SYNTHESES BASED ON STROPHANTHIDIN

II. Synthesis of 3β, 5β, 10β, 14β-Tetrahydroxy-19-norandrostan-17-one

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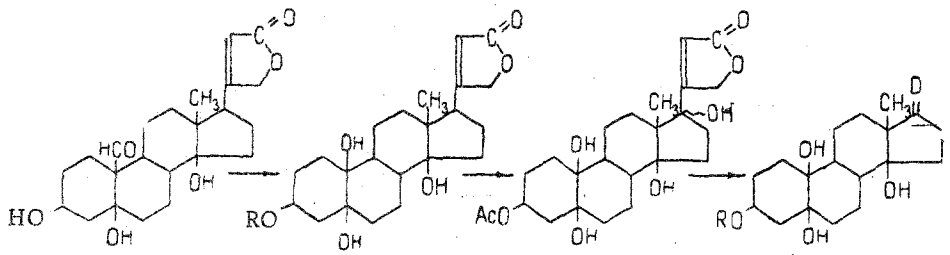
In a preceding communication [1] we showed the possibility of converting strophanthidin into 19-nor-11-deoxycorticosterone and 19-norprogesterone. For this purpose, the lactone ring of strophanthidin was converted by ozonization into an α-ketol chain and the aldehyde group in position 19 into a carboxyl group which was then easily eliminated.

We have attempted to destroy the lactone ring of strophanthidin completely in order to obtain 17-keto compounds. The latter can be used for the synthesis of estrogens or androgens with anabolic activity. As is well known, in alcoholic solutions strophanthidin (I) readily undergoes autoxidation under the action of atmospheric oxygen [2] with the formation of strophanthidinic acid [3]. However, in concentrated acetonic solution [4] the main product of autoxidation is 10β-hydroxy-19-norperiplogenin (II).

The methods of obtaining 17-ketones from cardiac aglycones via the products of ozonization or oxidation with potassium permanganate have several stages. In our opinion, oxidation with selenium dioxide, first used for the degradation of digitoxigenin [5] may be an interesting method suitable for this purpose. By selecting suitable conditions for the hydroxylation of 10β-hydroxy-19-norperiplogenin acetate (III) with selenious acid in boiling dioxane, we have obtained the 17-hydroxy product (IV) with a yield of 63–67%.



The presence in the UV spectrum of this compound of a maximum at 217 mμ (alcohol) and at 240 mμ (concentrated sulfuric acid) [6] and the presence in the UV spectrum of bands at 1750 and 1615 cm^{-1} show that the lactone ring has remained unattacked.

The tertiary nature of the hydroxy group introduced follows from the fact that compound (IV) is recovered unchanged after ordinary acetylation with acetic anhydride in pyridine. It was of interest to study how the additional hydroxy group affects the molecular rotation. For digitoxigenin acetate and its 17α-hydroxy derivative the increment due to an added hydroxy group was +585° [5], while for compounds (III) and (IV) the difference between the molecular rotations was −127°. Consequently, it is not excluded that under the conditions that we selected the introduction of a hydroxy group is accompanied by a change in the configuration of the lactone ring associated with a Walden inversion at the asymmetric C_{17} atom.

The oxidation of compound (IV) with potassium permanganate in acetone gave 3β, 5β, 10β, 14β-tetrahydroxy-19-norandrostan-17-one 3-acetate (V). The IR spectrum of this substance lacked the bands characteristic for a butenolide ring and exhibited an intense band at 1714 cm^{-1} corresponding to a keto group in a 5-membered ring.

The final product, 3β, 5β, 10β, 14β-tetrahydroxy-19-norandrostan-17-one (VI) was obtained by the hydrolysis of the acetate (V) with sodium hydrogen carbonate in aqueous methanolic solution.

Experimental

Thin-layer chromatography on a fixed layer of alumina (7% of gypsum) in a benzene–methanol (10: 1) system was used to identify the substances and follow the course of the reactions. The chromatograms were revealed with a saturated solution of antimony trichloride in chloroform or with iodine vapor. The melting points were determined in capillaries. They are given without correction for the emergent mercury thread.

10β-Hydroxy-19-norperiplogenin (II) from strophanthidin (I). This substance, obtained by a published method [4],

had mp 133–135°C/226–227°C (from methanol), $[\alpha]_D^{20}$ +35.4° (c 1.75; methanol). IR spectrum: 3400 (OH), 1780, 1745, 1630 (butenolide ring) cm^{-1}. Literature data: mp 130–135°C/205–218°C, $[\alpha]_D^{20}$ +33.2° (c 0.529; methanol) [4].

10β-Hydroxy-19-norperiplogenin 3-acetate (III). Compound (II) was acetylated with acetic anhydride in pyridine at room temperature. This gave a substance with mp 263–264°C (from methanol), $[\alpha]_D^{20}$ +48.1° (c 1.50; chloroform). Literature data: mp 261–275°C (from methanol), $[\alpha]_D^{20}$ +41.7° (c 0.527; chloroform) [4].

