[CONTRIBUTION FROM THE INSTITUTE OF APPLIED MICROBIOLOGY, UNIVERSITY OF TOKYO]

The Structure of Alantolactone

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The position of the lactone ring in the alantolactones has been determined and it was found that the lactonic hydroxyl must be located at C_7. Some results pertaining to the stereochemistry of alantolactone are discussed.

Alantolactone is a sesquiterpene lactone isolated, together with isoalantolactone and dihydroisoalantolactone, from the roots of *Inula Helenium*. These three compounds on catalytic hydrogenation give the same tetrahydroalantolactone and must thus have identical carbon skeletons. The structures of these lactones were established about twenty-five years ago and were shown to be normal isoprenoids of the eudalene type and Ruzicka, *et al.*,[2] suggested formula I for alantolactone, which has the same skeleton as santonin. Attempts to correlate these lactones with santonin have been made recently by a number of workers,[3-5] but entirely without success.

In the course of our studies on the subject we have found that there are marked differences between the properties of tetrahydroalantolactone and desoxotetrahydrosantonin, which Ruzicka, *et al.*, assumed to be stereoisomers: *e.g.* (1) the glycol III produced by the action of lithium aluminum hydride on the former affords a dibenzoate, while that obtained from the latter gives only a monobenzoate.[5d] (2) The diketo carboxylic acid IV derived from 4-ketotetrahydroalantolactone showed none of the characteristic properties of β-diketones, that is, it gives no pyrazole derivative with hydrazine and no color reaction with ferric chloride.[5b] (3) The keto group in the keto carboxylic acid XIII obtained from tetrahydroalantolactone can be reduced readily over platinum catalyst,[5e] but that from desoxotetrahydrosantonin cannot.[6] (4) The diketo carboxylic acid V from santonin was not identical with the corresponding product from alantolactone.[5c] These facts led us to question the position of the lactone ring in alantolactone as suggested by Ruzicka.

Ruzicka, *et al.*, claimed to have obtained a keto carboxylic acid VI when crude alantolactone, containing dihydroisoalantolactone, was subjected to ozonolysis followed by further oxidation of the products with potassium permanganate.[2a] The formation of VI was the only evidence available at that time from which the position of the lactone ring could be deduced. The yield of keto acid, however, was extremely low; from 150 g. of the lactone they obtained only 2.4 g. of the semicarbazone of VI. Moreover, the material used (melting point 66–72°) was somewhat impure and it is doubtful whether the keto acid VI was indeed derived from alantolactone rather than from another substance present in alanto-oil. To settle this problem we have performed the following experiments and the results have enabled us to conclude that the lactonic hydroxyl is located at C_7 and alantolactone should therefore be represented by II and not I. Similarly isoalantolactone and dihydroisoalantolactone must contain the skeleton shown in II.

Tetrahydroalantolactone (VII) was converted to the methyl ester VIII of the corresponding hydroxy acid, tetrahydroalantolic acid. The ester is fairly unstable due to its tendency to relactonize to the starting lactone, and the material used in this study showed a melting point of 120–123° (Ukita, *et al.*, m.p. 124–127°[7a]; Hansen, m.p. 114°[8]). Oxidation of VIII with sodium dichromate in acetic acid afforded methyl 7-ketotetrahydroalantolate (IX), which was treated with methylmagnesium iodide to give 7-methyltetrahydroalantolactone (X) in a 44% yield. It is of interest to mention that in the presence of excess Grignard reagent, the yield of the expected glycol XI was only 1%. The structure of X is based on molecular composition, infrared spectrum (ν_{max} 1762 cm.$^{-1}$, γ-lactone), and on the fact that it was soluble in alkali but recovered unchanged after acidification. Reduction of X with lithium aluminum hydride yielded a glycol XII. Dehydrogenation of X with selenium afforded a hydrocarbon, which showed ultraviolet light absorption characteristic of substituted naphthalenes. Its picrate and styphnate melted at 102–103 and 149°, respectively. The infrared absorption spectrum of this hydrocarbon resembles closely that of 2,3,5-trimethylnaphthalene, and because the ring C–H out-of-plane bending vibrations are known to be highly characteristic[9] we have synthesized 2,5-dimethyl-3-ethylnaphthalene for comparison with the above hydrocarbon. The compound was synthesized by a method similar to Bradfield's for 2,5-dimethyl-3-isopropylnaphthalene.[10] *o*-Tolylacetyl chloride was condensed with ethylzinc iodide to give *o*-methylbenzyl ethyl ketone, which was converted, by condensation with ethyl α-bromopropionate, followed by dehydration and hydrogenation, to ethyl γ-*o*-tolyl-α-methyl-β-ethylbutyrate. Ring closure of

