sodium hydroxide in 60% aqueous methanol. The product was obtained after the usual work-up and the infrared spectrum showed it to be unchanged starting material.

Another 2-mg. sample of Xa was similarly allowed to stand overnight in 4% ethanolic potassium hydroxide. The infrared spectrum of the oily product was not comparable to either Xa or XIa and showed infrared absorption at 1709 cm.$^{-1}$. A sample of 3β,17β-dihydroxyandrostane-16-one (XIa) similarly treated resulted in a product with an identical infrared spectrum.

Rearrangement of 3β,16β-Dihydroxyandrostan-17-one Diacetate (VIIIb) with Acetic Acid–Hydrochloric Acid.—A solution of 20 mg. of VIIIb in 4 cc. of glacial acetic acid containing 0.2 cc. of concentrated hydrochloric acid was allowed to stand for 48 hours. Dilution with ice-cold water was followed by immediate extraction with chloroform which was washed with water, dried and evaporated. The residue was crystallized from petroleum ether to give crystals with a m.p. 176–179° undepressed on admixture with authentic 3β,17β-diacetoxyandrostan-16-one (XIb). The mother liquors were evaporated and an infrared spectrum of the residue showed it also to be 90% XIb.

Acknowledgment.—The author wishes to express his thanks to Dr. T. F. Gallagher for his advice and interest in this work, and Dr. David K. Fukushima for his helpful discussion. He also wishes to thank Beatrice S. Gallagher and staff for the infrared spectra. The technical assistance of Rosemarie Lehman and Maria Tomasz is also gratefully acknowledged.

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C(16)–C(18) Rearrangements of Steroid Alkaloids

BY JOHN C. SHEEHAN, RICHARD L. YOUNG AND PHILIP A. CRUICKSHANK

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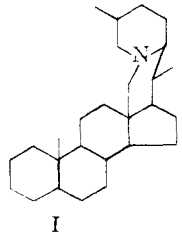
Skeletal rearrangements of certain 18-substituted solanidane alkaloids are described in which the nitrogen migrates between C(16) and C(18). Upon heating solanidane-18-oic acids with acetic anhydride a lactam was formed between C(18) and the nitrogen, while an acetoxy group was introduced at C(16). Acid hydrolysis of these 16α-acetoxy lactam derivatives regenerated the starting solanidane-18-oic acid. Lithium aluminum hydride reduction of 16α-chloro or 16α-tosyloxy lactam derivatives also led to regeneration of the solanidane skeleton. Similar reduction of 16α-acetoxy or 16-desoxy lactam derivatives afforded products free of oxygen at C(18) in which the new ring system had been retained. Hofmann or Emde degradations of isorubijervine monotosylate also were shown to afford compounds with this new skeleton.

The presence of substituents on C(16) and C(18) of steroids has been shown to have a profound effect on physiological activity.[1] As a result there has been considerable interest recently in the preparation of steroids substituted at these positions.[2] Among the naturally occurring steroid derivatives only the alkaloid isorubijervine (VI) is known to have substituents at both of these carbon atoms.[3] The β-nitrogen at C(16) and the hydroxyl at C(18) offer a unique relationship, and their proximity permits an opportunity to study interactions of substituents at these positions.

When solutions of solanidane-18-oic acids are heated under reflux in acetic anhydride solution, a skeletal rearrangement occurs to give the new ring system I for which we propose the name "cevanidane."[4] In the products of this acetolysis reaction the new E ring is in the form of a lactam, and an acetoxy group is introduced at C(16),



I

the site of the C–N bond cleavage.[5] This reaction is illustrated by the conversion of 3β-acetoxy-5-solanidene-18-oic acid (IX) to 3β,16α-diacetoxy-18-oxo-5-cevanidene (X). Regeneration of the solanidane skeleton from certain 16-substituted-18-oxocevanidane derivatives also takes place readily. Hydrolysis of the lactam ring in the presence of the 16α-acetoxy group led to formation of solanidane-18-oic acid. Reduction of the lactam ring with lithium aluminum hydride in the presence of more easily displaceable 16-substituents (tosyloxy or chloro) gave isorubijervine derivatives. These reactions illustrate the facile interconversion of the solanidane (II) and cevanidane (I) ring systems.

No naturally occurring alkaloid has yet been found to have the cevanidane skeleton. The ring system is of considerable interest in that it can be looked upon as the normal steroid analog of cevane (III). The alkaloids of the veratrum group,[6] of which isorubijervine (VI) is a member, can be assigned to one of three skeletal classifications: the solanidane (II) skeleton of isorubijervine (VI), the cevane (III) skeleton of germine, and the skeleton IV found in jervine and veratramine. Only solanidane has the normal steroid skeleton; the other two have a C-nor-D-homo steroid ring system. The cevanidane ring system (I) thus exemplifies a "missing link" between the solanidane and cevane types of alkaloids.

Interaction between C(18) and the nitrogen

(1) J. Fried and A. Borman, *Vitamins and Hormones*, **16**, 303 (1958).

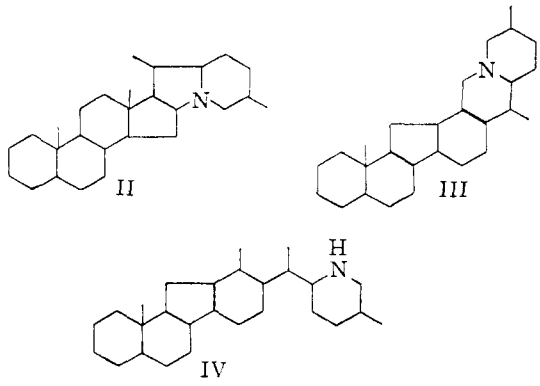
(2) See L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 689–696, 863–867, for summary of recent literature.

(3) (a) F. L. Weisenborn and D. Burn, THIS JOURNAL, **75**, 259 (1953); (b) S. W. Pelletier and W. A. Jacobs, *ibid.*, **75**, 4442 (1953).

(4) This name was chosen to indicate the relationship of the ring system to that of *ce*vane (III) and sol*anidane* (II).

(5) Intramolecular reactions of carboxyl derivatives with γ- or δ-dialkylamino groups have been reported by R. L. Clarke, A. Mooradian, P. Lucas and T. J. Slauson, THIS JOURNAL, **71**, 2821 (1949). Upon heating γ- or δ-dialkylamino acid chlorides, lactams and alkyl chlorides are formed. This reaction is analogous to that obtained with solanidane-18-oic acids in acetic anhydride, and suggests that the acetolysis proceeds *via* activation of the carboxyl as a mixed anhydride.

