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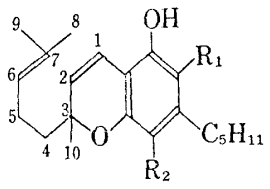
Cannabichromenic Acid, a Genuine Substance of Cannabichromene[1)]

Cannabichromene (CBC), one of the active constituents of hemp, was isolated by Gaoni and Mechoulam[2a)] and by Korte, *et al.*,[2b)] and assigned the structure (I). Recently, Korte[3)] mentioned the isolation of cannabichromenic acid (CBCA), a genuine substance of CBC in the living plants, but the detail has not been presented. We wish to report the isolation and the structural elucidation of CBCA (IIa).

The mixture of the acids was obtained as pale yellow syrup from the benzene percolate of the hemp, according to Schultz's procedure.[4)] Column chromatography of this mixture on silica gel yielded tetrahydrocannabinolic acid (THCA),[1)] as a major component, and cannabidiolic acid (CBDA)[5)] with hexane–EtOAc elution in a ratio of 5:1 to 3:1. Successive development of the column with the same solvent system (1:1) finally afforded a new substance (A), which gave the methyl ester (B) on methylation with diazomethane in ether at 10°. The nuclear magnetic resonance (NMR) spectrum of B was in good agreement with that of CBC except for the signal of methyl protons at 3.91 ppm and the absence of one of the phenyl protons at 6.15 ppm, and strongly suggested that A was CBCA. This was confirmed by the conversion of A to CBC on heating with toluene as in the formation of tetrahydrocannabinol (THC) from THCA.[1)] Physical constants are as follows; CBCA: relative t_R[6)] 1.06 [specimen cannabidiol (CBD) 1.00 (t_R 3.54 min), CBC 1.06, Δ^2-THC 1.32, cannabigerol (CBG) 1.64, cannabinol (CBN) 1.64]; CBCA-trimethylsilate (TMS): relative t_R 3.79 [CBD-TMS 1.00 (t_R 2.03 min), CBC-TMS 1.29, Δ^2-THC-TMS 1.48, CBG-TMS 1.67, CBN-TMS 1.95, CBDA-TMS 2.31, THCA-TMS 3.74], $[\alpha]_D^{18}$ +4.8° (c=0.69, chloroform). *Anal.* Calcd. for $C_{22}H_{30}O_4$: C, 73.74; H, 8.37. Found: C, 73.24; H, 8.53. UV λ_{max}^{EtOH} mμ (ε): 253 (24100), 259 (23900), 290 (4200), 326 (2900). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3100, 2800—2400 (sh), 1640, 1618, 1560. CBCA-Methyl ester: *Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.19; H, 8.60. Found: C, 74.69; H, 8.80. UV λ_{max}^{EtOH} mμ (ε): 256 (22900), 263 (23800), 293 (3600), 326 (2300). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2550, 1730, 1642, 1620, 1560. NMR (in $CDCl_3$) δ: 0.92 (3H, triplet), 1.40 (3H), 1.59 (3H), 1.68 (3H), 3.91 (3H), 5.09 (1H), 5.47 (1H, doublet, J=10.5 cps), 6.21 (1H), 6.75 (1H, doublet, J=10.5 cps).



I : R_1=R_2=H
IIa : R_1=COOH, R_2=H
IIb : R_1=H, R_2=COOH

In the two possible structures of CBCA, *i.e.* IIa and IIb, the former is supported by the evidence that IR spectra of CBCA in various concentrations indicates the presence of intramolecular hydrogen bond between the carboxyl and the hydroxyl groups, and consistent biogenetically with the structure of THCA, concerning the location of carboxyl group.

CBCA exclusively was observed in the seedling almost one week prior to the appearance of THCA.

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1) This forms Part II of "Cannabis." Part I: *Chem. Pharm. Bull.* (Tokyo), **15**, 1075 (1967).
2) *a*) Y. Gaoni and R. Mechoulam, *Israel J. Chem.*, **3**, 65 (1965); *Chem. Commun.*, **1966**, 20; *b*) U. Claussen, F.v. Spulak, and F. Korte, *Tetrahedron*, **22**, 1477 (1966).
3) The 24th Annual Meeting of Pharmaceutical Society of Japan, Kyoto, April 1967; U. Claussen, F.v. Spulak, and F. Korte, *Tetrahedron*, **24**, 1021 (1968).
4) O.E. Schultz and G. Haffner, *Arch. Phram.*, **293**, 1 (1960).
5) Z.Krejci, M. Horak, and F. Santavy, *Pharmazie*, **14**, 349 (1959); O.E. Schultz and G. Haffner, *Z. Naturforsch.*, **14b**, 98 (1959).
6) GLC was conducted in the following conditions : Shimadzu GC-1B (FID) with 1.5% SE-52 column (2.25 m × 4 mm), column temperature 229°, sample heater 290°, carrier gas : N_2, 20 ml/min, 3.0 kg/cm^2.

