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

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

MASAITI YANAGITA AND KOJI YAMAKAWA

Received November 25, 1958

The monobromo derivative (II) of γ-tetrahydrosantonin (I) was submitted to the same reactions as reported earlier for the derivative of α-tetrahydrosantonin. The reaction sequence (II → III → IV → VII) gave conclusive evidence for the structure (II) of the bromoketone. The acid (VII) from the olefin (IV) was readily isomerized to IX with acid. Acetolysis of the bromoketone (II) led to the more stable epimer (XII) of the ketol acetate, while lead tetraacetate oxidation of I afforded only the less stable epimer (XIII). The transformations of these ketol acetates were undertaken as described for the α-isomer. Marked differences in reactivity were observed in various types of reaction of the isomeric pairs of the α- and γ-series, in which the isomers of the α- series were always more reactive. This steric situation is in accord with the generality suggested previously for the juncture isomers of the simpler decalin systems.

In an earlier paper of this series,[1] some reactions of the monobromo derivative of α-tetrahydrosantonin have been described, by which the 2-bromo structure for this compound was definitely proved. From the reasons discussed there[1] and for the purpose of comparison, it is desirable to extend the same sequence of reactions (II→III→IV→VII) to the monobromo derivative of γ-tetrahydrosantonin (I), which is of *cis*-decalin type.

Like the monobromide in the α-series,[1] the monobromo-γ-tetrahydrosantonin (II), prepared from I with bromine,[3] possesses the bromine atom in the equatorial position, as evidenced by the shift of absorption maxima in the ultraviolet ($\Delta\lambda_{max}^{CHCl_3}$ −37 mμ and $\Delta\lambda_{max}^{EtOH}$ −34 mμ)[4,5] and infrared spectra ($\Delta\nu_{C=O}$ +15 cm.$^{-1}$)[6] over those of the parent ketone (I). Sodium borohydride reduction of the bromoketone (II) resulted in an almost quantitative yield (95%) of one isomer (III) of the bromohydrin, and no evidence for the simultaneous production of the other isomer was obtained. This indicated that the borohydride reduction of II proceeded in more highly stereoselective manner than in the α-series.[1] The bromohydrin was refluxed with methanolic potassium hydroxide for 4 hr. to give the parent ketone (I), identified as the semicarbazone. From this, it is deduced that in the bromohydrin (III), the hydroxyl group at the 3-position is *cis*- to the bromine, assuming an axial conformation. The configuration of this hydroxyl group was further supported by the observation that catalytic hydrogenation of the bromohydrin with palladium-charcoal in an alkaline medium led quantitatively to the known hexahydrosantonin (VI), where the hydroxyl group was previously proved to be axial.[7] Zinc dust and acetic acid hydrogenation of III gave in 82% yield an olefin, but requiring much longer reaction period compared with the α-series.[1] The Δ^2-structure (IV) for this olefin was based on the infrared spectrum, $\nu_{C=C}$ 1653 cm.$^{-1}$ and $\nu_{CH=}$ 718 and 697 cm.$^{-1}$ (*cis*-disubstituted double bond)[1,8] and the nonidentity with the Δ^3-isomer reported previously.[9] Catalytic hydrogenation of IV gave the 3-desoxy-γ-tetrahydrosantonin (V),[9] prepared by the Clemmensen reduction of I. As compared with the Δ^2-olefin in the α-series, IV was more difficulty oxidized with permanganate in pyridine solution in the presence of magnesium sulfate. The only product, isolated in 25% yield, was a diacid, m.p. 220–222°. When the oxidation period was shortened, a glycol (VIII), besides the diacid, was obtained in 10% yield, the structure of which followed from the analytical data and the mode of its formation.

In the α-series, the oxidation of tetrahydrosantonin with fuming nitric acid was shown to afford the diacid identical with the compound obtained from the Δ^2-olefin with permanganate.[1] In contrast to this result, oxidation of γ-tetrahydrosantonin (I) with fuming nitric acid, which took place more slowly, led in a very low yield (17%) to a diacid, m.p. 248–250°, differing from the above acid. For these two diacids, three structures (VII, IX, X) are possible, of which the last one, assuming a boat form, appears most unlikely. On analogy with the α-series, the lower melting diacid may be assigned the structure (VII) retaining the original lactone ring, and hence, the other isomer the struc-

(1) Paper XIX, K. Yamakawa, *J. Org. Chem.*, **24**, 897 (1959).

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

(3) (a) M. Yanagita and A. Tahara, *J. Org. Chem.*, **20**, 959 (1955). (b) M. Yanagita and H. Ogura, *J. Org. Chem.*, **23**, 1268 (1958) and related references cited there.

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

(5) Obviously, these decreases of the absorption maxima are unusual, but the similar anomaly has been reported with the ultraviolet spectrum of *cis*-9-methyl-3-decalone 2,4-dinitrophenylhydrazone (ref. 10).