(6) For a review see K. J. Morgan and J. A. Barltrop, *Quart. Revs.*, **12**, 34 (1958).



atom of isorubijervine has been observed previously.[3] Tosylation of isorubijervine or any of its derivatives retaining the 18-hydroxyl group affords a neutral, salt-like compound which was assigned the structure XXVIII. Reduction of the quaternary salt with sodium in alcohol gave two compounds, solanidine (V), formed by cleavage of the C(18)–N bond, and an isomeric compound called "pseudosolanidine" which the authors felt had structure XXX, formed by cleavage of the C(16)–N bond.[3b] No evidence was offered which could rule out the alternative structures formed by cleavage of C(22)–N or C(26)–N bonds. That structure XXX is correct has been confirmed by establishing that the same ring system is formed in this reaction and in the acetolysis of the solanidane-18-oic acids.

The solanidane to cevanidane rearrangement observed during acetolysis of solanidane-18-oic acids and during cleavage of isorubijervine tosylates, and the reverse rearrangement with certain 16-substituted-18-oxocevanidanes, suggest a possible biogenetic relationship between the cevane and solanidane groups of alkaloids. Rearrangement of rings C and D of normal steroids to products with a C-nor-D-homo ring system has been demonstrated,[7] and has been suggested as evidence that jervine and veratramine are biogenetically related to the steroids.

The 18-oxocevanidanes were obtained in very pure form in 80–90% yields by diluting the hot acetic anhydride solutions with water; the neutral products crystallized spontaneously. Three examples were studied: conversion of 3β-acetoxy-5-solanidene-18-oic acid (IX) to 3β,16α-diacetoxy-18-oxo-5-cevanidene (X), conversion of solanidane-3-one-18-oic acid[8] (XIVa) to 16α-acetoxy-18-oxocevanidane-3-one (XVa), and conversion of 4-solanidene-3-one-18-oic acid[9] (XIVb) to 16α-acetoxy-18-oxo-4-cevanidene-3-one (XVb). Attempts to effect this skeletal transformation with thionyl chloride or phosphorus oxychloride did not afford characterizable products, although lactam formation apparently had taken place to some extent as evidenced by infrared absorption at 1630 cm.$^{-1}$.

Assignment of a structure to the cevanidane derivatives was based on the nature of the acetoxy group introduced during the acetolysis of the solanidane-18-oic acids. Mild alkaline hydrolysis of the acetolysis products afforded quantitatively the corresponding hydroxy compounds XVI. Oxidation of the hydroxyl group with chromic acid[10] or chromium trioxide in pyridine[11] gave a new carbonyl with infrared absorption at 1740 cm.$^{-1}$(XXI). This is strong evidence that the new carbonyl is a ketone situated in a 5-membered ring,[12] and the acetoxy group hence most probably is at C(16). Cleavage of the C(26)–N bond during acetolysis of the solanidane-18-oic acids would have introduced a primary acetoxy group, which upon saponification and oxidation would have given an aldehyde or carboxylic acid. Although cleavage of the C(22)–N bond would also have led to the ultimate formation of a ketone, its presence in a nine-membered ring would be expected to have infrared absorption in the 1705–1720 cm.$^{-1}$ region.[12]

Regeneration of the solanidane ring system from certain 16-substituted 18-oxocevanidane derivatives occurs readily during hydrolytic or reductive processes. When 16α-acetoxy-18-oxocevanidane (XVa) was heated under reflux in an acetic acid–hydrochloric acid solution or was heated with phosphoric acid, the acetolysis reaction was reversed and solanidane-3-one-18-oic acid (XIVa) was recovered in high yield. Lithium aluminum hydride reduction of 16α-tosyloxy-18-oxocevanidane-3-cycloethylene ketal (XIXa) or of 16α-chloro-18-oxocevanidane-3-cycloethylene ketal (XXa) gave 18-hydroxysolanidane-3-cycloethylene ketal (XIIIa) in good yield. This compound was characterized by cleavage of the ketal to give 18-hydroxysolanidane-3-one (XIIa), identical in all respects with a sample prepared by Oppenhauer oxidation of dihydroisorubijervine.[3a] Acetate and 2,4-dinitrophenylhydrazone derivatives of the two samples also were identical in all respects.

Assignment of an α-configuration to the 16-substituents of the cevanidane derivatives has been based in part on the ease with which rearrangement to the solanidane skeleton takes place. During both hydrolytic and reductive conditions an SN2 displacement of the 16-substituent by nitrogen would seem to be the most logical mechanism for the observed reaction. Introduction of the acetoxy group in the α-configuration would also seem most reasonable during the acetolysis of solanidane-18-oic acids by a concerted α-attack of acetate on C(16) and β-attack of carboxyl on the nitrogen atom.

The importance of the transannular 16–18 interactions in reactions of 18-oxocevanidanes becomes apparent upon reduction of C(16) to methylene. The lactam ring of 18-oxocevanidane-3-cycloethylene ketal (XXIII) is extremely stable to hydrolysis. Heating a solution of this compound in acetic acid–hydrochloric acid under reflux for two weeks resulted only in ketal cleavage; 18-oxocevanidane-3-one (XXIV) was recovered

(7) R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey and N. L. Wendler, THIS JOURNAL, **76**, 4013 (1954).

(8) Y. Sato and W. A. Jacobs, *J. Biol. Chem.*, **191**, 63 (1951).

(9) L. A. Cohen, Ph.D. Thesis, Massachusetts Institute of Technology, 1952, p. 31.

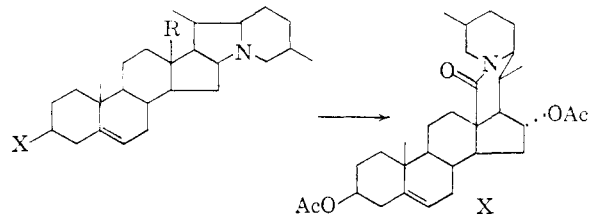
(10) Y. Sato and N. Ikekawa, *J. Org. Chem.*, **24**, 1367 (1959).

(11) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

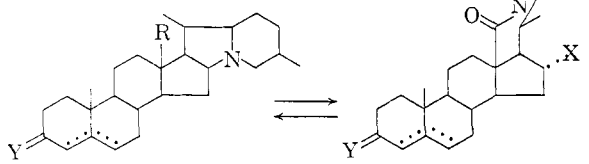
(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Second Edition, John Wiley and Sons, Inc., New York, N. Y., 1958.

in 74% yield. Removal of the 16-substituents was accomplished by the Huang-Minlon modification of the Wolff–Kishner reduction[13] of 18-oxocevanidane-16-one-3-cycloethylene ketal (XXII); XXII was prepared from 16α-hydroxy-18-oxocevanidane-3-cycloethylene ketal (XVIIIa) by oxidation with chromium trioxide in pyridine.

Lithium aluminum hydride reduction of 16α-acetoxy-18-oxocevanidane derivatives proceeded with retention of the cevanidane ring system; the lactam was reduced to the corresponding tertiary amine, and the acetoxy group was converted to hydroxyl. By this procedure 3β,16α-dihydroxy-5-cevanidene (XI) was prepared from 3β,16α-diacetoxy-18-oxo-5-cevanidene (X) and 16α-hydroxycevanidane-3-cycloethylene ketal (XXVa) from 16α-acetoxycevanidane-18-oxocevanidane-3-cycloethylene ketal (XVIIa). Attempts to reduce partially the lactam of XVIIa to a carbinolamine[14] were unsuccessful; low temperatures and/or stoichiometric quantities of lithium aluminum hydride gave mixtures of 16α-hydroxy-18-oxocevanidane-3-cycloethylene ketal (XVIIIa) and the fully reduced XXVa.

