CHEMISTRY AND STRUCTURE-ACTIVITY RELATIONSHIPS OF CANNABINOIDS: AN OVERVIEW

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I. INTRODUCTION

In the past 20 years the general increase in the illicit use of marijuana, the steady lowering of the age at which young people first experiment with the substance, and the increasing number of high school students who use it on a daily basis, have given cause for grave concern to society. Thus marijuana has become the subject of intense socio-political controversy. However, the recent use of marijuana and its active constituent, tetrahydrocannibinol, for the treatment of glaucoma and as an antinauseant in patients undergoing cancer chemotherapy, has revived public interest in its therapeutic potential.

The present article gives an overview of the synthesis of (-)-delta-1-3,4-trans-tetrahydrocannabinol (THC) and its metabolites in man and the known SAR in cannabinoids.

The term 'cannabinoids' is used for the typical C_{21}-groups of compounds present in Cannabis Sativa L. (family Moraceae) and includes their analogs and transformation products (10,11,18).

As shown in Figure 1, two different numbering systems, dibenzopyran and monoterpenoid, are generally used for cannabinoids. In the present article the monoterpenoid numbering system is used.

(-)-3,4-Trans-delta-1-THC, (1) the main pharmacologically active constituent of marijuana, is a resin which is optically

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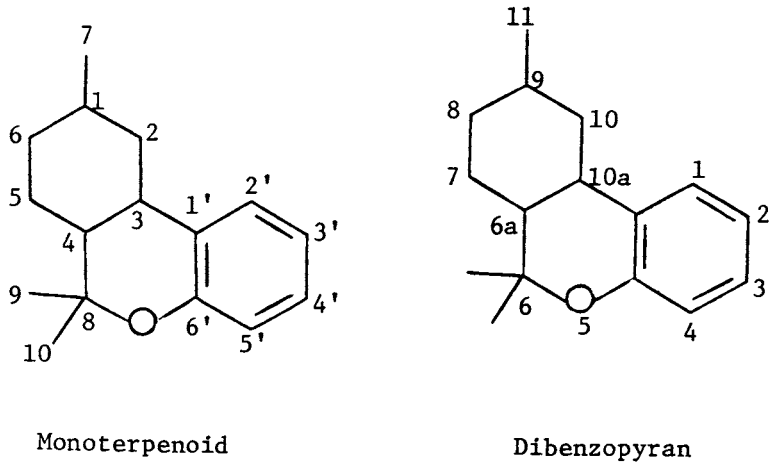


Monoterpenoid Dibenzopyran

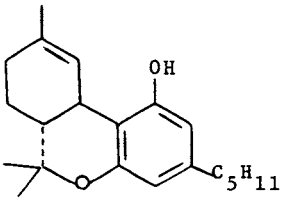
FIGURE 1. Numbering systems used in cannabinoids.

active and is generally referred to as delta-1-THC. It is also known as delta-9-THC based on the dibenzopyran numbering system. The other physiologically active isomer is delta-6-THC (2; alternate name delta-8-THC) and is found only in a few varieties of the plant. The isomers with a 3,4-cis ring junction are cis-delta-1-THC (3) and (cis-delta-6-THC (4), both of which have been synthesized, but only 3 has been found in the plant so far. On theoretical grounds the trans compounds (1 and 2) are expected to be more thermodyamically stable compared to the cis compounds 3 and 4. In the trans series, delta-6-THC (2) is more stable than delta-1-THC (1), since 1 is easily isomerized to (2) on treatment with acids. The main interest pharmacologically, therefore, centers on the thermodynamically less stable trans-delta-1-THC (1) and its various derivatives and metabolites. This has posed many synthetic problems, because during chemical reactions the more stable derivatives of trans-delta-6-THC (2) are mostly found.

II. SYNTHESIS

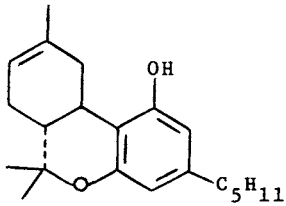
With this background let us now examine the various syntheses for (-)-delta-1- and delta-6-THCs (1 and 2). The various approaches to sterospecific syntheses are shown in Fig. 2.

Since the structure of delta-1-THC is not complex, the basic strategy can be envisioned as joining of the aromatic



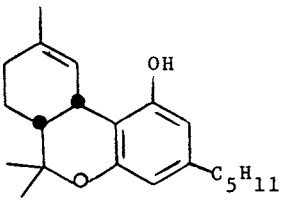
Δ^1 - THC

1



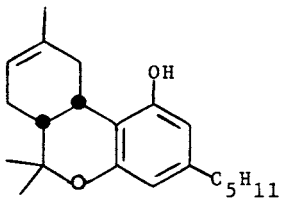
Δ^6 - THC

2



cis - Δ^1 - THC

3



cis - Δ^6 - THC

4

and the alicyclic parts of the molecule by condensation of olivetol with an optically active monoterpene. Mainly, it is the selection of the monoterpene and the reaction conditions which dictate or control the position of the double bond in the delta-1- or delta-6-position in the final product.

