[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF "SYNTEX," S. A.]

Steroids. I. 3-Thio-enol Ethers of Δ^4-3-Keto Steroids

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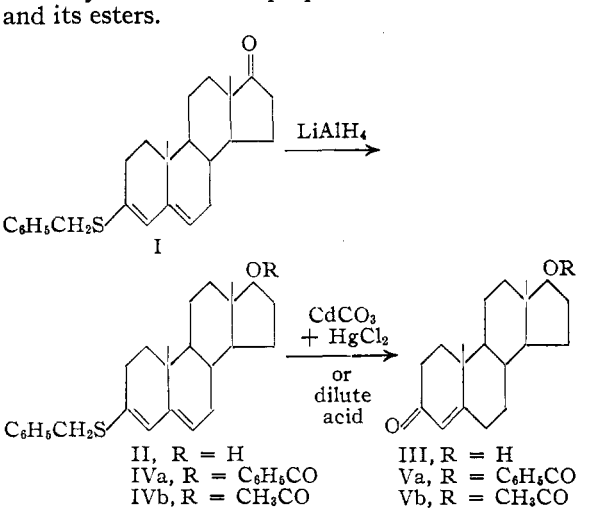
The reaction of 3-keto steroids with alcohols in the presence of condensing agents is well known.[1a,b,c,d] In the case of Δ^4-3-keto steroids, the reaction with monohydric alcohols leads preferably to 3-enol ethers while with glycols cyclic ketals are formed.[2]

It is to be expected that analogous reactions will occur with mercaptans and thioglycols. Bernstein and Dorfman[3] and Hauptmann[4] reported some thioenol ethers and mercaptols of cholestenone, dehydrocholic acid and cholestanone.[5]

We decided to study the exact reaction conditions for the condensation of Δ^4-androstene-3,17-dione with benzyl mercaptan. In order to avoid the reaction of the 17-keto group, as it occurs in the case of dehydroisoandrosterone acetate and several mercaptans,[6,7] we carried out the condensation either at room temperature with anhydrous zinc chloride and sodium sulfate in dioxane solution or by azeotropic distillation of the benzene solution of equimolar quantities of the ketone and mercaptan in the presence of *p*-toluenesulfonic acid. In both cases the resulting product was the well-characterized 3-benzylthioenol ether of Δ^4-androstene-3,17-dione (I). This product can be reconverted easily into the parent ketone by known methods, *e. g.*, with cadmium carbonate and mercuric chloride or by acid hydrolysis.

A very important reaction of the 3-enol ethers (and also of the 3-ketals) of Δ^4-androstene-3,17-dione is their reduction to the corresponding derivatives of testosterone.[1d] The best known method for this reduction is with sodium and alcohol. Applying this method to our 3-thioenol ethers, we encountered difficulties to accomplish the reduction of the 17-keto group without altering the thioenol ether group, while the reaction of these compounds with alkyl-magnesium halides (Miescher[5]) takes place very neatly, involving only the 17-keto group and leaving the 3-grouping unaffected. We found, however, that the 17-keto group of the 3-benzylthioenol ether of Δ^4-androstene-3,17-dione (I) can be transformed into the hydroxyl group with lithium aluminum hydride[8] whereby the 3-benzylthioenol ether of testosterone (II) is obtained in good yield. This latter compound can be hydrolyzed by means of dilute mineral acids or cadmium carbonate and mercuric chloride to testosterone (III). By careful acylation of the 3-benzylthioenol ether of testosterone (II) the corresponding esters (IV) are obtained. The mild hydrolysis of these 3-thioenol-ether 17-esters with cadmium carbonate and mercuric chloride leads to the corresponding esters of testosterone (V). It is obvious that the preceding reactions represent a new synthesis for the preparation of testosterone and its esters.



II, R = H
IVa, R = C_6H_5CO
IVb, R = CH_3CO

III, R = H
Va, R = C_6H_5CO
Vb, R = CH_3CO

The thioenol ethers described in this paper are well-crystallized substances which are fairly alkali resistant. They are stable in acid-free solvents but in presence of traces of acids they decompose rapidly with development of vile-smelling vapors. They also decompose under the influence of light and must be stored in dark containers.

As an interesting alternative we also studied the reaction between Δ^4-androstene-3,17-dione and monothioglycol since the latter compound contains simultaneously a hydroxyl and a sulfhydryl group. In analogy to the reaction of the Δ^4-3-keto-compounds with ethylene glycol[2] and dithioglycol[4,5] we expected the formation of a cyclic hemithioketal (VI).

Theoretically two other compounds might also be formed: the 3-(β-hydroxyethyl)-thioenol ether (VII) and the 3-(β-mercaptoethyl) enol ether (VIII) of androstenedione.

The formation of other theoretically possible reaction products, where the double bond of the

(1) (a) Schwenk, Fleischer and Whitman, THIS JOURNAL, **60**, 1702 (1938); (b) Schwenk and Whitman, U. S. Patent 2,246,540; (c) Westphal, Serini and Köster, U. S. Patent 2,294,433; (d) Köster U. S. Patent 2,363,338.

(2) Fernholz, U. S. Patent 2,356,154.

(3) Bernstein and Dorfman, THIS JOURNAL, **68**, 1152 (1946).

