PREPARATION OF 10β-HYDROPEROXIDES OF THE PREGNANE SERIES

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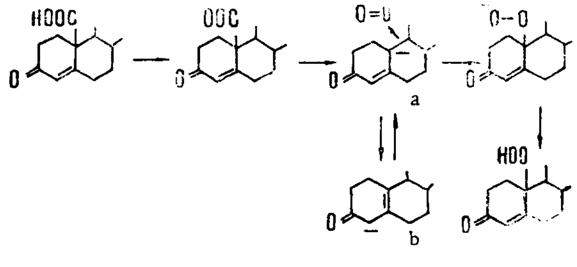
We have previously [1] reported on the oxidation with atmospheric oxygen of a compound of a new class – 3,17-dioxo-19-norandrost-4-ene-10β-carboxylic acid – in acetone solution. This reaction forms the corresponding 10β-hydroperoxide with a yield of 60-80%.

Continuing our investigation, we have made use of this reaction to obtain hydroperoxides of the pregnane series – 10β-hydroperoxy-16α, 17α-dimethyl-19-norpregn-4-ene-3,20-dione (VIa) and 10β-hydroperoxy-19-norpregn-4-ene-3,20-dione (VIb) – from the corresponding acids (Va, b). These compounds were synthesized in order to study their biological activity. We are the first to have obtained the hydroperoxide (VIa). The synthesis of the hydroperoxide (VIb) from 3,20-dioxopregn-4-ene-19-carboxaldehyde is mentioned in a patent [2], but no physicochemical characteristics of this compound are given.

We have investigated the influence of solvents and various catalysts on the oxidation of the compounds under consideration. Of the ten solvents tested (ethyl acetate, heptane, benzene, dioxane, chloroform, pyridine, methanol, butanol, isobutanol, and acetone), the best proved to be acetone since in this solvent only small amounts of by-products are formed. The oxidation takes place in more complicated fashion and more slowly in methanol: according to GLC in addition to the initial acid and the main reaction product – the 10β-hydroperoxide – four by-products were detected, two of which were isolated and were identified as 19-norandrost-4-ene,3,17-dione and 19-norandrost-5-ene-3,17-dione (and similarly in the pregnane series). In the other solvents under the oxidation conditions only the products of the decarboxylation of the acid – isomeric 19-norandrostene-3,17-diones (or 19-norpregnene-3,20-diones) – are formed.

As catalysts we have tested ferric chloride [3], sodium hydroxide [4], and benzoyl peroxide [5, 6]. A catalytic amount of ferric chloride added to a solution of the acid being oxidized in acetone caused no change in the rate of the reaction. The presence of a catalytic amount of alkali accelerated the decomposition of the acid to the isomeric 19-nor compounds. In the reaction solution, the initial acid had disappeared after 4 h and the spots of the by-products had increased in size (TLC results); the yield of hydroperoxide did not exceed 50% (iodometric titration). The addition of a radical initiator – benzoyl peroxide – to a solution of the acid in acetone did not change the rate of the reaction. Thus, it may be assumed that free radicals do not take part in the oxidation process. This was confirmed by recording the electron spin resonance spectrum. It is obvious that the formation of the hydroperoxide takes place by an ionic mechanism – through the stabilization of the carbanions (a and b) formed by the decarboxylation of the acid with the subsequent addition of oxygen.



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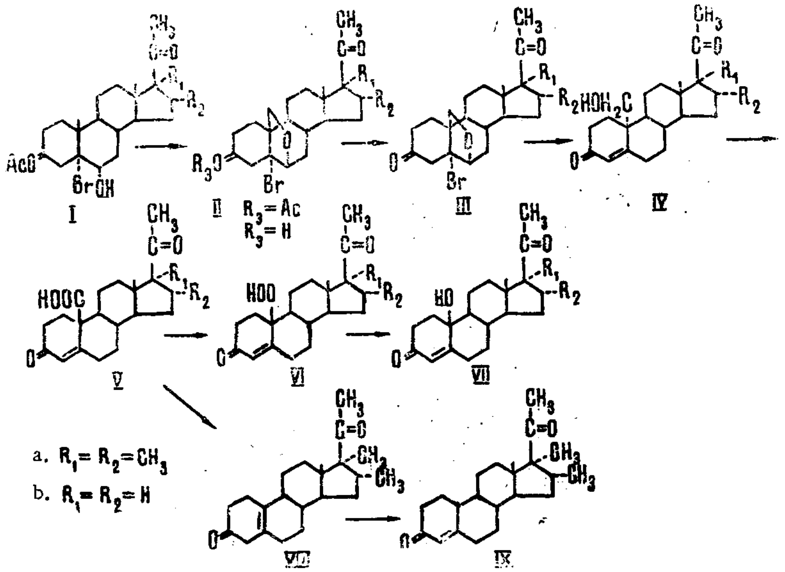
The pregnane hydroperoxides were obtained under the optimum conditions – air was bubbled through a solution of the acid in acetone at 35-40°C for 30-35 h. The yields of the hydroperoxides (IVa) and (VIb) were 75% and 72%, respectively. The structures of the hydroperoxides were confirmed by a positive iodine test and by the results of IR and NMR spectroscopy. Reduction of the hydroxy peroxides (VIa) and VIb) with trimethylphosphite gave 10β-hydroxy derivatives (VIIa) and (VIIb).

