TRANSFORMED STEROIDS

COMMUNICATION 19. CIRCULAR DICHROISM AND RETRO-ALDOL CLEAVAGE OF 3β, 20-DIHYDROXY-20-METHYLPREGN-5-EN-16-ONES THAT ARE ISOMERIC WITH RESPECT TO C-17

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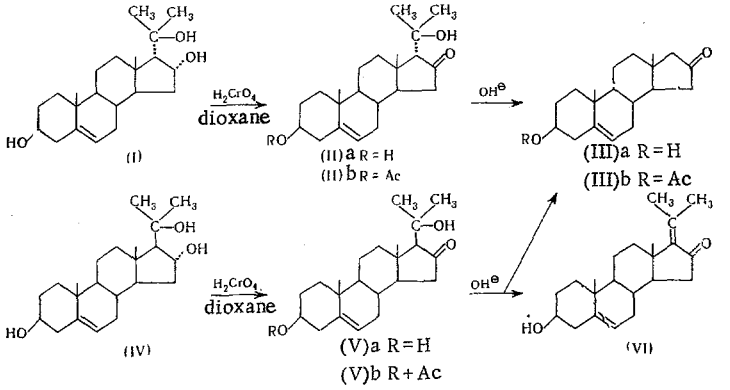
UDC 542.91+547.92

In a previous communication [1] we described the synthesis of 3β,20-dihydroxy-20-methyl-17α-pregn-5-en-16-one acetate (IIb) and found that under the action of alkali this ketone undergoes cleavage extremely readily at the $C_{17} - C_{20}$ bond with formation of the known 3β-hydroxyandrosten-16-one (IIIa). This proved the presence of a keto group at C-16 in the ketone (IIb) and confirmed the structure of the triol (I) obtained by the rearrangement of 16α,17α-epoxypregn-5-ene-3β,20α-diol under the action of methylmagnesium iodide [1]. The structure and configuration at C-17 of the ketone (IIa) corresponding to the acetate (IIb) was further confirmed by the measurement of circular-dichroism curves for the 16-ketones (IIa) and (Va), which are isomeric with respect to C-17. We synthesized 3β, 20-dihydroxy-20-methylpregn-5-en-16-one (Va) by the oxidation of the triol (IV) [2] with 8 N chromic acid. Because of the poor solubility of the triol (IV) in acetone, the oxidation was conducted in dioxane. By the acetylation of the oxidation product (Va) we obtained the acetate (Vb). The isomer with respect to C-17 – 20-methyl-17α-pregn-5-ene-3β,16α,20-triol (I) – was oxidized under the same conditions with formation of the ketone (IIa), whose acetate (IIb) was identical to the product which we described earlier [1].

The low vibration frequency of the carbonyl group in the five-membered ring found in the IR spectra of the ketones (IIa) and (Va) (1710 and 1735 cm^{-1} respectively) is probably to be explained by the presence of an intramolecular hydrogen bond between the 16-carbonyl group and the 20-hydroxyl. The structure of the ketones (IIb) and (VB) was confirmed by the PMR spectra and circular-dichroism curves of the corresponding keto diols (IIa) and (Va)



It is well known that steroid 16-ketones show a strongly negative Cotton effect, determined in the main by the asymmetry of the cyclopentane ring itself [3]. It was shown earlier that an equatorial 17β-substituent scarcely affects the character and amplitude of the rotatory dispersion curve of 16-keto steroids, whereas a 17α-bromine atom changes the sign of the Cotton effect [4]. As we have found, the 17β-(1-hydroxy-1-methylethyl) group in the ketone (Va), in accordance with data in the literature for 17β-substituted 16-keto steroids [4], scarcely affects the amplitude of the circular-dichroism curve of 3β-hydroxyandrost-5-en-16-one (IIIa), whereas the 17α-(1-hydroxy-1-methylethyl) group in the ketone (IIa), as a result of its positive contribution in the Cotton effect, reduces the amplitude of the circular-dichroism curve of the 17-unsubstituted ketone (IIIa) appreciably while not changing the sign of the Cotton effect.

