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TRANSFORMED STEROIDS.

100.* PATHS FOR THE SYNTHESIS OF 16α,17α,21-TRIHYDROXY-20-KETO SYSTEMS IN STEROIDS

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The presence of the 16α,17α,21-trihydroxy-20-keto grouping is of great importance for the appearance of the biological activity of steroid drugs. It is sufficient to point out that this grouping appears directly in the structure of Synalar and triamcinolone and in the form of the 16,17-ketal in the structure of triamcinolone acetonide, olgestone acetophenonide, etc. The paths for synthesizing this grouping have been far from completely exhausted. Only two methods for the hydroxylation of the 21-methyl group and two methods for the synthesis of the 16α,17α-diol system have found application in industry [2]. The former are the bromination and iodination of the methyl ketone side chain followed by the acetolysis of the 21-halo ketone, and the latter are the cis-hydroxylation of the Δ^{16} bond with the aid of $KMnO_4$ or its epoxidation, opening of the 16,17α-epoxy-20-ketone by HBr and saponification of the bromhydrin. The methods themselves and combinations of them have a number of shortcomings, which make their use difficult. All this forced us to turn to the study of the possibilities of other paths for the synthesis of the trihydroxyketo grouping, particularly the method previously developed in [3], which involves the cis opening of the 16,17α-oxide ring in the presence of hydrazines.

The model compound 16,17α-epoxy-5α-pregnan-3β-ol-20-one (I), which lacks a Δ^5 bond, was selected as the object of investigation, and both possible reaction sequences, i.e., with initial introduction of the 21-acetoxy group followed by the synthesis of the 16,17-vic-diol system and vice versa, were studied.

The bromination of I in the presence of a solution of HCl in absolute methanol produces the 21-bromide (II) with a small yield, probably due to the partial opening of the oxide ring. The replacement of the bromine by an acetoxy group is effected by boiling the 21-bromide (II) in acetone with AcOK. The cis opening of the 16,17α-epoxide 21-acetate (III) by acetic acid in the presence of semicarbazide proceeds, as previously shown for the Δ^5 series [4], very slowly (~10 days), and an attempt to accelerate the reaction by heating resulted in the formation of a mixture of products. The removal of the semicarbazone protection from the 5α-pregnan-3β,16α,17α,21-tetrol-20-one 16,21-diacetate 20-semicarbazone formed (IV) by standard methods (with pyruvic acid, acetylacetone, and $NaNO_2$ in AcOH) is not possible even under severe conditions; i.e., the original semicarbazone is recovered, or a complex mixture of reaction products forms. The treatment of semicarbazone IV in an acetone solution of concentrated $HClO_4$ for the purpose of the simultaneous removal of the protection from the 20-keto group and the synthesis of the isopropylidene derivative results in the loss of the 21-acetoxy group and the formation of 16α,17α-isopropylidenedioxypregnanolone (V). The mechanism of this hydrogenolysis is unclear; however, it has definite analogies in the dehydration of the 17-hydroxyl group under acid conditions known for the 20-semicarbazone [5]. In any case the path described for the synthesis of the 16α,17α,21-trihydroxy-20-keto system with the use of semicarbazide is not promising.

*For communication 99 see [1].

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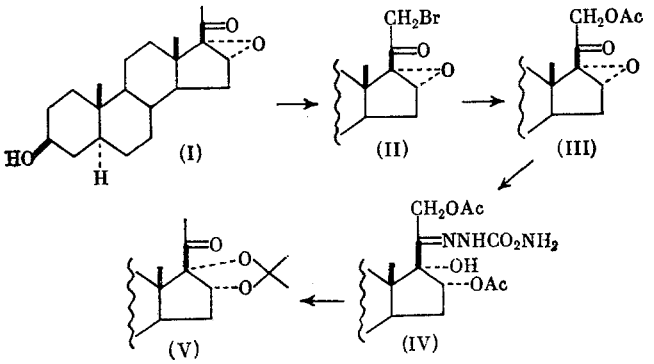
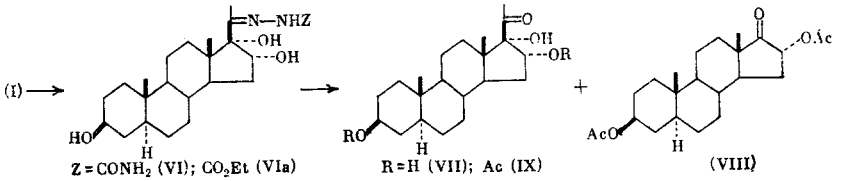
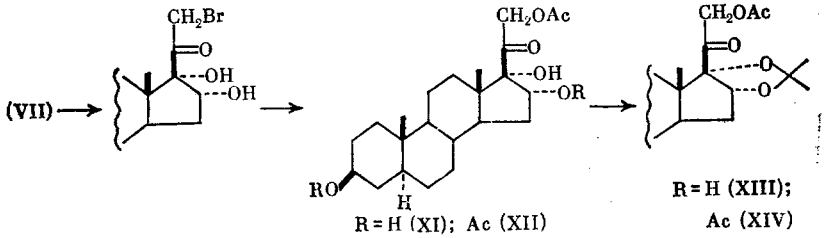


