An Aromatization Reaction of a Cross-conjugated Dienone System with Zinc. III.[1] A Novel Synthetic Method for Estrone and A-Ring Aromatic Corticoids from the Corresponding 1,4,9(11)-Trienone System of Steroids[2]

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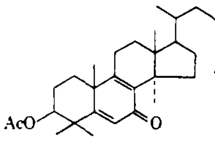
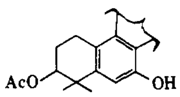
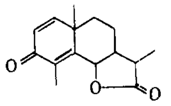
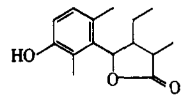
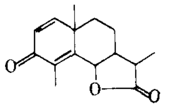
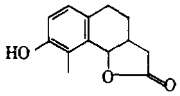
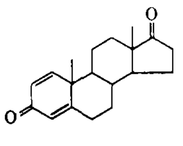
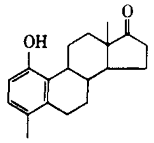
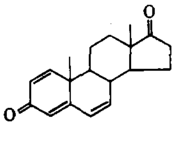
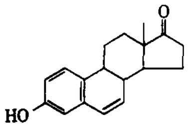
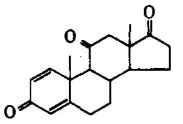
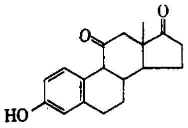
Refluxing androsta-1,4,9(11)-triene-3,17-dione with zinc dust in various solvents, such as pyridine or dimethylformamide containing a small amount of water afforded 9-dehydroestrone in excellent yield. The optimum reaction conditions also were investigated. 3,17α,21-Trihydroxy-19-norpregna-1,3,5,(10),9(11)-tetraen-20-one was synthesized from 17α,21-dihydroxypregna-1,4,9(11)-triene-3,20-dione by this reaction.

In previous papers of this series,[1,3-5] we described an aromatization reaction of cross-conjugated dienone and trienone systems of cross-conjugated dienone and trienone systems with zinc in various solvents, and the results of this reaction are summarized in Table I.

TABLE I

Starting substance	Solvent	Product	Yield, %	Ref.
	Acetic acid		85	4
	Ethylene glycol		10	1, 3, 5
	Pyridine		40	
	Pyridine		75	1, 3
	Pyridine Ethylene glycol		15-20	1, 3
	Pyridine		80	1, 3

These results prompted us to extend this aromatization reaction to a 1,4-dien-3-one system containing an additional double bond at the 9(11)-position. It was found that the 1,4,9(11)-trien-3-one system aromatized smoothly to a phenol with concomitant loss of the angular methyl group in excellent yield. We wish to describe in this paper the details of this new synthetic method which was used for the synthesis of an estrogenic hormone and A-ring aromatic corticoid steroids as well as the reaction conditions of this aromatization reaction. It was shown that this rearrangement was influenced by the presence of water in the solvent.

When the androsta-1,4,9(11)-triene-3,17-dione (I) was treated with zinc in acetic acid it was converted smoothly into a yellow compound, m.p. 240–242°, whose infrared spectrum showed the absence of an aromatic ring, a six-membered saturated or unsaturated ring ketone and hydroxyl absorptions, and whose ultraviolet absorption spectrum exhibited maxima at 340, 355, and 375 mμ (ε, 35,000, 54,000, and 49,000). Based on the above properties the product was thought to be a dimeric polyene compound[6] as described previously.[1]

However, if pyridine or ethylene glycol were used as the solvent instead of acetic acid, the characteristic absorption maximum of the starting material disappeared within thirty minutes and two new maxima appeared at 262 and 290 mμ. These maxima are typical of a phenol with an additional conjugated double bond.[7] After processing the reaction mixture in the usual manner, an alkali-soluble phenol, m.p. 257–259°, was obtained, which on acetylation gave an acetate (IIb), m.p. 125–126°. Methylation yielded a methyl ether (IIc), m.p. 142–144°. Catalytic hydrogenation of IIa with palladium on charcoal quantitatively afforded estrone, which was characterized by direct comparison with natural estrone and its acetate. This reaction clearly established the structure of the phenolic product as 3-hydroxyestra-1,3,5(10),9(11)-tetraen-17-one (II).[7] Hogg and Magerlein[7] have prepared this compound by pyrolysis of I, and its physical properties are identical with our product. It is noteworthy that the elimination of the angular methyl group which occurred with C—C bond fission and with concomitant aromatization of ring A takes place under such mild conditions and in excellent yield.

