PREPARATION OF THE FORMATES OF ISOMERIC 5,6-BROMOHYDRINS OF THE PREGNANE SERIES

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In a preceding paper [1] we have reported the preparation of isomeric 5,6-bromohydrins by the reaction of 3-acetates of pregn-5-enols with Dibromantin [1,3-dibromo-5,5-dimethylhydantoin] in the presence of perchloric acid in ethyl acetate. Continuing an investigation of the influence of the solvent on the course of the reaction, we have found that when this reaction is performed in dimethylformamide, it is not the free bromohydrins but their formates (II) and (III) that are formed. The latter have been isolated and characterized in the pregnane series – both the 3-acetate 6-formate of 5α-bromo-3β,6β-dihydroxypregnan-20-one (IIa) and the 3-acetate 5-formate of 6β-bromo-3β,5α-dihydroxypregnan-20-one (IIIa). Their separation was based on their different solubilities in dimethylformamide. The 6-formate (IIa), which is sparingly soluble in dimethylformamide, precipitated from the reaction medium, and the mixture of the formates (IIa) and (IIIa) remaining in solution in the dimethylformamide was precipitated with water. Fractional crystallization from acetone yielded the 5-formate (IIIa). On a thin-layer chromatogram (TLC, Silufol, heptane–ethyl acetate (3:2) system, chromogenic agent conc. sulfuric acid] compound (IIa) (R_f 0.41) was colored blue and compound (IIIa) (R_f 0.37) yellow. We established the structures of (IIa) and (IIIa) on the basis of their chemical transformations, and it was confirmed by the results of elementary analysis and by IR and NMR spectroscopy.

The conversion under the action of zinc dust in acetic acid of a mixture of (IIa) and (IIIa) into pregnenolone acetate (Ia) shows that no skeletal rearrangements take place in the compounds under consideration. Alkaline hydrolysis of the formate (IIa) gave the 5β,6-oxide (VIIa) identical with the product formed by the alkali treatment of the bromohydrin (Va), which shows the β orientation of the formyloxy group. Finally, the structure of (IIa) was confirmed by its formation from the bromohydrin (Va) and formic acid.

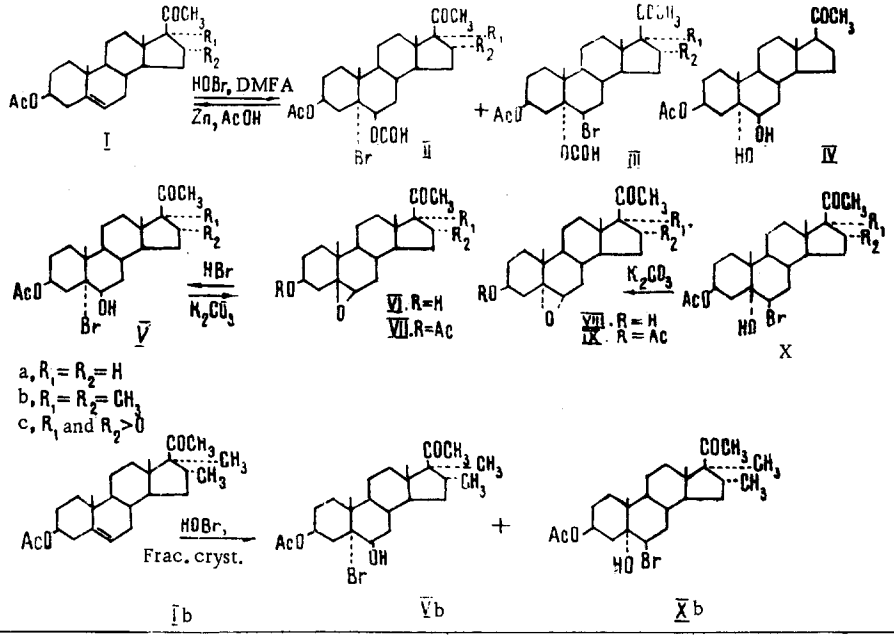

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TABLE 1. Relative Retention Times and Proportions of the Components in the Mixture Analyzed

