An Aromatization Reaction of a Cross-conjugated Dienone System with Zinc. V. Aromatization of Santonin with Zinc[1]

S. M. SHARIF,[2] S. NOZOE, K. TSUDA, AND N. IKEKAWA

Institute of Applied Microbiology, University of Tokyo, Bunkyo-Ku, Tokyo, Japan

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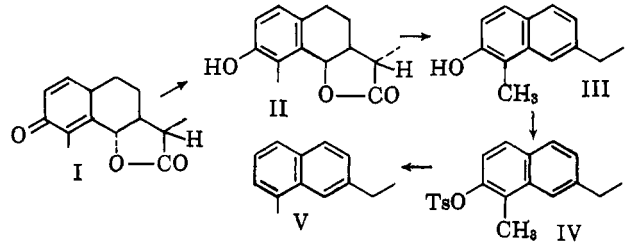
Treatment of santonin with zinc in refluxing dimethylformamide containing a small amount of water afforded a new 1-desmethyldesmotroposantonin (II). This aromatization reaction occurred with concomitant elimination of the angular methyl group. The configuration of the lactone ring was unchanged.

In a previous communication[1] we reported that compounds having a cross-conjugated dienone system easily undergo an aromatization reaction on treatment with zinc in various solvents to form phenolic compounds. The course of this reaction was determined by the structural elucidation of the aromatization product of lanosta-5,8-dien-3-one with zinc[3,4] in this laboratory and the aromatization reaction was applied to steroidal 3-keto-$\Delta^{1,4}$-dienone systems. It was observed that $\Delta^{1,4}$-diene-3-one systems having an additional olefinic linkage at the 6,8- or 9(11)-position underwent aromatization of ring A with elimination of the 19-angular methyl group[5-7] while androsta-1,4-diene-3,17-dione and androsta-1,4-diene-3,11,17-trione gave the *p*-cresol type rearrangement product[8] and 9//10 seco aromatized compounds,[9] respectively.

In the present paper the authors wish to report another example concerning the aromatization of ring A with concomitant elimination of the angular methyl group. It is a well established fact that the acid-catalyzed isomerization of santonin involves the migration of the angular methyl group to the 1-position giving desmotroposantonin[10] but a reaction with the elimination of the methyl group has never been reported. Thus a 3-keto-1,4-diene system like santonin possessing a methyl group at the 4-position would be expected to undergo such a reaction. Treatment of santonin with zinc in refluxing dimethylformamide in the presence of small amount of water for thirty minutes yielded a crystalline phenolic product (II), m.p. 228–229°, in 20–40% yield. The ultraviolet spectrum exhibited a characteristic absorption band of phenolic chromophore at 286.5 mμ (ε 2820). The infrared spectrum exhibited a band at 812 cm.$^{-1}$ which is characteristic of the out-of-plane vibration for two adjacent aromatic hydrogen atoms. The n.m.r. spectrum showed the presence of one methyl group on the benzene ring. Its analytical values corresponded with the composition of $C_{14}H_{16}O_3$. In addition to the spectral and analytical data, the evolution of methane gas during the reaction was detected by the gas chromatography which suggested the elimination of the angular methyl group.



To prove the skeleton of this phenolic product (II), dehydrogenation with palladium on charcoal was attempted. As expected, there was obtained an alkyl naphthol (III)[11] which on tosylation and subsequent reduction with palladium on charcoal and hydrazine under a hydrogen atmosphere[12] afforded a naphthalene (V)[13,14] that gave a known picrate, m.p. 73–74°, and a styphnate, m.p. 125–126°. A close similarity of infrared absorption of naphthalene (V) with that of 1,7-diethylnaphthalene in the fingerprint region showed it to have the decalin skeleton with substituents at C-1 and C-7.

Since this phenolic product, desmethyldesmotroposantonin (II) is dextrorotatory, the hydrogen at the 6-position is assumed to have the β-configuration. Huang-Minlon[15] has shown that *cis*-fused lactones (of the desmotroposantonin series) and hyposantonin all having 6β(H) configuration are dextrorotatory. Cocker[16] has also prepared a dextrorotatory desmotroposantonin of a *trans* lactone with a 6β(H) configuration under mild conditions by the action of acetyl chloride and acetic anhydride on santonin.

In the infrared absorption most of the *trans*-butanolides exhibit >C=O stretching frequency at 1789–1790 cm.$^{-1}$ and the acetate (VI) displays a maximum at 1783 (in chloroform). The *trans* fusion of the lactone was also proved by the isomerization of compound II by the action of sulfuric acid in acetic anhydride[16] into the acetate (VII) of the more stable *cis*-fused levorotatory lactone. This acetate (VII) exhibits the butanolides (>C=O) maximum at 1767 cm.$^{-1}$, quite compatible with those of *cis*-fused lactones. On the other hand, II with acetic anhydride in pyridine afforded a different lactone acetate (VI) which is dextrorotatory. The treatment of II with *p*-toluenesulfonic acid in benzene afforded the *cis* lactone di-

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

(2) 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.

