

SPIRAN ISOLATION IN THE DIENONE-PHENOL REARRANGEMENT  
OF STEROIDAL p-QUINOLS

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**Abstract:** The neutral form of the spirocation intermediate in the dienone-phenol rearrangement of a steroidal p-quinol has been isolated, providing a direct prove of the accepted mechanism. Changing acidic conditions, phenolic products were obtained.

Although the dienone-phenol rearrangement of steroidal dienones has been exhaustively studied for its potential application to the synthesis of estrogenic steroids<sup>1</sup>, few work has been done with steroidal p-quinols such as 1<sup>2</sup>. These compounds join to a dienone structure an hydroxyl group in a position (C-10) directly involved in this acid-catalyzed rearrangement.

We wish to communicate the isolation of a spiran in the acid-catalyzed rearrangement of the p-quinol 1 (10 $\beta$ -hydroxy-1,4-estradien-3,17-dione). To our knowledge, no spiran has ever been isolated in the dienone-phenol rearrangement of steroidal dienones. The result here reported provides a direct prove of the commonly accepted mechanism<sup>1</sup> by means of isolation of the postulated spirocationic intermediate as its neutral form.

The p-quinol 1<sup>3</sup> was treated with p-toluenesulfonic acid in acetone under reflux in a nitrogen atmosphere. The reaction was monitored by t.l.c. and showed no further evolution after 17 h. After titration with solid bicarbonate and usual work up followed by SiO<sub>2</sub> gel column chromatography, the spiroendione 2 (72%) and the acetone addition product 3 (28%) were isolated. Both reaction products 2 and 3 are unknown and their structures were established by spectroscopic analysis<sup>4</sup>. The result can be rationalized by the following formal mechanism (fig. 2):

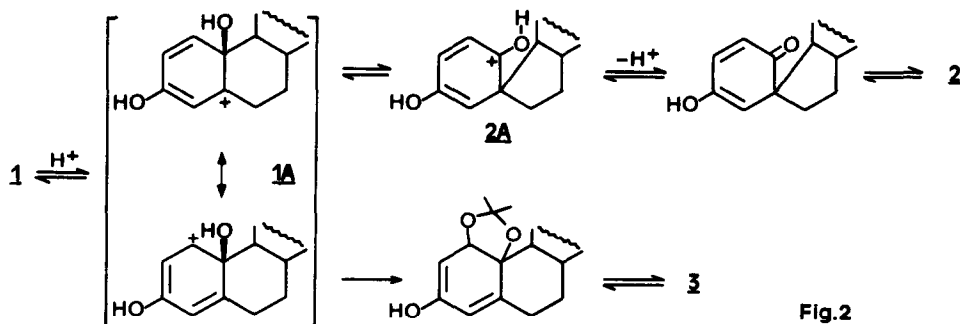
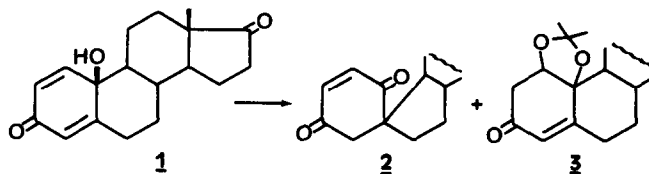
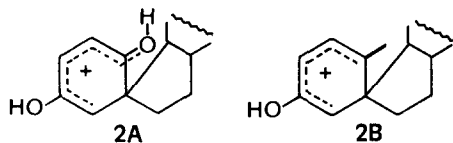


Fig.2

Assuming the generally accepted reaction pathways for the dienone-phenol rearrangement (DPR)<sup>1</sup>, a first 1,2-shift of the C9-C10 bond on the protonated dienone (1A) will lead to the spirocation 2A. At this stage, the second 1,2-shift (which would lead to a phenolic product) doesn't take place, and the neutral form of the cation 2A (2) is isolated. The absence of this second migration can be explained comparing the spirocation 2A here formed with the equivalent spirocation 2B, which is usually postulated as an intermediate in the DPR when



the angular substituent is an alkyl group. The first 1,2-shift to the spirocation 2B converts a dienone into a carbocation. 2B can not be stabilized, and a second 1,2-shift of the C9-C5 bond towards C4 is forced, affording the DPR products. However, the spirocation 2A is a protonated endione and its neutral form can be isolated by loss of a proton.

