Anal. Calcd for $C_{13}H_9N_3$: C, 75.34; H, 4.38. Found: C, 75.52; H, 4.43.

2,2'-Bipyrazine (XXV).—Pyrazine carboxylic acid (12.4 g) was dissolved in a slight excess of aqueous ammonia and the solution was evaporated to dryness. The residue was added to a saturated solution of cupric acetate and allowed to stand overnight. The crude precipitated copper(II) salt of the pyrazine carboxylic acid was filtered and dried. Pyrolysis of the salt was carried out at atmospheric pressure in a short-path still and yielded 0.55 g (7%) of product crystallizing from hexane, mp 183–184°.

Anal. Calcd for $C_8H_6N_4$: C, 60.75; H, 3.82. Found: C, 61.08; H, 3.80.

4,4'-Bipyrimidine (XXII).—The preparation of XXII was carried out in exactly the same manner as that employed for XXV. From 12.4 g of pyrimidine-4-carboxylic acid was obtained 0.39 g (5%) of product, mp 203–204°.

Anal. Calcd for $C_8H_6N_4$: C, 60.75; H, 3.82. Found: C, 60.86; H, 3.99.

3,3'-Bipyridazine (XXI).—A mixture of 8 g of pyridazine and 0.8 g of 5% palladium on carbon was stirred and refluxed for 24 hr. The mixture was cooled, diluted with 25 ml of chloroform, and filtered. The spent catalyst was twice extracted with 25 ml of chloroform. The filtrate and chloroform extracts were combined and the volatile material was removed *in vacuo*. The residue of crude XXI was sublimed at 130° (50 μ) and crystallized from ether to give 0.79 g (10%) of product, mp 224–226°. The molecular weight was found to be 155 (osmometer); calculated molecular weight was 158.

Anal. Calcd for $C_8H_6N_4$: C, 60.75; H, 3.82; N, 35.43. Found: C, 61.08; H, 3.94; N, 35.09.

2-Bromo-4-phenylpyrimidine (XXIII).—A mixture of 8.6 g of 2-hydroxy-4-phenylpyrimidine and 40 g of phosphorus oxybromide was heated at 150° for 4 hr. The mixture was cooled and treated with 300 g of ice. The aqueous solution was made alkaline with sodium hydroxide solution (10°) and extracted with ether. The ethereal extracts were dried over magnesium sulfate, filtered and the ether was removed *in vacuo*. The residue was crystallized from benzene to give 5.8 g (58%) of product, mp 84–85°.

Anal. Calcd for $C_{10}H_7BrN_2$: C, 51.06; H, 3.11. Found: C, 51.31; H, 3.20.

4,4'-Diphenyl-2,2'-bipyrimidine (XXIV).—A mixture of 4.7 g of 2-bromo-4-phenylpyrimidine, 5 g of activated copper powder, and 75 ml of dimethylformamide was stirred and heated at reflux for 6 hr. The dimethylformamide was removed *in vacuo* and the residue was washed several times with 50 ml of aqueous ammonia containing 5% of potassium cyanide. The dry solid was extracted with chloroform. The extracts were dried over magnesium sulfate, filtered, and the chloroform was removed *in vacuo*. The residue was crystallized from ether to give 0.62 g (20%) of product, mp 155–156°.

Anal. Calcd for $C_{20}H_{14}N_4$: C, 77.40; H, 4.55. Found: C, 77.60; H, 4.73.

Registry No.—III, 10239-68-6; IV (Z = C_6H_5), 10198-67-1; IV (Z = Py), 10198-68-2; V (X = C_6H_5), 10198-69-3; V (X = C_6H_5) picrate, 10198-70-6; V (X = Py), 10198-71-7; V (X = Py) picrate, 10198-72-8; VI (R′ = CH_3O), 10198-73-9; VII (R = H), 10198-74-0; VII (R = CH_3), 10198-75-1; VII (R = C_6H_5), 10198-76-2; VIII (Y = H), 10235-65-1; VIII (Y = CH_3), 10198-77-3; VIII (Y = C_6H_5), 10198-78-4; IX (Y = CH_3), 10198-79-5; IX (Y = CH_3) picrate, 10198-80-8; IX (Y = C_6H_5), 10198-81-9; IX (Y = C_6H_5) picrate, 10198-82-0; IX (Y = H), 10198-83-1; X (R = C_5H_4N), 10198-84-2; XI (R = H), 10198-85-3; XI (R = C_5H_4N), 10198-86-4; XII, 10198-87-5; XIII, 10198-88-6; XIV (R = C_5H_4N), 10198-89-7; XV (R = C_6H_5), 10198-90-0; XV (R = C_5H_4N), 10198-91-1; XV (R = CH_3), 10198-92-2; XVI, 10198-93-3; XVIII, 10198-94-4; XX, 10198-95-5; XXI, 10198-96-6; XXII, 2426-94-0; XXIII, 10198-98-8; XXIV, 10198-99-9; XXV, 10199-00-5; 4-(1-piperidyl)-2,6-bis(2-pyridyl)pyrimidine, 10199-01-6.

Synthesis and Transformations of a Heptacyclic Triazoline Derived from Pseudodiosgenin

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Displacement of the *p*-toluenesulfonate function of pseudodiosgenin 27-*p*-toluenesulfonate with potassium azide in dimethylformamide was followed by a 1,3-dipolar cycloaddition to the enol ether olefinic bond of ring E to furnish a triazoline derivative. Protonation of the triazoline in methanol solution led to abrupt evolution of nitrogen with genesis of a secondary amino methyl ketal. Transformation products of the methyl ketal include the hemiketal, the ethyl ketal, an enol ether tertiary amide originating from hemiketal dehydration, and a 16β-hydroxy acetylamino ketone resulting from opening of the ketal ring system.

The versatile pseudodiosgenin 27-*p*-toluenesulfonate (**1**),[1] prepared in 80% yield by selective hydrolysis of the 3β-homoallylic ester function of pseudodiosgenin 3β,27-di-*p*-toluenesulfonate, has proved useful as an intermediate in the synthesis of solasodine,[2] N-methylsolasodine,[3] a diosgenin ring-F thia counterpart,[1] and the novel hexacyclic hemiketal **6** arising from participation of the ring-E enol ether olefinic bond in a solvolytic ring closure.[4] In these, and in related transformations, *p*-toluenesulfonate displacement has been shown to proceed normally, without side-chain rearrangement through a 1,2-hydrogen migration.

