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Cyclic Ketals of 4-Androstene-3,17-dione

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A careful examination of the reaction of 4-androstene-3,17-dione with one mole of ethylene glycol in the presence of *p*-toluenesulfonic acid has revealed that the nature of the dioxolanes formed is dependent on the catalyst–steroid ratio. The preparation of the 17-dioxolane of 4-androstene-3,17-dione is described. By applying the principles elucidated in the study of the formation of dioxolanes, the 3-oxathiolane of 4-androstene-3,17-dione has been prepared. Calculations involving the molecular rotations of the various dioxolanes confirm the previously assigned structures for 5-androstene-3,17-dione-3-dioxolane and for 5-androstene-3,17-dione-bisdioxolane. The position of the double bond in various oxathiolanes is discussed.

Two of the three possible dioxolane derivatives of 4-androstene-3,17-dione, obtained by the action of ethylene glycol in the presence of *p*-toluenesulfonic acid, are 5-androstene-3,17-dione-3-dioxolane (II), m.p. 194° and 202°, and 5-androstene-3,17-dione-3,17-bisdioxolane (III), m.p. 173°.[1] The bisdioxolane is the sole product when more than two moles of ethylene glycol are employed. On the other hand, it has been reported that when approximately one mole of ethylene glycol is used under similar conditions a separable mixture of 3-dioxolane and bisdioxolane results,[1c] with the former predominating.

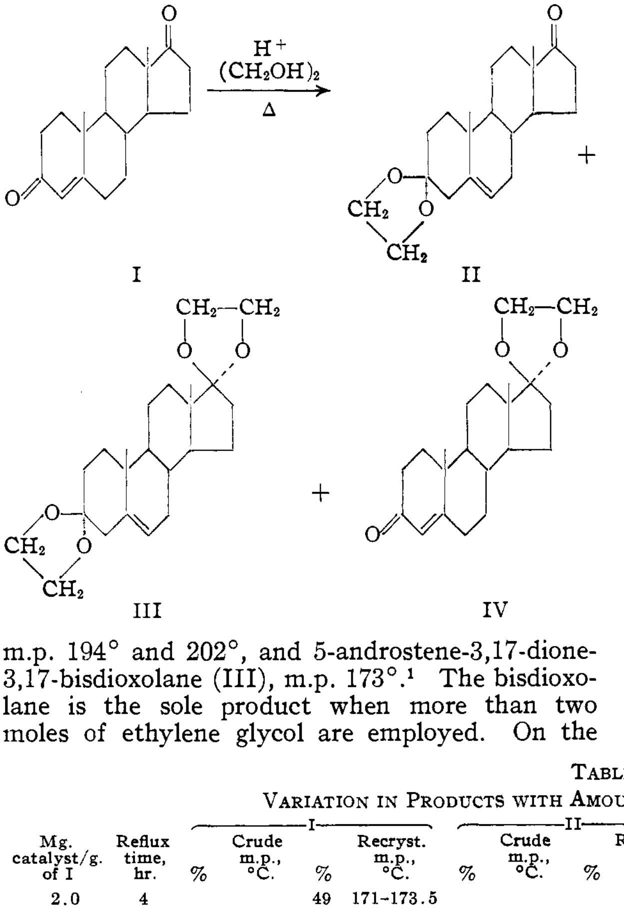

TABLE I

VARIATION IN PRODUCTS WITH AMOUNT OF *p*-TOLUENESULFONIC ACID[a]

Mg. catalyst/g. of I	Reflux time, hr.	I %	I Crude m.p., °C.	I %	I Recryst. m.p., °C.	II %	II Crude m.p., °C.	II %	II Recryst. m.p., °C.	III %	III Crude m.p., °C.	III %	III Recryst. m.p., °C.	IV %	IV Crude m.p., °C.	IV %	IV Recryst. m.p., °C.
2.0	4			49	171–173.5												
2.0[b]	4			62	161–166			4	190–195								
10.0	4	21	150–165	8	159–168			50	185–192			8	165–169.5				
20.0	4	27		18	160–165	21	170–185	8	185–192	30	160–167	19	166–169	10	136–144	6	145–147
25.0	4	15				17	170–191	9	188–192	22	155–172	15	171–172.5	30	130–138	18	142–145
100	1	6	158–166							11	145–165	8	160–165	43	130–141	27	144–147
100	4									10		7	168–171	46	120–143	23	135–140
115	1/2	21	150–166											29	130–145	18	146–148
100[c]	4	28	145–162	17	155–160							9	167–171	45	130–140	25	144–147

[a] The actual yield of product in each instance probably lies between the crude and the purified yields since the recoveries upon crystallization were often poor. [b] Chromatographed on three times as much Florisil as the other experiments. [c] This reaction was run at ten times the usual dilution resulting in improved recoveries of all the products.

