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Santonin and Related Compounds. XXI.[1] 3-Keto-5-hydroxy-α-santanic Acid-*a*[2]

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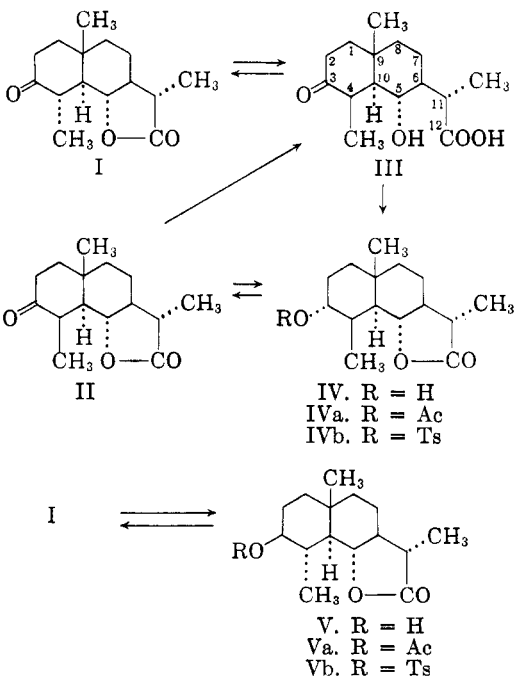
It was conclusively elucidated that both the ketohydroxy acid (III) and the ketodiol (VIII) derived from tetrahydro-α-santonin-*b* (I) (*trans*-decalin type) possessed the same configuration of the methyl group at the 4- position as in tetrahydro-α-santonin-*a* (II) (*trans*-decalin type). The 3-desoxydiol-*a* (X), newly obtained from the ketodiol (VIII), formed mono- and bis-*p*-nitro- and -3,5-dinitrobenzoates (Xa, b, c, d) under controlled reaction conditions, but the diol-*b* (XII) formed only mono-*p*-nitro- and -3,5-dinitrobenzoates (XIIa,b) even under drastic conditions. From these results, it appears that the methyl group at the 4- position is axial in the ketohydroxy acid-*a* (III), ketodiol-*a* (VIII), and 3-desoxydiol-*a* (X). 3-Desoxyhydroxy acid-*a* (XIV) produced *via* 3-desoxylactone-*a* (XI) (*trans*-decalin type) from the 3-desoxydiol-*a* (X) was readily oxidized to keto acid-*a* (XV), which isomerized into the *cis*-fused one (XIX) under alkaline conditions.

In a previous paper of this series,[3] it was reported that the *trans*-fused tetrahydro compound from β-santonin, the more stable isomer-*b* was converted to the less stable isomer-*a* by means of opening and careful closure of the lactone ring with cold concentrated sulfuric acid (corresponding to the sequence I → III → II in the α-santonin series). This course involving migration of the methyl group at the 4-position from equatorial to axial position was explained on the basis of conformational analysis. It seemed desirable, however, to establish these steric relationships by chemical means. Because of scarcity of β-santonin at hand, structural examination was made with *trans*-fused tetrahydroketone-*a* and -*b* (II and I)[2] of α-santonin, which are the respective epimers at the 11- position of the isomer-*a* and -*b* of β-santonin series. In order to convert the more stable tetrahydro-ketone-*b* (I) into the less stable isomer-*a* (III), 3-keto-5-hydroxy-α-santanic acid-*a* (III)[4] from I was treated with cold concentrated sulfuric acid by the same procedure employed for the corresponding reaction in the β-santonin series cited above. Unexpectedly, there resulted a substantial recovery of the starting ketone (I) and no



(1) Part XX, M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **24**, 903 (1959).

(2) For definition of the nomenclature and the numbering used in this paper, see Part XVIII of this series (ref. 3) (*cf.* Part XIII).

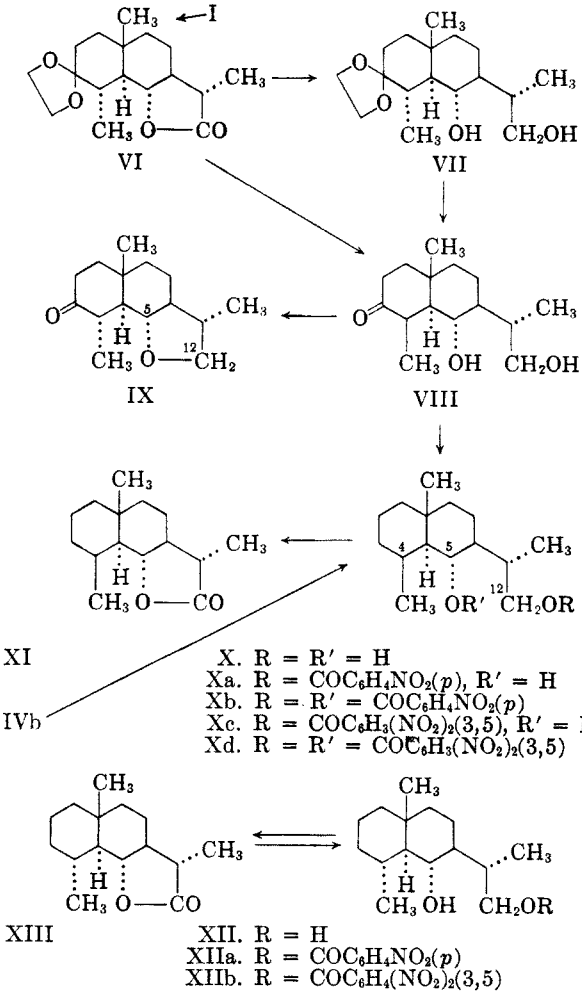
(3) M. Yanagita and H. Ogura, *J. Org. Chem.*, **23**, 1268 (1958).

(4) Wienhaus and Öttingen, and Tahara obtained the keto-hydroxy acids (m.p. 85–115° and 95–97°) with no description about the configuration. The present specimen showed the melting point of 140° (*cf.* Experimental).

evidence for the formation of II could be obtained from this reaction. As shown below, the lactone ring opening of the tetrahydro-ketone-*b* (I) was accompanied by inversion of the methyl group at the 4- position resulting in formation of the keto-hydroxy acid (III), which was also formed from tetrahydro-ketone-*a* (II) by the same procedure. It is clear that in spite of careful treatment of this hydroxy-ketone with sulfuric acid, the 4-methyl group was again inverted to the original position on lactonization. This indicates that the spatial arrangement of the methyl group at the 21- position could have a considerable influence on the relative stability of the methyl group at the 4- position.

It has already been shown that catalytic hydrogenation of tetrahydro-ketone-*a* (II) with platinum oxide in acetic acid gave one isomer (IV) of the hexahydrosantonin,[5] which was also prepared directly from *a*-santonin by similar hydrogenation.[6] The alcohol (IV), whose newly formed hydroxyl group was assigned the axial orientation (*trans* to the angular methyl group),[5,6] was now found to be almost quantitatively prepared from II by sodium borohydride in methanol. By the same procedure, the hydroxy acid (III) gave the same alcohol (IV) in a good yield, indicating that the methyl group at the 4- position in III possesses the same configuration as that in the ketone-*a* (II). It is notable that hydrogenation of the carbonyl group in II with these reagents proceeded in a highly stereoselective manner. On the other hand, the ketone-*b* (I) was catalytically hydrogenated with platinum oxide mainly to the corresponding alcohol (V) with smaller amount of an epimer.[5,6] The alcohol (V), in which the hydroxyl group was assigned the equatorial position (*cis* to the angular methyl group),[5,6] was also obtained almost quantitatively by reduction with sodium borohydride and converted to the original ketone (I) in a moderate yield by oxidation with chromium oxide–acetic acid. It is obvious that the C—O bond of the lactone ring in the ketone-*b* (I) must be much more sterically hindered by the methyl group at the 4- position than that in the ketone-*a* (II). The difference of such steric interference naturally increases by opening of the lactone ring in these ketones, as indicated by formation of the same hydrolysis product from both ketones. For establishment of the configuration of the methyl group at the 4- position in these ketones, it seemed of interest to examine the relative reactivity of the hydroxyl group in suitably constructed epimers at the 4- position.

