[Contribution from the Faculty of Pharmaceutical Sciences, University of Tokyo, and Department of Chemistry, National Institute of Health]

Santonin Analogs. IV. On the Structure of "Iso"-tetrahydroalantolactone[1]

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The structure of an isomeric tetrahydroalantolactone, "iso"-tetrahydroalantolactone, obtained by catalytic hydrogenation of dihydroalantoglycol which is derived from dihydroalantolactone, was investigated as to its relationship with ordinary tetrahydroalantolactone. A structure Ib′ having β-orientated hydrogen at C_{10}-position instead of the α-orientation in tetrahydroalantolactone, was proposed for this new isomeric lactone.

Recently Tsuda, *et al.*,[2] reported that the hydroxyl group of the lactonic linkage of alantolactone must be at the C_7-position instead of C_8 as formerly proposed by Ruzicka, *et al.*[3]

The results of conformational analysis of the tetrahydroalantolactone by Šorm, *et al.*,[4,5] Tanabe[6–8] and Cocker, *et al.*,[9] allow the assignment of structure Ib to tetrahydroalantolactone.

These investigations, however, were not concerned with the positions of the double bonds in the structures of the original alantolactone and isoalantolactone or their dihydro derivatives, dihydroalantolactone (Ia′) and dihydroisoalantolactone (Ia).

In the third paper of this series,[10] we reported an interesting difference between dihydroalantolactone and dihydroisoalantolactone in their behavior to catalytic hydrogenation. Thus with the consumption of one mole of hydrogen, dihydroisoalantolactone (Ia) quantitatively gives tetrahydroalantolactone (Ib); however, under similar reaction conditions dihydroalantolactone (Ia′) gives both Ib and a deoxy acid (II) by hydrogenolysis of the lactonic ring. The latter acid was identified as the saturated acid derived from "sesquibenihiol" formerly reported by Katsura.[11]

This paper deals with a further study of this interesting difference between the two dihydrolactones Ia and Ia′ as well as with a study of a new isomeric tetrahydroalantolactone derived from dihydroalantolactone.

Dihydroisoalantolactone is converted to a glycol (IIIa) by reduction with lithium aluminum hydride, and IIIa is reconverted to Ia with sodium dichromate in acetic acid. This reversibility shows that lithium aluminum hydride induces no steric change besides the reductive opening of the lactonic ring in IIIa.

Further, on hydrolysis with dilute alkali and subsequent methylation with diazomethane, Ia gave methyl dihydroisoalantolate (IVa) which is unstable and is transformed back to Ia on treatment with acid or standing at room temperature. Methyl dihydroisoalantolate (IVa) is oxidized with sodium dichromate to the oily methyl 7-ketodihydroisoalantolate (Va) and further converted to 7-ketodihydroisoalantolic acid (VIa) by alkaline hydrolysis. The latter was methylated again to Va.

Methyl 7-ketodihydroisoalantolate (Va) is reduced to glycol IIIa and dihydroisoalantolactone (Ia), respectively, by lithium aluminum hydride and sodium borohydride.

The observations in this series of reactions show that no steric change occurs during conversion of Va to VIa and that both compounds contain the isopropionic acid side chains in equatorial orientations. Thus the stereochemical relations at C_6, C_9, C_{10} and C_{11} are the same in Va and IIIa.

A similar series of reactions was performed on tetrahydroalantolactone (Ib), and the corresponding derivatives were obtained: glycol IIIb, methyl tetrahydroalantolate (IVb), methyl 7-ketotetrahydroalantolate (Vb) and 7-ketotetrahydroalantolic acid (VIb).

Catalytic hydrogenation of glycol IIIa and methyl 7-ketodihydroisoalantolate (Va) with platinum oxide in glacial acetic acid yields the respective saturated derivatives IIIb and Vb, belonging to the tetrahydroalantolactone (Ib) series.

The glycol IIIa′ obtained from dihydroalantolactone (Ia′) with lithium aluminum hydride was again convertible to starting material by chromic oxidation. However, the saturated glycol IIIb′ obtainable by catalytic reduction of the glycol IIIa′ with platinum oxide in glacial acetic acid is isomeric with the saturated glycol IIIb derived from tetrahydroalantolactone (Ib). Further, the saturated lactone Ib obtained from IIIb′ by chromic oxidation is isomeric, with tetrahydroalantolactone (Ib) and is convertible to IIIb′ by reduction with lithium aluminum hydride.

Methyl dihydroalantolate (IVa′) obtained by alkaline hydrolysis and subsequent methylation of Ia′ is also unstable, reverting to the original lactone. On chromic oxidation, IVa′ gave methyl 7-ketodihydroalantolate (Va′).

Unlike the similar ketonic acid VIa in the dihydroisoalantolactone series, a ketonic acid (VIa′) from hydrolysis of Va′ showed a maximum absorption at 240 mμ characteristic of a double bond conjugated with a carbonyl group. Further, on methylation, VIa′ no longer reverted to the starting methyl ester Va′ but gave a new isomeric ester Va″, which also showed similar absorption in the ultraviolet. Such absorption was never observed

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(1) Previous paper in this series, T. Ukita and S. Nakazawa, *Pharm. Bull.*, **2**, 299 (1954).

