The Absolute Configuration at C_7 of α- and β-Desmotroposantonin[1]

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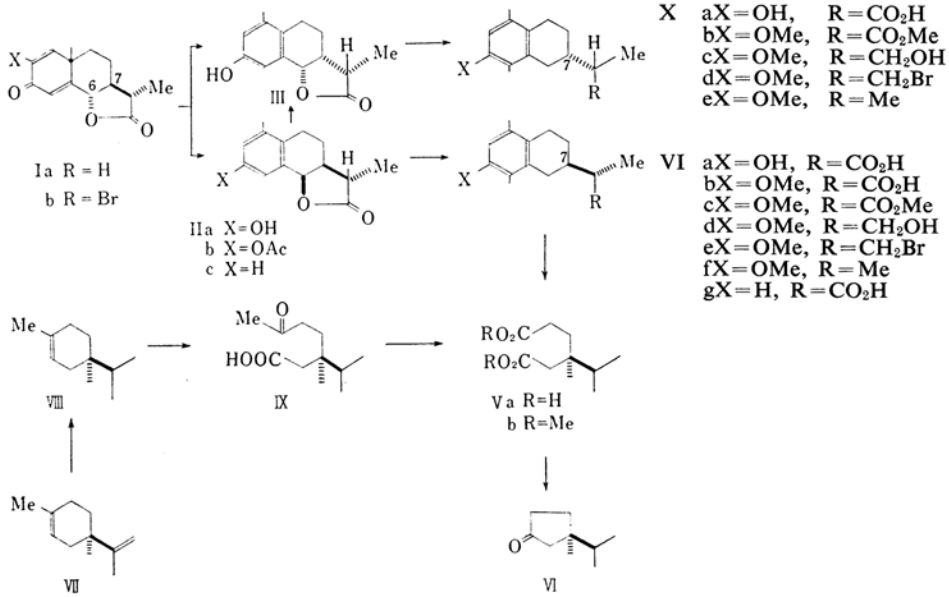
(Received September 21, 1963)

Although the bulk of evidence,[2] mainly deduced from the stereochemistry of α- (IIa) and β-desmotroposantonin (III), strongly favors the (R)-configuration at position 11 of (−)-α-santonin (Ia), recent publications[3,4] have confirmed Abe's assignment[5] of the (S)-configuration at this center.

Not only to settle this discrepancy, but also in order fully to understand the mechanism of the well-known peculiar cycle of rearrangements in the desmotroposantonin series,[6] the determination of the absolute configuration of α- and β-desmotroposantonin, which have not been established on a firm ground, seems imperative.

Acetyl (−)-α-desmotroposantonin (IIb) prepared from (−)-α-santonin following Huang-Minlon's procedure[7] was first hydrolyzed to (−)-α-desmotroposantonin (IIa), which was then reduced with zinc powder in acetic acid to afford (+)-α-desmotroposantonous acid (IVa).[8] After methylation with dimethyl sulfate, the methyl ether IVb which resulted was esterified with diazomethane to the methyl ester IVc. The methyl ester of (+)-α-desmotroposantonous acid methyl ether was reduced with lithium aluminum hydride to the alcohol IVd, which was converted with phosphorus tribromide/pyridine to the bromide IVe. The bromide was refluxed with lithium aluminum hydride to afford the methyl ether IVf; b. p. 145~155°C/3 mmHg, n_D^{29} 1.5328, $[\alpha]_D^{25}$ +60.0° (in ethanol). Exhaustive ozonolysis of the methyl ether IVf, followed by



1) A preliminary commncication has appeared in this Bulletin, **35**, 1904 (1962).

2) Cf. inter alia. W. Cocker and T. B. H. McMurry, *Tetrahedron*, **8**, 181 (1960), and the literatures cited in our preceding paper on the absolute configuration of (−)-α-santonin.

3) D. H. R. Barton, T. Miki, J. T. Rinhey and R. J. Wells, *Proc. Chem. Soc.*, **1962**, 112; J. D. Asher and G. A. Sim, ibid., **1962**, 111.

4) M. Nakazaki and H. Arakawa, ibid., **1962**, 152.

