6α-Methyl-Δ⁴-3-ketones (VIIIa, b, c and d). General Procedure.—One gram of 3-keto-5α-hydroxy-6β-methyl derivative (IIIa, b, c and d) was dissolved (or slurried) in 50 ml. of chloroform, cooled in an ice–salt-bath and saturated with hydrogen chloride gas. After 25 minutes nitrogen was bubbled through to remove some of the hydrogen chloride. The solution was washed 3 times with water, dried over magnesium sulfate, filtered and the solvent removed. The residue was recrystallized from acetone–SSB to give from 55–75% yield of the 6α-methyl derivatives in Table I.

The 6β-methyl isomers VII also can be epimerized using this procedure.

3-(1-Pyrrolidinyl)-6-methyl-3,5-androstadien-17-one (XIIIa).—To 100 mg. of 5α-hydroxy-6β-methylandrostane-3,17-dione (IIIa) in 2 ml. of boiling methanol was added 0.1 ml. of pyrrolidine. The solution was heated for about one minute and part of the methanol was allowed to evaporate under a stream of nitrogen. The crystals were collected, washed with fresh methanol and dried, m.p. 172–180° dec., λ_{max}^{MeOH} 281 mμ, a_M 17,900; λ_{max}^{ether} 284 mμ, a_M 23,150.

Anal. Calcd. for $C_{24}H_{34}NO$: C, 81.79; H, 9.72; N, 3.97. Found: C, 81.46; H, 10.15; N, 3.90.

Using the above procedure 6α- and 6β-methyl-4-androstene-3,17-diones (VIIa and VIIIa) were converted to the same enamine.

KALAMAZOO, MICH.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS, THE STATE UNIVERSITY]

Leuckart Reduction of Cholestan-3-one

BY RONALD R. SAUERS

RECEIVED MARCH 18, 1958

Leuckart reductive amination of cholestan-3-one gave 39–57% yields of several 3β-alkylaminocholestanes: piperidino, dimethylamino, benzylamino, pyrrolidino, diethylamino and N-methylbenzylamino. Smaller amounts (5–9%) of the 3α-isomers were isolated in some cases.

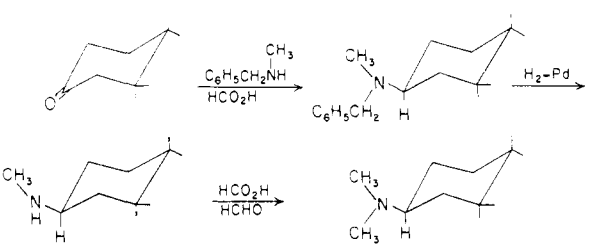
In connection with another project it was desirable to develop a convenient synthetic procedure for the preparation of relatively large amounts of 3β-mono- and dialkylaminocholestanes. The present methods for the preparation of 3β-aminoalkyl steroids suffer from marked limitations caused by undesirable side reactions, uncertain stereochemistry or unduly long synthetic procedures. For example, 3β-alkylamino steroids have been prepared from the corresponding 3α-tosylates (or halides) by heating with an amine.[1-3] In addition to the inconvenience involved in the preparation of 3α-tosylates, this method is also limited by the ease of diaxial elimination of toluenesulfonic acid.

Another general synthesis of 3β-alkylamino steroids involves, for example, reaction of amines with 3β-chlorocholest-5-ene to give 3β-alkylaminocholest-5-enes. Catalytic reduction of the Δ⁵-double bond leads to 3β-alkylaminocholestanes.[1-4] The success of this method depends largely on the nucleophilicity of the amine involved. Poor nucleophiles react *via* the homoallylic cation to give products of retained configuration, whereas the more nucleophilic amines react by the SN2 mechanism to give inverted products. Further, 3,5-cycloamines also have been isolated from this reaction.[5-10]

Finally, 3β-dimethylamino steroids have been prepared by formic acid–formaldehyde methylation of the corresponding 3β-amines. Preparation of the 3β-amines is tedious, however, involving sodium–alcohol reduction of the oximes of 3-ketosteroids.[11-13]

It appeared that Leuckart reductive amination might prove to be a useful method for the preparation of steroidal amines not only because of the high degree of stereospecificity expected (*vide infra*) but also because of the availability of the starting materials (*i. e.*, steroidal ketones). These expectations were realized experimentally when it was found that reaction of cholestan-3-one with secondary amines and formic acid gave 40 to 57% yields of 3β-dialkylaminocholestanes. Smaller amounts (5–9%) of the corresponding 3α-isomers could sometimes be isolated by chromatography of the crystallization liquors. The stereochemistry of the products was deduced from comparisons of the physical constants with literature values, and/or comparisons with the physical constants and infrared spectra of unambiguously prepared samples of the 3α-isomers.

