absolute ethanol (*c* 0.039): $[\alpha]_{600}$ +54°, $[\alpha]_{400}$ +354°, $[\alpha]_{315}$ + 2695°, $[\alpha]_{275}$ −2269°, $[\alpha]_{260}$ −1710°.

Dipole Moments.—The dipole moment instrument used has been described earlier.[4] The dipole moments were measured in benzene and dioxane solutions and the calculations were carried out essentially by the method of Halverstadt and Kumler[28] utilizing an IBM 650 computer programmed as described earlier.[29] Atomic polarization has been taken into account approximately by setting it equal to 10% of the molar refractivity. The latter was calculated from Tables.[30] The data are summarized in Table III.

TABLE III

DIPOLE MOMENTS

(Benzene solution, 25°C.)

N_2	d_{12}	ϵ_{12}
2β-Fluoroandrostane-3,17-dione—MR 89.36 cc.		
0.00000000	0.873502	2.2752
0.00020643	0.873727	2.2784
0.00043190	0.873941	2.2816
0.00126987	0.874711	2.2941
0.00196165	0.875243	2.3039
$\alpha = 14.653$	$\epsilon_1 = 2.2753$	$d_1 = 0.87354$
$\beta = 0.889$	$P_{2\infty} = 292.5$	$\mu = 3.15 \pm 0.02$ D.
2α-Fluoroandrostane-3,17-dione		
0.00000000	0.873562	2.2760
0.000299878	0.873797	2.2855
0.000407469	0.873870	2.2890
0.000593583	0.874124	2.2947
0.000724309	0.874211	
$\alpha = 31.506$	$\epsilon_1 = 2.2761$	$d_1 = 0.87353$
$\beta = 0.940$	$P_{2\infty} = 538.2$	$\mu = 4.69 \pm 0.10$ D.

Appendix

Calculation of the Resultant Dipole Moment from Any Number of Separate Group Moments.—The individual dipoles are vectors (v_i), the magnitudes of which are the group moments, and the directions of which are given by the coordinates of the atom at the negative end of the dipole minus the coördinates of the atom at the positive end, $(x_i, y_i, z_i) = (\Delta x, \Delta y, \Delta z)$, these being the quantities available from the measurements on the models. The bond length (L_i) of the group dipole is:

$$L_i = (x_i^2 + y_i^2 + z_i^2)^{1/2}$$

and this length is related to the group moment (μ_i) by

$$\mu_i = k_i L_i$$

For each v_i, k_i must be calculated. The projections of v_i on the axes then are:

$$v_i = (k_i x_i, k_i y_i, k_i z_i)$$

The resultant moment is given by

$$\mu = [(\sum_i k_i x_i)^2 + (\sum_i k_i y_i)^2 + (\sum_i k_i z_i)^2]^{1/2}$$

As a check on the accuracy of the measurement of the coördinates of the various atoms, the resultant moment was then recalculated as above, except that instead of calculating L_i from the coördinates it was given the computer as input, since this quantity is known to be just the bond length between the atoms which make up v_i. The value of μ obtained here was then compared with the value obtained by the previous method. A variation of more than about 0.05 D. for each vector (or of more than 0.15 D. in the present cases) between the moments calculated by the two methods indicated that the coördinates had not been measured with sufficient accuracy.

An IBM 650 program was written with the aid of a GATE compiler which took as input five quantities for each vector (x_i, y_i, z_i, L_i, μ_i), carried out the calculation, and gave as output two values of the resultant (μ) calculated as outlined. Taking the various sources of error into account, it is felt that the resultant moments calculated are accurate to 0.1 D. per vector (0.3 D. in the present cases) or better.

Acknowledgment.—The authors are indebted to Dr. P. D. Klimstra of G. D. Searle and Co., Chicago, for furnishing them with samples of the 2-fluoroandrostane-3,17-diones, to C. L. Neumann for measuring some of the dipole moments, and to Dr. Merle Emerson for the proton magnetic resonance spectra and helpful discussion regarding them.

[28] I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, **64**, 2988 (1942).

[29] N. L. Allinger and J. Allinger, *J. Org. Chem.*, **24**, 1613 (1959).

