117. SYNTHESIS OF 5α-HYDROXY-6-OXOSTEROIDS WITH A δ-LACTONE RING E

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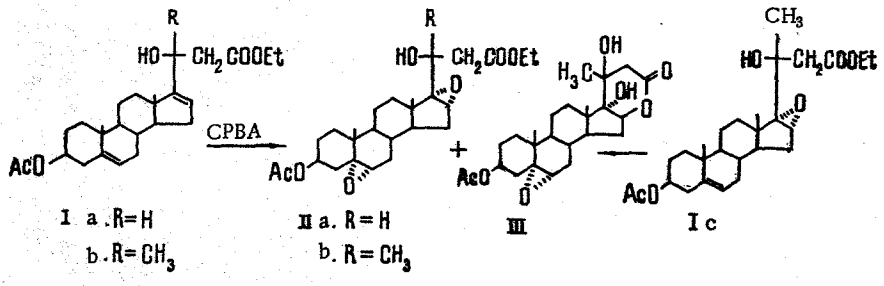
The paper is devoted to the synthesis of steroidal 5α-hydroxy-6-oxolactones from ethyl esters of 5,6-dienic acids. By epoxidating the latter it has been shown that, in addition to the usual formation of 5,6-oxides, opening of the 16α,17-oxide ring initially formed takes place and this is accompanied by intramolecular cyclization to a 17,20-dihydroxy-β-lactone. The trans-opening of the 5α,6α-epoxide in the epoxy-δ-lactone and subsequent oxidation with N-bromosuccinimide has led to a new representative of steroidal δ-lactones — the 23,16-δ-lactone of the 3-acetate of 3β,5α,16β,17α,20ξ-pentahydroxy-6-oxo-24-norcholan-23-oic acid.

The present investigation was performed within the framework of a program of study of the relationship between the structure and biological function of steroids with an additional lactone ring E and oxygen-containing substituents at the C-5 and C-6 centers. In this communication we consider the synthesis of 5α(OH),17α,20ξ-dihydroxy-6-oxolactones.

As the initial compounds we selected ethyl esters of 5,6-dienic acids (Ia, b) [1]. It was proposed to transform them into the desired porducts by the following scheme: epoxidation, trans-opening of the 5,6-epoxides with simultaneous lactonization to ring E, and oxidation of the 6-hydroxy group. As was found, the epoxidation of the dienes (Ia) and (Ib) with m-chloroperbenzoic acid (CPBA) in CH_2Cl_2 took place smoothly to give the corresponding 5α,6α:16α,17α-diepoxides (IIa, b), the 21,24-dinorsteroid (IIa) being characterized in the form of a 20ξ-acetate.



The sterochemistry of the oxide rings was assigned on the basis of general considerations concerning the preferential nature of the approach of an electrophilic reagent from the less hindered α-region of the steroid. The structure was confirmed by the nature of the fragmentation in the mass spectrum (the presence of the peaks of ions corresponding to M, M − $CO_2C_2H_5$, and M − CH_3COOH) and by the signals in the PMR spectrum with δ 2.8 ppm, having a spin—spin coupling constant of 4 Hz, and 3.0 ppm from the 6β and 16β protons [2]. An interesting fact proved to be that, under the conditions of the epoxidation of the 24-norsteroid (Ib), in addition to the diepoxide (IIb) the 5,6α-epoxy-δ-lactone (III) (mp 282-287°C) was formed, its yield increasing with a rise in the reaction temperature (boiling CH_2Cl_2). On the basis of literature analogies [3], it may be assumed that the chlorobenzoic

