REACTIVITY OF ETHANEDIYL S,S-ACETALS - 5.§ ON THE AROMATIZATION OF THE RING A IN 3-OXOSTEROID DERIVATIVES

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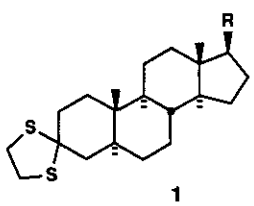
Abstract - Ethanediyl *S,S*-acetal (1,3-dithiolane) derivatives of 3-oxosteroids, when treated with bromine in anhydrous chloroform at room temperature, undergo ring A aromatization following a dienone-benzene like steroidal skeleton rearrangement that leads to 1,4-dithian fused 4-methylestranes. The 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[1-3] 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 17ß-acetoxy-5α-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. ^{1}H And ^{13}C nmr spectra of these compounds (see Table 1) were, in fact, consistent with the presence of a



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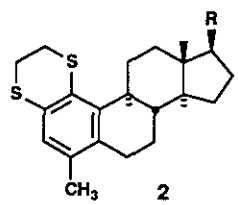
a) R = $OCOCH_3$

b) R = C_8H_{17}



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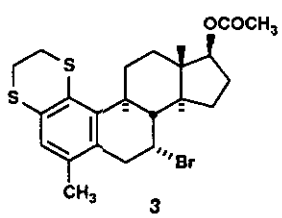

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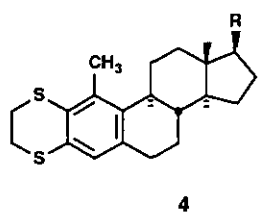

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Table 1 - Relevant ^{1}H and ^{13}C Nmr Signals (δ; $CDCl_3$) of Compounds (**2a**), (**2b**), and (**3**).

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*)	==
SCH_2CH_2S	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*)
CH_3COO	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}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}H nmr spectrum of **3** displayed a sharp peak (δ 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,[4] 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[5] 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,[6] 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 5α-cholestan-3-one (**1b**), under the same conditions, undergoes an analogous rearrangement and ring A aromatization leading to the sole compound (**2b**).

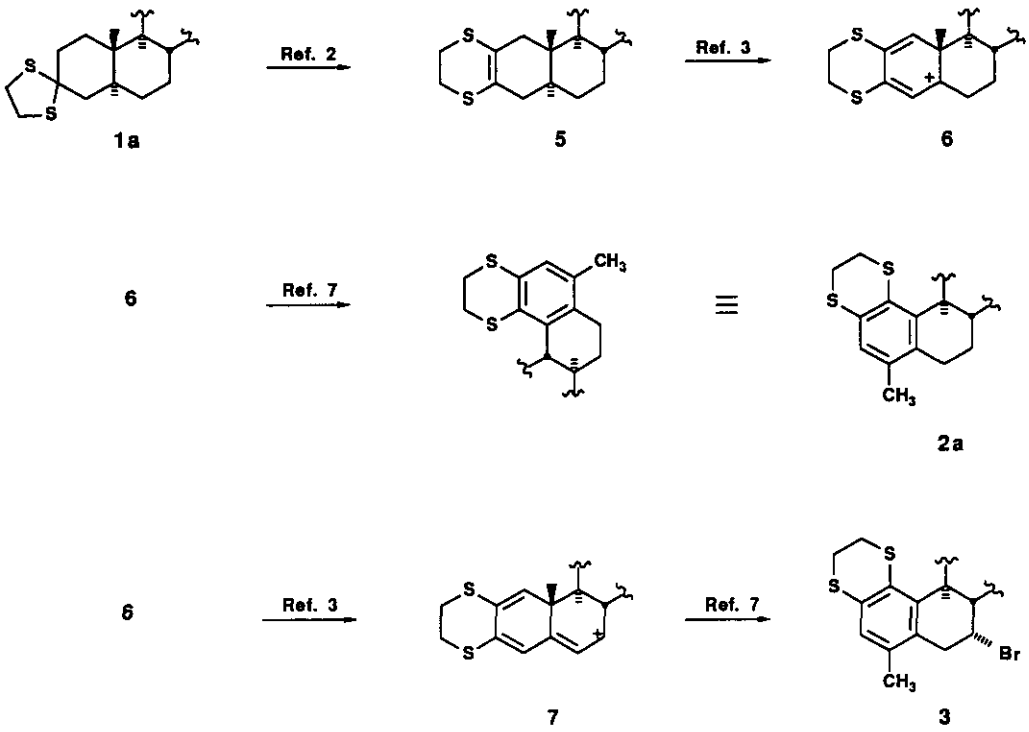
A mechanistic interpretation of the formation of both **2a** and **3** under our experimental conditions can be attempted in view of the already reported mechanisms operating in the conversion of cyclohexanone *S,S*-ethanediyl derivatives into benzo-1,4-dithians[3] and the steroid dienone-benzene rearrangement[7,8] 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.[2] 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,[3] to lead to the formation of hydrogen bromide and the carbocation (**6**). The latter cannot eliminate an α-proton to give ring aromatization and, hence, undergoes two subsequent [1,2] sigmatropic rearrangements[7,8] 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 α-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,[9] 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

Ethanediyl *S,S*-acetals were prepared from the parent ketones according to reported procedures.[10] Anhydrous chloroform was made from reagent grade solvent (Carlo Erba) according to literature procedures.[11] Commercially available bromine (Carlo Erba) was purified and dried immediately before use.[12] Flash chromatography was performed on Merck silica gel 60 (400-230 mesh). ^{1}H Nmr spectra were recorded on a Bruker WH (270 MHz) instrument in $CDCl_3$ solution.

Reaction of 17ß-acetoxy-5α-androstan-3-one ethanediyl *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_2SO_4), 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); ^{1}H and ^{13}C nmr: see Table 1; m/z = 402 (M^+). *Anal.* Calcd. for $C_{23}H_{30}O_2S_2$: 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); ^{1}H and ^{13}C nmr: see Table 1; m/z = 481 (M^+). *Anal.* Calcd for $C_{23}H_{29}O_2BrS_2$: C, 57.37; H, 6.07. Found: C, 57.42; H, 6.12.

Under the same conditions, 5α-cholestan-3-one ethanediyl *S,S*-acetal (**1b**) afforded the sole compound (**2b**) (80% yield),[13] mp 62-63° C (from *n*-hexane); ^{1}H and ^{13}C nmr: see Table 1; m/z = 456 (M^+). *Anal.* Calcd for $C_{29}H_{44}S_2$: C, 76.25; H, 9.71. Found: C, 76.30; H, 9.76.

Preparation of **3**. The reaction of 17ß-acetoxy-5α-androstan-3-one ethanediyl *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_3SiH (1.4 g; 12.0 mmol), in anhydrous *n*-hexane (10 ml) cooled in an ice bath, solid anhydrous $AlCl_3$ (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_2CO_3 was then added to quench the reaction mixture, and the organic layer was washed with water (3 x 10 ml) until neutral, dried (Na_2SO_4), 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); ^{1}H nmr: δ 4.70 (1H, *dd*, J = 7.7, 1.2 Hz, CHOAc), 3.30-3.15 (4H, *m*, SCH_2CH_2 S), 2.04 (3H, *s*, CH_3COO); m/z = 406 (M^+). *Anal.* Calcd for $C_{23}H_{34}O_2S_2$: 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**.

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