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REVIEW ARTICLE

Chemistry and Pharmacology of Marijuana

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Keyphrases ☐ Marijuana—chemistry and pharmacology review ☐ Tetrahydrocannabinol—chemistry and pharmacology review ☐ Psychotomimetic agents—marijuana, review ☐ Cannabinoids—chemistry and pharmacology review

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"Cannabis is used throughout the world for diverse purposes and has a long history characterized by usefulness, euphoria or evil, depending on one's point of view. To the agriculturist cannabis is a fiber crop; to the physician of a century ago it was a valuable medicine; to the physician of today it is an enigma; to the user, a euphoriant; to the police, a menace; to the traffickers, a source of profitable danger; to the convict or parolee and his family, a source of sorrow." (1).

As in so many other areas of drug research, real progress can be achieved in the understanding of the pharmacology and biogenesis of a naturally occurring drug only when the chemistry has been well established and the researcher has at his disposal pure compounds of known composition and stereochemistry. The last decade produced the necessary know-how in the chemistry of the Cannabis constituents so that chemists could devise practical and novel synthetic schemes to provide the pharmacologists with such materials. The precise biological effects of this intoxicant, known to man for several centuries, still remain to be elucidated; no doubt the next decade will yield such information.

Although the current world literature on Cannabis numbers some 2000 publications, few of these papers meet the criteria of modern scientific investigation. The purposes of this review are to provide the pharmaceutical scientist with current information relevant to his areas of specialization and to review the recent literature pertaining to this subject through December 1970.

The plant *Cannibis sativa* L. (family Cannabinaceae), the source of marijuana, is a tall annual weed. It sometimes reaches a height of 4.57 m. (15 ft.), depending on the part of the world where it is grown. It grows in almost any waste or fertile area. The weed is dioecious; that is, the male reproductive parts (stamens) are on one plant and the female parts (pistils) are on another. The male plants usually grow taller than the female plants (Fig. 1). The chemical substances responsible for the euphoric effect of marijuana are found primarily in a sticky resin that covers the female flowers and adjacent leaves. Although this resin is the prime

Figure 1—*Hemp plant* (C. sativa). *The active substances in the drug are contained principally in a sticky yellow resin that covers the flower clusters and top leaves of the ripe plant. (Reprinted, with permission, from "Marihuana" by L. Grinspoon (8), copyright December 1969, by Scientific American, Inc., all rights reserved.)*

source of the euphoric principles, other parts of the female as well as the male plants contain these same active principles (2, 3). This was shown by recent investigations, which uncovered one of the psychotomimetic substances, Δ^9-tetrahydrocannabinol, in the male plant (4). Other parts of the plant, namely, the seed, seed oil, seed oil cake, and fiber (hemp), are important and useful economic products.

Of the many preparations derived from the plant, marijuana (more commonly referred to as "pot" or "grass") is undoubtedly the most common one, at least in the United States. It is prepared simply by drying the flowering tops of the plants and is probably a mixture of male and female flowers in most cases.

The most potent of the plant preparations is hashish or charas. These preparations are the unadulterated resins from the flowering tops of cultivated female plants. The bhang of India is prepared from uncultivated female plants by cutting the tops of the plants and boiling or steeping them in water or milk. This decoction is either drunk or dried and smoked, and its potency is nearly equivalent to that of marijuana. Ganja, also of Indian origin, is prepared in the same way as bhang, except that only tops from very carefully selected cultivated female plants are used. This selectivity for plants of high resin content results in a preparation that is more potent than marijuana. Bhang, ganja, and other preparations such as Moroccan kif, Brazilian macohna, and South African dagga (all nearly equivalent to marijuana) are terms seldom encountered in the United States, since most of the *C. sativa* used here is in the form of dried flowering tops, that is, marijuana (5, 6) (Table I). It is estimated that 2–3 million people throughout the world use a variety of Cannabis preparations (7, 8).

Table II shows the tetrahydrocannabinol potency of a variety of plants grown in Mississippi from seeds obtained in different locations (2). Table I lists some of the Cannabis preparations and their composition.

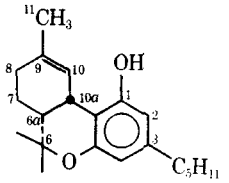
The plant *C. sativa* can vary widely in its chemical constituents, depending on the geography of the source material, the age of the harvested sample, the storage conditions, and other factors (10, 11).

NOMENCLATURE AND NUMBERING SYSTEM OF CANNABINOIDS

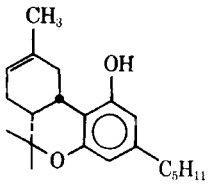
The term "cannabinoid" will be used in this report to refer to the group of compounds typical of, and present in, *C. sativa* as well as to their analogs and transformation products. This definition is adopted from Mechoulam and Gaoni (11), who originally proposed it in 1967.

At least four different numbering systems have been used in publications relating to the cannabinoids. A few research groups (7, 11–13) regarded the cannabinoids as substituted monoterpenes. The advantage of the monoterpene numbering system lies in the relationship of the cannabinoids to their biogenetic terpene precursor without the necessity of changing the numbering of specific carbon atoms. This system has disadvantages also (*i.e.*, in the monoterpene numbering system, the 3′—OH group in Δ^1-tetrahydrocannabinol becomes 2′—OH in cannabidiol). The dibenzopyran numbering system utilizes the formal chemical rules for the numbering of pyran-type compounds and was adopted by the National Institute of Mental Health (NIMH) (14) and the earlier publications of Adams (15). The formal (Chemical Abstracts) numbering system will be used throughout this report for those compounds containing the carbon skeleton corresponding to that of dibenzopyran. Both systems are shown here.

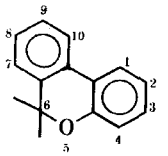
formal dibenzopyran numbering (used in this review)



Δ^9-*trans*-tetrahydrocannabinol

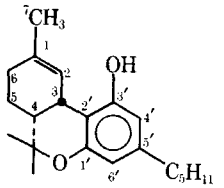


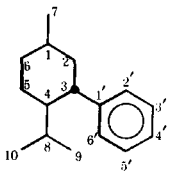
Δ^8-*trans*-tetrahydrocannabinol



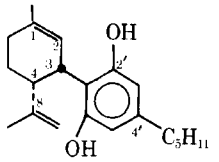
dibenzopyran numbering

monoterpenoid numbering (used in this review for terpenelike compounds only, *i.e.*, cannabidiol)





Δ′-*trans*-tetrahydrocannabinol



cannabidiol

CHEMICAL RESEARCH ON CANNABIS

It is beyond the scope of this review to present and discuss fully the investigations on the chemistry of Cannabis constituents reported over a period of 120 years. Rather, the present review attempts to summarize the pertinent chemistry relevant to an understanding of the biological effects of Cannabis and to review the chemistry of Cannabis that has appeared since the last review (7). Much of the older work was surveyed by Blatt (16); Adams (15) summarized his own work, and Todd (17) reviewed the field up to 1946. Since that time the chemistry of hashish was reviewed by Mechoulam and Gaoni (11), Korte *et al.* (18), Downing (19), two Ciba Foundation Symposia in 1965 (20) and in 1969 (21), and several shorter reviews (22–25).

Table I—Names for Common Preparations (9)

Name	Composition
Hashish Charas (India)	Pure resin from tops of female hemp plants; most potent material
Ganja (India)	Flowering tops of specially cultivated female plants; highly potent; used in smoking mixtures, beverages, and sweets
Bhang (India, Middle East)	Dried, uncultivated, mature, female plants; used in smoking mixtures and beverages
Marijuana (United States and Europe) Kif (Morocco) Dagga (South Africa) Macohna (Brazil)	Entire plant with variable proportions of leaves and flowering tops; used as smoking mixtures and as beverages; potency varies greatly; names such as "Panama red" and "Acapulco gold" describe highly potent preparations

Chemistry of the Natural Cannabinoids—In 1857, the Smith brothers (26) of Edinburgh showed that the physiologically active principle of Cannabis was contained in the alkali-insoluble, high boiling portion of the hemp resin, which was obtained by alcoholic extraction of the plant. No significant progress was made until 1897 when three Cambridge chemists, Wood, Spivey, and Easterfield (27), after effecting considerable purification of the resin through distillation, were able to isolate a crystalline acetate from the acetylated resin. Upon hydrolysis, the acetate yielded a phenolic compound which they called cannabinol.

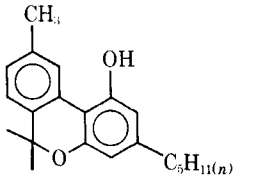
About 30 years later, Cahn (28) began work on the subject through his studies on cannabinolactone, a degradation product of cannabinol. As a result, he correctly deduced the structure of cannabinolactone, which was confirmed by Bergel and Vogel (29) by synthesis. These results led to a partial structure for cannabinol, which was not clarified until the 1940's when Cahn's colleagues in Britain and Adams and coworkers in America reopened the investigation. At this time, Adams *et al.* (30) isolated a new substance, cannabidiol, from marijuana; the same substance was isolated by Jacob and Todd (31) from Egyptian hashish. Both cannabinol and cannabidiol lacked hashish activity when tested on rabbits, so it was concluded that the active material remained in the noncrystalline portion of the esterified resin.

The locations of the hydroxyl groups in cannabidiol, which were determined from its pyrolysis products with pyridine hydrochloride, together with the fact that cannabinol also is present in hemp, made it certain that cannabinol was correctly represented by I (17).

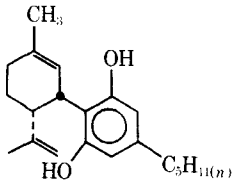
Table II—Δ^9-Tetrahydrocannabinol Potency of Marijuana Plants Grown in Mississippi from Various Seed Sources (2)

Seed Source	Percent Δ^9-Tetrahydrocannabinol
France	0.085
Italy	0.041–0.068
Mexico:	
Male plants	1.47
Female plants	1.31
Sweden	0.021
Turkey	0.05–0.40

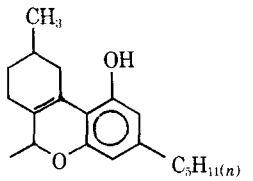
This structure was quickly confirmed by two independent syntheses of cannabinol by Adams *et al.* (32) and Ghosh *et al.* (33). Later, the structure of cannabidiol was clarified and shown to correspond to II (34, 35), although the position of the double bond in the ring was not known with certainty until 1963 (36).



cannabinol
I



cannabidiol
II



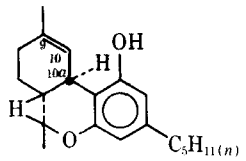
$\Delta^{6a,10a}$-tetrahydrocannabinol

IIIa

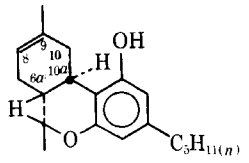
The synthetic route used by the former authors (29) produced an intermediate tetrahydrocannabinol, $\Delta^{6a,10a}$-tetrahydrocannabinol (IIIa), which was found to exhibit a high degree of marijuanalike activity in animals and in man. Concurrently, Adams and Baker (37) also established a synthetic route for IIIa, which was almost identical to the one reported by Ghosh *et al.* (33). It was also shown by Adams *et al.* (38) that cannabidiol (II) can be cyclized under acidic conditions to yield a mixture of optically and physiologically active tetrahydrocannabinols. In 1942, another group, working at the U. S. Bureau of Narcotics, succeeded in isolating a highly purified active fraction from the resin (39). Although no definite structure was offered for this substance, it was assumed to be a tetrahydrocannabinol isomer.

The discovery of the activity of $\Delta^{6a,10a}$-tetrahydrocannabinol led to the synthesis and pharmacological examination of a wide variety of related analogs in the hope of elucidating the relationship between chemical constitution and hashish activity. Some of these compounds were found to be many times more active than the semisynthetic tetrahydrocannabinol isomers. The results of these studies are discussed in detail later in this review. In spite of the progress achieved in the area of synthesis, the active natural constituents were not obtained pure; consequently, their structures were not fully elucidated.

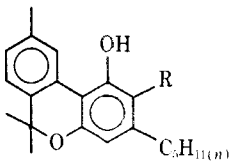
Knowledge of Cannabis has developed rapidly over the past 10 years as a result of intensive chemical investigations, which have considerably clarified its rather complex chemistry. This renewed interest is probably the combined result of its rapidly increasing use among the young, a reevaluation of its possible use as a medicinal, and a greater refinement of instrumental and chemical techniques. A host of new substances has been isolated from the resin (hashish), most of which have now been successfully characterized and synthesized. Among those substances isolated are



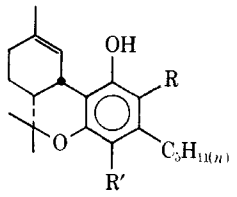
Δ^9-*trans*-tetrahydrocannabinol
IV



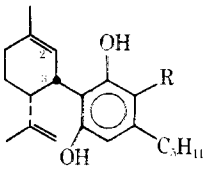
Δ^8-*trans*-tetrahydrocannabinol
V



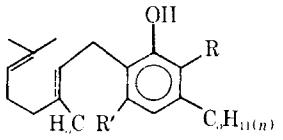
I: R = H, cannabinol
VI: R = COOH, cannabinolic acid



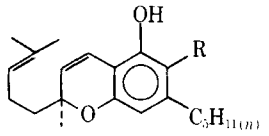
VII*a*: R = COOH, R′ = H
Δ^9-tetrahydrocannabinol acid A
VII*b*: R = H, R′ = COOH
Δ^9-tetrahydrocannabinol acid B



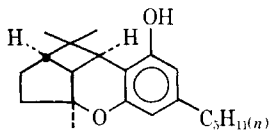
II: R = H, cannabidiol
VIII: R = COOH, cannabidiolic acid



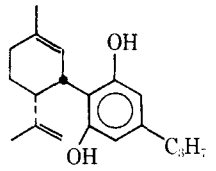
IX*a*: R = H, R′ = OH, cannabigerol
IX*b*: R = COOH, R′ = OH, cannabigerolic acid
IX*c*: R = H, R′ = OCH_3, cannabigerol methyl ether



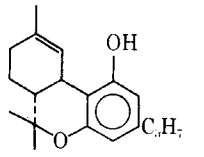
X*a*: R = H, cannabichromene
X*b*: R = COOH, cannabichromenic acid



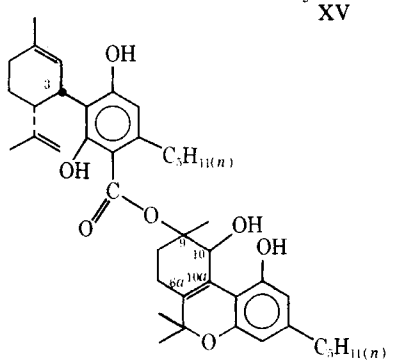
cannabicyclol (cannabipinol)
XI



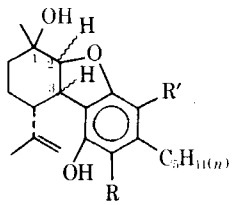
cannabidivarin
XII



n-propyl analog of Δ^9-tetrahydrocannabinol
XV



cannabitriol ester of cannabidiolic acid
XIII



XIV*a*: R = COOH, R′ = H, cannabielsoic acid A
XIV*b*: R = H, R′ = COOH, cannabielsoic acid B

structures of *C. sativa* cannabinoids

(−)-Δ^9-*trans*-tetrahydrocannabinol (IV), the generally accepted psychoactive principle, whose structure and stereochemistry have now been fully elucidated.

Isolation and Structure Elucidation of Naturally Occurring Cannabinoids—Column chromatography has been, without doubt, the major technique used in effecting the isolation of the naturally occurring cannabinoids. Usually an extract is made of the flowering tops or resin of the plant with petroleum ether. By repeated extraction with this solvent, all the active ingredients in the crude resin can be dissolved. The remaining inactive materials contain mostly phenolic polymers, small amounts of cannabielsoic acids, which can be extracted by benzene. The petroleum ether extract is separated into acidic and neutral fractions, both of which, on column chromatography, yield numerous cannabinoids and some unidentified sesqui- and triterpenes (7, 11). Adsorption chromatography (40), partition chromatography (40), preparative TLC (13), and countercurrent distribution (41) have been used with success by some workers, and it is not unusual to find two of these methods used together. The procedure used by Mechoulam and Gaoni (11) typifies the flexibility of column chromatography to effect separation of the cannabinoids:

> *"A hexane extract of hashish was separated into acidic and neutral fractions. The latter was chromatographed on Florisil or acid-washed alumina. The following identified compounds were eluted in order of increasing polarity: cannabidiol (II) (eluted with 5% ether in pentane), Δ^9-THC (IV), cannabinol (I), cannabichromene (Xa) and cannabigerol (IXa) (eluted with 15% ether in pentane). Repeated chromatography was needed to effect full separation. When the cannabidiol fractions were chromatographed on acid-washed alumina containing 12% silver nitrate, another component, cannabicyclol (XI), could be separated. Cannabichromene (Xa) and cannabigerol (IXa) could likewise be separated by the silver nitrate–alumina column. Cannabidiol, m.p. 66–7°, cannabicyclol, m.p. 152–3° and cannabigerol, m.p. 51–3°, were crystallized directly, while Δ^9-THC and cannabichromene were further purified by the preparation of crystalline derivatives and hydrolysis to the parent compound. Chromatography of the esterified acidic fraction yieldedcann abigerolic (IXb), cannabinolic (VI), and cannabidiolic (VIII) acids (as esters). The column chromatographic separations were monitored by thin-layer chromatography."*

The compounds isolated from the active neutral fraction are shown in Table III. A number of other workers described various methods of isolation and detection of Cannabis substituents (10, 42–48).

Earlier in this report, the structural elucidations of cannabinol (I) and cannabidiol (II) were briefly discussed. The structure of cannabinol was well established by two independent syntheses; the structure of cannabidiol was certain, except for the position of the double bond in the ring. The correct position of this double bond was not deduced until 1963 when NMR measurements showed the presence of only one olefinic proton in the compound (36). Additional support for this assignment was obtained from the NMR spectra of tetrahydrocannabidiol and its monoepoxide (11).

The relative stereochemistry of the two asymmetric centers, C_3 and C_4, in cannabidiol was deduced to be *trans* from an analysis of the coupling constants of the protons at these centers and by degradative evidence (36).

Cannabidiolic acid was first assigned Structure VIII (49, 50) (except for the position of the double bond), mainly on the basis of its conversion to cannabidiol by decarboxylation. The position of the carboxyl group was established by its IR and NMR spectra. The peak at 1698 cm.$^{-1}$ in the IR was assigned to an aromatic carboxyl group; in the NMR spectrum, only one aromatic proton was observed (51).

