TECHNICAL NOTE

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Synthetic Tetrahydrocannabinol

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ABSTRACT: This paper presents the synthetic route used and the identification of the precursors and reaction products in a clandestine laboratory manufacture of cannabidiol (CBD), Δ^9-cis-tetrahydrocannabinol (Δ^9-cis-THC), and Δ^9-trans-tetrahydrocannabinol (Δ^9-trans-THC).

KEYWORDS: toxicology, tetrahydrocannabinol, chemical analysis

Early cannabinoid (Fig. 1) chemistry mainly focused on the naturally occuring cannabinoids cannabidiol (CBD), and Δ^9-trans-tetrahydrocannabinol (Δ^9-trans-THC) (Table 1). The isolation and structural elucidation of CBD [*1*] in 1963 and Δ^9-trans-THC [*2,3*] in 1964 led to an interest in their syntheses.

The first practical syntheses of CBD and Δ^9-trans-THC was reported by Mechoulam and Gaoni in 1966 [*4*], followed by Taylor et al [*5*], Petrzilka and Sikemeier [*6*], Farenholtz et al [*7*], Jen et al [*8*] in 1967, and Razdan et al [*9*] in 1974.

The approaches followed by these researchers were similar in that they all employed olivetol

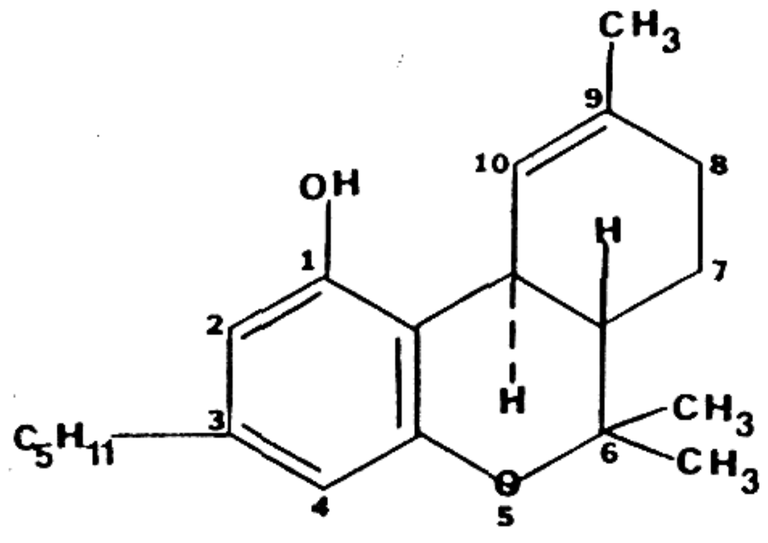

FIG. 1—*Skeletal cannabinoid structure.*

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TABLE 1—*Cannabinoid structural differences and specific orientation.*[a]

	Structural Cannabinoid Differences		
	C-11 proton orientation	Ring C	Ring B
Δ^9-trans-THC	alpha	C = C, 9-10	...
Δ^8-trans-THC	alpha	C = C, 8-9	...
Δ^9-cis-THC	beta	C = C, 9-10	...
Cannabidiol	alpha	C = C, 9-10	C = CH_2,6 OH, 5

[a]The numbering system used here conforms to *Chemical Abstracts* nomenclature of dibenzo [*b,d*] pyran compounds. "A" represents the phenolic ring; "B" the pyran ring; and "C" the remaining ring.

and a terpenoid derivative (for example, verbenol, *p*-menthadien-2,8,-1-ol, citral). Resultant reactant products and their ratios varied depending on which terpenoid, solvent, and reaction conditions were used. Figure 2 shows possible reaction products obtained from the reaction of olivetol with a terpenoid.

A sample from a clandestine laboratory was identified as a synthetic THC mixture based on the presence of precursors and resultant reaction products. The purpose of this paper is to present the synthetic route employed and the instrumental techniques used to identify the precursors in the synthetic THC mixture. Cannabidiol (CBD), Δ^9-trans-tetrahydrocannabinol (Δ^9-trans-THC) and Δ^9-cis-tetrahydrocannabinol (Δ^9-cis-THC) were identified in the reaction mixture.

Experimental Procedures

Gas chromatographic/mass spectroscopic (GC/MS) data was obtained on a Finnigan Model 3300 quadrupole electron impact/mass spectrometer (EI-MS) interfaced via jet separator to a Finnigan Model 9500 gas chromatograph. The electron energy was 70 eV and the carrier gas was helium.

Gas liquid chromatographic (GLC) data was obtained on a Hewlett Packard Model 5880 A fitted with a 1.8-m by 4-mm inside diameter glass column packed with 3% OV-1.

Proton magnetic resonance data were obtained on a Varian Model 390, 90-MHz unit. Spectra were recorded at probe temperature (33°C). Chemical shifts are reported in ppm delta. $CDCl_3$ was used as a solvent.

C_{13} nuclear magnetic resonance (NMR) data were acquired on a Nicolet 200-mHz unit with a P_2 for 90° at 9.9 Ms and 30° tip magnetization, acquisition time of 83 μs, and delay at 500 Ms.

Standard cannabidiol, Δ^8-trans-THC, and Δ^9-trans-THC were obtained from the National Institute of Drug Abuse (NIDA), Research Technology Branch in Rockville, MD.

Identification of Compounds

The precursors identified from the clandestine laboratory were olivetol (5-pentylresorcinol), citral, and boron trifluoride etherate. The olivetol was present as a white crystalline material and was identified using NMR (Fig. 3).

A yellow, highly aromatic oil was identified as citral by NMR spectroscopy. Citral from natural sources is a mixture of two geometric isomers, geranial and neral (Fig. 4). Figure 5 shows the NMR spectrum of the mixture.

