of the products being checked by melting point and mixture melting points.

IX (contaminated with the corresponding thiolsulfonate ester) (m.p. 110–114°) was suspended in dry carbon tetrachloride and boiled for 30 min. The material was recovered unchanged. Treatment of IX with 100% ethanol gave an immediate precipitate of a very pale yellow, highly crystalline solid (m.p. 145–146°) [lit. m.p. of III (Ar = 2-nitrophenyl) = 143°]. Treatment of IX with distilled water yielded a residue of m.p. 143–144° which showed no mixture melting point depression with the corresponding product from ethanol.

X (contaminated with the corresponding thiolsulfonate ester) (m.p. 125–132°) yielded a pale yellow crystalline solid (m.p. 144–145°) upon treatment with 100% ethanol [lit. m.p. of III (Ar = 2-nitro-4-chlorobenzene) = 145°]. The same product resulted from treatment of this nitrate with distilled water.

The ultraviolet spectrum of 2,4-dinitrobenzenesulfenyl nitrate was determined in acetonitrile solvent using a Cary recording spectrophotometer (model 14): λ_{max} = 245 mμ (ϵ_{max} 11,540).

Infrared spectra were determined using a Perkin–Elmer Infracord spectrophotometer. It was noted that even Nujol promoted decomposition of the nitrates and thus all infrared spectra were made using potassium bromide disks. The detailed spectra of $ArSONO_2$, ArSCl, and $ArSO_2SAr$ (Ar = 2,4-dinitrophenyl) have been deposited in the collection of the Instrumentation Research Center, Los Angeles, California,[8] from whom copies may be obtained at minimal cost. The spectral patterns clearly differentiate the three products.

Acknowledgment.—The assistance of Dr. John A. Biles, University of Southern California, School of Pharmacy, in the X-ray irradiations and interpretations and the support of the Office of Scientific Research, United States Air Force, and of the Stauffer Chemical Company are gratefully acknowledged.

(8) Intra-Science Research Foundation, Instrumentation Research Center, 2404 Wilshire Boulevard, Los Angeles 57, Calif.

A Convenient Stereospecific Synthesis of Axial Amines in Some Steroidal, Decalyl, and Cyclohexyl Systems[1]

JACK L. PINKUS, GERALDINE PINKUS, AND THEODORE COHEN

Contribution No. 1137 from the Department of Chemistry, University of Pittsburgh, Pittsburgh 13, Pennsylvania

Received July 5, 1962

It has been shown that ammonolysis of a variety of equatorial sulfonate esters in steroidal, decalyl, and cyclohexyl systems furnishes axial amines free of structural and stereochemical isomers. The simplicity, the exceedingly high stereospecificity, and the nonreductive nature of the reaction makes this the preferred method for the synthesis of axial amines.

In connection with studies on substitution reactions in rigid systems, we have sought to develop a simple method for the stereospecific synthesis of cycloalkyl axial amines. Two popular routes to axial amines have been platinum-catalyzed hydrogenation in acetic acid solution[2–5] or lithium aluminum hydride reduction of the appropriate oxime.[4,6–9] Although the first of these methods is widely used, it suffers from several disadvantages. The alcohol, which is the usual starting material in these reactions, must be oxidized to the ketone and the latter converted to oxime. The oxime is sometimes a mixture of *syn* and *anti* isomers[10,11] and is thus difficult to purify. Often the hydrogenation is not reproducible and it frequently gives poor yields,[8,12] an important side product being secondary amine.[12,13] Furthermore, the axial amine obtained is usually contaminated with varying amounts of the equatorial isomer and in one case, that of coprostanone oxime, the equatorial amine appears to be formed exclusively.[4] Another factor that limits the utility of this method is its reductive nature which precludes the preparation of axial amines bearing reducible groups. Reduction of the oxime with lithium aluminum hydride furnishes mixtures, containing both equatorial and axial amines, which are usually difficult to separate. Although separation of the epimeric amines *via* their amide derivatives is sometimes possible, the very hindered axial amides are difficult to cleave.[2,12]

The Hofmann and Curtius reactions have also been used in some instances, but the preparation of the requisite axial carboxylic acid involves a multistep sequence entailing severe losses.[14,15] Occasionally, reductive amination of the appropriate cyclic ketone with ammonium formate has been

(1) This work was supported by grants from the Health Research and Services Foundation and from the Frederick Gardner Cottrell Fund of the Research Corporation.

