PHARMACOLOGICAL REVIEWS

Vol. 23, No. 4
Printed in U.S.A.

CHEMISTRY OF MARIHUANA

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This review of the chemistry of the constituents of marihuana is a very brief one. Much has been written on the importance of the marihuana problem from many points of view. The lack of good data on what marihuana does to the user is fundamentally related to the state of the chemical knowledge. In spite of the fact that much work has been done on its chemistry, only recently has the chemist begun to solve his problems. The chemist must make his contributions before the biologist and clinician can provide good data. Most of the biological and

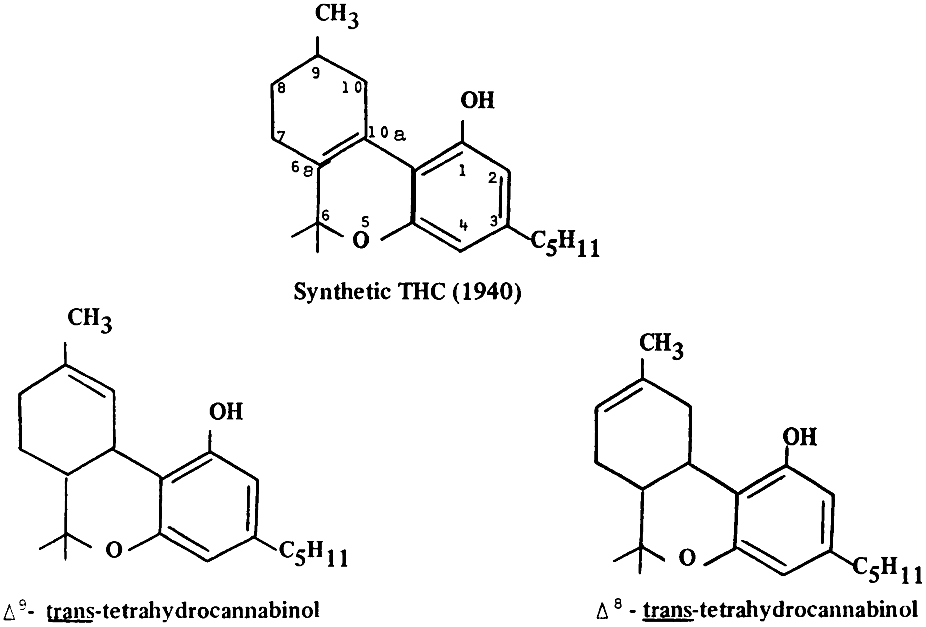


FIG. 1. The alicyclic double bond of earlier synthetic THC was in the 6a,10a position while the natural materials have it in the 9,10(Δ^9-THC) or the 8,9(Δ^8-THC) position.

clinical data published prior to 1966 were open to question since the materials used in these researches were not fully defined. It was about that time that the structure of natural tetrahydrocannabinol (THC) became known and was prepared synthetically. To be sure, much good work was done in the period from 1930 to 1940 and many compounds were synthesized, but the synthetic THC prepared in that period had the double bond in the wrong place as shown in the structures in figure 1. The 1940 vintage of THC had the double bond between two of the rings. Today, we know that the plant contains mainly Δ^9-*trans*-tetrahydrocannabinol (Δ^9-THC), with some of its THC content being Δ^8-*trans*-tetrahydrocannabinol (Δ^8-THC). We also know that Δ^9-THC is somewhat unstable and readily isomerizes with acids to Δ^8-THC.

In 1967, Petrzilka and co-workers (6–8) published a practical method for the synthesis of Δ^8- and Δ^9-THC. Also about this time, many of the other compounds in marihuana, which are related to THC, were becoming known structurally. The gas chromatography method of analysis had been published, so it became possible at the end of 1967 for the National Institute of Mental Health (NIMH) to formulate a rational program of marihuana research.