The configuration of 3β-(N-methyl)-benzylaminocholestane was demonstrated by its conversion to the known 3β-dimethylaminocholestane.



The preparation of 3β-dimethylaminocholestane

(1) F. Šorm and L. Lábler, *Chem. Listy*, **46**, 484 (1952).
(2) L. C. King and M. J. Bigelow, THIS JOURNAL, **74**, 3338 (1952).
(3) H. C. Richards, C. W. Shoppee, J. C. P. Sly and G. H. R. Summers, *J. Chem. Soc.*, 1054 (1956).
(4) C. W. Shoppee, B. D. Agashe and G. H. R. Summers, *ibid.*, 3107 (1957).
(5) G. R. Vavasour, H. I. Bolker and A. F. McKay, *Can. J. Chem.*, **30**, 933 (1952).
(6) P. L. Julian, A. Magnani, E. W. Meyer and W. Cole, THIS JOURNAL, **70**, 1834 (1948).
(7) J. H. Pierce, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 690 (1955).
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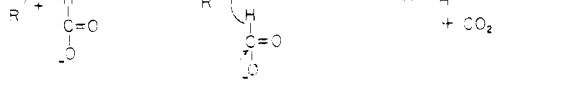
(10) F. Šorm, L. Labler and V. Černý, *Chem. Listy*, **47**, 418 (1953).
(11) D. P. Dodgson and R. D. Haworth, *J. Chem. Soc.*, 67 (1952).
(12) L. Lábler, V. Černý and F. Šorm, *Chem. Listy*, **48**, 1058 (1954).
(13) C. W. Shoppee, D. E. Evans, H. C. Richards and G. H. R. Summers, *J. Chem. Soc.*, 1649 (1956).

was modified somewhat by the substitution of dimethylformamide for the dimethylamine. The normal procedure with dimethylamine was unsuccessful probably because of the volatility of this base.

Attempts to prepare monoalkylaminocholestanes by reaction of cholestanone with a primary amine and formic acid met with limited success. Whereas with benzylamine a 39% yield of 3β-benzylaminocholestane was obtained, cyclohexylamine gave only 9% of the 3β-isomer.

The obtention of mainly the 3β-isomers is consistent with the recent views on the stereochemistry and mechanism[14-16] of formic acid reductions. Thus it can be seen that the most favorable approach of formate ion would be from the less hindered α-side of the steroid molecule



Application of "stereoelectronic control"[17] or "product development control"[18] arguments lead to the same stereochemical conclusions.

Experimental[19]

General.—Commercial 98–100% formic acid was used throughout unless otherwise noted. Cholestanone was prepared from commercial cholesterol by reduction to cholestanol[20] followed by oxidation to cholestanone.[21] The reductive aminations were carried out in a 25-ml. round-bottomed flask equipped with an efficient stirrer and condenser. After heating for the indicated times, the contents were cooled and stirred vigorously with 10 ml. of 3 *N* hydrochloric acid. The hydrochlorides were filtered and washed with water and ether. Basification with potassium hydroxide solution liberated the free amines which were extracted into ether. The ether solutions were washed with water and dried over sodium sulfate. The ether was removed *in vacuo* and the products purified by crystallization and/or chromatography.

3β-(N-Piperidino)-cholestane.—Cholestanone (1.98 g., 0.005 mole), piperidine (2.0 ml., 0.020 mole) and formic acid (1.5 ml., 0.040 mole) were heated at 175–180° for 10 hours. There was obtained 1.25 g. (53%) of 3β-(N-piperidino)-cholestane as colorless needles on crystallization of the basic product from acetone–methylene chloride; m.p. 146–149°, $[\alpha]_D$ +22° (lit.[2] 146–147°, $[\alpha]_D$ +23°).

A picrate was prepared in ether and crystallized as plates from ethanol, m.p. 185–186.5°.

Anal. Calcd. for $C_{38}H_{60}N_4O_7$: C, 66.64; H, 8.83; N, 8.18. Found: C, 66.34; H, 8.77; N, 8.38.

Evaporation of the combined crystallization liquors followed by chromatography on alumina gave 0.22 g. (9%) of 3α-(N-piperidino)-cholestane on elution with low-boiling petroleum ether. The melting point was 96–100° and the infrared spectrum was identical with that of an authentic sample prepared below.