Before describing transformations of the ketones (I and II), it is necessary to mention the result concerning the derivatives of I reported by Matsumura, Iwai, and Ohki.[7] These workers found that



the diol ketal (VII), prepared from the ketal (VI) of I with lithium aluminum hydride, gave only mono-*p*-nitrobenzoate in which the hydroxyl group at the 5- position remains unaffected, whereas the keto-diol (VIII) from VII formed a mono- or a bis-*p*-nitrobenzoate depending on the amount of *p*-nitrobenzoyl chloride used. Furthermore, these workers[8] stated that the diol (XII), prepared from 3-desoxytetrahydro-*a*-santonin-*b* (XIII) by reduction with lithium aluminum hydride, formed only a mono-*p*-nitrobenzoate, as the diol ketal (VII). From these results it seems probable to suggest that the methyl groups at the 4- position in the diol ketal (VII) and in the diol (XII) are both equatorial, whereas the keto-diol (VIII) possesses the axial 4-methyl group. However, three derivatives in question differ from each other in the substituents at the 3- position. In view of the fact that a small variation of the molecular structure frequently causes a significant change in the reaction rate, this comparison about the configuration of a methyl group at the 4- position in the above diols cannot be made. Consequently, preparation of the epimeric diol-*a* (X) was attempted.

(5) W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4549 (1956).

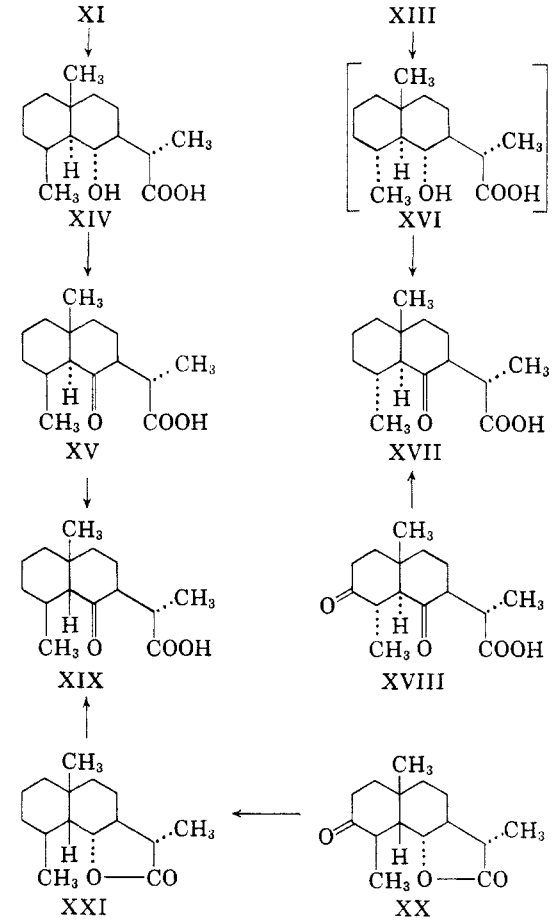
(6) B. Riniker, Thesis, E. T. H. Zürich, 1955.

(7) H. Matsumura, I. Iwai, and E. Ohki, *J. Pharm. Soc. Japan*, **75**, 687 (1955).

(8) H. Matsumura, I. Iwai, E. Ohki, and K. Kanzaki, *J. Pharm. Soc. Japan*, **75**, 689 (1955).

As the first route to X, reduction of the tosylate of hexahydrosantonin-*a* (IV) with lithium aluminum hydride[9] came into consideration. In preliminary experiments, this reaction gave an oil which was resistant to crystallization. The second line of approach to X involved reductive removal of the carbonyl group in the keto-diol (VIII) mentioned above. This keto-diol-*a* (VIII), prepared in a good yield directly from VI by hydride reduction, was subjected to the Martin-Clemmensen reduction in the usual manner. Surprisingly, the carbonyl group in VIII showed considerable resistance to this hydrogenation. The only product, obtained in a practically quantitative yield, was a dehydrated compound, in which the carbonyl group remained untouched, as shown by the formation of a 2,4-dinitrophenylhydrazone and the infrared spectrum, $\gamma_{C=O}$ 1712 cm.$^{-1}$ (cyclohexanone). It may be assumed that the product possesses the tetrahydrofuran structure (IX). The structure of IX was further supported by the infrared spectrum, γ_{C-O} 1125 cm.$^{-1}$, probably corresponding to the cyclic ether,[10] and the absence of a hydroxy band which was proved by inability to form a benzoate and resistance to the Clemmensen reduction. The keto-diol (VIII) was readily cyclized to IX with hydrochloric acid or *p*-toluenesulfonyl chloride, paralleling the smooth conversion of the 3-desoxy-diol-*b* (XII) into the corresponding tetrahydrofuran compound.[11] A few examples[12] involving such an unusual resistance of a ketone to the Clemmensen reduction have been recorded in the literature, and the reason for these abnormal results including the present case is entirely obscure. Removal of the keto group in VIII was readily effected by the Huang-Minlon modification of the Wolff-Kishner reduction, leading to a satisfactory yield of the desired product (X). The latter is differentiated from the above diol-*b* (XII) by comparison of melting point and infrared spectrum. In view of easy sublimation of X, the oily reduction product from the tosylate (IVb) mentioned above, was heated with sea-sand *in vacuo* and the diol-*a* (X) was obtained in a fair yield. This indicates that the methyl group at the 4- position has the same conformation in the tetrahydro-ketone-*a* (II), the hydroxy acid (III), and the keto-diol (VIII).

The diol-*a* (X) was subjected to acylation with *p*-nitro- or 3,5-dinitrobenzoyl chloride in pyridine by the Deninger-Einhorn method. By controlling the amount of the reagent (1.1 molar equivalents) and the reaction temperature to 0°, the mono-*p*-nitro-(Xa) or the mono-3,5-dinitrobenzoate (Xc) was formed. On the other hand, excess of the reagent (2.4 molar equivalents) and reaction at room temperature for 48 hr. resulted in the formation of the bis-*p*-nitro- (Xb) or the bis-3,5-dinitro benzoate (Xd) in a reasonable yield. From a steric viewpoint, it is obvious that the monobenzoates (Xa and Xc) possess the benzoyl group at the C-12 position. These results are in contrast to the above-cited fact regarding XII[8] and clearly indicate that the hydroxyl group at the 5- position in X is less hindered than that in XII, supporting these structures of the diols.



This steric explanation found further support in the following observation. The lactone (XI), prepared from the diol (X) by chromium trioxide oxidation, was hydrolyzed to a relatively stable hydroxy acid (XIV), whereas the epimeric acid (XVI) from the lactone (XIII) was so unstable that it could not be isolated in a pure state. It has been previously reported[13a] that oxidation of the hydroxy

(9) M. E. Wall and S. Serota, *J. Am. Chem. Soc.*, **78**, 1747 (1956).

(10) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., John Wiley & Sons, Inc., New York, 1958, p. 114.

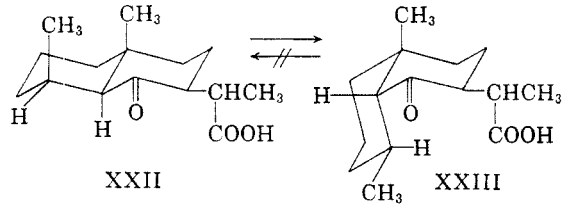
(11) O. Kovacs, V. Herout, M. Herak, and F. Sorm, *Collection Czechoslov. Chem. Communs.*, **21**, 225 (1956).

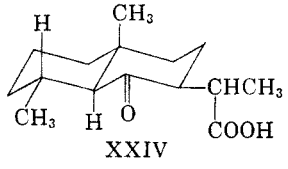
(12) For example see, W. T. Smith, Jr., *J. Am. Chem. Soc.*, **73**, 1883 (1951).