Compound	Relative retention time	Amt. in the reaction mixture, %	Ratio of the 5β,6- to the 5α,6-oxides
3β-Hydroxypregna-5,16-dien-20-one acetate	1,00*	—	—
Ia	1,11	7,0	—
VIIa	2,70	54,0	2,77
IXa	3,35	19,5	1,00
Ib	1,52	1,5	
VIIb	3,09	64,5	2,80
IXb	3,93	23,0	1,0
Ic	1,26	2,0	
VIIc	2,74	54,5	1,56
IXc	3,78	35,0	1,00

*The relative retention times are referred to HPDA, the retention time of which was 2.3 min.

Alkaline hydrolysis converted the formate (IIIa) into the 5α,6-oxide (IXa), identical with a sample obtained previously [1]. It was impossible to convert the bromohydrin (Xa) into the formate (IIIa) by the esterification of the tertiary hydroxy group.

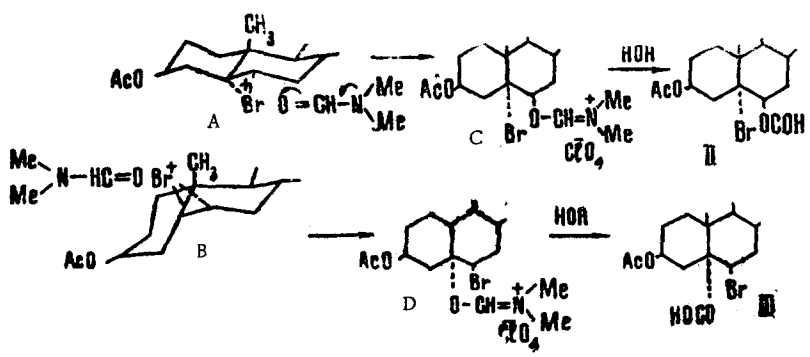
The NMR spectra of (IIa) and (IIIa) differ by the signals of the protons at C_3, which are located at 5.35 ppm for (IIa) and 4.7 ppm for (IIIa). The upfield shift of the signal of the proton in the spectrum of (IIIa) can be explained by a 1,3-diaxial interaction of the proton with the formyl group at C_5. The reaction of 16,17-disubstituted pregnenolones (Ib and Ic) with Dibromantin in the presence of perchloric acid in dimethylformamide takes place similarly. According to TLC, the reaction forms a mixture of the less polar 6β-formate (IIb) (R_f 0.41) and the more polar 5α-formate (IIIb) (R_f 0.36) and, respectively, the 6β-formate (IIc) (R_f 0.37) and the 5α-formate (IIIc) (R_f 0.31). To confirm the structures of the 6β-formate (IIb) and the 5α-formate (IIIb), we obtained the isomeric bromohydrins (Vb) and (Xb) by the reaction of (Ib) with hypobromous acid in ethyl acetate. According to GLC [Silufol, benzene–methanol (23 : 2) system], the bromohydrin (Vb) is less mobile (R_f 0.34) than its isomer (Xb) (R_f 0.48), which agrees with the results that we have obtained previously on the mobility of bromohydrins as a function of their structure [1]. The IR spectrum of (Vb) has an absorption band at 3620 cm^{-1} corresponding to a secondary hydroxy group, while in the spectrom of (Xb) an absorption band at 3595 cm^{-1} characterizes a tertiary hydroxy group. The configurations of the bromohydrins obtained for the first time were confirmed by their NMR spectra and by their conversion into the corresponding 5,6-oxides (VIIb) and (IXb). The latter have not been described in the literature and were therefore characterized by their elementary analyses and their IR and NMR spectra.

On treatment with alkali, the bromohydrin (Vb) and its formate (IIb) form one and the same 5β,6-oxide (VIIb), which shows the identity of the arrangement of the substituents at C_5 and C_6. The reaction of hypobromous acid with the 5β,6-oxide (VIIb) [which is formed in the alkaline hydrolysis of the formate (II)] in acetic acid solution gave the bromohydrin (Vb).

