UDC 547.659.1

37. **Katsumi Tanabe**: The Structure of Alantolactone. II.[1] The Conversion of Alantolactone into Dihydroeudesmol.

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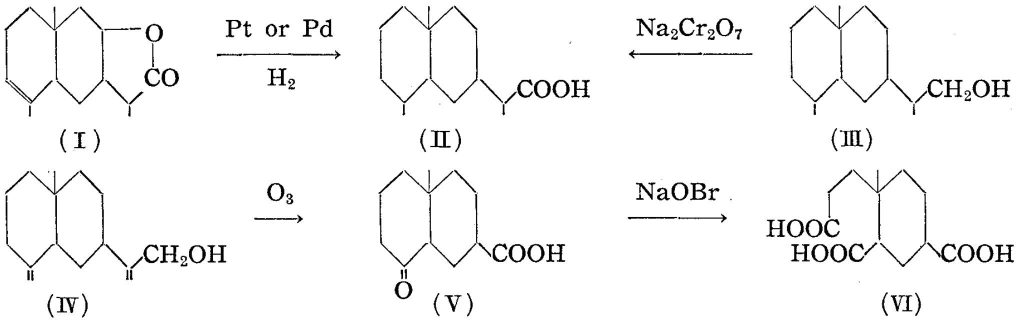
Ukita and Nakazawa[2] isolated a monocarboxylic acid from the reaction mixture of catalytic hydrogenation of dihydroalantolactone (I) and identified the acid with 1,10-dimethyl-7-(2′-carboxyethyl)decalin (II), prepared by the oxidation of tetrahydrosesquibenihiol (III). Katsura[3] previously reported that sesquibenihiol (IV) on subjecting to ozonolysis followed by further oxidation with sodium hypobromite furnished the same tricarboxylic acid (VI) as had been obtained previously from the α- and β-selinenes.[4]



On the basis of the above informations we assumed alantolactone to have a *trans*-decalin structure and discussed briefly the configurations of the lactone ring in the preceding paper.[1] However, some questions remained regarding the assumption made at that time concerning the decalin structure. The tricarboxylic acid (VI) had not been identified reliably with that derived from selinene by mixed fusion and the molecular rotation value was not also recorded, Katsura having reported merely that the melting point and analytical values were in good agreement. The two acids, therefore, cannot be considered as unequivocally identical.

Moreover, Katsura obtained the acid (VI) by oxidation of a ketocarboxylic acid (V), which possesses a carbonyl group at a position adjacent to the ring juncture, in an alkaline medium over a fairly prolonged period. Accordingly, the case must be taken into consideration where the decalin skeleton has already isomerized into a more stable *trans*-fused system during this stage.

The configuration of the A/B ring juncture should be settled first and the present study is concerned with this problem.

Kavács, *et al.*[5] stated that the glycol (VIII), obtained by the action of lithium aluminum hydride on tetrahydroalantolactone (VII), when refluxed with *p*-toluenesulfonic acid in benzene solution for 30 minutes, gave an unsaturated primary alcohol in a good yield. The author's result was, however, different from their's and the glycol was recovered unchanged nearly quantitatively under the above conditions. Either by a more prolonged heating or by replacing the solvent with toluene it was dehydrated to an unsaturated primary alcohol (IX) in a poor yield in addition to an oxide (X) having

