TRANSFORMED STEROIDS

COMMUNICATION 66. STEREOCHEMISTRY AND MECHANISM OF REACTION OF HYDRAZONES OF STEROIDAL 20-KETO 16α,17α-OXIDES WITH THIOACETIC ACID

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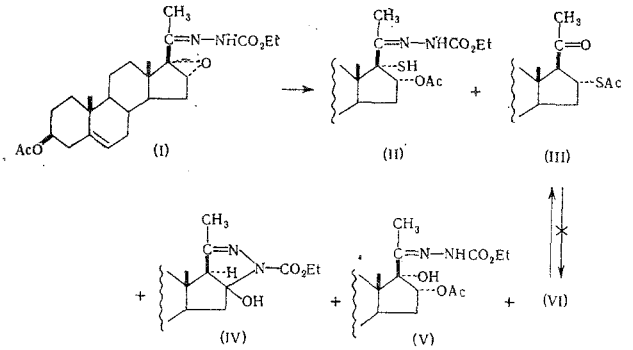
Previously it was shown that the reaction of the hydrazones of steroidal 20-keto 16α,17α-oxides with nucleophilic reagents can be used to synthesize the difficultly available 17α-substituted 16α-hydroxy-20-keto steroids [1, 2]. The results of a detailed study of this reaction using thioacetic acid [3] as the nucleophilic reagent are described in the present communication. The synthesis of compounds, containing either the thiol or the thiolacetate group at C-17, also represents independent interest for studying the relation between the structure (configuration) and the activity of modified steroids.

As it proved, the 20-carbethoxyhydrazone of 16α,17α-epoxypregn-5-en-3β-ol-20-one (I) reacts easily with AcSH at room temperature in the presence of an inhibitor of free radical processes, like hydroquinone, to give a mixture of products that contains at least seven compounds, from which the following compounds were isolated by chromatographing on silica gel and identified: pregn-5-ene-3β,16α-diol-17α-thiol-20-one 3,16-diacetate carbethoxyhydrazone (II), pregn-5-en-3β-ol-16α-thiol-20-one 3,16 diacetate (III), hydroxypyrazoline (IV), and pregn-5-ene-3β-16α,17α-triol-20-one 3,16-diacetate carbethoxyhydrazone (V).

The principal reaction product is the thiol hydrazone (II), which was isolated in ~60% yield by the recrystallization of its chromatographically inseparable mixture with product (VI) of unestablished structure, which could not be isolated in the pure state. Thiolacetate (III) was isolated by heating the mother liquor from the above-indicated mixture, which contains compound (VI), with pyruvic acid in AcOH for a short time. The removal of the hydrazone protection, with the formation of thiolacetate (III), proceeds



with exceeding ease even when the reaction mixture is chromatographed on silica gel. This can evidently explain the isolation of thiolacetate (III) from the reaction mixture, the structure of which was unequivocally proved by comparing with an authentic specimen of (III) [4]. Despite the fact that compound (III) is formed from substance (VI) under the conditions of removing the hydrazone protection, or even during

