Analgesic Properties of the Tetrahydrocannabinols, Their Metabolites, and Analogs

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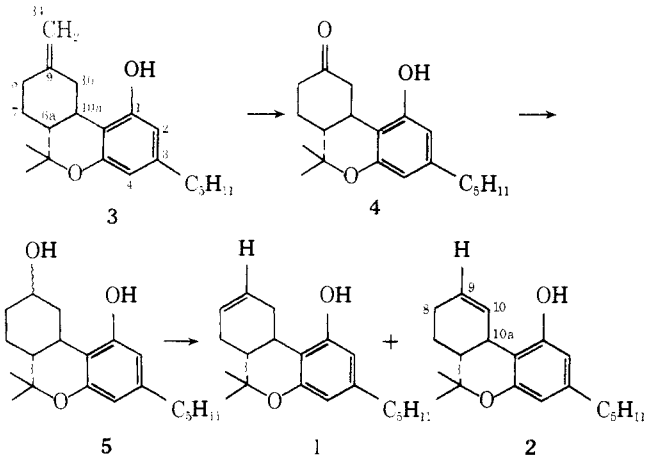
The tetrahydrocannabinols from marihuana were found to have moderate analgesic activity in mice by the hot-plate test (sc administration). Of the several metabolites of these two compounds tested, only the 11-hydroxy derivatives were more potent than the parent compounds. Analogs 1 and 2 (9-demethyl relatives which cannot be metabolized to 11-hydroxy compounds), both of which produce a pharmacological profile generally similar to that of Δ^8- and Δ^9-THC, were analgesically inert. This suggests that metabolism to 11-hydroxy congeners may be necessary for the mediation of analgesic activity in the mouse hot-plate test but not for other pharmacologic effects produced by these substances which we have examined.

The active constituents of marihuana, Δ^8-tetrahydrocannabinol (Δ^8-THC) and Δ^9-tetrahydrocannabinol (Δ^9-THC),[1] have been reported by a number of investigators to exhibit analgesic properties in laboratory animals. Thus, the oral ED_{50} for Δ^9-THC in mice was reported by Sofia et al.[2] to be 11.6 mg/kg in the tail-pinch and acetic acid writhing tests and 10.3 mg/kg in the hot-plate test. Chesher et al.[3] reported that the ED_{50} for both Δ^8- and Δ^9-THC, orally, was 5.0 mg/kg in mice in the hot-plate test. Still other investigators have reported that Δ^9-THC produces analgesia similar in potency to morphine in rats or mice.[4] Analgesic properties of Δ^9-THC have also been described in cats, and monkeys,[5] and dogs.[6] However, Dewey et al. could not show a significant antinociceptive effect using the tail flick test in mice[7] and found the antinociceptive effect of Δ^8- and Δ^9-THC to be weak and inconsistent in a number of other tests.[8]

We were interested in examining structure–analgesic activity relationships of the THC's. In particular it was of interest to determine whether the analgesic activity of the THC's was attributable to the parent compounds, their metabolites, or both. Other investigators have postulated that many of the biological effects of Δ^8- and Δ^9-THC are actually due to the primary metabolite in each case, 11-hydroxy-Δ^8-THC and 11-hydroxy-Δ^9-THC,[9] respectively. There is, however, evidence that the parent THC's also contribute significantly to some of the biological actions of the THC's. Perez-Reyes et al. found no difference in the potency and time of onset of cardiac effects and subjective "high" following infusion of 11-hydroxy-Δ^9-THC or Δ^9-THC to human subjects.[10] In addition, we have previously reported that 9-nor-Δ^8-THC (1, Scheme I),[11] which cannot be converted to an 11-hydroxy metabolite, produces a pharmacologic profile generally similar to that of Δ^8-THC. Compound 1 and the Δ^9 relative (2), whose synthesis is described below, provide a means of examining the role of 11-hydroxylation in the pharmacologic behavior of Δ^8- and Δ^9-THC. The analgesic properties (in mice) of 1 and 2, the parent Δ^8- and Δ^9-THC's, and some of the metabolites of these parent compounds are herein described.

Scheme I



Chemistry. The synthetic route reported previously[11a] for 1 has now been found to provide small amounts of 2. The keto compound, (−)-9-nor-9-oxohexahydrocannabinol (4),[12] was the key intermediate in the synthesis of 1 and 2 (Scheme I). It was prepared in about 54% yield by treating (−)-$\Delta^{9(11)}$-THC (3)† with OsO_4 and $NaIO_4$[13] in THF–water. Reduction of 4 with $NaBH_4$ gave the mixture of alcohols, 5, in essentially quantitative yield. Dehydration of 5 using *p*-toluenesulfonic acid in refluxing benzene gave (isolated) yields of 61% of 1 and 4.4% of 2. Final separation of 2 from 1 required preparative thin-layer chromatography.