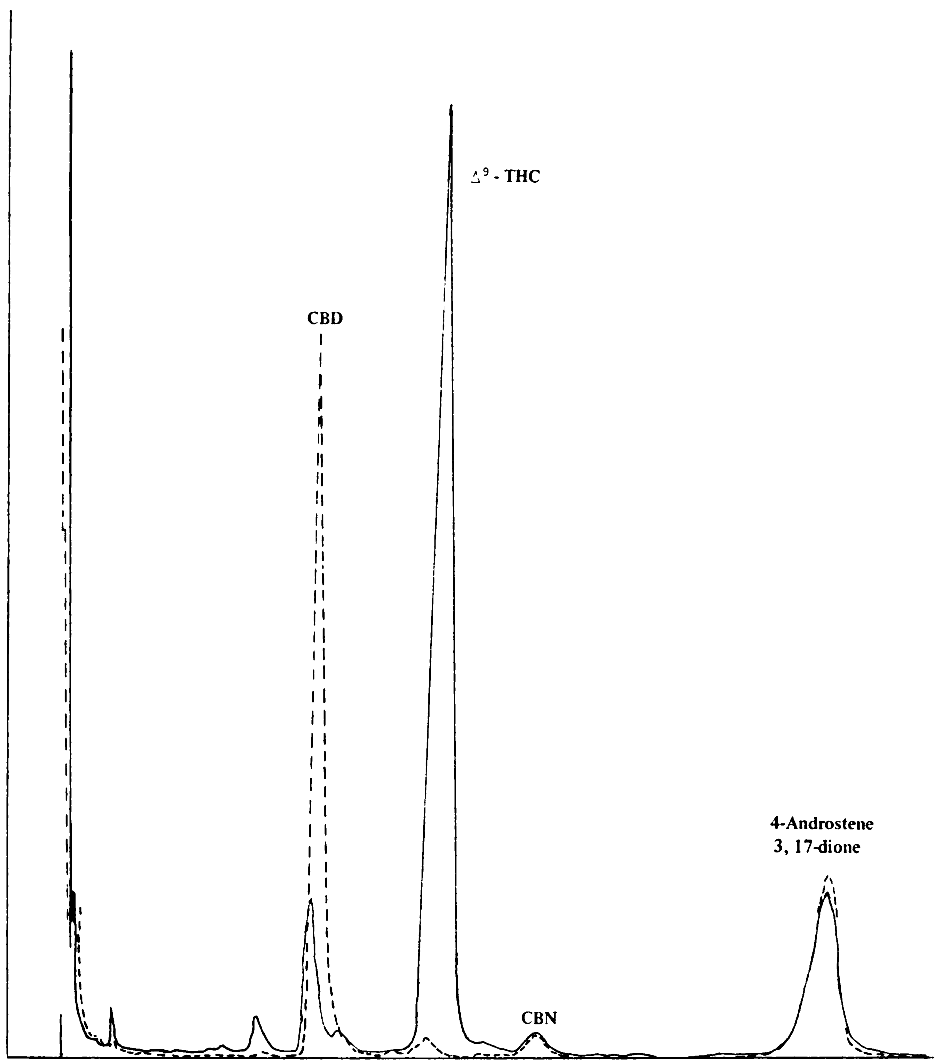


FIG. 2. Extract of *Cannabis sativa* L.: — Mexican; ----- Turkish.

The National Program on Marihuana as to concepts and functions was described on February 16, 1969, to the Committee on Problems of Drug Dependence by Dr. Morton G. Miller (5), Acting Director for Special and Collaborative Programs, NIMH. His talk was published in the report from that conference. I quote from his talk: "The program is seen as a joint effort between NIMH and the scientific community." The direct contract mechanism is being used primarily for the development of sufficient supplies of standardized materials both natural and synthetic; to conduct initial animal and human toxicity studies; to develop bioassay techniques; and to initiate high-priority studies of foreign populations where marihuana use has been present for many years. The bulk of the program is being conducted by means of research grants.

The need for fully defined and standardized materials for research has been recognized and stated on several occasions. In Dr. Miller's talk, he explained why it was necessary for NIMH to undertake the task of providing needed research materials. Tetrahydrocannabinol has been assumed to be the chemical responsible for the major physiological action of marihuana. This assumption needs verification; therefore, materials of natural origin which have been treated the least possible for each intended use must be supplied and compared with highly purified chemical constituents. If synthetic chemicals are used, their full relationship to those occurring in the plant must be established.

The base material is manicured marihuana, which is composed of leaves and flowering tops and freed of most stems and seeds from *Cannabis sativa* L. The

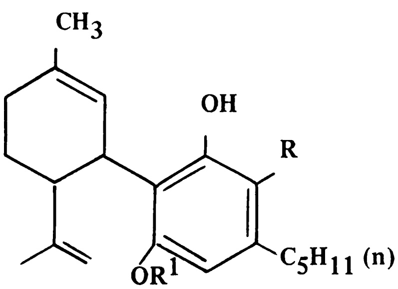
TABLE 1

Analysis of drug and hemp types of marihuana over three growing seasons

	CBD	Δ^9-THC	Δ^9-THC + CBN	
			CBN	CBD
Drug-type marihuana analysis				
Mexican				
Miss. grown (F_1)	0.31	3.7	0.11	12.5
Miss. grown (F_2)	0.19	3.9	0.17	22.1
Miss. grown (F_3)	0.18	3.7	0.22	22.2
Thailand				
Thailand material	0.14	4.8	0.12	36.6
Miss. grown (F_1)	0.18	3.4	0.11	20.6
Hemp-type marihuana analysis				
Minnesota				
Wild material	1.7	0.04	0.15	0.11
Miss. grown (F_1)	1.6	0.08	0.14	0.14
Turkish				
Miss. grown (F_1)	3.1	0.16	0.19	0.12
Miss. grown (F_2)	2.1	0.06	0.05	0.05
Miss. grown (F_3)	1.9	0.62	0.8	0.37

