

# REACTIVITY OF ETHANEDIYL S,S-ACETALS - 5.8 ON THE AROMATIZATION OF THE RING A IN 3-OXOSTEROID DERIVATIVES

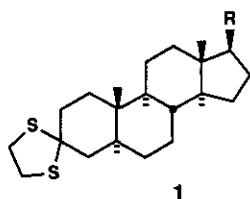
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**Abstract** - Ethanediyl S,S-acetal (1,3-dithiolane) derivatives of 3-oxosteroids, when treated with bromine in anhydrous chloroform at room temperature, undergo ring A aromatization following a dienone-benzene like steroidal skeleton rearrangement that leads to 1,4-dithian fused 4-methylestranes. The easy replacement of the sulphur atoms may afford 4-methylestranes with variously substituted A rings.

As a part of our current interest in ring expansion reactions<sup>1-3</sup> of ethanediyl S,S-acetals (1,3-dithiolanes) from substituted cyclohexanones, we report in this paper the results obtained when 1,3-dithiolane derivatives of 3-oxosteroids are treated with excess bromine in anhydrous chloroform at room temperature. Indeed, the 1,3-dithiolane derivative of 17 $\beta$ -acetoxy-5 $\alpha$ -androstan-3-one (1a) under such conditions (threefold excess bromine) affords two reaction products: a major one, which was assigned structure (2a), having a rearranged steroidal skeleton and the ring A aromatized, fused to a six member 1,4-dithian ring, along with a minor one (mainly occurring when a larger excess bromine is utilized) which turned out to be a C-7 brominated derivative of 2a, being assigned structure (3).

The attribution of both structures (2a) and (3) was performed essentially on spectroscopic grounds. <sup>1</sup>H And <sup>13</sup>C nmr spectra of these compounds (see Table 1) were, in fact, consistent with the presence of a



a) R = OCOCH<sub>3</sub>

b) R = C<sub>8</sub>H<sub>17</sub>

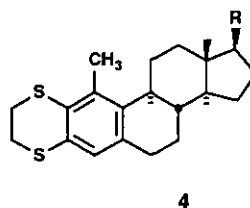
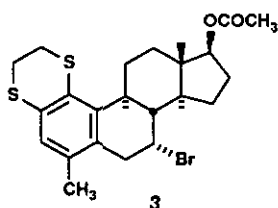
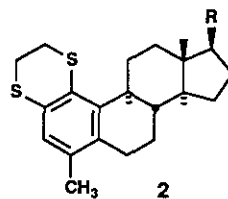


Table 1 - Relevant  $^1\text{H}$  and  $^{13}\text{C}$  Nmr Signals ( $\delta$ ;  $\text{CDCl}_3$ ) of Compounds (2a), (2b), and (3).

| H/C*                              | 2a                           | 3                            | 2b                 |
|-----------------------------------|------------------------------|------------------------------|--------------------|
| C3-H                              | 7.02 (s)                     | 7.05 (s)                     | 7.02 (s)           |
| C17-H                             | 4.75 (dd, $J = 7.7, 1.2$ Hz) | 4.75 (dd, $J = 7.7, 1.2$ Hz) | ==                 |
| C7-H                              | ==                           | 4.51 (m)                     | ==                 |
| $\text{SCH}_2\text{CH}_2\text{S}$ | 3.40-3.10 (m)                | 3.45-3.15 (m)                | 3.40-3.15 (m)      |
| C19-H                             | 2.15 (s)                     | 2.13 (s)                     | 2.18 (s)           |
| $\text{CH}_3\text{COO}$           | 2.05 (s)                     | 2.05 (s)                     | ==                 |
| C18-H                             | 0.87 (s)                     | 0.87 (s)                     | 0.72 (s)           |
| C1                                | 130.5 (s)                    | 130.5 (s)                    | 130.5 (s)          |
| C2                                | 134.3 (s)                    | 134.1 (s)                    | 133.9 (s)          |
| C3                                | 128.7 (d)                    | 128.7 (d)                    | 128.5 (d)          |
| C4 or C5                          | 134.1 or 134.8 (s)           | 134.3 or 134.5 (s)           | 133.9 or 134.9 (s) |
| C10                               | 141.7 (s)                    | 141.3 (s)                    | 141.6 (s)          |
| C19                               | 18.3 (q)                     | 19.3 (q)                     | 19.1 (q)           |
| C7                                | ==                           | 51.5 (d)                     | ==                 |
| SC-CS                             | 29.1-29.5 (t)                | 29.3-29.6 (t)                | 29.3-30.0 (t)      |