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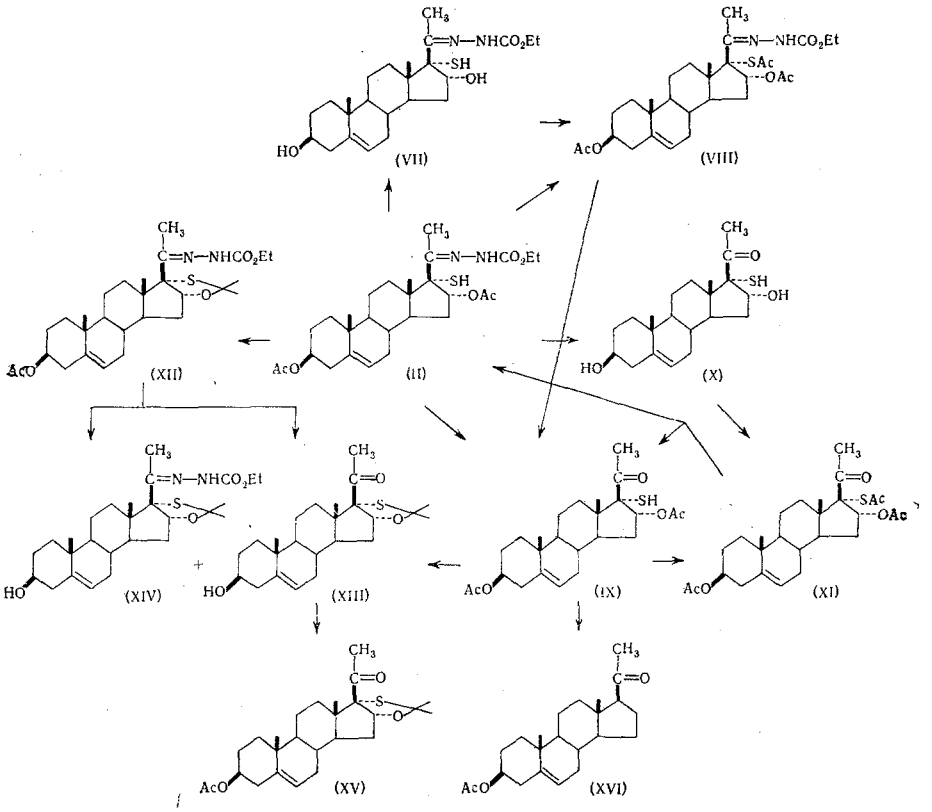
chromatographing on silica gel, product (VI) is not the hydrazone of thiolacetate (III), which was specially shown by comparing it with an authentic specimen of the hydrazone that was obtained by counter synthesis. In view of the unestablished structure of product (VI) the paths for the formation of thiolacetate (III) from it will not be discussed in the present paper. Compounds (IV) and (V) were identified by comparison with authentic specimens [5, 6].

The removal of the hydrazone protection in thiol (II) was accomplished by heating it with pyruvic acid in AcOH at 100°C, in which connection pregn-5-ene-3β-16α-diol-17α-thiol-20-one 3,16-diacetate (IX) was obtained in 30% yield.* The formation of the latter is also observed when hydrazone (VIII), obtained by the acetylation of hydrazones (II) and (VIII) with Ac_2O in pyridine, is heated under analogous conditions. Pregn-5-ene-3β-16α-diol-17α-thiol-20-one (XI) was obtained in ~90% yield when hydrazone (II) was refluxed for a short time in methanol that contained dilute HCl solution. Thiols (IX) and (X) are easily acetylated with Ac_2O in pyridine to give pregn-5-ene-3β-16α-diol-17α-thiol-20-one 3,16,17-triacetate (XI). It should be mentioned that thiolacetates (VIII) and (XI) have a lower chromatographic mobility on silica gel than the thiols (II) and (IX) corresponding to them. This observation is in agreement with the rule previously mentioned by us.

The absence of epimerization in the step of removing the hydrazone protection, with the formation of thiol (IX), was established by the resynthesis of hydrazone (II), which was accomplished by heating triacetate (XI) with carbethoxyhydrazine in AcOH for a long time. However, the reaction proceeds with great difficulty and in low yield, requires a large excess of carbethoxyhydrazine and, as can be seen from the scheme, is accompanied by partial hydrolysis of the thiolacetate group.



Multiplet signals are observed in the NMR spectra of hydrazone (II) and thiol (IX), respectively in the 5.9 and 5.75 ppm region, which were assigned to the 16β-protons at the 16α-acetoxy group [2]. The possible isomeric structure, with a tertiary acetate group at C-17, was rejected on this basis. The characteristic strong shift of the signal from the proton at C-16 downfield when going from the 16-hydroxy compounds (VII) and (X) to their 16-acetates (II) and (IX) ($\Delta\delta$ 0.8 and 0.85 ppm, respectively) is found to be in agreement with this.

It is also interesting to mention that the desulfurization of thiol (IX) over Raney Ni is accompanied by elimination of the acetate group at C-16, which leads to the known pregn-5-en-3β-ol-20-one 3-acetate

*The reaction is accompanied by a partial saponification of the 16-acetoxy group.

