ethylene glycol was heated under reflux for 45 min. The open flask was then heated until the temperature of the reaction mixture reached 200°, a reflux condenser was attached and refluxing was continued for a further 2 hrs. The solution was cooled, water was added, and the product was isolated with ether. The oily residue was chromatographed on alumina. Elution with hexane yielded first androstane and then androstan-11-one. The latter was purified most conveniently by pressing between filter paper; it weighed 1.62 g. (30%) and showed m.p. 45–47°, $[\alpha]_D$ + 65°. The analytical sample, obtained by high-vacuum distillation, showed m.p. 49–50°, $[\alpha]_D$ + 65°, ν_{max} 1700 cm.$^{-1}$ (reported:[3] m.p. 50–52°).

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.26; H, 10.85.

Testane-3,11,17-trione (IIIb). The saponification of 10 g. of pregnane-17α,21-diol-3,11,20-trione 21-acetate (Ib) suspended in 400 cc. of methanol was carried out by means of 1 g. of potassium hydroxide[18] in 5 cc. of water, as described above in the allo series. Addition of 1.5 cc. of glacial acetic acid, concentration to 200 cc., addition of 800 cc. of water, and ice-cooling resulted in the precipitation of 7.91 g. (88%) of pregnane-17α,21-diol-3,11,20-trione (IIb), m.p. 231–232° (reported:[19] m.p. 233–235°). This material (7.5 g.), dissolved in 300 cc. of glacial acetic acid and 300 cc. of water, was oxidized with 100 g. of sodium bismuthate as described above. The product was isolated by benzene extraction and the dried solution was evaporated and chromatographed on alumina. Elution with benzene and crystallization from ether furnished 4.73 g. (76%) of testane-3,11,17-trione (IIIb), m.p. 130–132°, $[\alpha]_D$ + 144° (reported:[12] m.p. 132–133°, 135–136°, $[\alpha]_D$ + 148°).

Testan-11-one (IVb). Testane-3,11,17-trione (4 g.) was reduced with 8 cc. of hydrazine hydrate in 50 cc. of diethylene glycol in the presence of 5 g. of potassium hydroxide and 5 cc. of water, as described previously. The product was isolated with ether and chromatographed on alumina. Elution with hexane and crystallization from ether yielded 2.41 g. (66%) of testan-11-one, m.p. 118–121°, $[\alpha]_D$ + 54°. The analytical sample showed m.p. 121–122°, $[\alpha]_D$ + 55°, ν_{max} 1700 cm.$^{-1}$.

Anal. Calcd. for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 82.91; H, 10.78.

Allopregnan-11-one (VIa). Allopregnane-3,11,20-trione (Va) (4.5 g.)[15] was reduced with 8 cc. of hydrazine hydrate in 80 cc. of diethylene glycol together with 8 g. of potassium hydroxide in 8 cc. of water, as described above for the preparation of IVa. The cooled reaction mixture was diluted with water, the precipitate was collected, dried, and chromatographed on alumina. Elution with hexane and crystallization from ether-methanol led to 2.44 g. (59%) of allopregnan-11-one with m.p. 101–104°. The analytical sample exhibited m.p. 108–109.5°, $[\alpha]_D$ + 60°, ν_{max} 1700 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.74; H, 11.33.

Pregnan-11-one (VIb). Pregnane-3,11,20-trione (Vb) (5 g.)[16] in 100 cc. of diethylene glycol was reduced with 10 cc. of hydrazine hydrate, 10 g. of potassium hydroxide, and 10 cc. of water, as described previously. The product was extracted with ether and chromatographed on alumina. Crystallization of the fractions eluted with hexane from ether-methanol yielded 1.91 g. (42%) of pregnan-11-one, m.p. 106–109°, $[\alpha]_D$ + 52°. A further purified specimen showed m.p. 111–113°, $[\alpha]_D$ + 54°, ν_{max} 1700 cm.$^{-1}$ (reported:[4] m.p. 112–114°, $[\alpha]_D$ + 56°).

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(19) L. H. Sarett, *J. Am. Chem. Soc.*, **70**, 1454 (1948).