(2) K. Tsuda, K. Tanabe, I. Iwai and K. Funakoshi, This Journal, **79**, 1009 (1957).

(3) L. Ruzicka, P. Pieth, Th. Reichstein and L. Ehmann, *Helv. Chim. Acta*, **16**, 268 (1933).

(4) Ö. Kovács, V. Herout, M. Horák and F. Šorm, *Collection Czechoslov. Chem. Commun.*, **21**, 225 (1956).

(5) V. Benešová, V. Sýkora, V. Herout and F. Šorm, *Chemistry & Industry*, 363 (1958).

(6) K. Tsuda, K. Tanabe, I. Iwai and K. Funakoshi, This Journal, **79**, 5721 (1957).

(7) K. Tanabe, *Pharm. Bull.*, **6**, 214 (1958).

(8) K. Tanabe, *ibid.*, **6**, 218 (1958).

(9) W. Cocker and T. B. H. McMurry, *Proc. Chem. Soc.*, 147 (1958).

(10) T. Ukita and S. Nakazawa, *Pharm. Bull.*, **2**, 239 (1954).

(11) S. Katsura, *Nippon Kagaku Kaishi*, **63**, 1465 (1942).

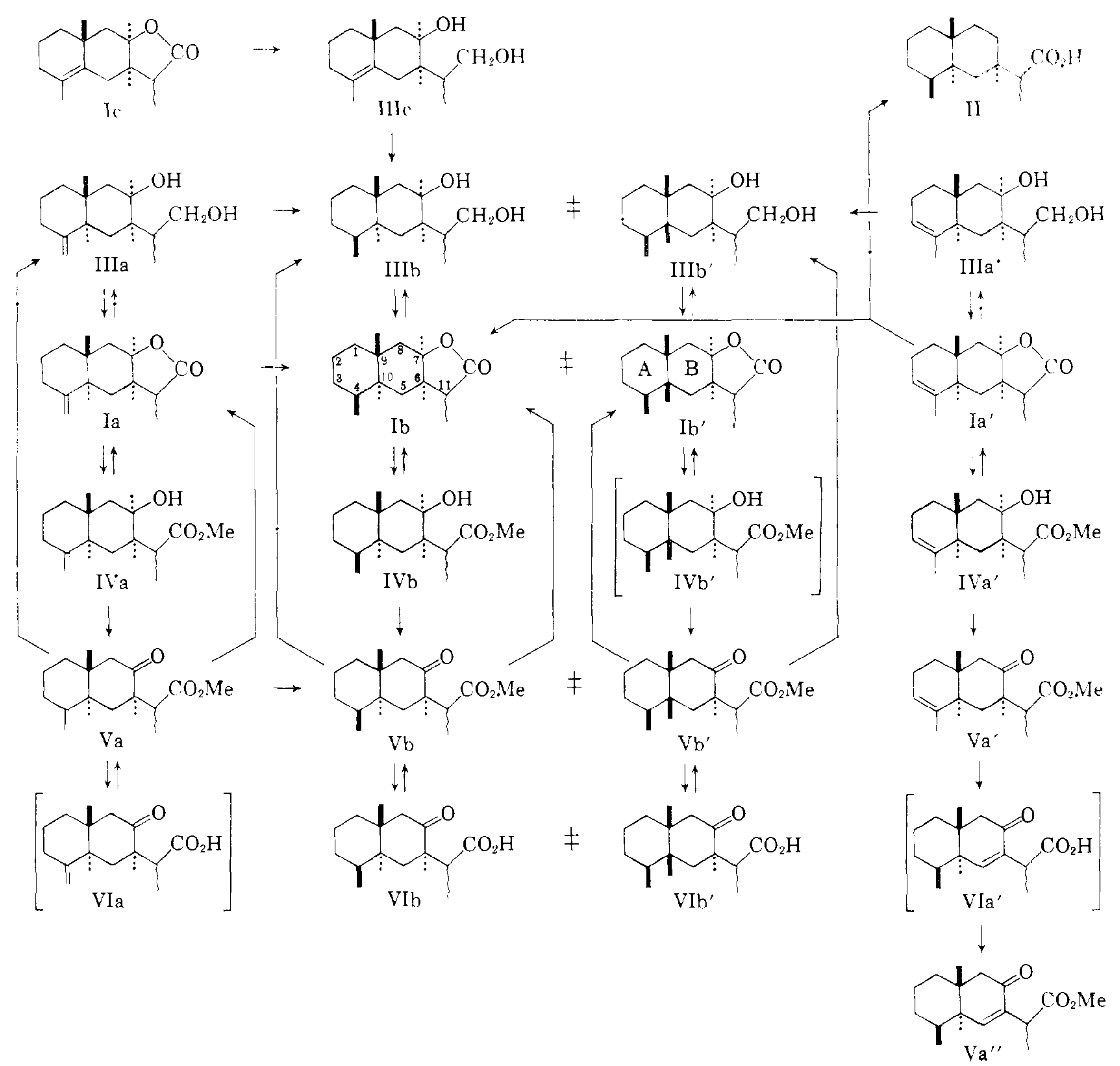

Chart.

