PREPARATION OF ISOMERIC 5,6-BROMOHYDRINS OF ANDROSTANE AND PREGNANE

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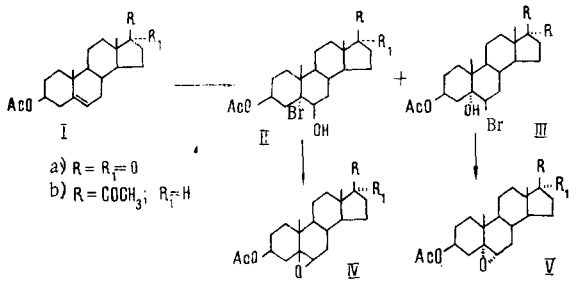
UDC 547.92+542.957.2

Steroid bromohydrins are used as intermediates in the synthesis of medicinal preparations – for example, the antiinflammatory 9α-fluorine-substituted corticosteroids, gestagens, and anabolitics of the 19-norsteroid series. The synthesis of the latter, in particular, uses 5α-bromo-6β-hydroxy compounds of the pregnane and androstane series. The usual method for their preparation is the reaction of acetates of Δ^5 compounds with hypobromous acid in dioxane [1-7], tetrahydrofuran [8], aliphatic ethers [9, 10], acetone [11], or a mixture of acetone and dioxane [12]. However, this reaction has been insufficiently studied. The papers mentioned describe the production of only one isomer of the bromohydrin with a yield of 50-75%.

On studying this reaction, we have found that the addition of hypobromous acid to the 5,6 double bond of steroids takes place ambiguously; simultaneously with the 5α-bromo-6β-hydroxy compounds (IIa, b, and VII), the isomeric 6β-bromo-5α-hydroxy compounds (IIIa, b, and VIII) are formed. As we have shown, the ratio of the isomers depends on the nature of the initial Δ^5-steroid and, to a great extent, on the solvent in which the reaction is performed. This dependence has been studied for the case of the preparation of the 3-acetate of 5α-bromo-3β,6β-dihydroxyandrostan-17-one (IIa) from dehydroepiandrosterone acetate (I) by the action of Dibromantin* in the presence of perchloric acid in various solvents. To isolate the (IIa) from the reaction mixture we used its capacity for forming sparingly soluble adducts with chloroform [13]. This enabled us to separate the mixture of isomers with quantitative yield. Below we give the dependence of the ratio of the isomers of the bromohydrin of dehydroepiandrosterone acetate on the solvent.

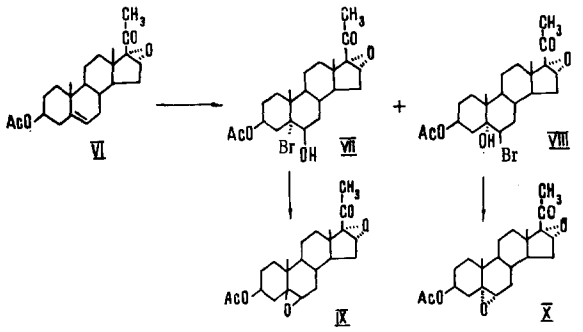
Solvent	Ratio of the 5α-bromo-6β-hydroxy isomer (IIa) to the 6β-bromo-5α-hydroxy isomer (IIIa)
Dioxane	2 : 3
THF	1 : 1
Ether	3 : 2
Ethyl acetate	3.2 : 1.2

The best ratio of the isomers in favor of the 5α-bromo-6β-hydroxy compound, which is used in the synthesis of the 19-norsteroids, was obtained in ethyl acetate.



*1,3-Dibromo-5,5-dimethylhydantoin.

All-Union Chemical and Pharmaceutical Scientific-Research Institute. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 72-77, January-February, 1972. Original article submitted October 13, 1971.



In the pregnane series in this solvent, the reaction takes place with the formation of a mixture of the 5α-bromo-6β-hydroxy (IIb) and 6β-bromo-5α-hydroxy (IIIb) isomers in the same ratio. The bromohydrins of the pregnane series (IIb, IIIb, VII, and VIII) do not give an adduct with halogeno hydrocarbons. The separation of these isomers was based on their different solubilities in ethyl acetate. The bromohydrins (IIb) and (VII), which are sparingly soluble in ethyl acetate, precipitated from the reaction mixture, and the isomers (IIIb) and (VIII) remaining in solution were purified by fractional crystallization.