In addition to giving the proper molecular ion in the high-resolution mass spectrum, the structure of 2 was confirmed by its 100-MHz NMR spectrum. Chemical shifts and coupling constants relevant to the structural assignment are summarized in Table I. Also shown for comparison are the corresponding data for Δ^9-THC at 220 MHz.[14] The spectrum of 2 is essentially the same as that of Δ^9-THC except that 2 lacks the 11-methyl and has an extra olefinic absorption at δ 5.65 for the H_9 olefinic proton. Assignment of the olefinic protons in 2 was based on the relative chemical shifts and double-resonance studies. The H_{10} proton would be expected to lie in the deshielding region of the aromatic ring, similar to the olefinic proton of Δ^9-THC. Therefore, the proton at δ 6.61 was assigned as H_{10} (H_{10} absorbs at δ 6.33 in Δ^9-THC) and the proton at δ 5.65 as H_9. This also agrees favorably with the fact that H_9 in 1 absorbs at δ 5.78. The H_{10} absorption appeared as a doublet of quartets and the H_9 absorption as an unresolved doublet of multiplets. Irradiation of the H_9 multiplet caused the H_{10} doublet of quartets to collapse to a single broadened multiplet ($J_{9,10}$ = 10 Hz) as would be expected for two cis-olefinic protons. Also, irradiation of H_{10a} (δ 3.24) resulted in collapse of the H_{10} absorption to a doublet of triplets ($J_{10,10a}$ = 2 Hz). This suggests that the original two quartets in the H_{10} absorption were actually overlapping triplets. The two triplets which result upon irradiation of H_{10a} are probably due to H_{10} coupling equally to the two H_8 protons ($J_{8,10}$ = 2 Hz).

Results

The results of analgesic testing in mice are shown in Table II and structures of the compounds are shown in Chart I. All compounds were given subcutaneously in a mixture of Emulphor EL-620, ethanol, and saline[15] which was inactive in both analgesic tests. Each compound was examined in the hot-plate test.[16] For comparison Δ^8-THC and 11-hydroxy-Δ^8-THC were also examined in mice in the

† A generous supply of (−)-$\Delta^{9(11)}$-THC was obtained from Dr. R. E. Willette, NIDA, Rockville, Md.

Table I. NMR Data for **2** and Δ^9-THC[a] in $CHCl_3$

Proton	Δ^9-THC		2	
	Chemical shifts, δ	Coupling constants, Hz	Chemical shifts, δ	Coupling constants, Hz
OH	4.87		4.98	
Aromatic	6.15, 6.29	$J_{2,4} = 1.8$	6.10, 6.25	$J_{2,4} = 1.8$
C_6-CH_3's	1.41, 1.09		1.36, 1.04	
ω-CH_3	0.89	$J = 6.0$	0.82	$J = 6.0$
H_9			5.65	$J_{9,10} = 10.0$
H_{10}	6.33		6.61	$J_{9,10} = 10.0$ $J_{10,8} = 2.0$ $J_{10,10a} = 2.0$
H_{10a}	3.22	$J_{10a,6a} = 10.9$	3.24	$J_{10a,6a} = 10.0$

[a] NMR of Δ^9-THC is 220 MHz and 100 MHz for **2**.

Nilsen test[17] in which electrical current applied to the tail rather than heat is the nociceptive stimulus.

The naturally occurring isomers, (−)-Δ^8-THC and (−)-Δ^9-THC, are approximately equipotent in the hot-plate test. The ED_{50}'s for these two compounds reported herein (8.8 and 9.6 mg/kg, respectively) are comparable to the oral ED_{50}'s reported previously.[2,3] One of the unnatural isomers, (+)-Δ^8-THC, was inactive at 50 mg/kg.

In both series of compounds the 11-hydroxy metabolite was approximately five times as potent as the parent THC. Of the other monohydroxylated metabolites examined, only 8α-hydroxy-Δ^9-THC showed low-grade activity and 8β-hydroxy-Δ^9-THC was inactive at 20 mg/kg. The more polar compounds resulting from further metabolism of monohydroxylated metabolites were typically less active or inactive. Both 9-nor-9-carboxy-Δ^8-THC and 9-nor-9-carboxy-Δ^9-THC were inactive as was 8β,11-dihydroxy-Δ^9-THC. Although 8α,11-dihydroxy-Δ^9-THC showed some analgesic activity, it appeared to be weaker than either of its possible precursors, 8α-hydroxy-Δ^9-THC or 11-hydroxy-Δ^9-THC. The two synthetic analogs, **1** and **2**, were inactive in the hot-plate at the doses indicated in Table II.