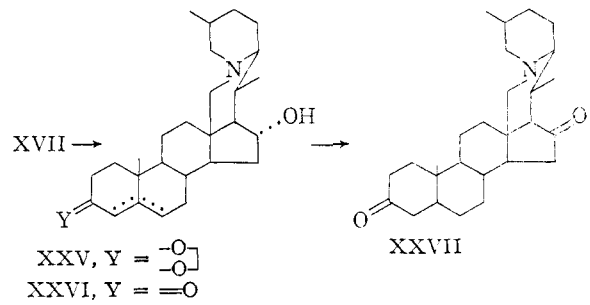


V, X = -OH, R = $-CH_3$
VI, X = -OH, R = $-CH_2OH$
VII, X = -OH, R = -CHO
VIII, X = -OAc, R = -CHO
IX, X = -OAc, R = $-CO_2H$

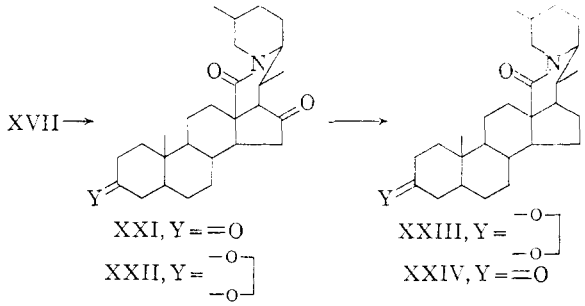


XII, Y = =O, R = $-CH_2OH$
XIII, Y = ⌐O O⌐, R = $-CH_2OH$
XIV, Y = =O, R = $-CO_2H$

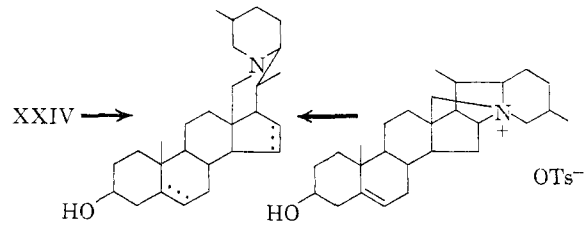
XV, Y = =O, X = -OAc
XVI, Y = =O, X = -OH
XVII, Y = ⌐O O⌐, X = -OAc
XVIII, Y = ⌐O O⌐, X = -OH
XIX, Y = ⌐O O⌐, X = -OTs
XX, Y = ⌐O O⌐, X = -Cl



XXV, Y = ⌐O O⌐
XXVI, Y = =O
series "a": 5β-H; series "b": Δ^4 or Δ^5



XXI, Y = =O
XXII, Y = ⌐O O⌐
XXIII, Y = ⌐O O⌐
XXIV, Y = =O



XXIX, 5β-H; 15,16-dihydro
XXX, Δ^5; 15,16-dihydro
XXXI, Δ^5; Δ^{15}
XXVIII

Quaternization of 16α-hydroxycevanidane-3-cycloethylene ketal (XXVa) was effected readily by heating under reflux with methyl iodide in acetone. This is in contrast to the behavior of isorubijervine (VI) which apparently is unreactive toward quaternizing agents.[15] Failure to obtain quaternary salts with isorubijervine probably is due to the transannular C(18)-hydroxy–C(16)-nitrogen interaction. The α-configuration of the hydroxyl in the cevanidane derivatives precludes any such OH–N interaction, allowing normal quaternization of the tertiary amine. Hofmann degradation of 16α-hydroxycevanidane-3-cycloethylene ketal methiodide regenerated the starting amine XXVa.

Oxidation of 16α-hydroxycevanidane-3-one (XXVIa) with chromic acid in acetone[10] gave cevanidane-3,16-dione (XXVII) in quantitative yield. This compound had two absorption maxima in the carbonyl region of the infrared, one at 1710 cm.$^{-1}$ due to the 3-keto group and one at 1740 cm.$^{-1}$ due to the 16-keto group. Since the absorption of the 16-ketone is in the region normally encountered for a cyclopentanone there apparently is no N–C_{co} interaction with the tertiary nitrogen at C(18).[16] If the new carbonyl had been at C(22),

(13) D. Todd in "Organic Reactions," Vol. IV, Roger Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 378.

(14) V. M. Micovic and M. L. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).

(15) No quaternary salts of isorubijervine other than the "intramolecular" quaternary tosylate XXVIII have been reported in the literature. Attempts in our laboratory to effect the quaternization of isorubijervine with methyl iodide or methyl *p*-toluenesulfonate under a variety of conditions were unsuccessful.

(16) N. J. Leonard, J. A. Adamcik, C. Djerassi and O. Halpern, THIS JOURNAL, **80**, 4858 (1958).

the result of a C(22)–N cleavage of the original solanidane-18-oic acid, the probability is high that an N–C_{CO} interaction across the nine-membered ring would occur, with a corresponding shift of the carbonyl frequency to values below the expected 1720-1705 cm.$^{-1}$ region.

Lithium aluminum hydride reduction of 18-oxo-cevanidane-3-one (XXIV) gave 3β-hydroxycevanidane (XXIX). The "dihydropseudosolanidine" of Pelletier and Jacobs,[3b] obtained by hydrogenation of XXX, was identical in all respects with this compound.

Hofmann degradation of isorubijervine monotosylate afforded a single compound, 3β-hydroxy-5,16-cevanidiene (XXXI)[17]; formation of a compound with the solanidane skeleton is not possible under these conditions. Two moles of hydrogen was consumed by XXXI during hydrogenation to give 3β-hydroxycevanidane (XXIX).

p-Toluenesulfonate esters were prepared by treating the 16-hydroxy compounds with *p*-toluenesulfonyl chloride in pyridine at room temperature. When these reaction mixtures were heated under reflux the only product characterized was the corresponding 16-chloro derivative.[18]

The 3-cycloethylene ketals were prepared by the *p*-toluenesulfonic acid-catalyzed interaction of the ketone with ethylene glycol. Cleavage of the ketals was effected by warming in 50% aqueous acetic acid solution.[19]

Chromic acid oxidation of the isorubijervine hydroxymethyl group served to prepare the solanidane-18-oic acids used as precursors for the 18-oxo-cevanidane derivatives. Direct oxidation of dihydro-isorubijervine with Kiliani solution[20] afforded solanidane-3-one-18-oic acid (XIVa).[8] Preparation of 4-solanidene-3-one-18-oic acid (XIVb)[9] required two steps: initial oxidation of isorubijervine (VI) to 18-hydroxy-4-solanidene-3-one (XIIb) by the Oppenhauer procedure, followed by oxidation at C(18) with a modified Kiliani reagent. A three-step procedure was necessary for the preparation of 3β-acetoxy-5-solanidene-18-oic acid (IX): chromium trioxide oxidation of isorubijervine to give the 18-aldehyde VII,[9] acetylation of the 3-hydroxyl group (VIII), and further oxidation of the aldehyde to carboxyl with chromic acid.