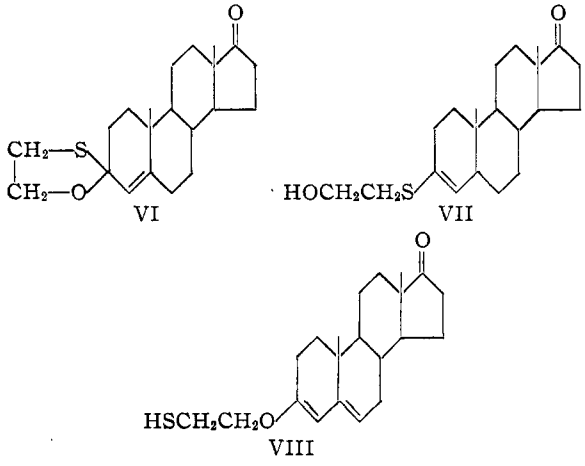
(4) Hauptmann, *ibid.*, **69**, 562 (1947).

(5) In one of his patents which recently became available to us (U. S. Patent 2,435,013), Miescher describes the reactions of androstene-3,17-dione with ethyl mercaptan and dithio-glycol, respectively. No characteristics of the corresponding reaction product are given. After the conclusion of our work a U. S. Patent (2,451-434) of Dorfman and Bernstein became available. This patent refers to the preparation of the ethylthioenol ether of testosterone propionate by the reaction of testosterone propionate with ethyl mercaptan. The product is described as a yellow viscous oil.

(6) Norymberska, Norymberski and Olalde, THIS JOURNAL, **70**, 1256 (1948).

(7) Levin and Thompson, *ibid.*, **70**, 3140 (1948).

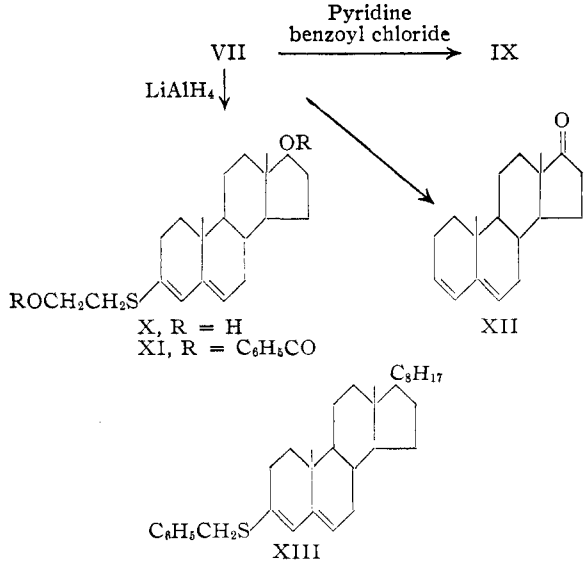
(8) Nystrom, Weldon and Brown, *ibid.*, **69**, 1197 (1947).



α,β-unsaturated ketone would react with the mercaptan seems remote since Hauptmann[4] was unable to obtain any sulfur-containing steroid compounds in the reaction of Δ^4-cholestene-3-one and benzyl mercaptan using as a catalyst, piperidine which is supposed to favor particularly the reaction between mercaptans and the α,β-double bond.

Working under different conditions we were able to isolate two compounds: using pyridine hydrochloride as condensing agent we isolated the thioenol ether (VII) and using zinc chloride and sodium sulfate or *p*-toluenesulfonic acid we obtained another compound which is probably the cyclic hemithioketal of the formula (VI).[9]

The thioenol ether (VII) behaves exactly as the 3-benzylthioenol ether of Δ^4-androstene-3,17-dione (I) and can be converted into the corresponding derivatives of testosterone by the same process as mentioned above. With benzoyl chloride and pyridine a monobenzoate (IX) can be prepared. The same reaction applied to the corresponding 17-hydroxy compound (X) which was obtained by the action of lithium aluminum hydride on (VII) gives a crystalline dibenzoate (XI).



In order to decide between formulas (VII) and (VIII) and for a definite proof of structure we submitted the compound to hydrogenolysis with Raney nickel. We obtained the known $\Delta^{3,5}$-androstadiene-17-one (XII), which proved beyond doubt structure (VII) for the compound obtained in the reaction of monothioglycol and androstenedione in presence of pyridine hydrochloride. Formula (VIII) can be excluded because on desulfuration one could expect a 3-ethyl ether of the androstane series. In order to establish the behavior of the double bonds of the thioenol ethers on desulfuration, it was necessary to submit several thioenol ethers of the androstane and cholestane series to hydrogenolysis under different conditions. As this reaction has not been described before we selected the following compounds for our study: 3-benzylthioenol ether of Δ^4-androstene-3,17-dione (I); 3-benzylthioenol ether of testosterone (II); 3-(β-hydroxyethyl)-thioenol ether of Δ^4-androstene-3,17-dione (VII); 3-(β-hydroxyethyl)-thioenol ether of testosterone (X) and 3-benzylthioenol ether of Δ^4-cholestenone (XIII).

This latter compound had not been prepared before. We obtained it by the reaction of equimolar quantities of benzyl mercaptan and Δ^4-cholestenone using as condensing agents either *p*-toluenesulfonic acid or zinc chloride and sodium sulfate. It seemed to us that if an excess of the mercaptan is used, the formation of the mercaptol predominates, whereas, using equimolar quantities, thioenol ethers are formed. However, Bernstein and Dorfman[3] reported the preparation of the 3-ethylthioenol ether of Δ^4-cholestenone using ethyl mercaptan in excess. We are inclined to regard this as an exception, due perhaps to the volatility of the mercaptan used. Hauptmann[4] using excess benzyl mercaptan obtained the corresponding mercaptol of Δ^4-cholestenone.