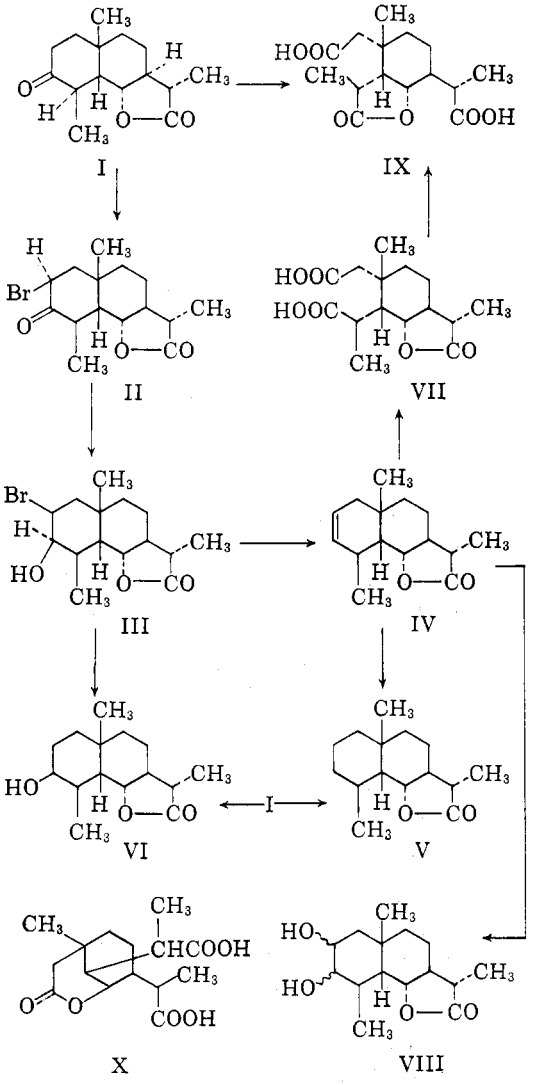
(6) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **74**, 2828 (1952).

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

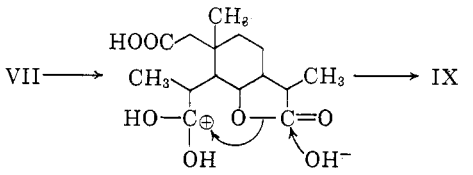
(8) L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, Methuen & Co. Ltd., London, 1954, p. 33.

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

ture (IX) with the inverted lactone ring. These formulations are supported by comparison of the infrared spectra. The lower melting diacid exhibited a single carbonyl band ($\nu_{C=O}^{Nujol}$ 1709 cm.$^{-1}$), which is similar to those of the diacid in the α-series[1] and of *cis*- and *trans*-1-methylcyclohexane-1,2-diacetic acid.[10,11] On the other hand, the higher melting di-



acid exhibited the carbonyl band as a doublet ($\nu_{C=O}^{Nujol}$ 1704 and 1733 cm.$^{-1}$), presumably being attributed to the different properties of the two carbonyl groups. Since the more stable diacid (IX) was completely recovered unchanged from the warm alkali solution by acidification, the less stable isomer (VII) would be expected to be converted to IX on alkali treatment. However, this expectation was not realized, and acidification on the alkali solution of VII gave only an oil, which could not be induced to crystallize. It is presumed that these two isomeric lactones did not form the same triacid on alkali hydrolysis. This isomerization was found to be readily effected by warming of VII with concentrated hydrochloric acid, giving a quantitative yield of IX. For explanation of this isomerization, a mechanism based on attack of a proton on the carboxyl oxygen of the carbonyl group in VII and subsequent inversion of the lactone ring in the resulting carbonium ion (XI) to form IX was proposed.



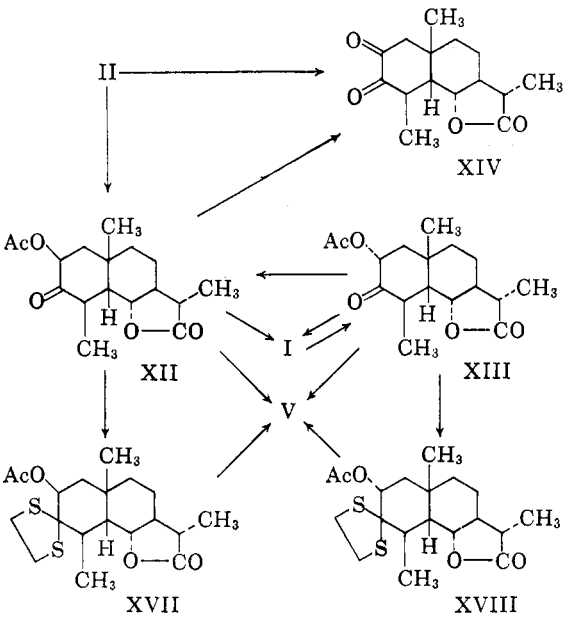
The foregoing result led to the conclusion that, like α-tetrahydrosantonin, the γ-isomer (I) was invariably attacked by electrophilic reagents (Br^+ or OH^+) at the 2-position, indicating the preference of the Δ^2- over the Δ^3-enolization of the carbonyl group at the 3-position.

Acetolysis of the 2-bromoketone (II) and lead tetraacetate oxidation of I were carried out as described with the corresponding compounds in the α-series. Refluxing of II with potassium acetate in acetic acid gave in 61% yield an epimer, m.p. 247°, of ketol acetate. Another epimer, m.p. 187–188.5°, was obtained from I by lead tetraacetate oxidation in glacial acetic acid. However, contrary to the case in the α-series,[1] the latter epimer was the only isoluble product even when the oxidation was conducted at the reflux temperature for 6 hr., and the lowering of the reaction temperature considerably reduced the yield of this product. On analogy with the formulation in the α-series,[1] the higher melting epimer of the ketol acetate is assigned the structure (XII) with the equatorial acetoxyl group, while the other epimer the structure (XIII) with the axial acetoxyl group. It was shown[1] that in the α-series, the ready conversion of the less stable ketol acetate into the other epimer was effected by refluxing in acetic acid for 6 hr. That XIII is inert to epimerization under these conditions is shown by the above observation on the lead tetraacetate oxidation of I. It was found, however, XIII was converted to XII completely after refluxing 24 hr. in acetic acid. This result gave conclusive evidence for the configuration of the acetoxyl group in the ketol acetates (XII and XIII). It seems of interest that on lead tetraacetate oxidation, both α-[1] and γ-tetrahydrosantonin were preferentially attacked at the 2-position by the acetoxyl radical from the axial side. Also, it is notable that each 2-bromoketone in both series on acetolysis gave, as the only isoluble product, the respective 2-ketol acetate bearing the acetoxyl group in the equatorial position. Though the yields of the ketol acetates were not so high (*ca.* 60%),

(10) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **21**, 500 (1956).