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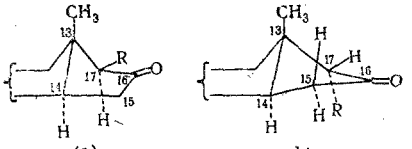
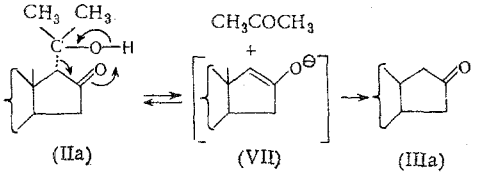
Our results are in agreement with views in the literature on the conformation of the five-membered D ring of steroids, which depends on the substituents present in the ring [5]. For C/D-trans steroids with a keto group at C-16 and a 17β-substituent the more favored conformation of the D ring is the conformation of the C-13 envelope (*a*), in which the 17β-substituent occupies the equatorial position and therefore does not influence the Cotton effect. 17α-Substituted 16-keto steroids, as a result of 1,3-interaction between the 17α-substituent and the α-hydrogen at C-14, probably exist in the preferred half-chair conformation (b), in which the 17α-substituent R and the 17β-hydrogen occupy quasiaxial and quasiequatorial positions, respectively [6]



The difference in the configuration of the 17-side chain in the epimeric pair of 16-ketones studied affects their behavior in chemical reactions. For example, the 16-ketones (IIa) and (Va) behave differently toward alkali. Whereas the acetate of the ketone (IIa) with the quasiaxial side chain is readily split at the $C_{17} - C_{20}$ bond with formation of (IIIa) under the action of an aqueous methanol solution of K_2CO_3 even at room temperature [1], the ketone (Va) with an equatorial side chain at C-17 is stable, even to the action of KOH at 20°. The ketone (Va) reacts with KOH only at the boil with formation of a mixture of two products with close R_f values, namely, the product of the degradation of the 17-side chain (IIIa) and the α,β-unsaturated ketone (VI). The structures of these compounds were assigned on the basis of TLC data and the IR spectra.

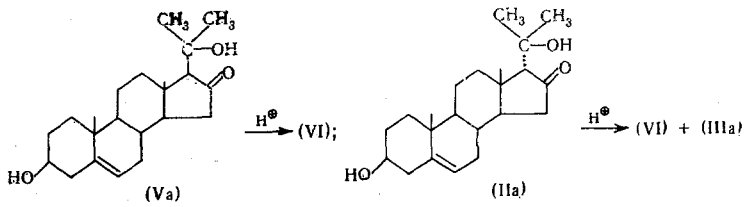
The elimination of the 17-side chain in 20-hydroxy 16-ketones is probably a retro-aldol reaction, i.e., a reaction that is the inverse of the aldol condensation. Both reactions appear to go by analogous mechanisms, in which an intermediate enol form of the 16-ketone is formed



Several examples of the retro-aldol cleavage of β-hydroxy ketones have been reported previously in the steroid series [7], but in the case of 20-hydroxy 16-ketones data have been reported only on the elimination of a 17β-side chain in the action of yeast on the ketols [8]. The stereochemistry of the retro-aldol reaction has been little studied, and data on the stereochemistry of the aldol condensation refers in the main to the subsequent state: the dehydration of the β-ketol formed into an α,β-unsaturated ketone. It is known that retro-aldolization under alkaline conditions may become the predominant course of reaction in the case of hindrance in the stage of the dehydration of the β-hydroxy ketone, the intermediate product of crotonic condensation. In the light of these data, the ketone with the 17α-side chain (IIa), in which the approach of the base to the proton at C-17 from the β-region is sterically hindered (as a result of interaction with the angular 18-methyl group), probably shows a high tendency to undergo retro-aldolization. Also, it must probably be supposed that the elimination of the quasiaxial side chain in (IIa) in retro-aldol reaction will go more readily than the elimination of the equatorial side chain in (Va) because of the operation of the stereoelectronic factor. We have previously [9] observed the elimination of a 17α-side chain in a 16-ketone of the 18-nor-17β-methyl-17α-pregna-5,13(14)-diene series under severe conditions (boiling with KOH in methanol). The difficulty of the retro-aldol reaction in this case may be explained by the fact that in presence of the 13(14)-double bond, which makes the D-ring planar, the character of the bonds at C-17 is probably close to bisectional [10], i.e., the 17β- and 17α-bonds are equally inclined to the plane of the ring. However, in this case the presence of a methyl group at C-17 may also have an effect.