For the hydrogenolytic desulfuration, we used the method described by Wolfrom and Karabinos.[10] The hydrogenolysis was carried out in two different series: in the first series the Raney nickel was partially deactivated according to the method of Spero, McIntosh and Levin.[11] These authors refluxed the acetone suspension of the catalyst during two hours and subsequently added the compound which was to be desulfurated, completing the reaction by further refluxing. In the second series of experiments fully active Raney nickel, prepared according to the method of Mozingo,[12a,b] was used in ethanol or dioxane as reaction medium.

With the deactivated catalyst we obtained $\Delta^{3,5}$-

(9) Investigation of this compound is now on the way in our laboratories. The results will be published at some future date.

(10) Wolfrom and Karabinos, THIS JOURNAL, **66**, 909 (1944).

(11) Spero, McIntosh and Levin, *ibid.*, **70**, 1907 (1948).

(12) (a) Mozingo, *Org. Syntheses*, **21**, 15 (1941); (b) in the classification of Adkins and Pavlic (THIS JOURNAL, **69**, 3039 (1947)) this Raney nickel is referred to as "catalyst W-2."

compounds throughout the whole series. With fully active catalyst the thioenol ethers of testosterone and cholestenone were desulfurated to the saturated compounds of the androstane and cholestane series, respectively.

When desulfurizing the thioenol ether of Δ^4-androstene-3,17-dione, a mixture of $\Delta^{3,5}$-androstadiene-17-one and androstan-17(β)-ol[13] was obtained. It is very probable that the first action of the Raney nickel on the thioenol ether molecule consists in the elimination of the sulfur atom. If the nickel catalyst is partially deactivated, its action ceases when desulfuration is complete, but with an active catalyst, and in a medium which does not exercise a deactivating action, the Raney nickel reduces the 17-keto group and then saturates the conjugated double bonds.

The simultaneous formation of the $\Delta^{3,5}$-androstadiene-17-one and androstan-17(β)-ol indicates that the carbonyl group of the thioether molecule acts as a partial deactivator of the nickel, hindering the saturation of the double bonds, but when it is reduced to the alcohol group its influence disappears and the double bonds are saturated.

The isolation of $\Delta^{3,5}$-androstadien-17-one from the desulfuration products of the thioenol ether of Δ^4-androstene-3,17-dione is the first direct evidence for this position of the double bonds in this compound, because under the extremely mild conditions of the desulfuration the shifting of the double bond is not likely to occur. That same position of the double bonds was suggested by some authors[1] for the enol ethers of the Δ^4-3-keto steroids but so far no direct proof for this assumption has been presented.

As additional evidence for the heteroannular location of the double bonds in our thioenol ethers, we may mention the fact that we failed to obtain an addition product with maleic anhydride, working in benzene solution under the usual conditions, while such an addition product would most likely have been formed in the case of a homoannular diene.

The ultraviolet absorption spectra of the thioenol ethers have an absorption maximum at 268 mμ; the corresponding enol ethers show a maximum at 240 mμ.[14] Gillam, *et al.*,[15] found a difference of 22 mμ between the absorption maxima of certain semicarbazones and thiosemicarbazones, and Bowden, *et al.*,[16] report a similar bathochromic effect of the –SR group attached to the ethylenic linkage. In the light of these findings and of the evidence presented above by ourselves, we feel justified in ascribing the Δ_λ of 28 mμ between the λ_{max} of the enol ethers and of the thioenol ethers (240–268 mμ) to the introduction of a sulfur-containing substituent, and not to any rearrangement in the steroid molecule itself.[17]

(13) We ascribe to this compound the β-configuration at C_{17} in accordance with the convention advanced in Fieser and Fieser "Natural Products Related to Phenanthrene," 3rd edition, Reinhold Publishing Corp., New York, N. Y., 1949, pp. 325-327.

(14) See ref. 1b; confirmed by measurements in this Laboratory.

(15) Gillam, *et al.*, *J. Chem. Soc.*, 486 (1942), (*C. A.*, **37**, 6251 (1943)).

(16) Bowden, *et al.*, *J. Chem. Soc.*, 948 (1946).

Experimental[18,19,20,21]

3-Benzylthioenol Ether of Δ^4-Androstene-3,17-dione (I).—(a) Pure Δ^4-androstene-3,17-dione (4.9 g., 0.017 mole) was dissolved in 25 cc. of anhydrous dioxane; 4 g. (0.034 mole) of benzyl mercaptan, 8 g. of freshly fused and pulverized zinc chloride and 8 g. of anhydrous sodium sulfate were added under external cooling. After seventeen hours at room temperature the orange-colored mixture was diluted with benzene, washed with water to remove the inorganic salts, dried over sodium sulfate and evaporated to dryness. The residue was crystallized from acetone–methanol whereby 3 g. (45%) of small pale-yellowish needles of I, m. p. 177–179°, $[\alpha]^{20}D$ −84°, λ_{max} 268 mμ, log E_m 4.15 was obtained.

Anal. Calcd. for $C_{26}H_{32}OS$: C, 79.54; H, 8.21; S, 8.16. Found: C, 79.59; H, 8.10; S, 7.88.

(b) A solution of 10 g. (0.035 mole) of Δ^4-androstene-3,17-dione in 100 cc. of benzene to which 5.3 g. (0.043 mole) of benzyl mercaptan and 0.5 g. of *p*-toluenesulfonic acid were added was refluxed for six hours. Every two hours 15 cc. of the azeotropic mixture was distilled off. After the end of the reaction the mixture was diluted with 100 cc. of benzene, washed neutral with 5% sodium carbonate solution and water, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was crystallized from acetone–methanol, whereby 7.5 g. (55%) of I, m. p. 177–179°, was obtained.

