B. Methylcyclohexane Solvent.[49]—No rearrangement was observed when adamantane was heated with aluminum chloride, using methylcyclohexane solvent. The details of the experiment were as with *endo*-trimethylenenorbornane (I).

Hydrogen–halogen Exchange with endo-Trimethylenenorbornane (I).—A 500-ml. 3-necked flask equipped with stirrer was charged with 100 g. (0.735 mole) of *endo*-trimethylenenorbornane (I) and 74 g. of *t*-butyl chloride and the reaction mixture cooled in an ice-bath. To this, 10 g. of aluminum chloride was added slowly and the reaction mixture was allowed to come to room temperature while stirring. A gas was given off, but the reaction did not appear to be exothermic. When heated on a steam-bath a vigorous evolution of gas took place, a sample of which was collected in a Dry Ice–acetone-bath. It did not decolorize bromine and boiled somewhat below 0°, properties compatable with isobutane, an expected reaction product. The reaction mixture refluxed at 52° initially, the boiling point of *t*-butyl chloride; the temperature then rose slowly to 65°, when the reaction was stopped. Water was added to decompose the aluminum chloride and the product was extracted with ether, washed with sodium carbonate and water and dried over sodium sulfate. Fractional distillation through a Vigreux column yielded solid starting material, b.p. 71–90° (14 mm.), and oily product, b.p. 90–125° (14 mm.), 21.2 g. Redistillation of the latter gave 11.4 g., b.p. 110–111° (17 mm.), characterized by infrared spectrum. Experiments conducted at lower temperatures failed to give any chloride product, only starting material.[27,28]

The chloride was dehydrohalogenated by 10 g. of sodium hydroxide in 114 g. of ethylene glycol at the boiling point. The olefin was distilled as it formed. After the appropriate preliminary isolation and purification steps, the olefin was distilled, b.p. 68–70° (17 mm.). The infrared spectrum was essentially identical with that of authentic *exo*-trimethylene-8-norbornene (VI,X = H) (*vide supra*).

Treatment of *exo*-Trimethylene-2-*exo*-norbornyl Chloride (XI, X = Cl) with $AlCl_3$.—A cold solution of 50 g. of *exo*-trimethylene-2-*exo*-norbornyl chloride[6] and 25 g. of isobutane was treated with 5 g. of $AlCl_3$. Stirring was continued overnight during which time the reaction mixture warmed to room temperature. Work-up revealed the presence of neither the expected hydrogen–halogen interchange product (III) nor of any rearranged product. The infrared spectrum of recovered chloride, b.p. 102–103° (13 mm.), was identical with that of the starting material.

A second experiment, omitting the isobutane and continuing the stirring at room temperature for 24 hours, also yielded only unchanged starting material, b.p. 106–107° (17 mm.), lit.[8] b.p. 102–104° (11–12 mm.).

Chromic Acid Oxidation of *endo*-Trimethylenenorbornane (I).—A reaction mixture consisting of 29.5 g. (0.226 mole) of *endo*-trimethylenenorbornane (I), 175 ml. of acetic acid and 175 ml. of acetic anhydride, and 47 g. (0.47 mole) of chromic anhydride was stirred at 80° for 90 minutes.[31] The solvent was stripped at reduced pressure, and the reaction mixture poured into water, extracted with ether, washed with sodium carbonate, and dried over sodium sulfate. Distillation gave the cuts: (1) b.p. up to 100° (15 mm.), 4.4 g. of solid, starting material; (2) b.p. 124–128° (15.5 mm), 3.8 g. of acetate, by infrared examination; (3) b.p. 128–176° (15 mm.), 2.5 g.; b.p. 176–177° (16 mm.), 2.3 g. The latter two cuts were highly oxygenated, because of the appearance of several bands in the carbonyl region of the infrared spectrum.

The acetate (3.8 g.) cut was saponified by 1.65 g. of potassium hydroxide dissolved in 15 ml. of ethanol and 1 ml. of water at reflux. After work-up, the product, b.p. 120–122° (16 mm.), was isolated by distillation; yield 1.15 g. (39%) of white solid, m.p. crude 94–109°. Besides the presence of a carbonyl band at 5.75 μ, the spectrum was identical with that of pure *endo*-trimethylene-5-*exo*-norbornyl alcohol (XII, X = OH), m.p. 135.6–136.0°.[33] Positive identification was made by derivatization.

***p*-Nitrobenzoate of XII, X = OH.**—The derivative was recrystallized six times from ethanol, m.p. 143.6–144.5°. *Anal.* Calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36. Found: C, 67.76; H, 6.25. The *p*-nitrobenzoate when made from authentic material[33] required 3 recrystallizations to give m.p. 144.6–145.2°, mixed m.p. 144.4–145.0°.

