melted at 120–210°. Recrystallization from xylene (Norite) gave 0.10 g. (5% yield) of tan crystals, m.p. 201–204°, which after sublimation at 190°/0.2 mm. gave white needles, m.p. 203.5–206° dec. Ultraviolet spectrum: λ_{max}, mμ (log ϵ): 246 (4.31), 312 (4.22).

Anal. Calcd. for $C_{16}H_{11}BrN_2$: C, 61.75; H, 3.56; N, 9.00. Found: C, 61.38; H, 3.83; N, 9.15.

Acknowledgment.—The authors are indebted to Dr. V. B. Fish of this laboratory for the microanalyses.

Reduction of Steroidal Enamines

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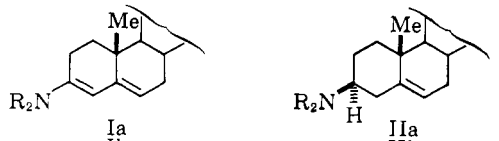
Further studies on the reduction of steroidal enamines with sodium borohydride and acetic acid have indicated that the mechanism involves initial protonation of the substrate followed by reduction of the immonium cation. Procedures are described for obtaining yields as high as 60% in the reduction of dienamines of type I and 70% in the case of simple enamines.

In connection with the total synthesis of racemic conessine,[1] we have studied further the previously reported[2] reduction of dienamines derived from α,β-unsaturated ketones. The present paper describes an improved procedure and also sheds some light on the mechanism of this type of reduction.

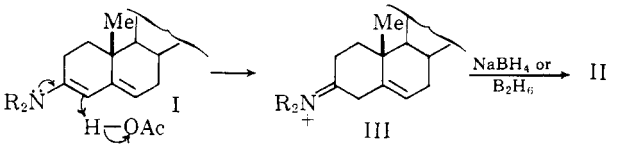


Ia Ib IIa IIb

a = conessine series, R_2 = Me_2
b = cholestane series, R_2 = —$(CH_2)_4$—

Our first observation of significance was that there was no reaction between the dienamine Ia (3,4-dehydroconessine) and sodium borohydride until *after* acetic acid was added to the reaction mixture. This point was demonstrated by observing no change in the characteristic ultraviolet spectrum, λ_{max} 265 mμ (ϵ 13,500), until acetic acid was added. When the product was isolated immediately after this acid treatment, we were surprised to find that it was not conessine (IIa) but rather an intractable solid which appeared to be an amine–borane as evidenced by a strong band at 4.2 μ in the infrared spectrum.[3] Since conversion to conessine was effected in 28–36% yield by decomposition of this complex with acetic acid at 100° for one hour, we entertained the hypothesis that diborane, produced from sodium borohydride and acetic acid,[4] was the reducing species.[5]

To test the above hypothesis, the more readily available dienamine, 3-N-pyrrolidylcholestadiene-3,5 (Ib),[6] was used. Reduction with sodium borohydride and acetic acid in tetrahydrofuran, followed by decomposition of the intractable intermediate complex (λ_{max} 4.2 μ)[3] with acetic acid at 100°, afforded the highly crystalline 3β-N-pyrrolidylcholestene-5 (IIb), m.p. 165–175° (polymorphic), in 44% yield. It is particularly noteworthy that the yield was increased to 60% when diglyme was used as solvent; therefore this promises to be the method of choice for reducing such dienamines. This result is to be compared with the attempted reduction of the dienamine Ib with diborane. The maximum due to the dienamine in the ultraviolet spectrum decreased relatively slowly, indicating that direct hydroboration was likewise slow compared with the reduction in the presence of acetic acid described above. When acetic acid was added to the diborane–dienamine mixture, rapid reaction ensued to give an amine–borane with an infrared spectrum which was essentially identical (including the band at 4.2 μ) with that of the complex described above. Heating with acetic acid gave the amine IIb, m.p. 159–172°, but in only 32% yield. The low yield by the diborane reduction as compared with the borohydride procedure was confirmed by repeated experiments. In addition, a comparatively large fraction of the total product from the diborane reaction appeared to consist of a stable boron compound (alkyl borane?) which was not eluted from alumina in the chromatographic purification.[7] It is therefore concluded that the sodium borohydride–acetic acid reduction does not proceed by hydroboration of the free enamine.



