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STEROIDS

XXXII. A Study of The Ketalization of 16α, 17α-Epoxy-4-pregnene-3,20-dione

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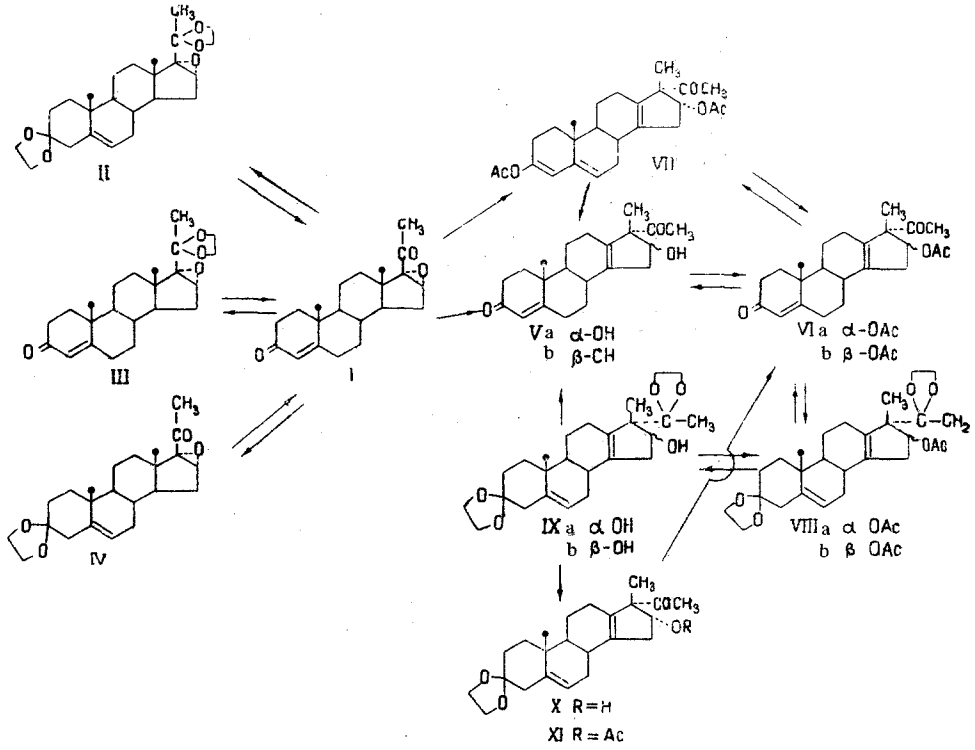
The 3,20-diketal of 16α, 17α-epoxy-4-pregnene-3,20-dione is the starting material for the preparation of 16β-alkyl derivatives of the corticosterioids [1] by the opening of the oxide ring with organometalic compounds [2,3]. The ketalization of the epoxyprogesterone (I) is carried out by the action of ethylene glycol in benzene in the presence of p-toluenesulfonic acid [4]. The low yield (~15%) of the 3,20-diketal of the epoxyprogesterone (II) is explained by the fact that the reaction takes place ambiguously (chromatography in a thin layer of silica gel shows the presence in the reaction mixture of not less than six substances according to the time of the reaction and the ratio of the reactants; data on the composition of this mixture are given below), and the isolation of (II) from the multicomponent reaction mixture is difficult. The performance of the ketalization of (I) by other methods [3, 5, 6] has not changed the general pattern of the reaction and has not given better results. The direct ketalization of (I) can form the 3,20-diketal (II), the 20-ketal (III), and the 3-ketal of the epoxyprogesterone (IV), and on the basis of the investigations of H. Herzog et al., on the ketalization of 3β-hydroxy-16α,17α-epoxy-5-pregnene-20-one [7], we may expect that (I) or its ketals (II)-(IV) will undergo the Wagner-Meerwein rearrangement.