[CONTRIBUTION FROM THE PHARMACEUTICAL INSTITUTE, KEIO-GIJUKU UNIVERSITY]

Santonin and Related Compounds. XII.[1] Stereoformulas of Tetrahydro-α-santonins[2]

MASAITI YANAGITA AND HARUO OGURA

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α, β, and γ-Tetrahydro-α-santonins were reassigned the stereoformulas III, VIII, and I on the basis of chemical evidence. Zinc-alcohol hydrogenation of the 5-dehydro-α-santoninic acid (VI, R = H) gave the Δ^1-3,5-diketo acid (VII, R = H), which was converted to santonic acid (XIV) with alkali. This offered strong support for the previously suggested mechanism of santonic acid formation from α-santonin (see ref. 15).

In the paper IV of this series,[3] it was described that α-santonin was catalytically hydrogenated to a mixture of three tetrahydro compounds, α, β, and γ, which are tentatively formulated as I, II, and III, respectively.

In these formulas, the configurations at the 5-, 6-, and 11-positions are the same as those in the α-santonin structure,[3] of which the former two were well established,[4,5] and the latter one remains obscure.[6] The assignment of the configurations at the juncture of two six-membered rings was based on molecular rotation differences, the relative reactivity toward bromine, and the mode of the preparations. However, these reasons for the formulations became questionable and revision of the above formulas seemed necessary on the following grounds.

(1) As shown in the paper VII of this series,[5]

(1) Paper XI, M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **22**, 291 (1957).

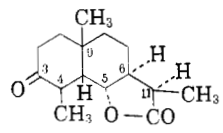
(2) This work was supported in part by the Grant in Aid for Scientific Research from the Ministry of Education of Japan.

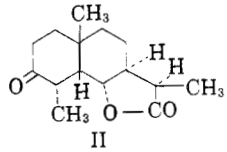
(3) M. Yanagita and A. Tahara, *J. Org. Chem.*, **20**, 959 (1955).

(4) For example see R. B. Woodward and P. Yates, *Chemistry & Industry*, 1391 (1954).

(5) A. Tahara, *J. Org. Chem.*, **21**, 442 (1956).

(6) Y. Abe, J. Miki, M. Sumi, and T. Toga, *Chemistry & Industry*, **1956**, 953.


I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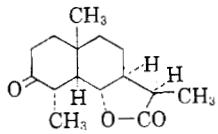
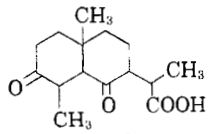
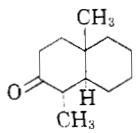
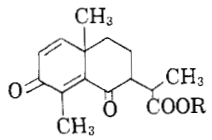
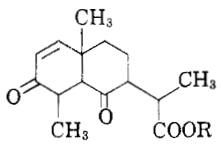
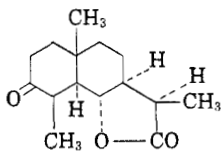

III


IVA,B


V


VI


VII

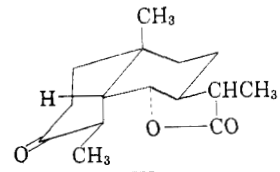

VIII

the α-3,5-diketo acid (IVA), prepared from α-tetrahydro compound (I), was proved to be thermodynamically more stable than the γ-diketo acid (IVB) from III. This relative stability of the two diketo acids is the reverse of that previously assumed.[3]

(2) In paper X[7] it was shown that catalytic hydrogenation of 4,9-dimethyl-Δ^4-3-octalone over palladium-charcoal resulted in a predominant formation of a *trans*-fused decalone (V). This unusual stereospecificity in the course of hydrogenation is difficult to reconcile with the *cis*-juncture of the six-membered rings in the α-tetrahydro compound (I), which is the chief product from α-santonin on similar hydrogenation.[3]

(3) It is known[8] that the 1,4-diketo-2,3-ene system in steroids, where the double bond terminates at the juncture of two six-membered rings, yielded the stable *trans*-fused compound predominantly on zinc–acetic acid hydrogenation, whereas with zinc-alcohol the *cis*-isomer is normally favored.