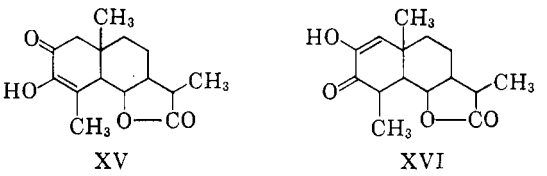
(11) M. Yanagita and K. Yamakawa, *J. Org. Chem.*, **22**, 291 (1957).

these acetolyses may be considered to occur in an stereospecific manner[12] and with no rearrangement. However, there remained a possibility that the acetolysis of the bromoketones would initially form the less stable epimer of the corresponding ketol acetate, followed by the complete epimerization to the other epimer. In the γ-series, this possibility can be excluded by the above observation that the less stable epimer (XIII) is inert to refluxing acetic acid under such conditions.



Reductive removal of the acetoxyl group in these ketol acetates with zinc dust in refluxing acetic acid proceeded much less readily, compared with that of the α-isomers.[1] Under the conditions employed for quantitative conversion of the more stable epimer of the α-ketol acetate into the parent ketone in the α-series, XIII was partly reduced to I, but XII was completely recovered unchanged. Even on prolonged reflux, the latter gave a 50% yield of I with a lesser amount of the recovered material. The similar difference in reactivity has been observed in reduction of the axial and equatorial acetoxyl groups in some ketol acetates of steroid.[13]

Clemmensen reduction or alkali treatment of the ketol acetates took place as in the case of the α-series,[1] giving, respectively the above 3-desoxy compound (V) or an α-diketone (XIV), as the single products isolated. The latter product, which was also obtained from the bromoketone II by treatment with alkali, showed positive ferric chloride test and gave a glyoxime, but, unlike the α-isomer,[1] no quinoxaline was formed on fusion with *o*-phenylenediamine. In the above hydrolysis of the acetate and the bromide, no evidence for formation of the expected ketol or diacid was obtained. The α-diketones in the α-and γ-series had, respectively, λ_{max}^{EtOH} 278.5 mμ (ε 10,000)[1] and 275.5 mμ (ε 6,600). For each of the α-diketones, two enol structures XV and XVI) are possible, whose maxima may be expected to be 280 mμ and 270 mμ, respectively.[11,14] From these data, it appears that both the α-diketones in the α- and γ-series exist predominantly in the Δ^8-enol structure (XV), and that the α-isomer tends mainly, but γ- isomer partly, to the enol form in keto-enol equilibration.



The ketol acetates (XII and XIII) were treated with ethane dithiol in the presence of boron trifluoride–ether complex to give the corresponding dimethylene thioketals (XVII and XVIII), both of which afforded the same 3-desoxy compound (V) on hydrogenolysis with Raney nickel. These sequences almost parallel those in the α-series.[1] However, unlike the α-isomer, XVIII could not be epimerized to XVII by refluxing with dioxane. Under more strenuous conditions it was converted to an untractable oil.

Previous works from our laboratory have shown that in the juncture isomers of the simple 9-methyl decalin compounds, the *cis*-isomer is always less reactive than the *trans* one.[11,15,16] In more complex decalin systems, a similar difference in reaction rates has been observed in bromination of the tetrahydrosantonins[3a] and their derivatives[17] in the α- and γ-series and of coprostan-3-one and cholestan-3-one.[18] Also, it has been reported by Evans and Shoppee[19] that methanolysis of tosylates of coprostanol proceeded more slowly than that of the

(12) It was reported [M. Provita, J. O. Jilek, L. Novk, E. Adlerover, V. Simak, and E. Knobloch, *Chem. Abstr.*, **50**, 4048 (1956)], that the α-monobromide of 2-methyl-2-carbethoxycyclohexanone afforded an epimeric mixture of the ketol acetate on acetolysis under similar conditions.

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

(14) L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd Ed., Reinhold Publishing Corp., New York, 1949, p. 195; F. E. King, T. J. King, and J. M. Ross, *J. Chem. Soc.*, 3995 (1954); N. L. Wendler and D. Taub, *Chem. & Ind. (London)*, 1237 (1957).

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

(16) Futaki [*J. Org. Chem.*, **23**, 451 (1958)] claimed that the relative reactivity of the juncture isomers of 2,9-dimethyl-3-decalone toward bromine is opposite to this generalization. On reinvestigation, however, it was found that this observation is erroneous and no apparent difference in reactivities exists in these isomers.

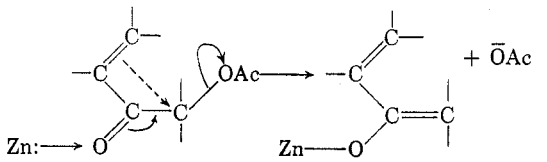
(17) M. Yanagita and H. Ogura, *J. Org. Chem.*, **23**, 443 (1958).

(18) O. H. Wheeler and J. L. Mateos, *J. Org. Chem.*, **22**, 605 (1957).

(19) D. D. Evans and C. W. Shoppee, *J. Chem. Soc.*, 540 (1953).

