night at room temperature and then poured into a stirred mixture of ice and water. The precipitate was separated, washed with water, dried, and recrystallized from methanol, affording 203 mg. of acetate (VI) as needles and prisms, m.p. 149–149.5°. The melting point was depressed on admixture with acetate (VII) to 123–126°; $[\alpha]^{20}\text{D}$ +121° (chloroform), ultraviolet $\lambda_{\max}^{\text{MeOH}}$ mμ (ϵ): 268 (523), 277 (506), infrared $\nu_{\max}^{\text{CHCl}_3}$ cm.$^{-1}$: 1783.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61; O, 23.33. Found: C, 70.16; H, 6.61; O, 23.34.

Hydrolysis of 6α(H),7α(H),11β(H)-1-Desmethyldesmotroposantonin Acetate (VII).—(a) A solution of 1.5 g. of acetate (VII) and 0.6 g. of potassium hydroxide in 22.5 ml. of methanol was set aside for 24 hr. at room temperature. The reaction mixture was acidified with 2% hydrochloric acid and poured into 100 ml. of water. The resulting precipitate was filtered, washed with water, and dried. A saturated solution of crude material in acetone was left for crystallization for 7–8 days at room temperature. The big prisms were then picked up mechanically from the mother liquor and recrystallized from acetone affording 563 mg. of product (VIII), m.p. 210–211°, $[\alpha]^{21}\text{D}$ +202.7° (ethanol), ultraviolet $\lambda_{\max}^{\text{MeOH}}$ mμ (ϵ): 288 (2981), infrared $\nu_{\max}^{\text{Nujol}}$ cm.$^{-1}$: 3376, 1751, 1596, 828, 818, $\nu_{\max}^{\text{CHCl}_3}$ cm.$^{-1}$: 1769.

Anal. Calcd. for $C_{14}H_{13}O_3$: C, 72.39; H, 6.94; O, 20.67. Found: C, 72.41; H, 6.87; O, 20.39.

(b) When the above mother liquor was concentrated another product (IX) crystallized from acetone as fine needles, m.p. 230° dec., ultraviolet $\lambda_{\max}^{\text{MeOH}}$ mμ (ϵ): 288 (3203), infrared $\nu_{\max}^{\text{CHCl}_3}$ cm.$^{-1}$: 3362, 1747.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; O, 20.67. Found: C, 72.54; H, 6.89; O, 20.87.

The acetate of IX has m.p. 147–148°, $[\alpha]^{19}\text{D}$ −169.3°(chloroform), infrared $\nu_{\max}^{\text{CHCl}_3}$ cm.$^{-1}$: 1766.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61; O, 23.33. Found: C, 69.93; H, 6.60; O, 23.25.

Action of *p*-Toluenesulfonic Acid on 6β(H),7α(H),11β(H)-1-Desmethyldesmotroposantonin (II).—(a) A solution of 1 g. of II and 100 mg. of *p*-toluenesulfonic acid in 2 ml. of benzene was refluxed for 30 hr. The reaction mixture was poured into water and the resulting light brown precipitate was collected and dissolved in ethyl acetate. The ethyl acetate solution was washed successively with saturated sodium bicarbonate solution and water. After drying over sodium sulfate and evaporation of the solvent 35 mg. of product (IX) was obtained which was recrystallized from acetone as leaflets, m.p. 230° dec. This substance was identical with IX by mixed melting point, infrared spectrum, and elemental analysis.

(b) When II was heated in a water bath with *p*-toluenesulfonic acid in benzene for 40 hr., the product (VIII) was obtained as big prisms m.p. 210°, which on acetylation with acetic anhydride and pyridine gave an acetate (VII).

Potassium Carbonate Isomerization of 6α(H),7α(H),11β(H)-1-Desmethyldesmotroposantonin (VIII).—A mixture of 250 mg. of VIII, 250 mg. of freshly ignited potassium carbonate, and 6.25 ml. of xylene was refluxed for 24 hr. The xylene was removed *in vacuo* and the residue extracted with acetone. The extract was washed with water, dried over sodium sulfate, and evaporated. The residue was recrystallized from acetone to afford 52 mg. of product (IX) as prisms, m.p. 230° dec.

