TRANSFORMED STEROIDS

COMMUNICATION 41. REACTION OF 3-ACETATE OF 16α, 17α-EPOXY-Δ⁵-PREGNEN-3β-OL-20-ONE WITH THIOLACETIC ACID AND SYNTHESIS OF Δ⁵-PREGNENE-3β, 16β, 17α-TRIOL-20-ONE 3-ACETATE, 16-THIONOACETATE

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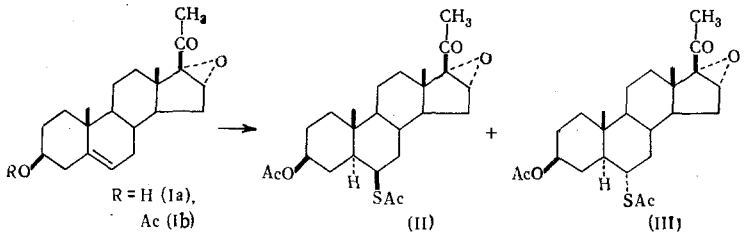
We had shown [1] that when 16α, 17α-epoxy-Δ⁵-pregnen-3β-ol-20-one (Ia) and its 3-acetate (Ib) are reacted with thiolacetic acid in the presence of acids (H_2SO_4, H_3PO_4, p-$C_7H_7SO_3H$) the reaction takes place without involving the 16α, 17α-epoxide ring. Stereochemically and structurally it proceeds in the same direction as under the classical radical conditions (UV light, CCl_4), i.e., exclusively at the Δ⁵-bond of the steroid molecule, giving the C_6-epimeric thiolacetates (II) and (III). The same direction and stereochemistry in the case of the reaction of oxides (Ia, b) with thiolacetic acid under ionic and homolytic conditions makes it possible to assume that in both cases the reaction is accomplished by the radical mechanism. The validity of such an assumption finds confirmation in the present paper, which is devoted to the reaction of oxides (Ia) and (Ib) with thiolacetic acid in the presence of inhibitors of free-radical processes



The reaction of oxides (Ia) and (Ib) * with thiolacetic acid in the presence of H_2SO_4 and free-radical addition inhibitors (SO_3 or hydroquinone) is accomplished only at the oxide ring and leads to the formation of a complex mixture which is composed of at least eight compounds, from which by chromatographing on silica gel were isolated and identified the following products†: Δ⁵-isopregnene-3β, 16α-diol-17β-thiol-20-one 3, 16-diacetate (Va), Δ⁵-pregnene-3β, 16β, 17α-triol-20-one 3-acetate, 16-thionacetate (IV), 17β-methyl-18-nor-Δ⁵,¹³-17-isopregnadiene-3β, 16α-diol-20-one 3, 16-diacetate (VI), Δ⁵-pregnene-3β, 16β, 17α-triol-20-one 3, 16-diacetate (VII), and 17aα-methyl-Δ⁵-D-homandrostene-3β, 16β; 17aβ-triol-17-one (VIII). In this connection the products of addition at the Δ⁵-bond were not detected. The main reaction product is 16β-thionoacetate (IV), which is apparently formed as the result of the exceedingly rare case of the thiolacetic acid reacting in the thiono form. We do not know of any cases for the direct preparation of thiono esters by the addition of thiolacetic acid to a multiple bond or to the oxide ring, for which reason we gave special

*Oxides (Ia) and (Ib) when reacted with thiolacetic acid give the same products, since thiolacetic acid is an acylating agent under the indicated conditions.

† The obtained products are arranged in the order of their decreasing chromatographic mobility.