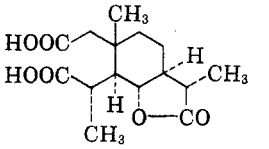
same derivatives of cholestanol. The present work added a number of examples involving the same relationship in reactivity of isomeric pairs in the α- and γ-tetrahydrosantonin series. This generality, however, which covers various types of reaction, is now referred only to the ring carbons at the 2- and 3-positions in the 9-methyl decalin systems. Furthermore, it is an outstanding problem whether the above generalization would be extended to the other positions in the 9-methyl decalin systems.[20,21]

It has been reported that the unsaturated ketol acetates with the double bond adjacent to the carbonyl group in the 9-methyl decalin systems were smoothly reduced to the ketone by treatment with zinc dust in hot acetic acid, acetic anhydride or xylene.[13,22,23] Compared with these previous results, the hydrogenolysis of the saturated ketol acetates of the tetrahydrosantonin, as described above, proceeded much less slowly under similar conditions. The greater reactivity of the unsaturated ketol acetate in this reaction can be readily rationalized by the assumption that in the unsaturated system (XIX), the ethylene double bond would accelerate the intermediate formation of the enol (XX) by the conjugation with the newly formed olefinic double bond and by its anchimeric assistance in the alkyl-oxygen fission, as pictured in XIX and XX.

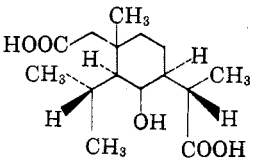


XIX XX

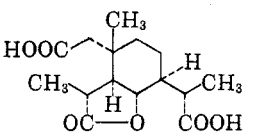
The marked difference in stabilities of the isomers of diacid lactone (XXI and VII, respectively) in the α- and γ-series, described above, will be discussed from a conformational viewpoint. In the triacid (XXII), resulting from the lactone ring opening of the α-isomer (XXI), the two α-propionic acid side chains are symmetrically arranged with respect to the hydroxyl group. Of these, the one at the 3-position should be strongly pushed by the adjacent bulky *gem*-substituents closer to the hydroxyl group than the other. This steric effect would prefer the formation of the inverted lactone (XXIII) rather than that of the original lactone (XXI). However, the former, which is represented by XXIV, is less favored than the latter (the conformation XXV) by a severe nonbonded interaction between the two methyl groups at the 4- and 5-position, the strength of which is nearly equivalent to the *meta*-diaxial effect. That the latter effect is much more significant than the steric interaction between the two substituents at the 2- and 5-positions, is shown by the reported results that XXI was completely recovered unchanged from the alkaline solution by acidification.[1] In the γ-series, the diacid-lactones (VII and IX) can be described by the conformations XXVI and XXVII, respectively. From the molecular models, it can seen that in XXVI, the axial α-propionic side chin should suffer severe steric repulsions by the adja-



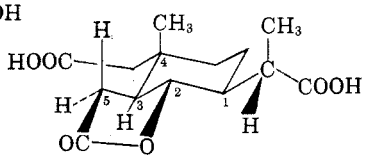
XXI



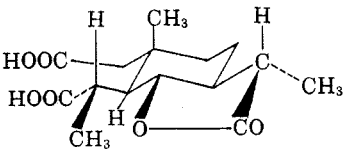
XXII



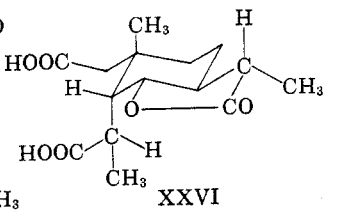
XXIII



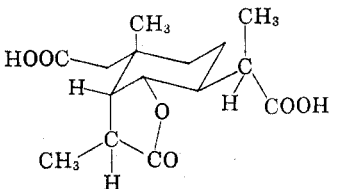
XXIV



XXV



XXVI

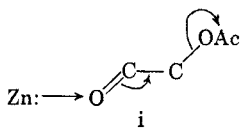


XXVII

(20) It has been recently reported [M. Idelson and E. I. Becker, *J. Am. Chem. Soc.*, **80**, 908 (1958)] that the tosylate of *cis*-9-hydroxylmethyldecalin is similarly resistant to hydrogenolysis with Raney nickel as the same derivatives of the *trans*- isomer, although the former appears more open than the latter. This indicates that the above generalization may not be extended at ease.

(21) It has been shown [H. B. Henbest and B. J. Lovell, *Chem. & Ind. (London)*, 278 (1956)] that on treatment with potassium bicarbonate, the percentage hydrolysis of each isomer of 3-acetoxy-5-hydroxy derivatives of coprostane. The relative reactivity of these compounds may be more strongly influenced by factors other than the present steric effect.

(22) R. B. Woodward *et al.* [*J. Am. Chem. Soc.*, **74**, 4223 (1952)] have offered an explanation for the mechanism of the facile removal of the acetoxyl group in the α-ketol acetate, as symbolized in i:

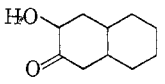


i

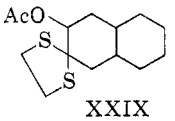
(23) C. Amendolla, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 1226 (1954); L. F. Fieser, *J. Am. Chem. Soc.*, **75**, 4377 (1953).

cent equatorial substituents as well as the axial *meta*-hydrogens on the cyclohexane ring. This interference would be greatly relieved by the formation of the lactone ring with the adjacent hydroxy group as in XXVII. Moreover, the rule that the *cis*-γ-lactone ring is more stable than the *trans*-one may strongly favor XXVII in stability over XXVI. These steric factors are responsible to the facile isomerization of VII into IX, cited here.

