and recrystallized from ethyl acetate–ethanol, m.p. 122° dec.

Anal. Calcd. for $C_{15}H_{26}N_2O \cdot 2C_6H_3N_3O_7$: C, 45.76; H, 4.55; N, 15.81. Found: C, 46.00; H, 4.84; N, 15.52.

Conversion of jamaidine to d-lupanine. A mixture of 100 mg. of jamaidine and 1 g. of phosphorus pentoxide was heated for 6 hr. at 170–180° under nitrogen. It was then cooled to room temperature and ice water was added to decompose the phosphorus pentoxide. The resulting solution was made strongly basic with potassium hydroxide and extracted with chloroform. The extract was dried, the solvent was evaporated, and the residue was submitted to evaporative distillation in high vacuum (0.01 mm.). A colorless oil (45 mg.) was obtained. The infrared spectrum carbon tetrachloride showed a band at 3021 cm.$^{-1}$ (—CH=CH—) and no hydroxyl absorption. The oil was dissolved in absolute ethanol and hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium-charcoal catalyst. The solution took up the calculated amount of hydrogen in 5 min. After another 15 min., during which no more hydrogen was absorbed, the catalyst was removed by filtration and the solution was evaporated. Two evaporative distillations of the residue yielded 35 mg. of thick colorless oil, $[\alpha]^{24}_{589}$ +78.5 (*c* 0.35, ethanol); the reported[8] rotation of *d*-lupanine is $[\alpha]^{20}_{D}$ +79.5. The infrared spectrum of the product was identical with that of an authentic sample of *dl*-lupanine. A picrate, m.p. 180–183° was prepared; the reported[8] melting point of *d*-lupanine picrate is 185°.

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(8) J. F. Couch, *J. Am. Chem. Soc.*, 59, 1469 (1937).

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, PUBLIC HEALTH SERVICE, U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE]

Chemistry of the Spiroaminoketal Side Chain of Solasodine and Tomatidine. IV.[1] Chemistry of the Tomatidine Side Chain

YOSHIO SATO, H. GEORGE LATHAM, JR., AND NOBUO IKEKAWA[2]

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Treatment of tomatidine with acetic anhydride yields an acetylated Δ^5-tetrahydropyridylallopregnane and a diacetylamino-5α,20(22)furostene derivative. With a zinc chloride-acetic anhydride-acetic acid solution tomatidine affords a Δ^1-tetrahydropyridylallopregnane derivative. The chemistry of these compounds is discussed.

In the previous papers of this series, solasodine and its derivatives were subjected to a series of reactions which revealed the interesting and interrelated chemistry of the spiroaminoketal system present in these alkaloids. Tomatidine has now been exposed to a similar series of reactions and, as expected, behaves in an analogous manner. The acetic anhydride treatment of tomatidine[3] (I. R = H) yields the crystalline 26-aminodiacetyl-5α-furost-20(22)en-3β-ol acetate (II) and an amorphous component which affords crystalline III. The oxidation and subsequent removal of the 16β-aminodiacetyl ester side chain of II to Δ^{16}-allopregnenolone (VI. R = H) have previously been reported.[3] The oxidative degradation to 3β-acetoxyallopregnenolone (VI. R = Ac) of the 26-aminoacetyl derivative V which is readily obtained from II by chromatography on an alumina column or from the acid catalyzed isomerization of *O,N*-diacetyltomatidine (Ia. R = Ac) has similarly been described.[4] The reversion of V to II can be effected by treatment of V with a solution of acetic anhydride and pyridine.

The above mentioned amorphous residue, obtained from the acetic anhydride treatment of tomatidine, possesses an ultraviolet absorption band at 236 mμ (log ϵ, 3.92) and characteristic infrared absorption bands at 5.78, 5.98, and 6.07 μ. These data are in close agreement with those obtained for the analogous product from solasodine[5] and are consistent for the assignment of an α,β-unsaturated acetylamino function[6,7] to this component. This is supported by the correct elemental analysis[4] (for structure III) as well as by the following transformation. Hydrolysis of the amorphous mass with hydrochloric acid in acetic acid yields the crystalline acetylamino ketone IV as in

(1) For previous papers of this series see *J. Org. Chem.*, 25, 789 (1960).

(2) Visiting Scientist, National Institutes of Health.

(3) Y. Sato, A. Katz, and E. Mosettig, *J. Am. Chem. Soc.*, 74, 538 (1952).