5) Y. Abe, T. Miki, M. Sumi and T. Toga, *Chem. & Ind.*, **1956**, 953; T. Miki, *J. Pharm. Soc. Japan* (*Yakugaku Zasshi*), **75**, 416 (1955).

6) J. Simonsen and D. H. R. Barton, "The Terpenes," II Ed., Vol. III, Cambridge Univ. Press (1955), p. 263.

7) Huang-Minlon et al., *J. Am. Chem. Soc.*, **65**, 1780 (1943).

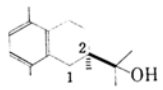
8) Elsevier's "Encyclopedia of Organic Chemistry," Series III, Vol. 12B, Elsevier Pub. Co. Inc., New York-Amsterdam (1948), pp. 3471, 3478.

peracetic acid oxidation, gave crude β-isopropyladipic acid (Va),[9] which was purified via dimethyl ester Vb. Heating the acid with barium hydroxide at 280~300°C following the procedure of Burger and Macbeth[10] gave 3-isopropylcyclopentan-1-one (VI), which was directly converted into the semicarbazone; m. p. 181~183°C, $[\alpha]_D^{31}$ +43.8° (in ethanol). Its identity with (R)-(+)-3-isopropylcyclopentan-1-one semicarbazone (m. p. 186~187°C, $[\alpha]_D^{26}$ +65.2° (in ethanol)) prepared from (R)-(+)-limonene (VII)[11] (via (+)-dihydrolimonene (VIII) and (+)-3-isopropylheptan-6-onic acid (IX)) was established by a mixed melting point comparison (181~183°C) and by a comparison of their infrared absorption spectra (in chloroform).

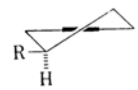
This correlation established the (R)-configuration at position 7. The fact that (+)-β-desmotroposantonin (III) has the opposite configuration from (−)-α-desmotroposantonin (IIa) at C_7 was confirmed by the conversion of the former, through the same sequence of conversions described in the α-series, into the enantiomer Xe (b. p. 110~120°C/0.1 mmHg, n_D^{29} 1.5322, $[\alpha]_D^{28}$ −65.2° (in ethanol)), which showed an infrared spectrum superimposable on that of the methyl ether IVf from (−)-α-desmotroposantonin (IIa).

It is of interest to note here that the compounds derived from (+)-α-desmotroposantonous acid (IVa) as well as from hyposantonous acid (IVg) and occidol (XII),[15] all of which have the same (R)-configuration at C_7, show dextrorotation, whereas the compounds Xa, Xb, Xc, Xd and Xe from the (−)-β-desmotroposantonous acid series all exhibit the opposite rotation (see the Experimental section).

Mill's rule[12] and Brewster's[13] model of optical activity extended to endocyclic compounds show that the cyclohexene derivative with a configuration similar to that of (+)-limonene (VII) exhibits dextrorotation. It is apparent from our experimental results that their rules can be extended to the tetralin series: *2-(R) substituted tetralin XII is dextrorotatory provided that the optical rotatory power of the conformational asymmetry XII is not exceeded by that of the side chain.*

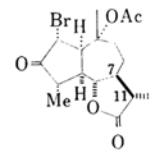


XI



XII

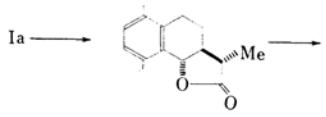
Thus having had established the absolute configuration of the C_7 asymmetric centers of α- and β-desmotroposantonin, our attention was next directed to correlating these centers of asymmetry with that of C_7 of (−)-α-santonin. The C_7 asymmetric center in (−)-α-santonin has been assigned the (R)-configuration[2] by correlating it with (+)-dihydrocarvon via carrison through a long series of degradations and synthetic works involving at least 20 compounds, among them artemisin, ψ-santonin, β-selinene, α- and β-eudesmol and costol. Since these natural compounds related to (−)-α-santonin are important relay substances in the stereochemistry of eudesmane-type sesquiterpene, it seems not superfluous to add other evidence to support the (R)-configuration at the asymmetric center C_7 of (−)-α-santonin. Especially is this so when it is reflected that the absolute configuration of C_{11} of bromoiso-α-photosantonic lactone acetate (XIII)[14] (and consequently that of santonin) has been assigned by X-ray crystal analysis with reference to this C_7 asymmetric center.



