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TRANSFORMED STEROIDS.

121. SYNTHESIS OF THE δ-LACTONE OF 3β-ACETOXY-16α-HYDROXY-6-OXO-24-NOR-5α-CHOL-17(20)-EN-23-OIC ACID

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The synthesis of the $\Delta^{17(20)}$-16α analog of natural chiogralactone is described. Attempts to introduce a 6-oxo group directly into the δ-lactone proved unsuccessful, since the first stage — saponification — took place with the formation of three products: the 3-hydroxy-δ-lactone, the 3-hydroxy-$\Delta^{20(22)}$-lactone, and the 15,17(20)-dienoic acid. The synthesis of the desired compound was effected from the ethyl ester of the 5,16-dienoic acid by the scheme 3-acetate→3-tosylate→6-hydroxy-3α,5α-cyclosteroid→6-oxo-3α,5α-cyclosteroid→6-oxo-5αH-δ-lactone. It has been shown that the cyclopropane ring in the 3α,5α-cyclosteroid δ-lactone is extremely stable under the conditions of acid treatments.

The aim of the present investigation was the synthesis of the 5αH-6-oxo-δ-lactone (VIII), the $\Delta^{17(20)}$-16α analog of natural chiogralactone [1]. An attempt to introduce a 6-oxo group directly into the lactone (I) via the 3α,5α-cyclosteroid showed that even in the first stage — saponification of the 3-acetoxy grouping in (I) the reaction did not take place unambiguously. Depending on the conditions (aqueous methanolic potash, sodium carbonate, 20°C, boiling), three products were formed: the $\Delta^{17(20)}$-3-hydroxylactone (IIa), the $\Delta^{20(22)}$-3-hydroxylactone (IIb), and the 15,17(20)-dienoic acid (IIIa). The structure of (IIa) was shown by its re-acetylation to (I); in the mass spectrum of the δ-lactone (IIb) there is an intense fragment (m/z = 111) which is characteristic for homoallyl cleavage at the C_{13-17}—C_{15-16} bonds. The acid (IIIa) was characterized in the form of the methyl ester (IIIb). It is formed as the result of the alkaline opening of the δ-lactone ring and the ready dehydration of the C_{16}-allyl alcohol on acid treatment. The positions of the double bonds in the ring and the side chain of (IIIb) were shown by comparing its UV spectrum (λ_{max} at 240 nm) with the spectra of the 16,20(22)-dienoic acids and their esters which we have obtained previously, in which λ_{max} is 270 nm, and also by the positions of the signals from the vinyl protons in the PMR spectrum (in a stronger field than those from the 16,20-(22)-dienes) [2, 3].

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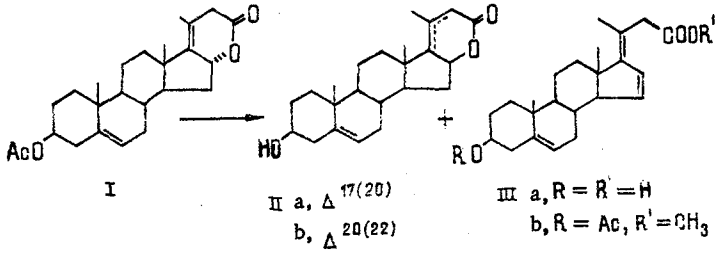
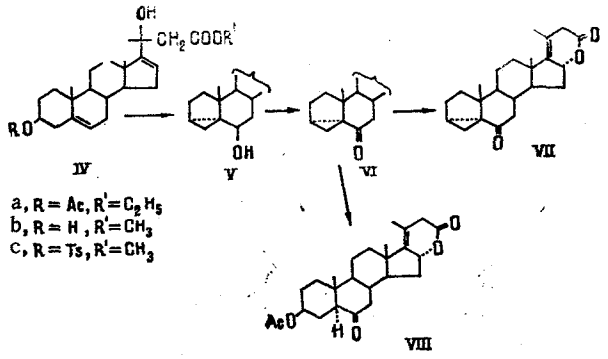