When **1** was allowed to react with potassium azide in dimethylformamide at 100° during 50 hr, rods melting at 224–230° with brisk ebullition were produced in 85% yield. The high melting point, accompanied by escape of nitrogen, together with absence of the enol ether absorption band from the infrared spectrum, inferred that tosylate displacement by azide ion had been followed by a 1,3-dipolar cycloaddition[5] to the dihydrofuranoid olefinic bond of ring E, affording the heptacyclic triazoline (**2**).[6]

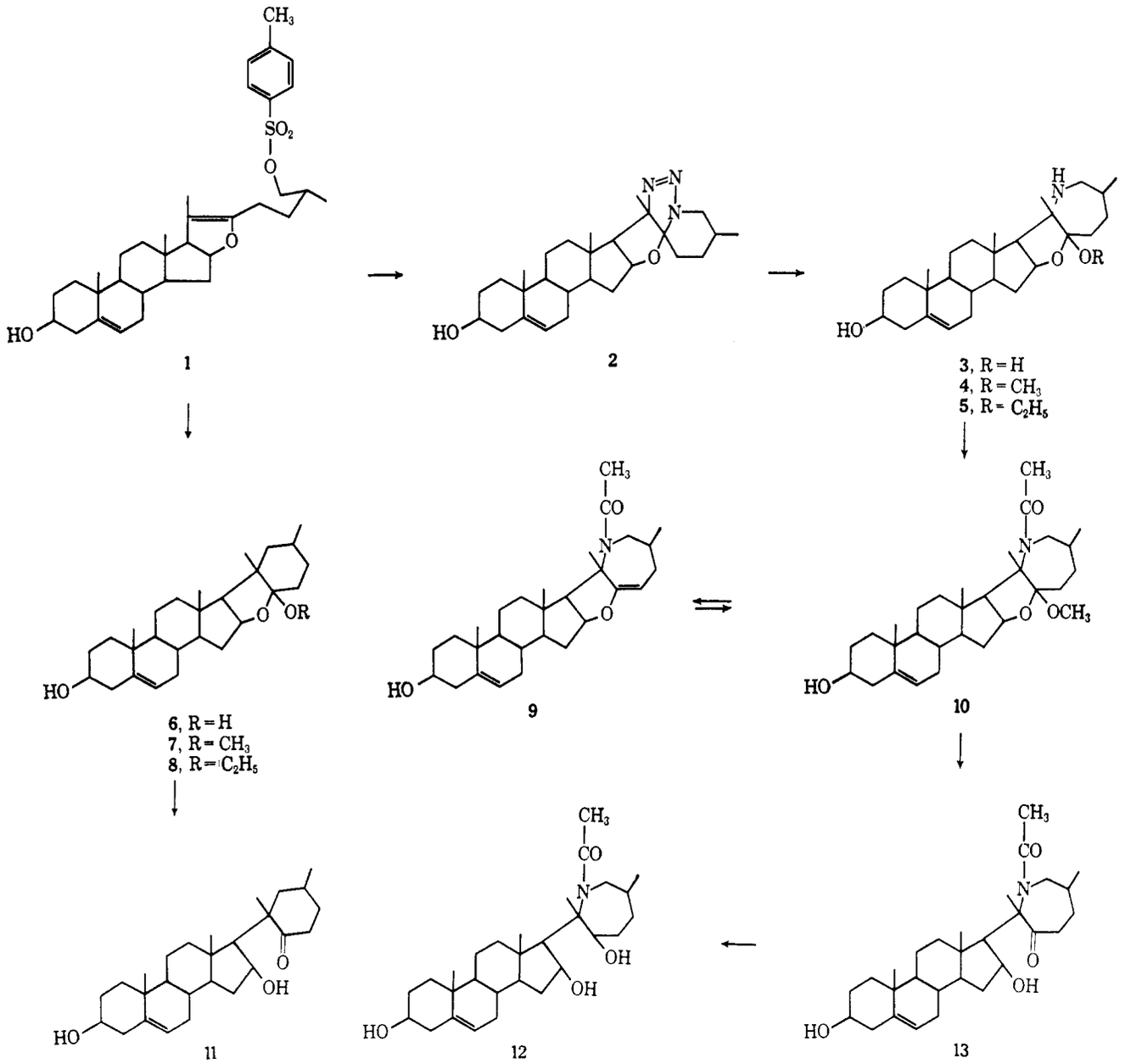
Acidification of a methanolic suspension of **2** with hydrochloric acid led to prompt dissolution with evolvement of nitrogen and thereafter to rapid crystal-

(1) F. C. Uhle, *J. Org. Chem.*, **27**, 2797 (1962).
(2) F. C. Uhle, *J. Am. Chem. Soc.*, **83**, 1460 (1961).
(3) F. C. Uhle, *J. Org. Chem.*, **32**, 792 (1967).
(4) F. C. Uhle, *ibid.*, **31**, 4193 (1966).

(5) For discussion of the concept of 1,3-dipolar cycloaddition, with a comprehensive review of examples, see R. Huisgen, *Angew. Chem.*, **75**, 604, 742 (1963); *Angew. Chem. Intern. Ed. Engl.*, **2**, 565, 633 (1963).

(6) Addition of organic azides to olefins, furnishing Δ^2-1,2,3-triazolines, was first observed by K. L. Wolff, *Ann.*, **394**, 23, 68 (1912); **399**, 274 (1913). For an account of subsequent study of the reaction, with references, see P. Scheiner, J. H. Schomaker, S. Deming, W. J. Libbey, and G. P. Nowack, *J. Am. Chem. Soc.*, **87**, 306 (1965).

SCHEME I



lization of a hydrochloride in nearly quantitative yield. Treatment of the hydrochloride with aqueous potassium hydroxide gave a secondary amine (mp 210–215°) which crystallized nicely from acetone. Although formation of a 20-hydroxysolasodine derivative had been expected[7] under these conditions, the compound appears to be the amino methyl ketal **4** incorporating a seven-membered hexahydroazepine ring (F) in a novel synthetic relative of the steroid alkaloids (see Scheme I).

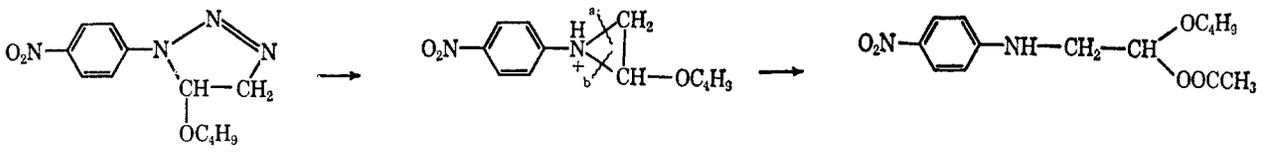
The nmr spectrum of **4** closely resembles the spectrum of the methyl ketal **7** produced by solvolysis of **1**. Prominent peaks include the signal at 192 cps arising from the methoxyl function, the signal at 62 cps resulting from the C-19 methyl group, and signals at 67 and 78 cps associated, respectively, with the C-18 and C-21 angular methyl groups. A doublet centered at 51 cps stems from the secondary methyl group of ring F.[8]

Methanolic hydrogen chloride converted the 3β-acetate of **2** to the hydrochloride of the 3β-acetate of **4**. Cautious liberation of the amine from its hydrochloride with 1 equiv of aqueous potassium hydroxide afforded the 3β-acetate of the secondary amino methyl ketal **4**. Treatment of **2** with *p*-toluenesulfonic acid in refluxing absolute ethanol, followed by neutralization with aqueous potassium hydroxide, furnished the ethyl ketal **5**, while decomposition of the triazoline in acidified aqueous media gave the hemiketal **3**.

