[CONTRIBUTION FROM THE PHARMACEUTICAL LABORATORY, MEDICAL SCHOOL, KEIO-GIJUKU UNIVERSITY]

Santonin and Related Compounds. XIII. Attempted Preparation of *trans*-3,5-Diketo-α-sant-Δ¹-enic Acid[1,2]

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Preparation of the acid (III) mentioned in the title was attempted by three different methods, but all proved unsuccessful. First, epimerization of the *cis*-Δ¹-diketo acid (I) into the *trans* isomer (III) could not be effected under the mild conditions employed. The second method, involving lactone-opening and subsequent oxidation of *trans*-Δ¹-dihydrosantonin (VI), gave not the desired acid (III), but an unidentified product. The third attempt of dehydrobromination of the 2-bromo-*trans*-diketo acid (IX) furnished only the enol lactone (XII) under rearrangement. Similar treatment of the bromide (XIII) of the *cis*-diketo acid (IV, R = H) resulted in a mixture of the Δ¹-diketo acid (I) and the same enol lactone. A possible explanation for the position of bromination in some pairs of the *cis* and *trans* series of 3-decalone systems is proposed.

In paper XII of this series,[1] we described the preparation of *cis*-3,5-diketo-α-sant-Δ¹-enic acid[3] (I) by selective hydrogenation of 3,5-diketo-α-santa-Δ¹,⁴-dienic acid (II) with zinc and ethanol. It seems of interest to prepare the *trans* isomer (III) of I for comparison of their behavior in some reactions, especially toward isomerization to santonic acid with alkali.[1]

It was reported[4] that the interconversion of *cis*- and *trans*-3,5-diketo-α-santanic acids (IV and V, both R=H) by isomerization was readily effected by warming with dilute alkali. Under similar conditions, isomerization of *cis*-Δ¹-diketo acid (I) into the *trans* isomer (III), which was expected to be more stable, was attempted. After careful examination of the reaction mixture, most of the starting acid was recovered and the *trans* acid could not be isolated. It is noteworthy that the *cis* configuration at the ring juncture in I is more resistant toward alkaline isomerization than the saturated *cis*-diketo acid (IV, R=H).

As a possible second route to the *trans* acid (III), the lactone opening and subsequent oxidation of *trans*-Δ¹-dihydro-α-santonin (VI) came under consideration. It had been disclosed from the authors' laboratory[5] that the 2-bromide of *trans*-tetrahydro-α-santonin (VII, R=Br) on collidine treatment gave only a low yield of the Δ¹-dihydro compound (VI) as the sole product isolated. In order to improve the reported result, dehydrobromination of the bromide (VII, R=Br) was performed with lithium chloride and dimethylformamide, which reagents are known to be effective in the dehydrohalogenation of α-halo-3-ketosteroids.[6,7] When the reaction was conducted under the conditions favorable for dehydrobromination of the bromoketosteroids,[6] the known chloro compound (VII, R=Cl)[8,9] was formed in a good yield. Since the halogen in α-chloro-3-ketosteroids was dehydrochlorinated by these reagents only at higher temperatures than the bromo analogs,[6,7] the bromide (VII, R=Br) was treated with these reagents at a higher temperature, in view of possible intermediate formation of the above chloro compound. There was indeed obtained a halogen-free mixture, but the desired Δ¹- compound could not be isolated from it. As mentioned previously with the 2-chloro-3-ketosteroids,[10] this chloro compound showed resistance toward hot collidine, but was readily reduced with zinc and ethanol to the parent ketone (VII, R=H). The location of the chlorine at the 2- position, which is not evident from the previous work,[8] can be given by the mode of its formation. It involves the above replacement reaction of halogens in the 2-bromo compound (VII, R=Br) where the location of bromine was confirmed,[11] and the direct chlorination of VII (R=H) with chlorine which possibly parallels 2-bromination with bromine.[5,11] Based on the ultraviolet spectrum, the

(1) Paper XII, M. Yanagita and H. Ogura, *J. Org. Chem.*, **22**, 1092 (1957).

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

(3) For the definition of the nomenclature employed and the numbering system used in this paper, see W. G. Dauben and P. D. Hance, *J. Am. Chem. Soc.*, **77**, 606 (1955). The term *cis-trans* refers to the configuration at the juncture of six-membered rings, corresponding to γ- and α-tetrahydrosantonins in our previous papers of this series, and the term α-β represents the α- and β-santonin series, which are epimers at the methyl group of the 11- position.

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

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

(6) R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

(7) J. J. Beereboom and C. Djerassi, *J. Org. Chem.*, **19**, 1196 (1954).

(8) E. Wedekind and K. Tettweiler, *Ber.*, **64**, 387 (1931).

(9) Since completion of this experimentation, a communication by W. Cocker and T. B. H. McMurry [*J. Chem. Soc.*, 4549 (1956)] appeared describing the same result. However, these authors obtained, in an unspecified yield, the chloro compound, the melting point of which was about 30° lower than that reported previously[8] and given in the present work. Unfortunately, the previous work[8] was overlooked by these authors.

(10) J. J. Beereboom, C. Djerassi, D. Ginsburg, and L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 3500 (1953).

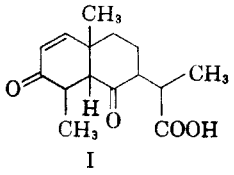
(11) Unpublished work.

chlorine in VII (R = Cl) was previously assigned an equatorial conformation,[9] and this was further evidenced by the shift (24 cm.$^{-1}$) in carbonyl absorption from the tetrahydroketone (VII, R = H) to the chloro compound (VII, R = Cl).[12]

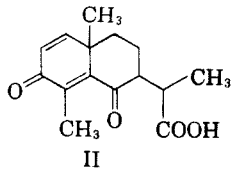
Two possible mechanisms were suggested by Holysz[6] for dehydrobromination of the 4-bromo-3-ketosteroids of the natural series (rings A/B: *cis*) into the Δ^4- compound with lithium chloride and dimethylformamide. The one involves an intermediate formation of a displacement product with an axial chlorine at the 4- position, a favorable conformation for ionic elimination. The other, which is considered more plausible, is a concerted mechanism with a transition state involving a six-membered ring between the bromide and the reagents. The above reaction of the bromo compound (VII, R = Br) with lithium chloride does not seem to follow either of the mechanisms of Holysz. It is reasonable to consider that the substitution of bromine by chlorine in VII (R = Br) gives an intermediate compound with axial chlorine, which, contrary to the case of steroids, may be immediately inverted to the stable equatorial position.

Attempt was made to transform the Δ^1-*trans*-dihydro compound (VI) into the desired *trans*-Δ^1-3,5-diketo acid (III) by lactone-opening and subsequent oxidation under similar conditions as described for the conversion of VII (R = H) to the corresponding diketo acid (V).[4] There was isolated, in low yield, unidentified crystals, which showed none of the characteristics expected of III, and was not further investigated.

