TRANSFORMED STEROIDS.

128. SYNTHESIS OF THE ISOMERIC 16α- AND 16β-LACTONES OF 3β,16-DIHYDROXY-24-NOR-5α-CHOLAN-23-OIC ACID

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The paper is devoted to the synthesis of steroids with an additional ring E consisting of a saturated lactone ring in forms isomeric at the 16-center. The basic intermediates for yielding such compounds were the products of the Reformatskii reaction with 3,16α-diacetoxypregn-5-en-20 one. The $\Delta^{20(22)}$-lactone was hydrogenated to the compound with a saturated lactone ring and a Δ^5 bond and to the fully saturated product. Its epimer at the 16-center was obtained from the ethoxycarbonyl triol forming the second product of the Reformatskii reaction. The dehydration of the latter gave a mixture of 20(21)- and 20(22)-enes, the hydrogenation of which led to the 3,16-diacetate of ethyl 24-norcholanoate. Subsequent saponification, methylation, oxidation, reduction, and cyclization led to the 6-deoxy analog of chiogralactone. The absolute configurations at C(16) of the three lactones obtained were determined by the Hudson–Klyne rule and were confirmed by analysis of the CD spectra. The unambiguity of the hydrogenation of the $\Delta^{20(22)}$ bonds of the intermediate compounds was confirmed by the PMR spectra.

The lactonization of 24-norcholanoic acids having a double bond or an α-oxide ring, leads to unsaturated or hydroxylated lactones with the α or β configuration at C(16) [1-4]. In the present communication we describe the synthesis of saturated 16α- and 16β-lactones from the readily accessible [5] 3β,16α-dihydroxypregn-5-en-20-one (I). In this case, unlike that described in [6], the Reformatskii reaction leads unambiguously to a mixture of the 20S- and 20R-isomers, as was confirmed by the presence of two signals from 18-CH_3 groups in the PMR spectrum. This directed nature of the reaction is apparently connected with the screening of the α region of the 16α-hydroxy group, competing with the usual hindrance of approach from the β region due to the 18-methyl group. At the same time, the δ-lactone (III) was formed as a reaction product, together with the 3β,16α,20ξ-triol (IIa). This obviously takes place as the result of spontaneous cyclization and dehydration, since a special treatment of the triol (IIa) with dehydrating agents does not cause a similar transformation.

The hydrogenation of the lactone (III) over PtO_2 with 1 mole of H_2 in AcOH led only to the 20- isomer of the Δ^5- lactone (IVa) contaminated with a small amount of its 5αH-saturated analog (IVb), which it was possible to eliminate only by crystallization. The Δ^5-lactone (IVa) obtained in this way has a PMR spectrum differing substantially from the initial one by the position and form of the signals of the 21-CH_3 group — three-proton doublet at δ 1.04 ppm, J = 6.5 Hz — and of the 18-CH_3 group — δ 0.77 ppm, as compared with δ 0.83 ppm for (III). The exhaustive hydrogenation of the lactone (III) also gave a mixture of (IVa) and (IVb), from which the latter was isolated after treatment with m-chloroperbenzoic acid (CPBA). In the PMR spectrum of (IVb) the signal from the 19-CH_3 group (δ 0.98 ppm) has shifted upfield. as compared with (IVa), and the 21-CH_3 group is represented by a three-proton doublet at δ 1.0 ppm with J = 6.5 Hz. Great interest is presented by the steric unambiguity of the hydrogenation of the lactone (III) at C(20) as is shown by the spectra of (IVa) and (IVb). It may be assumed that the 21-methyl group in (IVa) and (IVb) possesses the natural α configuration, thus being more remote from the 18-CH_3 group. In the case of the 21β configuration of the methyl group the appearance of strong 1,3-diaxial repulsion is unavoidable.