The gas generated from the above reaction was shown to be methane by gas phase chromatography.[8] The evolution of methane with ethylene glycol was more noticeable than in the case of pyridine, although the yield of the phenolic product in both cases was almost the same.

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(1) Previous paper II: K. Tsuda, E. Ohki, and S. Nozoe, *J. Org. Chem.*, **28**, 783 (1963).

(2) This paper constitutes Part XXXVIII of a series entitled "Steroid Studies," by K. Tsuda.

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

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

(5) K. Tsuda, S. Nozoe, and S. M. Sharif in press.

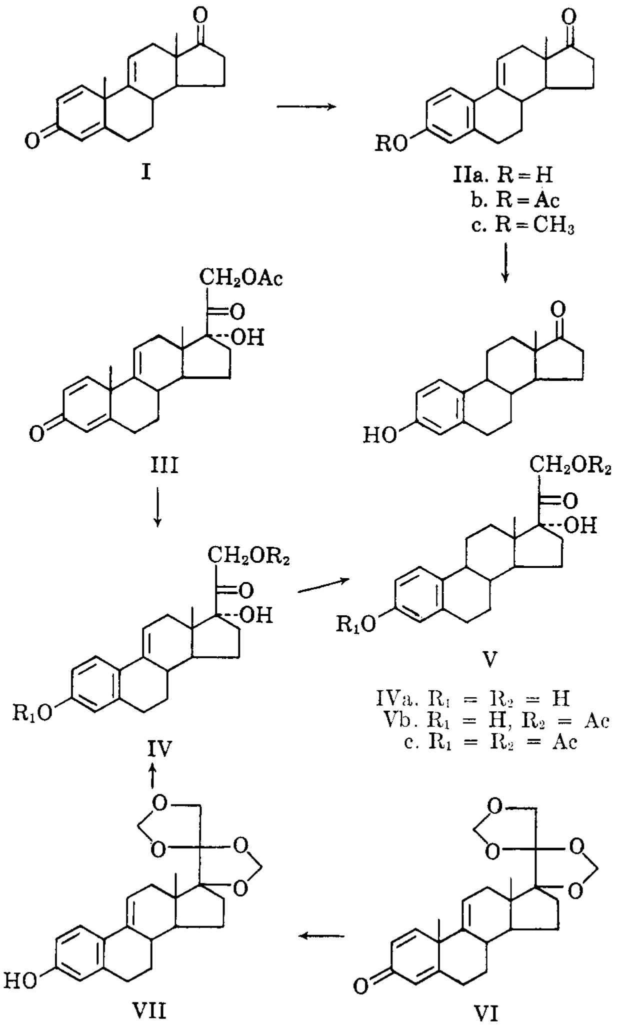
(6) P. Bladon and J. Redpath, *J. Chem. Soc.*, 2352 (1962).

(7) B. J. Magerlein and J. A. Hogg, *J. Am. Chem. Soc.*, **80**, 2220 (1958).

(8) C.E.C. Type 26-201 gas chromatography was used (column: silica gel, 1.2 m. carrier gas: He, 35 cc., min./temp. 28°.

The pyrolytic method of aromatizing the A-ring of dienone or trienone systems cannot be applied to cortico steroids since the side chain at C-17 is invariably affected by the drastic conditions. Thus the mild conditions of this type of aromatization seemed quite suitable for the preparation of aromatic A-ring cortical steroids.[9]

Treatment of 17α,21-dihydroxypregna-1,4,9(11)-triene-3,20-dione 21-acetate (III) with zinc in pyridine afforded 3,17α,21-trihydroxy-19-norpregna-1,3,5(10),9(11)-tetraen-20-one 21-acetate (IVb), m.p. 218–219°, which on alkaline hydrolysis gave 3,17α,21-trihydroxy-19-norpregna-1,3,5(10),9(11)-tetraen-20-one (IVa), m.p. 248–250° dec. Acetylation of IVa or IVb yielded the 3,21-diacetate (IVc), m.p. 188–190°.