(2) W. Hückel, R. Danneel, A. Gross, and H. Naab, *Ann.*, **502**, 99 (1933).

(3) D. Y. Curtin, R. D. Stolow, and W. Maya, *J. Am. Chem. Soc.*, **81**, 3330 (1959).

(4) C. W. Shoppee, D. E. Evans, H. C. Richards, and G. H. R. Summers, *J. Chem. Soc.*, 1649 (1956).

(5) G. Drefahl and S. Huneck, *Ber.*, **93**, 1961, 1967 (1960).

(6) D. E. Evans and G. H. R. Summers, *J. Chem. Soc.*, 906 (1957).

(7) R. A. B. Bannard and A. F. McKay, *Can. J. Chem.*, **33**, 1166 (1955).

(8) L. Labler, V. Černý, and F. Šorm, *Collection Czech. Chem. Commun.*, **19**, 1249 (1954).

(9) C. W. Bird and R. C. Cookson, *J. Chem. Soc.*, 2343 (1960).

(10) N. L. McNiven and J. Read, *ibid.*, 153 (1952).

(11) W. Hückel and W. Doll, *Ann.*, **526**, 103 (1936).

(12) Unpublished observations of Jack L. Pinkus.

(13) E. Breitner, E. Roginski, and P. N. Rylander, *J. Chem. Soc.*, 2918 (1959).

(14) W. G. Dauben, R. C. Tweit, and R. L. MacLean, *J. Am. Chem. Soc.*, **77**, 48 (1955).

(15) H. C. Richards, C. W. Shoppee, J. C. R. Sly, and G. H. R. Summers, *J. Chem. Soc.*, 1054 (1956).

employed to produce an epimeric mixture of formamides apparently richer in the axial isomer.[16,17]

We have considered other possible approaches to axial amines and have chosen to investigate the ammonolysis of equatorial cycloalkyl tosylates. It is known that acetolysis[18] and methanolysis[19] of equatorial tosylates furnish cleanly inverted substitution products. Since ammonia is more nucleophilic than these solvents, the results of ammonolysis should be no less stereospecific. Furthermore, the very favorable steric requirements of an ammonia molecule compared to those of a highly hindered axial[20] amine[21] should favor the formation of a primary amine rather than that of a secondary amine, arising from the competitive attack of product amine on starting material. Such competition is a serious problem in ammonolysis generally.[22]

Results which would appear to contradict these views are found in the well studied[23-25] ammonolysis reaction of cholest-5-en-3β-yl tosylate which yields five amines, cholest-5-en-3β-amine, cholest-5-en-3α-amine, 3α,5-cyclo-5α-cholestan-6β-amine, and two secondary amines. However, in this case, the nonstereospecific nature of the reaction at carbon 3 as well as the formation of rearranged and secondary amines is explicable on the basis of homoallylic participation which is known to occur in this system.[26] Such deviations from the aforementioned expectations might not be encountered in systems lacking this neighboring group effect. Indeed, Haworth, Lunts, and McKenna[25] have reported the isolation in 38% yield of *N*-acetyl-5α-cholestan-3α-amine from the acetylation of the basic fraction of the reaction product obtained by ammonolysis of 5α-cholestan-3β-yl tosylate. In addition, Shoppee and co-workers[4,27] have reported the isolation of axial amides in unspecified yield from acetylation of the ammonolysis product of 5β-cholestan-3α-yl tosylate and 5α-cholestan-6β-ol-3α-yl tosylate. In none of the foregoing cases was evidence presented for the absence of the equatorial epimer in the reaction product.

In order to evaluate the synthetic utility of this type of reaction, we have studied yields and stereospecificity in the ammonolysis of equatorial sulfonate esters varying both the alcohol and sulfonic acid moieties. The results are summarized in Table I. The reactions were performed by heating a stainless steel bomb, which contained two to twelve grams of ester suspended in 50–100 ml. of anhydrous ammonia, for 19–24 hours in a water bath. The bomb was cooled and the ammonia was allowed to evaporate. The neutral and basic materials were separated by extraction techniques. Evaporation of the ether layer containing the basic fraction furnished the pure amine. Alternatively, the dried ether extract of the basic reaction mixture, which contains both olefin and amine, could be chromatographed or treated with either acetic anhydride or hydrogen chloride to furnish the pure amine derivative.