Since cannabigerol (IX*a*) has two more hydrogens than cannabidiol (II) but the same number of double bonds, it was concluded that cannabigerol possesses one ring less than cannabidiol. Its optical inactivity suggested that the two asymmetric centers present in cannabidiol are absent in its structure. The NMR spectrum indicates that the aromatic protons are identical, that the two protons at C-8 are strongly deshielded and split by a single adjacent proton, and that an isopropylidene group is present. The fact that the UV spectrum is identical with that of cannabidiol indicates that the double bonds are unconjugated, either to each other or to the aromatic ring (52, 53). The structure of cannabigerol was corroborated by synthesis (52). Cannabigerol monomethyl ether (IX*c*) was also identified (54) from the benzene extract of hemp and characterized by its physical properties, NMR spectrum, and synthesis from cannabigerol.

The structure of Δ^9-*trans*-tetrahydrocannabinol (IV) was elucidated in 1964 by Mechoulam and Gaoni (55). The carbon skeleton was determined by dehydrogenation to cannabinol, and the position of the double bond and the stereochemistry at the asymmetric centers were determined from NMR measurements and by synthesis studies. NMR studies showed that the olefinic C_{10} proton of IV is strongly deshielded compared to the C_2 proton in cannabidiol (II). On the other hand, the C_3 proton of II is more strongly deshielded than the C_{10a} proton of IV. This effect is the result of the orientation of the aromatic ring with respect to the C_2 and C_3 protons of II and the C_{10} and C_{10a} protons of IV and could only be observed if the double bond were in the Δ^9-position in IV. The Δ^8-isomer (V) was first prepared semisynthetically by Adams *et al.* (34), and further chemical and spectroscopic evidence (13, 56) confirmed the structure and established the *trans* stereochemistry at C_{6a} and C_{10a}. Conversion of cannabidiol (II) into Δ^8-*trans*-tetrahydrocannabinol (V) confirmed the suggested structure, and subsequent synthesis corroborated the stereochemical assignments (12). The absolute configuration of Δ^8-tetrahydrocannabinol and of Δ^9-tetrahydrocannabinol at the chiral centers, C_{6a} and C_{10a}, is R (57). The key to this assignment is the degradative correlation of cannabidiol (II) to D(−)-menthane carboxylic acid, m.p. 65–66°,$[\alpha]_D$ −44°, derived from D(−)-menthol, whose absolute configuration is known.

A Δ^9-tetrahydrocannabinol homolog, in which the side chain is C_3H_7 (instead of C_5H_{11}) (XV), was recently found in a sample of Pakistani hashish. It is one-fourth as active as Δ^9-tetrahydrocannabinol in producing a cataleptic effect in mice (58).

The structures of cannabinolic acid (VI), cannabigerolic acid (IX*b*), and tetrahydrocannabinol acid A (VII*a*) (59, 60) were determined by comparison of their NMR spectra with those of the corresponding neutral compounds (I, IX*a*, and IV) and, in the cases of VI and IX*b*, by actual conversion to the corresponding neutral compounds (I and IX*a*) by decarboxylation. In the acids, VI and VII*a*, where the two aromatic positions are not equivalent, the position of the carboxyl group was shown to be adjacent to the free phenolic group on the basis of strong deshielding of the phenolic proton caused by hydrogen bonding (11). An isomeric Δ^9-tetrahydrocannabinol acid B (VII*b*) was also isolated and characterized (61).

The structure of cannabichromene (X*a*) was suggested in 1966 (62, 63) on the basis of the UV spectrum showing double-bond conjugation with an aromatic ring, while the NMR spectrum indicated that two of the olefinic protons are not flanked by additional hydrogen atoms, an isopropylidene grouping is present, and one of the methyl groups is alpha to an oxygen while two others are olefinic. The structure of cannabichromene (X*a*) was corroborated by comparison of its hydrogenated product with the hydrogenated product resulting from the cyclization of cannabigerol (IX*a*) (62). The structure of *dl*-cannabichromene (X*a*) was confirmed by Mechoulam *et al.* (64) [by the chloranil dehydrogenation of cannabigerol (IX*a*)] and by others

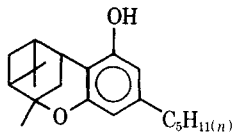
Table III—Constituents in Hashish, R_f Values, and Retention Times (VPC) of Some Natural Neutral Cannabinoids (7, 25)

	Yields[a]	R_f[b]	Retention Time[c]
Cannabicyclol (XI)	0.11	0.62	4 min., 33 sec.
Cannabidiol (II)	3.74 (1.4) (2.5)	0.58	5 min., 40 sec.
Δ^8-Tetrahydrocannabinol (V)	Not detected	0.57	7 min., 10 sec.
Δ^9-Tetrahydrocannabinol (IV)	3.30 (1.4) (3.4)	0.51	7 min., 52 sec.
Cannabinol (I)	1.30 (0.3) (1.2)	0.47	10 min., 12 sec.
Cannabichromene (X*a*)	0.19	0.43	5 min., 35 sec.
Cannabigerol (IX*a*)	0.30	0.42	9 min., 20 sec.

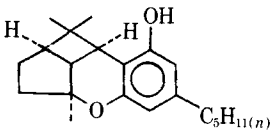
[a] As percent of hashish; determined by VPC. The numbers in parentheses are from two partial analyses of different batches. [b] Chromatoplates of silica gel. Elution with petroleum ether (b.p. 40–60°) and ether in a ratio of 4:1. [c] Column 2% OV-17 on Gas-Chromosorb Q: N_2 flow, 30 ml./min.; column temperature, 235°.

(65, 66). It is assumed (25) that naturally occurring cannabichromene is racemic, as in the related cannabichromenic acid (X*b*). This lack of optical activity points out that either cannabichromene is an artifact formed by a nonenzymatic oxidation of cannabigerol or that the intermediate formed by enzymatic oxidation is a symmetrical species. The lack of optical activity could also be due to the isolation procedure (25) involved in this compound. Pure cannabichromene shows no activity in the dog ataxia or monkey behavioral test in doses up to 10 mg./kg. (67). Cannabichromenic acid has been isolated from the benzene extract of hemp and shown to have Structure X*b* by NMR and by its ready conversion to cannabichromene (X*a*) with heat (68).

The structure of cannabicyclol (XI) was firmly established *via* an X-ray study of dibromocannabicyclol (69). The original formulation suggested for cannabicyclol (XVI) (11, 63) was revised to XI on the basis of its formation from cannabichromene (X*a*) by several chemical methods (69–72) and the X-ray study (69).



XVI

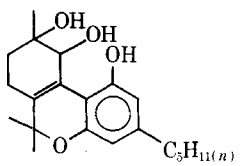


XI

Two tricyclic dihydrobenzofuran cannabinoids, cannabielsoic acid A (XIV*a*) and cannabielsoic acid B (XIV*b*), were isolated and characterized from the benzene extract of hashish in 0.08 and 0.04% yields, respectively (73). Compound XIV*a* was synthesized by an intramolecular photooxidative cyclization of cannabidiolic acid (VIII). The stereochemistry at C-2–C-3 was not confirmed but is probably *cis*.

Cannabidivarin (XII), a homolog of cannabidiol (II) in which the side chain on the phenyl ring is *n*-propyl (instead of *n*-pentyl), was also isolated from hashish. The structure and absolute configuration of cannabidivarin were determined by spectroscopic methods and confirmed by synthesis (74).

From the petroleum ether extract of hashish, the ester (XIII)[1] of cannabidiolic acid with tetrahydrocannabitriol was also isolated in small quantities (75). The alcohol moiety, tetrahydrocannabitriol (XVII), has not yet been isolated; it will in time, no doubt, also be found as a constituent of hashish.

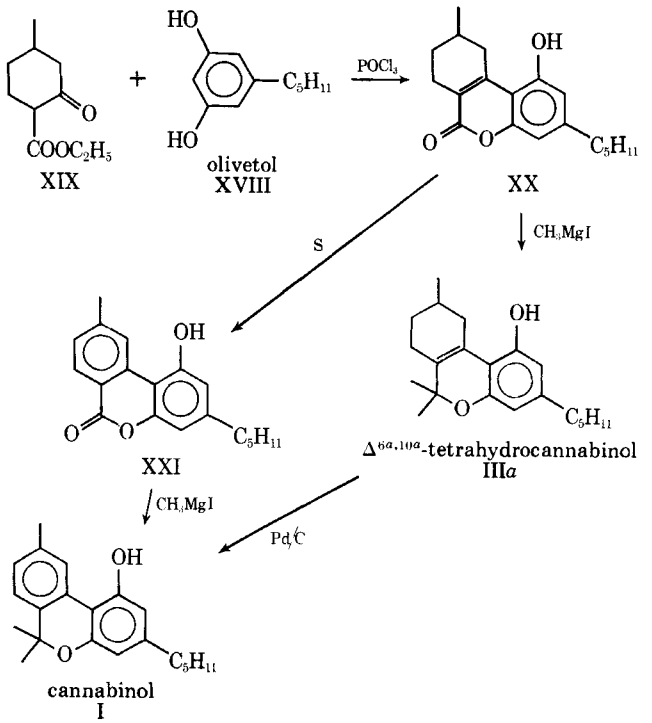


$\Delta^{6a,10a}$-tetrahydrocannabitriol
XVII

Other materials including noncannabinoid terpenes (76), nitrogen compounds (77), sugars (78), and phenolic compounds (77, 79) were isolated or detected in *C. sativa*.

Synthesis of Naturally Occurring and Structurally Modified Cannabinoids—Almost all of the noncarboxylic, naturally occurring cannabinoids that have been described were prepared synthetically or semisynthetically in the laboratory. These are cannabinol (I), cannabidiol (II), Δ^9-*trans*-tetrahydrocannabinol (IV), Δ^8-*trans*-tetrahydrocannabinol (V) (the corresponding *cis*-isomer of Δ^9-*trans*-tetrahydrocannabinol was also synthesized), cannabigerol (IX*a*), cannabichromene (X*a*), and cannabicyclol (XI). The syntheses of these compounds will be outlined.

In 1940, the biologically inactive cannabinol was the first cannabinoid to be synthesized by two groups working independently. One of the routes, followed by Adams and Baker (80), involved the condensation of ethyl 4-methyl-2-oxocyclohexanecarboxylate (XIX) with olivetol (XVIII) in the presence of phosphorus oxychloride. The resulting dibenzopyrone (XX) was dehydrogenated with sulfur and then treated with excess methylmagnesium iodide, yielding the desired product, cannabinol (I) (Scheme I).

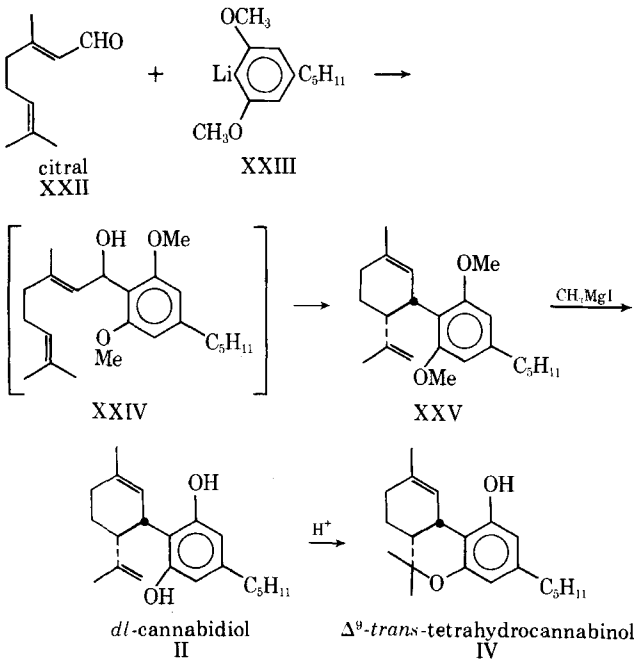


Scheme I—Synthesis of dl-$\Delta^{6a,10a}$-*tetrahydrocannabinol and of cannabinol*

Ghosh *et al.* (33, 81) made use of a similar route. They also produced the dibenzopyrone (XX), but they chose to treat it with methylmagnesium iodide before dehydrogenation. This latter route was of particular interest because the intermediate tetrahydrocannabinol (III*a*) was found to possess marijuanalike activity in animals and in man. Compound III*a* was also produced by Adams and Baker (37), who prepared a large series of $\Delta^{6a,10a}$-tetrahydrocannabinol homologs which will be discussed subsequently. Both groups described other routes for the synthesis of cannabinol (32, 82).

[1] The numbering system for this compound utilizes the dibenzopyran numbering system for the alcohol portion of the ester and the monoterpene numbering system for cannabidiolic acid.

The first total synthesis of *dl*-cannabidiol (II) and of *dl*-Δ^9-*trans*-tetrahydrocannabinol (IV), the major psychoactive principle of marijuana, was reported in 1965 by Mechoulam and Gaoni (83). Both of these cannabinoids were produced from the same reaction sequence (Scheme II). Citral (XXII) and the lithium



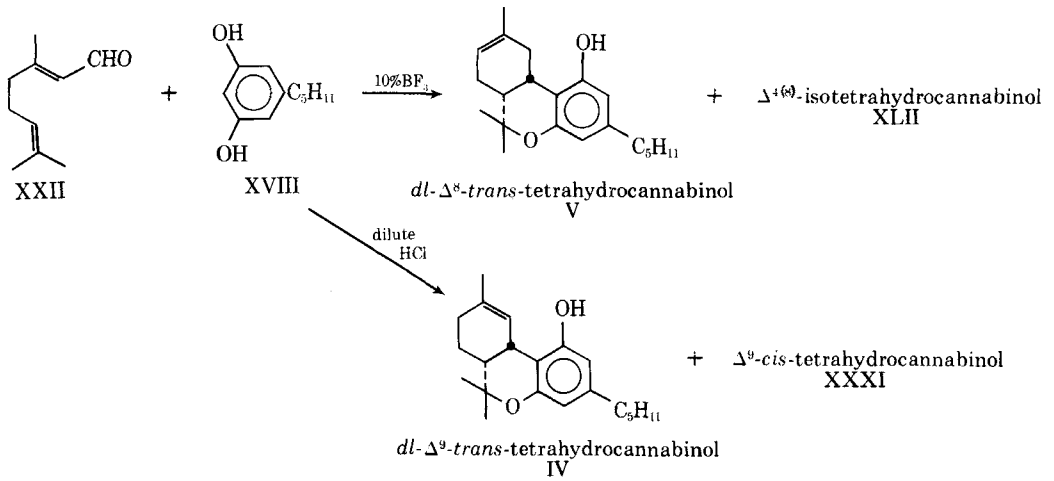
Scheme II—Synthesis of dl-*cannabidiol and of* dl-Δ^9-trans-*tetrahydrocannabinol*

salt of olivetol dimethyl ether (XXIII) were allowed to react at room temperature for 15 min.; the unresolved reaction mixture, presumably containing XXIV, was treated with *p*-toluenesulfonyl chloride in pyridine. The resulting cannabidiol dimethyl ether (XXV) was treated with excess methylmagnesium iodide, producing *dl*-cannabidiol (II). The diol was easily converted to *dl*-Δ^9-*trans*-tetrahydrocannabinol (IV) by treatment with 0.05% HCl in ethanol for 2 hr. The overall yield of IV was 2%. This synthesis was of little practical value since the yield was low, it was nonstereospecific, and it gave a racemic mixture. Numerous other investigators have since improved or modified this route or accomplished entirely new syntheses (47, 55, 84). Petrzilka *et al.* (85) reported a stereospecific synthesis of (−)-cannabidiol (II) in 25% yield by the condensation of (+)-*trans*- or (+)-*cis*-*p*-mentha-2,8-dien-1-ol (XXVIII) with olivetol (XVIII) in the presence of *N,N*-dimethylformamide dineopentylacetal (Scheme IVB).

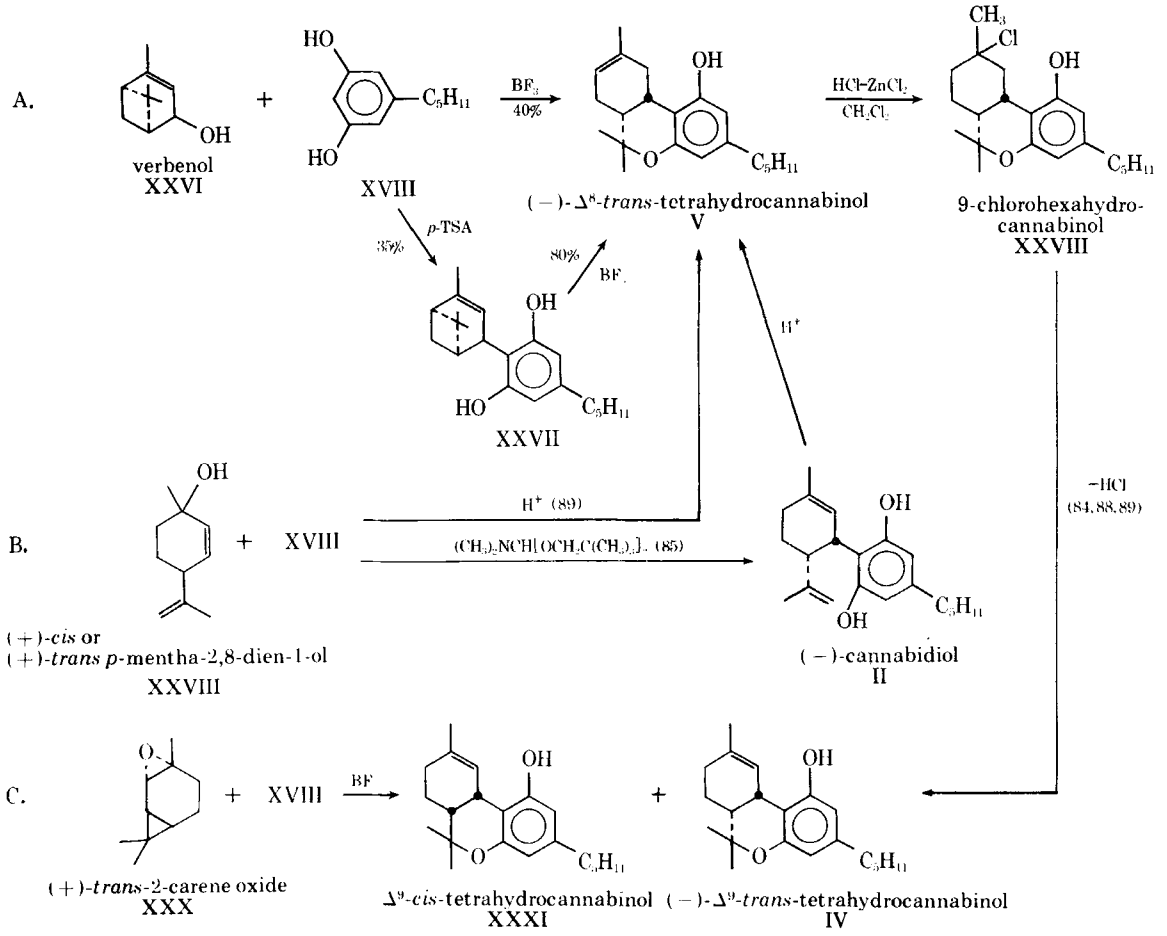
Taylor *et al.* (12) developed a facile one-step synthesis of *dl*-Δ^8- and *dl*-Δ^9-tetrahydrocannabinols. This procedure produces, in addition to the two *dl*-*trans*-tetrahydrocannabinol isomers, Δ^9-*cis*-tetrahydrocannabinol (XXXI) and $\Delta^{4(8)}$-isotetrahydrocannabinol (XLII), which are not found as naturally occurring cannabinoids (Scheme III). Citral (XXII) was reacted with olivetol (XVIII) in the presence of boron trifluoride and gave a mixture from which, after liquid column chromatography and vapor-phase chromatography, the *trans*-isomer (V) was recovered in 20% yield. The Δ^9-*cis*-isomer was formed by this condensation only under milder conditions (using very dilute HCl instead of boron trifluoride etherate).

dl-Δ^8-*trans*-Tetrahydrocannabinol (V) was also synthesized by Taylor and Strojny (86) *via* a Diels–Alder reaction. Fahrenholtz *et al.* (84) reported the synthesis of *dl*-Δ^9-*trans*-tetrahydrocannabinol and *dl*-Δ^8-*trans*-tetrahydrocannabinol, as well as of three unnatural isomers, *dl*-$\Delta^{9(11)}$-*trans*-tetrahydrocannabinol (LX), *dl*-$\Delta^{9(11)}$-*cis*-tetrahydrocannabinol, and *dl*-Δ^9-*cis*-tetrahydrocannabinol (LX). Their method involved a 10-step synthesis, in which the initial step was a von Pechman condensation of olivetol (XVIII) and diethyl α-acetoglutarate (LXIII). This method was employed by Nilsson *et al.* (87) for the synthesis of Δ^8- and Δ^9-tetrahydrocannabinol-^{14}C, which will be discussed later.