Scheme 1

The desired δ-lactone (VIII) was synthesized from the ethyl ester of the 5,16-dienoic acid (IVa) [3]. Using a scheme developed previously [4], the acetate (IVa) was transesterified to form the tosylate (IVc), which was then converted into the 6-hydroxy-3α,5α-cyclosteroid (V). The oxidation of (V) with CrO_3 in pyridine led smoothly to the 6-oxosteroid (VI). The subsequent treatment of (VI) in an acid medium (CH_3COOH–H_2SO_4) caused the cyclization of the side chain to form the δ-lactone (VII), as was shown by the mass spectrum (presence of a fragment with m/z 125 formed as the result of the cleavage of the C_{13-17}–C_{14-15} bonds [4]) and by the forms and positions of the signals in the PMR spectrum from the C_{21}–CH_3 and C_{16}–H protons. The cyclopropane ring in the i-steroid (VII) unexpectedly proved to be extremely stable, and only under severe conditions (prolonged boiling in CH_3COOH containing H_2SO_4) was it possible to obtain the 5αH-6-oxolactone (VIII), together with which a considerable amount of unidentified products was formed, obviously through the transformation of ring A. The δ-lactone (VIII) obtained differed from the natural phytosteroid chiogralactone by the presence of the 17(20) double bond and by the configuration at C(16).



Scheme 2

EXPERIMENTAL

Melting points were determined on a Kofler block. IR spectra were taken on a UR-10 spectrometer, and mass spectra on a Varian MAT CH-6 mass spectrometer with direct introduction of the samples into the ion source at an ionizing voltage of 70 V. PMR spectra were measured on a Tesla BS 497 instrument (internal standard HMDS) in $CDCl_3$. For TLC we used 5/40 mμ silica gel containing 13% of gypsum. The mixture was separated on columns containing 40/100 mμ SiO_2 in an atmosphere of N_2.

Saponification of the δ-Lactone of 3-Acetoxy-16α-hydroxy-24-norchola-5,17(20)-dien-23-oic acid (I). A. A solution of 150 mg of the lactone (I) in 15 ml of CH_3OH was treated with 0.25 ml of a 10% solution of K_2CO_3 in aqueous CH_3OH (1:1), and the mixture was left at 20°C for 24 h. Then it was neutralized with 2% HCl and was partially evaporated. The residue was diluted with water (30 ml) and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated. After chromatography on a column of SiO_2 with elution by ether, the following fractions were isolated:

1) 3β-Hydroxy-24-norchola-5,15(16),17(20)-trien-23-oic acid (IIIa) (40 mg); mp 184-186°C (from ether); IR spectrum (ν, cm^{-1}): 1050, 1240, 1580, 1620, 1700, 3345. UV spectrum (in ethanol; λ_{max}, nm): 240 (ε 9,700). Mass spectrum (m/z): 356 (M), 338 (M − 18), 312 (M − 44), 297 (M − 59). After the esterification of 100 mg of (IIIa) with CH_2N_2 (from 100 mg of methylnitrosourea and 0.36 ml of 40% KOH in 25 ml of ether) and acetylation of the

resulting product (130 mg in 3 ml of C_5H_5N and 0.8 ml of $(CH_3CO)_2O$), 80 mg of methyl 3β-acetoxy-24-norchola-5,15,17(20)-trien-23-oate (IIIc) was obtained in the form of an oil with R_f 0.55 (ether–hexane (1:1)). NMR spectrum (δ, ppm): 0.9-1.0 s (6 H, 18-CH_3, 19-CH_3), 1.9 g (6 H, acetate and 21-CH_3), 3.5 s (3 H, OCH_3), 4.43 m (1 H, 3-H), 5.32 (2 H, 6-H, CH=CH), 5.5 d (1 H, CH=CH, J 2 Hz);

2) 15 mg of the 3-hydroxylactone (IIa), mp 200-203°C (from ether). IR spectrum (ν, cm^{-1}): 1050, 1720, 3440, 3545. Mass spectrum (m/z): 356 (M), 338 (M − 18), 312 (M − 44), 297 (M − 59), 125 ($C_7H_9O_2$); and

3) 40 mg of the 3-hydroxy-$\Delta^{20(22)}$-lactone (IIb), mp 235-236°C (from ether). IR spectrum, (ν, cm^{-1}): 1065, 1680, 3445. Mass spectrum (m/z): 356 (M), 338 (M − 18), 323 (M − 15 − 18), 111 ($C_6H_7O_2$).