In actual fact, the deketalization of the oily product of the reaction led to the epoxyprogesterone (I) and a mixture of isomeric 16α,β-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-e,20-diones (Va Vb) formed by the Wagner-Meerwein rearrangement. The structure of the latter was confirmed by spectroscopic and analytical data. Compounds (Va) and (Vb) may be isomeric with respect to the position of the double bond (at C_{12} or C_{13}) [7] in accordance with the mechanism of the rearrangement [8] and with respect to the configuration of the hydroxy group at C_{16}, depending upon the mechanism of the opening of the oxide ring. The acetylation of the mixture of (Va) and (Vb) gave a mixture of isomeric acetates (VIa) and (VIb) which, in contrast to the alcohols (Va) and (Vb), had identical mobilities in a thin fixed layer of silica gel, and different R_f values (Table 1). Alkaline hydrolysis of the mixture of acetates (VIa) and (VIb) led to the formation of a mixture of (Va) and (Vb). It was impossible to separate this mixture either by chromatography or by recrystallization, but the corresponding isomeric acetates (VIa) and (VIb) were obtained in the individual form. The acetate (VIa) was isolated by repeated recrystallization of the mixture of (VIa) and (VIb), while the acetate (VIb) could not be isolated from the mixture, and it was synthesized in the following way:



From the epoxyprogesterone (I) under the conditions appropriate to the Wagner-Meerwein rearrangement [8], we obtained the 3-enol acetate of the 16-acetate of 16α-hydroxy-17β-methyl-18-nor-17-iso-3,5,13-pregnatriene-3,20-

Table 1

Physicochemical Properties of Compounds (Va,b-IXa,b)

Compound	Configuration	Mp, °C	Solvent for crystallization	λ_{max}, mμ (log ε)	ν_{max}, cm^{-1}	$[\alpha]_D^{20}$, deg	R_f	Found, % C	Found, % H	Formula	Calculated, % C	Calculated, % H
(Va)	α	140.5—142	Acetone-hexane	238 (4.23)	3360, 1696, 1660	+76	0.12	76.86	8.62	$C_{21}H_{28}O_3$	76.99	8.58
		141—142		238 (4.26)	3370, 1695, 1665	+82						
(Vb)	β	134—135.5		238 (4.25)	3440, 1698, 1670	+136	0.12	77.09	8.30			
		134 - 136		238 (4.24)	3420, 1695, 1669	+136						
(VIa)	α	148.5—150		238 (4.25)	1746, 1708, 1680	+154	0.48	74.81	8.16	$C_{23}H_{30}O_4$	74.54	8.16
		149		238 (4.26)	1730, 1700, 1658	+152						
(VIb)	β	175—176	Acetone-hexane	238 (4.25)	1734, 1704, 1680	+105	0.43	74.85	8.14			
		169—171	Methanol	238 (4.25)	1734, 1708, 1675	+159						
(VIIIa)	α	131—133.5	Methanol	—	1726	—98	0.70	70.56	8.29	$C_{27}H_{38}O_6$	70.68	8.35
(VIIIb)	β	143.5—145		—	1744	—82	0.70	71.05	8.54			
(IXa)	α	128—130	Aqueous acetone	—	3540	—123	0.50	72.03	8.60	$C_{25}H_{36}O_5$	72.06	8.69
(IXb)	β	142—144	Acetone-hexane	—	3410	—135	0.33	72.06	8.88			

Note. Mixtures of the following compounds had the melting points shown: (Va) and (Vb)—122-124° C, (VIa) and (VIb)—118-120° C, (VIIIa) and (VIIIb)—120-121.5° C. In the sections for (Va,b) and (VIa,b), the physicochemical characteristics in the second lines of figures have been taken from the literature [10].

dione (VII), the structure of which was confirmed by its IR and UV spectra. Selective acid hydrolysis of (VII), leading to the elimination of the enol acetyl group and not affecting the acetyl group in position 16, gave the acetate (VIb). The other reaction product, formed in considerably smaller amounts, was a mixture of (Va) and (Vb). Raising the concentration of the hydrochloric acid during hydrolysis increased the amount of this mixture. The alkaline hydrolysis of the enol acetate (VII) also formed a mixture of the alcohols (Va) and (Vb). An attempt to obtain the isomeric alcohols (Va) and (Vb) in the individual form by the hydrolysis of the corresponding acetates (VIa) and (VIb) was unsuccessful. The saponification of the acetal group at C_{16} always gave a mixture of (Va) and (Vb). The synthesis of the alcohols (Va) and (Vb) in the individual form was effected in the following way.