Table II. Analgesic Data

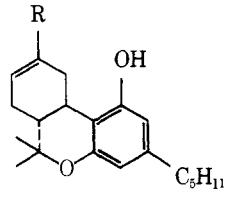
Compound	Analgesic ED_{50}, mg/kg[a]	
	Hot-plate	Nilsen
(+)-Δ^8-THC	Inactive at 50	
(−)-Δ^8-THC	8.8 (6.2–12.5)	Inactive at 20
(−)-11-Hydroxy-Δ^8-THC	1.9 (1.4–2.7)	5.4 (3.2–8.9)
(−)-9-Nor-9-carboxy-Δ^8-THC	Inactive at 50	
(±)-9-Nor-Δ^8-THC (1)	Inactive at 50	
(−)-Δ^9-THC	9.6 (7.4–12.5)	
(−)-11-Hydroxy-Δ^9-THC	1.9 (1.4–2.7)	
(−)-9-Nor-9-carboxy-Δ^9-THC	Inactive at 50	
(−)-9-Nor-Δ^9-THC (2)	Inactive at 20	
(−)-8β-Hydroxy-Δ^9-THC	Inactive at 20	
(−)-8β,11-Dihydroxy-Δ^9-THC	Inactive at 20	
(−)-8α-Hydroxy-Δ^9-THC	4/10 responded at 20	
(−)-8α,11-Dihydroxy-Δ^9-THC	2/10 responded at 20	
Morphine hydrochloride	1.2 (0.9–1.3)	

[a] 95% confidence limits are shown in parentheses.

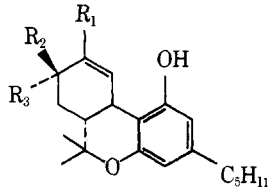
In the Nilsen test, 11-hydroxy-Δ^8-THC was about threefold less active than in the hot-plate test and Δ^8-THC was inactive at 20 mg/kg. Higher doses of Δ^8-THC were not tested to determine if its activity was also about threefold less than in the hot-plate test.

The potent antagonist of the narcotic analgesics, nalox-

Chart I



Δ^8-THC, R = CH_3
11-hydroxy-Δ^8-THC, R = CH_2OH
9-nor-9-carboxy-Δ^8-THC, R = COOH



Δ^9-THC, $R_1 = CH_3$; $R_2 = R_3 = H$
11-hydroxy-Δ^9-THC, $R_1 = CH_2OH$; $R_2 = R_3 = H$
9-nor-9-carboxy-Δ^9-THC, $R_1 = COOH$; $R_2 = R_3 = H$
8β-hydroxy-Δ^9-THC, $R_1 = CH_3$; $R_2 = OH$; $R_3 = H$
8α-hydroxy-Δ^9-THC, $R_1 = CH_3$; $R_2 = H$; $R_3 = OH$
8β,11-dihydroxy-Δ^9-THC, $R_1 = CH_2OH$; $R_2 = OH$; $R_3 = H$
8α,11-dihydroxy-Δ^9-THC, $R_1 = CH_2OH$; $R_2 = H$; $R_3 = OH$

one,[18] was examined for its ability to antagonize the analgesic activity of 11-hydroxy-Δ^8-THC. A subcutaneous dose of 1 mg/kg of naloxone given 10 min before 4 mg/kg of 11-hydroxy-Δ^8-THC completely abolished the analgesic response of the latter in the hot-plate test.

Discussion

Similar to a number of previous reports,[2-6] we have observed analgesic activity for the THC's in mice. However, we have also examined a number of their metabolites and synthetic analogs as well. Some structure–activity relationships are evident from our data. For instance, in both series of compounds, the 11-hydroxy compounds were the most active with nearly morphine-like potency. All of the more polar metabolites were much less active or inactive. This indicates that the 11-hydroxy compounds are not converted to any of the dihydroxy or carboxy compounds examined here before they are active. Compounds with an 8α-hydroxy retained some analgesic properties, unlike 8β-hydroxy compounds, but were much less active than the parent THC's or the 11-hydroxy compounds. Based on the inactivity of (+)-Δ^8-THC which is probably metabolized to the 11-hydroxy compound [(+)-Δ^9-THC is known to be metabolized to the corresponding 11-hydroxy compound],[19] it appears that only the levo isomers are active as analgesics. This is similar to other biological activities of the THC's where the levo isomers are considerably more potent than the dextro isomers.[19,20]