The re-acetylation of (IIa) gave a product identical according to its R_f value with the lactone 3-acetate (I).

B. When the 3-acetate (I) was subjected to similar treatment for 10-18 h, in addition to the saponification of the acetoxy group and the formation of a mixture of 3-hydroxylactones (TLC), some unchanged lactone (I) remained.

C. When 500 mg of the lactone (I) was boiled with 130 mg of a saturated solution of Na_2CO_3 in CH_3OH (2.7%) for 4 h and the reaction mixture was worked up in a manner similar to that described above, 210 mg of (IIIa) and 40 mg of (IIb) were obtained while (IIa) was formed in trace amounts.

Methyl 6,20-Dihydroxy-3α,5α-cyclo-24-norchol-16-en-23-oate (V). A solution of 2 g of the 3-acetate (IVa) in 90 ml of dioxane was treated with 10 ml of 1% KOH in CH_3OH. The homogeneous solution was left at 20°C for 3 h, and then it was neutralized with 2% HCl, diluted with water, and extracted with EtOAc, and the extract was dried and evaporated. This gave 1.9 g of methyl 3β,20ξ-dihydroxy-24-norchola-5,16-dien-23-oate (IVb) with mp 131-132°C (from acetone). IR spectrum (chloroform, ν, cm^{-1}): 1180, 1740, 3500-3610. A solution of 1.9 g of (IVb) in 15 ml of absolute pyridine cooled to 0°C was treated with 1.8 g of TsCl and the mixture was left at +5°C for 48 h. Then it was diluted with water and the aqueous layer was decanted off, while the residue – an oil – was dissolved in benzene and the solution was evaporated, to give 1.78 g of the tosylate (IVc) in the form of an amorphous powder. This was dissolved in 100 ml of acetone, and 1.5 g of $KHCO_3$ in 5 ml of water was added, after which the mixture was boiled until TLC showed that the initial substance had disappeared (10 h). The reaction mixture was partially evaporated and it was treated with water and extracted with EtOAc. The residue after evaporation (1.3 g) was separated by chromatography on SiO_2 in benzene–acetone (16:1). This gave 690 mg of the i-steroid (V) with mp 117-119°C (EtOAc–hexane). IR spectrum (ν, cm^{-1}); 1180, 1340, 1440, 1725, 3500-3600. Mol. wt. 388. Mass spectrum (cm/z): 388 (M), 373 (M − 15), 370 (M − 18), 355 (M − 18 − 15), 352 (M − 2 × 18), 337 (M − 2 × 18 − 15), 315 (M − 73).

Methyl 20-Hydroxy-6-oxo-3α,5α-cyclo-24-norchol-16-en-23-oate (VI). With stirring and cooling to 0°C, a solution of 300 mg of the i-steroid (V) in 10 ml of pyridine was added to a suspension of 600 mg of CrO_3 in 20 ml of absolute pyridine. The reaction mixture was stirred at 0°C for 2 h and was left at 20°C for 18 h. Then it was poured into 50 ml of saturated $NaHCO_3$ solution and extracted with ether, and the organic extracts were washed with dilute HCl and with water, dried over $MgSO_4$, and evaporated. This gave 260 mg of a mixture from which, by column chromatography, 140 mg of the 6-ketone (VI) was isolated in the form of an oil with R_f 0.68 [benzene–acetone (9:1)]. Mol. wt. 386. Mass spectrum (m/z): 386 (M), 368 (M − 18), 353 (M − 18 − 15), 313 (M − 73).