The second scheme for the cis opening of I with semicarbazide in AcOH followed by saponification by K_2CO_3 provides a good yield of the 20-semicarbazone of 5α-pregnan-3β,16α,17α-triol-20-one (VI). However, the attempt to remove the semicarbazone protection by the usual methods was unsuccessful, and the treatment of semicarbazone VI with $NaNO_2$ in AcOH resulted in the formation of a product of the degradation of the side chain, which was isolated and identified in the form of the 3,16-diacetate (VIII), along with 5α-pregnan-3β,16α,17α-triol-20-one (VII).



At the same time, the use of carbethoxyhydrazine instead of semicarbazide in this scheme showed that the formation of 5α-pregnan-3β,16α,17α-triol-20-one 20-carbethoxyhydrazone (VIa) proceeds with similar yields and that the removal of the hydrazone protection with the aid of acetylacetone is not accompanied by complications.

The bromination of triol VII by bromine in the presence of HCl in CH_3OH produces a good yield of the 21-bromide (X), which is converted into 5α-pregnan-3β,16α,17α,21-tetrol-20-one 21-acetate (XI) by boiling in acetone with AcOH and $N(Et)_3$. The structure of the latter and



its 3,16,21-triacetate (XII) is confirmed by the data from the physicochemical analysis. The treatment of the tetrol 21-acetate (XI) by acetone in the presence of $HClO_4$ at 20°C produces the 16,17-acetonide 21-acetate (XIII) with a good yield.

Thus, the use of carbethoxyhydrazine is more promising than that of semicarbazide for the synthesis of the 16α,17α,21-trihydroxy-20-ketosteroid system.

EXPERIMENTAL

The melting points were determined on a Kofler device. The PMR spectra were recorded on a Varian DA-60 IL spectrometer in a $CDCl_3$ solution, and the internal reference was TMS. The IR spectra were recorded on a UR-10 instrument with the use of samples molded with KBr.

16,17α-Epoxy-5α-pregnan-3β,21-diol-20-one 21-Acetate (III). A 1.6-ml portion of a 25% solution of HCl in abs. CH_3OH was added at 20°C to a solution of 2.12 g of 16,17α-epoxy-5α-pregnan-3β-ol-20-one (I) in 20 ml of CH_2Cl_2, and then a solution of 0.35 ml of Br_2 in 2 ml of CH_2Cl_2 was added dropwise. The mixture was stirred for 2 h, diluted with CH_2Cl_2, washed with an $NaHCO_3$ solution and water, and evaporated. This yielded 2.24 g of amorphous 16,17α-epoxy-5α-pregnan-3β-ol-20-one 21-bromide (II), mp 78-82°C. IR spectrum (ν, cm^{-1}): 1715, 3300-3530.

Next, 1.86 g of dry AcOK and 0.19 ml of AcOH were added to 1.24 g of the 21-bromide (II) in 7 ml of $(CH_3)_2CO$, the mixture was boiled with stirring for 6 h and diluted with water, and the precipitate formed was filtered, washed with water, and dried. This yielded 0.64 g of epoxide 21-acetate III, mp 179-182°C (from ether). IR spectrum (ν, cm^{-1}): 1235, 1723, 1758, 3400-3500, 3580. PMR spectrum (δ, ppm): 0.75 (s, 3 H, 18-CH_3), 1.00 (s, 3 H, 19-CH_3), 2.06 (s, 3 H, 21-OAc), 3.53 (broad line, H, 3-H), 3.57 (s, H, 3-OH), 3.68 (broad line, H, 16-H), 4.56 (s, 2 H, 21-CH_2).

5α-Pregnan-3β,16α,17α,21-tetrol-20-one 16,21-Diacetate 20-Semicarbazone (IV). A 0.24 g portion of semicarbazide was added to 1.03 g of epoxide 21-acetate III in 20 ml of AcOH, and the mixture was left to stand at 20°C for 18 days. The usual treatment yielded 0.96 g of semicarbazone IV, mp 156-160°C, which was used in the subsequent conversions without further purification.