(13) (a) H. Matsumura, I. Iwai, and E. Ohki, *J. Pharm. Soc. Japan*, **74**, 1206 (1954). (b) Keto-acid-*a* (XV) was purified by chromatography on alumina, but the purity was not examined in so unstable a liquid (see Experimental). Nevertheless, the acid (XV) formed a *s*-(*p*-nitrobenzyl)thiuronium salt (m.p. 168–169°) in 69% yield, which was obviously different from the *cis*-fused (XIX; m.p. 141–142°) and *trans*-fused salts (XVII; m.p. 175°) in both melting point and infrared spectrum.

acid (XVI) with chromium trioxide in pyridine gave the keto-acid-*α* (XVII) in a very low yield (12%), with a larger amount (70%) of the recovered lactone (XIII). This experiment was repeated but attempts to raise the yield of XVII with other oxidizing agents were unsuccessful. Compared with XVI, the epimer (XIV) was more readily oxidized with chromium trioxide under similar conditions, and the keto-acid-*a* (XV)[13b] was obtained in a better yield (63%) with a smaller amount of XI. This indicated that the methyl group at the 4- position in XVI had a stronger effect on the oxidation process than that in XIV. The *trans*-fused diketo-acid (XVIII)[14,15] was converted to XVII in a good yield by the Martin-Clemmensen reduction in the usual manner, as the reductive removal of only carbonyl group at the 3-position in XVIII was expected from the steric view point mentioned above. Furthermore, this result supported the equatorial configuration of the methyl group at the 4-position in XVIII.

The newly formed keto-acid-*a* (XV) was relatively less stable since it underwent conversion to the more stable crystalline isomer (XIX) merely upon distillation. Riniker[6] stated that the crystalline keto-acid obtained from XI by a similar oxidation of the ester of XIV, including alkaline hydrolysis of the product, possessed the same conformation as the stable isomer (XIX) on the basis of conformational analysis. It is obvious in view of steric considerations, that the keto-acid-*a* (XV) corresponding to the conformation of XXII should be much more hindered than its inverted isomer (XIX) corresponding to that of XXIII. It seems desirable, however, to give a decisive proof of it. The *cis*-fused 3-deoxy compound-*d* (XXI), prepared from tetrahydro-*α*-santonin-*d* (XX),[2,5,11,15,16] converted to the corresponding keto-acid-*d* (XIX) which was





completely identical with the more stable keto-acid (XIX) mentioned above, but in a poorer yield (16%), with reasonable recovery of the starting lactone-*d* (XXI). This keto-acid-*d* (XIX) was prepared in a good yield (67%) from the same lactone-*d* (XXI), *via* the methyl ester of the *cis*-fused hydroxy acid corresponding to the *trans*-isomer (XVI). Therefore, the less stable isomer (XV) has to belong to the *trans*-fused tetrahydro compound series, and the more stable isomer (XIX) to the *cis*-fused series. This ring inversion could be effected by 3% potassium hydroxide solution under the same condition employed for the equilibration reaction between the *trans*-fused 3,5-diketo-*α*-santanic acid (XVIII) and the corresponding *cis*-isomer, the 3-keto derivatives of XIX (*trans*/*cis* = 5/3).[14] The *trans*-fused isomer (XV) was thus quantitatively inverted to the *cis*-fused one (XIX), whereas no reverse reaction could proceed at all. It is of interest that the *cis*-fused keto-acid (XIX) could not be inverted to another isomer (XVII) possessing an all *trans*-conformation (XXIV), compared with the result of observation about the corresponding 3-keto derivatives. An effort is now being made in this laboratory to establish the steric aspects in the interconversions of the keto-acids compared with the diketo-acids.

EXPERIMENTAL[17]

All melting points were uncorrected. Rotations were determined in a 0.5-dm. microtube, unless otherwise noted.

Catalytic hydrogenation of α-santonin. (a) *In benzene.* *α*-Santonin (3.00 g.) was hydrogenated over platinum oxide (0.20 g.) in dry benzene (100 cc.), and absorption of 2.1 molar-equivalents (580 cc.) of hydrogen required 0.5 hr. After removal of the catalyst, the solution was evaporated to a small volume giving 1.20 g. (39%) of tetrahydro-*α*-santonin-*a* (II), colorless leaflets, m.p. 140°. Recrystallization from ethyl acetate gave colorless leaflets, m.p. and mixed m.p. 147°.[16]

The mother liquor from crystallization of II was evaporated to a colorless sirup, which was dissolved in ethanol (5 cc.) containing 3% hydrochloric acid (3 cc.). The solution was warmed for 0.5 hr. on a water bath. On cooling, the solution deposited 1.00 g. (33%) of tetrahydro-*α*-santonin-*b* (I) m.p. and mixed m.p. 152–154°.[15,16]

With Brady's reagent, it formed a 2,4-dinitrophenylhydrazone, m.p. 253°. Reported m.p. 248–249°.[6]

(b) *In dry acetone.* *α*-Santonin (3.00 g.) was hydrogenated over 0.02 g. of 5% palladium charcoal in dry acetone (30 cc.). Hydrogen (560 cc., 2 molar equivalents) was absorbed within 0.5 hr. Worked up as above, the residual sirup furnished 1.73 g. (58%) of tetrahydro-*α*-santonin-*a* (II), colorless leaflets, m.p. 126–135°, from a small amount of ethyl acetate. Recrystallization from ethanol afforded 1.23 g. (40%) of colorless leaflets, m.p. and mixed m.p. 141–143°.

(c) *Pressure hydrogenation over platinum oxide.* By an effective modification of the method reported by Kovacs *et al.*,[11] *α*-santonin (3.00 g.) was hydrogenated in methanol (30 cc.) over platinum oxide (0.15 g.) at room temperature and 100 atm. pressure. The catalyst was filtered off and the filtrate evaporated to a small volume, and a little water was added. There was obtained 2.10 g. of white needles, melting in the range 97–110°. Recrystallization from dilute methanol furnished 1.70 g. (55%) of white fine needles, m.p. 120–121°. Reported m.p. 135°.[11]

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

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

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

(17) Microanalyses were carried out by Mrs. C. Inayama of this school.

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found, C, 71.55; H, 9.46.

The hydrogenated product (0.64 g.) treated with acetic anhydride–pyridine as below, gave an acetate (IVa, 0.35 g., 47%), colorless needles, m.p. and mixed m.p. 199–200° (see below). This acetate (IVa) was hydrolyzed in 5% sodium hydroxide solution to the 3α-hydroxy tetrahydro-α-santonin-*a* (IV), m.p. and mixed m.p. 106–107° (see below).

The mother liquor of crystallization of the acetate (IVa) was evaporated to a white powder (0.15 g., m.p. 114°). Recrystallization from ethanol furnished colorless leaflets (0.05 g., m.p. 129°), which was chromatographed on alumina. Elution with benzene afforded 0.02 g. (0.7%) of another acetate (Va) as colorless plates, m.p. and mixed m.p. 138° (see below).

3-Keto-5-hydroxy-α-santanic acid-a (III). (a) *From tetrahydro-α-santonin-b* (I). Tetrahydro-α-santonin-*b* (I, 0.30 g.) was added to 5 cc. of 5% aqueous sodium hydroxide, and the mixture was warmed on a water bath for 10 hr. After cooling, the clear solution was washed with ether, acidified with 10% acetic acid under ice cooling, and extracted with chloroform. The dried chloroform solution was evaporated under reduced pressure, and the residual semisolid (0.30 g.) was washed with a small amount of benzene. Careful recrystallization from ethyl acetate gave 0.20 g. (63%) of the monohydrate of the keto-acid (III), colorless plates, m.p. 110°.

Anal. Calcd. for $C_{15}H_{24}O_4 \cdot H_2O$: C, 62.91; H, 9.15. Found: C, 62.88; H, 9.47.

The hydrate was dried *in vacuo* on phosphorus pentoxide (at room temperature, for 12 hr.), gave a white anhydrous acid (III) m.p. 140°; $\nu_{C=O}^{CHCl_3}$ 1709 cm.$^{-1}$ (Reported m.p. 95–97°,[14] and 85–115°.[18])

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.22; H, 9.39.