In view of the foregoing considerations we prefer the reduction mechanism depicted in the accompanying flowsheet which involves a preferential (rate-controlled) protonation at C-4 of the dienamine I leading to an immonium cation III which is attacked rapidly by hydride (or diborane) at C-3 to give II. The results indicate that protonation at C-4 is kinetically favored over protonation at C-6 when acetic acid is used.[8]

For purposes of comparison amine IIb was independently prepared by solvolysis of cholesteryl *p*-tolu-

(1) J. A. Marshall and W. S. Johnson, *J. Am. Chem. Soc.*, **84**, 1485 (1962).

(2) W. S. Johnson, V. J. Bauer, and R. W. Franck, *Tetrahedron Letters*, No. **2**, 72 (1962).

(3) *Cf.* M. F. Hawthorne, *Tetrahedron*, **17**, 117 (1962); H. C. Brown, K. J. Murray, L. J. Murray, J. A. Snover, and G. Zweifel, *J. Am. Chem. Soc.*, **82**, 4233 (1960); E. C. Ashby, *ibid.*, **81**, 4791 (1959).

(4) J. A. Marshall and W. S. Johnson, *J. Org. Chem.*, **28**, 595 (1963).

(5) G. Stork and G. Birnambaum, *Tetrahedron Letters*, No. **10**, 313 (1961), have already suggested this possibility.

(6) F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, **75**, 1918 (1953).

(7) Poor material recovery (<50%) was realized from such chromatographic purifications when diborane was used in contrast with high material recoveries (80–90%) when sodium borohydride and acetic acid was the reducing agent.

(8) Apparently this selectivity is lost with stronger acids. *Cf.* G. Opitz and W. Merz, *Ann. Chem.*, **652**, 139 (1962), for a detailed study of this process in the reduction of enamines derived from crotonaldehyde.

enesulfonate with pyrrolidine under the conditions described by Corey and Hertler.[9] A sample prepared in this manner had m.p. 166–175° which was unchanged on admixture with material obtained from the reduction experiments described above. The identity of these amines was further established by infrared spectral comparison. Hydrogenation of the unsaturated amine IIb over platinum in acetic acid, according to the conditions described by Haworth and co-workers for a similar conversion,[10] led to 3β-N-pyrrolidylcholestane, m.p. 130–132°, in 83% yield. This saturated amine was independently synthesized from 3-N-pyrrolidylcholestene-2[6] in 70% yield by reduction with sodium borohydride and acetic acid, but in only 31% yield when diborane and acetic acid was employed as the reducing agent. The identity of the amines obtained by catalytic and chemical reduction was established by infrared spectral comparison and mixture melting point.

Experimental

Conessine (IIa).—A solution of crude 3,4-dehydroconessine (Ia),[2] λ_{max}^{EtOH} 265 mμ (ε 13,500),[11] in 2.0 ml. of anhydrous dioxane was stirred under nitrogen with 150 mg. of pulverized sodium borohydride. Ultraviolet spectra taken after 3 min., 3 hr., 12 hr., and 16 hr. showed no decrease in extinction at 265 mμ.[11] However, the addition of 2.0 ml. of glacial acetic acid to the mixture resulted in the immediate disappearance of absorption at 265 mμ. When the reaction mixture was worked up at this point, in another experiment, by extraction with ether–ethyl acetate, a solid compound was obtained which could not be recrystallized, λ_{max} 4.2 μ (amine–borane —B—H).[3] Therefore, the above dioxane solution was heated under reflux for 1 hr.; a treatment which was shown to eliminate the absorption at 4.2 μ in the infrared spectrum. The cooled solution was made basic with 10% aqueous sodium hydroxide and extracted with ether. The combined ether layers were washed with water, saturated brine, and dried over anhydrous sodium sulfate. The solvent was removed, and the residue was chromatographed on 6 g. of alumina (Woelm, activity grade II). Elution with 25 to 50% ether in hexane afforded 42 mg. of crude solid conessine. Crystallization from acetone gave 24 mg. (28% yield) of conessine, m.p. 112–121°,[12] the infrared spectrum of which was identical to that of authentic material.

The yield in this reaction varied with the purity of the starting dienamine. Thus, in one experiment in which a very pure sample of dienamine Ia, $\lambda_{max}^{Et_2O}$ 271 mμ (ε 18,000), was used, conessine, m.p. 121–123°, was obtained in 36% yield,[13] even though the reaction conditions were probably less favorable than those described above.