To a solution of 2 g. of I in 200 cc. of ethanol, 3 cc. of concentrated hydrochloric acid and 3 cc. of water were added. After refluxing for two hours the mixture was poured into water, extracted with ether, washed neutral with water, sodium bicarbonate solution and water, dried over sodium sulfate and evaporated to dryness.[22] The residue on crystallization from acetone–hexane gave 1.2 g. of crystals, m. p. 166–170°, $[\alpha]^{20}D$ + 190° (in ethanol). A qualitative test of sulfur was negative; mixed with an authentic sample of Δ^4-androstene-3,17-dione it gave no depression.

To a solution of 2 g. of I in 250 cc. of acetone, 3 g. of freshly prepared cadmium carbonate and 3 g. of finely pulverized mercuric chloride were added. The mixture was refluxed for eight hours, the inorganic salts were filtered off and washed with acetone. The filtrate was concentrated to a volume of 50 cc., poured into water and ex-

(17) Moreover, we calculated the differences between the molecular rotations of our thioenol ethers and of the corresponding Δ^4-3-keto steroids and found in five out of seven cases a Δ_M of -873 ± 3 (in two cases the values differed by 10% from the above mean value; see note 20). This strongly levorotatory shift supports a $\Delta^{3,5}$ rather than a $\Delta^{2,4}$ location of the double bonds (see Fieser, ref. 13, p. 210) and comes near the corresponding values for the oxygen analogs (Δ_M about −760),[1a] thus suggesting once more that the oxygen-containing and the sulfur-containing enol ethers possess the same structure.

(18) The microanalyses were carried out by Dr. Carl Tiedcke, New York, N. Y., and in our microanalytical laboratory under the direction of Miss Amparo Barba.

(19) All the melting points were determined on the Kofler micro-melting point apparatus.

(20) The rotations of the sulfur-containing substances were determined in anhydrous dioxane; these compounds decompose rapidly in chloroform. The decomposition in dioxane, though somewhat slower, probably accounts for the 10% discrepancy in the molecular rotations of compounds II and VII (see note 17). Attempts to stabilize the dioxane solutions by the addition of a few drops of pyridine were not satisfactory. All determinations were carried out in appr. 2% solutions, using a 10-cm. tube of 2-cc. capacity.

(21) The ultraviolet absorption spectra were determined in alcoholic solution, using a Beckman Model DU Quartz Spectrophotometer with 1-cm. quartz cells.

(22) In the following, this procedure is briefly referred to as "usual workup."

tracted with ether. After the usual workup the residue was recrystallized from acetone–hexane. Androstenedione (1.1 g.) m. p. 167–172° was obtained, characterized by a mixed melting point with an authentic sample.

3-(β-Hydroxyethyl)-thioenol Ether of Δ⁴-Androstene-3,17-dione (VII).—A solution of 10 g. (0.035 mole) of Δ⁴-androstene-3,17-dione in 100 cc. of benzene, 3 g. (0.038 mole) of monothioglycol and 0.8 g. of pyridine hydrochloride in 10 cc. of absolute alcohol was refluxed for six hours. Every two hours 10 cc. of the azeotropic mixture was distilled off. At the end of the reaction the mixture was diluted with 100 cc. of benzene and worked up as described above. The residue was crystallized from methanol, whereby 4 g. (33%) of white prisms of VII, m. p. 166–177°, $[\alpha]^{20}D$ −113°, λ_{max} 268 mμ, log E_m 4.41 was obtained. From the mother liquors additional 2 g. (16.5%) could be collected on further standing.

Anal. Calcd. for $C_{21}H_{30}O_2S$: C, 72.78; H, 8.72; S, 9.25. Found: C, 72.74; H, 8.69; S, 9.15.

The hydrolysis of this thioenol ether was accomplished under the same conditions as described above for I. In both cases Δ⁴-androstene-3,17-dione was obtained, identified by melting points, mixed melting point and rotation.

The benzoate (IX) was prepared by dissolving 4 g. (0.011 mole) of VII in 10 cc. of anhydrous pyridine to which 5 g. (0.036 mole) of benzoyl chloride was added. The mixture was left standing at room temperature for eighteen hours, then diluted with pure chloroform and washed with 2% sulfuric acid, water, sodium carbonate solution and water until neutral, dried over sodium sulfate and concentrated to a residual volume of about 15 cc., diluted with 200 cc. of ether and quickly filtered. The filtrate was decolorized with charcoal and evaporated to dryness. The residue, after addition of methanol, became solid. After two crystallizations from chloroform–methanol, 2 g. (39%) of white plates, m. p. 209–211° was obtained; $[\alpha]^{20}D$ + 177.3°, λ_{max} 232 mμ, log E_m 4.38.[23]

Anal. Calcd. for $C_{28}H_{34}O_3S$: C, 74.62; H, 7.60; S, 7.11. Found: C, 74.59; H, 7.62; S, 7.28.

3-Benzylthioenol Ether of Δ⁴-Cholestenone (XIII).—This compound was prepared as described above under (b), using 5 g. (0.013 mole) of Δ⁴-cholestenone in 100 cc. of benzene, 2.5 g. (0.02 mole) of benzyl mercaptan and 0.3 g. of *p*-toluenesulfonic acid. Crystallization from acetone yielded 3.2 g. (50%) of white needles of XIII, m. p. 121.5–122°, $[\alpha]^{20}D$ −105°, λ_{max} 268 mμ, log E_m 4.31.

