of advantage as compared to the use of Pb-IV-acetate[9]. However, in the oxidation of **7** and **8**, no p-quinoid substances were detected. The main product of the reaction was the cleavage product **13** (70–80% yield).

Therefore, a number of indirect approaches to obtain **3** or the corresponding lactone **22** were tried: Oxidation of **9** yielded the p-quinol **14** and its previously known lactone **15**[11,5]. Since the isolation of **14** was accompanied by considerable loss of material, it was transformed into the more stabile **15** by gentle heating in glacial acetic acid/HCl 10:0.5; 27% yield; mp 100–102°C; MS [M+ 164]; UV [λ_{max}^{MeOH} 225, 343 nm, ε_{max} 15800,23]; IR [ν 1785, 1675, 1637, 1611 cm^{-1}]; NMR (acetone-d$_6$), [δ 7,15 and 6,26 ppm (4H, AA'BB'-system, J = 10,4 Hz) 3.04–2.31 ppm (4H, m)]. Excessive heating yields the coumarine **16**, the formation of which is in agreement with the rules for acid catalyzed rearrangements of free p-quinols[12]. The oxidation of **10** yields **17** and the corresponding lactone **18**; as described above, also **17** may be transformed into **18**, 17% yield; mp 115–116°C; MS [M+ 222]; UV [λ_{max}^{MeOH} 225, 301 nm, ε_{max} 12852,25]; IR [ν 1799, 1740, 1668, 1631, 1607 cm^{-1}]; NMR (CDCl$_3$) [δ 6.93 and 6.40 ppm (4H,AA'BB'-system, J = 10, 8 Hz) 2.74–2.42 ppm (3H, o, J$_{AB}$ = 15 Hz), 2.19 ppm (3H, s). In the oxidation of **11** no free p-quinol was obtained. Instead, besides the lactone **20**, 9% yield; mp 96–97°C; MS [M+ 180]; UV [λ_{max}^{MeOH} 226,290, ε_{max} 15450,23]; IR [ν 3470, 1774, 1669, 1633, 1611 cm^{-1}]; NMR (CDCl$_3$) [δ 6.94 and 6.37 ppm (4H, AA'BB'-system, J = 10, 5 Hz) 2,93–2,23 ppm (3H, ABX-system, J$_{AB}$ = 14, 1 Hz) 2.90 ppm (1 H, s, OH-group)], the stabile compound **19** was formed by nucleophilic attack of the side chain hydroxyl group at the β-carbon of the quinoid system, 30% yield; oil; MS [M+ 212]; UV [λ_{uuax}^{MeOH} 210, (284), (290), 324 nm, ε_{max} 8630, (150) (140), 30]; IR [ν 3680, 3590, 3440, 1730, 1745, 1682, 1610 cm^{-1}]; NMR (CDCl$_3$) [δ 6.75–6, 12 ppm (2H, AB-system, J = 9.75 Hz) 3.10–2.15 and 4.88–4.40 ppm (6H, ABX-

system), 3.76 ppm (3H, s) 3.92 ppm (1H, s, OH-group)]. Similarly, oxidation of **12** results in the formation of **21** in 54% yield. A tendency to intramolecular addition has also been observed with other similar p-quinols[4,5,7]. **19** may be transformed back to **20** by heating in glacial acetic acid/HCl. Upon reduction with Zn/glacial acetic acid and treatment with diazomethan **19** yielded the starting material **11** in 94% yield.

In numerous trials, using a series of different oxidation reactions and conditions, conversion of **20** into the desired lactone **22** was not successful. No azo-derivative corresponding to **22** could be detected using the sensitive DNPH reaction. In a different approach, however, the stabile enol-lacton-methylether of **22** was obtained.[13].

Summary. A proposed intermediate in the metabolic transformation of p-hydroxyphenylpyruvic acid into homogentisic acid has been synthetized. In an experiment with radioactive material in pig liver homogenate it could be shown that this compound does not occur as a free intermediate.

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Cannabidiol and its Pharmacokinetic Interaction with Δ^1-Tetrahydrocannabinol

Δ^1-Tetrahydrocannabinol (Δ^1-THC) and cannabidiol (CBD) are major constituents of marihuana. Although Δ^1-THC is thought to be mainly responsible for the biological activity of marihuana[1-3], interest has also centred on CBD because of its ability to potentiate the depressant effects of centrally active drugs such as the barbiturates[4,5] and Δ^1-THC[6,7]. The latter modification was of particular interest to us since it implies that CBD has a role in intoxication by marihuana and hashish.

CBD has been found to be a potent inhibitor of hepatic drug metabolism[8-10] and it has been suggested that it is by this mechanism that pharmacological interactions could take place[6,7,11]. Jones and Pertwee[11] noted that pretreatment of mice with large amounts of CBD causes higher levels of Δ^1-THC and 7-hydroxy-Δ^1-THC (1.4 and 2 times respect.) than is normally found in the brains of mice after administration of pure Δ^1-THC. The conditions of this experiment are not parallel to those where the influence of CBD on the effects of Δ^1-THC had been observed, but the inference that the interactions are the result of elevated brain levels of Δ^1-THC and its metabolites arizing from inhibition of the subsequent metabolism of these compounds, seems a reasonable one.