This mechanism assumes that the acidic conditions used are able to protonate the dienone but not the C10 hydroxyl group (in accordance with the corresponding tabulated pK<sub>a</sub><sup>5</sup>).

In order to confirm the mechanistic hypothesis and support the assumption that 2 arises from a "trapping" of the spiranic intermediate in the DPR, two kind of experiments were planned: the use of stronger acids with special emphasis in those that are typical reagents for the dienone-phenol rearrangement<sup>6</sup>, and the testing of the further evolution of the spiroendione 2 in acid media. Results are summarized in table 1.

In a first set of experiments, the p-quinol 1 was treated in the classical DPR acidic conditions (entries 2, 3 and 4) which combines stronger acidity than p-TsOH and acylating conditions. Aromatization of ring A is observed in all the cases with the isolation of the "meta" type or "para" type diphenols or their acetyl derivatives (4, 5 and 6). When a strong and dehydrating acid as H<sub>2</sub>SO<sub>4</sub> 97% was used (entry 5), 9(11)-dehydroestrone (7) was obtained, arising from a loss of water and further rearrangement to the styrenic system.

On the other hand, the formation of 2 is reversible. Addition of water before titration in the work up of the reaction with p-TsOH shows that 2 goes partially back to 1. Furthermore, treatment of 2 with HClO<sub>4</sub> in THF yields 1 again (entry 6, table 1).

The behaviour of 1 in those different acidic conditions and the fact of reversibility in the conversion 1 ⇌ 2, are in agreement with the previous proposed mechanism for the p-quinol-spiroendione rearrangement (fig. 3). Classifying the acid media in three types (A, B and C), we can conclude:

- if the tertiary hydroxyl group is protonated (type A) dehydration and aromatization occurs
- if the acid media is not strong enough to protonate the hydroxyl group in C10 (type B), the spirocation formed after the first migration corresponds to a protonated endione, and its neutral form can be isolated as the spiroendione 2 (according to fig 2)
- if the conditions are also acylating (type C), a dienone-phenol rearrangement, probably via the 10-acyloxy derivative, takes place. The acetoxy substituent in C10 would avoid the possibility to stabilize the carbocation formed after the first migration forcing a second 1,2-shift to a phenolic product.

TABLE 1

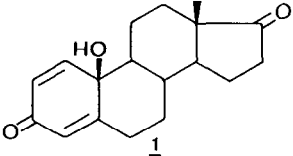
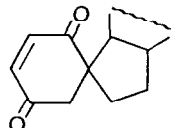
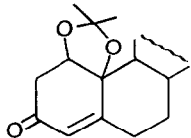
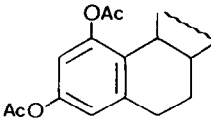
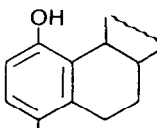
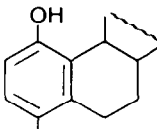
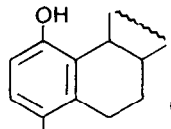
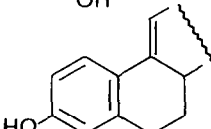
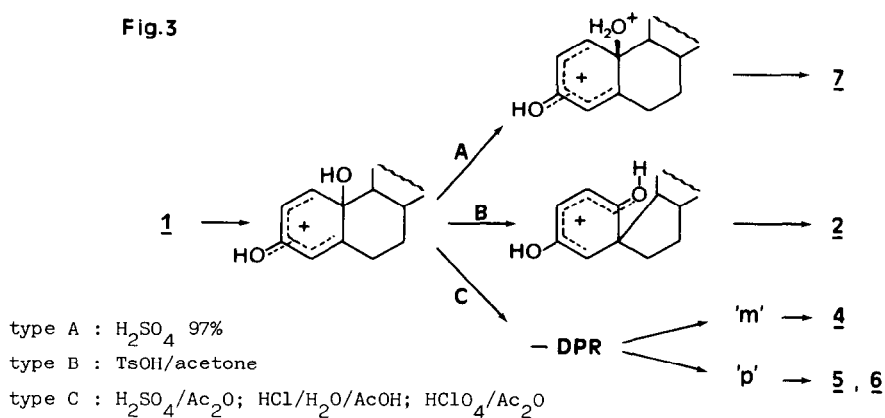
ENTRY	SUBSTRATE	ACIDIC CONDITIONS	REACTION PRODUCTS (% yield)
1		TsOH acetone	 <u>2</u> (42)  <u>3</u> (14)
2	<u>1</u>	H <sub>2</sub> SO <sub>4</sub> Ac <sub>2</sub> O	 <u>4</u> (23)
3	<u>1</u>	HCl H <sub>2</sub> O AcOH	 <u>5</u> (17)
4	<u>1</u>	HClO <sub>4</sub> Ac <sub>2</sub> O	 <u>5</u> (14)  <u>6</u> (23)
5	<u>1</u>	H <sub>2</sub> SO <sub>4</sub> 97%	 <u>7</u> (26)
6	<u>2</u>	HClO <sub>4</sub> THF	<u>1</u> (20)