(7) F. C. Uhle, *Tetrahedron Letters*, 3099 (1964). Transformation of Δ^2-1,2,3-triazolines to β-amino alcohols through the intervention of dilute aqueous mineral acids was described by K. Alder and G. Stein, *Ann.*, **501**, 1 (1933).

(8) Attribution of the signal at 62 cps in the spectra of both **4** and **7** to the C-19 methyl group rests on comparison with the spectrum of diosgenin whose C-19 methyl resonance is seen at 62 cps. Of the two remaining angular methyl signals, one is found at 67 cps in the spectra of both **4** and **7**; it therefore doubtless arises from the C-18 methyl group. Hence, the signal at 78 cps in the spectrum of **4** and at 71 cps in the spectrum of **7** may be allotted to the C-21 methyl group which is considered to occupy the β orientation in **7** and probably also in **4**. The unusually low-field position of the C-18 and C-21 methyl resonances may be explained if the 22-methoxyl function is assigned the β configuration since models reveal the proximity of groups thus disposed. The stereochemistry of rings E and F deserves further scrutiny, however.

SCHEME II



14 15 16

Interconversion of the hemiketal **3**, the methyl ketal **4**, and the ethyl ketal **5** was less readily achieved than is interrelation of the corresponding **6**, **7**, and **8** derived from solvolysis of **1**. Although dissolution of the hemiketal **6** in methanol suffices for instantaneous methylation to the methyl ketal **7**, the secondary amino hemiketal **3** was recovered unchanged from refluxing methanol. Moreover, the hemiketal **3** was not converted to the methyl ketal **4** in methanol containing 1% *p*-toluenesulfonic acid at 25°, requiring exposure at reflux temperature. Cleavage of the methyl ketal **4** to the hemiketal **3** occurred less easily than does conversion of **7** to **6** which progresses rapidly in cold, aqueous acetic acid.

Acetylation of the methyl ketal **4** with acetic anhydride in pyridine at 25° gave the handsomely crystalline 3β-acetate of the amide **10** in 80% yield. Ester hydrolysis with dilute, aqueous potassium hydroxide afforded the 3β-ol (**10**). Acetylation of the hemiketal **3** with acetic anhydride in pyridine at 0° proceeded less well to give the 3β,N-diacetate whose 22-hydroxyl function resisted methylation in refluxing methanol. Addition of a trace of *p*-toluenesulfonic acid to a methanolic solution of the hemiketal 3β,N-diacetate at 25°, however, promptly led to deposition of needles of the 3β-acetate of the methyl ketal **10**.

Elimination of the elements of methanol from the 3β-acetate of **10** with refluxing acetic anhydride, with *p*-toluenesulfonyl chloride in refluxing pyridine, or with glacial acetic acid at 25° gave the 3β-acetate of the enol ether **9**. Brief alkaline saponification of the 3β-acetate afforded the 3β-ol (**9**). Transformation of **10** to **9** was accompanied by a pronounced negative rotation shift (+52 to −150°) reminiscent of the equally marked negative rotation change (−3 to −153°) associated with conversion of **7** to an enol ether. Acidification of a methanolic solution of the enol ether **9** with a crystal of *p*-toluenesulfonic acid caused swift reversion to the methyl ketal **10**.

Treatment of the 3β-acetate of **10**, or of the 3β-acetate of **9**, with *p*-toluenesulfonic acid in refluxing methanol during several hours followed by ester hydrolysis with dilute aqueous potassium hydroxide furnished the 16β-hydroxy acetylamino ketone **13** resulting from opening of ring E. Severance of the cyclic ketal system parallels formation of the 16β-hydroxy ketone **11** from **7**, effected readily by refluxing glacial acetic acid. When **10** was allowed to react with refluxing acetic acid, however, **13** was not produced.

Although the infrared spectrum convincingly characterizes **13** as a ketone, the compound failed to combine with hydroxylamine, or with *p*-nitrophenylhydrazine under any of the conditions chosen. When **13** was allowed to react with sodium borohydride in isopropyl alcohol at 25° during 10 days, 25% of the crystalline triol **12** was isolated. The sluggishly reactive nature of the ketone appears strange in view of the normal behavior of **11**. Presumably the α-methyl and β-acetylamino groups conspire in hindering approach to the carbonyl function.

Exposure of the 3β-acetate of **10** to refluxing formic acid, in attempted ketal hydrogenolysis analogous to formic acid reduction of **7**,[4] followed by alkaline ester hydrolysis, gave 20% of high-melting plates of undetermined structure whose infrared spectrum displayed a prominent carbonyl band at 5.9 μ. The compound was encountered again as a minor component after prolonged treatment of the 3β-acetate of **10** with *p*-toluenesulfonic acid in refluxing ethanol, followed by brief ester saponification with dilute aqueous potassium hydroxide. The major product of this foray proved to be the hemiketal **3**. Apparently the initially opened 16β-hydroxy acetylamino ketone underwent reclosure to the hexacyclic system after slow amide hydrolysis in part had taken place in the acid medium. Failure attended efforts to prepare a 16β-hydroxy ketone in which the secondary amino group remained free. Likewise unavailing were attempts to produce a relative of the enol ether **9** with an unsubstituted secondary nitrogen function.

Serious effort to isolate a thermolysis product from **2** was not undertaken. Protracted exposure of the 3β-acetate of **2** in refluxing xylene led only to partial recovery of unchanged triazoline.[9] Photolytically elicited expulsion of nitrogen might prove of interest.[10]

Since the new ring system of **3** cannot be degraded to helpful reference compounds, classical structure proof is infeasible. Assignment rests on internal consistency of the chemical evidence, on kinship to the hemiketal **6** originating from solvolysis of **1**, and on a mechanistic interpretation assuming preferred, unilateral fission of a transient aziridinium ion.