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

Tertiary Amines from Methiodides and Lithium Aluminum Hydride[1]

BY ARTHUR C. COPE, ENGELBERT CIGANEK, LEE J. FLECKENSTEIN AND MELVIN A. P. MEISINGER

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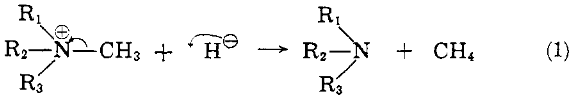
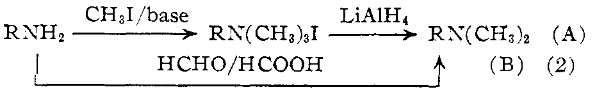
Suitable conditions for a little-used general synthesis of N,N-dimethyl tertiary amines from primary amines are described. The primary amine is treated with methyl iodide and a base, and the methiodide so obtained is reduced with lithium aluminum hydride in boiling tetrahydrofuran, forming a tertiary amine and methane. This method is compared with a standard procedure for methylating primary amines, the Clarke–Eschweiler reaction (treatment with formaldehyde and formic acid) in the preparation of N,N-dimethyl-(+)-neomenthylamine, N,N-dimethyl-(−)-menthylamine and (−)-N,N,α-trimethylbenzylamine. In each case the tertiary amines obtained by the two methods had identical optical rotations, indicating that the Clarke–Eschweiler method proceeds without epimerization of the carbon atom to which the amino group is attached.

The reduction of a quaternary ammonium salt to a tertiary amine with lithium aluminum hydride was first reported by Kenner and Murray[2] who suggested that this reaction proceeds by an SN2 displacement by hydride ion on the N-methyl group.



$$R_1R_2R_3\overset{\oplus}{N}{-}CH_3 + H^{\ominus} \longrightarrow R_1R_2R_3N + CH_4 \qquad (1)$$

Other methods of removing a methyl group from a quaternary salt involve treatment with potassium thiophenolate in triethylene glycol at 150–220°[3] or with ethanolamine at elevated temperatures.[4] It has been known for a long time that primary amines may be converted easily into quaternary iodides by the action of methyl iodide in the presence of a base. Combination of this method with lithium aluminum hydride reduction of the quaternary iodides to tertiary amines seemed to offer an attractive way of converting primary amines into N,N-dimethyl tertiary amines (path A in eq. 2), especially in cases where the standard method for dimethylating primary amines, treatment with formaldehyde and formic acid (the Clarke–Esch-



$$\begin{tikzcd} RNH_2 \arrow[r, "CH_3I/base"] \arrow[rr, bend right, "HCHO/HCOOH"'] & RN(CH_3)_3I \arrow[r, "LiAlH_4"] & RN(CH_3)_2 \end{tikzcd} \quad \begin{matrix}(A)\\(B)\end{matrix} \quad (2)$$

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[1] (1) Supported in part by the Office of Ordnance Research, U. S. Army, under Contract No. DA-19-020-ORD-4542.

[2] (2) G. W. Kenner and M. A. Murray, *J. Chem. Soc.*, 406 (1950).

[3] (3) E. R. Trumbull, J. Häberli and H. Ammon, Abstracts of Papers, American Chemical Society Meeting, Chicago, Ill., Sept. 7–12, 1958, p. 76-P.

[4] (4) S. Hünig and W. Baron, *Chem. Ber.*, **90**, 395 (1957).

weiler reaction,[5] path B in equation 2), gives low yields or is suspected to proceed with epimerization of a neighboring asymmetric center (see below).

In connection with other studies carried out in these laboratories, the following tertiary amines have been prepared by reduction of the corresponding methiodides: *cis*-2-phenylcyclohexyldimethylamine (78%),[6] 4-cycloöctenyldimethylamine (90%),[7] N,N-dimethylcyclononylmethylamine (80%),[8] *endo*-5-dimethylamino-2-norbornene (31%),[9] N,N-dimethyl-2-*t*-butyl-3,3-dimethylbutylamine (88%),[10] N,N-dimethyl-(−)-menthylamine (75%),[11] N,N-dimethyl-(+)-neomenthylamine (87%)[11] and *cis*-2-dimethylaminocyclohexanol (11%).[12] The yields given in parentheses are not necessarily the highest that are obtainable, since in these cases the method described below for quantitatively following the progress of the reduction was not used. The reduction of methiodides to tertiary amines with lithium aluminum hydride has been applied in a few cases by other workers.[13,14]

The method consists in treatment of the methiodide with a large excess of lithium aluminum hydride in anhydrous tetrahydrofuran at the reflux temperature; in cases where the reaction is slow, higher-boiling solvents like dioxane or N-methylmorpholine may be used to advantage. The progress of the reduction may be followed easily by measuring the amount of gas evolved. The gas was identified as methane on the basis of its mass spectrum,[15] a finding which serves to substantiate the mechanism suggested for this reaction. The methiodides used in this study and the products of their reduction with lithium aluminum hydride are shown in Table I. These results, together with those published elsewhere (see above) show that this method of preparing tertiary amines from methiodides appears to be generally applicable, giving good to excellent yields with the exception of methiodides containing a benzyl or α-methylbenzyl group, where attack of the hydride ion on the benzyl carbon atom (with formation of toluene or ethylbenzene and trimethylamine) competes with displacement on an N-methyl group. Other substituted benzyl groups and allyl or substituted allyl groups also would be expected to undergo some displacement by hydride, with reduction in the yield of the N,N-dimethylamines.