Table 2

Chemical Shifts* in Compounds (V)–(IX)

Compound	H_{C_4} (s)**	H_{C_6} (m)	$H_{C_{16}}$ (tr)	H_{CH_2} (d)	H_{CH_3OAc} (s)	H_{CH_3CO} (s)	$H_{CH_3C(O)O}$ (s)	$H_{CH_3(C_{17})}$ (s)	$H_{CH_3(C_{19})}$ (s)
(Va)	5.71	—	4.11	—	—	2.09	—	1.22	1.10
(Vb)	5.70	—	4.49	—	—	2.06	—	1.12	1.12
(VIa)	5.72	—	5.13	—	1.95	2.06	—	1.17	1.11
(VIb)	5.73	—	5.45	—	2.14	2.04	—	1.03	1.13
(VII)	5.67	5.37	5.13	—	1.95	2.07	—	1.13	0.96
(VIIIa)	—	5.45	5.26	3.90	2.01	—	1.19	1.11	0.97
(VIIIb)	—	5.35***		3.84	1.99	—	1.18	0.95	0.98
(IXa)	—	5.30	4.05	3.90	—	—	1.25	0.90	1.00
(IXb)	—	5.35	4.31	3.89	—	—	1.16	0.93	0.93
(X)	—	5.36	4.13	3.89	—	2.04	—	1.17	0.96
(XI)	—	5.39	5.13	3.92	1.97	2.06	—	1.16	0.96

*Expressed in ppm relative to TMS.

**(s)–singlet, (m)–multiplet, (tr)–triplet, (d)–doublet.

***Multiplet with an intensity of two proton units.

The acetates (VIa) and (VIb) were subjected to ketalization by the above-described method, giving the 3,20-diketals of the 16-acetates of 16α- and 16β-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-diones, (VIIIa) and (VIIIb), respectively. Saponification of the acetal groups in the latter in an alkaline medium led to the formation of the isomeric 3,20-diketals of 16α- and 16β-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-diones, (IXa) and (IXb). This shows that the saponification of the acetal group in position 16 does not cause isomerization of the compounds when the carbonyl group in position 20 has ketal protection. The deketalization of (IXa) and (IXb) gave (Va) and (Vb), the acetylation of which again led to the acetates (VIa) and (VIb), respectively. The pairs of isomeric compounds (Va, b)–(IXa, b) that we obtained showed clear depressions of the melting points when mixed and had different optical activities (see Table 1).

The structure of compounds (V)–(IX) was established on the basis of spectroscopic (IR and UV) and analytical data and was confirmed by their conversion into the initial compounds [(VIIIa, b) and (VIa, b), and (IXa, b) and (VIIIa, b)]. Some differences were found in monotypical reactions in the (a) and (b) series. The saponification of (VIIIb) and the acetylation of (IXb) required more severe conditions than the same processes for (VIIIa) and (IXa), and the removal of the ketal protection on the carbonyl group in position 20 took place with greater ease for compounds (VIIIa) and (IXa) than for (VIIIb) and (IXb). Thus it was possible to isolate the 3-ketal of 16α-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-dione (X) by the chromatographic separation of a mixture of (IXa) and (X) obtained after the saponification of (VIIIa) which had been isolated from the preceding stage of ketalization without recrystallization. The structure of (X) and its acetate (XI) was established on the basis of their IR, UV, and NMR spectra. The deketalization of the 3-ketal of the 16-acetate of 16α-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-dione (XI) led to the acetate (VIa).