(4) See Part I, Y. Sato, N. Ikekawa, and E. Mosettig, *J. Org. Chem.*, 25, 783 (1960).

(5) See Part II, Y. Sato and N. Ikekawa, *J. Org. Chem.*, 25, 786 (1960).

(6) G. Rosenkrantz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, 21, 520 (1956).

(7) R. Griot and T. Wagner-Jauregg, *Helv. Chim. Acta*, 42, 121, 605 (1959).

the case of the solasodine derivative.[5] The Δ^2-tetrahydropyridines are known for their ease of hydrolysis to acylamino ketones.[8] Finally, the amorphous substance afforded crystalline III when seeded with a crystalline sample of III prepared by treating tomatidine with a solution of zinc chloride, acetic anhydride, and acetic acid mixture and reacting the resultant so-called pseudotomatidine "B" with acetic anhydride in pyridine. Product III thus prepared by this alternate route proved to be identical with III obtained from the amorphous substance.

The site of unsaturation in III is most probably located at the Δ^{22}-position since the NMR spectrum[9,10] indicates vinyl proton absorption. This would fulfill the requirements of a Δ^{22}-structure but not the alternate $\Delta^{20(22)}$-formulation. Endocyclic double bonds are recognized generally to possess greater stability than their exocyclic homologs.[11]

Since pseudotomatidine "B" (VIII) exhibits the same prominent infrared spectra bands (5.76 μ, OAc; 5.99 μ, —C=N—; hydrochloride, 4.0, 4.94, 5.88 μ; perchlorate, 5.90 μ)[12] and undergoes the same reactions as pseudosolasodine "B",[13] it is regarded as its counterpart and accorded the formulation VIII. Treatment of VIII with methyl iodide gives the methiodide IX which with alkali yields the *N*-methyl derivative X.[14] The latter conversion can be reversed by addition of hydrogen iodide. Interestingly IX or X can be converted to *N*-methyltomatidine (XI) by vigorous treatment with alcoholic alkali. Similarly tomatidine (I) is regenerated when an alcoholic solution of VIII is vigorously refluxed with base. Milder saponification yields first the 3-alcohol of VIII. The *N*-acetylated derivative of VIII, (III) has also been found to undergo conversion to tomatidine by prolonged treatment with alcoholic base. The catalytic reduction (platinum oxide, acetic acid) of VIII and the subsequent hydrolysis of the resulting dihydro derivative forms predominantly the higher melting isomer of dihydrotomatidine[15] (XII).

Analogous to *O,N*-diacetylsolasodine,[16] the acid catalyzed isomerization of *O,N*-diacetyltomatidine (Ia) with hydrochloric acid in methanol leads to the formation of 26-acetylamino-22-methoxy-5α-furostan-3β-ol acetate (VII) which can readily be converted to the 26-acetylamino-20(22)furostene derivative V by refluxing with glacial acetic acid. The formation of VII is attributed to the nucleophilic attack of methoxide ion on C-22.[16] In the presence of aqueous acetic acid VII is easily transformed into the corresponding 22-hydroxy compound VIIa.

EXPERIMENTAL[17]

Treatment of tomatidine (I) *with acetic anhydride.*[3,4] A mixture of 500 mg. of tomatidine and 30 ml. of acetic anhydride was refluxed vigorously for 3 hr. The excess reagent was removed *in vacuo* and the oily residue crystallized from methanol-water. The 26-aminodiacetyl derivative II amounted to 230 mg. (35%). The mother liquor was evaporated to dryness and the residue chromatographed on alumina. Fractions eluted with benzene-ether (1:1) consisted principally of *O,N*-diacetyltomatidine (68 mg., 11%). Subsequent elutions with ether yielded 98 mg. (15%) of an amorphous component which displayed the following spectra: $\lambda_{max}^{C_2H_5OH}$ 236 mμ (log ϵ, 3.92); $\lambda_{max}^{CHCl_3}$ 5.78 μ (acetoxy), 5.99, 6.08 μ. When this amorphous substance was dissolved in hexane-ether and seeded with III resulting from the interaction of pseudotomatidine "B" with acetic anhydride and pyridine (see below), 53 mg. of crude crystals (m.p. 148–167°) were obtained. Upon recrystallization from hexane, plates, m.p. 169–172°, $[\alpha]_D^{20}$ +190°, $\lambda_{max}^{C_2H_5OH}$ 236 mμ (log ϵ, 3.88) were secured. It agreed in melting point, mixture melting point, rotation, and infrared spectrum with a sample of III prepared from the acetylation of pseudotomatidine "B" (VIII). The oily mother liquor, after removal of crystalline III, displayed an infrared spectrum similar to III and possessed an ultraviolet absorption maximum at 234 mμ (log ϵ, 3.85) and rotation of +78° ($CHCl_3$).