Fig.3



Conclusion: The p-quinol 1 undergoes the dienone-phenol rearrangement leading to the expected "meta" type or "para" type diphenols or derivatives. On treatment with a weaker acid in a non-acylating conditions a spiroendione (2) is obtained. Mechanistically this compound represents, to our knowledge, the first isolation of the neutral form of the postulated spirocation intermediate in the dienone-phenol rearrangement of steroidal compounds<sup>7</sup>.

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#### REFERENCES AND NOTES

1. C. Djerassi, "Steroid Reactions", Holden-Day Inc, 373 (1963)  
H. Kokociuska, R. Zalewski, Comm.Czech.Pol.Colloq.Chem.Phys.Org.Chem. 2nd, 200 (1980).
2. A.M. Gold, E. Schwenk, J.Am.Chem.Soc. 80, 5683 (1958).
3. The p-quinol 1 was obtained by dye-sensitized photooxygenation of estrone: P. Lupón, J. Gómez, J.-J. Bonet, Angew.Chem. 95, 757 (1983).
4. All new compounds isolated gave satisfactory spectral (<sup>1</sup>H-NMR, <sup>13</sup>C-NMR, IR, MS, UV) and analytical data. Selected data for 2 (9(10 → 5)abeo-1-estren-3,10-17-trione):  
<sup>1</sup>H-NMR (200MHz, CDCl<sub>3</sub>) δ: 0.81 (3H, s, 18-CH<sub>3</sub>); 2.79(1H, dxd, J 16, 0.8Hz, 4-CHeq); 3.06(1H, d, J 16Hz, 4-CHax); 6.70(1H, d, J 11Hz, 1-CH); 6.74(1H, dxd, J 11, 0.8Hz, 2-CH)  
<sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ: 13.98/q 18-C; 40.7/d 9-C; 48.5/s 13-C; 50.8/t 4-C; 51.1/d 8-C; 56.3/s 5-C; 59.2/d 14-C; 140.6/d + 141.2/d 2-C + 1-C; 198.2/s + 202.2/s 3-C + 10-C; 219.6/s 17-C; 22.3/t; 23.7/t; 27.3/t; 31.6/t; 35.0/t; 35.6/t.  
Absolute configuration of C-5 can not be established from this spectral information. A 5S configuration is suggested according to the proposed mechanism. X-Ray diffraction analysis is in progress.  
Selected data for 3:  
IR( $\bar{\nu}$ , cm<sup>-1</sup>): 1745, 1675, 1630, 1380, 1370  
<sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.95(3H, s, 18-CH<sub>3</sub>); 1.30(3H, s) + 1.35(3H, s) (CH<sub>3</sub>)<sub>2</sub>C; 2.62(2H, m, 2-CH<sub>2</sub>); 4.50(1H, b, 1-CH); 5.70(1H, d, J 2Hz, 4-CH)
5. R.F. Childs, Rev.Chem.Intermediates 3, 285 (1980) and references therein.
6. Dienone-phenol rearrangement of steroidal p-quinols are poorly documented in the literature; see ref. 1. We considered necessary to prove if 1 actually undergoes this rearrangement.
7. It has been published recently another isolation of a spiran from an acid-catalyzed rearrangement of a bromo-enone steroid: T. Koga, Y. Nogami, Tetrahedron Lett. 27(37), 4505 (1986).

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