From an experiment performed substantially as described by Koster and Inhoffen, and by Fernholz, using one mole of ethylene glycol, we have now isolated 4-androstene-3,17-dione-17-dioxolane (IV), m.p. 146–148°. Subsequent careful examination of the reaction conditions revealed that the amount of *p*-toluenesulfonic acid used is critical within narrow limits in determining the nature of the products. The results observed upon varying the amount of catalyst, followed by chromatographic separation of the products, are summarized in Table I.

These experiments show that the 3-dioxolane II is the important product at low catalyst–steroid ratios while at higher catalyst–steroid ratios the 17-dioxolane IV is formed. While the mechanism of ketal formation is well understood[2] it is not readily apparent why the observed shift in the site of reaction should occur. A consistent interpretation may be constructed based on several arbitrary assumptions. If it is assumed that the 3-keto-Δ^4-system captures almost all of the protons from the catalyst at low catalyst–steroid ratios, then reaction must occur almost exclusively at the 3-position. At higher catalyst–steroid ratios, it might be presumed that both the 3- and 17-carbonyl groups capture significant numbers of protons. If it is then assumed that the rate of reaction is considerably more rapid at 17- than at 3-, it follows that the 17-dioxolane is isolated in preponderant amount. From the data, it appears that at cata

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(1) (a) H. Koster and H. H. Inhoffen, U. S. Patent 2,302,636; (b) E. Fernholz, U. S. Patent 2,356,154; (c) E. Fernholz, U. S. Patent 2,378,918.

(2) W. A. Waters, "Physical Aspects of Organic Chemistry," Fourth Edition, D. Van Nostrand Co., Inc., New York, N. Y., 1950, p. 336.

TABLE II

MOLECULAR ROTATIONS OF DIOXOLANES

Compound or group	M_D (Dioxane)	M_D ($CHCl_3$)	ΔM_D ($CHCl_3$)
Androstane-3,17-dione-3-dioxolane		+270	
4-Unsaturation			+159
5-Unsaturation			−298
4-Androstene-3,17-dione-3-dioxolane		+429 (theory)	
5-Androstene-3,17-dione-3-dioxolane		−28 (theory)	
Androstene-3,17-dione-3-dioxolane (II)		−67 (obsd.)	
Androstane-3,17-dione-bisdioxolane		−38	
4-Androstene-3,17-dione-bisdioxolane		+121 (theory)	
5-Androstene-3,17-dione-bisdioxolane		−336 (theory)	
Androstene-3,17-dione-bisdioxolane (III)		−254 (obsd.)	
Androstane-3,17-dione-bisoxathiolane		−163	
4-Androstene-3,17-dione-bisoxathiolane		−4 (theory)	
5-Androstene-3,17-dione-bisoxathiolane		−461 (theory)	
Androstene-3,17-dione-bisoxathiolane[3]		−244 (obsd.)	
4-Androstene-3,17-dione	+497		
4-Androstene-3,17-dione-17-oxathiolane[3]	+159		
17-Oxathiolane group (replacing carbonyl)	−338		
4-Androstene-3,17-dione-3-oxathiolane	+935 (obsd.)		
4-Androstene-3,17-dione-bisoxathiolane	+597 (theory)		
Androstene-3,17-dione-bisoxathiolane	*ca.* −244 (obsd.)		

lyst–steroid ratios of about 20–25 mg. per g. a transition period is reached and the two positions compete for the one mole of ethylene glycol on about equal terms.

The previous investigators[1] invariably described the use of "a crystal" or "several crystals" of *p*-toluenesulfonic acid, rather than any weighed amount. Apparently these designations correspond approximately to 10 mg., which may explain why IV was never observed as a reaction product. It is also of interest that the catalyst is consumed during the reaction at low catalyst–steroid ratios (*e.g.*, 10 mg./g.), the reaction testing almost neutral at the end of the reflux period.