Experimental[21]

3β-Acetoxy-5-solanidene-18-oic Acid (IX).—A solution of 4.14 g. (0.01 mole) of isorubijervine in 100 ml of 90% acetic acid was cooled in an ice-bath; 0.70 g. of chromium trioxide dissolved in 10 ml. of 90% acetic acid was added during 30 minutes. After standing at room temperature for 18 hours, the excess chromium trioxide was destroyed with alcohol, and the solvents removed under reduced pressure. The oily residue was taken up in 50 ml. of water and the product precipitated by making the solution basic with 10% aqueous sodium carbonate. Recrystallization from ethanol gave 3.18 g. (77%) of 3β-hydroxy-5-solanidene-18-al (VII),[9] m.p. 214–215°, $[\alpha]^{28}D$ + 5.5° (*c* 0.7, $CHCl_3$); ν_{max}^{KBr} 3300, 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_2$: C, 78.78; H, 10.04; N, 3.41. Found: C, 78.31; H, 10.24; N, 3.96.

A solution containing 1.0 g. of 3β-hydroxy-5-solanidene-18-al (VII) in 10 ml. of acetic anhydride and 10 ml. of pyridine was stored 16 hours at room temperature. After dilution with ice-water the mixture was made basic with 10% aqueous sodium carbonate and the product extracted with several portions of methylene chloride. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Crystallization of the solid residue from methanol–water afforded 0.70 g. (64%) of 3β-acetoxy-5-solanidene-18-al (VIII), m.p. 203–203.5°.

Anal. Calcd. for $C_{29}H_{43}NO_2$: C, 76.78; H, 9.55; N, 3.09. Found: C, 76.95; H, 9.50; N, 3.00.

To 0.25 g. of VIII dissolved in 60 ml. of acetone there was added 0.3 ml. of a chromic acid oxidizing solution.[22] After 20 minutes at room temperature the mixture was made basic with 20 ml. of saturated aqueous sodium bicarbonate and was concentrated to a small volume. The solid was collected by filtration and washed thoroughly with 95% ethanol; upon evaporation to dryness the filtrate left a solid residue which was transferred to a filter and washed thoroughly with water; 0.24 g. (90%) of sodium 3β-acetoxy-5-solanidene-18-oic acid was obtained.

An aqueous suspension of the sodium salt was adjusted to *p*H 6–7 with hydrochloric acid and acetic acid, and the acid IX recovered as its hydrochloride by extraction with methylene chloride. The product was crystallized from methylene chloride and acetone, m.p. 296–298°, $[\alpha]D$ −13° (*c* 0.69, $CHCl_3$).

Anal. Calcd. for $C_{29}H_{43}NO_4 \cdot HCl$: C, 68.82; H, 8.76; N, 2.67; Cl, 7.01. Found: C, 68.90; H, 8.58; N, 2.74; Cl, 7.23.

4-Solanidene-3-one-18-oic Acid (XIVb).—To 1.6 g. of 18-hydroxy-4-solanidene-3-one[23] (XIIb) dissolved in 80 ml. of 90% acetic acid there was added 24 ml. of Kiliani reagent.[20] The reaction was stirred 12 hours in a melting ice-bath, after which excess oxidizing reagent was destroyed by adding 10 ml. of ethanol. The mixture was diluted with water, made basic with concentrated ammonium hydroxide, and exhaustively extracted with chloroform. After drying over anhydrous magnesium sulfate the extracts were evaporated to dryness, and the oily residue crystallized by trituration with acetone; the yield of 4-solanidene-3-one-18-oic acid (XIVb) was 0.83 g. (53%), m.p. 278–281°. Recrystallization from methylene chloride–acetone gave pure material, m.p. 282–285°, $[\alpha]D$ 108° (*c* 1.79, $CHCl_3$).

Anal. Calcd. for $C_{27}H_{39}O_3N$: C, 76.19; H, 9.24; N, 3.29. Found: C, 76.19; H, 9.46; N, 3.53.

Preparation of 18-Oxocevanidanes.—A 3 to 5% solution of the solanidane-18-oic acid (or its sodium salt) in acetic anhydride was heated under reflux for 2–3 hours. Sufficient water was added to the hot solution to hydrolyze completely the acetic anhydride, and the heating under reflux was continued for 15 min. The reaction mixture was then diluted with hot water until the product began to crystallize. After cooling, a product of sufficient purity for further reactions was collected.

A. 3β,16α-Diacetoxy-18-oxo-5-cevanidene (X).—From 0.48 g. of sodium 3β-acetoxy-5-solanidene-18-oate (IX) and 15 ml. of acetic anhydride there was obtained 0.33 g. (66%) of 3β,16α-diacetoxy-18-oxo-5-cevanidene (X), m.p. 227.5–230°. Recrystallization from ethanol–water gave an analy-

(17) The exact position of the double bond in the D ring has not been established. A Δ^{15}-structure is favored since the Hofmann degradation is known to give preferentially the less highly substituted olefin.

(18) Reaction conditions such as this normally afford dehydration of alcohols: O. Wintersteiner and M. Moore, THIS JOURNAL, **65**, 1511 (1943). Formation of chloro compounds is a known reaction with phosphorus oxychloride–pyridine or thionyl chloride–pyridine mixture: see R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 91–92.

(19) E. P. Oliveto, T. Clayton and E. B. Hershberg, THIS JOURNAL, **75**, 486 (1953).

(20) H. Kiliani, *Ber.*, **46**, 676 (1913). This reagent has the composition: 53 g. of chromium trioxide, 80 g. of concentrated sulfuric acid and 400 ml. of water.

(21) All melting points are corrected. Analyses were by S. M. Nagy, Massachusetts Institute of Technology, Cambridge, Mass., or by A. Bernhardt, Max Planck Institute, Mulheim, Germany. Infrared spectra were obtained with a Perkin–Elmer model 137 spectrophotometer.

(22) This solution consists of 26.72 g. of chromium trioxide dissolved in 23 ml. of concentrated sulfuric acid and diluted to 100 ml. of water; C. Djerassi, R. R. Engle and A. Bowen, *J. Org. Chem.*, **21**, 1547 (1956).

(23) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **159**, 617 (1945).

tical sample, m.p. 228.5–230.5°, $[\alpha]^{23}D$ −75.2° (*c* 0.95, $CHCl_3$); ν_{max}^{KBr} 1735, 1725, 1630, and 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{31}H_{45}NO_5$: C, 72.76; H, 8.86; N, 2.74. Found: C, 72.86; H, 8.89; N, 2.66.

