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Santonin and Related Compounds. XIX.[1] Some Transformation Reactions of 2-Bromo-α-tetrahydrosantonin

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The 2-bromo structure (II) for the monobromo derivative of α-tetrahydrosantonin (I) was definitely proved by the reaction sequence (II → IV → VI → VIII). The 2-bromoketone (II) on acetolysis afforded the more stable epimer (IX) of the ketol acetate, which was also prepared from I with lead tetraacetate in reflux acetic acid. When the latter reaction was performed at the lower temperature, the other epimer (X) was obtained almost quantitatively. Epimerization of X to IX was effected by refluxing with acetic acid. Both ketol acetates were reduced to the parent ketone (I) or 3-desoxy-α-tetrahydrosantonin (VII), respectively, with zinc dust-acetic acid or by the Clemmensen method. The dimethylene thioketals (XIV and XV) of the ketol acetates gave the 3-desoxy compound (VII) on reduction with Raney nickel. Compound XV could be easily epimerized to XIV.

It has been reported[2] that treating α-(I) and γ-tetrahydrosantonin[3] with bromine gave exclusively the 2-bromo compounds. The evidence for the 2-bromo structure of these derivatives was principally based on the fact that on collidine treatment, each of these bromoketones gave a Δ^1-dihydrosantonin (III) as the sole product isolated. However, because the yields of the dihydro compounds were small, the allocation of bromine in the bromoketones, though it appears very logical, cannot be considered conclusive. Moreover, previous work has shown that dehydrobromination of the 2-bromo derivative of 9-methyl-3-decalones with γ-collidine was always accompanied by rearrangement,[4,5] and that 4,9-dimethyl-3-decalones, both *cis*- and *trans*- fusions, were invariably brominated at the 4-position rather than the 2-position.[6,7] In view of these observations, the slight possibility of 4-bromination in the tetrahydrosantonins cannot be completely excluded. It seems to us worthwhile to unequivocally establish the structure of these bromoketones. The present paper reports on a study of the derivatives of α-tetrahydrosantonin (I), possessing the *trans*-decalin system.

The monobromo derivative of I was subjected to the same sequence of reactions (II→IV→VI→VIII) employed earlier for the proof of the position of bromine in the 2-bromo derivative of 9-methyl-3-decalone.[4,5b] Reduction of the bromoketone with sodium borohydride in ethanol at room temperature proceeded stereospecifically, and one of two possible bromohydrin isomers was obtained as a crystalline solid in a 74% yield. It is generally accepted that a *cis*-bromohydrin is converted by alkali to a ketone whereas its *trans*-isomer readily gives an epoxide. Upon treatment with methanolic potassium hydroxide, the present bromohydrin was unaffected at room temperature, but when heated to reflux, it was converted to the parent ketone (I) in a good yield. This result clearly favored the *cis*-structure (IV) for the bromohydrin.

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

(2) M. Yanagita and A. Tahara, *J. Org. Chem.*, **20**, 959 (1955); *cf.* M. Yanagita and H. Ogura, *J. Org. Chem.*, **22**, 1092 (1957).

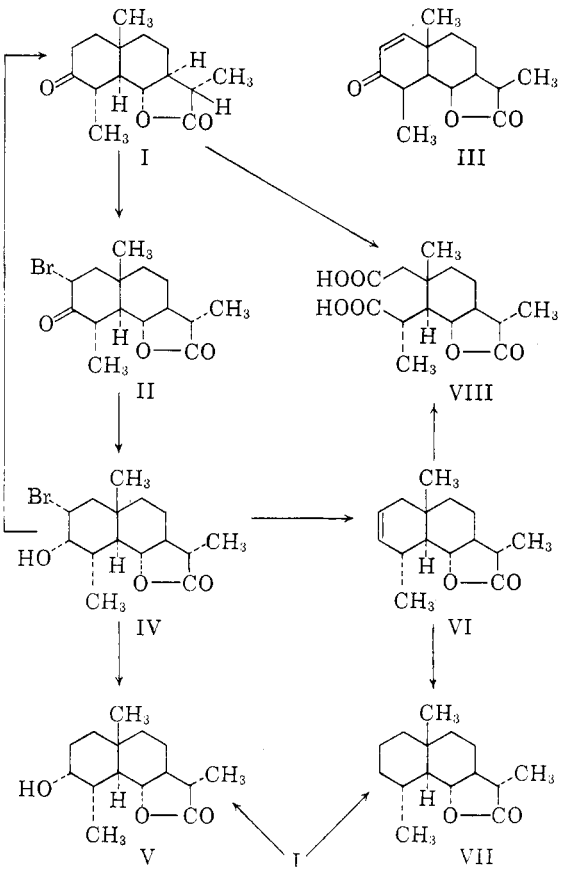
(3) The prefixes α and γ are used in this and following papers in conformity to the original paper in this series (ref. 2); *cf.* ref. 11b.

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

(5) (a) M. Yanagita and A. Tahara, *J. Org. Chem.*, **18**, 792 (1953); (b) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **21**, 500 (1956).