The acetate of IX was obtained as silky needles from methanol, m.p. 147–148°.

Acknowledgment.—S. M. S. wishes to express his thanks to Dr. T. Miki of the Takeda Chemical Industries, Ltd., Osaka, Japan, for his coöperation and sage counsel during the course of this work. We are indebted to Misses H. Yamanouchi and K. Hayashi for microanalyses and to Miss Arimoto for infrared spectral data. One of us (S. N.) is grateful to the Japan Society for Promotion of Science for the award of research fellowship.

An Aromatization Reaction of a Cross-conjugated Dienone System with Zinc.[1] VI. Synthesis of A-Ring Anilino Steroids[2]

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The aromatization reaction of cross-conjugated dienone systems with zinc, which converts androsta-1,4,9(11)-triene-3,17-dione to Δ^9-dehydroestrone, was applied to an oxime derivative of 17-acetoxyandrosta-1,4,9(11)-trien-3-one in order to synthesize an A-ring aniline derivative, 3-amino-1,3,5(10),9(11)-estratetraen-17-ol acetate. By the same reaction 3-amino-1,3,5(10),9(11)-estratetraen-17-ol acetate was also obtained from the 2,4-dinitrophenylhydrazone derivative of androsta-1,4,9(11)-trien-3-on-17-ol acetate.

In the previous report of this series we described the aromatization reaction of the A-ring of cross-conjugated dienone or trienone systems of steroids with zinc.[1,4–6] In that study it was shown that a steroidal $\Delta^{1,4}$-dien-3-one system having an additional double bond at the 9(11)- or 8-position, *e.g.*, androsta-1,4,9(11)-trien-3,7-one and androsta-1,4,8-trien-3,17-one, underwent aromatization of the A-ring with concomitant elimination of the C-19 angular methyl group to afford 9(11)-dehydroestrone[5] and Δ^8-dehydroestrone,[6] respectively.

It was envisaged that on heating with zinc the cross-conjugated keto oxime derivative would also undergo an aromatization reaction with the elimination of the angular methyl group to form aniline derivatives. Since santonin, under the influence of zinc affords an aromatized product, 6β(H), 7α(H), 11β(H)[7,8]-1-desmethyldesmotroposantonin,[9] its oxime on treatment with zinc would be expected to form the corresponding aniline derivative. The action of zinc dust and alcoholic sulfuric acid on santonin oxime has been known to furnish the corresponding primary amine, santoninamine, which can be converted by simple treatment with nitrous acid or with boiling water to hyposantonin[10] *via* the corresponding secondary alcohol and with loss of water.

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

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

(3) This paper will constitute a part of the dissertation to be submitted by S. M. Sharif, in partial fulfillment of the requirements for the D.Sc. degree at the University of Tokyo.

(4) K. Tsuda, E. Ohki, and S. Nozoe, in press.

(5) K. Tsuda, E. Ohki, and S. Nozoe, in press.

(6) K. Tsuda, S. Nozoe, and Y. Okada, in press.

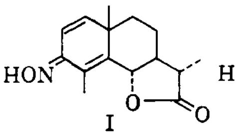
(7) J. D. M. Asher and G. A. Sin, *Proc. Chem. Soc.*, 111 (1962).

(8) D. H. R. Barton, *ibid.*, 112 (1962).

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

(10) J. Simonsen, "The Terpenes," Vol. III, Cambridge University Press, London, 1952, p. 253.

