

PHOTOCHEMICAL REACTIONS OF CANNABIDIOL CYCLIZATION TO Δ^1 -TETRAHYDROCANNABINOL AND OTHER TRANS FORMATIONS

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Abstract—Irradiation of cannabidiol (I) in methanol gave mainly 1-methoxy-dihydrocannabidiol (II, both isomers). Irradiation of I in cyclohexane gave a complicated mixture from which, in addition to starting material, the following compounds were isolated: Δ^1 tetrahydrocannabinol (III), Δ^8 iso-tetrahydrocannabinol (IV), 8,9-dihydrocannabidiol (V), and 3'-cyclohexylcannabidiol (VI).

IN A review of the pharmacological work of his group with natural and synthetic cannabinoids Loewe¹ mentions that “. . . unwirksamen Cannabidiol wurde nach Ultraviolett-bestrahlung ein wirkstoffgehalt nachgewiesen, der auf Umwandlung von 2% in THC[†] hindeutet.”[‡] We have been unable to find a report in the chemical literature on this experiment.

A related experiment has been reported by Korte and Sieper,² who exposed cannabidiol (I) to UV light of different energies and temperatures of 15° and 60°. Only one compound was formed in considerable amount and it was not identical with natural THC; these experiments are likewise reported only in a review which lacks experimental details. The criteria for identity seem to be TLC comparisons. Hively,³ in a Thesis, reported that cannabidiolic acid diacetate (VIIb) on irradiation with UV light gave $\Delta^{1(6)}$ THC (VIII). Experimental conditions and product yield of this unusual transformation were not divulged.

In view of this divergence of results we undertook to reinvestigate the photoreactivity of cannabidiol.⁴ Our interest also stemmed from the possibility that the close proximity of photoreactive groups in I could result in interesting photoreactions.

As we expected the formation of Δ^1 THC or $\Delta^{1(6)}$ THC all irradiations were monitored by monkey tests. The sensitivity of this species to THC (50–100 γ /kgr)⁵ assured the detection of any formation of active cannabinoids in yields as low as 1%.

From irradiation of cannabidiol in either benzene (in a Pyrex vessel) or t-butanol (in a Corex vessel) we were able to isolate only starting material (*ca* 90%). However, irradiation of cannabidiol in methanol with a Hanovia 450 watt lamp in a Corex vessel gave a mixture from which, on chromatography we isolated four compounds. The least polar material was shown to be the starting material (32% recovery). The compound eluted next was a dimeric product to which we tentatively assign the dimeric structure IX on the basis of NMR and mass spectral data (Experimental). The third compound eluted from the column was 1 α -methoxy-dihydrocannabidiol (IIa), obtained as an oil (8%),

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† Tetrahydrocannabinol.

‡ (Free Translation) On UV irradiation of inactive cannabidiol it was possible to ascertain the presence of an active principle; this suggested that approximately 2% of the substance had been converted into THC.

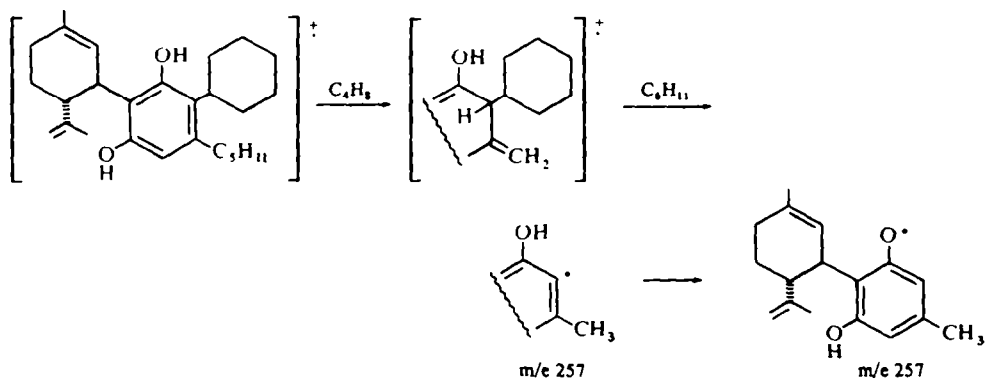
followed by the isomeric 1 β -methoxy-dihydrocannabidiol (IIb), m.p. 114–115° (29%). In both isomers the mass spectra have the M⁺ peak at 346; the base peak is at 314 indicating the facile loss of methanol, to yield a cannabidiol-type ion. The other peaks of each spectrum are essentially identical to those of cannabidiol.⁶ The NMR spectra of both IIa and IIb possess all the expected signals (Experimental). Of special interest are the two aromatic protons which appear as *two* peaks. By comparison, in cannabidiol they form a sharp singlet.⁷ We assume that the observed non-equivalence of the aromatic protons is due to the increased steric hindrance to free rotation of the aromatic ring as a result of the presence of an additional hydrogen at C₂. It is possible that the groups on C₁ have a certain buttressing effect on the C₂ protons thus increasing the steric hindrance. The most significant difference between the NMR spectra of IIa and IIb is the position of the C₁ methyls, which are at δ 1.18 and 1.39 respectively. In related 1-methoxy-1-methylcyclohexanes the axial Me has been observed to appear in lower field.⁸ Hence we assume that in IIb the C₁ Me group is axial and in IIa it is equatorial. This is expected on mechanistic grounds. Marshall⁹ and Kropp⁹ have independently shown that photochemical methanol addition across a double bond takes place *via* an ionic mechanism, and that the compound with the OMe group in the equatorial position predominates in the reaction products. In our case the ratio of IIb to IIa is 3.6 : 1.

