[Contribution from the Pharmaceutical Research Institute, Medical School, Keio-Gijuku University]

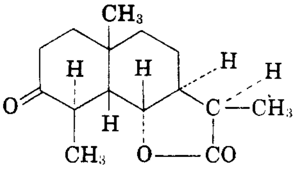
Santonin and Related Compounds. VII. Diketo Acids from Tetrahydrosantonins

AKIRA TAHARA

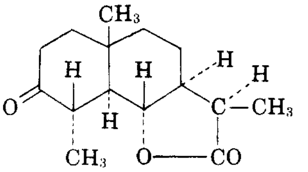
Received December 30, 1955

The α- and γ-diketo acids (IIIa and IIIb), prepared by oxidation from the α- and γ-tetrahydrosantonins (Ia and Ib) respectively, were reacted with various reagents, and on the basis of the results of these reactions, the proposed structures (Ia and Ib) for the tetrahydrosantonins have been discussed.

In the previous paper of this series,[1] the configurational structures Ia and Ib were proposed, respectively, for α- and γ-tetrahydrosantonins, prepared from α-santonin by catalytic hydrogenation.



Ia

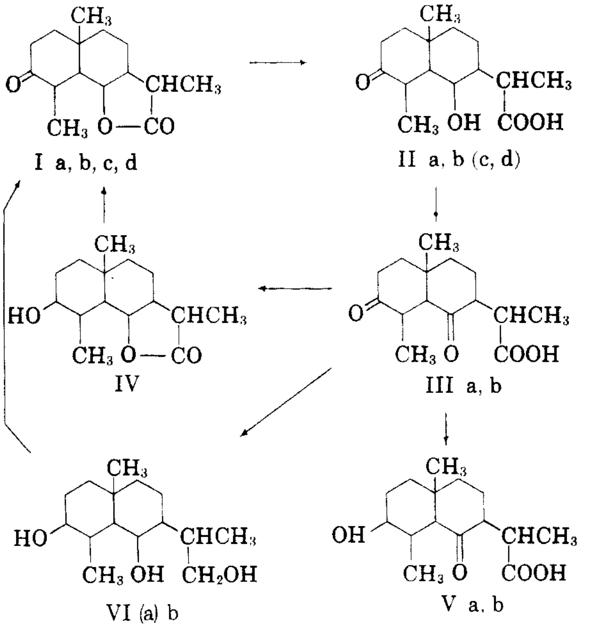


Ib

Since these formulations were derived from the configurational structure of santonin,[2] which was assigned mainly on the basis of molecular rotation differences, it is necessary to further elucidate the stereoformulas of tetrahydrosantonins (I) by chemical methods.

Recently, Matsumura, Iwai, and Ohki[3] reported that α-tetrahydrosantonin (Ia) was converted to a diketo acid (IIIa) in a low yield on hydrolytic opening of the lactone ring followed by oxidation of the resulting alcohol with chromium trioxide in pyridine. The diketo acid is of key importance to the stereochemistry of α-tetrahydrosantonin (Ia), since the introduction of the ketone group into the 5-position eliminates one asymmetric center and, moreover, permits facile isomerization at the 6- and the 10-positions to the sterically favored isomers.

For the purpose of improving the conversion of Ia into IIIa, the procedure reported by Wienhaus and Oettingen[4] for preparing the intermediate hydroxy acid, α-tetrahydrosantoninic acid (IIa), was followed, and was found to afford a good yield of IIa in high purity. On similar hydrolysis, γ-tetrahydrosantonin (Ib) gave the corresponding hydroxy acid (IIb), the melting point of which is close to that reported for "β-tetrahydrosantoninic acid" obtained from "β-tetrahydrosantonin"[1] by these authors.[4] The hydroxy acids (II) are unstable and readily gave back the parent *trans*-lactones (I) with acid or by heating above their melting points.



After several efforts to raise the yield of the α-diketo acid (IIIa) from Ia, a slight modification of the reported procedure[3] was found to give a twofold increase in the yield of the diketo acid (IIIa) with a large quantity of the recovered lactone, but the use of N-bromosuccinimide or N-bromoacetamide as an oxidation reagent gave no better results. γ-Tetrahydrosantonin (Ib), on similar hydrolysis and oxidation with chromium trioxide-pyridine, was converted to the corresponding diketo acid (IIIb) in better yield than that of IIIa from Ia. Both the diketo acids formed only monosemicarbazones.