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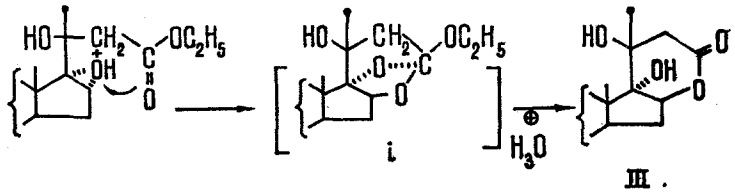
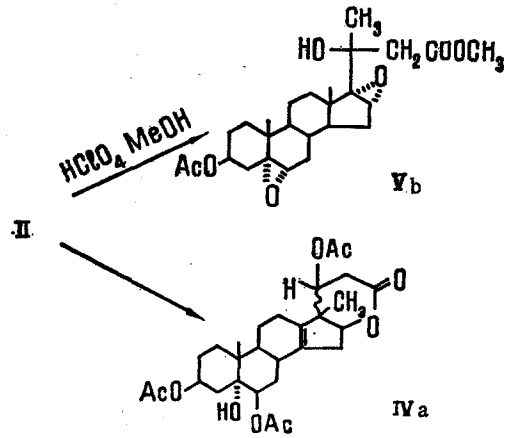
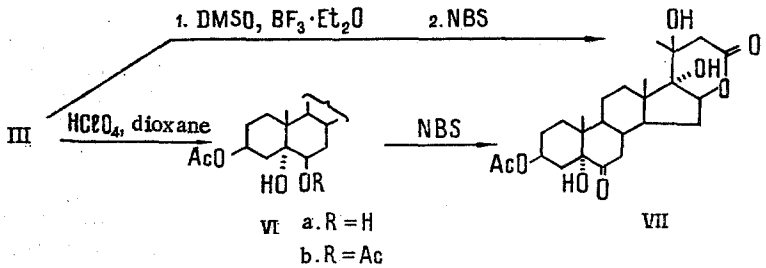
acid liberated in the epoxidation reaction first catalyzes the isomerization of the epoxy ester (IIb) and protonates the oxygen of the 16α,17α-oxide ring formed initially. The opening of the epoxide takes place by the intramolecular attack by the carbonyl oxygen of the ethoxycarbonyl group with the formation of the intermediate orthoester (i), the cleavage of which on further treatment is apparently accompanied by cyclization according to a S_N2 mechanism with inversion of the configuration of the oxide ring in the following way:



The same components are formed on the treatment of the monoepoxide (Ic) [4] with CPBA.



The structure of the 5α,6α-epoxylactone (III) was shown by the fragmentation in its mass spectrum: the presence of the peaks of the molecular ion and of ions characteristic for 17α-20-dihydroxy-δ-lactone (M − 18) and (M − 18 − 60). Compound (III) is sparingly soluble in the majority of organic solvents. The PMR spectrum of (III) in pyridine contains signals corresponding to the 18-CH_3, 19-CH_3, 21-CH_3, and 6-H protons and to an acetate group. A similar transformation into a 17α,20-dihydroxy-δ-lactone was not, however, observed when the diepoxides (IIa, IIb) were treated with strong protonic acids ($HClO_4$) or Lewis acids ($BF_3 \cdot Et_2O$). In the presence of a strong external nucleophile [5], together with the opening of the 5,6-oxide ring and lactonization in the hydroxyl functions at C-20 and C-17 are apparently involved, which is accompanied by rearrangements in ring E. A short exposure of the diepoxide (IIb) to $HClO_4$ in methanol led only to transesterification and to the formation of (Vb).



A study of the opening of the 5α,6α-oxide ring in the epoxylactone (III) showed that the 5,6 position is sterically hindered, and the influence of the remote δ-lactone ring E is apparently shown, as we have reported previously [4] in the bromination of a Δ^5-17,20-

dihydroxylactone. The choice of reaction conditions was dictated by the solubility of (III). When (III) was treated with $HClO_4$ in dioxane (20°C, 3 h) the oxide ring opened with the formation of (VIa), but 50% of the initial oxide remained unchanged. On the other hand, increasing the time of the reaction (until the epoxide had disappeared completely) led to the appearance of numerous by products. The opening of the epoxide (III) with boron trifluoride etherate in dimethyl sulfoxide [6] gave a mixture of the 5α,6β-diol (VIa) and the hydroxyketone (VII). The most rational approach to the 6-ketone (VII) proved to be the oxidation of a mixture of (VIa) and (III) with N-bromosuccinimide in dioxane [7]. Under these conditions the diol (VIa) was smoothly oxidized, and chromatographic separation of the mixture led to the 3-acetate of 3β,5α,16β,17α,20ξ-pentahydroxy-6-oxo-23-norcholan-23-oic acid 23,16β-δ-lactone (VII) with mp 269-271°C. Structure (VII) was confirmed by a fragmentation in the mass spectrum that is characteristic for such lactones. The PMR spectrum contained signals corresponding to protons at C-18, C-19 and C-21 and to an acetate group.