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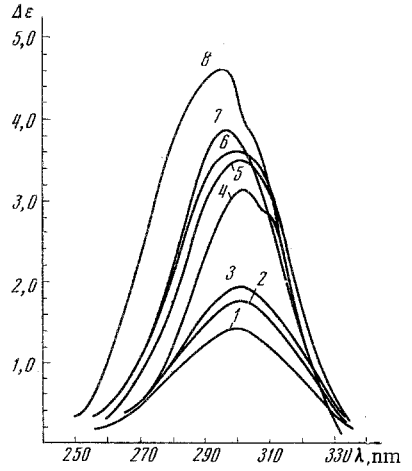
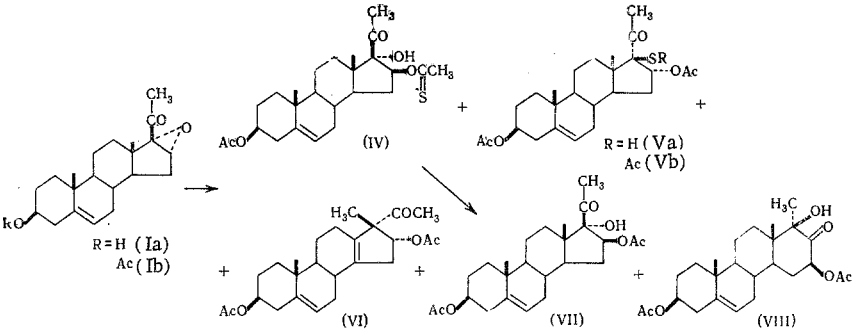
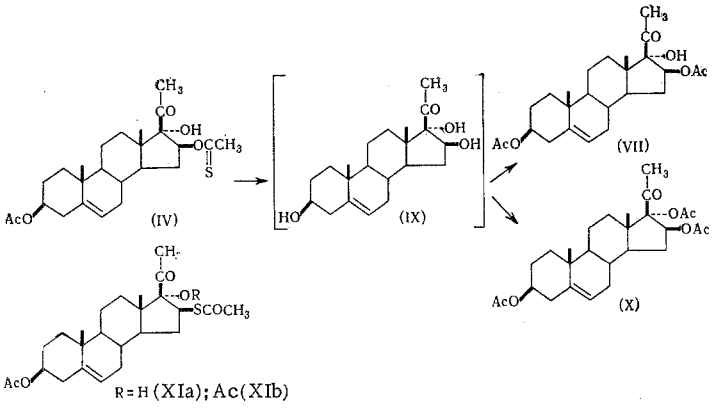


Fig. 1. Circular dichroism curves: 1) Δ^5-pregnene-3β, 16β, 17α-triol-20-one 3-acetate, 16-thionoacetate (IV) (in C_2H_5OH); 2) 3,16-diacetate (VII) (in 16β-methyl-Δ^5-pregnene-3β, 17α-diol-20-one 3-acetate (in C_2H_5OH); 4) Δ^5-pregnene-3β, 16α, 17α-triol-20-one 3, 16-diacetate (in dioxane); 5) Δ^5-pregnene-3β, 17α-diol-20-one 3-acetate (in C_2H_5OH); 6) Δ^5-pregnene-3β, 16α, 17α-triol-20-one 3, 16-diacetate (in C_2H_5OH); 7) Δ-isopregnene- 3β, 16α-diol-17β-thiol-20-one 3, 16-diacetate (Va) (in dioxane); 8) Δ^5-pregnene-3β, 16α-diol-17β-thiol-20-one 3, 16, 17-triacetate (Vb) (in dioxane).

attention to proving the structure of thiono ester (IV). The structure assigned to thionoacetate (IV) was based on all of the obtained chemical and physicochemical data



Thionoacetate (IV) is a very labile compound, and even on standing under the reaction conditions, i.e., in thiolacetic acid, in the presence of H_2SO_4 and hydroquinone, at 20°C, it is easily converted to the known diacetate (VII) [2]. For this reason it is possible to assume that the formation of substantial amounts of diacetate (VII) when the (I) oxides are reacted with thiolacetic acid is the consequence of a secondary process for the transformation of thiono ester (IV) under the reaction conditions. The same must also be said regarding the sulfur-free products (VI) and (VIII) that were detected in the reaction mixture, which, in all of their characteristics, proved to be identical with the previously obtained compounds [2], and do not depress the mixed melting point



Thionoacetate (IV) on standing is easily saponified in methanol, acidified with H_2SO_4, giving Δ^5-pregnene-3β, 16β, 17α-triol-20-one (IX), which was identified by acetylating it to the known diacetate (VII).