Isomerization of the α-diketo acid by warming with dilute alkali afforded a mixture, from which the α- and γ-isomers were isolated in about 50% and 30% yields, respectively. Starting with the γ-isomer (IIIb), the resulting isomeric mixture gave

---

(1) Yanagita and Tahara, *J. Org. Chem.*, **20**, 959 (1955).

(2) Woodward and Yates, *Chemistry & Industry*, 1391 (1954); Corey, *J. Am. Chem. Soc.*, **77**, 1044 (1955).

(3) Matsumura, Iwai, and Ohki, *J. Pharm. Soc. Japan*, **74**, 1206 (1954).

(4) Wienhaus and Oettingen, *Ann.*, **397**, 219 (1913).

50% of IIIa and 17% of IIIb. The equatorial conformations of the methyl groups at the 4-position in the tetrahydrosantonins (Ia and Ib) were established previously[1] and the α-propionic acid residues at the 6-position are considered to be equatorial, as shown below. Apparently the above transformations of III involve isomerizations at both the 10- and the 4-positions. It is known[5] that in bicyclic six-membered ring systems with angular methyl groups the *trans* form is slightly more stable than the *cis* form.[6] From this generalization, it may be seen that the predominant formation of the α-isomer (IIIa) on isomerization of the diketo acids is not in agreement with the respective assignments of *cis* and *trans* configurations at the juncture of the six-membered rings for the α- and γ-diketo acids, derived from the structures of Ia and Ib, respectively. Investigation of this problem is now being made.

To establish the configurations of the hydroxyl groups of the lactone rings in the tetrahydrosantonins (I), the diketo acids were subjected to reduction with sodium and ethanol, which is known to convert the alicyclic ketones predominantly into alcohols with an equatorial hydroxyl group.[7] Each reduction product was lactonized by acid treatment, followed by oxidation of the resulting alcohol (presumably IV) with chromium trioxide to a keto lactone. When the reduction was conducted on a small scale, both IIIa and IIIb yielded, along with a small amount of Ia, two new isomers of the tetrahydro compound (I), m.p. 162–163° (Ic) and m.p. 96–98° (Id). It is likely that the reduction of cyclic ketones with too small an amount of sodium and ethanol does not afford the expected alcohols with an equatorial hydroxyl group, especially when the ketone group to be reduced is considerably sterically hindered, as in the present case. The use of a sufficient amount of the reagents on reduction of IIIa is expected to give the normal product. When the reduction of IIIa with sodium and ethanol was carried out in a fourfold scale, in which the reaction took place more violently, the yield of Ia was markedly raised, and the new isomers were not isolated from the reaction mixture. This result gave support for the equatorial orientation (*trans* to the angular methyl group) of the hydroxyl group of the lactone ring in the α-tetrahydro compound (Ia), and consequently in the γ-isomer (Ib).

The two new isomers of the tetrahydro compound were subjected to the hydrolysis and oxidation under the conditions employed for the conversions of I into III. Thereupon the one (Ic) of the higher m.p. was converted to the α-diketo acid (IIIa) and the other (Id) of the lower m.p. to the γ-diketo acid (IIIb). From these results, it can be seen that Ic and Id are different, respectively, from Ia and Ib only in the configuration of the hydroxyl group of the lactone ring, which must be axial and form *cis*-lactones in the new isomers.

The reconversion of the IIIa to Ia with sodium and boiling ethanol shows that the α-propionic acid residue at the 6-position in these compounds must occupy a stable equatorial conformation. It follows that the same residue in Ib must also be equatorial, since the configurations at the 6-position in Ia and Ib are the same, as established previously.[1]

Catalytic hydrogenation of the α- and γ-diketo acids in the presence of platinum gave rise, respectively, to the corresponding monoketo acids (Va and Vb). These structures, in which the keto group at the 5-position remains untouched, were assigned on the basis of the failure to form lactone rings on treatment with acid and to react with 2,4-dinitrophenylhydrazine under the usual conditions. The same monoketo acids were obtained in comparable yields from IIIa and IIIb on treatment with sodium borohydride at room temperature. When the borohydride reduction was conducted at elevated temperature and on prolonging the reaction time, small amounts of the corresponding lactone fractions (IV), with the predominant acids (V), were isolated after acid treatment of the reaction mixtures from III. The lactone fraction from IIIa was oxidized with chromium trioxide-pyridine to Ic, whereas the lactone fraction from IIIb gave no crystalline products under the same conditions.

