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ACYLATIVE CONVERSION OF STEROIDAL THIOKETALS TO THIOENOL ETHERS

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A recent communication (1) describes the action of boron trifluoride etherate and acetic anhydride on 3-ethylene and 3-diethyl ketals of the 5α-androstane type. These are converted to Δ^2-enol ethers with simultaneous addition of an acetyl group at the 2-position.

We wish to report studies on the acylative scission of ethylenethioketals which were conducted prior to the publication of Youssefyeh (1). Our studies have shown that any set of conditions which can be considered to form intermediate acyl carbonium ions (2) can effect the cleavage of the sulfur to (steroidal) carbon bond of an ethylenethioketal to form a thioenol ether. Boron trifluoride etherate with carboxylic acid anhydrides or chlorides, trifluoroacetic anhydride with acids, trifluoroacetic acid or trichloroacetic acid or p-toluenesulfonic acid or hydrogen chloride with anhydrides have all been successfully employed, and no doubt many other Lewis acids could serve as well. It is apparent that the experimental conditions commonly employed for the acylation of highly-hindered steroidal carbinols are precisely those which result in cleavage of an ethylenethioketal, as described below.

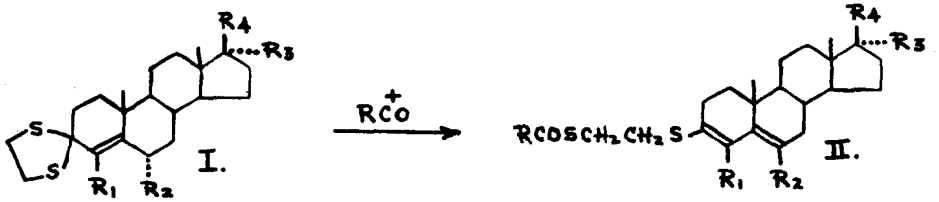
Our efforts were directed towards determining the minimum conditions for converting various ethylenethioketals to their corresponding β-acylthioethylthioenol ethers without further reactions of addition to the newly-

formed double bonds (1) and with avoidance of D-ring rearrangements (3). The most generally useful reagent mixture was boron trifluoride etherate plus acetic anhydride, with added acetic acid as a moderator of activity.

Treatment of 6α-methyl-4-pregnen-17α-ol-3,20-dione acetate 3-ethylenethioketal (Ia; m.p. 269-274°; $[\alpha]_D$ + 87.0°) with trifluoroacetic acid, acetic anhydride and acetic acid at 80° for 15 minutes yielded 80% of 3-(β-acetylthioethylthio)-6-methyl-3,5-pregnadien-17α-ol-20-one acetate (IVa; m.p. 134-135°; $[\alpha]_D$ -166.3°; λλmax. 235, 276 mμ., 5.76, 5.82, 5.90, 6.25, 8.77 μ.). Other combinations such as: boron trifluoride etherate, acetyl chloride, ether and methylene chloride at 25° for 1 hr.; trifluoroacetic anhydride and acetic acid at 60° for 10 minutes; p-toluenesulfonic acid, acetic anhydride and acetic acid at 25° for 2 hrs.; trichloroacetic acid, acetic anhydride and acetic acid at 80° for 3 1/2 hrs.; ethereal hydrogen chloride and acetic anhydride at 30° for 7 days also afforded IVa in 70-80% yield from Ia. Treatment of Ia with trifluoroacetic anhydride and cyclopropanecarboxylic acid at 25° for 15 minutes afforded 65% of the cyclopropylcarbonyl analog IVb (m.p. 92-94°; $[\alpha]_D$ -154.2°; λλmax. 234, 277 mμ., 5.78, 5.82, 5.95, 6.25, 8.88 μ.). In similar fashion, Ia with benzoic anhydride or benzoyl chloride and boron trifluoride etherate in ether-methylene chloride afforded 75% of the benzoyl analog IVc (m.p. 139-140°; $[\alpha]_D$ -137.0°; λλmax. 239, 273 mμ., 5.78, 5.83, 6.00, 6.28, 6.33, 8.90 μ.).