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(2) (a) L. Ruzicka and J. A. van Melsen, *Helv. Chim. Acta*, **14**, 397 (1931); (b) L. Ruzicka and P. Pieth, *ibid.*, **14**, 1090 (1931); (c) L. Ruzicka, P. Pieth, Th. Reichstein and L. Ehmann, *ibid.*, **16**, 268 (1933).

(3) Mme. C. Asselineau, Mme. S. Bory and E. Lederer, *Bull. soc. chim. France*, 1524 (1955).

(4) O. Kovàcs, V. Herout, M. Horak and F. Sorm, *Collection Czechoslov. Chem. Communs.*, **21**, 225 (1956).

(5) (a) H. Matsumura, I. Iwai and E. Ohki, *J. Pharm. Soc. Japan*, **74**, 738 (1954); (b) **74**, 1029 (1954); (c) **74**, 1206 (1954); (d) H. Matsumura, I. Iwai, E. Ohki and K. Kanzaki, *ibid.*, **75**, 689 (1955); (e) I. Iwai, E. Ohki and K. Kanzaki, *ibid.*, **76**, 1381 (1956).

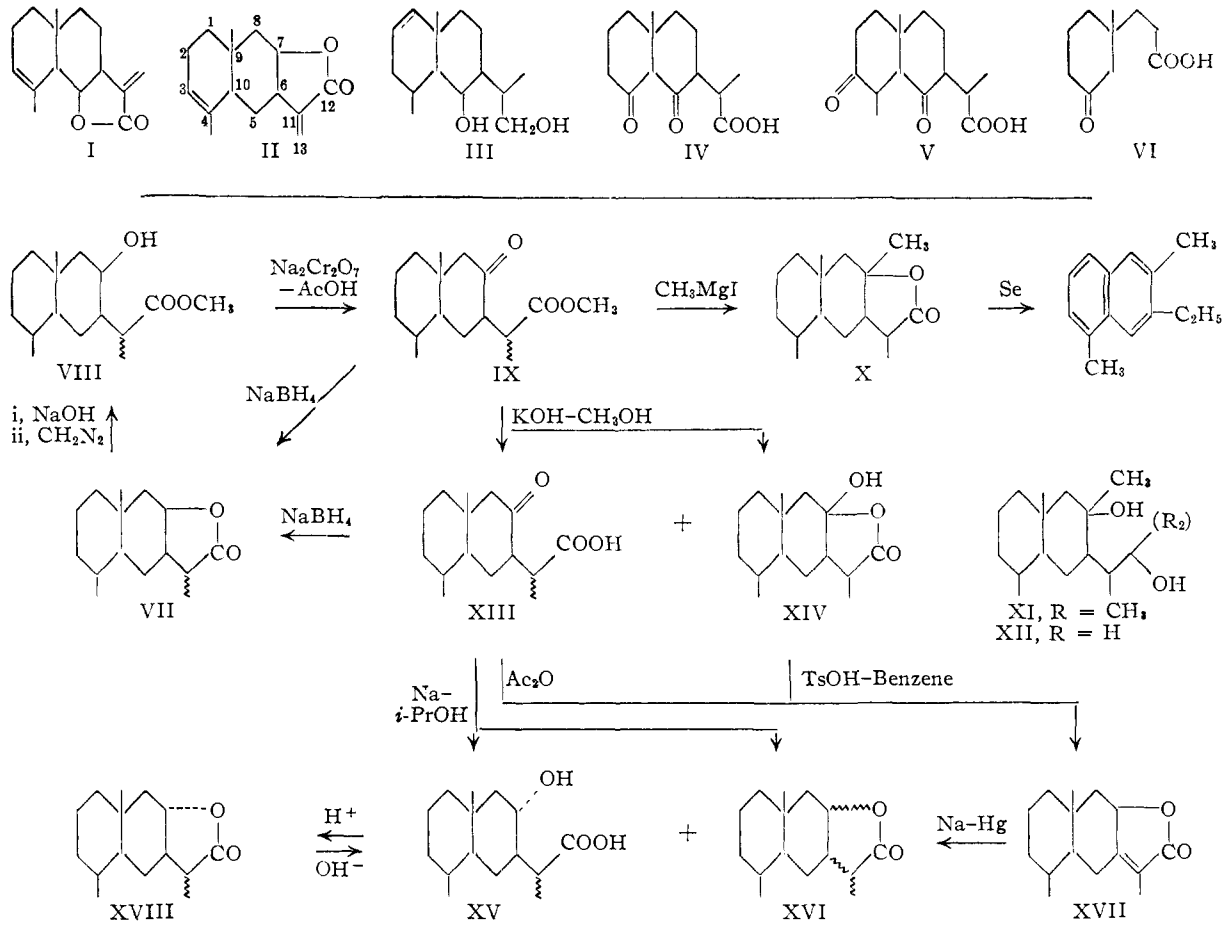
(6) A. Tahara, *J. Org. Chem.*, **21**, 442 (1956).