Anal. Calcd. for $C_{34}H_{50}S$: C, 83.27; H, 10.26; S, 6.53. Found: C, 83.42; H, 10.14; S, 6.66.

3-Benzylthioenol Ether of Testosterone (II).—The flask of a Soxhlet extraction apparatus was charged with a solution containing 2 g. (0.053 mole) of lithium aluminum hydride in 800 cc. of anhydrous ether and 3 g. (0.008 mole) of I was placed in the extractor thimble. The solution was warmed until all the thioenol ether had been transferred to the reaction flask. The mixture was then cooled externally with ice and, under continuous stirring, water was added dropwise to decompose the excess hydride and the complex formed during the reaction. When decomposition was complete, 300 cc. of benzene was added in order to dissolve the product completely. The benzene–ether solution was washed with water, dried over sodium sulfate and evaporated to dryness. After recrystallization from methanol with a drop of pyridine, 2 g. (66%) of white needles, m. p. 168–169°, $[\alpha]^{20}D$ −126.2°, λ_{max} 268 mμ, log E_m 4.20 was obtained.

Anal. Calcd. for $C_{26}H_{34}OS$: C, 79.12; H, 8.68; S, 8.12. Found: C, 79.22; H, 8.68; S, 8.28.

The hydrolysis of II with hydrochloric acid was carried out as described above for I: To a solution of 1 g. of II in ethanol, 3 cc. of hydrochloric acid and 3 cc. of water were added. After two hours refluxing, the mixture was poured into water, the product extracted with ether and worked up as usual. By several recrystallizations from acetone–hexane, 0.5 g. (68%) of testosterone (III) m. p. 150–152°, $[\alpha]^{20}D$ +104.2° (in methanol) was obtained. The mixed melting point with an authentic sample of testosterone gave no depression. The sulfur test was negative.

To a solution of 2 g. of II in 250 cc. of acetone, 3 g. of cadmium carbonate and 3 g. of mercuric chloride were added. The mixture was refluxed for two hours and the reaction product worked up as in previous examples. By repeated recrystallizations from acetone–hexane 0.9 g. (61%) of testosterone (III), m. p. 150–51° mixed m. p. 150–153°, $[\alpha]^{20}D$ + 103.4° (in methanol) was obtained. The sulfur test was negative.

3-Benzylthioenol Ether of Testosterone Benzoate (IVa).—To a solution of 4 g. (0.01 mole) of II in 8 cc. of anhydrous pyridine, 5 g. (0.035 mole) of benzoyl chloride was added and the mixture was left standing at room temperature for fourteen hours. It was then diluted with chloroform, washed with 2% sulfuric acid, water, sodium carbonate solution and water until neutral, dried over sodium sulfate and concentrated to a residual volume of 20 cc. Ether was added and the solution was quickly filtered, decolorized with charcoal and evaporated to dryness. After crystallization from methanol, 2 g. (40%) of white needles was obtained which, after recrystallization from acetone–methanol, melted at 160–161°, $[\alpha]^{20}D$ −59.3°, λ_{max} 228, 268 mμ; log E_m 4.46, 4.32.

Anal. Calcd. for $C_{33}H_{38}O_2S$: C, 79.47; H, 7.68; S, 6.42. Found: C, 79.59; H, 7.80; S, 6.69.

To a solution of 0.7 g. of IVa in 200 cc. of alcohol, 3 drops of concentrated hydrochloric acid and 3 cc. of water were added. After two hours of refluxing, the product was worked up as in the previous example. By crystallization from methanol, 0.35 g. (64%) of testosterone benzoate (Va), m. p. 190–192° was obtained, which gave no depression when mixed with an authentic sample.

3-Benzylthioenol Ether of Testosterone Acetate (IVb).—A flask containing a mixture of 10 cc. of anhydrous dioxane and 10 cc. of pyridine was cooled externally with ice and 9 g. (0.11 mole) of acetyl chloride was added dropwise. To this mixture, which was kept in the ice-bath, a solution of 1.5 g. (0.004 mole) of II in 20 cc. of anhydrous dioxane was added dropwise. It was left standing at room temperature during one hour and then poured into water. It was extracted with ether and the ether solution washed with 2% sulfuric acid solution and water until neutral, dried over sodium sulfate and evaporated to dryness. After crystallization from methanol with a drop of pyridine, 1 g. (60%) of white needles, m. p. 110°, $[\alpha]^{20}D$ −134° was obtained.

Anal. Calcd. for $C_{28}H_{36}O_2S$: C, 77.01; H, 8.31; S, 7.34. Found: C, 76.98; H, 8.39; S, 7.19.

To a solution of 0.6 g. of IVb in 100 cc. of ethanol, 3 drops of concentrated hydrochloric acid and 3 cc. of water were added. After two hours of refluxing, the mixture was poured into water and worked up as usual. The residue was taken up in hexane and the solution decolorized with charcoal. By crystallization, 0.2 g. (44%) of testosterone acetate (Vb) m. p. 139–140°, $[\alpha]^{20}D$ + 89° was obtained, which gave no depression when mixed with an authentic sample. The sulfur test was negative.