Transformations of (VI) on Its Treatment with Sulfuric and Acetic Acids. A solution of 300 mg of the ketone (VI) in 3 ml of CH_3COOH was treated with 2% H_2SO_4 until a turbidity appeared and it was then heated at 50-55°C for 4 h. After the end of the reaction (TLC), the mixture was poured into water and was extracted with EtOAc, and the organic layer was treated with $NaHCO_3$ and with water and was dried and evaporated. The residue (270 mg) was chromatographed on a column of SiO_2 in the benzene–acetone (20:1) system. This led to the isolation of 50 mg of the δ-lactone of 3β-acetoxy-16α-hydroxy-6-oxo-24-nor-5α-chol-17(20)-en-23-oic acid (VIII) in the form of an oil with R_f 0.6 [benzene–acetone (9:1)]. IR spectrum (ν, cm^{-1}): 1220, 1310, 1720. Mol. wt. 414. Mass spectrum (m/z): 368 (M − 28), 370 (M − 44), 352, 326, 311 (M − 59). PMR spectrum (δ, ppm): 0.96, 1.04 s (6 H, 18-CH_3,

19-CH_3), 1.86 s (3 H, 21-CH_3), 2.02 s (3 H, acetate), 5.0 m (2 H, 3-H, 16-H). The remainder consisted of an complex mixture of substances difficult to separate (TLC). When the experiment was repeated under the same conditions, 280 mg of (VII) was obtained in the form of an oil with R_f 0.4 [benzene–acetone (9:1)]. IR spectrum (ν, cm^{-1}): 1230, 1380, 1460, 1550, 1690, 1750. Mol. wt. 354. Mass spectrum (m/z): 354 (M), 336 (M − 18), 326, 125 ($C_7H_9O_2$). PMR spectrum (δ, ppm): 0.65 m (cyclopropane), 0.88, 0.94 s (6 H, 18-CH_3, 19-CH_3), 1.78 s (3 H, 21-CH_3), 4.95 m (1 H, 16-H). The lactone of the i-steroid (VII) (50 mg) in 0.5 ml of CH_3COOH containing 2% of H_2SO_4 was additionally heated at 65°C for 9 h, and after treatment similar to that described above the mixture of products was acetylated under the usual conditions. After working up and chromatographic separation, a series of products was obtained one of which coincided in terms of R_f with (VII). No formation of (VIII) was observed.

SUMMARY

The δ-lactone of 3β-acetoxy-16-hydroxy-6-oxo-24-nor-5α-chol-17(20)-en-23-oic acid — the $\Delta^{17(20)}$-16α analog of natural chiogralactone — has been synthesized.

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WITHASTEROIDS OF *Physalis*.

III. PHYSANOLIDE AND 4β-HYDROXYWITHANOLIDE E

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Two withanolides have been isolated from the epigeal part of *Physalis viscosa* L. One of them with the compositions $C_{28}H_{38}O_8$ has been identified as 4β-hydroxywithanolide E, and for the second, which has been called physanolide, the structure of 14α,17β,20R-trihydroxy-1,4-dioxo-22R-witha-5,24-dienolide has been proposed on the basis of its UV, IR, PMR, and mass spectra, and also the results of a partial synthesis of 14α-hydroxyandrost-5-ene-1,4,17-trione, obtained by its oxidation.

Continuing a study of *Physalis viscosa* L. [1, 2], from an aqueous extract of the epigeal part of the plant we have isolated two more compounds which have been assigned to the withanolide group on the basis of their UV, IR, PMR, and mass spectra.

Analysis of the spectral characteristics and physicochemical constants of the withanolide (I) $C_{28}H_{38}O_8$, and of its acetate and oxidation products (III, IV) has enabled us to identify this substance as the 4β-hydroxywithanolide E isolated previously from *Ph. peruviana* L. [3, 4].

The detection in the UV spectrum of compound (VIII), $C_{28}H_{38}O_7$, which has been called physanolide, of an intense maximum at 233 nm (log ε 4.1), in the PMR spectrum of two three-proton singlets at δ 1.86 and 1.90 ppm, and in the mass spectrum of a fragment with m/e 125 shows the presence of an unsaturated lactone ring in the side-chain of the new withanolide.

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