(XVI) [4], which also testifies to the tertiary character of the thiol grouping. The configuration of the substituents of the thiol 3,16-diacetate (IX), and consequently, also of all of the obtained compounds in this series, follows from the NMR spectra and the results of studying the circular dichroism curves, both in the region of the $n \rightarrow \pi^*$ transition of the carbonyl chromophore and in the region of the $n \rightarrow \sigma_5^*$ transition of the oxathiolane derivatives [7, 8]. This cis-arrangement of the vicinal thiol and acetate groups was also confirmed by the formation of the oxathiolane derivative (XIII)† when thiols (IX) and (X) are refluxed in acetone in the presence of $HClO_4$. The preparation of the identical oxathiolane derivative (XIII) from oxathiolane hydrazone (XII) indicates the absence of epimerization at C-17 in the step of converting thiols (IX) and (X) to compound (XIII). The absence of epimerization at C-16 was shown by the NMR spectra (when going from thiol (IX) and its hydrazone (II) to compounds (XII)-(XV) the signals of the C-18 protons of the angular CH_3 groups remain practically unchanged).

Consequently, the results obtained in studying the reaction of 16α,17α-epoxypregnenolone carbethoxyhydrazone (I) with AcSH reliably corroborate the previously adopted mechanism for the opening of the oxide ring in the presence of the hydrazone fragment, which includes the predominant cleavage of the C_{17}–O bond, the insertion of the nucleophilic reagent (SAc) at the C_{17}-center from the less shielded α-region of the molecule, and subsequent $C_{17} \rightarrow C_{16}$-acyl migration. The presence of hydroxypyrazoline (IV) in the reaction mixture is also additional proof of the initial cleavage of the C_{17}–O bond, and is evidently explained by the competing reaction of elimination of the 16-proton and subsequent cyclization. The reaction products of oxide (I) with the thiono form of thioacetic acid were not detected [9] in the present study. It is possible that the diacetate carbethoxyhydrazone (V) isolated from the reaction mixture is a secondary hydrolysis product of the formed thiono ester, with subsequent acylation of the secondary OH group.

EXPERIMENTAL METHOD

The melting points were determined on a Kofler block. The IR spectra were taken on a UR-10 instrument as KBr pellets. The NMR spectra (60 MHz) were taken in $CDCl_3$, using HMDS as the internal standard. The angles of rotation were measured on a Hilger Watts spectropolarimeter.

Reaction of 16α,17α-Epoxypregn-5-en-3β-ol-20-one 3-Acetate 20-Carbethoxyhydrazone (I) with Thioacetic Acid. A solution of 5 g of the keto oxide hydrazone (I) in 20 ml of distilled AcSH, to which 0.20 g of hydroquinone had been previously added, was allowed to stand at 20° overnight. The excess AcSH was evaporated in vacuo, the residue was diluted with water, and the obtained precipitate was filtered, washed with water, and dried in the air. We obtained 6.16 g of product, from which by chromatographing on a column (SiO_2, ether–hexane), with subsequent recrystallization of the obtained fractions and separation of the mother liquods by TLC, we isolated the following.‡

1) 3.3 g of pregn-5-ene-3β,16α-thiol-20-one 3,16-diacetate carbethoxyhydrazone (II), mp 181.5-184° (from MeOH); $[\alpha]_D^{22}$ −154.02 (C 1.418, $CHCl_3$). Infrared spectrum (ν, cm^{-1}): 1245, 1520, 1715, 1739, 3300. NMR spectrum (δ, ppm): 0.73 (s, 3H–18-CH_3); 0.93 (s, 3H–19-CH_3); 1.25 (t, 3H–CH_3 of hydrazone fragment); 1.87 (s, 3H–21-CH_3); 1.94 (s, 3H–3-OAc); 1.99 (s, 3H–16-OAc); 4.5 (broad line, H–3-H); 4.2 (qu., 2H–CH_2 of hydrazone fragment); 5.3 (broad line, H–6-H), 5.9 (broad line H–16-H); 7.75 (s, H–NH). Found: C 62.92; H 7.90; S 5.93; N 5.20%. $C_{28}H_{42}O_6SN_2$. Calculated: C 62.90; H 7.92; S 5.98; N 5.24%.