A. From Verbenol

In 1967, Mechoulam, et al., described a synthesis of (-)-delta-6-THC (2) from verbenol, a pinane derivative, and olivetol in the presence of acid catalysts (12). They visualized that the attack by olivetol will be favored from the side opposite the bulky dimethyl-methylene bridge in verbenol and will thus provide stereochemical control of the reaction to give mainly trans products. The final conversion of delta-6-

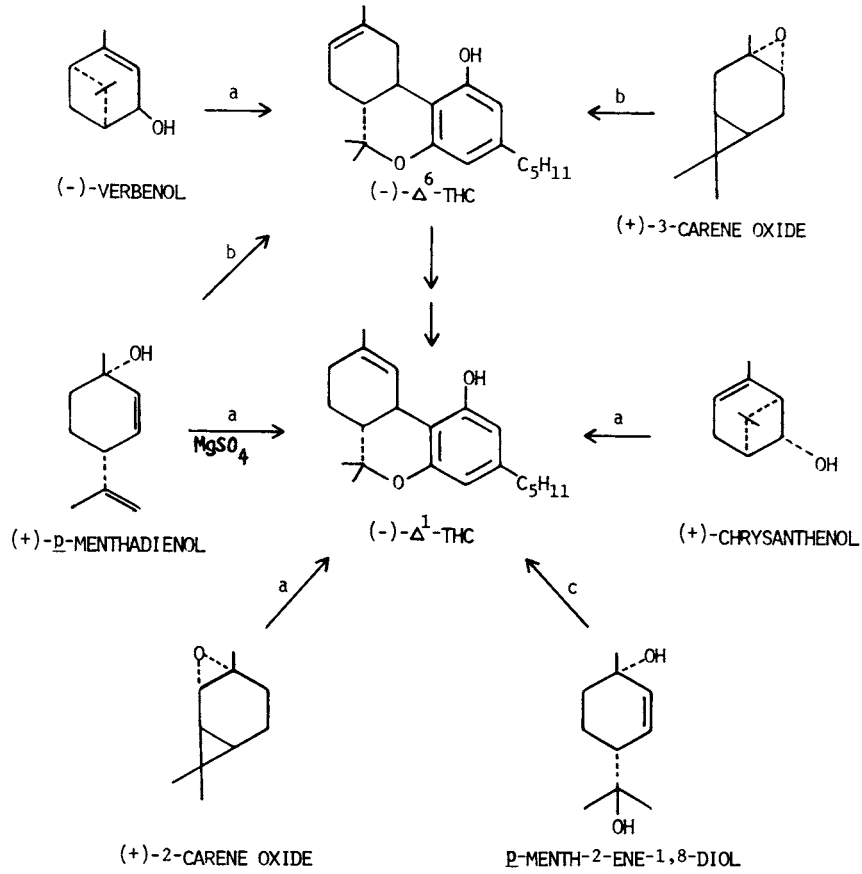


FIGURE 2. Various stereospecific syntheses of delta-1-THC. Reagents used with olivetol: a. BF_3:Et_2O; b. p-TSA; c. $ZnCl_2$.

THC (2) to delta-1-THC (1) was achieved by the addition of gaseous hydrochloric acid to the double bond of 2 followed by dehydrochlorination with sodium hydride in THF. A mixture of 1 and 2 was thus obtained which was separated by careful chromatography. Following the same sequence of reactions the unnatural (+)-delta-6- and (+)-delta-1-THC were similarly prepared from (+)-verbenol.

B. From Chrysanthenol

It is apparent that the mechanism of the verbenol route is

likely to involve a common allylic cation, since both cis- and trans-verbenols give the same products. However, on mechanistic grounds Razdan, et al., reasoned that by virtue of the position of the double bond, verbenol can lead only to delta-6-THC since the double bond has to migrate into that position during the ring opening of the cyclobutane ring (19). On the other hand, on the basis of similar arguments, they thought chrysanthenol should lead directly to delta-1-THC. This was indeed found to be the case albeit the yield was moderate (19).

C. From p-Menthadienol

A facile entry into cannabinoids utilizing (+)-p-menthadienol was demonstrated by Petrzilka, et al., in 1967 (15). By condensing the olivetol in the presence of weak and strong acids they obtained (-)-cannabidiol and (-)-delta-6-THC (2) respectively. Presumably 2 was being formed via the intermediates cannabidiol > delta-1-THC > delta-6-THC, since both cannabidiol and delta-1-THC are known to give delta-6-THC in nearly quantitative yields on treatment with p-TSA. The delta-6-THC obtained by this procedure was accompanied by many by-products typical of all THC syntheses, and was purified by very careful column chromatography. It was converted to delta-1-THC by the usual procedure of addition and elimination of HCl but these authors improved the yield (claimed 100%) of delta-1-THC in the dehydrochlorination step.

Because of the commercial availability of the starting terpene, (+)-cis/trans-p-methadienol, this route was further developed by Razdan and co-workers (20) for the preparation of kilogram quantities of 1 and 2 at Arthur D. Little, Inc., Cambridge, MA, for the National Institute of Mental Health. They reported that the dehydrochlorination procedure was very sensitive to reaction conditions and showed (glc) that under the best conditions a mixture of 95% 1 and 5% (-)-delta-1-THC (7) was always obtained. This new THC was completely characterized by isolation from this mixture by chromatography on silver nitrate-silica gel(21).