EXPERIMENTAL

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

Epoxidation of the 3-Acetate of Ethyl 3β,20ξ-Dihydroxy-21,24-dinorchola-5,16-dien-23-oate (Ia). A solution of 100 mg of (Ia) in 10 ml of CH_2Cl_2 was treated with 100 mg of CPBA. The homogeneous solution was left in the dark at 20°C for 24 h, and then it was washed successively with 10% Na_2SO_3, $NaHCO_3$, and NaCl, and it was dried over $MgSO_4$ and evaporated. The residue was acetylated by 0.5 ml of $(CH_3CO)_2O$ in 2 ml of pyridine. After the usual working up and chromatographic purification on SiO_2 in the ether–hexane (1:1) system, 60 mg of the 3,20ξ-diacetate of ethyl 3β,20ξ-dihydroxy-5α,6α,16α,17α-diepoxy-21,24-dinorcholan-23-oate (IIa) was obtained with mp 125-128°C (from hexane–acetone). IR spectrum (ν, cm^{-1}): 1030, 1040, 1180, 1250, 1730 (sh), 1750 (in KBr). Molecular weight 504. Mass spectrum (m/e): 504 (M), 444 (M − 60), 429 (M − 60 − 15), 384 (M − 2 × 60), 371 (M − 60 − 73). PMR spectrum (δ, ppm) 0.87 s (3 H, 18-CH_3), 1.08 s (3 H, 19-CH_3), 1.24 t (J = 7 Hz, 3 H, OCH_2CH_3), 2.00, 2.05 s (6 H, acetate groups), 2.48 d (J = 6.5 Hz, 2 H, 22-CH_2), [2.88 d (J = 4 Hz, 1 H), 3.18 d (J = 3 Hz, 1H) − epoxide protons]; 4.9 c.m. (1 H, 3-H), 4.11 q (J = 7 Hz, 2 H, OCH_2CH_3), 5.92 t (J = 6.5 Hz, 1 H, 20-H). When (Ia) was epoxidized with p-nitroperbenzoic acid in $CHCl_3$ (20°C, 48 h), from 250 mg of diene was isolated 170 mg of (IIa) with mp 125-128°C, giving no depression of the melting point with the sample described above and identical with it in all spectral characteristics. On epoxidation with CPBA at 42°C, the main product was (IIa).

Acid Cleavage of the Diepoxide (IIa). A solution of 230 mg of the diepoxide (IIa) in 10 ml of acetone was treated with 10 drops of $HClO_4$ (67%) and 0.5 ml of water, and 40 min after the disappearance of the initial substance (TLC) the reaction mixture was neutralized with $NaHCO_3$ solution, the solvent was evaporated off, and the residue was treated with 10 ml of water and was extracted with EtOAc. After drying over $MgSO_4$ and evaporation, the residue (210 mg) was acetylated with 0.5 ml of $(CH_3CO)_2O$ in 1 ml of pyridine. After 18 h, the reaction mixture was worked up in the usual way, and by chromatographic separation on SiO_2 with the ether–hexane (1:1 and 9:1) and ether systems, 100 mg of a chromatographically homogeneous oily substance was obtained with R_f 0.67 (ether) which apparently consisted of the 3,6,20-triacetate of 3β,5α,6β,16β,20ξ-pentahydroxy-17β-methyl-18,21,24-trinorchol-13-en-23-oic acid 23,16β-δ-lactone (IVa). IR spectrum (ν, cm^{-1}): 1040, 1250, 1380, 1600 (sh), 1735, 3450 (in $CHCl_3$). Molecular weight 518. Mass spectrum (m/e): 518 (M), 500 (M − 18), 458 (M − 60), 440 (M − 60 − 18), 398 (M − 2 × 60), 380 (M − 2 × 60 − 18), 367, 338 (M − 3 × 60), 320, 305. PMR spectrum (ν, ppm): 1.05, 1.08 s (6 H, 18-CH_3, 19-CH_3), 1.95, 1.99 s (9 H, acetate groups), 2.55 m (2 H, 22-CH_2), 3.47 c.m. (2 H, OCH), 4.73 m (1 H, OCH), 5.09 m (1 H, OCH). The same product was formed when the diepoxide (IIa) was treated in glacial CH_3COOH with p-TsOH (100-105°C, 4 h), R_f 0.66 (ether).