3-(β-Hydroxyethyl)-thioenol Ether of Testosterone (X).—Under the same conditions as described above for I, 3 g. of VII was treated in a Soxhlet apparatus with an excess of lithium aluminum hydride yielding, after crystallization from methanol with a drop of pyridine, 2 g. (66%) of white needles m. p. 175–177°, $[\alpha]^{20}D$ −161.3°.

Anal. Calcd. for $C_{21}H_{32}O_2S$: C, 72.36; H, 9.25; S, 9.19. Found: C, 72.38; H, 9.46; S, 9.09.

Following the method described above for II, 1.5 g. of X was hydrolyzed with hydrochloric acid and 1 g. (80%) of testosterone m. p. 151–153°, $[\alpha]^{20}D$ +103° (in methanol), was obtained. The mixed m. p. gave no depression. The sulfur test was negative.

On hydrolysis with cadmium carbonate and mercuric chloride under the conditions described above for II, 2 g. of X yielded 1.4 g. (85%) of testosterone m. p. 151°,

(23) In view of this unexpected dextrorotation and the absence of the typical absorption maximum at 268 mμ, we abstain from assigning a structural formula to IX.

$[\alpha]^{20}D$ + 104.6° (in methanol) which gave no melting point depression.

The **dibenzoate (XI)** was prepared by applying to a solution of 1 g. of X in 5 cc. of pyridine, to which 3 g. of benzoyl chloride was added, the treatment described for II. After crystallization from methanol, 0.5 g. (31%) of tiny plates was obtained, m. p. 131–133°, $[\alpha]^{20}D$ −58.5°, λ_{max} 230, 268 mμ, log E_m 4.57, 4.22.

Anal. Calcd. for $C_{35}H_{40}O_4S$: C, 75.50; H, 7.24; S, 5.75. Found: C, 75.60; H, 7.30; S, 5.65.

Working as described for IVa, 2 g. of dibenzoate yielded 0.4 g. (28%) of testosterone benzoate, m. p. 188–193°. Mixed with an authentic sample of m. p. 192–194° the mixture melted at 188–193°.

Probable Hemithioketal of Δ^4-Androstene-3,17-dione: First Method.—Five grams (0.017 mole) of the diketone and 1.4 g. (0.17 mole) of monothioglycol were dissolved in 10 cc. of anhydrous dioxane. Seven grams of freshly fused and pulverized zinc chloride and 7 g. of anhydrous sodium sulfate were added and the mixture was left standing at room temperature for sixteen hours. It was then diluted with benzene, washed with water, dried and evaporated to dryness, leaving 5.5 g. of an oily residue, which was subsequently chromatographed on a column of 100 g. of aluminum oxide (Alorco F-20), using portions of 300 cc. of benzene–hexane 1:1 for each fraction of the elution. Fraction 1 yielded 0.9 g. and fraction 8 yielded 0.2 g. of an oil. The combined crystalline fractions 2–7 (3.7 g.) with melting points ranging from 178 to 193°, were recrystallized several times from methanol yielding 2.5 g. (41%) of white needles, m. p. 190–193°, λ_{max} 238 mμ, log E_m 4.30.

Anal. Calcd. for $C_{21}H_{30}O_2S$: C, 72.78; H, 8.72; S, 9.25. Found: C, 73.02; H, 8.86; S, 8.93; $[\alpha]^{20}D$ +52.4°.

Second Method.—Ten grams (0.035 mole) of the diketone was dissolved in 100 cc. of benzene and 3.5 g. (0.045 mole) of monothioglycol was added. The mixture was refluxed for six hours and every two hours 10 cc. of the azeotropic mixture was distilled off. Proceeding as described in previous examples, by several crystallizations from methanol 3 g. (25%) of white needles, m. p. 190–193° was obtained. An additional crop of 2 g. (16%) was obtained from the mother liquors.

The mixed m. p. of the crystals obtained by these two methods gave no depression.

On hydrolysis with hydrochloric acid, 2 g. of this product gave 1.3 g. of Δ^4-androstene-3,17-dione, m. p. 168–170°.

On hydrolysis with cadmium carbonate and mercuric chloride, 2 g. of the product gave 1.5 g. of Δ^4-androstene-3,17-dione.

Hydrogenolysis of 3-Benzylthioenol Ether of Δ^4-Androstene-3,17-dione (I). Method A with Fully Active Raney Nickel.—To a solution of 4 g. (0.01 mole) of I in 100 cc. of dioxane, a suspension of 30 g. of Raney nickel in 100 cc. of ethanol, prepared according to Mozingo[12] was added and the whole was refluxed for eight hours. The nickel was filtered off and the solvent was removed under reduced pressure leaving 3 g. of a solid residue, which was dissolved in 38 cc. of absolute ethanol and 3.8 cc. of acetic acid; 3 g. of Girard reagent T was added. After refluxing for one hour the mixture was poured into water, containing a quantity of sodium hydroxide sufficient to neutralize 9/10 of the acetic acid. From the aqueous mixture, the non-ketone fraction was extracted with ether, the ether solution was washed with water, dried and evaporated; by recrystallization from hexane, 0.3 g. (8%) of androstan-17(β)-ol, m. p. 163°, $[\alpha]^{20}D$ + 12° (in chloroform) was obtained. This compound has been prepared by Marker[24] who reports a m. p. 166°. Mixed with an authentic sample of 166° the mixture melted at 163–166°. The tetranitromethane test and the sulfur test were negative.

Anal. Calcd. for $C_{19}H_{32}O$: C, 82.55; H, 11.65. Found: C, 82.68; H, 11.74.

(24) Marker, THIS JOURNAL, **62**, 2523 (1940).