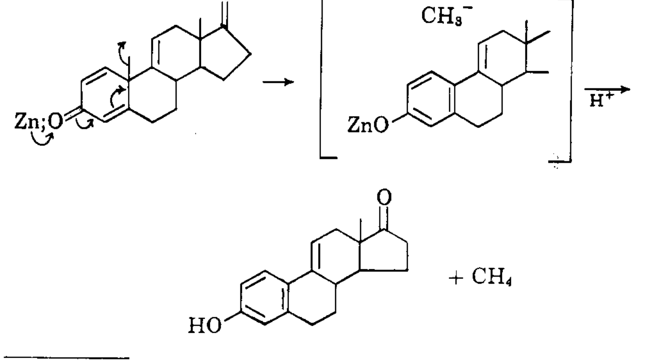
The bismethylenedioxy derivative of III was treated in the same manner to afford the corresponding phenolic compound (VII) which on hydrolysis with aqueous acetic acid regenerated IVa. Catalytic hydrogenation of IVb gave a dihydro derivative (Vb), m.p. 184–186°. Acetylation of Vb yielded a diacetate (Vc), m.p. 167–168°.

In order to establish the optimum reaction conditions the aromatization reaction was examined more thoroughly using androsta-1,4,9(11)-triene-3,17-dione (I). The time required for the reaction varies with the relative amounts of zinc used, the activity of the zinc, the concentration of water in the solvent and temperature. During the investigation of the reaction conditions a considerable retardation of the reaction time was observed when dry pyridine was used and when a relatively large amount of starting material to a solvent was used. It was found that the yield of the product increased with a shorter reaction time by the addition of a small amount of water to the system.

That water is necessary for this reaction was shown by the following experiment. The aromatization of compound I was effected by placing in two separate flasks identical quantities of zinc, carefully dried pyridine, and trienone I. Before heating the reaction mixtures, a small amount of water (*cf.* Experimental) was added to one flask. The mixture was heated to reflux and the course of the reaction followed by ultraviolet spectroscopy. After two hours, the cross-conjugated dienone band completely disappeared from the reaction mixture containing water. The reaction mixture which did not contain water was unchanged even after eight hours, but when subsequently treated with a small amount of water, the trienone was aromatized as in the first case. With increasing amounts of water, (*cf.* Experimental) in pyridine, the yield of the desired product decreased and formation of a polyenic substance become apparent. Thus it is clear that water is essential for the reaction and that its concentration is critical.

To study the effect of the solvent in this reaction, various solvents were tried, *e.g.*, pyridine, picoline, collidine, quinoline, piperidine, dimethylformamide, ethanol, *t*-butyl alcohol, *n*-amyl alcohol, ethylene glycol. Among these, dimethylformamide, pyridine, and piperidine were found in the presence of water to give a quantitative yield of phenolic product by ultraviolet analysis. We found that the reaction proceeded in almost all solvents to a greater or lesser extent except acidic ones. Toluene or xylene in the presence of water could also be used, although with a longer reaction time and a poor yield.

We now wish to suggest either of two possible reaction courses involving an ionic or a radical mechanism although at present the experimental evidence is not sufficient to confirm either mechanism rigorously. Brewster[10] has suggested a chemisorption mechanism for active metal reduction of carbonyl groups. If these reactions proceed *via* a chemisorption mechanism, one can assume the following ionic mechanism. In this case, the proton source is thought to be water in the solvent.



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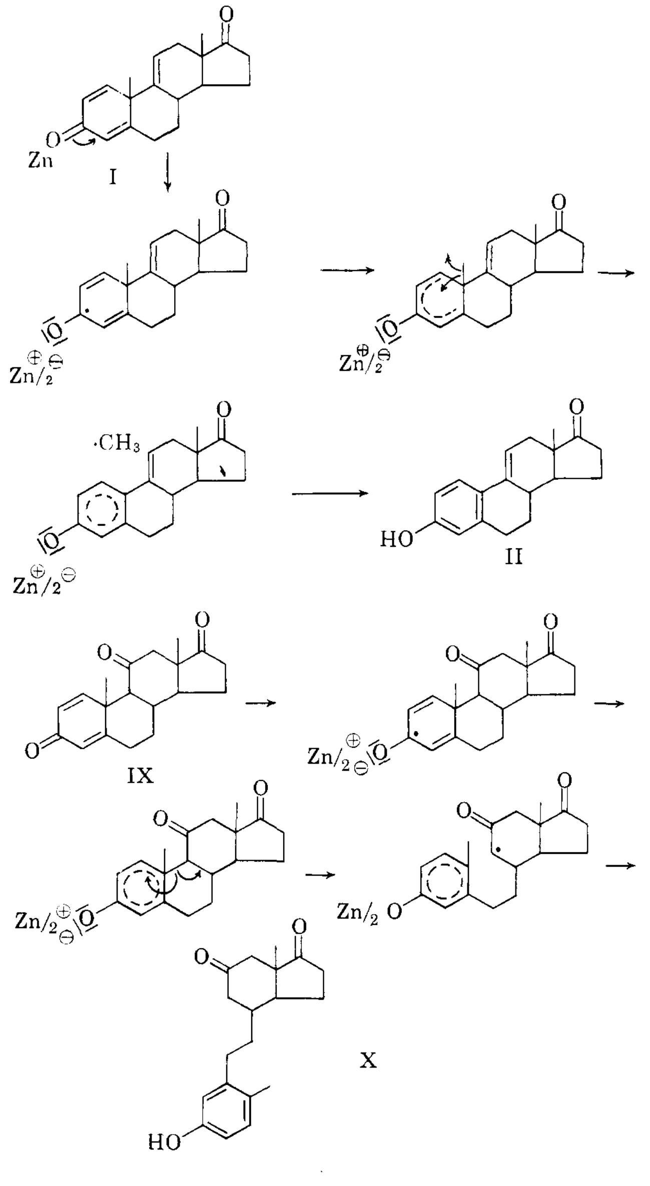
[9] B. J. Magerlein and J. A. Hogg, *J. Am. Chem. Soc.*, **80**, 2226 (1958).