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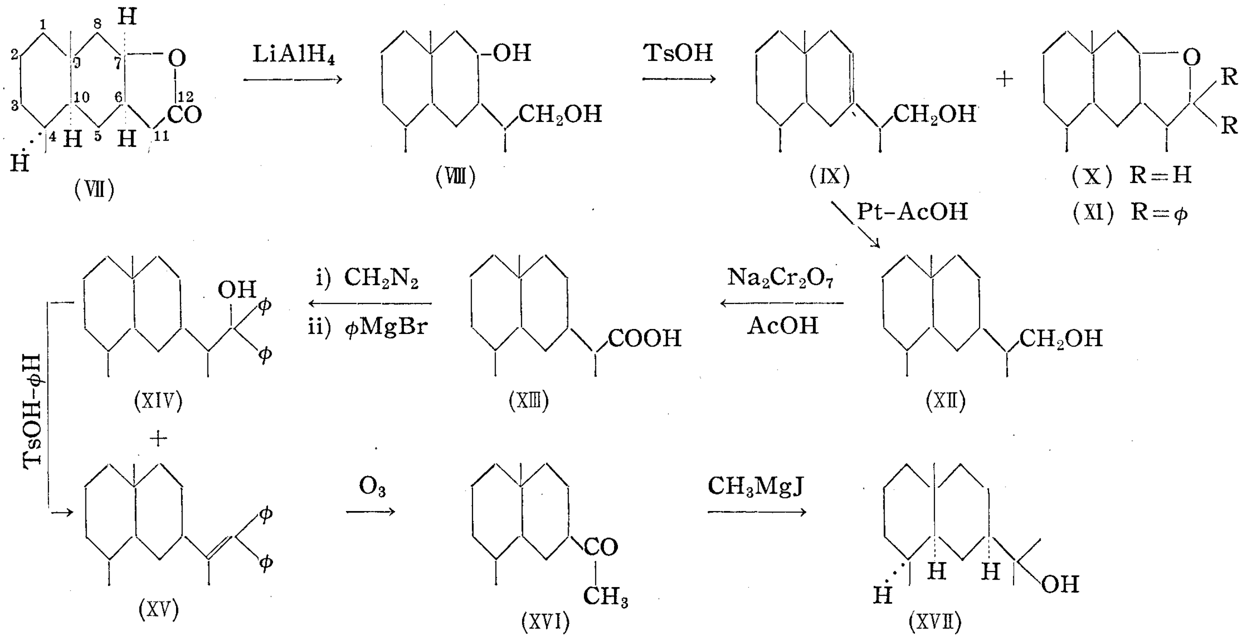
[1] Part I. K. Tsuda, K. Tanabe, I. Iwai, K. Funakoshi: J. Am. Chem. Soc., **79**, 5721(1957).

[2] T. Ukita, S. Nakazawa: This Bulletin, **2**, 239(1954).

[3] S. Katsura: Nippon Kagaku Zasshi, **63**, 1465(1942).

[4] α- and β-Selinenes belong to the *trans*-decaline type, since they afford the same dihydrochloride as that derived from eudesmol.[8]

[5] Ö. Kovács, V. Herout, M. Horák, F. Šorm: Collection Czechoslov. Chem. Communs., **21**, 225(1956).



a tetrahydrofuran structure. The 6–7 position of the double bond in (IX) was assigned from its infrared absorption at 1670 and 808 cm^{-1}(trisubstituted olefin). The structure of (X) was based on the analytical values, absence of coloration with tetranitromethane, and on its ready elution from alumina (Brockmann grade II) with petroleum ether.[6]

The oxide (X) was also obtained as a major product by treatment of (VIII) with *p*-toluenesulfonyl chloride in pyridine, affording the expected ditosylate only in a poor yield. The reaction of phenylmagnesium bromide on tetrahydroalantolactone (VII) also gave the analogous oxide (XI), probably produced by the elimination of water from a phenyl-substituted glycol as an intermediate. Such a tendency of the hydroxyl group at 7 to cyclize readily to a tetrahydrofuran ring may give an evidence to our assumption that alantolactones belong to 7-O axial *cis*-lactone.[1]

(IX) was catalytically hydrogenated in acetic acid and the product, without further purification, was oxidized with sodium dichromate to a monocarboxylic acid (XIII), which was characterized as the amide of m.p. 139~140°, $[\alpha]_D^{27}$ +35.2°. The same monocarboxylic acid (m.p. 70~72°) was isolated when the mixture of alantolactones, probably containing isoalantolactone, was subjected to hydrogenolysis in the presence of platinum oxide in acetic acid solution at 50°. The acid thus obtained can be considered as identical with the monocarboxylic acid (m.p. 65~67°; the amide, m.p. 138~140°, $[\alpha]_D^{17}$ +31.7°) reported by Ukita, *et al.*[2]

The methyl ester of (XIII) was treated with phenylmagnesium bromide and the reaction product was separated through alumina column into the corresponding tertiary alcohol (XIV), m.p. 140~141°, and its dehydrated product (XV), m.p. 109~110°, the former being easily dehydrated to the latter on heating with *p*-toluenesulfonic acid in benzene solution.