3β-N-Pyrrolidylcholestene-5 (IIb). (a) Sodium Borohydride and Acetic Acid Reduction.—A mixture of 50 mg. of 3-N-pyrrolidylcholestadiene-3,5,[6] m.p. 136–141°, and 25 mg. of sodium borohydride in 1.5 ml. of anhydrous tetrahydrofuran was stirred under nitrogen, and 0.5 ml. of glacial acetic acid was added dropwise. A 0.5-ml. aliquot was removed, made basic with 10% sodium hydroxide, and extracted with ether–ethyl acetate. The extracts were washed with water, saturated brine, and dried over anhydrous granular sodium sulfate. Removal of solvent left 14 mg. of colorless solid, $\lambda_{max}^{CCl_4}$ 4.2 μ (amine–borane —B—H).[3]

The remainder of the reaction mixture was refluxed for 1 hr., and the product was isolated as above to give 36 mg. of crude solid, $\lambda_{max}^{CCl_4}$ 3.61 μ (—C—H alpha to N), 6.03 μ (C=C). Recrystallization from ethanol afforded 16 mg. (44% yield allowing for removal of the aliquot) of lustrous white plates, m.p. 165–175°. The infrared spectrum of this material was identical with that of material prepared as described below (part b). Admixture of the two substances gave no depression in melting point.

The utilization of diglyme as the solvent led to a substantial improvement in yield. Thus, a solution of 50 mg. of 3-N-pyrrolidylcholestadiene-3,5,[6] m.p. 136–141°, and 20 mg. of sodium borohydride in 2.0 ml. of anhydrous diglyme was stirred under nitrogen during the dropwise addition of 2.0 ml. of glacial acetic acid. The mixture was allowed to stand for 10 min. and heated on a steam bath for 1 hr. The crude product was isolated as described above and crystallized from ethanol to give 30 mg. (60% yield) of 3β-N-pyrrolidylcholestene-5, m.p. 160–172°. The mother liquors afforded 17 mg. (34% yield) of an oil, the infrared spectrum of which was nearly identical with that of crystalline amine IIb.

(b) **Diborane–Acetic Acid Reduction.**—To a solution of 235 mg. of 3-N-pyrrolidylcholestadiene-3,5,[6] m.p. 136–141°, in 10.0 ml. of anhydrous tetrahydrofuran was added, under nitrogen, 1.25 ml. of 0.3 *M* diborane in tetrahydrofuran. After 3 hr. at room temperature, 1 ml. of acetic acid was cautiously added. Work-up of a small sample of the reaction mixture afforded a solid amine–borane which had infrared spectral characteristics identical with those of the corresponding material from part a of this experiment (see above). The solution was heated under reflux for 1 hr., then cooled, made basic with 10% aqueous sodium hydroxide, and extracted with ether. The extracts were washed with water, saturated brine, and dried over anhydrous sodium sulfate. The solvent was removed and the residue was chromatographed on 15 g. of alumina. Elution with 5 to 25% ether in hexane afforded 87 mg. of solid, $\lambda_{max}^{CCl_4}$ 3.61 μ (C—H alpha to N). Crystallization from absolute ethanol gave 76 mg. (32% yield) of colorless plates, m.p. 159–172°. Repeated recrystallization gave material, m.p. 168–175°, unchanged on further recrystallization. Evidence that this product is polymorphic, rather than a mixture of isomers, was provided by its hydrogenation to give, in high yield, the sharp melting dihydro compound (see below).

Anal. Calcd. for $C_{31}H_{53}N$: C, 84.67; H, 12.15; N, 3.19. Found: C, 84.4; H, 12.2; N, 3.3.

(c) **Solvolysis of Cholesteryl *p*-Toluenesulfonate.**—The conditions of Corey and Hertler[9] were used. A solution of 11.00 g. of cholesteryl *p*-toluenesulfonate and 6.30 g. of pyrrolidine in 50 ml. of anhydrous dimethylformamide was stirred under nitrogen at 80° for 16 hr. The cooled solution was diluted with water, made strongly basic with 10% sodium hydroxide, and extracted with ether. The combined ether layers were thoroughly washed with water, saturated brine, and dried over anhydrous sodium sulfate. This ether solution was then treated with anhydrous hydrogen chloride until no more precipitate formed. The solid amine hydrochloride was removed by filtration, washed with dry ether, and made basic with 10% sodium hydroxide containing a little ethanol to promote solubility of the salt. The basic mixture was extracted with ether, and the extracts were washed with water, saturated brine, and dried over anhydrous sodium sulfate. Removal of solvent gave 7.10 g. (80% yield) of crude brown oily amine. This oil was dissolved in a small amount of ether and cooled, affording 0.65 g. (7%) of colorless solid, m.p. 150–175°. Recrystallization from absolute ethanol gave 0.47 g., m.p. 160–170°. An additional recrystallization from absolute ethanol yielded 0.38 g. of lustrous white plates, m.p. 166–175°, unchanged by further recrystallization from absolute ethanol. Mixture melting point and infrared spectral comparison established the identity of this material with the amine IIb prepared as described in parts a and b of this experiment.