The initial acids were prepared from the acetates of the bromohydrins via the 6β,19-oxides in the following way [7,8]:



It is interesting to note the effect of the long-range influence of groups on the occurrence of the reactions described. We worked with a substance having no substituents in the 16 and 17 positions and also with 16α, 17α-dimethyl derivatives.

The reaction of the 3-acetate of 5α-bromo-3β, 6β-dihydroxy-16α, 17α-dimethylpregnan-20-one (Ia) with lead tetraacetate led to rapid oxidative cyclization – in 30 min (yield of the oxide (IIa) 96%) – while the 3-acetate of 5α-bromo-3β,6β-dihydroxypregnan-20-one (Ib) reacted with lead tetraacetate more slowly – 1.5 h (yield of the oxide (IIb) 81%). In the oxidation of the 19-alcohols (IVa and IVb) with the Jones reagent to the corresponding acids (Va, VIb), a considerable retardation of the reaction was found in the case of the 16α, 17α-dimethyl-substituted 19-alcohol (IVa). The oxidation of (IVa) required 4 h for completion while the oxidation of (IVb) took place completely in 2 h.

EXPERIMENTAL

The NMR spectra were obtained on a JNM-4H-100 instrument in $CHCl_3$ and $CDCl_3$ with HMDS as the standard; the UV spectra were taken in 96% ethanol; the IR spectra of mulls of the substances in paraffin oil were recorded on a Perkin-Elmer 457 instrument; and the specific rotations were determined in chloroform on an ÉLPU-0.1 instrument.

3β-Acetoxy-5α-bromo-16α, 17α-dimethyl-6β, 19-epoxypregnan-20-one (IIa, R_3=Ac). With stirring, 8.4 g of lead tetraacetate (washed on the funnel with dry benzene and dried in the vacuum of an oil pump) and 1.2 g of iodine were added rapidly to 5.32 g of the 3-acetate of 5α-bromo-3β,6β-dihydroxy-16α, 17α-dimethylpregnan-20-one (Ia) in 150 ml of dry benzene. The reaction mixture was heated to 40-50°C and then the illumination (two 200-W lamps) was switched on and the mixture was brought to the boil. A precipitate of lead diacetate separated out, and the starting material and the lead tetraacetate gradually passed into solution. The mixture was boiled with illumination for 30 min. At the end of the reaction, the pronounced iodine coloration of the mixture had lightened considerably. After the reaction mixture had cooled to room temperature, the lead diacetate that had deposited was filtered off and was washed several times with dry benzene. The combined benzene solutions were washed with a 3% solution of sodium sulfite for decoloration and then with water to neutrality and were dried with calcined sodium sulfate. The solvent was evaporated off in vacuum at a temperature not exceeding 40°C. This gave 5.1 g (96%) of (IIa, R_3=Ac). After reprecipitation with ether from methylene chloride the compound (IIa), with the composition $C_{25}H_{37}O_4Br$, had mp 163-165°C, $[\alpha]_D -17°$. IR spectrum: 1730, 1695, 1240 cm^{-1}. NMR spectrum, ppm: 0.71 (18–CH_3), 0.84 (16–CH_3), 1.036 (17–CH_3), 2.005 (3–$OOCCH_3$), 2.06 (21–CH_3), 3.687 (19–CH_2), 3.863 (6–H), 5.17 (3–H).