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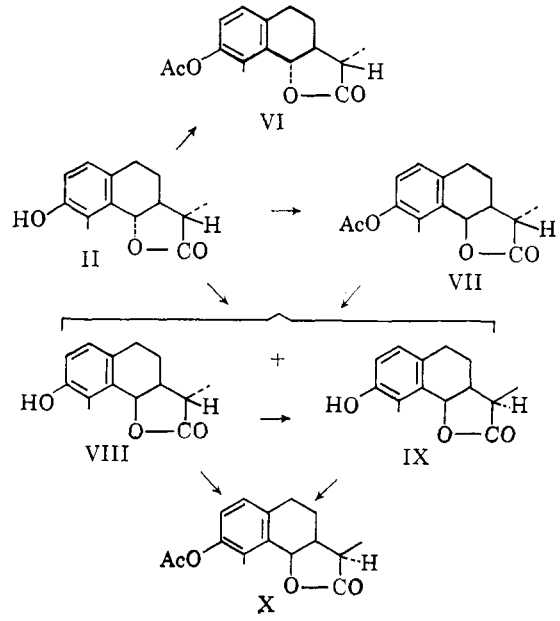
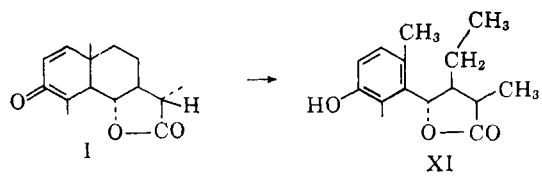
(16) W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4430 (1955).

rectly which on acetylation gave acetate VII. The same reaction under vigorous conditions effected inversion at C—11 and led to another levorotatory lactone (IX). The lactone (IX) gave a different acetate (X) which was not identical with any reported above. However, it exhibited an expected $\rangle C{=}O$ maximum at 1766 cm.$^{-1}$ for *cis* lactones. The hydrolysis of acetate VII with methanolic potassium hydroxide also yielded VIII and IX as the major and minor products, respectively. The latter was shown to be the 11(H) epimer of VIII by the treatment of VIII under known conditions of anhydrous potassium carbonate in refluxing xylene, which on acetylation gave an acetate (X).



From the above facts the lactone (II) was assigned the 6β(H), 7α(H), 11β(H) configuration,[17,18] and it was also concluded that the aromatization reaction does not change the original lactone configuration of santonin just as in case of the zinc dust reduction of santonin to santonone.[19]

Another aromatization reaction was carried out on santonin with zinc and ethylene glycol which yielded a different phenolic product (XI). This change was also accompanied with the evolution of considerable amount of methane gas and the ultraviolet spectrum of the crude product exhibited a characteristic phenolic chromophore at 280 mμ. However, analytical values of the purified product from alumina column chromatography, corresponded to the composition $C_{15}H_{20}O_3$.



From the infrared absorption it was concluded that there were two adjacent hydrogens on the benzene ring and that the unchanged lactone ring was retained. The n.m.r. spectrum showed the presence of two aromatic methyl groups and a triplet centered at 9.25 p.p.m. showed the presence of an ethyl group. Although the product (XI) could not oxidized to a desired carboxylic acid, on the basis of analytical and spectral data the product was assigned the structure $C_{15}H_{20}O_3$. Further studies concerning this problem are in progress.

Experimental[20]

6β(H),7α(H),11β(H)-1-Desmethyldesmotroposantonin (II).—A mixture of 20 g. of santonin, 200 g. of activated zinc, 200 ml. of dimethylformamide, and 15 ml. of water was refluxed with stirring for 30 min. The zinc was removed, the filtrate diluted with water and extracted with ethyl acetate. The extract was washed successively with 2% hydrochloric acid (400 ml.), 10% sodium bicarbonate, and water. After drying over sodium sulfate the solvent was removed *in vacuo* to leave a crystalline residue. Recrystallization of the residue from acetone yielded 3.22 g. (17.1 %) of product (II) as fine needles, m.p. 228–229°, $[\alpha]^{19}D$ +115° (chloroform), ultraviolet λ_{max}^{MeOH} mμ (ϵ): 286.5 (2820), infrared ν_{max}^{Nujol} cm.$^{-1}$: 3440 (OH), 1768 (lactone), 1606, 1588 (aromatic), 811 (2 H on benzene ring).

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; O, 20.67. Found: C, 72.63; H, 6.89; O, 20.85.