When santonin oxime[11] (I) was refluxed with zinc in dimethylformamide in the presence of a small amount of water,[5] there was obtained a crystalline aniline derivative (II) in 9.94% yield, m.p. 195.5–196.5°. This product showed the characteristic ultraviolet absorption band of aniline at 274 mμ (ε 14,227). The infrared spectrum and analytical values also supported its structure. Further proof of the structure of this product (II) was obtained by its conversion on treatment with nitrous acid to a known, 6β(H), 7α(H), 11β(H)-1-desmethyldesmotroposantonin (III), which has previously been characterized.[9]



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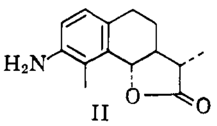

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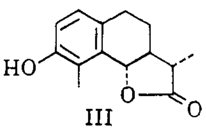


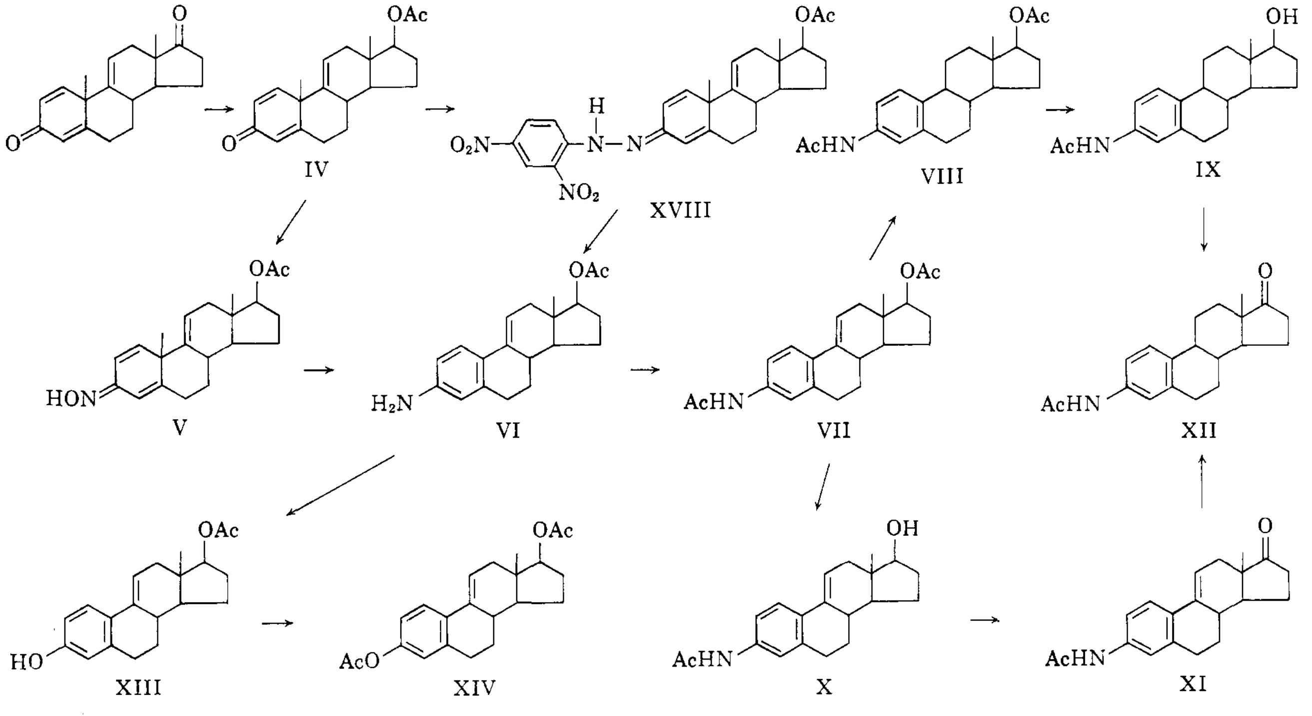
III

The successful results of this reaction prompted its application to steroidal compounds to synthesize the amine derivatives of estrone and estradiol. Gold, *et al.*, have reported the formation of aniline derivatives of steroids by a different reaction. They prepared 3-amino-1,3,5-(10)-estratrien-17-one and related compounds from the corresponding 10-acetoxy-1,4-estradien-3,17-one by refluxing with benzylamine followed by the treatment with dilute sulfuric acid.