The androstan-17(β)-ol acetate was prepared by heating a solution of 0.5 g. of androstan-17(β)-ol in 20 cc. of acetic anhydride on a steam-bath for one hour. The excess anhydride was removed under reduced pressure and the residue crystallized from methanol–water, yielding 0.3 g. of androstan-17(β)-ol acetate, m. p. 72–75°, $[\alpha]^{20}D$ +5° (in chloroform).

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.48; H, 10.52.

Kuwada and Miyasaki[25] describe a 17-acetoxyandrostane melting at 82°, but we did not have an opportunity to compare their product with ours.

The androstan-17(β)-ol benzoate was prepared by adding 3 g. of benzoyl chloride to a solution of 1 g. of androstanol in 8 cc. of anhydrous pyridine. The mixture was left standing at room temperature for sixteen hours, then diluted with chloroform, washed with 2% sulfuric acid and then with water until neutral, dried and evaporated. After recrystallization from methanol and acetone–methanol, 0.8 g. of white needles, m. p. 159–161°, $[\alpha]^{20}D$ + 51.7° (in chloroform) was obtained.

Anal. Calcd. for $C_{26}H_{36}O_2$: C, 82.05; H, 9.53. Found: C, 82.04; H, 9.64.

The aqueous mixture of the hydrogenolysis of I, which still contained the ketone fraction, was acidified with hydrochloric acid and extracted with ether. After the usual workup, 2.5 g. (66%) of white plates m. p. 85–87°, $[\alpha]^{20}D$ −21° (in chloroform) was obtained by crystallization from methanol–water. Mixed with a sample of $\Delta^{3,5}$-androstadien-17-one, obtained by dehydration of dehydroisoandrosterone with phosphorus pentoxide, following the method of Burrows, *et al.*,[26] no depression of the melting point was observed. The tetranitromethane test was positive; the sulfur test was negative.

Anal. Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.24; H, 9.75.

$\Delta^{3,5}$-Androstadien-17-one has been isolated by Wolfe, Fieser and Friedgood[27] who report a m. p. 88–89° and has also been prepared by other authors.[28,29]

The oxime was prepared by dissolving 0.5 g. of the ketone in 50 cc. of methanol to which 0.3 g. of hydroxylamine hydrochloride and 0.5 g. of sodium acetate were added. After refluxing for three hours, the solution was poured into water and worked up as usual. By recrystallization from methanol–water, 0.3 g. of the oxime, m. p. 165–167°, was obtained. This compound has also been prepared by Wolfe, Fieser and Friedgood,[27] who report m. p. 164–166°.

Hydrogenolysis of I. Method B, with Partially Deactivated Raney Nickel.—A suspension of 20 g. of Raney nickel in 100 cc. of acetone was refluxed for one hour, 2 g. of I in 100 cc. of acetone was added and refluxing was continued for four hours. The nickel was filtered off and washed with acetone. The solution was evaporated to dryness and the residue was recrystallized from methanol–water, yielding 0.65 g. (48%) of white plates, m. p. 87–89°, of $\Delta^{3,5}$-androstadien-17-one. The mixed melting point with the above test compound gave no depression. The tetranitromethane test was positive; the sulfur test negative.

Hydrogenolysis of 3-Benzylthioenol Ether of Testosterone (II). Method A.—Two grams of II was dissolved in 100 cc. of alcohol and 20 g. of Raney nickel was added. After refluxing for four hours, the reaction mixture was worked up as described above for I, and by crystallization from hexane, 1.2 g. (86%) of androstan-17(β)-ol, m. p. 165–166°, was obtained. The tetranitromethane test and the sulfur test were negative.

(25) Kuwada and Miyasaki, *J. Pharm. Soc. Japan*, **57**, 870–880 (1937), quoted after *C. A.*, **32**, 1275 (1938).

(26) Burrows, Cook, Roe and Warren, *Biochem. J.*, **31**, 950–961 (1937).

(27) Wolfe, Fieser and Friedgood, THIS JOURNAL, **63**, 582 (1941).

(28) Butenandt, *et al.*, *Ber.* **71B**, 198–204 (1938), quoted after *C. A.*, **32**, 2538 (1938).

(29) Ross, *J. Chem. Soc.*, 25–27 (1945).

Method B.—Working as described for I, 3 g. of II yielded, after crystallization from ethanol, 1.8 g. (87%) of needles, m. p. 156°, $[\alpha]^{20}D$ −139° (in chloroform). The tetranitromethane test was positive and the sulfur test negative.

Anal. Calcd. for $C_{19}H_{28}O$: C, 83.76; H, 10.35. Found: C, 83.79; H, 10.40.

This is the $\Delta^{3,5}$-androstadien-17(β)-ol previously described by Butenandt[28] and also by Kuwada and Miyasaki[25] who report m. p. 153–155°.

The acetate, prepared in the usual manner, melted at 128°. Kuwada and Miyasaki[25] report m. p. 126°, $[\alpha]^{20}D$ −155° (in chloroform).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.20; H, 9.61. Found: C, 80.26; H, 9.64.

In order to obtain an authentic specimen for comparison, we also prepared $\Delta^{3,5}$-androstadien-17-ol by the following method, which is essentially the one followed by Butenandt[28] but with some modifications: one gram of testosterone was dissolved in 200 cc. of anhydrous ether. This solution was added dropwise to a boiling solution of 0.8 g. of lithium aluminum hydride in 200 cc. of anhydrous ether. After working up the reaction mixture as described in previous examples, a residue was obtained which was a mixture of isomeric androstenediols. These were dissolved in 300 cc. of ethanol and after addition of 10 cc. of hydrochloric acid, refluxed for two hours. The product was poured into water and worked up as usual. By crystallization from ether–hexane, 0.5 g. of $\Delta^{3,5}$-androstadien-17(β)-ol, m. p. 158° was obtained.