The third line of approach to III involved the bromination-dehydrobromination of the *trans*-diketo acid (V) in the usual manner. The starting material (V) has been previously prepared by the two different methods, both of which are unsuitable for our purpose. Thus, the hydroxy acid, prepared from the *trans*-tetrahydro compound (VII, R = H) by lactone opening, was reported to give a rather poor yield of V on oxidation with chromium trioxide. Another method, consisting in hydrogenation of the methyl ester of $\Delta^{1,4}$-diketo acid (II) followed by hydrolysis to the free acid,[13] appears tedious. It has been found now that direct hydrogenation of the $\Delta^{1,4}$-diketo acid (II) itself over Raney nickel in the presence of potassium carbonate in dilute methanol resulted in 80% yield of V in a sterically pure state.

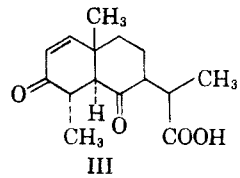


I

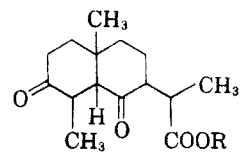


II

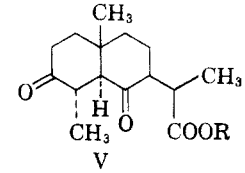
(12) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1953).
(13) H. Matsumura, I. Iwai, and Ohki, *J. Pharm. Soc. Japan*, **75**, 1043 (1955).



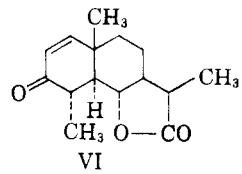
III



IV



V



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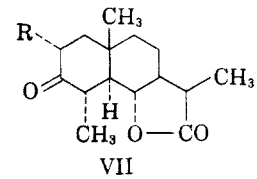
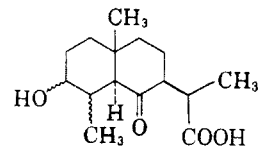
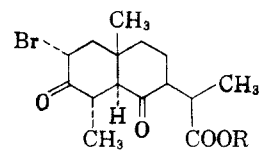


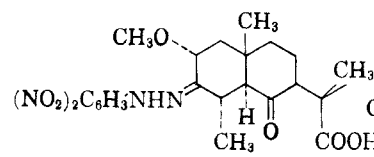
VII



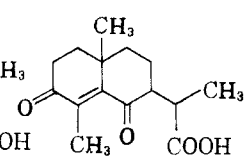
VIII



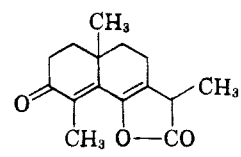
IX



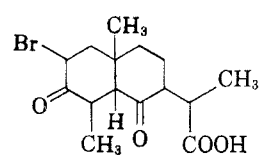
X



XI



XII



XIII

On hydrogenation of II with platinum black in acetic acid, a hydroxy acid (VIII) was formed in 78% yield, which was oxidized to the *trans*-diketo acid (V), indicative of the *trans* fusion of VIII. This hydroxy acid was unaffected by warm hydrochloric acid (no lactone formation) and did not give a 2,4-dinitrophenylhydrazone. These results show that in this hydrogenation, the keto group at the 3- position in II was highly selectively reduced to the hydroxy group, while the severely hindered keto group at the 5- position was preserved, as in the case of the saturated 3,5-diketo acids (IV and V, both R = H).[4] The hydroxy acid,[4] previously obtained by hydrogenation of V (R = H), is isomeric but not identical with VIII, probably being different in the configuration at the 3- and/or 4- positions.

Treatment of the *trans*-diketo acid (V) with one mole of bromine in chloroform afforded a monobromo compound (IX, R = H), as the single product, in 90% yield. Similar bromination of the methyl ester of V led to the ester of the mono-

bromide (IX) in low yield. To establish the position of bromine, the monobromide (IX, R=H) was treated with Brady's reagent[14] to give the 2,4-dinitrophenylhydrazone of the methoxyl derivative (X). This hydrazone proved identical with the same derivative of the methoxyl compound, prepared from 2-methoxy-*trans*-tetrahydro-α-santonin (VII, R=OCH_3) by lactone-opening and subsequent oxidation with chromium trioxide. Compound VII (R=OCH_3) had previously been obtained from the 2-bromo compound cited above (VII, R=Br) by reaction with Brady's reagent followed by hydrolysis.[5] Accordingly, the monobromide of the *trans*-diketo acid (V) must possess the 2-bromo structure (IX), excluding the possibility that the bromine may be located at other positions α to the keto groups. An equatorial orientation of the bromine in IX, which was rendered likely by conformational analysis,[12] was indicated by the shift in carbonyl absorption (12 cm.$^{-1}$) from the diketo acid (V) to IX.[12]

Dehydrobromination of the bromodiketo acid (IX) was carried out with hot collidine, forming 1.02 moles of the collidine salt. Unexpectedly, there was obtained a neutral brown oil, along with a lesser amount of acidic product. From the latter fraction, the desired Δ^1- compound (III) could not be isolated. The neutral oil, which refused to crystallize, was converted to 2,4-dinitrophenylhydrazone. Use of lithium chloride and dimethylformamide in place of collidine furnished a similar result, but the two fractions were obtained in higher yields.

It had been announced[15,16] that *rac*-Δ^4-3,5-diketo acid (XI) was converted, on heating by itself, to the enol lactone (XII) as yellow crystals, the melting point of which was variable. On repetition, it was found that the yield of XII was somewhat raised by conducting the pyrolysis at a lower temperature. Similar formation of enol lactone may be expected to take place in the above reaction of the bromide (IX) with a base. Indeed, analogous treatment of XI with lithium chloride and dimethylformamide at a high temperature furnished a neutral brown sirup, which was converted to its 2,4-dinitrophenylhydrazone. The latter was shown to be identical with the derivative of crystalline enol lactone (XII) and also with that of the neutral oil obtained above from the bromide (IX). Consequently, it is obvious that the dehydrobromination of the bromide (IX) with bases is attended with rearrangement to give the Δ^4- compound, as the sole product isolated.

Another interesting method for preparing the enol lactone (XII) has been reported involving selective hydrogenation of the enol lactone of the $\Delta^{1,4}$-diketo acid (II) over Raney nickel in the presence of pyridine in ether solution.[16] In the present work, it was found that hydrogenation of the $\Delta^{1,4}$-enol lactone into XII in a comparable yield was also achieved by using palladium-charcoal as a catalyst in acetone in the absence of a base. Similarly, the $\Delta^{1,4}$-diketo acid (II) itself can be reduced to the Δ^4-diketo acid (XI) in a fair yield. The latter was further hydrogenated with zinc and ethanol to the *cis*-diketo acid (IV, R=H), providing evidence for the location of the double bond between the keto groups in XI.