[30] A. I. Vogel, W. T. Cresswell, G. J. Jeffrey, and J. Leicester, *Chem. Ind.* (London), 358 (1950).

An Aromatization Reaction of a Cross-conjugated Dienone System with Zinc. II. Aromatization of Steroidal 1,4-Dien-3-one and 1,4,6-Trien-3-one System with Zinc[1]

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Treatment of androsta-1,4-diene-3,17-dione, androsta-1,4-diene-3,11,17-trione, and androsta-1,4,6-triene-3,17-dione with zinc in pyridine gave rise to the corresponding *p*-cresol type of rearrangement product, a 9,10-seco derivative and 6-dehydroestrone, respectively. When acetic acid was used as a solvent in this reaction, these cross-conjugated dienone or trienone derivatives were converted to the polyenic bissteroids.

In a previous communication,[2] we described a new type of dienone–phenol rearrangement of cross-conjugated dienone or trienone systems, involving aromatization of ring A with concomitant elimination of the C-19 angular methyl group.

In 1953, Barton and Thomas[3] reported the rearrangement of 3β-acetoxylanosta-5,8-dien-7-one with zinc in acetic acid to a phenolic substance, whose structure

[1] This paper constitutes Part XXXVII of a series entitled "Steroid Studies" by K. Tsuda.

[2] K. Tsuda, E. Ohki, S. Nozoe, and N. Ikekawa, *J. Org. Chem.*, **26**, 2614 (1961).

[3] D. H. R. Barton and B. R. Thomas, *J. Chem. Soc.*, 1842 (1953).

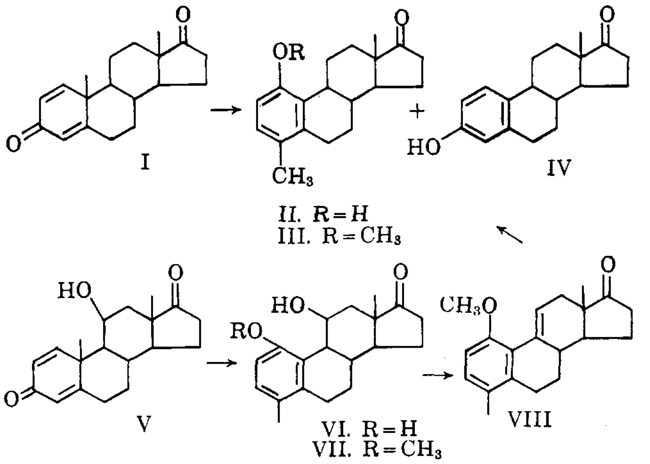
was elucidated by the present authors on the basis of its n.m.r. spectrum, which showed no aromatic methyl group and only aromatic protons.[4] Moreover, the elimination of a methyl group during the reaction was indicated by the evolution of methane which was identified by gas chromatography. From the above results the structure of the phenolic product was shown to be 3β-acetoxy-19-norlanosta-5,7,9-trien-7-ol, which resulted from the aromatization of ring B with elimination of the angular methyl group.

This novel type of aromatization reaction, involving the fission of a C—C bond, has prompted further studies with steroidal A-ring cross-conjugated dienone or trienone systems in order to synthesize estrogen type compounds.

Treatment of 1-dehydrotestosterone acetate with zinc in boiling acetic acid afforded a neutral compound,[5] m.p. 233–236°, which exhibited ultraviolet absorption maxima[6] at a longer wave length region 326, 340, and 357 mμ; ε 40,000, 66,000, and 69,000. This compound, however, did not show characteristic aromatic absorption bands in the infrared spectrum. On the other hand, the molecular weight determination and elemental analysis showed that the composition corresponded to $C_{42}H_{54}O_4$. Similar treatment of androsta-1,4,6-triene-3,17-dione also gave a corresponding dimeric substance containing the polyene chromophore, $\lambda_{\max}^{\mathrm{MeOH}}$ 363, 380, and 404 mμ, ε 40,000, 69,000, and 73,000, which decomposed at 260° with evolution of methane.

Treatment of androsta-1,4-diene-3,17-dione (I) with zinc in pyridine or ethylene glycol instead of acetic acid as a solvent gave a product exhibiting the characteristic absorption maximum of a phenolic chromophore at around 285 mμ. Purification of the crude product gave 80% of 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (II)[7] and 4% of estrone (IV). The identity of the products was proved by direct comparison with authentic specimens.