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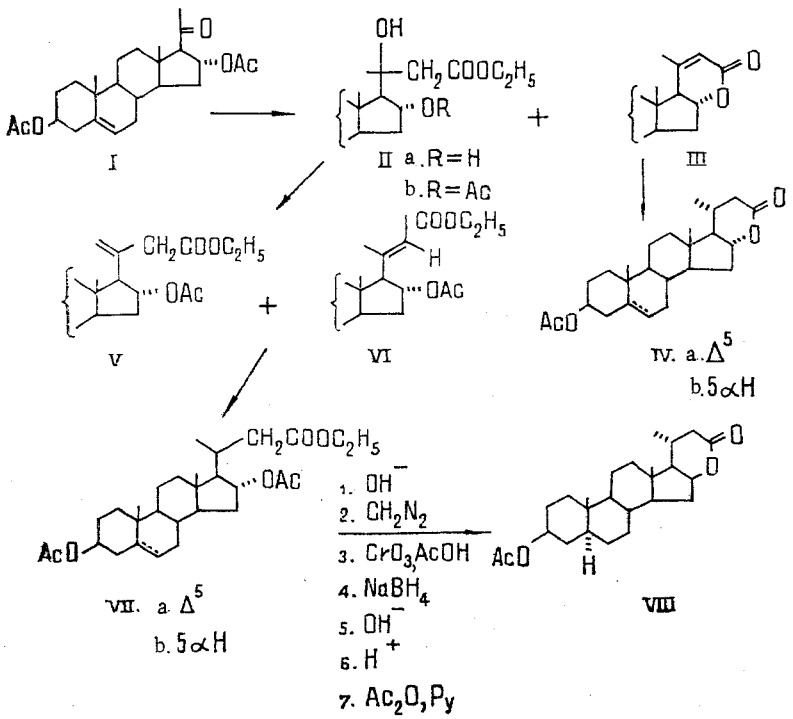

The dehydration of the triol (IIb) with the aid of $POCl_3$ in pyridine led to a mixture of the 5,20(21)- and 5,20(22)-dienes (V) and (VI) in a ratio of 1:2.5, which were characterized after separation on SiO_2. The isomer (VI) having in its PMR spectrum the signal from the 21-CH_3 group in the form of a broadened singlet 2.2 ppm possesses [1] the E configuration with respect to the $\Delta^{20(22)}$-bond.

The exhaustive hydrogenation of the mixture of (V) and (VI) in AcOH over PtO_2 led to the saturated diacetate (VIIb), identical in relation to its constants with a compound described in the literature [7] the stereochemistry of which of C(20) was not established. In this case, as well, so far as can be judged from the unambiguity of the PMR spectra of (VIIb), the hydrogenation took place stereoselectively. It is stated in the literature [8] that such stereoselective hydrogenation is characteristic for a $\Delta^{20(21)}$ bond, and for E isomers with respect to the $\Delta^{20(22)}$ bond of dehydrocholesterol and leads to the natural 20R compounds. On this basis, we may assume the same configuration at C(20) for the diacetate (VIIb), as well. An attempt to obtain the Δ^5-diacetate (VIIa) using one equivalent of H_2 in hydrogenation led to an unresolvable mixture of (VIIa) and (VIIb). Epoxidation of the latter with CPBA showed that a considerable part of it consisted of the saturated diacetate (VIIb).

The possibility of using the diacetate (VIIb) for the synthesis of saturated lactone with the 16β configuration was checked with the aid of the unseparated mixture of diacetates (VIIa) and (VIIb). With this aim, the mixture was subjected to successive saponification, methylation at the carboxy group with the aid of diazomethane, oxidation with CrO_3 in AcOH, reduction with $NaBH_4$, and cyclization. From the reaction products we isolated the δ-lactone (VIII) — the 6-deoxo analog of the natural chiogralactone [9] — the structure of which was confirmed by its physicochemical characterization. The PMR spectrum of the lactone (VIII) has characteristic multiplets from 3αH and 16αH protons with δ 4.63 ppm and a three-proton doublet from the 21-CH_3 group with δ 1.13 ppm and a spin—spin coupling constant J = 6.5 Hz, which shows the α configuration of this group. The presence of one three-proton signal from the 19-CH_3 group together with literature information on the stereochemistry of the hydrogenation of a Δ^5 bond [10] is evidence in favor of the 5αH configuration of (VIII). The absolute configuration at C(16) of the lactones (III), (IVa and b), and (VIII) was determined on the basis of the Hudson—Klyne rules [11] (from the difference of the molecular rotations of the δ-lactone and its K salt in a 0.1 N methanolic solution of KOH). The difference $\Delta[M]_D$ that we obtain for (VIII) was −162.97°, and since it is negative the δ-lactone oxygen has the β configuration and (VIII) belongs to the L series. In the case of (IVa), $\Delta[M]_D$ amounts to +79° and since this difference is positive, the δ-lactone oxygen has the α configuration and (IVa) and, consequently, (III) and (IVb) are assigned to the D series:

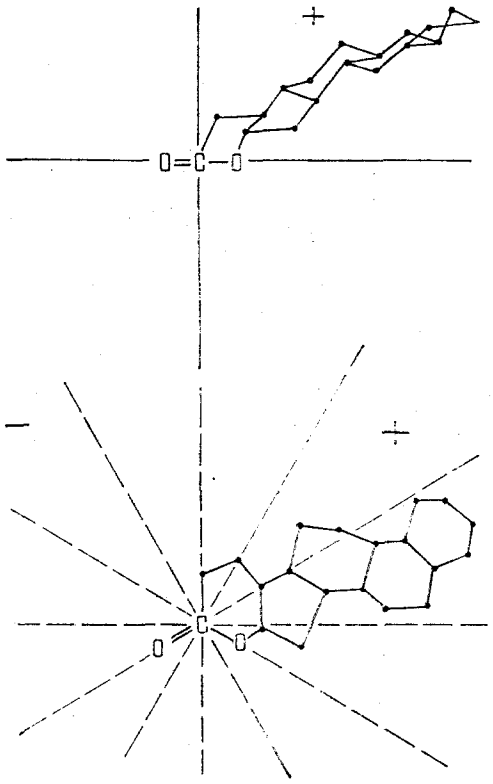

Fig. 1

Steroid	$[M]_D$	$\Delta[M]_D$	Steroid	$[M]_D$	$\Delta[M]_D$
δ-Lactone (VIII)	−50.65°		δ-Lactone (IVa)	−165°	
K salt	+112.32°	−162.97°	K salt	−244°	+79°

The assignment of the δ-lactones to the given series was also made on the basis of a comparison of their CD spectra. In the analysis of the CD spectra of the lactones (IVa and b) and (VIII), the most preferred half-chair conformation [12] was assumed for the lactone ring:

Number of the compound	CD		Stereochemistry at C-16
	Δε	λ_{max}, nm	
IVa	+3.74	218	16βH
IVb	+2.6	217	16βH
VIII	−0.62	216	16αH

Compounds (IVa) and (IVb) have a positive Cotton effect (CE) of the $n \rightarrow \pi^*$ transition of the lactone chromophore. Analysis of the CD spectra from the point of view of the Klyne sector rule permitted the conclusions that rings D and E had the trans linkage. A consideration of a projection of the molecules along the bisectrix of the O—C=O angle using the anti-octant rule also predicts a positive CE. A consideration of the molecule projected on the plane passing through the lactone group also permits a curve with a positive CE to be expected (Fig. 1) [12].

For compound (VIII), the CE of the $n \rightarrow \pi^*$ transition of the lactone chromophore has a small negative value. In actual fact, if we consider a molecule with the cis linkage of rings D and E from the point of view of the above-mentioned rules, then according to the first of them a weak negative CE is to be expected, and according to the second, if the fact that the main "weight" of the molecule is located above the plane of the O—C=O chromophore, i.e., in the front sectors, is taken into account — a negative sign of the CE should again be expected (see Fig. 2).

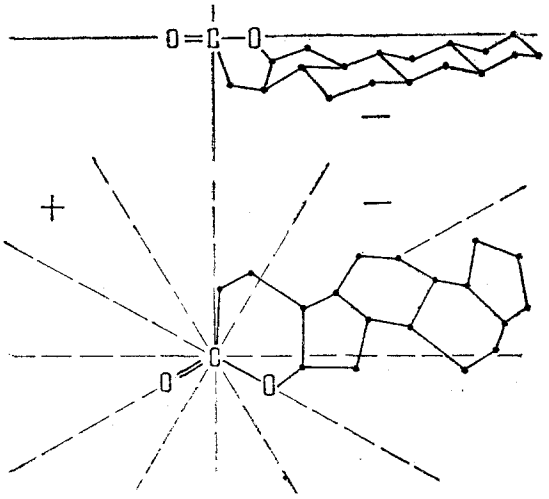

Fig. 2

EXPERIMENTAL

Melting points were determined on a Kofler block. IR spectra were measured on a UR-20 spectrometer, and UV spectra on a Unicam SP-700 in C_2H_5OH. Mass spectra were taken on a Varian MAT CH-6 mass spectrometer with the direct introduction of the samples into the ion source at an ionizing voltage of 70 eV. PMR spectra were measured on Tesla BS 497 and Bruker M-250 instruments with a working frequency of 250 MHz in $CDCl_3$ (using TMS as internal standard). CD spectra were taken on a Jobin Yvon Dichrographe-3 instrument at 20-23°C in CH_3CN using solutions with a concentration 1 mg in 1 ml and a cell with a length of 0.1 cm.