Since, as described above, the bromo-*trans*-diketo acid (IX) behaved abnormally on dehydrobromination, the *cis* isomer (XIII) was subjected to the same sequence of reactions. Bromination of the *cis*-diketo acid (IV) took place less readily than that of the *trans* isomer (V). Collidine treatment of the *cis*-monobromide (XIII) resulted in the formation of 0.97 mole of collidine salt, and the isolation of the *cis*-Δ^1-diketo acid (I), the normal product, in a low yield. In addition, a lesser amount of the enol lactone (XII) was isolated from the neutral fraction, as its 2,4-dinitrophenylhydrazone. Use of lithium chloride and dimethylformamide gave both products in better yields. In this case, however, there is a possibility that the bromide of the *cis*-diketo acid (IV, R=H) might be isomerized to the bromide of the more stable *trans*-isomer (V, R=H) on treatment with hot collidine, producing the unsaturated enol lactone (XII). Reported facile interconversion between these isomeric diketo acids with alkali[4] seems to favor this possibility. On heating IV with collidine, the starting ketone was substantially recovered and the *trans* isomer could not be detected. This excluded the foregoing possibility, indicating that the *cis*-bromide (XIII), unlike the *trans*-bromide (IX), on treatment with a base furnished a mixture of the double-bond isomers. The 2-bromo structure (XIII) for the *cis*-bromo-diketo acid can be assigned on the basis of its transformation to the Δ^1- compound (I) on dehydrobromination, since, in the 9-methyl-3-decalone systems, the 4-monobromo compound is unlikely to undergo rearrangement to the Δ^1-compound (I) on treatment with a base, especially when the bromine is tertiary.[17] From the relative stability to acid, the bromine in XIII may be assigned an equatorial conformation, though the shift in carbonyl absorption due to α-bromine is small (3 cm.$^{-1}$).[12]

It is interesting that, of the isomers of the bromodiketo acids, the *trans* fused one (IX) showed a much greater tendency to undergo rearrangement during dehydrobromination. A similar example is found in the results reported with the isomers of

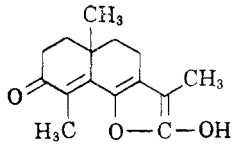
(14) A saturated methanolic solution of 1 part of 2,4-dinitrophenylhydrazine in 4 parts of concentrated sulfuric acid.

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

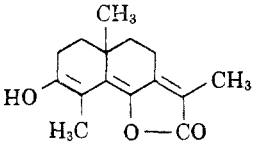
(16) M. Nishikawa, K. Morita, and H. Hasegawa, *J. Pharm. Soc. Japan*, **75**, 1202 (1955).

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

2,4-dibromo-9-methyl-3-decalone, of which the *trans* isomer on collidine treatment is rearranged into the $\Delta^{4,5}$-dienone, whereas the *cis* isomer forms the normal $\Delta^{1,4}$-dienone.[18] It is also noted that the Δ^4-diketo acid (XI) readily forms the enol lactone ring on heating, while the *cis*-Δ^1-diketo acid (I) remains unaffected. The facile dehydration in the former may be due to an electronic factor which favors elimination by the formation of a linear-conjugated dienone system. The two structures XIV and XV for the enol lactone (XII) were proposed by Nishikawa *et al.*[16] on the basis of ultraviolet and infrared absorption spectra. These formulations find further support in our observation that 3,5-diketo-β-sant-Δ^4-enic acid, a C_{11}-methyl epimer of XI, was converted to the same enol lactone by a similar procedure.[19] The unsuccessful recovery of the crystalline enol lactone from the usual solvent on heating may be attributed to the possible formation of a tautomeric equilibrium between the keto (XII) and the enol forms (XIV or XV or both) in the solution. The mutarotation[15] of the enol lactone in alcohol supports this assumption.



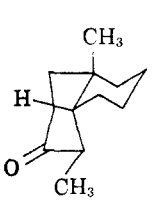
XIV



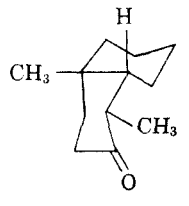
XV

It is recorded that bromine preferentially attacks the 4- position in *cis*-4,9-dimethyl-3-dedalone[17] and in the 3-ketosteroids of the natural series.[20] On the other hand, *cis*-tetrahydro-α-santonin is reported to be brominated at the 2- position,[5] like the *cis*-diketo acid (V) described above.

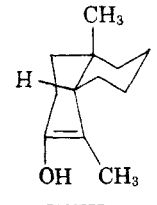
Dreiding[21] proposed an interesting rationalization for the position of bromination in the juncture isomers of 3-decalones and 3-ketosteroids in connection with the direction of enolization, which is governed by the steric (skew interaction) and the electronic factors (hyperconjugation effect). It was postulated by this author that, in 3-ketosteroids of the natural series, an enolization toward the 4- position is more favored by one less skew interaction than that toward the 2- position, agreeing with the bromination result of these ketones. The 4- bromination of *cis*-4,9-dimethyl-3-decalone can be connected with preference of Δ^3-enolization (XVIII and XIX, respectively) in the two conformations (XVI and XVII), which are more stabilized by the above factors than the Δ^2-enolization.



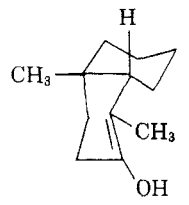
XVI



XVII

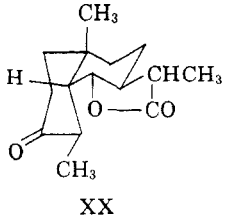


XVIII

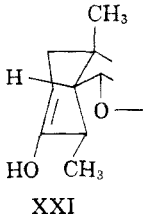


XIX

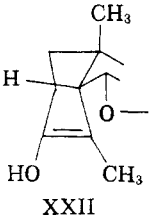
The bromination of *cis*-tetrahydro-α-santonin at the 2- position seems to be inconsistent with the stability of an enol structure which is governed by the above factors. In this case, however, a new non-bonded interaction must be considered to appear between the hydroxyl group of the lactone ring and the methyl group at the 4- position. This interaction, the strength of which is equivalent to that of the *meta*-diaxial effect in the cyclohexane ring, may be expected to play an important part in determining the direction of enolization in this molecule. Examination of molecular models showed that the strength of this interaction remains almost unchanged in the Δ^2-enol structure (XXI). On the other hand, the enolization toward the 4- position (XXII) causes a closer proximity of the two referred substituents, by which the interaction should be increased to exert a severe steric hindrance to uniplanar arrangement of the double bond. Thus, in XX, the steric factor outweighs the electronic effect, favoring the Δ^2-enolization (XXI) which is in agreement with the result of bromination in this ketone.



XX



XXI



XXII

In two possible conformations[1] of the *cis*-diketo acid (IV), an analogous steric interference is assumed to exist between the methyl group at the 4- position and the keto group at the 5- position. The 2- bromination of IV is similarly explained on the basis of preference of the Δ^2-enolization which is conceivable for the same reasons as stated for XX.