TABLE 1. Data of NMR Spectra (δ, ppm relative to HMDS)

Compound	CH_3 at C_{18}	CH_3 at C_{19}	OAc at C_3	OAc at C_{16}	OAc at C_{17}	CH_3 at C_{21}	$SCOCH_3$ or $OCSCH_3$ at C_{16}	$SCOCH_3$ at C_{17}	H* at C_6	H* at C_{16}	H* at C_3	OH at C_{17}
Va	0,95	0,95	1,95	2,04	—	2,31	—	—	5,25	5,57	4,45	—
Vb	0,93	0,97	1,93	1,88	—	2,20	—	2,23	5,26	5,75	4,43	—
IV	0,83	0,94	1,92	—	—	2,09	2,47	—	5,25	5,17	4,5	3,45
VII	0,87	0,96	1,94	1,96	—	2,12	—	—	5,3	4,6	4,5	3,46
XIa	0,67	0,93	1,93	—	—	2,11	2,19	—	5,26	3,58†	4,5	3,48
XIb	0,60	0,92	1,90	—	1,93	2,07	2,19	—	5,28	3,64	4,5	—

*Broad line.

†Triplet.

Thionacetate (IV) is not acetylated by acetic anhydride in pyridine, which testifies to the presence of a 17-tertiary hydroxyl group, while it is converted to the 3, 16, 17-triacetate of Δ^5-pregnene-3β, 16β, 17α-triol-20-one (X) when it is acetylated with acetic anhydride in glacial acetic acid. The obtained result is in good agreement with the exceeding ease of the acid hydrolysis of thioester (IV), while the formation of triacetate (X) under these conditions can be depicted by the above-given reaction scheme. All of these facts make it possible to assign the structure of the thionoacetate to compound (IV), while its conversion under mild conditions to diacetate (VII) and triacetate (X) unequivocally indicates the presence of a 16β-thionoacetate group in it.

A comparison of the physicochemical characteristics of thionoacetate (IV) and the isomeric thiol-acetate, namely Δ^5-pregnene-3β, 17α-diol-16β-thiol-20-one 3, 16-diacetate (XIa), the synthesis of which will be described in a subsequent communication, also corroborates the structure of (IV).

Thus, in the UV spectra of thionoacetate (IV) and thiolacetate (XIa) are respectively observed highly intense bands at 245 nm (ε 8316) and 235 nm (ε 4212), which are characteristic for the $\pi - \pi^*$ transition of the thioketo and carbonyl chromophores in thiolacetates [3, 4]. An important difference in the UV spectra of the compared compounds is also the presence in the case of ester (XIa) of a weak band in the long-wave region at 271 nm (ε 146), which is characteristic for the $n - \pi^*$ transition of thiolacetates [3], and the absence of absorption in this region for ester (IV). These data make it possible to exclude the structure of the thiolacetate for ester (IV). In addition, the frequency of a carbonyl group attached to sulfur was not detected in the IR spectrum of ester (IV), but in the 1200-1300 cm^{-1} region are observed two clearly distinguishable intense bands at 1280 and 1245 cm^{-1}, which were respectively assigned to the stretching vibrations of the C=S [5] and OAc groups.

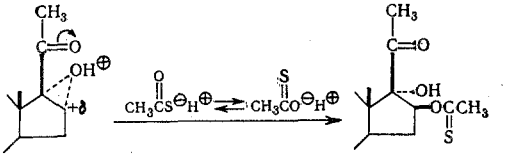
A comparison of the positions of the signals in the NMR spectra from the protons of the angular methyl, acetyl and methylketo group in thionoacetate (IV) and thiolacetates (XIa, b) on the one hand, and the 3, 16-diacetate (VII), on the other hand (Table 1), and of the literature analogs [6], make it possible to verify the structural identity of these compounds. However, in the NMR spectra of the thiol ester (XIa) or its 17-acetate (XIb) and the thiono ester (IV) are present important differences, which make it possible to assign them to the indicated series. This difference consists, first, in the position of the signal of the proton at C_{16}, which suffers a strong paramagnetic shift (5.17 ppm) in the O-ester (IV) when compared with the signal of this proton in the S-esters (XIa) and (XIb) (3.58 and 3.64 ppm). This deshielding of the proton at C_{16} in thiono ester (IV) when compared with its thiol analog (XIa) can be predicted if the greater electronegativity of the oxygen when compared with sulfur is taken into account. In addition, the singlet signal of the methyl protons of the thionoacetate group in (IV) is manifested further downfield than that of the thiolacetate group in (XIa). Since the thioketo group manifests a greater anisotropic effect than the oxygen analog, the signals of the alkyl group in the thiono ester (IV) appear further downfield, which is in agreement with the literature data [7]. As can be seen from Table 1, it is impossible to obtain conclusive information regarding the configuration of the substituents at C_{16} and C_{17} in thiono ester (IV) on the basis of the data of the NMR spectra.