TABLE I

Ester	% yield of axial amine[a]	Isolated as
5α-Cholestan-3β-yl tosylate	70	Acetamide
	72	Free base
5α-Cholestan-3β-yl methanesulfonate	63	Acetamide
	59[b]	Free base
Menthyl tosylate	39	Acetamide
Menthyl brosylate	39	Acetamide
Menthyl *p*-methoxybenzenesulfonate	37	Acetamide
trans-4-*t*-Butylcyclohexyl tosylate	37	Hydrochloride
trans-cis-2-Decalyl tosylate[c]	41	Acetamide
	28[d]	Free base

[a] Unsaturated compounds are the major accompanying products. [b] Isolated by chromatography on alumina of the total non-acidic reaction product. [c] This *trans* fused decalin derivative is named according to W. G. Dauben, R. C. Tweit, and C. Mannerskantz, *J. Am. Chem. Soc.*, **76**, 4420 (1954). [d] The difference between the amide and the amine yields is ascribed to the unavoidable loss entailed in isolation of the amine by distillation. Purification by distillation is however almost certainly unnecessary.

The 5α-cholestan-3α-amine isolated from ammonolysis of the corresponding equatorial tosylate was shown to be analytically and optically pure without recrystallization.[28] Its structural and stereochemical purity was further shown by a controlled chromatographic analysis in which none of the more difficultly eluted equatorial amine was detected and by conversion to its sharp melting acetamide,[29] which was uncontaminated by the

(16) J. Read, A. M. R. Cook, and M. I. Shannon, *J. Chem. Soc.*, 2223 (1926).

(17) J. Read and G. J. Robertson, *ibid.*, 2168 (1927).

(18) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, **77**, 5562 (1955).

(19) N. Pappas, J. A. Meschino, A. A. Fournier, and H. R. Nace, *ibid.*, **78**, 1907 (1956).

(20) W. G. Dauben and K. S. Pitzer, "Steric Effects in Organic Chemistry," M. S. Newman, ed., John Wiley and Sons, Inc., New York, N. Y., 1956, chap. 1.

(21) H. C. Brown, D. H. McDaniel, and O. Häfliger, "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, ed., Academic Press Inc., New York, N. Y., 1955, pp. 634–643; G. S. Hammond, "Steric Effects in Organic Chemistry," M. S. Newman, ed., John Wiley & Sons, Inc., New York, N. Y., 1956, pp. 454–460.

(22) R. T. Morrison and R. N. Boyd, "Organic Chemistry," Allyn and Bacon, Inc., Boston, Mass., 1959, p. 532.

(23) P. L. Julian, A. Magnani, E. W. Myer, and W. Cole, *J. Am. Chem. Soc.*, **70**, 1834 (1948).

(24) R. D. Haworth, J. McKenna, and R. G. Powell, *J. Chem. Soc.*, 1110 (1953).

(25) R. D. Haworth, L. H. C. Lunts, and J. McKenna, *ibid.*, 986 (1955).

(26) C. W. Shoppee, *ibid.*, 1147 (1946); S. Winstein and R. Adams, *J. Am. Chem. Soc.*, **70**, 838 (1948); C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 3361 (1952).

(27) J. H. Pierce, H. C. Richards, C. W. Shoppee, B. J. Stephenson, and G. H. R. Summers, *ibid.*, 694 (1955).

(28) This is particularly fortunate since the amine is difficult to recrystallize in satisfactory yield.

(29) The amine derivatives reported in Table I were obtained as sharp melting solids as isolated directly from the reaction mixture.

higher melting epimer.[30] The basic fractions from the ammonolysis of the other tosylates listed in Table I contained exclusively the desired (liquid) amines judging from the purity of their derivatives listed in the table.[29] In addition, the stereochemical purity of the axial *trans-trans-2*-decalylamine was established by gas chromatography employing 20% Carbowax 20 M on silanized and base-washed Chromosorb W.[31a]

This simple stereospecific synthesis of axial[31b] amines starting from readily available materials appears to be considerably superior to any of the published methods.[32] The relatively mild and nonreductive reaction conditions should make this synthesis widely applicable. The apparent independence of amine yield on the nature of the sulfonate leaving group could also be very useful. If one of the esters is inconvenient to purify, others could be used. This independence is also of interest theoretically and is being investigated further.