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

(7) *Cf.* M. Yanagita and H. Ogura, *J. Org. Chem.*, **23**, 443 (1958).



The equatorial orientation of bromine in the bromoketone (II), which was rendered likely from conformational analysis,[8] was established by the shifts of the carbonyl absorption in the ultraviolet ($\Delta\lambda_{max}$ -5.5 mμ)[9] and infrared spectra ($\Delta\nu$ $+23$ cm.$^{-1}$)[10] over the parent ketone (I). It is most likely that the bromine in the bromohydrin takes up the same equatorial position. Consequently, it is deduced that the hydroxyl group in the bromohydrin may be axially oriented. This deduction was confirmed by the observation that the bromohydrin was catalytically reduced to one isomer of the hexahydrosantonin, in which the axial character of the hydroxyl group at the 3-position has been established.[11] It is to be noted that the predominant formation of the *cis*-bromohydrin from the 2-bromoketone (II) with borohydride is in a remarkable contrast to the result of similar reduction of 2α-bromocholestan-3-one, which gave chiefly the *trans*-bromohydrin with the newly-formed hydroxyl group at the equatorial position.[12] This may be attributed to an increase in steric hindrance to the carbonyl group due to the combined effects of the two α-oriented, adjacent, bulky substituents, as suggested previously for explanation of the same stereochemical course of borohydride reduction of the 2α,4α-dihalo-3-ketosteroids.[13] This consideration was supported by the previous result[11a] that borohydride reduction of α-tetrahydrosantonin (I), unlike the case of II, reesulted in the predominant formation of an epimer of the hexahydrosantonin (V), carrying the equatorial hydroxyl group at the 3-position.

Reduction of the bromohydrin (IV) with zinc dust and acetic acid afforded in 67% yield an olefin (VI), which was differentiated from the known Δ^3-isomer[11b] by comparisons of the melting points and rotational data. It had the infrared absorption bands at 1662 and 678 cm.$^{-1}$, indicating the presence of a *cis*-disubstituted double bond.[4,5b,14] The olefin was quantitatively hydrogenated over platinic oxide to 3-desoxy-α-tetrahydrosantonin (VII) reported previously[15] Permanganate oxidation of the olefin was carried out in pyridine solution at low temperature with addition of magnesium sulfate in keeping the mixture neutral to litmus paper. There was obtained a diacid in 50% yield. The same acid was also formed in comparable yield directly from I by oxidation with hot concentrated nitric acid. From these modes of the preparation, it may be presumed that the diacid (VIII) preserved the original lactone ring, which is considerably stable to acid. The diacid was quantitatively recovered from the hot alkaline solution by acidification, showing that the lactone ring in the diacid possesses the most favorable of the possible isomeric structures.[16] Ozonolysis of the olefin (VI), which seems to be the most promising method for preparing the diacid, was attempted under various conditions, but even when methanol[17] was used as a solvent at low temperature, no crystalline products were obtained.[18]

(8) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1953).

(9) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

(10) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952).

(11) (a) B. Riniker, Thesis, E. T. H. Zürich, 1955. (b) W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4549 (1956).

(12) L. F. Fieser and X. A. Dominguez, *J. Am. Chem. Soc.*, **75**, 1704 (1953); E. J. Corey, *J. Am. Chem. Soc.*, **75**, 4832 (1953); H. B. Henbest and T. I. Wrigle, *J. Chem. Soc.*, 4596 (1957): *Cf.* J. J. Beereboom, C. Djerassi, D. Ginsburg, and L. F. Fieser [(*J. Am. Chem. Soc.*, **75**, 3500 (1953)] reported that borohydride hydrogenation of 2-chlorocholestan-3-one resulted in an epimeric mixture, consisting of almost an equal amount of *cis*- and *trans*-chlorohydrins.

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

(14) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, 1954, p. 31.

(15) (a) Wedekind and K. Tettweiler, *Ber.*, **64**, 387 (1931). (b) Ö. Kovács, V. Herout, M. Herák, and F. Šorm, *Collection Czeckoslov. Chem. Commun.*, **21**, 225 (1956).

(16) With respect to this point, a more detailed argument including *cis*-series will be made in the following paper of this series XX.

(17) Methanol was reported to be an excellent solvent for ozonolysis; for example see P. S. Bailey, *J. Am. Chem. Soc.*, **78**, 3811 (1956).