2) 0.6 g of pregn-5-en-3β-ol-16α-thiol-20-one 3,16-diacetate (III), mp 182-187°, which was chromatographically the same and did not depress the mixed melting point with an authentic specimen [5].

3) 1 g of a mixture of compounds (II) and (VI), which was obtained after recrystallizing the carbethoxyhydrazone (II). A solution of this mixture in 8 ml of AcOH and 2 ml of 50% pyruvic acid solution was heated at 100° for 10 min. After the usual workup and recrystallization from MeOH we isolated 0.3 g of thiolacetate (III), mp 178-181°, which was identical with the previously isolated sample. The mother liquor from the recrystallization was separated by TLC (SiO_2, 3:1 ether–hexane). As the result of the separation we isolated an additional 0.2 g of carbethoxyhydrazone (II) and 0.21 g of a mixture, which was

† An examination of the Dreiding models shows that the formation of the 17β(S),16α(O)-oxathiolane trans-derivative, although it is fairly improbable, is still possible and requires a greater strain of the ring and a distortion of the valence angles in rings D, B, C, and A. However, a study of the dichroism curves of oxathiolanes (XIII) and (XV) completely excludes a trans-coupling with ring D for them [7, 8].

‡ The yields (in g) are given on the basis of the chromatographically pure unrecrystallized products.

composed of thiolacetate (III) and pregn-5-ene-3β,16α-diol-17α-thiol-20-one 3,16-diacetate (IX), with a predominance of thiolacetate (III) in the mixture.

4) 0.2 of pregn-5-ene-3β,16α,17α-triol-20-one 3,16-diacetate carbethoxyhydrazone (V), mp 221-232° (from MeOH), which was identical with an authentic specimen [6].

5) 0.3 g of androst-5-ene-3β-[16,17-c]-2-hydroxy-3'-carbethoxy-5'-methylpyrazoline 3-acetate (IV), mp 204-207° (from acetone–hexane). Infrared spectrum (ν, cm^{-1}): 1260, 1700, 1722, 3470. NMR spectrum (δ, ppm): 0.6 (s, 3H–18-CH_3); 0.94 (s, 3H–19-CH_3); 1.25 (t, 3H–CH_3 of hydrazone fragment); 1.94 (s, 6H-3-OAc, 21-CH_3); 2.96 (s, H–OH); 4.5 (broad line, H–3-H); 4.2 (qu., 2H–CH_2 of hydrazone fragment); 5.28 (broad line, H–6-H).

A solution of 0.07 g of hydroxypyrazoline (IV) in 2 ml of absolute dioxane, containing 1 drop of H_2SO_4, was kept at 20° for 0.5 h. After workup and recrystallization from aqueous acetone we obtained 0.056 g of androst-5-enol-3β-[16,17-c]-3'-carbethoxy-5'-methylpyrazole 3-acetate, mp 163-166°, which was chromatographically the same and did not depress the mixed melting point with an authentic specimen [5].

Pregn-5-ene-3β,16α-diol-17α-thiol-20-one Carbethoxyhydrazone (VII). A solution of 0.18 g of hydrazone (II) in 5 ml of CH_3OH, containing 1 drop of conc. H_2SO_4, was kept at 20° for 24 h, after which it was diluted with water, and the precipitate was filtered and dried on the filter. After recrystallization from acetone–hexane we isolated 0.08 g of thiol (VII), mp 173-178°, 218° (decompn.); $[\alpha]_D^{22}$ −137.3 (C 0.313, $CHCl_3$). Infrared spectrum (ν, cm^{-1}): 1530, 1712, 3200-3600. NMR spectrum (δ, ppm): 0.74 (s, 3H–18-CH_3); 0.94 (s, 3H–19-CH_3); 1.25 (t, 3H–CH_3 of hydrazone fragment); 1.9 (s, 3H–21-CH_3); 3.5 (broad line, H–3-H); 4.2 (qu., 2H–CH_3 of hydrazone fragment); 5.1 (broad line, H–16-H); 5.28 (broad line, H–6-H).