[10] J. H. Brewster, *ibid.*, **76**, 6361 (1954); **76**, 6364 (1954).

On the other hand, the formation of the *p*-dienone–phenol rearrangement product from the 1,4-dien-3-one system which has no double bond at C-9 might be explained by a chemisorption of the 1,4-dien-3-one compound on zinc metal with the zinc acting zinc as a Lewis acid by its electron pump character.[10] As shown above, the addition of the double bond at C9–11 in a position allylic to the C_{10}–C_{19} linkage favors the elimination of the methyl group. The formation of polyenic bis compounds from the 1,4-dien-3-one system and the 1,4,9-(11)-trien-3-one system, respectively, may also be explained by this mechanism, that is, reduction of these reactants to pinacolic dimers and subsequent conversion convert to polyenic bis compounds.

Alternatively, it is not unreasonable to assume that the reaction proceeds through a radical intermediate. The reaction products are the same as those of the pyrolytic method which has been widely accepted to proceed by a free radical mechanism. The formation of 9-dehydroestrone from trienone (I) and the 9,10 seco compound (X)[1] from the corresponding 11-keto derivative (IX) may be interpreted as follows. Zinc can coordinate with the carbonyl group and, *via* one electron transfers to the A-ring, effect the formation of the radical intermediate, which has five π-electrons in the A-ring. This might induce homolytic fission of the C_{10}—C_{19} bond or C_9—C_{10} bond with subsequent stabilization of the A-ring as a six π-electron system.



It is known that the homolytic fission of a C—C bond on an unsaturated compound is most likely to occur at an allylic position.[11] Accordingly, one might expect that the C_{10}—C_{19} bond is more likely to undergo homolytic rupture than the C_9—C_{10} bond in the trienone I. However the 11-keto derivative IX would be expected to undergo homolytic fission at the C_9—C_{10} bond rather than the C_{10}—C_{19} bond, since the former is more activated by the carbonyl group than the latter. The dimeric product obtained from I with zinc in acetic acid was assumed to be formed by dimerization of this radical intermediate. The role of water is not clear now; however, it is thought to be the proton donor in this reaction.

A further extension of this reaction involving the aromatization of a 1,4,8-trien-3-one system is now underway in this laboratory and will be published in a forthcoming paper.

Experimental[12]

3-Hydroxyestra-1,3,5(10),9(11)-tetraen-17-one (IIa).—A mixture of 564 mg. of androsta-1,4,9(11)-triene-3,17-dione (I), 20 ml. of pyridine containing 0.2 ml. of water, and 10 g. of freshly activated zinc dust was heated under reflux with stirring for 20 min. After cooling, the zinc was removed by filtration and washed with ethyl acetate. The solvents were distilled *in vacuo*, and the residue was crystallized from methanol to give 500 mg. of estrone (II), m.p. 250–256°, as leaflets. Recrystallization from methanol raised the m.p. to 256–258° (lit.,[8] 255–257°); λ_{max} 262.5 mμ (ε 18,000), 298 mμ (ε 3000).

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.52; H, 7.48.