1-Methyl-7-ethyl-2-naphthol (III).—A mixture of 3 g. of II and 7 g. of 30% palladium on charcoal was heated at 260–270° in a metal bath for 12 hr. under a carbon dioxide atmosphere. The sublimed material in the long condenser was collected to afford 900 mg. of crude naphthol (III) which was used in the next reaction without further purification. Pure product melted at 93–94°.

1-Methyl-7-ethyl-2-naphthol O-Tosylate (IV).—A solution of 750 mg. of crude naphthol (III) and 834 mg. of *p*-toluenesulfonyl chloride in 4 ml. of pyridine was left overnight at room temperature. The mixture was poured into the ice–water and the resulting precipitate was washed thoroughly with water, dried, and recrystallized from methanol to yield 600 mg. of pure tosylate (IV) as needles, m.p. 114–115.5°, ultraviolet λ_{max}^{MeOH} mμ (ϵ): 280.5 (5372), 272.5 (5984), infrared $\nu_{max}^{CHCl_3}$ cm.$^{-1}$: 1365, 1178.

Anal. Calcd. for $C_{20}H_{20}O_3S$: C, 70.57; H, 5.92; O, 14.10. Found: C, 70.58; H, 5.89; O, 13.83.

1-Methyl-7-ethylnaphthalene (V).—A mixture of 150 mg. of tosylate (IV), 90 mg. of 30% palladium on charcoal, 15 ml. of ethanol, and 0.3 ml. of hydrazine hydrate (80% solution) was refluxed under a hydrogen atmosphere for 2 hr. The catalyst was removed by filtration and the filtrate was poured into ice–water. The resulting emulsion was extracted with petroleum ether and the extract was dried over sodium sulfate. The solvent was removed to leave 64 mg. of naphthalene (V) as a colorless oil; infrared ν_{max}^{Nujol} cm.$^{-1}$: 925, 875, 828, 750.

The picrate of V has m.p. 93–94° (lit.,[13,14] m.p. 94°).

Anal. Calcd. for $C_{19}H_{17}O_7N_3$: C, 57.14; H, 4.29; O, 28.05; N, 10.52. Found: C, 56.94; H, 4.61; O, 27.78; N, 10.62.

The styphnate of V has m.p. 125–126° (lit.,[13,14] m.p. 126°).

Anal. Calcd. for $C_{19}H_{17}O_8N_3$: C, 54.94; H, 4.13; O, 30.82; N, 10.12. Found: C, 54.95; H, 4.19; O, 30.98; N, 10.30.

Action of Acetic Anhydride and Sulfuric Acid on 6β(H),7α(H),-11β(H)-1-Desmethyldesmotroposantonin (II).—To a solution of 250 mg. of II in 4 ml. of acetic anhydride was added 1 drop of concentrated sulfuric acid and the mixture was heated on water bath for 20 min. The reaction mixture was poured into cold water, and the resulting precipitate was washed with water and dried to afford 211 mg. of crude acetate (VII). Recrystallization from methanol gave pure material as fine needles, m.p. 159.5–160.5°, $[\alpha]^{19.5}D$ −155.7°(chloroform), ultraviolet λ_{max}^{MeOH} mμ (ϵ): 268.5 (1714), 277 (1737), infrared $\nu_{max}^{CHCl_3}$ cm.$^{-1}$: 1767.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61; O, 23.30. Found: C, 69.92; H, 6.54; O, 23.45.

6β(H),7α(H),11β(H)-1-Desmethyldesmotroposantonin Acetate (VI).—A solution of 250 mg. of II in a mixture of 2 ml. of pyridine and 2 ml. of acetic anhydride was allowed to stand over-

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(19) Grassi-Cristaldi, *Gazz. chim. ital.*, **22**, II, 126 (1892).

(20) All melting points are uncorrected.

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°; $[\alpha]^{20}D$ +121° (chloroform), ultraviolet λ_{max}^{MeOH} mμ (ε): 268 (523), 277 (506), infrared $\nu_{max}^{CHCl_3}$ 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°, $[\alpha]^{21}D$ +202.7° (ethanol), ultraviolet λ_{max}^{MeOH} mμ (ε): 288 (2981), infrared ν_{max}^{Nujol} cm.$^{-1}$: 3376, 1751, 1596, 828, 818, $\nu_{max}^{CHCl_3}$ cm.$^{-1}$: 1769.

Anal. Calcd. for $C_{14}H_{18}O_3$: 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 λ_{max}^{MeOH} mμ (ε): 288 (3203), infrared $\nu_{max}^{CHCl_3}$ 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°, $[\alpha]^{19}D$ −169.3°(chloroform), infrared $\nu_{max}^{CHCl_3}$ 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°.

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

K. TSUDA, S. NOZOE, T. TATEZAWA, AND S. M. SHARIF[3]

Institute of Applied Microbiology, University of Tokyo, Bunkyo-Ku, Tokyo, Japan

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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 Δ^{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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(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.

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

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

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