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Total Synthesis of Hydroxyhopanone

Hydroxyhopanone is a typical representative of naturally occurring triterpenoid which belongs to hopane group. In 1958 Schaffner, *et al.*[1] synthesized one of its acidic dehydration product, hopenone-I (Ⅵ), starting from α-onocerin. However, in their synthesis the asymmetries at C_{17} and C_{21} had been lost and regeneration of these asymmetries producing a natural triterpenoid was hitherto unsuccessful. We now report the synthesis of the compound which possesses all asymmetries and oxygenated functions identical with those of natural triterpenoid, hydroxyhopanone (Ⅱa).

The key-intermediate of the synthesis is gammaceran-3-on-21-ol (Ia) which can be derived from α-onocerin according to the methods by Schaffner, *et al.*[1] or more conveniently by Tsuda, *et al.*[2] On tosylation with *p*-toluenesulfonyl chloride and pyridine or on mesylation with methanesulfonyl chloride and pyridine, it easily formed a tosylate (Ic), m.p. 150°, $C_{37}H_{56}O_4S$, and mesylate (Ib), m.p. 200~201°, $C_{31}H_{52}O_4S$, respectively. The tosylate (Ic) was then subjected to solvolysis under reflux 20 hours in dioxane-water with presence of $CaCO_3$[3] and the product was separated by alumina chromatography into a hydroxy-fraction (~20%) and an unsaturated fraction (~80%). The hydroxy-fraction when crystallized from methanol formed colorless needles (~15%), m.p. 247~250°, which was proved to be completely identical (melting point and mixed melting point, IR, NMR, and TLC comparisons.) with natural hydroxyhopanone (Ⅱa) crystallized from the same solvent.*1

The unsaturated fraction was further separated by $AgNO_3$-silica gel chromatography into two compounds. One of them (Ⅲ) (~20%) was found to be identical with hopenone-a,*2 a dehydration product of hydroxyhopanone by $POCl_3$-pyridine. The other compound (Ⅳ) (~40%), m.p. 267~271°, $C_{30}H_{48}O$, was elucidated as gammacer-20-en-3-one (Ⅳ) since it showed two olefinic protons at δ 5.42 and 5.38 in its nuclear magnetic resonance (NMR) spectrum. Hydrogenation of this in acetic acid over PtO_2 gave, as expected, tetrahymanol (Ⅴ), m.p. 312~314°, being identified with the specimen obtained by the alternative synthesis.[2] Careful examination of the mother liquor from Ⅲ and Ⅳ by combination of gas chromatography and thin-layer chromatography (TLC) over $AgNO_3$-silica gel plate

*1 The m.p. and crystalline form of hydroxyhopanone depend on the solvent of crystallization. For example, the specimen crystallized from $CHCl_3$-MeOH showed m.p. 268~271°, fine needles.

*2 The reported specimens[4] of hopenone-a (Ⅲ) and hopenone-b (Ⅶa) seem to be impure. They were now obtained in pure forms, m.p. 207~209° and m.p. 219~220°, respectively, by $AgNO_3$-silica gel chromatography.