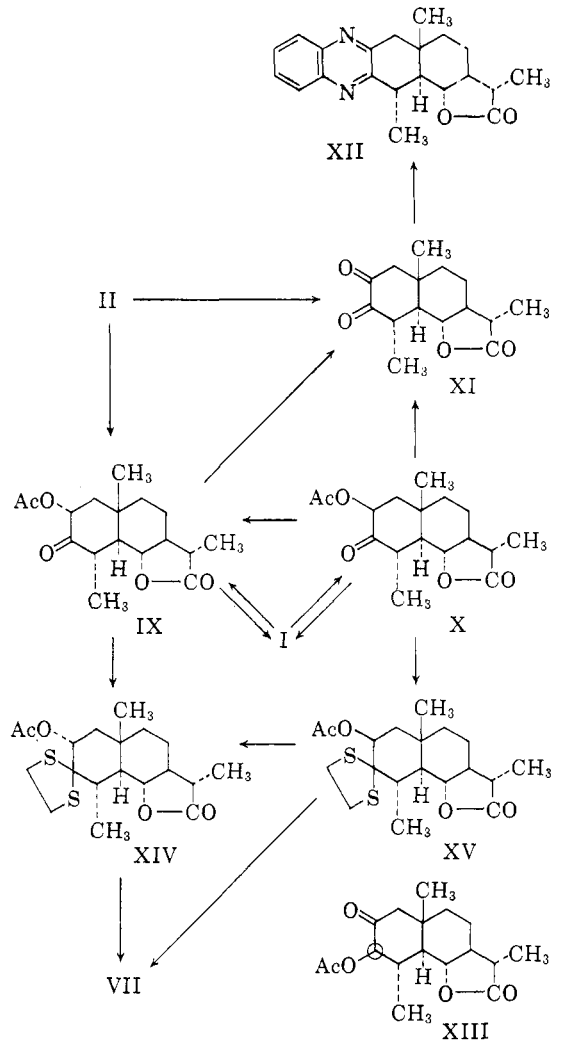
(18) A similar instance was found in a recent paper describing ozonolysis of the acetate of Δ^2-anhydroisodihydroresin, which gave only a poor yield of the oily ester of the diacid corresponding to VIII [C. Djerassi, F. W. Donovan, S. Burstein, and R. Mauli, *J. Am. Chem. Soc.*, **80**, 1972 (1958)].

The reaction sequence mentioned above clearly showed that the olefin (VI) has the double bond between the 2- and 3-positions, and hence, the previous formula (II) of the bromoketone is beyond doubt.

It is known that on acetolysis, the α-bromo-3-ketosteroids frequently yield rearranged product,[19] while the simple 2-bromo-3-decalone gives the normal ketol acetate.[4,5] It seems of interest to examine the reaction of the above bromoketone (II) with the acetate ion. Refluxing II with potassium acetate in glacial acetic acid led in 58% yield to one isomer, m.p. 199–200°, of the ketol acetate. The same compound could be quantitatively obtained in one step from I by oxidation with lead tetraacetate in refluxing glacial acetic acid. When the latter reaction was conduced on a water-bath, another isomer, m.p. 171.5–172.5°, was secured in 90% yield. That the discrepancy of the melting points of these two forms is due to isomerism rather than dimorphism was shown by comparisons of their infrared spectra and by preparation of dissimilar 2,4-dinitrophenylhydrazones. It is reasonably assumed that the acetoxyl group in the higher-melting epimer (IX) occupies an equatorial (*trans* to the angular methyl group) and the one in the lower-melting epimer (X) an axial conformation (*cis* to the angular methyl group). This assumption was confirmed by complete transformation of X into IX by refluxing with acetic acid for 6 hours, indicating that IX is the more stable compound. A similar instance in steroid chemistry is the oxidation of 23-bromo-22α,5α-spirostan-3-one with lead tetraacetate on the steam bath to give the 2α(axial)-acetoxyl compound.[20]

In order to hydrolyze the acetoxyl group, the ketol acetates (IX and X) were allowed to stand in 0.25*N* potassium hydroxide solution at room temperature for 2 hours. From either reaction mixture, the same α-diketone (XI), showing positive ferric chloride test, was isolated in good yield. It was characterized as a glyoxime and quinoxaline (XII). The bromoketone (II) on the same treatment with alkali afforded the identical diketone. There was no evidence for the expected α-ketol or diacid (VIII) in these reactions. Even when the alkaline hydrolysis of the bromoketone was conducted under a stream of nitrogen, the α-diketone (XI) was the only product isolated.

The slight possibility that the ketol acetate would have the structure XIII resulting from α-ketol rearrangement during acetolysis could not be excluded. It has been reported that in the ketol acetates of steroid[21] and of the simple cyclic compound,[22] which possess the carbonyl group in conjugation with the double bond, the acetoxyl group was readily eliminated by brief refluxing with zinc in acetic acid (or acetic anhydride). The same method of reduction was tried on ketol acetates IX and X, but both were completely recovered. When the refluxing time was prolonged to 24 hours, even the more stable ketol acetate (IX) was quantitatively reduced to the parent ketone (I). This completely eliminated XIII as a possible structure for the ketol acetate.



Hoping to prepare the 2-oxygenated compound by elimination of the carbonyl group, the ketol acetates (IX and X) were subjected to reduction by the Martin modification of Clemmensen method. Both reactions gave in good yields the same product, the 3-desoxy-tetrahydrosantonin (VII). This result was not unexpected, since some examples have been recorded involving elimination of only the hydroxyl group or the two oxygen functions of ketol (not its acetate) on reduction by the Clem-

(19) L. F. Fieser and M. A. Romero, *J. Am. Chem. Soc.*, **75**, 4716 (1953).