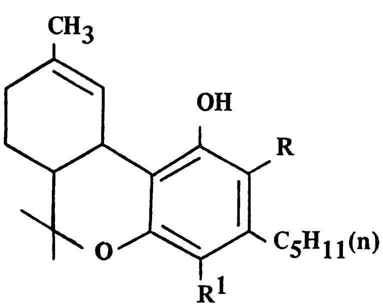
manicured marihuana is the form smoked by most users in the United States. This material is unavailable for research except through NIMH. Even confiscated marihuana is now channeled through NIMH, when made available from the Bureau of Narcotics. Confiscated marihuana is of unknown history and is often adulterated.

To obtain manicured marihuana for use and extraction, a planned program for growing, extraction and analysis was sponsored by NIMH. Material and seeds have been collected from various parts of the world and used in the program. The seeds were planted and grown under conditions to give plant material of suitable quality for research. Analysis of various cultigens have shown two dominate variants which we have classified as drug type and hemp type. Pictures of the wild and cultivated marihuana were shown. Figure 2 is a typical gas chromatogram of each.



R & R^1 = H	Cannabidiol (CBD)
R = COOH, R^1 = H	Cannabidiolic Acid (CBDA)
R = H, R^1 = CH_3	Cannabidiol Monomethylether (CBDM)
R = COOH, R = CH_3	Cannabidiolic Acid Monomethylether (CBDAM)

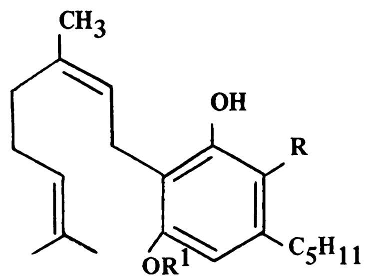
FIG. 3. Cannabidiol and its derivatives that occur in marihuana.



R & R^1 = H	Δ^9- <u>trans</u>-Tetrahydrocannabinol (Δ^9- THC)
R = COOH, R^1 = H	Δ^9- Tetrahydrocannabinolic Acid (Δ^9- THCA) (A)
R = H, R^1 = COOH	Δ^9- Tetrahydrocannabinolic Acid (Δ^9- THCA) (B)

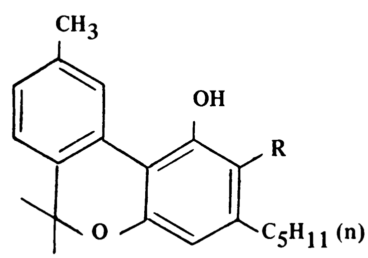
FIG. 4. Δ^9-Tetrahydrocannabinol and its derivatives that occur in marihuana.

Analysis of marihuana is being done by gas chromatography which, when compared with standards, allows for the detection and quantitation of the cannabinoid compounds (1, 2). Cannabinoids are tetrahydrocannabinols (THC) and related chemicals. The major ones in the plant are Δ^9-THC, cannabidiol (CBD) and cannabinol (CBN). In table 1 showing the analysis of representatives of drug and hemp types of marihuana over three growing seasons. Also the structures of the naturally occurring cannabinoids are in figures 3 to 8.



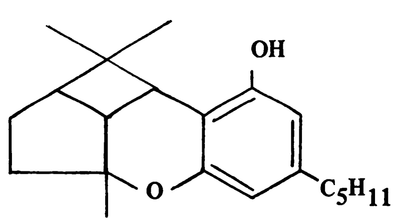
R & $R^1 = H$	Cannabigerol (CBG)
$R = COOH$, $R^1 = H$	Cannabigerolic Acid (CBGA)
$R = H$, $R^1 = CH_3$	Cannabigerol Monomethylether (CBGM)
$R = COOH$, $R^1 = CH_3$	Cannabigerolic Acid Monomethylether (CBGAM)

FIG. 5. Cannabigerol and its derivatives that occur in marihuana.



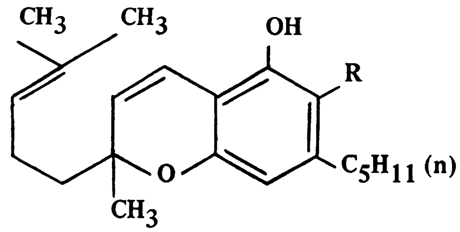
$R = H$	Cannabinol
$R = COOH$	Cannabinolic Acid

FIG. 6. Cannabinol and its derivative that occurs in marihuana.