for the parent methyl ester Va′. Thus the double bond originally contained in Va′ is assumed to migrate to the α,β-position of the carbonyl group on alkaline treatment.[12]

"Iso"-tetrahydroalantolactone (Ib′) behaved thoroughly analogously in a further series of reactions similar to those performed for tetrahydroalantolactone (Ib). Thus it gave methyl "iso"-tetrahydroalantolate (IVb′), methyl 7-keto-"iso"-tetrahydroalantolate (Vb′) and 7-keto-"iso"-tetrahydroalantolic acid (VIb′). However, these derivatives were again the isomers of the corresponding ones, IVb, Vb and VIb involved in the series of tetrahydroalantolactone (Ib).

The physical constants of these isomeric derivatives of tetrahydroalantolactone and "iso"-tetra-

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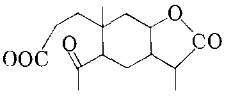
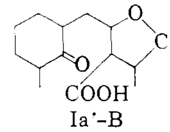
[12] These differences in the corresponding derivatives of dihydroalantolactone (Ia′) and dihydroisoalantolactone (Ia), *i.e.*, occurrence of isomeric tetrahydroglycols IIIb′ and IIIb from IIIa′ and IIIa, respectively, and the migration of the double bond on alkaline treatment of Va′ could be attributed to the difference in the positions of the double bond in the structure of Ia′ and Ia, as they give the same tetrahydroalantolactone by direct hydrogenation and further IIIa′ and IIIa are respectively convertible to Ia′ and Ia. As reported in the third paper of this series,[10] the constant melting points and specific rotations after repeated recrystallization of Ia and Ia′, reveal that these materials are not mixtures of isomers but pure individuals. Furthermore, the position of the double bonds in these materials was confirmed by the investigations of their ozonolysis products.

Especially, on ozonolysis, Ia′ gave a ketolactonic acid, $C_{15}H_{22}O_5$, (Ia′-A) as an only oxidation product. Although Ia′-A gave no crystalline condensation products with ketone reagents, *i.e.*, 2,4-dinitrophenylhydrazine or *p*-nitrophenylhydrazine, it gave both a positive iodoform reaction and a coloration with sodium nitroferricyanide and a methyl ester which gave three characteristic absorptions in the infrared corresponding to lactonic (1770 cm.$^{-1}$), carboxylic (1740 cm.$^{-1}$) and ketonic (1710 cm.$^{-1}$) carbonyl groups.

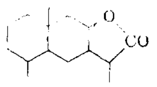
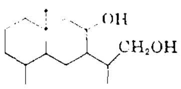
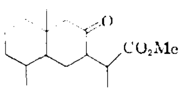
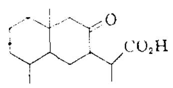

Ia′-A


Ia′-B

From these results, the ketolactonic acid should be represented with the alternative structure of Ia′-A or Ia′-B. However, the structure (Ia′-B) may be excluded by the fact that a ketohydroxylic acid obtained by alkaline hydrolysis of methyl ester of the ketolactonic acid did not show the properties of a β-hydroxylic acid, expected if the starting material had structure Ia′-B.

Thus the double bond involved in dihydroalantolactone (Ia′) must be located at the C_{3-4} instead of the C_{10-5} position.

TABLE I

Compounds Series				
Tetrahydroalantolactone	M.p. 141-143° $[\alpha]^{18}\mathrm{D}$ +15.0° $[M]\mathrm{D}$ +35	M.p. 111-113° $[\alpha]^{23}\mathrm{D}$ − 7.9° $[M]\mathrm{D}$ −19	B.p. 95°[a] $[\alpha]^{16}\mathrm{D}$ − 6.0° $[M]\mathrm{D}$ −16	M.p. 153-154° $[\alpha]^{16}\mathrm{D}$ +0.8° $[M]\mathrm{D}$ +2
"Iso"-tetrahydroalantolactone	M.p. 136-137° $[\alpha]^{18}\mathrm{D}$ +37.9° $[M]\mathrm{D}$ +90	M.p. 126-128° $[\alpha]^{23}\mathrm{D}$ +23.9° $[M]\mathrm{D}$ +57	B.p. 116°[b] $[\alpha]^{16}\mathrm{D}$ +34.1° $[M]\mathrm{D}$ +91	M.p. 118-119° $[\alpha]^{16}\mathrm{D}$ +41.9° $[M]\mathrm{D}$ +86

[a] At 0.05 *mm.* [b] At 0.1 *mm.*

hydroalantolactone series are summarized in Table I.