to support structure VI. It gave a well crystallizable *N,O*-diacetyl derivative (VII), m.p. 177–179.5°, which was hydrogenated with palladium on charcoal to 3-acetamido-1,3,5(10)-estratrien-17-ol acetate (VIII), m.p. 213–214°, λ_{max} 248 mμ (ε 16,422), 288 mμ (shoulder).[12]

In order to secure further evidence of the structure, the anilino steroid (VI) was diazotized with sodium nitrite and the resulting diazonium salt was hydrolyzed by heating in acid to give Δ^9-dehydroestradiol 17-acetate (XIII).[13] The acetylation of XIII furnished the diacetate (XIV), m.p. 149–150°, which was identical with an authentic sample of Δ^9-dehydroestradiol 3,17-diacetate[13] prepared from Δ^9-estrone by lithium aluminum hydride reduction followed by acetylation. These reactions clearly established the structure of the aromatic product as 3-amino-1,3,5(10),9(11)-estratetraen-17-ol acetate. The hydrolysis of the diacetate (VII) with methanolic potassium hydroxide provided X which on oxidation with chromium trioxide gave XI. Hydrogenation of XI with palladium on charcoal afforded a substance (XII) which was also obtained by the hydrolysis of VIII and subsequent oxidation of the resulting compound (IX) with chromium trioxide.

Another phase of this study involved the preparation of the dinitrophenylhydrazone derivative (XVIII) of the compound IV and its aromatization with zinc.



Treatment of 17-acetoxyandrosta-1,4,9(11)-trien-3-one oxime (V) with zinc in refluxing dimethylformamide in the presence of a small amount of water yielded an aromatic amine (VI) in good yield (76.7%), m.p. 178–182°. The product exhibited an ultraviolet absorption maximum at 276 mμ (ε 16,816) which is characteristic of an aromatic amine possessing a conjugated double bond. The infrared absorption was also characteristic of an aromatic amine. The substance was crystallized with difficulty but could be obtained in pure form which gave the correct elemental analysis

Hecker has also prepared 3-aminoestra-1,3,5(10)-trien-17-ol from the corresponding *p*-quinol and 2,4-dinitrophenylhydrazine, followed by reduction of the resulting azo compound.[14] Treatment of the hydrazone (XVIII) with zinc in refluxing dimethylformamide afforded a crude material which on alumina column chromatography gave an almost quantitative yield of product (VI). The reaction product was converted into an acetyl derivative which was shown to be identical with acetate (VII) by the usual physical tests.

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[11] Ref. 10, p. 269.

[12] A. M. Gold and E. Schwenk, *J. Am. Chem. Soc.*, **81**, 2198 (1959).

[13] K. Tsuda, S. Nozoe, and Y. Okada, in press.

[14] E. Hecker, *Chem. Ber.*, **92**, 3198 (1959).

Experimental[15]

3-Desoxy-3-amino-6β(H),7α(H),11β(H)-1-desmethyldesmotroposantonin (II).—A mixture of 6.0 g. of santonin oxime, 60 g. of activated zinc, 60 ml. of dimethylformamide, and 7.5 ml. of water was refluxed with stirring for 1.5 hr. After removal of the zinc the filtrate was poured into water, extracted with ether, dried over sodium sulfate, and the solvent removed *in vacuo*. The noncrystalline residue was chromatographed on alumina. Elution with benzene afforded 562 mg. of crude product (II). Recrystallization from methanol gave 221 mg. of pure product, m.p. 195.5–196.5, $[\alpha]^{22.5}\mathrm{D}$ +163° (EtOH, *c* 1.03), ultraviolet $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (ε): 276 (14,227), infrared $\nu_{\max}^{\mathrm{Nujol}}$ cm.$^{-1}$: 3495, 3390, 3280 (primary amine), 1780 (lactone), 1630, 1600 (aromatic).