Experimental[34]

Reaction of *trans-cis*-2-Decalyl Tosylate with Anhydrous Ammonia.—A mixture of 12.09 g. (0.0392 mole) of tosylate,[35,36] m.p. 64.5–65.5° (reported[35] m.p. 62.5–63°), recrystallized from *n*-pentane, and 90 ml. of anhydrous ammonia was placed in a steel bomb[37] which was maintained at 95–100° for 22.5 hr. The bomb, cooled below −40°, was opened and the ammonia allowed to evaporate. The residual solids were treated with 300 ml. of 2 *N* aqueous sodium hydroxide, and the mixture extracted with 150 ml. of ether. The aqueous layer was further extracted with three 55-ml. portions of ether. The combined ether extracts were washed with 20 ml. of water, then extracted with four 15-ml. portions of 1 *N* hydrochloric acid. The acid extract, after washing with 15 ml. of ether, was cooled to 0° and made basic with 20 ml. of 3 *N* sodium hydroxide solution. The cloudy mixture was extracted with three 35-ml. portions of ether; the extracts were then washed with three 10-ml. portions of water, shaken with decolorizing carbon, and filtered through Drierite to furnish a clear ether solution. After adjusting the volume to 110 ml., the solution was left over Drierite in a nitrogen atmosphere at 2° for 2 hr.

To a 10-ml. aliquot of the dried ether solution was added 0.35 ml. (3.5 mmoles) of acetic anhydride and the solution was allowed to remain at room temperature for 50 min. The clear reaction mixture was evaporated *in vacuo* on a rotary evaporator at room temperature; 5 ml. of methanol was added to the semisolid residue and evaporated as before. The addition of 5 ml. of methanol was repeated and the solution heated at reflux for 5 min. on the steam bath. The methanol was evaporated and the crystalline residue was dried in a vacuum desiccator containing solid potassium hydroxide for 24 hr. to furnish 0.282 g. (41%) of *N*-acetyl-*trans-trans*-2-decalylamine, m.p. 128–130°, m.p. of the resolidified melt (plates) 130.0–131.2°. Recrystallization from a mixture of acetone and water afforded 0.241 g. (35%) of minute prisms, m.p. 130–131°, resolidifying at 130° and remelting at 131–132° (lit.,[33,38] m.p. 130°). The epimer, *N*-acetyl-*trans-cis*-2-decalylamine, has the m.p. 163°.[33,38]

The main portion of the ether solution was concentrated and distilled through a short Vigreux column to give one fraction, 1.684 g. (28%) of *trans-trans*-2-decalylamine, b.p. 63–66°/2.5–3.0 mm., n^{24}D 1.4888, *N*-acetyl derivative, m.p. 130–131°.

Reaction of *trans*-4-*t*-Butylcyclohexyl Tosylate with Anhydrous Ammonia.—A mixture of 2.000 g. (0.00644 mole) of *trans*-4-*t*-butylcyclohexyl tosylate[18] and 50 ml. of anhydrous ammonia was placed in a steel bomb which was maintained at 95–100° for 24 hr. At the end of this period, the bomb was opened in the usual manner and the ammonia allowed to evaporate. The residue was then mixed with ether and 10% sodium hydroxide solution. The ether layer was separated, washed with 10% sodium hydroxide solution, then with water, and extracted with 10% hydrochloric acid. The acidic aqueous extract was made basic with 10% sodium hydroxide solution and extracted with ether. An anhydrous ethereal solution of hydrogen chloride was added to the dried (Drierite) extract to furnish the amine hydrochloride and the solvent was then removed under reduced pressure. The yield of *cis*-4-*t*-butylcyclohexylamine hydrochloride was 0.450 g. (37%), m.p. 275° (capillary method, corrected). After one recrystallization from a mixture of acetone and isopropyl alcohol the hydrochloride melted at 281–282° (capillary method, corrected), reported[3] m.p. 283°. The *trans*-4-*t*-butylcyclohexylamine hydrochloride is reported[3] to melt at 330° (uncor.).

Reaction of Menthyl Tosylate with Anhydrous Ammonia.—A mixture of 3.207 g. (0.0106 mole) of menthyl tosylate[39,40] and 50 ml. of anhydrous ammonia was heated at 95–100° in a steel bomb for 20 hr. The product amine was isolated in the usual way and acetylated in warm acetic anhydride to furnish a white solid. After cooling, the reaction mixture was mixed with water and then extracted with ether. The ether extract was washed with 10% sodium bicarbonate solution, then with water, dried over Drierite,

(30) The melting point of the free base is not a good criterion of its purity. Shoppee, *et al.*,[4] reported the m.p. 87–88°. We have also obtained samples melting in this range as well as a higher melting modification, m.p. 104.0–104.5°, produced by recrystallization from anhydrous ether at −77°. Interconversion of the two forms is discussed in the Experimental section. The amine obtained from our ammonolysis reactions was consistently the higher melting form apparently admixed with traces of the lower melting form which causes considerable softening at about 97° and melting at about 101–102°.