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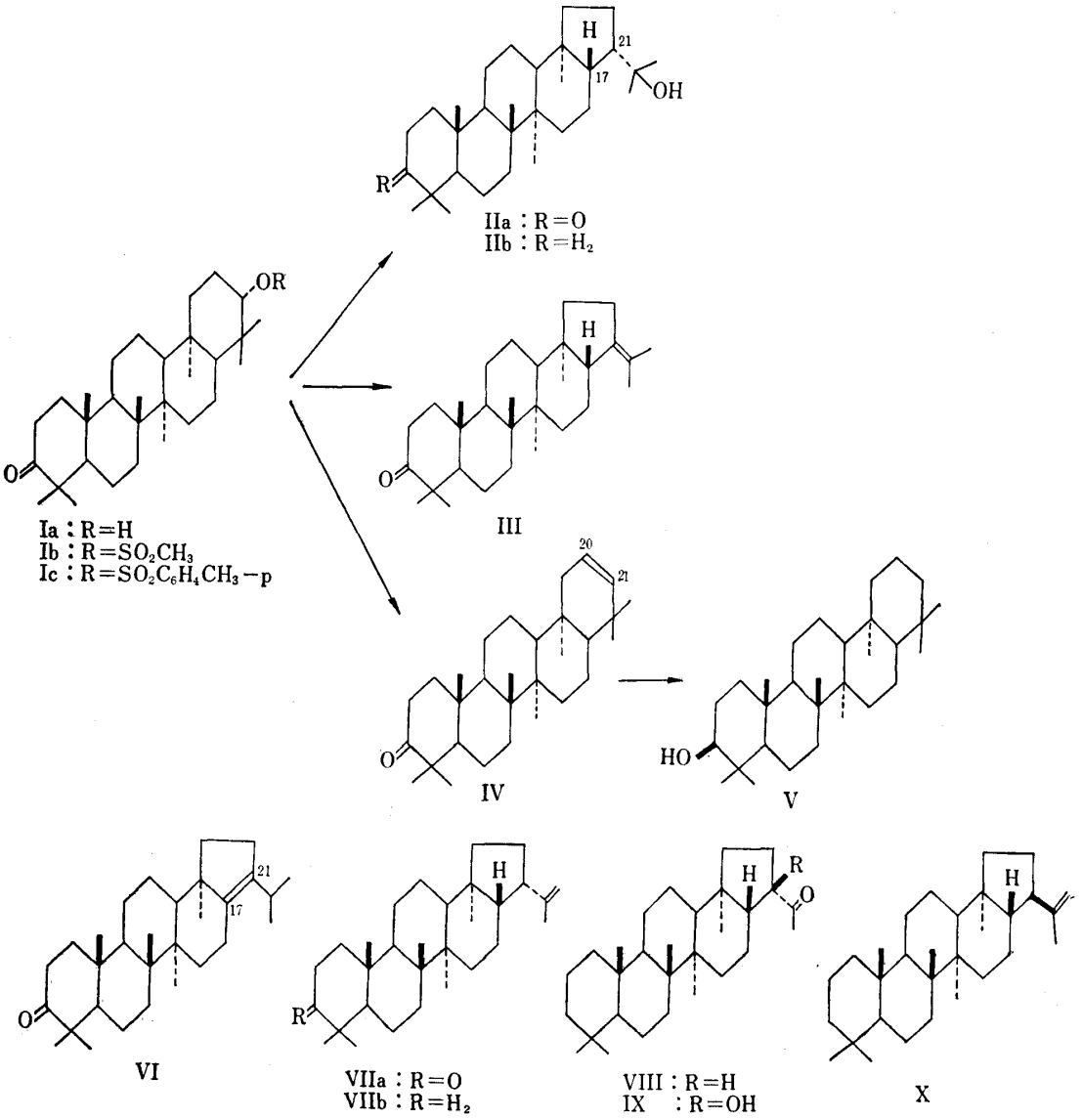

Chart 1.

demonstrated that hopenone-b (Ⅶa) was also formed in smaller amount, but the formation of hopenone-I (Ⅵ) being negligible.

Changing the solvent of solvolysis into DMF-water was found to increase the yield of Ⅳ, however, $CaCO_3$ was not the major factor of the formation of Ⅳ because solvolysis (2 hours) of the mesylate (Ib) in dioxane-water without $CaCO_3$ also afforded Ⅳ as the major product.

As our synthetic precursor of I, α- and β-onocerin, has been synthesized[5,6] and hydroxyhopanone (Ⅱa) was already transformed into diplopterol (Ⅱb),[4] diploptene (Ⅶb),[7] moretene (X),[7] adiantone (Ⅷ),[4] and hydroxyadiantone (Ⅸ),[8] the above transformation provides the total syntheses of these naturally occurring triterpenoids of hopane (or norhopane) and 21α-hopane group.