3β-Acetoxy-5α-bromo-6β, 19-epoxypregnan-20-one (IIb, R_3=Ac). From 20.5 g of (Ib) in 600 ml of benzene, 32 g of lead tetraacetate, and 4.6 g of iodine by boiling for 1.5 h was obtained 16.45 g (81%) of (IIb) with mp 148-150°C, $[\alpha]_D + 54.5°$. Without purification, the technical product was used in the following stage. Literature data – mp 152-154°C, $[\alpha]_D + 58°$ [9].

5α-Bromo-3β-hydroxy-16α, 17α-dimethyl-6β, 19-epoxypregnan-20-one (IIa, R_3=H). For hydrolysis, 3.4 g of (IIa, R_3=Ac) was dissolved in 70 ml of methanol, and a solution of 2 g of potassium carbonate in 8 ml of water was added and the mixture was boiled for 1 h. After cooling, the solution was shaken with a small amount of activated carbon and filtered, and the filtrate was evaporated in vacuum to small volume and then water was added with cooling. The precipitate that deposited was filtered off and was washed with water to neutrality. This gave 3.24 g of (IIa, R_3=H), with the composition $C_{23}H_{35}BrO_3$. After recrystallization from 10 volumes of methanol, mp 218.5-219.5°C, $[\alpha]_D - 20°$. IR spectrum, cm^{-1}: 3500, 1680. NMR spectrum, ppm: 0.699 (18–CH_3), 0.818 (16–CH_3), 1.01 (17–CH_3) 2.02 (21–CH_3), 3.75 (19–CH_2), 3.98 (6–H), 3.1 (3–H).

5α-Bromo-3β-hydroxy-6β, 19-epoxypregnan-20-one (IIb, R_3=H). The hydrolysis of 5 g of (IIb, R_3=Ac) (150 ml of methanol, 2.7 g of potassium carbonate, and 11 ml of water) under the conditions described above gave 4.16 g of (IIb, R_3=H) with mp 180-181.5°C, $[\alpha]_D + 61°$. Literature data – mp 179-180°C, $[\alpha]_D + 61°$ [9].

5α-Bromo-16α, 17α-dimethyl-6β, 19-epoxypregnane-3,20-dione (IIIa). At 10°C, 7.8 ml of a solution of chromium trioxide (an aqueous solution of which 10 ml contained 2.7 g of chromium trioxide and 2.3 ml of conc. sulfuric acid) was added dropwise to a cooled solution of 5.2 g of (IIa, R_3=H) in 105 ml of methylene chloride, and the mixture was stirred at room temperature for 2 h, after which time the initial compound had disappeared [TLC; benzene–methanol (23 : 2) system]. The organic layer was poured off and the chromium salts were washed with methylene chloride. The combined solution was washed with water to neutrality, dried, and evaporated in vacuum at a bath temperature ≈ 30°C. This gave 5.2 g of the crystallizing dione (IIIa), which was used in the following stage without purification.

5α-Bromo-6β, 19-epoxypregnane-3,20-dione (IIIb). The oxidation of 13.7 g of (IIb, R_3=H) (275 ml of methylene chloride and 20.5 ml of chromium trioxide solution) was performed under the conditions described above. After working up, 13.96 g of substance (IIIb) was obtained, and this was used without purification in the following stage.

19-Hydroxy-16α, 17α-dimethylpregn-4-ene-3,20-dione (IVa). To a suspension of 5.2 g of (IIIa) in 100 ml of isopropanol were added 52 g of zinc dust and 1.65 ml of acetic acid. The reaction mixture was boiled for 5 h. Then it was cooled to 40°C and the zinc dust was filtered off and carefully washed with methylene chloride. The combined solutions were washed with 2% hydrochloric acid (to isomerize the Δ^5 bond) and with water to neutrality. After drying over sodium sulfate, the solvent was evaporated off, the crystalline residue was mixed with 10 ml of ethyl acetate, and after cooling the solid matter was filtered off. This gave 3.6 g (85%) of (IVa). After recrystallization from ethyl acetate the (IVa) with the composition $C_{23}H_{34}O_3$, had mp 217.5-219°C, $[\alpha]_D + 81.5°$. UV spectrum: λ_{max} 242 nm (log ε 4.24). IR spectrum, cm^{-1}: 3350, 1700, 1660, 1610. NMR spectrum, ppm: 0.68 (18–CH_3), 0.81, (16–CH_3), 1.00 (17–CH_3), 2.04 (21–CH_3), 3.95 (19–CH_2), 5.86 (4–H).