From the mixtures of formates of 16,17-disubstituted pregnenolones, only the 6β isomers (IIb) and (IIc) were isolated. The structure of (IIc) was confirmed by its IR and NMR spectra and its conversion into the 5β,6-oxide (VIIc), identical with a sample obtained previously [1]. The NMR spectra of (IIb) and (IIc) have very similar values of the signals of the protons at C_3 and C_6 in the 5.4-5.5-ppm region and the signal of a proton at 8.01 and 9.7 ppm characteristic of a formyl group.

We judged the quantitative ratio of the isomeric formates indirectly – from the ratio of the 5β,6- and 5α,6-oxides (VIIa, b, c) and (IXa, b, c) obtained by treating the reaction mixtures with potassium carbonate in methanol and subsequent acetylation. The results of gas-liquid chromatography are given in Table 1.

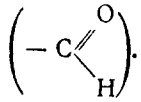
From the ratio of the 5β,6- and 5α,6-oxides it must be concluded that the 6β-formyloxy derivatives (IIa, IIb, and IIc) predominate in the reaction mixtures. This can be explained by stereochemical factors favoring the preferential formation of an intermediate α-oriented bromonium ion (A) rather than the β ion (B). The reaction of the α- and β-bromonium ions with a nucleophilic agent – dimethylformamide – forms the intermediate compounds C and D, the hydrolysis of which leads to the corresponding formyloxy derivatives (II and III).

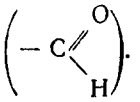


A similar explanation of the addition of dimethylformamide to an α-bromonium ion has been given previously by H. Reimann [2], K. Morita [3], and D. Klinot [4] in the study of the addition of halogens to Δ^2 and Δ^5 double bonds.

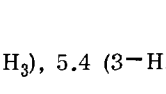
EXPERIMENTAL

The NMR spectra were obtained on a JNM-4H-100 instrument in $CDCl_3$ with hexamethyldisiloxane as standard; the IR spectra of 1% solutions of (IIa, b, c; IIIa, Vb, and Xb) were taken in chloroform and those of the other compounds in the form of mulls in paraffin oil on a Perkin-Elmer 457 instrument; the specific rotations were determined in chloroform on an ÉLPU-0,1 instrument. The ratio of the isomers (VIIa, b, c) and (IXa, b, c) was determined in a JEOL model-810 gas chromatograph with a flame-ionization detector. The stainless-steel column (60 × 0.3 cm) was filled with 2% of XE-60 on Chromosorb WHMDS (80-100 mesh). The temperature of the column was 200°C, that of the detector 225°C, and that of the sample inlet unit, 230°C. The rate of flow of the carrier gas, helium, at the outlet was 50 ml/min. The molecular weights were determined mass spectrometrically. The amounts of C, H, and Br found in compounds (IIa, IIIa, IIb, IIc, Vb, Xb, VIIb, and IXb) corresponded to the calculated figures.

3-Acetate 6-Formate of 5α-Bromo-3β,6β-dihydroxypregnan-20-one, $C_{24}H_{35}O_5Br$ (IIa) and the 3-Acetate 5-Formate of 6β-Bromo-3β,5α-dihydroxypregnan-20-one $C_{25}H_{35}O_5Br$ (IIIa). With heating to 60°C, 5 g of pregnenolone acetate was dissolved in 80 ml of dimethylformamide and the solution was rapidly cooled to 15°C (the reaction was performed at this temperature), and 12.2 ml of 10% perchloric acid solution was slowly added. A microcrystalline precipitate deposited. Then 2.4 g of Dibromantin was added to the reaction mixture in portions over 30 min. The mixture became transparent and after 5-10 min a precipitate deposited. The mixture was stirred for another 30 min and the precipitate was filtered off and was washed on the funnel with a 10% solution of sodium sulfite and with water to neutrality. This gave 2 g of (IIa). After recrystallization from acetone, mp 178-179°C (decomp.), $[\alpha]_D$ −27.5°C. IR spectrum, cm^{-1}: 1727, 1710, 1250, 1175. NMR spectrum, ppm: 0.57 (18−CH_3), 1.25 (19−CH_3), 1.97 (3−OOCCH_3) 2.07 (21−CH_3), 5.35 (3−H), 5.40 (6−H), 8.24  . Found mol. wt. 484. Calculated mol. wt. 483.42.