In connection with other studies it was of interest to compare the stereospecificity of this method with that of the Clarke–Eschweiler reaction. Carbonyl compounds have been found among the products of this latter reaction in a number of cases.[6,14,16–20]

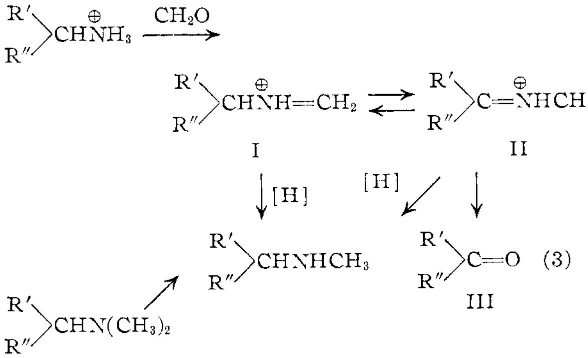
TABLE I

REDUCTION OF QUATERNARY IODIDES $RN(CH_3)_3I$ WITH LITHIUM ALUMINUM HYDRIDE IN TETRAHYDROFURAN

R	Reacn. time, hr.	*t*-Amine, %	Hydrocarbons, %
Cyclohexyl[a]	160	94[b]	0
Cycloöctyl[c,d]	72	72[e,f]	—[g]
Benzyl[h]	116	37[i]	52[j]
(−)-α-Methylbenzyl[k]	43	40[k]	43[l]
(+)-Neomenthyl[k]	24	74[f,k]	4[m]
trans-1,2-Bis-(dimethylamino)-cyclohexane bis-methiodide[k]	48	96[f,n]	—[g]

[a] Prepared in 90% yield from N,N-dimethylcyclohexylamine and methyl iodide, m.p. 268° dec.; A. Skita and H. Rolfes, *Ber.*, **53**, 1242 (1920), report m.p. 277°. [b] B.p. 75° (45 mm.), $n^{25}D$ 1.4515; J. D. Roberts and V. C. Chambers, THIS JOURNAL, **73**, 5030 (1951), report b.p. 75° (47 mm.), $n^{25}D$ 1.4517. [c] K. Ziegler and H. Wilms, *Ann.*, **567**, 1 (1950). [d] Reduced in N-methylmorpholine at 90–95°. [e] Isolated as the picrate, m.p. 197–198°, undepressed by admixture with an authentic sample; A. C. Cope and L. L. Estes, THIS JOURNAL, **72**, 1128 (1950). [f] The reduction was not followed quantitatively, and the value therefore does not necessarily represent the optimum yield. [g] Not determined. [h] Prepared in 88% yield from N,N-dimethylbenzylamine and methyl iodide, m.p. 178–180° dec.; M. Tiffenau and K. Fuhrer, *Bull. soc. chim. France*, [4] **15**, 162 (1914), report m.p. 178–179°. [i] B.p. 77° (25 mm.), $n^{25}D$ 1.4987. [j] Toluene. [k] See Experimental section. [l] Ethylbenzene. [m] Mixture containing 2-menthene, according to its retention time on gas chromatography and a positive test for unsaturation. [n] Isolated as the bis-hydrochloride.

It has been proposed[17] that these by-products arise through isomerization of the intermediate I to structure II, which on hydrolysis yields the carbonyl compound III (eq. 3). Establishment of the equilibrium I → II may lead to partial or complete epimerization of the carbon atom to which the nitrogen function is attached, if it is an asymmetric center. Indirect evidence for such an epimerization has been reported in the Clarke–Eschweiler methylation of *cis*-2-phenylcyclohexylamine.[6] The method of direct quaternization of the primary amine followed by reduction of the methiodide (path A in equation 2), on the other hand, may be



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[5] M. L. Moore, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 301.

[6] A. C. Cope and C. L. Bumgardner, THIS JOURNAL, **79**, 960 (1957).

[7] A. C. Cope and C. F. Howell, to be published.

[8] A. C. Cope, E. Ciganek, C. F. Howell and E. E. Schweizer, *ibid.*, **82**, 4663 (1960).

[9] A. C. Cope and N. A. LeBel, unpublished results.

[10] A. C. Cope and D. L. Ross, to be published.

[11] A. C. Cope and E. M. Acton, *ibid.*, **80**, 355 (1958).

[12] A. C. Cope, E. Ciganek and J. Lazar, to be published.

[13] N. G. Gaylord, "Reductions with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp. 787–793.