The structures of the bromohydrins were established on the basis of elementary analysis and IR and NMR spectra. The IR spectra have strong absorption bands characteristic for a hydroxy group: in a dilute solution (0.01% in CCl_4) the absorption of a secondary hydroxy group at 3630 cm^{-1} in the spectra of (IIa, b, and VII) and of a tertiary hydroxy group at 3600 and 3590 cm^{-1}, respectively, in the spectra of (IIIa, b, and VIII), which is in harmony with information on a decrease in the frequency of vibrations on passing from a secondary to a tertiary hydroxy group [14].

The configurations of the bromohydrins obtained were determined from the NMR spectra. In all the spectra, weak-field signals in the 5.0-5.7 ppm region are assigned to the proton at C-3 to which the acetoxy group is attached. The nature of the splitting – a seven-line structure with a half width of 15 Hz (the result of interaction with the four neighboring methylene protons) [15] – shows the axial arrangement of the protons at C-3 in all the bromohydrins which, in its turn, confirms the trans linkage of rings A and B. Narrow signals in the 3.94-4.35 ppm region (half-width 3.75 Hz) relate to the protons at C-6. This value of the half width of the lines of the proton signals is due to two factors: the equatorial nature of the proton and the presence of only two vicinal neighbors [15]. What has been said above permits the conclusion that in all the isomers the bromine atom and the hydroxy group have the trans-diaxial arrangement.

As can be seen from the Table, the signals of the 6α protons of the bromohydrins (IIa, b, and VII) show some downfield shift in comparison with their structural isomers, and the 3α proton is deshielded by a 5α bromine atom to a greater extent than by a 5α hydroxy group. For all the compounds given above, the chemical shifts of the protons of the angular methyl groups show poor agreement with the calculated values from the empirical rule of additivity. This is apparently due to the deformation of the skeleton through the strong 1,3-nonbound interactions of the substituents in the trans-diaxial position [15].

The structures of the 6β-bromo-5α-hydroxy compounds (IIIa, b and VII), which we isolated for the first time, are confirmed by their conversion into the known 5α,6-oxides (Va, b and X) [16, 17]. The 5α-bromo-6β-hydroxy compounds (IIa, b and VII) are converted correspondingly into the 5β,6-oxides (IVa, b and IX). The constants of the oxides (IVa, b) corresponded to those given in the literature [18, 19]. The oxide (IX), which we obtained for the first time, was characterized by its IR and NMR spectra.

Chromatography in a thin layer of silica gel (Silufol) in the benzene–8% methanol system showed a dependence of the mobility of the bromohydrins on their structures: the 6β-bromo-5α-hydroxy isomers, which contain a tertiary hydroxy group, are more mobile than the 5α-bromo-6β-hydroxy isomers with a secondary hydroxy group. The substances have the following R_f values: IIa – 0.41, IIIa – 0.65, IIb – 0.53, IIIb – 0.62, VII – 0.53, VIII – 0.77. Under the conditions of chromatographic monitoring on silica gel, the bromohydrins are not converted into the oxides.

The formation of structural isomers of the bromohydrins can be explained by the following mechanism:

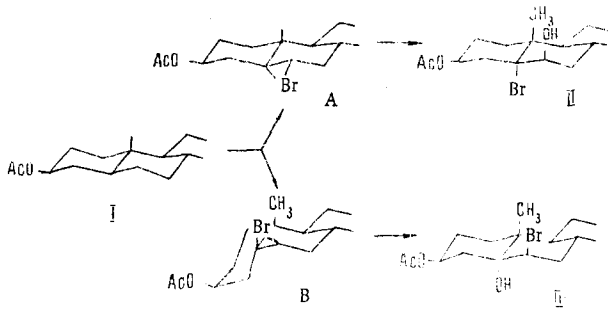
The electrophilic Br^+ attacks the olefin (I) from the α and the β sides with the formation of the cyclic bromonium cations A and B. On subsequent attack by a OH^- anion, the opening of the rings in the case of the 5α,6-bromonium ion takes place with the rupture of the C_6–Br bond, and in the case of the 5β-6-bro-

TABLE 1. Chemical Shifts in the NMR Spectra of the Bromohydrins Obtained (δ, ppm)

Compound	Chemical shifts						Solvent
	18–CH_3		19–CH_3		3H	6–H	
	singlet		singlet		multiplet	multiplet	
	found	calc.	found	calc.			
IIa	0,7	0,91	1,46	1,40	5,7	4,355	C_5H_5N
IIb	0,8	0,66	1,4	1,37	5,407	4,122	$CHCl_3$
IIIa	0.61	0,94	1,31	1,167	5,505	4,35	C_5H_5N
IIIb	0,66	0,69	1,35	1,142	5,05	3,968	$CHCl_3$
VII	1,05	1,076	1,35	1,38	5,215	4,15	$CDCl_3$
VIII	1,08	1,109	1,35	1,15	5,016	3,940	$CDCl_3$

monium ion at the C_5–Br bond with the formation of the trans-diaxial bromohydrins (II) and (III), respectively.

