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A NEW TETRAHYDROCANNABINOLIC ACID

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A major component of hashish is the acid I (1) which, though inactive per se, is converted on smoking into the active Δ^1-tetrahydrocannabinol (Δ^1-THC) (II) (2). We wish to report now the presence in some hashish samples of a second Δ^1-THC acid, III, which on heating, and presumably on smoking, is likewise converted into Δ^1-THC.

In order to differentiate between the two acids we suggest that acid I be named " Δ^1-THC acid A" and III " Δ^1-THC acid B".

Careful chromatography of the cannabinoid acidic material of a hashish sole on silicic acid (Merck, 70-325 mesh) yielded cannabidiolic acid (3), (eluted with 10% ether in pet. ether), Δ^1-THC acid B (eluted with 50% ether in pet. ether) and cannabigerolic acid (3) (eluted with ether). In this hashish sample III was present in 0.5% over-all concentration. The physical constants of Δ^1-THC acid B are as follows: m.p. 184-5° (d)(from $CHCl_3$),$[\alpha]_D^{CHCl_3}$ -202°; λ_{max}^{EtOH} 216mμ (ϵ, 27800), 250mμ (sh) (ϵ, 3210), 285mμ (sh) (ϵ, 1680); δ (ppm) in $CDCl_3$, 0.87 ($C\underline{H}_3$, tr), 1.20, 1.56, 1.68 (3 $C\underline{H}_3$, s), 2.70-3.70 (3 H, benzylic, mult.), 6.30 (1 H, olefinic, br), 6.50 (1 H, aromatic, s), no peaks above 7.25 ($CHCl_3$); $\nu_{max}^{CHCl_3}$ 1710 cm^{-1} (strong) (COOH); mass spectrum, very similar (4) to that of Δ^1-THC in addition to mass numbers 358 (M^+) and 343 (M^+ -15).

On TLC (silica gel; development with 88% benzene- 10% methanol - 2% acetic acid) Δ^1-THC acid B is considerably more polar than Δ^1-THC acid A.

The structure of III is further elucidated by the chemical correlations indicated in the Chart[*]. Some salient data are indicated below the formulas in the Chart. The I.R. spectra are particularly illuminative. In the B series the carboxyl and carbomethoxyl groups absorb between

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[*] All new compounds gave correct analytical values and have the expected spectroscopic properties.

1710 cm^{-1} and 1725 cm^{-1}, while those in the A series absorb at 1615 cm^{-1} to 1650 cm^{-1}. Of special interest are also the coversions with borontrifluoride etherate of compounds of the B series into those of the A series. We believe that this isomerization takes place by opening of the pyran ring (with borontrifluoride etherate) and cyclization with the alternative phenolic group to, what appears to be, a thermodynamically more stable system.

A comparison of the U.V. and I.R. spectral properties of Δ^1-THC acid B (III) with those of Δ^1-THC acid A (I)[‡] indicate that in III there is loss of coplanarity of the carboxyl group due to steric hindrance. In I this effect is minimized, apparently by hydrogen bonding with the free phenolic group.

The acid B (III) was found in hashish soles which contain very little or none of the acid I. It is conceivable that the differences in THC acid content may be due to biochemical variation and may have chemotaxonomic importance.

Both Δ^1-THC acids A and B showed no psychotomimetic activity in rhesus monkeys (5) when administered i.v. in doses up to 10mg/kgr.

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[‡] λ^{EtOH}_{max} 221mμ (ε, 26500), 260mμ (ε, 7900), 303mμ (ε, 4100); δ (CCl_4), 0.92, 1.10, 1.43, 1.65 (methyl groups), 6.15 (aromatic H), 6.38 (olefinic H), 12.75 and 11.95 (each 1 H, due to H bonded OH and COOH); $\nu^{CHCl_3}_{max}$ 1615 cm^{-1} (strong) (COOH).

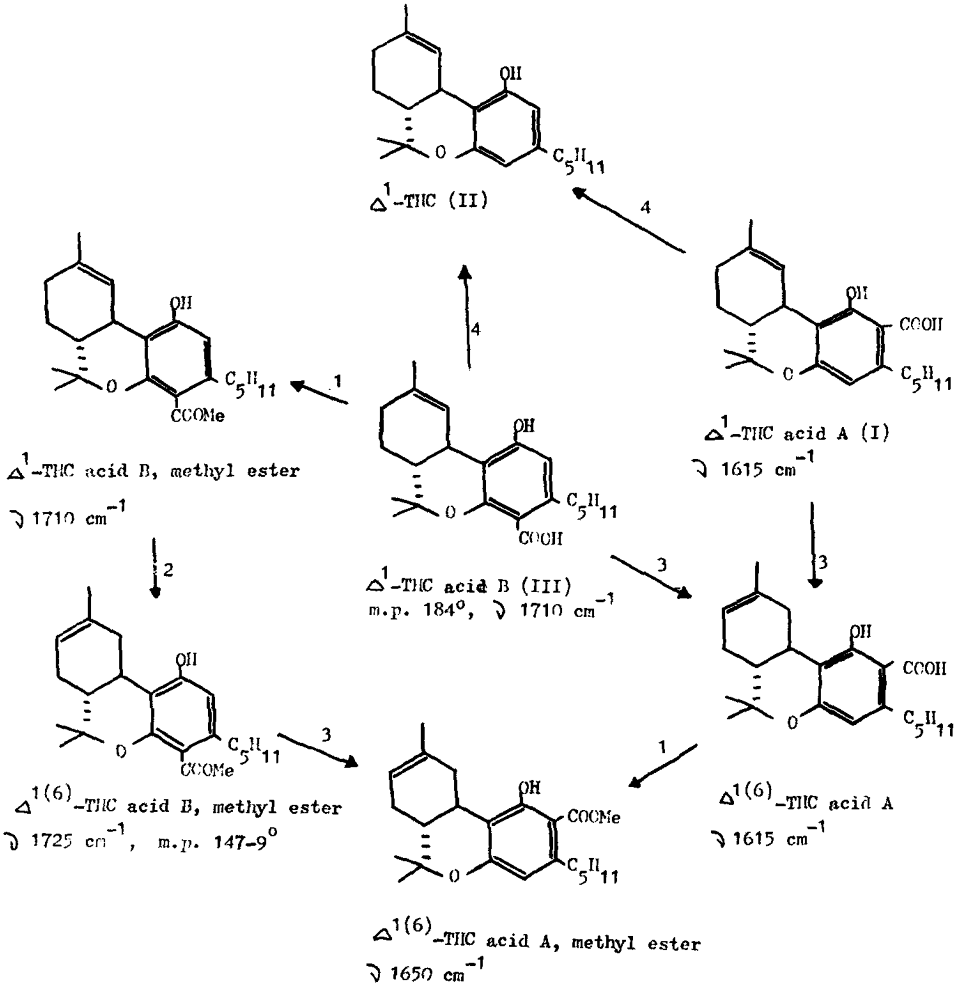

Chart. Interrelations of the THC acids

Reagents: 1) CH_2N_2; 2) p - toluene sulphonic acid, benzene, 80°; 3) BF_3 etherate, r.t. in CH_2Cl_2; 4) 140°.