Precedent for generation of the hemiketal **3** from **2** may be gleaned from the work of Huisgen, Möbius, and Szeimies who have studied the reaction of organic azides with simple, open-chain and cyclic enol ethers.[11] In the thermolabile Δ²-1,2,3-triazolines secured by *cis* addition, the outer, electrophilic azide nitrogen atom invariably was found to unite with the nucleophilic center β to the oxygen function. On thermolysis, the adduct from the cyclic dihydrofuran and *p*-nitrophenylazide evolved nitrogen to afford the imido ester N-[dihydro-2(3H)-furylidene]-*p*-nitroaniline which gave γ-butyrolactone and *p*-nitroaniline on acid hydrolysis. The addition

(9) The thermolability of simple Δ²-1,2,3-triazolines varies greatly. Occasionally, azide–olefin preparative addition must be carried out at relatively low temperature to forestall decomposition. Thermolysis products often comprise a mixture of anil and aziridine. For a review of aziridine chemistry, see P. E. Fanta in "Heterocyclic Compounds with Three- and Four-membered Rings," Part I, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp 524–575.

(10) *Cf.* P. Scheiner, *J. Org. Chem.*, **30**, 7 (1965), who found irradiation with ultraviolet light a means of converting Δ²-1,2,3-triazolines to aziridines in good yield without concomitant anil formation.

(11) R. Huisgen, L. Möbius, and G. Szeimies, *Chem. Ber.*, **98**, 1138 (1965); R. Huisgen and G. Szeimies, *ibid.*, **98**, 1153 (1965).

products from open-chain enol ethers, typified by the adduct **14** from *n*-butyl vinyl ether and *p*-nitrophenylazide, attained stability on heating by loss of a molecule of alkanol to form triazoles.

When **14** was treated with acetic acid in benzene at 50°, however, the product proved to be not the anticipated 1-*p*-nitroanilino-1-*n*-butoxy-2-acetoxyethane but the acetal derivative 1-*p*-nitroanilino-2-*n*-butoxy-2-acetoxyethane (**16**) which gave the 2,4-dinitrophenylhydrazone of *p*-nitroanilinoacetaldehyde with 2,4-dinitrophenylhydrazine in acid solution (see Scheme II). The sequence was considered to proceed through intermediacy of the aziridinium ion **15** which, as a consequence of charge distribution referable to the ether oxygen, opened at position b, rather than at a. The fully established, simpler structures thus offer support for conclusions reached with the steroid derivatives.

Experimental Section[12]

3β-Hydroxy-22(27)-imino-20(N)-azo-25α-5-furostene (2).—A magnetically stirred mixture of 569 mg (0.001 mole) of pseudodiosgenin 27-*p*-toluenesulfonate (**1**),[1,4,13] 243 mg (0.003 mole) of potassium azide, and 12 ml of dimethylformamide was kept at 100° during 50 hr. (Shorter reaction periods gave lower yields.) The cooled solution was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Recrystallization from a mixture of dichloromethane and acetone afforded 375 mg (85%) of rods: mp 224–230° with brisk ebullition; $[\alpha]_D$ −87°; infrared spectrum 6.15 (w), 6.9, 7.25, 7.4, 7.85, 8.0, 8.2, 8.4, 8.7, 8.8, 9.0, 9.3, 9.6, 9.8, 10.1, 10.35, 10.5, 10.7, 10.9, 11.0, 11.4, 12.0, 12.1, 12.3, 12.7, 13.5 μ.

Anal. Calcd for $C_{27}H_{41}N_3O_2$ (439.62): C, 73.76; H, 9.40; N, 9.56. Found: C, 74.02; H, 9.39; N, 9.57.

3β-Acetoxy-22(27)-imino-20(N)-azo-25α-5-furostene (2 3β-Acetate).—A mixture of 220 mg (0.0005 mole) of **2**, 1 ml of acetic anhydride, and 4 ml of anhydrous pyridine was kept at 25° during 20 hr. The solution was diluted with aqueous potassium chloride to give a precipitate which was collected by filtration, washed with water, and dried. Recrystallization from a mixture of dichloromethane and methanol gave 206 mg (85%) of hexagonal plates: mp 214–222° with brisk bubbling; $[\alpha]_D$ −92°; infrared spectrum 5.8, 8.05 (acetate), 6.9, 7.0, 7.3, 7.4, 7.9, 8.2, 8.45, 8.7, 8.85, 9.0, 9.65, 9.85, 10.2, 10.4, 10.5, 10.7, 10.8, 10.95, 11.4, 12.0, 12.3 μ.

Anal. Calcd for $C_{29}H_{43}N_3O_3$ (481.66): C, 72.31, H, 9.00; N, 8.72. Found: C, 72.01; H, 8.74; N, 8.77.

When a solution of 48 mg (0.0001 mole) of **2** 3β-acetate in 3 ml of xylene was heated under reflux during 24 hr and concentrated to give a residue which was recrystallized from acetone, affording 8 mg of dense plates, mp 214–222° with evolution of nitrogen, the infrared spectrum was identical with that of the starting **2** 3β-acetate.

3β-Acetoxy-22β-methoxy-20(27)-imino-25α-5-furostene Hydrochloride (4 3β-Acetate Hydrochloride).—To a solution of 134 mg (0.00028 mole) of **2** 3β-acetate in 2 ml of methanol was added 1 drop of 6 *N* aqueous hydrochloric acid. Prompt dissolution with vigorous evolution of nitrogen was followed by immediate crystallization of the hydrochloride. After 30 min at 0°, the precipitate was collected by filtration to afford 136 mg (96%): mp 220–230°; infrared spectrum 5.8, 8.05 (acetate), 3.8, 3.9, 4.0, 6.3 (hydrochloride), 6.8, 6.9, 7.2, 7.3, 8.45, 8.55, 8.7, 9.05, 9.3, 9.45, 9.7, 10.2, 10.3, 10.55, 10.95, 11.7 μ.

3β-Acetoxy-22β-methoxy-20(27)-imino-25α-5-furostene (4 3β-Acetate).—To a magnetically stirred solution of 134 mg (0.00026 mole) of **4** 3β-acetate hydrochloride in 30 ml of 80% aqueous ethanol was added dropwise 1.3 ml of an aqueous solution containing 14.6 mg (0.00026 mole) of potassium hydroxide. After the mixture had been stirred during 5 min, it was concentrated to give a residue which was diluted with water and extracted with ether. The ethereal extract was washed with water, dried, and concentrated. Recrystallization of the remainder from acetone afforded 96 mg (79%) of rods: mp 154–162°; $[\alpha]_D$ −35°; infrared spectrum 5.8, 8.05 (acetate), 6.8, 6.85, 6.95, 7.3, 8.5, 8.65, 9.2, 9.3, 9.5, 9.7, 9.8, 10.2, 10.4, 10.8, 11.0, 11.8 μ.