In the *trans*-fused 3-decalone rings, the relative stability of two enol structures may be predicted

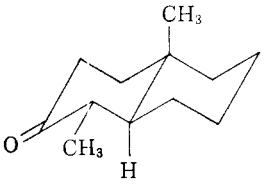
(18) M. Yanagita and A. Tahara, *J. Org. Chem.*, **18**, 792 (1953); *cf.* M. Yanagita, K. Yamakawa, A. Tahara, and H. Ogura, *J. Org. Chem.*, **20**, 1767 (1955).

(19) Unpublished work.

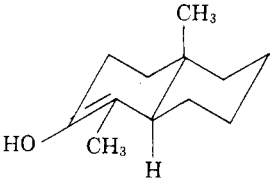
(20) C. W. Shoppee and E. Shoppee in E. H. Rodd's *Chemistry of Carbon Compounds*, Elsevier Publishing Company, New York, 1953, Vol. II B, p. 833.

(21) A. S. Dreiding, *Chem. & Ind. (London)*, 1419 (1954).

only by the hyperconjugation effect, when the other factors operating between the ring substituents are equal.[21,22] Thus, in the 3-keto-steroids of allo series (rings A/B; *trans*), this effect favors the Δ^2-enol structure, being in harmony with the 2- bromination of these ketones.[20] The 4-bromination in *trans*-4,9-dimethyl-3-decalone (XXIII) can be similarly rationalized by the Δ^3-enolization (XXIV) due to the electronic factor.

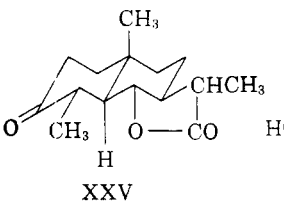


XXIII

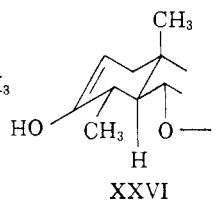


XXIV

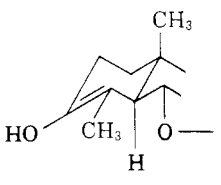
On the other hand, the 2- bromination of *trans*-tetrahydro-α-santonin (VII, R=H), which is described by XXV, is assumed to be attributable to the nonbonded interaction between the two substituents at the 4- and 5- positions which prefers the Δ^2-structure (XXVI) rather than the Δ^3-structure (XXVII) as in the case of the *cis* isomer (XX). The same steric interpretation can be adapted for the 2- bromination of the *trans*-diketo acid (V).



XXV



XXVI



XXVII

EXPERIMENTAL[23]

All temperatures are uncorrected. Rotations were determined in a 0.5-dm. semimicro tube; infrared absorption spectra were measured with a Perkin-Elmer model 21 double-beam spectrophotometer.

Attempted isomerization of cis-3,5-diketo-α-sant-Δ¹-enic acid (I). This reaction was carried out by the procedure employed previously for the isomerization of the *cis*-diketo acid (IV) into the *trans* isomer (V).[4] To a solution of 0.15 g. of the Δ^1-*cis*-diketo acid (I)[1] in 2 cc. of methanol was added 6 cc. of 3% aqueous potassium hydroxide, and the mixture was warmed on a water bath for 15 min. After cooling, the mixture was acidified with dilute sulfuric acid, saturated with sodium chloride, and extracted with ether. Evaporation of the dried ether solution left a colorless oil (0.15 g.) which, on treatment with ether-petroleum ether, gave 0.07 g. (47%) of the starting material (I), m.p. 175° (mixed m.p.) (after recrystallization from benzene-petroleum ether). The mother liquor of the crystals furnished a colorless oil (0.08 g.), which was chromatographed on silica gel (80-mesh, 1 × 20 cm.). Elution with benzene-ethanol (1:1) afforded an oil (0.07 g.), which was treated with diazomethane in ether. The methylation product was again chromatographed on alumina (1.2 × 20 cm.) and eluted with benzene-petroleum ether (1:1). The more readily eluted fraction gave a methyl ester (0.02 g.) of the starting ketone as prisms, m.p. (mixed m.p.) 100°; reported m.p. 99°.[1] From the less readily eluted fraction was obtained an oil (0.03 g.), which formed a *2,4-dinitrophenylhydrazone* (0.03 g.) as a yellow crystalline powder. Recrystallization from methanol gave yellow needles, m.p. 191–192°. It caused no depression of the melting point on admixture with the same derivative, m.p. 191–192° (after recrystallization from methanol), prepared from the methyl ester of the starting acid (I) with Brady's reagent. It had $\lambda_{max}^{CHCl_3}$ 259 mμ (log ε 4.06) and 373 mμ (log ε 4.42).

Anal. Calcd. for $C_{22}H_{26}O_7N_4$: C, 57.64; H, 5.72. Found: C, 58.07; H, 5.46.

Reaction of 2-bromo-trans-tetrahydro-α-santonin (VII, R = Br) *with lithium chloride and dimethylformamide.* A solution of 0.20 g. of the bromide (VII, R = Br) and 0.078 g. of lithium chloride in 4 cc. of dimethylformamide was heated at 95–100° for 2 hr. in a stream of nitrogen. The reaction mixture was diluted with ether and was washed successively with water, dilute sulfuric acid, bicarbonate solution, and water. Evaporation of the ether extract left 0.12 g. (70%) of the 2-chlorotetrahydrosantonin (R = Cl), m.p. 201° (dec.). Recrystallization from ethanol gave colorless platelets, m.p. 208° (dec.); $[\alpha]_D^{11}$ +14.3° (*c*, 0.28; EtOH) and +16.2° (*c*, 0.87; $CHCl_3$). It melted at 210° on admixture with a sample described in the following paragraph. Cocker and McMurry[9] gave m.p. 178–179° (variable); $[\alpha]_D^{23}$ +19.3° (*c*, 0.4; $CHCl_3$), for the chloro compound prepared in a similar way.

Anal. Calcd. for $C_{15}H_{21}ClO_3$: C, 63.26; H, 7.43. Found: C, 63.26; H, 7.09.

2-Chloro-trans-tetrahydro-α-santonin (VII, R = Cl). This was prepared by the modification of a previous method which was described only briefly.[8] Into a solution of 0.05 g. of *trans*-tetrahydro-α-santonin[5] (VII, R = H) in 3 cc. of chloroform was introduced chlorine gas (1.2 equivalents), generated from 10 mg. of potassium permanganate, at room temperature. The reaction mixture was washed with water, dried, and evaporated to leave 0.04 g. (70%) of the chloro compound (VII, R = Cl) as colorless platelets, m.p. 205° (dec.). Recrystallization from ethanol raised the m.p. to 213° (dec.); reported, m.p. 214° (dec.).[8]

The chloro compound (10 mg.) was refluxed with 30 mg. of zinc dust (activated with copper salt) in 5 cc. of ethanol for 15 hr. on a water bath. After removal of zinc, the reaction solution was evaporated, and the residue was dissolved in benzene. Washing, drying, and evaporation of the benzene solution gave 5 mg. of tetrahydrosantonin (VII, R = H)[5] as colorless leaflets, m.p. 150°. Recrystallization from ethanol raised the m.p. to 151° (mixed m.p.).