A study of the circular dichroism (CD) curve of thiono ester (IV) and its comparison with the curves shown in Fig. 1 for the standard samples lends support to the configuration of the substituents in the D ring that is assigned on the basis of the chemical data. It is known that a positive Cotton effect in the

pregnane series is associated with the 20-keto chromophore of the 17β-acetyl side chain [8]. Compound (IV) manifests a positive Cotton effect, and consequently has a β-orientation of the 17-acetyl group. As can be seen from Fig. 1, the CD curve of thionoacetate (IV) almost coincides with the curves that are shown for the standard compounds with a known β-configuration of the substituents at C_{16}, and has a much smaller amplitude when compared with the 16-unsubstituted pregnenediol. A similar rule has been mentioned repeatedly in the literature and is a generally accepted fact at the present time, namely, that the insertion of a 16β-substituent in the 17β-acetyl derivatives is accompanied by a substantial decrease in the CD amplitude, whereas 16α-substituents affect to a lesser degree (usually in the direction of increasing the amplitude) or else are completely without effect on the Cotton effect [8-10].

As can be seen from the reaction schemes, together with the main product of opening the keto oxides (Ia, b) by thiolacetic acid, namely thiol ester (IV), is also formed thiol (Va), which was assigned the indicated structure on the basis of the elemental analysis, the data of IR and NMR spectroscopy, the CD, and its behavior in the acetylation reaction. In the IR spectrum of this compound is observed absorption in the 2550 cm^{-1} region, which is characteristic for the thiol grouping. In the NMR spectrum of thiol (Va), in the regions 0.95, 1.95, 2.04 and 2.31 ppm, are found single lines with a relative integral intensity of 6:3:3:3, which can be respectively assigned to the protons of the angular methyl groups at C_{18} and C_{19}, the acetate groups at C_3 and C_{16}, and the methyl groups at C_{20}. A multiplet is observed downfield in the 5.57 ppm region, which was assigned to the proton at C_{16}, which is in agreement with the literature data for 16α-acetoxypregnanes [11, 12]. On the basis of this the possible isomeric structure, with a tertiary acetate group at C_{17} and a secondary thiol group at C_{16}, was excluded. The NMR spectrum of thiol acetate (Vb), obtained by the acetylation of thiol (Va) with acetic anhydride in pyridine, does not contradict the assigned structure (see Table 1). The signals of the methyl protons of 18-CH_3 and 21-CH_3 in compounds (Va) and (Vb), which respectively appear in the regions 0.95-0.93 and 2.31-2.2 ppm, are deshielded, which is in agreement with the iso-orientation of the 17-acetyl group [13]. These data, together with the fact that thiol (Va) does not give an oxathiolane derivative when heated with acetone under acid conditions, while its acetate (Vb) differs in its properties from the epimeric 3, 16, 17-triacetates of Δ^5-pregnene-3β, 16ξ-diol-17ξ-thiol-20-ones, obtained by us by other routes, speaks in support of the validity of the configuration assigned to it. It should be mentioned that the CD curves of compounds (Va) and (Vb), taken in dioxane, are characterized by a positive Cotton effect in the region of the $n-\pi^*$ transition of the $C_{20}=O$ group, and larger amplitudes. As we had already shown, sulfur-containing substituents, found in the α-position to the $C_{20}=O$ chromophore, exert a substantial effect on the amplitude and sign of the Cotton effect [14]. For this reason the simple use of the above indicated correlations in order to determine the configuration of the C_{17}-center of steroidal 20-ketones, when sulfur-containing substituents are present in them in the 17-position, without taking into account the contribution made by the latter in the Cotton effect, is wrong. This problem will be discussed in more detail in a special communication.