The question of isomerism in the two series of compounds (Va)–(IXa) and (Vb)–(IXb) was answered by means of their NMR spectra (Table 2). The presence in the spectra of the isomeric alcohols (Va) and (Vb) of a signal at ~5.70 ppm with an intensity of one proton unit and the absence of other signals in the 5–6 ppm region characteristic for vinyl protons permitted the conclusion that (Va) and (Vb) have a double bond at C_{13} and not at C_{12}, since in the latter case signals would be observed from two vinyl protons. The signals in the 5.13 and 5.45 ppm regions for the acetates (VIa) and (VIb) cannot be given to a vinyl proton because they disappear in the deacetylated compounds (Va) and (Vb) and signals appear at 4.11 and 4.49 ppm, respectively. The shifts mentioned, and also the shifts at 5.26 and 5.36 ppm for (VIIIa) and (VIIIb) and at 4.05 and 4.31 ppm for the deacetylated compounds (IXa) and (IXb) must be given to the signal of the proton at C_{16}. Consequently, compounds (Va), (VIa), (VIIIa), and (IXa) differ from compounds (Vb), (VIb), (VIIIb), and (IXb), not by the position of the double bond, but by the configuration of the hydroxy group at C_{16}. The compounds of series (a) have the signals from the protons at C_{16} in a stronger field by ~0.3 ppm than those of series (b), with the exception of (VIIIa) and (VIIIb). The signals of the protons at C_{16} in the 5.13, 4.13, and 5.13 ppm region for compounds (VII), (X), and (XI), respectively, make it possible to assign them to the (a) series. Although on the basis of the NMR spectra of (V)–(IX), it can be rigorously established that the compounds of series (a) are epimeric with the compounds of

series (b) at the C_{16} hydroxy group. Nevertheless, the data mentioned cannot assign a particular configuration of the hydroxy group to this series of compounds.

The compounds of series (a) were given the α-configuration and those of series (b) the β-configuration of the hydroxy group on the basis of the mass spectra of the two epimeric pairs of compounds (Va)–(VIa) and (Vb)–(VIb).

Table 3

Some Characteristic Peaks (% of Total Ionization) in the Mass Spectra of Compounds (Va, b) and (VIa, b)

Compound	(Va) (α–OH)	(Vb) (β–OH)	(VIa) (α–OAc)	(VIb) (β–OAc)
M^+	0.05	0.07	0.01	0.03
$\frac{M^+ - H_2O}{M^+ - AcOH}$ or	1	0.6	1.2	0.9
$\frac{M^+ - H_2O}{M^+}$ or $\frac{M^+ - AcOH}{M^+}$	20	8.5	120	30

In actual fact, in the mass spectra of the alcohols (Va) and (Vb) the ratio of the peaks $\frac{M^+ - H_2O}{M^+}$, which expresses the degree of dehydration under electron impact, is higher for the α-isomer (Va) than for the β-isomer (Vb) (Table 3), which agrees with the results given in the literature [9]. In the mass spectra of the corresponding acetates (VIa, b) an analogous rule is found in the ratio of the peaks $\frac{M^+ - AcOH}{M^+}$. At the same time, the greater intensity of the $M^+ - CH_3CO$ peak for the α-isomer (Va) shows the trans arrangement of the $COCH_3$ and OAc groups and, consequently, the α-configuration of the OAc group. In their physical characteristics, the compounds (Va, b) and their acetates (VIa, b) (see Table 1) are similar to the compounds obtained earlier from 16α,17α-epoxy-4-pregnene-3-20-dione (I) and 16β,17β-epoxy-4-isopregnene-3,20-dione [10], respectively, by the action of hydrogen fluoride on the latter. The compounds from the α-oxide were assigned the α-configuration of the hydroxy group and those from the β-oxide, the β-configuration without definite proof. The mass spectrometric investigations carried out have confirmed these assumptions.

