A New Type of Cannabinoid. Synthesis of Cannabielsoic Acid A by a Novel Photo-oxidative Cyclisation

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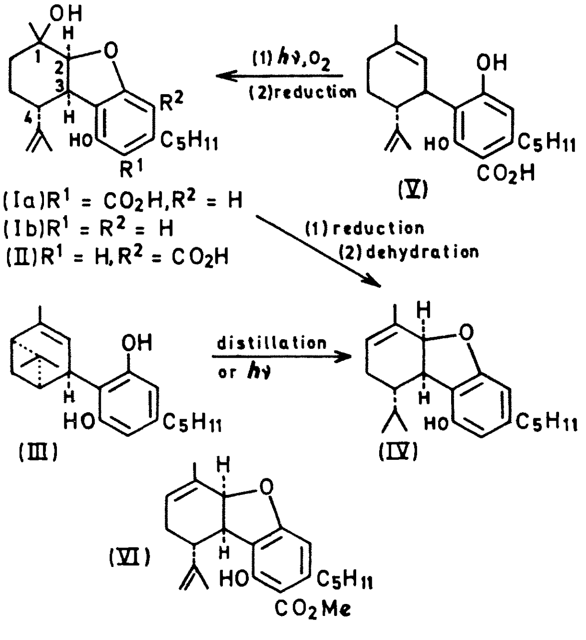
Summary Two tricyclic dihydrobenzofuran cannabinoids have been isolated and one of them has been synthesized by an intramolecular photo-oxidative cyclisation which involves attack by a phenoxy-group and molecular oxygen on a double bond.

The active Δ^1-tetrahydrocannabinol (Δ^1-THC)[1] is extracted from hashish by petroleum ether. An inactive mixture is obtained from the residue on subsequent treatment with benzene. Gas chromatography† of this mixture shows the presence of components with retention time equivalent to that of Δ^1-THC. In view of the analytical importance of this observation we have investigated the compounds responsible for this coincidence.

Silica gel chromatography of the above described benzene extract gave, on elution with ethyl acetate, cannabielsoic acids A (Ia) as an oil (0·08% yield).‡ The n.m.r. spectrum of the methyl ester of (Ia) indicates the presence of (i) one aromatic proton, (ii) a terminal methylene group, (iii) two methyl groups, one of which is vinylic (δ 1·83) and the other is apparently α to an oxygen (1·46), (iv) the C-2 proton at 4·12 (d, J 5·2) which appears as a singlet on irradiation of the C-3 proton, (v) the C-3 proton at 3·38 (dd, $J_{2,3}$ 5·2, $J_{3,4}$ 9·0) which collapses to a doublet on irradiation of the C-2 proton, and (vi) a hydrogen-bonded phenolic group (11·3). A hydroxy-group is present which does not undergo acetylation. The most plausible structure that fits the above data and the $C_{23}H_{32}O_5$ formula (M^+ 388) is the methyl ester of (Ia). A synthetic correlation with olivetylpinene[2] (III) supports the suggested structure.§ On distillation or on irradiation in methanol for 24 hr. (Q 81 Hanau lamp, Corex filter), (III) is isomerized to (IV). The same compound is obtained from (Ib) [produced by decarboxylation of (Ia)] by reduction and dehydration.

Cannabidiolic acid[3] (V) in cyclohexane was irradiated for



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† 2% OV-17 on Chromosorb Q at 240°.

‡ A second component, cannabielsoic acid B (II) was isolated in 0·04% yield. The elucidation of its structure will be presented in the full paper.

§ Satisfactory n.m.r. and i.r. spectra were obtained for all new compounds.

160 hr. (same lamp, quartz vessel); oxygen was bubbled throughout the reaction. In the dark no reaction takes place. The mixture obtained was reduced with sodium bisulphite. On chromatography two isomers were obtained, (Ia) (17%) and 1-iso-(Ia) (16%). When the reduction was omitted the corresponding hydroperoxides (positive KI–starch test) were obtained in addition to the tertiary alcohols. On irradiation (same lamp, Pyrex vessel), or on reduction, the hydroperoxides were converted into (Ia) and 1-iso-(Ia) respectively. The methyl ester of (Ia) and 1-iso-(Ia) gave the same product (VI) on dehydration.

The stereochemistry at C-2–C-3 is probably *cis*. This is deduced from the fact that radical processes which form related tricyclic dihydrobenzofuran systems (*cf.* Pumerer's ketone[4,5]) give the more stable *cis*-compounds.

As a total synthesis of (V) has been reported[6] the conversion of (V) into (Ia) represents a formal total synthesis of the latter.

The above reaction apparently represents the first recognized example of a new photo-oxidative cyclisation. A very recent publication[7] describes a related oxidation, which, in our opinion, may be induced by light.

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