(20) J. Herran, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **76**, 5531 (1954).

(21) F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 4712 (1953).

(22) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4233 (1952).

mensen reaction or modifications of it.[23] Another possible route is the hydrogenolysis of the thioketal derivative of the ketol acetate. Unlike the parent ketone (I),[15b] both IX and X remained unaffected on treatment with ethane dithiol in acetic acid using *p*-toluenesulfonic acid as a catalyst. Replacement of toluenesulfonic acid by boron trifluoride–ether complex gave thioketals (XIV and XV) in quantative yields. It was found that the thioketal (XV) of the less stable ketol acetate was readily epimerized to XIV by refluxing with dioxane for 20 hours. By the same procedure, the ketol acetate (IX) itself was epimerized quantitatively to X. Such a ready epimerization of the thioketal merits attention, because, unlike the ketol acetate, this compound is devoid of the enolizable function adjacent to the migrating group. Upon desulfurization with Raney nickel in dioxane or ethanol by the conventional procedure, both thioketals were converted to the above 3-desoxy compound (VII) with simultaneous elimination of the acetoxyl group. This result is somewhat unexpected, but after completion of this experimentation, a similar observation on Raney nickel hydrogenation of the dimethylene thioketal of the 3β-acetoxy-2-keto-steroid was reported.[24]

EXPERIMENTAL[25]

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.

α- and γ-Tetrahydrosantonins. According to the procedure described previously,[2] 1-α-santonin was hydrogenated over palladium-charcoal. α-Tetrahydrosantonin (I), obtained in 56% yield, had m.p. 153–156°; $\lambda_{max}^{CHCl_3}$ 289 mμ (ε 21.2); $\nu_{C=O}^{Nujol}$ 1701 cm.$^{-1}$ (cyclohexanone ring) and 1777 cm.$^{-1}$ (γ-lactone).

γ-Tetrahydrosantonin, obtained in 22% yield, had m.p 100–103°; $\lambda_{max}^{CHCl_3}$ 289 mμ (ε 30) and λ_{max}^{EtOH} 286 mμ (ε 40); $\nu_{C=O}^{Nujol}$ 1709 (cyclohexanone ring) and 1764 cm.$^{-1}$ (γ-lactone).

2-Bromo-α-tetrahydrosantonin (II). This was prepared from α-tetrahydrosantonin (I) with bromine as described previously.[2] It had m.p. 144–146°; $\lambda_{max}^{CHCl_3}$ 283.5 mμ (ε 30.0); $\nu_{C=O}^{CHCl_3}$ 1733 (cyclohexanone ring) and 1776 cm.$^{-1}$ (γ-lactone), $\nu_{C=O}^{Nujol}$ 1727 (cyclohexanone ring), and 1770 cm.$^{-1}$ (γ-lactone).

Reduction of 2-bromo-α-tetrahydrosantonin (II) *with sodium borohydride.* To an ice-cooled solution of 1.0 g. of the bromoketone (II) in 80 cc. of ethanol was added, dropwise, a solution of 0.12 g. of sodium borohydride in 50 cc. of ethanol with stirring within about 30 min. The stirring was continued 6 hr. at room temperature, and the mixture was allowed to stand overnight. Evaporation of the ethanol at reduced pressure left a white solid, which was treated with 10% sulfuric acid and extracted with ether. The ether solution was washed with water, dried and evaporated to give a pale yellow oil (0.98 g.) which partly solidified in a refrigerator. Trituration with a small amount of 70% ethanol afforded 0.74 g. (74%) of the *2-bromohexahydrosantonin* (IV) as colorless prisms, melting in the range 84–93°. Recrystallization from the same solvent and then 99% ethanol gave colorless silky needles, m.p. 91–93°; $[\alpha]_D^{26}$ +12.7° ($CHCl_3$; *c* 1.57); $\nu_{OH}^{CHCl_3}$ 3497 cm.$^{-1}$ and $\nu_{C=O}^{CHCl_3}$ 1770 cm.$^{-1}$ (γ-lactone).

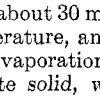
Anal. Calcd. for $C_{15}H_{23}BrO_3$: C, 54.38; H, 6.95. Found: C, 54.12; H, 7.29.

Reaction of the 2-bromohexahydrosantonin (IV) *with methanolic alkali.* (*a*) *At room temperature.* The above bromohydrin (IV, 0.09 g.) was allowed to stand in a solution of 0.05 g. of potassium hydroxide in 10 cc. of methanol 3 days. After acidification, the solution was evaporated under reduced pressure, and the residue was mixed with water and extracted with ether. Evaporation of the ether solution gave a pale yellow oil (0.07 g.), from which only the starting material, m.p. and mixed m.p. 90–93°, was isolated as a crystalline solid.

(b) *At reflux temperature.* The bromohydrin (IV, 0.20 g.) was refluxed 3 hr. in the same alkali solution described above in (a). The crystalline product (0.14 g., 93%), melting in the range 122–137°, was purified by passing the solution in benzene through alumina (5 g.) and then recrystallized from dilute ethanol to give colorless plates, m.p. 153–155°. It showed no depression of the melting point on admixture with α-tetrahydrosantonin (I).

