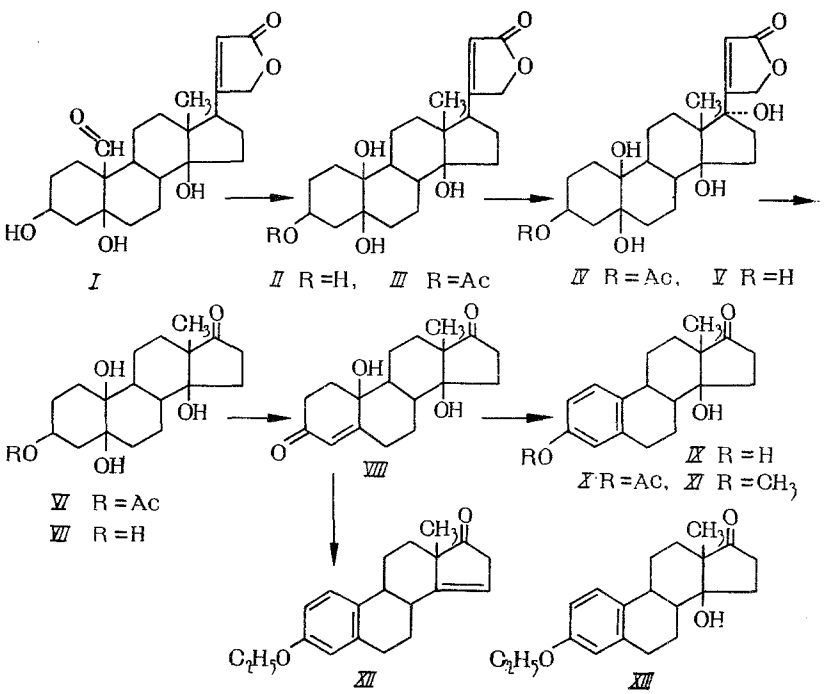
SYNTHESES OF ANDROSTANE AND ESTRONE DERIVATIVES ON THE BASIS OF STROPHANTIDIN

A. Kh. Sharipov and N. K. Abubakirov

UDC 615.357.6.012

At the present time, when the transition from cardenolides to a corticosteroid type of compounds and progestogens is well known, the application of cardenolides to the preparation of androgens and estrogens has been little studied. The oxidation of cardenolides to etianic acids, followed by the elimination of the 17-carboxylic acid group by the Barbier-Wieland reaction, is a multistep and not very convenient process [1].

In a preceding publication [2], the possible conversion of strophantidin (I) into compounds of the androstane series was shown. The autooxidation of strophantidin and the oxidation of 10β-hydroxy-19-norperiplogenin acetate (II) by selenic acid in boiling dioxane led to the formation of 3β,5β,10β,14β,17α-pentahydroxy-19-norcarden-(20:22)-olide acetate (IV). The NMR spectrum of this compound showed butenolide ring signals at 4.93 τ and 4.48 τ (I = 18, cps $C_{21}\begin{matrix}H\\H\end{matrix}$) and 3.47 τ ($C_{22}$–H), and indicates the appearance of



an additional hydroxy group. The absence of the C_{17}-proton signal at 7.3 τ, and the presence of physiological activity in the 17α-hydroxystrophantidin acetate [3], obtained under similar conditions, confirm the 17α-position of the hydroxy group introduced.

The saponification of IV by potassium bicarbonate in an aqueous methanol solution gave 3β,5β,10β, 14β,17α-pentahydroxy-19-norcarden-(20:22)-olide (V).

Compound IV served as an intermediate in the transition from cardenolides to the derivatives of 17-ketoandrostane with a 14β-hydroxy group.

Institute for Chemistry of Plant Substances, Academy of Sciences, Uzbek SSR, Tashkent. Translated from Khimiko-Farmatsevticheskii Zhurnal, No. 5, pp. 5-9, May, 1969. Original article submitted November 12, 1968.

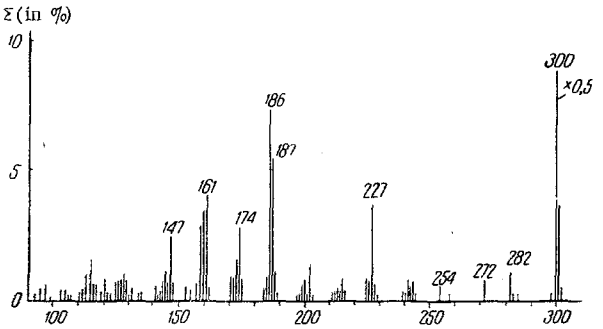


Fig. 1. Mass spectrum of 14β-hydroxyestrone methyl ester (XI).