(8) A. Lipp, *Ann.*, **289**, 173 (1896); A. Lipp and E Widnmann, *Ber.*, **38**, 2471 (1905).

(9) Peak assignment at 71 c.p.s. (relative to benzene). J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958) give a range of 71 to 78 c.p.s. (corrected from 40 to 60 meg.) for the vinyl protons of a Δ^{22} bond. Spectra were measured in deuterochloroform solution at 0.1*M* concentration on a Varian 60 meg. NMR spectrometer (4300-C) with tetramethylsilane as internal and benzene as external standards. We are deeply indebted to Dr. L. Cohen of this Institute for the measurements and interpretation of the NMR spectra of these compounds.

(10) Proton resonance shift (69 c.p.s.) was also observed for the analogous product obtained from solasodine.[5] Since the reaction of acetic anhydride with solasodine proceeds most likely in the same manner as with tomatidine, the Δ^{22}-position appears as the most tenable one for the corresponding unsaturated tetrahydropyridyl derivative obtained from solasodine. The $\Delta^{20(22)}$ structure proposed for the amorphous product after removal of the Δ^{22} compound seems doubtful since shifts were observed (63 c.p.s., C_6 proton, and 76 c.p.s., C_{23} proton) indicating the presence of Δ^5 and Δ^{22} unsaturation in the molecule. Studies of the remaining amorphous component, after removal of the *N*-acetyl-$\Delta^{22(23)}$-derivative, of both solasodine and tomatidine are being continued.

(11) R. B. Turner and R. H. Garner, *J. Am. Chem. Soc.*, **80**, 1424 (1958).

(12) N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.*, **76**, 2781 (1954).

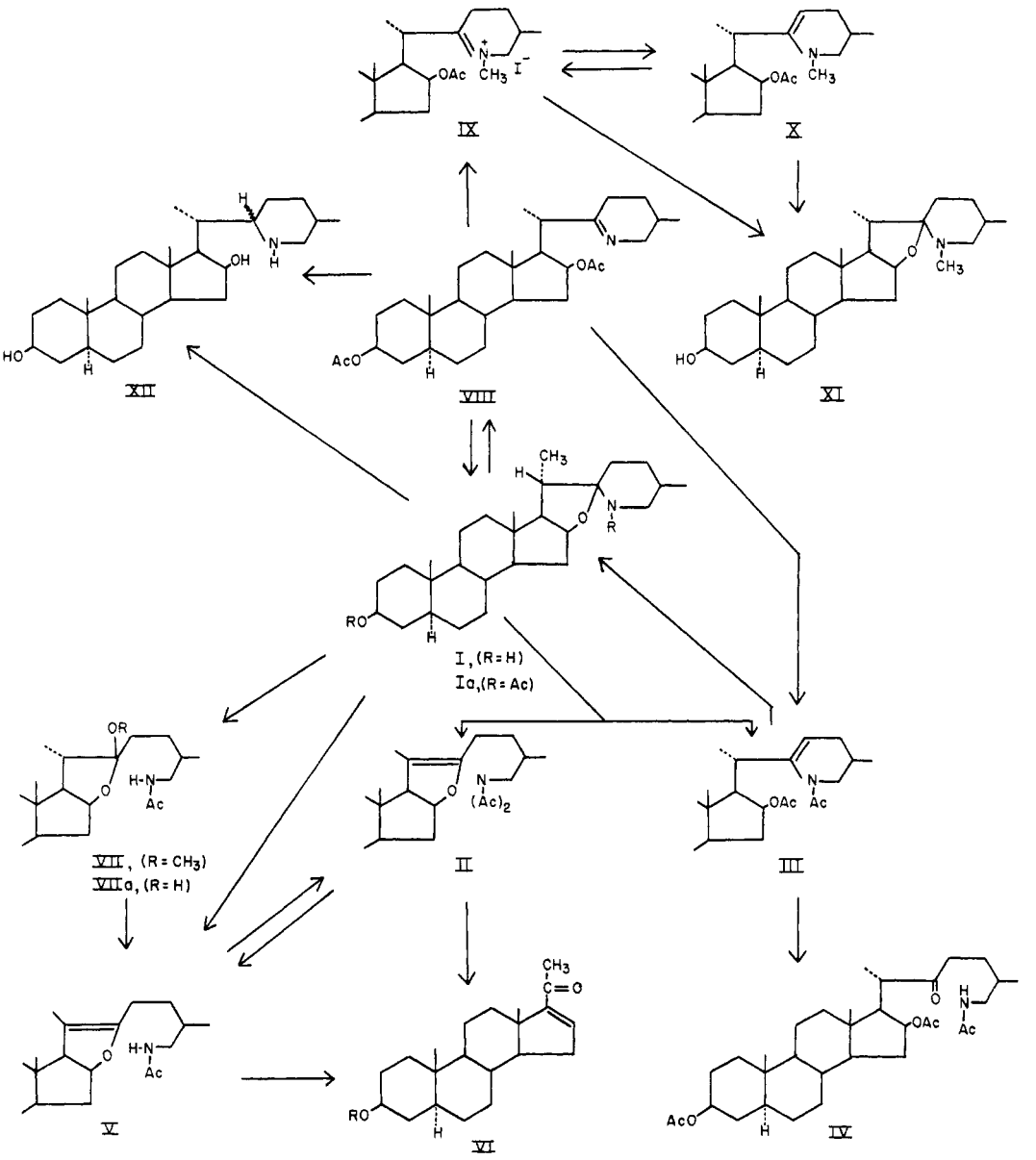
(13) Y. Sato, H. G. Latham, Jr., and E. Mosettig, *J. Org. Chem.*, **22**, 1496 (1957).