3α-(N-Piperidino)-cholestane.—A solution of 1.0 g. of cholestanyl tosylate in 4.0 ml. of piperidine was heated at reflux for 17 hours. The crude basic product was filtered through alumina in low-boiling petroleum ether and crystallized from acetone, m.p. 97–100°, $[\alpha]_D$ +23° (lit.[2] 98–100°, $[\alpha]_D$ +26°).

The picrate crystallized as plates from ethanol, m.p. 199–203°.

Anal. Calcd. for $C_{38}H_{60}N_4O_7$: C, 66.64; H, 8.83; N, 8.18. Found: C, 66.43; H, 8.82; N, 8.05.

3β-Dimethylaminocholestane.—Reaction of 1.42 g. (0.0037 mole) of cholestanone, 0.54 ml. (0.0147 mole) of formic acid and 1.05 g. (0.014 mole) of dimethylformamide at 165° for 5 hours gave a 53% yield (0.80 g.) of 3β-dimethylaminocholestane as colorless needles from acetone, m.p. 104–105°, $[\alpha]_D$ +28° (lit. 103–105°[10] and 105–106°[8]; $[\alpha]_D$ +25°,[12] +23°[8]).

Evaporation of the combined mother liquors followed by chromatography on alumina gave 0.080 (5%) of colorless plates, m.p. 88–91° (from acetone). The infrared spectrum of this material was identical with that of an authentic sample of **3α-dimethylaminocholestane**, m.p. 90.5–92°, $[\alpha]_D$ +21°, prepared from cholestanone oxime *via* catalytic reduction and methylation[12,13]; reported for 3α-dimethylaminocholestane: m.p. 91°, $[\alpha]_D$ +21°[1]; m.p. 90.5–91.5°, $[\alpha]_D$ +22°.[8]

3β-(N-Benzyl)-methylaminocholestane.—Heating a mixture of 0.99 g. (0.0025 mole) of cholestanone, 1.21 g. (0.01 mole) of N-benzylmethylamine and 0.75 ml. of formic acid at 170° for 8 hours gave 0.5 g. (41%) of 3β-(N-benzyl)-methylaminocholestane as colorless plates from acetone; m.p. 87.5–90.5°. The analytical sample melted from 89.5–91.5°, $[\alpha]_D$ +22°.

Anal. Calcd. for $C_{35}H_{57}N$: C, 85.47; H, 11.68; N, 2.85. Found: C, 85.56; H, 11.76; N, 2.69.

3β-Methylaminocholestane.—Debenzylation of 0.946 g. (0.0019 mole) of 3β-(N-benzyl)-methylaminocholestane in 100 ml. of absolute ethanol proceeded smoothly in the presence of 0.10 g. of 10% palladium-on-charcoal. After filtration of the catalyst, the ethanol was removed *in vacuo*. Crystallization of the product from acetone gave 0.355 g. (46%) of 3β-methylaminocholestane as colorless plates, m.p. 83–85.5° (solidified) and 90.5–92.5°, $[\alpha]_D$ +22°.

Anal. Calcd. for $C_{28}H_{51}N$: C, 83.71; H, 12.80; N, 3.49. Found: C, 83.85; H, 12.95; N, 3.60.

Methylation of 0.100 g. of this amine was accomplished by heating at reflux for 3 hours in a solution of 1.0 ml. of 90% formic acid and 0.75 ml. of 37% formaldehyde. The product weighed 0.92 g. (88%) after one crystallization from acetone and melted from 100–105°. A mixture melting point with 3β-dimethylaminocholestane prepared above was 101.5–105.5°.

3β-(N-Pyrrolidino)-cholestane.—Reaction of 3.86 g. (0.01 mole) of cholestanone with 3.3 ml. (0.04 mole) of pyrrolidine and 3.0 ml. (0.08 mole) of formic acid for 6 hours on the steam-bath gave 2.5 g. (57%) of 3β-(N-pyrrolidino)-cholestane as colorless plates from acetone, m.p. 128.5–131.5°, $[\alpha]_D$ +26°.

Anal. Calcd. for $C_{31}H_{55}N$: C, 84.28; H, 12.55; N, 3.17. Found: C, 84.07; H, 12.55; N, 3.34.

The picrate crystallized as plates from ethanol, m.p. 211–214°.

Anal. Calcd. for $C_{37}H_{58}N_4O_7$: C, 66.24; H, 8.71; N, 8.35. Found: C, 66.47; H, 8.62; N, 8.11.

3α-(N-Pyrrolidino)-cholestane.—A solution of 1.0 g. of cholestanyl tosylate in 3.0 ml. of pyrrolidine was heated at reflux for 12 hours. There was obtained 0.6 g. of crude 3α-(N-pyrrolidino)-cholestane, m.p. 77–82°. Crystallization from acetone raised the melting point to 80–82°, $[\alpha]_D$ +27°.