(31) (a) Unpublished results of Dr. M. Malaiyandi; (b) Preliminary experiments by Dr. M. Malaiyandi indicate that the pure equatorial *trans-cis*-2-decalylamine can be prepared in 13–15% yield by ammonolysis of the corresponding axial ester, *trans-trans*-2-decalyl tosylate.

(32) For example, there are only a few reports in the literature of the preparation of 5α-cholestan-3α-amine as the free base. In these cases, the yields have been reported only for the noncrystallizable liquid (4% yield)[3] and the crude solid (46%).[4] In the case of *cis*-4-*t*-butylcyclohexylamine, a 10.5% yield was reported.[3] Although *d*-neomenthylamine has been prepared previously, the yields are not stated and it is clearly poor in one preparation.[17,18] The properties of *trans-trans*-2-decalylamine have been studied and the synthetic method is stated but the yields in the synthesis are not reported.[2,33]

(33) W. Hückel, *Ann.*, **533**, 1 (1937).

(34) Melting points unless otherwise indicated were determined on a Kofler block utilizing polarized light with a stage calibrated thermometer and they are therefore corrected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. Rotations were determined in chloroform. The petroleum ether used had the b.p. 64–66°.

(35) I. Moritani, S. Nishida, and M. Murakami, *J. Am. Chem. Soc.*, **81**, 3420 (1959).

(36) We thank Mr. Edmond J. Jankowski for preparing this compound.

(37) The bomb (5.5 in. × 1.5 in. i.d.) was made by Mr. Albert E. Harrison of our machine shop from 1/4-in.-thick No. 316 stainless steel tubing with a 3/8-in. stainless steel bottom threaded in and hydrogen welded at the seam. At the top, a stainless steel flange was threaded to the outside of the tube and hydrogen welded at the joint. The flange (3.5-in. o.d.) contained a groove suitable for a 2 1/8 in. × 2 1/2 in. × 3/16 in. rubber O-ring and six threaded bolt holes for 10 × 32 socket head machine screws. The bomb was sealed with a circular 3/8-in.-thick stainless steel plate (3.5-in. diameter) fitted with a groove and bolt holes. In operation, the top is sealed by turning the bolts down firmly with an Allen wrench. Before adding anhydrous ammonia or opening the bomb, the contents and bomb are thoroughly cooled below −40° in a Dry Ice–acetone bath.

(38) W. Hückel, *Ann.*, **451**, 109 (1926).

(39) H. Phillips, *J. Chem. Soc.*, 2584 (1925).

(40) W. Hückel and H. Sauerland, *Ann.*, **592**, 190 (1955).

and evaporated *in vacuo* to furnish the *N*-acetyl-*d*-neomenthylamine as fine needles, 0.825 g. (39%), m.p. 165–168°. After recrystallization from a mixture of petroleum ether and ethyl acetate, the amide melted at 166.5–167.5° (lit.,[41] m.p. 169–170°). The specific rotation of the amide obtained in this experiment cannot be used as a measure of the stereospecificity of the ammonolysis reaction because the optical purity of our tosylate is unknown. Of the widely differing rotation values found in the literature,[39,42-45] in no case was any criterion of optical purity reported. The divergent values may be due in part to a spontaneous decomposition of the tosylate which has been observed with a sample stored *in vacuo* at 25°. A 2-g. sample of sharp melting tosylate liquefied within 1 day when stored in an Abderhalden apparatus at 1-mm. pressure.

Menthyl Brosylate.—To a solution of 23.42 g. (0.150 mole) of *l*-menthol (97% optically pure) in 20 ml. of dry pyridine was added in one portion 38.33 g. (0.150 mole) of *p*-bromobenzenesulfonyl chloride. After the reaction mixture became warm, the flask was cooled in an ice bath and the contents soon solidified. Dry pyridine (30 ml.) was added and the mixture was allowed to remain at room temperature for 48 hr. The reaction mixture was shaken with ether and water, and the layers were separated. The organic layer was washed with water, 10% sodium bicarbonate solution, 10% hydrochloric acid, and again with water. The ether solution was dried over Drierite and evaporated to furnish the brosylate which, after one recrystallization from ethanol, was obtained as needles weighing 46.5 g. (83%) with the m.p. 88–93° (capillary method). A second recrystallization from ethanol gave brosylate with the m.p. 89–90° (capillary method). The ester decomposed slowly unless stored under nitrogen and refrigerated.

