TRANSFORMED STEROIDS

COMMUNICATION 36.* SYNTHESIS AND OPENING OF 20-CARBETHOXYHYDRAZONE OF 16α-DEUTERODEHYDROPREGNENOLONE 16β,17β-OXIDE

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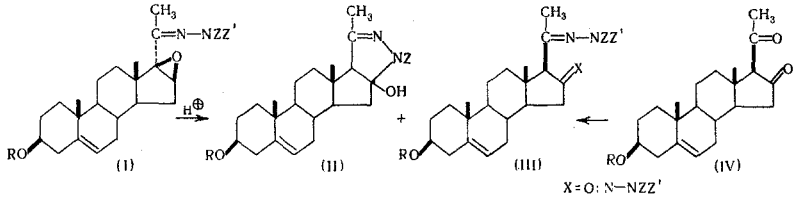
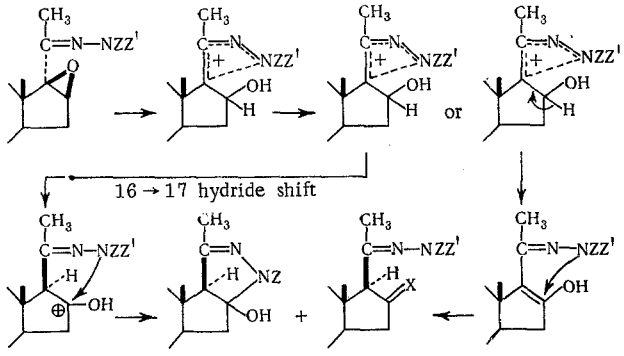
In studying the reaction for the opening of the oxide ring of the 20-hydrazones of dehydropregnenolone 16β,17β-oxide (I) we established [2, 3] that either the 16,17-hydroxypyrazolines (II) or the 16,20-diketone derivatives (III) are formed here. By counter synthesis from the corresponding diketone (IV) it was shown that cleavage of the C-17–O bond occurs exclusively here



Since the same direction of the reaction is retained when going from the monosubstituted hydrazones (Z = H) to the disubstituted hydrazones (Z = Z' = Ph), then the key step of the reaction is evidently the reversible shift of the free electron pair of nitrogen with the formation of a cation, which is stabilized in a definite configuration at C-17 [4, 5]. The further transformation of such a cation can occur either via the 16 → 17-hydride shift or with the ejection of a proton at C-16 and the formation of the Δ^{16}-bond. The hydride shift seemed more probable at this stage of the investigation, which is facilitated by the conformational driving force that arises when the conformation of the side chain is changed from α- to β-



In order to answer this question we ran the indicated reaction using 16β,17β-epoxy-16α-deuteropregnenolone (V). Here the retention of deuterium in the obtained hydroxypyrazoline would unequivocally indicate the progress of the 16 → 17-hydride shift.

* See [1] for Communication 35.

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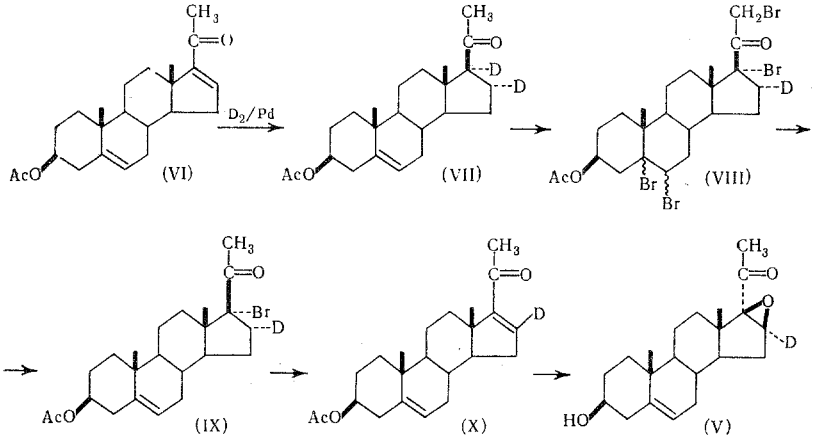
The starting deutero oxide (V) was obtained by the scheme given in [6], and was worked out in advance on nondeuterated compounds