A particularly interesting result is the inactivity of synthetic compounds **1** and **2** in the hot-plate test at two- to threefold higher doses than the ED_{50}'s for Δ^8- and Δ^9-THC; yet both **1** and **2** exhibit the potency of Δ^8- and Δ^9-THC in a number of behavioral and physiological tests.[11,21] Therefore, in those tests we have speculated that the 11-hydroxy metabolites were not necessary for activity, but we did not rule out the possibility that an alternative metabolite of **1** or **2** is responsible for this profile of activity.

As for the hot-plate test, however, the inactivity of **1** and **2** suggests that the 11-hydroxy metabolites may be necessary for the analgesic activity of the THC's. Of interest in this regard was the finding that 20 min after injection of Δ^9-THC in mice the ratio of Δ^9-THC to 11-hydroxy-Δ^9-THC in the brain was 5.3.[22] If the 11-hydroxy metabolite is actually the analgesically active form, then 11-hydroxy-Δ^9-THC should be roughly six times as potent as Δ^9-THC following injection, assuming similar distribution patterns. We have found 11-hydroxy-Δ^9-THC to be five times as potent as Δ^9-THC. Also noteworthy in this respect was the finding that SKF 525-A, a hepatic microsomal oxidase inhibitor, caused a nearly threefold increase in brain levels of 11-hydroxy-Δ^9-THC with almost no effect on levels of Δ^9-THC itself following administration of Δ^9-THC to mice.[23] Pretreatment with SKF 525-A both enhanced and prolonged Δ^9-THC analgesia in mice in the hot-plate.[4a]

Our results suggest, therefore, that the 11-hydroxy metabolites may be the analgesically active forms of Δ^8- and Δ^9-THC in mice. Even if the analgesic activity is not entirely dependent on these metabolites, it would appear that they are required for optimal activity.

Questions have been posed regarding the nature of THC analgesia. Concern was expressed that when given by injection the analgesia in some cases may actually have been the result of nonspecific irritant properties of the phenolic cannabinoids.[24] In view of the inactivity of (+)-Δ^8-THC under conditions where (−)-Δ^8-THC is active, any local irritant properties would appear to play a minor role in THC analgesia in the hot-plate test. Additional concern has been expressed that at doses required for analgesia the THC's also cause decrements in motor activity.[25] Therefore, what we and others have observed in testing of the THC's and referred to as analgesia may not reflect a change in the pain threshold but rather a retardation of the animal's physical capacity to respond to a nociceptive stimulus.[25] It remains to be determined whether the hot-plate test and other analgesic tests are predictive of analgesic properties, if any, of the cannabinoids in man. At least one report has appeared suggesting that Δ^9-THC decreases rather than increases the pain threshold in man when administered by smoking.[25]

Our finding that naloxone antagonized 11-hydroxy-Δ^8-THC analgesia suggests, but certainly does not prove, that the cannabinoids and morphine may share a common component in their mechanisms of producing analgesia. In addition, at least one instance of cross tolerance between Δ^9-THC analgesia and morphine analgesia has been reported.[5] This also suggests that THC analgesia may in some respects resemble the morphine-type of analgesia.

In summary, it was found that the 11-hydroxy metabolites were the most potent analgesics in mice of all the cannabinoids tested. Examination of the naturally occurring THC's, many of their metabolites, and some synthetic analogs has suggested that in mice the active analgesic form may be the 11-hydroxy metabolites.

Experimental Section

All spectra were recorded using instrumentation of the Section on Analytical Services and Instrumentation of this laboratory. Compounds being tested for analgesia were injected subcutaneously as a suspension in Emulphor EL-620, ethanol, and saline.[15]

(−)-9-Nor-9-oxohexahydrocannabinol (4). To 15.0 g (0.05 mol) of (−)-$\Delta^{9(11)}$-THC (**3**) in 250 ml of THF and 100 ml of H_2O were added 0.25 g of OsO_4 and 30 g of finely powdered $NaIO_4$. This mixture was rapidly stirred under N_2 for 2 days at room temperature, and then all the solvents were removed under vacuum. The dark oily residue was dissolved in Et_2O and then washed with 5% $NaHCO_3$, 5% HCl, and water, and then dried (Na_2SO_4) and evaporated to give 14.0 g of dark oil. Chromatography over 350 g of silica gel using Et_2O–ligroine (bp 30–60°) gave 8.1 g (54%) of **4** as a golden oil. The spectral and chromatographic properties of **4** were identical with a sample of the racemic ketone prepared according to the method of Fahrenholtz et al.[12a]

