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38. **Katsumi Tanabe**: The Structure of Alantolactone. III.[1] Configurations of 4-Methyl Group in Tetrahydroalantolactone and Several 3-Hydroxytetrahydroalantolactones.

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The asymmetric center at 4 in tetrahydroalantolactone is produced by catalytic hydrogenation of the 3-4 or 4-15 double bond in alantolactone or isoalantolactone, respectively. The catalytic addition of hydrogen is known to occur from the less hindered side of a molecule, and consequently the 4-methyl group was postulated to be β-orientated.[2] The present study was carried out to confirm this problem by chemical procedures.

Matsumura, Iwai, and Ohki[3] treated dihydroisoalantolactone (I) with selenium dioxide in boiling alcohol and isolated 3-hydroxydihydroisoalantolactone (II) which on catalytic hydrogenation gave 3-hydroxytetrahydroalantolactone (III). The oxidation product of (III) with chromium trioxide was passed through alumina column for the purpose of purification and they obtained 3-oxotetrahydroalantolactone (X), m.p. 169~171°, $[\alpha]_D^{15}$ −32.3°, which was reduced by Clemmensen's method to give the so-called β-tetrahydroalantolactone (XII), m.p. 117~119°, $[\alpha]_D^{21}$ −22.6°.

When (III) was oxidized with sodium dichromate in acetic acid it afforded 3-oxotetrahydroalantolactone (IV) of m.p. 189~191°, which on passing through basic alumina, isomerized quantitatively into (X), m.p. 170~171°. Desulfurization of 3-ethylenethioketals of (IV) and (X) with Raney nickel respectively gave tetrahydroalantolactone (IX), m.p. 142~143°, $[\alpha]_D^{23}$ +15.4°, and an isomeric tetrahydroalantolactone (XII), m.p. 120~121°, $[\alpha]_D^{23}$ −37.5°, the latter compound being believed to be identical with β-tetrahydroalantolactone cited above. The 4-methyl group in (IV) was thus found to have the same configuration as in tetrahydroalantolactone.

In view of the condition under which the isomerization of (IV) into (X) occured, it is beyond question that the basicity of the adsorbent has caused epimerization of 4-methyl group located *alpha* to the carbonyl group into a more stable form.[4] It follows therefore that tetrahydroalantolactone and β-tetrahydroalantolactone must have the 4-methyl group respectively in β(axial)- and α(equatorial)-orientations.

During the course of this work, Cocker and McMurry[6] reported analogous reactions on santonin series and they showed that 3-oxo-4,5,11α(*H*),6β(*H*)-eudesman-6,13-olide(4β-methyl) epimerizes into 3-oxo-5,11α(*H*),4,6β(*H*)-eudesman-6,13-olide(4α-methyl) when heated in an aqueous sodium hydroxide solution.

Treatment of the alcohol (III) with phosphoryl chloride in pyridine gave 2,3-dehydrotetrahydroalantolactone (VI), m.p. 139~142°, which on catalytic hydrogenation afforded tetrahydroalantolactone. The wide range of the melting point of (VI) may be due to the

