ether, yielding short pillars, m.p. 62°. This substance is optically inactive, and when admixed with the above *dl*-*O,O*-dimethyl-*N*-methylcoclaurine (III), m.p. 62°, no melting point depression was observed.

***dl*-*N*-Methylcoclaurine (*dl*-1-(4'-hydroxybenzyl)-6-methoxy-7-hydroxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline) (IV).**

By a method similar to that employed in the previous paper³⁾, coclaurine (I) was treated with formalin and formic acid, and the resultant product was purified through its oxalate, colorless slender needles, m.p. 122~123°. The free base, colorless prisms, m.p. 161~162°, $[\alpha]_D^{25} = \pm 0^\circ$. *Anal.* Calcd. for $C_{16}H_{15}O_2(OCH_3)(NCH_3)$: C, 72.21; H, 7.07; OCH_3 , 10.37; NCH_3 , 5.01. Found: C, 71.92; H, 6.95; OCH_3 , 10.44; NCH_3 , 4.37.

Methylation of *dl*-*N*-Methylcoclaurine (IV) with Diazomethane.

N-Methylcoclaurine (IV) was methylated by the same method as that employed in the case of the above *O,O*-dimethylcoclaurine, and the residue left after removal of ether was purified as the oxalate, which was then liberated by diluted sodium hydroxide solution. The product was recrystallized from a mixture of ether and petroleum ether to colorless short pillars, m.p. 62° (sint. 58°). On admixture with *dl*-*O,O*-dimethyl-*N*-methylcoclaurine (III), derived from the above *O,O*-dimethylcoclaurine, it showed no melting point depression.

Summary

The authors have prepared *dl*-*O,O*-dimethylcoclaurine (II) and *dl*-*O,O*-dimethyl-*N*-methylcoclaurine, viz., *dl*-1-(4'-methoxybenzyl)-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (III), starting with natural *dl*-coclaurine (I), and some comments have been made on their data. From these results, it has been clarified that the *d*-, *l*- and *dl*-form of the substance (III) all show the same melting point of 62°.

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232. Tyunosin Ukita, Reiko Matsuda and Satoshi Nakazawa: On the Santonin Analogs. I. Synthesis of 1,2-Dihydroxytetrahydro-alantolactone from Dihydro-alantolactone.

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The bicyclic sesquiterpene lactones obtainable from the rhizome of *Inula Helenium* have been studied from the chemical structural point of view by many authors, especially closely by Ruzicka, et al.^{1~3)}, Hansen^{4~7)}, and Bredt and Posth⁸⁾.

In spite of the great difficulty of separating and purifying these lactones because of their structural resemblances, Ruzicka, et al.²⁾ separated them after 300 times' repeated fractional recrystallization into three components, alantolactone, $C_{15}H_{20}O_2$, m.p. 71°, isoalantolactone, $C_{15}H_{20}O_2$, m.p. 110°, and dihydro-isoalantolactone, $C_{15}H_{22}O_2$, m.p. 168°, $[\alpha]_D^{25} = +72.0^\circ$, and assigned the structures (I), (II) and (III) respectively to them.

After recrystallizing them further 700 times, Ruzicka, et al.³⁾ found that the melting points of both (I) and (II) rose a little higher, so that he entertained a doubt

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3) L. Ruzicka, P. Pieth, Th. Reichstein, L. Ehmann: *Ibid.*, **16**, 268 (1933).

4) Karl Fr. W. Hansen: *Ber.*, **64**, 67 (1931).

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6) Karl Fr. W. Hansen: *Ibid.*, **64**, 1904 (1931).

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as to the purities of these lactones and their stability during recrystallization.

From the properties of degradation products of these lactones, however, it seems certain that their main components were of the structures shown by (I) and (II), respectively.

It was reported that reduction of (I) by sodium amalgam, and of (II) by sodium ethoxide, yielded dihydro-alantolactone (IV)⁸⁾, m.p. 123°, and dihydro-isoalantolactone (III)⁹⁾, m.p. 168°, respectively, and also that both (IV) and (III) absorbed one mole of hydrogen by catalytic reduction to yield the same tetrahydro-alantolactone (VI), m.p. 139~140°, $[\alpha]_D^{25} = +15.2^{\circ 1)}$.

Further, an attempt to obtain dihydro-alantolactone by catalytic hydrogenation of alantolactone was made by Ruzicka¹⁾, but as to the product obtained, m.p. 129~130°, $[\alpha]_D = -24.6^{\circ}$, he reserved final confirmation of its purity, because he could obtain only a mixture of tetrahydro-alantolactone and dihydro-isoalantolactone from isalantolactone by the similar procedure.