Matsumura, Iwai, and Ohki[9] reported the ready formation of the methyl ester of the α-diketo acid (IVA) by zinc–acetic acid hydrogenation of methyl 5-dehydro-α-santoninate (VI, R = CH_3), which was prepared from α-santoninic acid by chromium trioxide oxidation followed by esterification. On similar treatment, the free acid (VI, R = H) also was found to give the α-diketo acid but in a lower yield. On the other hand, the free acid (VI, R = H) was reduced with zinc-ethanol to afford a good yield of a monounsaturated acid (VII, R = H). The latter compound, in which the location of the double bond was proved by the ultraviolet absorption spectrum, λ_{max}^{MeOH} 225 mμ (log ϵ 3.84),[10] was readily hydrogenated over palladium-charcoal to the γ-3,5-diketo acid (IVB) quantitatively. Zinc-ethanol hydrogenation of the ester (VI, R = CH_3) to VII (R = CH_3) was less satisfactory than that of the free acid. Obviously, these observations are incompatible with the respective assignments of the *cis*- and *trans*-ring junctures in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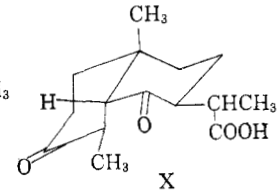
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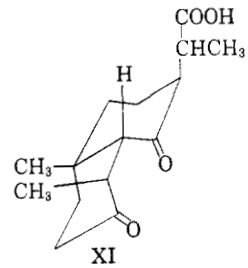
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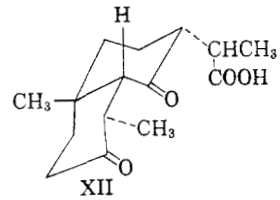
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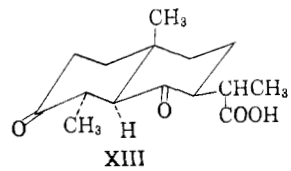
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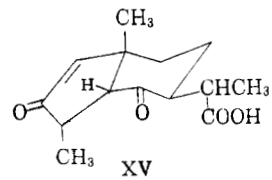
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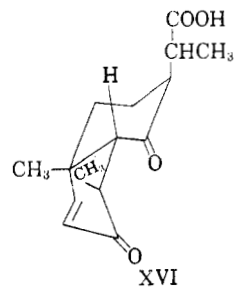
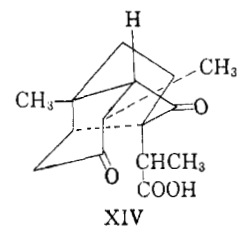

XVI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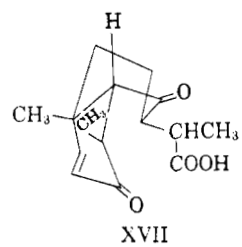
XVII

(7) M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956).

(8) Budziarek and Spring, *J. Chem. Soc.*, **1953**, 956.

(9) H. Matsumura, I. Iwai, and E. Ohki, *J. Pharm. Soc. Japan*, **75**, 1043 (1955).

(10) L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd Ed., Reinhold Publishing Corp., New York, 1949, p. 190.

the α- and γ-diketo acids (IVA and IVB), derived from the tetrahydro formulas I and III, respectively.

Based on the evidences cited above, α-tetrahydrosantonin must be reassigned the formula III and the γ-isomer I, reversing to those proposed previously.[3] Consequently the β-isomer, which differs from the α-isomer only in the configuration of the methyl group at the 4-position, should be formulated as VIII in place of II.[11]

Thus, it is seen that the known correlation between the molecular rotation differences and the juncture configurations of the rings A and B in steroids,[12] which is responsible for the false formulations of I to III, cannot be applied to the tetrahydrosantonins.

It is generally accepted that a simple *cis*-3-decalone might exist in two conformations.[13] The γ-tetrahydrosantonin (I), though it is *cis*-fused, should take up only one conformation IX, since the decalone ring in this compound is fixed by fusion of the *trans*-lactone ring. The γ-3,5-diketo acid (IVB) might be described by the conformations X and XI. In these two, the former possesses the ring substituents at the 4- and 6-positions in equatorial conformation, while in the latter the corresponding groups are axial. It is clear that in the ring conversion equilibrium of these conformations, X is much favored. Since the γ-diketo acid (IVB) contains three labile asymmetric centers α to the keto group, a possibility must be considered that alkali treatment of this acid would give, together with the α-isomer (IVA), the alternative *cis*-isomer (XII), being formed through XI by inversion of its axial ring substituents.