After the present work was completed, an interesting paper of Ali and Owen[24] has appeared describing the studies on the 2-hydroxy-3-decalone (decalin 2,3-ketol) bearing no substituent at the ring juncture. Certain properties reported for these ketols and their derivatives are markedly different from those of analogous compounds with the angular methyl group at the ring juncture which were described in the present and earlier papers[25] of this series. First, it was shown[24] that both *cis*- and *trans*-ketols (XXVIII) are rather stable to alkali, as indicated by the mode of its preparation involving the alkaline hydrolysis of the 2-chloro or 2-acetoxy-decalone. This is in a sharp contrast to the unsuccessful attempt on isolation of the ketol from hydrolysis of the analogous derivatives of 9-methyl-3-decalone[11,25] and tetrahydrosantonins. Second, each isomer of dimethylene thioketals



XXVIII



XXIX

(XXIX) of the ketol acetate was readily reduced with Raney nickel into the individual acetoxy compound in the usual manner, unlike the same derivatives (*e.g.* XVII and XVIII) of tetrahydrosantonins. From these observations, it is obvious that in the simpler 3-decalone systems, the angular methyl group at the 9-position exerts a significant influence on the course of reactions of these compounds, causing an increase in the reactivity of the substituent at the 2-position. Compared with the juncture isomers in the decalin systems, in this case, an enhancement in the steric compression of the whole molecule increases significantly the reactivity of the substituent.

EXPERIMENTAL[26]

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.

γ-Tetrahydrosantonin (I). According to the method reported by Cocker and McMurry,[7] sodium santoninate (from 2.5 g. of α-santonin) was hydrogenated over platinic oxide to give the tetrahydro acid (2.33 g.), melting in the range 95–100°. Recrystallization from dilute ethanol gave colorless plates (1.56 g., 62%), m.p. 194°. Reported,[7] m.p. 190–191°.

This acid (1.53 g.) was heated to reflux 2 hr. in benzene (30 cc.) with *p*-toluenesulfonic acid (0.4 g.). The reaction mixture was washed with sodium bicarbonate and water, and after drying, evaporated to leave 1.41 g. (99%) of γ-tetrahydrosantonin (I), melting in the range 94–103°. Recrystallization from dilute ethanol gave colorless prisms, m.p. and mixed m.p. 101–103°. The absorption spectra of I was given in a previous paper.[1]

2-Bromo-γ-tetrahydrosantonin (II). This was prepared from γ-tetrahydrosantonin (I) with bromine as described previously.[3a] It had m.p. 145.5–146° (dec.); $\lambda_{max}^{CHCl_3}$ 252 mμ (ε 71) and λ_{max}^{EtOH} 252 mμ (ε 65); $\nu_{C=O}$ 1770 (γ-lactone) and 1724 cm.$^{-1}$ (cyclohexanone ring) (Nujol). Reported,[3a] m.p. 144–146°.

Reduction of 2-bromo-γ-tetrahydrosantonin (II) *with sodium borohydride.* According to the procedure described earlier for 2-bromo-α-tetrahydrosantonin,[1] the 2-bromo-ketone (II, 1.0 g.) was reduced with sodium borohydride (0.12 g.). A white complex solid from the reaction was decomposed by refluxing 2 hr. in 50 cc. of benzene with 3 cc. of 10% hydrochloric acid. The benzene solution was washed with bicarbonate solution, and evaporated to give 0.95 g. (95%) of *2-bromo-hexahydrosantonin*, m.p. 210–214° (dec.). Recrystallization from ethanol afforded colorless needles, m.p. 215–217° (dec.); $[\alpha]_D^{26}$ −13.8° ($CHCl_3$; *c* 0.87); $\nu_{C=O}$ 1764 cm.$^{-1}$ (γ-lactone), and ν_{OH} 3472 and 1292 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{15}H_{23}BrO_3$: C, 54.38; H, 6.95. Found: C, 54.48; H, 6.69.

Reaction of the 2-bromohexahydrosantonin (III) *with methanolic alkali.* This was carried out similarly as described earlier for the 2-bromohexahydrosantonin in the α-series.[1] A solution of 0.14 g. of the bromohydrine (III) and 0.025 g. of potassium hydroxide in 5 cc. of methanol was heated to reflux 4 hr. The product was a viscous oil (0.11 g.) which could not be induced to crystallize. The oil formed 0.075 g. of a semicarbazone, melting in the range 205–215° (dec.). Recrystallization from ethanol afforded colorless plates, m.p. 240–242° (dec.), undepressed on admixture with the same derivative of γ-tetrahydrosantonin.[3a]

Anal. Calcd. for $C_{16}H_{25}O_3N_3$: N, 13.67. Found: N, 13.93.

Catalytic hydrogenation of the 2-bromohexahydrosantonin (III) *in basic medium.* Hydrogenation of 0.20 g. of the bromohydrin (III) over palladium-charcoal was carried out exactly as described earlier for the 2-bromohydrin in the α-series.[1] There was obtained 0.165 g. (98%) of crystalline solid, melting in the range 203–210°. Recrystallization from ethanol afforded colorless prisms, m.p. 210–212°. It showed no depression of the melting point on admixture with the hexahydrosantonin (VI), prepared by hydrogenation of γ-tetrahydrosantonin (I) with platinic oxide essentially by the method reported previously.[7]

Reduction of the 2-bromohexahydrosantonin (III) *with zinc dust and acetic acid.* Essentially as described earlier for the bromohydrin in the α- series,[1] 0.50 g. of the bromohydrin (III) was heated to reflux with zinc dust (1.0 g.) in glacial acetic acid (10 cc.), but the refluxing time was prolonged to 16 hr. There was obtained 0.29 g. (82%) of the Δ^2-olefin (IV) as colorless needles, melting in the range 82–90°. Recrystallization from petroleum ether gave colorless needles, m.p. 88–90°; $[\alpha]_D^{26}$ +20.0° ($CHCl_3$; *c* 1.40); $\nu_{C=O}$ 1770 cm.$^{-1}$, $\nu_{C=C}$ 1653 cm.$^{-1}$, $\nu_{HC=}$ 718 and 692 cm.$^{-1}$ (Nujol).