Similar to Ib, Ib′ showed infrared absorption at 1760 cm.$^{-1}$ specific for a *cis* fused lactone ring[13,14] and the reversibility between Vb′ and VIb′ reveals the equatorial position of the isopropionic acid side chain at the C_6-position of Vb′. These observations suggest axial substitution for the hydroxylic radical concerned with the lactone ring in Ib′.

These relations are entirely similar in the case between Vb and Ib, and no difference in the stereochemical sequences at C_6 and C_7 in both Ib and Ib′ is to be expected.

Further, because no configurational change at C_{11} during catalytic hydrogenation of IIIa′ to IIIb′ is expected, there is no steric difference at the C_{11}-positions of Ib and Ib′.

Tsuda and Tanabe[2] have reported two C_{11}-isomers of tetrahydroalantolactones (m.p. 108–109° and m.p. 74–75°) having *trans* fused lactone rings. One of the present authors has synthesized a C_4-isomer of tetrahydroalantolactone (Ib)[15] which was also reported by Iwai, *et al.*,[16] and Tanabe.[8]

None of these known isomers of tetrahydroalantolactone was identical with "iso"-tetrahydroalantolactone.

From the above evidence for "iso"-tetrahydroalantolactone Ib′ the only remaining difference between this new isomer and tetrahydroalantolactone (Ib) is the steric isomerism at the C_{10}-position, and thus it may be concluded that Ib′ has a *cis* fusion between rings A and B.

There are several instances in steroid chemistry in which 5β-steroids are more dextrorotatory than 5α-derivatives.[17] As shown in Table I all derivatives of "iso"-tetrahydroalantolactone are more dextrorotatory than the corresponding derivatives of tetrahydroalantolactone.

As a result of the above discussion and on the basis of the experimental observations, the authors propose structure Ib′ for "iso"-tetrahydroalantolactone.

As for the mechanism for the occurrence of Ib′, some migration of the double bond in dihydroalantolactone (Ia′) is assumed to occur prior to the hydrogenation of IIIa′ to IIIb′.

Another isomer of dihydroalanto glycol IIIc containing the double bond at its C_{4-10}-position, an isomer which will be reported in the following paper of this series, was catalytically hydrogenated under conditions similar to those used in the case of IIIa′. The product of this reaction, however, was tetrahydroalantolactone (Ib). This result is comparable to the hydrogenation of γ-eudesmol to dihydroeudesmol.[18]

Another possibility of obtaining the 10β-isomer of IIIb is hydrogenation of the dihydroalanto glycol containing a double bond at C_{10-5}. This will be the subject of further investigation.

Experimental[19]

Dihydroisoalantolactone (Ia) and Dihydroalantolactone (Ia′).—A mixture of dihydroisoalantolactone (Ia) and dihydroalantolactone (Ia′) (6 g.) obtained by the reduction of a mixture of alantolactone, isoalantolactone and dihydroisoalantolactone by aluminum amalgam,[20] was fractionally recrystallized from ethanol to obtain *ca.* 3.5 g. of dihydroisoalantolactone (Ia), m.p. 171–172°, $(\alpha)^{26}\mathrm{D}$ +44.1° (*c* 1.36, abs. ethanol), and 2 g. of dihydroalantolactone (Ia′), m.p. 133.5–134°, $(\alpha)^{26}\mathrm{D}$ −49.5° (*c* 2.5, abs. ethanol). On further recrystallization both materials showed each constant melting points and specific rotations.

Ketolactonic Acid (Ia′-A) Obtained from Dihydroalantolactone (Ia′).—Compound Ia′ (2 g.) was ozonized in 30 ml. of chloroform, and the sirupy ozonide obtained after removal of the solvent was decomposed with 10 ml. of water and distilled with steam. The residue was extracted with ether and the ether-soluble product was extracted with 5% sodium bicarbonate solution to separate it into acidic (0.7 g.) and neutral (1.3 g.) products. The acidic product solidified to a crystalline mass which was recrystallized from ethyl acetate to colorless prisms, m.p. 193–195°. *Anal.* Calcd. for $C_{15}H_{22}O_5$: C, 63.83; H, 7.80; COOH, 15.96. Found: C, 63.48; H, 7.52; COOH, 15.72 (monobasic acid).

After mild oxidation of the neutral fraction with potassium permanganate, the acidic product obtained (0.8 g.) was methylated with diazomethane to furnish colorless crystals with m.p. 128–130°, $(\alpha)^{17}\mathrm{D}$ +175.8° (*c*, 0.99 ethanol); $\nu_{\max}^{\mathrm{CHCl_3}}$ 1770 (lactonic-carbonyl), 1740 (carboxylic carbonyl) and 1710 cm.$^{-1}$ (ketonic carbonyl). *Anal.* Calcd. for $C_{16}H_{24}O_5$: C, 64.86; H, 8.10. Found: C, 65.14; H, 7.87.