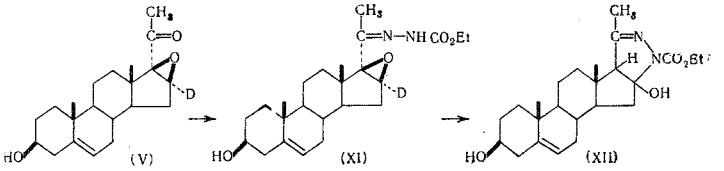


The deuteration of dehydropregnenolone acetate (VI) on 10% Pd/C catalyst in ethyl acetate gave 16α,-17α-dideuteropregnenolone acetate (VII). The bromination of the latter in acetic acid led to the 5,6,17,21-tetrabromide (VIII). The latter was treated first with sodium iodide and then with sodium bisulfite, as a result of which was obtained 16α-deutero-17α-bromopregnenolone acetate (IX). Finally, the dehydrobromination of (IX) with lithium chloride in dimethylformamide [7] gave 16-deuterodehydropregnenolone acetate (X). The total yield of compound (X), when calculated on the starting dehydropregnenolone acetate (VI), was 27.4%.

The conversion of deuterodehydropregnenolone acetate (X) to deutero oxide (V) was effected by the bromination of the Δ^5-bond, addition of hypobromous acid, debromination, and closure of the oxide ring [2]. All of the obtained intermediate products were identified by comparing them directly with the nondeuterated samples. The amount of deuterium was checked by mass spectrometry. Here it was found that the (VII) sample contained 1.2 atoms of deuterium per molecule. Toward the end of the indicated sequence of reactions the amount of deuterated oxide in the (V) sample was 0.45 atom of deuterium per molecule of steroid.

The treatment of deutero oxide (V) with hydrazinecarboxylic ester and a small amount of acetic acid in dioxane led to the carbethoxyhydrazone of oxide (XI), which was then treated with acetic acid [2]. The thus obtained pyrazoline (XII) proved to be identical with the authentic sample. Its mass spectrum contains the molecular peak (M^+) and peak $(M + 1)^+$ in a ratio that differs by only 5 relative % from the ratio of these peaks in the nondeuterated sample of the pyrazoline.

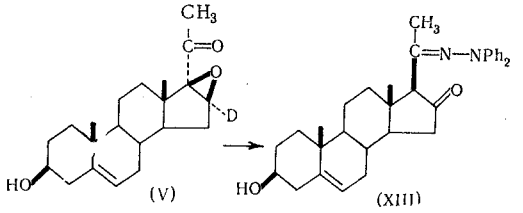
As a result, complete elimination of the deuterium occurs as the result of opening the hydrazone of 16α-deuteropregnenolone 16β,17β-oxide (XI)



The obtained results cause us to reject the possibility of the 16 → 17-hydride shift and testify in support of the fact that the reaction proceeds via the ejection of the 16-proton and the formation of the Δ^{16}-bond. It is interesting to mention that, as was shown by the authors of [8], the treatment of the 20-semicarbazone of 16β-methyl-17α-hydroxysteroids, i.e., steroids that have the same configuration of the 16-substitutuent, which is also true in our case, with acetic acid also leads to the loss of the 16-proton and the formation of the Δ^{16}-bond. At the same time, the semicarbazones of 16α-methyl-17α-hydroxysteroids undergo the Wagner–Meerwein rearrangement under these conditions. These authors believe that the facile dehydration of 16β-methylsteroids is explained by a decrease in the steric contraction when going to a planar arrangement of the side chain and the 16-methyl group. However, such an assumption does not explain a different progress of the reaction of 16α-methylsteroids and seems poorly applicable to the described

case. Rather it should be assumed that the reverse migration of the electron pair to the nitrogen atom facilitates cleavage of the C-16–H(α) bond.

In addition, we ran the opening of deutero oxide (V) in acetic acid in the presence of diphenylhydrazine



Based on the mass-spectral data, the thus obtained Δ^5-pregnen-3β-ol-16,20-dione 20-diphenylhydrazone (XIII) also does not contain deuterium, and in its constants is the same as the diketone monohydrazone previously described by us [4].

EXPERIMENTAL METHOD

The melting points were determined on a Kofler block. The mass spectra were taken on a MKh-1303 mass spectrometer, with insertion of the substance into the ion source at a heating temperature of 120°, a chamber temperature of 150°, and an ionizing voltage of 40 V. The IR spectra were taken on a UR-10 instrument in KBr. For the thin-layer chromatography (TLC) we used KSK silica gel (5-15 μ) free of iron traces on microplates with development using I_2 vapors and a solution of vanillin in H_2SO_4.