(−)-9-Nor-9-hydroxyhexahydrocannabinol (5). To 1.5 g (0.005 mol) of **4** in 50 ml of MeOH at room temperature was carefully added 0.3 g of $NaBH_4$. The mixture was stirred for 1 hr. Then 10 ml of H_2O was added, and the mixture was evaporated to dryness under vacuum. The residue was taken up in Et_2O–H_2O and the Et_2O layer washed with additional H_2O and dried (Na_2SO_4). Evaporation of the solvent gave 1.5 g (100%) of white glassy **5** which resisted attempts at crystallization. The spectral and chromatographic properties of **5** were identical with a known sample of the racemic alcohol.[11a]

(−)-9-Nor-Δ^8-THC (1) and (−)-9-Nor-Δ^9-THC (2). A mixture of 150 ml of C_6H_6, 4.2 g (0.013 mol) of **5**, and 0.3 g of *p*-toluenesulfonic acid was refluxed for 6 days under N_2 with a Dean-Stark trap. The mixture was evaporated to a gummy mass which was dissolved in a small amount of ligroine (bp 30–60°) and chromatographed over silica gel with ligroine–acetone. When the eluent was 5% acetone, a 2.4-g (61%) fraction of nearly pure **1** was collected (the spectral and chromatographic properties were identical with the known racemic 9-nor-Δ^8-THC).[11a] Immediately thereafter a small fraction was collected containing a mixture of **1** and **2**. Essentially pure **2** (0.170 g, 4.4%) was isolated on 2-mm-thick silica gel plates after eluting each plate three times with ether–ligroine (bp 30–60°) (1:9). NMR spectral data for **2** are shown in Table I and discussed in the text; $[\alpha]^{20}D$ −218° (EtOH). Anal. Calcd *m/e* for $C_{20}H_{28}O_2$, 300.2089; found, 300.2067.

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Synthesis and Antitumor Properties of New Glycosides of Daunomycinone and Adriamycinone

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The synthesis of 4′-*epi*-daunorubicin and of 4′-*epi*-adriamycin was performed by condensation of 2,3,6-trideoxy-3-trifluoroacetamido-4-*O*-trifluoroacetyl-α-L-*arabino*-hexopyranosyl chloride with daunomycinone or the protected adriamycinone derivative **17**, respectively. Both the α and β anomers were obtained and characterized. All new compounds are biologically active in cultured cells and the α anomers display noticeable activity in experimental tumors in mice. Interestingly, 4′-*epi*-adriamycin (**4**) appears nontoxic to cultured heart cells up to a concentration of 5 μg/ml.

Our continuing concern with the glycosidic antitumor agents belonging to the anthracycline family of antibiotics[1,2] and with the structure–activity relationships of new derivatives of daunorubicin (**1**) and of adriamycin (**2**) with modifications in the amino sugar moiety[3] has prompted us to the synthesis and the biological evaluation of stereoisomers of **1** and of **2** in which the amino sugar residue is configurationally different with respect to the parent antibiotics. Synthesis of analogs of **1** with the sugar moiety substituted by D-glucose and D-glucosamine has been reported.[4] We now report the synthesis and biological activity of 4′-*epi*-daunorubicin (**3**), the corresponding β anomer **6**, 4′-*epi*-adriamycin (**4**), and its β anomer **7**. In the new compounds the natural amino sugar, daunosamine (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose), is replaced by the corresponding 4-epi analog (3-amino-2,3,6-trideoxy-L-*arabino*-hexose).

Synthesis. Compounds **3** and **6** were obtained by coupling daunomycinone with 2,3,6-trideoxy-3-trifluoroacetamido-4-*O*-trifluoroacetyl-α-L-*arabino*-hexopyranosyl chloride (**16**) in the conditions of the Koenigs–Knorr reaction to give, after removal of the *O*-trifluoroacetyl group with methanol, the mixture of the *N*-trifluoroacetyl derivatives **5** and **8**. Removal of the protective group by mild alkaline treatment gave, after chromatographic separation, the glycosides **3** and **6**, which were isolated as the crystalline hydrochlorides. In order to obtain glycosides **4** and **7**, adriamycinone was converted to the dioxolane derivative

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