PREPARATION OF 16-SUBSTITUTED 3-HYDROXYESTRA-1, 3,5(10)-TRIENE-17-ONES STARTING WITH THE BROMINATION OF ESTRONE ACETATE

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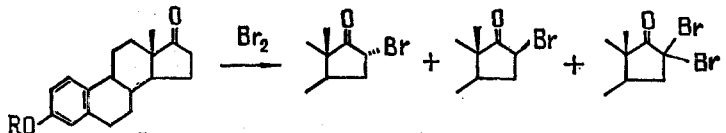
The bromination of estrone acetate (Ia) leads to a mixture of acetates of 16α-bromo-16β-bromo-, and 16,16-dibromoestrone (IIa, IIIa, and IVa) in a ratio of 63:28:9. On treatment with an aqueous methanolic solution of potash, depending on the conditions, a mixture of (IIa) and (IIIa) gives 3,16α-dihydroxyestra-1,3,5(10)-trien-17-one (V) or 3,17β-dihydroxyestra-1,3,5(10)-trien-16-one (VI). When 5 g of (Ia) was brominated with 2.8 g of Br_2 in chloroform and the products were chromatographed on silica gel, 0.36 g of (IVa), $C_{20}H_{22}Br_2O_3$, mp 165-166°C (from ether) 0.37 g of (IIIa), mp 169-170.5°C, 4.6 g of a mixture of (IIa) and (IIIa), 30 mg of (Ia) and 0.2 g of a mixture of 16α- and 16β-bromoestrones was obtained. The action of potash on a mixture of (IIa) and (IIIa) in aqueous MeOH at 20°C led to the epimerization of the (IIa) into (IIIa) and then the conversion of the latter into (V) with mp 203.5-206°C; diacetate with mp 172-173°C (acetone–ethanol). Similarly, but with heating (98°C, 3 h), a mixture of (IIa) and (IIIa) was converted into (VI), with mp 234-236°C. Characteristics of the IR and PMR spectra of the compounds obtained are given.

The introduction of alkyl, halogen, or oxygen-containing substituents into position 16 of the estrone or estradiol molecule greatly affects the biological activity of these compounds and not infrequently leads to the appearance of new hormonal properties [1-3]. One of the methods for the functionalization of position 16 in ring D of steroids is the bromination of 17-keto compounds [4, 5]. To obtain 16-bromo derivatives of 1,3,5(10)-estratrienes the corresponding 17-enol acetates are brominated [6, 9] in order to avoid the possible bromination of the aromatic ring A [6]. However, the performance of the direct bromination of estratriene-17-ones is of interest, since it permits the corresponding 16-bromo derivatives to be obtained by the shortest route.

In the present paper we report on the compounds obtained by the direct bromination of estrone acetate and on the conversion of 16-bromo derivatives of estrone into 16-oxygen-containing compounds under the action of a base.

By treating estrone acetate (Ia) in chloroform with bromine in the presence of a few drops of an ethanolic solution of hydrogen bromide as reaction initiator we obtained a mixture of acetates of the 16-monobromoestrones ((IIa) and (IIIa), the main products) and the acetate of 16,16-dibromoestrone (IVa):



I II III IV

a R = Ac
b R = H

In contrast to the bromination of a 17-enol acetate, leading to the formation of the 16α-bromo epimer exclusively [8], the bromination of estrone acetate takes place nonstereo-

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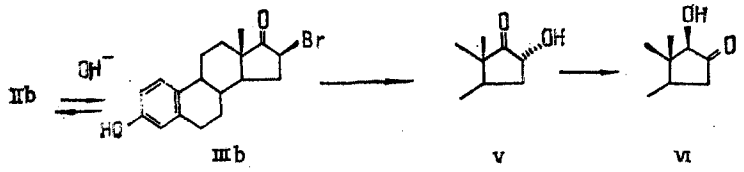
specifically, giving a mixture of the acetates of 16α- and 16β-bromoestrones (IIa) and (IIIa) in a ratio of 7:3. The acetate of 16β-bromoestrone, being distinguished by somewhat higher chromatographic mobility than its epimer, was separated from the latter by chromatographing the bromination product on silica gel. In the PMR spectrum of the 16β-bromo epimer (IIIa), the signal of the angular methyl group, undergoing the spatial influence of the 16β-bromine atom, is observed in a weaker field (1.12 ppm) as compared with the analogous signals of estrone acetate (Ia) and of the 16α epimer (IIa) – 0.92 and 0.94 ppm, respectively. The signals of the proton in position 16 appear in the spectrum in the form of a triplet (J = 9 Hz) at δ = 4.15 ppm for the 16β-bromo epimer and a multiplet at δ = 4.60 ppm for the 16α-bromo epimer.

