INFLUENCE OF A SUBSTITUENT AT C_3 ON THE DIRECTION OF BROMINATION OF ESTRA-1,3,5(10)TRIEN-17-ONES

O. I. Fedorova, L. S. Morozova,
L. M. Alekseeva, and G. S. Grinenko

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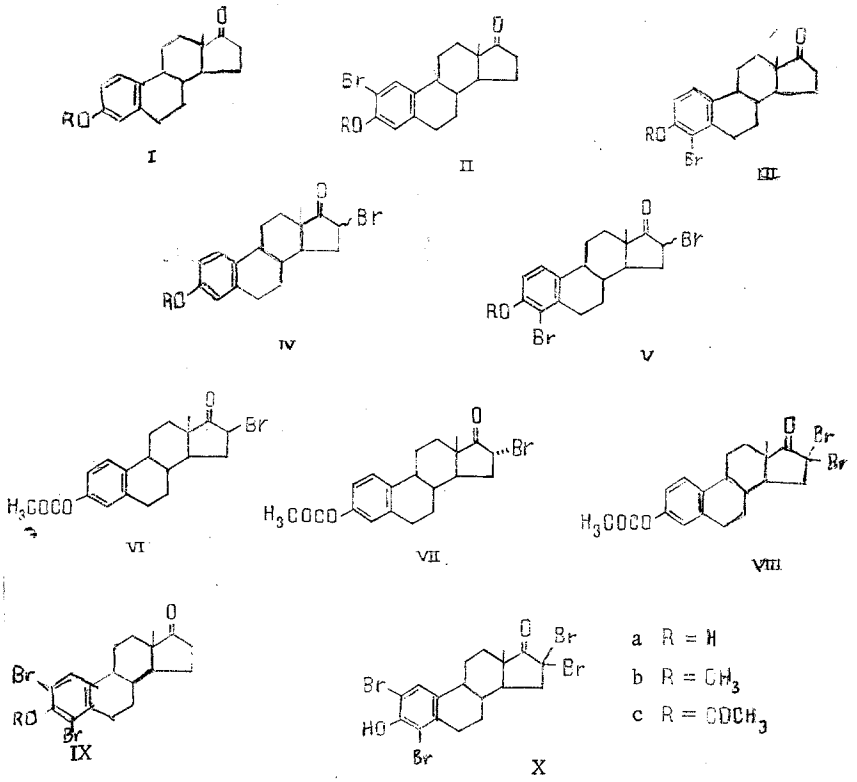
The influence of a C_3 substituent on the direction of bromination of estra-1,3,5(10)-trien-17-one is discussed: Estrone and its methyl ether give mainly derivatives bromine-substituted in ring A, while the bromination of estrone acetate leads to the production of 16-mono- and 16,16,dibromo-substituted estrones.

The preparation of halogen-substituted estra-1,3,5(10)-triene-17-ones is one of the methods for functionalizing the steroid molecule which permits passage to unsaturated or oxygen- and amino-substituted compounds. Some halogen-substituted estratrienones possess a useful biological activity; for example, the 16-halogen derivatives of the methyl ether of estrone have shown a high antilipid activity [1].

Various methods of introducing halogen atoms into the estra-1,3,5(10)-trien-17-one molecule leading to 2-, 4-, or 16-mono-halogen-substituted or 2,4-dihalogen-substituted compounds are known. The influence of halogenating agents on the direction of halogenation has also been discussed: Depending on the reagent used it is possible to obtain 2-, 4-, or 16-halogen-substituted estra-1,3,5(10)-trien-17-ones [2-4]. A dependence of the direction of bromination on the solvent has also been observed [2].

We have studied the influence of a substituent in position 3 on the direction of the direct bromination of estra-1,3,5(10)-trien-17-one. By the reaction of the latter with bromine in methylene chloride in the presence of catalytic amounts of hydrochloric acid it was



A. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 327-330, May-June, 1984. Original article submitted May 26, 1983.

