BYPRODUCTS OF THE CONVERSION OF DIOSGENIN INTO $\Delta^{5,16}$-PREGNADIEN-3β-OL-20-ONE ACETATE

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Byproducts of the conversion of diosgenin into $\Delta^{5,16}$-pregnadien-3β-ol-20-one acetate (I) by the method described previously [1] have been investigated. Cyclopseudodiosgenin, the (22 → 16) lactones of 3β,16β-dihydroxy-Δ^5- and of 3β,16β,20β-trihydroxy-Δ^5-bisnorcholenic acid (III, IV, and V respectively) were isolated. Derivatives of the latter have been obtained.

We showed previously that the conversion of diosgenin into pseudodiosgenin acetate can proceed under mild conditions (3 h, 180°C) as long as the pseudomerization is conducted in a mixture of acetic anhydride and acetic acid. This observation was used in the industrial method of obtaining (I) from diosgenin [2, 3].

Results are reported in this communication of a study of some byproducts formed during this process and which accumulate in the alcoholic mother liquors after recrystallization of technical (I). The mother liquors were condensed, the residue was dissolved in benzene, and the benzene solution extracted exhaustively with 20% sodium hydroxide solution. About 3% (I), based on diosgenin, was isolated by crystallization from the benzene solution treated in this way and also from the mother liquor as the semicarbazone. The residues were subjected to saponification with methanolic potassium hydroxide solution. The precipitate obtained after acidification of the alkaline extracts and of the products of alkaline hydrolysis was extracted with ether, and then with chloroform. Two compounds were isolated from the ether extract. One proved to be cyclopseudodiosgenin (III). The structures of (III) and of the acetate (IIIa) obtained from it were demon-

TABLE 1. Values of Chemical Shifts (δ) in the PMR Spectra of Steroidal Lactones, Cyclohemiacetals and Their Derivatives (in ppm)

Compound	Chemical shift									Solvent
	18-CH_3 singlet	19-CH_3 singlet	21-CH_3 singlet	3-H multiplet	16-H multiplet	6-H doublet	22-H	4-H	CH_3CO	
IV	0,78	1,04	1,34[1]	3,49	4,95	5,37				$CDCl_3$
IVa	0,80	1,06	1,33	4,58	4,95	5,39			2,04 (acetoxy group)	$CDCl_3$
V	0,76	0,89	1,71	3,73	4,91	5,24				pyridine
Vb	0,88	1,07	1,82	4,62	4,97	5,39			2,05, 2,07 (2 acetoxy groups)	$CDCl_3$
VI	0,77	0,88	1,70		5,2			5,71 (multiplet)		pyridine
VII	1,03	1,04	1,58	3,75	4,95	5,38	5,18 (multiplet)			$CDCl_3$
VIIa	1,03	1,07	1,81	4,63	4,89	5,42	6,1 (singlet)		2,05, 2,07 2,14 (3 acetoxy groups)	$CDCl_3$

*Doublet.

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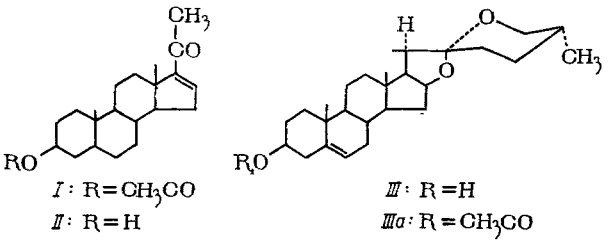
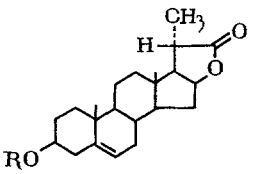
strated by analyses, by the transformation of these substances into pseudodiosgenin acetate on boiling with acetic anhydride and also on the basis of the change in optical rotation on heating them with ethanolic hydrochloric acid and conversion into diosgenin.

The structure of the second substance was established as (IV) and its acetate as (IVa) by analyses, IR, and PMR spectra. The acetate of this lactone has been described previously [4,5].