Anal. Calcd. for $C_{16}H_{23}BrO_3S$: C, 51.20; H, 6.18; Br, 21.29. Found: C, 50.95, 51.13; H, 6.18, 6.20; Br, 21.19, 21.40.

Menthyl *p*-Methoxybenzenesulfonate.—The ester was prepared in 86% yield in the same manner as described for the brosylate except that the reaction mixture was allowed to stand at room temperature for 92 hr. The ester crystallized from ethanol as glittering sturdy needles, m.p. 109.0–109.5°.

Anal. Calcd. for $C_{17}H_{26}O_4S$: C, 62.55; H, 8.03; S, 9.82. Found: C, 62.65, 62.64; H, 7.73, 7.77; S, 9.89, 10.01.

Reaction of Menthyl Brosylate with Anhydrous Ammonia.—A run employing 0.010 mole of menthyl brosylate and 50 ml. of anhydrous ammonia at 95–100° for 30 hr. worked up as in the menthyl tosylate ammonolysis furnished the *N*-acetyl-*d*-neomenthylamine in 35% yield. Another run using the same amounts of starting materials but carried out at 78° for 24 hr. gave the acetamide in 39% yield.

Reaction of Menthyl *p*-Methoxybenzenesulfonate with Anhydrous Ammonia.—A run employing 0.010 mole of menthyl *p*-methoxybenzenesulfonate and 50 ml. of anhydrous ammonia at 95–100° for 24 hr. furnished the *N*-acetyl-*d*-neomenthylamine in 37% yield.

Reaction of 5α-Cholestan-3β-yl Tosylate with Anhydrous Ammonia.[46] **Run A.**—A mixture of 4.70 g. (0.0086 mole) of the finely ground tosylate[47,48] and 85 ml. of anhydrous ammonia in a steel bomb was maintained at 95–100° for 20.5 hr. After the cooled bomb was opened and the ammonia evaporated, the solid residue was triturated with 100 ml. of anhydrous ether. Ethereal hydrogen chloride was added dropwise to this mixture until no further precipitation of the amine hydrochloride could be observed. The solids, a mixture of the *p*-toluenesulfonic acid and hydrogen chloride salts of ammonia and 5α-cholestan-3α-amine were removed by filtration, added to a mixture of 70 ml. of 1 *N* sodium hydroxide solution and 15 ml. of dioxane and vigorously stirred for 20 min. The resulting oily mixture was extracted with four 50-ml. portions of ether; the combined ether extracts were dried over anhydrous potassium carbonate and evaporated under reduced pressure. The residue of 5α-cholestan-3α-amine, after drying for 2 hr. at 50°/0.25 mm., weighed 2.40 g. (72%) and had the m.p. 98–103°, $[\alpha]^{29}D$ +27.3° (*c* 3.8), reported[4] m.p. 87–88°, $[\alpha]D$ +27° (chloroform). The product was submitted for analysis without further purification.

Anal. Calcd. for $C_{27}H_{49}N$: C, 83.65; H, 12.74; N, 3.61. Found: C, 83.84; H, 12.36; N, 3.63.

Acetylation of the amine in ether with acetic anhydride at 20° furnished needles of *N*-acetyl-5α-cholestan-3α-amine having, as initially isolated, the m.p. 217.5–218.0° and $[\alpha]^{29}D$ +36° (*c* 4.6), reported[4,49] m.p. 217–218°, $[\alpha]D$ +36° (chloroform); m.p. 216–217°, $[\alpha]D$ +37° (chloroform). Recrystallization from ethyl acetate gave fine needles, m.p. 217–218°, $[\alpha]^{28}D$ +36° (*c* 1.0). The initially isolated α-acetamide was shown to be uncontaminated with the higher melting epimer,[4] *N*-acetyl-5α-cholestan-3β-amine, m.p. 245–246°, $[\alpha]D$ +12° (chloroform). In previous work,[12] a mixture of α- and β-amines containing mainly the α-amine, obtained[4] from the catalytic hydrogenation of 5α-cholestan-3-one oxime, furnished upon acetylation a mixture of acetamides, which when placed on the Kofler block and viewed under polarized light melted first near the reported melting point of the α-acetamide while crystals of the β-acetamide could be clearly discerned adjacent to and in the melt of the α-acetamide up to its reported melting point.

