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

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O^6,2′-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).

and a pKa value of 8.2. Hydrogenation of II with palladised barium sulfate afforded needles (III) in good yield, m.p. 238° from ethanol (*Anal.* Calcd. for $C_9H_{10}O_6N_2$: C, 44.63; H, 4.16; N, 11.57. Found : C, 44.76; H, 4.31; N, 11.41). III gave a single ultra violet absorbing spot on paper electrophoresis ($R_{2'\text{-deoxyuridine}}$ 1.2, R_{II} 0.48 in 0.05*M* borate buffer, pH 9.2) and ultra violet absorption spectra ($\lambda_{max}^{pH 2}$ 252 mμ; $\lambda_{min}^{pH 2}$ 225 mμ; $\lambda_{max}^{pH 5}$ 252 mμ; $\lambda_{min}^{pH 5}$ 225 mμ; $\lambda_{max}^{pH 12}$ 254 mμ; $\lambda_{min}^{pH 12}$ 233 mμ). About the same time when we had obtained II in our laboratory, Chang reported the synthesis of a novel compound besides 5-iodo-2′-deoxycytidine by the iodination of 2′-deoxycytidine and postulated the former compound to be 5-iodo-O^6,5′-6-hydroxycyclodeoxyuridine.[3)]

By analogy with Chang's observations and structural assignments, we assigned II the structure 5-iodo-O^6,2′-6-hydroxycyclouridine.[*3]

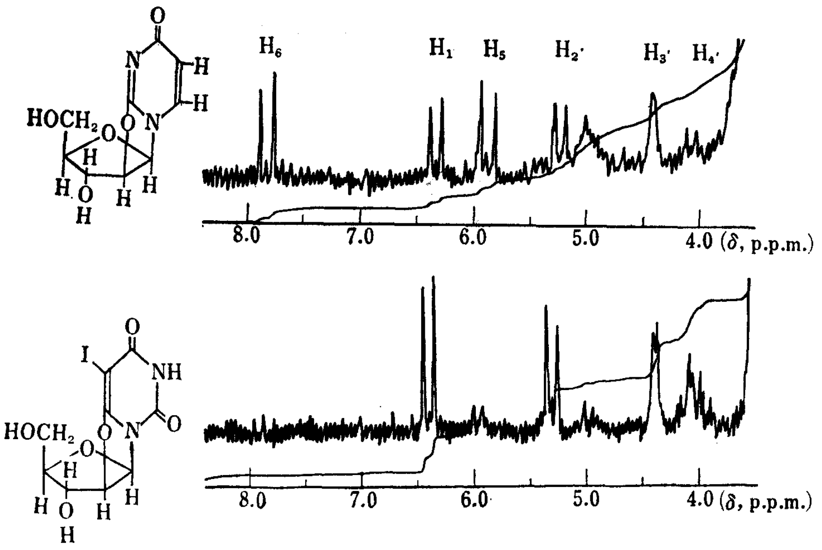

Fig. 1.

The nuclear magnetic resonance (NMR) spectrum[*4] of II clearly demonstrated the lack of the H_6 signal, which was seen in the spectrum of O^2,2′-cyclouridine (Fig. 1), thus supporting the correctness of the proposed structure.

Crystals of II are orthorhombic and belong to space group $P2_12_12_1$. The unit cell containing four molecules is of the dimensions, a=9.03, b=17.46 and c=7.09 Å. Diffraction measurements were made with a linear diffractometer to obtain 1198 independent data. The coordinates of iodine atom were determined from a three