A brown fuming liquid was identified as boron trifluoride etherate by NMR spectroscopy. The NMR spectrum obtained is shown in Fig. 6.

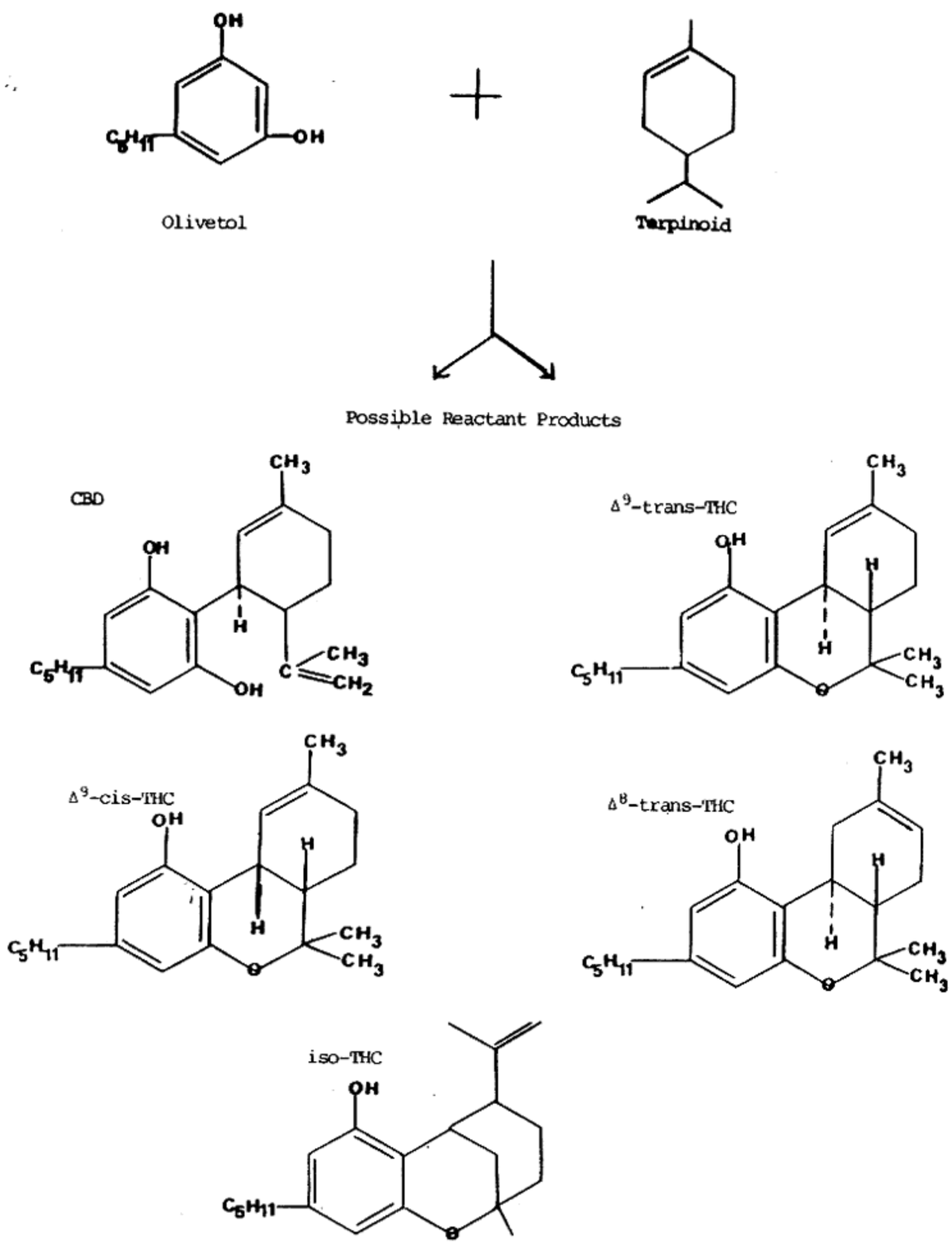

FIG. 2—*Possible products of olivetol and terpenoid reaction.*

In addition to these pure chemicals, three resinous mixtures were analyzed (Samples 1, 2, and 3). Methanol extracts of these mixtures were chromatographed at 240° on a 3% OV-1 1.8 m (6-ft) column (Fig. 7). Table 2 lists the peaks obtained and their retention times. The relative abundance of each component is denoted by parentheses. The retention time for Δ^8-trans-THC is given for comparison purposes.

Mass spectral data for GLC Peaks A, B, and D were identical to those produced for standard citral, CBD, and Δ^9-trans-THC, respectively. Peak C has a molecular ion of 314 AMU and a base peak of 243 AMU. The peak at 231 AMU is at 80% relative intensity. This *m/e* fragmentation is consistent with that published by Vree et al [*10*] for Δ^9-cis-THC. Smith and Kempfert [*11*] report a similar fragmentation but with considerable ratio differences.