Pregn-5-ene-3β-16α-diol-17α-thiol-20-one 3,16,17-Triacetate Carbethoxyhydrazone (VIII). A solution of 0.8 g of hydrazone (II) in 15 ml of C_5H_5N was acetylated at 20° with 8 ml of Ac_2O for 24 h. The excess Ac_2O was neutralized with methanol, and the obtained reaction mixture was poured into water and extracted with ether. The ether extract was washed with dilute HCl solution, then with water, and dried over Na_2SO_4. Evaporation of the ether gave 0.83 g of product, from which by recrystallization from ether–hexane we isolated 0.58 g of carbethoxyhydrazone (VIII), mp 148-152° (decompn.); $[\alpha]_D^{24}$ −148.7 (C 0.62, $CHCl_3$). NMR spectrum (δ, ppm): 0.71 (s, 3H–18-CH_3); 0.93 (s, 3H–19-CH_3); 1.81 (s, 3H–16-OAc); 1.85 (s, 3H–21-CH_3); 1.96 (s, 3H–3-OAc); 2.23 (s, 3H–SAc); 4.5 (broad line, H–3-H); 6.32 (broad line, H–16-H); 7.68 (s, H–NH). Found: C 61.85; H 8.07; S 5.38; N 5.03%. $C_{29}H_{44}O_7SN_2$. Calculated: C 61.68; H 7.85; S 5.66; N 4.96%. By chromatographing the mother liquor we isolated an additional 0.148 g of (VIII) and 0.08 g of the starting hydrazone (II).

A solution of 0.07 g of hydrazone (VII) in 2 ml of pyridine was acetylated with 0.7 g of Ac_2O under the above-described conditions. After the usual workup and purification employing TLC (SiO_2, 4:1 ether–hexane) we obtained 0.05 g of triacetate (VIII), mp 143-148° (from ether–hexane), which was chromatographically the same and did not depress the mixed melting point with the above-described specimen.

Pregn-5-ene-3β-16α-diol-17α-thiol-20-one 3,16-Diacetate (IX). A solution of 0.5 g of hydrazone (II) in 4 ml of glacial AcOH, containing 2 ml of 50% pyruvic acid solution, was heated at 100° for 5 h, after which it was diluted with water. The obtained precipitate was filtered, washed with water, and dried on the filter. We obtained 0.45 g of product, from which by employing TLC (SiO_2, 3:1 ether–hexane) we isolated 0.14 g of thiol (IX), mp 152-156.5° (from CH_3OH); $[\alpha]_D^{21}$ −179.7 (C 1.008, $CHCl_3$). Infrared spectrum (ν, cm^{-1}): 1250, 1702, 1735. NMR spectrum (δ, ppm): 0.77 (s, 3H–18-CH_3); 0.94 (s, 3H–19-CH_3); 1.95 (s, 3H–3-OAc); 2.00 (s, 3H–16-OAc); 2.23 (s, 3H–21-CH_3); 4.5 (broad line, H–3-H); 5.75 (broad line, H–16-H). Found: C 66.40; H 8.01; S 7.13%. $C_{25}H_{36}O_5S$. Calculated: C 66.94; H 8.09; S 7.21%.

A solution of 0.22 g of hydrazone (VIII) in 2 ml of glacial AcOH, containing 0.5 ml of 50% pyruvic acid solution, was heated at 100° for 40 min, after which it was worked up as described above. We obtained 0.09 g of thiol (IX), mp 145-152°, which was identical with the previously isolated specimen.