A portion of the α-amine was recrystallized from a mixture of ethanol and water to afford microcrystals, m.p. 105–106°, $[\alpha]^{29}D$ +27.4° (*c* 3.0). Acetylation in the usual manner gave, in quantitative yield, the α-acetamide, m.p. 216–217°. Most attempts to recrystallize the amine from a mixture of ethanol and water at 0–20° usually furnished the amine as an oil.

Low temperature recrystallization of the α-amine from ether at −30 to −77° afforded microcrystals which melted sharply at some temperature within the range 100–104° with occasional softening or slight melting at about 98° and which exhibited unchanged specific rotation. However, in one instance, when recrystallization occurred slowly during a period of several hours to furnish a few massive prisms, the m.p. was 104.0–104.5°. If the amine, in a nitrogen atmosphere, was heated above its m.p. to 120–130°, the temperature at which the melt crystallized appeared to affect the melting point of the resolidified amine. A sample of melt kept at 83° for 90 min. was rubbed with a glass rod while the temperature was lowered to 78° whereupon the melt solidified rapidly. After being allowed to cool to room temperature, the amine had the m.p. 98.0–101.5°. Another sample of melt, cooled slowly in an oil bath from 130° began to crystallize at about 65°. After slow cooling to room temperature, the m.p. was 87–88°.

A sample of the α-amine, m.p. 98–103°, was evaporatively distilled in a sublimation apparatus at a bath temperature of 150° and <0.01 mm. pressure. The white crystalline amine which deposited on the cold finger melted mainly at 101.5–103.0° with a portion of the crystals, about 10%, melting at 87–89°. The sample was allowed to cool slowly on the hot stage to room temperature; the resolidified amine had the m.p. 88.0–89.0°. The melting point of this cooled and resolidified sample was again essentially unchanged, m.p. 88.0–89.5°. In some instances the amine exhibited a double

(41) J. Read and G. J. Robertson, *J. Chem. Soc.*, 2209 (1926).
(42) T. P. Hilditch, *ibid.*, 224 (1911).
(43) H. G. Rule and G. Smith, *ibid.*, 1482 (1931).
(44) R. S. Tipson, M. A. Clapp, and L. H. Cretcher, *J. Org. Chem.*, **12**, 133 (1947).
(45) E. R. Alexander and A. G. Pinkus, *J. Am. Chem. Soc.*, **71**, 1786 (1949).
(46) We thank Mr. L. Dennis McKeever for technical assistance in this experiment.
(47) I. Malunowicz, J. Fajkoš, and F. Šorm, *Collection Czech. Chem. Commun.*, **25**, 1359 (1960).
(48) W. Stoll, *Z. physiol. Chem.*, **207**, 147 (1932).
(49) H. B. Henbest and W. R. Jackson, *J. Chem. Soc.*, 954 (1962).

melting point. For example, a sample of amine isolated from an ammonolysis run by chromatography on alumina of the mixture of neutral (olefin) and basic reaction products melted at 86.0–90° with the exception of a few minute crystals which remained in the melt and began to grow rapidly at 90°. When the temperature reached 94° the sample was completely crystalline and remelted at 102–103° with slight softening from 101.5–102.0°.

From a similar 19-hr. run, the α-amine was precipitated from the ether solution containing both the basic and neutral products as its hydrochloride which without further purification was cut back to the α-amine, minute needles, m.p. 103–104°, $[\alpha]^{27}D$ +27.4° (*c* 9.5). A portion of the α-amine was dried with phosphorus pentoxide for 24 hr. at 25°/1 mm. and submitted for analysis.

Anal. Calcd. for $C_{27}H_{49}N$: C, 83.65; H, 12.74; N, 3.61. Found: C, 83.77, 83.87; H, 12.28, 12.40; N, 3.88, 3.62.

Run B.—A run was carried out at 95–100° for 19 hr. employing 3.000 g. (5.53 mmoles) of tosylate and 50 ml. of anhydrous ammonia. The residue obtained after evaporation of the ammonia was dissolved in 50 ml. of dioxane (some brown material did not dissolve). After the addition of 2.0 g. of potassium hydroxide in a minimum volume of warm ethanol, the dioxane solution was heated on a steam bath for 15 min. The cooled solution was shaken with water and ether. The layers were separated and the water layer was extracted with ether. The combined ether extract was dried over sodium sulfate. One quarter of the ether solution was evaporated on a rotary evaporator. Upon addition of 0.5 ml. of acetic anhydride to the residue, a white solid formed immediately. The mixture was left at 25° for 16 hr., filtered and the solid washed with cold ether to furnish 0.416 g. (0.97 mmole, thus the total yield of α-amine would be 70%) of *N*-acetyl-5α-cholestan-3α-amine, m.p. 214–215°.