4-Chlorotestosterone acetate 3-ethylenethioketal (Ib; m.p. 177-178°; $[\alpha]_D$ +136.1°) treated with trifluoroacetic anhydride and acetic acid at 25° for 7 minutes yielded 90% of 3-(β-acetylthioethylthio)-4-chloro-3,5-androstadien-17β-ol acetate (IVd; m.p. 107-108°; $[\alpha]_D$ -64.4°; λλmax. 228, 278 mμ., 5.78, 5.90, 6.38, 8.81 μ.). The same reagents, plus added methylene chloride, in 1 1/4 hrs. at 25° converted 17α-methyltestosterone acetate 3-ethylenethioketal (Ic; m.p. 221-223°; $[\alpha]_D$ + 100.0°) to 60% of

TABLE 1: Thioketals to Thioenol Ethers



Ia: R_1 = H; R_2 = CH_3; R_3 = OAc; R_4 = Ac	IVa: R = CH_3; R_1 = H; R_2 = CH_3; R_3 = OAc; R_4=Ac
Ib: R_1 = Cl; R_2, R_3 = H; R_4 = OAc	IVb: R = C_3H_5; R_1 = H; R_2 = CH_3; R_3 = OAc; R_4=Ac
Ic: R_1, R_2 = H; R_3 = CH_3; R_4 = OAc	IVc: R = C_6H_5; R_1 = H; R_2 = CH_3; R_3 = OAc; R_4=Ac
Id: R_1, R_2 = H; R_3 = C≡CH; R_4 = OAc	IVd: R = CH_3; R_1 = Cl; R_2, R_3 = H; R_4 = OAc
Ie: R_1, R_2 = H; R_3 + R_4 = O	IVe: R = CH_3; R_1, R_2 = H; R_3 = CH_3; R_4 = OAc
If: R_1, R_2, R_3 = H; R_4 = Ac	IVf: R = CH_3; R_1, R_2 = H; R_3 = C≡CH; R_4 = OAc
Ig: R_1, R_2, R_3 = H; R_4 = C_8H_{17}	IVg: R = CH_3; R_1, R_2 = H; R_3 + R_4 = O
	IVh: R = CH_3; R_1, R_2, R_3 = H; R_4 = Ac
	IVi: R = CH_3; R_1, R_2, R_3 = H; R_4 = C_8H_{17}

the thioenol ether IVe (m.p. 117-118°; $[\alpha]_D$ -105.5°; $\lambda\lambda$max. 233, 268 mμ., 5.80, 5.91, 6.26, 8.83 μ.).

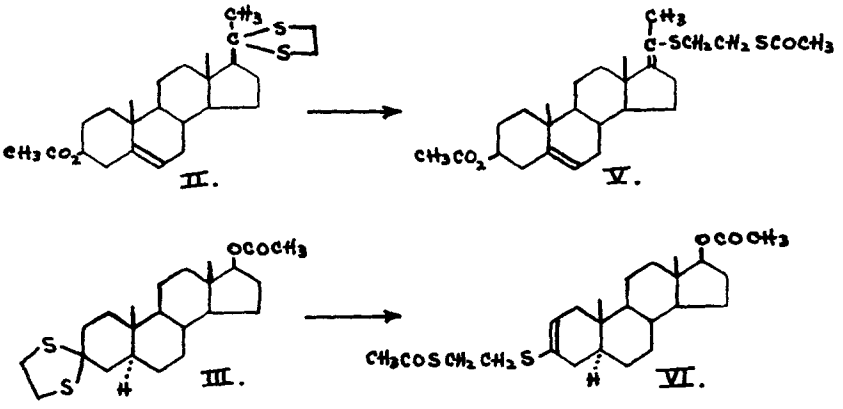
Ethisterone acetate 3-ethylenethioketal (Id; m.p. 255-259°; $[\alpha]_D$ +63.5°) when treated with boron trifluoride etherate, acetic anhydride and acetic acid at 25° for 8 minutes (or with trifluoroacetic anhydride, acetic acid and methylene chloride at 25° for 30 minutes) yielded 70-80% of the thioenol ether IVf (m.p. 130-131°; $[\alpha]_D$ -197.3°; $\lambda\lambda$max. 232, 270 mμ., 3.08, 5.79, 5.92, 6.25, 8.80 μ.). The same conditions convert 4-androstene-3,17-dione 3-ethylenethioketal (4, Ie) to 85% of the corresponding thioenol ether IVg (m.p. 124-126°; $[\alpha]_D$ -100.0°; $\lambda\lambda$max. 230, 270 mμ., 5.78, 5.91, 6.24, 8.80 μ.).

