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Received April 4, 1967

[Chem. Pharm. Bull. 15(7)1075~1076(1967)]

UDC 581.19 : 547.99 : 582.635.3

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.

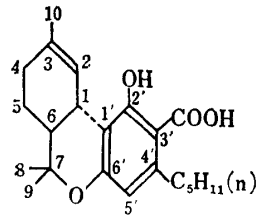

Chart 1. Δ^2-Tetrahydrocannabinolic Acid

*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.

1) F. Korte, M. Haag, U. Claussen : Angew. Chem., **77**, 862 (1965).
2) The 24th Annual Meeting of Pharmaceutical Society of Japan in Kyoto (April 8, 1967).
3) Y. Gaoni, R. Mechoulam : Tetrahedron, **22**, 1481 (1966).
4) E.C. Taylor, K. Lenard, Y. Shvo : J. Am. Chem. Soc., **88**, 367 (1966).

Quantitative separation of the phenol carboxylic acids and phenols according to Schultz's method including basic extraction of the acids,[5] followed by gas chromatographic separatory estimation of each component, indicated that after the storage of dried sample of (I) for four months at room temperature, 93% of marihuana components was found as phenol carboxylic acid, in which the ratio of CBDA, Δ^2-THCA and CBNA was 6/89/5, while 70% of the components was converted into phenols during the storage of dried sample of (I) at 35° for two months.

Since no detectable amount of phenols was observed on thin-layer chromatography in the methanol percolate of the fresh leaves of Mexican, Japanese, and Indian hemp, it seems quite obvious that marihuana components are preserved as phenol carboxylic acid form in the living plants, the decarboxylation being effected by the external factors such as temperature and light in the course of drying and storage after the harvest.

We are deeply grateful to Dr. Y. Gaoni for the authentic sample of Δ^2-tetrahydrocannabinol and to Prof. M. Fujita, for cannabidiol. Thanks are also due to Mr. H. Okabe for NMR spectra, to Miss K. Soeda for UV spectra and to Mr. M. Shido for the elemental analyses.

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Received April 21, 1967

5) O. E. Schultz, G. Haffner: Arch. Pharm., **293**, 1 (1960).

[Chem. Pharm. Bull. 15(7)1076~1079(1967)]

UDC 547.963.07

O⁶,2′-6-Hydroxycyclouridine

5-Iodo-2′-deoxycytidine has been used clinically for the treatment of herpes simplex keratitis in human eyes.[1] In line with the idea that a certain analogous nucleoside may have a similar effect, we have undertaken the investigations to synthesize 1-β-D-arabinofuranosyl-5-iodocytosine (I).

The iodination of 1-β-D-arabinofuranosylcytosine (CA) in the presence of iodic acid under the conditions described by Chang and Welch,[2] gave I in 25% yield as colorless needles which melted at 205~206° (decomp.) after recrystallization from water (*Anal.* Calcd. for $C_9H_{12}O_5N_3I$: C, 29.29; H, 3.27; N, 11.39; I, 34.38. Found: C, 29.38; H, 3.16; N, 11.36; I, 34.00). The reaction mixture, after removal of the crystals of I, was treated with activated charcoal and then with Dowex-50 (H^+) to isolate another crystals (II), platelets, m.p. 255° (decomp.)*1 from water (*Anal.* Calcd. for $C_9H_9O_6N_2I$: C, 29.35; H, 2.47; N, 7.61; I, 34.50. Found: C, 29.47; H, 2.48; N, 7.56; I, 34.36), showing a single ultra violet absorbing spot on paper chromatogram (R_{CA}*2 1.3 in *iso*-PrOH-NH_4OH-H_2O; 7:1:2), ultra violet absorption spectra ($\lambda_{max}^{pH\,5}$ 265 mμ; $\lambda_{min}^{pH\,5}$ 242 mμ; $\lambda_{max}^{pH\,11}$ 263 mμ; $\lambda_{min}^{pH\,11}$ 243 mμ)

*1 It darkened gradually above 230° with evolution of iodine gas.
*2 The ratio of the migration distance of a sample to that of CA.
1) K. Ikeda, E. Yoshida, S. Uchida, Y. Kitani: Jap. Rev. Clin. Opthal., **58**, 1039 (1964).
2) P. K. Chang, A. D. Welch: Biochem. Pharmacol., **8**, 327 (1961).