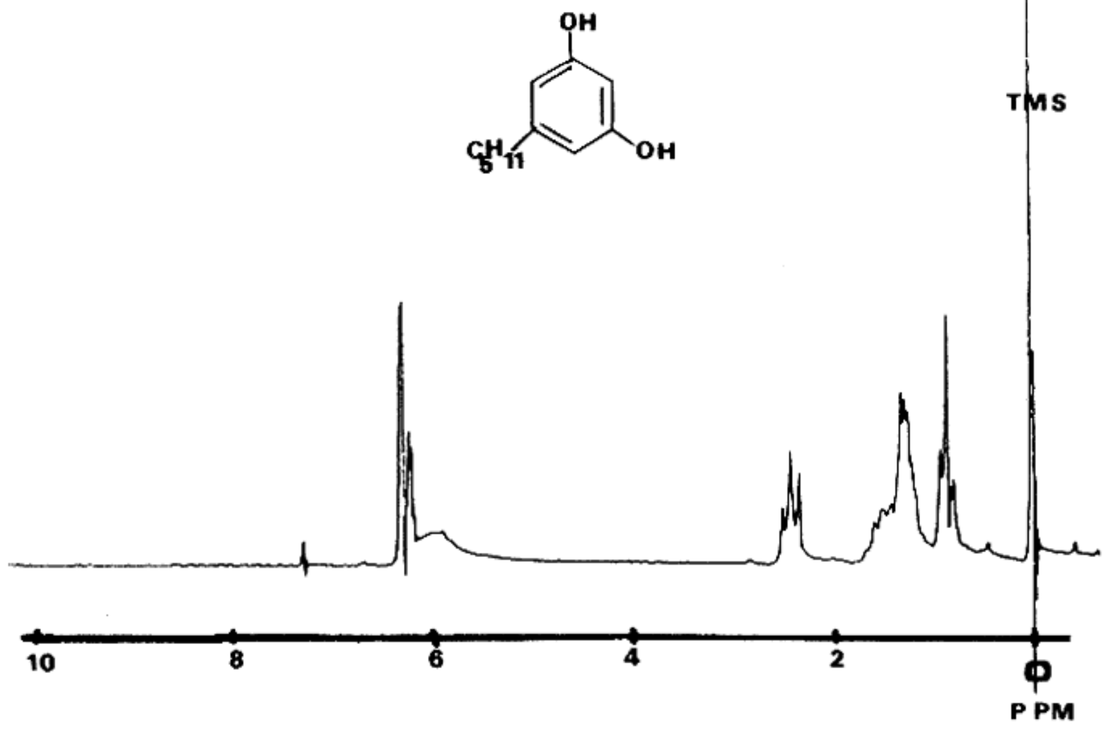

FIG. 3—*NMR spectrum of olivetol.*

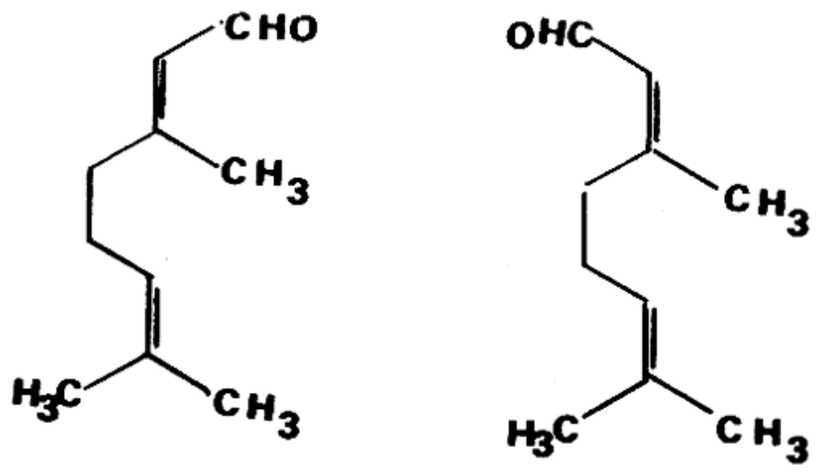

FIG. 4—*Geranial (citral A) on left and neral (citral B) on right.*

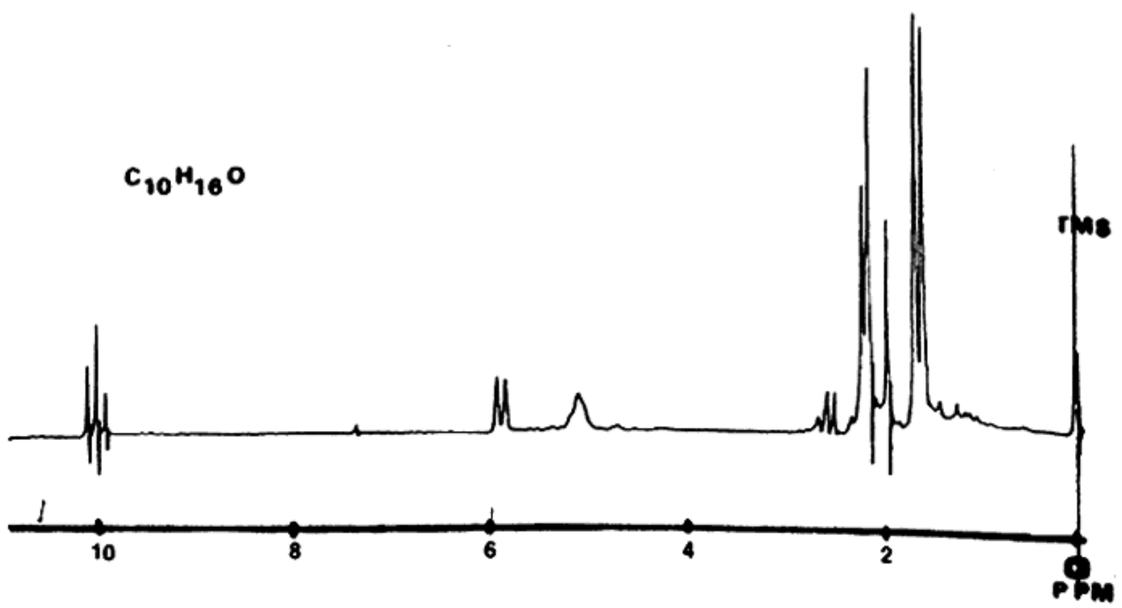

FIG. 5—*NMR spectrum of citral.*

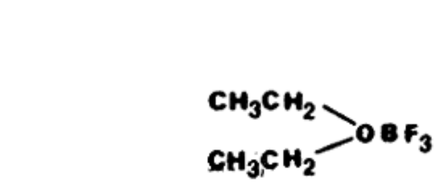

FIG. 6—*NMR spectrum of boron trifluoride etherate.*

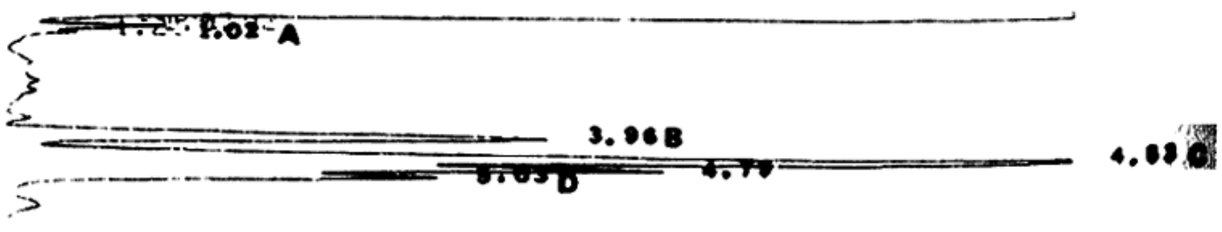

FIG. 7—*GLC of Sample 2 with Δ^8-trans-THC added.*

TABLE 2—*GLC retention times (min).*

Sample	Peak A	Peak B	Peak C	Peak D
1	1.02 (2)	3.95 (1)	4.53 (6)	...
2	1.02 (0.5)	3.96 (3)	4.53 (10)	5.03 (2)
3	1.02 (13)	...	4.50 (1)	...
Δ^9-THC	...	...	...	5.03
CBD	...	3.95	...	...
Citral	1.02	...	...	...
Δ^8-THC	...	...	4.79	...

Figures 8 through 11 represent the *m/e* fragmentation from 200 to 330 AMU for CBD, Δ^9-cis-THC, Δ^8-trans-THC, and Δ^9-trans-THC, respectively.

Using preparative high pressure liquid chromatography (HPLC), CBD, Δ^9-cis-THC, and Δ^9-trans-THC were obtained from the three mixtures. Their NMR spectra are presented in Figs. 12, 13, and 14. The NMR spectrum of standard Δ^8-trans-THC is presented for comparison purposes (Fig. 15).

The NMR spectrum obtained for GLC Peak C is consistent with that of Δ^9-cis-THC. C_{13} data for Peak C were used for confirmation because of discrepancies in NMR data reported in the literature [*5, 7, 12–14*].

Table 3 lists the experimental values obtained and the literature values for comparison.

Discussion

A commercial publication, *Basic Drug Manufacture* [*16*] includes a procedure for the synthesis of *d*,1-Δ^9-3,4-trans-THC using citral, olivetol, methylene chloride, and boron trifluoride etherate. The resultant reaction product is extracted with 10% sodium hydroxide and then acidified to remove unreacted olivetol. The organic layer contains mixed isomers of THC. The outlined procedure is very similar to a scheme published by Taylor et al [*5*] with a resultant mixed isomer product of Δ^9-cis-THC and Δ^9-trans-THC. The synthetic method outlined in *Basic Drug Manufacture* was followed by the author and the resultant reaction