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possible to obtain 2-, 4-, and 16-bromine-substituted compounds. The presence in position 3 of a substituent affecting the electron density of the aromatic ring A facilitates (where it increases the electron density) or suppresses (where it decreases the electron density) bromination in ring A. Thus, the bromination of estrone (Ia) with an equimolar amount of bromine formed mainly a mixture of 2- and 4-monosubstituted estrones (IIa and IIIa), and only about 15% of 2,16- and 4,16-dibromo derivatives of estrones (IVa and Va). With a 1.5-fold increase in the amount of bromine the proportion of the latter rose to 24%. The formation of 2,4-dibromine-substituted or 2,4,16-tribromine-substituted estrones was insignificant. Thus, when estrone is brominated in chloride it is primarily positions 2 and 4 of the molecule that are subjected to attack by the bromine, while substitution at C_2 is somewhat preferred over substitution at C_4. This preference became overwhelming when estrone methyl ether (Ib) was brominated: Under similar conditions, the 2,16-dibromo derivative (IIb) was formed almost exclusively. However, in this case, even with an excess of bromine, the reaction does not go to completion. In addition to electronic factors, the nature of the brominating agent and the solvent used obviously exert a strong influence on the selectivity of C_2- or C_4-bromination. For example, Schwenk et al. [5] observed the predominant formation of 4-monobromoestrone when estrone was brominated in acetic acid or with N-bromoacetamide in ethanol.

In the bromination of estrone acetate (Ic), in contrast to that of estrone and its methyl ether, substitution took place in ring D even when an excess of bromine was used. The acetates of 16β- and 16α-bromoestrone (VI and VII) were formed, with, in minor amount, the acetate of 16,16-dibromoestrone (VIII). The further bromination of the mixture of 16β- and 16α-bromoestrones acetates after their isolation took place with difficulty, giving 16,16-dibromoestrone acetate. Other compounds isolated from the products of this reaction were 2,16-dibromoestrone (IVa), and 2,4,16,16-tetrabromoestrone (X). It is characteristic that these compounds containing bromine in ring A had not an acetoxy but a hydroxy group in position 3. Obviously, under the conditions of prolonged bromination in the presence of hydrogen bromide partial hydrolysis of the acetate took place with the formation of the C_3-alcohol, facilitating bromination in ring A.

The presence of these compounds in the bromination products was established from the nature of the multiplicity of the signals of the aromatic protons of ring A and of the C_{16} protons of ring D in the PMR spectra. Thus, in the spectra of the 2-bromine-substituted estratrienones (IIa and b), the signals of the protons were observed in the form of two singlets at 7.38-7.48 and 6.6-6.85 ppm, respectively. The spectra of the 4-bromo derivatives (IIIa, b) were characterized by the presence of two doublets ($J_{1,2}$ = 9 Hz) relating to the protons at C_1 and C_2 (δ = 7.2-7.3 and 6.9-7 ppm). The assignment of the signals of the protons at C_1, C_2, and C_4 was made on the basis of the comparison of the spectra of compounds (II) and (III) and of unsubstituted estrone. The assignment made was in harmony with the spectra of 2,4-dibromoestrone and its methyl ether (IXa and b), in each of which the proton in the C_1 position is represented by a singlet in the 7.4-7.5 ppm region.

EXPERIMENTAL

IR spectra were taken on a Perkin-Elmer 457 instrument in paraffin oil, PMR spectra on a XL-100 spectrometer (Varian) in $CDCl_3$, with TMS as internal standard. The chemical shifts are given in the δ scale. Mass spectra were taken on a MAT-112 instrument (Varian) at an energy of the ionizing electrons of 70 eV, a temperature of the ionizing chamber of 180°C, and with direct introduction of the sample into the source. Lachema 40/100 silica gel was used for column chromatography, and the fractions were analyzed by thin-layer chromatography (Silufol plates, Czechoslovakia).

Brominaton of Estra-1,3,5(10)-trien-17-ones. At room temperature, 2 drops of a 10% solution of hydrochloric acid in methanol and, over 30 min, a solution of 1.26 mmole (experiment A) or 1.8 mmole (experiment B) of bromine in 25 ml of methylene chloride was added to 1.2 mmole of a 3-substituted estra-1,3,5(10)-trien-17-one in 30 ml of methylene chloride. The reaction mixture was stirred for 30 min and was poured into a 10% aqueous solution of sodium bicarbonate. The layers were stirred for 5 min, and the methylene chloride layer was separated off, washed with water, dried over calcinated sodium sulfate, and evaporated. The residue was crystallized from ether or chromatographed on silica gel.

