EXPERIENTIA

Vol. 28 - Fasc. 2 Pag. 121-248 15. 2. 1972

SPECIALIA

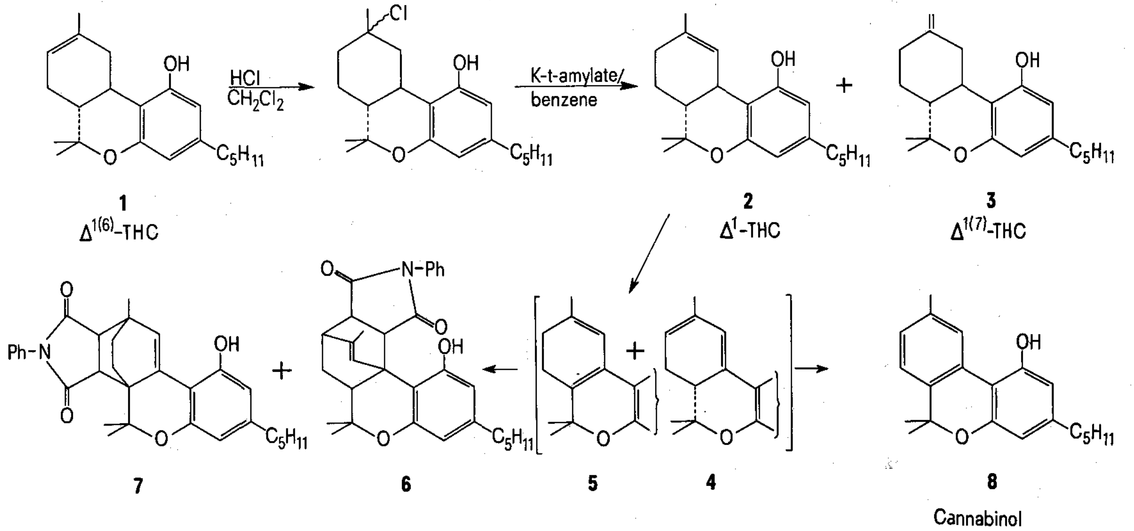
Hashish VI[1]: Conversion of (−)-$\Delta^{1(6)}$-Tetrahydrocannabinol to (−)-$\Delta^{1(7)}$-Tetrahydrocannabinol. Stability of (−)-Δ^{1}- and (−)-$\Delta^{1(6)}$-Tetrahydrocannabinols

The recent report[2] on the total synthesis of (−)-$\Delta^{1(7)}$-tetrahydrocannabinol (THC) (**3**) prompts us to record our findings at this time. PETRZILKA et al.[3], have claimed a quantitative conversion of (−)-$\Delta^{1(6)}$-THC (**1**) to (−)-Δ^{1}-THC (**2**) by addition and then stereospecific elimination of hydrogen chloride. However, following their procedure we find that the formation of **2** from **1** is always accompanied by 3–5% of **3**.

We have found that **3** can be easily isolated from the mixture by chromatography on silver nitrate-silica gel[4] followed by chromatography on silica gel thus constituting a total synthesis of (−)-$\Delta^{1(7)}$-THC (**3**). The synthesis of (±) **3** has been reported earlier/[5].

The mixture (**2**, 92%; **3**, 6%; others, 2%)[6] as obtained after dehalogenation and workup was chromatographed through 100 times its weight of silver nitrate-silica gel in a 5-ft × 0.5-in column and eluted with hexane (flow rate 3.6 ml/min), then with 98:2, 95:5, 90:10 and finally 50:50 hexane/ether mixtures. The desired materials **2** and **3** were enriched in the 98:2 and 90:10 fractions, respectively. Fractions enriched in **3** from various silver nitrate-silica gel colums were combined (1.23 g) and chromatographed on 100 g of silica gel (Brinkman 70–250 mesh) packed in a 5-ft × 0.5-in column. Hexane was passed at a flow rate of 7 ml/min (with external pressure) and the eluant was changed to 96:4 hexane/ether mixture and monitored fractions were collected. A total of 0.3 g of colorless resin was obtained[7]; (*m/e*; 314); $[\alpha]_D^{26}$ $-19.8°$ (c, 3.2; chloroform); NMR ($CDCl_3$) δ, 0.87 (t, 3H), 1.04, 1.39 (s, 6H), 3.73 (m, 1H, C_3-benzylic), 4.74 (br s, 2H, exocyclic), 6.04 and 6.23 (d, J = 1.5 cps, 2H, aromatic); IR showed a strong band at 885 cm^{-1} ($CH_2{=}C<$).