It appears that it is Δ^1-THC (rather than its hydroxylated metabolite) in the brain which is responsible for

most of the 'cannabis effect'[12,13]. Assuming there is little or no blood-brain barrier[14,15] to this compound, blood levels of Δ^1-THC are probably the most easily measured indicator of Δ^1-THC intoxication and it would be expected that co-administration of CBD and Δ^1-THC would result in elevated Δ^1-THC blood levels.

Propylene glycol solutions of Δ^1-THC (1 mg; ca. 0.1% cannabinol) and CBD (1 mg) were administered i.v. both separately and as a mixture, to male rats (ca. 145 g). The disappearance of these cannabinoids from the blood was followed for 10 min by GLC according to the procedures reported elsewhere[16,17]. One rat was used for each analysis and, as in our previous work[16,17], these results were found to be highly reproducible provided rats of similar weights were used. It was found that the disappearance rates for CBD and Δ^1-THC in the mixture, were identical to those determined when they were administered separately (see Figures). The blood level curves are biphasic but no work has been undertaken to characterize them further.

The route of administration of the cannabinoids is of particular importance to the onset and duration[18-20] of the biological effects being studied. We have reported that after i.v. administration, the metabolism of Δ^1-THC to cannabinol (CBN) in the rat is extremely rapid –

the CBN blood level reaching a peak 4% of the Δ^1-THC level within 40 sec of injection[17] — and that the onset of Δ^1-THC intoxication (as evidenced by sluggishness, lack of grooming etc.[16]) is also very fast (ca. 3 min). We conclude that, if the mechanism of the interaction of CBD with Δ^1-THC in the rat is by inhibition of the metabolism

Fig. 1. The disappearance of Δ^1-THC from the blood of rats. A) 1 mg Δ^1-THC injected i.v. alone; B) 1 mg Δ^1-THC injected i.v. with 1 mg CBD.

Fig. 2. The disappearance of CBD from the blood of rats. A) 1 mg CBD injected i.v. alone; B) 1 mg CBD injected i.v. with 1 mg THC.

of Δ^1-THC and, as we discussed earlier, if this does result in elevated Δ^1-THC blood levels, then the onset of this effect must be very much slower than the onset of the Δ^1-THC metabolism and intoxication after i.v. administration. On the other hand, the possibility that changes in concentration of the metabolites of Δ^1-THC or CBD may be contributing to the overall effects, also cannot be eliminated.

Summary. Co-administration of cannabidiol with Δ^1-tetrahydrocannabinol was found to have no effect on the rate of disappearance of Δ^1-tetrahydrocannabinol from the blood of rats. The implications of this finding are discussed.

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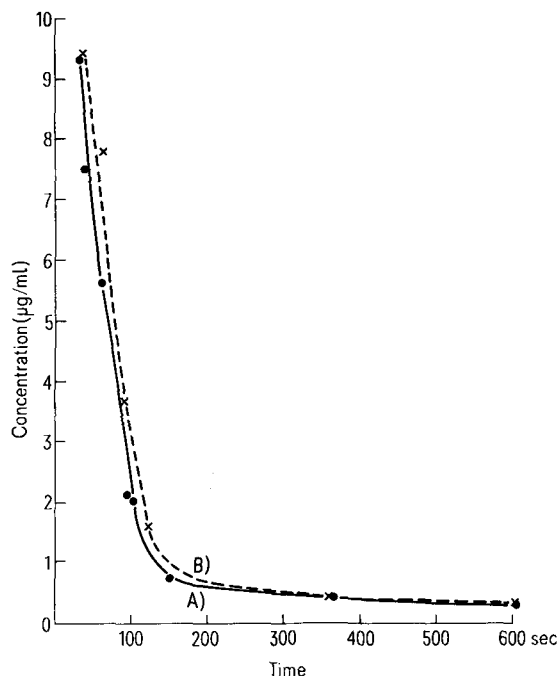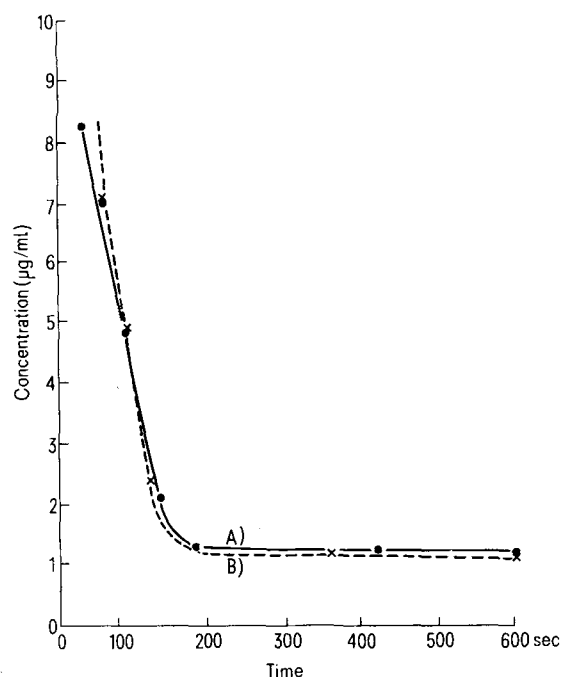
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