It showed obvious depression of the melting point on admixture with I and II, respectively.

(b) *From tetrahydro-α-santonin-a* (II). Tetrahydro-α-santonin-*a* (II, 0.40 g.) was treated as described above, giving 0.30 g. (70%) of the hydroxy-acid (III), m.p. 96°. Recrystallization from ethyl acetate afforded colorless plates, m.p. 112°, undepressed on admixture with the monohydrate of III.

Lactonization of the acid (III). (a) *By concentrated sulfuric acid.* When the hydroxy acid (III, 0.10 g.) was treated as previously reported,[3] it gave white leaflets (0.09 g., the melting range showed 139–146°), and showed 145–152° on admixture with tetrahydro-α-santonin-*b* (I). Recrystallization from ethyl acetate raised the melting point to 154–155° (mixed m.p. with I).

(b) *In glacial acetic acid containing trace of concentrated sulfuric acid.* The hydroxy-acid (III, 0.01 g.) was dissolved in glacial acetic acid (0.5 cc.). After adding trace of concentrated sulfuric acid, the reaction mixture was allowed to stand at room temperature for 8 hr. Worked up as usual, it gave white leaflets (0.005 g.), m.p. 148–150°, undepressed on admixture with I. But it showed obvious depression of the melting point on admixture with the isomer-*a* (II).

(c) *By 2,4-dinitrophenylhydrazine in glacial acetic acid.* To a solution of the hydroxy acid (III, 0.01 g.) in acetic acid (0.4 cc.) was added 2,4-dinitrophenylhydrazine (0.01 g.). After standing for 8 hr., the reaction mixture was evaporated *in vacuo* at room temperature, and then fine yellow needles (0.01 g.) were deposited as a 2,4-dinitrophenylhydrazone of I, m.p. 253° (mixed m.p.).

3β[19]*-Hydroxy-tetrahydro-α-santonin-b* (V, R = H). To a solution of tetrahydro-α-santonin-*b* (I, 0.50 g.) in methanol (30 cc.) was added dropwise, 0.10 g. of sodium borohydride in 0.5 cc. of water. After standing at room temperature for 2 hr., the mixture was acidified with 10% hydrochloric acid and the solvent was evaporated under reduced pressure, and the residue was mixed with water and extracted with benzene, washed with water, dried, and evaporated. There was obtained 0.47 g. (93%) of the 3β-hydroxy-tetrahydro-α-santonin-*b* (V), m.p. 167°. Recrystallization from benzene-petroleum ether afforded colorless plates, m.p. 168–169°; $\lambda_{max}^{CHCl_3}$ 3472, 1770, 1460, 1385, 1143, 1119, 1047, 1013, 983, 935 cm.$^{-1}$ Reported,[5] m.p. 171–172°.

To a solution of the hexahydro compound (V, 0.05 g.) in glacial acetic acid (1 cc.), was added dropwise, 0.01 g. of chromium trioxide in the same solvent (1 cc., containing 0.02 cc. water) under stirring. After stirring was continued for 0.5 hr. at room temperature, the solution was poured into water, and taken up in chloroform. The chloroform solution was washed with aqueous sodium bicarbonate and then with water. Evaporation of the dried chloroform solution left 0.04 g. (81%) of the pure ketone (I) as colorless plates, m.p. and mixed m.p. 152–153°.

An *acetate* (Va, R = Ac) obtained in 85% yield from the hexahydro compound (V) by the usual procedure, was recrystallized from ethanol affording colorless plates, m.p. 139°; $[\alpha]_D^{14}$ +64.2° (*c* 0.37; $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 1773, 1733, 1458, 1379, 1250, 1134, 1047, 1026 (sh.), 1010, 983, 939 cm.$^{-1}$ Reported[5] m.p. 143°; $[\alpha]_D$ +63.1°.

A *tosylate* (Vb, R = Ts.). To an ice cold solution of V (0.05 g.) in pyridine (0.5 cc.) was added *p*-toluenesulfonyl chloride (0.05 g.). After standing at room temperature for 7 days, the reaction mixture was poured into ice water, and the separated white needles was filtered, washed with water, and dried, giving 0.06 g. (74%) of the tosylate (Vb), m.p. 135–140°. Recrystallization from methanol gave colorless needles, m.p. 155°; $[\alpha]_D^{15}$ +55.8° (*c* 0.57; $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 1779, 1610, 1460, 1362, 1176, 1135, 1098, 1015, 993, 935, 862, 835 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{30}O_5S$: C, 64.99; H, 7.44. Found: C, 65.27; H, 7.78.

3α[19]*-Hydroxy-tetrahydro-α-santonin-a* (IV, R = H). (a) *From tetrahydro-α-santonin-a* (II) *by sodium borohydride.* Tetrahydro-α-santonin-*a* (II, 0.80 g.) was dissolved in methanol (15 cc.), and sodium borohydride (0.08 g.) in water (0.4 cc.) was added. The reaction mixture was carried out as described above for IV, giving 0.75 g. (93%) of the 3α-hydroxytetrahydro-α-santonin-*a* (IV) as colorless needles, m.p. 103–104°. Recrystallization from aqueous ethanol afforded colorless needles, m.p. 107–108°; $[\alpha]_D^{18}$ +36.2° (*c* 1.43; $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 3448, 1776, 1460, 1385, 1149, 1126, 1047, 1028, 1015, 990, 910 cm.$^{-1}$ Reported,[5] m.p. 108–110°; $[\alpha]_D^{20}$ +36.0° (*c* 0.95).

(b) *From tetrahydro-α-santonin-a* (II) *by catalytic hydrogenation.* Tetrahydro-α-santonin-*a* (II, 1.00 g.) was hydrogenated over platinum oxide (0.03 g.) in glacial acetic acid. About 1 molar equivalent (88 cc.) of hydrogen was absorbed within 1 hr. The catalyst was filtered off and the filtrate was evaporated under reduced pressure, gave 1.00 g. (99%) of IV, as white needles, m.p. 89–92°. Recrystallization from ethanol and then from acetone–petroleum ether raised the melting point to 107°, undepressed on admixture with an authentic specimen. From the hexahydro compound (IV), the acetate (IVa) was formed by the usual method (see below).

(c) *From 3-keto-5-hydroxy-α-santanic acid-a* (III). To the solution of hydroxy acid (III, 0.05 g.) in methanol (5 cc.), dropwise, an aqueous solution of sodium borohydride (0.02 g. in 0.1 cc. water) was added. After standing at room temperature for 1 hr., the reaction mixture was saturated with sodium chloride and then extracted with ether. The organic layer was washed with aqueous sodium bicarbonate, water, dried, and evaporated. There was obtained 0.04 g. (85%) of a hexahydro-α-santonin-*a* (IV) as colorless needles, m.p. 100–102°. Recrystallization from benzene-petroleum ether raised the melting point to 107–108° (mixed m.p.). From the hexahydro compound (IV), the acetate (IVa) was formed by the usual method (see below).

(18) Wienhaus and Ottingen, *Ann.*, 397, 219 (1913).

(19) Relative configurations were expressed as α or β for the groups except to be designated according to the definition[3] of the nomenclature in this series.

An *acetate* (IVa, R = Ac), obtained in 80–90% yield from the hexahydro compound (IV) by the usual method, was recrystallized from ethanol, giving colorless prisms, m.p. 200–201°; $[\alpha]_D^{14}$ +19.4° (*c* 1.13; $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 1776, 1733, 1456, 1372, 1250, 1149, 1127, 1042, 1029, 1018, 995, 935 cm.$^{-1}$ [reported,[5] m.p. 199–200°; $[\alpha]_D^{20}$ +15.4° (*c* 0.72)].

The acetate (IVa) was hydrolyzed with 3% methanolic sodium hydroxide. Acidification of the reaction mixture gave the original hexahydro compound (IV) as colorless needles, m.p. and mixed m.p. 108–109°.