For TLC we used silica gel 50/40 μm (+13% of gypsum). Mixtures were separated on columns of SiO_2 40/100 μ in an atmosphere of N_2. Specific rotations were measured on a Spectropol-1 instrument at c 0.5 mg/ml.

Reformatskii Reaction with 3,16α-Diacetoxypregn-5-en-20-one (I). A. With vigorous stirring, 1.3 g of (I) and 1.5 ml of $BrCH_2CO_2Et$ was added to a suspension of 750 mg of activated Zn in 10 ml of a mixture of absolute benzene and ether (1:1), and the mixture was boiled for 2 h. After treatment with 2 N HCl, extraction with EtOAc, drying of the extract with $MgSO_4$ and evaporation, the residual oil was separated by chromatography in ether–heptane systems (1:8, 1:6, 1:4, and 1:2). The products were: 1) 200 mg of the 3-acetate of ethyl 3,16α,20ξ-trihydroxy-24-norchol-5-en-23-oate (IIa), $C_{27}H_{42}O_6$, mp 170-173° (ether–hexane). IR spectrum (ν, cm^{-1}): 1260, 1725, 3500-3610 (in $CHCl_3$). Mass spectrum (m/z): 402 (M − 60), 384 (M − 60 − 18), 366 (M − 60 − 2 × 18); 2) 170 mg of the 3-acetate of 3,16α-dihydroxy-24-norchola-5,20(22)-dien-23-oic acid 23→16-δ-lactone (III), $C_{25}H_{34}O_4$, mp 222-226°C (from CH_3OH). IR spectrum (ν, cm^{-1}): 1250, 1620, 1720 (in $CHCl_3$). Mass spectrum (m/z): 338 (M − 60), 323 (M − 15 − 60). PMR spectrum, (δ, ppm): 0.83 s (3 H, 18-CH_3), 1.04 s (3 H, 19-CH_3), 2.04 s (6 H, 21-CH_3, acetate), 4.60 m (2 H, 3-H, 16-H), 5.40 m (1 H, 6-H), 5.76 br.s (1 H, 22-H). In addition very small amounts of ADP (70 mg) and (I) (60 mg) were isolated.

B. After the performance of the reaction under the conditions described above starting with 2.4 g of (I), the crude product obtained (2.4 g) was acetylated with 3 ml of Ac_2O in 30 ml of pyridine, and after the usual working up the mixture was separated by chromatography in ether–heptane systems (1:3 and 1:2). This gave: 1) 900 mg of the 3,16α-diacetate (IIb), $C_{29}H_{44}O_7$, mp 168-170°C (from CH_3OH). Mass spectrum (m/z): 444 (M − 60), 429 (M − 60 − 15), 329 (M − 60 − 45), 384 (M − 2 × 60). PMR spectrum (δ, ppm): 0.65, 0.85 s (6 H, 18-CH_3), 1.35 s (3 H, 21-CH_3), 2.01 s (6 H, acetates), 4.16 q (J = 6.5 Hz, 2 H, OCH_2CH_3), 4.56 m (1 H, 3-H), 1.02 s (3 H, 19-CH_3), 1.26 t (J = 6.5 Hz, 3 H, OCH_2CH_3), 5.32 m (2 H, 6-H, 16-H); and 2) 450 mg of the lactone (III), identical with the sample obtained in the separation of the mixture before acetylation.

Hydrogenation of the Lactone (III). The hydrogenation of 1.1 g of the lactone (III) was carried out in 100 ml of AcOH in the presence of 100 mg of PtO_2 until 1 mole of H_2 (69 ml) had been absorbed. After the usual working up of the reaction mixture and two crystallizations, 102 g was obtained of the 3-acetate of 3,16α-24-norchol-5-en-23-oic acid 23→16α-δ-