As little is known about the stability of Δ^{1}-THC (**2**) except that it darkens on exposure to air and is slowly converted to cannabinol[8], we determined the stability of Δ^{1}- and $\Delta^{1(6)}$-THCs under various conditions.



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[1] For part V see R. K. RAZDAN and G. R. HANDRICK, J. Am. chem. Soc. *92*, 6061 (1970).

[2] J. W. WILDES, N. H. MARTIN, C. G. PITT and M. E. WALL, J. org. Chem. *36*, 721 (1971).

[3] T. PETRZILKA, W. HAEFLIGER and C. SIKEMEIER, Helv. chim. Acta *52*, 1102 (1969).

[4] 80–100 mesh having an assay 20% $AgNO_3$, 66% SiO_2 and 16% H_2O.

[5] K. E. FAHRENHOLTZ, M. LURIE and R. W. KIERSTEAD, J. Am. chem. Soc. *89*, 5934 (1967).

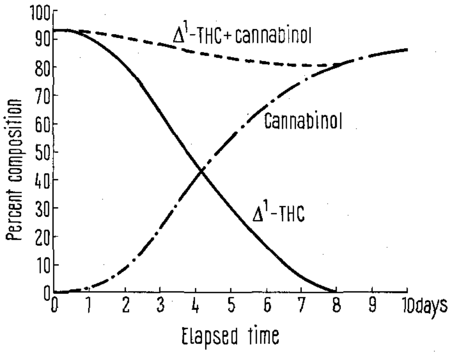

Fig. 1. Stability of Δ^1-THC on porous media at 80°C.

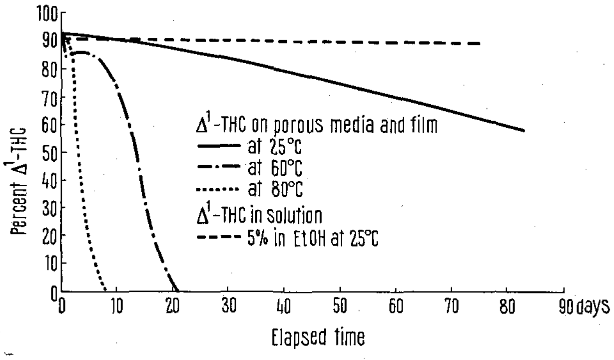

Fig. 2. Effect of temperature on Stability of Δ^1-THC.

Accelerated aging tests were carried out by heating samples on filter paper in an oven at controlled temperatures. Sections of filter paper (Whatman No. 1 or Reeve-Angel 934 AH glass fibre) were spotted with 0.25-ml aliquots of a solution of **2** (1.0 g THC/5 ml hexane) to give residual spots approximately 2 cm in diameter. The samples were placed in an oven at 80°C and after specific intervals were extracted into 5 ml of CCl_4 for analysis by gas chromatography[6]. (—)-$\Delta^{1(6)}$-THC (**1**) showed no change in composition after 7 days at 80°C, whereas under the same conditions (—)-Δ^1-THC (**2**) disappeared completely (Figure 1) with the concomitant appearance of cannabinol[9] (**8**). At 60°C the rate of decomposition of Δ^1-THC was slower and at 25°C[10] it appeared to be a linear function of time (Figure 2). After 1 month at 25°C there was 10% loss of **2** and at the end of 10 months nearly 75% had disappeared.

When the stability of **2** was determined at 80°C but in an atmosphere of nitrogen[11], the qualitative changes in composition were the same as in air, although the rate of deterioration of **2** was slower. Thus, one-half of Δ^1-THC had disappeared after 4 days' exposure to air at 80°C, whereas it took 7 days under nitrogen atmosphere to produce a similar change in composition. The oxidative conversion of **2** to cannabinol (**8**) can be envisioned as proceeding through the intermediate dienes **4** and **5** and this postulated mechanism has been confirmed by trapping the dienes with a dienophile.