Pregn-5-ene-3β,16α-diol-17α-thiol-20-one (X). A solution of 0.1 g of hydrazone (II) in 3 ml of CH_3OH, containing 0.3 ml of dilute HCl solution (1:1), was refluxed for 1.5 h, in which connection the reaction course was checked by TLC. The reaction mass was diluted with water, and the precipitate was filtered, washed with water, dried on the filter, and recrystallized from acetone–hexane. We obtained 0.04 g of thiol (X), mp 192-196°; $[\alpha]_D^{22}$ −100.8 (C 0.247, $CHCl_3$). Infrared spectrum (ν, cm^{-1}): 1690, 2530, 2560, 3200-3600. NMR spectrum (δ, ppm): 0.78 (s, 3H–18-CH_3); 0.93 (s, H–19-CH_3); 2.23

(s, 3H–21-CH_3); 3.42 (broad line, H–3-H); 4.9 (broad line, H–16-H); 5.28 (broad line, H–6-H). From the mother liquor by employing TLC (SiO_2, 4:1 ether–hexane) we isolated an additional 0.03 g of thiol (X).

Pregn-5-ene-3β,16α-diol-17α-thiol-20-one 3,16,17-Triacetate (XI). A solution of 0.2 of thiol (IX) in 4 ml of C_5H_5N and 2 ml of Ac_2O was kept at 20° overnight. After the usual workup and recrystallization from CH_3OH we obtained 0.15 g of the 3,16,17-triacetate (XI), mp 244-255° (decompn.); $[\alpha]_D^{24}$ −189.3 (C 0.235, $CHCl_3$). Infrared spectrum (ν, cm^{-1}): 1250, 1710, 1733. NMR spectrum (δ, ppm): 0.73 (s, 3H –18-CH_3); 0.93 (s, 3H–19-CH_3); 1.85 (s, 3H–16-OAc); 1.96 (s, 3H–3-OAc); 2.2 (s, H–21-CH_3); 2.28 (s, 3H–SAc); 4.5 (broad line, H–16-H). Found: C 65.99; H 7.72; S 6.30%. $C_{27}H_{38}O_6S$. Calculated: C 66.10; H 7.81; S 6.52%.

A solution of 0.22 g of thiol (X) in 10 ml of C_5H_5N and 2.2 ml of Ac_2O was kept at 20° overnight. After the usual workup we obtained 0.023 g of product, the recrystallization of which from methanol gave 0.19 g of the 3,16,17-triacetate (XI), mp 248-251.5°, which was identical with the previously obtained sample.

Pregn-5-ene-3β,16α-diol-17α-thiol-20-one 3,16-Diacetate Carbethoxyhydrazone (II). A solution of 0.045 g of triacetate (XI) and 0.4 g of carbethoxyhydrazine in 2 ml of AcOH was kept at 100° for 11 h, after which the mixture was diluted with water, and the obtained precipitate was filtered, washed with water, dried on the filter, and separated employing TLC (1:1 ether–hexane). We obtained 0.012 g of carbethoxyhydrazone (II), mp 181.5-184° (from CH_3OH) and 0.011 g of thiol (IX), mp 152-156° (from CH_3OH), which in all of their characteristics coincided with the previously isolated specimens.

3-Acetoxypregn-5-en-3β-ol-20-one-[17,16α-d]-1',3'-oxathiolane Carbethoxyhydrazone (XII). A solution of 0.2 g of hydrazone (II) in 10 ml of anhydrous acetone, containing 0.2 ml of 70% $HClO_4$ solution, was refluxed for 1.5 h, with a continuous check of the reaction course employing TLC, after which the acetone was evaporated in vacuo to a volume of 2-3 ml. The residue was diluted with water, and the obtained precipitate was filtered, washed with water, and dried on the filter. The obtained product was separated employing TLC (2:1 ether–hexane). We isolated: 1) 0.11 g of hydrazone (XII), mp 129-135° (from CH_3OH); $[\alpha]_D^{24}$ −51.09 (C 0.503, $CHCl_3$). Infrared spectrum (ν, cm^{-1}): 1250, 1530, 1710–1740. 3200-3600. NMR spectrum (δ, ppm): 0.65 (s, 3H–18-CH_3); 0.93 (s, 3H–19-CH_3); 1.42 and 1.55 (s, 3H–CH_3 of oxathiolane ring); 1.85 (s, 3H–21-CH_3); 1.94 (s, 3H–3-OAc); 5.3 (broad line, H–6-H); 4.5 (broad line, H–3-H); 5.8 (broad line, H–16-H); 7.62 (s, H–NH). Found: C 65.41; H 8.28; S 6.22; N 5.21%. $C_{29}H_{44}O_5SN_2$. Calculated: C 65.39; H 8.33; S 6.07; N 5.26%. 2) 0.04 g of thiol (IX), mp 152-156° (from CH_3OH), which was identical with the above-obtained specimen.