16α,17α-Isopropylidenedioxy-5α-pregnan-3β-ol-20-one (V). A solution of 0.74 g of semicarbazone IV in 3.7 ml of acetone, 2.3 ml of CH_3OH, and 0.78 ml of 68% $HClO_4$ was heated at 60°C for 8 h and then diluted with water. The precipitate formed was filtered, washed with water, and dried. This yielded 0.31 g of acetonide V, mp 193-198°C (from ether), which did not show melting-point depression in a sample with a known specimen. IR spectrum (ν, cm^{-1}): 1713, 3350-3520.

5α-Pregnan-3β,16α,17α-triol-20-one 20-Semicarbazone (VI). A 0.16-g portion of semicarbazide was added to 0.83 g of I in 15 ml of AcOH, and the mixture was left to stand overnight at 20°C. The usual treatment yielded 0.94 g (82%) of 5α-pregnan-3β,16α,17α-triol-20-one 16-acetate 20-semicarbazone, mp 262-264°C (from CH_3OH).

A solution of 0.5 g of the latter in 50 ml of CH_3OH was treated with 1.5 ml of a 10% aqueous solution of K_2CO_3 and left to stand overnight at 20°C. The usual treatment yielded 0.48 g (56%) of semicarbazone VI, mp 248-249°C (from ether). IR spectrum (ν, cm^{-1}): 1445, 1480, 1580, 1660, 1680, 3210-3530.

Removal of Semicarbazone Protection from 5α-Pregnan-3β,16α,17α-triol-20-one 20-Semicarbazone (VI) with the Aid of $NaNO_2$ in AcOH. A solution of 8.55 g of $NaNO_2$ in 4 ml of water was added to 2.85 g of semicarbazone VI in 12 ml of AcOH, and the mixture was left to stand overnight at 20°C. Then urea was added, and the reaction mixture was extracted by $CHCl_3$. The extract was washed with a solution of $NaHCO_3$ and water and evaporated. This yielded 2.07 g of a mixture of two compounds. A 0.1-g portion of the mixture was acetylated with 2 ml of pyridine and 1 ml of Ac_2O to form 0.107 g of a mixture of acetates, from which the following were isolated by TLC on SiO_2 in a 2:1 ether—hexane system: 1) 40 mg of androstan-3β,16α-diol-17-one 3,16-diacetate (VIII), mp 186-187°C (from ether). IR spectrum (ν, cm^{-1}): 1740-1760. PMR spectrum (δ, ppm, $CDCl_3$): 0.85 (s, 3 H, 18-CH_3), 0.94 (s, 3 H, 19-CH_3), 2.00 (s, 3 H) and 2.08 (s, 3 H, 3-OAc and 16-OAc), 4.65 (broad line, H, 3-H), 5.4 (broad line, H, 16-H). Mass spectrum (m/e): M^+ 390. 2) 60 mg of 5α-pregnan-3β,16α,17α-triol-20-one 3,16-diacetate (IX), mp 153-158°C. PMR spectrum (δ, ppm): 0.7 (s, 3 H, 18-CH_3), 0.81 (s, 3 H, 19-CH_3), 2.00 (s, 3 H), 2.04 (s, 3 H), 2.23 (s, 3 H, 21-CH_3, 3-OAc, and 16-OAc), 4.65 (broad line, H, 3-H), 5.67 (broad line, H, 16-H).

5α-Pregnan-3β,16α,17α-triol-20-one 20-Carbethoxyhydrazone (VIa). A solution of 1.5 g of carbethoxyhydrazine in 5 ml of AcOH was added to 2 g of I in 50 ml of AcOH, and the mixture was left to stand overnight at 20°C. The usual treatment yielded 1.6 g (55%) of 5α-pregnan-3β,16α,17α-triol-20-one 16-acetate 20-carbethoxyhydrazone, mp 263-266°C (from an acetone—hexane mixture), to a solution of which in 50 ml of CH_3OH were added 6 ml of 10% K_2CO_3, and the mixture was left to stand at 20°C for 3 h. The usual treatment yielded 1.4 g (∿100%) of diol hydrazone VIa, mp 240-242°C.

5α-Pregnan-3β,16α,17α-triol-20-one (VII). A solution of 1.4 g of VIa in 35 ml of AcOH, 2.8 ml of acetylacetone, and 6 ml of water was heated at 85-95°C for 45 min and then diluted with water. The precipitate formed was filtered, washed with water, and dried. This yielded 770 mg of triol VII, mp 210-213°C, 231-233°C (from aqueous acetone). IR spectrum (ν, cm^{-1}): 1690, 3420.