Lithium aluminum hydride reduction of the α-diketo acid (IIIa) resulted in the formation of a neutral oily product (presumably a stereoisomeric mixture of VI), which gave a good yield of Ic on oxidation with chromium trioxide-pyridine. The γ-diketo acid (IIIb) was similarly reduced to a neutral crystalline product, to which a possible structure VIb is assigned from the mode of formation and analytical figures. Contrary to the neutral oil from IIIa, VIb gave no identifiable products on chromium oxidation, and this unsuccessful attempt in the γ-series is in line with the foregoing observations on the oxidation of the hydroxy lactone (IV) of the same series.

The unreactivity of the ketone groups at the 5-position in the diketo acids (III) and the monoketo acids (V) is shown in the above cited behaviors of these compounds against ketone reagents and in the relative resistance to hydrogenation with platinum or borohydride. This may be associated with the considerable steric hindrance effected by the neighboring groups. Based on the postulation of Barton,[7] it may be seen that these ketone groups in III and V were sterically hindered dominantly by the substituents at the 4-, 6-, and 10-positions, and the ring carbon at the 4-position. Difficulties encountered in the oxidation of the tetrahydrosantoninic

---

(5) Turner, *J. Am. Chem. Soc.*, **74**, 2118 (1952).

(6) Barton, *J. Chem. Soc.*, 1029 (1952).

(7) Contrary to this generality, Bachmann, *et al.*, [*J. Org. Chem.*, **19**, 222 (1954)] stated that some hetero-bicyclic six-membered ring systems with angular methyl groups are slightly more stable in the *cis*-configuration.

acids (II) into the diketo acids (III) may be due to the similar steric effects as well as the facile reconversions to the lactones (I).

It is generally accepted[8] that reduction of the hindered ketone groups in the six-membered rings with lithium aluminum hydride or sodium borohydride results largely in hindered (axial) hydroxyl groups. From this argument, it is clear that the formation of Ic from IIIa on metal hydride reduction followed by oxidation affords further support for the axial orientation of the hydroxyl group of the lactone ring in Ic, and consequently in Id.

In conclusion, a remark should be made on the previously reported stereoisomers of the diketo acid (III), the configurations of which remain obscure. The one,[9] derived from *l*-artemisin, has m.p. 192°, close to that of IIIb, but since no other properties are recorded for it, it is impossible to compare the two isomers more precisely. The other,[3] which is derived from *l*-dihydroisoalantolactone through a stereoisomer of tetrahydrosantonin (I), has m.p. 156–157°, close to that of IIIa, but lack of the identity of the two isomers was reported.[3]

EXPERIMENTAL[10]

All melting points were taken on a Kofler block, unless otherwise noted, and were uncorrected. Rotations were determined in a 0.5-dm. semimicro tube with ethanol as the solvent.

α-Tetrahydrosantoninic acid (IIa). This substance was prepared from α-tetrahydrosantonin (Ia) with dilute alkali by the procedure reported by Wienhaus and Oettingen.[4] It was found that on warming with 3% aqueous sodium hydroxide, Ia dissolved to give a clear solution in a few minutes. The product (90%) was recrystallized from ethanol by addition of water; prisms, m.p. 95–97°. Reported,[4] m.p. 85–115°. This acid was readily relactonized to Ia by acid treatment for a few minutes or by heating above its m.p.

γ-Tetrahydrosantoninic acid (IIb). This was prepared from γ-tetrahydrosantonin (Ib) by the procedure for IIa reported by Wienhaus and Oettingen.[4] It took about 1 hour to dissolve Ib in 3% aqueous alkali by warming. The product (80%), m.p. 165°, was recrystallized from ethanol by addition of water to give crystals, m.p. 196–197°.