\*  $^{13}\text{C}$  Nmr signals assignments were made by INEPT and off-resonance experiments.

pentasubstituted aromatic ring carrying a methyl group and a 1,4-dithian moiety. In addition, the  $^1\text{H}$  nmr spectrum of 3 displayed a sharp peak ( $\delta$  4.51) that could be ascribed to the proton geminal with the bromine atom. These data, however, could as well account for an alternative structure (4), also predictable on a mechanistic basis,<sup>4</sup> to be assigned to the main product resulting from the reaction of 1a with bromine. In the absence of any clearcut evidences, the choice between structures (2a) and (4) came out from the X-ray analysis<sup>5</sup> of the brominated product (3). The closest nmr features (see Table 1) of the latter in comparison with the main reaction product, and also the successful chemical conversion of pure 3 into 2a, by triethylsilane and aluminium trichloride,<sup>6</sup> enabled structure (4) to be definitely ruled out and the main reaction product to be unambiguously assigned structure (2a). The ethanediyl *S,S*-acetal of 5 $\alpha$ -cholestan-3-one (1b), under the same conditions, undergoes an analogous rearrangement and ring A aromatization leading to the sole compound (2b).

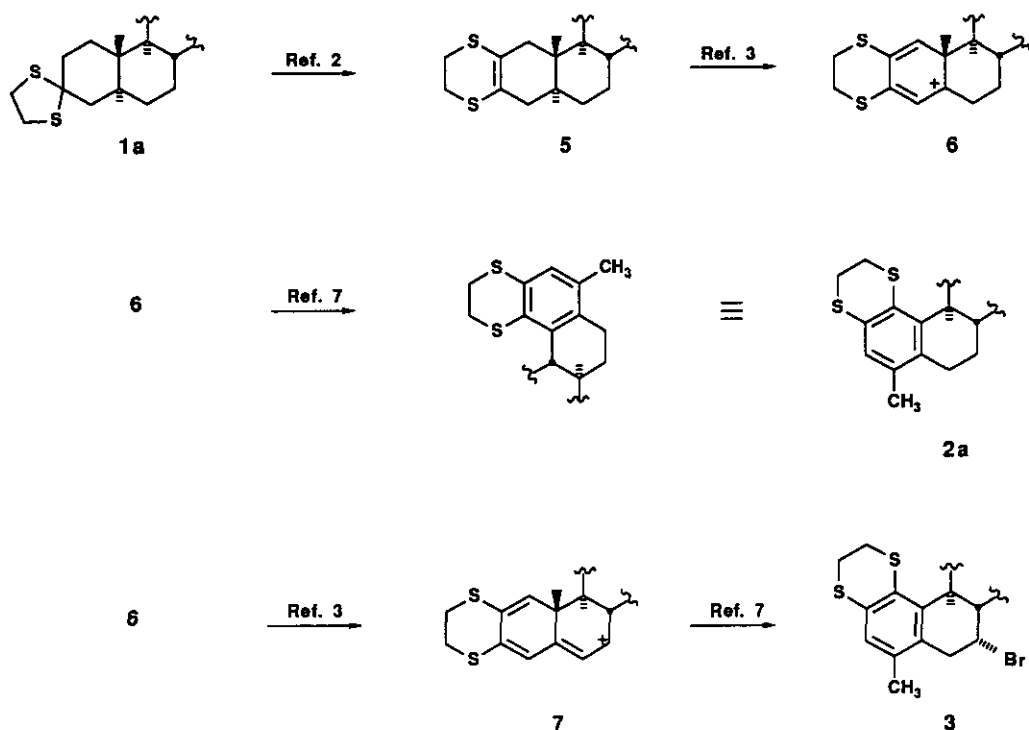
A mechanistic interpretation of the formation of both 2a and 3 under our experimental conditions can be attempted in view of the already reported mechanisms operating in the conversion of cyclohexanone *S,S*-ethanediyl derivatives into benzo-1,4-dithians<sup>3</sup> and the steroid dienone-benzene rearrangement<sup>7,8</sup> respectively.