16α,17α-Dideutero-Δ^5-pregnen-3β-ol-20-one Acetate (VII). A solution of 5 g of dehydropregnenolone acetate (VI), with mp 175-178°, in 250 ml of ethyl acetate was deuterated in a hydrogen flask at 20° over 10% Pd deposited on active carbon, using 98% D_2. The calculated amount of D_2 was absorbed in 18 h, after which the solution was filtered from the catalyst, evaporated, and the residue was dissolved in 250 ml of acetone, cooled to –10°, and a solution of 2 g of $KMnO_4$ in 140 ml of 85% acetone was added to it in order to remove the starting compound (–5°, 10 min), after which the mixture was treated with saturated $NaHSO_3$ solution and filtered. The residue on the filter was washed with acetone, and the combined filtrates were evaporated. The residue contained 4.5 g of acetate (VII), mp 146-152° (from CH_3OH). Infrared spectrum (ν, cm^{-1}): 1730, 1705, 1240. The mixed melting point with the starting acetate (VI) was 124-132°. The hydrogenation of 300 mg of acetate (VI) under analogous conditions led to 250 mg of pregnenolone acetate (VIIa); mp 146-151° (from CH_3OH), whose IR spectrum was identical with the IR spectrum of (VII). The mixed melting point of (VII) and (VIIa) was not depressed. The amount of deuterium, calculated on the basis of measuring the intensity of the peaks with m/e 301, 300, 299, and 298 (M – 60) in the mass spectrum of (VII) and comparison with the intensity of the corresponding peaks of (VIIa), proved to be equal to 1.2-1.3 atoms of deuterium per molecule of the steroid.

5,6,17,21-Tetrabromo-16-deuteropregnan-3β-ol-20-one Acetate (VIII). To a solution of 1.8 g of deutero acetate (VII) in 38 ml of CH_3COOH were added a solution of 0.3 ml of Br_2 in 1.5 ml of CH_3COOH and several drops of HBr in CH_3COOH, after which was slowly (1 h) added a solution of 0.6 ml of Br_2 in 3 ml of CH_3COOH. The mixture was kept at 35° for 5 min, cooled to 20°, and the obtained precipitate was filtered. We obtained 1.88 g of acetate (VIII); mp 163-167°. The analogous bromination of 1.8 g of acetate (VIIa) led to 1.5 g of 5,6,17,21-tetrabromopregnan-3β-ol-20-one acetate (VIIIa) with mp 169-172°, which was chromatographically identical with (VIII).

17α-Bromo-16α-deutero-Δ^5-pregnen-3β-ol-20-one Acetate (XI). To a solution of 1.88 g of the tetrabromo acetate (VII) in 100 ml of anhydrous acetone was added 5 g of NaI and the mixture was allowed to stand overnight at 20°, after which it was evaporated to dryness, treated with 10% $Na_2S_2O_3$ solution, and filtered. The precipitate was washed with water, dried, dissolved in a mixture of 8 ml of C_6H_6 and 8 ml of ether, and shaken with 10% $NaHSO_3$ solution (30 min). The organic layer was separated, washed with $NaHCO_3$ solution, then with water, and evaporated. The residue was treated with CH_3OH and the insoluble portion was filtered. We obtained 810 mg of acetate (IX); mp 142-146° (from CH_3OH). Infrared spectrum (ν, cm^{-1}): 1730, 1700, 1253. A similar treatment of 1.5 g of the tetrabromo acetate (VIIIa) gave 520 mg of 17α-bromo-Δ^5-pregnen-3β-ol-20-one acetate (IXa); mp 130-133° [its IR spectrum was identical with the IR spectrum of (IX)], whose mixed melting point with (IX) was not depressed.

16-Deuterodehydropregnenolone Acetate (X). To a solution of 1.3 g of the bromo acetate (IX) in 13 ml of dimethylformamide was added 350 mg of LiCl and the mixture was heated on the water bath for 4 h, after which it was diluted with water and extracted with ether. The ether extract was washed with water and evaporated. We obtained 790 mg of acetate (X); mp 165-170° (from CH_3OH). Infrared spectrum (ν, cm^{-1}): 1730, 1675, 1590, 1570, 1250. The mixed melting point with (VI) (mp 168-172°; infrared spectrum (ν, cm^{-1}): 1730, 1675, 1590, 1250) was not depressed.

The amount of deuterium in (X), determined on the basis of comparing the intensities of the peaks with m/e 297 and 296 (M – 60) in the mass spectra of (X) and (VI), was 0.45-0.47 atom of deuterium per molecule of the steroid.