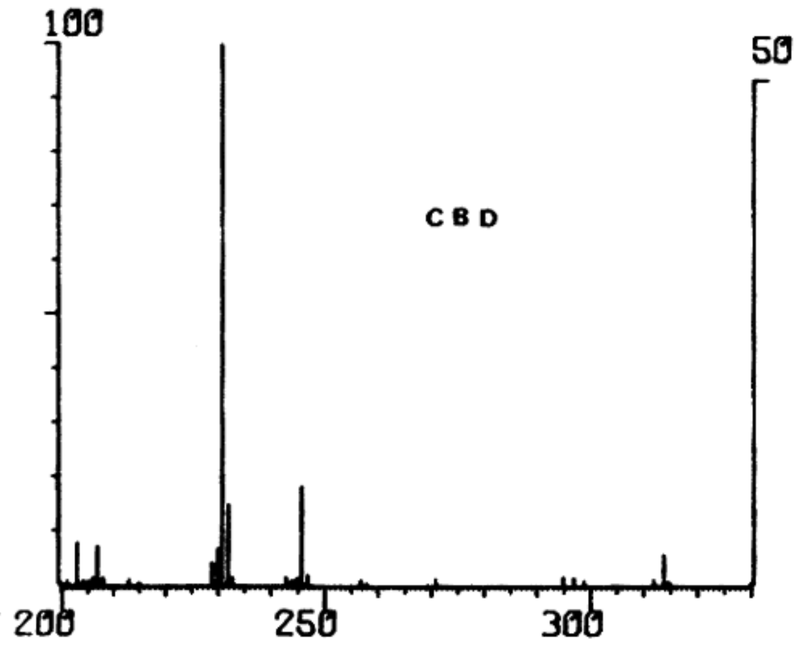

FIG. 8—*Partial mass spectrum of cannabidiol.*

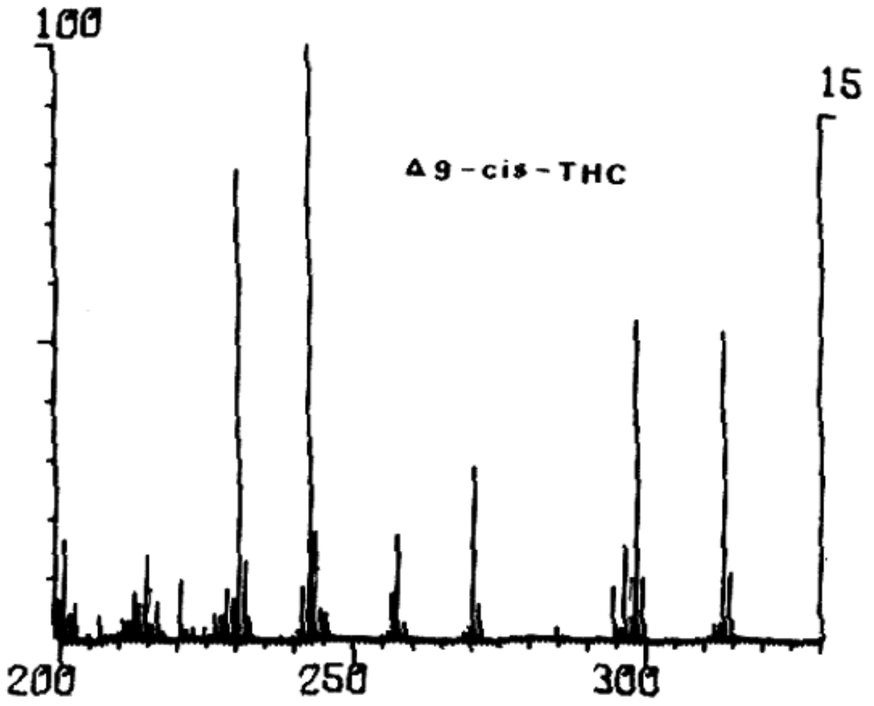

FIG. 9—*Partial mass spectrum of* Δ^9*-cis-tetrahydrocannabinol.*

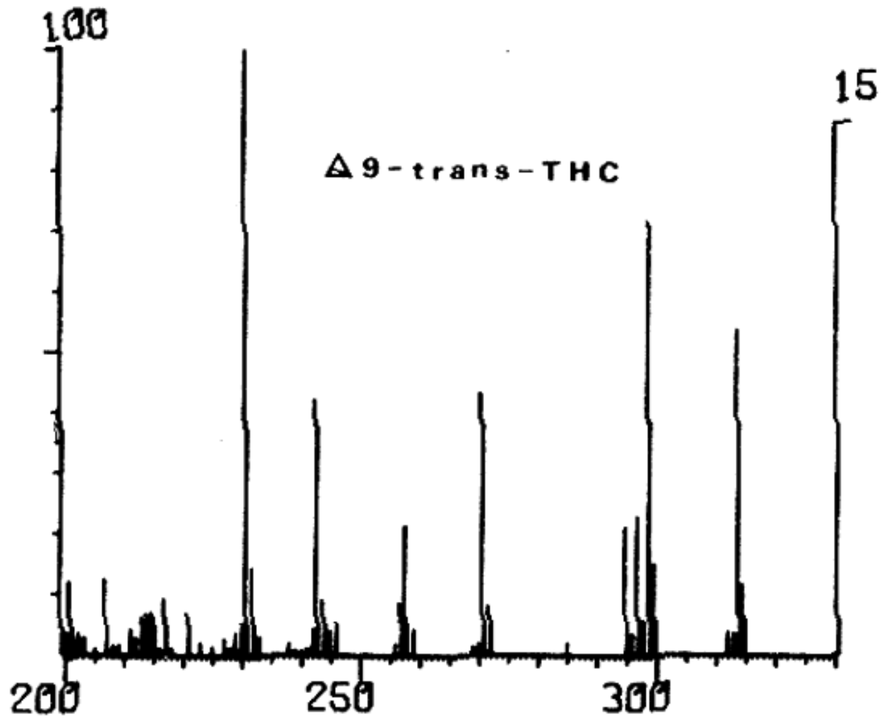

FIG. 11—*Partial mass spectrum of* Δ^9*-trans-tetrahydrocannabinol.*

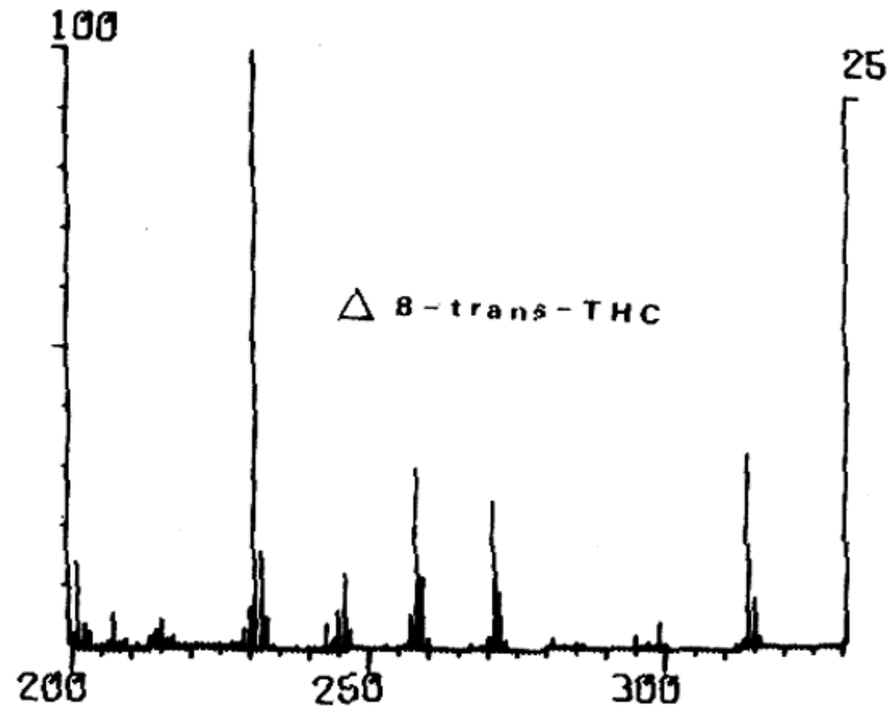

FIG. 10—*Partial mass spectrum of* Δ^8*-trans-tetrahydrocannabinol.*

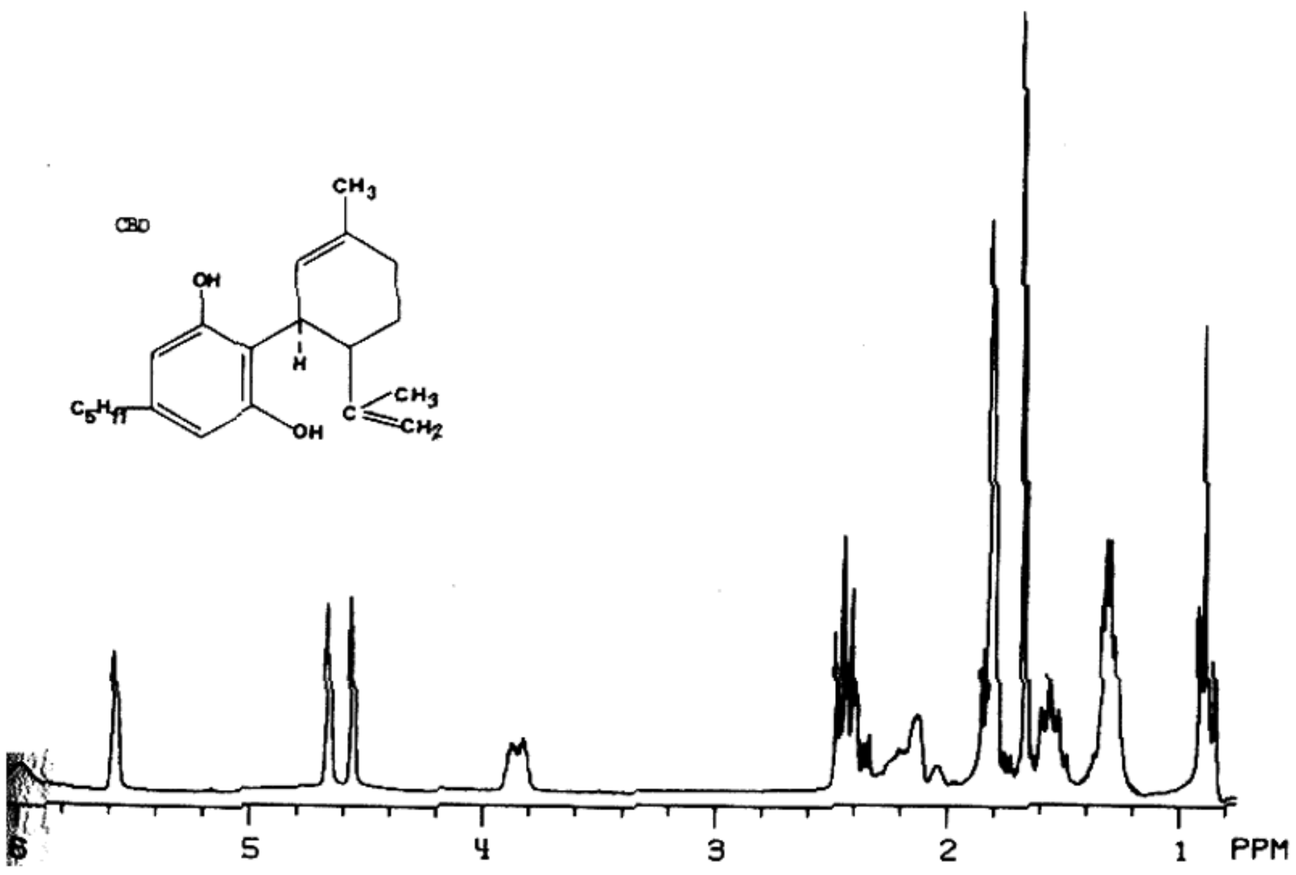

FIG. 12—*NMR spectrum of cannabidiol.*

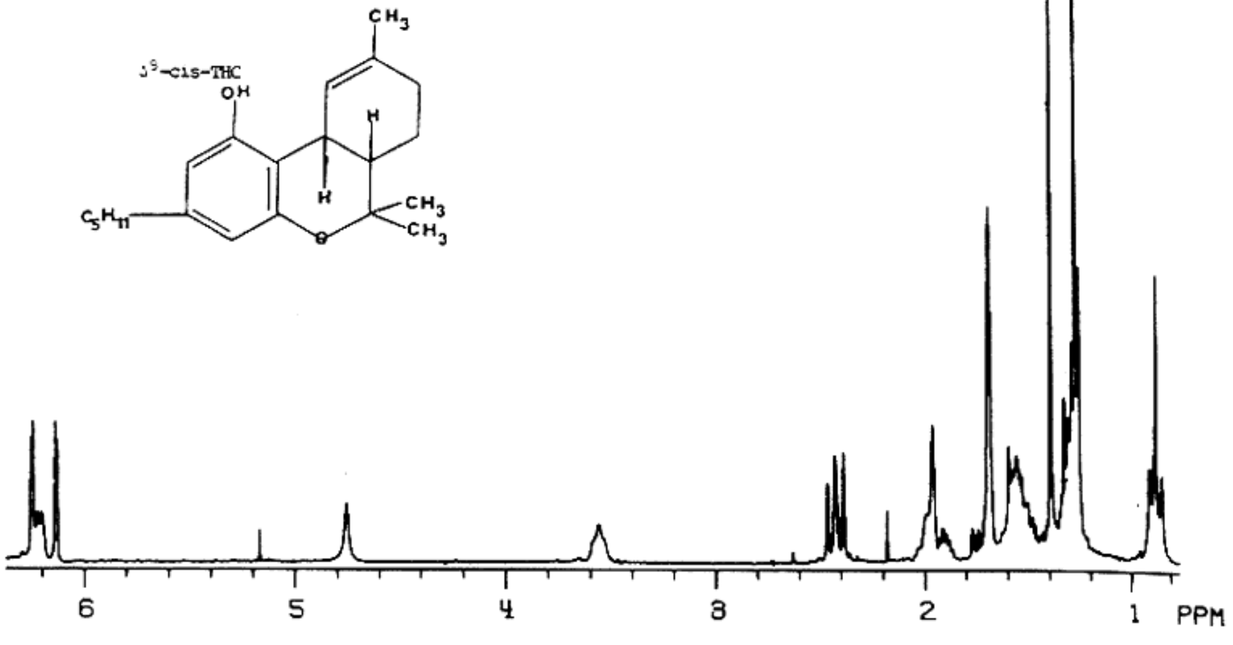

FIG. 13—*NMR spectrum of Δ^9-cis-tetrahydrocannabinol.*

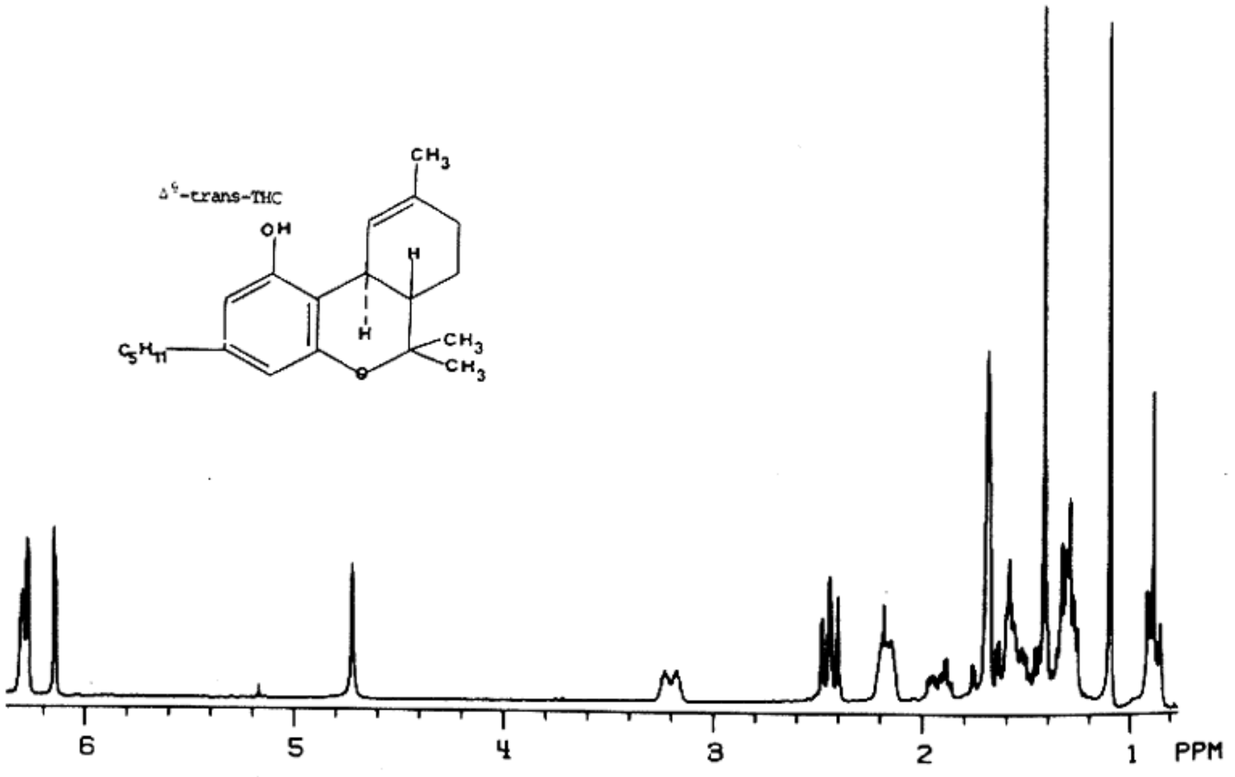

FIG. 14—*NMR spectrum of Δ^9-trans-tetrahydrocannabinol.*

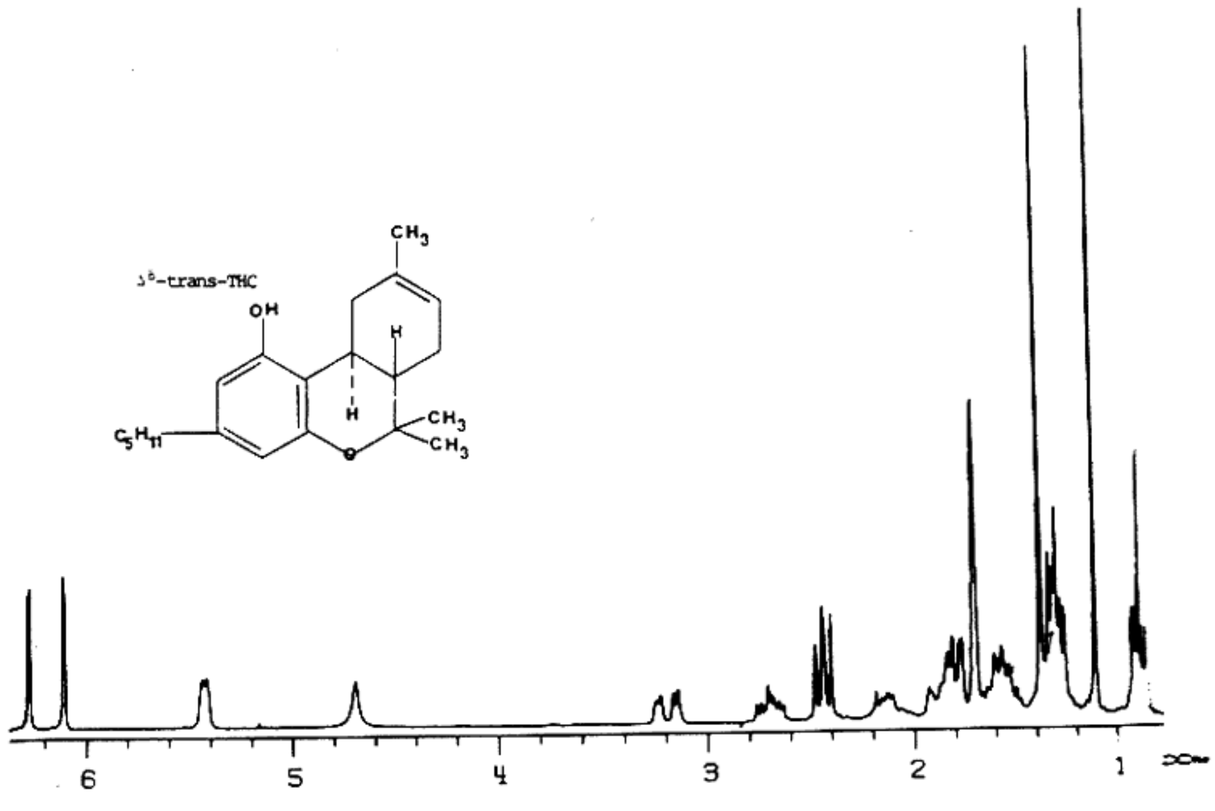

FIG. 15—*NMR spectrum of Δ^8-trans-tetrahydrocannabinol.*

TABLE 3—*Carbon-13 NMR data. Values reported in ppm.*

Experimental Values, GLC Peak C	Literature [15], Δ^9-cis-THC