Three stereospecific syntheses of the psychoactive tetrahydrocannabinol isomers were reported (Scheme IV). Mechoulam *et al.* (88) synthesized (−)-Δ^9-*trans*-tetrahydrocannabinol (IV) and (−)-Δ^8-*trans*-tetrahydrocannabinol by the condensation of (−)-verbenol (XXVI) with olivetol (XVIII) in the presence of *p*-



Scheme III—Synthesis of dl-Δ^8-*tetrahydrocannabinol and* dl-Δ^9-*tetrahydrocannabinol*



Scheme IV—Synthesis of optically active (−)-Δ⁸-trans-*tetrahydrocannabinol*, (−)-Δ⁹-trans-*tetrahydrocannabinol, and* (−)-*cannabidiol*

toluenesulfonic acid (*p*-TSA). The pinene derivative (XXVII) was treated with boron trifluoride etherate at room temperature, producing (−)-Δ⁸-*trans*-tetrahydrocannabinol (V). The tetrahydrocannabinol (V) could also be prepared directly by treating the reactants with boron trifluoride etherate. (−)-Δ⁹-*trans*-Tetrahydrocannabinol (IV) was prepared by treating V with a dry hydrochloric acid–zinc chloride mixture, followed by reaction of the halogenated product (XXVIII) with sodium hydride in tetrahydrofuran. The overall yield was 19% (Scheme IVA).

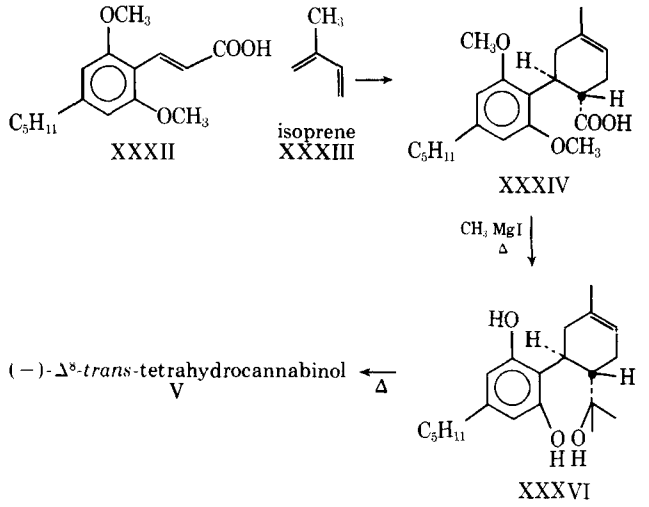
Petrzilka *et al.* (85, 89) also accomplished a stereospecific synthesis of these two psychoactive tetrahydrocannabinol isomers in a process that involves the condensation of olivetol with either (+)-*cis*- or (+)-*trans*-*p*-mentha-2,8-dien-1-ol (XXVIII) in the presence of acids (Scheme IVB). The (−)-Δ⁸-tetrahydrocannabinol (V) thus formed was converted to (−)-Δ⁹-tetrahydrocannabinol (IV) by the addition and elimination of hydrogen chloride in a manner similar to that of Mechoulam *et al.* (88). Potassium *tert*-amylate accomplished the dehydrogenation in benzene solution. *N,N*-Dimethylformamide dineopentylacetal was found to mediate the direct formation of (−)-cannabidiol (II) from XXVIII and XVIII (85).

Razdan and Handrick (90) reported an entry into the cannabinoids *via* carane derivatives; their one-step stereospecific synthesis leads to (−)-Δ⁸-*trans*-tetrahydrocannabinol (V) and (−)-Δ⁹-*trans*-tetrahydrocannabinol. Their method involves the interaction of (+)-*trans*-2-carene oxide (XXX) with an equimolar quantity of olivetol (XVIII) in the presence of *p*-toluenesulfonic acid to yield 23% of the Δ⁸-tetrahydrocannabinol isomer (V), 7% of Δ⁹-tetrahydrocannabinol (IV), and a complex mixture of other products. By modifying the molar ratio of the reactants or by employing 1% boron trifluoride etherate in methylene chloride, 28% of (−)-Δ⁹-*trans*-tetrahydrocannabinol (IV), Δ⁹-*cis*-tetrahydrocannabinol (XXXI), and a mixture of other products were obtained (Scheme IVC).

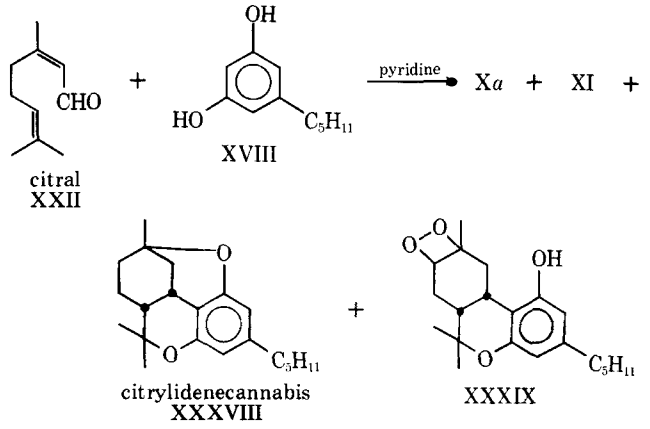
Jen *et al.* (91) reported a total synthesis of (−)-Δ⁸-*trans*-tetrahydrocannabinol (V), which involves the optical resolution of a racemic intermediate (XXXIV) (Scheme V). Fusion of the resulting (−)-XXXIV with methylmagnesium iodide gave the triol (XXXVI), which, on distillation and filtration in benzene through neutral Al_2O_3, gave a gum from XXXIV. Pure (−)-Δ⁸-*trans*-tetrahydrocannabinol was separated from the gum by preparative GLC.

Δ⁹- and Δ⁸-Tetrahydrocannabinol incorporating ^{14}C, tritium, and deuterium (87, 92–96) were synthesized for metabolism studies. Methods for these syntheses will be discussed in the section dealing with metabolism studies.

Cannabigerol (IX*a*) was synthesized by Mechoulam and Gaoni (52) by heating geraniol (XXXVII) with



Scheme V—Synthesis of (−)-Δ⁸-trans-tetrahydrocannabinol involving resolution of an intermediate (91)



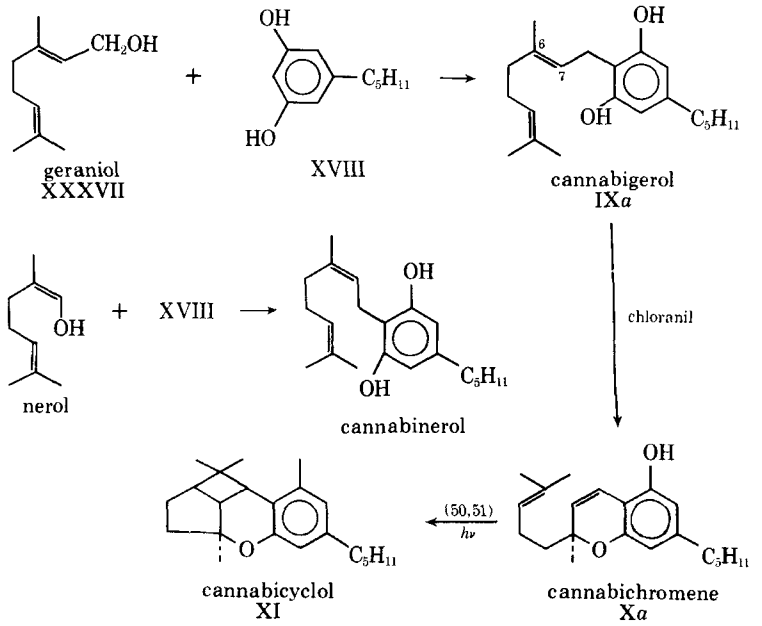
Scheme VII—Pyridine-catalyzed condensation products of olivetol with citral

olivetol (XVIII) in methylene chloride in the presence of *p*-toluenesulfonic acid at 20° (Scheme VI). The *cis*-isomer, cannabinerol, was similarly prepared in 39% yield from nerol and olivetol, confirming the geometry of the C_6—C_7 bond in cannabigerol (53).

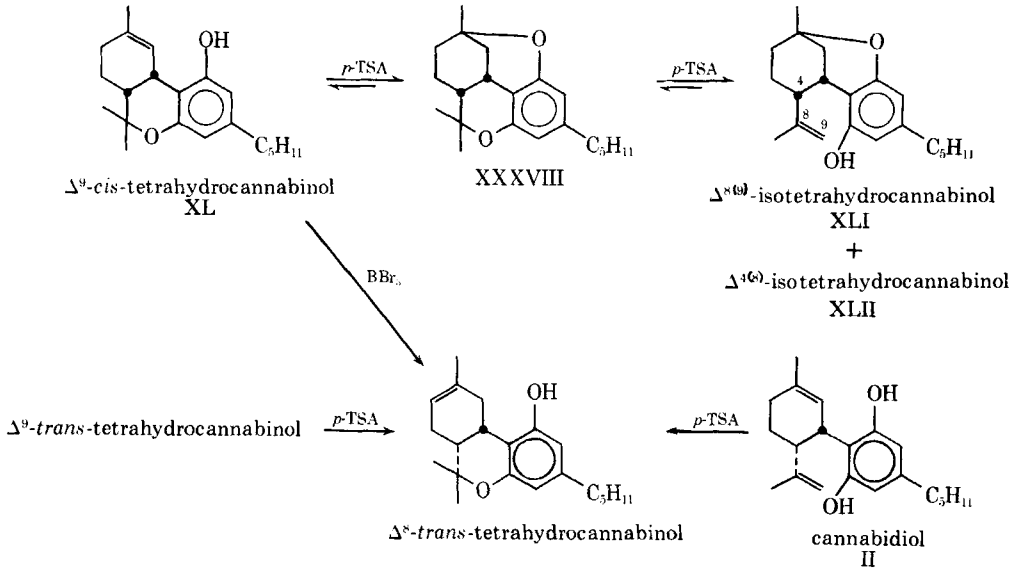
Mechoulam *et al.* (64) also prepared *dl*-cannabichromene (X*a*) by the dehydrogenation of cannabigerol (IX*a*) (in 45% yield) with chloranil (tetrachloroquinone) (Scheme VI). Cardillo *et al.* (97) synthesized *dl*-cannabichromene from geranyl bromide.

Crombie *et al.* (65, 72) prepared cannabicyclol (XI) from cannabichromene (X*a*) by photochemical means. Kane and Razdan (66) synthesized *dl*-cannabicyclol (XI) and *dl*-cannabichromene (X*a*) by heating equimolar quantities of citral (XXII) with olivetol (XVIII) in pyridine (Scheme VII). A third component isolated from this reaction mixture was the tetracyclic ether (XXXVIII), which had previously been obtained by the treatment of cannabigerol with chloranil (64). Razdan and Kane (98) subsequently reported the isolation of still another compound, a cyclic peroxide (XXXIX), from this pyridine-catalyzed reaction.

The isolation of XXXVIII in this reaction mixture and the observation that similar compounds were formed by varying the structure of the phenolic reactant (replacing olivetol with orcinol) led these authors to conclude that the reaction between substituted resorcinols and citral (XXII) in the presence of pyridine to form tetracyclic ethers of type XXXVIII is a general one. Such tetracyclic ethers will form isotetrahydrocannabinol derivatives of types XLI and XLII by reaction with *p*-toluenesulfonic acid (64, 66, 99, 100). An example for the interconversion of Δ⁹-*cis*-tetrahydrocannabinol (XL) to Δ⁸-*trans*-tetrahydrocannabinol was reported (101), and it was further shown that XL, XXXVIII, XLI, and XLII are interconvertible (71) (Scheme VIII). On the basis of this equilibrium and other results, Razdan and Zitko (71) proposed a mechanism of such acid-catalyzed transformations in cannabinoids. These authors concluded that in cannabinoids that have one of the oxygens tied



Scheme VI—Synthesis of cannabigerol, cannabichromene, and cannabicyclol



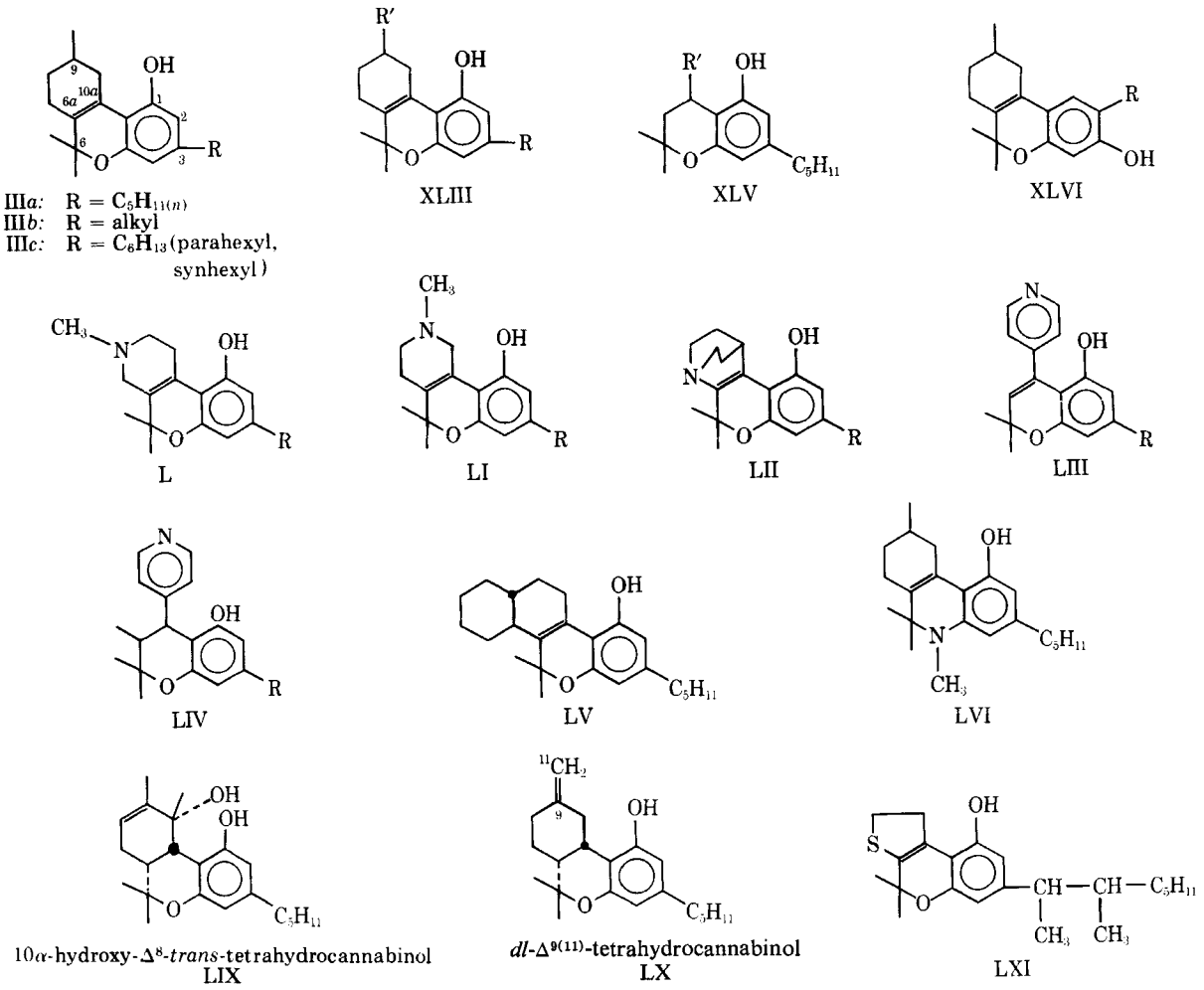
Scheme VIII—Acid-catalyzed transformations of Δ⁹-trans-*tetrahydrocannabinol*, Δ⁸-trans-*tetrahydrocannabinol*, *and* Δ⁹-cis-*tetrahydrocannabinol*

up in the form of a pyran ring, acid catalysts such as *p*-toluenesulfonic acid, which can protonate a double bond, affect transformation with retention of stereochemistry at the ring junction. However, nonprotonic acid catalysts such as BBr_3 or BF_3 effect interconversions with inversion at the ring junction to the more thermodynamically stable *trans*-form.

A general method developed for the synthesis of cannabinoid acids, utilizing methylmagnesium carbonate, was applied to the synthesis of Δ⁹-tetrahydrocannabinol acid A (VII*a*), cannabidiolic acid (VIII), and cannabigerolic acid (IX*b*) (102).