1,10-Dimethyl-7-acetyldecalin (XVI) was isolated in a pure state on regenerating its semicarbazone (m.p. 206~208°), which was produced from the ozonolysis reaction mixture of (XV). On treatment of (XVI) with methylmagnesium iodide, according to the procedure of Ruzicka, *et al.*,[7] it afforded dihydroeudesmol (XVII), m.p. 84~85°, $[\alpha]_D^{27}$ +17.5°, which was proved to be identical with the authentic specimen by mixed fusion and infrared spectra.

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[6] cf. C. Asselineau, S. Bory, E. Lederer : Bull. soc. chim. France, **1955**, 1524.

[7] L. Ruzicka, A. H. Wind, D. R. Koolhaas : Helv. Chim. Acta, **14**, 1132(1931).

Eudesmol was established by Riniker, *et al.*[8] to have a *trans*-decalin structure by correlation with steroids, and, thus, alantolactone including isoalantolactone and dihydroisoalantolactone must have a *trans*-decalin structure and at the same time should be represented by (Ⅶ) and not by its mirror image.

The present study was carried out under the kind guidance of Prof. K. Tsuda of the University of Tokyo for which the author is deeply grateful. The author wishes to express his appreciation to Prof. S. Shibata of the University of Tokyo for providing a sample of eudesmol, to Mr. M. Matsui, Director of this Laboratory, and to Dr. S. Yoshida and Dr. I. Iwai of this Laboratory for their kind encouragements. Thanks are due to Mr. T. Onoe, Miss C. Furukawa, and Miss H. Ohtsuka for microanalyses, and to Mr. H. Shindo and Mr. O. Amakasu for the infrared spectral measurement.

Experimental[9]

Glycol (VIII)—Tetrahydroalantolactone(m.p. 142~143°, $[\alpha]_D^{25}$ +11.5°) was treated with $LiAlH_4$ in dehyd. ether and the product was recrystallized from hexane to give the glycol (Ⅷ) in colorless needles, m.p. 112~113.5, $[\alpha]_D^{25}$ −8.1°(c=2). *Anal.* Calcd. for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found : C, 75.14; H, 11.90.

A solution of (Ⅷ)(2.4 g.) and *p*-toluenesulfonyl chloride (5 g.) in pyridine (20 cc.) was set aside overnight at room temperature, the mixture was poured into ice-water, acidified with HCl, and extracted with ether. The ether extract was washed with aq. $NaHCO_3$ solution, dried, and the solvent was removed. The residual oily substance (2.5 g.) was dissolved in hexane and stored in an ice-box overnight. The deposited crystalline precipitate was recrystallized from hexane to afford the ditosylate of (Ⅷ) in colorless needles, m.p. 105°; yield, 146 mg. *Anal.* Calcd. for $C_{29}H_{40}O_6S_2$: C, 63.47; H, 7.35. Found : C, 63.82; H, 7.36.

The mother liquor separated from the ditosylate was passed through an alumina (Brockmann grade II) column and the column was eluted with petr. ether. Removal of the solvent gave an oily residue, which was distilled to give an oxide (X) as a colorless liquid, b.p_5 125~128°, n_D^{24} 1.4980; yield, 1.59 g. *Anal.* Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found : C, 80.97; H, 11.47.

Dehydration of (VIII)—After refluxing a solution of (Ⅷ)(6 g.) and *p*-toluenesulfonic acid (1 g.) in dehyd. benzene (150 cc.) for 2 hrs., the solvent was concentrated at an ordinary pressure to about 20 cc. and then at a reduced pressure to dryness. The residue was dissolved in hexane (30 cc.) and stored in an ice-box. The deposited crystalline mass was recrystallized from hexane to give unchanged glycol, m.p. 112~113°; yield, 4 g.