As a result, the ionic opening of the oxide ring of 16α, 17α-epoxy-Δ^5-pregnen-3β-ol-20-one (Ia) with thiolacetic acid in the presence of free-radical addition inhibitors takes place with a predominant cleavage of the $C_{16}-O$ bond of the starting oxide and the formation of the 16β-thiono ester (IV), which is apparently the product of the direct reaction of the keto oxides (I) with the thiono form of thiolacetic acid. It is possible to assume that the thiolacetic acid attacks the site of the lowest electron density of the formed oxonium ion by its more electronegative O-center



Together with this, a small amount (~6%) of the 16-diacetate (Va) is obtained, which is formed as the result of the cleavage of the oxide ring in the C_{17} position and the insertion of the thiolacetic acid anion as its thiol form at the indicated C_{17}-center. The mechanism for the formation of (Va) has as yet not been completely elucidated.

EXPERIMENTAL METHOD

The melting points were determined on a Kofler block. The IR spectra were taken on an UR-10 instrument as KBr pellets. The NMR spectra were taken on a DA-60 IL NMR-spectrometer at an operating

frequency of 60 MHz in $CDCl_3$ solution. The internal standard was hexamethyldisiloxane. The UV spectra were taken in C_2H_5OH solution. The angles of rotation were measured on a Hilger Watts spectropolarimeter in $CHCl_3$. The CD curves were taken on a Roussel Jouan dichrograph (C ~ 1 g/liter).

Reaction of 16α, 17α-Epoxy-Δ⁵-pregnen-3β-ol-20-one 3-Acetate (Ib) with Thiolacetic Acid in the Presence of SO_3. To a solution of 5 g of keto oxide (Ib) in 28 ml of freshly distilled CH_3COSH was added a mixture of 3 ml of CH_3COSH and 0.5 ml of 100% H_2SO_4, containing traces of SO_3. The reaction mass was allowed to stand at room temperature for 48 h, after which the excess CH_3COSH was evaporated in vacuo, and the residue was diluted with water. The aqueous layer was extracted with ether, and the ether extract was washed with $NaHCO_3$ solution, and then dried over $MgSO_4$. After distilling off the ether we obtained 5.6 g of an oily product, which, when subjected first to chromatographing on a column (SiO_2, eluant = ether – hexane mixture, in succession 1:6 1:4, 1:3, 1:2), and to TLC on SiO_2, gave,* together with 0.42 g of unreacted oxide (Ib):

1. 1.1 g of Δ⁵-pregnene-3β, 16β, 17α-triol-20-one 3-acetate, 16-thionoacetate (IV), mp 190-194.5°, $[\alpha]_D^{21}$ −94.3 (C 1.018 in $CHCl_3$), R_f 0.51. Infrared spectrum (ν, cm^{-1}): 1245, 1280, 1700, 1725, 3380-3600. Ultraviolet spectrum (in ethanol): 245 nm (ε 8316), 318 nm (ε 158). Found: C 66.78; H 7.98; S 7.14%. $C_{25}H_{36}O_5S$. Calculated: C 66.94; H 8.09; S 7.21%.
2. 0.31 g of Δ⁵-isopregnone-3β, 16α-diol-17β-thiol-20-one 3, 16-diacetate (Va), mp 178-181° (from methanol), R_f 0.58. Infrared spectrum (ν, cm^{-1}): 1245, 1689, 1738, 2555, 3450. Found: C 66.79; H 8.00; S 7.15%. $C_{25}H_{36}O_5S$. Calculated: C 66.94; H 8.09; S 7.21%.
3. 1.33 g of Δ⁵-pregnene-3β, 16β, 17α-triol-20-one 3, 16-diacetate (VII), mp 174-175° (from methanol); R_f 0.17. The material coincides chromatographically and does not depress the mixed melting point with an authentic sample [2].
4. 0.51 g of 17β-methyl-18-nor-Δ⁵,¹³-isopregnadiene-3β, 16α-diol-20-one 3, 16-diacetate (VI), mp 215-217° (from aqueous acetone); R_f 0.35. The material coincides chromatographically and does not depress the mixed melting point with an authentic sample [2].
5. 0.5 g of 17aα-methyl-Δ⁵-D-homoandrostene-3β,16β, 17aβ-triol-17-one 3,16-diacetate (VIII), mp 254-256° (from methanol), R_f 0.13, which was identical with the authentic specimen [2].