The residue (2.58 g) after the distillation of the ethyl acetate in vacuum was chromatographed on 78 g of alumina. A mixture of benzene and ether (19 : 1) eluted 1.22 g of (IVa) with the composition $C_{23}H_{36}O_3$, mp 217.5-219°C and 0.3 g of 3β, 19-dihydroxy-16α,17α-dimethylpregn-4-ene-20-one with mp 190-192°C, $[\alpha]_D - 50.9°$. IR spectrum, cm^{-1}: 3370, 1690. NMR spectrum, ppm: 0.72 (18–CH_3), 0.80 (16–CH_3), 0.99 (17–CH_3), 2.04 (21–CH_3), 3.53 (3–H), 3.73 (19–CH_2), 5.687 (4–H).

19-Hydroxypregn-4-ene-3,20-dione (IVb). The analogous opening of the oxide ring of 13.96 g of (IIIb) (275 mg of isopropanol, 140 g of zinc dust, and 4.6 ml of acetic acid) gave 7 g (61.7%) of (IVb) with mp 161-164°C. After recrystallization from a threefold amount of ethyl acetate, mp 167-169°C, $[\alpha]_D + 179°$. According to the literature – mp 169-171°C, $[\alpha]_D + 182°$ [9].

The 3β, 19-Dihydroxy-16α, 17α-dimethylpregn-4-en-20-onecarboxylic Acid (Va). A solution of 3 g of (IVa) in 300 ml of acetone (the acetone had been purified by being mixed with an aqueous solution of chromium trioxide followed by distillation) was cooled to 10°C and, in a current of argon, 10 ml of chromic acid was added dropwise. The solution was stirred at room temperature for 4 h, the progress of the reaction being monitored by TLC [Silufol, benzene–methanol (23 : 2) system]. The excess of chromic acid was decomposed with a small amount of isopropanol, and then 300 ml of benzene was added to the reaction mixture and it was stirred and the organic layer was separated from the insoluble chromium salts. The organic layer was washed three times with saturated common salt solution and once with water. After drying the solvent was evaporated off in vacuum at a bath temperature not exceeding 40°C. The crystallization from acetone gave 2.6 g (83.5%) of (Va), $C_{23}H_{32}O_4$, with mp 166-167°C, $[\alpha]_D + 116°$. UV spectrum: λ_{max} 246 nm (log ε 4.09). IR spectrum, cm^{-1}: 3700 (0.02% solution in CCl_4), 1720, 1690, 1635. NMR spectrum, ppm: 0.68 (18–CH_3), 0.83 (16–CH_3), 0.998 (17–CH_3), 2.04 (21–CH_3), 5.89 (4–H).

3,20-Dioxopregn-4-ene-19-carboxylic Acid (Vb). At 10°C, 11.7 ml of a solution of chromic acid was added to a solution of 3.87 g of (IVb) in 200 ml of acetone. Oxidation was performed at room temperature for 2 h, and the reaction mixture was worked up as described above. This gave 3.7 g (91.5%) of (Vb) with mp 145-147°C, $[\alpha]_D + 100°$. Literature data – mp 147-149°C, $[\alpha]_D + 94°$ [9].

10β-Hydroperoxy-16α, 17α-dimethyl-19-norpregn-4-ene-3,20-dione (VIa). Air was bubbled through a suspension of 2.26 g of the acid (Vb) in 23 ml of acetone at 30-35°C for 30 h. TLC [fixed layer of silica gel; benzene–methanol (23 : 2) system] showed the presence of the initial acid and of two less polar spots which may be assigned to 16α, 17α-dimethyl-19-norpregn-4-ene-3,20-dione and its Δ^5 isomer. The precipitate that had deposited from the reaction mixture was filtered off and washed with a small amount of benzene. This gave 1.17 g (53%) of (VIa), with the composition $C_{22}H_{32}O_4$. After recrystallization from methanol, mp 188-189°C (decomp.), $[\alpha]_D + 55°$. UV spectrum: λ_{max} 238 nm (log ε 4.19). IR spectrum, cm^{-1}: 3280, 1700, 1660, 1620. NMR spectrum, ppm: 0.608 (18–CH_3), 0.768 (16–CH_3), 0.88 (17–CH_3), 1.946 (21–CH_3), 6.097 (4–H).