Bromination of Estrone (Ia). A. Estrone (7.45 g) was brominated as in the first experiment, and the resulting mixture of bromine-substituted compounds was acetylated with acetic

anhydride in pyridine at room temperature, to give 10.21 g of a mixture of acetates. This mixture was chromatographed on silica gel. Benzene and then a mixture of benzene and ether successively eluted the following fractions: 1.3 g of a mixture of the acetates of 2,16- and 4,16-dibromoestrones (IVc and Vc) in a ratio of 7:4, from which 0.2 g f the acetates of 2,16α and 2,16β-bromoestrones in a ratio of 7:3 was obtained; 6.87 g of a mixture of the acetates of 2- and 4-monobromoestrones (IIc and IIIc in a ratio of 7:5); and 1.34 g of estrone acetate (Ic), mp 123-123°C [sic].

B. Estrone (3.33 g) was brominated as in experiment B. From the mixture of bromo derivatives obtained, 1.3 g of a crystalline mixture of 2- and 4-monobromoestrones (IIa) in a ratio of 5:3 was isolated by crystallization. The mother solution yielded 3.5 g of a mixture of monobromo- and dibromoestrones (2:1) with the 2-bromo-substituted compounds predominating. No 2,4-dibromo or 2,4,16-tribromo compounds were detected in the reaction mixture.

Acetate of 2,16-dibromoestrone (IVc): a mixture of the 16α- and 16β- epimers (7:3), mp 165-168°C. IR spectrum, ν_{max}^{Nujol}, cm^{-1}: 1760 ($COCH_3$); 1745 (CO); 1590 (C=C). PMR spectrum (ppm): 7.48 (singlet, 1 H at C_1); 6.85 (singlet, 1 H at C_4); 4.60 (multiplet, βH at C_{16}); 4.16 (triplet, J = 4 Hz, αH at C_3); 2.34 (singlet, 3 H, $COCH_3$); 1.12 (singlet, 3 H at C_{18} for the β-Br epimer); 0.94 (singlet, 3 H at C_{18} for the α-Br epimer); M^+ 468 and 472.

2-Bromoestrone acetate (IIc): PMR spectrum, ppm: 7.52 (singlet, 1 H at C_1); 6.84 (singlet, 1 H at C_4); 2.34 (singlet, $COCH_3$); 0.91 (singlet, 3 H at C_{18}).

4-Bromoestrone acetate (IIIc): PMR spectrum, ppm: 7.32 (doublet, J = 9 Hz, 1 H at C); 6.98 (doublet, J = 9 Hz, 1 H at C_2); 2.35 (singlet, 3 H, $COCH_3$); 0.92 (singlet, 3 H at C_{18}).

Bromination of Estrone Methyl Ether (Ib). Estrone methyl ether (Ib) (3.9 g) was brominated as in experiment B. The product contained approximately equal amounts of the methyl ethers of 2,16α- and 2,16β-dibromoestrones (IVb) (78%) and the methyl ether of estrone (22%). By crystallization from this mixture 1.18 g of the methyl ether of 2,16β-dibromoestrone (IVb) was isolated: $C_{19}H_{22}Br_2O_2$, mp 221-222°C (from methanol); IR spectrum, ν_{max}^{Nujol}, cm^{-1}: 1750, 1600, 1380, 1256, 1240, 1042-1050, 880, 725, 680. PMR spectrum, ppm: 7.40 (singlet, 1 H at C_1); 6.60 (singlet, 1 H at C_4); 4.20 (triplet, J = 4 Hz, α-H at C_{16}); 2.81 (singlet, OCH_3); 1.2 (singlet, 3H at C_{18}).

Bromination of Estrone Acetate (Ic). The bromination of 3.84 g of estrone acetate as in experiment B gave a mixture of the acetates of 16β- and 16α-monobromoestrones (VI and VII) and of 16,16-dibromoestrone (VIII). The amount of the last-mentioned compound in the mixture was, according to TLC, 10%. No appreciable amounts of compounds brominated in ring A were detected.