(14) The double bond in X is probably endocyclic (Δ^{22}) rather than $\Delta^{20(22)}$ as depicted previously[13] for the solasodine analog. Oxidation of X has never yielded any significant amounts of 3β-acetoxy-Δ^{16}-allopregnene-20-one as would be expected of a compound with a $\Delta^{20(22)}$-bond.

(15) Y. Sato and H. G. Latham, Jr., *J. Am. Chem. Soc.*, **78**, 3146 (1956).

(16) See Part III, Y. Sato and N. Ikekawa, *J. Org. Chem.*, **25**, 789 (1960).

(17) Melting points were taken on the Kofler block and are uncorrected. Microanalyses were performed by the Microanalytical Services Unit of this laboratory under the direction of Mr. Harold G. McCann. The infrared spectra were taken on the Model 21 Perkin-Elmer Infrared Spectrometer by Messrs. H. K. Miller and R. T. Brown of this Laboratory. "Woelm" alumina grade 1 was used as adsorbent for chromatography unless otherwise stated. We thank Dr. E. Becker and Mr. R. B. Bradley for the NMR measurements.



The last fractions of the chromatogram eluted with ether-methanol (0.5%) afforded 214 mg. (35%) of the pseudo derivative V.

Pseudotomatidine "B" (VIII). To 1 g. of tomatidine was added 35 ml. of a zinc chloride solution (prepared by dissolving 8 g. of zinc chloride in a mixture of 70 ml. of acetic anhydride and 30 ml. of glacial acetic acid) and the solution allowed to stand overnight. The reaction mixture was then poured into ice water. After standing for 30 min., ammonium hydroxide was added to the mixture until alkaline. The copious precipitate was crystallized from aqueous methanol to yield 900 mg. of crude crystals which when twice recrystallized from aqueous acetone melted at 132–136°, $[\alpha]_D^{20}$ +6.5° ($CHCl_3$), $\lambda_{max}^{CHCl_3}$ 5.76 μ (OAc); 5.99 μ (—C=N—): hydrochloride, 4.0, 4.94, 5.88 μ; perchlorate, 5.90 μ.

Anal. Calcd. for $C_{31}H_{49}O_4N$: C, 74.51; H, 9.88. Found: C, 74.62; H, 9.80.

3β,16β-Diacetoxy-20-(2'-Δ²'-N-acetyl-5'-methyltetrahydropyridyl)-5α-pregnane (III). A solution of 180 mg. of pseudotomatidine "B" (VIII) in 2 ml. of pyridine and 1.5 ml. of acetic anhydride was allowed to stand overnight at room temperature and poured into ice water. The product which crystallized as plates (180 mg.) from hexane melted at 166–170°. Recrystallization from the same solvent gave a product of m.p. 170–172°, $[\alpha]_D^{20}$ +190° ($CHCl_3$), $\lambda_{max}^{C_2H_5OH}$ 236 mμ (log ϵ, 3.90).