The third bromination product – 16,16-dibromoestrone acetate (IV) – was formed in an amount of 5-10% of the mixture of substances when the excess of bromine taken in the reaction was about 10%. In this case, we observed no formation of estrone derivatives brominated in ring A. With an increase in the amount of bromine the percentage of the 16,16-dibromoestrone acetate in the mixture rose. In the region of the signals of aromatic protons in the PMR spectrum of this compound the pattern characteristic for a 3-substituted aromatic ring A is retained: doublet of C_1–H (7.20 ppm, $J_{1,2}$ = 8 Hz), quartet of C_2–H (6.88 ppm, $J_{1,2}$ = 8 Hz, $J_{2,4}$ = 3 Hz), and the signal of C_4–H (6.84 ppm). At the same time, the spectrum lacks the signals of protons at C_{16} in the region from 4.00 to 4.60 ppm that are observed in the spectrum of the 16α-bromo and 16β-bromo epimers (IIa) and (IIIa). The chemical shift of the signal of the angular methyl group in the 16,16-dibromo derivative (IVa) is close to that of the analogous methyl group in the 16β-bromo epimer (IIIa).

The instability of 16-bromine-substituted 17-ketosteroids in an alkaline medium has been discussed in the literature. Thus, under the action of sodium methanolate, a 16α-bromine atom is replaced by a hydroxy group [8], and under the action of an aqueous solution of caustic potash in tert-butanol 3β-acetoxy-16α-bromo-5β-androstane-11,17-dione gives 3β,17β-dihydroxy-5β-androstane-11,16-dione [4] with a yield of 50%.

We have observed successive transformations of the 16-bromo derivatives of estrone in an aqueous methanolic solution of potash. Initially, at room temperature, a mixture of 16α- and 16β-bromoestrones (ratio of the acetates (IIa) and (IIIa) taken in the reaction 7:3) was enriched with the 16β epimer, and then it was slowly converted into a 16α-hydroxyestrone (V); after 1 h from the beginning of the reaction the mixture contained 16α- and 16β-bromoestrones ((IIb) and (IIIb)) in a ratio of 3:7, and after 20 h the ratio of the epimers (IIb) and (IIIb) had not changed but a considerable amount of 16α-hydroxyestrone (V) had appeared. Heating accelerated the conversion of the 16 bromoestrone into 16α-hydroxyestrone which under these conditions undergoes a ketol rearrangement, giving the more stable 16-ketoestradiol (VI). The latter can be obtained from a mixture of (IIa) and (IIIa) in quantitative yield.



IIIb V VI

The transformations of 16-bromoestrone into 16α-hydroxyestrone apparently involve a mechanism of the substitution of α-bromo ketones which includes the intermediate isomerization of 16α-bromoestrone into the 16β epimer [8]. Here it is important that the epimeric 16-bromine-substituted estrones form 16α-hydroxyestrone exclusively.

Thus, the direct bromination of estrone acetate gives products of substitution in ring D. The epimeric 16-bromine-substituted derivatives (IIa) and (IIIa) can readily be converted into 16-oxygen-containing derivatives of estrone.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 457 instrument in paraffin oil, and PMR spectra on a Varian XL-100 spectrometer in $CDCl_3$ solution with TMS as internal standard, the values of the chemical shifts being given in the δ scale. Mass spectra were recorded on a Varian MAT-112 instrument at an energy of the ionizing electrons of 70 eV and a temperature of the ionization chamber of 180°C, with the direct introduction of the sample into the ion source.