As shown above, under acid and alkaline conditions the alcohols (Va) and (Vb) undergo epimerization at C_{16}, giving a mixture of epimers. It is possible that epimerization takes place by a retroaldolization mechanism [7, 11], since; 1) when an acetylated hydroxy group is present in position 16 isomerization under acid conditions does not take place (alkaline conditions led to the saponification of the acetal group), the enol acetate (VII) is converted into the acetate (VIa) but not into a mixture of (VIa) and (VIb); and 2) the ketal protection of the carbonyl group at C_{20} makes it possible for compounds (VIIIa) and (VIIIb) to undergo saponification of the acetal group in position 16 without the epimerization of compounds (IXa) and (IXb).

Compounds (V)–(IX) obtained by the Wagner-Meerwein rearrangement enable the composition of the mixture formed in the ketalization of (I) to be established. The mixture contains ketals of the epoxyprogesterone: the 3,20-diketal (II), (R_f 0.7), the 20-ketal (III), (R_f 0.51), and the 3-ketal (IV), (R_f 0.81) (it was impossible to isolate this in the pure state), and the rearrangement products: a mixture of (Va) and (Vb) (R_f 0.12), the 3-ketal (X) (R_f 0.21), and the 3,20-diketal (IXb) (R_f 0.33). The compounds were identified by means of thin-layer chromatography with reference samples and by the chromatographic separation of the mixture into individual fractions (A, B, C, and D) (see Experimental) containing two or three compounds and their deketalization, leading to the epoxyprogesterone (I), the alcohols (V), or mixtures of them.

Experimental

The IR spectra were taken on a UR-10 instrument in the form of mulls in paraffin oil, the UV spectra on an SF-4 spectrophotometer in ethanolic solution, and the NMR spectra on a JNM-4H-100 instrument with a standard frequency of 100 MHz in solution in deuterated chloroform with tetramethylsilane as internal standard. The mass spectra were obtained on an MKh-1303 instrument fitted with an inlet system for the direct introduction of the sample into the ion source at an electron energy of 70 eV and a temperature of 140–145° C. The NMR spectra were recorded and interpreted by Yu. N. Sheinker and L. Alekseeva, and the mass spectra by V. I. Zaretskii and V. G. Zaikina. Chromatography was performed on plates with a thin layer of silica gel of type KSK(150–200 mesh) fixed with gypsum in the chloroform–

acetone (9.5 : 0.5) system (if no other system is referred to) with subsequent detection of the substances by treatment with phosphomolybdic acid at 100° C for 5 min. Preparative chromatography was carried out on silica gel of the same type. The specific rotations were determined for 1% solutions in chloroform at 20° C. Solutions intended for evaporation in vacuum were dried with anhydrous sodium sulfate.

Deketalization. One part by weight of the substance was boiled with a 50-fold amount of aqueous acetic acid for 10–15 min. Solution was treated in two ways: a) by evaporation to dryness; b) by dilution with water, filtration of the precipitate, and washing with water.

Acetylation. 1) One part by weight of acetic anhydride was added to one part by weight of the substance in ten parts by weight of dry pyridine, and the mixture was left at room temperature for a day with subsequent working up in the usual way.

2) One part by weight of substance was boiled with 30 parts by weight of acetic anhydride for 1 hr. The solvent was evaporated off to dryness.

Alkaline hydrolysis. One part by weight of the substance was treated with 50 ml of 2% caustic potash in methanol. The solution was neutralized with acetic acid and evaporated to dryness. The residue was washed with water. Where an oil was formed, it was extracted with methylene chloride and the extract was washed with water and evaporated to dryness.