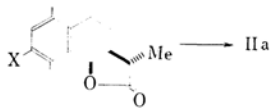
XIII

Hyposantonin (XIV)[15] derived from (−)-α-santonin under very mild conditions, which possesses the original asymmetric configurations of C_6, C_7 and C_{11} of santonin intact, appears a convenient intermediate with which to link (−)-α-santonin and α-desmotroposantonin. During the course of their study of hyposantonylquinol, Asahina and Momose[16] nitrated hyposantonin to obtain a mononitro derivative which they named 2-nitrohyposantonin. Since the same compound could be prepared from isohyposantonin (XVa), which has a cis lactone ring, it is evident that the epimerization at C_6, reminiscent of the process from santonin to α-desmotroposantonin, intervenes during the nitration, implying that the proper name should be 2-nitroisohyposantonin (XVb). The diazotization of 2-amino-isohyposantonin (XVc) prepared from the nitro compound XVb afforded (−)-α-desmotroposantonin (IIa). Thus, this sequence of reactions seems to provide evidence that (−)-α-desmotroposantonin (IIa) and isohyposantonin (XVa) have the same absolute configuration at C_7 and C_{11}.

9) J. v. Braun and G. Werner, *Ber.*, **62**, 1050 (1929).
10) G. Burger and K. Macbeth, *J. Chem. Soc.*, **1946**, 145.
11) A. J. Birch, *Ann. Reports*, **47**, 191 (1950).
12) J. A. Mills, *J. Chem. Soc.*, **1952**, 4975.
13) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5493 (1959).
14) J. D. M. Asher and G. A. Sim, *Proc. Chem. Soc.*, **1926**, 111.
15) Ref. 8, p. 3456 and M. Nakazaki, This Bulletin, **35**, 1387 (1962).
16) Y. Asahina and T. Momose, *Ber.*, **71**, 1421 (1938).



XIV



XVa R=H
b R=NO_2
c R=NH_2

However, since Asahina and Momose used rather severe conditions (concentrated nitric acid and concentrated sulfuric acid in acetic acid) in the nitration reaction, during the nitration a rearrangement similar to (−)-α-desmotroposantonin (IIa)→(+)-β-desmotroposantonin (III) may intervene simultaneously. To clarify this point, 2-aminoisohyposantonin (XVc) was diazotized; the deamination of the diazonium compound with hypophosphorous acid[17] gave back the starting compound, isohyposantonin (XVa) implying that no such inversion occured. Thus, the configuration of (−)-α-santonin at C_7 can be related with that of (−)-α-desmotroposantonin; this (R)-configuration at C_7 of (−)-α-santonin is completely in accord with the results obtained from the X-ray crystal analysis of 2-bromosantonin (Ib) by the Glasgow group.[18]

Experimental*

A) The α-Desmotroposantonin Series

Acetyl (−)-α-Desmotroposantonin (IIb).[7]—Twenty grams of (−)-α-santonin was slowly stirred into a mixture of 120 cc. of acetic anhydride and 2 cc. of concentrated sulfuric acid at room temperature. After the solution had been kept at room temperature overnight, the crystals which precipitated were filtered and washed with water. The mother liquor was added to 500 cc. of ice water, and the crystals which deposited were filtered and washed with water. Recrystallization of the combined crystals from ethanol gave 20 g. of IIb (m. p. 155～156°C (lit.[7] m. p. 156～157°C)).

(−)-α-Desmotroposantonin (IIa).[7]—To 20 g. of acetyl-(−)-α-desmotroposantonin (IIb), a mixture of 20 g. of potassium hydroxide, 50 cc. of water and 200 cc. of methanol was added. The mixture was refluxed for 5 hr, and the methanl was distilled off. The residue was dissolved in 200 cc. of water, and the solution was made acidic with concentrated hydrochloric acid. After the crystals had been filtered and washed with water, they were recrystallized from ethanol to give 12 g. of IIa (m. p. 190～192°C). The mother liquor was concentrated to yield the second crop of crystals (m. p. 186～190°C (lit.[7] m. p. 194°C)).

