Department of Chemistry,
Tohoku University,
Sendai

Morio Kishi (岸 守男)
Tadahiro Kato (加藤忠弘)
Yoshio Kitahara (北原喜男)

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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 C₁₇ and C₂₁ 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°, C₃₇H₅₆O₄S, and mesylate (Ib), m.p. 200~201°, C₃₁H₅₂O₄S, respectively. The tosylate (Ic) was then subjected to solvolysis under reflux 20 hours in dioxane-water with presence of CaCO₃,³⁾ 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 AgNO₃-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 POCl₃-pyridine. The other compound (IV) (~40%), m.p. 267~271°, C₃₀H₄₈O, 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 PtO₂ 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 AgNO₃-silica gel plate

*¹ The m.p. and crystalline form of hydroxyhopanone depend on the solvent of crystallization. For example, the specimen crystallized from CHCl₃-MeOH showed m.p. 268~271°, fine needles.

*² The reported specimens⁴⁾ 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 AgNO₃-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 (V) being negligible.

Changing the solvent of solvolysis into DMF-water was found to increase the yield of V, however, CaCO₃ was not the major factor of the formation of V because solvolysis (2 hours) of the mesylate (Ib) in dioxane-water without CaCO₃ also afforded V as the major product.

As our synthetic precursor of I, α - and β -onocerin, has been synthesized^{5,6)} and hydroxyhopenone (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 21 α -hopane group.

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Faculty of Pharmaceutical Sciences,
Osaka University,
Toyonaka, Osaka

Yoshisuke Tsuda (津田喜典)
Masao Hattori (服部征雄)

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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 -

Chart 1. Δ^2 -Tetrahydrocannabinolic Acid

tetrahydrocannabinol (Δ^2 -THC) 1.23, Δ^3 -THC*² 1.15, cannabiniol (CBN) 1.51); trimethylsilylate, RRT 3.25 (CBD 1.00, Δ^2 -THC 1.33, CBN 1.75),*³ $[\alpha]_D^{25} -220^\circ$ ($c=0.75$, CHCl_3), *Anal.* Calcd. for $\text{C}_{23}\text{H}_{30}\text{O}_4$: C, 73.71; H, 8.44. Found: C, 73.17; H, 8.78. UV $\lambda_{\text{max}}^{\text{cyclohexane}}$ $m\mu$ (ϵ): 224 (20300), 278 (12000), 310 (4800), IR $\nu_{\text{max}}^{\text{CHCl}_3}$ 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: $[\alpha]_D^{25} -231^\circ$ ($c=1.12$, CHCl_3), *Anal.* Calcd. for $\text{C}_{23}\text{H}_{32}\text{O}_4$: C, 74.16; H, 8.35. Found: C, 74.44; H, 8.89. UV $\lambda_{\text{max}}^{\text{cyclohexane}}$ $m\mu$ (ϵ): 224 (18000), 274 (10700), 309 (4300), IR $\nu_{\text{max}}^{\text{CHCl}_3}$ 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: $[\alpha]_D^{25} -159^\circ$ ($c=0.97$, CHCl_3), *Anal.* Calcd. for $\text{C}_{30}\text{H}_{35}\text{O}_7\text{N}$: 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.

*¹ Considering with biosynthetic pathway of marihuana components,³⁾ the authors propose the new numbering system, available both in cannabiniol 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. $\times$ 4 mm.), column temperature 225°, sample heater temperature 280°, carrier gas: N_2 , 22.5 ml./min., 3.0 kg./cm², 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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