Reaction of a 1,4-dienone having an 11β-hydroxyl function[8] with zinc in pyridine afforded an alkali-soluble phenol, m.p. 222–223° (VI). To prove the structure of this product, its methyl ether (VII) was dehydrated with methanesulfonyl chloride in dimethylformamide to give the 9-dehydrophenol (VIII) which on hydrogenation with palladium on charcoal furnished the known compound (III).



I

II. R=H
III. R=CH₃

IV

V

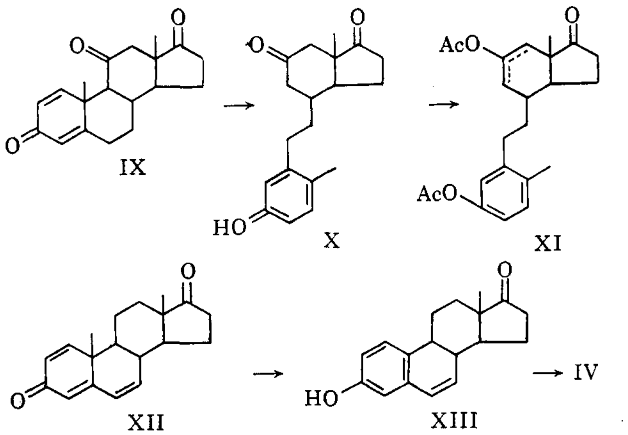
VI. R=H
VII. R=CH₃

VIII

Androsta-1,4-diene-3,11,17-trione (IX) was rearranged by zinc in pyridine to form a phenolic compound, m.p. 212–214°, which exhibited a characteristic ultraviolet absorption maximum at 280 mμ. The infrared spectrum showed the presence of two adjacent hydrogen atoms on the aromatic ring and by elemental analysis the composition was shown to be $C_{19}H_{24}O_3$. On the assumption that the C-10 methyl group was still attached to the A-ring, only a 9,10-seco structure was favorable. Refluxing this phenol (X) with acetic anhydride in the presence of potassium acetate, afforded a diacetate (XI) which did not contain a six-membered ring ketone; therefore, it is more likely that the 11-keto group was acetylated in the enol form. Since the double bond of the enol acetate is not conjugated with the aromatic ring as determined by the ultraviolet spectrum, it was assumed that 9-10 bond fission had occurred during the aromatization. Hogg, *et al.*,[9] by the pyrolytic cleavage of IX have prepared 3-hydroxy-9,10-seco-androsta-1,3,5(10)-triene-11,17-dione (X), whose physical properties agreed in all respects with our phenol. The identity of these phenols was proved by mixed melting point and by infrared spectra comparison with a sample prepared by Hogg's method.

The 1,4,6-trien-3-one system, which gives a *meta*-cresol type of rearrangement product under acid-catalyzed reaction conditions,[10] was next studied. Treatment of androsta-1,4,6-triene-3,17-dione (XII) with zinc in pyridine or ethylene glycol afforded 15–20% of an alkali soluble phenol (XIII) containing an additional conjugated double bond, whose structure was proved by the hydrogenation to natural estrone.[11] Since the presence of the double bond at the C-6 position gave rise to XIII, it is apparent that the double bond causes the reaction of angular C-methyl elimination.

The details of this aromatization reaction and discussion of the mechanism will be reported in the later paper.



IX

X

XI

XII

XIII

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[4] K. Tsuda, E. Ohki, J. Suzuki, and H. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **9**, 131 (1961).

[5] Petrow, *et al.*, also obtained a similar polyenic bis compound by zinc and sodium acetate in acetic acid from cholesta-1,4-dien-3-one [D. N. Kirk, D. K. Patel, and V. Petrow, *J. Chem. Soc.*, 1046 (1957)].

[6] From the ultraviolet data, the structure of this polyenic bis compound seemed to be similar to the compound which was also obtained by P. Bladon, and J. Redpath, *ibid.*, 2352 (1962).