Anal. Calcd for $C_{30}H_{47}NO_4$ (485.68): C, 74.18; H, 9.75; N, 2.88. Found: C, 74.13; H, 9.75; N, 2.99.

3β-Hydroxy-22β-methoxy-20(27)-imino-25α-5-furostene Hydrochloride (4 Hydrochloride).—To a suspension of 266 mg (0.0006 mole) of **2** in 3 ml of methanol was added 2 drops of 6 *N* aqueous hydrochloric acid. Rapid dissolution of the triazoline, accompanied by lively evolution of nitrogen, was followed by prompt crystallization. The mixture was warmed during a few minutes to complete the reaction. After 2 hr at 0°, the precipitate was collected by filtration, washed with methanol, and dried to give 261 mg (92%) of rods which were recrystallized from methanol: mp 265–275°; $[\alpha]_D$ −21°; infrared spectrum 3.7 (m), 3.9 (m), 4.0 (m), 6.25 (m), (hydrochloride), 6.8, 7.2, 8.6, 8.7, 9.2, 9.4, 9.5, 9.8, 10.0, 10.2, 10.3, 10.6, 11.0, 11.8 μ.

Anal. Calcd for $C_{28}H_{46}ClNO_3$ (480.11): C, 70.04; H, 9.65; N, 2.92. Found: C, 69.41; H, 9.54; N, 3.03.

Treatment of the hydrochloride with aqueous methanolic potassium hydroxide, followed by recrystallization of the product from a mixture of dichloromethane and acetone gave **4**.

3β-Hydroxy-22β-methoxy-20(27)-imino-25α-5-furostene (4). A. From 2.—A mixture of 354 mg (0.0008 mole) of **2**, 304 mg (0.0016 mole) of *p*-toluenesulfonic acid hydrate, and 10 ml of methanol was heated under reflux during 1 hr. The cooled solution was made basic by addition of 200 mg of potassium hydroxide in 2 ml of water. The solution was concentrated to give a residue which was diluted with water and extracted with ether. The ethereal extract was washed with water, dried, and concentrated. Recrystallization of the remainder from a mixture of dichloromethane and acetone afforded 298 mg (84%) of rods: mp 210–215°; $[\alpha]_D$ −31°; infrared spectrum 3.0, 3.1, 6.85, 6.95, 7.2, 7.25, 7.4, 8.0, 8.1, 8.4, 8.6, 8.7, 8.9, 9.15, 9.25, 9.35, 9.75, 9.9, 10.1, 10.3, 10.4, 10.6, 10.85, 11.1, 11.65, 12.0, 12.2, 12.5, 13.0 μ; nmr spectrum (in deuteriochloroform, relative to TMS = 0) 192 (OCH_3), 62 (C-19), 67 (C-18), 78 (C-21), 51 ppm (doublet) (C-26).

Anal. Calcd for $C_{28}H_{45}NO_3$ (443.65): C, 75.80; H, 10.22; N, 3.16; OCH_3, 7.00. Found: C, 75.60; H, 9.95; N, 3.30; OCH_3, 6.98.

B. From 3.—A mixture of 44 mg (0.0001 mole) of the hemiketal **3**, 40 mg of *p*-toluenesulfonic acid hydrate, and 5 ml of methanol was kept at 25° during 20 hr. The solution was made basic with 200 mg of potassium hydroxide in 2 ml of water, concentrated, and extracted with ether. The ethereal extract was washed with water, dried, and concentrated. Crystallization from a mixture of dichloromethane and acetone (difficulty soluble) gave 20 mg of needles shown by infrared spectrum to be unchanged **3**. All fractions were recombined and the treatment with *p*-toluenesulfonic acid in methanol was repeated during 1 hr at reflux temperature. After 4 days at 25° the solution was made basic with 200 mg of potassium hydroxide in 2 ml of water, concentrated, and extracted with ether. The ethereal phase was washed with water, dried, and concentrated. Crystallization of the residue from a mixture of dichloromethane and methanol gave 26 mg (59%) of needles, mp 200–207°, whose infrared spectrum was identical with that of **4** prepared from **2**.

When a solution of 88 mg (0.0002 mole) of **4** in 1 ml of 80% aqueous acetic acid was kept at 25° during 30 min, followed by addition to a solution of 1 g of potassium hydroxide in 30 ml of water, affording a precipitate which was collected, washed with water, dried, and triturated with acetone, the infrared spectrum of the 71 mg (85%) of needles, mp 179–184°, demonstrated them to be unchanged **4**.

3β-Hydroxy-22β-ethoxy-20(27)-imino-25α-5-furostene (5). A. From 2.—A mixture of 88 mg (0.0002 mole) of **2**, 76 mg (0.0004 mole) of *p*-toluenesulfonic acid hydrate, and 5 ml of ethanol was heated under reflux during 2 hr. After 20 hr at 25°, the solution was made basic with 200 mg of potassium hydroxide in 2 ml of water, concentrated, and extracted with ether. The ethereal extract was washed with water, dried, and concentrated. Recrystallization of the residue from a mixture of dichloromethane and acetone gave 65 mg (71%) of needles, mp 164–171°. A

(12) Melting points were observed on a calibrated micro hot stage and are corrected. Ethereal solutions were dried over anhydrous magnesium sulfate. Concentrations were carried out under diminished pressure with a rotating evaporator. Infrared spectra were recorded from potassium bromide disks with a Perkin-Elmer spectrophotometer, Model 137. Microanalyses were performed by Dr. S. M. Nagy, Massachusetts Institute of Technology, Cambridge, Mass. Rotations were measured at concentrations of 1% in chloroform at 25° by Huffman Laboratories, Wheatridge, Colo.

(13) For comments on preparation of the starting pseudodiosgenin, see F. C. Uhle, *J. Org. Chem.*, **30**, 3915 (1965).

second recrystallization gave 52 mg of needles: mp 170–176°; $[\alpha]_D$ −46°; infrared spectrum 6.9, 7.0, 7.2, 7.3, 7.4, 8.8, 9.3, 9.45, 9.8, 10.05, 10.1, 10.35, 10.9, 11.0, 11.8, 13.2 μ.

Anal. Calcd for $C_{29}H_{47}NO_3$ (457.67): C, 76.10; H, 10.35; N, 3.06; OC_2H_5, 9.85. Found: C, 76.26; H, 10.45; N, 3.21; OC_2H_5, 9.82.

B. From 3.—A mixture of 52 mg (0.00012 mole) of the hemiketal **3**, 50 mg (0.00026 mole) of *p*-toluenesulfonic acid hydrate, and 5 ml of ethanol was heated under reflux during 1 hr. After 20 hr at 25°, the solution was made basic with aqueous potassium hydroxide, concentrated, and extracted with ether. The ethereal solution was washed with water, dried, and concentrated. Crystallization of the residue from acetone afforded 35 mg (63%) of dense needles, mp 172–176°, whose infrared spectrum was identical with that of the ethyl ketal prepared from **2**.