The chloro compound (VII, R = Cl, 40 mg.) was heated with γ-collidine at 275–180° for 20 min. in a stream of nitrogen. Working up of the mixture as usual afforded crystals (28 mg.) m.p. 130°, which were recrystallized from ethanol to give the starting material (13 mg.) as plates, m.p. 205° (mixed m.p. 107°). The mother liquor of recrystallization afforded a further amount of the starting material, m.p. 200° (after chromatography on alumina).

Attempted conversion of Δ¹-trans-dihydro-α-santonin (VI) *to the Δ¹-diketo acid* (III). The Δ^1-dihydro compound (VI) was subjected to hydrolysis of the lactone ring and subsequent oxidation, principally according to the procedure de-

(22) D. A. H. Taylor, *Chem. & Ind.* (*London*), 250 (1954).

(23) Microanalyses were carried out by Miss Ch. Shibuya and the ultraviolet measurements by Miss M. Suzuki.

scribed previously for the preparation of the *trans*-diketo acid (V) from *trans*-tetrahydrosantonin[4] (VII, R = H).

Compared with the tetrahydro compound[24] (VII, R = H), the dihydro compound (VI, 0.12 g.) more readily dissolved in 6% potassium hydroxide (2 cc.) on warming on a water bath. The alkali solution was washed with ether and slowly acidified with 10% sulfuric acid under cooling with a mixture of sodium chloride and ice, and was at once extracted with ether-chloroform (10:1). After addition of 3 drops of pyridine, the extract was dried over sodium sulfate and the solvent was distilled off under reduced pressure. The residue was mixed with a mixture of 0.10 g. of chromium trioxide and 3 cc. of pyridine and was stored in an ice box for 36 hr. Treatment as described previously[4] furnished an acidic fraction (nonlactonic fraction) as a colorless oil (0.07 g.), which was chromatographed on silica gel (80 mesh, 0.8 × 13 cm.). Elution with petroleum ether-benzene (1:1) gave a minute amount of crystals, m.p. 134° (after recrystallization from petroleum ether-benzene). This material, which formed no precipitates with Brady's reagent and exhibited no ultraviolet absorption bands corresponding to the α,β-unsaturated ketone, was not further investigated.

Similar treatment of *cis*-Δ^1-dihydrosantonin gave only a minute amount of crystals, m.p. 156° (after recrystallization from petroleum ether-benzene). This material showed no characteristics of the α,β-unsaturated ketone, obviously being different from the Δ^1-*cis*-diketo acid (I), m.p. 190–191°.[1]

2-Bromo-trans-3,5-diketo-α-santanic acid (IX, R = H). To a solution of 0.30 g. of the above described *trans*-diketo acid (V, R = H),[4] m.p. 148° ($\nu_{C=O}^{CHCl_3}$ 1706 cm.$^{-1}$), in 5 cc. o chloroform was added, dropwise, a solution of 0.19 g. of bromine in 2 cc. of the same solvent under cooling. Bromine absorption proceeded rapidly. The reaction mixture was washed with water, dried over sodium sulfate, and evaporated to a small bulk. Addition of a small amount of petroleum ether precipitated 0.35 g. (90%) of almost white needles, m.p. 143° (dec.). Recrystallization from ethyl acetate–petroleum ether gave white needles, m.p. 152° (dec.); $[\alpha]_D^{11}$ −73.8° (*c*, 0.43; EtOH), $\nu_{C=O}^{CHC}$ 1718 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{21}BrO_4$: C, 52.18; H, 6.13. Found: C, 52.00; H, 6.19.

Methyl 2-bromo-trans-3,5-diketo-α-santonate (IX, R = CH_3). (*a*) The above bromide (IX, R = H) was treated with an ether solution of diazomethane under ice cooling. The methyl ester was obtained as colorless leaflets (0.02 g., 96%), m.p. 132°. Recrystallization from benzene–petroleum ether raised the melting point to 137°, undepressed on admixture with a sample described just below.

(*b*) Methyl ester (V, R = CH_3), prepared from the *trans*-diketo acid (V, R = H) with diazomethane,[25] was brominated with bromine as described above for the acid (V, R = H). The product was a colorless oil, which partly crystallized from ether on addition of petroleum ether as colorless leaflets (44%), m.p. 132°. Further recrystallization from benzene–petroleum ether raised the melting point to 137–138°; $[\alpha]_D^{14}$ −92.3° (*c*, 0.87; EtOH).

Anal. Calcd. for $C_{16}H_{23}BrO_4$: C, 53.49; H, 6.45. Found: C, 53.93; H, 6.34.

2-Methoxy-trans-3,5-diketo-α-santanic acid 2,4-dinitrophenylhydrazone (X). (*a*) The above bromo acid (IX, R = H, 0.05 g.) was dissolved in Brady's Reagent (a solution of 0.04 g. of 2,4-dinitrophenylhydrazine and 0.05 cc. of concentrated sulfuric acid in 3 cc. of methanol). On standing at room temperature, the hydrazone (X) soon deposited as a yellow crystalline powder (0.06 g., 93%), m.p. 196°. Three crystallizations from methanol afforded fine yellow needles, m.p. 201°, undepressed on admixture with a sample described below (*c*).

Anal. Calcd. for $C_{22}H_{28}N_4O_8$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.51; H, 5.95; N, 11.98.

(*b*) 2-Methoxy-*trans*-tetrahydro-α-santonin (VII, R = OCH_3),[5] m.p. 135°, was subjected to hydrolysis-oxidation, essentially according to the procedure described earlier for the preparation of V (R = H) from VII (R = H).[4] A hydroxy acid, prepared from the methoxy lactone (VII, R = OCH_3, 0.10 g.), was treated with a mixture of chromium trioxide (0.06 g.) and pyridine (1 cc.) under cooling. After standing at 5–10° for 12 hr., the mixture was worked up as usual. The starting material (0.05 g.) was recovered as crystals, m.p. 130–132°, from the neutral fraction. The acidic fraction, a colorless oil (0.01 g.), formed a small amount of 2,4-dinitrophenylhydrazone (X), m.p. 196° (after recrystallization from methanol).

(*c*) Oxidation of the above hydroxy acid with chromium trioxide in acetic acid at higher temperature somewhat improved the result. To a stirred solution of chromium trioxide (0.18 g.) in acetic acid (5 cc.) containing a drop of water was added, dropwise, the alkaline solution of the hydroxy acid, prepared from the methoxy lactone (VII, R = OCH_3, 0.01 g.), at 20–25°. The addition was completed in about 30 min. and the stirring was continued further for 30 min. To decompose the excess of chromium trioxide, aqueous solution of sodium bisulfate was added, the mixture was diluted with water, and extracted with ether. The ether extract was washed three times with sodium chloride-saturated water and then with bicarbonate solution. Evaporation of the ether solution left the starting lactone (0.01 g.), m.p. 133° (mixed m.p.).