(7) (a) T. Ukita and S. Nakazawa, *Pharm. Bull.*, **2**, 299 (1954); (b) **2**, 239 (1954).

(8) K. F. W. Hansen, *Ber.*, **64**, 943 (1931).

(9) W. L. Mosby, THIS JOURNAL, **74**, 2564 (1952).

(10) A. E. Bradfield, B. H. Hegde, B. Sanjiva Rao, J. L. Simonsen and A. E. Gillam, *J. Chem. Soc.*, 667 (1936).



the ester with sulfuric acid gave 2,5-dimethyl-3-ethyl-1,2,3,4-tetral-1-one, which was reduced with lithium aluminum hydride to 2,5-dimethyl-3-ethyl-1,2,3,4-tetral-1-ol. The dimethylethyltetralol was dehydrogenated with selenium to 2,5-dimethyl-3-ethylnaphthalene, which was identical with that obtained from X as shown by complete identity of their infrared spectra and undepressed mixed melting points of the corresponding picrates and styphnates.

The following experiments have provided some information concerning the configuration of alantolactone. Alantolactone is probably a *trans*-decaline, since Ukita and Nakazawa[7b] have recently converted it to sesquibenihiol derivatives and the latter had previously been correlated with selinene by Katsura.[11] Both the keto ester IX[5e] and the keto acid XIII derived from IX by saponification give the original tetrahydroalantolactone on reduction with sodium borohydride. The stability of both IX and XIII to alkali indicate that the C_6-side chain is already in the more stable equatorial configuration. The carbonyl group at C_7 may be expected to be sterically more hindered than that at C_2 in A/B *trans*-fused steroids because of the space demanding C_6-propionic residue, and, indeed, it does not react with carbonyl reagents under the usual conditions. Such a carbonyl is known to afford predominantly an axial hydroxyl group when reduced with the relatively bulky sodium borohydride.[12] The observed reductions of both IX and XIII with this reducing reagent, together with the reported fact that the glycol III readily eliminates water to give an unsaturated primary alcohol,[4] seem to provide evidence for the axial configuration of the lactonic hydroxyl. The lactone ring in the alantolactones is thus *cis*-fused.