Acetate of IIa.—Acetylation of IIa with acetic anhydride and pyridine gave acetate (IIb), m.p. 125–126°; λ_{max} 226 mμ (ε 8500), 258.5 mμ (ε 15,000), 290 mμ (ε 2700), 299.5 mμ (shoulder).

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.18; H, 7.11.

Methyl Ether of IIa.—Methylation of Ia with dimethyl sulfate in aqueous methanol containing potassium hydroxide afforded the methyl ether (IIc), m.p. 142–144° (lit.,[8] 142–145°); λ_{max} 263 mμ (ε 17,300), 297 mμ (ε 2600).

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.81; H, 7.85. Found: C, 80.72; H, 7.79.

The structure of IIa was confirmed by hydrogenation to estrone, which was identical in all respects with the natural hormone. The aromatization of androsta-1,4,9(11)-triene-3,17-dione was carried out according to the above mentioned procedure, varying the amounts of water in the reaction. The yield of the product was determined by the measurement of ultraviolet absorption intensity at 263 mμ. The results of these experiment are summarized in Table II.

3,17α,21-Trihydroxy-19-norpregn-1,3,5(10),9(11)-tetraen-20-one 21-Acetate (IVb).—A mixture of 760 mg. of 17,21-dihydroxypregn-1,4,9(11)-triene-3,20-dione 21-acetate in 20 ml. of pyridine containing 0.5 ml. of water and 15 g. of zinc dust was heated under reflux for 30 min. After removal of the zinc dust from the reaction mixture, the filtrate was poured into 200 ml. of water and extracted with ethyl acetate. The extract was washed with dilute hydrochloric acid to remove the pyridine and successively washed with dilute sodium bicarbonate solution and water. Evaporation of the solvent and trituration of the residue with methanol afforded 420 mg. of IVb as leaflets. Recrystallization from methanol gave 210 mg. of an analytical sample of IVb, m.p. 218–219°; $[\alpha]_D$ +174° (*c* 1.21); λ_{max} 263 mμ (ε 18,000) 298 mμ (ε 3100); ν_{max} 3420, 1735, 1717, 1630, 1618, 1574, 1495, 813 cm.$^{-1}$.

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(11) R. C. Fuson, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 15.

(12) All melting points are uncorrected; all rotations were measured in chloroform solution. Methanol was used for the ultraviolet spectra and Nujol paste for the infrared spectra.

TABLE II

Amount of water, ml.	Yield, %	Reaction period, min.
0[a]	Recovered[a]	480[a]
0[b]	80	240
0.07	90	60
.18	100	10
.36	100	15
.72	100	35
1.8	70	35[b]
7.2	55	60[c]
10.8	37	60[c]
14.4	32	60[c]

[a] Reaction procedures are different: see discussion. [b] Pyridine distilled over potassium hydroxide was used. [c] Formation of dimeric polyenes (λ_{max} 339, 375, 356 mμ) were apparent.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.49; H, 7.33.

3,17α,21-Trihydroxy-19-norpregna-1,3,5(10),9(11)-tetraen-20-one 3,21-Diacetate (IVc).—A solution of 160 mg. of IVb in 4 ml. of acetic anhydride and 4 ml. of pyridine was permitted to stand at room temperature for 24 hr. The solution was poured into ice–water and the crystals collected by filtration to give 140 mg. of diacetate (IVc), as needles, m.p. 188–190°; $[\alpha]_D$ +136°; λ_{max} 226 mμ (ε 8500), 258.5 mμ (ε 16,000), 290 mμ (ε 2700), 299.5 mμ (shoulder); ν_{max} 3540, 1738, 1631, 1606, 1589, 1230, 1213 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84. Found: C, 69.99; H, 6.85.

3,17α,21-Trihydroxy-19-norpregna-1,3,5(10),9(11)-tetraen-20-one (IVa).—To a solution of 100 mg. of IVb in 20 ml. of methanol was added a solution of 100 mg. of potassium bicarbonate in 2 ml. of water. The reaction mixture was allowed to stand for 24 hr. at room temperature. The mixture was neutralized with acetic acid and evaporated to dryness *in vacuo*. The residue was dissolved in methanol and undissolved inorganic substance was removed by filtration. Recrystallization from acetone gave 78 mg. of IVa, m.p. 248–250° dec.; $[\alpha]_D$ +176°; λ_{max} 262.5 mμ (ε 18,000), 299.5 mμ (ε 3000).

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 72.58; H, 7.37.