Ketalization of 16α,17α-epoxy-4-pregnene-3,20-dione (I). A mixture of 150 ml of dry benzene and 0.3 g of p-toluenesulfonic acid monohydrate was boiled for 20 min with a Dean and Stark trap. To the boiling solution were added 5 g of (I) in 50 ml of dry benzene and 20 ml of freshly distilled ethylene glycol. The solution was boiled for 5 hr and was then washed with a 1% solution of sodium carbonate; the steroids were extracted from the aqueous layer with benzene twice, and the benzene was washed with water and evaporated to dryness. The resulting oil (6.34 g), containing substances with R_f 0.81, 0.7, 0.53, 0.33, 0.21, and 0.12, was chromatographed on silica gel. The eluate was collected in three fractions:

Fraction I—benzene eluted 5.36 g of a mixture of five substances with R_f 0.81, 0.70, 0.53, 0.33, and 0.21.

Fraction II—methylene chloride eluted 0.15 g of oily substances with R_f 0.33 and 0.21 (fraction C).

Fraction III—ethyl acetate eluted 0.65 g of an oil with R_f 0.12.

The oily mixture of fraction I was treated with methanol and the precipitate that deposited was filtered off and washed with methanol. Three recrystallizations from methanol with the addition of pyridine (50 : 1) gave 0.84 g (13.5%) of the 3,20-diketal (II) with mp 183–185° C $[\alpha]_D^{20}$ −20°, R_f 0.7 and 0.6 [ethyl acetate—cyclohexane (2 : 3)]. Literature data—mp 183.5–185° C, $[\alpha]_D^{24}$ −24° [4].

The mother liquor after the separation of (II) contained three compounds (R_f 0.81, 0.70, and 0.53)—fraction A. The deketalization of fraction A led to substance (I) with mp 200–202° C, R_f 0.7 and 0.49 [ethyl acetate—cyclohexane (2 : 3)]. The deketalization of fraction C gave a mixture of substances with R_f 0.12.

The oil of fraction III (0.65 g) was crystallized from a mixture of acetone and hexane (7 : 3), giving 0.2 g of a mixture of 16α- and 16β-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-diones (Va, b) with mp 122–124° C; UV spectrum: λ_{max} 238 mμ (log ε 4.25); IR spectrum: ν_{max} 3500, 3430, 1690, 1613 cm^{-1}.

Found, %: C 76.94; H 8.44. Calculated for $C_{21}H_{28}O_3$, %: C 76.99; H 8.58.

The oily mixture (3.1 g) obtained from fraction I after the isolation of (II) was rechromatographed on silica gel. Benzene eluted 1.33 g of an oil (R_f 0.81, 0.7, 0.53, and 0.33) which crystallized on standing. Acetone was added and the precipitate was filtered off and twice recrystallized from acetone. This gave 0.25 g of the 20-ketal of 16α,17α-epoxy-4-pregnene-3,20-dione (III) with mp 195–197° C; R_f 0.53; UV spectrum: λ_{max} 242 mμ (log ε 4.53); IR spectrum: ν_{max} 1670, 1620 cm^{-1}.

Found, %: C 74.51; H 8.87. Calculated for $C_{23}H_{31}O_4$, %: C 74.15; H 8.66.

Methylene chloride eluted 0.8 g of an oil (R_f 0.53 and 0.33; fraction B.) The deketalization of this gave a mixture of (I) and (Va,b). Ethyl acetate eluted 0.85 g of an oil (R_f 0.21 and 0.12; fraction D), the deketalization of which gave a mixture of (Va) and (Vb). The deketalization of 3 g of a mixture of substances (R_f 0.81, 0.7, 0.53, 0.33, 0.21, and 0.12) was carried out by method a. The precipitate was recrystallized from methanol to give 0.51 g of (I), mp 202–204° C. The sample gave no depression of the melting point in admixture with (I).

The mother liquor was evaporated and the residue was passed in a solution of methylene chloride through a layer of silica gel (3 × 4 cm). Both methylene chloride containing 10% of ethyl acetate and ethyl acetate eluted 1.85 g of an oil. After recrystallization from acetone–hexane (7 : 3), 0.3 g of (Va,b) with mp 120–121° C was obtained.