[14] J. McKenna and J. B. Slinger, *J. Chem. Soc.*, 2759 (1958).

[15] We are indebted to Dr. K. Biemann and his associates for the determination.

[16] H. Rupe, F. Buxtorf and F. Flatt, *Helv. Chim. Acta*, **13**, 1026 (1930).

[17] H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

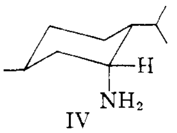
[18] W. E. Parham, W. T. Hunter, R. Hanson and T. Lahr, *ibid.*, **74**, 5646 (1952).

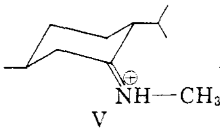
[19] C. A. Grob, H. Kny and A. Gagneux, *Helv. Chim. Acta*, **40**, 130 (1957).

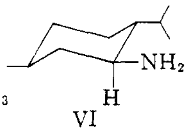
[20] B. B. Gent and J. McKenna, *J. Chem. Soc.*, 137 (1959).

expected to be stereospecific inasmuch as this sequence does not involve the asymmetric center.

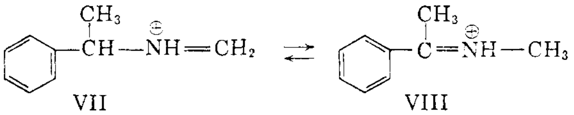
The stereospecificity of these two methods was compared in the methylation of (+)-neomenthylamine (IV), (−)-menthylamine (VI) and (−)-α-methylbenzylamine. Establishment of the equilibrium I → II in the Clarke–Eschweiler methylation of IV and VI would lead to the formation of


IV


V


VI

the isomerized intemediate V (corresponding to II in eq. 3) which on reduction by formic acid and further reaction with formaldehyde would be expected to give rise to a mixture of the two epimeric tertiary amines. This assumption is based on the stereochemical course of the reduction of enamines with formic acid[21] and of the Leuckart reaction[22]; in these reactions hydrogen is added from the least hindered side to the double bonds of intermediates which are similar to V. In V the side of the isopropyl group is only slightly more hindered as evidenced by the fact that menthone, on catalytic hydrogenation in acid solution as well as on reduction by the Meerwein–Ponndorf–Verley method, yields mixtures of both epimeric alcohols in which the product of hydrogen addition from the side opposite to the isopropyl group, neomenthol, predominated only slightly over menthol (74:26 and 66:34, respectively, for the two reactions).[23] (−)-α-Methylbenzylamine also was chosen for study because in an equilibrium VII → VIII (corresponding to I → II in equation 3) VIII would be favored


VII VIII

because of its increased resonance stabilization and accordingly this would be expected to be a particularly favorable case for partial epimerization during the Clarke–Eschweiler methylation. Snyder and Brewster[24] submitted (+)-α-methylbenzylamine to the Clarke–Eschweiler methylation and converted the (+)-N,N-α-trimethylbenzylamine so obtained to its methiodide, which had a specific rotation (in water at 26°) of +11.88°. The same methiodide, prepared by Biilman, Jensen and Jensen[25] by direct quaternization of (+)-α-methylbenzylamine, had a specific rotation (in ethanol at 20°) of +19.60°. These results might be interpreted as indicating that some epimerization did indeed occur during the Clarke–Eschweiler methylation. It should be noted that the methiodide of (+)-N,N-dimethyl-β-phenylisopropylamine prepared from (+)-β-phenylisopropylamine by methylation by the Clarke–Eschweiler method, followed by treatment of the tertiary amine with methyl iodide, had the same specific rotation as the methiodide prepared by direct quaternization of the primary amine.[18] In this case, however, there is no resultant increase in resonance stabilization to favor isomerization to an intermediate corresponding to II (eq. 3).

(+)-Neomenthylamine (IV) was prepared by the treatment of (−)-menthyl tosylate with excess ammonia. The reaction was very sluggish, and approximately 40% of the tosylate was recovered; however, a 40% yield (based on starting material not recovered) of the amine was obtained. Considerable elimination to yield menthene also was observed, as expected by analogy with the solvolysis of *trans*-4-*t*-butylcyclohexyl tosylate (in which the tosyl group also occupies an equatorial position).[26] Purification of IV was accomplished by conversion to its N-formyl derivative, which was crystallized to constant rotation. Treatment of the pure amine with formaldehyde and formic acid gave a 67% yield of N,N-dimethyl-(+)-neomenthylamine, having a rotation of $\alpha^{24}\text{D}$ +53.39°. The tertiary amine prepared by direct quaternization followed by reduction of the methiodide with lithium aluminum hydride had a rotation of $\alpha^{24}\text{D}$ + 53.47°. The N,N-dimethyl-(+)-neomenthylamine prepared by the two methods was shown by gas chromatography to be free of N,N-dimethylmenthylamine. Methylation of (−)-menthylamine (VI) by the Clarke–Eschweiler method gave a 71% yield of N,N-dimethyl-(−)-menthylamine, having a rotation of $\alpha^{26}\text{D}$ −51.20°. It contained no N,N-dimethylneomenthylamine as shown by gas chromatography. The N,N-dimethyl-(−)-menthylamine prepared previously[11] by direct quaternization followed by reduction of the methiodide had a rotation of $\alpha^{25}\text{D}$ −51.20°. Menthone was not detected among the products of the Clarke–Eschweiler methylation of IV and VI.