On alkaline hydrolysis, the methyl ester gave the same ketolactonic acid Ia′-A in the theoretical yield. Both this acid and the methyl ester furnished no crystalline 2,4-dinitrophenylhydrazone or *p*-nitrophenylhydrazone by the usual method, but they gave a positive iodoform reaction and sodium nitroferricyanide coloration.

Reduction of Dihydroisoalantolactone (Ia), Tetrahydroalantolactone (Ib), Dihydroalantolactone (Ia′) and "Iso"-tetrahydroalantolactone (Ib′) with Lithium Aluminum Hydride to Dihydroisoalanto Glycol (IIIa), Tetrahydroalanto Glycol (IIIb), Dihydroalanto Glycol (IIIa′) and

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(13) J. H. Brewster and C. H. Kucera, THIS JOURNAL, **77**, 4564 (1955).

(14) T. Kanzawa, H. Kamio, M. Sumi and M. Nishikawa, *ibid.*, **80**, 3705 (1958).

(15) S. Nakazawa, THIS JOURNAL, **82**, 2229 (1960).

(16) H. Matsumura, I. Iwai and E. Ohki, *Yakugaku Zasshi*, **74**, 738 (1954).

(17) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 1949, p. 211.

(18) F. J. McQuillin and J. D. Parrack, *J. Chem. Soc.*, 2973 (1956).

(19) All melting points are uncorrected.

(20) T. Ukita, R. Matsuda and S. Nakazawa, *Yakugaku Zasshi*, **72**, 796 (1952).

TABLE II

Products	Crystals, colorless	M.p., °C.	Formula	Calcd. C	Calcd. H	Found C	Found H	$[\alpha]^t_{\text{D}}$ (*c* 2.5, EtOH), *t*, °C.
IIIa	Prisms	129–131	$C_{15}H_{26}O_2$	75.63	10.92	76.08	10.97	+46.0 (16)
IIIb	Needles	111–113	$C_{15}H_{28}O_2$	75.00	11.66	75.05	11.50	− 7.9 (23)
IIIa′	Cubelets	83–85	$C_{15}H_{26}O_2$	75.63	10.92	75.43	10.98	+30.8 (24)
IIIb′	Prisms	126–128	Identified with IIIb′ obtained in the next experiment.					

"Iso"-tetrahydroalanto Glycol (IIIb′), Respectively.—A solution of 1 g. of Ia in 100 ml. of ether was added dropwise to a solution of 0.4 g. of lithium aluminum hydride in 70 ml. of ether at room temperature under stirring. After additional stirring for 2 hours at the same temperature the mixture was treated in the usual manner to yield 1.01 g. of crude product IIIa. Also 0.5 g. of Ib, 3 g. of Ia′ and 0.12 g. of Ib′ were reduced with the same reagent as in the case of Ia to give the corresponding product IIIb, IIIa′ and IIIb′ in the theoretical yields. These crude products were recrystallized from petroleum ether to pure compounds having the properties given in Table II.

Catalytic Hydrogenation of Dihydroalanto Glycol (IIIa′) to "Iso"-tetrahydroalanto Glycol (IIIb′).—A solution of 2.0 g. of dihydroalanto glycol (IIIa′) in 20 ml. of glacial acetic acid was reduced catalytically with active platinum prepared from 0.50 g. of Adams platinum oxide in 20 ml. of same solvent. After consumption of 243 ml. of hydrogen in 5 hours, at 22°, 761 mm. (calcd. for one mole, 209 ml.), the mixture was treated in the usual manner to obtain 1.95 g. of crystalline product. Recrystallization from petroleum ether gave colorless prisms of IIIb′, m.p. 126–128°, $(\alpha)^{23}_{\text{D}}$ +23.9° (*c* 2.5, ethanol). *Anal.* Calcd. for $C_{15}H_{28}O_2$: C, 75.00; H, 11.66. Found: C, 74.80; H, 12.04. On admixture of this glycol (IIIb′) with tetrahydroalanto glycol (IIIb) a depression of the melting point (90–97°) was observed.

Oxidation of Dihydroisoalanto Glycol (IIIa), Tetrahydroalanto Glycol (IIIb), Dihydroalanto Glycol (IIIa′) and "Iso"-tetrahydroalanto Glycol (IIIb′) to Dihydroisoalantolactone (Ia), Tetrahydroalantolactone (Ib), Dihydroalantolactone (Ia′) and "Iso"-tetrahydroalantolactone (Ib′), Respectively.—To solutions of 0.12 g. of IIIa, IIIb and IIIa′ or 1.35 g. of IIIb′ in 10 ml. or 100 ml. of glacial acetic acid was added dropwise a solution of 0.1 or 1.13 g. of sodium dichromate in 5 or 50 ml. of the same solvent under stirring at room temperature. Stirring was continued at the same temperature for 2 hours and the mixture was treated as usual to give the theoretical yields of crude crystalline products. In the cases of the oxidation of IIIa, IIIb and IIIa′, the products were recrystallized from ethanol to give colorless needles m.p. 171–173° Ia, m.p. 141–143° Ib, m.p. 128–130° Ia′, which were, respectively, identified with dihydroisoalantolactone, tetrahydroalantolactone and dihydroalantolactone.