Through these communications, the physical constants of alantolactone and dihydro-alantolactone are very obscure, in contrast to those of isalantolactone and dihydro-isoalantolactone, and this is probably due to the difficulty of completely separating alantolactone from other compounds because of its lowest melting point, and due to the fact that the melting point of dihydro-alantolactone was also the lowest among those of many reduction products.

This paper describes a new method to obtain the pure dihydro-alantolactone without opening the lactone rings during the reaction, and also its conversion into 1,2-dihydroxy-tetrahydro-alantolactone, which may be used as a starting material in the syntheses of some santonin analogs.

The distillation of the ether extract of the original roots *in vacuo* gave an oil, b.p.₁ 148~152°, which solidified into a crystalline mass on standing. After separating the small amount of oily substance, the crystals were reduced with aluminum amalgam in alcohol. Although the melting point of the reduction product was not constant, depending upon the quality of the original roots used (in one case, m.p. 110~132°, and in another, m.p. 114~140°), it was easily separated by recrystallization from alcohol into two parts with constant melting points having the same molecular formula, $C_{15}H_{22}O_2$, the one as colorless needles, m.p. 171~172°, $[\alpha]_D^{25} = +44.1^{\circ}$, and the other as colorless prisms, m.p. 133.5~134°, $[\alpha]_D^{25} = -49.5^{\circ}$.

From these data of the reduction products, the latter must be dihydro-alantolactone, and the former, dihydro-isoalantolactone. The rotatory power of the latter (III), however, was a little lower than that reported by Ruzicka²⁾, though its melting point was constant and over that of his data (m.p. 168°) after repeated recrystallization⁹⁾.

Dihydro-isoalantolactone thus obtained absorbed just one molar equivalent of hydrogen on catalytic hydrogenation with Adams' platinum oxide yielding tetrahydro-alantolactone, m.p. 141~143°, $[\alpha]_D^{18} = +15.0^\circ$. Further, on ozonolysis, it gave an oxidation product, $C_{14}H_{20}O_3$, m.p. 197~199°, $[\alpha]_D^{18} = +15.1^\circ$, a keto-lactone, in good yield, for which the structural formula (V) was assigned by Ruzicka, et al²⁾.

On catalytic hydrogenation of dihydro-alantolactone with palladium, tetrahydro-alantolactone (VI) was also obtained after the consumption of one molar equivalent of hydrogen. From the oxidation product of dihydro-alantolactone with ozone, an acid was obtained, which was purified through its methyl ester, $C_{16}H_{24}O_5$, m.p. 128~130°, $[\alpha]_D^{17} = +175.8^\circ$, to a crystalline compound, $C_{15}H_{22}O_5$, m.p. 193~195°.

These products might correspond to the keto-lactonic acid (VII) and its methyl ester (VIII) obtained by Hansen⁷⁾.

Oxidation of dihydro-alantolactone thus obtained with perhydrol in acetic acid yielded an oxide-lactone $C_{15}H_{22}O_3$ (IX), m.p. 203°, $[\alpha]_D^{27} = -34.9^\circ$, which was stable against permanganate in acetone solution and against bromine in acetic acid solution. This oxide-lactone (IX) was hydrolyzed by 2 molar equivalents of alcoholic alkali solution and then acidified to give a product, $C_{15}H_{24}O_4$ (X), m.p. 235~237° (decomp.), $[\alpha]_D^{27} = -9.4^\circ$, which was much more insoluble in ether than the above oxide-lactone and unstable against some oxidizing agent such as chromic acid, and which was dehydrated to a diene-lactone $C_{15}H_{20}O_2$, m.p. 105~110°, (XI), by heating with 95% formic acid.

From these reactions, the product (X) must have the structure, 1,2-dihydroxy-tetrahydro-alantolactone, derived from Ruzicka's structure for alantolactone (I).

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Experimental

Mixture of Lactones—2 kg. of the strips of roots of *Inula Helenium* was extracted with ether for about 10 days at room temperature, and then the ether was removed. After separating the crystalline lactone mixture by filtration, the oily residue was set for steam distillation to obtain further amounts of crystalline lactone. Or the above concentrated ethereal solution was washed with 5% sodium carbonate solution, and the neutral portion was distilled under reduced pressure. The main fraction, b.p.₁ 148~152° solidified into crystalline mass on standing, from which crystals were separated from oily substance by pressing. Yield: 1% of the original roots.

The crystals thus obtained were a mixture consisting of alantolactone, isalantolactone, and dihydro-isoalantolactone. The melting point usually lay between 70~120° and was not constant according to the quality of original roots.