B. 16α-Acetoxy-18-oxo-4-cevanidene-3-one (XVb).—A 90% yield of XVb was obtained from 0.72 g. of 4-solanidene-3-one-18-oic acid (XIVb) in 15 ml. of acetic anhydride. After recrystallization from ethanol–water the substance was analytically pure: m.p. 242–244.5°, $[\alpha]^{23}D$–6.3° (*c* 0.9, $CHCl_3$); ν_{max}^{KBr} 1730, 1665, 1620, and 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{41}NO_4$: C, 74.48; H, 8.84; N, 3.00. Found: C, 74.62; H, 8.93; N, 3.04.

C. 16α-Acetoxy-18-oxocevanidane-3-one (XVa) was obtained in 89% yield from 1.5 g. of solanidane-3-one-18-oic acid[8] (XIVa) in 50 ml. of acetic anhydride. Recrystallization from ethanol–water afforded material of m.p. 255.5–258.5°, $[\alpha]^{21}D$ −40.5° (*c*-1.0, $CHCl_3$); ν_{max}^{KBr} 1730, 1710, 1630 and 1240 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{43}NO_4$: C, 74.16; H, 9.23; N, 2.98. Found: C, 74.43; H, 9.19; N, 2.80.

Acid Hydrolysis of 16α-Acetoxy-18-oxocevanidane-3-one.—A solution of 0.23 g. of 16α-acetoxy-18-oxocevanidane-3-one (XVa) in 10 ml. of acetic acid and 10 ml. of constant boiling hydrochloric acid was heated under reflux for 6 days. After cooling the mixture was diluted with 30 ml. of water (no turbidity developed) and extracted with ether. The aqueous phase was neutralized to *p*H 6 with solid sodium carbonate and re-extracted with methylene chloride. Removal of the methylene chloride from the extracts after drying over magnesium sulfate left a gum which solidified upon trituration with ether; m.p. 296–300°, $[\alpha]D$ + 65° (*c* 1.05, pyridine). A mixture melting point with authentic solanidane-3-one-18-oic acid (XIVa) was undepressed; infrared spectra (KBr disk) of the two materials were identical. The yield of solanidane-3-one-18-oic from this hydrolysis was 0.17 g. (82%). Similar results were obtained with phosphoric acid upon heating at 150° for 2 hours or with an acetic acid–48% hydrobromic acid mixture upon reflux for several days.

16α-Hydroxy-18-oxo-cevanidane-3-one (XVIa).—Saponification of the acetate group was readily effected with methanolic potassium hydroxide. From 1.17 g. of 16α-acetoxy-18-oxo-cevanidane-3-one (XIVa) and 1.0 g. of potassium hydroxide dissolved in 25 ml. of methanol there was obtained 1.04 g. (98%) of product. The reaction mixture was left at room temperature for 15 hours, then acidified with 10% aqueous hydrochloric acid and diluted with water on a steam-bath until the product crystallized. Recrystallization from methanol–water gave analytically pure 16α-hydroxy-18-oxo-cevanidane-3-one (XVIa) as its monohydrate, m.p. 135° dec. followed by resolidification and m.p. 217–218°, $[\alpha]^{24}D$ −19° (*c* 1.1, pyridine); ν_{max}^{KBr} 3400, 1710 and 1630 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_3 \cdot H_2O$: C, 72.77; H, 9.73; N, 3.14. Found: C, 72.59; H, 9.72; N, 3.24.

A tosylate derivative of this compound was prepared by the action of *p*-toluenesulfonyl chloride on XVIa in pyridine solution at room temperature. After recrystallization from acetone–water the product had m.p. 180–182°.

Anal. Calcd. for $C_{34}H_{47}NO_3S$: C, 70.19; H, 8.14; N, 2.41. Found: C, 69.94; H, 8.12; N, 2.25.

18-Oxocevanidane-3,16-dione (XXI).—A solution of 90 mg. of 16α-hydroxy-18-oxocevanidane-3-one (XVIa) in 20 ml. of 90% acetic acid was treated with 2.0 ml. of Kiliani reagent.[20] The reaction mixture was left at room temperature for 15 hours then was diluted with 100 ml. of water and extracted with chloroform. After washing with 5% aqueous sodium bicarbonate the combined extracts were dried over anhydrous magnesium sulfate and evaporated to dryness. Crystallization of the solid residue from absolute methanol gave 18-oxocevanidane-16-one-3-dimethyl ketal, m.p. 192–193°, ν_{max}^{KBr} 1740 and 1630 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{45}NO_4$: C, 73.84; H, 9.62. Found: C, 73.99; H, 9.33.

Upon warming the dimethyl ketal in 50% acetic acid, followed by dilution with water, 18-oxocevanidane-3,16-dione (XXI) was obtained. Recrystallization from acetone–water afforded material of m.p. 222–225°, $[\alpha]D$ −148 (*c* 1.0 pyridine); ν_{max}^{KBr} 1740, 1719 and 1630 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{39}NO_3$: C, 76.19; H, 9.24; N, 3.29. Found: C, 75.66; H, 9.17; N, 3.36.

16α-Chloro-18-oxocevanidane-3-one.—A pyridine solution (25 ml.) containing 0.60 g. of 16α-hydroxy-18-oxo-cevanidane-3-one and 0.60 g. of *p*-toluenesulfonyl chloride was heated under reflux for 16 hours. After cooling, the reaction mixture was poured into 100 ml. of water, and the oil which separated was induced to crystallize by trituration. Recrystallization from methanol–water gave 0.48 g. (80%) of 16α-chloro-18-oxocevanidane-3-one, m.p. 218–228°. A second recrystallization from the same solvent gave an analytical sample, m.p. 229–231°, $[\alpha]D$ −3.9° (*c* 1.0, pyridine); ν_{max}^{KBr} 1710, 1630 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{40}NO_2Cl$: C, 72.70; H, 9.04: N, 3.14; O, 7.17; Cl, 7.95. Found: C, 72.72, 72.76; H, 9.04, 9.14; N, 3.15; O, 7.27; Cl, 7.23.

Preparation of Cycloethylene Ketals.[19]—To a 2% solution of the 3-ketone in anhydrous benzene there was added 4% by volume of ethylene glycol and a trace of *p*-toluenesulfonic acid. The mixture was heated under reflux in a Soxhlet extractor containing anhydrous magnesium sulfate in the thimble. After 12 hours one pellet of potassium hydroxide dissolved in 5 ml. of methanol was added, and the mixture washed with 5% aqueous sodium bicarbonate. After drying over anhydrous magnesium sulfate the benzene was evaporated to leave a solid residue of product.

A. 16α-Acetoxy-18-oxocevanidane-3-cycloethylene Ketal (XVIIa).—From 5.6 g. of 16α-acetoxy-18-oxocevanidane-3-one (XVa) there was obtained 6.07 g. (98%) of XVIIa. The product was crystallized from 95% ethanol, m.p. 249–251°, $[\alpha]D$ −54° (*c* 1.44, pyridine).