Catalytic hydrogenation of the 2-bromohexahydrosantonin (IV) *in alkaline medium.* A solution of 0.20 g. of the bromohydrin (IV) and 1.5 g. of potassium hydroxide in 20 cc. of ethanol was shaken under an atmosphere of hydrogen in the presence of palladium-charcoal (prepared from 2 cc. of 1% palladium chloride solution and 0.04 g. of charcoal). Uptake of one equivalent of hydrogen required about 3 hr. After removal of the catalyst, the hydrogenation mixture was acidified and then evaporated under reduced pressure. The oily residue was mixed with water and extracted with ether, and the dried ether solution was evaporated to leave an oil (0.16 g.) which solidified partly. This was chromatographed on 5 g. of alumina, and elution with benzene gave crystals, m.p. 135–140°, which were recrystallized from ethanol to afford colorless needles, m.p. 143–144°. It showed no depression of the melting point on admixture with the hexahydrosantonin (V), m.p. 143–144°, prepared by catalytic hydrogenation of I with platinic oxide as reported previously.[11]

Reduction of the 2-bromohexahydrosantonin (IV) *with zinc dust and acetic acid.* A solution of 0.98 g. of the bromohydrin (IV) in 10 cc. of glacial acetic acid was refluxed with 1.7 g. of acid-washed zinc dust 3 hr. After removal on zinc by filtration, the reaction mixture was poured into ice water. There was obtained 0.465 g. (67%) of the Δ^2-olefin (VI), m.p. 139–144.5°, which was crystallized from petroleum ether to give colorless plates, m.p. 143–144.5°; $[\alpha]_D^{22}$ +6.4° (EtOH, *c* 0.94); $\nu_{C=O}^{Nujol}$ 1776 cm.$^{-1}$ (γ-lactone) and $\nu_{C=C}^{Nujol}$ 1662 cm.$^{-1}$ (*cis*-CH=CH—), 720 and 687 cm.$^{-1}$ (*cis*-



—C=C—).

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.09; H, 9.71.

Catalytic hydrogenation of the olefin (VI) in ethanol over platinic oxide gave in quantitative yield a crystalline product, melting in the range 120–135°. Recrystallization from ethanol furnished colorless plates, m.p. 150–153°; $\nu_{C=O}^{Nujol}$ 1770 cm.$^{-1}$ (γ-lactone). It showed no depression of the melting point on admixture with the 3-desoxy-α-tetrahydrosantonin (VII), prepared by the Clemmensen reduction of I was reported previously.[15]

Oxidation of the Δ^2-olefin (VI) *with potassium permanganate.* A solution of 0.20 g. of the Δ^2-olefin (VI) in 3.4 cc. of pyridine was mixed with a solution of 3.2 g. of manganese sulfate hydrate in 3.4 cc. of water. To this mixture was added, in

(23) V. Prelog, K. Shenker, and H. H. Gunthard, *Helv. Chim. Acta.*, **35**, 1598 (1952); M. N. Huffman and M. H. Lott, *J. Am. Chem. Soc.*, **75**, 4327 (1953); M. Cordon, J. D. Knight, and D. J. Cram, *J. Am. Chem. Soc.*, **76**, 1643 (1954).

(24) J. C. Sheehan and W. F. Erman, *J. Am. Chem. Soc.*, **79**, 6050 (1957).

(25) Microanalyses were carried out by Mrs. Ch. Inayama and the ultraviolet measurements by Miss M. Suzuki, both of this school.

small portions, 3.2 g. of powdered potassium permanganate with rigorous stirring cooling with ice. After the addition was completed in about 1.5 hr., the stirring was maintained 2 hr. with cooling and then at room temperature for 5 hr. After decomposition of an excess of permanganate and removal of the manganese dioxide, the yellow solution was evaporated under reduced pressure to a small volume, acidified with hydrochloric acid and extracted with ethyl acetate. The ethyl acetate solution was shaken with aqueous bicarbonate, and the bicarbonate solution was acidified and extracted with ethyl acetate. Evaporation of the dried ethyl acetate solution afforded a pale yellow viscous oil (0.23 g.) which partly solidified on standing in a refrigerator for a week. Trituration with a little ethyl acetate gave 0.145 g. (57%) of colorless prisms, melting in the range 179–183°. Recrystallization from water raised the melting point to 193–195°; $\nu_{C=O}^{Nujol}$ 1783 (γ-lactone) and 1715 cm.$^{-1}$ (carboxyl). It showed no depression of the melting point on admixture with the diacid (VIII) described in the following paragraph.

Anal. Calcd. for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.11; H, 7.17.