Epoxidation of the 3-Acetate of Ethyl 3β,20ξ-Dihydroxy-24-norchola-5,16-dien-23-oate (Ib). A solution of 1.7 g of the diene (Ib) in 100 ml of CH_2Cl_2 was treated with 3 g of CPBA. After 20 h (20°C), the mixture was worked up as described for (Ia). This gave 1.5 g of an oily mixture from which by titration with ether we isolated 170 mg of the 3-acetate of

3β,16β,17α,20ξ-tetrahydroxy-5α,6α-epoxy-24-norcholan-23-oic acid 23,16β-δ-lactone (III), mp 282-287°C (EtOAc—ether). IR spectrum (ν, cm^{-1}): 1040, 1250, 1360, 1380, 1705, 1730, 3380, 3510 (in KBr). Molecular weight 448. Mass spectrum (m/e): 448 (M), 430 (M − 18), 412 (M − 2 × 18), 388 (M − 60), 370 (M − 60 − 18), 352 (M − 60 − 2 × 18), 346 (M − 60 − 42). Compound (III) is sparingly soluble in ether, $CHCl_3$, THF, and CH_3OH. PMR spectrum (δ, ppm in pyridine): 0.76, 0.92 s (18-CH_3, 19-CH_3), 1.3 s (21-CH_3), 1.84 s (acetate group), 2.88 m (6-H).

Part (380 mg) of the filtrate after the removal of the (III) was chromatographed on a column of SiO_2. Elution with the ether—hexane (1:3 and 1:1) systems yielded 100 mg of the diepoxide (IIb) with mp 181-184°C (from CH_3OH). IR spectrum (ν, cm^{-1}): 910, 960, 1040, 1250, 1340, 1380, 1710, 1740, 3510 (in KBr). Molecular weight 476. Mass spectrum (m/e): 476 (M), 458 (M − 18), 443 (M − 18 − 15), 385 (M − 18 − 73). PMR spectrum (δ, ppm): 0.92 s (3 H, 19-CH_3), 1.02 s (3 H, 18-CH_3), 1.2 t (J = 7 Hz, 3 H, OCH_2CH_3), 1.28 s (3 H, 21-CH_3), 1.92 s (3 H, acetate), 2.28 d (2 H, J = 4 Hz, CH_2), 2.8 d (1 H, J = 4 Hz, 6β-H), 3.08 s (1 H, 16β-H), 4.1 (2 H, J = 7 Hz, OCH_2CH_3), 4.48 s (1 H, OH), 4.8 m (1 H, 3-H). When epoxidation was carried out at 42°C, 700 mg of the diene (Ib) yielded 220 mg of the δ-lactone (III). From 1.7 g of the diene (Ib), 700 mg of the δ-lactone (III) and 500 mg of the diepoxide (IIb) were obtained.

Epoxidation of the 3-Acetate of Ethyl 3β,20ξ-Dihydroxy-16α,17α-epoxy-24-norchol-5-en-23-oate (Ic). A solution of 100 mg of the monoepoxide (Ic) [4] and 200 mg of CPBA in 10 ml of CH_2Cl_2 was kept in the dark at 20°C for three days. After a working up process similar to that for (Ia), 20 mg of (III) was obtained with mp 250°C, having the same R_f values and giving no depression of the melting point with authentic (III), together with 50 mg of the diepoxide (IIb), mp 175-178°C, identical with the sample described above.