Anal. Calcd. for $C_{14}H_{17}O_2N$: C, 72.70; H, 7.41; O, 13.84; N, 6.06. Found: C, 72.45; H, 7.47; O, 13.80; N, 6.06.

When the above amine (II) was treated with an ice-cooled sodium nitrite solution in dilute hydrochloric acid and the mixture warmed to 60° for 5 min. a light yellow product was separated. The physical properties of a recrystallized sample, m.p. 227–229°, were identical in all respects to an authentic sample of 6β(H),7α(H),11β(H)-1-desmethyldesmotroposantonin.

17-Acetoxy-1,4,9(11)-androstatrien-3-one Oxime (V).—To a solution of 4.28 g. of androsta-1,4,9(11)-triene-3,17-dione in 780 ml. of methanol was added 852 mg. of sodium borohydride at 0° with stirring. After 1 hr. stirring 3 ml. of acetic acid was added to decompose the unchanged sodium borohydride and the stirring was continued for another 30 min. the reaction mixture was concentrated to a volume of about 50 ml. then poured into water and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated *in vacuo*. The residue was crystallized once from acetone–*n*-hexane to afford 2.65 g. of androsta-1,4,9(11)-trien-17-ol-3-one, m.p. 147–148°. Without purification this product was acetylated in the usual manner to yield an acetate (IV), m.p. 136.5–137°. To a solution of 2.15 g. of this acetate in 20 ml. of ethanol and 1.1 ml. of pyridine was added 465 mg. of hydroxylamine hydrochloride and the mixture refluxed for 2 hr. Evaporation of the solvent left a crystalline residue which was washed with water, dried, and recrystallized from acetone to yield 1.62 g. of oxime (V), m p. 221–223°, $[\alpha]^{21.5}\mathrm{D}$ +26.6° (EtOH, *c* 0.89), ultraviolet $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (ε): 249 (9152), infrared $\nu_{\max}^{\mathrm{Nujol}}$ cm.$^{-1}$: 3147, 1666 (oxime), 1745 (acetate).

Anal. Calcd. for $C_{21}H_{27}O_3N$: C, 73.87; H, 7.97; O, 14.06; N, 4.10. Found: C, 73.97; H, 8.05; O, 13.88; N, 4.47.

3-Amino-1,3,5(10),9(11)-estratetraen-17-ol Acetate (VI).—A mixture of 1 g. of oxime (V), 30 g. of zinc, and 20 ml. of dimethylformamide containing 1 ml. of water was heated under reflux for 1 hr. After removal of the zinc the filtrate was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated to give 700 mg. of crude product (VI), m.p. 167–169°. An analytical sample was prepared by recrystallization from methanol, m.p. 178–182°, $[\alpha]^{21}\mathrm{D}$ +168.6° (EtOH, *c* 0.33), ultraviolet $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (ε): 277 (16,816), infrared $\nu_{\max}^{\mathrm{Nujol}}$ cm.$^{-1}$: 3526, 3426 (amino), 1723 (acetate), 1629, 1500 (aromatic), 812 (aromatic H).

Anal. Calcd. for $C_{20}H_{25}O_2N$: C, 77.13; H, 8.09; N, 4.50. Found: C, 77.28; H, 8.13; N, 4.48.

***N*-Acetyl Derivative of VI.**—This was prepared by the treatment of VI with acetic anhydride in pyridine in the usual manner and had m.p. 177–179.5°, $[\alpha]^{22}\mathrm{D}$ +107.6° (EtOH, *c* 1.29), ultraviolet $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (ε): 274.5–281 (broad, 15,000), infrared $\nu_{\max}^{\mathrm{Nujol}}$ cm.$^{-1}$: 3455, 3365 (NH), 1731 (acetate), 1685 (amide).

Anal. Calcd. for $C_{22}H_{27}O_3N$: C, 74.75; H, 7.70; O, 13.58; N, 3.96. Found: C, 74.49; H, 7.74; O, 13.88; N, 4.07.