Oxidation of α-tetrahydrosantonin (I) *with nitric acid.* To 5 cc. of fuming nitric acid (d = 1.52) containing 0.02 g. of ammonium vanadate was slowly added 0.50 g. of α-tetrahydrosantonin (I), and soon an exothermic reaction took place under violent evolution of a brown-red gas. After standing overnight, the reaction mixture was diluted with 4 cc. of water and evaporated under reduced pressure to leave a red viscous oil, which was dissolved in ethyl acetate. The ethyl acetate solution was filtered, and the filtrate was repeatedly shaken with aqueous bicarbonate. Acidification of the combined bicarbonate solutions afforded 0.33 g. (55%) of colorless prisms (VIII), melting in the range 189–195°. Recrystallization from water raised the melting point to 193–195°; $[\alpha]_D^{26}$ −15.0° (EtOH; *c* 1.27). The infrared absorption spectrum of this sample was superimposable on that of the sample above mentioned.

Anal. Calcd. for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.00; H, 7.62.

A solution of the diacid (0.05 g.) in 5% sodium hydroxide (1 cc.) was warmed on a water bath for 30 min. Acidification of the alkaline solution gave back the parent material in a quantitative yield.

Reaction of 2-bromo-α-tetrahydrosantonin (II) *with anhydrous potassium acetate.* The 2-bromoketone (II, 0.30 g.) was heated to reflux with 0.45 g. of anhydrous potassium acetate in 3 cc. of glacial acetic acid 4 hr. The light-brown mixture was poured into 20 cc. of ice water and extracted with ether, and the ether solution was washed with 10% sodium carbonate and then with water. Evaporation of the dried ether solution left a pale yellow oil (0.24 g.), which soon solidified mostly. Trituration with ethanol gave 0.16 g. (57.5%) of the *trans-2-acetoxy-α-tetrahydrosantonin* (IX) as colorless plates, m.p. 191–196°. Recrystallization from ethanol raised the melting point to 198–200°; $[\alpha]_D^{26}$ +41.3° ($CHCl_3$; *c* 1.33) λ_{max}^{EtOH} 283 mμ (ϵ 26.2); $\nu_{C=O}^{CHCl_3}$ 1739 (acetyl), 1730 (cyclohexanone ring) and 1770 cm.$^{-1}$ (γ-lactone).

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.41; H, 7.65.

In the above reaction system, use of ethanol instead of acetic acid gave the same product (IX) in lower yield.

Oxidation of α-tetrahydrosantonin (I) *with lead tetraacetate in glacial acetic acid.* (a) *At reflux temperature.* The α-tetrahydrosantonin (I, 0.50 g.) was heated to reflux with 1.0 g. of lead tetraacetate in 100 cc. of glacial acetic acid for 6 hr. in an oil bath. After cooling, the acetic acid was mostly evaporated under reduced pressure, and the residue was mixed with aqueous bicarbonate and shaken with chloroform. After removal of the insoluble material by filtration, the chloroform extract was again washed with aqueous bicarbonate and then with water, and dried. Evaporation of the chloroform left 0.63 g. (quantitative) of the *trans*-ketol acetate (IX), melting in the range 180–198°. Recrystallization from ethanol afforded colorless plates, m.p. 199–200°, undepressed on admixture with the sample described in the preceding paragraph.

With Brady's reagent,[7] it formed in 76% yield a *2,4-dinitrophenylhydrazone* as yellow crystals, melting in the range 213–223° (dec.) which was recrystallized from ethanol to give yellow needles, m.p. 226–228° (dec.).

Anal. Calcd. for $C_{23}H_{28}N_4O_8$: C, 56.55; H, 5.78; N, 11.47. Found: C, 56.91; H, 5.97; N, 11.05.

(b) *On the boiling water bath.* A solution of 0.30 g. of the α-tetrahydrosantonin (I) in 100 cc. of glacial acetic acid was heated with 0.6 g. of lead tetraacetate 6 hr. on the boiling water bath. The reaction mixture was worked up as described above in (a), and there was obtained 0.335 g. (90%) of the *cis-2-acetoxy-α-tetrahydrosantonin* (X) as a crystalline solid, m.p. 166–172°. Recrystallization from ethanol gave colorless plates, m.p. 171.5–172.5°; $[\alpha]_D^{26}$ +49.7° ($CHCl_3$; *c* 1.53); λ_{max}^{EtOH} 285 mμ (ϵ 30.4); $\nu_{C=O}^{CHCl_3}$ 1739 (acetyl), 1730 (cyclohexanone ring) and 1770 cm.$^{-1}$ (γ-lactone).

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.17; H, 7.86.

With Brady's reagent, it formed in 85% yield a *2,4-dinitrophenylhydrazone,* melting in the range 162–175°. Recrystallization from ethanol afforded orange-yellow plates, m.p. 207–210°.

Anal. Calcd. for $C_{23}H_{28}N_4O_8$: C, 56.55; H, 5.78; N, 11.47. Found: C, 56.61; H, 5.47; N, 11.73.

Conversion of cis-2-acetoxy-α-tetrahydrosantonin (X) *into the trans-epimer* (IX). The *cis*-ketol acetate (X, 0.05 g.) was heated to reflux in 1.5 cc. of glacial acetic acid 6 hr. Evaporation of the acetic acid under reduced pressure gave quantitatively the *trans*-acetoxyketone (IX), melting in the range 188–200°. Recrystallization from ethanol furnished colorless prisms, m.p. and mixed m.p. 198–201°.