The first step of the overall conversion consists of the formation of 2,3-dihydro-1,4-dithiin (5), involving consumption of one bromine mole.<sup>2</sup> As a matter of fact, the reaction of specially prepared 5 with only two bromine equivalents affords 2a (and occasionally 3) in nearly quantitative yield; in addition, 5 is isolated,

beside 2a and starting 1a, when the reaction of the latter with bromine is quenched before getting to completion. The sequential action onto 5 of the remaining two bromine moles can be assumed, by analogy with already reported results,<sup>3</sup> to lead to the formation of hydrogen bromide and the carbocation (6). The latter cannot eliminate an  $\alpha$ -proton to give ring aromatization and, hence, undergoes two subsequent [1,2] sigmatropic rearrangements<sup>7,8</sup> and final hydrogen bromide elimination to afford the main reaction product (2a). Accordingly, six moles of hydrogen bromide were evolved during the reaction.

The formation of the C-7  $\alpha$ -brominated derivative (3) could not be satisfactory rationalized. It can be tentatively accounted for by considering that the elimination of a C-6 *vic*-proton from the carbocation (6) may afford an heteroannular triene which, in its turn, undergoes sulfur attack by bromine and hydrogen bromide elimination leading to a new carbocation (7). The latter, by bromide addition at C-7 and several subsequent steps including the above mentioned [1,2] sigmatropic rearrangements finally gives 3.

Considering that the sulfur atoms of the dithian moiety can be conveniently either removed or replaced by alkyl groups,<sup>9</sup> this conversion represents a suitable way to prepare estrane-like steroids having unusual substituents on the ring A. It is also noteworthy that ethanediyl *O,S*-acetals and *N*-acyl-1,3-thiazolidine derivatives of 3-oxosteroids exhibit the same behaviour as their corresponding *S,S*-acetals leading to interesting structures like the biologically relevant *N*-acylbenzo-1,4-thiazines and *N*-acyl-phenothiazines.



Scheme 1 - Main Steps of the Conversion of 1a into 2a (and 3) by Treatment with Bromine in Anhydrous Chloroform.

## EXPERIMENTAL

Ethanediyyl *S,S*-acetals were prepared from the parent ketones according to reported procedures.<sup>10</sup> Anhydrous chloroform was made from reagent grade solvent (Carlo Erba) according to literature procedures.<sup>11</sup> Commercially available bromine (Carlo Erba) was purified and dried immediately before use.<sup>12</sup> Flash chromatography was performed on Merck silica gel 60 (400-230 mesh). <sup>1</sup>H Nmr spectra were recorded on a Bruker WH (270 MHz) instrument in CDCl<sub>3</sub> solution.

Reaction of 17 $\beta$ -acetoxy-5 $\alpha$ -androstan-3-one ethanediyyl *S,S*-acetal (1a) with bromine. To a solution of the title compound (1.00 g; 2.5 mmol) in anhydrous chloroform (70 ml), at room temperature and under magnetic stirring, bromine (1.10 g; 6.9 mmol) dissolved in the same solvent (20 ml) is added dropwise over few minutes. Stirred for 5 h at room temperature (tlc monitoring), the reaction mixture is then quenched by adding excess solid sodium hydrogen carbonate: the chloroform layer is extracted with 5N aq. sodium thiosulfate (2 x 25 ml), washed with water until neutral, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated *in vacuo*. The oily crude residue, flash-chromatographed on silica gel (95:5 light petrol ether:benzene), afforded both chromatographically pure semicrystalline products (2a) and (3), beside some unchanged starting product (14%).

2a (0.70 g; 80% yield), mp 149-151° C (from methanol); <sup>1</sup>H and <sup>13</sup>C nmr: see Table 1; m/z = 402 (M<sup>+</sup>). *Anal.* Calcd. for C<sub>23</sub>H<sub>30</sub>O<sub>2</sub>S<sub>2</sub>: C, 68.61; H, 7.51. Found: C, 68.73; H, 7.62.