In the reaction of the ketone (Va) with perchloric acid in dioxane the only reaction product was the α,β-unsaturated ketone (VI). In the analogous treatment of the isomeric ketone (IIa), apart from the α,β-unsaturated ketone (VI), the product of retro-aldol reaction – 3β-hydroxyandrost-5-en-16-one (IIIa) – is formed. The retro-aldol cleavage of the $C_{17} - C_{20}$ bond is observed also in the chromatography of the ketone (IIb) on florisil. It should be noted that in the last case there occurs also the isomerization of the side chain

with formation of the ketone (Vb) with the more stable equatorial configuration of the side chain



EXPERIMENTAL

Melting points were determined in a Kofler block. Angles of rotation were measured with a Hilger-Watts polarimeter. Circular-dichroism (CD) curves were determined with a Roussel-Jouan dichrograph on ethanol solutions of concentration about 1 g/liter at room temperature. IR spectra were determined with a UR-10 instrument on samples pelleted with KBr. PMR spectra were determined in chloroform-d with an RS-60 radiospectrometer at 60 MHz with hexamethyldisiloxane as internal standard. For TLC we used microscope slides with a bound layer of KSK silica gel, grain size 10-30 mμ.

3β-Hydroxyandrost-5-en-16-one (IIIa) [1]. CD: $[\theta]_{350}0$; $[\theta]_{322}$ −4.850 (shoulder (sh.)); $[\theta]_{315}$ −8.570; $[\theta]_{308}$ −14.300 (sh.); $[\theta]_{298}$ −18.350 (max.); $[\theta]_{292}$ −16.500 (sh.); $[\theta]_{285}$ −13.200; $[\theta]_{250}$ −43. Γ = 37 mμ.

3β,20-Dihydroxy-20-methylpregn-5-en-16-one (Va). 20-Methylpregn-5-ene-3β,16α,20-triol (IV) (0.30 g) was dissolved with heating in 350 ml of dioxane, and then at 20° 1 ml of 8 N chromic acid was added dropwise with stirring. After 15 min 20 ml of methanol was added to the solution, stirring was continued further for 10 min, and then the solution was poured into water and extracted with chloroform. Solvent was removed in a vacuum, and the residue was recrystallized from ethyl acetate. We obtained 0.082 g of 3β,20-dihydroxy-20-methylpregn-5-en-16-one (Va), mp 197-199°. Found: C 76.37; H 9.66%. $C_{22}H_{34}O_3$. Calculated: C 76.26; H 9.89%. IR spectrum: 1735, 3530 cm^{-1}. CD: $[\theta]_{350}0$; $[\theta]_{320}$ −10.500; $[\theta]_{305}$ −19.130 (max.); $[\theta]_{285}$ −10.260; $[\theta]_{250}0$. Γ = 37 mμ.

3β,20-Dihydroxy-20-methylpregn-5-en-16-one Acetate (Vb). The mother liquors from the crystallization of the ketone (Va) were acetylated with 1 ml of acetic anhydride in 5 ml of pyridine at room temperature for 18 h. After the usual treatment we isolated 0.200 g of 3β,20-dihydroxy-20-methylpregn-5-en-16-one acetate (Vb), mp 172.5-173° (mixture of acetone and hexane). $[\alpha]_D$ −169.9° (C 0.536, ethanol). Found: C 74.12; H 9.26%. $C_{24}H_{36}O_4$. Calculated: C 74.19; H 9.34%. IR spectrum: 1250, 1730, 3530 cm^{-1}. PMR spectrum (δ, ppm): 5.48 (H at double bond); 4.50 (3αH); 3.75 (OH); 1.98 (3β-OAc); 1.24 (2 CH_3 at C-20); 1.17 (19-CH_3); 0.89 (18-CH_3).

3β,20-Dihydroxy-20-methyl-17α-pregn-5-en-16-one (IIa). With stirring at 16° in an atmosphere of nitrogen 8 N chromic acid was added dropwise to a solution of 1.85 g of 20-methyl-17α-pregn-5-ene-3β,16α,20-triol (I) in 750 ml of dioxane (dissolution was effected by heating) until the spot of the original triol (I) disappeared from the chromatogram (3.2 ml of chromic acid was required). Methanol (25 ml) was added to the mixture, stirring was continued for 10 min, and then the mixture was poured into water and extracted with chloroform. Solvent was driven off in a vacuum, and the residue was crystallized from ethyl acetate. We obtained 0.440 g of 3β,20-dihydroxy-20-methyl-17α-pregn-5-en-16-one (IIa), mp 148-150°; $[\alpha]_D^{22}$ −179.8° (C 0.97, acetone). Found: C 76.08; H 9.81%. $C_{22}H_{34}O_3$. Calculated: C 76.26 H 9.89%. IR spectrum: 1710, 3410, 3560 cm^{-1}. $[\theta]_{350}0$; $[\theta]_{328}$ −5.280; $[\theta]_{317}$ −10.220 (sh.); $[\theta]_{309}$ −12.090 (max.); $[\theta]_{303}$ −10.750 (sh.); $[\theta]_{290}$ −6.600; $[\theta]_{250}0$. Γ = 39 mμ.