9) Hansen (see footnote 4) reported the melting point as 174° for dihydro-isoalantolactone, but no data of rotatory power of this compound was found in his articles.

Reduction of the Lactone Mixture with Aluminum Amalgam.—To 6 g. of the above lactone mixture (m.p. 72~77°), dissolved in 132 cc. of alcohol, was added aluminum amalgam prepared from 10.5 g. of pure aluminum leaf, and the mixture was warmed on a water bath for 5 hrs. under stirring. After removing the solvent from the reaction mixture, the residue was dried and then extracted with ether using a Soxhlet apparatus. On evaporating the solvent from dried extract, the residue solidified into a crystalline mass.

Separation of Dihydro-alantolactone (IV) and Dihydro-isoalantolactone (III).—The whole reduction product thus obtained from above lactone mixture was fractionally recrystallized from alcohol to colorless prisms, m.p. 133.5~134°, (yield, ca. 40%) and colorless needles, m.p. 171~172° (yield, ca. 60%). The former is dihydro-alantolactone (IV) and the latter dihydro-isoalantolactone (III).

Dihydro-alantolactone—*Anal.* Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.76; H, 9.68, $[\alpha]_D^{26} = -49.5^\circ$ (2.5% in ab. alcohol solution).

Dihydro-isoalantolactone—*Anal.* Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.60; H, 9.53. $[\alpha]_D^{26} = +44.1^\circ$ (1.36% in ab. alcoholic solution).

Catalytic Hydrogenation of Dihydro-isoalantolactone and Dihydro-alantolactone: Tetrahydro-alantolactone (VI).—To 0.7 g. of dihydro-isoalantolactone, dissolved in 70 cc. of glacial acetic acid, was added 0.35 g. of Adams' platinum oxide, and the mixture was reduced catalytically under 766 mm. at 14°. The mixture absorbed 73 cc. of hydrogen. (Calcd. for one double bond: 71.0 cc.).

The solvent was removed from the filtered solution and the residue was recrystallized from alcohol to colorless needles, m.p. 141~143° (yield, 0.69 g.). The product was stable both against potassium permanganate in acetone solution and bromine in glacial acetic acid solution.

0.12 g. of dihydro-alantolactone was reduced similarly with 6% palladium charcoal in 40 cc. of alcohol under 763 mm. at 19°. The mixture absorbed ca. 17 cc.* of hydrogen (Calcd. for one double bond: 12.5 cc.).

From the filtered reaction mixture, after evaporation of the solvent and recrystallization of the residue from alcohol, 0.1 g. of colorless needles, m.p. 141~143°, was obtained. The mixture of both reduction products melted without depression. *Anal.* Calcd. for $C_{15}H_{24}O_2$: C, 76.27; H, 10.17. Found: C, 76.04; H, 10.40. $[\alpha]_D^{18} = +15.0^\circ$ (10.046 mg./cc. in alcohol).

Ozonolysis of Dihydro-isoalantolactone: Keto-lactone (V).—The solution of 2 g. of dihydro-isoalantolactone, m.p. 170~173°, in 30 cc. of dry chloroform was saturated with ozonized oxygen. After removal of the solvent at 40° under reduced pressure, the residual ozonide was decomposed with 10 cc. of water to separate colorless crystals. The product (V) was recrystallized from alcohol to colorless needles, m.p. 197~199°. Yield, 1.6 g. *Anal.* Calcd. for $C_{14}H_{20}O_3$: C, 71.18; H, 8.47. Found: C, 70.78; H, 8.47. $[\alpha]_D^{18} = +15.1^\circ$ (9.959 mg./cc. in alcohol).

Ozonolysis of Dihydro-alantolactone: Keto-lactonic Acid (VII).—2 g. of dihydro-alantolactone, m.p. 128~131°, was dissolved in 30 cc. of dry chloroform, and saturated with ozonized oxygen. After removal of the solvent the syrupy ozonide was decomposed with 10 cc. of water to give an oily product, which was distilled with steam and the distillate (150 cc.) was extracted with ether.

The ethereal solution was extracted with 5% sodium bicarbonate solution to remove acidic matters. From the dried neutral ethereal solution, after removal of the solvent, was obtained 1.3 g. of an oily product.

To this oil, dissolved in 20 cc. of acetone, under cooling and stirring, was added a 4% potassium permanganate solution, and the reaction mixture, after decolorizing with thiosulfate, was extracted with ether.

The ethereal solution was extracted with 5% sodium bicarbonate solution to separate the acidic product, which on acidifying the aqueous layer, was obtained as an oily substance.