A *tosylate* (IVb, R = Ts) was obtained in 93% yield from the hexahydro compound (IV) by the same procedure as in Vb. Recrystallization from ethanol furnished colorless plates, m.p. 168–169° (dec. 170°); $[\alpha]_D^{15}$ +20.0° (*c* 1.70; $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 1776, 1608, 1456, 1357, 1174, 1126, 1098, 1017, 996, 946, 849 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{30}O_5S$: C, 64.99; H, 7.44. Found: C, 65.33; H, 7.19.

Tetrahydro-α-santonin-b-3-ketal (VI). By a slight modification of the procedure previously reported,[7] the ketal (VI) was obtained in 70% yield from tetrahydro-α-santonin-*b* (I), as colorless plates, m.p. 168°; $[\alpha]_D^{14}$ +26.1° (*c* 5.4; $CHCl_3$). Reported,[7] m.p. 167–168.5°; $[\alpha]_D^{5}$ +23.4°.

α-Santan-5,12-diol-b-3-ketal (VII). By an effective modification of the method,[7] the ketal (VI, 0.40 g.) was reduced in absolute ether-benzene solution with lithium aluminum hydride, gave 0.35 g. (86%) of VII, as colorless needles, m.p. 145°. Recrystallization from acetone raised the melting point to 149°; $[\alpha]_D^{16}$ −10.7° (*c* 6.7; $CHCl_3$). Reported,[7] m.p. 149–151°; $[\alpha]_D^{5}$ −14.0°.

3-Keto-α-santan-5,12-diol-a (VIII). (a) By an effective modification of the method,[7] the diol ketal (VII, 0.17 g.) was treated with sulfuric acid in acetone, giving 0.11 g. (76%) of VIII, as colorless needles, m.p. 119–120°; $\nu_{max}^{CHCl_3}$ 3413 (OH), 1706 cm.$^{-1}$ (C=O) (reported,[7] m.p. 117–118°).

(b) The above keto-diol (VIII) was also prepared directly from the ketal (VI) as follows: To an ethereal solution (60 cc.) of lithium aluminum hydride (0.6 g.), the ketal (VI, 2.00 g.) in absolute ether benzene (6:1, 60 cc.) was added dropwise, with stirring (1 hr.). After heating under reflux with stirring for 3 hr., the reaction mixture was cooled with water, and cold dilute sulfuric acid (7%, 30 cc.) was added into the reaction mixture with careful stirring. After the mixture was heated under reflux for 1 hr., the organic layer was separated and washed with water. Evaporation of the dried solution left 1.20 g. (70%) of VIII, as colorless needles m.p. 117–118° (mixed m.p.).

3-Keto-α-santan-5,12-oxide (IX). (a) *Clemmensen method.* By an effective modification of the procedure previously reported,[3] the ketodiol (VIII, 0.80 g.) in toluene (2 cc.) was heated to reflux for 24 hr. with amalgamated zinc (prepared from 2.0 g. of zinc and 0.08 g. of mercuric chloride) in 3 cc. of concentrated hydrochloric acid and 2 cc. of water. One cc. each of concentrated hydrochloric acid was added to the refluxed reaction 3 times during a period of 5 hr. After cooling, benzene was added to the reaction mixture, and the organic layer was separated, washed with water, dried, and evaporated. There was obtained 0.73 g. (98%) of an oxide (IX) as colorless plates, m.p. 70–75°. Recrystallization from petroleum ether raised the melting point to 84–85°; $[\alpha]_D^{28}$ +11.8° (*c* 3.4; $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 1712 (C=O), 1125 cm.$^{-1}$ (tetrahydrofuran).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.47; H, 9.99.

It showed obvious depression of the melting point (71–77°) on admixture with the starting material (VIII, m.p. 118–119°).

With Brady's reagent, IX gave in 70% yield a *2,4-dinitrophenylhydrazone*, which was recrystallized from ethyl acetate to golden yellow plates, m.p. 188–189°.

Anal. Calcd. for $C_{21}H_{28}O_5N_4$: C, 60.56; H, 6.78; N, 13.45. Found: C, 60.55; H, 6.66; N, 13.61.

(b) *With hydrochloric acid.* The keto-diol (VIII, 0.05 g.) in toluene (1 cc.) was mixed with concentrated hydrochloric acid (0.3 cc.) and water (0.1 cc.), and then the mixture was heated to reflux for 16 hr. On working up as described for (a), the oxide (IX, 0.04 g., 86%) was obtained as colorless plates, m.p. and mixed m.p. 83–84°.

(c) *With p-toluenesulfonic acid.* The keto-diol (VIII, 0.03 g.) was dissolved in benzene (2 cc.), which was heated under reflux with *p*-toluenesulfonic acid (monohydrate, 0.01 g.) for 0.5 hr. After cooling, the benzene solution was washed with aqueous sodium bicarbonate. Evaporation of the dried solution left a pale yellow sirup (IX, 0.02 g., 72%), which furnished in 57% yield the 2,4-dinitrophenylhydrazone, m.p. 188–189° (mixed m.p.).

(d) *Deninger-Einhorn method.* To a cold solution of the keto-diol (VIII, 0.16 g.) in pyridine (1.5 cc.) was added *p*-toluenesulfonyl chloride (0.16 g.). After standing at room temperature for 5 days, the reaction mixture was poured into ice water, and taken up in ether. The ether solution was washed, successively, with water, 5% hydrochloric acid, aqueous sodium bicarbonate, and then water. Evaporation of the dried ethereal solution left a colorless sirup (IX, 0.12 g., 80%), which gave in 60% yield of the 2,4-dinitrophenylhydrazone, m.p. 188–189° (mixed m.p.).

The oxide (IX, 0.05 g.) was treated with Clemmensen reduction the same condition as mentioned in (a), giving quantitative recovery of the starting material as colorless plates, m.p. and mixed m.p. 83–84°.

α-Santan-5,12-diol-a (X, R = H). (a) *From 3-keto-α-santan-5,12-diol-a* (VIII). To a solution of metallic sodium (0.31 g.) in diethylene glycol (9 cc.) was added the keto-diol (VIII, 1.30 g.) and hydrazine hydrate (80%, 0.65 cc.). After refluxing for 2 hr. at 180–190° (bath temperature) the condenser was removed. The reaction continued until the bath temperature had reached 200–210°, when reflux continued for 5 hr. After cooling, the reaction mixture was poured into an equal amount of water and extracted with ether. The ethereal solution was washed with water, dried, and evaporated, giving 1.07 g. (87%) of the diol (X) as white needles, m.p. 100–103°. Recrystallization from ethanol or sublimation *in vacuo* (2 mm., 85–90°) gave colorless prisms, m.p. 107–108°; $[\alpha]_D^{28}$ −28.2° (*c* 2.2; $CHCl_3$) and $[\alpha]_D^{30}$ −21.5° (*c* 2.6; EtOH); λ_{max}^{Nujol} 3226, 1107, 1025 cm.$^{-1}$ (OH).

Anal. Calcd. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 74.93; H, 11.94.

(b) *From 3α-hydroxy-tetrahydro-α-santonin-a* (IV). A solution of the tosylate (IVb, 0.20 g.) in absolute benzene-ether (6:1, 7 cc.) was added dropwise, with stirring to the solution of lithium aluminum hydride (0.06 g.) in absolute ether (6 cc.). After reflux with stirring for 10 hr., excess reagent in the cooled reaction mixture was decomposed with water and then 5% hydrochloric acid. The separated organic layer was washed with water, dried, and evaporated, giving a pale yellow sirup (0.11 g.), which was chromatographed on alumina (10 g.). Elution with benzene-ethanol (1:1) afforded a pale yellow sirup (0.10 g.), which was sublimated at 3 mm. (85–90°, bath temperature), gave 0.06 g. (51%) of the diol (X) as colorless needles, m.p. and mixed m.p. 107–108°.