Very recently, Klyne[14] discussed the stability of the cyclohexanones by making allowances for the three kinds of nonbonded interactions, *viz.* 2- and 3-alkylketone effects and the skew-butane interaction. By application of this argument to the present *cis*-diketodecalins (X and XII), the values of nonbonded energy differences for the conformations X and XII are calculated to be approximately 5.1 and 5.2 kcal. mole^{-1}, respectively. With the *trans*-isomer (IVA), the corresponding value for the conformation XIII is almost the same (5.3 kcal. mole^{-1}). These would imply that the three conformations should be of nearly equal stability. In fact, alkali isomerization of the diketo acid (IVA or IVB), as reported previously,[5] gave rise to a mixture of these isomers, in which the *trans*-isomer was predominant. No detection of the alternative isomer of IV was reported in this reaction. The failure in the conversion of X into XII seems not in accordance with Klyne's rule, but this anomaly is corrected by assigning a value <0.8 kcal. mole^{-1} to the 2-alkylketone effect, as in the case of the isomers of 9-methyl-4-decalone, which presented an exception to this rule.

In their brilliant work on elucidation of the structure of santonic acid (XIV), Woodward and his collaborators[15] suggested a possible mechanism for the formation of santonic acid from α-santonin, which proceeds through the hypothetical intermediate possessing the structure (VII, R = H). It may be expected that the compound VII which is now available will afford santonic acid with alkali under analogous conditions. This expectation was confirmed and the yield of santonic acid was comparable to that from α-santonin. For VII, which is *cis*-locked, two conformations XV and XVI, corresponding respectively to X and XI of the γ-diketo acid, would be adopted, in which the former carrying the ring substituents in equatorial position should be much more stable. Conversion of XV into XVI possibly passes through an intermediate XVII, where the ring with double bond is inverted and the other ring assumes a boat form. From the examination of molecular models, it can be seen that transformation of the Δ^1-3,5-diketo acid (VII) into santonic acid proceeds only by way of the conformation XVII, carrying the carbon atoms at the 1- and 6-positions in proximity. It is reasonable to consider that the isomerization of XVII to santonic acid (XIV) under strongly basic conditions involves a bond formation between the above two ring carbons by internal Michael condensation and subsequent inversion of the axial methyl group at the 4-position to an equatorial conformation. Woodward and Yates[4] assigned the same configuration to santonic acid, but in a different expression.

EXPERIMENTAL[16]

All melting points were uncorrected. Rotations were determined in a 0.5-dm. microtube with ethanol as the solvent.

5-Dehydro-α-santoninic acid (VI, R = H). This was prepared from α-santoninic acid with chromium trioxide–pyridine[9] (yield, 62%) or chromium trioxide–acetic acid[7] (yield, 63%) by the procedures previously reported. Recrystallization from ethyl acetate or dilute methanol gave plates, m.p. 135–136°; λ_{max}^{MeOH} 248 mμ (log ϵ 4.08), $[\alpha]_D^{24}$ −130.4° (*c* 0.77). Reported, m.p. 134–136°;[9] λ_{max}^{MeOH} 248 mμ (log ϵ 4.11)[7]; $[\alpha]_D^{15}$ −82.6° (*c* 2.1, $CHCl_3$)[9] and $[\alpha]_D^{24}$ −120° (*c* 1, EtOH).[17]

The *methyl ester* was prepared with diazomethane as reported previously.[9,17] After chromatographic separation, the petroleum ether elutions gave 76% of the crude ester, m.p. 78°, which was recrystallized from ether–petroleum ether to afford prisms, m.p. 86°; $[\alpha]_D^{24}$ −115.0° (*c* 0.40).

(11) During the later stages of this investigation C. Djerassi kindly informed us that, based on the study of rotatory dispersion curves, the configurations at the juncture of two six-membered rings in α-, β-, and γ-tetrahydrosantonins (I, II, and III) should be revised as described in this paper.

(12) Ref. 10, p. 212.

(13) A. S. Dreiding, *Chemistry & Industry*, 1954, 1419.

(14) W. Klyne, *Experientia*, 12, 119 (1956).

(15) R. B. Woodward, F. J. Brutschy, and H. F. Baer, *J. Am. Chem. Soc.*, **70**, 4216 (1948).

(16) Microanalyses were by Miss C. Shibuya, and the ultraviolet measurements by Miss M. Suzuki.