3β-N-Pyrrolidylcholestane. (a) Sodium Borohydride–Acetic Acid Reduction.—A mixture of 100 mg. of 3-N-pyrrolidylcholestene,[6] m.p. 100–110°, and 200 mg. of sodium borohydride in 5.0 ml. of anhydrous tetrahydrofuran was stirred under nitrogen while 3.0 ml. of glacial acetic acid was added dropwise over a 20-min. period. The mixture was heated under reflux for 1 hr., cooled, made basic with 10% sodium hydroxide, and extracted with ether. The combined ether layers were washed with water, saturated brine, and dried over anhydrous sodium sulfate. Removal of solvent left the crude solid amine which was recrystal-

(9) E. J. Corey and W. R. Hertler, *J. Am. Chem. Soc.*, **81**, 5209 (1959).

(10) R. D. Haworth, J. McKenna, and G. H. Whitfield, *J. Chem. Soc.*, 1102 (1953).

(11) It was necessary to measure the ultraviolet spectrum rapidly in order to minimize the loss of extinction due to slow decomposition of the enamine in ethanol.

(12) Apparently the melting point of conessine is lowered considerably by traces of impurities.

(13) Unpublished results of R. W. Franck.

lized from absolute ethanol to give 70 mg. (70%) of colorless plates, m.p. 121–127°. Repeated recrystallization from absolute ethanol raised the melting point to 130–131.5°.

Anal. Calcd. for $C_{31}H_{55}N$: C, 84.28; H, 12.55; N, 3.17. Found: C, 84.0; H, 12.5; N, 3.2.

(b) **Diborane–Acetic Acid Reduction.**—A solution of 120 mg. of 3-N-pyrrolidylcholestene,[6] m.p. 100–110°, in 5.0 ml. of anhydrous tetrahydrofuran was treated, under nitrogen, with 1.0 ml. of 0.3 *M* diborane in tetrahydrofuran. The solution was stirred at room temperature for 1 hr., cautiously treated with 2.0 ml. of glacial acetic acid, and heated at reflux for 1 hr. The product was isolated as described above to afford a yellow oil which was chromatographed on 10 g. of alumina. Elution with 2% ether in hexane afforded 52 mg. of crude solid. Recrystallization from absolute ethanol gave 37 mg. (31% yield), m.p. 130–132°. The infrared spectrum of this material was identical with that of the specimen prepared as described above in part a of this experiment. A mixture of these substances melted at 130–132°.

(c) **Catalytic Hydrogenation.**—The procedure of Haworth and co-workers[10] was used. A solution of 60 mg. of 3β-N-pyrrolidylcholestene-5, m.p. 166–173°, in 3 ml. of acetic acid was hydrogenated over 50 mg. of platinum oxide (Engelhard Industries Inc.) at 45 p.s.i. for 12 hr. The catalyst was removed by filtration, and the filtrate was made basic with 10% sodium hydroxide and extracted with ether. The combined ether layers were washed with water, saturated brine, and dried over anhydrous sodium sulfate. The solvent was removed, and the residue crystallized from absolute ethanol, affording 50 mg. (83% yield) of colorless plates, m.p. 130–132°, undepressed on admixture with the specimens described above in parts a and b of this experiment. The infrared spectra of all these specimens were identical.

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C-19 Functional Steroids. III.[1] 2,19-Disubstituted Androstane and Cholestane Derivatives[2]

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The synthesis of 2,19-disubstituted androstane and cholestane derivatives is described. Photolysis of the nitrite ester of 5α-androstane-2β,3α,17β-triol 3,17-diacetate gave *syn*-19-oximino-5α-androstane-2β,3α,17β-triol 3,17-diacetate, the structure of which was established by its n.m.r. spectrum. Further chemical modification of the oxime ultimately resulted in the preparation of 3,17-dioxo-2β-hydroxy-5α-androstan-19-oic acid 2,19-lactone. Lead tetraacetate oxidation of 5α-androstane-2β,3α,17β-triol 3,17-diacetate afforded 2β,19-epoxy-5α-androstane-3α,17β-diol diacetate which, through a series of steps, formed 2β,19-epoxy-17β-hydroxy-5α-androstan-3-one.