Deninger-Einhorn reactions of α-santan-5,12-diol-a (X). (a) *With p-nitrobenzoyl chloride at lower temperature.* To a cold solution of the diol (X, 0.10 g.) in pyridine (6 cc.) was added 1.1 molar equivalents of *p*-nitrobenzoyl chloride (0.08 g.). After standing in refrigerator at 0° for 48 hr., the reaction mixture was poured into ice water, and the separated solid was taken up in ether. The ethereal solution was washed, successively, with 10% hydrochloric acid, water, aqueous sodium bicarbonate and water, giving 0.12 g. (75%) of the mono-*p*-nitrobenzoate (Xa), as white needles, m.p. 150°. Recrystallization from benzene raised the melting point to 165–166°; $\lambda_{max}^{CHCl_3}$ 1727, 1531, 1350, 1277, 1166, 1103, 1053, 1038, 1016, 974 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02; N, 3.60. Found: C, 67.77; H, 8.06; N, 3.50.

(b) *With p-nitrobenzoyl chloride at room temperature.* To a cold solution of the diol (X, 0.15 g.) in pyridine (10 cc.) was added 2.4 molar equivalents of *p*-nitrobenzoyl chloride (0.30 g.). After standing at room temperature for 48 hr., the reaction mixture was treated as above. The bis-*p*-nitrobenzoate (Xb, 0.25 g., 74%) m.p. 160–164° deposited as white needles, which was recrystallized from ethanol (contained small amount of ethyl acetate) to white needles, m.p. 169–170°; $\lambda_{max}^{CHCl_3}$ 1727, 1534, 1348, 1274, 1172, 1117, 1104, 1017 cm.$^{-1}$

Anal. Calcd. for $C_{29}H_{34}N_2O_8$: C, 64.67; H, 6.36; N, 5.20. Found: C, 64.44; H, 6.40; N, 5.14.

It showed obvious depression (139–142°) of the melting point on admixture with the mono-*p*-nitrobenzoate (Xa).

To a cold solution of the mono-*p*-nitrobenzoate (Xa, 0.05 g.) in pyridine (3 cc.) was added the same reagent (0.05 g.). After standing at room temperature for 48 hr., the reaction mixture was treated as above, giving 0.06 g. (87%) of the bis-*p*-nitrobenzoate (Xb) as white needles, m.p. and mixed m.p. 168–169°.

(c) *With 3,5-dinitrobenzoyl chloride at lower temperature.* The diol (X, 0.15 g.) was treated at lower temperature as described above, with 1.1 molar equivalents of 3,5-dinitrobenzoyl chloride (0.16 g.), giving crude product as a white powder (0.21 g., the melting range of 120–134°). The material was triturated with ethanol (0.5 cc.) at room temperature. After removal of an insoluble substance (0.005 g.), solvent was evaporated with addition of a small amount of benzene, and then deposited the mono-3,5-dinitrobenzoate (Xc, 0.12 g., 45%) as white needles, m.p. 135–138°. Recrystallization from benzene raised the melting point to 141–142°, $\lambda_{max}^{CHCl_3}$ 1736, 1553, 1348, 1280, 1167, 1081, 1036, 1003, 987, 920 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{30}N_2O_7$: C, 60.81; H, 6.96; N, 6.45. Found: C, 60.88; H, 6.93; N, 6.43.

The mother liquor from crystallization of Xc gave a white powder (0.08 g.), which was chromatographed on alumina (6 g.). Elution with benzene afforded an additional 0.03 g. (total 0.15 g., 54%) of the monobenzoate (Xc) as white needles, m.p. and mixed m.p. 141–142°. The following fractions, eluted with ethyl acetate, afforded 0.05 g. (33%) of the starting diol (X) as colorless needles, m.p. and mixed m.p. 103–104° (sublimation at 3 mm.).

An ethanol insoluble substance was recrystallized from ethyl acetate–ethanol (2:1), giving the bis-3,5-dinitrobenzoate (Xd, described below) as white needles, m.p. 181–182° (mixed m.p.).

(d) *With 3,5-dinitrobenzoyl chloride at room temperature.* The diol (X, 0.15 g.) was treated at room temperature as described above for (b), with 2.2 molar equivalents of the reagent (0.32 g.), giving 0.34 g. (87%) of the bis-3,5-dinitrobenzoate (Xd) as white needles, m.p. 162°. Recrystallization from ethyl acetate–ethanol (2:1) raised the melting point to 181–182°; $\lambda_{max}^{CHCl_3}$ 1736, 1553, 1347, 1277, 1167, 1075, 1034, 1005, 980, 953, 921 cm.$^{-1}$

Anal. Calcd. for $C_{29}H_{32}N_4O_{12}$: C, 55.41; H, 5.13; N, 8.91. Found: C, 55.42; H, 5.05; N, 8.77.

The mono-3,5-dinitrobenzoate (Xc, 0.02 g.) was treated with the same reagent (0.02 g.) in pyridine, as described above for (b), giving 0.02 g. (70%) of the bis-3,5-dinitrobenzoate (Xd), m.p. and mixed m.p. 181–182°.

Deninger-Einhorn reactions of α-santan-5,12-diol-b (XII, R = H). (a) *With p-nitrobenzoyl chloride.* The diol-*b* (XII, 0.05 g.) was treated at room temperature as described above for Xb, with 2.4-molar equivalents of the reagent (0.10 g.), giving a mono-*p*-nitrobenzoate (XIIa, 0.07 g., 86%) as white needles, m.p. 120°. Recrystallization from ethanol containing small amount of ethyl acetate, raised the melting point to 135–136°; $\lambda_{max}^{CHCl_3}$ 1730, 1613, 1534, 1351, 1279, 1117, 1104, 1017, 975 cm.$^{-1}$ (reported,[8] m.p. 134–135.5°).

The mono-*p*-nitrobenzoate (XIIa, 0.05 g.) was warmed with the same reagent (0.05 g.) in pyridine at 60° for 5 hr. The starting material (0.05 g.) was recovered, m.p. and mixed m.p. 135°.

(b) *With 3,5-dinitrobenzoyl chloride.* The diol-*b* (XII, 0.05 g.) was treated at room temperature as described above, with 2.0 molar equivalents of the reagent (0.11 g.), giving 0.10 g. of semicrystalline product. Recrystallization from ethanol gave 0.07 g. (54%) of mono-3,5-dinitrobenzoate (XIIb) as white needles, m.p. 140°; $\lambda_{max}^{CHCl_3}$ 1736, 1635, 1552, 1347, 1279, 1166, 1075, 1025, 978, 911 cm.$^{-1}$

Anal. Calcd. for $C_{22}H_{30}N_2O_7$: C, 60.81; H, 6.96; N, 6.45. Found: C, 60.73; H, 6.73; N, 6.85.

3-Desoxytetrahydro-α-santonin-a (XI). (a) *With chromium trioxide in acetic acid.* To a solution of chromium trioxide (0.14 g., 1.2 molar equivalents) in glacial acetic acid (5 cc.) and water (0.2 cc.), added dropwise the diol-*a* (X, 0.20 g.) in glacial acetic acid (2 cc.) at 15–20° with stirring. After stirring was continued for 1 hr. at 20°, the solution was poured into twice volume of water to decompose the excess chromium trioxide with aqueous sodium bisulfite. The deposited colorless leaflets were filtered and washed with water, showing m.p. 142° (0.13 g.). The crude product was taken up in ether and washed with aqueous sodium bicarbonate, water, and dried, giving the 3-desoxytetrahydro-α-santonin-*a* (XI, 0.12 g., 61%) as colorless plates, m.p. 149°. Recrystallization from ethanol raised the melting point to 151–152°; $[\alpha]_D^{27}$ +57.6° (*c* 2.64; $CHCl_3$); λ_{max}^{Nujol} 1776 (γ-lactone), 1460, 1388, 1332, 1189, 1155, 1133, 1117, 1030, 1014 cm.$^{-1}$ (reported,[6] m.p. 153–155°, $[\alpha]_D$ +46.7°; and m.p. 155–157°, $[\alpha]_D$ +47.5°).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.49; H, 10.11.

A residual semisolid, obtained from the mother liquor of XI was worked up as above. The residual semicrystalline mixture was triturated with petroleum ether. Recrystallization from ethanol furnished an additional 0.02 g. (total 0.14 g., 71%) of XI, m.p. 145–148° (mixed m.p.).