We have found that a resinous material was obtained by heating equimolar quantities of **2** and N-phenylmaleimide at 80°C for 6 days. The resin was dissolved in ether and chromatographed on Florisil. Elution with 15:85 ether/petroleum ether (b.p. 30–60°) gave an amorphous solid, which NMR showed to be a 1:1 mixture of the adducts **6** and **7**. NMR: δ ($CDCl_3$), 0.85 (t, ω-methyl), 0.86 (s, methyl at a bridgehead), 0.98, 1.31 (s, *gem* dimethyl), 1.82 (s, br, olefinic methyl), 2.35 (t), 2.38 (m), 6.01, 6.21 (J = 1 cps, aromatic), 6.0 (br, olefinic), 7.26 (m, aromatic). IR showed a strong peak at 1700 cm^{-1}. The mass spectrum confirmed the molecular formula $C_{31}H_{35}NO_4$ (*m/e*, 485). The quantities of the adducts **6** and **7** were estimated on the basis of the NMR signal of the methyls in the alicyclic ring at δ 1.82 and 0.86.

We ascribe the difference in the stability between **1** and **2** to the activity of the C_3 benzylic-allylic proton in **2**, which facilitates the formation of the dienes **4** and **5** and hence cannabinol.

The addition of antioxidants[12] BHA, BHT, nordihydroguaiaretic acid, and ascorbic acid did not improve the stability of Δ^1-THC when examined in accelerated filter paper tests at 80°C. However, in a comparative study of the stability of **2** as a 5% solution in ethanol, hexane and CCl_4 at room temperature, we found that ethanol prevented apparent decomposition (Figure 2)[13]. After 75 days there was no deterioration of Δ^1-THC, whereas 12% decomposition had occurred in hexane and CCl_4 at the end of 2 months. Furthermore, in uncontrolled experiments we have found that 1% ethanol solutions of **2** did not discolor or change in composition (GLC) after 1 year of storage at 0–5°C.

Further work along these lines is in progress[14] and will be reported elsewhere.

Zusammenfassung. Die Synthese von (—)-$\Delta^{1(7)}$-Tetrahydrocannabinol (THC) auf (—)-$\Delta^{1(6)}$-THC wird beschrieben. Das Hauptprodukt der oxidativen Zerstörung von Δ^1-THC ist Cannabinol. Beschleunigte Versuche der Luftoxidation von Δ^1-THC und $\Delta^{1(6)}$-THC haben gezeigt, dass das letztere beständiger ist. Dieser Unterschied kann mit der Reaktivität des C_3-benzylisch-allylischen Wasserstoffes in Δ^1-THC erklärt werden.

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Arthur D. Little, Inc., Cambridge (Mass. 02140, USA),
5 July 1971.

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[6] All percentage purity are based on GLC assay. A 6-ft × 1/4-in glass column packed with 2% OV-17 on 100–200 mesh Gas Chrom Q at 240° was employed in conjunction with a Perkin-Elmer Model 900 Gas Chromatograph equipped with a flame ionization detector.

[7] The identity was further confirmed by comparison on GLC with an authentic sample of (±) **3** kindly supplied by Dr. K. E. Fahrenholtz.

[8] R. Mechoulam, Science *168*, 1159 (1970). – R. F. Turk, J. E. Manno, N. C. Jain and R. B. Forney, J. Pharm. Pharmac. *23*, 190 (1971).

[9] Identified by m.p., mixed m.p. with an authentic sample, NMR, and GLC.

[10] The stability of **2** at 25 °C was studied by placing 0.15-ml aliquots of a hexane solution (4.0 g Δ^1-THC/12 ml hexane) onto glass microscope slides and exposing the resulting smears to air and light at ambient temperature under normal laboratory conditions. At specific intervals the samples were extracted into CCl_4 and analyzed by GLC.

[11] Under the experimental conditions it was not possible to remove air completely.

[12] Various concentrations were tried.

[13] The apparent increase at 60 °C in percent Δ^1-THC between days 1 and 10 is ascribed to experimental error in the analytical procedure.

[14] Acknowledgment: This work was supported by National Institute of Mental Health Contract No. PH-43-68-1340.

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