The general structure of IIb is supported by its ready conversion to Δ^{11} THC (VIII) on treatment with boron trifluoride etherate in methylene chloride.

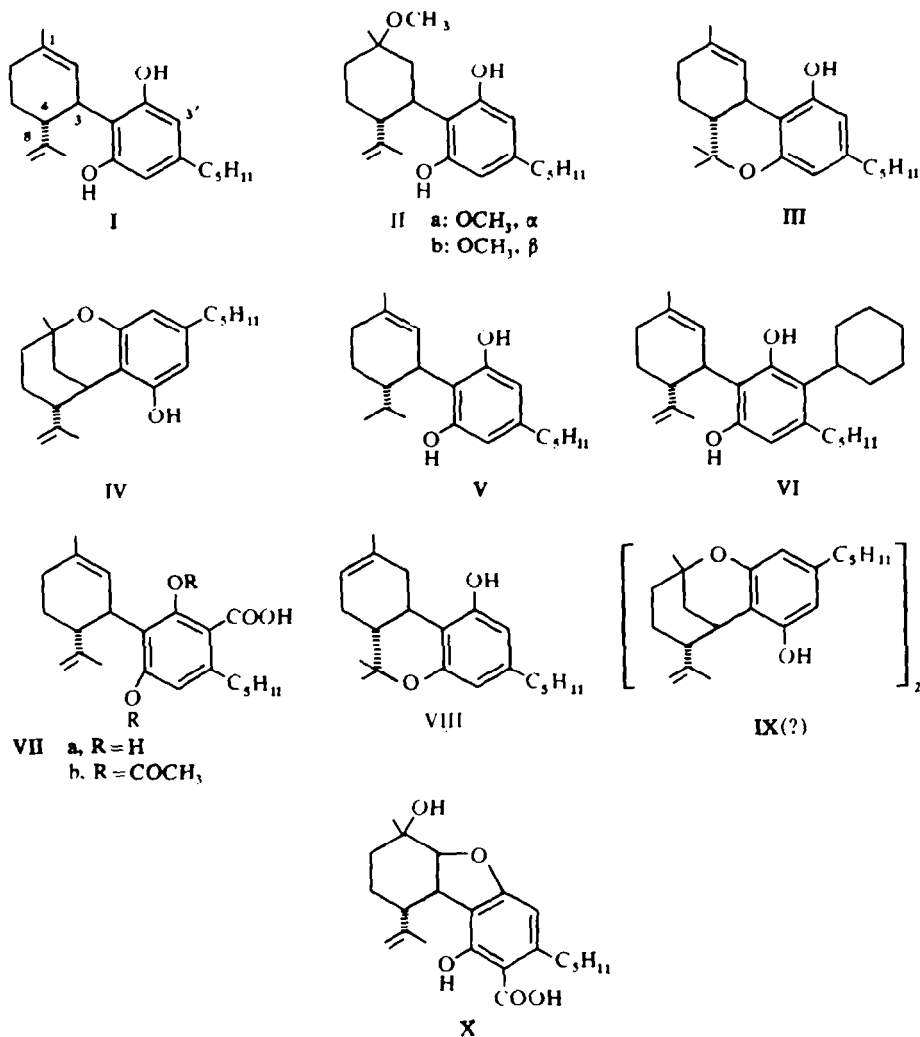
Irradiation of cannabidiol (I) in cyclohexane with a Hanau Q-81, 70 watt lamp in a quartz vessel, gave a mixture quite different from the one described above. On chromatography the following compounds were isolated (in order of increasing polarity): a new compound (3%), whose molecular weight of 396 (mass spectrum) and NMR spectrum (one aromatic proton only, the vinylic methyls and vinylic terpene moiety identical to those in cannabidiol) indicate structure VI; 8,9-dihydrocannabidiol (V)¹⁰ (8%); starting material (25%); Δ^8 -iso-tetrahydrocannabinol (IV)¹⁰ (13%) and Δ^1 -THC (III)⁴ (13%).