Structure–Activity Relationships in Cannabinoids—As mentioned earlier in this review, a compound, Δ⁶ᵃ,¹⁰ᵃ-tetrahydrocannabinol (III*a*), possessing marijuanalike activity but not occurring as a constituent of Cannabis, was prepared in 1940 by Ghosh *et al.* (33) and by Adams and Baker (37), independently of each other. The biological activity of this compound led Adams and others (83, 85, 86, 103, 104) to prepare a large series of closely related tetrahydrocannabinols (III*b*). The general method of synthesis employed by Adams *et al.* (105–109) involved ethyl 4-methyl-2-oxocyclohexanecarboxylate (XIX) (Scheme I), with an appropriate 5-alkylresorcinol in the presence of phosphorus oxychloride. Further conversion of the resulting pyrone with excess methylmagnesium iodide yielded the desired 3-alkyl-6*a*,10*a*-tetrahydrocannabinol (III*b*) (105). Loewe (110) showed that two major properties of Cannabis—the ability to block the blink reflex in rabbits [Gayer test (111)] and the ability to cause ataxia in the dog—were in part combined in the same molecule and in part embodied in different structures. Pharmacological data on the early cannabinoids were generally limited to either the Gayer test or the dog ataxia test. Of the tetrahydrocannabinols prepared in the 1940's, the most active compound on the basis of the dog ataxia and Gayer tests proved to be the one with a dimethylheptyl side chain [III*b*, R = $CH(CH_3)CH(CH_3)C_5H_{11}$]. Adams *et al.* (112) subsequently also synthesized the optically active *d*- and *l*-forms of Δ⁶ᵃ,¹⁰ᵃ-tetrahydrocannabinol (III*a*); they found that the *d*-form of III*a* had about 40% of the activity of the racemic III*a* and that the *l*-form had four to five times the physiological potency of the *d*-form. These optically active isomers were prepared by treating olivetol with the *d*- and *l*-forms of ethyl 4-methyl-2-oxocyclohexanecarboxylate. The potency of the dimethylheptyl analog [III*b*, R = $CH(CH_3)$-$CH(CH_3)C_5H_{11}$] led Aaron and Ferguson (113) to prepare the eight possible isomers of this compound. Their method, the same as used by Adams and Baker (80) (Scheme I), involves the resolution of the appropriate resorcinol into four isomers and their subsequent treatment with the (+)- and (−)-forms of ethyl 4-methyl-2-oxocyclohexanecarboxylate (XIX). The biological activity of these isomers has not yet been reported. One isomer of III, in which R is hexyl (III*c*, parahexyl, synhexyl, pyrahexyl), was studied in man (114) and found to have behavioral effects similar to those of the natural cannabinoids (115).

Other compounds were synthesized by Adams *et al.* (105, 116); the position of the methyl group in the cyclohexene ring was altered (XLIII) or more than one methyl group was added. This research group (117) also prepared a few compounds in which the 6-position of III*a* was substituted by higher alkyl groups. This was accomplished by reacting the appropriate Grignard reagent with the pyrone (XX) formed in the first step of the general reaction scheme. A more drastic alteration of the basic cannabinol structure, which eliminated the cyclohexane ring of III*a*, was achieved by Adams *et al.* (118) in a synthesis of XLV (R′ = CH_3). Ethyl acetoacetate was condensed with olivetol in benzene, using phosphorus oxychloride as the catalyst. The resulting coumarin was treated with methylmagnesium iodide, yielding the bicyclic product XLV (R′ = CH_3) (118). The 3-butyl derivative of XLV (R′ = C_4H_9) also was prepared by this method. Most of these compounds prepared by Adams *et al.* (118) were active in the dog ataxia test.



synthetic analogs of cannabinol

The pharmacological tests using rabbits and dogs measure only two aspects of the pharmacology of these substances. So far there is no evidence that the powerful psychotomimetic effects of *C. sativa* and its synthetic analogs in man have any relationship to the results of these tests in animals. The following conclusions can be drawn on the basis of the activity of these series compounds (III, XLIII, XLV, and XLVI).

1. In the series of compounds (105) with unbranched side chains, activity increases with an increase in the length of the carbon chain, reaching a maximum with the *n*-hexyl homolog and falling off with the higher homologs.

2. In the secondary series of compounds (106) (III*b*, R = *sec*-alkyl), in all except one case, the secondary groups produce molecules more active than the isomeric normal groups, and the activity increases with an increase in chain length. The *sec*-octyl homolog is higher in potency than the natural tetrahydrocannabinol isolated at that time.

3. Additional branching and lengthening of the *sec*-alkyl chain (107) in III*b* increase the potency to the point where the dimethylheptyl homolog is about 70 times more potent than is natural tetrahydrocannabinol.

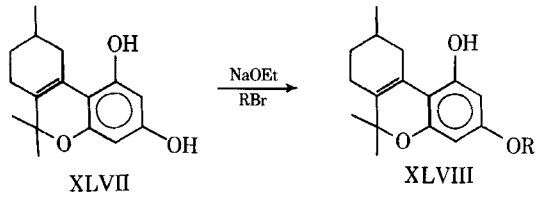
4. More potent compounds result from side-chain branching (R) close to the benzene ring rather than in more distant positions (108).

5. Further branching or extension beyond a seven-carbon chain appears to decrease activity, but, because of the longer duration of action of these higher homologs, it is impossible to determine where the peak of activity occurs in the alkyl series (108, 109).

6. Structural changes in the pyran and/or in the cyclohexene ring result in a decrease in activity.

Using essentially the method established by Adams (105–109), Avison *et al.* (119) and Taylor *et al.* (120) synthesized positional isomers (XLVI) with varying alkyl side chains on the aromatic ring. In some instances, such compounds showed marijuanalike and analgesic activity (119).

Bergel *et al.* (121) reported the synthesis (Scheme IX) of four derivatives (XLVIII), in which the *n*-amyl group in III is replaced by *n*-alkoxy groups. These were prepared by treating the dihydroxy pyran (XLVII) with the appropriate alkyl bromide. These workers also prepared a water-soluble derivative, the disodium tetrahydrocannabinyl phosphate, which showed no hashish activity in the Gayer test. Of the alkoxy derivatives (XLVIII), only the *n*-hexyloxy derivative (R = C_6H_{13}) appeared to show activity in doses between 10 and 20 mg./kg. by the Gayer test. The activity was only feeble, however. None of the other compounds showed any activity in doses up to 20 mg./kg.



XLVII XLVIII

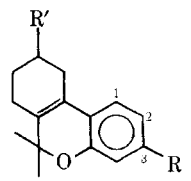
R = C_4H_9; C_5H_{11}; C_6H_{13}; C_7H_{15}

Scheme IX

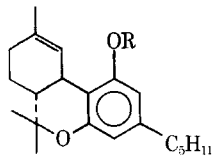
By a similar method (121), Alles *et al.* (122) synthesized two series of alkoxy and acyloxy derivatives (XLIII). They are distinguished from Bergel's compounds by the absence of the 1-hydroxy group and, in another series, the additional absence of the 9-methyl group (R′ = H). Neither of these two series of pyrans exhibited any significant degree of marijuana activity in dogs or rabbits.

Razdan (123) and Howes (124) prepared and tested water-soluble derivatives of Δ^9-tetrahydrocannabinol (XLIX*a* and *b*). The ether (XLIX*a*) was found to have a different profile than Δ^9-tetrahydrocannabinol, whereas the ester (XLIX*b*) showed similar properties to Δ^9-tetrahydrocannabinol (IV), although the compound was less active. The activity of the ester (XLIX*b*) was probably due to the *in vivo* hydrolysis to the phenolic cannabinoid (IV).

A number of nitrogen analogs of tetrahydrocannabinol were prepared and evaluated for their marijuanalike activity. Anker and Cook (125) synthesized L and its dihydro derivative in 1946, and they reported it to have no analgesic activity. No mention was made of other CNS effects of these compounds. In contrast to these earlier findings, Pars *et al.* (126) reported, in 1966, the synthesis of the isomeric nitrogen analog (LI) and its dihydro derivative; they found these compounds to be active on the CNS and to produce ataxia and motor deficits in mice, cats, dogs, and monkeys. Homologs of this azatetrahydrocannabinol, in which the side-chain R was varied, were also prepared by substituting 4-carbethoxy-*N*-methyl-3-piperidone for ethyl 4-methyl-2-oxocyclohexanecarboxylate in the general method for the synthesis of $\Delta^{6a,10a}$-tetrahydrocannabinol (III*a*) described in Scheme I. The activity of these nitrogen analogs encouraged these workers to prepare other aza-derivatives [LII (127), LIII (128), and LIV (128)], a sulfur analog [LXI (129)], and a "steroidal" analog



XLIII



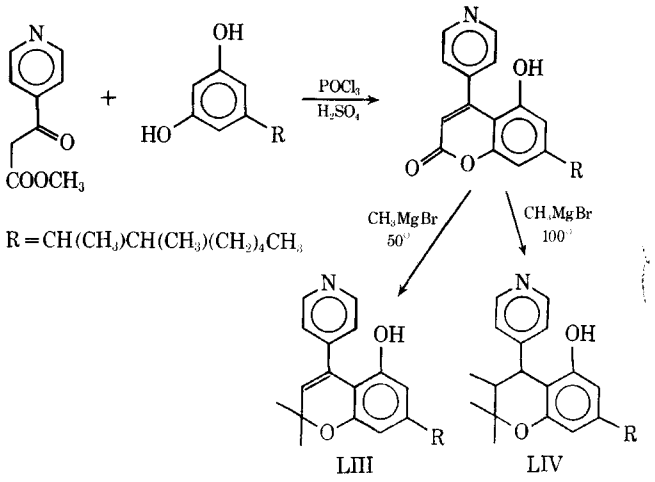
XLIX

R = CH_3; C_5H_{11}; OC_2H_5; $OCCH_3$; OCC_3H_7 (O)

R′ = H, CH_3

a) R = $-(CH_2)_2\overset{H}{\overset{+}{N}}(CH_2CH_3)_2Cl^-$

b) R = $C(CH_2)_3\overset{H}{\overset{+}{N}}(CH_2CH_3)_2Cl^-$ (O)



R = $CH(CH_3)CH(CH_3)(CH_2)_4CH_3$

LIII LIV

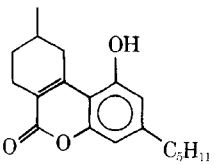
Scheme X—Grignard addition to 4-pyridylcoumarins (128)

[LV (130)]. These were all active on the CNS, except the "steroidal" analog (LV) (129, 131, 132).

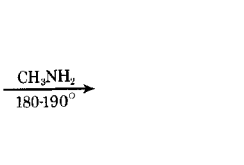
The effects of the aza-analog (LI) [R = $CH(CH_3)$-$CH(CH_3)C_5H_{11}$] were qualitatively similar to those of the sulfur analog (LXI) also containing a dimethylheptyl side chain (129). These investigators speculated that the introduction of a heterocyclic atom into the molecule enhances passage through the blood–brain barrier. Adams (16) previously reported that the tetrahydrocannabinol analogs (III) containing a dimethylheptyl side chain were considerably more active than those with the *n*-C_5H_{11} chain (110, 133). This may explain the activity of these heterocyclic analogs as compared with Δ^8-tetrahydrocannabinol (V) and Δ^9-tetrahydrocannabinol (IV).

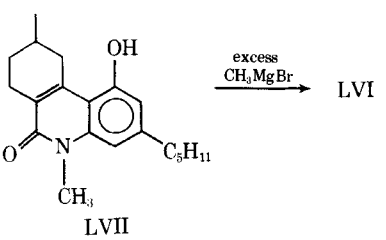
The synthesis of LIII and LIV involves a Grignard reaction with the 4-pyridylcoumarin prepared from methyl 3-oxo-3-(4-pyridyl)propionate and 5-(1,2-dimethylheptyl)resorcinol. The Grignard addition resulted in the usual 1,2-addition to give LIII at 50°, as well as the unexpected addition of a third mole of Grignard reagent to the double bond of the chromene to yield the 2,2,3-trisubstituted chroman (LIV) (128) (Scheme X).

A 5-azatetrahydrocannabinol analog was prepared in 1968 but was found to lack any CNS activity (134). The dibenzopyrone (XX), prepared by the method of



XX





LVII

Scheme XI

Adams and Baker (80) (Scheme I), was treated with methylamine to give the amide (LVII), which was converted to the 5-azatetrahydrocannabinol analog (LVI) with excess methylmagnesium bromide (Scheme XI).

The two isomeric 10-hydroxy-Δ^8-*trans*-tetrahydrocannabinol analogs were prepared and evaluated in the monkey (7). 10α-Hydroxy-Δ^8-*trans*-tetrahydrocannabinol (LIX) is almost as active as Δ^8-tetrahydrocannabinol (V), but the isomeric 10β-hydroxy-Δ^8-tetrahydrocannabinol is not active at 0.5 mg./kg.

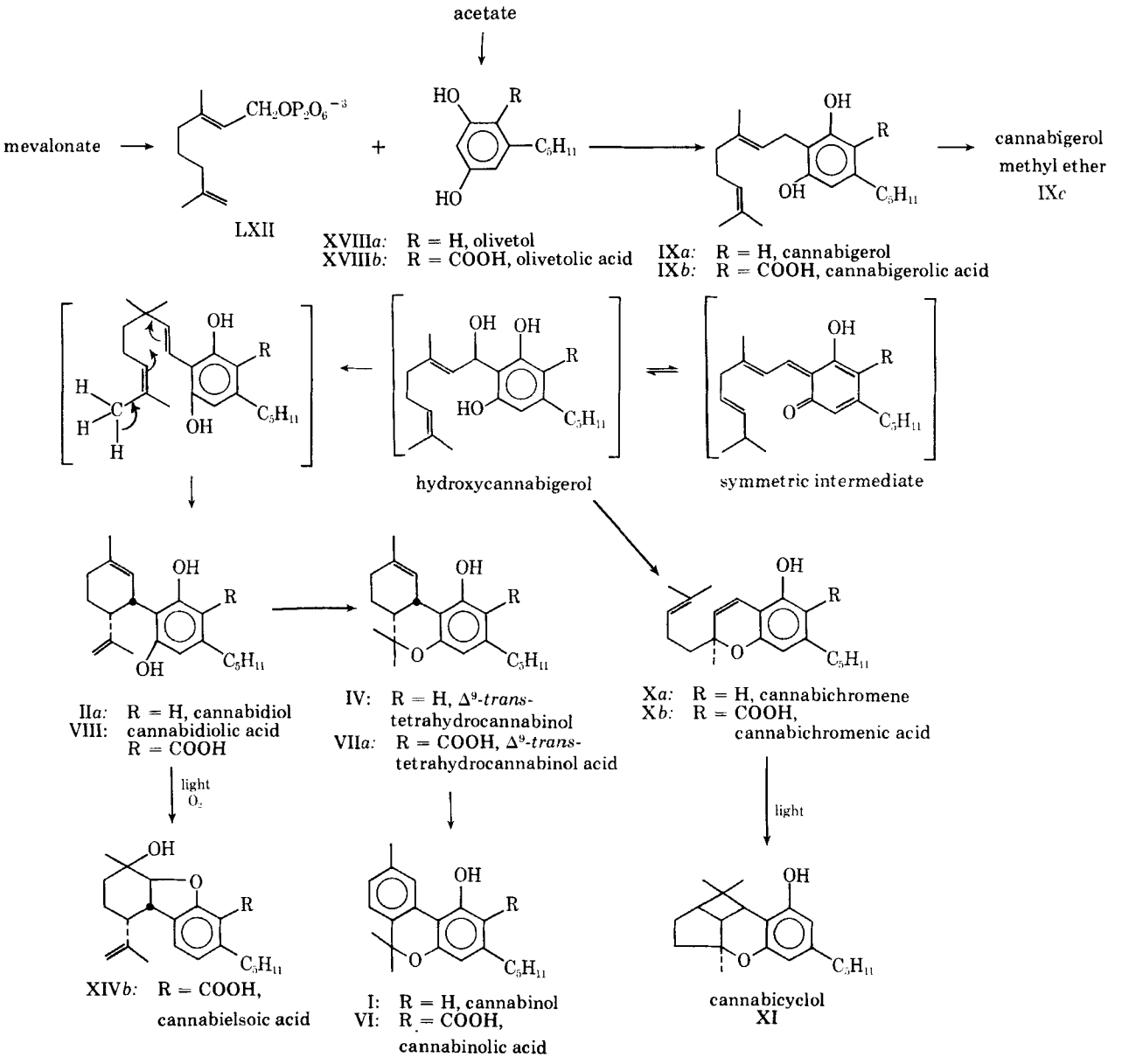
Three unnatural isomers of tetrahydrocannabinol were synthesized by Fahrenholtz *et al.* (84) in the course of their synthesis of *dl*-Δ^9-*trans*-tetrahydrocannabinol and *dl*-Δ^8-*trans*-tetrahydrocannabinol, referred to earlier. One of these isomers, $\Delta^{9(11)}$-*trans*-tetrahydrocannabinol (LX), was reported to be inactive (7). $\Delta^{8(9)}$-Isotetrahydrocannabinol (XLI), the synthesis of which has been discussed (Scheme VIII), was reported to be physiologically active by Razdan and Pars (131) at 10 mg./kg. in the mouse, and it was found to be inactive by Edery and Grunfeld (135) when tested in the monkey.

The structure–activity relationships in the cannabinoids can be summarized as follows:

1. In the $\Delta^{6a,10a}$-tetrahydrocannabinol series (III*b*), changes in the side chain of the aromatic ring can bring a considerable increase in activity, the most active compound being the dimethylheptyl compound. Synhexyl (III*b*, R = C_6H_{13}) shows strong activity orally (115), whereas $\Delta^{6a,10a}$-tetrahydrocannabinol (III*a*) is inactive up to 400 mcg./kg. (smoking) (136).

2. The major psychotomimetically active compound present in hashish is (−)-Δ^9-*trans*-tetrahydrocannabinol (67, 136–138). This compound is active on smoking and on ingestion (115, 136).

3. As with $\Delta^{6a,10a}$-tetrahydrocannabinol (III*a*), changes in the side chain of the natural cannabinoids cause a sharp increase in activity in the rhesus monkey. The most active compound is Δ^9-tetrahydrocannabinol, in which the side chain is dimethylheptyl (7).



Scheme XII—Postulated biogenesis of cannabinoids

4. Acetylation of the free hydroxyl in Δ^9-tetrahydrocannabinol (IV) or Δ^8-tetrahydrocannabinol (V) reduces the activity (7). The diethylaminobutyrate ester hydrochloride (XLIX*b*) is water soluble; it shows similar activity to Δ^9-tetrahydrocannabinol, although it is less active (123, 124).