(−)-α-Methylbenzylamine was methylated with formic acid and formaldehyde to give the corresponding tertiary amine in 78% yield, $\alpha^{28}\text{D}$ −63.12°. Acetophenone (3%) was also isolated from the reaction mixture. The formation of a considerable quantity of neutral high-boiling material indicates that the carbonyl compound was formed in larger amounts but reacted further under the condition of the methylation. The (−)-N,N,α-trimethylbenzylamine prepared by the reduction of the methiodide (Table I) had a rotation of $\alpha^{28}\text{D}$ −62.94°. Methylation of the tertiary amine prepared by the Clarke–Eschweiler procedure yielded a methiodide having specific rotations (in water and in ethanol) essentially identical with those of the product of direct quaternization of the primary amine. It was found that the specific rotation of an alcoholic solution of (−)-N,Nα-trimethylbenzylamine methiodide was considerably higher than that of an aqueous solution. The difference in rotation of the methiodides prepared earlier[24,25] by the two methods may therefore be attributable to the fact that the rotations were measured in different solvents.

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(21) N. J. Leonard and R. R. Sauers, THIS JOURNAL, **79**, 6210 (1957), and references cited there.

(22) R. R. Sauers, *ibid.*, **80**, 4721 (1958); *cf.* also references in ref. 21.

(23) W. Hückel and C. Z. Khan Cheema, *Chem. Ber.*, **91**, 311 (1958).

(24) H. R. Snyder and J. H. Brewster, THIS JOURNAL, **71**, 291 (1949).

(25) E. Billman, K. A. Jensen and H. B. Jensen, *Bull. soc. chim. France*, [5] **3**, 2295 (1936).

(26) S. Winstein and N. J. Holness, THIS JOURNAL, **77**, 5562 (1955).

The results show that the Clarke–Eschweiler reaction proceeds without epimerization of the three amines investigated, despite the fact that a carbonyl compound was isolated in one case. This is in agreement with the finding of McKenna and Slinger[14] that both (+)-bornylamine and (−)-isobornylamine, on methylation by the Clarke–Eschweiler procedure, yielded the corresponding N,N-dimethyl derivatives "without appreciable epimerization" although camphor was formed in both cases in a yield of 17%. If the formation of carbonyl compounds in the Clarke–Eschweiler methylation proceeds by the sequence shown in eq. 3, then it must be postulated that the isomerized Schiff base II is converted entirely to the carbonyl compound III and undergoes neither reconversion to the isomeric I nor reduction to the secondary amine.

Inasmuch as the stereospecificity of the Clarke–Eschweiler reaction observed in this investigation may be expected to hold for the methylation of most primary amines, this procedure remains the most convenient and economical general method for the preparation of N,N-dimethyl tertiary amines. The reaction of methiodides with lithium aluminum hydride, however, should prove to be a valuable supplementary method in certain instances in which the Clarke–Eschweiler reaction gives poor yields. On occasion also it might be desirable to prepare a tertiary amine through the quaternary salt because the salt can be purified by recrystallization.

Experimental[27]

Preparation of Quaternary Iodides by Direct Quaternization.—A mixture of the primary amine (0.1 mole), sodium bicarbonate (0.3 mole), methyl iodide (0.3 mole) and methanol (*ca.* 10 times the volume of the primary amine) was heated under reflux with stirring (magnetic stirrer) for 75 hours. Methyl iodide was added after 24 and 48 hours; the total amount of methyl iodide used was about 0.45 mole. The reaction mixture was evaporated to dryness under reduced pressure, using a rotary evaporator, and the residual solid was extracted three times with boiling chloroform (each time with 10 times the volume of the primary amine used in the preparation). The combined extracts were cooled, filtered, and evaporated to dryness. The residual crude methiodide was recrystallized from absolute alcohol and dried under reduced pressure. In a number of preparations the evaporated reaction mixture was dried and used for the reduction without prior separation of the methiodides from the inorganic salts by chloroform extraction.