3 (0.10 g; 3% yield), mp 144-145° C (from *n*-hexane); <sup>1</sup>H and <sup>13</sup>C nmr: see Table 1; m/z = 481 (M<sup>+</sup>). *Anal.* Calcd for C<sub>23</sub>H<sub>29</sub>O<sub>2</sub>BrS<sub>2</sub>: C, 57.37; H, 6.07. Found: C, 57.42; H, 6.12.

Under the same conditions, 5 $\alpha$ -cholestan-3-one ethanediyyl *S,S*-acetal (1b) afforded the sole compound (2b) (80% yield),<sup>13</sup> mp 62-63° C (from *n*-hexane); <sup>1</sup>H and <sup>13</sup>C nmr: see Table 1; m/z = 456 (M<sup>+</sup>). *Anal.* Calcd for C<sub>29</sub>H<sub>44</sub>S<sub>2</sub>: C, 76.25; H, 9.71. Found: C, 76.30; H, 9.76.

Preparation of 3. The reaction of 17 $\beta$ -acetoxy-5 $\alpha$ -androstan-3-one ethanediyyl *S,S*-acetal (1a), carried out as reported above but with a substrate:bromine ratio equal to 1:3, gave the expected 2a and its C-7 brominated derivative 3 in 70% and 15% yield respectively.

Conversion of 3 into 2a. To a mixture of pure 3 (0.50 g; 1.0 mmol) and Et<sub>3</sub>SiH (1.4 g; 12.0 mmol), in anhydrous *n*-hexane (10 ml) cooled in an ice bath, solid anhydrous AlCl<sub>3</sub> (0.05 g; 0.4 mmol) was added in one portion under magnetic stirring. The resulting suspension was heated at 40° C for 1 h. 2N Aq. Na<sub>2</sub>CO<sub>3</sub> was then added to quench the reaction mixture, and the organic layer was washed with water (3 x 10 ml) until neutral, dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated *in vacuo*. The semicrystalline residue after crystallization

from MeOH afforded pure **2a** (0.25 g; 63% yield), mp 148-150° C. In the mother liquors its C-17 hydroxy derivative was present in appreciable amount (about 20%).

5,6-Dihydro-1,4-dithiin(5) from the reaction of 1a with bromine. The reaction of **1a** (0.90 g; 2.5 mmol) with bromine (0.60 g; 3.7 mmol) in anhydrous chloroform (70 ml) was carried out under the conditions reported above. After 2 h the reaction mixture was quenched and worked up as usual. The oily crude residue, flash chromatographed on silica gel (95:5 light petrolether:benzene), afforded unreacted starting dithiolane (**1a**) (0.40 g; 45% yield), as the main product, beside a mixture of 1,4-benzodithian (**2a**) (0.15 g; 10% yield) and 5,6-dihydro-1,4-dithiin (**5**) (0.45 g; 30% yield), mp 188-189° C (from *n*-hexane); <sup>1</sup>H nmr: δ 4.70 (1H, *dd*, *J* = 7.7, 1.2 Hz, CHOAc), 3.30-3.15 (4H, *m*, SCH<sub>2</sub>CH<sub>2</sub>S), 2.04 (3H, *s*, CH<sub>3</sub>COO); *m/z* = 406 (M<sup>+</sup>). *Anal.* Calcd for C<sub>23</sub>H<sub>34</sub>O<sub>2</sub>S<sub>2</sub>: C, 67.93; H, 8.43. Found: C, 67.81; H, 8.35.

1,4-Benzodithian(2a) from the reaction of 5 with bromine (1:2). To a solution of 5,6-dihydro-1,4-dithiin (**5**) (0.90 g; 2.5 mmol) in anhydrous chloroform (50 ml) at room temperature under magnetic stirring, bromine (0.80 g; 5.0 mmol) dissolved in the same solvent (15 ml) is added dropwise over few min. Stirred for 5 h at room temperature and worked up as usual, the crude product afforded after flash chromatography essentially **2a** (0.80 g; 82% yield), accompanied by traces of **3**.

#### ACKNOWLEDGMENT

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