(+)-α-Desmotroposantonous Acid (IVa).[19]—Into a mixture of 50 g. of (−)-α-desmotroposantonin (IIa), 1.2 l. of acetic acid and 100 cc. of water, 300 g. of zinc powder were vigorously stirred (Vibro-Mischer). After the solution had been refluxed and stirred for 16 hr., the excess zinc powder was filtered, and the zinc power was washed with hot acetic acid on a Buchner funnel. The combined filtrate and washing were concentrated under reduced pressure. The crystals which were precipitated by adding water to the residue were collected and washed with water. Recrystallization from ethanol yielded 44 g. of (+)-α-desmotroposantonous acid (IVa) (m. p. 176～178°C). Further recrystallization from 75% acetic acid yielded needles (39 g.) melting at 177～179°C; $[\alpha]_D^{25}$+77.6° (*c* 1.81 in ethanol), (lit.[8] m. p. 182～183°C, $[\alpha]_D$+75° (in ethanol)).

(+)-α-Desmotroposantonous Acid Methyl Ether (IVb).—In an atmosphere of nitrogen, 21 g. of (+)-desmotroposantonous acid (IVa) was dissolved in 127 cc. of 6.5% aqueous sodium hydroxide. When 3.4 g. of dimethyl sulfate was added to the stirred solution, a solid deposited which was then dissolved by adding 70 cc. of water and heating the solution at 50°C. In a period of 1 hr., 10.2 g. of dimethyl sulfate was added; the reaction mixture was then stirred at 80°C for 2 hr. After 20 cc. of 6.5% of aqueous sodium hydroxide was added, the reaction mixture was made acidic with concentrated hydrochloric acid and kept in a refrigerator overnight. The crystals which were deposited were filtered and washed with water. The product weighed 22 g. and melted at 114～117°C after recrystallization from 70% acetic acid; $[\alpha]_D^{25}$+69.5° (*c* 1.21 in ethanol) (lit.[8] m. p. 116～117°C, $[\alpha]_D^{26}$+72.2° (in ethanol)).

Methyl Ester of (+)-α-Desmotroposantonous Acid Methyl Ether (IVc).—A solution of 34 g. of (+)-α-desmotroposantonous acid methyl ether in 60 cc. of methanol was added into a chilled solution of diazomethane in ether prepared from 42 g. of nitrosomethylurea, and the mixture was kept in a refrigerator overnight. The excess diazomethane was decomposed with a small amount of acetic acid. After the reaction mixture had been washed with saturated aqueous sodium chloride to remove the methanol, it was dried over calcium chloride and freed from the solvent. The residue was distilled to yield 33.5 g. of an oil, b. p. 128～140°C/10^{-2} mmHg, n_D^{27} 1.5293, $[\alpha]_D^{27}$+82.0° (*c* 1.82 in ethanol).

Found; C, 73.62; H, 8.82. Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75%.

The Alcohol IVd.—In a stream of nitrogen, a solution of 33.5 g. of methyl ester IVc in 40 cc. of ether was stirred into suspension of 3.7 g. of lithium aluminum hydride in 350 cc. of anhydrous ether at room temperature. After the reaction mixture had been gently refluxed for 1.5 hr., the excess lithium

17) N. Kornblum, "Organic Reactions," Vol. 2, 262 (1948).

18) J. D. Asher and G. A. Sim, *Proc. Chem. Soc.*, **1962**, 335.

* All melting and boiling points are uncorrected. The analyses were performed in the Microanalytical Laboratory of the Shionogi Pharm. Co. through the courtesy of Dr. Kenichi Takeda, which is gratefully acknowledged.