Bromination of a Mixture of 16β- and 16α-Bromoestrone Acetates. To a solution of 14.37 g of a mixture (3:7) of 16β- and 16α-bromoestrone acetates (VI and VII) in 100 ml of methylene chloride was added 0.2 ml of a 10% solution of hydrochloric acid in methanol and then, over 1 h, a solution of 8 g of bromine in 70 ml of methylene chloride. The reaction mixture was stirred at room temperature for 3 h and was worked up in the manner described above. This gave 19 g of a mixture of bromine-substituted compounds which was chromatographed on 200 g of silica gel. Benzene–hexane (5:1) in benzene eluted successively: 2.48 g of 2,4,16,16-tetrabromo-3-hydroxyestra-1,3,5(10)-trien-17-one (X); 1.8 g of a mixture of 2,16- and 4,16-dibromo-3-hydroxyestra-1,3,5(10)-trien-17-ones (IVa and Va); and 6.63 g of acetate of 16,16-dibromo-3-hydroxyestra-1,3,5(10)-trien-17-one (VIII). Benzene–ether (95:5 and 90:10) yielded 3.69 g of a mixture of the acetates of 16β- and 16α-bromo-3-hydroxyestra-1,3,5(10)-trien-17-ones (VI and VII) and 0.1 g of the acetate of 16α-bromo-3-hydroxy-estra-1,3,5(10)-trien-17-one.

2,4,16,16-Tetrabromo-3-hydroxyestra-1,3-5(10)-trien-17-one (X): $C_{18}H_{18}Br_4O_2$ mp 114-115°C (from ethanol and acetone). UV spectrum ν_{max}^{Nujol}, cm^{-1}: 3450 (OH); 1758 (CO); 1582 and 1556 (=C). M^+: 582, 590. PMR spectrum, ppm: 7.37 (singlet, 1 H at C_1); 5.85 (singlet, OH); 1.13 (singlet, 3 H at C_{18}).

Acetate of 16,16-dibromo-3-hydroxyestra-1,3,5(10)-trien-17-one (VIII), mp 164-165°C; according to the literature [6], mp 165-166°C.

Acetate of 16α-bromo-3-hydroxyestra-1,3,5(10)-trien-17-one, mp 168.5-169.5°C (from ethanol); according to the literature [7], mp 169-171°C.

CONCLUSION

The result of the direct bromination of estra-1,3,5(10)-trien-17-one depends substantially on the nature of the substituent at C_3: Estrone and its methyl ether give mainly compounds bromine-substituted in ring A, while the bromination of estrone acetate leads to 16-mono- and 16,16-dibromo-derivatives.

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THERMAL DECOMPOSITION OF 2-HYDROXYBENZYLAMINES

V. I. Vinogradova and M. S. Yunusov

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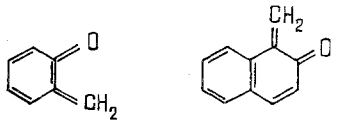
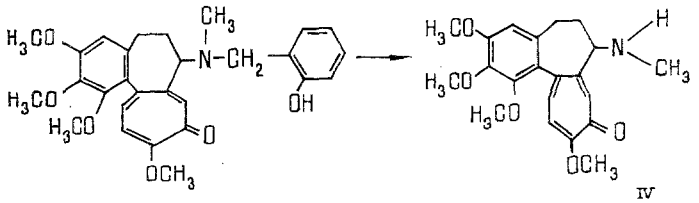
The results are given of the preparation of a number of 2-hydroxybenzylamines and their thermal decomposition. The thermolysis reactions and the formation of the corresponding amines take place smoothly and with good yields.

The convenient method of retrodiene decomposition of 2-hydroxybenzylamines [1, 2] and of 2-hydroxy-1-naphthylmethylamines [3, 4], which is used for the regeneration of O-quinone methide compounds (I, II), has been discussed in the literature.



I II

In the thermolysis of the alkaloids speciosine (III), Kiselev et al. [5] isolated the nitrogen-containing moiety of the molecule — colchamine (IV) — in 52% yield.



III IV

It was of interest to study the possibility of using salicylaldehyde for blocking the amino group and its subsequent debenzylation under pyrolysis conditions. With this aim, we have synthesized a number of substances (Table 1) by condensing amines and salicylaldehyde followed by sodium tetrahydroborate reduction according to the scheme.

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR, Tashkent.

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