Razdan, et al., developed a modification of Petrzilka's cannabinoid synthesis utilizing BF_3-Et_2O/CH_2Cl_2 in the presence of $MgSO_4$ as the dehydrating agent (22). By this process delta-1-THC (1) of very high optical purity was formed in a simple one-step synthesis in 50% yield (glc) and was isolated in 31% yield after a simple and quick column chromatography (22). The purity of delta-1-THC was > 96% by glc and, in contrast to Petrzilka's process, no delta-6-THC (2) is formed under the new conditions. Furthermore, by a slight change in

the reaction conditions of the new process, (-)-cannabidiol was obtained on a preparative scale.

D. From Carene Oxides

In 1970, Razdan and Handrick reported an entry into cannabinoids from carene derivatives (23). Treatment of (+)-trans-2-carene oxide and olivetol in the presence of acids gave mainly a mixture of (-)-trans- (1) and (-)-cis-delta-1-THC (3), from which the former was isolated by preparative gas chromatography. As expected, other transformation products such as iso-THCs were also formed during this reaction but no cannabidiol was detected. These results were interpreted as suggesting that the mechanism is different from the p-menthadienol route and that trans- and cis-delta-1-THCs are first formed which are then converted into their transformation products.

Recently, Montero has reported in a thesis that (+)-3-carene oxide and olivetol give delta-6-THC (2) and the corresponding diadduct, on refluxing in benzene with p-TSA (13).

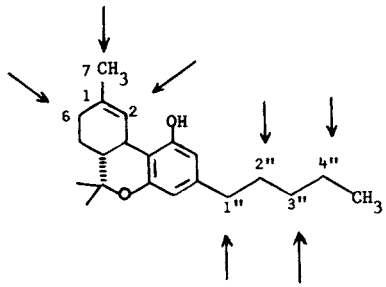
E. From p-Menth-2-ene-1,8-diol

Handrick, et al., (Fig. 2) have recently used another readily available monoterpene p-menth-2-ene-1,8-diol (4) in the synthesis of (-)-delta-1-THC (1) (7). This synthon was selected to facilitate the ring formation at C-8 by the presence of a hydroxyl group rather than a double bond as in p-menthadienol. A variety of catalysts were studied and the best yield of 1 with the least amount of by-products was found to be with anhydrous $ZnCl_2/CH_2Cl_2$. The material was purified by preparative high pressure liquid chromatography (HPLC). Although the quality of 1 was excellent the isolated yield provided no advantage over the p-methadienol route.

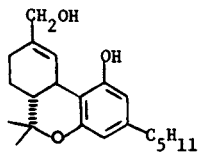
Of all the procedures described above, as stated earlier, Petrzilka's process as developed by Razdan and co-workers (20) is presently used in the large scale preparation of delta-1-THC. Modification of Petrzilka's process ($BF_3 \cdot Et_2O/MgSO_4$) by Razdan, et al., (22) has also been developed (24) to produce a 50 g lot of 1 of very high purity. The purification is simplified by using preparative HPLC, thus avoiding large scale column chromatography. At present, this method is being scaled up by the National Cancer Institute.

III. METABOLITES OF TETRAHYDROCANNABINOLS

Extensive literature (1,10,11,28) has appeared in recent years describing the various metabolites of THC isomers isolated from *in vivo* or *in vitro* studies. These have been



Δ^1 - THC



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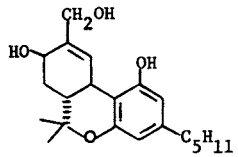
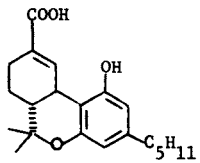
equiactive with Δ^1 - THC



6

a 6 α, inactive

b 6 β ?



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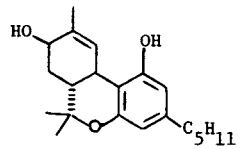
inactive



8

a 6α , 1/10th activity

b 6β , 1/4th activity

FIGURE 3. Sites of metabolism and the known metabolites of delta-1-THC in man.

carried out on a wide variety of animal species and in some cases different animal organ homogenates have been utilized. Important sites of metabolism of delta-1- and delta-6-THC and the metabolites of delta-1-THC so far identified in man (27) are shown in Figure 3. The hydroxylation at the 7-position appears to be the major initial point of attack in nearly every species tested, including man. This metabolite, 7-hydroxy-delta-1-THC, is pharmacologically equiactive with delta-1-THC, and still others are active to different degrees. This has complicated the understanding of marijuana activity in man. The problems associated with the synthesis of these metabolites in the delta-1-series are somewhat similar to those encountered in the synthesis of delta-1-THC itself as has already been discussed in the introduction. Thus a number of synthetic procedures which work satisfactorily in the delta-6 series prove to be inadequate in the delta-1 series. For the purpose of this review only the synthesis of delta-1-THC metabolites identified in man are discussed.