19) Following the procedure of G. R. Clemo, *J. Chem. Soc.*, **1934**, 1343.

aluminum hydride was decomposed with 5 cc. of ethyl acetate. Water was added until the aluminum hydroxide deposite in an easily filterable state (about 50 cc. of water was required). The aluminum hydroxide was then filtered and washed with ether thrice. The combined ether solution was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, and freed from the solvent. When the residue was distilled, 28.1 g. of a viscous colorless liquid (b. p. 160~180°C/10^{-2} mmHg) was collected in a 94% yield. $[\alpha]_D^{27}$+60.8° (*c* 2.90 in ethanol).

Found: C, 77.0; H, 9.7. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74%.

Phenylurethane. — The recrystallization of the phenylurethane, prepared by the usual method, from ethanol gave prismatic crystals; m. p. 125~126°C, $[\alpha]_D^{27}$+47.3° (*c* 0.65 in ethanol).

Found: C, 75.2; H, 8.2. Calcd. for $C_{23}H_{29}O_3N$: C, 75.17; H, 7.95%.

The Bromide IVe.—Into a chilled (−5~10°C) mixture of 12.0 g. of phosphorus tribromide, 1.7 g. of pyridine and 8 cc. of benzene, a mixture of 28.1 g. of the alcohol IVd, 30 cc. of benzene and 0.6 g. of pyridine was stirred over 4 hr., during which time the temperature was kept constant. After being stirred at this temperature for 2 hr., the reaction mixture was warmed on a water bath (40~50°C) for 2 hr. and then poured on 200 g. of crashed ice and extracted with ether. The ether extract was washed with aqueous sodium hydrogen carbonate, water and saturated sodium chloride solution successively, and then dried over calcium chloride. Removal of the solvent gave a residue which was distilled to yield 18.4 g. (51% yield) of a liquid (b. p. 150~160°C/10^{-2} mmHg, n_D^{29} 1.5638, $[\alpha]_D^{28}$+66.4° (*c* 2.24 in ethanol)).

Found: Br, 22.8. Calcd. for $C_{16}H_{23}OBr$: Br, 22.49%.

The Methyl Ether IVf.—Into a slurry of 2.9 g. of lithium aluminum hydride in 30 cc. of anhydrous tetrahydrofuran, a solution of 18 g. of the bromide in 20 cc. of tetrahydrofuran was stirred over a 1/2 hr. period. The exothermic reaction was observed, and the reaction mixture was gently refluxed for another 2 hr. The cold mixture was diluted with 180 cc. of ether, and the excess reducing reagent was decomposed with a small amount of ethyl acetate. The mixture was decomposed by a dropwise addition of water until aluminum hydroxide was deposited in an easily filterable state. The ether solution was filtered, and the collected aluminum hydroxide was washed with ether three times. The ether filtrate and washings were combined and washed with water and with a saturated sodium chloride solution. After being dried over calcium chloride, the solution was concentrated to afford the residue, which was distilled to give 12.0 g. of a liquid (92.4% yield) (b. p. 145~155°C/3 mmHg, n_D^{29} 1.5328, $[\alpha]_D^{25}$+60.0° (*c* 2.52 in ethanol)).

Found: C, 83.0; H, 10.4. Calcd. for $C_{16}H_{24}O$: C, 82.70; H, 10.41%.