The oxidation product of IIIb′ was recrystallized from petroleum ether and ethanol to colorless needles of m.p. 136–137°, $(\alpha)^{20}_{\text{D}}$ + 37.9° (*c* 2.5, ethanol), $\nu^{\text{CHCl}_3}_{\text{max}}$ 1760 cm.$^{-1}$ (*cis* fused lactone). *Anal.* Calcd. for $C_{15}H_{24}O_2$: C, 76.27; H, 10.17. Found: C, 75.97; H, 10.17. Admixture of this lactone Ib′ with tetrahydroalantolactone (Ib) gave a depression of melting point (103–109°).

Hydrolysis and Methylation of Dihydroisoalantolactone (Ia), Tetrahydroalantolactone (Ib) and Dihydroalantolactone (Ia′) to Methyl Dihydroisoalantolate (IVa), Methyl Tetrahydroalantolate (IVb) and Methyl Dihydroalantolate (IVa′), Respectively.—To ethanolic solutions of 1 g. of Ia, Ib or Ia′ was added a slight excess of 5% sodium hydroxide solution and the mixtures were refluxed on a water-bath for 2 hours. After removal of ethanol by distillation and addition of 30 ml. of water, the cooled mixtures were neutralized with 50% acetic acid under ice cooling. The oily products were extracted with ether and the ethereal solutions were methylated with diazomethane to obtain the crude esters in the theoretical yield. Recrystallization from petroleum ether gave products with the properties given in Table III. These esters reverted to the respective starting lactones on standing at room temperature.

Oxidation of Methyl Dihydroisoalantolate (IVa), Methyl Tetrahydroalantolate (IVb), Methyl Dihydroalantolate (IVa′) to Methyl 7-Ketodihydroisoalantolate (Va), Methyl 7-Ketotetrahydroalantolate (Vb) and Methyl 7-Ketodihydroalantolate (Va′), Respectively.—To a solution of 1.5 g. of IVa in 40 ml. of glacial acetic acid was added dropwise a solution of 0.57 g. of sodium dichromate in 5 ml. of the same solvent at room temperature with stirring. After 2 hours additional stirring at the same temperature, the mixture was treated in the usual manner to furnish 1.5 g. of colorless oily product. This was purified by distillation; Va, b.p. 95–97° (0.05 mm.). *Anal.* Calcd. for $C_{16}H_{24}O_3$: C, 72.73; H, 9.09. Found: C, 72.80; H, 8.88. Each 0.5 g. of IVb and 5.9 g. of IVa′ was likewise oxidized with sodium dichromate to obtain the respective products Vb and Va′.

TABLE III

Products	Crystals, colorless	M.p., °C.	Formula	Analyses, % Calcd. C	Analyses, % Calcd. H	Analyses, % Found C	Analyses, % Found H
IVa	Cubelets	103–106	$C_{16}H_{26}O_3$	72.18	9.77	72.50	9.59
IVb	Needles	124–127	$C_{16}H_{28}O_3$	71.64	10.45	71.78	10.26
IVa′	Needles	103–105	$C_{16}H_{26}O_3$	72.18	9.77	72.41	9.53

Compound Vb: colorless oil, b.p. 95° (0.05 mm.) $[\alpha]^{16}_{\text{D}}$ −6.0° (*c* 2.5, ethanol). *Anal.* Calcd. for $C_{16}H_{26}O_3$: C, 72.18; H, 9.77. Found: C, 72.49; H, 9.72.

Its 2,4-dinitrophenylhydrazone; pale yellow needles (from ethyl acetate–petroleum ether), m.p. 118–120° dec. *Anal.* Calcd. for $C_{22}H_{30}O_6N_4$: C, 59.19; H, 6.73; N, 12.56. Found: C, 59.37; H, 6.43; N, 12.15.

Compound Va′: b.p. 110–112° (0.08 mm.) $[\alpha]^{20}_{\text{D}}$ −46.9° (*c* 2.6, ethanol). *Anal.* Calcd. for $C_{16}H_{24}O_3$: C, 72.73; H, 9.09. Found: C, 73.11; H, 8.81.

Its 2,4-dinitrophenylhydrazone: pale yellow needles (from ethyl acetate–petroleum ether), m.p. 188–190° dec. *Anal.* Calcd. for $C_{22}H_{28}O_6N_4$: C, 59.46; H, 6.31; N, 12.61. Found: C, 59.40; H, 6.40; N, 12.84.