The direction of the opening of the intermediate bromonium cation depends both on conformational and on electronic factors. In the intermediate cation A, the ionization of the C_5–Br bond is inhibited by the –I effect of the 3β-acetoxy group, and because of this, the main reaction product is the bromohydrin (II). In the intermediate B, the conformational factor is predominant: the ionization of the C_5–Br bond leads to the thermodynamically more stable product with the trans linkage of the rings. This corresponds completely to the mechanism for the opening of the 5α,6- and 5β,6-oxide rings of 3β-acetoxysteroids.



The possibility of the formation of 5α,6- and 5β,6-cyclic intermediate iodonium cations has been discussed by Bowers et al. [20] in an explanation of the anomalous addition of FI to Δ^5-steroids.

EXPERIMENTAL

The NMR spectra were obtained on a JNM-4H-100/100 MHz instrument with tetramethylsilane as standard. The IR spectra of 0.01% solutions of compounds (IIa) and (IIIa) in carbon tetrachloride and of mulls of the other compounds in paraffin oil were taken on a UR-10 instrument. The specific rotations were determined in chloroform on a ÉLPU-0.1 instrument. The C, H, and Br figures found corresponded to the calculated values.

3-Acetate of 5α-Bromo-3β,6β-dihydroxyandrostan-17-one (IIa) and the 3-Acetate of 6β-Bromo-3β,5α-dihydroxyandrostan-17-one (IIIa). At 10-12°C, 240.7 ml of a 10% solution of perchloric acid and 48 g of Dibromantin were added to a solution of 100 g of dehydroepiandrosterone acetate in 600 ml of ethyl acetate. The mixture was stirred at a temperature not exceeding 15°C for 45 min. Then 330 ml of a 10% aqueous solution of sodium sulfite and 263 ml of chloroform were added to it. The mixture was heated at 45°C for 1 h and was cooled to –5°C. A crystalline precipitate of the adduct (IIa) deposited. The precipitate was filtered off and was washed on the filter with 196 ml of chloroform and with water to neutrality. This gave 76.6 g of (IIa) with the composition $C_{21}H_{31}O_4Br$, mp 172-172.5°C (decomp.), $[\alpha]_D^{20} \pm 0°$. Literature data: mp 173-175°C, $[\alpha]_D^{20} +0°$, and mp 171-172°C, $[\alpha]_D^{20} +1.9°$ [1, 2]. IR spectrum: 3630, 1740 cm^{-1}; for NMR spectrum, see Table 1.

The reaction solution was washed to neutrality and evaporated in vacuum, and the resulting mixture of the isomers (IIa) and (IIIa) was treated with chloroform, giving an additional 3% of (IIa). The total yield of (IIa) was 61%. The chloroform solution, containing mainly the isomer (IIIa), was evaporated to small volume (60 ml), and 42 ml of ether was added. The precipitate that deposited was filtered off and washed with ether, giving (IIIa), $C_{21}H_{31}O_4Br$, mp 178-179°C (decomp.), $[\alpha]_D^{20} -13.5°$. IR spectrum: 3600, 1740 cm^{-1}; for NMR spectrum, see Table 1.

3-Acetoxy-5α,6-epoxyandrostan-17-one (Va). A solution of 80 g of (IIIa) in 1200 ml of ethanol was treated with 23 g of anhydrous potassium acetate, the mixture being boiled for 18 h. After the solvent had been distilled off completely in vacuum, the residue was dissolved in 300 ml of methylene chloride, and the solution was washed to neutrality. The residue of (Va) was recrystallized from a 20-fold amount of ethyl acetate. This gave (Va), $C_{21}H_{30}O_4$, mp 221.5-223°C, $[\alpha]_D^{20} -12°$. Literature data: mp 220-222°C, $[\alpha]_D -12°$ and mp 222-224°C, $[\alpha]_D^{20} -12°$ [17].

3-Acetate of 6β-Bromo-3β,5α-dihydroxyandrostan-17-one (IIIa) [21]. At 16-18°C, 0.6 ml of a 16% (d=1.21) acetic acid solution of hydrogen bromide was added dropwise to a suspension of 0.5 g of (Va) in 4 ml of glacial acetic acid. After 2 h, 9-10 ml of water was added with ice-water cooling. The precipitate was filtered off and was washed with 33% acetic acid and with water to neutrality. This gave 0.6 g (98%) of (IIIa) with mp 178.5-180°C.

A sample of (IIIa) gave no depression of the melting point in admixture with a sample of (IIIa) obtained by the separation of the mixture of the isomers (IIa) and (IIIa) through the adduct of (IIa) with chloroform.