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.60; H, 9.56.

Catalytic hydrogenation of the olefin (IV) with platinic oxide gave quantitatively the 3-desoxy-γ-tetrahydrosantonin (V), melting in the range 75–83°. Recrystallization from ethanol afforded colorless plates, m.p. 85–86°. It showed no depression of the melting point on admixture with a sample, prepared by the Clemmensen reduction of I as reported previously.[9]

(24) M. E. Ali and L. N. Owen, *J. Chem. Soc.*, 2111 (1958).

(25) M. Yanagita and A. Tahara, *J. Org. Chem.*, **18**, 792 (1953); *cf.* reference 10.

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

Oxidation of the Δ^2*-olefin* (IV) *with potassium permanganate.* Under the same conditions as described for the α-Δ^2-olefin,[1] 0.2 g. of the above olefin (IV) was oxidized with potassium permanganate, except the powdered permanganate was added in a period of 3.5 hr. and then the mixture was stirred 3 hr. in the ice bath. There was obtained 0.04 g. (25%) of the *diacid* (VII), melting in the range 204–216°. Recrystallization from water afforded colorless prisms, m.p. 220–222°; $[\alpha]_D^{26}$ −4.28° (EtOH; c 1.40); $\nu_{C=O}$ 1709 (carboxyl) and 1795 cm.$^{-1}$ (γ-lactone) (Nujol).

Anal. Calcd. for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.17; H, 7.59.

Hoping to raise the yield of VII, the oxidation was conducted under the milder conditions. Thus, to a cooled mixture of 0.48 g. of the olefin (IV) and 8.0 g. of magnesium sulfate hydrate in 8.5 cc. of pyridine was added 0.65 g. of potassium permanganate with vigorous stirring. The addition was completed in about 2 hr., and the stirring was continued for additional 1 hr. After an excess of permanganate was decomposed with methanol, the mixture was filtered, and the residual manganese dioxide was washed with 40 cc. of hot water. The wash water, combined with the filtrate, was allowed to stand in a refrigerator overnight. The separated *glycol* (VIII, 0.05 g.), melting in the range 140–165° was recrystallized from ethanol to give colorless prisms, m.p. 176°; $[\alpha]_D^{26}$ −24.2° ($CHCl_3$; c 0.33).

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.19; H, 8.80.

The aqueous filtrate, removed from VIII, was worked up as described earlier for the olefin in the α-series.[1] There was obtained 0.08 g. of the diacid (VII), melting in the range 191–215°, which was recrystallized from water to give colorless prisms, m.p. and mixed m.p. 220–222°.

Oxidation of γ*-tetrahydrosantonin* (I) *with nitric acid.* This oxidation was carried out at higher temperatures than that described earlier for the α- isomer.[1] To a 2 cc. of fuming nitric acid (d = 1.52) containing 0.01 g. of ammonium vanadate was slowly added 0.2 g. of γ-tetrahydrosantonin (I). Contrary to the case of the α- isomer, the reaction at room temperature was only slightly exothermic and no apparent evolution of a red gas was observed. The mixture was heated 3 hr. on a water bath. The acidic oily product, which solidified partly, was triturated with a little ethyl acetate to give 0.04 g. (17%) of the *diacid* (IX), melting in the range 240–247°. Recrystallization from water afforded colorless prisms, m.p. 248–250°; $[\alpha]_D^{26}$ −22.4° (EtOH; c 1.07); $\nu_{C=O}$ 1704, 1733 (carboxyl), and 1770 cm.$^{-1}$ (γ-lactone) (Nujol).

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

A solution of 0.02 g. of IX in 0.5 cc. of 5% aqueous sodium hydroxide was heated on a water bath for 30 min. Acidification of the solution yielded 0.018 g. (90%) of the starting material.

Conversion of VII *into* IX *with acid.* The diacid (VII, 10 mg.) was heated 2 hr. in 0.2 cc. of concentrated hydrochloric acid. The solution was evaporated under reduced pressure to leave IX as pale yellow crystals, m.p. 238–245°. Recrystallization from water afforded colorless prisms, m.p. and mixed m.p. 247–250°.

Treatment of VII with alkali as described above for IX gave a viscous oil, which could not be induced to crystallize.

Reaction of 2-bromo-γ*-tetrahydrosantonin* (II) *with anhydrous potassium acetate.* Essentially as described for the α-isomer,[1] acetolysis of the bromoketone (II) was carried out, but the refluxing period in acetic acid was prolonged. Thus, a mixture of 1.0 g. of the 2-bromoketone (II) and 1.5 g. of anhydrous potassium acetate in 10 cc. of glacial acetic acid was refluxed 10 hr. The mixture was poured into ice water (60 cc.), and *cis-2-acetoxy-*γ*-tetrahydrosantonin*[27] (XII) separated as colorless crystals (0.57 g., 61%), melting in the range 197–206°. Recrystallization from ethanol afforded colorless needles, m.p. 247°; $[\alpha]_D^{26}$ −36.0° ($CHCl_3$; c 1.00); λ_{max}^{EtOH} 275 mμ (ϵ 45.0); $\nu_{C=O}$ 1770 (γ-lactone), 1745 (cyclohexanone ring), and 1733 cm.$^{-1}$ (acetyl) (in $CHCl_3$ solution).

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.49; H, 7.72.