3β, 5β, 10β, 14β, 17α-Pentahydroxy-19-norcard-20(22)-enolide 3-acetate (IV). A solution of 18 g of selenious acid in 10 ml of water was added to 720 ml of freshly purified dioxane, and this was followed by 6 g of the acetate (III). The mixture was boiled for 45 hr. Then the solution was concentrated in vacuum. The dry residue was dissolved in 1 *l* of a mixture of chloroform and methanol (4:1), and the solution was neutralized with sodium carbonate, washed with water, dried with sodium sulfate, and evaporated to dryness.

After crystallization from chloroform–methanol (1:1), 3.9 g of the 17-hydroxycardenolide (IV) was obtained with mp 283–285°C, $[\alpha]_D^{20}$ −25.8° (c 2.02, pyridine). UV spectrum: λ_{max} 217 mμ (log ε 4.16) in alcohol; 240, 435, 495 mμ (log ε 4.19, 3.62, 3.48, respectively) in concentrated sulfuric acid. IR spectrum: 3540, 3485 (OH), 1750, 1615 (butenolide ring), 1730 (C=O), 1275 (C–O–C) cm^{-1}.

Found, %: C 63.80; H 7.98. Calculated for $C_{24}H_{34}O_8$, %: C 63.97; H 7.60.

3β, 5β, 10β, 14β-Tetrahydroxy-19-norandrostan-17-one 3-acetate (V) from the 17-hydroxycardenolide (IV). 2 g of finely ground potassium permanganate was added to a solution of 2 g of the 17-hydroxycardenolide (IV) in 750 ml of freshly purified acetone, and the mixture was heated with stirring to 50–52°C until it became decolorized. Then another 2.5 g of potassium permanganate was added in small portions. The reaction was stopped when a sample on a thin-layer chromatogram showed the absence of the starting material. The mixture was concentrated in vacuum. The residue was dissolved in 50 ml of 10% sulfuric acid and the solution was exhaustively extracted with chloroform–methanol (2:1).

The chloroform-methanol extract was washed with sodium carbonate solution and water, dried with sodium sulfate and evaporated to dryness. The residue (1.35 g) was chromatographed on a column of alumina (Brockmann activity grade 2–2.5). The column was eluted first with benzene and then with benzene containing a gradually increasing concentration of chloroform. The fraction eluted with benzene–chloroform (1:1) and with chloroform gave, after recrystallization from methanol, 1.05 g of the acetate of the 17-ketone (V) with mp 180–181°C, $[\alpha]_D^{20}$ +32.0° (c 2.69; methanol). IR spectrum: 3470 (OH), 1735 (C=O), 1265 (C–O–C), and 1714 (C = O at position 17) cm^{-1}.

Found, %: C 65.39; H 8.32. Calculated for $C_{20}H_{30}O_6$, %: C 65.55; H 8.25.

3β, 5β, 10β, 14β-Tetrahydroxy-19-norandrostan-17-one (VI) from the acetate (V). 3 g of the acetate (V) in 330 ml of methanol was mixed with 7.5 g of potassium hydrogen carbonate in 120 ml of water. The solution was kept at 37°C for 2 days and was then exhaustively extracted with chloroform–methanol (3:1). The extract was neutralized, washed with water, dried with sodium sulfate, and concentrated in vacuum. The residue crystallized on treatment with chloroform. Yield 2.6 g. The 17-ketone (VI) had mp 225–226°C (from methanol), $[\alpha]_D^{20}$ +46.9° (c 0.77; methanol). IR spectrum: 3410 (OH) and 1730 (C=O) cm^{-1}.

Found, %: C 67.30; H 8.69. Calculated for $C_{18}H_{28}O_5$, %: C 66.64; H 8.70.

Summary

With strophanthidin as starting material, 3β, 5β, 10β, 14β-tetrahydroxy-19-norandrostan-17-one has been obtained by a five-stage synthesis.

REFERENCES

1. M. B. Gorovits and N. K. Abubakirov, DAN SSSR, 136, 1082, 1960; ZhOKh, 34, 2456, 1964.
2. R. Mauli, Ch. Tamm, and T. Reichstein, Helv. Chim. Acta., 40, 284, 1957; W. Kreis, Ch. Tamm, and T. Reichstein, Helv. Chim. Acta, 40, 593, 1957.
3. M. B. Gorovits, F. S. Khristulas, and N. K. Abubakirov, ZhOKh, 31, 1381, 1961.
4. J. Binkert, E. Angliker, and A. von Wartburg, Helv. Chim. Acta., 45, 2122, 2139, 1962; A. von Wartburg, Helv. Chim., Acta, 46, 591, 1963.
5. N. Danieli, Y. Masur, and F. Sondheimer, Tetrah. Lett., 26, 1281, 1962.
6. K. Repke and S. Kleschewski, Arch. exp. Path. Pharmac., 239, 131, 1960; S. D. Nikonovits and N. K. Abubakirov, ZhOKh, 34, 2658, 1964.

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