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Abstract

Full Text

Chemistry

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A NEW SYNTHESIS OF 19-NOR-11-DEOXYCORTICOSTERONE ACETATE

(Presented by Academician M. M. Shemyakin, 6 IX 1960)

19-Nor-11-deoxycorticosterone acetate was first synthesized by Ehrenstein ([1]) from strophanthidin, but the amorphous product, evidently consisting of stereoisomers, possessed no biological activity. Later, another group of investigators ([2], [3]) carried out the synthesis of 19-nor-11-deoxycorticosterone acetate starting from 19-nor-17-ethynyltestosterone. The substance obtained proved to be twice as active as the natural hormone. Barber and Ehrenstein ([4]), also on the basis of strophanthidin, synthesized 19-nor-11-deoxy-10 ϵ, 14 β, 17 α-corticosterone. As is characteristic of all corticosteroids of the 17 series with cis fusion of rings C and D, the synthesized compound did not possess any appreciable mineralocorticoid action.

On the basis of strophanthidin we have carried out a new synthesis of 19-nor-11-deoxycorticosterone acetate with a configuration corresponding to that of natural 11-deoxycorticosterone.

The lactone ring of strophanthidin was converted into an α-ketol side chain by ozonization. In cardiac aglycones this reaction is usually ([5], [6]) carried out in three stages. The ozonide formed in the first stage is reduced with zinc dust in acetic acid to the ester of glyoxalic acid. The latter, under the action of potassium bicarbonate in aqueous methanol, is saponified to the ketol. The side chain at C_{17} retains the β-orientation, although there are data ([7]) indicating that under alkaline hydrolysis the possibility of its isomerization is not excluded. Under mild acid hydrolysis isomerization (see ([8])) does not occur.

In our experiments the process of converting the lactone ring (I) into the α-ketol side chain (V) was practically carried out in one stage. A solution of strophanthidin (VI) in acetone was ozonized at $-72°$ until a blue color appeared. The acetone was evaporated at room temperature, the residue was dissolved in aqueous ethanol and left for slow evaporation at 36–37° for 2–3 days. Apparently, the following reactions occur successively under these conditions: decomposition of the ozonide (II) with formation of the ester of glyoxalic acid (III), oxidation of the aldehyde group of glyoxalic acid to the carboxyl group, and spontaneous hydrolysis of the resulting acid ester of oxalic acid (IV) to the ketol (V). That the process proceeds in just this way is confirmed by the fact that, in the mother

SovietRxiv

Reaction scheme showing conversion of strophanthidin lactone ring (I) through ozonide (II), glyoxalic ester (III), oxalic acid ester (IV), to ketol (V).

Figure 1: Reaction scheme showing conversion of strophanthidin lactone ring (I) through ozonide (II), glyoxalic ester (III), oxalic acid ester (IV), to ketol (V).

Reaction scheme: conversion of (VI) through (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI) to (XVII) 19-nor-11-deoxycorticosterone acetate.

Figure 2: Reaction scheme: conversion of (VI) through (VII), (VIII), (IX), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI) to (XVII) 19-nor-11-deoxycorticosterone acetate.

liquor after separation of the ketol, oxalic acid was detected and identified in the form of its anilide.

Simultaneously, either during ozonization (strophanthidin is already readily oxidized in air to strophanthidinic acid), or during oxidation of the aldehyde group of glyoxalic acid, the aldehyde group at C_{10} is oxidized to a carboxyl group, so that the final product of ozonization is $3\beta, 5, 14, 21$-tetraol-20-OH-14-isopregnane-19-carboxylic acid $C_{21}H_{32}O_7$ (VII), m.p. 216–217° and $[\alpha]_D^{21} = +64.8^\circ \pm 1^\circ$ ($C = 2.59\%$ in methanol). Yield 68–70%.

With acetic anhydride in pyridine, the tetraoxyketo acid (VII) obtained gives the diacetate (VIII), m.p. 208–209° and $[\alpha]_D^{22} = +40.2^\circ \pm 0.5^\circ$ ($C = 1.66\%$ in methanol).

At the second stage of the synthesis, dehydration of the hydroxyl group at C_{14}, carried out by heating substance (VII) with a 1% solution of hydrogen chloride in methanol, led to the amorphous product (X). At the same time, the formation of a small amount (1–1.5%) of another neutral product, $C_{21}H_{30}O_6$ (IX), m.p. 265–268° and $[\alpha]_D^{28} = +164.5^\circ \pm 2.5^\circ$ ($C = 1.48\%$ in pyridine), was observed; this product apparently is the 19,8-lactone of $3\beta, 5, 8, 21$-tetraol-20-OH-14-pregnane-19-carboxylic acid and has a structure analogous to the lactone of strophanthidinic acid (*), as well as to the lactone obtained under similar conditions in the dehydration of $3\beta, 5, 14$-triol-21-nor-$14\beta, 17\alpha$-pregnane-19,20-dicarboxylic acid ([4,10]).