Anal. Calcd. for $C_{31}H_{47}NO_5$· C, 72.47; H, 9.22; N, 2.73. Found: C, 72.40; H, 9.24; N, 2.41.

B. 16α-Acetoxy-18-oxo-5-cevanidene-3-cycloethylene Ketal (XVIIb).—A quantitative yield of XVIIb was obtained from 0.43 g. of 16α-acetoxy-18-oxo-4-cevanidene-3-one (XVb). Recrystallization from cyclohexane afforded the analytical sample, m.p. 102° dec. The material analyzed as a cyclohexane solvate.

Anal. Calcd. for $C_{31}H_{45}NO_5 \cdot C_6H_6$: C, 74.58; H, 9.64. Found: C, 74.19; H, 9.51.

C. 16α-Hydroxy-18-oxocevanidane-3-cycloethylene Ketal (XVIIIa).—From 450 mg. of 16α-hydroxy-18-oxo-cevanidane-3-one (XVIa) there was obtained 475 mg. (100%) of 16α-hydroxy-18-oxo-cevanidane-3-cycloethylene ketal (XVIIIa), m.p. 155–157°. Recrystallization from acetone–water gave material of m.p. 157–159°, $[\alpha]D$ −23.5° (*c* 0.68, pyridine); ν_{max}^{KBr} 3300 and 1630 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{45}NO_4$: C, 73.84; H, 9.62. Found: C, 74.01; H, 9.55.

Reaction of XVIIa with *p*-toluenesulfonyl chloride in pyridine at room temperature afforded 89% of **16α-tosyloxy-18-oxocevanidane-3-cycloethylene ketal (XIXa).** Crystallization from acetone–water gave pure material of m.p. 169–171°, $[\alpha]D$ −37° (*c* 1.05, pyridine).

Anal. Calcd. for $C_{36}H_{51}NO_6S$: C, 69.08; H, 8.21. Found: C, 69.09; H, 8.21.

D. 16α-Chloro-18-oxocevanidane-3-cycloethylene Ketal (XXa).—An 84% yield (1.43 g.) of XXa was obtained from 1.54 g. of 16α-chloro-18-oxocevanidane-3-one; m.p. 247.5–249.5° from ethanol. Recrystallization from cyclohexane gave pure material, m.p. 252–254°, $[\alpha]D$ −21° (*c* 1.0, pyridine); ν_{max}^{KBr} 1630 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{44}ClN_3O$: C, 71.06; H, 9.05; N, 2.86. Found: C, 70.75; H, 9.32; N, 2.90.

18-Oxocevanidane-16-one-3-cycloethylene Ketal (XXII).—A solution of 2.0 g. of 16α-hydroxy-18-oxocevanidane-3-cycloethylene ketal (XVIIIa) in 60 ml. of pyridine was added to 0.535 g. of chromium trioxide in 30 ml. of pyridine. After 16 hours at 25° the mixture was diluted with water and extracted with a 1:1 benzene–ether mixture. The combined extracts were washed with water, dried over Drierite and concentrated under reduced pressure. Crystallization of the residue from methanol–acetone gave 1.30 g. of pure 18-oxocevanidane-16-one-3-cycloethylene ketal (XXII). Concentration of the mother liquors and reoxidation under the same conditions afforded an additional 0.64 g. of product; the total yield was 98%. Recrystallization from methanol–acetone gave an analytical sample, m.p. 282–284.5° after

softening at 276°, $[\alpha]D$ −133° (*c* 1.46, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 1740, 1620, 1250 and 1160–1060 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{43}N$: C, 74.16; H, 9.23; N, 2.98. Found: C, 73.88; H, 9.11; N, 3.00.

18-Oxocevanidane-3-cycloethylene Ketal (XXIII).—A mixture of 1.30 g. of 18-oxocevanidane-16-one-3-cycloethylene ketal (XXII), 10 ml. of anhydrous hydrazine and 10 g. of potassium hydroxide in 170 ml. of ethylene glycol was distilled slowly until the temperature reached 190°. An additional 10 ml. of hydrazine was then added and the distillation continued for 3 hours. After cooling, the mixture was diluted with 200 ml. of water and exhaustively extracted with methylene chloride. The combined extracts were washed with water, dried over Drierite, and taken to dryness under reduced pressure. Crystallization from methanol afforded 0.90 g. (71%) of 18-oxocevanidane-3-cycloethylene ketal (XXIII). An analytical sample recrystallized from methanol had m.p. 203–205°, $[\alpha]D$ + 20° (*c* 1.05, $CHCl_3$); ν_{max}^{KBr} 1620, 1260 and 1180–1080 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{43}O_3N$: C, 76.43; H, 9.95; N, 3.07. Found: C, 76.52; H, 9.87; N, 3.18.

18-Oxocevanidane-3-one (XXIV). Attempted Hydrolysis of Lactam.—A solution of 60 mg. of 18-oxocevanidane-3-cycloethylene ketal (XXII) in 15 ml. of glacial acetic acid and 5 ml. of 20% hydrochloric acid was heated under reflux in a nitrogen atmosphere for 2 weeks. The residue remaining after removal of the solvent under reduced pressure was crystallized from methylene chloride–hexane to give 40 mg. (74%) of 18-oxocevanidane-3-one (XXIV), m.p. 196–200°. Recrystallization from the same solvents afforded material of m.p. 202–203°, $[\alpha]D$ −27° (*c* 1.20, $CHCl_3$); ν_{max}^{KBr} 1715, 1626 and 1340 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_2$: C, 78.78; H, 10.04; N, 3.40. Found: C, 78.51; H, 10.09; N, 3.41.

Lithium Aluminum Hydride Reduction.—The lithium aluminum hydride reductions were carried out in tetrahydrofuran (THF) solution with a large excess of the reducing agent. Reaction mixtures usually were heated under reflux for 12–18 hours, after which excess hydride was decomposed by the addition of ethyl acetate. Further processing of the reaction mixture was by one of two procedures[24]: (1) The inorganic salts were precipitated by the addition of a small amount of water dissolved in tetrahydrofuran (THF); after filtering, the salts were thoroughly washed with hot tetrahydrofuran (THF), and the combined filtrate evaporated to afford the solid products. (2) The reaction mixture was diluted with a 20% aqueous solution of sodium and potassium tartrate, and the resultant mixture extracted with methylene chloride; after drying, the combined extracts were evaporated to give the products.

A. 18-Hydroxysolanidane-3-cycloethylene Ketal (XIIIa). I. From 16α-Chloro-18-oxocevanidane-3-cycloethylene Ketal (XXa). Reduction of 0.55 g. of XXa with 0.15 g. of lithium aluminum hydride in 10 ml. of tetrahydrofuran (THF) afforded 0.30 g. of (59%) of 18-hydroxy-3-cycloethylene ketal (XIIIa); work-up was by procedure 1. Recrystallization from ethanol gave an analytical sample, m.p. 227.5–230.5°, $[\alpha]^{25}D$ +30° (*c* 2.0, $CHCl_3$).