lactone (IVa), $C_{26}H_{36}O_4$, mp 218-220°C (from CH_3OH). IR spectrum (ν, cm^{-1}): 1270, 1725 (in $CHCl_3$). Mass spectrum (m/z): 340 (M − 60), 325 (M − 60 − 15). PMR spectrum (δ, ppm): 0.77 s (3 H, 18-CH_3), 1.04 s (6 H, 19-CH_3, overlapping with d, J = 6.5 Hz, 21-CH_3), 2.05 s (3 H, acetate), 4.44 m (2 H, 3-H, 16-H), 5.25 m (1 H, 6-H). The exhaustive hydrogenation of (III) formed a mixture of (IVa) and the 3-acetate of 3,16α-dihydroxy-24-norcholan-23-oic acid 23 → 16α-δ-lactone (IVb), which was separated from (IVa) by epoxidation of 500 mg of the mixture with 850 mg of CPBA in 25 ml of CH_2Cl_2. The usual working up and chromatographic separation with ether—heptane systems (1:3 and 1:4) gave 100 mg of (IVb), $C_{25}H_{38}O_4$, mp 235-238°C (from EtOAc), R_f 0.51 [benzene—acetone (9:1)]. IR spectrum (ν, cm^{-1}): 1250, 1730 (in $CHCl_3$). Mass spectrum (m/z): 342 (M − 60), 327 (M − 60 − 15). PMR spectrum (δ, ppm): 0.74 s (3 H, 18-CH_3), 0.98 s (3 H, 19-CH_3), 1.0 d (J = 6.5 Hz, 21-CH_3), 2.05 s (3 H, acetate), 4.34 m, (2 H, 3-H, 16-H).

Dehydration of the 3,16-Diacetate of Ethyl 3,16α,20ξ-Trihydroxy-24-norchol-5-en-23-oate (IIb). A solution of 460 mg of (IIb) in 10 ml of pyridine was treated at the boil with 1 ml of $POCl_3$. After 0.5 h the mixture was treated with water and extracted with ether; the extracts were washed with 2% HCl and with water and were dried with $MgSO_4$ and evaporated. After separation of the mixture by the ether—heptane (1:3) system, the following products were obtained: 1) 60 mg of the 3,16-diacetate of ethyl 3,16α-dihydroxy-24-norchola-5,20(21)-dien-23-oate (V), $C_{27}H_{42}O_6$, R_f 0.59 [ether—hexane (1:4)]. IR spectrum (ν, cm^{-1}), 1250, 1645, 1725, 3020 (in $CHCl_3$). Mass spectrum (m/z): 426 (M − 60), 366 (M − 2 × 60), 351 (M − 2 × 60 − 15), 330, 305, 293. PMR spectrum, (δ, ppm): 0.66 s (3 H, 18-CH_3), 1.02 s (3 H, 19-CH_3), 1.26 t (J = 6.5 Hz, 3 H, OCH_2CH_3), 2.03 s (6 H, acetates), 4.15 q (J = 6.5 Hz, 3 H, OCH_2CH_3), 4.6 m (1 H, 3-H), 5.08 m (2 H, 21-CH_2), 5.34 m (2 H, 6-H, 16-H); and 2) 150 mg of 3,16-diacetate of ethyl 3,16-dihydroxy-24-norchola-5,20(22)-dien-23-oate (VI), $C_{27}H_{42}O_6$, R_f 0.50 [ether—hexane (1:4)]. IR spectrum (ν, cm^{-1}): 1250, 1645, 1725 (in $CHCl_3$). Mass spectrum (m/z): 426 (M − 60), 366 (M − 2 × 60), 351 (M − 2 × 60 − 15). UV spectrum (λ_{max}, nm): 227 (ε 6667). PMR spectrum (δ, ppm): 0.66 s (3 H, 18-CH_3), 1.02 s (3 H, 19-CH_3), 1.28 t (J = 6.5 Hz, 3 H, OCH_2CH_3), 2.03, 2.01 s (6 H, acetates), 2.2 br.s (3 H, 21-CH_3), 4.09 q (J = 6.5 Hz, 2 H, OCH_2CH_3), 5.4-5.31 m (2 H, 6-H, 16-H), 5.70 m (1 H, 22-H); and 140 mg of a mixture of (V) and (VI).