Alkali treatment of cis- and trans-2-acetoxy-α-tetrahydrosantonin (X *and* IX). The *trans*-ketol acetate (IX, 0.05 g.) was dissolved in 10 cc. of 0.25*N* ethanolic potassium hydroxide to give a clear solution, which showed a strong yellow fluorescence. On keeping the solution at room temperature 1 hr., the fluorescence disappeared. After standing an additional 1 hr., the pale yellow solution was acidified and evaporated under reduced pressure. The residue was mixed with water and extracted with ether. The ether extract was dried and evaporated to furnish 0.04 g. (94%) of a yellow viscous oil, which almost completely solidified in a refrigerator; m.p. 155–158°. Recrystallization from ethanol gave colorless prisms, m.p. 159–160°, undepressed on admixture with 2-keto-α-tetrahydrosantonin (XI), prepared from the bromoketone (II) as described in the following paragraph. It showed a dark violet coloration with ferric chloride.

The same treatment of the *cis*-ketol acetate (X) with alkali gave, in a comparable yield, the diketone (XI), m.p. and mixed m.p. 158–160°.

Alkali treatment of 2-bromo-α-tetrahydrosantonin (II). Essentially as described in the preceding paragraph, the bromoketone (II, 0.20 g.) was treated with 0.25*N* ethanolic potassium hydroxide (40 cc.). The alkali reaction showed the same yellow fluorescence as described with IX. Evaporation of the ether extract left 0.11 g. (73%) of *2-keto-α-tetrahydrosantonin* (XI), m.p. 148–156°. Recrystallization from ethanol furnished colorless prisms, m.p. 159–160°; $[\alpha]_D^{26}$ +108° ($CHCl_3$; *c* 1.33); λ_{max}^{EtOH} 278.5 mμ (ϵ 10,000); $\nu_{C=O}^{CHCl_3}$ 1642 (α,β-unsaturated ketone) and 1757 cm.$^{-1}$, $\nu_{C=C}^{CHCl_3}$ 1667 cm.$^{-1}$, and $\nu_{OH}^{CHCl_3}$ 3413 cm.$^{-1}$ The infrared spectrum indicated that the α-diketone exists chiefly in an enol form.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.93; H, 7.55.

It formed in good yield a *glyoxime,* m.p. 238–241° (dec.), by the conventional method. Recrystallization from ethanol gave colorless needles, m.p. 245–246° (dec.). It showed a pink coloration with nickel salt.

Anal. Calcd. for $C_{15}H_{22}N_2O_4$: C, 61.20; H, 7.53; N, 9.52. Found: C, 60.98; H, 7.69; N, 9.79.

According to the procedure reported by Sheehan and Erman,[24] the diketone (0.05 g.) was heated with the same amount of *o*-phenylenediamine at 150–160° 30 min. in a stream of nitrogen gas. The crude product, a light-brown viscous oil, was dissolved in ethyl acetate, and on standing overnight, the acetate solution deposited 0.03 g. (47%) of a *quinoxaline* (XII) as yellow crystals, melting in the range 250–265°. Recrystallization from ethyl acetate gave yellow silky needles, m.p. 268–271°.

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.95; H, 7.32; N, 8.46.

In attempting to isolate an intermediate, an α-ketol, the alkali hydrolysis of II was conducted in a stream of nitrogen gas to avoid the air-oxidation. Unlike the above reactions, the strong fluorescence of the alkali solution did not disappear even after keeping the solution at room temperature 2 hr. The solution was immediately acidified, but the only product isolated was the α-diketone (XI) and no evidence for the α-ketol was found in the reaction mixture.

Reduction of the trans-2-acetoxy-α-tetrahydrosantonin (XI) *with zinc and acetic acid.* A solution of 0.10 g. of the *trans*-ketol acetate (IX) in 2 cc. of glacial acetic acid was heated to reflux with 1.0 g. of acid-washed zinc dust 24 hr. After removal of the zinc, the reaction mixture was evaporated under reduced pressure, and the residue was mixed with aqueous bicarbonate and extracted with ether. The ether solution was water washed, dried and evaporated to leave 0.08 g. (quantitative) of α-tetrahydrosantonin (I), melting in the range 128–144°. Recrystallization from ethanol gave colorless plates, m.p. and mixed m.p. 154–156°.

In preliminary experiments, attempts were made to remove the acetoxy group in the ketol acetate by the procedure reported earlier for related compounds.[20,21] Thus, each epimer (IX or X) of ketol acetate was heated to reflux with zinc dust in acetic acid (or acetic anhydride) 10 min., but the starting material was completely recovered. Even on prolongation of the reflux time to 1 hr., IX was completely recovered while X gave a mixture probably consisting of IX and X resulting from partial epimerization.