After the addition of 20 ml of a 10% solution of sodium sulfite, a precipitate deposited from the dimethylformamide solution, and this was filtered off and washed with water to neutrality. This gave 1.77 g of (IIIa). An analytical sample was isolated by recrystallization from acetone, mp 175-176.5°C (decomp.), $[\alpha]_D$ 0°C. IR spectrum, cm^{-1}: 1727, 1697, 1245, 1175. NMR spectrum, ppm: 0.64 (18−CH_3), 1.35 (19−CH_3), 1.97 (3−OOCCH_3), 2.07 (21−CH_3), 4.7 (3−H), 5.13 (6−H), 8.08  .

Water was added to the mother solution until precipitation was complete. The precipitate was filtered off and washed with water. This gave 3.8 g of a mixture of (IIa), (IIIa), and a more polar substance. The mixture was chromatographed on a 30-fold amount of silica gel. A mixture of benzene and ether (19 : 1) eluted 0.3 g of (IIa) and 2.9 g of a mixture of (IIa) and (IIIa); and a mixture of benzene and methanol (19 : 1) eluted 0.3 g of the 3-acetate of 3β,5α,6β-trihydroxypregnan-20-one (IV), mp 224-225°C, $[\alpha]_D$ +30.4°. Mol. wt: found, 392; calculated, 392.49. IR spectrum, cm^{-1}: 3630, 1725, 1705, 1250. Literature figures [5]: mp 228-230°C; $[\alpha]_D$ +36°.

3-Acetate 6-Formate of 5α-Bromo-3β,6β-dihydroxy-16α,17α-dimethylpregnan-20-one, $C_{26}H_{39}O_5Br$ (IIb). With heating to 80°C, 5 g of the acetate of 16α,17α-dimethylpregnenolone (Ib) was dissolved in 150 ml of dimethylformamide. Rapid cooling formed a suspension, and to this suspension were added 12.2 ml of a 10% solution of perchloric acid at 15°C and 2.4 g of Dibromantin over 30 min. The reaction mixture was stirred for 40 min, and the precipitate was filtered off and was washed with 10% sodium sulfite solution and with water to neutrality. This gave 2.95 g of (IIb). After recrystallization from acetone, mp 194°C (decomp.), $[\alpha]_D$ −83°. IR spectrum, cm^{-1}: 1725, 1695, 1255, 1175. NMR spectrum, ppm: 0.66 (18−CH_3), 0.80 (16−CH_3), 1.026 (19−CH_3), 1.25 (17−CH_3), 1.94 (3−OOCCH_3), 2.06 (21−CH_3), 5.4 (3−H, 6−H), 8.01  .

From the mother solution, water precipitated 3.8 g of a mixture of (IIb), (IIIb), and an unidentified more polar compound. The isomers (IIb) and (IIIb) have very similar polarities, and therefore it is impos-

sible to separate them by recrystallization. Chromatographic separation on a column of silica gel is also impossible because of their lability.

3-Acetate 6-Formate of 5α-Bromo-3β,6β-dihydroxy-16α,17-epoxypregnan-20-one, $C_{24}H_{34}O_6Br$ (IIc). Under similar conditions, 5 g of the acetate of 16α,17-epoxypregnenolone (Ic), 2.4 g of Dibromantin, 80 ml of dimethylformamide, and 12.2 ml of a 10% solution of perchloric acid gave 6.7 g of a mixture of (IIc), (IIIc), and (Vc). The mixture was dissolved in 8 ml of chloroform, and 16 ml of ether eluted 0.6 g of (Vc) contaminated with small amounts of (IIc) and (IIIc). Pure (Vc) with mp 169-172°C (decomp.), $[\alpha]_D$ −17.2°, was isolated by fractional crystallization from ethyl acetate.