(b) *With chromium trioxide in pyridine.* To a solution of the desoxy diol-*a* (X, 0.50 g.) in pyridine (6 cc.) was added a complex of chromium trioxide (0.81 g.) in pyridine (12 cc.). After standing at room temperature for 24 hr. the precipitate on addition of ether, was filtered off and then the ethereal solution was washed, successively, with aqueous sodium bicarbonate, water, 10% hydrochloric acid, and water. Evaporation of the dried ethereal solution afforded 0.12 g. (49%) of XI as colorless plates, m.p. 148–149°. Recrystallization from ethanol raised the melting point to 150–151° (mixed m.p.). It showed obvious depression (*ca.* 30°) of the melting point on admixture with XIII described below.

3-Desoxy-tetrahydro-α-santonin-b (XIII), was prepared in 68% yield, from α-santan-5,12-diol-*b* (XII, m.p. 154–155°)[11] by oxidation with chromium trioxide in pyridine, as described for XI, m.p. and mixed m.p. 152°.[3,6,11]

5α-Hydroxy-α-santanic acid-a (XIV). After the 3-desoxytetrahydro-α-santonin-*a* (XI, 0.25 g.) was dissolved in methanol (3 cc.) and 5% sodium hydroxide (10 cc.), the solution was heated on a water bath under reflux for 5 hr. The methanol was removed under reduced pressure, the aqueous alkaline solution was washed with ether, and acidified with cold 10% hydrochloric acid. The acidic solution was extracted with ether, which was washed with water. Evaporation of the dried ethereal solution under reduced pressure, furnished 0.20 g. (74%) of the hydroxy acid (XIV) as white needles, m.p. 130°. Recrystallization from ether–petroleum ether raised the melting point to 148–149°; $[\alpha]_D^{28}$ +64.1° (*c* 0.97; $CHCl_3$); λ_{max}^{Nujol} 3236, 2604, 1773, 1681 cm.$^{-1}$

Anal. Calcd. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.77; H, 10.26.

It showed obvious depression (*ca.* 20°) of the melting point on admixture with the starting lactone (XI).

A *s-(p-nitrobenzyl)thiuronium salt*[20] *of* XIV was prepared

(20) R. L. Shriner, R. C. Fuson, and D. Y. Curtin "The Systematic Identification of Organic Compounds," 4th ed., John Wiley & Sons, Inc., New York, 1956, p. 202.

from the hydroxy acid (XIV, 0.03 g.) and *p*-nitrobenzyl thiuronium chloride (0.05 g.) in ethanol (1.5 cc.). The solution was concentrated under reduced pressure to deposit white needles (0.05 g., 91%), m.p. 148–150° (turned to brown). Recrystallization from minimum amount of ethanol, raised the melting point to 153–154° (turned to brown).

Anal. Calcd. for $C_{23}H_{35}N_3O_5S$: C, 59.33; H, 7.58. Found: C, 59.16; H, 7.70.

The hydroxy acid (XIV, 0.05 g.) was heated under reflux on a water bath in methanol (2 cc.) and 5% hydrochloric acid (1 cc.) for 1 hr. The solution was condensed under reduced pressure, and the residue was extracted with ether, washed with water, dried, and evaporated. Recrystallization of the residue from ethanol, afforded 0.04 g. (86%) of the starting lactone (XI) as colorless plates, m.p. and mixed m.p. 150–151°.

5-Keto-α-santanic acid-a (XV). The hydroxy acid (XIV, 0.10 g.) was added to a solution of chromium trioxide (0.10 g.) in pyridine (2 cc.). After standing at room temperature for 72 hr., the precipitate formed on addition of ether, was filtered off and then the ethereal solution was extracted with aqueous sodium bicarbonate. The alkaline solution was acidified with hydrochloric acid and warmed on a water bath for 0.5 hr. After cooling, the separated oil was extracted with ether. The ethereal solution was again extracted with aqueous sodium bicarbonate, which was acidified with 10% hydrochloric acid and taken up in ether. Evaporation of the dried ethereal solution left 0.05 g. (63%) of the keto-acid (XV) as colorless oil, the attempt of crystallization of which was unfruitful after it was chromatographed on alumina. Furthermore, it could not form the 2,4-dinitrophenylhydrazone by the usual method.

A *s-(p-nitrobenzyl)thiuronium salt of* XV was obtained in 69% yield, by the same procedure as described for XIV, as white fine needles (m.p. 162–163°). Recrystallization from ethanol, afforded white leaflets, m.p. 168–169° (turned to orange), λ_{max}^{Nujol} 1706, 1527, 1408, 1130, 1105 cm.$^{-1}$

Anal. Calcd. for $C_{28}H_{33}N_3O_5S$: C, 59.58; H, 7.18; N, 9.06. Found: C, 59.42; H, 7.03; N, 8.88.

Inversion of 5-keto-α-santanic acid-a (XV) *to 5-keto-α-santanic acid-d* (XIX). (a) *By only heating.* The keto-acid (XV, 0.22 g.) was heated *in vacuo* (2 mm.) at 180–190°. A distilled colorless sirup was readily crystallized to colorless needles (0.12 g., 55%), m.p. 152–154°. The residue from the above distillation was crystallized from petroleum ether to the same crystal (0.07 g., total 86%), m.p. and mixed m.p. 156–157°. Recrystallization from petroleum ether furnished colorless needles, m.p. 159–160.5°. It showed no depression of the melting point on admixture with an authentic specimen of 5-keto-α-santanic acid-*d* (XIX), obtained from *cis*-fused tetrahydro-α-santonin-*d* (XXI) described below.

(b) *By 3% potassium hydroxide solution.* The keto-acid (XV, 0.07 g.) was heated on a water bath in dioxan (0.5 cc.) and 3% potassium hydroxide (1.4 cc.) as reported previously.[14] The acidified solution was extracted in ether. Evaporation of the dried ethereal solution left 0.06 g. (86%) of XIX as white needles, m.p. 153–155°. Recrystallization from petroleum ether raised the melting point to 159–160.5° (mixed m.p.).

5-Keto-α-santanic acid-b (XVII). (a) *From 3-desoxytetrahydro-α-santonin-b* (XIII). The 3-desoxy compound (XIII, 1.00 g.) was dissolved in an aqueous potassium hydroxide (3%, 40 cc.) and a minimum amount of ethanol (3 cc.). After distillation of organic solvent, the ice cold reaction mixture was acidified with dilute acetic acid and extracted with ether. To the ethereal solution of the acid (XVI) was added a few drops of pyridine to prevent relactonization, as reported previously.[14] After distillation of the ether under reduced pressure, the residual crude acid (XVI) was mixed with a mixture of 2 g. of chromium trioxide and 17 cc. of pyridine. The mixture was allowed to stand at room temperature over night. Ether was added to the reaction mixture, the precipitate was filtered off, and the ethereal solution was washed successively with 10% hydrochloric acid, water, and saturated sodium bicarbonate. The alkaline solution was acidified with 10% hydrochloric acid and heated on a water bath for 0.5 hr., and the separated oil was taken up in ether. The ethereal solution was extracted with aqueous sodium bicarbonate. The combined ethereal solution was dried and evaporated to give 0.70 g. (70%) of recovered XIII (m.p. and mixed m.p. 150–151°). The alkaline solution was acidified with 10% hydrochloric acid, and extracted with ether. Evaporation of the dried ethereal solution left 0.17 g. (16%) of the keto-acid-*b* (XVII) as colorless prisms, m.p. 80°. Recrystallization from petroleum ether melting point raised to 95–96° (reported, m.p. 98–99°).

A *s-(p-nitrobenzyl)thiuronium salt of* XVII was prepared in 96% yield by the method as described for XV, as white fine needles, m.p. 175° (turned to orange) (from ethanol), λ_{max}^{Nujol} 1709, 1524, 1404, 1117, 1092 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{33}N_3O_5S$: C, 59.58; H, 7.18; N, 9.06. Found: C, 59.69; H, 7.42; N, 8.82.