Reduction of XIII with sodium and isopropyl alcohol gave a hydroxy acid XV of m.p. 174° dec., in addition to a small amount of an isomeric tetrahydroalantolactone (XVI; m.p. 108–109°) identical with a product obtained previously by us from a butenolide XVII by reduction with sodium amalgam.[5b] On treatment with *p*-toluenesulfonic acid in benzene solution or with dilute acid, XV was converted to a new isomer of tetrahydroalantolactone (XVIII), m.p. 74–75°, which was hydrolyzed to XV by alkali. It is well known that such reductions afford predominantly equatorial hydroxyls and it seems very probable that the lactone ring fusion of this new isomer is *trans*.

The infrared absorption spectra of the three isomeric lactones mentioned above and of another one of m.p. 71°[8,13] were measured in Nujol mull, and strong bands in the region from 800 to 1400 cm.$^{-1}$ are shown at 963 and 1170 cm.$^{-1}$ (m.p. 147°), 958 and 1175 cm.$^{-1}$ (m.p. 71°), 998 and 1008 cm.$^{-1}$ (m.p. 75°), and 990 cm.$^{-1}$ (m.p. 109°).

(11) S. Katsura, *J. Chem. Soc. Japan*, **63**, 1465 (1942).

(12) W. G. Dauben, E. G. Bianz, Jr., J. Jin and R. A. Micheli, THIS JOURNAL, **78**, 3752 (1956).

(13) In view of the stereochemical course of reaction, this lactone might be assumed to be the C_{11}-epimer of that of m.p. 147°.

Kanzawa, *et al.*,[14] have reported recently that C_5–O axial *cis*-lactones in the santonin series give rise to two strong infrared bands near 960 and 1150 cm.$^{-1}$, while in the *trans*-lactones a strong band appears near 1030 cm.$^{-1}$. The above empirical rule applied to the alantolactone series, supports our views that the naturally occurring type of lactones belongs to the *cis*-series,[15] whereas the lactone of m.p. 75°, first obtained in our laboratory and possibly also that of m.p. 109°, are *trans*-lactones. The stereochemical relationships of the four lactones are now under further investigation.[16]

When the keto ester IX was saponified a small amount of a crystalline substance of m.p. 141–143° was also obtained, which was assumed from its infrared spectrum (ν_{max} 3390 and 1770 cm.$^{-1}$; OH and γ-lactone, respectively) to be 7-hydroxytetrahydroalantolactone (XIV). This hydroxylactone could be dehydrated readily to the known butenolide XVII on heating with *p*-toluenesulfonic acid in benzene solution or by treatment with phosphoryl chloride in pyridine.

Experimental[17]

Tetrahydroalantolactone (VII).—The crystalline lactone fraction from the extract of the finely powdered roots of *Inula Helenium* was hydrogenated over platinum catalyst in ethanol at 50°. The product thus obtained was recrystallized several times from 95% ethanol to give tetrahydroalantolactone, m.p. 142–143°, $[\alpha]^{25}D$ +11.5° (*c* 5, $CHCl_3$).[18]

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.20; H, 10.24. Found: C, 75.98; H, 10.15.

Methyl Tetrahydroalantolate (VIII).—A mixture of tetrahydroalantolactone (20 g.) and an aqueous sodium hydroxide solution (4%; 150 cc.) was heated on a steam-bath with stirring until all of the crystals had dissolved. The solution was cooled in ice, diluted with ether (150 cc.), and neutralized with an equivalent amount of dilute acetic acid with vigorous stirring. The ether layer was separated and treated immediately with an ethereal solution of diazomethane. The ester thus obtained was recrystallized from 95% ethanol; m.p. 120–123°. The analytical sample was produced by three recrystallizations of this material from 95% ethanol, colorless cubes of m.p. 122–124°, $[\alpha]^{25}D$ +16.1° (*c* 5, $CHCl_3$).