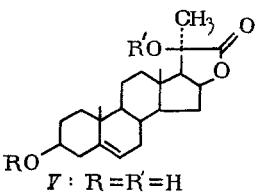


I: R=CH$_3$CO
II: R=H

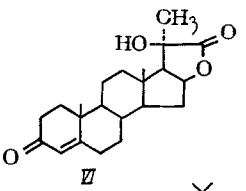
III: R=H
IIIa: R=CH$_3$CO



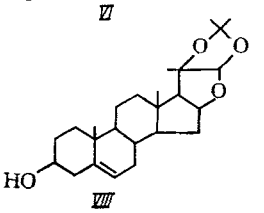
IV: R=H
IVa: R=CH$_3$CO



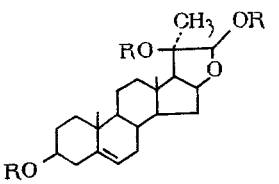
V: R=R'=H
Va: R=CH$_3$CO, R'=H
Vб: R=R'=CH$_3$CO
Vв: R=C$_6$H$_5$CO, R'=H



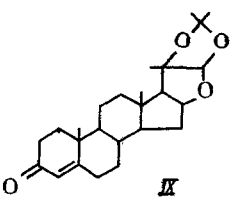
VI



VII



VIII: R=H
VIIIa: R=CH$_3$CO



IX

A crystalline substance of composition $C_{22}H_{32}O_4$, mp 309-310°, $[\alpha]_D^{20}$ −68.3° (concn. 0.5, pyridine) was isolated from the chloroform extract. Structure (V) has been assigned on the basis of analytical data, IR, and PMR spectra, and also chemical properties. There was an absorption band at 1750 cm^{-1} (lactone) in the IR spectrum of this compound and also two bands in the region of hydroxyl hydrogen stretching vibrations, i.e., near 3450 and 3300 cm^{-1}.

On acetylating (V) (acetic anhydride, pyridine at 20°, 24 h) the 3-acetate (Va) was obtained and on prolonged interaction with the same reagents (about 100 h) a mixture of diacetate (Vb) with a small amount of monoacetate was formed. These were separated by crystallization and chromatography. On interacting (V) with benzoyl chloride in pyridine the monobenzoate (Vc) was formed.

A multiplet of one proton strength was observed in the PMR spectra of (IV, IVa, V, and Vb) (see Table 1) in the 4.97-4.91 ppm region. In compounds (IV) and (IVa), the structures of which have been shown previously, this signal was assigned to the proton at C_{16}. The presence of an analogous multiplet signal in compounds (V) and (Vb), obtained for the first time, made possible the assignment of the same type of steroid γ-lactone structure to this compound.

On Oppenauer oxidation of (V) the ketolactone (VI) was obtained, which contained absorption bands at 1663 (Δ^4-3-keto), 1765 (lactone), and 3345 cm^{-1} (hydroxyl) in the IR spectrum and confirmed the presence of a tertiary hydroxyl group in (V). It follows, on the basis of PMR spectral data on (IV), (V), and (Vb) that the tertiary hydroxyl group in (V) is at C_{20}. This follows from the sizes of the chemical shifts of the C_{20} methyl group signal, which has the following values of δ: 1.34, 1.74, and 1.78 ppm respectively in the spectra of the compounds mentioned.

Such a displacement of the signal of protons towards lower field and also the change in the form of the signal in the spectra of (V) and (Vb) (singlet) compared to (IV) (doublet) shows that in (IV) the methyl group is geminal with proton and in (V) and (Vb) geminal with a hydroxy or acetoxy group.

On reducing (Vb) with lithium aluminum hydride the (22 → 16) cyclohemiacetal of 3β,16β,20β-trihydroxy-Δ^5-bisnorcholenic aldehyde (VII) was obtained, the structure of which, and of the triacetate (VIIa) obtained from it, was demonstrated by analyses and by IR and PMR characteristics.

A multiplet (sextet) signal was observed in the PMR spectrum of (VII) at δ 4.95 ppm and also a singlet at δ 5.18 ppm each having an intensity of one proton unit. The signal at δ 4.95 ppm as in compounds (IV), (IVa), (V), and (Vb) pertains to the proton at C_{16} which indicates the retention of ring E in (VII). The singlet signal with δ 5.18 ppm we have ascribed to the proton at C_{22} (in an O−CH−O grouping) which is in keeping with the formation of a cyclohemiacetal. The PMR spectrum of (VIIa) gives further confirmation of the assignments made. The proton at C_{16} retains the value of the chemical shift with δ 4.89 ppm but a singlet, which was attributed to the proton at C_{22}, is displaced significantly towards lower field on substitution of the hydroxyl group at C_{22} by an acetoxy group. [The formation of polyacetals was observed on reducing the (18 → 11β) and (18 → 20) lactones of pregnane 18-carboxylic acid with lithium aluminum hydride [6]. It was shown that the presence of a carbonyl keto, hydroxy, or ester grouping together with the lactone group was necessary for the reduction of lactones in cyclohemiacetals.]