(17) M. Nishikawa, K. Morita, and H. Hagiwara, *J. Pharm. Soc. Japan*, **75**, 1199 (1955).

Reported, m.p. 68–69°[9] and m.p. 81°[71]; $[\alpha]_D^{15}$ −62.5° (*c* 2.8, $CHCl_3$)[9] and $[\alpha]_D^{24}$ −112.8° (*c* 1, EtOH).[17]

Zinc–acetic acid reduction of 5-dehydro-α-santoninic acid (VI, R = H). To a solution of 0.50 g. of the above 5-dehydro acid (VI, R = H) in 10 cc. of glacial acetic acid was added 0.75 g. of activated zinc dust (treated with dilute hydrochloric acid). The mixture was heated to reflux for 4 hr. After cooling, the precipitate was filtered off, and the filtrate was evaporated under reduced pressure. The residual viscous oil was dissolved in ether, and the ether solution was washed successively with sodium chloride–saturated water, sodium bicarbonate solution, and water. Evaporation of the dried ether solution gave a neutral oil (0.04 g.), which could not be induced to crystallize even after treatment with pyridine–chromium trioxide in the cold to remove any contaminating alcohol. The bicarbonate solution was acidified and extracted with ether, and the ether solution was dried and evaporated. The residual oil (0.45 g.), which partly solidified, was dissolved in 1 cc. of pyridine, mixed with a solution of chromium trioxide (0.20 g.) in pyridine (4 cc.), and allowed to stand in a refrigerator overnight. After working up as usual, there was obtained 0.22 g. (44%) of an acidic product, which was recrystallized from dilute ethanol to give plates, m.p. 97°.[18] After drying *in vacuo* at 60°, the dehydrated material showed the m.p. 152.5°. It melted at 150.5° on admixture with the α-3,5-diketo acid, m.p. 147–148°, reported previously.[5,19]

In this reduction, use of ethanol–acetic acid in place of acetic acid alone somewhat improved the result. To a refluxing solution of 0.10 g. of the 5-dehydro acid (VII, R = H) in 5 cc. each of acetic acid and ethanol was added 1.5 g. of activated zinc dust in three portions. After the refluxing was continued for 1.5 hr., the reaction mixture was filtered and evaporated under reduced pressure, and the residual oil was extracted with benzene. Evaporation of the dried benzene solution left an oil (0.10 g.), which on treatment with petroleum ether gave 0.06 g. (60%) of a solid (IVA), m.p. 67°. Recrystallization from a mixture of 5% hydrochloric acid and methanol afforded prisms, m.p. 80°, which after drying *in vacuo* at 60° showed the m.p. and mixed m.p. 147–148°.

Zinc-ethanol reduction of 5-dehydro-α-santoninic acid (VI, R = H). To a refluxing solution of 1.0 g. of the 5-dehydro acid (VI, R = H) in 70 cc. of 99% ethanol was added 8 g. of activated zinc dust in four portions. The refluxing was continued for 10 hr. and a yellow color was developed in the early stages of the reaction, which eventually disappeared. The cooled reaction mixture was filtered, the colorless filtrate was evaporated, and a small amount of acetone was added. Filtration and evaporation of the acetone solution gave an oil (0.95 g.), which on treatment with petroleum ether afforded 0.88 g. (88%) of the Δ^1-3,5-diketo acid (VII, R = H), as a microcrystalline solid, m.p. 185°. Recrystallization from benzene by addition with petroleum ether raised the m.p. to 190–191°.

To a solution of this material (0.10 g.) in 2 cc. of acetone was added 10 cc. of 5% hydrochloric acid and the mixture was warmed on a water bath for 30 min. The acetone solution was allowed to stand in a refrigerator under spontaneous evaporation of the solvent and there was obtained 0.08 g. (80%) of plates, m.p. 173°. Recrystallization from ethanol by addition of water raised the m.p. to 178°; λ_{max}^{MeOH} 225 mμ (log ε 3.84); $[\alpha]_D^{24}$ −213.8° (*c* 0.53). It melted at 190° on admixture with the above form, m.p. 190–191°. Probably dimorphism is the cause of the different melting points of these two forms. The substance of the lower melting point was used for analysis.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.60; H, 7.81.