Anal. Calcd. for $C_{29}H_{47}NO_3$: C, 76.10; H, 10.35; N, 3.06. Found: C, 76.20; H, 10.31; N, 3.09.

II. From 16α-Tosyloxy-18-oxo-cevanidane-3-cycloethylene Ketal (XIXa).—A 45% yield of 18-hydroxysolanidane-3-cycloethylene ketal was obtained using the same quantities and procedure as described above for the chloro compound. The purified product had a m.p. 227–230° (mixture m.p. with material from reduction of chloro compound was undepressed), $[\alpha]^{25}D$ + 30° (*c* 2.0, $CHCl_3$).

Anal. Calcd. for $C_{29}H_{47}NO_3$: C, 76.10; H, 10.35; N, 3.06. Found: C, 76.04; H, 10.33; N, 2.93.

B. 16α-Hydroxycevanidane-3-cycloethylene Ketal (XXVa).—From 0.514 g. of 16α-acetoxy-18-oxocevanidane-3-cycloethylene ketal (XVIIa) there was obtained a quantitative yield (0.46 g.) of 16α-hydroxycevanidane-3-cycloethylene ketal (XXVa); the product was isolated from the reaction mixture by procedure 2. Two recrystallizations from acetone afforded material of m.p. 212.5–216°, $[\alpha]D$ −23.7° (*c* 1.2, pyridine).

Anal. Calcd. for $C_{29}H_{47}NO_3$: C, 76.10; H, 10.35; N, 3.06. Found: C, 76.45; H, 10.58; N, 3.25.

C. 3β,16α-Dihydroxy-5-cevanidene (XI).—A quantitative yield of XI was obtained upon reduction of 0.45 g. of 3β, 16α-diacetoxy-18-oxo-5-cevanidene with 0.40 g. of lithium aluminum hydride in 25 ml. of THF; procedure 2 was utilized for isolation of the product. Recrystallization from ethanol–water gave the analytical sample, m.p. 229–233°, $[\alpha]D$ −35.5° (*c* 2.4, pyridine).

Anal. Calcd. for $C_{27}H_{43}NO_2 \cdot {}^1/_2H_2O$: C, 76.73; H, 10.49; N, 3.31. Found: C, 76.37; H, 10.27; N, 3.28.

D. 3β-Hydroxycevanidane (XXIX).—This compound, isolated by procedure 2, was prepared from 40 mg. of 18-oxocevanidane-3-one (XXIV). After crystallization from acetone the substance had m.p. 207–209°, $[\alpha]D$ +30° (*c* 0.605, $CHCl_3$); recrystallization from the same solvent afforded an analytical sample, m.p. 211–212°.

Anal. Calcd. for $C_{27}H_{45}NO$: C, 81.14; H, 11.25; N, 3.51. Found: C, 81.03; H, 11.32; N, 3.64.

A mixture m.p. of this compound with the "dihydropseudosolanidine," m.p. 209–211°, $[\alpha]D$ + 30° (*c* 1.0, $CHCl_3$), prepared according to Pelletier and Jacobs,[3b] was not depressed. Infrared spectra (KBr disk) of the two materials were identical.

18-Hydroxysolanidane-3-one (XIIa). A. By Hydrolysis of 18-Hydroxysolanidane-3-cycloethylene Ketal (XIIIa).—Approximately 25 mg. of the ketal XIIIa dissolved in 5 ml. of 50% acetic acid was heated for 30 minutes on a steam-bath. After removal of the solvents under reduced pressure the residue was crystallized from acetone–water containing a trace of potassium carbonate. The product had m.p. 217–220°, $[\alpha]D$ + 56° (*c* 1.0, pyridine).

A 2,4-dinitrophenylhydrazone derivative was prepared and recrystallized from methylene chloride–ethanol; m.p. 244.5–245.5°.

Anal. Calcd. for $C_{33}H_{47}N_5O_5$: C, 66.75; H, 7.99; N, 11.80. Found: C, 66.96; H, 7.91; N, 12.25.

B. By Oxidation of Dihydroisorubijervine.—An Oppenhauer oxidation of dihydroisorubijervine by the procedure of Weisenborn and Burn[3a] gave authentic 18-hydroxysolanidane-3-one, m.p. 215–217°, $[\alpha]D$ + 57° (*c* 1.0, pyridine). A mixture m.p. with the material obtained by hydrolysis of the 3-cycloethylene ketal was undepressed, and the two gave identical infrared spectra (KBr disk).

The 2,4-dinitrophenylhydrazone of this compound had m.p. 242–243°; there was no depression of the m.p. upon admixture with the derivative obtained above.

18-Acetoxysolanidane-3-one.—A mixture containing 60 mg. of 18-hydroxysolanidane-3-cycloethylene ketal (XXVa), 1 ml. of acetic anhydride, and 2 ml. of pyridine was heated on a steam-bath for 1 hour. After cooling, the acetylation mixture was poured over cracked ice and the resultant solution made basic with potassium carbonate. The product was extracted with methylene chloride. After removal of the solvent under reduced pressure, the residue was warmed with 60% acetic acid; concentration left an oil which solidified upon trituration with 5% aqueous potassium carbonate. Recrystallization from acetone–water gave pure 18-acetoxysolanidane-3-one, m.p. 176.5–178.5°, $[\alpha]^{28}D$ + 55° (*c* 1.2, pyridine); reported[25] m.p. 179°.

Anal. Calcd. for $C_{29}H_{45}NO_3$: C, 76.44; H, 9.95; N, 3.07. Found: C, 76.37; H, 9.38; N, 2.85.

16α-Hydroxycevanidane-3-cycloethylene Ketal Methiodide.—A mixture of 0.30 g. of 16α-hydroxycevanidane-3-cycloethylene ketal (XXVa), 6 ml. of methyl iodide, 5 g. of potassium carbonate and 50 ml. of acetone was heated under reflux with stirring for 18 hours. The hot mixture was filtered and the filter cake washed thoroughly with acetone. Evaporation of the filtrate gave a solid residue which was triturated with ether and with chloroform; crystallization of the remaining material from water gave 0.26 g. (66%) of methiodide, m.p. 271–275°.

Anal. Calcd. for $C_{30}H_{50}NO_2I$: C, 60.09; H, 8.41; I, 21.17. Found: C, 59.85; H, 8.26; I, 21.19.

16α-Hydroxycevanidane-3-one (XXVIa).—The ketal group of 16α-hydroxycevanidane-3-cycloethylene ketal (XXVa) was cleaved by warming the compound in 20% aqueous acetic acid on a steam-bath for 30 minutes. Removal of

(24) W. G. Brown in "Organic Reactions," Vol. VI, Roger Adams, Ed., John Wiley and Sons, Inc., New York, N. Y., 1951, p. 469.