Anal. Calc'd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.37; H, 9.09.

Like IIa, this material is readily relactonized by acid treatment or heating above its m.p.

α-Diketo acid (IIIa). (a) This was prepared from α-tetrahydrosantonin (Ia) by a slight modification of the method reported by Matsumura, Iwai, and Ohki.[3] To the ether extract containing IIa, prepared from 3.19 g. of α-tetrahydrosantonin (Ia) as reported previously,[4] was added a few drops of pyridine to prevent relactonization. After distillation of the ether under reduced pressure and low temperature, the residue was mixed with a mixture of 3 g. of chromium trioxide and 20 cc. of pyridine. The mixture was warmed at 40–50° for about 1 hour and allowed to stand at room temperature overnight. Ether was added to the reaction mixture, the precipitate was filtered off, and the ether solution was washed successively with 20% sulfuric acid, water, and sodium carbonate. Evaporation of the ether gave 450 mg. of recovered Ia. The carbonate solution was acidified and heated in a water-bath for a few minutes, and the separated oil was taken up in ether. The ether solution was washed with saturated sodium carbonate and evaporated to give an additional 690 mg. of Ia (total 35%). The carbonate solution was acidified and the precipitate was filtered after standing in a refrigerator overnight. The crystals so obtained were recrystallized from dilute ethanol to prisms, m.p. 77–79°, which resolidified under loss of water of crystallization.

Anal. Calc'd for $C_{15}H_{22}O_4 \cdot H_2O$: H_2O, 6.7. Found: H_2O, 6.2.

The dehydrated material was recrystallized from a mixture of ether and petroleum ether to give crystals, m.p. 147–148°, $[\alpha]_D^{13}$ −59.9° (*c*, 1.7). Reported,[3] m.p. 146–149°, $[\alpha]_D^{20}$ −61.2° (*c*, 2.99; $CHCl_3$).

Anal. Calc'd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.51; H, 8.25.

It formed a *monosemicarbazone*, m.p. 227–229°, after recrystallization from ethanol.

Anal. Calc'd for $C_{16}H_{25}N_3O_4$: N, 13.00. Found: N, 13.38.

(*b*) α-Tetrahydrosantonin (Ia) was oxidized with N-bromosuccinimide by application of the method reported by Fry[11] for the preparation of 5-benzyloxy-2-cyclohexanone-1-acetic acid from the corresponding γ-lactone. To a warmed alkaline solution of IIa, prepared from 500 mg. of Ia and 2 cc. of 2 *N* sodium hydroxide by hydrolysis, was added 100 mg. of monobasic potassium phosphate, whereupon two layers separated. N-Bromosuccinimide (390 mg.) was added to the mixture in a water-bath at 40°, and the bath temperature was raised to 50° within 10 minutes. After this temperature was maintained for about 30 minutes, the chilled solution was shaken with ether and the ether solution was worked up as described above (*a*). There was obtained 80 mg. (15%) of the α-diketo acid (IIIa), m.p. 130–136°, after drying at 60° in a vacuum, and there was recovered 200 mg. (40%) of Ia in a less pure state than from the above chromium trioxide oxidation. Recrystallization of IIIa from a mixture of ether and petroleum ether raised the m.p. to 146–147° (mixture m.p.).

When N-bromoacetamide was used instead of N-bromosuccinimide, 300 mg. of Ia gave, with recovery of 60 mg. of Ia, 100 mg. of an acidic crystalline product containing a bromine atom. Debromination of this acid with zinc dust and ethanol gave 40 mg. (13%) of IIIa, m.p. 130–135°, after drying in a vacuum at 60°.

γ-Diketo acid (IIIb). This substance was prepared from Ib by the procedure described for IIIa in the preceding experiment. There was obtained in 45% yield the γ-diketo acid (IIIb) and Ib was recovered in 20% yield. Recrystallization of IIIb from dilute ethanol gave prisms, m.p. 186–187°, $[\alpha]_D^{25}$ −138.5° (*c*, 2.1).

Anal. Calc'd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.78; H, 8.66.

It formed a *monosemicarbazone*, m.p. 241–243°, after recrystallization from ethanol.

Anal. Calc'd for $C_{16}H_{25}N_3O_4$: N, 13.00. Found: N, 13.17.