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Synthesis of Purpnigenin

Purpnigenin is a digitenol of the simplest structure initially isolated from *Digitalis purpurea* L. leaves as a glycoside purpnin.[1] The structure **6** was determined by Ishii[2] by identification of an oxidation product with unambiguously prepared authentic sample. We wish here to describe the partial synthesis of purpnigenin starting with 3β-acetoxypregna-5,16-dien-20-one(**1**). Our synthetic method has its significance in that one may find general applicability in the syntheses of other digitenols such as purprogenin.[3]

3β-Acetoxypregna-5,16-dien-20-one(**1**) was converted by the known method of Solo and Singh[4] into 3β-acetoxypregna-5,14,16-trien-20-one(**2**). Saturation of the 16 double bond in the trienone(**2**) was achieved by the reduction either with triphenyltin hydride or with triethylsilane in the yields of 80%.[5] 3β-Acetoxypregna-5,14-dien-20-one(**3**) thus obtained had mp 148—150°[6] and showed the following spectral data that supported the structure; nuclear magnetic resonance (NMR)[7]: 0.87 (18-H), 1.03 (19-H), 2.03 (OAc), 2.15 (21-H), 5.13 (15-H, peak width at half-height=5 cps), 5.38 (6-H, half-width=9 cps); infrared absorption spectrum (IR) (KBr) cm^{-1}: 1738 (OAc), 1710 (20-one); ORD (c=0.102, MeOH) $[M]_D^{20}$ (mμ): +3895 (311) (peak), −7230 (268) (trough). The dienone **3** was then oxidized with an equimolar amount of monoperphthalic acid giving a single monoepoxide, mp 158°, in the yield of 65%.[8] That this is a 14,15-oxide was confirmed by NMR in which 15-H was observed as a singlet at 3.31,[9] and 6-H at 5.28 as a broad peak with half height width of 9 cps. The stereochemistry **4** was deduced from the known steric course of epoxidation[10] and supported by ORD which showed positive Cotton effect (a=+103).[11]

1) *a*) D. Satoh, H. Ishii, Y. Oyama, and T. Okumura, *Yakugaku Zasshi*, **75**, 1573 (1955); *b*) *Idem.*, *Chem. Pharm. Bull.* (Tokyo), **10**, 37 (1962); *c*) H. Freitag, S. Spengel, H.H.A. Linde, and K. Meyer, *Helv. Chim. Acta*, **50**, 1336 (1967).
2) H. Ishii, *Chem. Pharm. Bull.* (Tokyo), **9**, 411 (1961); *Idem.*, *ibid.*, **10**, 351, 354 (1962).
3) D. Satoh and J. Morita, *Chem. Pharm. Bull.* (Tokyo), **16**, 178 (1968); M. Fukuoka and H. Mitsuhashi, *ibid.*, **15**, 2007 (1967).
4) A.J. Solo and B. Singh, *J. Org. Chem.*, **30**, 1658 (1965).
5) The novel feature of this reduction method was presented at the 88th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April, 1968. Experimental details will be reported in a full paper.
6) Melting points were taken with a Yanagimoto Micro Melting Point Apparatus and uncorrected. Satisfactory elemental analytical data were obtained for all new compounds.
7) NMR spectra were measured using deuteriochloroform as solvent unless indicated otherwise and are quoted as δ(ppm) down field from tetramethylsilane as internal standard.
8) Treatment of **3** with N-bromoacetoamide in an acetate buffer, followed by alumina chromatography, afforded 3β-acetoxy-14β, 15β-epoxypregn-5-en-20-one which will serve as a precursor in the synthesis of 12-deoxyisoramanone.[1a]
9) K. Tori, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, **29**, 1136 (1964); A.D. Cross, *J. Am. Chem. Soc.*, **84**, 3206 (1962).
10) H. Ishii, *Chem. Pharm. Bull.* (Tokyo), **10**, 354 (1962) ; H. Hasegawa, Y. Sato, and K. Tsuda, *ibid.*, **11**, 1275 (1963) ; D. Satoh and J. Morita, *ibid.*, **16**, 178 (1968).
11) K.M. Wellman and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 60 (1965).