Oxidation of γ*-tetrahydrosantonin* (I) *with lead tetraacetate in glacial acetic acid.* (a) *On the boiling water bath.* As described earlier for α-tetrahydrosantonin, 0.10 g. of the γ-ketone (I) was heated 6 hr. with 0.20 g. of lead tetraacetate in 20 cc. of glacial acetic acid on the boiling water bath. There was obtained 15 mg. (12%) of *trans-2-acetoxy-*γ*-tetrahydrosantonin* (XIII), melting in the range 160–175°. Recrystallization from ethanol afforded colorless prisms, m.p. 187–188.5°; $[\alpha]_D^{26}$ −24.3° ($CHCl_3$; c 1.73); λ_{max}^{EtOH} 274 mμ (ϵ 90.0); $\nu_{C=O}$ 1776 (γ-lactone), 1770 (cyclohexanone ring), and 1733 cm.$^{-1}$ (acetyl) (in $CHCl_3$ solution).

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.13; H, 7.84.

(b) *At reflux temperature.* As described earlier for the α-isomer,[1] the above reaction mixture was heated to reflux 6 hr. The *trans*-acetoxyketone (XIII, 0.05 g., 40%), melting in the range 170–184°, was obtained, which gave the pure sample, m.p. and mixed m.p. 187–188.5° (from ethanol).

Even when the reflux time was prolongated to 12 hr., the yield of XIII could not be improved.

Conversion of trans-2-acetoxy-γ*-tetrahydrosantonin* (XIII) *into the cis-epimer* (XII). The *trans*-ketol acetate (XIII, 0.02 g.) was heated to reflux 24 hr. in glacial acetic acid (3 cc.). Evaporation of the solution under reduced pressure gave quantitatively the *cis*-ketol acetate (XII), m.p. 235–241°, which was recrystallized from ethanol to give the pure sample, m.p. and mixed m.p. 246–248°.

Alkali treatment of cis- and trans-2-acetoxy-γ*-tetrahydrosantonin* (XII *and* XIII). As described earlier for the α-isomer,[1] a solution of the *cis*-ketol acetate (XII, 0.05 g.) in 0.25*N* ethanolic potassium hydroxide, which showed a strong yellow fluorescence, was allowed to stand 3 hr. at room temperature. There was obtained 0.03 g. (70%) of *2-keto-*γ*-tetrahydrosantonin* (XIV), melting in the range 140–150°. Recrystallization from ethanol gave colorless plates, m.p. 174–176°; $[\alpha]_D^{26}$ −190° ($CHCl_3$; c 0.60); λ_{max}^{EtOH} 275.5 mμ (ϵ 6600); $\nu_{C=O}$ 1684 (α,β-unsaturated ketone) and 1789 cm.$^{-1}$ (γ-lactone), $\nu_{C=C}$ 1658 cm.$^{-1}$ and ν_{OH} 3484 cm.$^{-1}$ (free) (in $CHCl_3$ solution). It showed a dark violet coloration with ferric chloride.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 67.99; H, 7.32.

A *glyoxime*, m.p. 220–226° (dec.), obtained in a moderate yield, was recrystallized from ethanol to give colorless prisms, m.p. 230–232° (dec.). It showed a light red 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, 61.55; H, 7.39; N, 9.53.

Exactly as described above, the *trans*-ketol acetate (XIII 0.05 g.) was treated with alkali to give 0.015 g. (35%) of the same diketone (XIV), melting in the 160–170°; the pure sample, m.p. and mixed m.p. 175–176° (from ethanol).

Alkali treatment of 2-bromo-γ*-tetrahydrosantonin* (II). Treatment of the bromoketone (II, 0.20 g.) with alkali, exactly as described earlier for the α- isomer,[1] gave 0.05 g. (31%) of the above α-diketone (XIV), m.p. 166–173°; the pure sample, m.p. and mixed m.p. 174–176° (from ethanol).

Reduction of cis- and trans-2-acetoxy-γ*-tetrahydrosantonin* (XII *and* XIII) *with zinc and acetic acid.* As described earlier for *trans*-2-acetoxy-α-tetrahydrosantonin,[1] 0.05 g. of the *cis*-ketol acetate (XII) was heated to reflux 24 hr. with zinc dust (0.3 g.) in glacial acetic acid (2.5 cc.). There resulted complete recovery of the starting material, m.p. and mixed m.p. 235–247°. When the refluxing was continued 50 hr. with 0.5 g. of zinc dust in the above system,

(27) The term *cis-trans-* refers to the configuration of the acetoxyl group in relation with the angular methyl group at the 9- position; *cf.* ref. 1.

there was obtained an oil which solidified mostly. Fractional recrystallization from ethanol afforded 0.01 g. of the starting material (XII), m.p. 225–235°; the pure sample, m.p. and mixed m.p. 247–249°. On standing for a few days, the mother liquors of XII deposited 0.02 g. (50%) of γ-tetrahydrosantonin as colorless prisms, m.p. 88–94°; the pure sample, m.p. and mixed m.p. 98–100° (from dilute ethanol).

The *trans*-ketol acetate (0.05 g.), as described above, was refluxed 24 hr. with zinc dust to give an oil which solidified mostly. Trituration with a little methanol afforded 0.025 g. (62%) of γ-tetrahydrosantonin (I), m.p. 83–90°; the pure sample, m.p. and mixed m.p. 98–100° (from methanol).

Clemmensen reduction of cis- and trans-2-acetoxy-γ-tetrahydrosantonin (XII *and* XIII). Employing the conditions described earlier for 2-acetoxy-α-tetrahydrosantonin,[1] the *cis*-ketol acetate (XII, 0.10 g.) was reduced by the Martin modification of the Clemmensen method. There was obtained 0.07 g. (92%) of the 3-desoxy-γ-tetrahydrosantonin (V), m.p. 73–81°; the pure sample, m.p. and mixed m.p. 85–86° (from ethanol).