Reduction of Methiodides.—The reduction was carried out in a three-necked flask fitted with an efficient reflux condenser, a magnetic stirrer and an electric heating mantle. The condenser was connected through a drying tube (Drierite) to a gasometer. Anhydrous tetrahydrofuran (distilled from sodium; *ca.* 15 ml. for each gram of methiodide) and lithium aluminum hydride (0.5 mole) were introduced into the flask and the mixture was heated under reflux for one hour. The finely ground methiodide (0.1 mole) was added in a single portion and the mixture was heated under reflux with stirring until the evolution of methane had ceased. A cold 25% aqueous solution of sodium hydroxide (2 moles) was added very slowly with stirring to the cooled (ice-bath) reaction mixture, which was then steam distilled until no more basic material came over. The distillate was acidified with concentrated hydrochloric acid and concentrated to a small volume. In preparations in which isolation of any hydrocarbon formed in the reduction was desired, the acidified distillate was extracted three times with pentane before concentration. The isolation of the hydrocarbons from the pentane solution is described below. The amine was liberated from the solution of its hydrochloride by addition of sodium hydroxide pellets and extracted with ether. The combined ether extracts were dried over potassium hydroxide pellets for 4 hours. The tertiary amine was obtained by distillation of the dried ether solution through a semi-micro column.

To isolate the hydrocarbons the pentane extracts were washed with sodium carbonate solution and water and dried over magnesium sulfate. The pentane and most of the tetrahydrofuran were removed by distillation through a semi-micro column; the residue was distilled without fractionation and the resulting mixture of tetrahydrofuran, 1-butanol (from reduction of the solvent, tetrahydrofuran) and hydrocarbon was analyzed by gas chromatography using Silicone oil (30% on base-washed firebrick) as the stationary phase. The yield of hydrocarbon was calculated from the gas chromatogram. Small samples of the hydrocarbons were isolated by preparative gas chromatography and identified by their infrared spectra.

Clarke–Eschweiler Methylation.—The primary amine (0.1 mole) was dissolved, with external cooling, in 98–100% formic acid (0.5 mole), and a 37% aqueous solution of formaldehyde (0.3 mole) was added at once. The mixture was heated to 100°; the heating bath was removed as soon as gas evolution set in. After the evolution of carbon dioxide had ceased, the mixture was heated under reflux for 5–6 hours. The cooled reaction mixture was poured into ice-cold 10% hydrochloric acid (0.11 mole), the aqueous solution was extracted four times with ether, the combined ether extracts were washed with sodium carbonate solution and water, and dried over magnesium sulfate. Distillation through a semi-micro column afforded the ketonic fraction. The amine was isolated from the acidified aqueous solution as described for the isolation from the lithium aluminum hydride reduction.

(−)-α-Methylbenzylamine.—D,L-α-Methylbenzylamine (Eastman Kodak Co. white label) was resolved with (+)-tartaric acid by the method of Theilacker and Winkler.[28] The third crop of the acid tartarate was crystallized from water (1.8 times the amount of the salt), and the resulting crystals were combined with the second crop and again crystallized from water. This was repeated after addition of the first crop; the yield of (−)-α-methylbenzylamine (+)-hydrogen tartarate, $[\alpha]^{29}_{\mathrm{D}}$ + 12.80° (in water, *c* 8) (lit.[29] $[\alpha]_{\mathrm{D}}$ + 13.0° to + 13.2°, *c* 8 in water), was 55%. The amine, recovered in 94% yield, had b.p. 93–94° (32 mm.), n^{25}_{D} 1.5244, d^{28}_{4} 0.951, α^{28}_{D} − 37.34°, $[\alpha]^{28}_{\mathrm{D}}$ − 39.26° (lit.[28] d^{22}_{4} 0.950, α^{22}_{D} − 38.30°, $[\alpha]^{22}_{\mathrm{D}}$ −40.3°). It formed a carbonate with extreme ease, and all operations were therefore carried out with the exclusion of atmospheric carbon dioxide.

(−)-N,N,α-Trimethylbenzylamine. (A) By the Clarke–Eschweiler Method.—The tertiary amine obtained in 78% yield had b.p. 85° (20 mm.), n^{25}_{D} 1.5005, $d^{28.2}_{4}$ 0.901, $\alpha^{28.2}_{\mathrm{D}}$ −63.12°, $[\alpha]^{28.2}_{\mathrm{D}}$ −70.05° (lit.[30] n^{14}_{D} 1.5025, d^{16}_{4} 0.8986, α^{20}_{D} −32.24°, *l* 0.5). The methiodide, obtained in 96% yield from the tertiary amine by treatment with methyl iodide, melted at 156–157° dec. after one crystallization from ethanol; $[\alpha]^{28.4}_{\mathrm{D}}$ −13.59° (*c* 12.3 in water) (lit.[25] m.p. 156.5–157°, $[\alpha]^{20}_{\mathrm{D}}$ −19.60°, *c* 2.5 in ethanol). From the neutral fraction there was obtained a 3.2% yield of acetophenone and a high-boiling residue weighing *ca.* three times as much as the ketone. The yields obtained in the Clarke–Eschweiler methylation of unresolved α-methylbenzylamine were 79% of N,N,α-trimethylbenzylamine, b.p. 88° (22 mm.), n^{25}_{D} 1.5003 (lit.[31] b.p. 71° at 11 mm., n^{25}_{D} 1.5000) and 4% of acetophenone, b.p. 77° (8 mm.), m.p. of the 2,4-dinitrophenylhydrazone 250°, undepressed by admixture with an authentic sample.