3,16-Diacetate of 16α-hydroxy-17β-methyl-18-nor-17-iso-3,5,13-pregnatriene-3,20-dione (VII). 1) A mixture of 5 g of (I) in 300 ml of acetic anhydride and 0.3 g of p-toluenesulfonic acid was boiled for 3 hr. The solution was evaporated to dryness and the residue was passed in benzene solution through a layer of silica gel (3 × 5 cm). The benzene was distilled off to dryness and the residue was recrystallized to methanol to give 2.11 g of (VII) with mp 173–174.5° C [from methanol and acetone–hexane (1 : 3.5)]; $[\alpha]_D$ – 136° ; UV spectrum: λ_{max} 236 mμ (log ε 4.31); IR spectrum: ν_{max} 1758, 1650, 1608 cm^{-1}; R_f 0.75.

Found, %: C 72.86; H 7.56. Calculated for $C_{25}H_{32}O_5$, %: C 72.78; H 7.82.

2) A mixture of 1 g of (VIa), 20 ml of acetic anhydride, and 0.02 g of p-toluenesulfonic acid was boiled for 2.5 hr. The solvent was distilled off to dryness and the residue was chromatographed on silica gel. Benzene eluted 0.52 g of an oil which recrystallized from methanol and gave 0.3 g of (VII) with mp 172–174.5° C.

Hydrolysis of the 3,16-diacetate of 16α-hydroxy-17β-methyl-18-nor-17-iso-3,5,13-pregnatriene-3,20-dione (VII). 1) Acid hydrolysis. A boiling solution of (VII) in 150 ml of methanol was treated with 3 ml of concentrated hydrochloric acid. The solution was left at room temperature for 3 hr. After this the solvent was distilled off to dryness and the residue was chromatographed on silica gel. Benzene eluted 4.5 g of a substance with R_f 0.48. After recrystallization from methanol, 2.45 g of the 16-acetate of 16α-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-dione (VIa) was obtained (see Table 1). Methylene chloride and ethyl acetate eluted 0.5 g of a mixture of (Va) and (Vb).

2) Alkaline hydrolysis. 2.85 g of (VII) was hydrolyzed as described above. After acetylation of the mixture of (Va) and (Vb) the residue was recrystallized from methylene to give 1.4 g of a mixture of (VIa) and (VIb) with mp 110–120° C.

16-Acetate of 16β-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-dione (VIb). 1) The acetylation of 0.59 g of a mixture of (Va) and (Vb) was carried out by method 1. This yielded 0.35 g of a substance with R_f 0.43 and 0.48. Successive recrystallizations from methanol (once) and ethanol (twice) gave 0.2 g of the 16-acetate of 16β-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-dione (VIb) (see Table 1).

2) Compound (VIIIb) (0.11g) was deketalized and the oily residue (R_f 0.43) was recrystallized from methanol to give 0.05 g of (VIb) with mp 173–175° C.

3) Compound (Vb) (0.22g) was acetylated by method 2. After recrystallization from methanol, 0.12 g of (VIb) with mp 171–174° C was isolated. The samples gave no depression of the melting point with an analytical sample. Their IR spectra were identical.

16-Acetate of 16α-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-dione (VIa). 1) Obtained by the acid hydrolysis of (VII) (see above).

2) After the deketalization of 0.1 g of (XI), the oily residue (R_f 0.48) was recrystallized from methanol to give (VIa) with mp 136–139° C.

3) Compound (Va) (0.05 g) was acetylated by method 1. Compound (VIa) was isolated with mp 138–140° C (from methanol). None of the samples gave a depression of the melting point in admixture with an analytical sample.