On a similar treatment, the *trans*-ketol acetate (XIII, 0.10 g.) gave 0.07 g. (92%) of the 3-desoxy compound (V), m.p. 69–76°; the pure sample, m.p. and mixed m.p. 85–86° (from ethanol).

Dimethylene thioketals of cis- and trans-2-acetoxy-γ-tetrahydrosantonin (XII *and* XIII). As described earlier for the 2-acetoxy-α-tetrahydrosantonin,[1] 0.34 g. of the *cis*-ketol acetate (XII) was allowed to stand 48 hr. with 0.3 cc. of ethane dithiol and 0.7 cc. of boron trifluorid-ether complex in 5 cc. of acetic acid. The crude dimethylene thioketal (XVII, quantitative), melting in the range 140–161°, was recrystallized from ethanol to give 0.22 g. (57%) of colorless prisms, m.p. 176–177.5°; $[\alpha]_D^{26}$ −58.3° ($CHCl_3$; *c* 1.27); $\nu_{C=O}$ 1783 (γ-lactone) and 1751 cm.$^{-1}$ (acetyl) (in $CHCl_3$ solution).

Anal. Calcd. for $C_{19}H_{28}O_4S_2$: C, 59.36; H, 7.28. Found: C, 59.61; H, 7.12.

By the same procedure, the *trans*-ketol acetate (XIII, 0.50 g.) formed the dimethylene thioketal (XVIII, 0.59 g., 95%), melting in the range 130–152°. Recrystallization from ethanol gave 0.46 g. (74%) of colorless prisms, m.p. 163–165.5°; $[\alpha]_D^{26}$ −32.3° ($CHCl_3$; *c* 1.33); $\nu_{C=O}$ 1779 (γ-lactone) and 1748 cm.$^{-1}$ (acetyl) (in $CHCl_3$ solution).

Anal. Calcd. for $C_{19}H_{28}O_4S_2$: C, 59.36; H, 7.28. Found: C, 59.25; H, 7.57.

Attempted epimerization of the dimethylene thioketal (XVIII) *of* XIII. Exactly as described earlier for the *cis*-acetoxy thioketal in the α- series,[1] the dimethylene thioketal (XVIII) was heated to reflux in dioxane, but the starting material was completely recovered. When the refluxing time was prolonged to 50 hr., XVIII was converted to an oil which could not be induced to crystallize.

Reduction of the dimethylene thioketals (XVII *and* XVIII) *of the ketol acetates with Raney nickel.* As described earlier for the same derivatives of the ketol acetate in the α-series,[1] 0.06 g. of the dimethylene thioketal (XVII) of the *cis*-ketol acetate was heated to reflux 30 hr. with Raney nickel (0.6 g.) in dioxane (10 cc.). There was obtained 0.03 g. (82%) of the above 3-desoxy-γ-tetrahydrosantonin (V), m.p. 63–72°; the pure sample, m.p. and mixed m.p. 85–86°.

By the same procedure, the dimethylene thioketal (XVII) of the *trans*-ketol acetate was converted to the 3-desoxy compound (V) in good yield.

Acknowledgment. The authors wish to thank Mr. K. Kotera of the Tanabe Seiyaku Co. Ltd., Osaka, Japan, for determination and interpretation of the infrared spectra in this work.

SHINJUKU-KU
TOKYO, JAPAN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX S.A.]

Steroids. CXIX.[1] The Preparation of Some Vicinal Glycols in the Cortical Hormone Series

JOHN A. ZDERIC, HUMBERTO CARPIO, AND CARL DJERASSI

Received January 28, 1959

Osmylation of Δ⁶-dehydrocortisone acetate and Δ⁶-dehydro-9α-fluorohydrocortisone acetate proceeds in dioxane solution to yield the corresponding 6α,7α-dihydroxy analogs of cortisone acetate and 9α-fluorohydrocortisone acetate. When Δ⁶-dehydroprednisone acetate is similarly treated a mixture of 6α,7α-dihydroxyprednisone acetate and 1α,2α-dihydroxy-Δ⁶-dehydrocortisone acetate is obtained.

The findings that in the cortical hormone series 16α-hydroxylation[2] as well as 16α,17α-acetal or ketal formation[3] markedly influence biological properties prompted us to investigate a number of steroid vicinal glycols. This paper reports the synthesis of four such compounds.

Thus when Δ⁶-dehydrocortisone acetate (Ia)[4] was allowed to stand for four or five days at room temperature in dioxane solution with osmium tetroxide there was obtained, following hydrogen sulfide decomposition of the osmic ester,[5] a mixture of starting material and 6α,7α-dihydroxycortisone acetate (IIa). This mixture was readily resolved by chromatography to provide the pure 6α,7α-dihydroxy compound (IIa), characterized as its 6α,7α-acetonide (III). In our hands the addition of small quantities of pyridine[2] to the osmylation mixture did not improve the yield.

An identical procedure with Δ⁶-dehydro-9α-

(1) Paper CXVIII. H. J. Ringold, J. Perez Ruelas, E. Batres, and C. Djerassi. *J. Am. Chem. Soc.*, in press.

(2) S. Bernstein, R. A. Lenhard, W. S. Allen, M. Heller, R. Littel, S. M. Stolar, L. I. Feldman, and R. H. Blank, *J. Am. Chem. Soc.*, **78**, 5693 (1956).

(3) J. Fried, A. Borman, W. B. Kessler, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **80**, 2338 (1958).

(4) V. R. Mattox, E. L. Woroch, G. A. Fleisher, and E. C. Kendall, *J. Biol. Chem.*, **197**, 261 (1952).

(5) D. H. R. Barton and D. Elad, *J. Chem. Soc.*, 2090 (1956).