The preparation of steroids having favorable myotrophic/androgenic ratios, relative to testosterone itself, has been accomplished by a variety of structural alterations of the testicular hormone.[4] The purpose of the work described in the present paper was to prepare steroids for pharmacological evaluation of the effects of introduction of lactone and cyclic ether functions involving C-19 and C-2 in androstane derivatives[5]; the resulting final compounds are analogs of 2-hydroxymethylene-17α-methyl-17β-hydroxy-5α-androstan-3-one (oxymetholone), a clinically useful anabolic agent.

Access to the C-19 functional steroids was gained by the use of selective intramolecular reactions. Prior work[6] has shown that intramolecular attack from 6β and 11β oxygen functions can be used to operate on C-19. Since 2,19-disubstituted steroids were sought in the present work, the use of 2β-hydroxy steroid starting materials, in which the hydroxyl group is in a 1,3-diaxial relationship to the C-19 angular methyl group, was investigated.

After a number of orienting experiments in the cholestane series, which are described in the Experimental section,[7] 2α-bromoandrostan-3-one[8] was reduced with $LiAl(t\text{-}BuO)_3H$ in tetrahydrofuran[9] to afford excellent yields of I, which on treatment with alkali, gave the pure β-epoxide III. In both the cholestane and androstane series, it was found that the use of $LiAl(t\text{-}BuO_3)H$ gave stereochemically homogeneous 2α-bromo-3β-ols, in contrast to the mixture of epimeric alcohols obtained[10,11] in the cholestane series by the use of sodium borohydride. The 17-hydroxy group in III was blocked by acetylation to form IV. An attempt was made to benzoylate III using benzoyl chloride in pyridine solution. It was hoped ultimately to secure compounds having a benzoate group at C-17 and an acetate at C-3 so that a selective hydrolysis could be carried out. However, the epoxide was cleaved by pyridinium chloride and only 3α-chloro-5α-androstane-2β,17β-diol dibenzoate was obtained.

(1) Paper II, R. Kwok, and M. E. Wolff, *Chem. Ind.*, (London), 1194 (1962).

(2) Preliminary accounts of portions of this work have been presented in ref. 1 and at the 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962, p. 43N. This investigation was supported by a PHS research grant (A-5016) from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service.

(3) From the Ph.D. thesis of R. Kwok, University of California, 1963.

(4) For a recent review, see B. Camerino and G. Sala, "Progress in Drug Research," Vol. 2, E. Jucker, ed., Interscience Publishers, Inc., New York, N. Y., 1960, pp. 71–134.

(5) Some of the compounds resulting from this and other work are currently being evaluated biologically, and the results of these tests will be presented separately.

(6) The following basic routes for C-19 functionalization in steroids have been developed: Ultraviolet irradiation of 6β-nitrites, D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Am. Chem. Soc.*, **82**, 2640 (1960); ultraviolet irradiation of 6β-hypochlorites, M. Akhtar and D. H. R. Barton, *ibid.*, **83**, 2213 (1961), and J. S. Mills and V. Petrow, *Chem. Ind.*, (London), 946 (1961); lead tetraacetate oxidation of 6β-hydroxy steroids, A. Bowers, L. C. Ibañez, M. E. Cabezas, and H. J. Ringold, *Chem. Ind.*, (London), 1299 (1960); lead tetraacetate oxidation of 11β-hydroxy steroids in presence of iodine, Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Experientia*, **17**, 475 (1961); ultraviolet irradiation of 11-oxo steroids, H. Wehrli, M. S. Heller, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **44**, 2162 (1961).

(7) After the completion of this phase of our work, the preparation of VI by a similar method was reported: K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).

(8) A. Butenandt and H. Dannenberg, *Ber.*, **71**, 1681 (1938).

(9) J. Fajkos, *Collection Czech. Chem. Commun.*, **24**, 2284 (1959).

(10) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 4832 (1953).

(11) L. F. Fieser and W. Y. Huang, *ibid.*, **75**, 4837 (1953).