Bromination of Estrone Acetate (Ia). At room temperature, a solution of 2.8 g of bromine in 70 ml of chloroform and two drops of a 10% solution of hydrogen bromide in acetic acid was added to a solution of 5 g of estrone acetate in 70 ml of chloroform. The solution was stirred for 20 min and was poured into an aqueous solution of sodium bicarbonate. After the usual working up, a product was obtained (6.89 g), which was chromatographed on silica gel (Lachema, L 40/100). Benzene–ether (95:5) eluted successively: fraction 1 – 0.36 g of 16,16-dibromoestrone acetate (IVa); fraction 2 – 0.8 g of a mixture of (IV) and 16β-bromoestrone acetate (IIIa) from which 0.37 g of 16β-bromoestrone acetate (IIIa) was obtained by crystallization from ether; and fraction 3 – 4.6 g of a mixture of 16α- and 16β-bromoestrone acetates ((IIa) and (IIIa)) in a ratio of 7:3. Benzene–ether (90:10) eluted 0.21 g of a mixture of 16α-bromoestrone acetate and estrone acetate from which, after recrystallization from ether, 30 mg of estrone acetate (Ia) was obtained with mp 123-124°C. Then 0.2 g of a mixture of 16α- and 16β-bromoestrones was eluted.

16,16-Dibromoestrone acetate (IVa). $C_{20}H_{22}Br_2O_3$, mp 165-166°C (from ether). IR spectrum, ν, cm^{-1}: 1753, 1758, 1600, 1580, 1500. PMR spectrum, ppm: 1.14 (3H, CH_3); 2.27 (3H, $COCH_3$); 6.84 (1 H, C_4–H); 6.88 (1 H, quartet, $J_{1,2}$ = 8 Hz, $J_{2,4}$ = 3 Hz, C_2–H); 7.20 (1 H, $J_{1,2}$ = 8 Hz, C_1–H); M^+ 470.

16β-Bromoestrone acetate (IIIa), mp 169-170.5°C. IR spectrum, ν, cm^{-1}: 1747, 1758, 1600, 1580, 1690. PMR spectrum, ppm: 1.12 (3 H, CH_3); 2.30 (3 H, $COCH_3$); 4.15 (1 H, J = 9 Hz, C_{16}–H); 6.84 (1 H, C_4–H); 6.86 (1 H, quartet, $J_{1,2}$ = 8 Hz, $J_{2,4}$ = 3 Hz, C_2–H); 7.2 (1 H, doublet, $J_{1,2}$ = 8 Hz, C_1–H); according to the literature [7]: mp 170-173°C.

16,16-Dibromoestrone (IVb). A solution of 1 g of potash in 12 ml of water was added to a solution of 2 g of dibromoestrone acetate (IVa) in 50 ml of methanol. The mixture was stirred at room temperature for 30 min and was poured into water. The mixture was acidified with hydrochloric acid, and the precipitate was filtered off, washed on the filter with water, and dried. This gave 1.77 g of 16,16-dibromoestrone (IVb): $C_{18}H_{20}Br_2O_2$, mp 183-183.5°C (decomp.) after recrystallization from ethanol, mp 188-189°C. IR spectrum, ν, cm^{-1}: 3430, 1750, 1610, 1500; PMR spectrum: 1.14 (3 H, singlet, CH_3); 6.56 (1 H, C_4–H); 6.60 (1 H, quartet, $J_{1,2}$ = 8 Hz, $J_{2,4}$ = 3 Hz, C_2–H); 7.10 (1 H, doublet, $J_{1,2}$ = 8 Hz, C_1–H). Mass spectrum: M^+ 428.

Hydrolysis of a Mixture of 16α- and 16β-Bromoestrone Acetates ((IIa) and (IIIa)). A. 16-Bromoestrones. A solution of 3 g of potash in 20 ml of water was added to a solution of 1 g of a mixture of acetates containing 70% of the 16α epimer (IIa) and 30% of the 16β epimer (IIIa) in 30 ml of methanol and 30 ml of dioxane. The reaction mixture was stirred at room temperature for 30 min, poured into water, acidified with hydrochloric acid, and extracted with chloroform. This gave 0.96 g of a mixture of 16α- and 16β-bromoestrones (IIb and IIIb) in a ratio of 30:70. PMR spectrum for 16α-bromoestrone (ppm): 0.94 (3 H, singlet, CH_3); 4.60 (1 H, multiplet, C_{16}–H); 6.62 (1 H, C_4–H); 6.66 (1 H, quartet, $J_{1,2}$ = 8 Hz, $J_{2,4}$ = 3 Hz, C_2–H); 7.16 (1 H, doublet, $J_{1,2}$ = 8 Hz, C_1–H); for 16β-bromoestrone (ppm): 1.12 (3 H, singlet, CH_3); 4.15 (1 H, triplet, J = 9 Hz, C_{16}–H); 6.66 (1 H, C_4–H); 6.62 (1 H, C_2–H); 7.16 (1 H, C_1–H).