VI *via* Hydrazone.—To a solution of 1.5 g. of 2,4-dinitrophenylhydrazine in 30 ml. of methanol and 2.5 ml. of concentrated sulfuric acid was added dropwise and with continuous shaking a solution of 1.63 g. of androsta-1,4,9(11)-trien-3-on-17-ol acetate in 5 ml. of methanol. The bright red precipitate which formed was removed and dried to afford 2.8 g. of crude hydrazone (XVIII), m.p. 201–204°. Analytically pure sample was obtained by recrystallization from ethyl acetate as scales, m.p. 207–208°, ultraviolet $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (ε): 251–257 (broad, 22,288), 392.5 (36,977).

Anal. Calcd. for $C_{27}H_{30}O_6N_4$: C, 64.02; H, 5.97; O, 18.95. Found: C, 64.27; H, 6.07; O, 18.95.

A mixture of 0.5 g. of the above hydrazone (XVIII), 20 g. of zinc, 20 ml. of dimethylformamide, and 2.5 ml. of water was refluxed with stirring for 45 min. until the reaction mixture became colorless. During reflux the color of the reaction mixture changed to brown, green, and colorless after the time intervals of 15, 20, and 40 min., respectively. At the colorless stage the reaction was stopped, the zinc removed, the filtrate poured into water and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated to leave a brownish residue. The product which could not be purified by crystallization was applied to an alumina column and eluted with benzene. The first two fractions afforded 331 mg. of crystalline product which on recrystallization from acetone had m.p. 177–179°, undepressed on admixture with VI. Its acetate melted at 177–179°.

3-Acetamido-1,3,5(10)-estratrien-17β-ol Acetate (VIII).—A solution of 270 mg. of VII in 10 ml. of ethyl acetate was shaken with 10% palladium on charcoal under a hydrogen atmosphere for 30 min. The catalyst was removed and the solvent evaporated. The residue was recrystallized from methanol to afford 145 mg. of product (VIII), m.p. 213–214° (lit., 213–213.5°),[12] $[\alpha]^{21}\mathrm{D}$ +45.4°(EtOH, *c* 1.15), ultraviolet $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (ε): 248.4 (16,422), infrared $\nu_{\max}^{\mathrm{Nujol}}$ cm.$^{-1}$: 1737, 1663 (amide).

Anal. Calcd. for $C_{22}H_{29}O_3N$: C, 74.33; H, 8.22; O, 13.50; N, 3.94. Found: C, 74.31; H, 8.29; O, 13.90; N, 3.90.

3-Acetamido-1,3,5(10),9(11)-estratetraen-17β-ol (X).—To a solution of 500 mg. of VII in 100 ml. of methanol was added a solution of 100 mg. of potassium hydroxide in 1 ml. of water and the mixture heated under reflux for 1 hr. The reaction mixture was then concentrated to a volume of about 2–3 ml. and poured into water. The resulting precipitate was removed and dried to afford 370 mg. of crude product (X), m.p. 194–199°. An analytically pure sample was obtained by recrystallization from aqueous methanol as needles, m.p. 195–200°, $[\alpha]^{21}\mathrm{D}$ +143° (EtOH, *c* 1.02), ultraviolet $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (ε): 275–280 (broad, 25,800), infrared $\nu_{\max}^{\mathrm{Nujol}}$ cm.$^{-1}$: 3539, 3295 (OH,NH), 1640 (amide).

Anal. Calcd. for $C_{20}H_{25}O_2N \cdot H_2O$: C, 72.92; H, 8.26; O, 14.51; N, 4.25. Found: C, 72.84; H, 8.24; O, 14.86; N, 4.20.