The oxidation of IV by potassium permanganate in acetone and the hydrolysis of the product gave 3β,5β,10β,14β-tetrahydroxy-19-norandrostane-17-one (VII). The yield of this compound was 18.4% on the starting strophantidin. VII proved to be physiologically active. According to the preliminary information*, its anabolic activity determined according to Hersnberger [4], is 0.3, and the androgenic, 0.1 (M/A = 3) compared with testosterone.

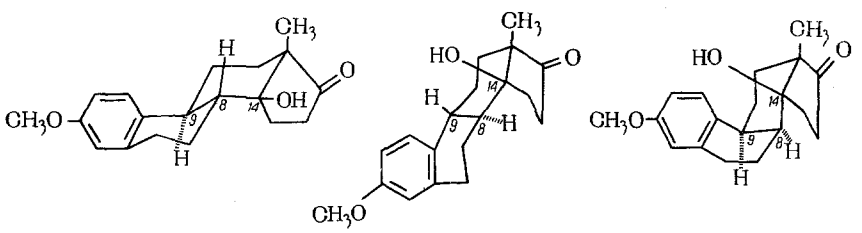
The catalytic dehydration of VII by platinum in an oxygen atmosphere gave 10β,14β-dihydroxy-19-norandrost-4-ene-3,17-dione (VIII) [5]. Tests for biological activity showed that the latter has a 0.61 anabolic activity and 0.3 (M/A = 2.03[1]) androgenic activity, compared to testosterone propionate. This indicates that VII and VIII are moderate anabolic substances.

Compound VIII proved to be a convenient intermediate for the preparation of estrone types of compounds. The C_{10}-hydroxy group in Δ^4-3-ketone is highly mobile, and even on heating with glacial acetic acid, a 14β-hydroxyestrone (IX) is formed. Aromatization of the A ring in the presence of small amounts of strong acids proceeds even more readily. Compound IX is easily obtained even at room temperature, if VIII is shaken with glacial acetic acid containing 1% of hydrochloric acid.

If the reaction time is increased, 3-acetate (X) is also formed together with hydroxyestrone. Etherification of the C_3-hydroxy group in the aromatization process under the influence of strong acids has already been noted in alcoholic solutions of 10-hydroxy-3-keto-Δ^4-steroids [6].

Compound X was synthesized directly from hydroxyestrone by the usual method, i.e., acetylation by acetic anhydride in pyridine. It was identical with a sample of X obtained from the unsaturated dione.

Methylation of X by a solution of diazomethane in ether yields the methyl ether of 14β-hydroxyestrone (XI). The hydroxyestrone ether thus obtained has the natural 8β,9α-configuration, and differs in its properties from 8α,9α- and 8α,9β-isomers of 14β-hydroxyestrone, recently synthesized by Torgov and co-workers [7]. A comparison of the mass spectra of XI† and its 8α,9β- and 8α,9α-isomers [8] shows an appreciable difference in the intensities of the characteristic peaks (see Fig. 1):



The best information on the variation in the structure of 14β-hydroxyestrone gives the dehydration peak with m/e 282 $(M-18)^+$. Dehydration under an electron impact in the isomeric 14-hydroxyestrones takes place mainly at the expense of the C_{14}-hydroxy group and the C_9-hydrogen atom, since under such conditions the 1,3-elimination of the elements of water is most probable in steroid systems [9, 10]. Besides it has been shown [8] that in analogous ketols, 50-94% of the hydrogen lost in the form of H_2O is related to the C_9-position.

The degree of dehydration is very dependent on the mutual configuration of the C_9-hydrogen atom and the C_{14}-hydroxy group, and is markedly decreased on transition from the cis-1,3-diaxial configuration (25% Σ in the case of 8α,9β,14β-isomer) to the trans-configuration (1% Σ and 4.5% Σ in the case of 8β,9α,14β-

* Tests on physiological activity of VII and VIII were carried out by T. I. Barkova (Institute of the Chemistry of Natural Compounds, Moscow).

† The mass spectrum of XI was measured by V. I. Zaretskii (Institute of The Chemistry of Natural Compounds, Moscow).

and 8α,9α,14β-isomers). The highest degree of dehydration under electron impact is characteristic of the hydroxy groups axial with respect to the ring, in this case to the ring C, which loses a hydrogen atom (4.5% Σ in the case of 8α,9α,14β-isomer) [10, 11]. Therefore, the low intensity (1%) of the dehydration peak $(M-H_2O)^+$ in the mass spectrum of XI indicates an equatorial configuration of the 14β-hydroxy group, and consequently, an 8β,9α,14β-configuration of XI.