5α-Pregnan-3β,16α,17α-triol-20-one 21-Bromide (X). Two drops of a solution of Br_2 in CH_2Cl_2 (0.06 ml Br_2 in 1 ml CH_2Cl_2) and 0.2 ml of a 25% solution of dry HCl in abs. CH_3OH were added to a suspension of 0.52 g of triol VII in 10 ml of CH_2Cl at 20°C with stirring, and then the remaining Br_2 solution was added dropwise. The mixture was stirred until the Br_2 was completely absorbed

(∿30 min), and the precipitate of the bromide was filtered. This yielded 0.55 g of cis-diol 21-bromide X, mp 159-162°C. IR spectrum (ν, cm^{-1}): 1720-1733, 3210-3540.

5α-Pregnan-3β,16α,17α,21-tetrol-20-one 21-Acetate (XI). A solution of 0.2 g of X in a mixture of 11 ml of acetone, 2.1 ml of AcOH, and 2.1 ml of $(C_2H_5)_3N$ was boiled for 3 h and then diluted with water. The precipitate formed was filtered, washed with water, and dried. This yielded the following products: 1) 0.13 g of cis-diol 21-acetate XI, mp 199-203°C (from aqueous acetone). IR spectrum (ν, cm^{-1}): 1715, 1730, 3410-3440. Mass spectrum (m/e): 348 (M^+ − AcOH). 2) 5α-pregnan-3β,16α,17α,21-tetrol-20-one 3,16,21-triacetate (XII), mp 198-200°C (from aqueous acetone). IR spectrum (ν, cm^{-1}): 1705, 1733-1745, 3460. PMR spectrum (δ, ppm): 0.70 (s, 3 H, 18-CH_3), 0.8 (s, 3 H, 19-CH_3), 2.00 (s, 3 H), 2.04 (s, 3 H), and 2.14 (s, 3 H, 21-OAc, 3-OAc, and 16-OAc), 4.65 (broad line, H, 3-H), 4.92 (s, 2 H, 21-CH_2), 5.65 (broad line, H, 16-H). Mass spectrum (m/e): 432 (M^+ − AcOH).

16α,17α-Isopropylidenedioxy-5α-pregnan-3β,21-diol-20-one 21-Acetate (XIII). A 0.08-ml portion of 68% $HClO_4$ was added to a suspension of 0.05 g of tetrol XI in 2 ml of acetone, and the mixture was left to stand at 20°C for 15 min. Then the mixture was diluted with water, and the precipitate formed was filtered, washed with water, and dried. The following products were obtained: 0.04 g of acetonide 21-acetate XIII, mp 185-188°C (from aqueous acetone). IR spectrum (ν, cm^{-1}): 1730, 1750, 3430-3500. PMR spectrum (δ, ppm): 0.625 (s, 3 H, 18-CH_3), 0.80 (s, 3 H, 19-CH_3), 1.22 (s, 3 H) and 1.47 (s, 3 H, acetonide CH_3), 2.15 (s, 3 H, 21-OAc), 3.50 (broad line, H, 3-H), quartet with centers at 4.7 and 5.12 (2 H, 21-CH_2), 5.1 (broad line, H, 16-H). Mass spectrum (m/e): M^+ 448. 16α,17α-Isopropylidenedioxy-5α-pregnan-3β,21-diol-20-one 3,21-diacetate (XIV): mp 160-162°C (from aqueous acetone). IR spectrum (ν, cm^{-1}): 1730, 1735, 1750. PMR spectrum (δ, ppm, CCl_4): 0.53 (s, 3 H, 18-CH_3), 0.79 (s, 3 H, 19-CH_3), 1.15 (s, 3 H) and 1.40 (s, 3 H, acetonide CH_3), 2.04 (s, 3 H) and 1.88 (s, 3 H, 21-OAc and 3-OAc), 4.51 (broad line, H, 3-H), quartet with centers at 4.6 and 4.93 (2 H, 21-CH_2), 4.8 (broad line, H, 16-H).

CONCLUSIONS

1. Two schemes for the synthesis of the 16α,17α,21-trihydroxy-20-keto system in 5α-steroids with the use of the cis opening of 16,17α-oxides of 20-ketosteroids in the presence of reagents on the carbonyl group have been realized.

2. The use of carbethoxyhydrazine provides better yields of 5α-pregnan-3β,16α,17α-21-tetrol-20-one.

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