Anal. Calcd. for $C_{33}H_{51}O_5N$: C, 73.16; H, 9.49. Found: C, 73.18; H, 9.66.

Forty milligrams of the above *N*-acetyltetrahydropyridyl derivative III was refluxed with 10 ml. of methanolic potassium hydroxide (10%) for 13 hr. The product which was recrystallized from methanol-water melted at 199–203° and proved to be tomatidine (melting point, mixture melting point, and infrared spectrum).

3β,16β-Diacetoxy-26-acetylaminocholestan-22-one (IV). A solution of 80 mg. of III in 0.6 ml. of 3*N* hydrochloric acid and 3 ml. of acetic acid was allowed to stand for 50 min. at room temperature and poured on ice. After addition of ammonia water to the solution, the product was chromatographed on alumina. The ether-methanol (1%) eluate yielded 44 mg. of crystals (from acetone-hexane) which melted at 126–130°, $\lambda_{max}^{CHCl_3}$ 2.88 μ (N—H), 5.77 μ (OAc and CO), 5.98, 6.57 μ (HN—Ac), $[\alpha]_D^{20}$ +13° ($CHCl_3$). $\lambda_{max}^{C_2H_5OH}$ 287 mμ (log ϵ, 1.91).

Anal. Calcd. for $C_{33}H_{53}O_6N$: C, 70.80; H, 9.54. Found: C, 70.48; H, 9.40.

Hydrolysis of the amorphous substance in the same manner also yields IV.

Methiodide of pseudotomatidine "B" (IX). One hundred milligrams of pseudotomatidine "B" (VIII) with 10 ml. of acetone and 1 ml. of methyl iodide were placed in a sealed reaction flask and allowed to stand at room temperature for 68 hr. Upon concentration and addition of hexane, slightly yellowish granular crystals were obtained (72 mg.). They melted at 252–255°.

Anal. Calcd. for $C_{32}H_{52}O_4NI$: C, 59.90; H, 8.17. Found: C, 60.10; H, 8.09.

When the salt was dissolved in methanol and the solution made basic by dropwise addition of sodium carbonate solution (5%), N-*methylpseudotomatidine* (X) was obtained. Recrystallized from aqueous acetone, the compound crystallized as rods and melted at 151–153°, $\lambda_{max}^{CHCl_3}$ 5.80, 6.08 μ. When a solution of X in ether is treated with an alcoholic solution of hydriodic acid, it reforms the methiodide (IX).

Anal. Calcd. for $C_{32}H_{51}O_4N$: C, 74.81; H, 10.01. Found: C, 75.11; H, 10.19.

N-*Methyltomatidine* (XI). Sixty milligrams of *N*-methylpseudotomatidine "B" (X) was refluxed for a period of 7 hr. with 14 ml. of methanolic potassium hydroxide (5%), concentrated *in vacuo* and water added to the residue. The precipitate was twice recrystallized from aqueous acetone. It formed plates which melted at 218–220°; its infrared spectrum somewhat resembled tomatidine in the finger print region, $\lambda_{max}^{CHCl_3}$ 2.78, 10.25, 10.43, 11.00, 11.30, 11.45 μ.

Anal. Calcd. for $C_{28}H_{47}O_2N$: C, 78.27; H, 11.03. Found: C, 78.10; H, 10.78.

When the methiodide IX was used in place of X, XI was likewise obtained.

Hydrolysis of pseudotomatidine "B" (VIII). (a). (With 2% methanolic potassium hydroxide). A solution of 400 mg. of pseudotomatidine "B" (VIII) in 40 ml. of methanolic potassium hydroxide (2%) was refluxed for 45 min., concentrated, and water added. The product (330 mg.), m.p. 100–107°, was chromatographed on neutral alumina, and the fraction (189 mg.) eluted with 1% methanol in ether afforded rectangular plates which melted at 157.5–161°, $[\alpha]_D^{20}$ +21° ($CHCl_3$), after recrystallization from aqueous methanol. Its infrared spectrum ($CHCl_3$) displayed bands at 2.78 μ (OH), 5.78 μ (OAc), 5.98 μ (—C=N—). It is the 3-alcohol of VIII.

Anal. Calcd. for $C_{29}H_{47}O_3N$: C, 76.10; H, 10.35. Found: C, 76.26; H, 10.21.