5. Substitution on the aromatic ring of Δ^8-tetrahydrocannabinol (V) with a methyl group retains activity, while substitution with a carbomethoxy or hydroxyl group eliminates it (7).

6. α-Hydroxylation of Δ^8-tetrahydrocannabinol at the 10-position results in a compound almost as active as Δ^8-tetrahydrocannabinol, whereas the isomeric β-hydroxy compound is inactive in the monkey (7).

7. 11-OH-Δ^9-Tetrahydrocannabinol (LIV), a minor metabolite of Δ^9-tetrahydrocannabinol in man (139), is equally as active as Δ^9-tetrahydrocannabinol in animals.

8. Substitution of a hetero atom into the cyclohexene ring (LI, LXI) produces analogs that are qualitatively similar to the natural tetrahydrocannabinols when evaluated in animals (129).

9. Relationships of structure to activity of the many compounds synthesized to date will be clarified only when these compounds are studied in man.

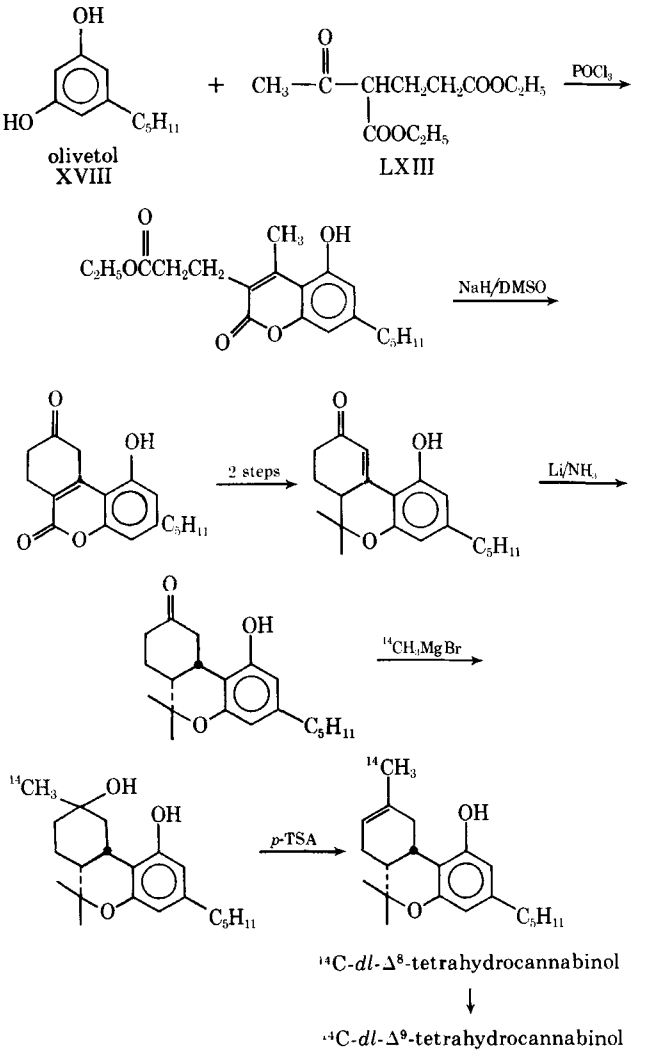
BIOGENESIS

Mechoulam (7) and Mechoulam and Gaoni (11) suggested a biogenetic scheme for the generation of cannabinoids. It was based upon a postulation, offered by Todd (17) and Sinonsen and Todd (140), in 1942, that the cannabinoids originated in the plant from a condensation of a terpene derivative with olivetol. Since definitive labeling experiments are lacking, the scheme proposed by Mechoulam (Scheme XII) seems to account for the various Cannabis constituents that have been found to date. It is suggested that geranyl pyrophosphate (LXII) (Scheme XII) condenses with olivetolic acid (XVIII*b*) [or olivetol (XVIII*a*)], resulting in the formation of cannabigerolic acid (IX*b*) [or cannabigerol (IX*a*)]. Since a direct cyclization of cannabigerol to cannabidiol (II*a*) is not possible (cannabidiol is in a higher state of oxidation than cannabigerol), an oxidized intermediate that can cyclize to either cannabidiol (II*a*) or cannabichromene (X*a*) was postulated. Cannabichromene (X*a*), cannabichromenic acid (X*b*), and cannabicyclol (XI) so far have been found optically inactive. Mechoulam indicated that either the cyclization leading to these compounds passes through a symmetric intermediate or that their formation involves a nonenzymatic process.

It is still debated whether the neutral cannabinoids are authentic natural products or whether these compounds are artifacts formed by decarboxylation of the corresponding cannabinoid (21). The formation of Δ^8-tetrahydrocannabinol can be readily rationalized by the isomerization of Δ^9-tetrahydrocannabinol by acids (Scheme VIII). The Δ^9-tetrahydrocannabinol isomer in the presence of air is slowly oxidized to cannabinol and compounds of higher molecular weight through oxidative phenolic coupling (7).

METABOLISM AND DISPOSITION

Synthesis of Labeled Cannabinoids—Metabolic studies on Cannabis constituents were hampered in the past by the lack of labeled compounds necessary to investigate the metabolic fate of these drugs. The recent progress in the development of synthetic methods applicable to the synthesis of labeled compounds has made such studies possible. Miras (20), in 1965, produced small amounts of tetrahydrocannabinol-^{14}C by growing Cannabis plants in $^{14}CO_2$. When the labeled Δ^9-tetrahydrocannabinol that was isolated was administered intraperitoneally to a rat, 68% of the radioactivity was eliminated in the feces and 12% *via* the urine within 5 days (20). More recently, Burstein and Mechoulam (92) prepared the Δ^8-tetrahydrocannabinol isomer specifically labeled at the C-10 position by the isomerization of Δ^9-tetrahydrocannabinol with tritiated *p*-toluenesulfonic acid. Facile deuteration and tritiation of both Δ^8-tetrahydrocannabinol and Δ^9-tetrahydrocannabinol by the use of labeled trifluoroacetic acid were also reported (95). Agurell *et al.* (93, 96) prepared Δ^9-tetrahydrocannabinol with high specific activities by treating Δ^9-tetrahydrocannabinol with tritiated water in the presence of phosphoric acid. These authors pointed out that, although Δ^9-tetrahydrocannabinol-^{3}H is stable in biological systems, gas chromatographic analysis of metabolic products can result in the exchange of the



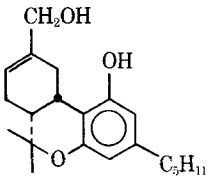
Scheme XIII—Total synthesis of ^{14}*C-dl-*Δ^8*-tetrahydrocannabinol and* ^{14}*C-dl-*Δ^9*-tetrahydrocannabinol (85) by the procedure of Fahrenholtz (84)*

label in the chromatograph, complicating the structural elucidation of the metabolites.

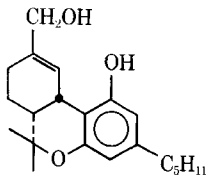
The synthesis of Δ^9- and Δ^8-tetrahydrocannabinol specifically labeled with ^{14}C at C-11 was accomplished by Nilsson *et al.* (87), essentially by the process developed by Fahrenholtz *et al.* (84). The synthetic sequence is shown in Scheme XIII. The label was introduced by the use of $^{14}CH_3Br$ in the final Grignard reaction.

Elimination and Distribution of Tetrahydrocannabinols—*Δ^9-Tetrahydrocannabinol*—The metabolism and distribution of Δ^9-tetrahydrocannabinol-^{14}C were studied in animals and man (93, 139, 141–144). Agurell *et al.* (93) showed that intravenously injected Δ^9-tetrahydrocannabinol-^3H was eliminated very slowly by the rat. About half of the administered drug remained in the body after 1 week, about 80% of the drug being excreted in the feces and the remainder being eliminated as metabolites in the urine. The elimination of Δ^9-tetrahydrocannabinol-^3H in the rabbit differs greatly from that in the rat. In the rabbit, the major elimination was *via* the kidneys, about 30% of the administered drug being excreted in the first 24 hr., in contrast to only a few percent excreted in the rat (141, 142). Nilsson *et al.* (142) identified one of the metabolites of Δ^9-tetrahydrocannabinol by an *in vitro* metabolism of Δ^9-tetrahydrocannabinol-^{14}C with rabbit liver as 11-hydroxy-Δ^9-tetrahydrocannabinol (LXIV). This metabolite was identified by the chemical conversion of LXIV to cannabinol (I) with *p*-toluenesulfonic acid and by mass and NMR spectrometry.

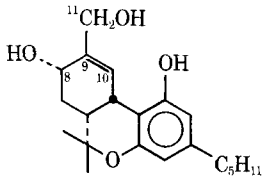
Working independently of the Nilsson group (142), Wall *et al.* (143) identified several *in vitro* metabolites from Δ^9-tetrahydrocannabinol-^3H from the 10,000-g supernatant prepared from male rat liver homogenate. These workers identified four *in vitro* oxidation products of Δ^9-tetrahydrocannabinol. After extraction and chromatography, Δ^9-tetrahydrocannabinol (IV), 11-hydroxy-Δ^9-tetrahydrocannabinol (LXIV), 8,11-dihydroxy-Δ^9-tetrahydrocannabinol (LXVI), and 11-acetoxy-Δ^9-



11-hydroxy-Δ^8-*trans*-tetrahydrocannabinol
LXV



11-hydroxy-Δ^9-*trans*-tetrahydrocannabinol
LXIV



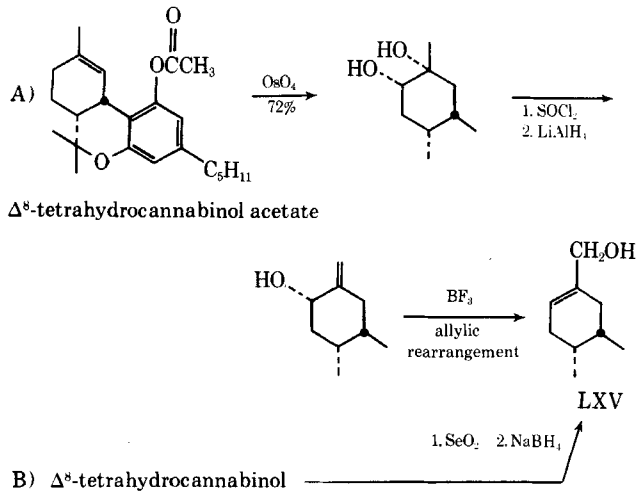
8,11-dihydroxy-Δ^9-*trans*-tetrahydrocannabinol
LXVI

identified metabolites of tetrahydrocannabinol

tetrahydrocannabinol, which is an artifact formed from LXIV during the extraction procedure, were identified. Preliminary behavioral and neuropharmacological examination of these metabolites indicated that 11-hydroxy-Δ^9-tetrahydrocannabinol (LXIV) was at least equipotent to Δ^9-tetrahydrocannabinol, whereas the dihydroxy metabolite (LXVI) was inactive. Subsequent to these earlier studies, this group found that the 11-hydroxy metabolites of Δ^8- and Δ^9-tetrahydrocannabinol are more active than the parent compounds (*viz.*, IV and V) when administered to mice by either the intravenous or intracerebral route; Christensen *et al.* (143) speculated that the 11-hydroxy metabolites may be the active forms of tetrahydrocannabinol in the mouse. A significant study, carried out at the National Institute of Mental Health (NIMH) (139), in which naive human volunteers were administered intravenously with 0.5 mg. of Δ^9-tetrahydrocannabinol-^{14}C, showed that its metabolites appear within 10 min. after administration and persist along with the precursor compound. These workers showed that 30% of the administered radioactivity was excreted in the urine and that less than 1% was unchanged Δ^9-tetrahydrocannabinol. This finding is significant for the development of assay procedures for the detection of Δ^9-tetrahydrocannabinol *via* urine samples. These results also indicated that less than 1% of the urinary radioactivity was unchanged Δ^9-tetrahydrocannabinol and that 11-hydroxytetrahydrocannabinol-^{14}C did not appear to account for more than a small percentage of the metabolites. Eighty percent of the metabolites still remained uncharacterized. About 50% of the radioactivity administered as Δ^9-tetrahydrocannabinol-^{14}C was recovered in feces, of which about 20% was the 11-hydroxytetrahydrocannabinol (LXIV) metabolite. Thus, after intravenous administration of Δ^9-tetrahydrocannabinol-^{14}C, the concentration in plasma rapidly declines, with a half-life of about 30 min.; two-thirds of the total radioactivity excreted in the urine is present during the 1st day. During this initial phase, the plasma contains higher concentrations of metabolites of Δ^9-tetrahydrocannabinol than of the parent drug.

In vitro studies (145) indicated that Δ^9-tetrahydrocannabinol was found to be 80–95% associated with lipoproteins. Lemberger *et al.* (139), in the NIMH studies in humans, pointed out that since Δ^9-tetrahydrocannabinol is a nonpolar compound, it may accumulate in fat or other tissue, such as lung, which has an affinity for drugs. Since the usual route of administration of marijuana is *via* inhalation, these findings are significant. Studies in animals confirmed that higher levels of Δ^9-tetrahydrocannabinol were present in the lungs than in other tissues (146, 147). The finding that Δ^9-tetrahydrocannabinol and its metabolites persists in humans for long periods indicates that the drug and its metabolites may accumulate in tissue when administered repeatedly.

Sofia and Barry (148) contend that the central depressant effect of Δ^9-tetrahydrocannabinol is attributable primarily to the parent compound rather than to the 11-hydroxy metabolites. Kubena and Barry (149) found that prolongation of barbital sleeping time in mice by Δ^9-tetrahydrocannabinol was enhanced when its hydroxylation to the 11-hydroxy metabolite was blocked by the microsomal enzyme inhibitor, SKF525A (β-diethylaminoethyldiphenyl propylacetate hydrochloride).



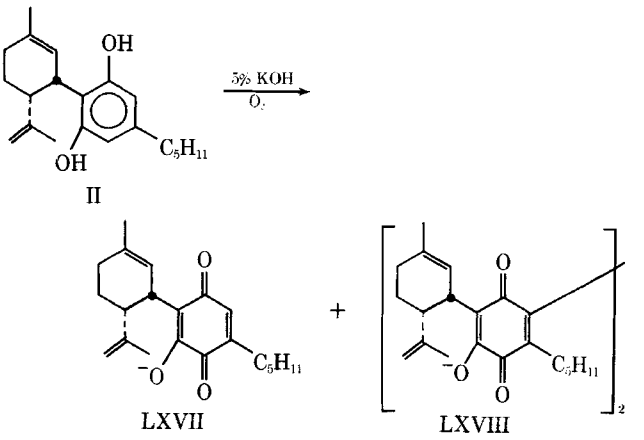
Scheme XIV—Synthesis of 11-hydroxy-Δ⁸-trans-tetrahydrocannabinol (65)

Δ⁸-Tetrahydrocannabinol—The metabolism of Δ⁸-tetrahydrocannabinol was studied in rabbits (150) and in rats (151). Δ⁸-Tetrahydrocannabinol-^{3}H, administered intravenously to rabbits, indicated that several water-soluble substances containing tritium were present. Treatment of the mixture with 0.1 *N* perchloric acid gave one major compound (150), which could also be obtained by incubation of Δ⁸-tetrahydrocannabinol-^{3}H with a homogenate of rabbit liver (152). This compound was identified as 11-hydroxy-Δ⁸-tetrahydrocannabinol (LXV) by mass spectrometry and chemical transformation to cannabinol (I) and was confirmed by synthesis (152, 153) (Scheme XIV). Synthetic 11-hydroxy-Δ⁸-tetrahydrocannabinol, when administered to monkeys (154), was active at approximately the same dose levels as Δ⁸-tetrahydrocannabinol. A synthesis of LXV in two steps, by oxidation of Δ⁸-tetrahydrocannabinol with selenium dioxide and reduction of the product with sodium borohydride (Scheme XIVB), was also reported (151). A modification of this procedure (153) involves the selenium dioxide oxidation of Δ⁸-tetrahydrocannabinol acetate, yielding 11-hydroxy-Δ⁸-tetrahydrocannabinol diacetate. This method was similarly applied to the synthesis of LXV in 1% yield from Δ⁸-tetrahydrocannabinol. Foltz *et al.* (151), in studies with Δ⁸-tetrahydrocannabinol-^{14}C, found approximately 13% of the radioactivity in the liver 30 min. after injection into rats. The major metabolite produced *in vivo* was LXV, which was also formed by hepatic microsomes *in vitro*. These studies confirmed that the behavioral effects of this metabolite (LXV) in rats were similar to those imparted by Δ⁸- and Δ⁹-tetrahydrocannabinol.

QUALITATIVE AND QUANTITATIVE ANALYSIS OF CANNABIS CONSTITUENTS

The analysis of cannabinoids received considerable attention by numerous groups. Beam (155), in 1911, reported that hashish extracts give a deep-purple color with a 5% ethanolic potassium hydroxide solution. Because of the importance of Cannabis identification for legal purposes, this test was subjected to numerous studies regarding its specificity, reliability, and sensitivity (10). Out of 120 plant species examined, only two, *Rosmarinus officinalis* and *Salvia officinalis*, give a weakly positive reaction; out of 48 pure substances of vegetable origin, consisting of such diverse chemical types as monoterpenes, sesquiterpenes, and aromatic compounds, only juglone, which is a quinone, developed a color close to that of the Beam test.

Curiously, the identification of hashish is based on the presence of the physiologically inactive constituents, cannabidiol (II) and cannabigerol (IX*a*), and their corresponding acids. The active constituent in Cannabis, Δ⁹-tetrahydrocannabinol, gives a negative Beam test. Mechoulam *et al.* (156) clarified the chemical basis for the Beam test (Scheme XV). Under the reaction condi-



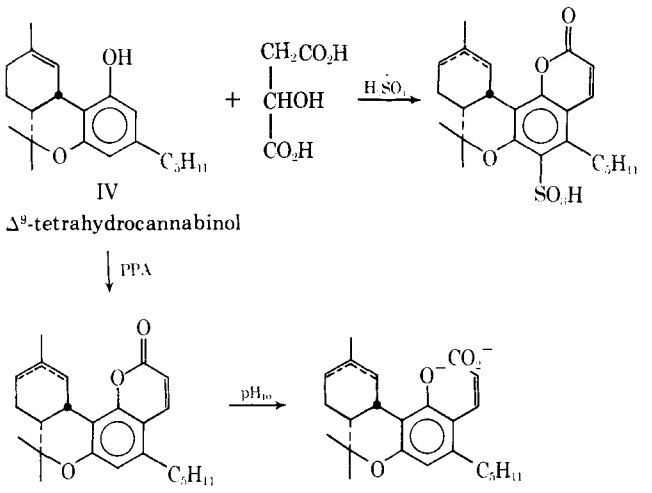
Scheme XV—Chemical basis for Beam test

tions of this test, cannabidiol (II) is oxidized to the monomeric quinone (LXVII) and the dimeric quinone (LXVIII). The violet color is due to the anions of these hydroxyquinones. Oxidation of Δ⁸-tetrahydrocannabinol with *m*-chloroperbenzoic acid similarly produces the quinone (LXVII). TLC is now used more widely for qualitative analysis. Korte and Sieper (46) employed silica gel impregnated with dimethylformamide and cyclohexane as the solvent. Numerous other solvent systems have been used, the R_f values being affected by the solvent (25, 43–45, 157). Mechoulam (7) and Gaoni and Mechoulam (25) reported a system in which chromatoplates of silica gel were eluted with petroleum ether (b.p. 40–60°)–ether in a ratio of 8:2, and the plates were sprayed with potassium permanganate solution. The R_f values of the major neutral cannabinoids are tabulated in Table III (7, 25).

