From the benzene eluate, 17 mg. of impure 3β-acetoxy-5,16-pregnadien-20-one were obtained, which yielded 6 mg. of the pure specimen. The aqueous layer from the ether extract was acidified with hydrochloric acid and reextracted with ether. This after acetylation yielded 143 mg. of crude lactonic material which was chromatographed on acidic alumina. From the ether eluate, 30 mg. of lactone VII, m.p. 212–215° (from acetone-hexane), was obtained, which was identical (melting point, mixture melting point, infrared spectrum) with an authentic specimen prepared from another source.[9]

Tetrahydrosolasodine (VIII) *from amorphous mixture.* The amorphous mixture (177 mg.) was dissolved in 6 ml. of acetic acid and reduced catalytically with 94 mg. of platinum oxide. In about 30 min. the consumption (2 moles) of hydrogen ceased. Although the tetrahydro derivative was chromatographed, it refused to crystallize,[12] $[\alpha]_D^{29}$ +24° ($CHCl_3$).

A part of the triacetate (64 mg.) was therefore hydrolyzed in methanolic potassium hydroxide (10%) for 3 hr. and the product crystallized from aqueous methanol. It formed prisms, m.p. 288–292°, $[\alpha]_D^{29}$ −8.7° ($CHCl_3$), identical in respect to melting point and infrared spectrum with an authentic specimen of tetrahydrosolasodine obtained from the direct reduction of solasodine.[15]

Conversion of IIA *and the amorphous mixture into pseudosolasodine B* (X). (a) The amorphous mixture (225 mg.) was refluxed with 15 ml. of acetic acid for 3 hr. The acetic acid was removed *in vacuo* and the residue chromatographed on alumina. The fraction eluted with ether (175 mg.) crystallized from methanol as plates, m.p. 184–191°, and agreed in properties (melting point and infrared spectrum) with an authentic specimen[3] prepared from the interaction of a solution of zinc chloride-acetic anhydride-acetic acid with solasodine.

Anal. Calcd. for $C_{31}H_{47}O_4N$: C, 74.81; H, 9.52. Found: C, 74.58; H, 9.43.

The treatment of IIA in the same manner also gave X in good yields.

(b) A solution of 130 mg. of amorphous IIA and IIB in 20 ml. of benzene-ether (1:1) containing hydrogen chloride gas (slow bubbling for *ca.* 5 min.) was allowed to stand overnight at 5°. The product was chromatographed on alumina. The ether eluate (45 mg.) proved to be X.

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(15) H. Rochelmeyer, *Arch. Pharm.*, **277**, 329 (1939).

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The Chemistry of the Spiroaminoketal Side Chain of Solasodine and Tomatidine. III.[1] The Reaction of *O,N*-Diacetylsolasodine in Acidic Media

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The isomerization of *O,N*-diacetylsolasodine in nonpolar media forms the pseudo derivative, 26-acetylamino-5,20(22)-furostadien-3β-ol acetate in good yields. Aqueous or alcoholic acidic media promote the formation of C-22 substituted 26-acetylaminofurostene derivatives. The chemistry of the 22-hemiketal and alkoxyketals is discussed.

In the course of our investigations of the acid-catalyzed isomerization of the diacetates of the steroidal alkaloids, tomatidine, and solasodine[1] several interesting new compounds were obtained from the treatment of these diacetyl derivatives with mineral acid in polar solvents. In the presence of aqueous hydrochloric acid in dioxane[3] diacetylsolasodine (I) yields, along with the known pseudo compound II,[1] the 22-hydroxyl derivative III. This structure was deduced from the proposed course of the pseudomerization reaction (VIII→IX→X) and confirmed by spectroscopic and chemical data.