16β,17β-Epoxy-16α-deutero-Δ^5-pregnen-3β-ol-20-one (V). To a solution of 1 g of acetate (X) in 34 ml of absolute ether was added a solution of 0.15 ml of Br_2 in 10 ml of CH_3COOH and the resultant solution was diluted with ether and neutralized with $NaHCO_3$. The ether solution was evaporated and the residue was treated with CH_3OH and filtered. We obtained 1 g of the 5,6-dibromo derivative, which without purification was dissolved in 28 ml of purified t-C_4H_9OH, and to the solution were added 8 ml of water and 1 drop of 67% $HClO_4$ solution. Then to the cooled mixture was added 1 g of $CH_3CONHBr$ and the mixture was allowed to stand for 4 days at 5°. Then the excess HOBr was decomposed with 10% $Na_2S_2O_3$ solution and the reaction mass was poured into 100 ml of water. After 1 h the obtained precipitate was filtered and washed with water. We obtained 1.25 g of the tribromohydrin, mp 153-154° (from CH_3OH), which was dissolved in 16 ml of anhydrous acetone and treated with 1.7 g of NaI. After 1.5 h a saturated solution of $Na_2S_2O_3$ was added until the brown color disappeared and the mixture was diluted with water and extracted with ether. The solvent was evaporated and the addition of CH_3OH caused the residual oil to crystallize. We obtained 0.57 g of the bromohydrin, which was dissolved in 18 ml of CH_3OH, a solution of 0.65 g of K_2CO_3 in 0.4 ml of water was added and the mixture was refluxed for 2 h. The solution was cooled, diluted with water, and the obtained product was filtered. We obtained 330 mg of deutero oxide (V); mp 141-144° (from CH_3OH). The mixed melting point of (V) and the ordinary β-oxide (Va) (mp 143-145°) [2] was not depressed.

The amount of deuterium in (V), calculated on the basis of comparing the intensities of the peaks with m/e 329 and 328 (M^+) in (V) and (Va), was 0.42-0.44 atom of deuterium per molecule of the steroid.

Carbethoxyhydrazone of Deutero Oxide (XI). To a solution of 150 mg of deutero oxide (V) in 3 ml of absolute dioxane were added a solution of 150 mg of hydrazinecarboxylic ester in 0.45 ml of absolute dioxane and 0.03 ml of CH_3COOH and the mixture was kept at 20° for 5 h, after which it was allowed to stand overnight at 5°. The reaction mass was diluted with water and the obtained product was filtered and recrystallized from THF–hexane. We obtained 120 mg of hydrazone (XI); mp 175-178° (in a capillary).

Opening of Carbethoxyhydrazone of Deutero Oxide (XI). A solution of 120 mg of hydrazone (XI) in 2 ml of CH_3COOH was allowed to stand at 20° for 2.5 h, after which it was diluted with water and the obtained precipitate was filtered, dried, and rubbed with ether. We obtained 100 mg of pyrazoline (XII); mp 208-211°. Infrared spectrum (ν, cm^{-1}): 3410-3480, 3230-3300, 1730, 1630, 1440, which is identical with the spectrum of authentic pyrazoline (XIIa) [1]. The mixed melting point with the authentic pyrazoline (XIIa) was not depressed.

The mass spectrum of (XII) contained the peaks m/e 417 and 416 (M^+), with a 1 : 3 ratio of the intensities. In the authentic pyrazoline (XIIa) this ratio is 1 : 3.5.

Δ^5-Pregnen-3β-ol-16,20-dione 20-Diphenylhydrazone (XIII). To a solution of 170 mg of deutero oxide (V) in 5 ml of CH_3COOH was added 170 mg of diphenylhydrazine and the mixture was allowed to stand for 24 h at 20°, after which the product was precipitated with water, filtered, dried in the air, and washed with ether. We obtained 130 mg of diphenylhydrazone (XIII) with mp 205-206° (from CH_3OH), whose IR spectrum was identical with that of the authentic compound [4, 5], and whose mixed melting point with the latter was not depressed. The mass spectra of (XIII) and the authentic diketone diphenylhydrazone proved to be completely identical.

CONCLUSIONS

1. The opening of the oxide ring of the hydrazones of the 16α-deutero-16β,17β-oxides of steriods proceeds with a cleavage of the C-17–O bond and is accompanied by the complete elimination of deuterium from the 16-position.

2. The obtained results testify in support of the fact that the formation of the 16,17-hydroxypyrazoline and the monohydrazone of the 16,20-diketone does not proceed through the 16 → 17-hydride shift, but rather through the step of the Δ^{16}-16-vinyl alcohols.

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