The bicarbonate solution was acidified and extracted with ether. Evaporation of the dried ether solution gave a colorless oil (0.02 g.), which formed the 2,4-dinitrophenylhydrazone (X, 0.01 g.), m.p. 191°. Two recrystallizations from methanol afforded fine yellow needles, m.p. 200°.

Dehydrobromination of 2-bromo-trans-3,5-diketo-α-santanic acid (IX, R = H). (*a*) *With γ-collidine.* The above bromo acid (IX, R = H, 0.10 g.) was heated with purified collidine (b.p. 169–170°) at 175–180° for 20 min. in a stream of nitrogen. After cooling, the mixture was diluted with ether and the separated collidine salt (0.06 g. 1.02 moles) was filtered off. The filtrate was washed successively with dilute sulfuric acid, water, and sodium bicarbonate. Evaporation of the dried ether solution gave a brown sirup (0.02 g.), which formed a 2,4-dinitrophenylhydrazone (0.02 g.). Recrystallization from ethyl acetate gave beautiful orange leaflets, m.p. 241° (dec.). It showed no depression of the melting point on admixture with the same derivative of the enol lactone (XII) of the Δ^4-diketo acid, described below.

The above bicarbonate wash, showing a green fluorescence, was acidified and extracted with ether. Evaporation of the dried ether solution left a red sirup (0.01 g.), which was methylated with diazomethane. The ester (0.01 g.) was chromatographed on alumina (0.8 × 12 cm.) and the elution with petroleum ether–benzene (1:1) furnished a minute amount of white needles, m.p. 166°, which is described below (*b*).

(*b*) *With lithium chloride and dimethylformamide.* A solution of 0.25 g. of the bromo acid (IX, R = H) and 0.10 g. of lithium chloride in 2 cc. of dimethylformamide was heated at 150–155° (oil bath temperature) for 30 min. in a stream of nitrogen. The reaction mixture was worked up as described above for the bromotetrahydro compound (VII, R = H). There was obtained, as a neutral product, a light brown sirup (0.08 g.) which (0.06 g.) formed the *2,4-dinitrophenylhydrazone* (0.07 g.) of the enol lactone (XII) as beautiful light orange leaflets, m.p. 240–241° (dec., mixed m.p.) (after recrystallization from ethyl acetate).

Anal. Calcd. for $C_{21}H_{22}N_4O_6$: C, 59.15; H, 5.20. Found: C, 58.95; H, 5.49.

Methylation of the above bicarbonate-soluble fraction gave the same methyl ester (0.01 g.), m.p. 167° (mixed m.p.

(24) H. Matsumura, I. Iwai, and E. Ohki, *J. Pharm. Soc. Japan*, **74**, 1206 (1954).

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

166°) (after recrystallization from petroleum ether), as obtained in (*a*). It had λ_{max}^{MeOH} 253.5 mμ (log ε 3.83), which is obviously different from the absorption band (λ_{max}^{MeOH} 225 mμ) of the *cis*-Δ¹-diketo acid (I).[1] Also the nonidentity of this ester with methyl ester of the Δ⁴-3,5-diketo acid (XI), m.p. 61°, described below, is shown by a large discrepancy of the melting point, though the ultraviolet absorption maxima of the two esters are practically identical in position.

3,5-Diketo-α-santa-Δ¹,⁴-dienic acid (5-dehydro-α-santoninic acid) (II). This compound, m.p. 138°, was prepared from α-santoninic acid as reported previously.[1] It had $\nu_{C=O}^{CHCl}$ 1704 cm.⁻¹ and 1661 cm.⁻¹ (cross-conjugated dienone). With Brady's reagent, it formed a *2,4-dinitrophenylhydrazone* as a crystalline powder in 70% yield. Recrystallization from glacial acetic acid gave fine needles, m.p. 248°; $\lambda_{max}^{CHCl_3}$ 263 mμ (log ε 4.27), 310 mμ (log ε 3.81), and 395 mμ (log ε 4.62).

Anal. Calcd. for $C_{21}H_{22}N_4O_7$: C, 57.01; H, 5.01. Found: C, 56.99; H, 5.13.

Enol lactone of 3,5-diketo-α-santa-Δ¹,⁴-dienic acid. With a slight modification of the method reported previously,[15] this compound was prepared from the above acid (II) (0.30 g.) by heating at 170–180° and 1-mm. pressure for 15 min. The molten mass, partly crystallized, was dissolved in chloroform. The chloroform solution was washed with sodium bicarbonate solution, dried over magnesium sulfate, and evaporated to give yellow crystals (0.20 g.). Recrystallization from ether-chloroform furnished yellow plates, m.p. 147°; $[\alpha]_D^{15}$ +182.5° (*c*, 1.07; $CHCl_3$); reported, yellow solid, m.p. 135°,[26] and beautiful yellow needles, m.p. 166°; $[\alpha]_D^{18}$ +187°.[15] The discrepancy of the melting points of the latter and our sample may be due to dimorphism, since the values of the optical rotation of these substances are almost the same.

The acetate was prepared from the enol lactone by refluxing with acetic anhydride as reported previously.[15] It was obtained as yellow plates, m.p. 114–116°, after recrystallization from ether–petroleum ether. The acetate was also obtained in 50% yield directly from the Δ¹,⁴-diketo acid (II, 0.05 g.) by gentle refluxing with acetic anhydride (0.5 cc.) for 30 min.

3,5-Diketo-α-sant-Δ⁴-enic acid (XI). The above Δ¹,⁴-diketo acid (II, 2.00 g.), m.p. 138°, was dissolved in 50 cc. of purified acetone and was shaken in hydrogen over 0.4 g. of 0.6% palladium-charcoal. After 181 cc. (1.06 equivalents) of hydrogen was absorbed in about 2 hr., the gas uptake almost ceased. Removal of the catalyst and evaporation of the solvent afforded 2.0 g. of a colorless oil, which crystallized from ethyl acetate by addition of petroleum ether, as colorless plates (1.07 g., 54%), m.p. 129°. Further recrystallization from dilute ethanol raised the melting point to 138°, which was obviously depressed on admixture with the *trans*-diketo acid (V), m.p. 147–148°.[4] It had λ_{max}^{MeOH} 255 mμ (log ε 4.08); $\nu_{C=O}^{CHCl_3}$ 1689 cm.⁻¹ (α,β-unsaturated ketone), and $[\alpha]_D^{25}$ +100.0° (*c*, 0.5; EtOH).

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.72; H, 7.78.

The mother liquor of the crude crystals (XI) gave an additional 0.25 g. (total 66%) of XI, m.p. 105°, identified as 2,4-dinitrophenylhydrazone described just above.