Interconversion of the α- and γ-diketo acids (IIIa and IIIb) *by isomerization.* To a solution of 60 mg. of the α-diketo acid (IIIa) in 0.3 cc. of dioxane was added 1 cc. of 3% aqueous sodium hydroxide and the mixture was warmed in a water-bath for 20 minutes. The pale yellow reaction mixture was acidified with sulfuric acid and immediately the first crop of crystals separated which were filtered after standing at room temperature for about 1 hour. The second and third crops of crystals were obtained from the mother solution after standing for 2 days each. The first crop (30

---

[8] Klyne, *Progress in Stereochemistry*, Academic Press Inc., New York, 1954, Vol. 1, p. 74.

[9] Tettweiler, Engel, and Wedekind, *Ann.*, **492,** 105 (1932).

[10] Microanalyses were carried out by Miss Shibuya in this Laboratory, and Mr. Negishi and Mr. Abe, Daiichi Seiyaku Co., Ltd.

[11] Fry, *J. Org. Chem.*, **17,** 1484 (1952).

mg., 50%), m.p. 69–72°, was recrystallized from dilute ethanol to give α-diketo acid (IIIa), 77–79°, which showed m.p. and mixture m.p. 145–147°, after drying in a vacuum at 60°. The second crop (IIIb, 10 mg.), m.p. 160–168°, and the third (IIIb, 10 mg.), m.p. 165–170°, were combined and recrystallized from dilute ethanol to give crystals, m.p. and mixture m.p. 185–187°.

A solution of 30 mg. of the γ-diketo acid (IIIb) in 0.3 cc. of dioxane and 0.2 cc. of 3% aqueous sodium hydroxide was treated as described for IIIa. There were obtained 15 mg. (50%) of IIIa, m.p. 145–147° (after crystallization from dilute ethanol and drying in vacuum at 60°), and 5 mg. (17%) of IIIb, m.p. 185–187° (after recrystallization from dilute ethanol).

Reduction of the α-diketo acid (IIIa) *with sodium and ethanol.* (*a*) To a solution of 300 mg. of the α-diketo acid (IIIa) in 10 cc. of isopropyl alcohol was added, in small pieces, 600 mg. of metallic sodium with stirring, and the stirring was continued for 3 hours. To the suspension of the sodium salt so obtained, after addition of 25 cc. of iabsolute ethanol, there was added rapidly 2 g. of sodium in large pieces, with stirring. Gentle reflux took place, and, the sodium dissolved in 30 minutes. The red-brown reaction mixture was mixed with water and concentrated under reduced pressure at about 40° to remove most of the ethanol. The solution so obtained was acidified, heated for a few minutes in a water-bath, and after cooling, was extracted with ether. The ether solution was washed with saturated sodium carbonate, then with sodium chloride-saturated water, and dried. Evaporation of the ether gave 160 mg. of a neutral yellow oil (presumably IV), which, without purification, was treated with a mixture of chromium trioxide (160 mg.) and pyridine (1.6 cc.). The reaction mixture was allowed to stand at room temperature overnight and was worked up as described for the α-diketo acid (IIIa) from Ia. There was obtained 110 mg. of a pale yellow oil, a lactone fraction, which soon solidified partly. On chromatographic separation, the fraction eluted with carbon tetrachloride gave 15 mg. (5%) of crystals, which were recrystallized from a mixture of ether and petroleum ether to yield prisms (Ic), m.p. 162–163°, $[\alpha]^{31}_{D}$ −120.0° (*c*, 1.13). The substance showed an obvious depression of the m.p. on admixture with the α-isomer (Ia).

Anal. Calc'd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.62; H, 9.23.

The fraction eluted with carbon tetrachloride-chloroform (2:1) gave a minute quantity of crystals, which were crystallized from a mixture of ether and petroleum ether giving α-tetrahydrosantonin (Ia), m.p. and mixture m.p. 142–145°. From the mother liquor of Ia, crystals, m.p. 95–96°, were isolated, which on recrystallization from a mixture of ether and petroleum ether gave platelets (Id), m.p. 96–98°. This material showed an obvious depression of the m.p. on admixture with the γ-isomer (Ib).