Transformation of Δ⁵-Pregnene-3β, 16β, 17α-triol-20-one 3-Acetate, 16-Thionoacetate (IV) under the Conditions of the Preparation Reaction. A solution of 0.1 g of thionoacetate (IV) in 0.5 ml of CH_3COSH, to which had been previously added a drop of H_2SO_4 and 5 mg of hydroquinone, was allowed to stand at room temperature for 24 h. The workup was the same as described above. Separation of the reaction product by TLC (SiO_2, 1:2 ether–hexane mixture) gave 0.04 g of (VII), mp 173-176° (from methanol), which was identical with the previously obtained specimen.

Transformation of Δ⁵-Pregnene-3β, 16β, 17α-triol-20-one 3-Acetate, 16-Thionoacetate (IV) under the Conditions of the Acetylation Reaction. A mixture of 0.05 g of thionoacetate (IV), 0.7 ml of Ac_2O and 0.05 g of sulfosalicylic acid in 3 ml of glacial acetic acid was allowed to stand at room temperature for 4 days. The reaction mass was poured into water, and the precipitate was filtered, and then separated by TLC (SiO_2, ether–hexane, 1:2). We obtained 0.034 g of chromatographically pure Δ⁵-pregnene-3β, 16β, 17α-triol-20-one 3, 16, 17-triacetate (X), mp 202-203.5° (from aqueous methanol), which in all of its characteristics was identical with the authentic specimen and did not depress the mixed melting point with it.

Hydrolysis of Δ⁵-Pregnene-3β, 16β, 17α-triol-20-one 3-Acetate, 16-Thionoacetate (IV). A solution of 0.1 g of thionoacetate (IV) in 15 ml of absolute methanol, to which had been added 3 drops of conc. H_2SO_4, was allowed to stand at room temperature for a day. The reaction was accompanied by the liberation of H_2S. A precipitate was obtained on dilution with water, which was filtered, washed with water, and dried. We obtained 0.07 g of products with mp 136-156°, which was acetylated with 0.7 ml of Ac_2O in 1.8 ml of pyridine at 20° overnight. After the usual workup we isolated 0.08 g of a powder, the recrystallization of which from ether–hexane gave 0.015 g of the 3β, 16β-diacetate (VII), mp 172-178°, which was identical with the previously obtained specimen. The mother liquor was chromatographed (SiO_2, ether–hexane, 1:3) to give an additional 0.04 g of (VII).

* The given values are based on the chromatographically pure unrecrystallized products.

Δ^5-Isopregnene-3β, 16α-diol-17β-thiol-20-one 3, 16, 17-Triacetate (Vb). A solution of 0.035 g of the 3β, 16α-diacetate (Va) and 0.35 ml of Ac_2O in 0.8 ml of pyridine was allowed to stand at 20° for 2 days. The reaction mass was diluted with water, and the obtained precipitate was filtered. We obtained 0.029 g of product, the separation of which by TLC (SiO_2, ether–hexane, 1 : 2) gave 0.025 g of the 3, 16, 17-triacetate (Vb), mp 160-164° (from aqueous methanol). Infrared spectrum (ν, cm^{-1}): 1245, 1695, 1732.

CONCLUSIONS

1. A method was developed for opening the oxide ring of the 3-acetate of 16α, 17α-epoxy-Δ^5-pregnen-3β-ol-20-one with thiolacetic acid under ionic conditions.

2. The reaction proceeds with a predominant cleavage of the C_{16}–O bond of the oxide ring and attack of the C_{16}-center by the thiolacetic acid in the thiono form, with the formation of the 3-acetate, 16-thionoacetate of Δ^5-pregnene-3β, 16β, 17α-triol-20-one, the structure of which was assigned on the basis of the sum of the chemical and physicochemical methods.

3. A small amount (~6%) of the isomeric product of opening the ring is formed, which apparently arises as the result of the cleavage of the C_{17}–O bond of the starting oxide by the thiol form of thiolacetic acid.

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