When a solution of 46 mg of **4** and 0.3 ml of acetic acid in 1 ml of ethanol was kept at 25° during 3 days, followed by treatment with aqueous potassium hydroxide and recrystallization from acetone, the infrared spectrum of the product closely resembled that of the starting **4**.

3β,22β-Dihydroxy-20(27)-imino-25α-5-furostene (3). A. From 2.—To a suspension of 88 mg (0.0002 mole) of **2** in a mixture of 1 ml of water and 2 ml of ethanol was added 5 drops of 6 *N* aqueous hydrochloric acid. Rapid dissolution of **2** with evolution of nitrogen was followed by prompt crystallization of the hydrochloride. The mixture was diluted with 2 ml of water and stored at 0° during 1 hr. The precipitate was collected by filtration, washed with water, and dried to afford 94 mg (98%) of tiny needles of the hydrochloride: mp 258–268° (dark red melt); infrared spectrum 3.5, 3.7, 3.9, 4.0, 6.15, 6.25, 6.8, 8.6, 9.2, 9.5, 9.7, 9.8, 10.2, 11.0 μ.

To a solution of this hydrochloride in 12 ml of 80% aqueous ethanol was added a solution of 100 mg of potassium hydroxide in 1 ml of water. The clear solution was diluted with water to give a gelatinous precipitate which, after 1 hr at 0°, was collected by filtration, washed with water, and dried. Trituration with refluxing methanol, followed by storage at 0°, gave 63 mg (73%) of fine needles: mp 190–198°; $[\alpha]_D$ −93°; infrared spectrum 2.9, 2.95, 3.05, 3.3, 6.6, 6.75, 6.9, 7.0, 7.3, 7.35, 7.65, 7.8, 7.9, 8.0, 8.1, 8.2, 8.4, 8.45, 8.5, 8.65, 8.7, 8.9, 9.1, 9.3, 9.4, 9.55, 9.8, 10.1, 10.35, 10.4, 10.5, 10.85, 11.0, 11.3, 11.5, 11.7, 11.8, 12.0, 12.3, 13.0, 13.6, 14.2 μ.

Anal. Calcd for $C_{27}H_{43}NO_3$ (429.62): C, 75.48; H, 10.09; N, 3.26. Found: C, 75.32; H, 10.21; N, 3.78.

When a solution of 22 mg of the hemiketal **3** in 2 ml of methanol was heated under reflux during 2 hr and kept at 25° during 20 hr, crystals had deposited. After 2 hr at 0°, the precipitate was collected by filtration to afford 14 mg of fine needles which were shown by infrared spectrum to be unchanged **3**.

When a solution of 20 mg of the hemiketal **3** in 2 ml of acetic acid was heated under reflux during 10 min, concentrated, and treated with aqueous potassium hydroxide to give a precipitate which was collected by filtration, washed with water, dried, and recrystallized from acetone, 11 mg of unchanged **3**, identified by infrared spectrum, was recovered.

B. From 4.—A mixture of 44 mg (0.0001 mole) of the methyl ketal **4**, 100 mg of *p*-toluenesulfonic acid hydrate, 1 ml of water, and 4 ml of ethanol was heated under reflux during 20 hr. The solution was made basic with aqueous potassium hydroxide and extracted with ether. The washed and dried ethereal extract was concentrated to give a residue which was recrystallized from acetone to afford 22 mg, whose infrared spectrum was identical with that of **3** prepared from the triazoline **2**.

3β-Acetoxy-22β-hydroxy-20(27)-acetylimino-25α-5-furostene (3 3β,N-Diacetate).—A mixture of 43 mg (0.0001 mole) of **3**, 0.75 ml of acetic anhydride, and 2 ml of anhydrous pyridine was kept at 0° during 48 hr with frequent shaking. (Dissolution was complete after 45 hr.) The solution was diluted with aqueous potassium chloride to give a precipitate which was collected by filtration, washed with water, and dried. Crystallization from isopropyl alcohol gave 10 mg of needles, mp 159–179°. Recrystallization from methanol afforded 5.5 mg of fine needles: mp 164–174°; infrared spectrum 3.0 (hydroxyl), 5.8, 8.05 (acetoxyl), 6.15 (tertiary amide), 6.9, 7.2, 7.3, 7.9, 8.3, 8.5, 8.6, 8.8, 9.1, 9.3, 9.5, 9.6, 9.8, 10.0, 10.3, 10.4, 10.9, 11.6, 12.3, 13.8 μ.

This product was combined with mother liquor material from the 10 mg and dissolved in methanol. When a crystal of *p*-toluenesulfonic acid hydrate was added to the solution at 25°, long needles soon began to separate. After 1 hr at 0°, the product was collected by filtration to give 7 mg of needles, mp 199–210°, whose infrared spectrum was identical with that of **10** 3β-acetate.

3β-Acetoxy-22β-methoxy-20(27)-acetylimino-25α-5-furostene (10 3β-Acetate). A. From 4.—A mixture of 222 mg (0.0005 mole) of **4**, 2 ml of acetic anhydride, and 5 ml of anhydrous pyridine was kept at 25° during 20 hr. A copious precipitate of long needles had separated. After 5 hr at 0°, the crystals were collected by filtration to afford 211 mg (80%) of needles, mp 249–253°. Recrystallization from a mixture of dichloromethane and methanol gave needles: mp 249–253°; $[\alpha]_D$ +47°; infrared spectrum 5.8, 8.05 (acetate), 6.0 (tertiary amide), 6.8, 6.9, 7.0, 7.2, 7.3, 7.8, 8.3, 8.5, 8.6, 9.1, 9.25, 9.4, 9.5, 9.65, 9.8, 10.25, 10.35, 10.9, 11.0, 11.7 μ.

Anal. Calcd for $C_{32}H_{49}NO_5$ (527.72): C, 72.83; H, 9.36; N, 2.65. Found: C, 72.84; H, 9.33; N, 2.80.

B. From 9 3β-Acetate.—To a solution of 11 mg of the enol ether **9** 3β-acetate in 1 ml of methanol at 25° was added a crystal of *p*-toluenesulfonic acid hydrate. Within a few minutes at 25° needles began to deposit. After 2 hr at 25°, followed by 20 hr at 0°, the precipitate was collected by filtration to give 9 mg of needles, mp 205–220°, whose infrared spectrum was identical with that of **10** 3β-acetate.