Cyclohemiacetal (VII) readily formed an acetonide (VIII) which indicates the cis disposition of the two vicinal hydroxyl groups in its molecule. The product (IX) of Oppenauer oxidation of the acetonide contained, in its IR spectrum, an absorption band at 1687 cm^{-1} (Δ^4-3-keto). The absence of hyroxylic frequencies from the IR spectrum of this ketone indicated that the tertiary hydroxyl group (at C_{20}) takes part in the formation of acetonide.

Since, as is known, β oriented alcohols (attack at the less hindered rear side) are formed on lithium aluminum hydride reduction of steroidal carbonyl compounds, it is possible to propose a similar steric orientation for the hydroxyl group at the asymmetric center at C_{22}.

It is possible to propose the hydroxyl at C_{20} in lactone (V) as β (20 R) on the basis of studying molecular models, the ease of formation of cyclohemiacetal (VII), and the preparation from it of an acetonide.

Some byproducts of the dehydration of the diosgenin side chain have been reported previously [5, 7-9]. (IVa) was isolated, the formation of which was explained as the result of oxidation of a Δ^{22}-furostene derivative, a side product of the pseudomerization reaction of diosgenin formed under the influence of the pseudomerization catalyst viz. hydrochlorides of organic bases. The isolation of lactone (IV) by us from the reaction mixture (the pseudomerization of diosgenin was carried out in a mixture of acetic anhydride and acetic acid) made it possible to suggest that under these conditions the formation of the same byproduct, viz. a derivative of Δ^{22}-furostene, took place.

The formation of cyclopseudodiosgenin apparently takes place as a result of conversion of pseudodiosgenin acetate, remaining unchanged, under the further influence of the alkaline acidic reagents used.

Lactone (V) is seemingly formed as a product of incomplete oxidation of pseudodiosgenin acetate with chromic acid proceeding through the formation of 20α,22α-hydroxy (attack from the rear) which is then isomerized into the tertiary C_{20} alcohol which is being oxidized to the lactone. The oxidation of natural sapogenins into lactones of normal structure has been reported previously [10, 11].

EXPERIMENTAL

IR spectra were taken on a UR-10 spectrophotometer in Nujol. The PMR data which are presented in Table 1 were obtained on a 4H-100 spectrophotometer, working frequency 100 MHz. Solutions of substances were in deuterochloroform or pyridine, the standard was tetramethylsilane. All δ values are in ppm.

Melting points of substances were determined on a "Boetius" microhot-stage (GDR). Data are given for chromatography on thin layer plates of KSK silica gel, with gypsum as binder in the system benzene – methanol 100 : 7 (A) or 100 : 2 (B). Visualization was with concentrated sulfuric acid. Solutions of steroids were dried with anhydrous sodium sulfate prior to evaporation in vacuum.

$\Delta^{5,16}$-Pregnadien-3β-ol-20-one 3-Acetate (I). Preparation was from industrial mother liquors after the purification of technical (I) [12].

The residue (87.8 g) after evaporation of 1 liter isopropyl mother liquors from the purification of technical (I) (from 360 g diosgenin treated under standard conditions [3]) was dissolved in 500 ml benzene. The solution was treated with 80 ml 20% sodium hydroxide, then washed with water, with aqueous sodium bicarbonate solution, once again with water, and evaporated to dryness. After crystallization of the residue (73 g) from methanol, and then from isopropanol, 6.2-7 g (2-2.3%) (I) was obtained of mp 170-171° and $[\alpha]_D^{20}$ −34° (conc. 1, chloroform). The mother liquors (after recrystallization of the product from methanol and isopropanol) were combined and mixed with 50 ml 30% solution of potassium hydroxide in methanol. The mixture was stored for 72 h at 18-20° and then 300 ml benzene and 150 ml water were added to it. The lower layer (aqueous alcoholic alkali) was separated from the benzene, combined with the alkaline layer from the first treatment of the benzene solution, and freed from the latter by distillation in vacuum. After cooling, the alkaline solution was acidified with hydrochloric acid. The light brown solid isolated was washed with water and air dried (24.6 g).

The benzene solution of saponified products was washed with water, with 1% hydrochloric acid, with water, and evaporated to dryness in vacuum. The residue (28 g) was treated with an alcoholic solution of semicarbazide acetate. Semicarbazone (5.1 g) of mp 231° (with decomposition) was isolated. By decomposing the semicarbazone with formalin [13, 14] and recrystallizing the isolated product from methanol, 3.2 g 16-dehydropregnenolone (II) of mp 201-202° was obtained, acetylation of which gave 3.1 g (I) mp 169-170°.