For the synthesis of 7-hydroxy-delta-1-THC (5), Pitt, et al., (16) have developed a regioselective route utilizing a base-induced epoxide-allylic alcohol rearrangement followed by SN' displacement (Figure 4). Delta-1-THC acetate was con-

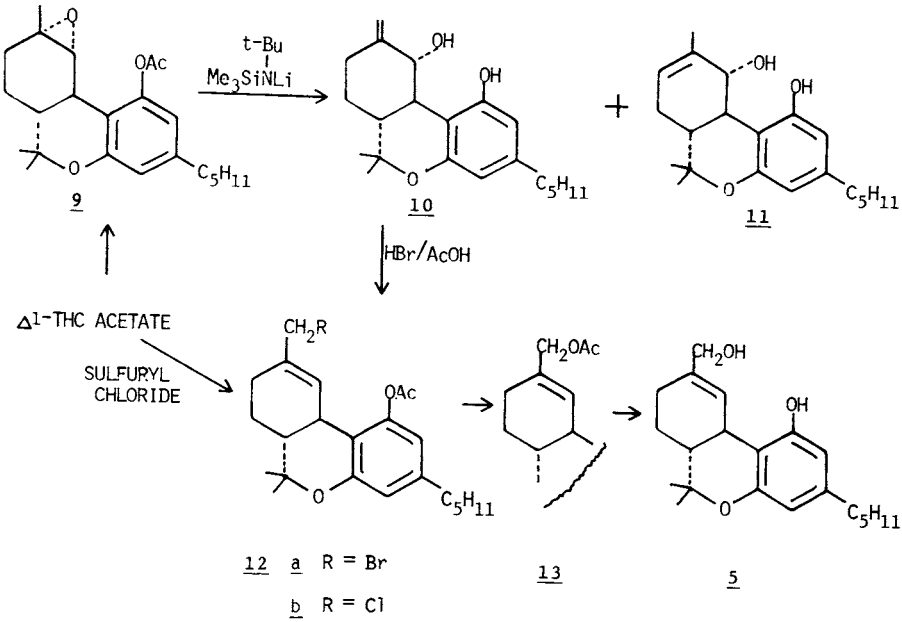


FIGURE 4. Synthesis of 7-hydroxy-delta-1-THC.

verted to the known alpha-epoxide 9 which was isomerized to a mixture of 10 and 11 containing mainly 10. Treatment with 5% HBr/AcOH formed 12a which on acetolysis with tetramethylammonium acetate in acetone followed by reduction with $LiAlH_4$ afforded the desired metabolite 5 in 20% yield. Alternatively, treatment of delta-1-THC acetate with sulfuryl chloride (17) gave a mixture containing 12b, which with silver acetate in acetic acid followed by hydrolysis with base, formed 5, albeit in poor yield (5%). Another metabolite 6-beta-hydroxy-delta-1-THC (8b) was also isolated (14%) from this synthesis.

Pitt, et al., also synthesized the carboxy metabolite 7 by selective acetylation of the phenolic hydroxyl group 5, oxidation (MnO_2,CH_3CN) to the aldehyde, and further oxidation with MnO_2 in methanol containing acetone cyanohydrin (16).

In a different approach, Razdan, et al., (25) (Figure 5) oxidized the exocyclic double bond of (-)-delta-1-THC (7) acetate (4) with m-chloroperbenzoic acid to the epoxide 15 which was hydrolyzed (basic conditions were used to avoid forming the delta-6-dehydration products) with 0.3N KOH/DMSO to form the triol 16. After acetylation, the diacetate alcohol 17 was

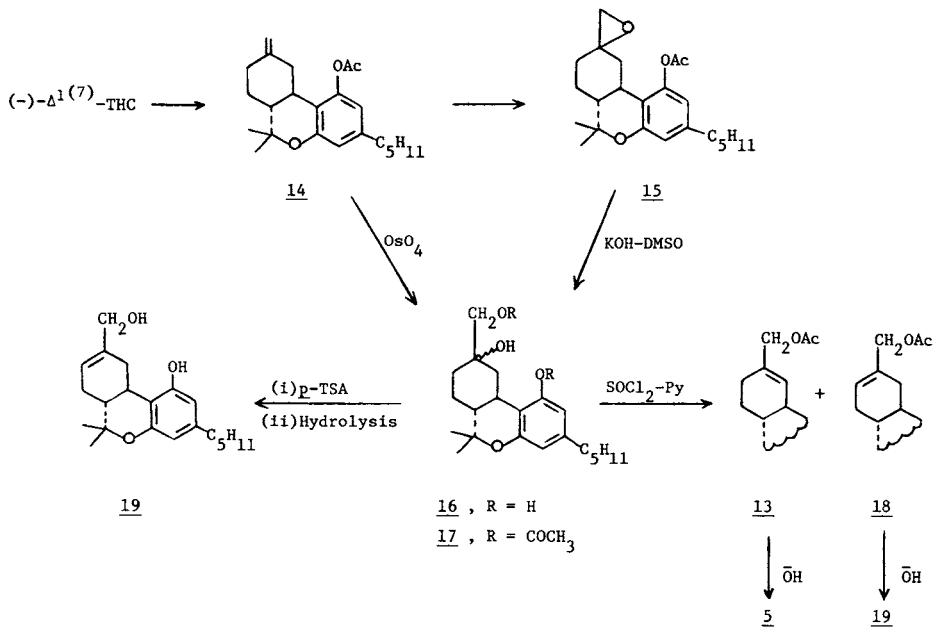


FIGURE 5. Synthesis of 7-hydroxy-delta-1-THC.