After the evaporation of the solvent, the residue (6 g) was chromatographed on 180 g of silica gel. A mixture of benzene and ether (19 : 1) eluted 3.86 g of (IIc). An analytical sample was obtained by crystallization from methanol, mp 186.5-187°C (decomp.), $[\alpha]_D$ −49°. IR spectrum, cm^{-1}: 1727, 1700, 1245, 1180. NMR spectrum, ppm: 1.12 (18−CH_3), 1.4 (19−CH_3), 2.09 (3−OOCCH_3, 21−CH_3), 5.4 (3−H), 5.51 (6−H), 9.7 (−C(=O)H).

Benzene−ether (9 : 1) eluted 0.46 g of (VIIc) and 0.63 g of (IXc), the constants and spectra of which were identical with those obtained previously [1].

3-Acetate of 5α-Bromo-3β,6β-dihydroxy-16α,17α-dimethylpregnan-20-one, $C_{25}H_{39}O_4Br$ (Vb) and the 3-Acetate of 6β-Bromo-3β,5α-dihydroxy-16α,17α-dimethylpregnan-20-one, $C_{25}H_{39}O_4Br$ (Xb). Over 30 min, 12.2 ml of 10% perchloric acid solution and 2.4 g of Dibromantin were added in four portions to a suspension of 5 g of the acetate of 16α,17α-dimethylpregnenolone (Ib) in 75 ml of ethyl acetate. The suspended matter dissolved completely. The solution was stirred for 45 min and was then washed with a 10% solution of sodium sulfite and with water to neutrality. After drying, the solvent was evaporated to 1/2 of the original volume. The precipitate that deposited was filtered off, giving 2.87 g of (Vc). After reprecipitation with ether from chloroform, the (Vb) had mp 160-161°C (decomp.), $[\alpha]_D$ −58.8°. IR spectrum, cm^{-1}: 3620, 1730, 1695; NMR spectrum (pyridine), ppm: 0.6 (18−CH_3), 0.77 (16−CH_3), 0.87 (19−CH_3), 1.44 (17−CH_3), 1.94 (3−OOCCH_3), 1.95 (21−CH_3), 4.35 (6−H), 5.66 (3−H).

The mother solution was again evaporated until a precipitate appeared. This was filtered off and was washed on the filter with a small amount of cooled ethyl acetate, giving 2.11 g of (Xb). After recrystallization from ethyl acetate, mp 208°C (decomp.), $[\alpha]_D$ −65.4°. IR spectrum, cm^{-1}: 3595, 1730, 1695. NMR spectrum, ppm: 0.82 (18−CH_3), 0.99 (16−CH_3), 1.11 (19−CH_3), 1.47 (17−CH_3), 2.1 (3−OOCCH_3), 2.15 (21−CH_3), 4.1 (6−H), 5.22 (3−H).

Acetate of 3β-Hydroxy-5β,6-epoxypregnan-20-one (VIIa). A mixture of 5.88 g of (IIa) and 6 g of calcined potassium acetate in 60 ml of absolute methanol was boiled for 1 h 45 min. Then the methanol was evaporated to incipient crystallization and was cooled with ice water and diluted with water. The precipitate was filtered off and was recrystallized from acetone. This gave 3.8 g of (VIIa). A pure sample was obtained by additional recrystallization from acetone, mp 134-136°C $[\alpha]_D$ +39°. Literature figures [5]: mp 137-139°C; $[\alpha]_D$ +43°.

Acetate of 3β-Hydroxy-16α,17α-dimethyl-5β,6-epoxypregnan-20-one, $C_{25}H_{38}O_4$ (VIIb). A. A mixture of 0.5 g of (IIb), 0.45 g of potassium acetate, 25 ml of methanol, and 2 ml of water was boiled for 1.5 h. Then, with cooling, water was added to the reaction mixture, and the resulting precipitate was filtered off and dried. The 0.26 g of (VIb) so isolated was acetylated with $Ac_2O-C_5H_5N$, giving 0.35 g of (VIIb). The latter was recrystallized from methanol, mp 194.5-196.5°C, $[\alpha]_D$ −33.4°.