(25) M. W. Klohs, M. D. Draper, F. Keller, W. Malesh and F. J. Petracek, THIS JOURNAL, **75**, 2133 (1953).

solvents under reduced pressure left a colorless oil which solidified upon trituration with 5% aqueous sodium bicarbonate. From 0.35 g. of XXVa there was obtained 0.31 g. (98%) of crude 16α-hydroxy-cevanidane-3-one (XXVIa); two recrystallizations from ethanol–water gave a pure sample, m.p. 207.5–210°, $[\alpha]^{25}D$ −42.7° (*c* 1.28, $CHCl_3$). A mixture m.p. with 18-hydroxysolanidane-3-one (XIIa), m.p. 217–220°, was depressed.

Anal. Calcd. for $C_{27}H_{43}NO_2$: C, 78.40; H, 10.48; N, 3.39. Found: C, 78.31; H, 10.54; N, 3.80.

The acetate was prepared by the pyridine–acetic anhydride procedure; m.p. 163–167.5° after recrystallization from acetone–water, $[\alpha]^{24}D$ −44° (*c* 1.22, pyridine). A mixture m.p. with 18-acetoxysolanidane-3-one, m.p. 174–176.5°, was depressed.

Anal. Calcd. for $C_{29}H_{45}NO_3$: C, 76.44; H, 9.95; N, 3.07. Found: C, 76.33; H, 9.90; N, 3.26.

Cevanidane-3,16-dione (XXVII).—To a solution of 0.11 g. of 16α-hydroxycevanidane-3-one (XXVIa) in 15 ml. of acetone there was added sufficient Kiliani reagent[20] to give a permanent orange color. Addition of a few drops of water gave a green oily phase which was removed by filtration through Celite. The filtrate was made basic with *N* aqueous sodium hydroxide and was diluted with water; an oil separated which solidified upon trituration to give a quantitative yield of cevanidane-3,16-dione (XXVII). Recrystallization from acetone–water gave pure material, m.p. 158–161°, $[\alpha]^{24}D$ −84° (*c* 1.02, pyridine), ν_{max}^{KBr} 1740 and 1710 cm.$^{-1}$.

Anal. Calcd. for $C_{27}H_{41}NO_2$: C, 78.78; H, 10.04; N, 3.40. Found: C, 78.66; H, 10.15; N, 3.67.

Hofmann Degradation of Isorubijervine Monotosylate.—Isorubijervine monotosylate (XXVIII)[3b] was added to a solution of 1 g. of potassium in 20 ml. of *t*-butyl alcohol. After heating the solution under reflux for 16 hours, the product was isolated by diluting the reaction mixture with water and extracting with methylene chloride. Removal of solvent from the extracts afforded 97 mg. (69%) of 3β-hydroxy-5,15-cevanidiene (XXXI), m.p. 227–230° after crystallization from acetone.

Anal. Calcd. for $C_{27}H_{40}NO$: C, 81.97; H, 10.45; N, 3.54. Found: C, 81.80; H, 10.36; N, 3.54.

Hydrogenation of 60.6 mg. of this material in glacial acetic acid over Adams catalyst gave 25 mg. of 3β-hydroxycevanidane (XXIX), m.p. 209–213°, $[\alpha]D$ + 32.5° (*c* 0.55, $CHCl_3$). Two moles of hydrogen was consumed during the reduction. A mixture m.p. with 3β-hydroxycevanidane prepared from 18-oxocevanidane-3-one (XXIV) was undepressed.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PRODUCTOS ESTEROIDES, S. A. DE C. V.]

Synthesis of 6-Methyl Steroids

BY LUIS MIRAMONTES, PASCUAL AGUINACO AND MIGUEL A. ROMERO

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A facile synthesis of 6α-methylprogesterone and 6α-methyl-17α-hydroxyprogesterone has been developed. A novel feature of the method involves the simultaneous attack at the nitrile and epoxide groups by methylmagnesium bromide on 5α,6α-epoxy-17-cyano-16-androsten-3β-ol acetate (III).

The introduction of a methyl substituent at the C-6 position of the steroid nucleus and the resulting enhancement of physiological properties has been the subject of several communications[1] during the past three years.

In all cases except that of the oxo reaction[1e,1f] the 6-methyl group has been introduced either by cleavage of the corresponding 5α,6α-epoxide with methylmagnesium halide or by adding this reagent to the 6-keto derivative. The nature of such a reaction imposes certain restrictions on its use, since any other substituents subject to attack by the Grignard reagent must be protected. The provision and removal of such protective groups has been a handicap in the synthesis of 6-methyl progestational and cortical steroids.

Petrow[1c] circumvented this problem in the synthesis of 6-methylprogesterone by treating the 5α,6α-epoxide of diosgenin with the Grignard reagent and degrading the adduct by normal procedures (the yield was not reported).

(1) (a) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek and J. A. Hogg, THIS JOURNAL, **78**, 6213 (1956); (b) H. J. Ringold, E. Batres and G. Rosenkranz, *J. Org. Chem.*, **22**, 99 (1957); (c) D. Burn, B. Ellis, V. Petrow, I. A. Stuart-Webb and D. M. Williamson, *J. Chem. Soc.*, 4092 (1957); (d) J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes and W. E. Dulin, THIS JOURNAL, **80**, 2904 (1958); (e) A. L. Nussbaum, T. L. Popper, E. P. Oliveto, S. Friedman and I. Wender, *ibid.*, **81**, 1228 (1959); (f) P. F. Beal, M. S. Rebenstorf and J. E. Pike, *ibid.*, **81**, 1231 (1959); (g) J. H. Fried, G. E. Arth and L. H. Sarett, *ibid.*, **81**, 1235 (1959).

In the present work we have taken a different approach to the synthesis of 6-methyl steroids of the pregnane series. Dehydroisoandrosterone acetate was converted to a mixture of isomeric 17-cyanohydrins by a modification of Heusser's method.[2] Dehydration of this mixture afforded the known nitrile II which, upon selective peroxidation and fractional crystallization, yielded 5α,6α-epoxy-17-cyano-16-androsten-3β-ol acetate (III). Attempts to perform a two-phase reaction on III with methylmagnesium bromide in benzene or toluene were fruitless. However, in anisole the reaction proceeded smoothly to give 3β,5α-dihydroxy-6β-methyl-16-pregnen-20-one (IV) which was consecutively hydrogenated (IX), oxidized and dehydrated to obtain the known 6β-methyl- (X) and 6α-methylprogesterone (XI).[1b]

Epoxidation of IV followed by oxidation and dehydration afforded 16α,17α-epoxy-6β-methyl-4-pregnene-3,20-dione (VI). This compound was epimerized (VII) and the 17α-hydroxyl group was then introduced by opening the epoxide with hydrogen bromide. Removal of the bromine with Raney nickel yielded 17α-hydroxy-6α-methylprogesterone (VIII) whose physical constants are in good agreement with those reported by Babcock, *et al.*[1d]

(2) H. Heusser, P. Th. Herzig, A. Fürst and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 1093 (1950).