Anal. Calcd. for $C_{26}H_{28}O_3$: C, 71.60; H, 10.52. Found: C, 71.37; H, 10.42.

Methyl 7-Ketotetrahydroalantolate (IX).—To a solution of VIII (18 g.) in acetic acid (300 cc.) was added slowly a solution of sodium dichromate (9 g.) in acetic acid (200 cc.) at room temperature with stirring. After 1 hour, the excess reagent was decomposed with ethanol, and the solution was concentrated to about 100 cc. under reduced pressure, water added, and extracted with ether. The extract was washed well with 5% aqueous sodium bicarbonate solution and with water, dried, and the solvent was removed. The residue was distilled at 134–135° (0.05 mm.) to give methyl 7-ketotetrahydroalantolate, $n^{18}D$ 1.4941, $[\alpha]^{25}D$ −26° (*c* 5, $CHCl_3$).

Anal. Calcd. for $C_{16}H_{28}O_3$: C, 72.14; H, 9.84. Found: C, 72.38; H, 9.80.

7-Methyltetrahydroalantolactone (X).—A solution of the keto ester (13.3 g.) in dry ether (100 cc.) was added to a solution of methylmagnesium iodide (magnesium, 5 g.; methyl iodide, 36 g.; dry ether, 100 cc.) in ice.

After standing overnight at room temperature, the solution was refluxed for 2 hours. The excess reagent was decomposed with 10% aqueous acetic acid solution, the ether layer separated, washed with aqueous sodium bicarbonate solution and dried. Removal of the solvent and fractional recrystallization of the residue from *n*-hexane gave a glycol XI and 7-methyltetrahydroalantolactone (X), as the less and the more soluble parts, respectively.

The glycol was recrystallized from *n*-hexane to give silky colorless needles, m.p. 199–200°, yield 160 mg. (1%).

Anal. Calcd. for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13. Found: C, 76.16; H, 11.83.

7-Methyltetrahydroalantolactone was recrystallized from *n*-hexane to give colorless needles, m.p. 99–100°, $[\alpha]^{25}D$ −0.8° (*c* 5, $CHCl_3$), yield 6.2 g. (44%).

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.72; H, 10.54.

Reduction of X with lithium aluminum hydride in dry ether gave a glycol XII, which was recrystallized from petroleum ether (b.p. 60–80°) to give colorless needles, m.p. 157–158°.

Anal. Calcd. for $C_{16}H_{30}O_2$: C, 75.53; H, 11.89. Found: C, 75.20; H, 11.84.

Dehydrogenation of 7-Methyltetrahydroalantolactone (X).—Five grams of X was heated with selenium (10 g.) at 280–300° for 44 hours. The benzene extract of the reaction mixture was condensed to about 30 cc. and chromatographed roughly on alumina (20 g.) to remove the tarry product. From the benzene eluate a colorless oil was obtained by distilling twice over sodium, b.p. 117–118° (1 mm.), yield 1.34 g. (36%); λ_{max}^{EtOH} 230, 275, 285, 295, 318 mμ (log ε 4.83, 3.54, 3.59, 3.38, 2.35, respectively).

The picrate crystallized from methanol in orange-red needles, m.p. 102–103°; the styphnate was deposited from methanol in orange-yellow needles, m.p. 149°.