3-Acetamido-1,3,5(10),9(11)-estratetraen-17-one (XI).—To a stirred solution of 311 mg. of X in 5 ml. of acetone was added dropwise 0.58 ml. of Kilianis reagent (66.7 mg. of chromium trioxide in 0.561 ml. of water). Upon addition of several drops of dilute aqueous sodium bicarbonate a sticky matter appeared which on standing for some time settled at the bottom of the flask. The supernatant material was removed and poured into water, then extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated. Recrystallization of the residue from methanol afforded 150 mg. of pure product (XI), m.p. 210–212°, $[\alpha]^{21.5}\mathrm{D}$ +289.5° (EtOH, *c* 1.01), ultraviolet $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (ε): 274.6–280 (broad, 27,535), infrared $\nu_{\max}^{\mathrm{Nujol}}$ cm.$^{-1}$: 3320 (NH), 1733 (five-membered ring ketone), 1662 (amide).

Anal. Calcd. for $C_{20}H_{23}O_2N$: C, 77.64; H, 7.49; O, 10.34; N, 4.53. Found: C, 77.51; H, 7.49; O, 10.34; N, 4.61.

3-Acetamido-1,3,5(10)-estratrien-17-one (XII).—Hydrogenation of XI with 10% palladium on charcoal in ethyl acetate was carried out as above to afford XII in 80% yield, m.p. 250–252° (lit., 255–256°), ultraviolet $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (ε): 248 (5449), 289 (313.4), infrared $\nu_{\max}^{\mathrm{Nujol}}$ cm.$^{-1}$: 3337 (NH), 1735 (five-membered ring ketone), 1661 (amide), 1610, 1526, 1500 (aromatic), 828 (aromatic H).

Anal. Calcd. for $C_{20}H_{25}O_2N$: C, 77.13; H, 8.09; N, 4.50. Found: C, 77.46; H, 8.23; N, 4.59.

3-Acetamido-1,3,5(10)-estratrien-17β-ol (IX).—Hydrolysis of VIII with methanolic potassium hydroxide was carried out as described above to afford IX, m.p. 257–258°, $[\alpha]^{21.5}\mathrm{D}$ +82° (EtOH, *c* 0.78), ultraviolet $\lambda_{\max}^{\mathrm{MeOH}}$ mμ (ε): 248.4 (5249), 289 (313.4), infrared $\nu_{\max}^{\mathrm{Nujol}}$ cm.$^{-1}$: 3358 (OH, NH), 1669 (amide).

Anal. Calcd. for $C_{20}H_{27}O_2N$: C, 76.64; H, 8.68; O, 10.21; N, 4.47. Found: C, 76.90; H, 8.81; O, 10.30; N, 4.63.

Δ^9-Dehydroestradiol 17-Acetate from 3-Amino-1,3,5(10),9-(11)-estratetraen-17-ol Acetate (XIII).—To a mixture of 220 mg. of VI, 3.5 ml. of tetrahydrofuran, and 2.0 ml. of 0.7 *N* sulfuric acid cooled in ice was added with stirring 150 mg. of sodium nitrite and the solution was allowed to stand at 0° for 20 min. After addition of 126 mg. of urea the resulting solution was brought to room temperature, then warmed on water bath for 10 min.

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(15) Melting points are uncorrected.

Upon cooling the mixture was poured into water and extracted with ethyl acetate. The residue was acetylated with acetic anhydride and pyridine in the usual manner to afford the diacetate (XIV). Recrystallization from methanol yielded the pure product, m.p. 149–150°. The product was identical by mixed melting point and infrared spectrum comparison with a sample prepared from the Δ^9-estrone.

Acknowledgment.—The authors are indebted to Misses H. Yamanouchi and K. Hayashi for the microanalyses and to Miss K. Arimoto for the infrared spectral data. One of the authors (S.N.) is grateful to the Japan Society for Promotion of Science for the award of research fellowship.

The Aluminum Phenoxide-catalyzed Reaction of Phenol with Dienes

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Shell Development Company, Emeryville, California

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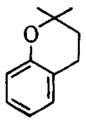
The reaction of phenol with dienes in the presence of aluminum phenoxide gives a mixture of alkenylphenols and chromans. With phenol and isoprene, a bisphenol possessing an unusual n.m.r. spectrum is also obtained. The mechanism of the reaction is discussed.