The Δ⁴-diketo acid (XI) with Brady's reagent formed, in 71% yield, a *2,4-dinitrophenylhydrazone*, which was recrystallized from ethyl acetate to afford orange needles, m.p. 224° (dec.); $\lambda_{max}^{CHCl_3}$ 265 mμ (log ε 4.27), 360 mμ (log ε 4.04) (shoulder), and 386 mμ (log ε 4.67).

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 56.40; H, 5.64.

A *semicarbazone* was obtained in 83% yield as colorless needles, m.p. 135° (dec.) from ethanol solution in the usual manner. Recrystallization from ethanol did not change the m.p.; $[\alpha]_D^{14}$ +240.0° (*c*, 1.33; EtOH).

Anal. Calcd. for $C_{16}H_{23}N_3O_4$: C, 59.79; H, 7.21. Found: C, 59.34; H, 7.38.

Methyl ester was prepared by treatment of the acid (XI, 0.03 g.) in ether with an ether solution of diazomethane. The ester (0.02 g.), m.p. 56°, was purified by passing the solution in petroleum ether–benzene (1:1) through alumina (0.8 × 13 cm.) and then recrystallized from petroleum ether. There were obtained colorless prisms, m.p. 61°; λ_{max}^{EtOH} 255 mμ (log ε 4.03) and $[\alpha]_D^{14}$ +93.5° (*c*, 0.51; EtOH). Drying in vacuum over P_2O_5 for 10 days caused no change in the melting point.

Anal. Calcd. for $C_{16}H_{22}O_4.H_2O$: C, 64.84; H, 8.16. Found: C, 64.90; H, 8.03.

The methyl ester formed, in 76% yield, a *2,4-dinitrophenylhydrazone*, which on recrystallization from ethyl acetate afforded orange needles, m.p. 226°.

Anal. Calcd. for $C_{22}H_{26}N_4O_7$: C, 57.63; H, 5.72. Found: C, 58.04; H, 5.47.

Zinc-ethanol reduction of 3,5-diketo-α-sant-Δ⁴-enic acid (IX). A solution of 0.10 g. of the above Δ⁴-diketo acid (XI) in 20 cc. of 99% ethanol was refluxed with 0.4 g. of zinc (activated with copper sulfate) on a water bath for 8 hr. Filtration of zinc and evaporation of the ethanol gave 0.10 g. of a colorless oil which was dissolved in ether. The ether solution was shaken with sodium bicarbonate, and the bicarbonate solution was acidified and extracted with ether. Evaporation of the dried ether extract left 0.05 g. (50%) of *cis*-3,5-diketo acid (IV) as colorless plates, m.p. 180°. Recrystallization from dilute ethanol raised the melting point to 185° (mixed m.p.); $\nu_{C=O}^{CHCl_3}$ 1709 cm.⁻¹ (unconjugated ketone).

With Brady's reagent, it gave a *2,4-dinitrophenylhydrazone*, as yellowish plates, m.p. 216° (dec.), after recrystallization from ethanol.

Anal. Calcd. for $C_{21}H_{26}N_4O_7$: C, 56.49; H, 5.87. Found: C, 56.76; H, 5.54.

To a solution of 0.03 g. of the *cis*-diketo acid (IV) in 5 cc. of methanol was added 0.1 cc. of concentrated sulfuric acid, and it was refluxed for 5 hr. on a water bath. Evaporation of methanol under reduced pressure left an oil, which was dissolved in ether. The ether solution was washed with aqueous sodium bicarbonate, dried, and evaporated. There was obtained *methyl ester* of IV (0.03 g., 95%), m.p. 116°, which was recrystallized from ether–petroleum ether to colorless prisms, m.p. 124°; $[\alpha]_D^{21}$ −150.0° (*c*, 0.4; $CHCl_3$).

Anal. Calcd. for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.98; H, 8.30.

trans-3,5-Diketo-α-santanic acid (V) *from the Δ¹,⁴-diketo-acid* (II). To a previously reduced mixture of 3 g. of Raney nickel and 1 g. of potassium carbonate in 30 cc. of methanol and 5 cc. of water was added a solution of 1.0 g. of the above Δ¹,⁴-diketo acid (II) in 10 cc. of methanol, and the resultant mixture was shaken in atmosphere of hydrogen. After 165 cc. (2.06 equivalents) of hydrogen was absorbed in 15 min., gas uptake ceased. The catalyst was filtered off, and the filtrate was acidified, diluted with aqueous sodium chloride–saturated solution, and extracted with ether. Evaporation of the dried ether extract gave the *trans*-diketo acid (0.8 g., 79%) as needles, m.p. 96°. Crystallization from dilute ethanol caused no changes in the melting point. The dehydrated material had the m.p. 149° (mixed m.p.); $\nu_{C=O}^{CHCl_3}$ 1706 cm.⁻¹ (unconjugated ketone). It showed no depression of the melting point on admixture with the same compound reported previously.[4]

With Brady's reagent, it formed, in 60% yield, a *2,4-dinitrophenylhydrazone*, as a yellow crystalline powder, which recrystallized from ethanol to needles, m.p. 185–186°.

Anal. Calcd. for $C_{21}H_{26}N_4O_7$: C, 56.49; H, 5.87. Found: C, 56.82; H, 5.50.

The esterification was smoothly effected by refluxing the acid (V, 0.05 g.) with a mixture of methanol (5 cc.) and concentrated sulfuric acid (0.1 cc.) for 3 hr., similarly as de-

(26) S. S. Medvedev, *Chem. Abstr.*, **21**, 2476 (1927); **22**, 1978 (1928).

scribed above for the methyl ester of the *cis* acid (IV). There was obtained the *methyl ester* (0.04 g., 76%) as colorless leaflets, m.p. 83.5° (after recrystallization from ether–petroleum ether). Reported,[13] m.p. 80–81°.

trans-5-Keto-3-hydroxy-α-santanic acid (VIII). A solution of 0.50 g. of the $\Delta^{1,4}$-diketo acid (II), m.p. 138°, in 15 cc. of glacial acetic acid was shaken in atmosphere of hydrogen in the presence of platinum black (prepared from 0.02 g. of platinic oxide). After 127 cc. (3.0 equivalents) of hydrogen was absorbed in 1.5 hr., the gas uptake almost ended. The catalyst was filtered off and the filtrate was evaporated to a small bulk under reduced pressure, and a small amount of water was added. On standing at room temperature, the solution deposited 0.40 g. (78%) of the hydroxy acid (VIII) as prisms, m.p. 174°. Recrystallization from ethyl acetate raised the m.p. to 181°; $[\alpha]_D^{18}$ +9.6° (*c*, 1.87; EtOH). It showed an obvious depression (*ca.* 20°) of the m.p. on an admixture with *cis*-5-keto-3-hydroxy-α-santanic acid, m.p. 182–183°, obtained previously by catalytic hydrogenation of the *cis*-diketo acid (IV, R = H).[4]

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.50; H, 9.28.