***o*-Methylbenzyl Ethyl Ketone.**—*o*-Tolylacetyl chloride, b.p. 108–109° (12 mm.), was prepared by the action of thionyl chloride on *o*-tolylacetic acid (m.p. 86–89°). A mixture of ethyl iodide (54.5 g.), ethyl acetate (9.6 g.) and toluene (19 g.) was cautiously heated with a zinc–copper couple (46 g.) in the presence of a catalytic amount of iodine[19] until the reaction began, thereafter heating was regulated to maintain gentle boiling for 15 minutes. The cooled solution of ethylzinc iodide thus prepared was decanted from the excess of the zinc–copper couple, and well cooled in a flask in ice, from which moisture was excluded. A mixture of *o*-tolylacetyl chloride (44 g.) and toluene (40 cc.) was slowly added (one drop/sec.) under mechanical stirring. After addition was completed the stirring was continued for another hour in ice, and then water (50 cc.) was added cautiously. The precipitate of zinc hydroxide was dissolved by adding dilute sulfuric acid (20%; 35 cc.). The product was extracted with ether, the extract washed with aqueous sodium bicarbonate solution, then with water, and dried. The solvent was removed, and distillation of the residue gave *o*-methylbenzyl ethyl ketone as a colorless oil, b.p. 121° (10 mm.), yield 41 g. (96.7%). The semicarbazone crystallized from ethanol in prismatic needles, m.p. 173–174°.

Anal. Calcd. for $C_{12}H_{17}ON_3$: C, 65.72; H, 7.81; N, 19.16. Found: C, 65.80; H, 7.75; N, 19.23.

Ethyl γ-*o*-Tolyl-α-methyl-β-ethylbutyrate.—A mixture of the ketone (45 g.), activated zinc (19 g.), ethyl α-bromopropionate (55 g.) and dry toluene (300 cc.) was heated on a sand-bath, the reaction being initiated by the addition of methylmagnesium iodide and iodine. After 10 hours the product was treated with ice and dilute hydrochloric acid, and the toluene solution was separated, washed with aqueous sodium bicarbonate solution, dried and evaporated. The

(14) T. Kanzawa, H. Kamio, M. Sumi and M. Nishikawa, Symposium on Infrared and Raman spectroscopy, at Osaka University (Oct. 15, 1956).

(15) Distinct absorption bands of the naturally occurring dihydroisoalantolactone also appear at 964 and 1170 cm.$^{-1}$.

(16) The 4-methyl group has been tentatively assigned to be β-methyl.[4]

(17) All melting points are uncorrected. Microanalyses were done by Misses T. Furukawa and H. Ohtsuka of the Takamine Research Laboratory, Sankyo Co., Ltd. Infrared spectra were measured on a Perkin–Elmer Model 21 double-beam recording spectrophotometer by Messrs. H. Shindo and O. Amakasu of the same laboratory.

(18) The m.p. and $[\alpha]D$ values are nearly the same as those reported by Ruzicka, *et al.*,[2b] (m.p. 141–141.5°, $[\alpha]D$ +11.05°), but lower than those recently reported by European workers (Mme. Asselineau, *et al.*,[3] m.p. 147–148°, $[\alpha]D$ +16°; Kovács, *et al.*,[4] m.p. 147–147.5 $[\alpha]D$ +14°). The infrared spectrum of our material, however, is in complete agreement with that of the French workers from 2 to 15 μ region. The difficulty we have encountered in raising its m.p. is probably due to small amounts of impurities such as stereoisomeric substances.

(19) *Cf.* F. L. Breusch and F. Baykut, *Ber.*, **86**, 684 (1953).

residue, b.p. 80–150° (1 mm.), was dehydrated by heating with potassium hydrogen sulfate (60 g.) for 2 hours at 195–200°. The product, without further purification, was reduced with hydrogen in the presence of Pd-C catalyst in alcoholic solution at 60°. After removal of the alcohol, ethyl γ-*o*-tolyl-α-methyl-β-ethylbutyrate distilled at 160–161° (12 mm.), yield 20 g. (43.5%, calcd. from the used ketone).

Anal. Calcd. for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.49; H, 9.43.

The fore-run, b.p. 110–130° (12 mm.), consisted mainly of the recovered ketone, the semicarbazone of which weighed 21 g.