The remaining ether solution was evaporated and the residue, 1.668 g. dissolved in the minimum volume of petroleum ether containing about 1% benzene, was chromatographed on 86 g. of Woelm alumina, activity grade III, in a column 2.0 × 28 cm., previously packed in petroleum ether. Elution with petroleum ether (200 ml.) gave 0.252 g. of an unsaturated oil which later solidified and had the m.p. 63–65°. Elution with petroleum ether–5% benzene (100 ml.), petroleum ether–10% benzene (100 ml.), and petroleum ether–50% benzene (100 ml.) afforded trace amounts of some solids and oils. Further elution with benzene (100 ml.) yielded 0.072 g. of a solid, m.p. 66–75°. Continued elution with benzene–50% ether (200 ml.) followed by pure ether (250 ml.) afforded 1.058 g. (63%) of the α-amine with variable melting point as described previously, *N*-acetyl derivative, m.p. 217–218°. Terminal elution with absolute ethanol (250 ml.) gave a few milligrams of oil. Total recovery from the column was 1.382 g. (83%). None of the β-amine was obtained. Previous experience[12] with a mixture of α- and β-amines showed that the slower moving[4] β-amine is stripped from the column in the terminal eluate.

5α-Cholestan-3β-yl Methanesulfonate.—A solution of 25.0 g. (0.0643 mole) of 5α-cholestan-3β-ol in anhydrous benzene was distilled to dryness. The residue was dissolved in 35 ml. of dry pyridine to which was added in one portion 55.6 g. (0.193 mole, 18.5 ml.) of methanesulfonyl chloride at room temperature. The reaction flask when warm was immersed in an ice bath. Within a few minutes crystallization began. After 1 hr. in the ice bath and 43 hr. at 25°, the reaction mixture was shaken with water and ether. The layers were separated and the ether layer was washed with water, 1 *N* hydrochloric acid, a 10% solution of sodium bicarbonate, and then water. The ether solution was dried with anhydrous sodium sulfate, shaken with decolorizing carbon, and filtered. The green filtrate was evaporated to furnish a discolored solid which was recrystallized three times from ethanol to afford 14.9 g. (50%) of the colorless methanesulfonate as needles, m.p. 113.5–115.5°, $[\alpha]^{26}D$ +14.1° (*c* 3.5). Further recrystallization from ethanol gave the analytical sample, m.p. 116.5–118.5°.

Anal. Calcd. for $C_{28}H_{50}O_3S$: C, 72.05; H, 10.80; S, 6.87. Found: C, 72.03, 72.07; H, 10.39, 10.25; S, 6.75, 6.64.

Reaction of 5α-Cholestan-3β-yl Methanesulfonate with Anhydrous Ammonia.—The run was carried out at 95–100° for 20.5 hr. employing 3.00 g. (0.00643 mole) of methanesulfonate and 50 ml. of anhydrous ammonia. The reaction mixture, after evaporation of the ammonia, was treated with potassium hydroxide in aqueous dioxane and the neutral and basic products extracted into ether. Acetic anhydride was added to one fifth of the dried ether solution to yield the α-acetamide, m.p. 215–216°, equivalent to a 63% yield of the α-amine. The remaining ether solution was chromatographed as in the aforementioned manner to afford a 59% yield (corrected for aliquot volume) of α-amine. The melting points of the various α-amine fractions were relatively sharp and all within the range previously noted.

NOTE ADDED IN PROOF.—A recent synthesis of 5α-cholestan-3α-amine (62% yield) and *d*-neomenthylamine hydrochloride (34% yield), achieved by reduction of the axial azide[49] obtained from the equatorial tosylate, was reported by A. K. Bose, J. F. Kistner, and L. Farber, *J. Org. Chem.*, **27**, 2925 (1962). *d*-Neomenthylamine has also been prepared previously [see A. C. Cope, E. Ciganek, L. J. Fleckenstein, and M. A. P. Meisinger, *J. Am. Chem. Soc.*, **82**, 4651 (1960)] from menthyl tosylate in an ammonolysis reaction carried out at 50–60° for 110 hr. These conditions resulted in 25% conversion and 40% recovery of the tosylate.