(B) By Reduction of the Methiodide.—The crude methiodide, obtained by direct quaternization of (−)-α-methylbenzylamine, weighed 6% more than the theoretical amount, m.p. 147–157°; it was reduced without further purification.

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(27) Melting points are corrected and boiling points are uncorrected. Gas chromatographic analyses were carried out using 180 × 0.8-cm. Pyrex tubes packed with 48/100-mesh firebrick (Johns-Manville) which was coated with the appropriate stationary phase. The samples were eluted with helium at 15 p.s.i. and thermal conductivity cells were used as detectors. Optical rotations are those of the pure liquids, unless otherwise stated, and were determined in tubes of 1 dm. length.

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A small sample, crystallized from ethanol, had m.p. 156–157°, $[\alpha]^{28.4}\mathrm{D}$ −13.64° (*c* 12.3 in water), $[\alpha]^{28.4}\mathrm{D}$ −20.54° (*c* 2.5 in ethanol). Reduction with lithium aluminum hydride gave (−)-N,N,α-trimethylbenzylamine (40% yield), b.p. 84–85° (30 mm.), $n^{25}\mathrm{D}$ 1.5004, $\alpha^{28.2}\mathrm{D}$ −62.94°, $[\alpha]^{28.2}\mathrm{D}$ −69.85°, and 43% of ethylbenzene. From unresolved α-methylbenzylamine the methiodide, m.p. 145–146° (lit.[32] m.p. 145–146°), was obtained in 90% yield after one crystallization from ethanol. Reduction of the purified methiodide gave N,N,α-trimethylbenzylamine in 67% yield, b.p. 87° (21 mm.), $n^{25}\mathrm{D}$ 1.5002, and 18% of ethylbenzene. The difference between the yields of the optically active and inactive amines presumably is due to the heterogeneous character of the reaction mixture which must not have been identical in all respects.

(−)-Menthyl *p*-Toluenesulfonate.—A solution of 100 g. of (−)-menthol (Matheson Co.) in 200 ml. of dry pyridine was cooled to 0° and added to a solution of 245 g. of *p*-toluenesulfonyl chloride in 320 ml. of pyridine, also cooled to 0°. Following addition of 120 ml. of pyridine to the mixture, it was permitted to stand at 10° for 36 hr., then poured into a 4-l. separatory funnel. The product which precipitated upon addition of 2 l. of water was taken up in 500 ml. of ether, and the aqueous phase was extracted three times with ether. After washing with two 250-ml. portions each of dilute hydrochloric acid, sodium bicarbonate solution and water, the combined ethereal solutions were dried over magnesium sulfate. Concentration of the solution gave a yellow solid, which was recrystallized from 140 ml. of acetone, giving 163 g. of (−)-menthyl *p*-toluenesulfonate, m.p. 92.0–93.7°. From the mother liquors a second crop, m.p. 91.9–93.5°, was isolated. The total yield was 189 g. (95%).

(+)-Neomenthylamine.—A mixture of 243.5 g. of (−)-menthyl *p*-toluene-sulfonate and 450 ml. of liquid ammonia was heated at 50–60° in a 1.5-l. stainless steel bomb for 110 hr. The bomb was cooled to room temperature and vented. Water (300 ml.) was added, and the mixture was filtered to remove 90 g. of unreacted (−)-menthyl *p*-toluenesulfonate. The organic phase of the filtrate was separated, the aqueous layer was extracted with three 50-ml. portions of ether, and the ethereal extracts were added to the original organic phase. The combined solutions were extracted three times with 2.5 *N* hydrochloric acid and dried over magnesium sulfate. Concentration of the dried solution gave 31 g. of a yellow liquid which partially crystallized on seeding with (−)-menthyl *p*-toluenesulfonate and was probably a mixture of menthene and 5–10 g. of starting material. A total of 95–100 g. (*ca.* 40%) of (−)-menthyl *p*-toluenesulfonate was recovered. The acidic extracts were made strongly alkaline with sodium hydroxide, the amine was taken up in petroleum ether, and the aqueous phase was extracted three times with petroleum ether. The combined extracts were dried over magnesium sulfate; on distillation 30.2 g. (25% conversion, *ca.* 40% yield, based on starting material not recovered) of (+)-neomenthylamine, b.p. 65–65.5° (3.8 mm.), was obtained. The amine had $\alpha^{31}\mathrm{D}$ + 10.3° (*c* 4.5 in chloroform) (lit.[33] $\alpha^{25}\mathrm{D}$ + 8.7°, *c* 1 in chloroform).