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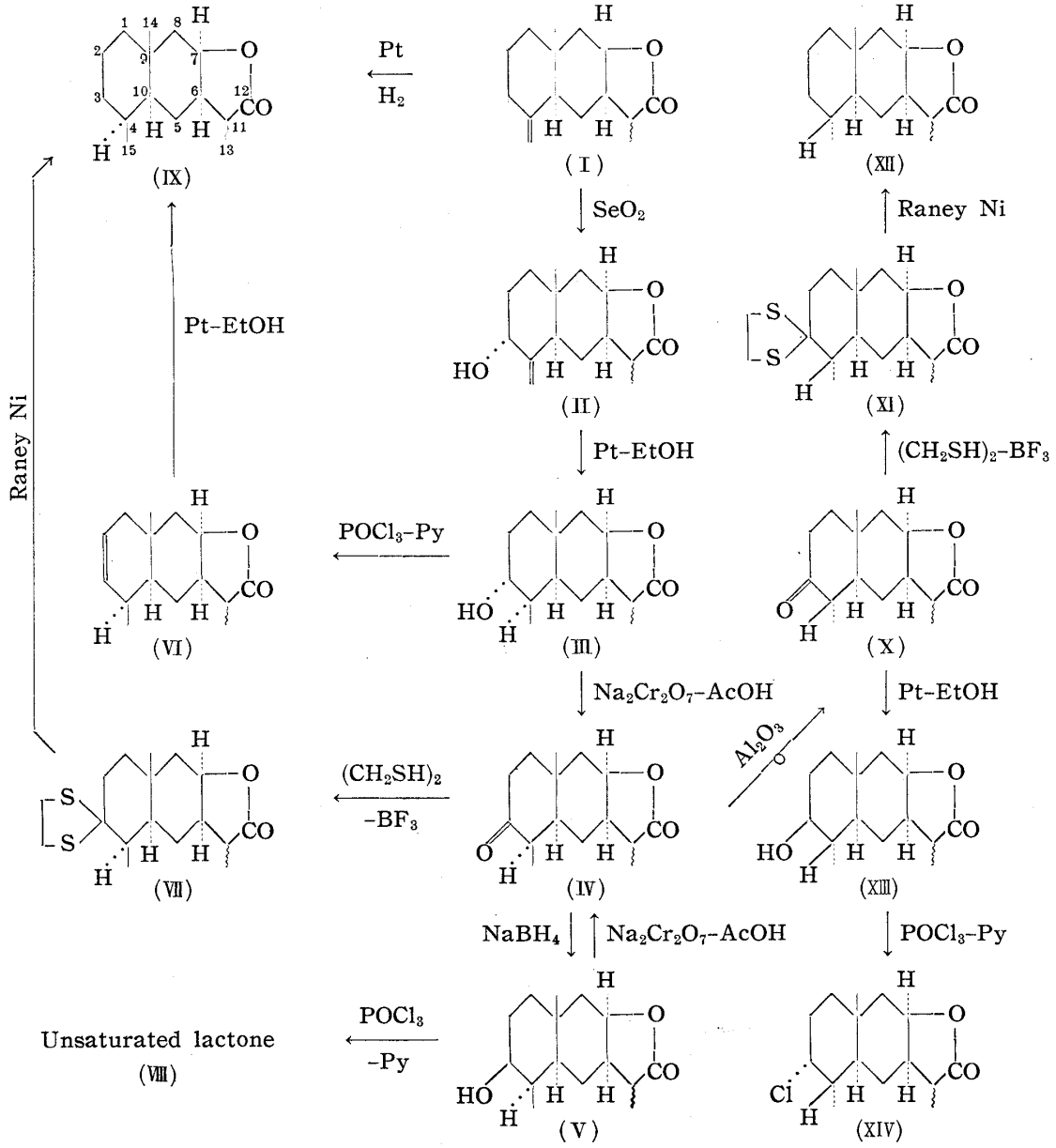
1) Part II: This Bulletin, **6**, 214(1958).
2) Ö. Kovács, V. Herout, M. Horák, F. Šorm: Collection Czechoslov. Chem. Communs., **21**, 225 (1956).
3) H. Matsumura, I. Iwai, E. Ohki: Yakugaku Zasshi, **74**, 738(1954).
4) The author has not encountered cases where the 11-methyl group in the alantolactones has epimerized under the same conditions, much less the configurations of the decalin and lactone ring.
5) The β-orientation was also confirmed for the 4-methyl group in dihydroeudesmol by the present study and in view of Part II of this series.[1]
6) W. Cocker, T.B.H. McMurry: J. Chem. Soc., **1956**, 4549.



contamination of a small amount of dihydroalantolactone (3-4 double bond), which was assumed from a strong absorption band at 711 cm^{-1}(*cis*-disubstituted olefin) and a weak band at 851 cm^{-1}(trisubstituted olefin) in its infrared spectrum.

The formation of (VI), the negative shift in molecular rotation on acetylation (Δ_1: $-60°$), and the negative molecular-rotational contribution of the hydroxyl group (Δ OH: $-38.6°$) indicate, according to the rule of Klyne and Stokes,[7] that the hydroxyl group in (III) introduced by the action of selenium dioxide is α-orientated.

When the keto-lactone (X) was hydrogenated with platinum oxide in ethanol it gave 3β-hydroxy-β-tetrahydroalantolactone (XIII), the β-orientation of the hydroxyl group being assumed from its respective positive values of $+30.2°$ and $+46.5°$ for Δ_1 and Δ OH, and also from the method of preparation. On treatment with phosphoryl chloride in pyridine (XIII) afforded 3α-chloro-β-tetrahydroalantolactone (XIV), the negative molecular-rotational contribution of chlorine indicating that the chlorine is α-orientated and this reaction thus involves a Walden inversion.

7) W. Klyne, W.M. Stokes: *Ibid.*, **1954**, 1979.

Reduction of the keto-lactone (IV) with sodium borohydride in 95% ethanol gave 3β-hydroxytetrahydroalantolacone (V). Epimerization of the 4-methyl group by basicity of the reagent during the reaction is excluded and (V) retains the methyl group in β-orientation, since the alcohol (V) was oxidized with sodium dichromate to the ketone (IV) again.