Anal. Calc'd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.61; H, 9.01.

(*b*) Reduction of IIIa was carried out on a larger scale. To a suspension of the sodium salt of IIIa, prepared from 1350 mg. of IIIa and 2.7 g. of metallic sodium, was added 100 cc. of absolute ethanol, followed by 9 g. of metallic sodium (in large pieces) rapidly. A violent reflux of ethanol took place, and a clear, pale yellow solution was worked up. The crude product (800 mg.) was oxidized, as described in (*a*). There was obtained a neutral oil (690 mg.), which was chromatographed on 25 g. of alumina (Brockmann, grade II). The fractions eluted with carbon tetrachloride and with chloroform gave only α-tetrahydrosantonin (Ia, 180 mg., 23%).

(*c*) To a suspension of the sodium salt (prepared from 150 mg. of IIIa and 300 mg. of sodium) in 8 cc. of isopropyl alcohol was added 15 cc. of absolute *n*-butanol (b.p. 117–118°) followed by 1 g. of metallic sodium. After addition of sodium, the mixture was heated until the sodium completely dissolved in the solution. The reaction was worked up and the product was oxidized, as described in (*a*), and there was obtained a neutral oil (70 mg.), which was chromatographed on alumina (3 g.). The fraction eluted with carbon tetrachloride gave 10 mg. of Ic, m.p. and mixture m.p. 158–160° (after recrystallization from a mixture of ether and petroleum ether).

Reduction of the γ-diketo acid (IIIb) *with sodium and ethanol.* The γ-diketo acid (430 mg.) was reduced with sodium and ethanol and oxidized with chromium trioxide-pyridine by the procedure described in the preceding experiment. On chromatographic separation of the product (160 mg.), the fraction eluted with carbon tetrachloride gave Ic, and the fraction eluted with carbon tetrachloride-chloroform (2:1) yielded Ia and Id.

α- and γ-Diketo acids (IIIa and IIIb) *from* Ic *and* Id, *respectively.* Ic (25 mg.) was subjected to hydrolysis of the lactone and subsequent oxidation of the resulting alcohol (II) by the procedure described above for IIIa and Ia. The product (15 mg., 60%) was recrystallized from dilute ethanol to give prisms, m.p. 75–78°, which, after drying in a vacuum (30°, 6 hours), showed m.p. 145–146°, undepressed on admixture with the α-diketo acid (IIIa).

On similar treatment, Id gave the γ-diketo acid (IIIb), m.p. and mixture m.p. 185–187° (after recrystallization from dilute ethanol).

Catalytic hydrogenation of α- and γ-diketo acids (IIIa *and* IIIb). A solution of 100 mg. of IIIa in 10 cc. of glacial acetic acid was shaken under an atmosphere of hydrogen in the presence of platinum black (prepared from 50 mg. of platinic oxide) until the gas absorption was complete. In 45 minutes, 17 cc. (16 cc. for one mole) of hydrogen was consumed. After filtration of the catalyst and distillation of acetic acid under reduced pressure, the residual oil was heated with dilute hydrochloric acid for a few minutes and extracted with ether. The ether solution was shaken with aqueous sodium carbonate, and the carbonate solution was acidified and extracted with ether. Drying and evaporation of the ether extract gave 70 mg. (70%) of an oil, which solidified, m.p. 150–152°. Recrystallization from dilute ethanol gave prisms (Va), m.p. 151–152°, $[\alpha]^{26}_{D}$ −40.0° (*c*, 0.9).

Anal. Calc'd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 66.65; H, 8.91.

It did not react with *2,4-dinitrophenylhydrazine* in ethanolic sulfuric acid at room temperature.

By the same procedure, IIIb was hydrogenated to give 80 mg. (80%) of Vb, which was recrystallized from dilute ethanol to give prisms, m.p. 182–183°, $[\alpha]^{27}_{D}$ −64.6° (*c*, 0.86).

Anal. Calc'd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 66.79; H, 9.00.