Pregn-5-en-3β-ol-20-one-[17,16α-d]-1',3'-oxathiolane (XIII) and Its 20-Carbethoxyhydrazone (XIV). A solution of 0.1 g of carbethoxyhydrazone (XII) in 3 ml of CH_3OH, containing 0.3 ml of dilute HCl solution (1:1), was refluxed for 2 h and 40 min, after which it was diluted with water, and the obtained precipitate was filtered, washed with water, and dried on the filter. Employing TLC we isolated: 1) 0.033 g of oxathiolane (XIII), mp 120-130°; 146-155° (from hexane). Infrared spectrum (ν, cm^{-1}): 1700, 3400. NMR spectra (δ, ppm): 0.69 (s, 3H–18-CH_3); 0.93 (s, 3H–19-CH_3); 1.34 and 1.54 (s, 3H–CH_3 of oxathiolane fragment); 2.20 (s, 3H–21-CH_3); 3.6 (broad line, H–3-H); 5.3 (broad line, 2H–6-H, 16-H).

2) 0.038 g of carbethoxyhydrazone (XIV), mp 123° (decompn.) (from acetone–hexane); $[\alpha]_D^{24}$ −55.9 (C 0.701, $CHCl_3$). Infrared spectrum (ν, cm^{-1}): 1540, 1700-1740, 3300, 3430. NMR spectrum (δ, ppm): 0.65 (s, 3H–18-CH_3); 0.90 (s, 3H–19-CH_3); 1.40 and 1.54 (s, 3H–CH_3 of oxathiolane fragment); 1.82 (s, 3H–21-CH_3); 3.4 (broad line, H–3H); 5.78 (broad line, H–16-H); 7.52 (s, H–NH).

A solution of 0.08 g of thiol (IX) in 2.5 ml of anhydrous acetone and 1 ml of CH_3OH, containing 3 drops of $HClO_4$ solution, was refluxed for 5 h, after which the solvent was evaporated in vacuo to a volume of 1 ml. The reaction mass was diluted with water, and the obtained precipitate was filtered, washed with water, and dried on the filter. Employing TLC (1:1, ether–hexane) we isolated 0.05 g of compound (XIII), mp 120-130, 146-155° (from hexane), which was completely identical with the described sample.

Pregn-5-en-3β-ol-20-one-[17,16α-d]1',3'-oxathiolane 3-Acetate (XV). A solution of 0.06 g of oxathiolane (XIII) and 0.6 ml of Ac_2O in 2 ml of C_5H_5N was kept at 20° overnight, after which it was worked up as described above. After recrystallization from CH_3OH we obtained 0.05 g of oxathiolane (XV), mp 151-156°; $[\alpha]_D^{22}$ −114 (C 0.377, $CHCl_3$). Found: C 69.71; H 8.32; S 6.94%. $C_{26}H_{38}O_4S$. Calculated: C 69.93; H 8.58; S 7.16%.

Pregn-5-en-3β-ol-20-one 3-Acetate (XVI). A solution of 0.1 g of thiol (IX) in 30 ml of absolute alcohol was refluxed over Raney Ni for 1 h and 10 min, after which it was kept at 20° for 2 h. The catalyst

was filtered, and the filtrate was evaporated. After evaporation we obtained 0.1 of product, the recrystallization of which from CH_3OH gave 0.034 g of the known 3-acetate (XVI), mp 146-150°, that in all of its characteristics was identical with the authentic specimen [4].

CONCLUSIONS

1. The steric and structural direction of the reaction of the 16α,17α-epoxypregnenolone hydrazone with thioacetic acid confirms the previously proposed mechanism for the opening of the hydrazones of oxides.

2. A method was developed for the synthesis of steroids of the pregnane series that contain sulfur at C-17.

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