Reaction at the 17-carbonyl group of 4-androstene-3,17-dione in preference to the 3-carbonyl has been observed before in the preparation of the corresponding oxathiolanes employing hemithioethylene glycol.[3] When Romo, *et al.*, employd *p*-toluenesulfonic acid as the catalyst in amounts exceeding our largest catalyst–steroid ratio, only the 17-oxathiolane and the bisoxathiolane were isolated. By employing the principle elucidated in the experiments described in this paper, that lower catalyst–steroid ratios favor reaction at 3-, we have now prepared the 3-oxathiolane of 4-androstene-3,17-dione.

Fernholz and Stavely[4] showed that migration of the double bond from 4- to 5- occurs during dioxolane formation with 3-keto-Δ^4-systems. No such conclusion has been reached with respect to the corresponding oxathiolane formation.[5] We have attempted to establish the course of oxathiolane and dioxolane formation at the 3-keto-Δ^4-system by the application of Barton's method of molecular rotation differences.[6] For our purpose it was necessary to prepare androstane-3,17-dione-3-dioxolane, the corresponding bisdioxolane and the corresponding bisoxathiolane. The molecular rotations of these and the androstene derivatives are given in Table II.

It is apparent that the experimental molecular rotations for II and III are in reasonable agreement with the values predicted for the 5-androstene derivatives. No definite conclusion can be drawn with respect to the location of the double bond in the bisoxathiolane of 4-androstene-3,17-dione on the basis of the calculation used to assign the configuration of the dioxolanes. The confusion may result from an interaction of unknown magnitude between the unsaturation and the asymmetric center at 3- (not present in the dioxolanes), or from a variation in the stereoisomer ratio at 3-, introduced during the formation of the oxathiolane, depending on the presence or absence of 4-unsaturation in the starting material. On the other hand, the high positive molecular rotation observed with the 3-oxathiolane of 4-androstene-3,17-dione makes it appear probable that the double bond is at 4- in this compound.[5] The difference in the methods of preparation of the two oxathiolanes may explain the striking difference in molecular rotation. Romo and co-workers[3] prepared the bisoxathiolane using twenty times as much *p*-toluenesulfonic acid as was employed by us in the preparation of the 3-oxathiolane. As in the case of the dioxolanes, we have observed that the catalyst was consumed during the reaction which might account for the failure of the double bond to migrate. It is likely that the reaction mixture used by the previous investigators[3] was strongly acid throughout the reflux period, thus catalyzing the shift of the double bond. In this connection it should be noted that

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(3) J. Romo, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 4961 (1951); G. Rosenkranz, St. Kaufmann and J. Romo, *ibid.*, **71**, 3689 (1949).

(4) E. Fernholz and H. Stavely, Abstracts of the 102nd Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 8–12, 1941, p. M39.

(5) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(6) For a survey of this work see L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Third Edition, Reinhold Publ. Corp., New York, N. Y., 1949, pp. 204–219.

Hauptmann,[7] in his preparation of a dithiolane of 4-cholestene-3-one, employed mild acid catalysis (anhydrous zinc chloride at room temperature) and obtained the product in which the double bond remained at 4-.

A calculated value for the molecular rotation of the bisoxathiolane[3] has been assembled assuming that the double bond in the 3-oxathiolane is at 4-. The observed value (−244) differs from the calculated value (+597) by 841 units in the direction of the contribution of the 5-double bond.

Experimental[8]

Dioxolanes of 4-Androstene-3,17-dione (II, III, IV).—To a mixture of 1.0 g. of 4-androstene-3,17-dione (I), 50 ml. of anhydrous C.P. benzene and 0.23 ml. of ethylene glycol was added the appropriate amount of *p*-toluenesulfonic acid. The reactants were brought to reflux quickly and the water which formed was removed by slow azeotropic distillation. After 4 hours of refluxing, the resulting solution was cooled, made alkaline with alcoholic sodium hydroxide and washed with water until neutral. After drying over magnesium sulfate, the solution was evaporated to dryness. The amorphous residue was dissolved in heptane and evaporated to dryness twice, in order to ensure complete removal of the benzene which interfered with the subsequent chromatogram. The residue was finally taken up in 150 ml. of heptane and placed on a column of 15 g. of Florisil (100–200 mesh, activated by heating at 140° for 16 hours) which had been previously prepared with heptane. Careful elution, during which a single solvent combination was used until no further steroidal eluate resulted before changing to another combination, gave the products in the order

Hexane	bisdioxolane (III)
Hexane–1% ether	3-dioxolane (II)
Hexane–2 to 5% ether	17-dioxolane (IV)
Hexane–10 to 100% ether	4-androstene-3,17-dione (I)
Ether–1% methanol	

Recrystallization of I, II and III was from methanol, and IV was from heptane. An analytical sample of IV melted at 146.2–148°, $[\alpha]^{25}\mathrm{D}$ +58.7° (1% in dioxane), ϵ_{241} 16.4 × 10^3 (ethanol).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.48; H, 9.34.