2,5-Dimethyl-3-ethyl-1,2,3,4-tetral-1-one.—The above ester (20 g.) was heated on a water-bath with sulfuric acid (80%; 150 cc.) for 1 hour, then the mixture was poured into water. The oil was extracted with ether, the solvent was removed, and the residue was refluxed with an excess of alcoholic potassium hydroxide solution for 30 minutes. After addition of water, the ketone was again collected in ether, the solution dried, and the solvent removed: the ketone then had b.p. 169–170° (10 mm.), yield 13 g. (81%). The 2,4-dinitrophenylhydrazone crystallized from ethyl acetate in fine needles, m.p. 205–206°.

Anal. Calcd. for $C_{20}H_{22}O_4N_4$: C, 62.81; H, 5.80; N, 14.65. Found: C, 63.15; H, 5.70; N, 14.66.

2,5-Dimethyl-3-ethyl-1,2,3,4-tetral-1-ol.—A solution of the ketone (12 g.) in dry ether (30 cc.) was added to a stirred solution of lithium aluminum hydride (1.5 g.) in dry ether (50 cc.) at room temperature. After 1 hour, the excess of the reagent was decomposed with dilute hydrochloric acid. The ether layer was separated, washed with water, and dried. Evaporation of the solvent gave 2,5-dimethyl-3-ethyl-1,2,3,4-tetral-1-ol, which was recrystallized from petroleum ether (b.p. 60–80°) to colorless needles, m.p. 101–102°.

Anal. Calcd. for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.40; H, 9.90.

2,5-Dimethyl-3-ethylnaphthalene.—The above tetralol (10 g.) was heated with selenium (20 g.) at 280–290° for 10 hours. The hydrocarbon thus obtained distilled over sodium at 120–121° (1.5 mm.), $n^{15}D$ 1.5988, yield 9 g.

Anal. Calcd. for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.28; H, 8.54.

The picrate: orange-red needles, m.p. 102–103° (from methanol).

Anal. Calcd. for $C_{20}H_{19}O_7N_3$: C, 58.11; H, 4.63; N, 10.17. Found: C, 58.19; H, 4.55; N, 10.18.

The styphnate: orange-yellow needles, m.p. 149° (from methanol).

Anal. Calcd. for $C_{20}H_{19}O_8N_3$: C, 55.94; H, 4.46; N, 9.79. Found: C, 55.71; H, 4.42; N, 9.81.

The picrate and styphnate showed no depression on mixed melting with those from X. The infrared spectra of the hydrocarbons derived from both sources were completely superimposable.

Saponification of Methyl 7-Ketotetrahydroalantolate (IX).—The keto ester (9 g.) was refluxed with potassium hydroxide (2 g.) in methanol (50 cc.) for 1 hour. The solution was poured into water (200 cc.) and extracted with ether. The aqueous layer was acidified to congo red and extracted with ether. The extract was washed with water, dried and the solvent was removed. The residue (8.3 g.) was dissolved in *n*-hexane (30 cc.) and stored in an ice-box overnight. The deposited crystalline substance (0.92 g.) was recrystallized from aqueous ethanol to afford 7-hydroxytetrahydroalantolactone in colorless leaflets, m.p. 141–143°, $[\alpha]^{25}D$ +10.5° (*c* 2, $CHCl_3$).

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.48; H, 9.57.

7-Ketotetrahydroalantolic acid (XIII) obtained from the mother liquor was a glassy substance and attempts to crystallize it ended in failure. When reduced with sodium borohydride (0.4 g.) in 95% ethanol (60 cc.) at room temperature, XIII (1 g.) was converted to tetrahydroalantolactone (0.68 g.), which was recrystallized from 95% ethanol to colorless needles, m.p. 141–142°. This proved identical by mixed melting point with the authentic tetrahydroalantolactone (VII).

Dehydration of the Hydroxy Lactone (XIV).—(1) A solution of XIV (200 mg.), pyridine (5 cc.), and phosphoryl chloride (5 drops) was allowed to stand overnight. The product obtained after the usual treatment was chromatographed on alumina (Brockmann grade III) with petroleum ether and then recrystallized from *n*-hexane to give colorless needles, m.p. 111–112°, which proved identical by mixed melting point with the butenolide XVII previously obtained from the keto acid XIII on heating with acetic anhydride.[8b]

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.91; H, 9.27.