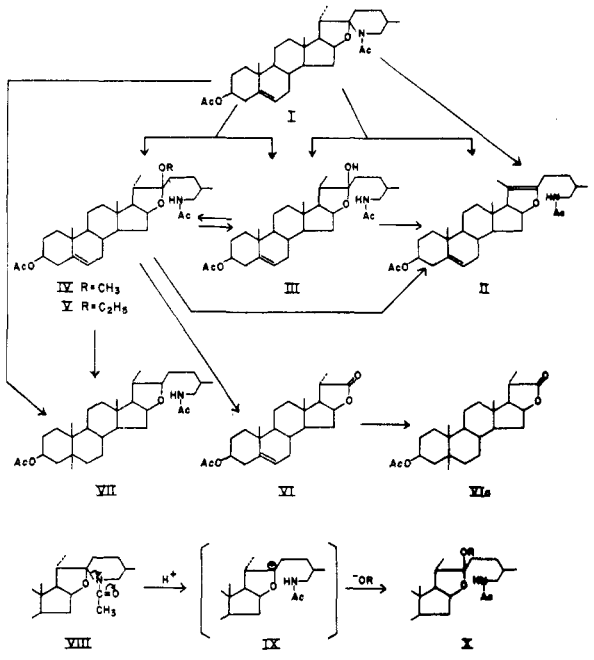
The infrared spectrum of III is characterized by the appearance of a hydroxyl absorption (2.78 μ) in addition to to the normal acetoxy (5.78 μ) and secondary amide function (2.90, 5.98, 6.60 μ). As would be expected III is readily converted into the pseudo derivative II by treatment with acetic acid. Structure III is further supported by the preponderant formation of the C-22 methoxy derivative IV when methanol is used as solvent in place of dioxane in its preparation from diacetylsolasodine. When ethanol is employed in place of methanol, the ethoxy derivative V is obtained, which can be converted to the methoxyl compound IV by allowing it to stand in a solution of methanol and acetic acid. The process is easily reversed (IV→V) by employing ethanol and acetic acid. By mild treatment with 80% acetic acid, these alkoxy derivatives IV and V are transformed into the hydroxyl compound III which, in turn, is readily reconverted into IV or V with acetic acid and the appropriate alcohol. More vigorous treatment with acetic acid converts compounds IV and V directly into II. This series of transformations parallels the sequence of reactions which Hirschman and Hirschman have found for the C-22 ketals obtained from kryptogenin.[4]

(1) For Part I and II see *J. Org. Chem.*, **25**, 783 (1960).

(2) Visiting Scientist, National Institutes of Health.

(3) Hydrochloric or perchloric acid (60%) in acetic acid also acts similarly.[1]

(4) H. Hirschman and F. B. Hirschman, *Tetrahedron*, **3** 243 (1958).



During the earlier phase of this work, before alkoxylation at C-22 was suspected, oxidative degradation of compounds IV and V were attempted. The principal substance isolated in these experiments was the lactone VI, accompanied by a small amount of 5,16-pregnadienolone acetate. The identity of VI was established by its reduction to the known tigogenin lactone (VIa).[5] It was also found that the C-22 alkoxy substituent can be reductively removed (platinum oxide–acetic acid) whereby 26-acetylamino-5α-furostan-3β-ol acetate (VII) is formed, which had been previously prepared from the catalytic reduction[6] of *O,N*-diacetylsolasodine.

As would be expected, in the absence of nucleophiles under anhydrous conditions the formation of these C-22 substituted by-products is avoided. For example *O,N*-diacetylsolasodine (I) is converted in good yields to the pseudo compound II (*ca.* 90%) in an anhydrous media (e.g., methylene chloride) with hydrogen chloride. Treatment of I with pyridine hydrochloride in dry pyridine also affords II in high yields (95%).

EXPERIMENTAL[7]

*26-Aminoacetyl-25*D*-furost-5-en-3β,22-diol 3-acetate* (III). A solution of solasodine diacetate (I) (105 mg.), 2*N* hydrochloric acid (0.5 ml.), and dioxane (6 ml.) was allowed to stand at room temperature for 30 min. Water and ammonium hydroxide were then added and the recovered product subjected to chromatography on alumina. The ether-methanol (0.2%) eluate yielded 66 mg. (63%) of pseudosolasodine diacetate (II), m.p. 128–134°, which upon recrystallization from acetone-hexane melted at 135–138°. It was identical (melting point, mixture melting point, infrared spectrum) with an authentic sample of II obtained previously.[1]

The fraction eluted with ether-methanol (5%) gave 27 mg. (26%) of the C-22 hydroxy derivative III, melting at 152–155° (plates from aqueous acetone) $[\alpha]_D^{20}$ −52° ($CHCl_3$). Its principal infrared absorption bands ($CHCl_3$) were located at 2.78 μ (OH), 2.90 μ (NH), 5.78 μ (OAc), and 5.98, 6.60 μ (HN—Ac).

Anal. Calcd. for $C_{31}H_{49}O_5N$: C, 72.19; H, 9.58. Found: C, 72.17; H, 9.58.

Solasodine diacetate (I) in acetic acid with hydrochloric or perchloric acid (60%) also affords II and III.[1]

*26-Aminoacetyl-22-methoxy-25*D*-furost-5-en-3β-ol acetate* (IV). To 300 mg. of *O,N*-diacetylsolasodine dissolved in 10 ml. of methanol was added 0.2 ml. of 6*N* hydrochloric acid and the solution allowed to stand for 15 min. at room temperature. Water and conc. ammonium hydroxide (0.5 ml.) were added and the precipitate chromatographed on alumina. The fraction eluted with ether-methanol (0.5%) yielded 270 mg. (85%) of the methoxy derivative, plates, (aqueous methanol) m.p. 141–144°; $[\alpha]_D^{20}$ −82° ($CHCl_3$).