Sodium borohydride reduction of the α-diketo acid (IIIa). (*a*) *At room temperature.* To a solution of 100 mg. of IIIa in 15 cc. of absolute methanol was added, dropwise, 60 mg. of sodium borohydride[12] in 30 cc. of the same solvent under stirring, and a slightly exothermic reaction took place with evolution of gas. After the stirring was continued for 1 hour, the solution was evaporated under reduced pressure, and the residue was mixed with water and extracted with ether. The ether solution was shaken with saturated aqueous sodium carbonate, and the carbonate solution was acidified and warmed in a water-bath for a few minutes. The crystals that separated were taken up in ether and the ether solution was again shaken with aqueous sodium carbonate. The carbonate solution was acidified, extracted with ether, and the ether was distilled to give 90 mg. (90%) of crystals, m.p. 142–145°, which were recrystallized from dilute ethanol to yield prisms, m.p. 150–152°, undepressed on admixture with Va in the preceding experiment.

In the above procedure, the ether solution shaken with

---

[12] The author wishes to thank Prof. Sugasawa, The Pharmaceutical Institute, Tokyo University, for the gift of this reagent.

aqueous sodium carbonate gave no detectable amount of neutral compound.

(*b*) *At higher temperature.* To a solution of 50 mg. of IIIa in 3 cc. of absolute ethanol was added a solution of 30 mg. of sodium borohydride in 20 cc. of the same solvent. After the exothermic reaction had subsided, the mixture was heated to reflux for 2 hours, and three 10-mg. portions of sodium borohydride were added to the refluxing solution over a 2-hour period. The reaction mixture was worked up as described above (*a*), and two crystalline products were obtained: an acid, m.p. 145–147° (40 mg.), and a neutral substance (10 mg.), m.p. 77–79°. The acid (Va) was recrystallized from dilute ethanol to give prisms, m.p. and mixture m.p. 150–152°. The neutral crystals, which possibly correspond to structure IV, were, without purification, oxidized with chromium trioxide-pyridine as described above. There was obtained 10 mg. of crystals, which were recrystallized once from dilute ethanol to give prisms (Ic), m.p. and mixture m.p. 157–158°.

Sodium borohydride reduction of the γ-diketo acid (IIIb). IIIb (100 mg.) was reduced with sodium borohydride (50 mg.) at room temperature by the procedure (*a*) described for IIIa in the preceding experiment. The acidic product (90 mg., 90%), m.p. 175–177°, was recrystallized once from dilute ethanol to give prisms (Vb), m.p. and mixture m.p. 180–181°. No neutral materials were isolated in this reaction.

Sodium borohydride reduction of IIIb (60 mg.) in refluxing ethanol by the procedure (*b*) described for IIIa, gave Vb (50 mg., 83%), m.p. 180–181° (after recrystallization from dilute ethanol), and a neutral oil (10 mg., 17%). Oxidation of this oil with chromium trioxide-pyridine gave no crystalline products.

Lithium aluminum hydride reduction of the α-diketo acid (IIIa). To a solution of 70 mg. of IIIa in 20 cc. of absolute ether was added 40 mg. of lithium aluminum hydride in the same solvent and the mixture was heated to reflux for 6 hours. To the cooled reaction was added dilute sulfuric acid to decompose the excess lithium aluminum hydride. The separated ether layer was washed with saturated sodium carbonate and then with sodium chloride-saturated water and dried. Evaporation of the ether gave an oil, which presumably consisted chiefly of a stereoisomeric mixture of VI. This oil was oxidized with chromium trioxide-pyridine, as described above, and there was obtained 40 mg. of a neutral oil which solidified slowly. Recrystallization from a mixture of ether and petroleum ether gave Ic, m.p. and mixture m.p. 162–163°.

Lithium aluminum hydride reduction of the γ-diketo acid (IIIb). IIIb (100 mg.) was reduced with lithium aluminum hydride by the procedure described for IIIa in the preceding experiment, except that the reaction mixture was heated to reflux for 12 hours. A neutral oily product (80 mg., 80%), which solidified, was triturated with petroleum ether and recrystallized from dilute ethanol to give crystals (VIb), m.p. 212–215° (in capillary). It is sublimable.

Anal. Calc'd for $C_{15}H_{28}O_3$: C, 70.24; H, 11.01. Found: C, 69.88; H, 10.97.

Oxidation of VIb with chromium trioxide-pyridine gave no crystalline products.

SHINJUKU-KU, TOKYO, JAPAN