Clemmensen reduction of the cis- and trans-2-acetoxy-α-tetrahydrosantonin (IX *and* X). The above *trans*-ketol acetate (IX, 0.1 g.) in 2 cc. of toluene was refluxed for 8 hr. with 1.0 g. of zinc amalgam in 1.5 cc. of concentrated hydrochloric acid and 0.5 cc. of water. Then, 1.5 cc. each of concentrated hydrochloric acid was added to refluxed reaction 3 times at intervals of 4 hrs. After removal of zinc amalgam, the reaction mixture was salted out and extracted with ether. The organic layer was washed with water, dried, and evaporated under reduced pressure. There was obtained 0.06 g. (84%) of the above 3-desoxy compound (VII) of I, melting in the range 135–147°. Recrystallization from ethanol afforded colorless plates, m.p. and mixed m.p. 150–153°.

By the same procedure, the *cis*-ketol acetate (X) was reduced to VII in almost the same yield.

Dimethylene thioketal (XIV) *of the trans-2-acetoxy-α-tetrahydrosantonin* (IX). To a solution of 0.81 g. of the *trans*-ketol acetate (IX) in 10 cc. of glacial acetic acid was added 0.5 cc. of ethanedithiol and 1.0 cc. of boron trifluoride–ether complex. After standing at room temperature 5 hr., the mixture was poured into 100 cc. of ice water, and the separated solid (XIV, 1.05 g., quantitative), m.p. 214–217°, was recrystallized from ethanol to afford colorless plates, m.p. 219–220°; $[\alpha]_D^{26}$ +27.9° ($CHCl_3$; *c* 1.47); $\nu_{C=O}^{CHCl_3}$ 1736 cm.$^{-1}$ (acetyl) and 1767 cm.$^{-1}$ (γ-lactone).

Anal. Calcd. for $C_{19}H_{28}O_4S_2$: C, 59.36; H, 7.28. Found: C, 59.03; H, 7.25.

According to the procedure reported previously for α-tetrahydrosantonin (I),[15b] the *trans*-ketol acetate (IX, 1.0 g.) in glacial acetic acid was allowed to stand 5 hr. with ethanedithiol in the presence of *p*-toluenesulfonic acid. However, the starting material was substantially recovered.

Dimethylene thioketal (XV) *of the cis-2-acetoxy-α-tetrahydrosantonin* (X). Employing the conditions described above for the *trans*-epimer (IX), the *cis*-ketol acetate (X, 0.85 g.) was treated with ethanedithiol using boron trifluoride–ether complex as a catalyst. There was obtained white solid (XV, 0.99 g., 94%), melting in the range 160–194°. Recrystallization from ethanol afforded colorless plates, m.p. 200–203°; $[\alpha]_D^{26}$ +35.6° ($CHCl_3$; *c* 0.87); $\nu_{C=O}^{CHCl_3}$ 1733 (acetyl) and 1770 cm.$^{-1}$ (γ-lactone).

Anal. Calcd. for $C_{19}H_{28}O_4S_2$: C, 59.36; H, 7.28. Found: C, 59.49; H, 7.32.

Like IX, X remained unaffected on treatment with ethanedithiol in the presence of *p*-toluenesulfonic acid.

Conversion of the dimethylene thioketal (XV) *of X into the trans-epimer* (XIV). A solution of 0.05 g. of the *cis*-acetoxy thioketal (XV) in 6 cc. of dioxane was refluxed 20 hr. Evaporation of the reaction solution under reduced pressure gave 0.05 g. (quantitative) of the *trans*-epimer (XIV), m.p. and mixed m.p. 219–220°.

When the reflux time was shortened to 12 hr., XV was almost completely recovered.

Like the thioketal (XV), the less stable ketol acetate (X) was completely epimerized to IX by the same procedure (refluxing 20 hr.), and was recovered on shortening of the reflux time (10 hr.).

Reduction of the dimethylene thioketal of trans-2-acetoxy-α-tetrahydrosantonin (XIV) *with Raney nickel.* A solution of 0.25 g. of the *trans*-acetoxy thioketal (XIV) in 30 cc. of purified dioxane was heated to reflux with 2.5 g. of Raney nickel on a water bath 10 hr. After removal of nickel, evaporation of the reaction mixture under reduced pressure left 0.14 g. (77%) of the above 3-desoxy compound (VII), m.p. 141–145°. Recrystallization from ethanol gave colorless plates, m.p. and mixed m.p. 150–153°.

Substitution of dioxane by ethanol in this reduction led to almost the same result, but using of acetone as a solvent gave only substantial recovery of the starting material.

Reduction of the dimethylene thioketal of cis-2-acetoxy-α-tetrahydrosantonin (XV) *with Raney nickel.* Exactly as described above for the *trans*-epimer (XIV), the *cis*-acetoxy thioketal (XV, 0.25 g.) was treated with Raney nickel in dioxane to give 0.16 g. (88%) of VII, m.p. and mixed m.p. 150–152° (after recrystallization from ethanol). Using ethanol in place of dioxane reduced the yield of VII to 77%, while use of acetone gave a quantitative recovery of the starting material.

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