Anal. Calcd. for $C_{32}H_{51}O_5N$: C, 72.55; H, 9.70; CH_3O—, 5.85. Found: C, 72.21; H, 9.81; CH_3O—, 5.65.

A fraction subsequently eluted with ether-methanol (3%) afforded 36 mg. (*ca.* 11%) of a mixture of the 3-alcohol and the C-22 hydroxy compound as judged from its infrared spectrum.

*26-Aminoacetyl-22-ethoxy-25*D*-furost-5-en-3β-ol acetate* (V). A solution consisting of solasodine diacetate (500 mg.), 6*N* hydrochloric acid (0.4 ml.), and ethanol (15 ml.) was allowed to stand for 1 hr. at room temperature and then for 1 hr. in the refrigerator (0°). The fine crystals which had precipitated amounted to 326 mg. (61%) and melted at 160–164°. This was recrystallized from acetone-hexane to form plates, m.p. 166–171°, $[\alpha]_D^{20}$ −75° ($CHCl_3$).

Anal. Calcd. for $C_{33}H_{53}O_5N$: C, 72.89; H, 9.82; EtO—, 8.28. Found: C, 72.88; H, 9.54; EtO—, 8.43.

To the mother liquor was added water and ammonia water and the precipitated product subjected to chromatography on alumina. The ether-methanol (0.5%) eluate yielded 70 mg. (14%) of starting material and 18 mg. (3%) more of the ethoxy derivative. A subsequent fraction (5% methanol in ether) gave 74 mg. (15%) of the C-22 hydroxy compound, m.p. 152–155°, identical in infrared spectrum with III obtained from the treatment of diacetylsolasodine with hydrochloric acid in dioxane.

Conversion of V *into* IV. Twenty milligrams of the ethoxy derivative V was dissolved in 2 ml. of methanol and 0.5 ml. of acetic acid and allowed to stand for 3 hr. at room temperature. The product which was crystallized twice from aqueous methanol melted at 140–143°. It was identical (melting point, infrared spectrum) with a sample of IV obtained directly from I.

Conversion of IV *into* V. The methoxy derivative IV (23 mg.) was allowed to stand for 5 hr. at room temperature in a mixture of ethanol (3 ml.) and acetic acid (0.6 ml.). The product, twice crystallized from acetone-hexane, melted at 164–169°. The substance agreed (melting point, infrared spectrum) with a sample of V prepared directly from I.

Conversion of IV *to* III. The methoxy compound IV (70 mg.) was dissolved in a solution consisting of 4 ml. of acetic acid and 0.8 ml. of water. After standing at room temperature for 2 hr. ether was added and the solution washed thoroughly with a dilute sodium bicarbonate solution. The residue, after removal of the ether, was either crystallized from aqueous acetone or chromatographed on alumina. The substance obtained from the ether-methanol (2%) eluate

(5) R. Tschesche and A. Hagedorn, *Ber.*, **68**, 1412 (1935).

(6) Y. Sato and H. G. Latham, Jr., *J. Am. Chem. Soc.*, **78**, 3150 (1956).

(7) Melting points were taken on the Kofler block and are uncorrected. Microanalyses were performed by the Institute's Analytical Service Laboratory under the direction of Dr. W. C. Alford. 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.

crystallized as plates from aqueous acetone and melted at 152–155°. It proved to be identical (melting point, mixture melting point, infrared spectrum) with III.

Conversion of V *to* III. The ethoxy derivative V (95 mg.) was dissolved in 6 ml. of aqueous acetic acid (80%) and treated in the same manner as described above for conversion of IV to III. The properties of the compound (melting point, infrared spectrum) agreed with an authentic sample of III.

Conversion of III *into* IV. III (14 mg.) was dissolved in a mixture of 1.5 ml. of methanol and 0.3 ml. of acetic acid and allowed to stand for 10 min. It was taken up in ether and the ethereal solution washed thoroughly with water, 5% sodium bicarbonate solution, and again water. The residue from the ether extract crystallized from aqueous acetone to yield plates melting at 140–143°. It was identical (melting point, mixture melting point, infrared spectrum) with IV obtained directly from the treatment of *O,N*-diacetylsolasodine with hydrochloric acid in methanol.