Anal. Calcd. for $C_{31}H_{55}N$: C, 84.28; H, 12.55; N, 3.17. Found: C, 84.11; H, 12.38; N, 3.39.

The picrate was crystallized from ethanol and melted from 199–203°.

Anal. Calcd. for $C_{37}H_{58}N_4O_7$: C, 66.24; H, 8.71; N, 8.35. Found: C, 66.23; H, 8.54; N, 8.42.

(14) For a review of the Leuckart reaction, see M. L. Moore in "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 301–330. For more recent references see ref. 16.

(15) D. S. Noyce and F. W. Bachelor, THIS JOURNAL, **74**, 4577 (1952).

(16) N. J. Leonard and R. R. Sauers, *ibid.*, **79**, 6210 (1957).

(17) E. J. Corey and R. A. Sneen, *ibid.*, **78**, 6269 (1956).

(18) W. G. Dauben, G. J. Fonken and D. S. Noyce, *ibid.*, **78**, 2579 (1956).

(19) Melting points were determined on a Kofler hot-stage and are corrected. Optical rotations were taken in chloroform. Microanalyses are by G. Robertson, Florham Park, N. J.

(20) E. B. Hershberg, E. Oliveto, M. Rubin, H. Staeudle and L. Kuhlen, THIS JOURNAL, **73**, 1144 (1951).

(21) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 139.

3β-Diethylaminocholestane.—A mixture of 0.99 g. (0.0025 mole) of cholestanone, 0.75 ml. of formic acid (0.02 mole) and 1.0 ml. (0.01 mole) of diethylamine was heated at 134° for 5 hours. The basic product was chromatographed on alumina. Elution with 700 ml. of low-boiling petroleum ether gave 0.18 g. of an oil which could not be induced to crystallize. This isomer may be assigned the 3α-configuration since it is the less polar of the two isomers (*vide infra*). The picrate crystallized as needles from ethanol, m.p. 176–179°.

Anal. Calcd. for $C_{37}H_{60}N_4O_7 \cdot {}^1/_2C_2H_5OH$: C, 65.58; H, 9.12; N, 8.05. Found: C, 65.37, 65.44; H, 8.78, 8.83; N, 7.98, 8.55.

Further elution with low-boiling petroleum ether containing benzene gave 0.52 g. of a solid which on crystallization from acetone gave 0.45 g. (41%) of 3β-diethylaminocholestane as colorless plates, m.p. 101.5–103.5°, $[\alpha]_D$ +20°.

Anal. Calcd. for $C_{31}H_{57}N$: C, 83.90; H, 12.94; N, 3.16. Found: C, 83.92; H, 13.24; N, 3.24.

The picrate crystallized as plates from ethanol, m.p. 137–139° (solidified) and 147–148°.

Anal. Calcd. for $C_{37}H_{60}N_4O_7$: C, 66.04; H, 8.99; N, 8.33. Found: C, 66.32; H, 9.19; N, 8.52.

3β- and 3α-Benzylaminocholestane.—Cholestanone (0.99 g., 0.0025 mole), benzylamine (1.07 g., 0.01 mole) and formic acid (0.75 ml., 0.02 mole) were heated at 174–179° for 9.5 hours. Hydrolysis of the formamide was effected directly by adding 4 ml. of concentrated hydrochloric acid and 30 ml. of absolute ethanol. Heating at reflux for 18 hours was followed by addition of 100 ml. of water. The precipitated hydrochloride salts were collected and washed with water and ether. Basification of the salts with potassium hydroxide solution followed by ether extraction gave a mixture of the two amines. Crystallization from acetone gave 0.465 g. (39%) of **3β-benzylaminocholestane** as colorless plates, m.p. 113–115°, $[\alpha]_D$ +16° (lit.[3] m.p. 114–115°, $[\alpha]_D$ +19°).

Chromatography of the residual basic material on alumina gave 0.15 g. of a solid on elution with 1:1 low-boiling petroleum ether–benzene. Crystallization from acetone gave 0.10 g. (8%) of **3α-benzylaminocholestane** as colorless plates, m.p. 74–76°, $[\alpha]_D$ +27° (lit.[3] m.p. 75–77°, $[\alpha]_D$ +27°).