3β-Hydroxy-22β-methoxy-20(27)-acetylimino-25α-5-furostene (10).—A mixture of 45 mg (0.00085 mole) of **10** 3β-acetate, 100 mg of potassium hydroxide, 1 ml of water, and 9 ml of ethanol was heated under reflux during 5 min. The solution was concentrated to give a residue which was diluted with water. The precipitate was collected by filtration, washed with water, dried, and recrystallized from acetone to afford 30 mg (73%) of needles, mp 250–255°. Recrystallization from a mixture of dichloromethane and acetone gave 20 mg of needles, mp 254–259°; $[\alpha]_D$ +52°; infrared spectrum 6.0 (sh), 6.1 (tertiary amide), 6.9, 7.0, 7.1, 7.2, 7.3, 7.8, 8.2, 8.6, 9.1, 9.3, 9.4, 9.8, 10.1, 10.35, 10.85, 11.8, 13.6 μ.

Anal. Calcd for $C_{30}H_{47}NO_4$ (485.68): C, 74.18; H, 9.75; N, 2.88. Found: C, 73.08; H, 9.67; N, 3.19.

3β-Acetoxy-20(27)-acetylimino-25α-5,22-furostadiene (9 3β-Acetate). A.—A solution of 53 mg (0.0001 mole) of **10** 3β-acetate in 2 ml of acetic anhydride was heated under reflux during 1 hr. The cooled solution was diluted with water to give a precipitate which was collected by filtration, washed with water, and dissolved in ether. The ethereal solution was dried and concentrated to give a residue which was crystallized from a mixture of dichloromethane and methanol, furnishing 40 mg (80%) of glistening plates: mp 212–222°; $[\alpha]_D$ −147°; infrared spectrum 5.8, 8.05 (acetate), 6.0 (sh), 6.05 (tertiary amide), 6.8, 6.9, 7.1, 7.3, 7.7, 8.3, 8.5, 8.6, 8.7, 9.1, 9.5, 9.7, 9.8, 10.4, 10.6, 11.0, 11.45, 12.1, 12.2, 12.7 μ.[14]

Anal. Calcd for $C_{31}H_{45}NO_4$ (495.68): C, 75.11; H, 9.15; N, 2.83. Found: C, 75.04; H, 9.07; N, 2.77.

B.—A mixture of 53 mg (0.0001 mole) of **10** 3β-acetate, 57 mg (0.0003 mole) of *p*-toluenesulfonyl chloride, and 1 ml of anhydrous pyridine was heated under reflux during 5 hr. The solution was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Recrystallization from a mixture of dichloromethane and methanol afforded 26 mg (53%) of plates, mp 200–217°, whose infrared spectrum was identical with that of the product prepared with refluxing acetic anhydride.

C.—To a solution of 10 mg of **10** 3β-acetate in 1 ml of glacial acetic acid was added dropwise sufficient water to cause complete precipitation. The deposit was collected by filtration to give tiny plates, mp 205–220°, whose infrared spectrum was identical with that of **9** 3β-acetate prepared with refluxing acetic anhydride or with *p*-toluenesulfonyl chloride in refluxing pyridine.

3β-Hydroxy-20(27)-acetylimino-25α-5,22-furostadiene (9).—A mixture of 61 mg (0.000123 mole) of **9** 3β-acetate, 100 mg of potassium hydroxide, 1 ml of water, and 4 ml of ethanol was heated under reflux during 30 min. The solution was concentrated to give a residue which was extracted with ether. The ethereal extract was washed with water, dried, and concentrated. Crystallization of the remainder from a mixture of dichloromethane and acetone gave 41 mg (73%) of plates: mp 269–273°; $[\alpha]_D$ −150°; infrared spectrum 5.98 (enol ether), 6.05 (tertiary amide), 6.9, 7.05, 7.25, 7.4, 7.5, 7.7, 8.0, 8.15, 8.3,

(14) Although in preliminary work[7] the band at 11.45 μ had been considered tentative evidence for terminal methylene unsaturation, the presence of a prominent maximum at this position of the rich fingerprint region must be only fortuitous.

8.45, 8.6, 8.75, 9.1, 9.2, 9.3, 9.45, 9.6, 9.75, 9.9, 10.35, 10.45, 10.65, 11.4, 12.15, 12.7, 13.6 μ.

Anal. Calcd for $C_{29}H_{43}NO_3$ (453.64): C, 76.78; H, 9.55. Found: C, 76.64; H, 9.62.

1-Acetyl-2-(3′β,16′β-dihydroxy-17′β-androst-5′-enyl)-2,6-dimethyl-3-oxohexahydroazepine (13). A. From 10 3β-Acetate.—A mixture of 106 mg (0.0002 mole) of **10** 3β-acetate, 50 mg of *p*-toluenesulfonic acid hydrate, and 5 ml of methanol was heated under reflux during 2 hr. The cooled solution was made basic with a solution of 100 mg of potassium hydroxide in 1 ml of water and was heated under reflux during 30 min. The solution was concentrated to give an aqueous residue which was extracted with ether. The ethereal extract was washed with water, dried, and concentrated. Recrystallization of the remainder from acetone afforded 70 mg (75%) of dense prisms: mp 220–230°; $[\alpha]D$ −64°; infrared spectrum 5.8 (ketone), 6.1 (tertiary amide), 6.9, 7.1, 7.25, 7.3, 7.5, 7.9, 8.0, 8.1, 8.35, 8.5, 8.6, 8.9, 9.15, 9.35, 9.6, 9.75, 9.9, 10.3, 10.4, 11.1, 11.4, 11.6, 12.3, 12.9, 13.6 μ.

Anal. Calcd for $C_{29}H_{45}NO_4$ (471.66): C, 73.84; H, 9.62; N, 2.97. Found: C, 73.80; H, 9.57; N, 2.93.

B. From 9.—A mixture of 20 mg of the enol ether **9**, 20 mg of *p*-toluenesulfonic acid hydrate, and 4 ml of methanol was heated under reflux during 4 hr. The solution was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Recrystallization from acetone gave 7 mg of prisms, mp 224–230°, whose infrared spectrum was identical with that of the product prepared from **10** 3β-acetate.

Treatment of 13 with *p*-Nitrophenylhydrazine.—A mixture of 37 mg (0.000078 mole) of **13**, 50 mg of *p*-nitrophenylhydrazine, 10 drops of acetic acid, and 5 ml of ethanol was heated under reflux during 20 hr. The solution was concentrated and extracted with ether. The ethereal extract was washed repeatedly with dilute acetic acid and with water, dried, and concentrated. Recrystallization of the residue from ethyl acetate gave 10 mg of colorless prisms, mp 230–233°, shown by infrared spectrum to be unchanged **13**.