Progesterone 3-ethylenethioketal (4, If) reacted with p-toluenesulfonic acid, acetic anhydride and acetic acid at 25° for 10 hrs. to afford 60% of the thioenol ether IVh (m.p. 79-80°; $[\alpha]_D$ -58.5°; $\lambda\lambda$max. 233, 269 mμ., 5.90, 6.29, 8.80 μ.). The same conditions converted 4-cholestenone 3-ethylenethioketal (5, Ig) to 65% of 3-(β-acetylthioethylthio) cholest-3,5-diene (IVi; $[\alpha]_D$ -47.0°; $\lambda\lambda$max. 232,271 mμ., 5.90, 6.22, 8.79 μ.), a viscous oil which was purified by chromatography on acidic alumina.

Treatment of pregnenolone acetate 20-ethylenethioketal (II; m.p. 198-200°; $[\alpha]_D$ -44.6°) with boron trifluoride etherate, acetic anhydride and acetic acid at 25° for 10 minutes formed the $\Delta^{17,20}$-thioenol ether V ($[\alpha]_D$ -29.6°; $\lambda\lambda$max. 252 mμ., 5.73, 5.87, 8.78 μ.), a relatively unstable oil purified by chromatography.

5α-Dihydrotestosterone acetate 3-ethylenethioketal (6, III) was our closest analog to the ketals of Youssefyeh (1). This thioketal underwent acetylative scission far less readily than any of those previously discussed. Boron trifluoride etherate, acetic anhydride and acetic acid

at 25° for 3 hrs. was inadequate for complete scission, but chromatography on acidic alumina yielded 50% of the Δ^2-thioenol ether VI as a colorless viscous oil ($[\alpha]_D$ +40.6°; $\lambda\lambda$ max. 227 mμ., 5.73, 5.88, 8.78 μ.). The spectral data clearly demonstrated opening of the thioketal without addition of acetyl to the double bond in this instance, as in all the others.



Acid-catalyzed hydrolysis (7) of the thioenol ethers IVa-i and V converted these to the ketones from which their precursor ethylenethioketals (and acetates) had been prepared. Similar hydrolysis of the Δ^2-thioenol ether VI, however, led to a mixture of dihydrotestosterone and its 3-ethylenethioketal (6). Obviously, to the extent that the terminal acetylthio group is hydrolyzed to mercaptan prior to hydrolysis of the thioenol ether, the mercaptan rapidly recloses to the ethylenethioketal which is not further affected by the conditions of acid hydrolysis.

In the foregoing discussion, the yields refer to purified products of the stipulated melting points. All compounds for which data are given appear to be new, and with the exception of IVi and V, they are supported by carbon and hydrogen analytical values within the accepted range. The

non-crystalline thioenol ethers IVi and V, although giving poor carbon values, did however give good yields of the appropriate ketones on acid hydrolysis as evidence of their structures.

Further investigations on the acylative opening of cyclic thioketals are being continued and will be reported in more detail at a later date.

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