3α- and 3β-Cyclohexylaminocholestane.—A mixture of 0.99 g. (0.0025 mole) of cholestanone, 0.99 g. (0.01 mole) of cyclohexylamine and 0.75 ml. of formic acid was heated at 176° for 8 hours. Hydrolysis of the amide under the conditions used for the benzylaminocholestanes gave a mixture of cyclohexylaminocholestanes which could not be separated by crystallization from acetone. Chromatography on alumina gave two fractions. Elution with 2:1 low-boiling petroleum ether–benzene gave 0.095 g. (8%) of **3α-cyclohexylaminocholestane**, m.p. 103.5–105.5°, $[\alpha]_D$ +21°.

Anal. Calcd. for $C_{33}H_{59}N$: C, 84.36; H, 12.66; N, 2.98. Found: C, 84.00; H, 12.31; N, 3.25.

Elution with benzene–ether mixtures gave 0.105 g. (9%) of **3β-cyclohexylaminocholestane**, m.p. 142–144.5° (colorless needles from acetone), $[\alpha]_D$ +18° (lit.[4] m.p. 140–141°, $[\alpha]_D$ +17°).

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE STATE UNIVERSITY]

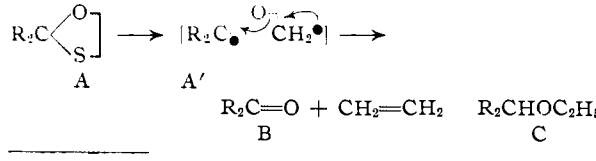
Studies in Organic Sulfur Compounds. X.[1] The Scope of the Raney Nickel Desulfurization of Cyclic Hemithioketals (1,3-Oxathiolanes and 1,3-Oxathianes)[2]

BY CARL DJERASSI, M. SHAMMA[3a] AND T. Y. KAN[3b]

RECEIVED JANUARY 20, 1958

The synthesis of 1,1-diphenyl-4-mercapto-2-butanol and thence of substituted 1,3-oxathianes has been described. A detailed parallel study of the desulfurization of 1,3-oxathiolanes and 1,3-oxathianes has led to the following results. In ketonic solvents, desulfurization of 1,3-oxathiolanes and 1,3-oxathianes proceeds in the same manner by "oxygen introduction" leading to the corresponding ketone and alcohol fragments in good yield. Modifications in the structure of the hemithioketal can alter the product composition to an appreciable extent and furnish a certain proportion of the corresponding substituted ethyl or propyl ether. The isolation of 3α-ethoxycholestane (XXIa) from several desulfurizations of spiro-(1,3-oxathiolane-2,3′-cholestane) (XX) has a bearing on the mode of formation and stereochemistry of this hemithioketal. A mechanism is proposed for the "oxygen introduction" step involving an intermediate hemiketal and this is based on the facile cleavage of hemithioketals under mild alkaline conditions. This observation greatly increases the utility of such derivatives as protecting groups for carbonyl functions. In benzene solution under anhydrous conditions, the desulfurization proceeds by different paths depending upon ring size. 1,3-Oxathiolanes yield almost exclusively the ketone and corresponding hydrocarbon, each in high yield and it is suggested that this reaction proceeds *via* a 1,4-diradical. On the other hand, the desulfurization of 1,3-oxathianes in benzene solution is more complex and leads to variable amounts of ketone, alcohol, ether and hydrocarbons.

The desulfurization of 5-membered hemithioketals (1,3-oxathiolanes) (A) with Raney nickel catalyst in acetone solution was found[4] to yield the corresponding ketone B rather than ethyl ether C and the following mechanism was suggested initially



A A′ B C

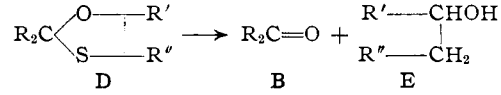
(1) Paper IX, C. Djerassi and J. Grossman, THIS JOURNAL, **79**, 2553 (1957).

(2) This work was carried out in part under contract No. DA-20-018-ORD-13474 with the Office of Ordnance Research, U. S. Army.

(3) (a) Postdoctorate Research Fellow (1955–1956); (b) Monsanto Predoctorate Research Fellow (1956–1957).

(4) J. Romo, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 4961 (1951).

Subsequently,[5] it was observed in work with appropriately substituted hemithioketals[6] (D) that the course of this Raney nickel desulfurization was more complex and that in addition to the ketone B an alcohol E corresponding to the other fragment was formed. In fact, the yield of B and E each exceeded 50% which meant that oxygen had to be introduced from an outside source.



D B E

We have now examined in more detail the structural and experimental scope of this reaction and have discovered that depending upon the circum-

(5) C. Djerassi, M. Gorman and J. A. Henry, *ibid.*, **77**, 4647 (1955).

(6) C. Djerassi, M. Gorman, F. X. Markley and E. B. Oldenburg, *ibid.*, **77**, 568 (1955).