(2) A mixture of XIV (560 mg.), *p*-toluenesulfonic acid (500 mg.) and benzene (50 cc.) was refluxed for 30 minutes. The solution was washed with aqueous sodium bicarbonate solution, dried and the solvent removed. The residue was dissolved in *n*-hexane and stored in an ice-box to afford the butenolide, m.p. 111–112°.

Reduction of 7-Ketotetrahydroalantolic Acid (XIII).—To a boiling solution of XIII (2.4 g.) in isopropyl alcohol (300 cc.) was added sodium in small portions (total amount, 24 g.) over 30 minutes. After all the sodium had been added, the mixture was refluxed vigorously for 3 hours, and an amount of isopropyl alcohol sufficient to dissolve the remaining sodium, was added. After further refluxing for 30 minutes, the mixture was cooled and neutralized with aqueous acetic acid solution in ice. The solution was concentrated under reduced pressure to about 200 cc., and extracted several times with ether. The ether solution was extracted again with 5% aqueous potassium carbonate solution. The potassium carbonate solution was neutralized with acetic acid, the deposited isomeric tetrahydroalantolic acid (XV) collected, washed with water, and dried. It weighed 1.8 g. (75%), m.p. 165–167° dec. Recrystallization from 95% ethanol afforded colorless leaflets, m.p. 174° dec., $[\alpha]^{25}D$ +66.6° (*c* 1.5, 95% EtOH).

Anal. Calcd. for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C, 70.81; H, 10.14.

The methyl ester obtained by treating the acid with diazomethane crystallized from aqueous alcohol to colorless leaflets, m.p. 72°, $[\alpha]^{25}D$ +61.3° (*c* 1.5, $CHCl_3$).

Anal. Calcd. for $C_{16}H_{28}O_3$: C, 72.14; H, 9.84. Found: C, 72.03; H, 10.03.

The ether layer was washed with water, dried, and the solvent was removed. The residue (0.25 g.) was purified on a column of alumina (Brockmann grade III) with petroleum ether. Recrystallization from aqueous methanol gave colorless needles, m.p. 108–109°, which proved identical by mixed melting point and infrared spectrum with the previously reported isomeric tetrahydroalantolactone obtained from XVII on sodium amalgam reduction.[5b]

Isomeric Tetrahydroalantolactone (XVIII).—(1) The hydroxy acid (XV; 75 mg.) was warmed with 10% hydrochloric acid (8 cc.) and methanol (5 cc.) on a steam-bath for 10 minutes. The solution was poured into water and extracted with ether. The extract was washed with 2% aqueous potassium carbonate solution, water, and dried. After removal of solvent, the residue (70 mg.) was purified by chromatography with alumina (Brockmann grade III) and petroleum ether, and recrystallized from a small amount of *n*-hexane to colorless needles, m.p. 74–75°, $[\alpha]^{25}D$ −29.3° (*c* 2, $CHCl_3$).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.50; H, 10.71.

(2) A solution of the hydroxy acid (800 mg.), *p*-toluenesulfonic acid (80 mg.) and benzene (70 cc.) was refluxed for 30 minutes. After washing with 3% aqueous potassium carbonate solution and water, benzene was removed under reduced pressure. The residue (700 mg.) was purified as above. The isomeric tetrahydroalantolactone thus obtained had m.p. 74–75°.

The lactone (m.p. 74–75°; 100 mg.) was refluxed with 1% methanolic potassium hydroxide solution (20 cc.) for 30 minutes. After addition of water (100 cc.), the solution was neutralized with dilute acetic acid. The deposited acid was collected and recrystallized from aqueous ethanol to colorless leaflets, m.p. 174° dec., which was identical with the starting hydroxy acid by mixed melting point.

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