Acid Cleavage of the Diepoxide (IIb). a) A solution of 30 mg of the diepoxide (IIb) in 15 ml of CH_3OH was treated with three drops of 67% $HClO_4$. After the disappearance of the initial substance (15 min at 20°C, TLC) the solvent was partially evaporated off and the remaining solution was diluted with water and extracted with EtOAc, the extract was washed with $NaHCO_3$ and with water and was dried over $MgSO_4$ and evaporated, and the residue was acetylated with 0.3 ml of $(CH_3CO)_2O$ in 1 ml of pyridine. After the usual working up the chromatographically homogeneous methyl 3β,20ξ-dihydroxy-5α,6α:16α,17α-diepoxy-24-norcholan-23-oate (V) was obtained with R_f 0.72 [ether—acetone (1:1)], IR spectrum (ν, cm^{-1}): 980, 1040, 1100, 1260, 1380, 1460, 1700, 3460, 3600 (in $CHCl_3$). Molecular weight 462. Mass spectrum (m/e): 462 (M), 444 (M − 18), 428, 412, 402 (M − 60), 360 (M − 60 − 42), 342 (M − 60 − 42 − 18).

A solution of 400 mg of (IIb) in 15 ml of dioxane was treated with eight drops of $BF_3 \cdot Et_2O$, and after the initial substance had disappeared (20°C, 18 h) the reaction mixture was diluted with CH_2Cl_2 and washed with water, and the organic layer was separated off, dried over $MgSO_4$, and evaporated. The residue was dissolved in 50 ml of dry benzene and the solution was treated with 20 mg of p-TsOH and was boiled for 20 min. After cooling, the solution was diluted with ether, washed with water and NaCl solution, dried over $MgSO_4$, and evaporated. The residue (290 mg) was acetylated with 1.5 ml of $(CH_3CO)_2O$ in 4 ml of pyridine. After the usual working up and chromatography of the mixture in the ether—acetone (5:1.4:1.3:1) systems, 100 mg of oily chromatographically homogeneous rearrangement product was obtained with R_f 0.68 [ether—acetone (1:1)]. IR spectrum (ν, cm^{-1}): 1040, 1250, 1730, 3440, 3580 (in $CHCl_3$). Molecular weight 492. Mass spectrum (m/e): 492 (M), 474 (M − 18), 450, 448, 430, 412, 408, 390, 388, 370, 352, 330. PMR spectrum (ν, ppm): 0.58 s, 1.1 s, 1.18 s (18-CH_3, 19-CH_3, 21-CH_3), 1.94 s (3 H, acetate group), 3.82 m (OCH).

Acid Cleavage of the 3-Acetate of 3β,16β,17α-20ξ-Tetrahydroxy-5α,6α-epoxy-24-norcholan-23-oic Acid 23,16β-δ-Lactone (III). a) A solution of 30 mg of (III) in 5 ml of dioxane was treated with a few drops of 67% $HClO_4$, and after 3 h at 20°C it was treated with water, extracted with EtOAc, dried, and the residue was acetylated with 0.5 ml of $(CH_3CO)_2O$ in 1 ml of pyridine. After working up, the 3,6-diacetate (VIb) was obtained in the form of an oil with R_f 0.69 [ether—acetone (3:1)]. Molecular weight 508. Mass spectrum (m/e): 508 (M), 490 (M − 18), 472 (M − 2 × 18), 457 (M − 2 × 18), 457 (M − 2 × 18 − 15), 448 (M − 60), 430 (M − 60 − 18), 412 (M − 60 − 42), 396, 388 (M − 2 × 60), 370 (M − 2 × 60 − 18), 352 (M − 2 × 60 − 2 × 18).