The formation of 3'-cyclohexylcannabidiol (VI) indicates the photochemical production of a cyclohexyl radical which reacts with an aryl radical.

An analysis of the mass spectrum of VI is of interest. The spectrum is essentially identical to that of cannabidiol (I)⁶ except for the molecular ion peak and one at 257 (40% abundance of the base peak *m/e* 231). We assume that the latter ion is formed through the loss of C₄H₈ due to a McLafferty rearrangement of the C₅H₁₁ side chain and subsequent loss of cyclohexyl radical.



By contrast, in cannabidiol the McLafferty rearrangement of the side chain is a minor cleavage.⁶ It seems that the presence of the bulky cyclohexyl group *ortho* to the pentyl side chain causes this effect. The cannabidiol ion-radical in the mass spectrum of VI (314, 70% of the base peak) is obtained when the *initial* cleavage involves the loss of cyclohexene.¹¹



The photochemical production of IV and Δ^1 THC (III) has precedence. Frater and Schmidt,¹² and Horspool and Pauson,¹³ have reported intramolecular Markovnikoff-type additions of phenols to double bonds. In our case the cyclizations are of the same type, i.e. they apparently proceed *via* the more stable tertiary cation or radical. We intuitively prefer the radical mechanism because cyclizations of cannabidiol with acids predominantly yield products formed through the Δ^8 double bond, while in the above

photochemical cyclization, additions to either double bond (in the same yield) are observed.

The formation of Δ^1 THC on irradiation, while of interest in itself, is probably of no importance in the conversion of cannabidiol into THC either in Nature, or as an artifact on storage of hashish and marihuana. If we assume that such a reaction does take place we have to expect to find the isomeric Δ^8 -ios-THC (IV) in either fresh Cannabis or illegal material. This compound has not been isolated from a natural source, though we have investigated numerous hashish samples.

The formation of the dihydrocompound V was unexpected. Photochemical reductions of double bonds usually take place when the double bond is conjugated or the solvent is a facile hydrogen donor. However a few cases of photochemical hydrogenations in which the above conditions are lacking have been reported.¹⁴ We assume that the reducing agent is an hydrogen radical formed from a phenolic group.

Irradiation of cannabidiolic acid diacetate (VIIb) in cyclohexane did not give $\Delta^{1(6)}$ THC, contrary to the previous report.³ However, our experimental conditions may have been different.

It was of interest to compare the photochemical behavior of cannabidiolic acid (VIIa) with that of cannabidiol (I). The acid (VIIa) remained essentially unchanged; 90% of the starting material was recovered. Under identical experimental conditions cannabidiol reacted at a much faster rate; only 25% of the starting material was present (*vide supra*). The products of the reaction with cannabidiolic acid (VIIa) were largely the cannabielsoic acids A (both isomers at C₁) (X)¹⁵ formed from traces of oxygen present in the nitrogen gas used. It seems that the carboxyl group stabilizes the phenoxy radical which, to the extent that it reacts, does so with the Δ^1 double bond at position C₂ in an anti-Markovnikoff fashion. A tertiary radical is produced on C₁ which reacts with molecular oxygen to yield after reduction, the cannabielsoic acids.

The reaction product, from which Δ^1 THC was isolated, was the only irradiation mixture, in doses up to 10 mg/kg, showed biological activity³ in rhesus monkeys. The effective dose of the mixture corresponded reasonably well with its Δ^1 THC content (13%).