Now that the hydroxyl group in (III) is most probably axial, and also in view of the method of preparation, the hydroxyl group in (V) must be equatorial. In this case, however, the differences of molecular rotation values were against the rule[7] and showed negative values for Δ_1(−84.6°) and ΔH(−114°). Moreover, the product (m.p. 103~105°) obtained on treatment of (V) with phosphoryl chloride and pyridine gave a yellow coloration with tetranitromethane and a negative Beilstein's test, indicating the presence of a double bond and the absence of halogen. The structure of this compound was not further investigated because of its poor yield.

Such anomalous behaviors of the equatorial hydroxyl group of (V) in molecular rotation and with phosphoryl chloride might be attributed, with a certain possibility, to the 1,3-diaxial non-bonded atom interaction of the methyl groups at 4- and 9-positions.

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Experimental[8]

Dihydroisoalantolactone (I)—The lactone fraction obtained from the benzene extract of the roots of *Inula Helenium* was repeatedly recrystallized from 99% EtOH. From 17 kg. of the finely powdered roots, 31 g. of dihydroisoalantolactone was isolated in colorless needles of m.p. 170~171°; $[\alpha]_D$ +39.5° (c=2.1). *Anal.* Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.83; H, 9.58.

3α-Hydroxydihydroisoalantolactone (II)—According to the method of Matsumura, *et al.*[3] a solution of SeO_2 (10 g.) in 90% EtOH (100 cc.) was added to a boiling solution of (I) (13 g.) in 95% EtOH (130 cc.) during 1 hr. and the mixture was refluxed for an additional 1.5 hrs. The cooled solution was separated from the deposited Se, concentrated to about 30 cc. under a reduced pressure, diluted with water, and extracted with ether. The ether extract was washed with 5% Na_2CO_3 solution, dried, and the solvent was evaporated. The residue (12 g.) was passed through alumina (400 g.) column. The eluate with a mixture of benzene and dehyd. ether (8:2) gave, after evaporation of the solvent, 5.5 g. of (II), which was recrystallized from benzene to colorless needles, m.p. 179~180°; $[\alpha]_D$ −12.5°(c=2). *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.65; H, 8.96.

3α-Hydroxytetrahydroalantolactone (III)—(II) (3 g.) in 95% EtOH was hydrogenated with PtO_2 (0.3 g.), absorbing 1.1 moles of hydrogen. The product was recrystallized from a mixture of benzene and hexane (1:1) to 3α-hydroxytetrahydroalantolactone in colorless needles of m.p. 143~144°; $[\alpha]_D$ −0.8°(c=3). *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.26; H, 9.67.

The acetate of (III) prepared with Ac_2O and pyridine showed m.p. 94~95°(from hexane), $[\alpha]_D$ −21° (c=2). *Anal.* Calcd. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.21; H, 8.83.

2,3-Dehydrotetrahydroalantolactone (VI)—A mixture of (III) (500 mg.), pyridine (5 cc.), and $POCl_3$ (0.3 cc.) was set aside at room temperature for 24 hrs. The solid obtained on dilution with water was collected and recrystallized from hexane to colorless needles of m.p. 139~142°, which consisted substantially of 2,3-dehydrotetrahydroalantolactone (VI). The probable contamination of dihydroalantolactone was not separated by chromatography on acid alumina.

(VI) (160 mg.) was hydrogenated in EtOH with PtO_2 (20 mg.), absorbing 17 cc. (1 mole) of H_2 at 29°, 755 mm. Hg. The product was recrystallized from hexane to tetrahydroalantolactone (IX), m.p. and mixed m.p. 142~143°.

3-Oxotetrahydroalantolactone (IV)—To a solution of (III) (2 g.) in AcOH (100 cc.) a solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (1 g.) in AcOH (30 cc.) was added dropwise and the solution was allowed to stand for 1 hr. at room temperature. The excess reagent was decomposed with EtOH, the solvent was removed under a reduced pressure, and the residue was diluted with water. The deposited precipitate was recrystallized from a mixture of hexane and benzene to 3-oxotetrahydroalantolactone (VI) of m.p. 189~191°,

8) Optical rotations were measured in $CHCl_3$ solution at 23°.

$[\alpha]_D$ −22.5°(c=2); yield, 1.28 g. *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.13; H, 8.87.

3-Oxo-β-tetrahydroalantolactone (X)—(IV) (145 mg.) in benzene solution was passed through a column of basic alumina (25 g., Brockmann grade I). The product was recrystallized from a mixture of hexane and benzene to 3-oxo-β-tetrahydroalantolactone (X) of m.p. 170~171°; $[\alpha]_D$ −34.8°(c=2). *Anal.* Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.26; H, 8.75.