B. 16α-Hydroxyestrone (V). A mixture of the acetates (IIa) and (IIIa) (3.58 g) was treated with potash as in paragraph A. The reaction mixture was kept at room temperature for 12 h and was then poured into 500 ml of water and the mixture was acidified with hydrochloric acid. The resulting precipitate was filtered off and washed on the filter with water, which gave 2.27 g of a mixture of 16α- and 16β-bromoestrones (IIb) and (IIIb) in a ratio of 25:75. The aqueous solution was extracted with methylene chloride. The extract was washed with water and evaporated in vacuum. The residue (0.8 g) was crystallized from ether and recrystallized from ethanol, to give 0.38 g of 16α-hydroxyestrone (V) with mp 203.5-206°C; according to the literature [10]: 205-206.5°C. IR spectrum, ν, cm^{-1}: 3540, 3360, 1725, 1620, 1580, 1500. PMR spectrum, in C_5D_5N, ppm: 0.92 (3 H, singlet, CH_3); 4.68 (1 H, multiplet, C_{16}–H); 7.0-7.4 (C_1–, C_2–, and C_4–H). 16α-Hydroxyestrone diacetate had mp 172-173°C (from acetone and ethanol). IR spectrum, ν, cm^{-1}: 1750, 1735, 1607, 1580. According to the literature [11]: mp 172-174.5°C.

C. 3,17β-Dihydroxyestra-1,3,5(10)-trien-16-one (VI). A solution of 12 g of potash in 70 ml of water was added to a solution of 6.7 g of a mixture of 16α- and 16β-bromoestrone acetates in 130 ml of methanol and 100 ml of dioxane. The mixture was boiled in a current of argon for 3 h and was then cooled and poured into one liter of cold water and acidified with hydrochloric acid. The resulting precipitate was filtered off, washed with water, and

dried, to give 4.57 g of 3,17β-dihydroxyestra-1,3,5(10)-trien-16-one (VI) with mp 229-231°C. After recrystallization from ethanol, mp 234-235°C; according to the literature [11]: mp 236-238°C. IR spectrum, ν, cm^{-1}: 3420, 3320, 1735, 1610, 1500. PMR spectrum (in C_5D_5N; ppm): 0.94 (3 H, singlet, CH_3); 4.05 (1 H, singlet, C_{17}—H).

SUMMARY

The direct bromination of estrone acetate gives predominantly a mixture of 16α- and 16β-bromo derivatives, and also 16,16-dibromoestrone acetate. Under the action of an aqueous methanolic solution of potash, the mixture of epimeric acetates is converted into 16α-hydroxyestrone which isomerizes on heating into 16-ketoestradiol.

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TRANSFORMATION OF THE AGLYCONES IN STEROID GLYCOSIDES. 1. SYNTHESIS OF 20β-ACETOXY-16β,23-EPOXY-21,24-DINOR-5α-CHOLANE-3β,17α-DIOL 3-O-[O-β-D-GLUCOPYRANOSYL-(1 → 2)-O-β-D-GLUCOPYRANOSYL-(1 → 4)-β-D-GALACTOPYRANOSIDE]

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The pathways of the chemical transformation of aglycones and their glycosides that do not affect the glycosidic chain are considered. Starting from 3β-hydroxy-5α-pregn-16-en-20-one 3-O-[O-β-D-glucopyranosyl-(1 → 2)-O-β-D-glucopyranosyl-(1 → 4)-β-D-galactopyranoside] the corresponding 16α(H),17α(OH)-dihydropyranone glycoside has been obtained. The latter has been converted into the polyacetate of a glycoside with a 17α,20β-dihydroxytetrahydropyran ring E. The structure and stereochemistry of the final compound have been shown from the results of the ^1H and ^{13}C NMR spectra and mass spectra.

In spite of the fact that the structure and biological action of steroid and triterpenoid glycosides has long been the object of broad studies [1-3] clarity has so far been lacking on what roles the glycoside and aglycone moieties of the molecule play here. The answer to this question to a considerable degree comes up against the difficulty or impossibility of obtaining from natural sources systematic sets of compounds having, for example, the same glycosidic chain with homologous or analogous aglycones. Apparently the production of such a set

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