The filtrate separated from the glycol was chromatographed on alumina. The fraction eluted with petr. ether gave 1.1 g. of a coloress liquid, b.p_{12} 148°, which proved identical with the oxide (X) described above by the comparison of their infrared spectra. The benzene eluate afforded 0.64 g. of an unsaturated alcohol (IX) as a colorless viscous liquid, b.p_4 140°(bath temperature). *Anal.* Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found : C, 80.75; H, 11.57.

1,10-Dimethyl-7-(2′-carboxyethyl)decalin (XIII)—(a) A solution of (IX)(500 mg.) in AcOH was shaken in H_2 atmosphere with PtO_2, absorbing about 1 mol. equiv. of H_2. After removal of the catalyst, a solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (250 mg.) in AcOH was added slowly to the filtrate and the mixture was set aside overnight at room temperature. The excess reagent was decomposed with EtOH and the solvent was removed under a reduced pressure. The residue was diluted with water and extracted with ether. The acidic portion was separated from the ether extract by shaking with 5% Na_2CO_3 solution, and converted to the amide by the usual procedure. The amide showed m.p. 139~140°, $[\alpha]_D^{27}$ +35.2°(c=2), after recrystallization from hydr. MeOH. Yield, 210 mg. *Anal.* Calcd. for $C_{15}H_{27}ON$: C, 75.89; H, 11.47; N, 5.90. Found : C, 75.86; H, 11.49; N, 5.94.

(b) A solution of 42 g. of a mixture of alantolactones (m.p. 120~130°) was shaken in AcOH with PtO_2(5 g.) in H_2 atmosphere at 50°, ca. 1.8 moles of H_2 being consumed. After filtration of the catalyst, the filtrate was concentrated at a reduced pressure and the residue was dissolved in ether. The separated acidic substance (16 g.) from the ether solution was worked up as above and was recrystallized from hydr. MeOH to give 1,10-dimethyl-7-(2′-carboxyethyl)decalin (XIII) as colorless cubelets, m.p. 70~72°, $[\alpha]_D^{25}$ +37.1°(c=2). *Anal.* Calcd. for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.91; H, 11.14.

The amide showed m.p. 139~140°, $[\alpha]_D^{24}$ +35.7°(c=2), after recrystallization from hydr. MeOH, which was proved to be identical by mixed melting point and the infrared spectra with that obtained through the route described above.

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[8] B. Riniker, J. Kolvoda, D. Arigoni, A. Fürst, O. Jeger, A.M. Gold, R.B. Woodward : J. Am. Chem. Soc., **76**, 313(1954).

[9] Optical rotation was measured in $CHCl_3$.

The methyl ester of (XIII) was prepared with CH_2N_2 and showed b.p$_{0.1}$ 92°; n_D^{24} 1.4835; $[\alpha]_D^{24}$ +42.5° (c=2).

Grignard Reaction of the Methyl Ester of (XIII)—A solution of the methyl ester (11 g.) of (XIII) in dehyd. ether (100 cc.) was added dropwise with stirring and cooling into an ether solution of PhMgBr prepared from 23.5 g. of bromobenzene and 3.56 g. of Mg. After the addition was completed, the solution was refluxed for 1 hr. The cooled mixture was hydrolysed with 10% AcOH solution, the ether layer separated, washed with 5% $NaHCO_3$ solution, and dried. After removal of the solvent the residue was chromatographed on alumina (200 g.). The petr. ether eluate after evaporation of the solvent yielded 8.5 g. of an uusaturated hydrocarbon (XV), which was recrystallized from 95% EtOH to colorless needles, m.p. 109~110°. *Anal.* Calcd. for $C_{27}H_{34}$: C, 90.44; H, 9.56. Found: C, 90.88; H, 9.47.