Conversion of III *into* V. III (18 mg.) was dissolved in a mixture of 1.5 ml. of ethanol and 0.3 ml. of acetic acid and was allowed to stand for 10 min. The product was crystallized from acetone-hexane and melted at 165–170°. It agreed in properties (melting point, rotation, infrared spectrum) with an authentic specimen of V prepared from I with hydrochloric acid in ethanol.

Conversion of V, IV *and* III *to* II. Fifty milligrams of the ethoxy derivative V was refluxed with 4 ml. of glacial acetic acid for 0.5 hr. After removal of the solvent *in vacuo* the residue was crystallized from acetone-hexane, m.p. 134–136°. It was identical in respect to melting point and infrared spectrum with an authentic specimen of II.

In a similar manner IV and III respectively were converted to II.

Oxidation of IV *and* V *to 3β-acetoxy-16β-hydroxy-5-bisnorcholenic 22 → 16-lactone* (VI). To a solution of IV (250 mg.) in 12 ml. of acetic acid there was added dropwise with stirring a solution of chromium trioxide (250 mg.) in 3 ml. of acetic acid (90%). The stirring was continued for 1½ hr. and the solution poured into ice water and extracted with ether. After the ethereal extract had been washed with water, 5% sodium bicarbonate solution, and again with water, the solvent was removed. The residue was refluxed with 10 ml. of methanolic potassium hydroxide (2%) for 40 min. partially concentrated, water added, and extracted with ether. The ethereal extract yielded 28 mg. of a neutral substance which was acetylated in the usual manner with acetic anhydride and pyridine. When this was chromatographed on alumina, the ether eluate yielded 8 mg. of a compound which was identified as slightly impure 5,16-pregnadien-20-one-3β-acetate from its infrared spectrum. The residual aqueous layer was acidified with hydrochloric acid and re-extracted with methylene chloride. Upon removal of the solvent, 62 mg. of an acidic substance was obtained. After acetylation with acetic anhydride and pyridine, the crude acetate was chromatographed on acid alumina. The ether eluate yielded 16 mg. (9%) of lactone, VI, m.p. 212–215° (acetone-hexane) $[\alpha]_D^{20}$ −90° ($CHCl_3$), $\lambda_{max}^{CS_2}$ 5.62 (lactone), 5.76 μ (acetate).

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.73; H, 9.02.

Oxidation of V in the same manner yielded the same lactone VI.

Reduction of VI *to the acetate of tigogenin lactone* (VIa). The unsaturated lactone VI (21 mg.) was dissolved in 3 ml. of glacial acetic acid and reduced in the presence of 50 mg. of 10% palladium-charcoal. With the consumption of 1 mole equivalent of hydrogen, the uptake ceased. The compound crystallized from acetone-hexane and melted at 210–213°. Its melting point, rotation, and infrared spectrum agreed with an authentic specimen of 3-acetate of tigogenin lactone.[5]

Hydrogenation of the ethoxy derivative V *to N-acetyltetrahydrosolasodine acetate* (VII). The ethoxy compound V (100 mg.) was dissolved in 4 ml. of glacial acetic acid and hydrogenated in the presence of 49 mg. of Adams catalyst. The uptake of hydrogen (2 mole equivalents) was rapid and ended in 20 min. The product was chromatographed on alumina. The ether-methanol (1%) eluate yielded needles, m.p. 139–141°, $[\alpha]_D^{20}$ −3° ($CHCl_3$). The melting point, and infrared spectrum of this substance were in agreement with *N*-acetyltetrahydrosolasodine-3-acetate[6] obtained directly from the catalytic reduction of *O,N*-diacetylsolasodine.

Anal. Calcd. for $C_{31}H_{51}O_4N$: C, 74.21; H, 10.25. Found: C, 74.41; H, 10.02.

Isomerization of I *to* II. (a) To a 5 ml. solution of methylene chloride containing hydrogen chloride gas (prepared by bubbling gaseous hydrogen chloride slowly for 3 min. into methylene chloride) there was added 110 mg. of solasodine diacetate; the reaction was allowed to stand at room temperature for 20 min. The solution was washed with 5% sodium bicarbonate solution and water and dried over anhydrous sodium sulfate. The residue, after removal of the solvent, was chromatographed on alumina. The fraction eluted with 0.5% methanol in ether yielded 99 mg. of a product melting at 129–133°. The infrared spectrum of this substance was in agreement with an authentic specimen of II.

(b) A solution of 132 mg. of solasodine diacetate in 20 ml. of dry pyridine containing approximately 0.8% hydrogen chloride was refluxed for 1.5 hr. and poured on ice. The product upon chromatography yielded 125 mg. (95%) of II, m.p. 129–134°.

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