Acetylation of 3β,20-Dihydroxy-20-methyl-17α-pregn-5-en-16-one (IIa). The acetylation of 0.400 g of the crystalline ketone (IIa) was effected with 1.5 ml of acetic anhydride in 6 ml of pyridine at room temperature. After 17 h the solution was poured into water, and the precipitate formed was filtered off, washed with water, and dried in air. We obtained 0.42 g of 3β,20-dihydroxy-20-methyl-17α-pregn-5-en-16-one 3-acetate (IIb), mp 158-160° after two crystallizations from a mixture of acetone and hexane. $[\alpha]_D^{24}$ −162.7° (C 0.519, ethanol). Found: C 74.14; H 9.46%. $C_{24}H_{36}O_4$. Calculated: C 74.19; H 9.34%. IR spectrum: 1250, 1730, 3495 cm^{-1}. PMR spectrum (δ, ppm): 545 (H at double bond); 4.50 (H adjacent to OAc); 4.15 (OH); 1.97 (OAc); 1.24, 1.18 (2CH_3 at C-20); 1.17 (19-CH_3); 0.95 (18-CH_3).

The substance in the mother liquor from the crystallization of the ketone (IIa) (0.836 g) was acetylated with 4 ml of acetic anhydride in 20 ml of pyridine at room temperature. After 16 h the mixture was poured

into water and extracted with ether. The extract was washed with water and vacuum-evaporated; methanol was added to the residue. The residue was chromatographed on 90 g of florisil. In gradient elution with the systems hexane varying to 1:1 hexane + ether and 1:1 hexane + ether varying to 3:1 hexane + ether we isolated: 1) 0.334 g of 3β-hydroxyandrost-5-en-16-one 3-acetate (IIIb), mp 131-132° (after three crystallizations from hexane), and 2) 0.430 g of a substance with mp 173-174.5° (after three crystallizations from a mixture of acetone and hexane), which was found to be identical to 3β,20-dihydroxy-20-methylpregn-5-en-16-one 3-acetate (Vb). IR spectrum: 1250, 1730, 3530 cm^{-1}.

Reaction of 3β,20-Dihydroxy-20-methylpregn-5-en-16-one (Va) with Aqueous-Methanolic KOH Solution. To a solution of 0.022 g of the keto diol (Va) in 2 ml of methanol we added 0.3 ml of 1 N KOH. When the solution had been stirred at room temperature for 12 h, the spot of the original keto (Va) on the chromatogram was unchanged. The solution was boiled until the keto diol (Va) had disappeared (1 h) and then neutralized with acetic acid and vacuum-evaporated. The residue was chromatographed preparatively on a layer of silica with a 4:1 mixture of ether and hexane as solvent. We then isolated 0.015 g of a mixture of two substances with close R_f values, chromatographically identical to (IIIa) and (VI). IR spectrum: 1620, 1710 ($\Delta^{17(20)}$-16-keto), 1720, 1750 (keto group at C-16 in 3β-hydroxyandrost-5-en-16-one),* 3400 (OH) cm^{-1}.

3β-Hydroxy-20-methylpregna-5,17(20)-dien-16-one (VI). Two drops of 72% $HClO_4$ were added to a solution of 7.0 mg of the keto diol (Va) in 2 ml of aqueous dioxane. At room temperature the spot of the original ketone (Va) on the chromatogram did not change for 12 h. The solution was heated for 1.5 h at 65°, cooled, and without treatment applied to a thin layer of silica and chromatographed with a 4:1 mixture of ether and hexane as solvent. We isolated 4.0 mg of the ketone (VI), mp 156-161° (after one crystallization from acetone. IR spectrum: 1618, 1705 ($\Delta^{17(20)}$-16-keto), 3410, 3500 (OH) cm^{-1}.

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CONCLUSIONS

1. 3β,20-Dihydroxy-20-methylpregn-5-en-16-ones isomeric with respect to C-17 were synthesized by the oxidation of the corresponding triols with chromic acid in dioxane.

2. The retro-aldol cleavage of steroid 20-hydroxy 16-ketones is probably directed by the stereoelectronic factor. Elimination of the side chain occurs readily under mild conditions in the case of the 17α-substituted 16-ketone, but does not occur under these conditions in the case of the 17β-isomer.

3. Analysis of the circular-dichroism curves of 17-(1-hydroxy-1-methylethyl) 16-keto steroids which are isomeric with respect to C-17 confirms the configuration of the side chain in these ketones.

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*See preceding communication.