Hydrogenation of IVb to 3,17α,21-Trihydroxy-19-norpregn-1,3,5(10)-trien-20-one 21-Acetate (Vb).—A solution of 372 mg. of IVb in 30 ml. of ethyl acetate was shaken with 40 mg. of 10% palladium on charcoal for 1 hr. under hydrogen. Filtration, evaporation and recrystallization from methanol gave 340 mg. of Vb as needles, m.p. 184–186°; λ_{max} 281 mμ (ε 2380), 288 mμ (shoulder).

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 71.11; H, 7.59.

3,17α,21-Trihydroxy-19-norpregna-1,3,5-(10)-trien-20-one 3,-21-Diacetate (Vc).—Acetylation of Vb was carried out by the usual procedure and recrystallization from methanol afforded Vc as needles, m.p. 167–168°; λ_{max} 213 mμ (ε 13,400), 268.5 mμ (ε 1000), 275.5 mμ (ε 1000).

Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.79; H, 7.24.

17α,21-Dihydroxypregna-1,4,9(11)-triene-3,20-dione BMD (VI).—To a solution of 1.5 g. of 17α,21-dihydroxypregn-1,4,9-(11)-triene-3,20-dione in 50 ml. of chloroform was added 13 ml. of concentrated hydrochloric acid and 13 ml. of 37% formalin. The mixture was shaken for 72 hr. at room temperature. The aqueous layer was separated and discarded. The chloroform solution was washed with aqueous sodium bicarbonate until it was neutralized, dried over sodium sulfate, and concentrated. Recrystallization of the residue from methylene chloride–methanol afforded 980 mg. of BMD compound (VI), m.p. 198–199°, as fine needles.

Anal. Calcd. for $C_{23}H_{28}O_5$: C, 71.85; H, 7.34. Found: C, 71.49; H, 7.14.

3,17α,21-Trihydroxy-19-norpregna-1,3,5(10),9(11)-tetraen-20-one BMD (VII).—A mixture of 400 mg. of VI and 15 g. of zinc dust in 20 ml. of pyridine was heated under reflux for 3 hr. After the usual work-up, recrystallization of the residue from methylene chloride afforded 300 mg. of VII, m.p. 247–248°, which was used for the next step without further purification.

Hydrolysis of VII with Aqueous Acetic Acid.—A mixture of 200 mg. of VII, 20 ml. of acetic acid, and 20 ml. of water was purged with nitrogen and heated to reflux for 6 hr. under nitrogen atmosphere. After standing at room temperature overnight the solvent was evaporated *in vacuo* to dryness. The residue was dissolved in 3 ml. of pyridine and 3 ml. of acetic anhydride. After storing at room temperature overnight, the solution was poured into ice-water. The aqueous suspension was extracted with methylene chloride, washed with water, and dried. Evaporation of the solvent and recrystallization of the residue from methanol afforded 65 mg. of 3,17α,21-trihydroxy-19-norpregn-1,3,5(10),-9(11)-tetraen-20-one, 3,21-diacetate (IVc), m.p. 183–184°. The melting point was undepressed on admixture with the sample prepared directly.

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An Aromatization Reaction of a Cross-conjugated Dienone System with Zinc. IV. Synthesis of 11-Hydroxyisoequilin and Aromatization of the Steroidal 1,4,8-Triene-3,11-dione System[1]

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11β-Hydroxyandrosta-1,4,8-triene-3,17-dione was prepared by the action of N-bromosuccinimide of 11β-hydroxyandrosta-1,4,9(11)-triene-3,17-dione and followed by dehydrobromination with collidine. The former was aromatized with zinc to give rise to 3,11β-dihydroxyestra-1,3,5(10)-trien-17-one, which was converted to equilenin by acid and estradiol with lithium in liquid ammonia. Refluxiug androsta-1,4,8-triene-3,11,17-trione with zinc in dimethylformamide afforded 3-hydroxyestra-1,3,5(10),8-tetraene-11,17-dione and 3-hydroxy-9,10-secoandrosta-1,3,5,X-tetraene-11,17-dione.

In a previous paper[3] of this series, it was reported that androsta-1,4,9(11)-triene-3,17-dione (I) was easily converted to 9-dehydroestrone (II) with zinc by the aromatization of ring A with concomitant elimination of the C-19 angular methyl group in excellent yield.

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(1) This paper constitutes Part XXXIX of a series entitled "Steroid Studies" by K. Tsuda.

(2) Sankyo Co., Ltd., Shinagawa, Tokyo, Japan.

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