153.2	153.4
107.9	107.9
142.4	142.1
109.9	109.5
154.7	154.7
109.3	109.3
76.1	76.1
40.0	40.0
20.6	20.7
29.7	29.7
134.9	134.3
121.9	122.0
31.5	31.4
25.2	25.2
25.9	25.8
23.6	23.6
35.3	35.3
30.5	30.5
31.5	31.5
22.5	22.5
14.0	14.0

products identified by GLC, GC-MS, and NMR (proton magnetic resonance [PMR] and C/13).

The final reaction product contained the same compounds found in Sample 2 (CBD, Δ^9-cis-THC, and Δ^9-trans-THC) in approximately the same proportions. Residue from the initial reaction of citral and olivetol contained the same compounds as those found in Sample 1 (citral, CBD, and Δ^9-cis-THC). The aqueous alkaline extract contained the same compounds as those found in Sample 3 (Δ^9-cis-THC and citral).

These samples represent the applied synthetic route leading to synthetic THC.

References

[1] Mechoulam, R. and Shvo, Y., *Tetrahedron Letters*, Vol. 19, 1963, p. 2073.

[2] Mechoulam, R. and Gaoni, Y., *Journal of the American Chemical Society*, Vol. 86, Feb. 1964, pp. 1646–1647.

[3] Mechoulam, R. and Gaoni, Y., *Journal of the American Chemical Society*, Vol. 87, 1965, p. 3273.

[4] Gaoni, Y. and Mechoulam, R., *Tetrahedron Letters*, Vol. 22, 1966, p. 1481.

[5] Taylor, E. C., Lenard, K., and Shvo, Y., *Journal of the American Chemical Society*, Vol. 88, No. 2, Jan. 1967, pp. 367–369.

[6] Petrzilka, T. and Sikemeier, C., *Helvetica Chimica Acta*, Vol. 50:5, No. 143, 1967, pp. 1416–1419.

[7] Farenholtz, K. E., Lurie, M., and Kierstead, R. W., *Journal of the American Chemical Society*, Vol. 89, No. 23, Nov. 1967, pp. 5934–5941.

[8] Jen, T. Y., Hughes, G. A., and Smith, H., *Journal of the American Chemical Society*, Vol. 89, No. 17, Aug. 1967, pp. 4551–4552.

[9] Razdan, R. K., Dalzell, H. C., and Handrick, G. R., *Journal of the American Chemical Society*, Vol. 96, No. 18, Sept. 1974, pp. 5860–5865.

[10] Vree, T. B., Breimer, D. D., van Ginneken, C. A. M., van Rossum, J. M., and Nibbering, N. M. M., *Journal of Chromatography*, Vol. 79, 1973, p. 81.

[11] Smith, R. M. and Kempfert, K. D., *Phytochemistry*, Vol. 16, 1977, pp. 1088–1089.

[12] Archer, R. A., Boyd, D. B., Demarco, P. V., Tyminiski, I. J., and Allinger, N. L., *Journal of the American Chemical Society*, Vol. 92, No. 17, Aug. 1970, pp. 5200–5206.

[13] Uliss, D. B., Razdan, R. K., Dalzell, H. C., and Handrick, G. R., *Tetrahedron Letters*, Vol. 49, Oct. 1975, pp. 4369–4372.

[14] Uliss, D. B., Razdan, R. K., Dalzell, H. C., and Handrick, G. R., *Tetrahedron Letters*, Vol. 33, 1977, pp. 2055–2059.

[15] Archer, R. A. and Johnson, D. W., *Journal of Organic Chemistry*, Vol. 42, No. 3, 1977, pp. 490–495.

[16] *Basic Drug Manufacture*, 20th Century Alchemist, Manhattan Beach, CA, 1973.