Treatment of 13 with Hydroxylamine.—A mixture of 35 mg (0.000075 mole) of **13**, 139 mg (0.002 mole) of hydroxylamine hydrochloride, 1 ml of pyridine, and 3 ml of ethanol was heated under reflux during 4 hr. The solution was diluted with aqueous potassium chloride to give a precipitate which was collected by filtration, washed with water, and dried. Recrystallization from methanol gave 4 mg, mp 223–232°, shown by infrared spectrum to be unchanged **13**. Crystallization of mother liquor material from acetone gave an additional 10 mg of **13**, mp 224–231°.

1-Acetyl-2-(3′,16′β-diacetoxy-17′β-androst-5′-enyl)-2,6-dimethyl-3-oxohexahydroazepine (13 3′β,16′β-Diacetate).—A solution of 47 mg (0.0001 mole) of **13** in 3 ml of acetic anhydride was heated under reflux during 1 hr. The cooled solution was diluted with water to give a precipitate which was collected by filtration, washed with water, and dissolved in ether. The ethereal solution was dried and concentrated. Crystallization of the residue from a mixture of dichloromethane and methanol afforded 33 mg (60%) of long, dense needles, mp 216–221°. Two additional recrystallizations gave needles: mp 219–221°; infrared spectrum 5.8 (ketone, acetate), 7.95 (acetate), 6.0 (tertiary amide), 6.8, 6.9, 6.95, 7.2, 7.3, 7.35, 7.4, 7.55, 8.4, 8.5, 8.85, 8.95, 9.2, 9.35, 9.65, 9.8, 10.0, 10.4, 11.0, 11.1, 11.3, 11.4, 11.7, 12.3, 12.7, 12.9, 13.6 μ.

Anal. Calcd for $C_{33}H_{49}NO_6$ (555.73): C, 71.32; H, 8.89. Found: C, 71.84; H, 9.00.

Acetylation of **13** with acetic anhydride, in anhydrous pyridine at 25° during 20 hr gave 48% of the same product. Although several analytical determinations gave values more nearly satisfactory for a monoacetate [Calcd for $C_{31}H_{47}NO_5$ (513.69): C, 72.48; H, 9.22.), failure of the 16′β-hydroxyl group to acetylate in refluxing acetic anhydride, at least, seems unlikely. The infrared spectrum of a thoroughly dried sample showed no appreciable hydroxyl absorption.

1-Acetyl-2-(3′β,16′β-dihydroxy-17′β-androst-5′-enyl)-2,6-dimethyl-3-hydroxyhexahydroazepine (12).—A mixture of 67 mg (0.00014 mole) of **13**, 100 mg (0.0026 mole) of sodium borohydride, and 40 ml of isopropyl alcohol was stirred magnetically at 25° during 10 days. The solution was concentrated to give a residue which was diluted with water. The precipitate was collected by filtration, washed with water, and dried. The infrared spectrum of the total product showed the carbonyl band at 5.8 μ still present, though much reduced in intensity. Crystallization from acetone gave 16 mg (25%) of needles from whose infrared spectrum the 5.8-μ band had virtually disappeared. Recrystallization from aqueous ethanol gave 10 mg of tiny needles: mp 222–232°; infrared spectrum 6.1 (sh), 6.2 (tertiary amide), 6.9, 7.0, 7.1, 7.25, 7.4, 8.9, 9.3, 9.4, 9.7, 9.9, 10.3, 10.5, 11.45, 11.7, 12.4, 14.2 μ.

Anal. Calcd for $C_{29}H_{47}NO_4$ (473.67): C, 73.53; H, 10.00. Found: C, 73.38; H, 9.94.

Treatment of 10 3β-Acetate with Refluxing Formic Acid.—To a boiling solution of 345 mg (0.0025 mole) of potassium carbonate in 5 ml of formic acid (prepared by cautious addition in the cold) was added 53 mg (0.0001 mole) of **10** 3β-acetate. When the solution was heated under reflux during 15 min a purple coloration slowly developed. The cooled mixture was diluted with aqueous potassium chloride to give a precipitate which was collected by filtration, washed with water, and dried. The product failed to crystallize from any solvent tried. A solution in ethanol was made basic with aqueous potassium hydroxide and heated under reflux during 30 min. The mixture was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Crystallization from a mixture of dichloromethane and acetone gave 10 mg (21%) of tiny, hexagonal plates: mp 271–272°; infrared spectrum 5.9 (s) (carbonyl), 6.1 (tertiary amide), 6.85, 6.9, 7.0, 7.2, 7.3, 7.4, 7.5, 7.6, 7.9, 8.0, 8.3, 8.4, 8.45, 8.95, 9.1, 9.35, 9.6, 9.8, 10.05, 10.3, 10.5, 10.8, 11.5, 11.8, 12.4, 12.5, 13.4, 13.8, 14.5 μ.

Prolonged Treatment of 10 3β-Acetate with *p*-Toluenesulfonic Acid in Refluxing Ethanol.—A mixture of 77 mg (0.000145 mole) of **10** 3β-acetate, 100 mg of *p*-toluenesulfonic acid hydrate, and 5 ml of ethanol was heated under reflux during 20 hr. To the cooled solution was added a solution of 200 mg of potassium hydroxide in 2 ml of water. The mixture was heated under reflux during 1 hr, concentrated, and extracted with ether. The ethereal solution was washed with water, dried, and concentrated. Recrystallization of the remainder from acetone gave 14 mg (22%) of needles, mp 175–190°, whose infrared spectrum was identical with that of the hemiketal **3**, unexpectedly demonstrating partial hydrolysis of the N-acetyl tertiary amide group under these conditions. Concentration of the mother liquors gave 5 ml (7%) of tiny plates, mp 266–271°, whose infrared spectrum was identical with that of the product from treatment of **10** 3β-acetate with refluxing formic acid. On the surmise that this substance might represent an acid transformation product of **13**, an acetic acid solution of the 16β-hydroxy ketone **13** was heated under reflux. Dilute aqueous potassium hydroxide treatment of the material precipitated with water gave only unchanged **13**, however. Further investigation of the compound was not undertaken.

Registry No.—**2**, 10239-67-5; **2** 3β-acetate, 10198-55-7; **3**, 10198-56-8; **3** 3β,N-diacetate, 10198-57-9; **4**, 10198-58-0; **4** hydrochloride, 10198-54-6; **4** 3β-acetate, 10198-59-1; **4** 3β-acetate hydrochloride, 10198-60-4; **5**, 10198-61-5; **9**, 10198-62-6; **9** 3β-acetate, 10232-01-6; **10**, 10198-63-7; **10** 3β-acetate, 10198-64-8; **12**, 10198-65-9; **13**, 10198-66-0; **13** 3′β,16′β-diacetate, 10235-64-0; pseudodiosgenin, 2309-38-8.

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