treated with $SOCl_2$/Py to give a mixture of the two metabolites as their diacetates 13 and 18. These were separated by HPLC and then hydrolyzed with base to yield 7-hydroxy-delta-1-THC (5). The overall yield of 5 from delta-1(7)-THC was 13%. Alternatively 17 was obtained from 14 by hydroxylation of the exocyclic double bond with OsO_4 in ether followed by acetylation. These syntheses were developed because delta-1(7)-THC became available in large quantities from the kilogram synthesis of delta-1-THC (20,21). The intermediate 17 also provided a facile route to the 7-hydroxy-delta-6-THC 19 (14). This was achieved by treatment with p-TSA followed by hydrolysis (overall yield, 75%).

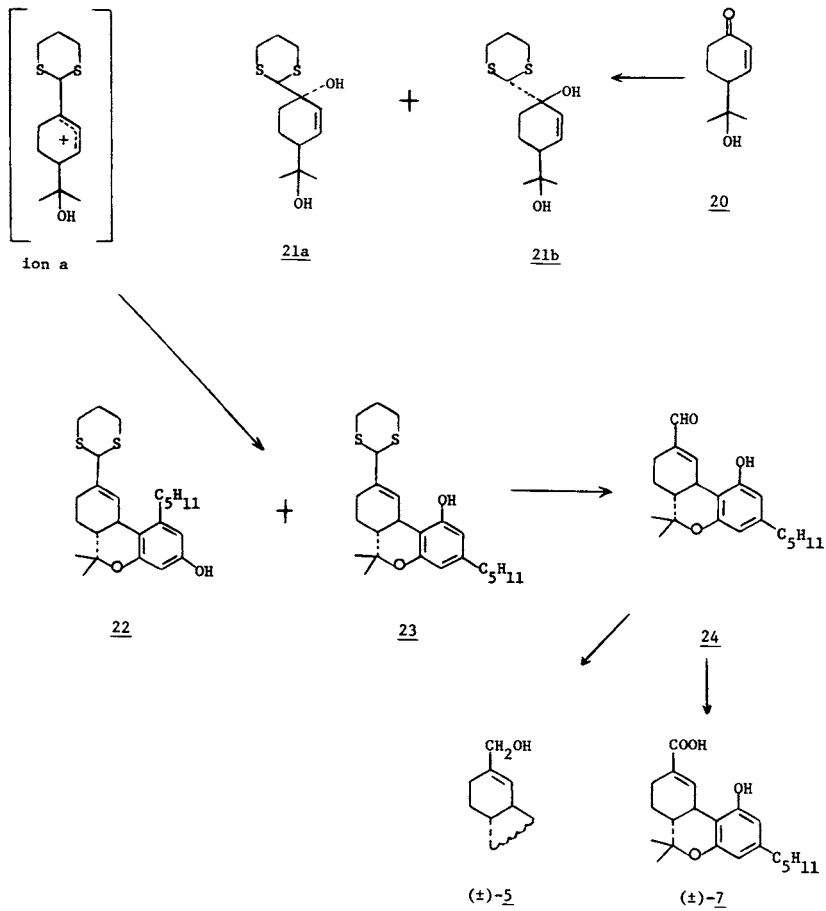


FIGURE 6. Synthesis of 7-substituted delta-1-THCs.

Uliss, et al., have recently reported a versatile route to 7-substituted delta-1-THC from the novel synthons 21a and 21b (26). This scheme (Figure 6) is based on the principal of reversal of reactivity of carbonyl compounds when masked as dithioacetals (i.e., umpolung). Interestingly, this route has resulted in the synthesis of delta-1 derivatives specifically, since, by introduction of the dithiane moiety into the THC structure, isomerization of the normally labile delta-1-unsaturation to the delta-6 isomer is effectively inhibited. The synthons 21a and 21b can be readily synthesized. Treatment with olivetol inthe presence of p-TSA gave amixture of delta-1-compounds 22 and 23 which was separated. The dithiane masking group in 3 was readily removed by HgO/BF_3-Et_2O togive the metabolite (+/-)-2 (3). This was converted by $LiAlH_4$ reduction to the metabolite (+/-)-5 or oxidized with MnO_2/ CH_3OH containing acetone cyanohydrin, to the metabolite (+/-)-7 (16).

The SeO_2 oxidation of delta-1-THC acetate followed by $LiAlH_4$ reduction also gave 5 in very poor yield (1%) (2).