Ethylenethioketals of (IV) and (X)—To a solution of (IV) (400 mg.) in AcOH (10 cc.) ethanedithiol (0.8 cc.) and BF_3 etherate (1 cc.) were added. The mixture was set aside overnight at room temperature, poured into water, and extracted with ether. The ether extract was washed with 5% $NaHCO_3$ solution, dried, and the solvent removed at a reduced pressure to dryness. The residue was recrystallized from 85% EtOH to ethylenethioketal (VII) in colorless needles m.p. 124~125°; $[\alpha]_D$ −30.4°(c=2). *Anal.* Calcd. for $C_{17}H_{26}O_2S_2$: C, 62.56; H, 8.03. Found: C, 62.71; H, 8.23.

Ethylenethioketal (XI) was prepared by the same procedure as above and showed m.p. 174°; $[\alpha]_D$ −24.2°(c=2). *Anal.* Calcd. for $C_{17}H_{26}O_2S_2$: C, 62.56; H, 8.03. Found: C, 62.89; H, 7.88.

Desulfurization of (VII) and (XI)—(VII) (200 mg.) was refluxed with Raney Ni (3 g.) in dioxane (40 cc.) for 8 hrs. The solution was separated from Ni and the solvent was evaporated. The residue was recrystallized from hexane to tetrahydroalantolactone (IX), m.p. and mixed m.p. 142~143°; yield, 145 mg.

Desulfurization of (XI) by the same procedure gave β-tetrahydroalantolactone (XII), which showed m.p. 120~121°(from hexane); $[\alpha]_D$ −37.5°(c=2). *Anal.* Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.37; H, 10.42.

3β-Hydroxytetrahydroalantolactone (V)—A solution of (IV) (150 mg.) in 95% EtOH (20 cc.) was treated with $NaBH_4$ (20 mg.). After 1 hr., the mixture was acidified with a few drops of AcOH, the solvent was removed under a reduced pressure, and the residue was extracted with ether. The product was recrystallized from a mixture of benzene and hexane to 3β-hydroxytetrahydroalantolactone as colorless leaflets, m.p. 165~166°. $[\alpha]_D$ −19.2°(c=2). *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.68; H, 9.50.

Acetate: m.p. 168°, $[\alpha]_D$ −55.1°(c=2). *Anal.* Calcd. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.27; H, 8.90.

(V) (70 mg.) in AcOH (6 cc.) was oxidized with $Na_2Cr_2O_7 \cdot 2H_2O$ (35 mg.) in AcOH (4 cc.). The product after recrystallization from hexane showed m.p. 187~190°, which proved identical with 3-oxotetrahydroalantolactone (IV) by admixture and the infrared spectra.

Action of $POCl_3$ in Pyridine on (V)—A solution of (V) (100 mg.), pyridine (5 cc.), and $POCl_3$ (2 drops) was set aside overnight at room temperature. The solid obtained on dilution with water was collected and recrystallized from hydr. EtOH to leaflets, m.p. 103~105°; yield, 15 mg.

3β-Hydroxy-β-tetrahydroalantolactone (XIII)—A solution of (X) (100 mg.) in 99% EtOH (30 cc.) was shaken in H_2 with PtO_2 (15 mg.), absorbing 1 mole of H_2. The product was recrystallized from a mixture of benzene and hexane to 3β-hydroxy-β-tetrahydroalantolactone (XIII) as colorless needles, m.p. 171~172°, $[\alpha]_D$ −16.1°(c=1.3). *Anal.* Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.67; H, 9.43.

Acetate: m.p. 153°; $[\alpha]_D$ −0.4°(c=3). *Anal.* Calcd. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.71; H, 8.95.

3α-Chloro-β-tetrahydroalantolactone (XIV)—A mixture of (XIII) (200 mg.), pyridine (3 cc.), and $POCl_3$ (0.2 cc.) was allowed to stand at room temperature for 20 hrs. The solid obtained on dilution with water was collected and recrystallized from a mixture of benzene and hexane to 3α-chloro-β-tetrahydroalantolactone (XIV) as colorless needles, m.p. 209~212°(decomp.); $[\alpha]_D$ −60.5°(c=2); yield, 180 mg. *Anal.* Calcd. for $C_{15}H_{23}O_2Cl$: C, 66.53; H, 8.56; Cl, 13.09. Found: C, 66.86; H, 8.55; Cl, 12.97.

Summary

The methyl group in 4-position of tetrahydroalantolactone and the so-called β-tetrahydroalantolactone was confirmed to be respectively β- and α-orientated. Several 3-hydroxytetrahydroalantolactones were prepared.

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