The mother liquor yielded 0.48 g of (VIa) with mp 185-187°C (decomp.). The total yield of (VIa) was 75%.

10β-Hydroperoxy-10-norpregn-4-ene-3,20-dione (VIb). The autooxidation of 3.2 g of (Vb) under similar conditions gave 1.6 g (52%) of (VIb), $C_{20}H_{28}O_4$; after recrystallization from methanol, mp 158.5-160°C (decomp.), $[\alpha]_D + 160°$. UV spectrum: λ_{max} 237 nm (log ε 4.19). IR spectrum, cm^{-1}: 3350, 1705, 1660, 1610. NMR spectrum, ppm: 0.61 (18–CH_3), 2.06 (21–CH_3), 5.92 (4–H).

The mother solution was evaporated to dryness in vacuum, the residue was dissolved in benzene, and the solution was washed three-four times with 5% sodium carbonate solution and with water to neutrality and was evaporated. This gave 0.6 g (20%) of (VIb) with decomp. p. 151-153°C. The total yield of (VIb) was 72%.

10β-Hydroxy-16α, 17α-dimethyl-19-norpregn-4-ene-3,20-dione (VIIa). A suspension of 0.5 g of (VIa) in 2.5 ml of methanol was treated with 0.25 ml of trimethyl phosphite. The temperature of the reaction mixture rose to 30-35°C. Then it was left at room temperature for 30 min and was poured into ice water. The precipitate was filtered off and washed with water. This gave 0.48 g (100%) of (VII), composition $C_{22}H_{32}O_3$; after recrystallization from methanol, mp 209-210°C, $[\alpha]_D + 48°$. UV spectrum: λ_{max} 237 nm (log ε 4.16). IR spectrum, cm^{-1}: 3460, 1680, 1660, 1618. NMR spectrum, ppm: 0.685 (18–CH_3) 0.762 (16–CH_3), 0.892 (17–CH_3), 1.940 (21–CH_3), 5.850 (4–H).

10β-Hydroxy-19-norpregn-4-ene-3,20-dione (VIIb). Compound (VIb) was converted into (VIIb) with quantitative yield under the conditions described above. After recrystallization from methanol, (VIIb) had the composition $C_{20}H_{28}O_3$, mp 168.5-169.5°C, $[\alpha]_D + 160°$. UV spectrum: λ_{max} 236 nm (log ε 4.164): IR spectrum, cm^{-1}: 3350, 1710, 1665, 1630. NMR spectrum, ppm: 0.614 (18–CH_3), 2.08 (21–CH_3), 5.68 (4–H).

16α, 17α-Dimethyl-19-norpregn-5-ene-3,20-dione (VIIIa). A mixture of 0.7 g of (V) and 1.5 ml of pyridine was heated at 60°C for 2 h. Then 3 ml of water was added to the cooled solution and after brief cooling the precipitate that had deposited (0.4 g) was filtered off, washed with water, and recrystallized from methanol. This was the dione (VIIIa), $C_{22}H_{32}O_2$, mp 136-137.5°C, $[\alpha]_D + 150°$. NMR spectrum, ppm: 0.60 (18–CH_3), 0.78 (16–CH_3), 0.95 (17–CH_3), 2.05 (21–CH_3).

16α, 17α-Dimethyl-19-norpregn-4-ene-3,20-dione (IXa). The isomerization of 0.2 g of (VIIIa) was performed in methanol solution in the presence of four drops of concentrated hydrochloric acid at room temperature. According to TLC [fixed layer of silica gel, benzene–methanol (23 : 2) system], the reaction was complete after 4 h. The methanol was evaporated off, and water was added to the residue. After cooling, the precipitate was filtered off and washed with water. Compound (IXa), recrystallized from methanol, had the composition $C_{22}H_{32}O_2$, mp 148.5-150.5°C, $[\alpha]_D + 24.3°$. IR spectrum, cm^{-1}: 1690, 1670, 1615. NMR spectrum: 0.62 (18–CH_3), 0.725 (16–CH_3), 1.0 (17–CH_3), 2.05 (21–CH_3), 5.79 (4–H).

SUMMARY

The synthesis of 10β-hydroperoxy-19-norpregn-4-ene-3,20-dione and its 16α, 17α-dimethyl derivative from the corresponding 10β-carboxylic acids has been effected. The influence of solvents and catalysts on the autooxidation of the acids has been studied.

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