The 6-alpha- and 6-beta-hydroxy-delta-1-THCs (8a and 8b) are the two other metabolites which have been identified in man. The latter, 8b was directly prepared (Figure 7) by bro-

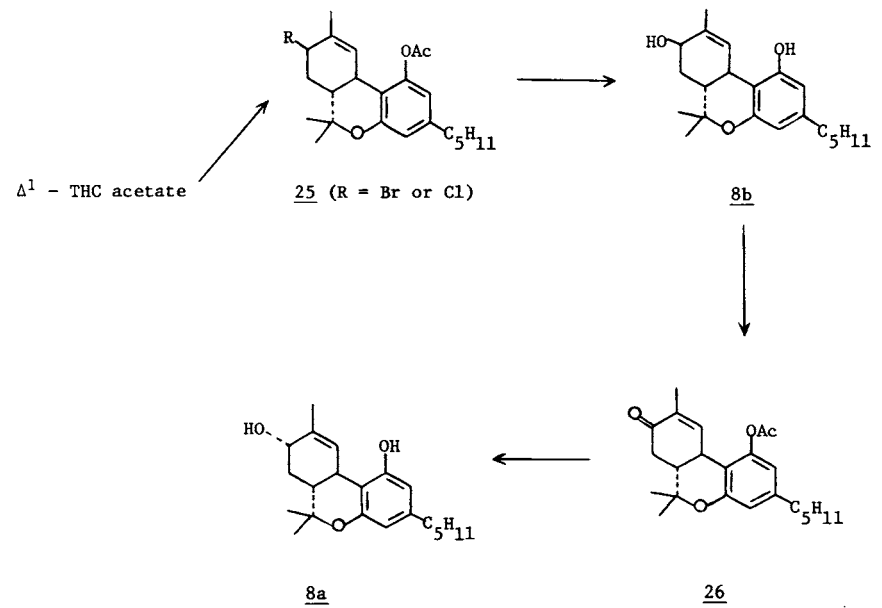


FIGURE 7. Synthesis of 6-beta-hydroxy-delta-1-THC.

mination of delta-1-THC acetate with N-bromosuccinimide (16) or sulfuryl chloride (17) followed by acetolysis and hydrolysis. The 6-alpha-metabolite 8a was prepared (16) from 8b by selective acetylation of the phenolic group and MnO_2 oxidation to 26 followed by $LiAlH_4$ reduction to 8a. It is interesting to note that 26 was also obtained by SeO_2 oxidation of delta-1-THC acetate.

The two dihydroxy metabolites 6a and 6b have been identified in humans (27) and were synthesized from the epoxide of delta-6-THC acetate (16). The sequence required epoxide-allylic alcohol rearrangement (BuLi), diacetylation, oxidation with OsO_4, acetylation of the primary 7-hydroxy group, dehydration ($SOCl_2$, pyridine) and finally saponification.

A few other metabolites from man have been observed by different workers but as yet none of them have been fully characterized.

Recent work from our laboratory has been directed to enlarge the scope of the versatile thioacetal route we reported (26) to 7-substituted delta-1-THCs from the snythons 21a and 21b (Figure 8). A practical synthesis of (+/-)-2'- and -3'-acetoxy olivetols was developed (5) and these were then converted to the corresponding metabolites (+/-)-2",7-dihydroxy-delta-1-THC, 27 (6) and (+/-)-3",7-dihydroxy-delta-1-THC, 28 (8), respectively, following essentially the sequence as shown in Figure 6. Until now, the metabolites with a functionalization both in the terpene portion and the aromatic side chain have not been synthesized. Thus they represent the first examples of such metabolites belonging to this class.

We have also found (Figure 8) that treatment of cannabidiol as its diacetate with N-bromosuccinimide gave the regiospecifically brominated compound 29 in >80% yield. Reaction with base including bicarbonate formed the novel delta-1-THC cannabinoid 30 (9). The 10-bromo-cannabidiol diacetate (29) is a key intermediate which has led to the synthesis of several 10-amino analogs of cannabidiol.

IV. SAR IN CANNABINOIDS

Based on CNS pharmacological profiles in laboratory animals the overall Structure-Activity Relationships (SAR) are summarized below:

1. Essentially a benzopyran structure with an aromatic hydroxyl group at 2'-position and an alkyl or alkoxyl group on the 4'-position are a requirement for activity.

2. The position and the environment around the aromatic hydroxyl group are very important for activity, viz.:

a. the OH at position C-2' is in itself necessary for CNS activity.
b. esterification of the phenol retains whereas etherification eliminates activity. Replacement of the OH by NH_2 retains while SH eliminates activity.
c. methyl substituents at C-2 in the alicyclic ring can significantly influence the CNS activity.

3. Substitution in the aromatic ring by electronegative groups, such as COOH or acetyl, eliminates activity, whereas alkyl and OH retain activity.

4. A minimum length of the aromatic side chain is a requirement for activity. Branching of the side chain, increases potency.