0.8 g. of the acidic product was methylated with diazomethane by the ordinary procedure, to furnish the methyl ester which was recrystallized from alcohol to colorless prisms, m.p. 128~130°. Yield, 0.7 g. *Anal.* Calcd. for $C_{16}H_{24}O_5$: C, 64.86; H, 8.10. Found: C, 65.14; H, 7.87. $[\alpha]_D^{17} = +175.8^\circ$ (9.954 mg./cc. in alcohol).

Hydrolysis of the methyl ester: To 0.16 g. of the methyl ester dissolved in 10 cc. of methanol was added 0.08% sodium hydroxide solution, the mixture was boiled on a water bath for 3 hrs. After cooling, the reaction mixture was neutralized and acidified with diluted hydrochloric acid. The oily substances separated was extracted with ether. The ethereal solution was again extracted with 5% sodium bicarbonate, and on acidifying the alkaline solution furnished a crystalline product which was recrystallized from ethyl acetate to colorless prisms, m.p. 193~195°. Yield, 0.1 g. *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 (for

* The amount of hydrogen absorbed was in slight excess in every repeated experiments than calculated in the case of dihydro-alantolactone, although the material used was reliable as to its purity and on its structure as discussed above. The reason for this phenomena will be dealt with in the near future.

monobasic acid).

Both this acid and the methyl ester furnished no crystalline 2,4-dinitrophenylhydrozone by the usual method but the acid gave positive iodoform reaction by iodine solution and caustic alkali.

Oxidation of Dihydro-alantolactone (IV) to Oxide-lactone (IX).—To 1.0 g. of (IV) in 20 cc. of glacial acetic acid 4 g. of 30% hydrogen peroxide was added, and the mixture was gently warmed on a water bath for 7 hrs. The crystals precipitated when the reaction mixture was poured into ice water, separated, and recrystallized from alcohol to colorless needles, m.p. 203°. Yield, 0.75 g.

This product did not decolorize permanganate in acetone solution, and bromine in glacial acetic acid. *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.95; H, 8.62. $[\alpha]_D^{27} = -34.9$ (in 2% pyridine solution).

Hydrolysis of Oxide-lactone (IX) to 1,2-Dihydroxy-tetrahydroalantolactone (X).—To 0.83 g. of (IX) in 40 cc. of methanol, 8.5 cc. of 3.2% sodium hydroxide solution (2 mol. equiv.) was added, the mixture warmed on a water bath for 15 min. after acidifying with dil. hydrochloric acid, and the reaction mixture was extracted with ethyl acetate. The ethyl acetate solution was washed with 3% sodium carbonate and then with water. The residue, obtained on removal of the solvent, was recrystallized from ethyl acetate or acetone to colorless platelets, m.p. 235–237°. Yield, 0.7 g. *Anal.* Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.01. Found: C, 66.84; H, 9.18. $[\alpha]_D^{27} = -9.4^\circ$ (in 6.6% pyridine solution).

Diene-lactone (XI)—0.4 g. of (X) was dissolved in 8 cc. of 95% formic acid, and boiled for 4 hrs. at 165° (bath temp.). Dark brown reaction mixture was poured into ice water, and the oil separated was taken up in ether. The ethereal solution was dried, evaporated and distilled under reduced pressure. The distillate, b.p.₁ 140–145° solidified to crystalline mass on standing, which was recrystallized, after separating a little amount of oil, from 50% alcohol to colorless plates, m.p. 105–110°. *Anal.* Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; Found: C, 77.32; H, 8.78.

Summary

The mixture of bicyclic sesquiterpene lactones obtained from the rhizome of *Inula Helenium* was reduced by aluminum amalgam and the reduction product was separated into dihydro-isoalantolactone and dihydro-alantolactone in a pure state. The dihydro-alantolactone was converted into 1,2-dihydroxytetrahydro-alantolactone.

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233. Tyunosin Ukita, Makoto Matsumoto and Tomie Tamura : Antibacterial Properties of Compounds containing the Tricarbonylmethane Group.

VIII.* Synthesis of 4-Hydroxycoumarins substituted with Unsaturated Aromatic Acyl Groups in 3-Positions, with respect to their Antibacterial Properties.

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In the previous paper of this series^{1, 2)}, the authors and collaborators reported on the syntheses and antibacterial properties of 4-hydroxycoumarins substituted with aliphatic saturated acyl groups in the 3-positions (I). The antibacterial activities of these compounds increased with the elongation of acyl-chain and reached a maximum at decanoyl derivative.

In Part V, K. Tomita³⁾ synthesized both series of 2,4-dihydroxy-3-acylquinolines (II) and *N*-alkylated 3-acyl-4-hydroxy-2-quinolones (III) which had nitrogen atom in place of oxygen in the pyrone ring of type (I) compounds, and found that all the compounds

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