Alkaline hydrolysis of the 16-acetate of 16α-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-dione (VIa) and the 16β-isomer (VIb). The hydrolysis of 0.55 g of (VIa) was carried out as described above. Recrystallization of the residue (R_f 0.12) from acetone–hexane gave 0.1 g of a mixture of (Va) and (Vb) with mp 120–122° C. Similarly, 0.72 g of (VIb) gave 0.2 g of (Va) and (Vb) with mp 124–125° C.

3,20-Diketal of the 16-acetate of 16α-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-dione (VIIIa). Compound (IXa) (0.5 g) was acetylated by method 2, giving 0.4 g of (VIIIa) (see Table 1).

Ketalization of the 16-acetate of 16α-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-dione (VIa). A mixture of 2.45 g of (VIa) in 125 ml of dry benzene, 5 ml of ethylene glycol, and 0.12 g of p-toluenesulfonic acid was boiled for 5 hr. After the working up described above, the oily residue, weighing 2.96 g (R_f 0.48, 0.7), was chromatographed on silica gel. Benzene eluted 2.3 g of a substance with R_f 0.7. Recrystallization of this from 80% aqueous methanol gave 2.1 g of a mixture of (VIIIa) and (XI) with mp 140–145° C, which was hydrolyzed with 2% caustic potash in methanol. The oily residue (1.91 g) was chromatographed on silica gel, and benzene eluted 1 g of a substance with R_f 0.5. After recrystallization from aqueous acetone, 0.88 g of the 3,20-diketal of 16α-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-dione (IXa) was obtained (see Table 1). Methylene chloride and ethyl acetate eluted 0.65 g of a substance with R_f 0.21. It was triturated with ether, and the precipitate was filtered off and washed with ether to give 0.2 g of the 3-ketal of 16α-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-dione (X), with mp 191–193° C (from aqueous acetone); R_f 0.21; ν_{max} 3530, 1697 cm^{-1}.

Found, %: C 74.17; H 8.44. Calculated for $C_{23}O_{32}O_4$, %: C 74.15; H 8.66.

The acetate of (X) and (XI), has mp 182–184° C (from methanol); R_f 0.7; IR spectrum: ν_{max} 1750, 1718 cm^{-1}.

Found, %: C 72.71; H 8.00. Calculated for $C_{27}H_{38}O_6$, %: C 72.43; H 8.27.

3,20-Diketal of the 16-acetate of 16β-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-dione (VIIIb). 1) A mixture of 3 g of (VIb) in 150 ml of benzene, 8 ml of ethylene glycol, and 0.15 g of p-toluenesulfonic acid was boiled for 7.5 hr with a Dean and Stark trap. After the working up procedure described above, the oily residue was triturated with ether and methanol, and the precipitate was filtered off and washed with methanol. This gave 2.6 g (72%) of (VIIIb) (see Table 1).

2) Compound (IXb) (0.19 g) was acetylated by method 2 to give 0.14 g of (VIIIb) with mp 140–143° C. The substance gave no depression of the melting point with an analytical sample.

3,20-Diketal of 16β-hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-dione (IXb). Compound (VIIIb) (2.4 g) was hydrolyzed as described above to give 2.00 g of (IX) (see Table 1).

16α-Hydroxy-17β-methyl-18-nor-17-iso-4,13-pregnadiene-3,20-dione (Va) and the 16β-epimer (Vb). Compound (IXa) (1 g) was deketalized by method a. The oily residue (R_f 0.12) was passed in ethereal solution through a layer of silica gel (3 × 5 cm). The ethereal solution was evaporated and the residue was triturated with ether, filtered off, washed with ether, and recrystallized from acetone–hexane (1 : 3.5). This yielded 0.22 g of (Va) (see Table 1). Analogously, 2 g of (IXb) gave 0.5 g of (Vb) (see Table 1).

Conclusions

The ketalization of 16α,17α-epoxy-4-pregnene-3,20-dione has been studied. The structures of the compounds formed by its direct ketalization and the compounds the formation of which are connected with the Wagner-Meerwein rearrangement have been shown.

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