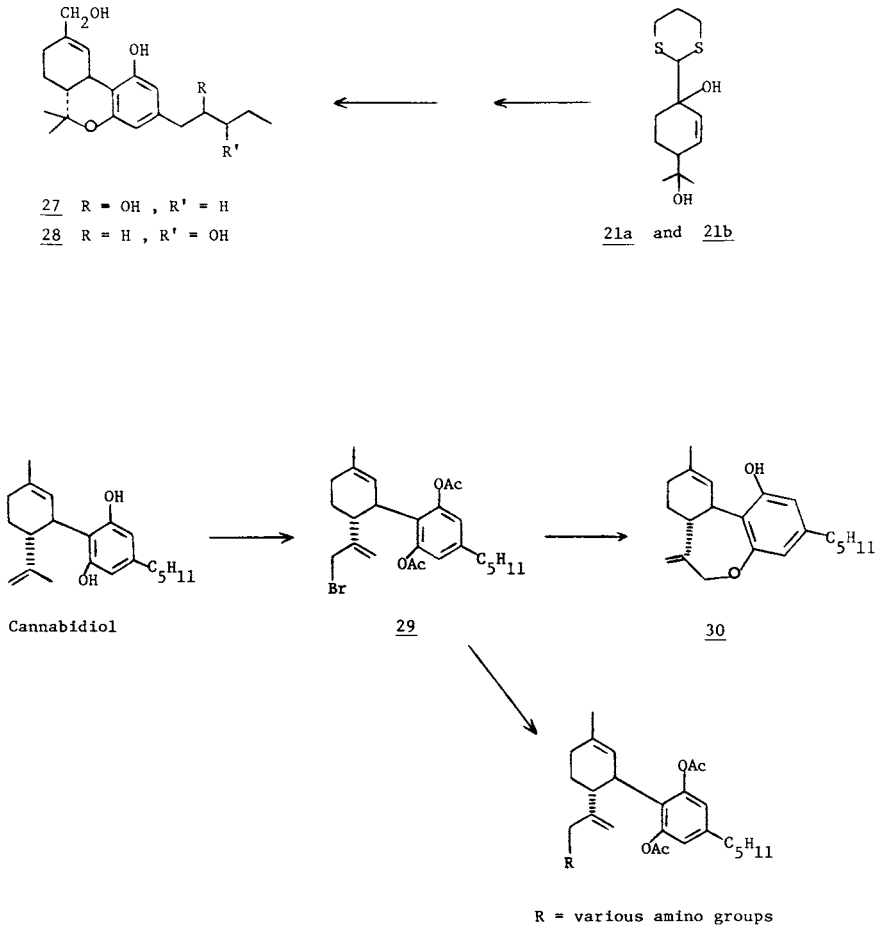


FIGURE 8. Synthesis of various THC derivatives. In last structure, R = various amino groups.

5. The gem-dimethyl group in the pyran-ring is optimum for activity. Replacement of pyran O by N and ring expansion by one carbon can retain activity.

6. In the alicyclic ring the position of the double bond in delta-1-, -6-, or -3-THC retains activity. A 3,4-trans junction increases and a cis junction decreases activity. The natural THCs are active in the 3R,4R series only. A methyl at C-1 increases activity but metabolism to the 7-hydroxymethyl is not a pre-requisite for THC activity.

7. The alicylic ring can be substituted by a variety of nitrogen and sulfur-containing rings without loss of CNS activity. With the nitrogen and sulfur analogs, the optimum CNS activity is obtained when the heteroatom is in a phenethyl orientation, i.e., inserted in place by C-1 or C-5.

8. Planarity of the alicyclic ring is not a necessary criterion for activity.

9. In both carbocyclic and heterocyclic analogs, opening the pyran ring generally decreases activity.

REFERENCES

1. Burstein, S., in "Cannabinoid Analysis in Physiological Fluids", ACS Symposium Series 98, (J. A. Vinson, ed.). American Chemical Society, Washington, D. C., 1979.
2. Ben-Zvi, Z., Mechoulam, R., and Burstein, S., Synthesis of delta-1- and delta-1(6)-tetrahydrocannabinol metabolites, Tetrahedron Lett. 4495-4497 (1970).
3. Ben-Zvi, Z., Burstein, S., 7-oxo-delta-1-tetrahydrocannabinol: a novel metabolite of delta-1-tetrahydrocannabinol, Res. Commun. Pathol. Pharmacol. 8:223-2239 (1974).
4. Dev, S., and Prasad, R. S., Chemistry of ayurvedic crude drugs, Tetrahedron 32:1437-1441 (1976) and references cited therein.
5. Duffley, R. P., Handrick, G. R., Uliss, D. B., Lambert, G., Dalzell, H. C., and Razdan, R. K., Synthesis of 2'-and3'-acetoxyolivetols [5-(2- and 3-acetoxypentyl)-1,3-benzenediols]: Key intermediates in the synthesis of tetrahydrocannabinolderivatives, Synth.733-736 (1980).
6. Duffley, R. P., Lambert, G., Dalzell, H. C., and Razdan, R. K., Hashish: Synthesis of (+/-)-2',11-dihydroxy-delta-9-tetrahydrocannabinol (THC), a metabolite of delta-9-THC. Experientia 37:931-932 (1981).
7. Handrick, G. R., Uliss, D. B., Dalzell, H. C., and Razdan, R. K., Hashish: Synthesis of (-)-delta-9-tetrahydrocannabinol (THC) and its biologically potent metabolite 3'-hydroxy-delta-9-THC, Tetrahedron Lett. 681-684 (1979).