The Exhaustive Ozonolysis of the Methyl Ether IVf.—A stream of ozone (about 2%) was passed into a solution of 6.0 g. of the methyl ether IVf in 70 cc. of acetic acid for 30 hr. at room temperature (28~29°C). To this reaction mixture, 5 cc. of 30% hydrogen peroxide was added, and the mixture was allowed to stand at room temperature overnight. After the mixture had been warmed on a water bath for 2 hr., a small amount of palladium on a carbon catalyst was added to decompose the excess peracetic acid. The mixture was heated on a water bath for 2 hr. and freed from the catalyst. Concentration under reduced pressure gave a sirup which was dissolved in 50 cc. of water and again concentrated at reduced pressure. This process of evaporation was repeated twice in order to remove the acetic acid. The brown, viscous sirup was dissolved in 30 cc. of methanol and treated with 150 cc. of a cold ether solution of diazomethane prepared from 13 g. of nitrosomethylurea. After being kept in a refrigerator overnight, the solution was washed with water and a saturated aqueous calcium chloride solution and dried over calcium chloride. Removal of the solvent gave a viscous brown liquid which was distilled to afford 1.9 g. of the ester Vb (b. p. 100~105°C/5 mmHg (bath temp. 140~150°C), n_D^{30} 1.4493). The ester Vb was saponified by heating it with 2 g. of potassium hydroxide in 20 cc. of methanol containing 0.5 cc. of water for 3 hr. After the methanl had been removed, water was added and the mixture was made strongly acidic with concentrated hydrochloric acid. The solution was saturated with sodium chloride and continuously extracted with ether for 10 hr. When the solvent was removed and the residue was heated with 0.1 g. of barium hydroxide (at 160~180°C for 1 hr., at 180~280°C for 2 hr. and at 280~300°C for 1 hr.), 0.8 g. of a pale yellow liquid with a pleasant smell was obtained. To this oil was added a mixture of 0.7 g. of semicarbazide hydrochloride and 0.8 g. of sodium acetate with a small amount of water; drops of alcohol were also added to remove any turbidity. The crystalline product which separated was recrystallized from ethanol twice and finally from water to give 0.05 g. of fine needles (m. p. 181~183°C, $[\alpha]_D^{31}$+43.8° (*c* 0.48 in ethanol)). A mixed melting point determination with (R)-(+)-3-isopropylcyclopentan-1-one semicarbazone (m. p. 186~187°C, $[\alpha]_D^{26}$+65.2° prepared from (R)-(+)-limonene (vide infra)) was 181~183°C. The infrared spectra of the two compounds in chloroform were indistinguishable.

Found: C, 59.2; H, 8.9; N, 22.7. Calcd. for $C_8H_{17}ON_3$: C, 58.98; H, 9.35; N, 22.93%.

B) β-Desmotroposantonin Series

(+)-β-Desmotroposantonin (III).[20]—A solution of 30 g. of (−)-α-santonin in 180 cc. of fuming concentrated hydrochloric acid, prepared by saturating concentrated hydrochloric acid with dried hydrogen chloride gas at 0~5°C, was sealed in a pressure bottle and kept at 36°C for 2 days, during which time a crystalline solid was deposited. After 1 l. of water had been added to the reaction mixture, the cream-colored crystalline solid was broken up, washed with water, and dried. The product, which weighed 29 g., was recrystallized from about 1 l. of ethanol to yield 20 g. crystals (m. p. 237°C (decomp.)).

20) Following the procedure of G. R. Clemo, *J. Chem. Soc.*, **1930**, 1110, 1114.

Concentration of the mother liquor gave 1.1 g. of the second crop (m. p. 230°C (decomp.), $[\alpha]_D^{26}$+108° (*c* 0.39 in ethanol)). (lit.[8] decomp. p. 260°C, $[\alpha]_D$+112.1°)).

(−)-β-Desmotroposantonous Acid (Xa).—Into a refluxing mixture of 31 g. of (+)-β-desmotroposantonin (III) in 950 cc. of acetic acid and 60 cc. of water, 190 g. of zinc powder was vigorously stirred with a Vibro-Mischer. Following the procedure described for the prepartion of IVa, 23 g. of needles (m. p. 174~175°C) were obtained after recrystallization from 70% acetic acid. Concentration of the mother liquor gave the second crop; 2.3 g., m. p. 170~174°C. $[\alpha]_D^{25}$ −56.9° (*c* 1.87 in ethanol) (lit.[21] m. p. 175°C, $[\alpha]_D$ −53.3° (in ethanol)).