VPC was extensively employed for the analysis of the cannabinoids (158, 159). The columns in use today are SE-30 (159–161), XE 60 (45), Carbowax 20M (162), OV-17 (163), and 2% OV-17 on Chromosorb Q at 235° (25). The retention times of the major natural cannabinoids are also tabulated in Table III. Mechoulam (7) pointed out that all the cannabinoid acids undergo decarboxylation at the high temperatures employed for VPC. Thus, a VPC analysis will give all the tetrahydrocannabinol available to a smoker in a certain sample. A methanol extraction is necessary to remove the tetrahydrocannabinol acids. Hydrocarbon extraction of the plant does not remove tetrahydrocannabinol acids. Preliminary treatment of the fresh plant by heating at 110° for 15 min. was effective for the decarboxylation of the tetrahydrocannabinol acids.

This method was utilized by Kimura and Okamota (209) for determining the tetrahydrocannabinol content in Cannabis. When exact determination of the cannabinoid content is required, decarboxylation can be prevented by esterification.

There is, at present, no generally accepted method useful for the detection and quantitation of the constituents of marijuana in mammalian materials. Bullock *et al.* (164) developed an analytical method based on the fluorescence produced with certain Cannabis constituents by condensation with malic acid (Scheme XVI



Scheme XVI—Chemical basis for fluorimetric method of analysis of cannabinoids (164)

and Table IV). This method was found useful for quantitating Δ^9-tetrahydrocannabinol in plasma samples containing at least 0.6 mcg. tetrahydrocannabinol in 2 ml.; given a 10-ml. sample, 0.05 mcg./ml. has been quantitated. The doses used in evaluating the method in the dog are, however, at least 20-fold greater than might be encountered with marijuana users on a milligrams per kilogram basis. In a study using blood samples obtained 20 min. after the subjects smoked a 400-mg. marijuana cigarette (0.9% tetrahydrocannabinol), no Δ^9-tetrahydrocannabinol was detected with two subjects. Blood levels of Δ^9-tetrahydrocannabinol must have been significantly below 0.05 mcg./ml. (165). This method has not been developed sufficiently to establish the amount of tetrahydrocannabinol metabolites present in plasma. By using a TLC separation prior to derivatization with malic acid, 1 mcg. of the 11-hydroxy metabolite (LXIV) was quantitated in dog and monkey feces (165). As pointed out by Lemberger *et al.* (139), little, if any, unchanged Δ^9-tetrahydrocannabinol may be excreted in the urine or feces.

Numerous detection methods for marijuana constituents (166–168), including smoke condensate (169, 170), were recently reported.

PHARMACOLOGY OF CANNABINOIDS

Animal Pharmacology—The early pharmacologic studies were carried out with extracts of Cannabis, such as "red oil," containing varying quantities of cannabinoids (7, 10, 11). Thus, much of the earlier data needed to be repeated when pure and standardized marijuana preparations became available.

Table IV—Excitation and Emission Maxima of Fluorescent Species Derived from Certain Cannabinoids with Malic Acid (164)

Compound	Excitation, nm.	Emission, nm.
Δ^9-Tetrahydrocannabinol (IV)	290	360
	380	470
Δ^8-Tetrahydrocannabinol (V)	290	360
	380	470
Cannabinol (I)	290	360
	370	460
Cannabidiol (II)	290	360
	370	460

Gershon (171) recently summarized the pharmacology of the cannabinoids in laboratory animals. Other significant reviews relating to the pharmacology of marijuana in animals appeared over the last 5 years (20, 21, 58). Recent investigations with pure Δ^9-tetrahydrocannabinol and with Δ^8-tetrahydrocannabinol in a variety of animal species corroborated, in general, the earlier findings of the psychopharmacological activity of marijuana extract (67, 154, 172). Scheckel *et al.* (138) studied the effects of *dl*-Δ^9-tetrahydrocannabinol (IV) and *dl*-Δ^8-tetrahydrocannabinol (V) in monkeys (intraperitoneally). They found that both isomers profoundly affect the behavior of monkeys, causing stimulation, depression, apparent hallucinations, and loss of ability or motivation to perform complex tasks. Studies with the synthetic levorotatory (−)-Δ^9-tetrahydrocannabinol (IV) and (−)-Δ^8-tetrahydrocannabinol (V) indicated that these isomers have the same type of activity as their racemates but are more potent. There was also a tendency for both drugs to increase tolerance to shock, but no general sedative or analgesic effects were observed. Mechoulam *et al.* (67) observed that, except for Δ^9-tetrahydrocannabinol, no other major active compounds were present in analyzed samples of hashish when administered intravenously to adult rhesus monkeys. The presence of only very minor quantities of Δ^8-tetrahydrocannabinol in these samples seems not to contribute appreciably to the biological activity of Cannabis. Such studies have not been carried out in humans, however.

Bicher and Mechoulam (173), working with these same two compounds, observed that 8 mg./kg. i.v. of either isomer in rabbits caused restlessness and increased motor activity and awareness. Also observed in most animals were a significantly increased cortical activity, a significantly lowered cortical arousal response threshold, and a prolonged length of ECoG arousal. These findings are contradistinct to morphine sulfate, which produced a decrease in frequency of ECoG waves and elevated the threshold of arousal response. The analgesic properties of both Δ^9- and Δ^8-tetrahydrocannabinol on mice and rabbits were found to be similar, 20 mg./kg. of the compounds being equivalent to 10 mg./kg. of morphine sulfate. LD_{50}'s of both compounds were greater than 1000 mg./kg. In the anesthetized dog, both isomers were shown by Razdan *et al.* (174) to potentiate epinephrine and norepinephrine in all parameters.

Marijuana extract, which consists of a mixture of both Δ^8- and Δ^9-tetrahydrocannabinol and other compounds, was reported (175) to prolong significantly the hexobarbital sleeping time and to increase significantly the amphetamine-induced activity in the mouse. Marijuana extract was found to be completely absent of hypnotic action in mice, rabbits, guinea pigs, cats, and dogs (176). There is some evidence that natural tetrahydrocannabinol possesses anticonvulsant activity (177).

Gill *et al.* (58) claimed that there are at least six pharmacologically effective components of Cannabis. Cannabis resin, given to mice, lowers body temperatures by up to 8°, produces analgesia and catalepsy, and prolongs pentobarbital sleeping time. Doses required for these effects ranged from 25 to 200 mg./kg., depending on the route of injection (58). In preliminary toxicity tests, the LD_{50} for a single dose lay between 1000 and 5000 mg./kg. when injected intraperitoneally at various dose levels. For doses repeated daily, it lay between 500 and 1000 mg./kg.

Other studies with marijuana extract indicated that, in the mouse, the duration of effects on body temperature and spontaneous activity correlates generally well with changes in brain amines (178). Striking aggressive behavior was shown to develop in starved rats treated with marijuana extract (179).

The parenteral administration of (−)-Δ^9-*trans*-tetrahydrocannabinol to pigeons demonstrated the behavioral tolerance to this drug (180). This procedure was used previously to demonstrate the behavioral tolerance to narcotics. These experiments showed not only that a marked tolerance develops to the behavioral effects of (−)-Δ^9-*trans*-tetrahydrocannabinol but also that the rate, pattern, and degree of tolerance development resemble, in some respect, those seen with narcotics. Previous failures to demonstate development of tolerance to the effects of marijuana in man and animals (137, 181, 182) may have been related to the route of administration, the purity of the drug, or the species examined.

A few studies were made on the teratogenic and mutagenic effects of Cannabis, only one of which was carried out on human subjects. In the studies carried out with marijuana extracts on cultured rat leucocytes, with rat embryonic cells in tissue culture, and with rat embryos whose mothers were treated with Cannabis resin, no chromosomal abnormalities were indicated and only slight mitotic inhibition was found (183). With pregnant rats injected intraperitoneally, incidences of fetal malformations, resorption of fetuses, and retarded development in the treated animals were significantly higher than in control groups (184). In contrast to these findings with marijuana extract, Borgen and Davis (185) found no teratogenic effects in rats injected with Δ^9-tetrahydrocannabinol in dosages up to 200 mg./kg. given throughout gestation.

The other naturally occurring cannabinoids were subjected to various pharmacological investigations. Cannabinol (I) was found devoid of any specific activity (30, 176, 186). Cannabidiol (II) demonstrated some antibiotic activity *in vitro* (11), but it was found devoid of hypnotic (176) as well as psychotomimetic activity (30), although it was shown to potentiate barbiturates (187). Recently, II was reported to cause severe motor deficit and ataxia in rabbits (10 mg./kg. i.v.) (181). Cannabigerol (IX*a*) also demonstrated antibiotic activity *in vitro* (11) but was devoid of psychotomimetic activity (154, 172). Cannabidiolic acid (VIII) and cannabichromene (X*a*) (67, 136, 154, 172) both were found ineffective as psychotomimetics; however, VIII demonstrated sedative and potent *in vitro* antibiotic activity (188), while X*a* produced ataxia and sedation in the dog (11) and loss of neuromuscular coordination in mice (15–30 mg./kg. s.c.) (174). Another cannabinoid possessing antibiotic activity is cannabigerolic acid (IX*b*). This compound's psychotomimetic activity has not been reported.

Natural cannabinoids whose biological activity has not been reported or who are inactive are cannabitriol ester of cannabidiolic acid (XIII), cannabinolic acid (VI), cannabigerol monomethyl ether (IX*c*), cannabidivarin (XII), cannabichromenic acid (X*a*), and cannabicyclol (XI).

Of the synthetic cannabinoids, parahexyl (III*c*) demonstrated the same order of activity as marijuana extract or chlorpromazine in suppressing the isolation-induced aggressive behavior in mice, the effective doses of all three being in the range of 3–5 mg./kg. i.p. (189). Parahexyl (III*c*) was shown to: (*a*) prolong hexobarbital sleeping time in mice (175), (*b*) have anticonvulsant activity in mice (177), and (*c*) lack hypnotic activity in five animal species (176). Loewe (176) demonstrated that a mixture of hexahydrocannabinols is active in the dog ataxia test.

$\Delta^{6a,10a}$-Tetrahydrocannabinol (III*a*) has actions in common with parahexyl and natural tetrahydrocannabinol; that is, it prolongs hexobarbital sleeping time and increases amphetamine-induced activity in the mouse (intraperitoneally) (175).

The pharmacological effects of the two most potent nonnatural cannabinoids synthesized to date, the dimethylheptylpyran [III*b*, $R=CH(CH_3)CH(CH_3)C_5H_{11}$] and the methyloctylpyran [III*b*, $R = CH(CH_3)C_7H_{15}$], were studied on cats and mice (190). Dagirmanjian and Boyd (190) reported that, in anesthetized cats, intravenous dimethylheptylpyran lowered blood pressure, depressed respiration, relaxed the gut, and depressed two polysynaptic reflexes, the knee jerk and the ipsilateral flexion reflex. The methyloctylpyran derivative produced similar effects to those of the dimethylheptylpyran derivative, but it was shorter acting and showed stimulatory action on the flexion reflex.

In mice, the barbiturate sleeping time was prolonged and amphetamine-induced activity was increased significantly by both drugs. The reported (190) 7-day LD_{50}'s in mice were 27 mg./kg. (17.5–41.6, 95% confidence level) for dimethylheptylpyran and 5.0 mg./kg. (3.5–7.0, 95% confidence level) for methyloctylpyran. The potencies in dogs and cats were not in the same order as the toxicities in mice. Boyd and Meritt (191) also reported that dimethylheptylpyran, in a dose of 0.2 mg./kg. i.v., increased the threshold for EEG arousal in the cat with acute preparations and increased the threshold for behavioral as well as EEG arousal with chronic preparations. A dose of 2.0 mg./kg. i.v. of thiopental was necessary to

produce similar results. Arousal was induced by electrical stimulation of the reticular formation.

Human Pharmacology—The knowledge of the pharmacologic effects of marijuana in humans is based chiefly on five important studies. The most comprehensive of these, the "La Guardia Report," was carried out by the New York Academy of Science in 1939 (182). However, it was not until 1967, when pure synthetic Δ^9-tetrahydrocannabinol became available, that the studies of Isbell *et al.* (136) in man were possible. Weil and his associates (137, 192, 193) studied "naive" and marijuana users and their responses to smoking marijuana. Hollister *et al.* (115) studied the clinical effects of Δ^9-tetrahydrocannabinol and synhexyl (IIIc) in man and found the effects quite similar to those observed with smoking marijuana. With high oral doses of Δ^9-tetrahydrocannabinol, these authors found disintegration of sequential thought which was related to impaired immediate memory (194).

Hollister *et al.* (115) also reported the biochemical effects in man from oral doses of Δ^9-tetrahydrocannabinol. These workers found:

1. The free fatty acids in the plasma remained unchanged (LSD elevated free fatty acids in plasma).

2. Glucose concentrations in the blood were unchanged.

3. Creatinine and phosphorus clearance were temporarily decreased.

Other studies with marijuana or pure synthetic derivatives were reported by Williams *et al.* (195), Clark and Nakashima (196), Pillard (197), Lemberger *et al.* (139), and the U. S. Army Chemical Research and Development Laboratories (211).

The significant findings of Isbell *et al.* (136) in humans, with pure (−)-Δ^9-*trans*-tetrahydrocannabinol rather than the crude extract, showed:

1. Regardless of the route of administration, (−)-Δ^9-*trans*-tetrahydrocannabinol (IV) caused no significant changes in pupillary size, respiratory rate, blood pressure, or threshold for elicitation of the knee jerk reflex.

2. Pulse rates were consistently elevated, and infection of the conjunctivae developed after large doses; 120 mcg./kg. orally and 50 mcg./kg. by smoking were recognized by patients as being similar to marijuana. [Other studies (115) showed that a range of 341–946 mcg./kg. orally produced similar marijuanalike effects (Table V)].

Table V—Dose in Relation to Physiological Effects in Man

Compound	Dose, mg. Oral	Dose, mg. Smoked[b]	Physiological Effects	Reference
Δ^9-Tetrahydrocannabinol[a]	9[c] 36[c]	2[c] 7.5[c]	Oral dose showed slow onset of action and longer duration. Smoking produced more rapid onset of action (seconds) but effects were briefer. Lower dose produced increased pulse rate, changes in mood, usually euphoric. Highest dose produced distortion in visual and auditory perception, depersonalization, and hallucinations resembling LSD.	136
Δ^9-Tetrahydrocannabinol[a]		2.25 9	Increased heart rate and reddening of the whites of the eyes. No changes in blood sugar. Marijuana-naive persons demonstrated impaired performance on simple intellectual and psychomotor tests which were dose related. Physiological and psychological effects reached maximum intensity within 0.5 hr. of inhalation and were completely dissipated within 3 hr.	137
Δ^9-Tetrahydrocannabinol[a]	20 40 60	6	Increased pulse rate; blood pressure fell slightly; at higher doses, orthostatic hypotension was observed. Conjunctival reddening was also constantly observed. Euphoria, sleepiness, and deep sleep at higher doses. Many psychotomimetic symptoms similar to LSD, mescaline, or psilocybin. Total food intake as well as hunger and appetite was increased.	115
Δ^9-Tetrahydrocannabinol[a]	50[c]		Impaired performance in complex reaction time, digit code memory, time estimation, hand steadiness, and reading comprehension. Suggested impairment of rapid decision making and short-term memory.	196
Δ^9-Tetrahydrocannabinol[a]		5	Impaired performance on pursuit meter and on performance tests.	202
$\Delta^{6a,10a}$-Tetrahydrocannabinol (III*a*)		7.5[c]	Activity similar to effects produced with Δ^9-tetrahydrocannabinol but considerably less potent.	115
		15[c]	No effects from smoking (400 mcg./kg.).	136
$\Delta^{6a,10a}$-Tetrahydrocannabinol (synhexyl, IIIc)	50–200	7.5	Activity like those with Δ^9-tetrahydrocannabinol but considerably less potent. Showed slower onset of symptoms, these being delayed by about 60 min. more than with Δ^9-tetrahydrocannabinol. The duration of action of synhexyl, however, was prolonged as compared to Δ^9-tetrahydrocannabinol.	115
$\Delta^{6a,10a}$-Tetrahydrocannabinol (III*b*, R = dimethylheptyl)	0.5–1.0 1.5–3.0 3.5–4.0		Fatigue, thirst, headache. Postural hypotension with temporary blurring or actual loss of vision on standing. Marked psychomotor retardation. Subjects stayed in bed and were unwilling or incapable of assuming an erect position. Sluggishness, inability to concentrate, and dimness and blurring of vision persisted for as much as 48 hr. Pulse rate increased when postural hypotension occurred but showed little or no change at higher dose levels.	210

[a] Δ^9-Tetrahydrocannabinol (IV) was extracted from hashish or marijuana and assayed for its tetrahydrocannabinol content or prepared synthetically. [b] In the compilation of these comparative doses, it was assumed that 50% of the active constituents introduced into the cigarette or occurring naturally in marijuana or hashish were destroyed by smoking. In some cases, dose was recalculated to indicate dose available to user. [c] All doses reported in micrograms per kilogram were converted to dose/75-kg. man if weight of man was not indicated.

3. Marijuana effects of (−)-Δ^9-*trans*-tetrahydrocannabinol (IV) are dose related.

4. The drug is about three times more potent when smoked than when ingested.

5. $\Delta^{6a,10a}$-Tetrahydrocannabinol (III*a*) produced no effects in doses up to 400 mcg./kg. by smoking [Hollister *et al.* (115) reported marijuanalike effects at half this dose], and synthetic cannabidiol dimethyl ether and cannabichromene produced no effects in doses up to 2.5 mg./kg. orally.