The use of aluminum phenoxide as a selective catalyst for the *ortho*-alkylation of phenol has been described.[1] In the cases of propylene and isobutylene good yields of 2,6-dialkylated phenols were obtained, whereas more complicated olefins gave somewhat poorer yields of mono- and dialkylated products. In the present paper we have examined the reaction of phenol with conjugated dienes.

Results

When phenol is treated with isoprene in the presence of aluminum phenoxide at low temperatures and low phenol–isoprene ratios, compounds I–IV may be isolated from the reaction mixture. As may be seen from Table I, the product distribution varies considerably with reaction conditions, although the reaction could not be directed to a particular product. The products obtained under these conditions are identical with those obtained by Bader[2] using phosphoric acid as catalyst, except that under his conditions the double bonds were partially hydrated.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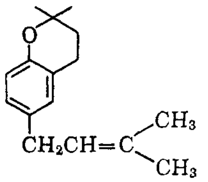

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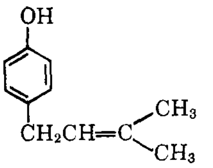

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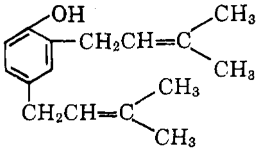


IV

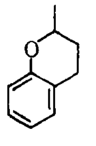
When the aluminum phenoxide-catalyzed reaction was carried out at higher temperatures (>100°) in the presence of excess phenol, chroman I was obtained (36%), accompanied by a new compound, bisphenol V (see next section), in 38% yield.

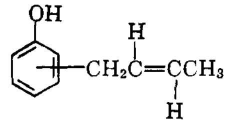
TABLE I

PRODUCT DISTRIBUTION IN THE ALUMINUM PHENOXIDE-CATALYZED REACTION OF PHENOL AND ISOPRENE

Reaction conditions			Product composition[a] (mole fraction)			
Phenol–isoprene	Temp. °C.	Solvent	I	II	III	IV
1.2:1	60	...	0.32	0.41	0.27	..
1.2:1	20	Benzene	0.35	0.52	0.14	..
1.2:2	80	...	0.38	0.25	0.24	0.13

[a] Combined yields average 70%.

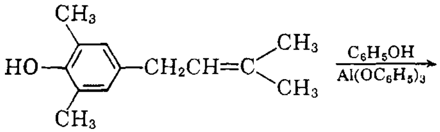

VI



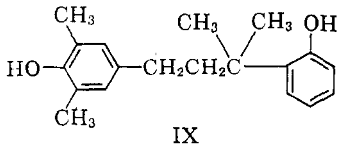
VIIa: *ortho*
VIIb: *para*

Under identical conditions, phenol reacted with 1,3-butadiene to give monoadducts VI, VIIa and VIIb in 5%, 8%, and 57% yields, respectively. Attempts to add a second mole of phenol to VIIb under more vigorous conditions failed. The relative sluggishness of the disubstituted olefin as compared with II (trisubstituted) is probably to be ascribed to weaker complex formation with aluminum phenoxide.

Similarly, 2,6-dimethylphenol reacted with isoprene in the presence of aluminum 2,6-dimethylphenoxide to give phenol VIII in 67% yield. Although VIII would not react further with 2,6-dimethylphenol, it did so with phenol to give an 89% yield of bisphenol IX. The structure of IX was not demonstrated, but inferred by analogy to bisphenol V (*vide infra*).



VIII



IX

The reaction also proceeded smoothly with β,β-dimethylstyrene to give phenol X in 75% yield. The structure of X was demonstrated by the occurrence in its n.m.r. spectrum of two sharp bands (area ratio 3:1) in the alkyl region, and by permanganate oxidation to acid XI.

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[2] A. R. Bader and W. C. Bean, *J. Am. Chem. Soc.*, **80**, 3073 (1958).