Oxidation of this hydroxy acid (VIII, 0.01 g.) with chromium trioxide-pyridine in the usual manner gave the *trans*-diketo acid (V, 5 mg.) m.p. 95° (after crystallization from dilute ethanol). The dehydrated sample had the m.p. 149° (mixed m.p.).

Enol lactone (XII) *of 3,5-diketo-α-sant-Δ⁴-enic acid* (XI). (*a*) *Pyrolysis of 3,5-diketo-α-sant-Δ⁴-enic acid* (XI). This reaction was conducted at a somewhat lower temperature than that reported previously. The above Δ^4-3,5-diketo acid (XI, 0.05 g.), m.p. 138°, was heated at 160–170° (oil bath temperature) and 1 mm. pressure for 30 min. Evolution of gas began at about 140°. The molten mass, partly crystallized, was rapidly recrystallized from ethanol to yellow plates (0.03 g., 64%), m.p. 181–182°. Reported, 184–187°[15] and 192–196°.[16] On recrystallization of this material, care must be taken, since on brief heating its solution in usual solvents did not give the parent crystals, but only a yellow sirup which could not be induced to crystallize even after chromatography on silica gel (eluted with petroleum ether–benzene).

With Brady's reagent, it formed a *2,4-dinitrophenylhydrazone*, which was recrystallized from ethyl acetate to orange leaflets, m.p. 240–241° (dec.).

Anal. Calcd. for $C_{21}H_{22}N_4O_6$: C, 59.15; H, 5.20. Found: C, 58.95; H, 5.49.

(*b*) *Reaction of the Δ⁴-diketo acid* (XI) *with lithium chloride–dimethylformamide.* This reaction was carried out similarly as described above for dehydrobromination of IX (R = H). Thus, the acid (XI, 0.05 g.) was heated with lithium chloride (0.02 g.) and dimethylformamide (0.5 cc.) at 160–165° (oil bath temperature) for 20 min. The starting acid (0.01 g.), m.p. 135° (mixed m.p. 137°) was recovered from the bicarbonate-soluble fraction. The neutral fraction, a yellow oil (0.03 g.), formed a 2,4-dinitrophenylhydrazone (0.03 g.) of the enol lactone (XII), which was recrystallized from ethyl acetate to orange leaflets, m.p. 242° (dec.) (mixed m.p. 241.5° with the above sample).

(*c*) *Hydrogenation of the enol lactone of 3,5-diketo-α-santa-Δ¹,⁴-dienic acid* (II). By the procedure described above for the preparation of the Δ^4-3,5-diketo acid (XI) from II, the enol lactone of the $\Delta^{1,4}$-diketo acid (II) was hydrogenated over 1.2% palladium-charcoal (0.1 g.) in purified acetone (10 cc.). Filtration of the catalyst and evaporation of the solvent gave XII (0.04 g., 57%), m.p. 178° (mixed m.p. 179–180° with the above sample).

2-Bromo-cis-3,5-diketo-α-santanic acid (XIII). Bromination of the *cis*-3,5-diketo acid (IV) was performed under more severe conditions than that of the *trans* isomer (V, R = H).

To a solution of 0.25 g. of IV in 5 cc. of chloroform 0.16 g. of bromine was added and allowed to stand at room temperature (20°) for 1.5 hr. The light yellow solution was worked up as described above for the *trans*-bromo acid (IX, R = H). The crude product crystallized as white needles (0.25 g., 77%), m.p. 153° (dec.), from ethyl acetate by addition of petroleum ether. Further recrystallization by the same procedure raised the m.p. to 163° (dec.); $[\alpha]_D^{12}$ −153.3° (*c*, 0.6; EtOH).

Anal. Calcd. for $C_{15}H_{21}BrO_4$: C, 52.18; H, 6.13. Found: C, 51.95; H, 6.60.

Dehydrobromination of 2-bromo-cis-3,5-diketo-α-santanic acid (XIII). (*a*) *With γ-collidine.* The above 2-bromo-*cis*-diketo acid (XIII, 0.13 g.) was heated with γ-collidine (1 cc.) at 175–180° (oil bath temperature) for 20 min. in a stream of nitrogen and worked up as described above for the *trans*-bromo acid (IX, R = H). The collidine salt amounted to 0.07 g. (0.92 mole). The bicarbonate-soluble fraction, a brown sirup (0.05 g.), partly crystallized (0.01 g.) from dilute ethanol. Further recrystallization from the same solvent furnished white plates, m.p. 176°. It showed no depression of the melting point on admixture with the Δ^1-*cis*-3,5-diketo acid (I), m.p. 178°.[1]

The mother liquor of the crude *cis*-acid was treated with Brady's reagent and gave a *2,4-dinitrophenylhydrazone*, an orange crystalline powder (0.01 g.), which was recrystallized from ethyl acetate to orange needles, m.p. 196° (dec.). It melted at 198° (dec.) on admixture with an authentic sample m.p. 201° (dec.), prepared from I with Brady's reagent and crystallized from ethyl acetate.

Anal. Calcd. for $C_{21}H_{24}N_4O_7$: C, 56.75; H, 5.44. Found: C, 57.04; H, 5.27.

The above neutral fraction, a brown sirup (0.03 g.), was converted to a 2,4-dinitrophenylhydrazone (0.015 g.) as orange crystalline powder. Recrystallization from ethyl acetate afforded orange leaflets, m.p. 242° (dec.), undepressed on admixture with the same derivative of enol lactone (XII) of the Δ^4-diketo acid, described above.

(*b*) *With lithium chloride and dimethylformamide.* The bromo acid (XIII, 0.03 g.) was treated with lithium chloride (0.015 g.) and dimethylformamide (0.3 cc.) as described for the *trans*-bromo acid (IX, R = H). The acidic fraction, a colorless sirup (0.01 g.), gave the *cis*-Δ^1-diketo acid (I, 0.005 g.), m.p. 165°, from ether by addition of petroleum ether. Recrystallization from ethyl acetate by addition of petroleum benzine raised the m.p. to 176° (mixed m.p. 177°). The neutral fraction, a yellow sirup (0.01 g.), formed 2,4-dinitrophenylhydrazone (0.01 g.) of the enol lactone (XII) of the Δ^4-compound, which on recrystallization from ethyl acetate had the m.p. 241° (dec.) (mixed m.p.).

Collidine treatment of cis-3,5-diketo-α-santanic acid (IV). The *cis*-diketo acid (IV, 0.05 g.) was heated with γ-collidine (0.7 cc.) under the same conditions as described above for the dehydrobromination of the *cis*-bromo acid (XIII). The bicarbonate-soluble fraction, a light brown sirup (0.05 g.), soon solidified on standing. Washing with dilute ethanol gave the starting material (0.04 g., 80%) as a colorless needles, m.p. 185° (mixed m.p.) (after recrystallization from dilute ethanol). As the neutral fraction, only a trace of a brown sirup was obtained.

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