The two forms of this acid quantitatively formed the same *semicarbazone*, which on crystallization from ethanol gave prisms, m.p. 222° (decomp.).

Anal. Calcd. for $C_{16}H_{23}N_3O_4$: C, 59.79; H, 7.21; N, 13.08. Found: C, 59.59; H, 7.51; N, 12.60.

A solution of 0.14 g. of the acid of the lower melting point in 30 cc. of ether was treated with the ether solution of diazomethane. When the yellow color of the diazomethane did not fade, an excess of the diazomethane was immediately decomposed with acetic acid. The ether solution was washed with sodium bicarbonate solution, dried, and evaporated, leaving a viscous oil (0.12 g.), which was chromatographed on alumina (0.8 × 12 cm.). Elution with benzene gave 0.09 g. (65%) of the *methyl ester* (VII, R = CH_3) as prisms, m.p. 88°. Recrystallization from petroleum ether raised the m.p. to 99°; λ_{max}^{MeOH} 226 mμ (log ε 4.06); $[\alpha]_D^{25}$ −188.6° (*c* 0.23). An analytical sample was dried over phosphorus pentoxide at room temperature for 5 days.

Anal. Calcd. for $C_{16}H_{22}O_4.H_2O$: C, 64.84; H, 8.16. Found: C, 64.54; H, 8.29.

The methyl ester (VI, R = CH_3) of the 5-dehydro acid was reduced with zinc-ethanol under similar conditions. A mixture of 0.05 g. of the methyl ester and 0.5 g. of zinc dust in 20 cc. of ethanol was refluxed for 3 hr. After addition of another 0.5 g. of zinc dust, the reflux was kept for 3 hr. further. Filtration of zinc and evaporation of the filtrate gave an oily residue, which was dissolved in a small amount of benzene and filtered. The benzene solution was evaporated to give a viscous oil, which could not be crystallized and was chromatographed on alumina (0.8 × 9.5 cm.). Elutions with petroleum ether–benzene gave 0.02 g. (40%) of the Δ^1-3,5-diketo acid methyl ester (VII, R = CH_3), m.p. 69°. Recrystallization from ether–petroleum ether afforded prisms, m.p. 95°, which melted at 97° on admixture with the above sample, m.p. 99°.

Catalytic hydrogenation of the Δ^1-3,5-diketo acid (VII, R = H). The above Δ^1-3,5-diketo acid (VII, R = H) (0.05 g.), m.p. 190–191°, was hydrogenated in acetone (10 cc.) over palladium-charcoal (prepared from 0.1 cc. of 1% palladium chloride solution and 0.01 g. of activated charcoal). One mole of hydrogen (4 cc.) absorbed rapidly. Removal of the catalyst and evaporation of the solvent afforded needles (0.05 g., 100%), m.p. 170°, which on recrystallization from dilute ethanol showed the m.p. 186°, undepressed on admixture with the γ-3,5-diketo acid (IVB), m.p. 186–187°.[5]

The other form, m.p. 178°, was similarly hydrogenated to the same product (IVB).

Conversion of the Δ^1-3,5-diketo acid (VII, R = H) *to santonic acid* (XIV). The above Δ^1-3,5-diketo acid (VII, R = H) was treated with alkali by the procedure previously reported for the conversion of α-santonin to santonic acid (XIV).[15] A solution of 0.10 g. of the Δ^1-diketo acid in potassium hydroxide solution (0.24 g. of KOH in 0.5 cc. of water) was heated to reflux for 1 hr. The solution was acidified and extracted with ether and the dried ether solution was evaporated to leave 0.07 g. (70%) of white crystals, m.p. 163°. Recrystallization from ethanol raised the m.p. to 170°; $[\alpha]_D^{19}$ −75.0° (*c* 0.24). It showed no depression of the melting point on admixture with santonic acid, m.p. 171°, prepared from α-santonin as reported previously.[15] Reported, m.p. 170–172° and $[\alpha]_D^{9}$ −74.1° (EtOH).[20]

SHINJUKU-KU, TOKYO, JAPAN

(18) It was 20° higher than the reported m.p. (76–78°),[5] the cause of which was not examined.

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(20) J. C. Simonsen and J. H. R. Barton, *The Terpenes*, 2nd Ed., The University Press, Cambridge, 1952, Vol. III, p. 295.