When mixed with a sample of the product obtained by method B (see above) the mixture melted at 156–158°.

Hydrogenolysis of the 3-(β-Hydroxyethyl)-thioenol Ether of Δ^4-Androstene-3,17-dione (VII). Method A.—Proceeding as described for I, 4 g. of VII yielded a crude reaction product of 2.7 g. (85%). After treatment with Girard reagent T, 0.7 g. (22%) of androstan-17(β)-ol, m. p. and mixed m. p. 162–164°, was obtained from the non-ketone fraction. The tetranitromethane test and the sulfur test were negative. The ketone fraction yielded 1 g. (32%) of $\Delta^{3,5}$-androstadien-17-one, m. p. 85–87°, $[\alpha]^{20}D$ −22° (in chloroform). The tetranitromethane test was positive; the sulfur test negative.

Method B.—Working as above, from 2 g. of VII, 1.3 g. (83%) of white plates of $\Delta^{3,5}$-androstadien-17-one, m. p. and mixed m. p. 87–88°, $[\alpha]^{20}D$ −21.5° (in chloroform) was obtained. The tetranitromethane test was positive; the sulfur test negative.

Hydrogenolysis of the 3-(β-Hydroxyethyl)-thioenol Ether of Testosterone (X). Method A.—Working as in previous examples, 2 g. of X yielded 1.3 g. (82%) of androstan-17(β)-ol, m. p. and mixed m. p. 164–166°. The tetranitromethane test and the sulfur test were negative.

The acetates prepared from this androstan-17(β)-ol and from the one obtained by hydrogenolysis of II were identical.

Androstan-17(β)-ol (0.5 g., 0.002 mole) was dissolved in 30 cc. of acetic acid. A solution of 1.5 g. (0.015 mole) of chromic anhydride in 10 cc. of 80% acetic acid was added. The mixture was left standing at room temperature for three hours, then poured into water and extracted with ether. After the usual workup and crystallization from methanol, 0.2 g. of white plates of androstan-17-one, m. p. 122°, $[\alpha]^{20}D$ + 103° (in chloroform) was obtained. The tetranitromethane test was negative.

Method B.—Working as in previous examples, 2 g. of X yielded 1.4 g. (90%) of needles of $\Delta^{3,5}$-androstadien-17-(β)-ol, m. p. and mixed m. p. 154–155°. The tetranitromethane test was positive, the sulfur test negative.

Hydrogenolysis of the 3-Benzylthioenol Ether of Δ^4-Cholestenone (XIII). Method A.—Working as in previous examples, 4 g. of XIII yielded after crystallization from methanol–ether, 2.5 g. (82%) of cholestane, m. p. 78–79°, $[\alpha]^{20}D$ + 23.7° (in chloroform). The tetranitromethane test and the sulfur test were negative.

Anal. Calcd. for $C_{27}H_{48}$: C, 87.01; H, 12.98. Found: C, 87.16; H, 12.72.

Method B.—Working as described above, 1.5 g. of XIII yielded 1 g. (88%) of crystals of $\Delta^{3,5}$-cholestadiene, m. p. 78–79°, $[\alpha]^{20}D$ −101° (in chloroform). The tetranitromethane test was positive and the sulfur test negative.

Anal. Calcd. for $C_{27}H_{44}$: C, 87.96; H, 12.03. Found: C, 87.82; H, 12.23.

The mixed melting point of the reaction products of method A and method B showed a marked depression.

Summary

1. Several thioenol ethers of Δ^4-3-keto steroids have been prepared.

2. The conversion of the thioenol ethers of Δ^4-androstene-3,17-dione and its esters to the corresponding testosterone derivatives has been accomplished by treatment with lithium aluminum hydride.

3. Evidence for the structure of the 3-thioenol ethers of Δ^4-3-ketosteroids has been given.

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Synthetic and Degradative Studies in the Isoquinoline Series. IV

BY G. FODOR, V. BRUCKNER, J. KISS AND J. KOVÁCS

In our recent communication of this series[1] an unequivocal synthesis of I and the proof of its structure by oxidative degradation was described. This compound was isomeric, but not identical, with that prepared by Pfeiffer, *et al.*,[2] from brasilin and formulated as I; consequently the structure of their compound became doubtful.[1]

Tetramethyl hematoxylonol oxime (II) was converted by the same authors[2] in two steps into an amphoteric compound to which we will refer below as "H." Oxidation of "H" with permanganate yielded metahemipinic acid (3,4-dimethoxyphthalic acid). Degradation with nitric acid furnished an acid ("A") only isolated as picrate. Acid "A" reacted with diazomethane under formation of a monomethyl derivative, which was again only isolated as picrate. On the basis of these facts Pfeiffer, *et al.*,[2] suggested for "H" structure IIIa and for acid "A" formula IVa. These structures were not confirmed by synthesis. Although the synthesis of the methyl ether of "H" from amide Vb was attempted, the obtained synthetic

(1) Bruckner, Fodor, Kovács and Kiss, THIS JOURNAL **70**, 2697 (1948).

(2) Pfeiffer, Breitbach and Scholl, *J. prakt. Chem.*, **2**, 154, 157 (1940).