3-Acetate of 5α-Bromo-3β,6β-dihydroxypregnan-20-one (IIb) and the 3-Acetate of 6β-Bromo-3β,5α-dihydroxypregnan-20-one (IIIb). A solution of 47.5 g of pregnenolone acetate in 300 ml of ethyl acetate was made at 40°C, and then the solution was cooled to 10°C and 120 ml of 10% $HClO_4$ and 24 g of Dibromantin were added over 30 min. A voluminous precipitate deposited 10 min after the addition of the Dibromantin. The mixture was stirred for 35 min, and 150 ml of a 10% aqueous solution of sodium sulfate was added. The precipitate was filtered off and was washed with water to neutrality. This gave 27.6 g of (IIb) with mp 150°C (decomp.). An analytical sample, after recrystallization from ethyl acetate, had mp 159.5-160°C (decomp.), $[\alpha]_D$ +8.1°. Literature data: mp 165-167°C, $[\alpha]_D$ +6.5° [6]. The ethyl acetate solution was washed with water to neutrality, and evaporated to small volume, whereupon it deposited 12 g of a mixture of (IIb) and (IIIb).

Two successive recrystallizations from ethyl acetate and methanol yielded (IIIb), $C_{23}H_{35}O_4Br$, with mp 196-198°C (decomp.), $[\alpha]_D$ −16°. IR spectrum: 3340, 1740, 1695, 1260 cm^{-1}. For the NMR spectrum, see Table 1.

3-Acetate of 5α-Bromo-3β,6β-dihydroxy-16α,17-epoxypregnan-20-one (VII) and the 3-Acetate of 6β-Bromo-3β,5α-dihydroxy-16α,17-epoxypregnan-20-one (VIII). Under similar conditions, 9.5 g of 3β-acetoxy-16α,17-epoxypregnan-5-en-20-one, 4.2 g of Dibromantin, and 13.2 ml of 10% perchloric acid solution gave 5.2 g of (VII), $C_{23}H_{33}O_5Br$. An analytical sample was obtained by fractional crystallization successively from ethyl acetate and chloroform, mp 173-174°C (decomp.), $[\alpha]_D$ −17.8°. IR spectrum: 3410, 1740, 1690, 1245 cm^{-1}. For the NMR spectrum, see Table 1.

The ethyl acetate solution contained 3.7 g of a mixture of the isomers (VII) and (VIII). Fractional recrystallization from ethyl acetate and acetone yielded (VIII), $C_{23}H_{33}O_5Br$, with mp 180-181°C (decomp.), $[\alpha]_D$ −37.4°. IR spectrum: 3420, 1745, 1695, 1245 cm^{-1}. For the NMR spectrum, see Table 1.

3-Acetoxy-5α,6-epoxypregnan-20-one (Vb). At the boiling point, 0.32 g of fused potassium acetate was dissolved in 3.2 ml of absolute methanol, and then a solution of 0.4 g of the bromohydrin (IIIb) in 1.5 ml of dry dioxane was added. The mixture was boiled for 40 min and was cooled with ice water. Then 8.7 ml of water was added, and the precipitate that deposited was filtered off and washed with water to neutrality. This gave 0.29 g of (Vb), mp 162-165°C. After recrystallization from methanol, the melting point of (Vb) was 167-167.5°C, $[\alpha]_D$ +16°. Literature data: mp 167-168°C, $[\alpha]_D$ +14° [22].

3-Acetoxy-5β,6,16α,17-diepoxypregnan-20-one (IX). Under the conditions described above, 0.48 g of the bromohydrin (VII), 0.39 g of potassium acetate, 3.9 ml of methanol, and 4.8 ml of dioxane yielded 0.36 g of (IX) with mp 203-206°C. After recrystallization from ethyl acetate, substance (IX) had the composition $C_{23}H_{32}O_5$, mp 208.5-210°C, $[\alpha]_D$ +31.5°. IR spectrum: 1725, 1700 cm^{-1}.

3β-Acetoxy-5α,6,16α,17-diepoxypregnan-20-one (X). Similarly, 0.21 g of the bromohydrin (VIII), 0.16 g of potassium acetate, 1.6 ml of methanol, and 1 ml of dioxane gave 0.15 g of (X) with mp 202-204°C, $[\alpha]_D$ −16°. Literature data: mp 202-204°C, $[\alpha]_D$ −18° [23].

SUMMARY

The formation of bromohydrins from 3-acetoxy-Δ^5-steroids has been studied. In addition to the 5α-bromo-6β-hydroxy compounds, their structural isomers, the 6β-bromo-5α-hydroxy compounds, are obtained. A mechanism for their formation is proposed.

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