6. The effects of smoked Δ^9-*trans*-tetrahydrocannabinol (75–225 mcg./kg.) were compared with those of LSD given intramuscularly in doses of 0.5–1.5 mcg./kg. Subjective effects between the two drugs were not readily distinguished, but objective differences were marked.

Weil's (137, 192, 193) pioneering studies investigated the effects of marijuana in a formal double-blind experiment, and they are claimed to be the first attempts to collect basic clinical and psychological information on the drug by observing its effects on marijuana-naive human subjects in a laboratory setting. From these studies (137, 192, 193), these investigators drew the following conclusions:

1. Persons naive to marijuana do not have strong subjective experiences, even after high doses of the drug.

2. Marijuana-naive persons demonstrate impaired performance on simple intellectual and psychomotor tests after smoking the drug. Regular users who get "high" show a much less marked degree of impairment on the same tests; in some cases, they even improve.

3. Smoking marijuana increases the heart rate moderately and dilates the conjunctival blood vessels but causes no change in the respiratory rate, the pupil size, or the blood sugar levels.

4. Physiological and psychological effects reach maximum intensity within 0.5 hr. of inhalation, are diminished after 1 hr., and are completely dissipated after 3 hr.

5. Moderate marijuana smokers differ little in personality from those who do not smoke the drug, but heavy smokers of marijuana are rather less conventional.

6. Marijuana smokers tend to drink little alcohol.

A number of studies reported the effects of smoking on the components of marijuana. A report in 1964 indicated that smoking has no effect on the active constituent of marijuana (presumably Δ^9- and Δ^8-tetrahydrocannabinol), although 40% of the resin constituents disappeared during smoking (198).

Da Silva (199) showed that the tetrahydrocannabinol constituents were still found in the smoke condensate from combustion of Cannabis, although cannabidiol, which was present in the crude drug, was absent from the smoke condensate. Further support of the thermal stability of the naturally occurring tetrahydrocannabinol was given by Claussen and Korte (200), but they claimed that about 98%, instead of 40%, of the cannabinoids present in marijuana was destroyed by the smoking process and that tetrahydrocannabinol carboxylic acid readily decarboxylated to form the active tetrahydrocannabinol. Mechoulam (7) supported this latter finding in stating that the cannabinoid acids are converted into the respective neutral compounds, rapidly when heated and slowly when stored. This is given as one of the reasons for the higher activity of marijuana following smoking as compared with ingestion (49, 50). Incomplete absorption of drug following ingestion may also be a reason for the higher activity by the inhalation route. The burning process destroys part of the natural tetrahydrocannabinol already present in the plant. These findings were also confirmed by Kimura and Okamota (209).

Lemberger *et al.* (139) pointed out that since Δ^9-tetrahydrocannabinol is found in the lungs *via* the inhalation route, a critical degree of tissue saturation must be attained before effective threshold levels of Δ^9-tetrahydrocannabinol can be achieved. This could explain, in part, the phenomenon of "reverse tolerance" seen in chronic users of marijuana.

Another recent study described a comparison of the effects of marijuana and alcohol on simulated driving performance (201). The authors concluded that subjects experiencing a "social marijuana high" demonstrated no significant differences in total errors as compared with control conditions, whereas the same subjects intoxicated with alcohol accumulated significantly more accelerator, brake, signal, speedometer, and total errors as compared with control conditions. Although these results indicate that smoking marijuana does not impair driving performance, it is difficult to extrapolate conclusions from simulated driving conditions to actual driving conditions.

A more recent study, using subjects that smoked either calibrated marijuana cigarettes (10 mg. Δ^9-tetrahydrocannabinol per cigarette) or placebo cigarettes, produced significant decrements in human motor and mental performance (202).

A study of 12 healthy marijuana smokers indicated a possible hepatotoxicity of Cannabis, because eight of the 12 subjects showed evidence of mild liver dysfunction (203).

Of the few studies on the effect of Cannabis on chromosomes, only one was carried out on human subjects. In this study, leucocyte cultures from four healthy adult subjects were treated with (−)-*trans*-Δ^8-tetrahydrocannabinol during the last 24 hr. of culturing. No more chromosomal aberrations were found in these specimens than those observed in cultures from normal, healthy persons (204). Unfortunately, tests with the Δ^9-isomer present in larger quantities have not been reported.

A few of the many published case histories of persons experiencing unusual psychological effects induced by smoking marijuana are worth noting. One report presents cases of six persons who experienced hallucinations of color design or marked changes in perception with their eyes open (205). Another report described adverse reactions experienced by 11 individuals in a student population. Their difficulties included panic, fear, gross confusion, depersonalization, disorientation, depression, and paranoia following the use of the drug (206). One author described clinical syndromes of acute toxic psychosis associated with Cannabis derivatives and environmental stress observed in 12 soldiers seen in Vietnam (189). These cases of perplexing psychotic

reactions usually cleared in 1–4 days, but a few lasted a week or longer. In all instances, this was the patient's first admitted exposure to marijuana; in each case, marked physical symptoms appeared soon after the subjects began to smoke (207). In another study, four individuals reported the recurrence, in the drug-free state, of visual or somatic sensations previously experienced during the marijuana reaction (208). The possibility of adulterants incorporated into the marijuana cannot be ruled out in any of these studies where the purity and source of the drug was not definitely established.

Quantitation of Dose in Relation to Clinical Phenomena—The availability of synthetic cannabinoids over the last 3 years and the accurate determination of the active constituents in marijuana have now made it possible to provide some indication of the dose–response relationship with oral and smoked marijuana. A comparison of these results with the synthetic cannabinoids such as $\Delta^{6a,10a}$-tetrahydrocannabinol (III*a*) and the side-chain homologs where the *n*-amyl group was substituted with an *n*-hexyl group (III*c*, synhexyl) or a dimethylheptyl group [III*b*, R = $CH(CH_3)CH(CH_3)C_5H_{11}$], some of which (*i.e.*, synhexyl) had previously been evaluated in man, was now possible.

When marijuana is smoked, the amount of the active component Δ^9-tetrahydrocannabinol delivered is still uncertain. For this review, it was assumed that an average cigarette consists of 500 mg. of marijuana, containing an average of 1% active ingredients. The smoking process would destroy 50% of the active constituents. (This is still a matter of controversy.) The dose delivered would thus be 2.5 mg. of Δ^9-tetrahydrocannabinol per cigarette. Similarly, doses reported in micrograms per kilogram have been converted to mg./75-kg. man. The results of the studies carried out at the U. S. Public Health Service in Lexington, Ky. (136), at the Veterans Administration Hospital at Palo Alto, Calif. (115), at Boston University (137), at the University of Utah (196), and at the U. S. Army Chemical Research and Development Laboratories, Edgewood, Md. (210), are summarized and tabulated in Table V. The following observations can be made.

1. Synthetic tetrahydrocannabinol and marijuana extracts are orally active, but doses equivalent in effect to those from smoking are about three times greater.

2. When smoked, tetrahydrocannabinol is rapidly absorbed and effects appear within seconds to minutes, lasting 2–3 hr. after a single cigarette. Oral doses delay onset of symptoms from 30 min. to 2 hr.

3. Synthetic tetrahydrocannabinol analogs (III*a*, III*b*, and III*c*) show similar physiological effects, although structure–activity relationships have not singled out any specific pharmacological effect, except possibly the hypotensive effect produced by the dimethylheptyl homolog (III*b*).

4. Both $\Delta^{6a,10a}$-tetrahydrocannabinol (III*a*) and synhexyl (III*c*) were considerably less potent than Δ^9-tetrahydrocannabinol both on oral administration and when smoked.

Summary of Pharmacological Effects in Man—NIMH summarized the present state of knowledge on the pharmacological effects of marijuana in September 1970 in a report to the Secretary of Health, Education and Welfare (211):

> *"Marijuana is not a narcotic. Neither is it primarily a stimulant, sedative, tranquilizer or hallucinogen, although it shares some properties with each of these. At the same time, it lacks many of their other properties. In small doses it produces stimulation followed by sedation. In high doses it acts as a hallucinogen and can produce subjective changes somewhat resembling those of small amounts of LSD. Unlike many drugs* (e.g., *opiates and amphetamines) which require increasingly higher dosages over time to produce the same effect, marijuana users frequently report that with repeated use smaller doses produce the original effects. The apparent rapid disappearance from the blood of such substances as Δ^9-THC and Δ^8-THC following their injection indicates that they are rapidly transformed into other compounds.*
>
> *"Marijuana shares with other psychoactive drugs the problem of adequately describing and defining its subjective effects. There is considerable variability in the way in which the different sensations produced are interpreted by the user. What appear to be similar subjective states may be quite differently interpreted by different users. The same effect may be pleasurable to one user and unpleasant, even frightening, to another. It may also be that those finding the experience predominantly pleasant are inclined to minimize or ignore the less pleasant effects.*
>
> *"Although the state of intoxication is frequently vivid as described by the user, an observer may see little change from a normal state. Mild states of intoxication often go completely undetected. The user's mood may be quite variable from being happy and gregarious to quiet and detached. At higher doses, speech may be slowed or slurred. Physiological changes are notably minimal. Increase in pulse rate and bloodshot eyes are the most obvious. Dry mouth and throat along with an increase in appetite are common. Other physiological effects often are inconsistent or not reproducible.*
>
> *"Generally, simple physical and psychological performances are not much affected in short-term, moderate dosages while more complicated physical and psychological performances may be impaired. This may be due to an effect of marijuana intoxication on immediate memory. There is, however, great variability between users and little is presently known about the effects of long-term, chronic use on performance. Subjectively, time distortion appears common, with users reporting that a minute appears more like several minutes passage of time. Other subjective effects range from pleasant relaxation to acute anxiety, loss of reality contact, hallucinations and panic. These latter reactions are less common and much more likely when unexpectedly large doses of active material are consumed.*
>
> *"As is true of other psychoactive drugs, much appears to depend on the expectations of the user and the circumstances under which he uses the drug (set and setting). The user's set, referring to his total psychological makeup, mood at time of use and personal expectations, makes a considerable difference in the effects experienced, especially in low to moderate dosages. The external conditions of use, or setting, also make a great deal of difference in the total experience. A user feeling emotionally secure in a pleasant setting free of fear of detection is likely to have a different experience from someone taking the drug under more anxiety-producing conditions. The more neutral setting of the research laboratory may produce still different experiences. It is generally conceded that the individual and group expectations involved in the typical circumstances of marijuana use are important although difficult-to-evaluate aspects of the drug reaction."*

REFERENCES

(1) T. H. Mikuriya, *Calif. Med.*, **110**, 34(1969).

(2) C. W. Waller, "The National Marihuana Program: First Annual Report," The National Institutes of Health, 1969.

(3) J. R. Valle, A. J. Lapa, and G. G. Barros, *J. Pharm. Pharmacol.*, **20,** 798(1968).
(4) N. R. Farnsworth, *J. Amer. Pharm. Ass.*, **NS9,** 410(1969).
(5) N. R. Farnsworth, *Science*, **162,** 1086(1968).
(6) A. T. Weil, *Sci. J.*, **1969,** 36.
(7) R. Mechoulam, *Science*, **168,** 1159(1970).
(8) L. Grinspoon, *Sci. Amer.*, **221,** 17(1969).
(9) G. S. Chopra, *Int. J. Addict.*, **4,** 215(1969).
(10) L. Grlic, *Bull. Narcotics*, **16,** 29(1964).
(11) R. Mechoulam and Y. Gaoni, *Fortschr. Chem. Org. Naturst.*, **25,** 175(1967).
(12) E. C. Taylor, K. Lenard, and Y. Shvo, *J. Amer. Chem. Soc.*, **88,** 367(1966).
(13) R. L. Hively, W. A. Mosher, and F. W. Hoffman, *ibid.*, **88,** 1832(1966).
(14) Anon., *Chem. Eng. News*, July 6, 1970.
(15) R. Adams, *Harvey Lect.*, **37,** 168(1941).
(16) J. Blatt, *J. Wash. Acad. Sci.*, **28,** 465(1938).
(17) A. R. Todd, *Experientia*, **2,** 55(1946).
(18) F. Korte, H. Sieper, and S. Tira, *Bull. Narcotics*, **17,** 35 (1965)
(19) D. F. Downing, *Quart. Rev.*, **16,** 133(1962).
(20) "The Ciba Foundation, Hashish: Its Chemistry and Pharmacology," G. E. W. Wolstenholme and J. K. Knight, Eds., Little, Brown, Boston, Mass., 1965.
(21) "The Botany and Chemistry of Cannabis," C. R. B. Joyce and S. H. Curry, Eds., Churchill, London, England, 1970.
(22) "Psychopharmacological Agents," M. Gordon, Ed., Academic, New York, N. Y., 1964, p. 555.
(23) Anon., *Bull. Narcotics*, **16,** 29(1964).
(24) O. E. Schultz, *Planta Med.*, **12,** 371(1964).
(25) Y. Gaoni and R. Mechoulam, *J. Amer. Chem. Soc.*, **93,** 217(1971).
(26) T. Smith and H. Smith, *J. Chem. Soc.*, **21,** 47(1857).
(27) T. B. Wood, W. T. N. Spivey, and T. H. Easterfield, *ibid.*, **75,** 20(1897).
(28) R. S. Cahn, *ibid.*, **1930,** 986; **1931,** 630; **1932,** 1342; **1933,** 1400.
(29) F. Bergel and K. Vogel, *Justus Liebigs Ann. Chem.*, **493,** 250(1932).
(30) R. Adams, D. C. Pease, and J. H. Clark, *J. Amer. Chem. Soc.*, **62,** 2194(1940).
(31) A. Jacob and A. R. Todd, *Nature*, **145,** 350(1940); *J. Chem. Soc.*, **1940,** 649.
(32) R. Adams, B. R. Baker, and R. B. Wearn, *J. Amer. Chem. Soc.*, **62,** 2204(1940).
(33) R. Ghosh, A. R. Todd, and S. Wilkinson, *J. Chem. Soc.*, **1940,** 1121.
(34) R. Adams, C. K. Cain, W. D. McPhee, and R. B. Wearn, *J. Amer. Chem. Soc.*, **63,** 2209(1941).
(35) R. Adams, S. Loewe, D. C. Pease, C. K. Cain, R. B. Wearn, B. R. Baker, and H. Wolff, *ibid.*, **62,** 2566(1940).
(36) R. Mechoulam and Y. Shvo, *Tetrahedron*, **19,** 2073(1963).
(37) R. Adams and B. R. Baker, *J. Amer. Chem. Soc.*, **62,** 2405 (1940).
(38) R. Adams, D. C. Pease, C. K. Cain, and J. H. Clark, *ibid.*, **62,** 2402(1940).
(39) H. J. Wollner, J. R. Matchett, J. Levine, and S. Loewe, *ibid.*, **64,** 26(1942).
(40) R. S. DeRopp, *J. Amer. Pharm. Ass., Sci. Ed.*, **49,** 756 (1960).
(41) F. Korte and H. Sieper, *Justus Liebigs Ann. Chem.*, **630,** 71 (1960).
(42) J. Karsen, J. H. Exler, and A. B. Svendesen, *Pharm. Weekbl.*, **104,** 583(1969).
(43) H. Aramaki, N. Tomiyasu, H. Yoshimura, and H. Tsukamoto, *Chem. Pharm. Bull.*, **16,** 822(1968).
(44) T. J. Betts and P. J. Holloway, *J. Pharm. Pharmacol., Suppl.*, **19,** 97S(1967).
(45) B. Caddy, F. Fish, and W. D. C. Wilson, *J. Pharm. Pharmacol.*, **19,** 851(1967).
(46) F. Korte and H. Sieper, *J. Chromatogr.*, **13,** 90(1964).
(47) U. Claussen and F. Korte, *Naturwissenschaften*, **53,** 541 (1966).
(48) L. Grlic, *J. Pharm. Pharmacol.*, **13,** 637(1961).
(49) J. Kabelik, Z. Kreju, and F. Santavy, *Bull. Narcotics*, **12** (3), 5(1960).
(50) O. E. Schultz and G. Haffner, *Arch. Pharm. (Weinheim)*, **291,** 391(1958).
(51) O. E. Schultz and G. Haffner, *Tetrahedron*, **21,** 1223(1965).
(52) R. Mechoulam and Y. Gaoni, *Proc. Chem. Soc. (London)*, **1964,** 82.
(53) R. Mechoulam and B. Yagen, *Tetrahedron Lett.*, **1969,** 5349.
(54) T. Yamauchi, Y. Shoyama, Y. Matsuo, and I. Nishioka, *Chem. Pharm. Bull.*, **16,** 1164(1968).
(55) R. Mechoulam and Y. Gaoni, *J. Amer. Chem. Soc.*, **86,** 1646(1964).
(56) Y. Gaoni and R. Mechoulam, *Tetrahedron*, **22,** 1481 (1966).
(57) R. Mechoulam and Y. Gaoni, *Tetrahedron Lett.*, **1967,** 1109.
(58) E. W. Gill, W. D. M. Palon, and R. G. Pertwee, *Nature*, **228,** 134(1970).
(59) F. Korte, M. Haag, and U. Claussen, *Angew. Chem.*, **4,** 872(1965).
(60) T. Yamauchi, Y. Shoyama, H. Aramaki, T. Azuma, and I. Nishioka, *Chem. Pharm. Bull.*, **15,** 1075(1967).
(61) R. Mechoulam, Z. Ben-Zvi, B. Yagnitinsky, and A. Shani, *Tetrahedron Lett.*, **1969,** 2339.
(62) R. Mechoulam and Y. Gaoni, *Chem. Commun.*, **1966,** 20.
(63) U. Claussen, F. Von Spulak, and F. Korte, *Tetrahedron*, **22,** 1477(1966).
(64) R. Mechoulam, B. Yagnitinsky, and Y. Gaoni, *J. Amer. Chem. Soc.*, **90,** 2418(1968).
(65) L. Crombie and R. Ponsford, *Chem. Commun.*, **1968,** 894.
(66) V. V. Kane and R. K. Razdan, *J. Amer. Chem. Soc.*, **90,** 6551(1968).
(67) R. Mechoulam, A. Shani, H. Edery, and Y. Grunfeld, *Science*, **169,** 611(1970).
(68) Y. Shoyama, T. Fujita, T. Yamauchi, and I. Nishioka, *Chem. Pharm. Bull.*, **16,** 1157(1968).
(69) M. J. Begley, G. D. Clarke, L. Crombie, and D. A. Whiting, *Chem. Commun.*, **1970,** 1547.
(70) B. Yagan and R. Mechoulam, *Tetrahedron Lett.*, **1969,** 5353.
(71) R. K. Razdan and B. Zitko, *ibid.*, **1969,** 4949.
(72) L. Crombie, R. Ponsford, A. Shani, B. Yagnitinsky, and R. Mechoulam, *ibid.*, **1968,** 5771.
(73) A. Shani and R. Mechoulam, *Chem. Commun.*, **1970,** 273.
(74) L. Vollner, D. Bieniek, and F. Korte, *Tetrahedron Lett.*, **1969,** 145.
(75) F. Von Spulak, U. Claussen, H. W. Fehlhaber, and F. Korte, *Tetrahedron*, **24,** 5379(1968).
(76) M. C. Nigam, K. L. Handa, I. C. Nigam, and L. Levi, *Can. J. Chem.*, **43,** 3372(1965).
(77) C. A. Salemink, E. Veen, and W. A. Kloet, *Planta Med.*, **13,** 211(1965).
(78) R. Hegnaver, *Chemotaxomonie der Pflanzen*, **3,** 350(1964).
(79) Y. Obata and Y. Ishikawa, *Agr. Biol. Chem.*, **30,** 619(1966).
(80) R. Adams and B. R. Baker, *J. Amer. Chem. Soc.*, **62,** 2401 (1940).
(81) R. Ghosh, A. R. Todd, and S. Wilkinson, *J. Chem. Soc.*, **1940,** 1393.
(82) R. Ghosh, A. R. Todd, and D. C. Wright, *ibid.*, **1941,** 137.
(83) R. Mechoulam and Y. Gaoni, *J. Amer. Chem. Soc.*, **87,** 3273(1965).
(84) K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *ibid.*, **88,** 2079(1966); **89,** 5934(1967).
(85) T. Petrzilka, W. Haefliger, C. Sikemeier, G. Ohloff, and A. Eschenmoser, *Helv. Chem. Acta*, **50,** 719, 1716, 2111(1967).
(86) E. C. Taylor and E. J. Strojny, *J. Amer. Chem. Soc.*, **82,** 5198(1960).
(87) J. L. G. Nilsson, I. M. Nilsson, and S. Agurell, *Acta Chem. Scand.*, **23,** 2207(1969).
(88) R. Mechoulam, P. Braun, and Y. Gaoni, *J. Amer. Chem. Soc.*, **89,** 4552(1967).
(89) T. Petrzilka, W. Haefliger, and C. Sikemeier, *Helv. Chem. Acta*, **52,** 1102(1969).
(90) R. K. Razdan and G. R. Handrick, *J. Amer. Chem. Soc.*, **92,** 6061(1970).
(91) T. Y. Jen, G. A. Hughes, and H. Smith, *ibid.*, **89,** 4551 (1967).
(92) S. Burstein and R. Mechoulam, *ibid.*, **90,** 2420(1968).