Cyclopseudodiosgenin (III). The solid (24.6 g), isolated in the preparation of (I), was extracted with ether (residue 14.9 g). The ether extract was shaken with a mixture of 7% aqueous sodium hydroxide solution and isopropyl alcohol (9 : 1), separated from the alkaline layer, washed with water, with 1% hydrochloric acid, and then with water until a neutral reaction was obtained. After drying, the ether solution was concentrated to small volume. On cooling a crystalline product was precipitated and filtered off (1.55 g). After recrystallization from methanol and chromatography on a column of aluminum oxide (activity grade II) (elution with chloroform) (III) of mp 191-192° was isolated in 0.28 g yield. It gave no depression of melting point with cyclopseudodiosgenin, $[\alpha]_D^{20}$ −87.7° (concn. 0.6, dioxan). Found, %: C 77.92, 77.85; H 10.30, 10.00. $C_{27}H_{42}O_5$. Calculated, %: C 78.21; H 10.21.

In a mixture of pyridine and acetic anhydride (III) gave the acetate (IIIa) of mp 184-185° which gave no depression of melting point on admixture with a specimen of cyclopseudodiosgenin acetate. Found, %: C 76.56, 76.31; H 9.81, 9.67. $C_{29}H_{44}O_4$. Calculated, %: C 76.27; H 9.71.

According to literature data [15], it had mp 190-195°, $[\alpha]_D^{20}$ −97° (dioxan). On heating (III) or (IIIa) with acetic anhydride pseudodiosgenin,acetate of mp 98-100° was obtained. According to literature data [15], it had mp 99-101°.

On boiling (III) or (IIIa) with a 1% solution of hydrochloric acid in alcohol, diosgenin was obtained of mp 204-206°, $[\alpha]_D^{20}$ −121° (concn. 1, chloroform).

(22 → 16)-Lactone of 3β,16β-Dihydroxy-Δ^5-bisnorcholenic Acid (IV). The alkaline layer [obtained from (III)] was acidified with hydrochloric acid after being cooled. The solid was washed with water, dried, and extracted with ether. The ether layer was treated with 5% sodium bicarbonate solution, washed with water, dried, and evaporated to dryness. The residue (2.8 g) was recrystallized from 38% isopropanol, and then from methanol. This gave 0.98 g (IV) of mp 219-221°, $[\alpha]_D^{20}$ −99.9° (concn. 1, chloroform). Found, %: C 76.92, 76.65; H 9.3, 9.2. $C_{22}H_{32}O_3$. Calculated, %: C 76.71; H 9.36.

IR spectrum: 3470 (hydroxyl), 1770 cm^{-1} (lactone). PMR spectrum, see Table 1. On acetylating (IV) (pyridine-acetic anhydride) the acetate (IVa) was obtained having mp 209-211° (from methanol), $[\alpha]_D^{20}$ −94.1° (concn. 1, chloroform). Found, %: C 74.71, 74.86; H 8.93, 8.88. $C_{22}H_{34}O_4$. Calculated, %: C 74.57; H 8.87. According to literature data [5] mp 211-212°, $[\alpha]_D$ −93.7° (chloroform). IR spectrum: 1755 (lactone), 1750 and 1255 cm^{-1} (acetoxy group). PMR spectrum, see Table 1.

(22 → 16)-Lactone of 3β,16β,20β-Trihydroxy-Δ^5-bisnorcholenic Acid (V). The residue (14.9 g) obtained from the isolation of (III) was extracted with chloroform. The extract was concentrated to small volume, cooled, and the solid, a finely crystalline substance, was filtered off. From this after two recrystallizations from methanol and drying in vacuum at 100° for 6 h, 0.63 g (V) was obtained of mp 309-310°, $[\alpha]_D^{20}$ −68.3° (concn. 0.5, pyridine). Found, %: C 73.39; 73.59; H 9.02, 9.09. $C_{22}H_{32}O_4$. Calculated, %: C 73.30; H 8.94. R_f (A) 0.31. IR spectrum: 3450 (unbonded hydroxyl), 3330 (bonded hydroxyl), 1750 cm^{-1} (lactone). PMR spectrum, see Table 1.

On acetylation with a mixture of acetic anhydride and pyridine (at 20°, 100 h) the diacetate (Vb) was obtained of mp 248-249° (from methanol), $[\alpha]_D^{20}$ 96° (concn. 1, chloroform). Found, %: C 69.93, 70.11; H 8.36, 8.37. $C_{26}H_{36}O_6$. Calculated, %: C 70.24; H 8.16. IR spectrum: 1790, 1730, 1265, and 1230 (acetoxy group), 1752 cm^{-1} (lactone). R_f (B) 0.84. PMR spectrum, see Table 1. By chromatographing the methanolic mother liquor on a column of alumina of activity grade II (elution with a mixture of benzene-methanol, 99 : 1), (Va) was obtained of mp 248-248.5° (from methanol). IR spectrum: 1755 (lactone), 3400 (hydroxyl), 1730 and 1240 cm^{-1} (acetoxy group). R_f (B) 0.34. Found, %: C 71.29, 71.50; H 8.26, 8.34. $C_{24}H_{34}O_5$. Calculated, %; C 71.61; H 8.51.