b) A mixture consisting of 220 mg of (III), 5 ml of $(CH_3)_2SO$, and 0.06 ml of $BF_3 \cdot Et_2O$ was heated at 60-80°C for 22 h. After cooling, it was treated with water and extracted with CH_2Cl_2, and the extracts were washed with water, dried over $MgSO_4$, and evaporated, and the

residue (160 mg) was chromatographed on SiO_2 with elution by the ether and ether–acetone (5:1) systems. This gave 60 mg of a mixture of the 5,6-diol (VIa) and the 5-hydroxy-6-ketone (VII). The molecular weight of (VIa) was 466 and that of (VII) 464. Mass spectrum (m/e) 466, 464, 448, 446, 430, 412, 404, 402, 388, 384, 370, 352. PMR spectrum (δ, ppm): 0.7, 0.94, 1.0, 1.2, 1.3 (18-CH_3, 19-CH_3, 21-CH_3), 2.0 s (acetate), 3.39, 4.55, 5.0.

Preparation of the 3-Acetate of 3β,5α,16β,17α,20ξ-Pentahydroxy-6-oxo-24-norcholan-23-oic Acid 23,16β-δ-Lactone (VII). a) A solution of 500 mg of (III) in 100 ml of dioxane was treated with 1 ml of 67% $HClO_4$. After 3 h at 20°C, it was neutralized with $NaHCO_3$ and evaporated; the residue was treated with water, filtered off, washed with water, and crystallized from acetone–ether. The reaction product (500 mg) consisted of a mixture of (III), R_f 0.64, and the diol (VIa), R_f 0.40 [ether–acetone (6:1)]. Without separation (in view of its extremely poor solubility in $CHCl_3$), this mixture was dissolved in 9 ml of dioxane and 1 ml of water and was treated with 380 mg of NBS. A day (20°C) after the disappearance of the (VIa) (TLC) the reaction mixture was washed with Na_2SO_3 solution (to eliminate bromine) and with water and was extracted with EtOAc, and the extract was dried over $MgSO_4$ and evaporated. The residue (350 mg) was separated twice on a column of SiO_2 in the ether–acetate (100:5) system. This gave 120 mg of the epoxylactone (III), mp 281–286°C (CH_3OH–ether), 40 mg of a mixture of (III) and (VII), and 55 mg of the 6-oxolactone (VII) with mp 269–271°C (CH_3OH–ether), the melting point of a mixture of (VII) and (III) being 236–256°C. IR spectrum (ν, cm^{-1}): 1040, 1280, 1370, 1390, 1715, 1735, 3440 (br.), 3480 (in KBr). Molecular weight 464. Mass spectrum (m/e): 464 (M), 446 (M − 18), 404 (M − 60), 388, 386. PMR spectrum (δ, ppm, in pyridine): 0.81, 0.92 s (6 H, 18-CH_3, 19-CH_3), 1.4 s (3 H, 21-CH_3), 1.92 s (3 H, acetate).

Under similar conditions, from 150 mg of a mixture of the diol (VIa) and (III) by reaction with NBS, after separation, 35 mg of (VII) with mp 248–254°C and 45 mg of a mixture of (III) and (VII) with mp 220–254°C were obtained.

b) A mixture of the products obtained on the treatment of (III) with $BF_3 \cdot Et_2O$ in $(CH_3)_2SO$ (50 mg) was treated in the same way as described above with 50 mg of NBS in dioxane–water (9:1) for two days. After chromatography on SiO_2 in the ether–acetone (50:2) system, 15 mg of the hydroxy ketone (VII), coinciding in R_f value with that described above was obtained, mp 248–254°C, melting point of a mixture with (VII) 248–254°C.

SUMMARY

1. It has been shown that in the epoxidation of esters of steroid polyenic acids, in addition to the usual formation of oxides, intramolecular cyclization to give 17α,20ξ-dihydroxy-δ-lactones takes place.

2. A new representative of the steroid δ-lactones — the 3-acetate of 3β,5α,16β,17α,20ξ-pentahydroxy-6-oxo-24-norcholan-23-oic acid 23,16β-δ-lactone (VII) — has been obtained by transformations of the 5α,6α-epoxide ring, in the epoxy-δ-lactone (III).

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