Methyl Ester Xb of (−)-β-Desmotroposantonous Acid Methyl Ether.—Twenty grams of sodium hydroxide was dissolved in 400 cc. of water, 280 cc. of which was then added to 25 g. of (−)-β-desmotroposantonous acid (Xa) in an atomosphere of nitrogen. Twenty grams of dimethyl sulfate was stirred into the solution over a 1~1/4 hr. period at room temperature, and the reaction mixture was heated at 70~80°C on a water bath for 2 hr. After the rest of the sodium hydroxide solution had been added, the reaction mixture was refluxed for 1 hr. After it had been acidified with concentrated hydrochloric acid, the viscous semisolid product which deposited was collected and dissolved in ether. The ether solution was washed with water and saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. Removal of the solvent gave a viscous oil which was dissolved in 20 cc. of methanol and treated with 300 cc. of an ether solution of diazomethane prepared from 31 g. of nitrosomethylurea. After being allowed to stand in a refrigerator 1 for 2 days, the excess diazomethane was decomposed with 1 cc. of acetic acid. The solution was washed with saturated aqueous calcium chloride, and dried over calcium chloride. The ether was removed and the residue distilled to give 21.0 g. of a liquid (b. p. 128~135°C/10^{-2} mmHg, n_D^{27} 1.5319, $[\alpha]_D^{27}$ −37.2° (*c* 2.13 in ethanol)).

Found: C, 73.6; H, 8.6. Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75%.

The Alcohol Xc.—The reduction of 21.0 g. of the methyl ester Xb with 2.4 g. of lithium aluminum hydride, as described in the preparation of the alcohol IVd, yielded 18 g. (95% yield) of the alcohol Xc (b. p. 160~180°C/10^{-2} mmHg, $[\alpha]_D^{27}$ −74.4° (*c* 3.12 in ethanol)).

Found: C, 76.8; H, 9.7. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74%.

Phenylurethane.—The phenylurethane prepared following the usual method was recrystallized from ethanol to give silky needles (m. p. 106~108°C, $[\alpha]_D^{28}$ −60.2° (*c* 0.93 in ethanol)).

Found: C, 74.9; H, 8.0. Calcd. for $C_{23}H_{29}O_3N$: C, 75.17; H, 7.95%.

The Bromide Xd.—Following the procedure described for the preparation of the bromide IVe, 17 g. of the alcohol Xc was converted into the bromide Xd (12.4 g., 57% yield) (b. p. 197~200°C/3 mmHg, n_D^{27} 1.5640, $[\alpha]_D^{27}$ −41.3° (*c* 1.58 in ethanol)).

Found; Br, 23.42. Calcd. for $C_{16}H_{23}OBr$: Br, 22.49%.

The Methy Ether Xe.—The reaction of 12.0 g. of the bromide Xd with 1.7 g. of lithium aluminum hydride in tetrahydrofuran, as described for the preparation of the methyl ether IVf, gave 8.0 g. of the methyl ether Xe, a colorless liquid (93% yield) (b. p. 110~119°C/0.1 mmHg, n_D^{29} 1.5322, $[\alpha]_D^{28}$ −65.1° (*c* 1.51 in etanol)). The infrared absorption spectra of the methyl ether IVf of the α-desmotroposantonin series and the methyl ether Xe of the β-desmotroposantonin series were indistinguishable.

Found: C, 82.6; H, 10.2. Calcd. for $C_{16}H_{24}O$: C, 82.70; H, 10.4%.

Isohyposantonin (XVa)[22].—To a solution of 3 g. of barium hedroxide hydrate in 30 cc. of water 0.5 g. of hyposantonin XIV was added; the mixture was warmed on a water bath to gave a clear solution. The solution was made acidic with concentrated hydrochloric acid to precipitate isohyposantonin. The crystalline isohyposantonin which separated was recrystallized from ethanol to yield prismatic crystals (m. p. 168~171°C, $[\alpha]_D^{32}$ −76.6° (*c* 0.51 in benene) (lit.[22] m. p. 167.5~168.5°C, $[\alpha]_D$ −73.7° (in benzene)).

2-Nitroisohyposantoin (XVb).[16]—The nitration of 1.5 g. of hyposantonin in 5 cc. of acetic acid with a mixture of 6 g. of concentrated sulfuric acid and 3 g. of concentrated nitric acid at 20~30°C gave 0.85 g. of needles after recystallization from ethanol (m. p. 174~176°C (lit.[16] m. p. 183°C)).