EXPERIMENTAL

Instrumentation. IR: Perkin-Elmer Model 137; UV: Unicam, SP 800A, solvent-ethanol; NMR: JEOL C-60H, recorded in CCl₄ with TMS at the internal reference standard; chemical shifts, δ , are expressed in ppm measured downfield from the reference; Mass spectra: Atlas CH4, 150°, 70eV; column chromatography: adsorbent Florisil (Ratio of adsorbent to compound, 100:1); TLC: Kieselgel GF₂₅₄ or PF₂₅₄ Merck, elution with light petroleum: ether; spray—a 0.5% soln of KMnO₄ in a saturated soln of cupric acetate; GLC: column, 2% OV-17 on gas Chrom Q, nitrogen flow, 30 cc/min. 1.8 m column (inside diam. 3 mm) temp 235° on a Packard chromatograph, Model 7821. Microanalyses were carried out by the Hebrew University microanalytical laboratory.

Irradiations were carried out in an apparatus consisting of two parts, and outer jacket and a dipper well. The dipper well was a water-cooled Hanovia 5 liter flask immersion well made of either quartz or Pyrex. The outer jacket was made of Pyrex glass fitted with N₂ inlet at the bottom and a septum-covered inlet in the midsection for withdrawing aliquots during irradiations. Different jackets varying in capacity from 130 to 180 ml were used. The side arm was connected to a condenser the top of which was joined to a mercury filled tube in order to prevent the entrance of air. The soln level was always kept above the mercury ark to prevent pyrolysis. N₂ was bubbled through the soln for 15 min before the irradiation, during which it was stopped.

The inert atmosphere was kept in the vessel throughout the reaction, which was magnetically stirred.

Materials. Cannabidiol, m.p. 66–67°; benzene, distilled over sodium; *t*-butanol, distilled; acetone (BDH) and MeOH (Mallinckrodt) analytical grade; cyclohexane, distilled over sodium; ether, dried and distilled over sodium; petroleum, dried over CaCl₂ and distilled, b.p. 60–80°. Known compounds were identified by direct comparison with authentic samples through their IR and NMR spectra as well as TLC and GLC.

Irradiation of I in benzene. Cannabidiol (I) (680 mg) in benzene (130 ml) in a Pyrex vessel was irradiated for 27 hr with a Hanau Q81 lamp. The solvent was evaporated and the product was chromatographed on a column. Pure starting material (630 mg) and a mixture of at least 3 compounds (30 mg) were obtained.

Irradiation of I in *t*-BuOH. Cannabidiol (500 mg) in *t*-BuOH (180 ml) in a quartz vessel (Corex filter) was irradiated for 3.5 hr with a Hanovia 450 watt lamp. Work-up as above gave starting material (440 mg) and a mixture of numerous compounds. (35 mg).

Irradiation of I in MeOH. Cannabidiol (I) (630 mg) in MeOH (180 ml) in a quartz vessel (Corex filter) was irradiated for 5 hr with a Hanovia 450 watt lamp. The solvent was evaporated and the oily mixture was chromatographed. Elution with 2% ether in light petroleum gave starting material (202 mg), followed by a compound to which we tentatively attribute the dimeric structure IX (65 mg); elution with 10% ether in light petroleum gave IIa followed by a mixture of IIa and IIb and then pure IIb. The mixture was separated on preparative TLC (elution mixture, 25% ether in light petroleum 4 consecutive runs) and the pure components were combined to give a total of 56 mg IIa and 200 mg IIb.

The oily IX has NMR signals at δ , 0.88 (t, 6H, terminal Me's), 1.28, 1.32 (C₁ Me's), 1.58 (s, C₈ Me's), 3.10 (br C₃—H), 4.42, 4.58 (together 4H, >C=CH₂), 5.98 (s, aromatic 2H), no signal attributable to a C₂ olefinic proton between 5.0 and 6.0; no H in offset up to 14 ppm; mass peaks, 626 (M⁺), 558, 314 (45% of base peak), 313 (2%; symmetrical cleavage of dimer), 299, 271, 258, 246, 231 (base peak), 193; ν_{\max}^{near} 888 cm⁻¹ (terminal methylene); λ_{\max} 283, 275 and 212 m μ (ϵ , 2490, 2570, 68 800). The acetate of IX has NMR signals at δ , 0.89 (t, 6H, terminal Me's), 1.35, 1.39 (C₁ Me's), 1.54 (s, C₈ Me's), 2.30 (6H, acetate Me's), 4.53 and 4.65 (together 4H, >C=CH₂), 6.62 and 6.66 (2 aromatic H); mass peaks 398 (25% of base peak), 356 (22%), 355 (25%, symmetrical cleavage of dimer), 314 (22%), 313 (25%), 273 (38%), 235, 231, 193 (base peak). $\nu_{\max}^{\text{C=O}}$ 884 cm⁻¹ (terminal methylene), 1770 cm⁻¹ (acetate), no OH.