It is known that the introduction of a 17α-alkyl substituent into androgenic rings often increases their anabolic activity, especially on per os administration. We found it interesting to introduce an alkyl radical into the 17-position of VIII. However, an attempt to protect the Δ^4-3-keto grouping by ethyl orthoformate in the presence of pyridine hydrochloride led to a 3-ethyl ether of 14β-hydroxyestrone (XIII). Another product is obtained together with ether XIII, to which we assigned the structure of 3-ethyl ether of Δ^{14}-estrone (XII).

EXPERIMENTAL

To identify and to follow the course of the reaction, thin-layer chromatography on a fixed aluminum oxide layer (7% calcium sulfate) was used in the systems benzene-methanol (7:1, 10:1) and benzene-chloroform (1:1). The chromatograms were developed by saturated solution of antimony trichloride in chloroform. The UV spectra were measured in 95% alcohol on SF-4 and EPS-3T (Hitachi) spectrophotometer and the IR spectra on the UR-10 spectrophotometer, and NMR spectra on the INM-4 H-100 with a working frequency of 100 mHz in deuteropyridine. Hexamethylenedisiloxane was the internal standard, and its signal was fixed as 10 (τ scale). The shift of the hydroxy group signals was produced by CF_3COOH.

3β,5β,10β,14β,17α-Pentahydroxy-19-norcardene(20:22)-olide (V). A solution of 1.9 g of potassium bicarbonate in 20 ml of water was added to a solution of 50 mg of IV in 15 ml of methanol. The mixture was left to stand for 24 h in a thermostat at 50°. The solution was neutralized by 2N sulfuric acid, filtered from potassium bisulfate and evaporated to dryness in vacuo. The dry residue was chromatographed on an aluminum oxide column. Thus, ~40 mg of V were isolated from fractions eluted by a mixture of chloroform-methanol (25:1). The product was recrystallized from methanol to yield compound V. Mp 251-252°; $[\alpha]_D^{20}$ +7.9 (c 0.76, methanol). UV spectrum: λ_{max} 218 mμ (log ε 4.12). IR spectrum: 3460-3380 (ν, OH), 1750, 1625 (butenolide ring) cm^{-1}. NMR spectrum: 8.88 (C_{18}–H), 5.79 (C_3–H), 4.92 and 4.48 (I = 18 cps, C_{21} ) τ values. Found, %: C 64.50; H 8.05. $C_{22}H_{32}O_7$. Calculated, %: C 64.68; H 7.90.

10β,14β-Dihydroxy-19-norandrost-4-ene-3,17-dione (VIII). A 1 g sample of VII was dissolved in 210 ml of freshly purified acetone, and stirred with a platinum catalyst (prepared by hydrogenating 1 g of PtO_2, H_2O in 160 ml of water) for two days over pure oxygen. The catalyst was filtered, the solution evaporated, and the dry residue dissolved in 30 ml of glacial acetic acid. The solution was boiled for 30 min while nitrogen was passed. The solvent was evaporated in vacuo, and the dry residue was chromatographed on an aluminum oxide column. Compound VIII was obtained in a yield of 0.63 g (67.4%) from fractions eluted by a mixture of benzene-chloroform (1:1). Mp 238-239° (from acetone); $[\alpha]_D^{20}$ +80° (c 0.81 methanol). UV spectrum: λ_{max} 234, 303 mμ (log ε 4.20, 190). IR spectrum: 3485 (ν, OH), 1730 (17, C=O), 1676 (3, C=O), 1635 (ν, C=C) cm^{-1}. NMR spectrum: 8.71 (C_{18}–H), 4.28 and 4.13 (OH at C_{10} and C_{14}), 3.6 (C_4–H) τ values. Found, %: C 71.20; H 8.07. $C_{18}H_{24}O_4$. Calculated, %: C 71.03; H 7.95.

14β-Hydroxyestrone (IX). A. A solution of 0.6 g of VIII in 45 ml of glacial acetic acid was heated for 12 h at 118° while a weak current of nitrogen was passed. The solution was concentrated in vacuo, and the residue chromatographed on an aluminum oxide column. Compound IX was obtained from fractions eluted by chloroform-alcohol (50:1) in a yield of 0.45 g (79.8%). Mp 215-218° (from chloroform-alcohol); $[\alpha]_D^{20}$ +94.9° (c 0.57, methanol). UV spectrum: λ max 281 mμ (log ε 3.40). IR spectrum: 3500, 3340, 3260 (ν, OH), 1734 (17, C=O), 1615, 1510 (Ar) cm^{-1}. Found, %: C 75.40; H 7.79. $C_{18}H_{22}O_3$. Calculated, %: C 75.49; H 7.74.

B. A solution of 0.2 g of VIII in 40 ml of glacial acetic acid containing 0.4 ml of concentrated hydrochloric acid was shaken for 25 min at room temperature. The solution was evaporated, and the residue chromatographed as described above. The yield of IX was 0.12 g (64.3%).