To 30 g. of (+)-neomenthylamine was added, with cooling, 10 g. of 98–100% formic acid. The resulting salt was heated at 150° for 2 hr. and at 180° for 7 hr. Water was removed by distillation from the melt, which solidified on cooling. The crude N-formyl-(+)-neomenthylamine was recrystallized 7 times from methanol to constant rotation, yielding 22.9 g. (58%) of the pure compound, m.p. 117–118°, $[\alpha]^{30}\mathrm{D}$ + 59.0° (*c* 5 in absolute ethanol) (lit.[11] m.p. 117.2–118.2°, $[\alpha]^{25}\mathrm{D}$ + 59.9°, *c* 5 in absolute ethanol). The N-formyl-(+)-neomenthylamine was heated under reflux with concentrated hydrochloric acid (3 times by weight of the amount of the N-formyl derivative) for 2 hr. The mixture was cooled, the amine was liberated by the addition of sodium hydroxide, and taken up in petroleum ether. The aqueous phase was extracted three times with petroleum ether, and the combined extracts were dried and concentrated. The residual amine was used without further purification.

N,N-Dimethyl-(+)-neomenthylamine. (A) By Clarke–Eschweiler Methylation.—The tertiary amine obtained in 67% yield had b.p. 69–73° (3.6 mm.), $n^{25}\mathrm{D}$ 1.4599–1.4602, $\alpha^{24}\mathrm{D}$ + 53.39° (lit.[11] b.p. 89–90° at 7 mm., $n^{25}\mathrm{D}$ 1.4600–1.4602, $\alpha^{25}\mathrm{D}$ + 52.82°). Gas chromatography, using Silicone oil as the stationary phase at 170°, showed that the product was uncontaminated by N,N-dimethylmenthylamine or other compounds.

(B) **By Reduction of the Methiodide.**—N,N-Dimethyl-(+)-neomenthylamine methiodide was obtained in 90% yield after one crystallization from acetone–pentane. The methiodide (11.7 g.) was reduced as described in the general procedure, but the tertiary amine was isolated using a somewhat different method. The cooled reaction mixture was hydrolyzed by careful addition of 20 ml. of water. Ether (100 ml.) was added, and the mixture was refluxed for 2 hr., cooled, and filtered. After the filter cake had been washed with ether, the filtrate and washings were concentrated by distillation. The residue was washed with five 50-ml. portions of water to remove tetrahydrofuran, and the remaining organic material was dissolved in pentane. The pentane solution was extracted with two 45-ml. portions of 2 *N* hydrochloric acid and two 25-ml. portions of water, and the aqueous acidic washings were combined and treated with a solution of 10 g. of sodium hydroxide in 50 ml. of water. The amine was taken up in pentane, the aqueous layer was extracted several times with pentane, and the combined extracts were dried over magnesium sulfate. The solvent was removed and the residue, on distillation through a semimicro column, gave 4.9 g. (74%) of N,N-dimethyl-(+)-neomenthylamine, b.p. 75–76.5° (4.5 mm.), $n^{25}\mathrm{D}$ 1.4600, $\alpha^{24}\mathrm{D}$ + 53.47°. Gas chromatography on Silicone oil at 170° showed the product to be homogeneous. The acid-washed pentane solution of neutral products was dried over magnesium sulfate and concentrated; short-path distillation of the residue yielded 0.20 g. (3.6%) of hydrocarbon, $n^{25}\mathrm{D}$ 1.4448. Addition of bromine gave a positive test for unsaturation, and gas chromatographic analysis, using a saturated solution of silver nitrate in tetraethylene glycol (30% on firebrick) as the stationary phase at 63°, showed the presence of two components. The retention time of one of the components on this column as well as one containing Silicone oil as the stationary phase (at 170°) was identical with that of 2-menthene.

N,N-Dimethyl-(−)-menthylamine.—Methylation of (−)-menthylamine[11] by the Clarke–Eschweiler method gave N,N-dimethyl-(−)-menthylamine in 71% yield, b.p. 67–67.5° (3.3 mm.), $n^{25}\mathrm{D}$ 1.4546–1.4549, $\alpha^{26}\mathrm{D}$ − 51.20° (lit.[11] b.p. 85° at 7 mm., $n^{25}\mathrm{D}$ 1.4552, $\alpha^{25}\mathrm{D}$ − 51.20°).

***trans*-1,2-Bis-(N,N-dimethylamino)-cyclohexane.**—The crude bis-methiodide of *trans*-1,2-bis-(N,N-dimethylamino)-cyclohexane, obtained from *trans*-1,2-diaminocyclohexane[34] by direct quaternization, was reduced with lithium aluminum hydride without prior purification. The acidified steam distillate was evaporated to dryness and gave a 96% yield (based on *trans*-1,2-diamino-cyclohexane) of crude bis-hydrochloride. The bis-picrate of *trans*-1,2-bis-(N,N-dimethylamino)-cyclohexane, prepared by addition of a saturated ethanolic picric acid solution to the bis-hydrochloride, had m.p. 213.5° dec. (lit.[34] 203–204°).

CAMBRIDGE, MASS.

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