Evaporation of the benzene eluate gave 1.6 g. of a diphenylcarbinol (XIV), which was recrystallized from 95% EtOH to colorless needles, m.p. 140~141°. *Anal.* Calcd. for $C_{27}H_{36}O$: C, 86.11; H, 9.64. Found: C, 85.65; H, 9.59.

After refluxing a solution of (XIV) (1.32 g.) and *p*-toluenesulfonic acid (0.15 g.) in benzene (60 cc.), the solution was washed with 5% Na_2CO_3 solution, dried, and the solvent was evaporated. The residue was recrystallized from 95% EtOH to (XV), m.p. 109~110°, which showed no depression of m.p. on admixture with that obtained above.

1,10-Dimethyl-7-acetyldecalin (XVI)—A solution of (XV) (4 g.) in $CHCl_3$ (100 cc.) at −10° was treated with ozonized oxygen until the solution gave no color with tetranitromethane. The solvent was evaporated under a reduced pressure. After the addition of water the mixture was allowed to stand for 3 hrs. and extracted with ether. The ether extract after evaporation of the solvent gave 4.1 g. of a viscous liquid, which was distilled at a reduced pressure and the fraction of b.p$_{12}$ 140~160° was collected. The semicarbazone of (XVI) was prepared from this fraction in the usual way and was recrystallized twice from MeOH to colorless leaflets of m.p. 206~208°; yield, 1.9 g. *Anal.* Calcd. for $C_{15}H_{27}ON_3$: C, 67.88; H, 10.26; N, 15.83. Found: C, 68.00; H, 10.10; N, 16.00.

The semicarbazone (1.4 g.) was heated at 110° for 2 hrs. in saturated oxalic acid solution. The regenerated dimethylacetyldecalin was collected with ether and distilled at a reduced pressure; b.p$_{12}$ 147~148°, n_D^{23} 1.4888; yield, 1.1 g.

Dihydroeudesmol (XVII)—(a) To an ether solution of MeMgI, prepared from 2.15 g. of MeI and 0.36 g. of Mg, a solution of (XVI) (1 g.) in dehyd. ether (20 cc.) was added with stirring and cooling. After the addition was completed, the solution was allowed to stand overnight, poured into ice water, acidified with tartaric acid solution, and extracted with ether. The dried ether extract was evaporated to give a crystalline mass, which was recrystallized from hydr. acetone to colorless needles. Dihydroeudesmol thus obtained had m.p. 84~85° and $[\alpha]_D^{27}$ +17.5° (c=2), which proved identical with the authentic sample described below by mixed fusion and the infrared spectra. *Anal.* Calcd. for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.10; H, 12.26.

(b) Eudesmol (m.p. 81~83°, $[\alpha]_D^{27}$ +30.5°) was hydrogenated in EtOH in the presence of PtO_2, absorbing 1 mol. equiv. of H_2. The product was repeatedly recrystallized from hydr. acetone to give dihydroeudesmol in colorless needles, m.p. 84~85°, $[\alpha]_D^{27}$ +17.0° (c=2).

Reaction of Phenylmagnesium Bromide with Tetrahydroalantolactone—A solution of tetrahydroalantolactone (2.36 g.) in dehyd. ether (150 cc.) was added dropwise into an ether solution of PhMgBr, prepared from bromobenzene (6.28 g.) and Mg (0.92 g.). Afer the addition was completed, the mixture was refluxed for 30 mins. On treatment in the usual way the product was chromatographed on alumina and the part (2.83 g.) eluted with petr. ether was recrystallized from 95% EtOH to (XI) as colorless needles, m.p. 157~158°. *Anal.* Calcd. for $C_{27}H_{34}O$: C, 86.58; H, 9.15. Found: C, 86.92; H, 9.46.

Another part (0.45 g.) eluted with benzene proved to be the unchanged tetrahydroalantolactone, m.p. 142~143°, after recystallization from hexane.

Summary

Alantolactone was converted to dihydroeudesmol and it was confirmed that the alantolactone series belongs to the *trans*-fused decalin type.

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