Acetylation of the trioxyketo acid (X) was carried out in two ways: with an equimolecular amount (more precisely, 1.25 g-mol) of acetic anhydride

and an excess of acetic anhydride. In both cases the acetylation products were amorphous. On testing by partition chromatography (system: chloroform—formamide; developer—alkaline solution of 3,5-dinitrobenzoic acid), the substance obtained by exhaustive acetylation was less polar and gave, on the paper chromatogram, a spot situated closer to the front ($R_f = 0.88 \pm 0.03$) than the product of incomplete acetylation ($R_f = 0.69 \pm 0.02$). Consequently, the sub-

stance obtained with an excess of acetic anhydride is a diacetyl derivative and corresponds to structural formula (XII). The other acetyl derivative must be a monoacetate, and, taking into account that in selective acetylation the primary hydroxyl at C_{21} is acetylated first[5], it should be assigned structure (XI).

Hydrogenation of the trioxoketo acid (X) in acetic acid over platinum gave crystalline compound (XIII), $C_{21}H_{34}O_6$, with m.p. 235-237° and $[\alpha]_D^{18} = 50.0° \pm 1.5°$ ($C = 1.40\%$ in methanol). Under analogous conditions, the monoacetyl derivative (XI) gave crystalline substance $C_{23}H_{36}O_7$ (XV), with m.p. 198-200° and $[\alpha]_D^{28} = +129.1° \pm 2°$ ($C = 1.27\%$ in methanol). The yield, calculated on the tetraoxoketo acid (VII), was 12%. In each case about 2 g-moles of hydrogen were consumed in the hydrogenation. This indicates that, along with reduction of the double bond at C_{14} and C_{15}, the ketone group at C_{20} is also reduced. Since hydrogenation of $\Delta^{14,15}$-steroids with β-configuration at C_{17}, as Plattner, Ruzicka, and co-workers[11] have shown, leads to a trans-configuration of rings C and D, it must be assumed that a similar transformation occurred in the present case as well.

The tetraoxyketo acid (XIII) with an excess of acetic anhydride gives the triacetate $C_{27}H_{40}O_9$ (XIV), with m.p. 171-172° and $[\alpha]_D^{18} = +60.9° \pm 2.5°$ ($C = 1.51\%$ in methanol). Acetylation of compound (XV) likewise gave the triacetate $C_{27}H_{40}O_9$ (XVI), with m.p. 209-210° and $[\alpha]_D^{28} 106.9 \pm 2.5°$ ($C = 1.44\%$ in methanol). It is noteworthy that the constants of triacetate (XIV) do not coincide with those of triacetate (XVI). Obviously, the reason is epimeric hydroxy compounds at C_{20}. It is difficult to judge their structure. On the basis of the difference in molecular rotations between the oxy steroids themselves and their acetyl derivatives[7,12,13], one can only assume that at C_{20} triacetate (XIV) has the β-configuration, and compound (XVI) the α-configuration.

The final conversion to 19-nor-11-deoxycorticosterone acetate (XVII) includes oxidation of the secondary hydroxyl groups at C_3 and C_{20} to ketone groups, dehydration of the tertiary hydroxyl group at C_5, and cleavage of the carboxyl group at C_{10}. Practically all of this is achieved in one stage by oxidation of compound (XV) with chromic anhydride and heating the crude oxidation product in glacial acetic acid. The yield, calculated on compound (XV), is 68%. At this stage the decarboxylation process proceeds readily. In syntheses using strophanthidin it was usually carried out by heating the substance in high vacuum[1] or by treatment with Girard reagent[4,14]. It does not seem possible to give a satisfactory explanation of the decarboxylation mechanism in the present case. It may only be noted that elimination of carbon dioxide occurs only after an α,β-unsaturated ketone group, polarizing the carbon-carbon bond between C_{10} and C_{19}, has entered the molecule. Therefore it cannot be excluded that here we are dealing with one of the varieties of oxidative-hydrolytic transformations[15].

The 19-nor-11-deoxycorticosterone acetate $C_{22}H_{30}O_4$ synthesized by us is a crystalline substance with m.p. 172-173° and $[\alpha]_D^{27} = +144.7° \pm 1.5°$ ($C = 1.19\%$ in chloroform). The IR spectrum is characterized by the following principal frequencies: 1622, 1667, 1728 cm^{-1}. Absorption in the ob-

SovietRxiv

hydroxyl groups is absent. According to literature data, 19-nor-11-deoxycorticosterone acetate, synthesized from 19-norandrostendione ([2,3]), has m.p. 173–174° and $[\alpha]_D = +150°$ (in chloroform).

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