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Tetrahydrocannabinolic Acid, a Genuine Substance of Tetrahydrocannabinol

Isolation of tetrahydrocannabinolic acid (abbreviated to THCA) was first described by F. Korte, *et al.*[1] in 1965, but in his latest lecture he mentioned that their sample was the molecular compound with dimethylformamide.[2]

We wish to report the isolation of pure Δ^2-THCA,*1 a main component in Mexican hemp cultivated in Japan (I), with the aid of chromatography on cellulose powder impregnated with dimethylformamide and *n*-hexane as an eluant, followed by preparative thin-layer chromatography with *n*-hexane-EtOAc. The physical constants and some properties are as follows, Δ^2-THCA : RRT 1.23 (specimen cannabidiol (CBD) 1.00, Δ^2-tetrahydrocannabinol (Δ^2-THC) 1.23, Δ^3-THC*2 1.15, cannabinol (CBN) 1.51); trimethylsilate, RRT 3.25 (CBD 1.00, Δ^2-THC 1.33, CBN 1.75),*3 $[\alpha]_D^{14}$ −220° (c=0.75, $CHCl_3$), *Anal.* Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found : C, 73.17; H, 8.78. UV $\lambda_{max}^{cyclohexane}$ mμ (ε) : 224 (20300), 278 (12000), 310 (4800), IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3500 (sh), 2700~2400, 1685 (sh), 1660 (sh), 1620, 1565, NMR p.p.m. : 0.93 (3H) (t), 1.12 (3), 1.45 (3), 1.67 (3), 6.25 (1), 6.48 (1). Δ^2-THCA-Methyl ester : $[\alpha]_D^{12}$ −231° (c=1.12, $CHCl_3$), *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.35. Found : C, 74.44; H, 8.89. UV $\lambda_{max}^{cyclohexane}$ mμ (ε) : 224 (18000), 274 (10700), 309 (4300), IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3570, 1720, 1640, 1615, 1567. NMR p.p.m. : 0.90 (3), 1.09 (3), 1.44 (3), 1.63 (3), 3.89 (3), 6.29 (1), 6.37 (1). *p*-Nitrobenzoate of Δ^2-THCA-methyl ester : $[\alpha]_D^{15}$ −159° (c=0.97, $CHCl_3$), *Anal.* Calcd. for $C_{30}H_{35}O_7N$: C, 69.08; H, 6.76; N, 2.69. Found : C, 69.24; H, 7.11; N, 2.76. No activity was observed on catalepsy test in mouse at one hundredfold concentration of Δ^2-THC. On boiling with benzene for seven hours, or by smoking test*4 Δ^2-THCA was decarboxylated to give Δ^2-THC.

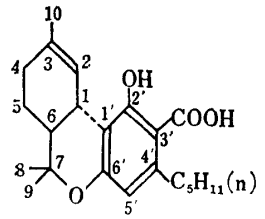

Chart 1. Δ^2-Tetrahydrocannabinolic Acid

*1 Considering with biosynthetic pathway of marihuana components,[3] the authors propose the new numbering system, available both in cannabinol and in cannabichromene.

*2 Prepared from Δ^2-1,6-*trans*-THC, isolated from the hemp, according to the method of Y. Gaoni and R. Mechoulam.[3]

*3 Gas liquid chromatography was run in the following conditions; Shimadzu GC-1B with 1.5% SE-52 column (2.25 m. × 4 mm.), column temperature 225°, sample heater temperature 280°, carrier gas : N_2, 22.5 ml./min., 3.0 kg./cm^2, RT of CBD : 5.33 min.

*4 Δ^3-THC was not observed in the condensate of the smoke of the hemp containing Δ^2-THCA, although Taylor, *et al.*[4] suggested the possibility of isomerization of Δ^2-THC to Δ^3-THC during GLC operation.

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