B. The analogous treatment of 0.5 g of the bromohydrin (Vb) (0.5 g of potassium carbonate, 25 ml of methanol, and 2 ml of water) and subsequent acetylation yielded 0.4 g of (VIIb), mp 194-195.5°C. It gave no depression of the melting point in admixture with the sample of (VIIb) obtained above. IR spectrum, cm^{-1}: 1730, 1690, 1250; NMR spectrum, ppm: 0.64 (18−CH_3), 0.82 (16−CH_3), 0.97 (17−CH_3, 19−CH_3), 1.98 (3−OOCCH_3), 2.04 (21−CH_3), 3.02 (6−H), 4.72 (3−H).

Acetate of 3β-Hydroxy-16α,17α-dimethyl-5α,6-epoxypregnan-20-one, $C_{25}H_{38}O_4$ (IXb). Under the conditions described, 0.5 g of (Xb) gave 0.36 g of (IXb) with mp 219-221.5°C; after recrystallization from methanol $[\alpha]_D$ −66°. IR spectrum, cm^{-1}: 1725, 1690, 1250. NMR spectrum, ppm: 0.61 (18−CH_3), 0.82 (16−CH_3), 0.98 (17−CH_3, 19−CH_3), 1.98 (3−OOCCH_3), 2.04 (21−CH_3), 2.86 (6−H), 4.83 (3−H).

3-Acetate of 5α-Bromo-3β,6β-dihydroxy-16α,17α-dimethylpregnan-20-one (Vb). At 18°C, 0.3 ml of a 16% acetic acid solution of hydrogen bromide was slowly added to a suspension of 0.25 g of (VIIb) in 3 ml of glacial acetic acid. After 2 h, 5 ml of water was added with cooling. The resulting precipitate was filtered off and was washed with water to neutrality, giving 0.3 g of (Vb), mp 159-160°C (decomp.), $[\alpha]_D$ −58°. The sample of (Vb) gave no depression of the melting point in admixture with a sample of the substance obtained by the reaction of (Ib) with hypobromous acid in ethyl acetate.

3-Acetate 6-Formate of 5α-Bromo-3β,6β-dihydroxypregnan-20-one (IIa). A mixture of 0.3 g of (Va) and 4 ml of 87% formic acid was kept at room temperature for 48 h. Then the reaction mixture was poured into ice water. The substance was extracted with chloroform, washed to neutrality, and dried. After the chloroform had been distilled off, the residue was crystallized from ether, giving 0.21 g of (IIa) with mp 175°C (decomp.). The IR spectrum was identical with that of the sample obtained previously.

3-Acetate of 3β-Hydroxypregnan-20-one (Ia). A mixture of (IIa) and (IIIa) (1 g) in 25 ml of glacial acetic acid was treated with 1 g of zinc dust in the boiling-water bath for 2 h. The zinc dust was filtered off and washed with ethyl acetate, and then the solvent was evaporated, the residue was treated with water, and the resulting precipitate was filtered off and washed with water to neutrality. After two recrystallizations from acetone, 0.4 g of (Ia) was obtained with mp 146.5-147.5°C, $[\alpha]_D$ +18°. It gave no depression of the melting point with an authentic sample. Literature figures [6]: mp 149-151°C; $[\alpha]_D$ +19°. The IR spectrum was identical with that of an authentic sample.

3-Acetate of 3β-Hydroxy-16α,17α-dimethylpregnan-20-one (Ib). The analogous treatment of 0.94 g of (IIb) with zinc dust in acetic acid gave 0.42 g of (Ib), mp 219.5-221°C, $[\alpha]_D$ −72°. Literature figures [7]: mp 218-219°C; $[\alpha]_D$ −62°. The IR and NMR spectra were identical with those of an authentic sample.

SUMMARY

The reaction of 3β-acetoxy-Δ^5-steroids with hypobromous acid in dimethylformamide has been studied. It has been shown that this reaction forms formates of bromohydrins.

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