[7] R. B. Woodward and T. Singh, *J. Am. Chem. Soc.*, **72**, 494 (1950); A. S. Dreiding and A. Voltman, *ibid.*, **76**, 537 (1954).

[8] B. J. Magerlein and J. A. Hogg, *ibid.*, **79**, 1508 (1957).

[9] B. J. Magerlein and J. A. Hogg, *Tetrahedron*, **2**, 80 (1958).

[10] C. Djerassi, C. Rosenkranz, J. Romo, J. Pataki, and St. Kaufman, *J. Am. Chem. Soc.*, **72**, 4540 (1950).

[11] St. Kaufman, J. Pataki, G. Rosenkranz, J. Romo, and C. Djerassi, *ibid.*, **72**, 4531 (1950).

Experimental[12]

Dimeric Polyene Compound from 17β-Acetoxyandrosta-1,4-dien-3-one.—To a solution of 500 mg. of 17β-acetoxyandrosta-1,4-dien-3-one in 20 ml. of acetic acid was added 10 g. of zinc dust.[13] The mixture was heated under reflux with stirring for 1 hr. After cooling the zinc was removed by filtration and the filtrate was poured into water. Filtration of the resulting precipitate and crystallization from methylene chloride–ether afforded 460 mg. of the dimeric polyene compound as needles, m.p. 233–236°; mol. wt., 560; λ_{max} 326 mμ (ε 40,000), 340 mμ (ε 66,000), 357 mμ (ε 69,000).

Anal. Calcd. for $C_{42}H_{56}O_4$: C, 80.73; H, 9.03 (for $C_{42}H_{54}O_4$: C, 80.99; H, 8.74). Found: C, 80.56; H, 8.99.

Dimeric Polyene Compound from Androsta-1,4,6-triene-3,17-dione.—The reaction was carried out as above using androsta-1,4,6-triene-3,17-dione and led to the polyene compound, m.p. 260° (dec. with evolution of methane); λ_{max} 363 mμ (ε 40,000), 380 mμ (ε 69,000), 402 mμ (ε 72,500).

Anal. Calcd. for $C_{38}H_{44}O_2.H_2O$: C, 82.87; H, 8.42. (for $C_{38}H_{42}O_2 \cdot H_2O$: C, 83.17; H, 8.08). Found: C, 83.23; H, 8.20.

Aromatization of Androsta-1,4-diene-3,17-dione (I) with Zinc.—To a solution of 800 mg. of androsta-1,4-diene-3,17-dione in 30 ml. of pyridine was added 15 g. of zinc dust. The mixture was heated under reflux for 2.5 hr. After cooling the zinc dust was removed by filtration and the filtrate was diluted with 200 ml. of water. The product was extracted with ethyl acetate. The extract was washed with 1% hydrochloric acid, 1% sodium bicarbonate, and water successively and dried. Evaporation of the solvent and crystallization from methanol afforded 500 mg. of 1-hydroxy-4-methyl-estra-1,3,5(10)-trien-17-one (II) as long needles, m.p. 251–253°, undepressed on admixture with an authentic sample. The infrared spectrum of this compound was identical with that of a known sample. All filtrates were combined and dissolved in ether. The ether solution was extracted with 5% potassium hydroxide solution. Acidification of the alkaline medium with dilute hydrochloric acid, extraction with ether, and evaporation afforded 30 mg. of estrone, m.p. 255–257°, undepressed on admixture with the natural hormone.

1,11β-Dihydroxy-4-methylestra-1,3,5(10)-trien-17-one (VI).—To a solution of 1 g. of 11β-hydroxyandrosta-1,4-diene-3,17-dione (V) in 40 ml. of pyridine was added 15 g. of zinc dust. The mixture was heated under reflux for 2 hr. After the usual work-up, concentration of the ether extract yielded 780 mg. of the crude product. Recrystallization from acetone gave an analytically pure sample of VI, m.p. 222–223°; $[\alpha]_D$ +249° (c 1.05); λ_{max} 282–286 mμ (ε 2340).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.87; H, 8.02.

