Total Synthesis of Hydroxyhopanone

Hydroxyhopanone is a typical representative of naturally occurring triterpenoid which belongs to hopane group. In 1958 Schaffner, *et al.* synthesized one of its acidic dehydration product, hoponenone-I (\(\text{Ib}\)), starting from \(\alpha\)-onocerin. However, in their synthesis the asymmetries at C\(_7\) and C\(_8\) 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 \(\alpha\)-onocerin according to the methods by Schaffner, *et al.* or more conveniently by Tsuda, *et al.* 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\(^\circ\), \(\text{C}_9\text{H}_9\text{O}_2\text{S}\), and mesylate (Ib), m.p. 200-201\(^\circ\), \(\text{C}_9\text{H}_9\text{O}_2\text{S}\), respectively. The tosylate (Ic) was then subjected to solvolysis under reflux 20 hours in dioxane-water with presence of CaCO\(_3\) and the product was separated by alumina chromatography into a hydroxy-fraction (\(\sim 20\%\)) and an unsaturated fraction (\(\sim 80\%\)). The hydroxyfraction when crystallized from methanol formed colorless needles (\(\sim 15\%\)), m.p. 247-250\(^\circ\), 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.*

The unsaturated fraction was further separated by \(\text{AgNO}_3\)-silica gel chromatography into two compounds. One of them (III) (\(\sim 20\%\)) was found to be identical with hopenone-a, a dehydration product of hydroxyhopanone by \(\text{POCl}_3\)-pyridine. The other compound (IV) (\(\sim 40\%\)), m.p. 267-271\(^\circ\), \(\text{C}_{30}\text{H}_{50}\text{O}\), was elucidated as gammaceran-20-en-3-one (IV) since it showed two olefinic protons at \(\delta 5.42\) and 5.38 in its nuclear magnetic resonance (NMR) spectrum. Hydrogenation of this in acetic acid over \(\text{PtO}_2\) gave, as expected, tetrahymanol (V), m.p. 312-314\(^\circ\), being identified with the specimen obtained by the alternative synthesis. Careful examination of the mother liquor from III and IV by combination of gas chromatography and thin-layer chromatography (TLC) over \(\text{AgNO}_3\)-silica gel plate

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*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\(^\circ\), fine needles.

*2 The reported specimens*\(^2\) of hopenone-a (III) and hopenone-b (\(\text{IIa}\)) seem to be impure. They were now obtained in pure forms, m.p. 207-209\(^\circ\) and m.p. 219-220\(^\circ\), respectively, by \(\text{AgNO}_3\)-silica gel chromatography.

demonstrated that hopene-\(b\) (\(\text{VIIa}\)) was also formed in smaller amount, but the formation of hopene-\(I\) (\(\text{V}\)) being negligible.

Changing the solvent of solvolysis into DMF-water was found to increase the yield of \(N\), however, CaCO\(_3\) was not the major factor of the formation of \(N\) because solvolysis (2 hours) of the mesylate (Ib) in dioxane-water without CaCO\(_3\) also afforded \(N\) as the major product.

As our synthetic precursor of I, \(\alpha\)- and \(\beta\)-nocicerin, has been synthesized\(^{4,5}\) and hydroxyhopanone (\(\text{IIa}\)) was already transformed into diploptoler (\(\text{IIb}\)), \(^4\) diploptene (\(\text{VIIb}\)), \(^7\) moretene (\(\text{X}\)), \(^7\) adamantone (\(\text{VII}\)), \(^4\) and hydroxy adamantone (\(\text{K}\)), \(^9\) the above transformation provides the total syntheses of these naturally occurring triterpenoids of hopane (or norhopane) and 21\(\alpha\)-hopane group.

Tetrahydrocannabinolic Acid, a Genuine Substance
of Tetrahydrocannabinol

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

We wish to report the isolation of pure $\Delta^2$-THCA, a main component in Mexican hemp cultured in Japan (1), 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, $\Delta^2$-THCA: RRT 1.23 (specimen cannabidiol (CBD) 1.00, $\Delta^2$-tetrahydrocannabinol (THC) 1.23, $\Delta^2$-THC 1.15, cannabidiol (CBD) 1.51), trimethylsilylate, RRT 3.25 (CBD 1.00, $\Delta^2$-THC 1.33, CBN 1.75), $^\alpha [\alpha]_D = -220^\circ$ (c = 0.75, CHCl$_3$), Anal. Calcd. for C$_{29}$H$_{38}$O$_5$: C, 73.71; H, 8.44. Found: C, 73.71; H, 8.78. UV $\lambda_{max}$ (nm) $\mu$ (e) : 224 (20300), 278 (12000), 310 (4800), IR $\nu_{max}$ 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). $\Delta^2$-THCA-Methyl ester : $[\alpha]_D = -231^\circ$ (c = 1.12, CHCl$_3$), Anal. Calcd. for C$_{30}$H$_{38}$O$_5$: C, 74.16; H, 8.35. Found: C, 74.44; H, 8.89. UV $\lambda_{max}$ (nm) $\mu$ (e) : 224 (18000), 274 (10700), 309 (4300), IR $\nu_{max}$ 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). $\rho$-Nitrobenzoate of $\Delta^2$-THCA-methyl ester : $[\alpha]_D = -159^\circ$ (c = 0.97, CHCl$_3$), Anal. Calcd. for C$_{36}$H$_{38}$O$_5$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 catatopy test in mouse at one hundredfold concentration of $\Delta^2$-THC. On boiling with benzene for seven hours, or by smoking test $\Delta^2$-THCA was decarboxylated to give $\Delta^2$-THC.

*1 Considering with biosynthetic pathway of marihuana components, the authors propose the new numbering system, available both in cannabidiol and in cannabinomone.

*2 Prepared from $\Delta^2$-1,6-trans-THC, isolated from the hemp, according to the method of Y. Gaoni and R. Mechoulam.

*3 Gas liquid chromatography was run in the following conditions; Shimadzu GC-1B with 1.5% SE-52 column (2.25 m x 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 $\Delta^2$-THC was not observed in the condensate of the smoke of the hemp containing $\Delta^2$-THCA, although Taylor, et al. suggested the possibility of isomerization of $\Delta^2$-THC to $\Delta^2$-THC during GLC operation.