2-Aminoisohyposantonin (XVc).[16]—The reduction of XVb (0.85 g.) with 5 g. of zinc powder and 0.6 g. of ammonium chloride in ethanol afforded 0.7 g. of crystals after washing and drying. Recrystallization from benzene yielded 0.65 g. of a pale yellow powderlike crystalline material (m. p. 188~191°C, $[\alpha]_D^{31}$ −168° (*c* 0.60 in benzene) (lit.[16] m. p. 193°C, $[\alpha]_D^{14}$ −165.7° (in chloroform)).

The Deamination of 2-Aminoisohyposantonin (XVc) to Isohyposantonin (XVa).—Into a chilled solution of 0.40 g. of 2-aminoisohyposantonin (XVc) in 15 cc. of 1 N hydrochloric acid, a solution of 0.12 g. of sodium nitrite in 2 cc. water was stirred. The reaction mixture was chilled at −5~0°C, and 8 cc. of 40% hypophosphorous acid was added over a 1 hr. period. After the solution had been allowed to stand in a refrigerator for 24 hr., the crystalline product was filtered, washed with water, and dried. Recrystallization from ethanol gave 0.20 g. of crystals (m. p. 168~169°C). A mixed melting point with isohyposantonin (m. p. 168~171°C) was 168~170°C. The infrared spectra in chloroform of the product and isohyposantonin were indistinguishable. $[\alpha]_D^{31}$ −73.6° (*c* 0.65 in benzene).

Found: C, 77.9; H, 7.8. Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88%.

(+)-3-Isopropylheptan-6-onic Acid (IX).—A stream of ozone (2%) was passed into a mixture of 80 cc. of acetic acid and 19.0 g. of (+)-dihydrolimonene (VIII) (b. p. 64~65°C/20 mmHg. $n_D^{21.5}$ 1.4555, $[\alpha]_D^{21.5}$ +100.8° (neat)) for 4 hr. at room temperature. The reaction mixture was diluted

21) Ref. 8, p. 3478.
22) Ref. 8, p. 3458.

with 10 cc. of water and oxidized by dropwise addition of a solution of 33 g. potassium permanganate in 500 cc. of water at 70°C with stirring. The oxidation mixture was filtered, and the manganese dioxide was washed with hot water. The washing was combined with the fiiltrate and was made acidic with concentrated hydrochloric acid and then extracted with ether. The ether extract was freed of the solvent and the residue was distilled to give 95 g. of a liquid (b. p. 132~137°C/0.8 mmHg, n_D^{22} 1.4557).

(+)-3-Isopropylcyclopentan-1-one (VI) Semicarbazone.[10]—A solution of 2.0 g. of the ketocarboxylic acid IX in 20 cc. of 5% sodium hydroxide was added to a chilled hypobromite solution prepared from 9 g. of bromine, 6 g. of sodium hydroxide and 100 cc. of water. After having been stirred for 4 hr., the reaction mixture was washed with ether and was then made acidic with concentrated hydrochloric acid. The mixture was continuously extracted with ether for 30 hr., and the extract was dried over anhydrous sodium sulfate. Removal of the solvent gave an oil which was distilled to give 0.4 g. of a liquid (b. p. 162~175°C/0.6 mmHg). A mixture of this crude β-isopropyladipic acid (Va) and 0.05 g. of barium hydroxide hydrate was heated in a salt bath. When the mixture was heated at 200~260°C for 1/2 hr. and then at 260~300°C for 2 hr., a pale yellow liquid was collected which was directly converted into the semicarbazone with 0.24 g. of semicarbazide hydrochloride, 0.29 g. of sodium acetate and a small amount of water. The crystals which deposited were collected and recrystallized from ethanol to give fine needles (m. p. 186~187°C, $[\alpha]_D^{26}$ +65.2° (*c* 0.62 in ethanol)).

Found: C, 58.8; H, 9.2; N, 22.8. Calcd. for $C_9H_{17}ON$: C, 58.98; H, 9.35; N, 22.93%.

The authors are very grateful to Mr. Eiichi Togashi, Shiono Koryo Kaisha, for his generous gift of (+)-limonene, and to the Nitto Kasei Co. for its financial support.

This work was partilally supported by a grant-in-aid for fundamental scientific research from the Ministry of Education, to which the authors' thanks are due.

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