1-Methoxy-4-methyl-11β-hydroxyestra-1,3,5(10)-trien-17-one (VII).—To a solution of 100 mg. of VI in 10 ml. of ethanol and 1.2 ml. of water containing 1 g. of potassium hydroxide solution was added a total of 1.5 ml. of dimethyl sulfate. When the reaction was completed, water was added to the reaction mixture. After standing for several hours the precipitated crystals were filtered. Recrystallization from acetone afforded 89 mg. of the methyl ether of VI, m.p. 213–214°; $[\alpha]_D$ +303° (c 1.4); λ_{max} 278 mμ (ε 2060), 285 mμ (ε 2130).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.63; H, 8.32.

1-Methoxy-4-methylestra-1,3,5(10),9(11)-tetraen-17-one (VIII).—To a solution of 70 mg. of VII in 2 ml. of dimethylformamide and 1.2 ml. of pyridine was added 0.2 ml. of methanesulfonyl chloride. After warming for 2 hr. at 80°, the dark reaction mixture was poured into cold dilute sodium bicarbonate solution and extracted with ether. The ether extract was washed with water and dried. The residue after concentration of the ether was crystallized from methanol to afford 58 mg. of VIII. Recrystallization from methanol afforded pure material of m.p. 120–121°; $[\alpha]_D$ +286° (c 1.36); λ_{max} 257 mμ (ε 13,540), 296 mμ (ε 3320).

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.26; H, 8.12.

Hydrogenation of VIII.—A solution of 296 mg. of VIII in 30 ml. of ethanol was shaken with 30 mg. of 5% palladium on charcoal for 1 hr. under hydrogen. Filtration, evaporation, and recrystallization from methanol gave 250 mg. of 1-methoxy-4-methylestra-1,3,5(10)-trien-17-one (III) as needles, m.p. 118–119°, undepressed on admixture with an authentic sample prepared by methylation of 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one. The infrared spectra of these compounds were identical.

3-Hydroxy-9,10-secoandrosta-1,3,5(10)-triene-11,17-dione (X).—The aromatization of androsta-1,4-diene-3,11,17-trione (IX) with zinc in pyridine was carried out as described for the corresponding 11β-hydroxy derivative and yielded 70% of 3-hydroxy-9,10-secoandrosta-1,3,5(10)-triene-11,17-dione (X) m.p. 212–214°; λ_{max} 280 mμ (ε 2360) (lit.,[10] 212–214°). No depression of the melting point was observed on mixing with the sample prepared by Hogg's method and the infrared spectra proved to be identical. Acetate: m.p. 118.5–119.5°; λ_{max} 266 mμ (ε 670), 273 mμ (ε 670).

Anal. Calcd. for $C_{24}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.73; H, 7.59.

Acetylation of X with Acetic Anhydride and Potassium Acetate.—A solution of 100 mg. of the seco compound (X) in 5 ml. of acetic anhydride containing 200 mg. of freshly fused potassium acetate was heated under reflux for 1 hr. After cooling the reaction mixture was poured into 30 ml. of ice–water containing 1 ml. of pyridine. Extraction with ether, evaporation, and trituration of the residue with methanol afforded diacetate (XI), m.p. 102–108°, as needles. Recrystallization from methanol raised the melting point to 108–109°; $[\alpha]_D$ +67° (c 1.3); λ_{max} 266 mμ (ε 654), 273 mμ (ε 650).

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 72.03; H, 7.30.

3-Hydroxyestra-1,3,5(10),6-tetraen-17-one (XIII).—To a solution of 900 mg. of androsta-1,4,6-triene-3,17-dione in 30 ml. of pyridine was added 20 g. of zinc dust. The mixture was heated under reflux for 2 hr. After the usual work-up, including the extraction with 5% potassium hydroxide solution, recrystallization from methanol yielded 136 mg. of 6-dehydroestrone (XIII), m.p. 258–260° (lit.,[11] 261–263°); λ_{max} 262 mμ (ε 8800), 304 mμ (ε 2700).

The structure of XIII was confirmed by hydrogenation to estrone, which was identical in all respects with the natural hormone. When ethylene glycol was used as a solvent instead of pyridine in the above experiment, almost identical results were obtained.

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[12] All melting points are uncorrected and all rotations were measured in chloroform solution. Methanol was used for the ultraviolet spectra.

[13] The zinc was activated by several washings with 5% hydrochloric acid, thorough washing with water, methanol, and ether, and dried *in vacuo*.