Hydrogenation of the Dienes (V) and (VI). The exhaustive hydrogenation of 500 mg of the dienes (V) and (VI) in 10 ml of AcOH over 50 mg of PtO_2 gave, after the usual working up, 340 mg of the 3,16-diacetate of ethyl 3,16-dihydroxy-24-nor-5α-cholan-23-oate (VIIb), $C_{29}H_{46}O_6$, mp 138-140°C (from hexane—ether) (lit. [7]: 138°C). Mass spectrum (m/z); 490 (M), 430 (M − 60), 415, 403, 371, 370, 366. PMR spectrum (δ, ppm); 0.73 s (3 H, 18-CH_3), 0.79 s (3 H, 19-CH_3), 0.93 d (J = 6.5 Hz, 3 H, 21-CH_3), 1.21 t (J = 6.5 Hz, 3 H, OCH_2CH_3), 1.98 s (6 H, acetates), 4.11 q (J = 6.5 Hz, 2 H, OCH_2CH_3), 4.6-4.97 m (2 H, 3-H, 16-H). The hydrogenation of 1.1 g of the mixture of dienes (V) and (VI) in 20 ml of AcOH over 160 mg of PtO_2 until 1 mole of H_2 had been absorbed gave, after the usual working up, 1.0 g of a mixture of (VIIb) and (VIIa), $C_{29}H_{44}O_6$. R_f 0.59 [ether—hexane (1:4)]. IR spectrum, (ν, cm^{-1}): 1250, 1730-1740 (in $CHCl_3$). Mass spectrum (m/z): 430, 428 (M − 60), 415 (M − 73), 370, 368. PMR spectrum (δ, ppm): 0.73 s (3 H, 18-CH_3), 0.99 s (3 H, 19-CH_3), 0.95 d (J = 6.5 Hz, 3 H, 21-CH_3), 1.23 t (J = 6.5 Hz, 3 H, OCH_2CH_3), 2.0 s (6 H, acetates), 4.13 q (J = 6.5 Hz, 2 H, OCH_2CH_3), 4.6-4.97 m (2 H, 3-H, 16-H), 5.32 m (6-H).

3-Acetate of 3,16β-Dihydroxy-24-nor-5α-cholan-23-oic Acid 23→16-δ-Lactone (VIII). Compound (VIIb) containing (VIIa) as an impurity (340 mg) was kept in 40 ml of 5% KOH in CH_3OH at 20°C for 18 h. Then the mixture was treated with saturated NaCl solution, acidified with 2% HCl, and extracted with EtOAc. The extracts were dried with $MgSO_4$ and evaporated. The residue was dissolved in 30 ml of $CHCl_3$—CH_3OH (1:10) and a solution of diazomethane prepared from 250 mg of nitrosomethylurea and 2 ml of 40% KOH in 30 ml of ether was added. After 24 h the solvent was evaporated off, giving 180 mg of the methyl ester of the 3,16-diol, with R_f 0.46 [ether—benzene (1:1)]; without additional purification, this was dissolved in 30 ml of AcOH and the solution was added dropwise to a solution of 275 mg of CrO_3 in 10 ml of AcOH. After 24 h at 20°C, the reaction mixture was treated with water and was extracted with ether and EtOAc. The extracts were washed with $NaHCO_3$ solution and with water and were dried with $MgSO_4$ and evaporated. This gave 175 mg of the 3,16-diketone, $C_{24}H_{36}O_4$, R_f 0.58 (ether—benzene) (1:1). IR spectrum (ν, cm^{-1}): 1710, 1730 (in $CHCl_3$). Mass spectrum (m/z): 388 (M), 373 (M − 15), 341 (M − 15 − 32). A solution of 170 mg of this product in 10 ml of DMFA was treated with a solution of 170 mg of $NaBH_4$ in 1 ml of water. After being stirred at 20°C for 18 h, the mixture was treated with 2% HCl, diluted with water, dried with $MgSO_4$, and

evaporated. The residue (150 mg) was saponified by boiling with 1.5 g of K_2CO_3, 10 ml of CH_3OH and 7 ml of water for 1 h. After cooling, the mixture was treated with water, acidified to pH 1, and extracted with EtOAc. After 18 h, the extracts were washed with $NaHCO_3$ solution and with water, dried with $MgSO_4$, and evaporated. The residue (100 mg) was acetylated with 0.5 ml of Ac_2O in 1 ml of pyridine. After the usual working up, chromatography in benzene—acetone (traces) permitted the isolation from the mixture formed of 35 mg of the δ-lactone (VIII), $C_{25}H_{38}O_4$, R_f 0.51 [benzene—acetone (9:1)]. IR spectrum (ν, cm^{-1}): 1260, 1730 (in $CHCl_3$). Mass spectrum (m/z): 342 (M − 60), 327 (M − 60 − 15). PMR spectrum (δ, ppm): 0.77 (3 H, 18-CH_3), 0.84 s (3 H, 19-CH_3), 1.12 d (J = 6.5 Hz, 3 H, 21-CH_3), 2.02 s (3 H, acetate), 4.63 m (2 H, 3-H, 16-H).

SUMMARY

1. It has been shown that the products of the Reformatskii reaction with 3,16α-diacetoxypregn-5-en-20-one may serve as the starting materials for passing to steroid δ-lactones isomeric at the C(16) center.

2. A correlation has been made between CD spectra and the stereochemistry of the C(16) center of the steroids with saturated δ-lactonic rings E that have been synthesized.

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