The identity of III was established by its melting point and the absence of carbonyl bonds in its infrared spectrum. The identity of II was established by its melting point, by the absence of any significant absorption in the ultraviolet around 240 mμ and by the presence of a strong bond in the infrared spectrum at 5.75 μ, characteristic of a carbonyl group contained in a five-membered ring. The identity of I was established by the absence of depression of melting point on admixture with starting material.

3-Oxathiolane of 4-Androstene-3,17-dione.—A mixture of 10 g. of I, 500 ml. of anhydrous C.P. benzene, 0.10 g. of *p*-toluenesulfonic acid and 2.89 ml. of hemithioethylene glycol was refluxed for four hours with slow azeotropic distillation and then processed as described in the preceding experiment. Elution of the chromatogram with hexane (300 ml. per fraction) gave four crystalline fractions: 0.37 g., m.p. 145–155°; 1.16 g., m.p. 150–155°; 0.44 g., m.p. 145–154°; 0.65 g., m.p. 151–160°. Recrystallization of the 1.16-g. fraction from ether–hexane afforded only 0.24 g. of 4-androstene-3,17-dione-3-oxathiolane, m.p. 167–170°, $[\alpha]^{25}\mathrm{D}$ +271° (1% in dioxane), showing no absorption around 240 mμ in the ultraviolet, strong band at 5.75 μ in the infrared (17-carbonyl).

Anal. Calcd. for $C_{21}H_{30}O_2S$: C, 72.80; H, 8.73. Found: C, 73.12; H, 8.40.

All other fractions from the chromatogram were oily and no other products were identified.

Dioxolanes of Androstane-3,17-dione.—A mixture of 2 g. of androstane-3,17-dione, 0.42 ml. of ethylene glycol, 0.20 g. of *p*-toluenesulfonic acid and 150 ml. of C.P. benzene was refluxed for one hour with concomitant slow azeotropic distillation. The reaction mixture was treated as described in the preceding experiments and a hexane solution of the product was chromatographed. From the 2% ether–hexane and 5% ether–hexane fractions there was obtained a total of 0.51 g., most of which melted between 148° and 155°. Recrystallization from hexane afforded androstane-3,17-dione-3-dioxolane, m.p. 155–156°, $[\alpha]^{25}\mathrm{D}$ +81.5° (1% in chloroform).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.76; H, 10.12.

All other fractions from the chromatogram were pooled and rechromatographed on 35 g. of activated alumina and 10 g. of Florisil. The product from the first five fractions (175 ml. each) eluted with 10% ether–hexane was crystallized from hexane at Dry Ice temperature yielding 0.10 g. of androstane-3,17-dione-3,17-bisdioxolane, m.p. 157.5–160°. Recrystallization from methanol afforded 0.05 g., m.p. 162–162.5°, $[\alpha]^{25}\mathrm{D}$ −10.3° (1% in chloroform). A mixture with a sample of 3-dioxolane depressed the melting point below 135°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.37; H, 9.69. Found: C, 73.25; H, 9.48.

Additional 3-dioxolane was recovered from the second chromatogram in the 15%–40% ether–hexane fractions. Starting material was recovered from the 60% ether–hexane to 100% ether fractions.

Bisoxathiolane of Androstane-3,17-dione.—A mixture of 1.0 g. of androstane-3,17-dione, 50 ml. of C.P. benzene, 0.100 g. of *p*-toluenesulfonic acid and 3 ml. of hemithioethylene glycol was refluxed for 4 hours with slow azeotropic distillation. Following the usual procedure, the residue was crystallized from ether–hexane without chromatography. There resulted 0.79 g. of androstane-3,17-dione-bisoxathiolane, m.p. 194–198°. Recrystallization from ether–pentane raised the melting point to 203–206°, $[\alpha]^{25}\mathrm{D}$ −40.7° (1% in dioxane).

Anal. Calcd. for $C_{23}H_{36}O_2S_2$: C, 67.62; H, 8.88. Found: C, 67.67; H, 9.05.

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[7] H. Hauptmann, THIS JOURNAL, **69**, 562 (1947).

[8] All melting points are corrected. Analyses and optical data were obtained by the Microanalytical and Physical Chemical Departments of this Laboratory.