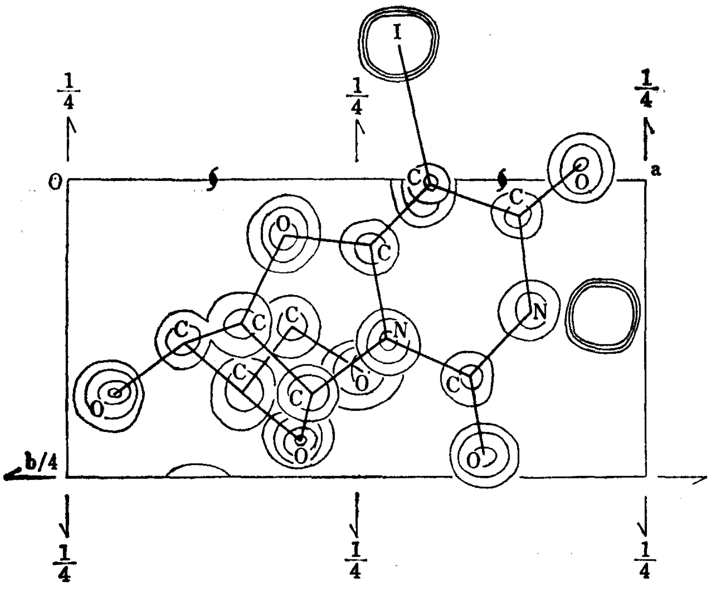

Fig. 2. 5-Iodo-O^6,2′-6-hydroxycyclouridine

[*3] Recently, Fox, *et al.* have reported the synthesis of the related compound which had suffered from the bond fission at the 3,4-position of the 5-fluoro-5,6-dihyro-O^6,2′-6-hydroxycyclouridine (J. J. Fox, N. C. Miller, R. J. Cushley : Tetrahedron Letters, **1966**, 4927).

[*4] Solvent : DMSO-d_6 containing a small amount of D_2O.

3) P. K. Chang : J. Org. Chem., **30**, 3913 (1965).

dimensional Patterson synthesis. For the solution of the coordinates of the light atoms, the minimum function method based on these coordinates of iodine atom ($x/2=0.42$, $y/b=0.39$, $z/c=0.29$) was carried out. Twenty one maxima were found in the diagram, of which eighteen must be true atoms considering the molecular formula. The detection of the three false peaks and assignment of the correst identities of C, N, O atoms were made by the analysis of the behavior of temperature factors in successive four cycles of least squares treatment. Thus the structure of the molecule was determined without ambiguity as shown in Fig. 2. The final R-value was 0.085.

When the alkali treatment*[5] was omitted on the iodination of CA, we obtained colorless needles (IV)*[6] in 43% yield, m.p. 210° (decomp.)*[7] from water (*Anal.* Calcd. for $C_9H_{10}O_6N_2I_2 \cdot H_2O$: C, 21.01; H, 2.35; N, 5.45; I, 49.30. Found : C, 21.01; H, 2.27; N, 5.48; I, 49.03), showing the lack of either H_6 or H_5 signal in the NMR spectrum (4.70, singlet). On treatment with alkali, IV gave II in good yield, therefore, the compound, on the basis of the elemental analysis and other physicochemical properties, was confirmed to be 5,5-diiodo-6-hydro (or 5,6-diiodo-5-hydro)-O^6,2′-6-hydroxycyclouridine.

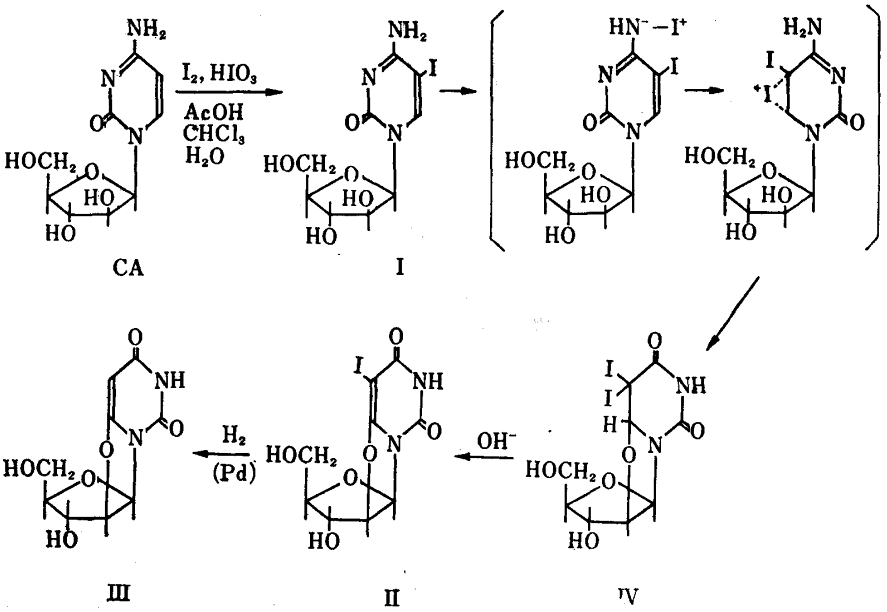

Chart 1.

Similar iodination of 1-β-D-arabinofuranosyluracil (UA) afforded 1-β-D-arabinofuranosyl-5-iodouracil (V), but II was not obtained in this case.