8. Handrick, G. R., Duffley, R. P., Lambert, G., Murphy, J. G., Dalzell, H. C., Howes, J. F., Razdan, R. K., Martin, B. R., Harris, L. S., and Dewey, W. L., 3'-Hydroxy- and (+/-)-3',11-dihydroxy-delta-9-tetrahydrocannabinol (THC); Biologically active metabolites of delta-9-THC, J. Med. Chem. 25:000 (1982).
9. Jorapur, V. S., Khalil, Z. H., Duffley, R. P., and Razdan, R. K., Hashish: Synthesis of a novel delta-9-tetrahydrocannabinol (THC) analog, Chem. Lett. 299-302 (1982).
10. Mechoulam, R. (ed.), "Marijuana, Chemistry, Pharmacology, Metabolism and Clinical Effects". Academic Press, New York, 1973.
11. Mechoulam, R., McCallum, N. K., and Burstein, S., Recent advances in the chemistry and biochemistry of cannabis, Chem. Rev. 76:75-112 (1976).
12. Mechoulam, R., Braun, P., and Gaoni, Y., Synthesis of delta-1-tetrahydrocannabinol and related cannabinoids, J. Amer. Chem. Soc. 94:6159-6165 (1972).
13. Montero, J. L., Ph. D. Thesis, Chromenes derivant de la phloroacetophenone; syntheses d'analogues et d'isosteres des cannabinoids. University of Lanqudoc, Montpelier, France; Chem. Abstr. 80:44430d (1976).
14. Nilsson, J. L. G., Nilsson, I. M., Agurell, S., Kermark, B. A., and Lagerlund, I, Metabolism of Cannabis XI: Synthesis of delta-7-tetrahydrocannabinol and 7-hydroxy-tetrahydrocannabinol, Acta Chem. Scand. 25:768-769 (1971).
15. Petrzilka,T., Haefliger, W., and Sikemeier, C., Synthese von haschisch-inhaltsstoffen, Helv. Chim. Acta. 52:1102-1134 91969).
16. Pitt, C. G., Fowler, M. S., Sathe, S., Sirivastava, S. C., and Williams, D. L., Synthesis of metabolites of delta-9-tetrahydrocannabinol, J. Am. Chem. Soc. 97:3798-3802 (1975).
17. Pitt, C. G., Hauser, F., Hawks, R. L., Sathe, S., and Wall, M. E., Synthesis of 11-hydroxy-delta-9-tetrahydrocannabinol, J. Amer. Chem. Soc. 94:8578-8579 (1972).
18. Razdan, R. K., in "Progress in Organic Chemistry", Vol. 8, (W. Carruthers, J. K. Sutherland, eds.). Butterworths, London, 1973.
19. Razdan, R. K., Handrick, G. R., and Dalzell, H. C., A one-step synthesis of (-)-delta-1-tetrahydrocannabinol from chrysanthenol, Experientia 31:16 (1975).
20. Razdan, R. K., Woodland, L. R., and Handrick, G. R., Large scale synthesis of (-)-trans-6a,10a-delta-8- and -delta-9-tetrahydrocannabinols, Arthur D.Little, Inc., Technical Report 3, to National Institute of Mental Health, Contract Ph-43-68-1339, January, 1972.

21. Razdan, R. K., Puttick, A. J., Zitko, B. A, and Handrick, G. R., Hashish VI: Conversion of (-)-delta-1(6)-tetrahydrocannabinol to (-)-delta-1(7)-tetrahydrocannabinol, Experientia 28:121-122 (1972).
22. Razdan, R. K., Dalzell, H. C., and Handrick, G. R., Hashish; a simple one-step synthesis of(-)-delta-1-tetrahydrocannabinol (THC) from p-mentha-2-,8-dien-1-ol and olivetol. J. Amer. Chem. Soc. 96:5860-5865 (1974).
23. Razdan, R. K., and Handrick, G. R., Hashish, A stereospecific synthesis of (-)-delta-1- and (-)-delta-1(6)-tetrahydrocannabinols, J. Amer. Chem. Soc. 92:6061-6062 (1970).
24. Razdan, R. K., Unpublished results from our laboratory.
25. Razdan, R. K., Uliss, D. B. and Dalzell, H. C., Hashish: Synthesis of 7-hydroxy-delta-1-tetrahydrocannabinol (THC); An important active metabolite of delta-1-THC in man, J. Amer. Chem. Soc. 95:2361-2362 (1973).
26. Uliss, D. B., Handrick, G. R., Dalzell, H. C., and Razdan, R. K., A terpenic synthon for delta-1-cannabinoids, J. Amer. Chem. Soc. 100:2929-2930 (1978).
27. Wall, M. E., Brine, D. R., Pitt, C. G., and Perez-Reyes, M., Identification of delta-9-tetrahydrocannabinol and metabolites in man, J. Amer. Chem. Soc. 94:8579-8581 (1972).
28. Wall, M. E., and Brine, D. R., in "Marihuana: Chemistry, Biochemistry and Cellular Effects" (G. G. Nahas, W. D. Paton, and J. E. Indanpaan-Heikkila, eds.). Springer-Verlag, New York, 1976.