Successive Hydrolysis, Methylation and Oxidation of "Iso"-tetrahydroalantolactone (Ib′) to Methyl 7-Keto-"iso"-tetrahydroalantolate (Vb′).—To 1.3 g. of "iso"-tetrahydroalantolactone (Ib′) dissolved in 15 ml. of ethanol was added 30 ml. of 5% sodium hydroxide solution, the mixture was refluxed on a water-bath for 2 hours, and the solvent was removed by distillation. The hydrolysate was methylated with diazomethane and the methyl ester was oxidized as described in the case of IVa to Va to give 1.27 g. of oily ester. This product was purified by distillation to give a colorless oily product Vb′, b.p. 115–116°, (0.1 mm.) $(\alpha)^{16}_{\text{D}}$ + 34.1° (*c* 2.5, ethanol). *Anal.* Calcd. for $C_{16}H_{26}O_3$: C, 72.18; H, 9.77. Found: C, 72.44; H, 9.66.

Hydrolysis of Methyl 7-Ketodihydroisoalantolate (Va) to 7-Ketodihydroisoalantolic Acid (VIa) and Methylation of the Latter to Va.—To 1.72 g. of methyl 7-ketodihydroisoalantolate (Va) dissolved in 5 ml. of ethanol was added 10 ml. of 5% sodium hydroxide solution. The mixture was refluxed on a water-bath for 2 hours, then treated in the usual manner to yield 1.55 g. of crude acidic product. As this product was difficult to recrystallize, it was methylated directly with diazomethane to give 1.60 g. of crude ester which was purified by distillation to a colorless oily product Va, b.p. 95–96° (0.05 mm.).

Hydrolysis of Methyl 7-Ketotetrahydroalantolate (Vb) and Methyl 7-Keto-"iso"-tetrahydroalantolate (Vb′) to 7-Ketotetrahydroalantolic Acid (VIb) and 7-Keto-"iso"-tetrahydroalantolic Acid (VIb′), Respectively.—To solutions of 0.54 g. of Vb and 0.77 g. of Vb′ dissolved in 10 ml. of ethanol was added 10 ml. of 5% sodium hydroxide solution. The mixtures were refluxed on a water-bath for 2 hours. The hydrolysates were treated as usual to give products VIb and VIb′ in yields of 0.5 and 0.7 g., respectively.

Compound VIb: recrystallized from aqueous methanol to colorless scales, m.p. 153–154°, $[\alpha]^{16}_{\text{D}}$ + 0.8° (*c* 2.5, ethanol). *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.43; H, 9.52; COOH, 17.86. Found: C, 71.42; H, 9.39; COOH, 18.15.

Its 2,4-dinitrophenylhydrazone: pale yellow needles (from ethyl acetate), m.p. 210–212° dec. *Anal.* Calcd. for $C_{21}H_{28}O_6N_4$: C, 58.33; H, 6.48; N, 12.96. Found: C, 57.91; H, 6.76: N, 12.80.

Compound VIb′: recrystallized from aqueous methanol to colorless prisms, m.p. 118–119°, $[\alpha]^{16}_{\text{D}}$ +41.9° (*c* 2.5, ethanol). Admixture of VIb′ with VIb showed a depression of melting point (102–106°). *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.43; H, 9.52; COOH, 17.86. Found: C, 71.44; H, 9.22; COOH, 17.81.

Methylation of 7-Ketotetrahydroalantolic Acid (VIb) and 7-Keto-"iso"-tetrahydroalantolic Acid (VIb′) to Methyl 7-Ketotetrahydroalantolate (Vb) and Methyl 7-Keto-"iso"-tetrahydroalantolate (Vb′), Respectively.—Portions of 0.25 g. of VIb and VIb′ were methylated with diazomethane in the usual manner, and the methyl esters obtained were identified with Vb and Vb′, respectively.

Hydrolysis and Methylation of Methyl 7-Ketodihydroalantolate (Va′) to the Isomeric Methyl 7-Ketodihydroalantolate (Va″).—To 5 g. of methyl 7-ketodihydroalantolate (Va′) dissolved in 10 ml. of ethanol was added 25 ml. of 5% sodium hydroxide solution. The mixture was refluxed on a water-bath for 2 hours, 4 g. of VIa′ was obtained from the hydrolysate by the usual isolation procedure. It was methylated directly with diazomethane to obtain 3.80 g. of oily product. This was purified by distillation to a colorless oil (Va″), b.p. 119–120° (0.02 mm.), $[\alpha]^{20}D$ +20.6° (*c* 2.6, ethanol), λ_{max}^{EtOH} 240 mμ (log ε 3.63). *Anal.* Calcd. for $C_{16}H_{24}O_3$: C, 72.73; H, 9.09. Found: C, 73.16; H, 9.21.

Reduction of Methyl 7-Ketodihydroisoalantolate (Va), Methyl 7-Ketotetrahydroalantolate (Vb) and Methyl 7-Keto-"iso"-tetrahydroalantolate (Vb′) with Sodium Borohydride to Dihydroisoalantolactone (Ia), Tetrahydroalantolactone (Ib) and "Iso"-tetrahydroalantolactone (Ib′), Respectively.—To solutions of 0.26 g. of Va, Vb or Vb′ in 10 ml. of methanol was added dropwise a solution of 0.03 g. of sodium borohydride in 10 ml. of the same solvent at room temperature with stirring. Stirring was continued at the same temperature for 3 hours, and the mixtures were neutralized with dilute hydrochloric acid. After evaporation of solvent under reduced pressure, 20 ml. of water was added to each residue. The mixtures were extracted with ether, and recrystallized from ethanol: the product from Va, colorless needles with m.p. 171–173°; that from Vb, colorless needles, m.p. 141–143°; and that from Vb′, colorless needles, m.p. 136–137°, were identified with Ia, Ib and Ib′, respectively.