On benzoylating (V) with benzoyl chloride in pyridine the monobenzoate (Vc) was obtained having mp 294-296° (from benzene), $[\alpha]_D^{20}$ −58.8° (concn. 0.36, chloroform). Found, %: C 74.82, 74.73; H 7.62, 7.53. $C_{29}H_{36}O_5$. Calculated, %: C 74.97; H 7.81.

IR spectrum: 3408 (hydroxyl), 1750 (lactone), 1718 cm^{-1} (aryl ester group). R_f (B) 0.39.

On Oppenauer oxidation of (V) the ketolactone (VI) was obtained having mp 260-262° (from methanol), $[\alpha]_D^{20}$ 0° (concn. 0.25, pyridine). Found, %: C 73.90, 73.53; H 8.34, 8.6. $C_{22}H_{30}O_4$. Calculated, %: C 73.77; H 8.43. IR spectrum: 3345 (hydroxyl), 1765 (lactone), 1663 cm^{-1} (Δ^4-3-keto). R_f (A) 0.34. PMR spectrum, see Table 1.

(22 → 16)-Cyclohemiacetal of 3β,16β,20β-Trihydroxy-Δ^5-bisnorcholenic Aldehyde (VII). A solution of 1.2 g (Vb) in a mixture of ether-benzene (1 : 1) was added to a suspension of 1.8 g lithium aluminum hydride in 150 ml ether. The mixture was stirred for 2 h at 18-20°, then heated at the boiling point for 4 h. Water (5 ml) was added to the cooled mixture, then 10% sulfuric acid until the fluid was acid, and then boiled for 30 min. The precipitate was filtered off, washed with water, and dried (0.93 g). The ether-benzene layer was washed with water, dried, and evaporated to dryness in vacuum. The residue (0.25 g) was added to the main quantity and recrystallized from chloroform, then from benzene, and dried in vacuum at 100° for 6 h. The product (VII) (0.62 g) which was obtained had mp 249-250°, $[\alpha]_D^{20}$ −42.07° (concn. 0.5, pyridine). Found, %: C 72.90, 73.03; H 9.56, 9.65. $C_{22}H_{34}O_4$. Calculated, %: C 72.89; H 9.45. IR spectrum: 3420 cm^{-1} (hydroxyl). R_f (A) 0.20. PMR spectrum, See Table 1.

On acetylating (VII) with a mixture of acetic anhydride in pyridine the acetate (VIIa) was obtained of mp 204-205° (from methanol), $[\alpha]_D^{20}$ −80° (concn. 0.25, chloroform). Found, %: C 68.96, 68.62; H 8.58, 8.50. $C_{28}H_{40}O_7$. Calculated, %: C 68.83; H 8.25. IR spectrum: 1740 and 1240 cm^{-1} (acetoxy group). R_f (B) 0.6. PMR spectrum, see Table 1.

Acetonide of (22 → 16)-Cyclohemiacetal of 3β,16β,20β-Trihydroxy-Δ^5-bisnorcholenic Aldehyde (VIII). A 2% acetone solution (12 ml) of hydrogen chloride was added to a solution of 0.7 g (VII) in dry acetone, kept for 40 min at 20°, neutralized with a 3% aqueous potassium hydroxide solution, and concentrated in vacuum. The residue was washed with warm water, filtered off, dried, and recrystallized from methanol. In this way 0.41 g (VIII) was obtained of mp 221-223°, $[\alpha]_D^{20}$ −103.9° (concn. 1, chloroform). Found, %: C 74.48; 74.45; H 9.30, 9.52. $C_{25}H_{38}O_4$. Calculated, %: C 74.58; H 9.52. IR spectrum: 3475 cm^{-1} (hydroxyl). R_f (A) 0.8.

On Oppenauer oxidation of (VIII),ketone (IX),was obtained of mp 268-269° (from methanol). Found, %: C 75.06, 74.84; H 9.14, 8.96. $C_{25}H_{36}O_4$. Calculated, %: C 74.96; H 9.06. IR spectrum: 1687 cm^{-1} (Δ^4-3-keto).

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