Cannabicyclol
(Cannabipinol)

FIG. 7. Cannabicyclol that occurs in marihuana.



R = H	Cannabichromene (CBC)
R = COOH	Cannabichromenic Acid (CBCA)

FIG. 8. Cannabichromene and its derivative that occurs in marihuana.

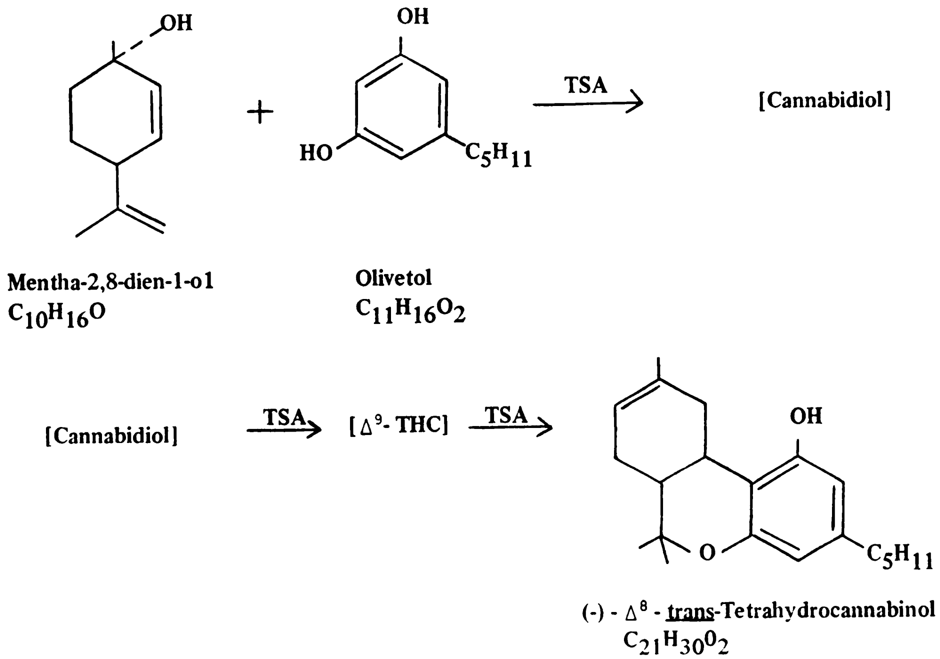


FIG. 9. Synthesis of Δ^8-*trans*-tetrahydrocannabinol. Toluene sulfonic acid (TSA) is used as the catalyst for condensation and ring closure in a non-hydroxylated solvent such as benzene.

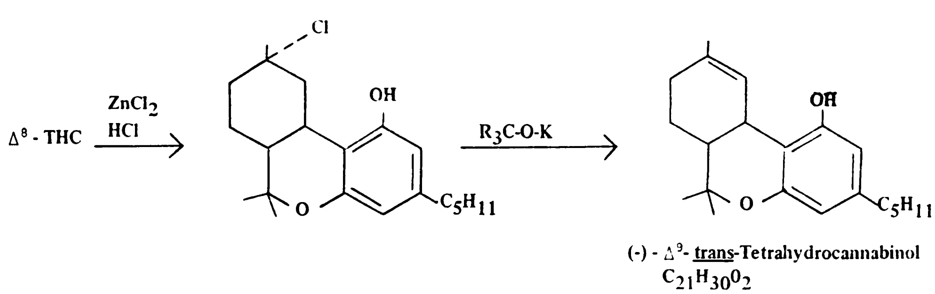


FIG. 10. Synthesis of pure Δ^9-tetrahydrocannabinol.

The total syntheses of Δ^9-THC with Olivetol and Mentha-2,8-dien-1-ol are presented in figures 9 and 10. A stepwise synthesis of the THC's was published by Petrzilka and Sikemeir (6–8); while Razdan *et al.* (9) telescoped these steps into one to obtain Δ^8-THC and then converted it after purification through the chloro-compound to Δ^9-THC. Both Δ^8- and Δ^9-THC were purified through column chromatography and high vacuum distillation. Essentially pure synthetic Δ^8- and Δ^9-*trans*-tetrahydrocannabinols are now available to researchers from NIMH. The THC's though totally synthetic in origin are identical with the THC's which have been isolated from *Cannabis sativa* L.

Pure Δ^8- and Δ^9-THC are thick, viscous oily materials at room temperature, and resinous solids when cold. They are soluble in organic solvents and insoluble in water. Though they are soluble in alcohol, they oil-out on diluting with water. Aqueous suspension can be made with Tween 80. The solubility properties have created difficulties for the biologist. The specific rotation of pure Δ^8 is -268 (c, 1.2% $CHCl_3$) and Δ^9-THC is -175 (c, 2% $CHCl_3$).

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