An attempt of purification of XVI was unfruitful: The 3-desoxy lactone (XIII, 1.00 g.) was dissolved as above to aqueous alkaline solution, and acidified with 3% hydrochloric acid under ice cooling, and extracted with ether. The dried ethereal solution was evaporated *in vacuo*. There was obtained the starting lactone XIII (0.95 g.) as colorless leaflets, m.p. and mixed m.p. 150–151°.

On the other hand, when 3-desoxytetrahydro-α-santonin-*b* (XIII) was oxidized with *N*-bromoacetamide by the method reported previously,[14] or aqueous alkaline permanganate solution, the starting material was recovered in 90% and 67% yield, respectively.

The keto-acid (XVII) was quantitatively recovered in the attempt of equilibration under the same alkaline condition as described for XV. With Brady's reagent, it could not form the 2,4-dinitrophenylhydrazone.

(b) *From 3,5-diketo-α-santanic acid-b* (XVIII). The keto-acid-*b* (XVII) was furnished in 77% yield from 3,5-diketo-α-santanic acid-*b* (XVIII)[14,15] by the Clemmensen reduction as described for IX (m.p. and mixed m.p. 97–98°).

3-Desoxytetrahydro-α-santonin-d (XXI). The Clemmensen reduction of *cis*-fused tetrahydro-α-santonin-*d* (XX, 2.00 g.)[16] was carried out as the same procedure as for IX. 3-Desoxy compound (XXI) was afforded in 96% yield as crude crystals (m.p. 76°), which was recrystallized from petroleum ether to colorless prisms, m.p. 85°; $[\alpha]_D^{31}$ −16.8° (*c* 1.67; EtOH); $\nu_{C=O}^{Nujol}$ 1772 cm.$^{-1}$ (γ-lactone) [reported,[11] m.p. 86–87° and $[\alpha]_D^{20}$ −27.9° ($CHCl_3$)].

5-Keto-α-santanic acid-d (XIX). (a) 3-Desoxytetrahydro-α-santonin-*d* (XXI, 0.40 g.) was dissolved in an aqueous potassium hydroxide (1.2%, 40 cc.), and was carried out the same procedure as described for *trans*-fused isomer (XVII). The crude hydroxy acid was oxidized in pyridine (6 cc.) with chromium trioxide (0.60 g.) as described for XI. There was obtained 0.07 g. (16%) of crude keto-acid-*d* (XIX) as white needles, m.p. 157°, and 0.22 g. (55%) of the starting lactone (XXI). Recrystallization from petroleum ether raised the melting point to 159–160.5°; $[\alpha]_D^{12}$ −88.5° (*c* 1.33; $CHCl_3$); $\nu_{C=O}^{CHCl_3}$ 1709 cm.$^{-1}$ (reported,[6] m.p. 159–160°, $[\alpha]_D$ −84.2°).

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.51; H, 9.64.

A *s-(p-nitrobenzyl)thiouronium salt of* XIX was prepared from the keto-acid (XIX, 0.05 g.) in the usual manner. There was obtained 0.08 g. (87%) of the salt as white leaflets, m.p. 138–139°. After recrystallization from ethanol the melting point raised to 141–142° (turned to brown); λ_{max}^{Nujol} 1700, 1521, 1393, 1155, 1115 cm.$^{-1}$

Anal. Calcd. for $C_{23}H_{33}N_3O_5S$: C, 59.58; H, 7.18; N, 9.06. Found: C, 59.67; H, 7.05; N, 9.04.

The keto-acid (XIX) was quantitatively recovered in the attempt of equilibration under the same alkaline condition as described for XV, and it could not form the 2,4-dinitrophenylhydrazone of XIX in the usual manner.

(b) The 3-desoxy compound (XXI, 0.50 g.) was dissolved in an aqueous potassium hydroxide (1.2%, 50 cc.). The ice cooled reaction mixture was acidified with dilute hydrochloric acid, and extracted with ether. The ethereal solution was esterified with diazomethane in the usual manner. To the residue, which was obtained on evaporation of the ethereal solution, was added a mixture of chromium trioxide (1 g.) in pyridine (10 cc.). After standing at room temperature for 72 hr., the reaction mixture was treated as usual, giving a colorless sirup (0.47 g.). It was hydrolyzed with an aqueous potassium hydroxide in methanol, and acidified with dilute hydrochloric acid. On cooling, 0.36 g. (67%) of XIX deposited as white needles, m.p. 150°, which was raised by recrystallization from petroleum ether to 160–161° (mixed m.p.).

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[CONTRIBUTION NO. 1055 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Reaction of Dicobalt Octacarbonyl with Some Acetylenic Compounds[1]

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The relative rates of reaction of acetylenic acids, alcohols, esters, ethers, halides, and hydrocarbons with dicobalt octacarbonyl have been determined. The differences in the relative reactivities are not great; however, carboxy-, carbomethoxy- and methylol- groups appear to enhance the reactivity when attached to the triple bonded carbon. The observed relative reactivities are not correlated with possible electronic effects. A decrease in relative reactivity can be traced to steric factors. An anomalous behavior of certain propargyl-type halides was found and has been attributed to a possible coupling reaction of these halides in the presence of dicobalt octacarbonyl.

In a recent investigation,[5] it was reported that dicobalt octacarbonyl reacts with acetylenic compounds producing acetylenic dicobalt hexacarbonyls and evolving carbon monoxide according to the reaction

$$R{-}C{\equiv}C{-}R' + Co_2(CO)_8 \longrightarrow RC_2R'Co_2(CO)_6 + 2CO. \quad (1)$$

A kinetic study of this reaction with hexyne-1 and with hexyne-2 has been made.[6] This investigation gave kinetic evidence that in solution a small amount of a reactive form of dicobalt octacarbonyl is present. Kinetic evidence was also found for an acetylenic dicobalt heptacarbonyl intermediate.[6]

The purpose of the present study was to determine the effect of various groups (R- and R'-) upon the rate of reaction. The relative reactivities of various acetylenic acids, alcohols, esters, ethers, halides, and hydrocarbons were determined from the half-lives of their reactions. These half-lives were obtained from a plot of volume of evolved carbon monoxide *versus* time. The half-life of the reaction with hexyne-1 was assigned a value of 100 on the relative reactivity scale and the relative reactivity of each acetylenic compound was calculated from

$$\text{Relative reactivity} = \frac{t_{1/2}\ (\text{hexyne-1})}{t_{1/2}\ (\text{acetylenic compound})} \times 100 \quad (2)$$

The average half-life ($t_{1/2}$) for hexyne-1 calculated from twenty-one individual experiments was found to be 320 seconds.

EXPERIMENTAL

Procedure. The rates of reaction of various acetylenic compounds were determined by measuring the rates of evolution of carbon monoxide. The apparatus and procedure that were used have been described in a previous paper.[6] Liquid acetylenes were introduced into the reaction flask with a hypodermic syringe. Standard solutions of acetylenic solids were prepared in toluene and aliquots of these solutions were injected into the reaction flask. The total volume of solution in the reaction flask was 50 ml.

The initial concentrations of both the dicobalt octacarbonyl and the acetylenic compound were 0.200 moles $l.^{-1}$ In all cases the reaction was carried out in toluene solution and at a temperature of 25°.

Materials. Toluene was obtained from the Neville Chemical Co., Pittsburgh, Pa. and was redistilled; b.p. 108–109°. Dicobalt octacarbonyl was obtained through the courtesy of the Bureau of Mines, Bruceton, Pa. The dicobalt octacarbonyl reagent was prepared in toluene solution as described in a previous paper.[6]

The acetylenic compounds were prepared with the purpose of obtaining pure materials; hence, no attempt was made to determine yields of the new compounds. These materials (as listed in Tables I, II and III) were obtained by the general syntheses or specific procedures as indicated below:

A. Alkylation (one- or two-step) of sodium acetylide in liquid ammonia.

(1) Abstracted from a portion of the Ph.D. Thesis of M. R. Tirpak, University of Pittsburgh (1958).

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