(93) S. Agurell, I. M. Nilsson, A. Ohlsson, and F. Sandberg, *Biochem. Pharmacol.*, **18,** 1195(1969).
(94) C. G. Pitt and M. E. Wall, *Tetrahedron Lett.*, **1969,** 321.
(95) M. L. Timmons, S. C. G. Pitt, and M. E. Wall, *ibid.*, **1969,** 3129.
(96) S. Agurell, B. Holmstadt, J. E. Lindgren, and R. E. Schultes, *Acta Chem. Scand.*, **23,** 903(1969).
(97) G. Cardillo, R. Cricchio, and L. Merlin, *Tetrahedron*, **24,** 4825(1968).
(98) R. K. Razdan and V. V. Kane, *J. Amer. Chem. Soc.*, **91,** 5190(1969).
(99) V. V. Kane and R. K. Razdan, *Tetrahedron Lett.*, **7,** 591 (1969).
(100) Y. Gaoni and R. Mechoulam, *Isr. J. Chem.*, **6,** 689(1968).
(101) Y. Gaoni and R. Mechoulam, *J. Amer. Chem. Soc.*, **88,** 5673(1966).
(102) R. Mechoulam and Z. Ben-Zvi, *Chem. Commun.*, **1969,** 343.
(103) P. B. Russell, A. R. Todd, S. Wilkinson, A. D. MacDonald, and G. Woolfe, *J. Chem. Soc.*, **1941,** 826.
(104) F. Korte, E. Dlugosch, and U. Claussen, *Justus Liebigs Ann. Chem.*, **693,** 165(1966).
(105) R. Adams, S. Loewe, C. Jelinek, and H. Wolff, *J. Amer. Chem. Soc.*, **63,** 6971(1941).
(106) R. Adams, H. H. Chen, and S. Loewe, *ibid.*, **67,** 1537 (1945).
(107) R. Adams, S. MacKenzie, Jr., and S. Loewe, *ibid.*, **70,** 664(1948).
(108) R. Adams, B. F. Aycock, Jr., and S. Loewe, *ibid.*, **70,** 662(1948).
(109) R. Adams, M. Harfenist, and S. Loewe, *ibid.*, **71,** 1624 (1949).
(110) S. Loewe, *J. Pharmacol. Exp. Ther.*, **84,** 78(1945).
(111) H. Gayer, *Arch. Exp. Pathol. Pharmakol.*, **129,** 312(1928).
(112) R. Adams, C. M. Smith, and S. Loewe, *J. Amer. Chem. Soc.*, **64,** 2087(1942).
(113) H. S. Aaron and C. P. Ferguson, *J. Org. Chem.*, **33,** 684 (1968).
(114) G. T. Stockings, *Brit. Med. J.*, **1,** 918(1947); C. S. Parker and F. Wrigley, *J. Ment. Sci.*, **96,** 276(1950); L. J. Thompson and R. C. Procter, *N. C. Med. J.*, **14,** 520(1953).
(115) L. E. Hollister, R. K. Richards, and H. K. Gillespie, *Clin. Pharmacol. Ther.*, **9,** 783(1968).
(116) R. Adams, S. Loewe, C. W. Theobald, and C. M. Smith, *J. Amer. Chem. Soc.*, **64,** 2653(1942).
(117) R. Adams, C. M. Smith, and S. Loewe, *ibid.*, **63,** 1973 (1941).
(118) R. Adams, C. K. Cain, and S. Loewe, *ibid.*, **63,** 1977(1941).
(119) A. W. D. Avison, A. L. Morrison, and M. Parkes, *J. Chem. Soc.*, **1949,** 952.
(120) E. C. Taylor, K. Lenard, and B. Voev, *Tetrahedron*, **23,** 77(1967).
(121) F. Bergel, A. L. Morrison, H. Rinderknecht, A. R. Todd, A. D. MacDonald, and G. Woolfe, *J. Chem. Soc.*, **1943,** 286.
(122) G. A. Alles, R. N. Icke, and G. A. Feigen, *J. Amer. Chem. Soc.*, **64,** 2031(1942).
(123) R. K. Razdan, personal communication.
(124) J. F. Howes, *Pharmacologist*, **12,** 258(1970).
(125) R. M. Anker and A. H. Cook, *J. Chem. Soc.*, **1946,** 58.
(126) H. G. Pars, F. E. Granchelli, J. K. Keller, and R. K. Razdan, *J. Amer. Chem. Soc.*, **88,** 3664(1966).
(127) R. E. Lyle, R. K. Razdan, F. E. Granchelli, and H. G. Pars, U. S. pat. 3,493,579 (1970).
(128) R. K. Razdan, W. R. Thompson, H. G. Pars, and F. E. Granchelli, *Tetrahedron Lett.*, **1967,** 3405.
(129) N. L. Dewey, L. S. Harris, J. F. Howes, J. S. Kennedy, F. G. Granchelli, H. G. Pars, and R. K. Razdan, *Nature*, **226,** 1266(1970).
(130) R. K. Razdan, H. G. Pars, F. E. Granchelli, and L. S. Harris, *J. Med. Chem.*, **11,** 377(1968).
(131) R. K. Razdan and H. G. Pars, in "The Botany and Chemistry of Cannabis," C. R. B. Joyce and S. H. Curry, Eds., Churchill, London, England, 1970.
(132) L. S. Harris, R. K. Razdan, W. L. Dewey, and H. G. Pars, *Chim. Ther.*, **1967,** 167.
(133) S. Loewe and R. Adams, *Fed. Proc.*, **6,** 352(1947).
(134) J. F. Hoops, H. Bader, and J. H. Biel, *J. Org. Chem.*, **33,** 2995(1968).
(135) H. Edery and Y. Grunfeld, private communication.
(136) H. Isbell, C. W. Gorodetszky, D. Jasinski, U. Claussen, F. Von Spulak, and F. Korte, *Psychopharmacologia*, **11,** 184(1967); H. Isbell and D. R. Jasinski, *ibid.*, **14,** 115(1969).
(137) A. T. Weil, N. E. Zinberg, and J. M. Nelsen, *Science*, **162,** 1234(1968).
(138) C. L. Scheckel, E. Boff, P. Dahlem, and T. Smart, *ibid.*, **160,** 1467(1968).
(139) L. Lemberger, S. D. Silberstein, J. Axelrod, and I. J. Kopin, *ibid.*, **170,** 1320(1970).
(140) J. Sinonsen and A. R. Todd, *J. Chem. Soc.*, **1942,** 188.
(141) S. Agurell, I. M. Nilsson, A. Ohlsson, and F. Sandberg, *Biochem. Pharmacol.*, **19,** 1333(1970).
(142) I. M. Nilsson, S. Agurell, J. L. G. Nilsson, A. Ohlsson, F. Sandberg, and M. Wahlquist, *Science*, **168,** 1228(1970).
(143) M. E. Wall, O. R. Brine, G. A. Brine, C. G. Pitt, R. I. Freudenthal, and H. D. Christensen, *J. Amer. Chem. Soc.*, **92,** 3466(1970); H. D. Christensen, R. I. Freudenthal, J. T. Gidley, R. Rosenfeld, G. Bregli, L. Testino, D. R. Brine, C. G. Pitt, and M. E. Wall, *Science*, **172,** 165(1971).
(144) S. Agurell, in "The Botany and Chemistry of Cannabis," C. R. B. Joyce and S. H. Curry, Eds., Churchill, London, England, 1970, p. 175.
(145) M. Wahlquist, I. M. Nilsson, F. Sandberg, and S. Agurell, *Biochem. Pharmacol.*, **19,** 2579(1970).
(146) H. A. Klausner and D. J. Dingel, *Pharmacologist*, **12,** 259 (1970).
(147) B. T. Ho, G. E. Fritchie, P. M. Kralik, F. L. Englert, W. M. McIsaac, and J. I. Heikkila, *J. Pharm. Pharmacol.*, **22,** 538(1970).
(148) R. D. Sofia and H. Barry, *Eur. J. Pharm.*, **13,** 134(1970).
(149) R. K. Kubena and H. Barry, *J. Pharmacol. Exp. Ther.*, **173,** 94(1970).
(150) S. Burstein, F. Menezes, E. Williamson, and R. Mechoulam, *Nature*, **225,** 87(1970).
(151) R. L. Foltz, A. F. Fentiman, Jr., E. G. Leighty, J. L. Walter, H. R. Drewes, W. E. Schwartz, T. F. Page, Jr., and E. B. Trutt, Jr., *Science*, **168,** 844(1970).
(152) Z. Ben-Zvi, R. Mechoulam, and S. Burstein, *J. Amer. Chem. Soc.*, **92,** 3468(1970).
(153) Z. Ben-Zvi, R. Mechoulam, and S. Burstein, *Tetrahedron Lett.*, **1970,** 4495.
(154) Y. Grunfeld and H. Edery, *Psychopharmacologia*, **14,** 200 (1969).
(155) W. Beam, Fourth Report Wellcome Tropical Research Lab. Chem. Sect. Khartoum B25, 1911; *ibid.*, Bulletin No. 3, 1915.
(156) R. Mechoulam, Z. Ben-Zvi, and Y. Gaoni, *Tetrahedron*, **24,** 5615(1968).
(157) M. J. deFaubert-Maunder, *J. Pharm. Pharmacol.*, **21,** 334(1969).
(158) C. G. Farmilo and T. W. M. Davis, *ibid.*, **13,** 767(1961).
(159) T. W. M. Davis, C. G. Farmilo, and M. Osadchuk, *Anal. Chem.*, **35,** 751(1963).
(160) U. Claussen, W. Borger, and F. Korte, *Justus Liebigs Ann. Chem.*, **693,** 158(1966).
(161) F. Toffoli, U. Avico, and E. Signoretti Ciranni, *Bull. Narcotics*, **20** (1), 55(1968).
(162) L. T. Heagsman, E. A. Walker, and D. T. Lewis, *Analyst (London)*, **92,** 450(1967).
(163) P. Lerner, *Bull. Narcotics*, **21** (3), 39(1969).
(164) F. J. Bullock, R. J. Bruni, and E. Werner, Abstracts 160th Natl. ACS Meeting, Chicago, Ill., Sept. 1970 (Anal 077).
(165) F. J. Bullock, personal communication.
(166) R. F. Turk, H. I. Dhavir, and R. B. Fornay, *J. Forensic Sci.*, **14,** 389(1969).
(167) L. Grlic, *Bull. Narcotics*, **20,** 256(1968).
(168) K. D. Parker, J. A. Wright, A. F. Halpern, and C. H. Hine, *ibid.*, **20,** 9(1968).
(169) H. Aramaki, N. Tomiyasu, H. Yoshimura, and T. Tsukamoto, *Eisei Kagaku*, **14,** 262(1968); through *Chem. Abstr.*, **70** 36122a(1969).
(170) T. Okamoto and K. Watanabe, *Yakugaku Zasshi*, **90,** 15(1970).
(171) S. Gershon, *Behav. Neuropsychiat.*, **1,** 9(1970).
(172) Y. Grunfeld and H. Edery, *Electroencephalogr. Clin. Neurophysiol.*, **27,** 219(1969).

(173) H. I. Bicher and R. Mechoulam, *Arch. Int. Pharmacodyn. Ther.*, **172,** 24(1968).
(174) R. K. Razdan, V. V. Kane, H. G. Pars, J. L. Kucera, D. H. Reid, L. S. Harris, W. L. Dewey, and J. F. Howes, Minutes 31st Meeting, Committee on Problems of Drug Dependence, NAS-NRC, 6135, 1969.
(175) J. C. Garriott, L. J. King, R. B. Forney, and F. W. Hughes, *Life Sci.*, **6,** 2119(1967).
(176) S. Loewe, *J. Pharmacol. Exp. Ther.*, **88,** 154(1946).
(177) J. C. Garriott, R. B. Forney, F. W. Hughes, and A. B. Richards, *Arch. Int. Pharmacodyn. Ther.*, **171,** 425(1968).
(178) D. Holtzman, R. A. Lovell, J. M. Jafee, and D. X. Freedman, *Science*, **163,** 1164(1969).
(179) E. A. Carlina, *Life Sci.*, **8,** 607(1969).
(180) D. E. McMillan, L. S. Harris, J. M. Frankenheim, and J. S. Kennedy, *Science*, **169,** 501(1970).
(181) F. Lipparini, A. Scotti DeCarolis, and V. G. Longo, *Physiol. Behav.*, **4,** 527(1969).
(182) Mayor's Committee on Marijuana: The Marijuana Problen in The City of New York: Sociological, Medical, Psychological and Pharmacological Studies, Jacques Cattell Press, Lancaster, 1944.
(183) P. A. Martin, *Lancet*, **1969,** 370.
(184) T. V. N. Persaud and A. C. Ellington, *ibid.*, **1968,** 406.
(185) L. A. Borgen and W. M. Davis, *Pharmacologist*, **2,** 259 (1970).
(186) R. Adams, D. C. Pease, J. H. Clark, and B. R. Baker, *J. Amer. Chem. Soc.*, **62,** 2197(1940).
(187) S. Loewe, *Arch. Exp. Pathol. Pharmacol.*, **211,** 175(1950).
(188) J. Kabelik, Z. Krejci, and F. Santavy, *Bull. Narcotics*, **12** (3), 5(1960); O. E. Schultz and G. Haffner, *Arch. Pharm. (Weinheim)*, **293,** 1(1960).
(189) J. Salustiano, K. Hoshino, and E. A. Carlina, *Med. Pharmacol. Exp.*, **15,** 153(1966).
(190) R. Dagirmanjian and E. S. Boyd, *J. Pharmacol. Exp. Ther.*, **135,** 25(1962).
(191) E. S. Boyd and D. A. Meritt, *ibid.*, **149,** 138(1965).
(192) N. E. Zinberg and A. T. Weil, *Nature*, **226,** 119(1970).
(193) A. T. Weil and N. E. Zinberg, *ibid.*, **222,** 434(1969).
(194) F. T. Melges, J. R. Tinklenberg, L. E. Hollister, and H. K. Gillespie, *Science*, **168,** 1118(1970).
(195) E. G. Williams, C. K. Himmelshack, and A. Wikler, *Pub. Health Rep.*, **61,** 1059(1946).
(196) L. D. Clark and E. N. Nakashima, *Amer. J. Psychiat.*, **125,** 379(1968); L. D. Clark, R. Hughes, and E. N. Nakashima, *Arch. Gen. Psychiat.*, **23,** 193(1970).
(197) R. C. Pillard, *New Engl. J. Med.*, **283,** 294(1970).
(198) C. Miras, S. Simos, and J. Kiburis, *Bull. Narcotics*, **16,** 13 (1964).
(199) J. B. Da Silva, *Rev. Fac. Farm. Bioquim. Univ. Sao Paulo*, **5** (1), 205(1967).
(200) U. Claussen and F. Korte, *Justus Liebigs Ann. Chem.*, **713,** 162(1968).
(201) A. Crancer, Jr., J. M. Dille, J. C. Delay, J. E. Wallace, and M. D. Haykin, *Science*, **164,** 851(1969).
(202) J. E. Manno, G. F. Kiplinger, S. E. Haine, I. F. Bennett, and R. B. Forney, *Clin. Pharm. Ther.*, **11,** 808(1970).
(203) M. C. Kew, I. Bersohn, and S. Siew, *Lancet*, **1,** 578(1969).
(204) R. L. Neu, H. O. Powers, S. King, and L. I. Gardner, *ibid.*, **1,** 675(1969).
(205) M. H. Keeler, *Dis. Nerv. Syst.*, **29,** 314(1968).
(206) M. H. Keeler, *Amer. J. Psychiat.*, **124,** 674(1967).
(207) J. A. Talbott and J. W. Teague, *J. Amer. Med. Ass.*, **210,** 299(1969).
(208) M. H. Keeler, C. B. Reifler, and M. B. Lipztin, *Amer. J. Psychiat.*, **125,** 140(1968).
(209) M. Kimura and K. Okamota, *Experientia*, **26,** 819(1970).
(210) U. S. Dept. of Commerce Report AD 342332, National Technical Information Service, Jan. 1970.
(211) "Marihuana and Health—A Preliminary Report," Dept. of Health, Education and Welfare, Sept. 1970.

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