By carrying out the iodination of CA in the presence of nitric acid under similar conditions to those described by Hunter[4] (the alkali treatment omitted), IV was obtained in 23% yield, however, I was not

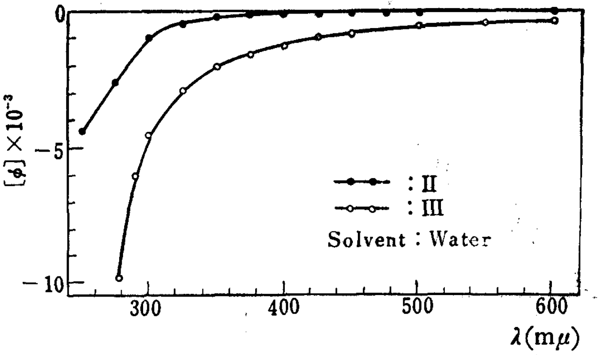

Fig. 3. ORD Curves of 5-Iodo-O^6,2′-6-hydroxycyclouridine (II) and O^6,2′-6-Hydroxycyclouridine (III)

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*[5] The method described by Chang and Welch[2] contains two processes; one of which is of course iodination, and the other is adjusting the pH of the iodinated reaction mixture to 10 with aqueous NaOH.

*[6] Paper chromatography (BuOH-AcOH-H_2O; 5:2:3) of the mother liquor, which was practically free from IV, demonstrated the formation of I.

*[7] It darkened gradually above 100° with evolution of iodine gas.

4) J.H. Hunter : C.A., **62**, 2812 (1965); U.S. Pat., 3,155,646.

obtained. The similar iodination of UV (the alkaline treatment was also omitted) gave V as the sole product.

At present, a possible mechanism for the formation of the O^6,2′-cyclostructure would be as summarized in Chart 1. The C$_4$-amino group in I thus may play an important role in the intramolecular iodination reaction, which in turn would be followed by the cyclic ether formation to yield Ⅳ.

The signs of the Cotton effect in Ⅱ and Ⅲ were both negative (Fig. 3). According to Ulbricht, *et al.*, who recorded a rule for predicting the sign of the Cotton effect with reference to the configuration of pyrimidine nucleosides,[5] the signs of the Cotton effect in Ⅱ and Ⅲ should be positive. Our results, therefore, present a discrepancy with their rule and more detailed studies should throw light on this problem.

Further attempts to synthesize O^6,3′-6-hydroxycyclouridine from 1-β-D-xylofuranosylcytosine are now in progress.

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5) T.L.V. Ulbricht, T.R. Emerson, R.J. Swan: Tetrahedraon Letters, **1966**, 1561.

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A Novel Skeletal Rearrangement of Aromatic N-Oxides upon Electron Impact

The formation of unstable oxaziridines in photochemical reactions of aromatic N-oxides has been postulated in order to account for the various photo-products such as oxazepines and pyridones.[1~7] The first step of these transformations is most conveniently depicted in terms of the n-π^* excited state of the N-oxides. The related reactions would be expected under the electron impact induced inoization as well, because the

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1) M. Ishikawa, Sa. Yamada, C. Kaneko: This Bulletin, **13**, 747 (1965); M. Ishikawa, Sa. Yamada, H. Hotta, C. Kaneko: *Ibid.*, **14**, 1102 (1966); C. Kaneko, Sa. Yamada: *Ibid.*, **14**, 555 (1966); C. Kaneko, Sa. Yamada, M. Ishikawa: Tetrahedron Letters, No. 19, 2145 (1966); C. Kaneko, Sa. Yamada: Rept. Res. Inst. Dental materials, Tokyo Medico-Dental Univ., **1966**, 804.
2) O. Buchardt, J. Becher, C. Lohse: Acta Chem. Scand., **20**, 2467 (1966); O. Buchardt, C. Lohse: Tetrahedron Letters, No. 36, 4355 (1966).
3) J. Streith, C. Sigwalt: *Ibid.*, No. 13, 1347 (1966).
4) E.C. Taylor, C.G. Spence: Chem. Commun., **1966**, 767.
5) M.J. Haddadin, C.H. Issidorides: Tetrahedron Letters, No. 8, 753 (1967).
6) O. Buchardt: *Ibid.*, No. 50, 6221 (1966).
7) C. Kaneko, Sa. Yamada, I. Yokoe: *Ibid.*, No. 39, 4701 (1966); C. Kaneko, Sa. Yamada, I. Yokoe, M. Ishikawa: *Ibid.*, No. 20, 1873 (1967).