14β-Hydroxyestrone acetate (X). A. A 0.16 g sample of IX was dissolved in 2 ml of pyridine and 2 ml of acetic anhydride. The solution was left to stand overnight at room temperature. The solvents were evaporated in vacuo, and the residue ground with a small amount of ice water, filtered and dried. The product was crystallized from chloroform, and 0.15 g of X were obtained. Mp 202-203°; $[\alpha]_D^{20}$ +107.6° (c 0.5, C=O), 1225 (ν, C=O), 1610, 1590, 1500 (Ar) cm^{-1}. Found, %: C 73.50; H 7.45. $C_{20}H_{24}O_4$. Calculated, %: C 73.15; H 7.37.

B. A 0.2 g portion of crude VIII was dissolved in 20 ml of glacial acetic acid containing 0.3 ml of concentrated hydrochloric acid. The solution was stirred for 3h at room temperature. The mixture was concentrated in vacuo, the residue chromatographed on a thin layer of silica gel. The product (0.13 g) was isolated from the fractions eluted by chloroform-benzene (1:1, 5:1), and was identical with X in its melting point, rotation, and passage through the chromatogram. NMR spectrum: 8.75 (C_{18}−H), 6.41 (CH_3-acetate), 4.17 (OH at C_{14}), 3.35 (I = cps, C_4−H), 3.20 (I_1 = 8 cps, I_2 = 3 cps, C_2−H), 2.82 (I = 8 cps, C_1−H) τ values.

Methyl Ether of 14β-Hydroxyestrone (XI). A 0.04 g sample of IX was dissolved in 5 ml of a mixture of chloroform and alcohol (2:1), and 50 ml of an ether solution of diazomethane added. The mixture was left to stand for 2 days at room temperature. The solution was evaporated, and the residue chromatographed on an aluminum oxide column. Compound XI (25 mg) was obtained from the fractions eluted by benzene-chloroform (1:5). Mp 162-163° (from benzene); $[\alpha]_D^{20}$ +88.3° (c 0.41, chloroform). UV spectrum: λ max 280, 285 mμ (log ε 3.39, 3.34). IR spectrum: 3505 (ν, OH), 1736 (17, C=O), 1620, 1590, 1516 (Ar), 1245 (Ar−O−C) cm^{-1}. Found, %: C 76.10; H 8.22. $C_{19}H_{24}O_3$. Calculated, %: C 75.97; H 8.05.

Ethyl Ethers of 14β-Hydroxyestrone (XIII) and Δ^{14}-Estrone (XII). A mixture of 0.3 g of VIII, 4 ml of ethyl orthoformate, 0.2 g of pyridine hydrochloride in 50 ml of dry thiophene-free benzene and 2 ml of absolute alcohol was refluxed on a water bath for two and a half hours. The more volatile solvents were evaporated in vacuo. The residue was dissolved in 100 ml of chloroform, washed with water, and dried over sodium sulfate. The solution was evaporated to dryness. The residue was chromatographed on an aluminum oxide column and eluted by diethyl ether. First, compound XII was eluted. $C_{20}H_{24}O_2$, mp 101-102° (from methanol); $[\alpha]_D^{20}$ +287° (c 1.12, chloroform). IR spectrum: 3070, 3037 (Ar, or ν−CH), 1746 (17, C=O), 1647 (ν, C=C), 1610, 1583, 1510 (Ar), 1240 (Ar−O−C) cm^{-1}. NMR spectrum in CCl_4: 8.94 (C_{18}−H), 8.68 (I = 7 cps, CH_3-ethoxy group), 7.20 (C_{16} ), 6.13 (I = 7 cps, CH_2-ethoxy group), 4.50 (C_{15}−H), 3.2 (Ar) τ values. The yield of XIII, $C_{20}H_{26}O_3$, was 0.16 g, mp 214-215° (from methanol); $[\alpha]_D^{20}$ +108 (c 0.91, chloroform). UV spectrum: λ max 222, 282, 288 mμ, (log ε 3.95, 3.30, 3.30). IR spectrum: 3425 (ν, OH), 1722 (17, C=O), 1611, 1575, 1505 (Ar), 1250 (Ar−O−C) cm^{-1}. NMR spectrum: 8.82 (I = 7 cps, CH_3-ethoxy group), 8.75 (C_{18}−H) 6.16 (I = 7 cps, CH_3-ethoxy group), 4.15 (OH at C_{14}), 3.32 (I = 3 cps, C_4−H), 3.17 (I_1 = 8 cps, I_2 = 3 cps, C_2−H), 2.81 (I = 8 cps, C_1−H) τ values.

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