(b). (With 5% methanolic potassium hydroxide). A solution of 90 mg. of VIII in 10 ml. of methanolic potassium hydroxide (5%) was refluxed for 3 hr. The reaction mixture was partially concentrated and water added until precipitation was induced. The substance (70 mg.) crystallized from aqueous methanol and melted at 201–204°. It agreed in melting point, mixture melting point, and infrared spectrum with an authentic sample of tomatidine.

Reduction of VIII. Four hundred milligrams of VIII were dissolved in 7 ml. of glacial acetic acid and reduced over 100 mg. of platinum oxide catalyst under atmospheric pressure. The absorption of gas ceased with the uptake of 1 mole equivalent of hydrogen. After removal of the catalyst by filtration, the filtrate was made alkaline with addition of ammonia water and the copious precipitate subjected to chromatography on alumina after drying. The fractions eluted with benzene and with ether gave 225 mg. of crystalline product which melted at 110–115° when crystallized from ether.

Anal. Calcd. for $C_{31}H_{51}O_4N$: C, 74.21; H, 10.25. Found: C, 73.51; H, 10.26.

Although its elemental analysis was not quite satisfactory, 136 mg. of the above dihydro derivative was subjected to hydrolysis by refluxing with 15 ml. of methanolic potassium hydroxide (5%) solution for 2 hr. The crude product which weighed 112 mg. was chromatographed over alumina. The early fractions (ether-methanol (0.5%) eluate) gave a small amount (18 mg.) of the low melting dihydrotomatidine A while the fractions eluted with 2% and 10% methanol in ether yielded 46 mg. of the high melting dihydrotomatidine B (m.p. 231–234°). The compound was identical in respect to melting point, mixture melting point, and infrared spectrum with an authentic specimen of dihydrotomatidine B,[15] (XII).

Anal. Calcd. for $C_{27}H_{47}O_2N$: C, 77.64; H, 11.34. Found: C, 77.31; H, 11.06.

O,N-Diacetyltomatidine with hydrochloric acid in methanol. A mixture of 250 mg. of *O,N*-diacetyltomatidine (IA), 15 ml. of methanol, and 0.2 ml. of 6*N* hydrochloric acid was allowed to stand for 15 min. at room temperature. The reaction mixture was made alkaline with 0.2 ml. of concd. ammonia water, partially concentrated, and diluted with water. The product was chromatographed over alumina. The ether-methanol (0.5%) eluate gave 185 mg. (73%) of the 22-methoxy compound VII, m.p. 141–144° (acetone), $[\alpha]_D^{20}$ −59° ($CHCl_3$).

Anal. Calcd. for $C_{32}H_{53}O_5N$: C, 72.27; H, 10.05. Found: C, 72.36; H, 10.07.

26-Aminoacetyl-5α-furost-20(22)-en-3β-ol acetate (V). A solution of 48 mg. of the 22-methoxy derivative, VII, in 3 ml. of glacial acetic acid was refluxed for 30 min. After removal of the solvent *in vacuo*, the residue was crystallized from acetone-hexane to yield the pseudo derivative V which melted at 128–131°. It agreed in properties (melting point, infrared spectrum) with an authentic sample of V.

Conversion of V *to* II. Twenty-eight milligrams of the pseudo derivative V was dissolved in a mixture of 0.5 ml. of pyridine and 0.25 ml. of acetic anhydride and refluxed for 1 hr. The excess reagents were removed *in vacuo* and the residue dissolved in ethanol. Water was added to incipient turbidity and the mixture allowed to stand. The compound which formed (20 mg.) was recrystallized from aqueous ethanol and melted at 98–101°. It proved to be identical (melting point and infrared spectrum) with II obtained directly from the acetic anhydride treatment of tomatidine.

26-Acetylamino-22-hydroxy-5α-furostan-3β-ol acetate (VIIa). A solution of the 22-methoxy compound, VII, (80 mg.) in aqueous acetic acid (5 ml. of 80%) was allowed to stand for 2 hr. at room temperature. It was taken up in ether and the ethereal solution washed with water, dilute sodium bicarbonate solution, and again with water. The product recovered from the ethereal extract was chromatographed over alumina. The ether-methanol (2%) eluate afforded 56 mg. of VIIa, m.p. 119–123° (acetone-hexane), $[\alpha]_D^{20}$ −27° ($CHCl_3$).

Anal. Calcd. for $C_{31}H_{51}O_5N$: C, 71.91; H, 9.93. Found: C, 72.15; H, 10.02.

BETHESDA, MD.