Reduction of Methyl 7-Ketodihydroisoalantolate (Va), Methyl 7-Ketotetrahydroalantolate (Vb) and Methyl 7-Keto-"iso"-tetrahydroalantolate (Vb′) with Lithium Aluminum Hydride to Dihydroisoalanto Glycol (IIIa), Tetrahydroalanto Glycol (IIIb) and "Iso"-tetrahydroalanto Glycol (IIIb′), Respectively.—(a) A solution of 0.2 g. of Va in 50 ml. of ether was added dropwise to a solution of 0.1 g. of lithium aluminum hydride in 50 ml. of ether at room temperature with stirring. Stirring was continued for an additional 2 hours at the same temperature and the mixture was treated as usual to give 0.21 g. of crystalline product. Recrystallization from petroleum ether gave colorless prisms, m.p. 129–131°, which were identified with dihydroisoalanto glycol (IIIa).

Similar reductions were performed on 0.26 g. of Vb and 0.13 g. of Vb′ and the products from Vb, colorless silky needles, were recrystallized from petroleum ether, m.p. 111–113°; the product from Vb′, colorless prisms, was recrystallized from the same solvent, *m.p.* 126–128°; these were respectively identified with tetrahydroalanto glycol IIIb and "iso"-tetrahydroalanto glycol (IIIb′).

(b) The esters Va, Vb and Vb′ obtained by remethylations of the free acids were reduced as in (a) and the resulting glycols were identified with IIIa, IIIb and IIIb′, respectively.

Catalytic Hydrogenation of Dihydroisoalanto Glycol (IIIa) to Tetrahydroalanto Glycol (IIIb).—Dihydroisoalanto glycol (IIIa) (0.24 g.) was hydrogenated catalytically over 0.12 g. of Adams platinum oxide; 29 ml. of hydrogen was consumed in 2 hours, at 23.5° (757.3 mm.) (calcd. for one mole, 25.3 ml.). After removal of the catalyst by filtration, and processing as usual, 0.24 g. of crude crystals was obtained. Recrystallization from petroleum ether gave colorless silky needles, m.p. 111–113°, identified with tetrahydroalanto glycol IIIb.

Catalytic Hydrogenation of Methyl 7-Ketodihydroisoalantolate (Va) to Methyl 7-Ketotetrahydroalantolate (Vb).—A solution of 0.36 g. of methyl 7-ketodihydroisoalantolate (Va) was hydrogenated catalytically with platinum in glacial acetic acid as described above. A total of 42.0 ml. of hydrogen was consumed in 2 hours, at 26° (758.3 mm.) (calcd. for one mole, 34.5 ml.). The mixture was treated in the usual manner yielding 0.33 g. of oily product, b.p. 100–103° (0.01 mm.); 2,4-dinitrophenylhydrazone, pale yellow needles (from ethyl acetate–petroleum ether), m.p. 118–120° dec. The 2,4-dinitrophenylhydrazone was identified with that from methyl 7-ketotetrahydroalantolate (Vb).

Reduction of Isomeric Dihydroalantolactone (Ic) with Lithium Aluminum Hydride to Isomeric Dihydroalanto Glycol (IIIc).—A solution of 0.12 g. of isomeric dihydroalantolactone (Ic) in 20 ml. of ether was added dropwise to 0.04 g. of lithium aluminum hydride in 20 ml. of ether at room temperature with stirring. After 2 additional hours stirring at room temperature, the mixture was treated in the usual manner to give 0.1 g. of crystalline product. This was recrystallized from petroleum ether to colorless prisms (IIIc), m.p. 127–130°. *Anal.* Calcd. for $C_{15}H_{26}O_2$: C, 75.63; H, 10.92. Found: C, 75.34; H, 10.80.

Catalytic Hydrogenation of Isomeric Dihydroalanto Glycol (IIIc) to Tetrahydroalanto Glycol (IIIb).—A solution of 0.1 g. of isomeric dihydroalanto glycol (IIIc) in 10 ml. of glacial acetic acid was reduced catalytically with 0.12 g. of Adams platinum oxide in 10 ml. of same solvent. After consumption of 12.5 ml. of hydrogen in 5 hours, at 29° (757 mm.) (calcd. for one mole, 10.9 ml.), the mixture was treated in the usual manner to yield 0.1 g. of crystalline product. Recrystallization from petroleum ether gave colorless silky needles, m.p. 111–113°, identified with tetrahydroalanto glycol (IIIb).

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