The oily IIa has NMR signals at δ 0.88 (t, 3H, terminal Me) 1.18 (C₁ Me), 1.63 (C₈ Me), 3.31 (4H, —OCH₃ and C₃—H), 4.50, 4.70 (2H, terminal methylene), 6.13, 6.22 (2 aromatic H); λ_{\max} 282, 275, 212 m μ (1170, 1190, 29000); $\nu_{\max}^{\text{CHCl}_3}$ 890 cm⁻¹ (terminal methylene); mass spectral peaks, 346 (M⁺, 31% of base peak), 314 (base peak, M⁺ —CH₃OH), 299, 271, 246, 231 (63% of base peak), 193.

The crystalline IIb, m.p. 114–115° (from light petroleum) has NMR signals a δ 0.88 (t, 3H, terminal Me), 1.39 (C₁ Me), 1.61 (C₈ Me), 3.20 (br. C₃—H), 3.31 (3H, —OH₃), 4.53, 4.73 (2H terminal methylene), 6.09, 6.12 (2 aromatic H); λ_{\max} 282, 274, 213 m μ (1210, 1310, 29500); $\nu_{\max}^{\text{CHCl}_3}$ 890 cm⁻¹ (terminal methylene); mass spectral peaks, 346 (M⁺, 65% of base peak), 314 (base peak, M⁺ —CH₃OH), 299, 271, 246, 231 (69% of base peak), 193; (Found: C, 76.18; H, 9.56. C₂₂H₃₄O₃ requires: C, 76.30; H, 9.84%). The diacetate of IIb has NMR signals at δ 0.88 (t, 3H), 1.18 (C₁ Me), 1.50 (C₈ Me), 2.22, 2.30 (s, 2 acetate Me's), 3.12 (—OCH₃), 4.45 (br, s, terminal methylene), 6.54, 6.71 (2 aromatic H).

Reaction of IIb with boron trifluoride. BF₃-etherate (0.5 ml) was dropped into a soln of IIb (180 mg) in CH₂Cl₂ (25 ml). After 15 min at room temp water (20 ml) was poured into the mixture. The organic layer was dried and evaporated. The oily residue (160 mg) was purified on preparative TLC (20% ether in light petroleum) to give Δ^8 THC (VIII) (80 mg).

Irradiation of I in cyclohexane. Cannabidiol (1.560 gr) in cyclohexane (150 ml) in a quartz vessel was irradiated for 22 hr with a Hanau Q81 lamp. The solvent was evaporated and the product was chromatographed on a column. Elution with 1% ether in light petroleum gave a mixture of VI and V.¹⁰ Further elution with the same solvents afforded a mixture of Δ^8 iso-THC (IV)¹⁰ and starting material (I). Elution with 2% ether in light petroleum gave Δ^1 THC (200 mg).

The mixture of VI and V was separated by preparative TLC (elution mixture, 5% ether in light petroleum, 2 consecutive runs) to give 45 mg of VI and 116 mg of V. The mixture of IV and I is not separated on GLC under our standard conditions. Separation between them was done on preparative TLC (25% AgNO₃ on silica gel PF₂₅₄; elution mixture, 10% ether in light petroleum) to give 200 mg of IV and 390 mg of I.

The oily VI, which is not eluted on GLC under our conditions, has NMR signals at δ 0.80 (t, 3H, terminal methyl), 1.68 (3H, C₁ methyl), 1.84 (3H, C₈ Me), 3.94 (C₃ —H), 4.27, 4.45 (2H, terminal methylene); mass spectral peaks, 396 (M⁺), 314, 299, 271, 257 (40% of base peak) 231 (base peak), 193. *R_f*-values of the above products on TLC (elution mixture 2% ether in light petroleum, 10 consecutive runs), are as follows: VI, 0.35, V, 0.29, I, 0.22, VIII, 0.19, IV, 0.18, III, 0.15.

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