and the analytical sample was crystallized from ethyl alcohol: mp 264–265 °C dec; $[\alpha]^{20}_D$ −36.5° (c 1.0, 1 N NaOH); TLC (silica gel) R_f in methyl alcohol 0.75, chloroform–methyl alcohol–28% aqueous ammonia (55:40:10) 0.80, n-butyl alcohol–acetic acid–H_2O (9:5:1) 0.50 (spots visualized with ninhydrin); NMR [100 MHz (D_2O, K_2CO_3, DSS)] δ 4.00–3.87 (complex d, 1 H, $-C(NH_2)-HCONH$), 3.70–3.40 (qd[a], 1 H $-C(OCH_3)H$), 3.30–3.10 (complex s, 3 H, $-OCH_3$), 2.90–2.75 (complex t, 1 H, $-NHC(CO_2H)H$), 1.70–1.35 (complex m, 3 H, $-CH_2CH-$), 1.30–1.10 (complex d, 3 H, CH_3CH-), 0.95–0.75 [complex d, 6 H, $-CH(CH_3)_2$]. Anal. ($C_{11}H_{22}N_2O_4$) C, H, N, O.

***N*-Carbobenzoxy-*O*-methyl-L-threonyl-L-threonine Benzyl Ester (10).** Compound **10** was prepared in 65% yield from **2**, **9**, and triethylamine in DMF in the same manner as *N*-carbobenzoxy-L-leucyl-*O*-methyl-L-threonine benzyl ester (4). The analytical sample was crystallized from an ethyl acetate–petroleum ether mixture, mp 105–106.5 °C. Anal. ($C_{25}H_{31}N_2O_7$) C, H, N.

***O*-Methyl-L-threonyl-*O*-methyl-L-threonine (11).** **10** was submitted to hydrogenolysis in the same manner as **5**. The yield of the product was 62%. An analytical sample was crystallized from ethyl alcohol: mp 224–225 °C dec; $[\alpha]^{20}_D$ −7.1° (c 1.10, 1 N NaOH); TLC (silica gel) R_f in chloroform–methyl alcohol–28% aqueous ammonia (55:40:10) 0.50, n-butyl alcohol–acetic acid–H_2O (9:5:1) 0.25 (spots visualized with ninhydrin); NMR [60 MHz (D_2O, K_2CO_3, DSS)] δ 4.33–4.25 (d, 1 H, $-C(CO_2H)HNHCO-$), 4.25–4.10 (d, 1 H, $-C(NH_2)HCONH-$), 4.10–3.80 (complex m, 2 H, $-C-(OCH_3)H-$), 3.45–3.41 (2 s, 6 H, $-OCH_3$), 1.33–1.22, 1.28–1.17 (2 d, 6 H, CH_3CH-). Anal. ($C_{10}H_{20}N_2O_5$) C, H, N, O.

Acknowledgment. This work was supported in part by the U.S. Army Medical Research and Development Command, Washington, D.C., under Contract DADA17-72-C2131. We thank Drs. T. Sweeney and E. A. Steck of the Walter Reed Army Institute of Research for making the antimalarial data available to us. Thanks are due to Professors R. Frank and D. D. Clarke for the 100-MHz NMR spectra. The expert technical assistance of Messrs. D. Gawiak and A. Grefig is gratefully acknowledged. This is contribution no. 1534 from the Army Research Program on Malaria.

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Some 11-Substituted Tetrahydrocannabinols. Synthesis and Comparison with the Potent Cannabinoid Metabolites 11-Hydroxytetrahydrocannabinols

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A series of compounds was prepared in which the 11-hydroxyl of 11-hydroxy-Δ^8-THC, the potent metabolite of Δ^8-THC, was replaced by a methyl, methoxy, amino, or acetamido group. All of the compounds tested produced behavioral changes in dogs, but only the methoxy compound has analgesic properties in mice. An isosteric oxime was inactive in mice.

The primary active constituents of marihuana, Δ^8- and Δ^9-THC, are rapidly metabolized in vivo to their respective 11-hydroxy derivatives (Chart I). The parent compounds and their 11-hydroxy metabolites have similar pharmacological profiles.[2,3] In a variety of tests in different species, including monkeys,[4] mice,[5] rats,[6] dogs,[7] and man,[8] the 11-hydroxy metabolites have been reported to be more potent than the parent compounds. However, in at least one experiment utilizing human subjects the potency of the 11-hydroxy-Δ^9-THC was the same as the parent Δ^9-THC.[9]

We were interested in the analgesic properties of cannabinoids and recently reported[10] that the 11-hydroxy metabolites were more potent in mice than the parent

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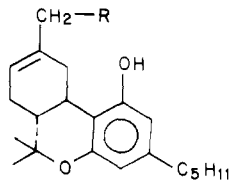
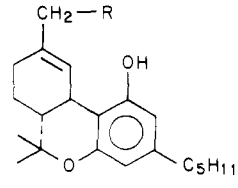
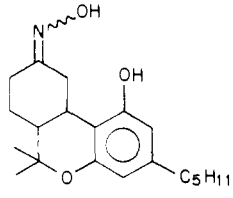
Chart I



Δ^8-THC, R = H
11-OH-Δ^8-THC, R = OH
1, R = CH_3
2, R = OCH_3
3, R = NH_2
4, R = $NHC(=O)CH_3$

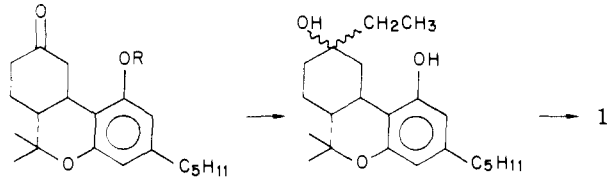


Δ^9-THC, R = H
11-OH-Δ^9-THC, R = OH



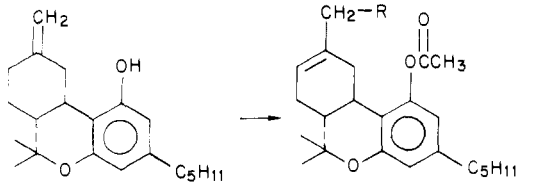
5

Scheme I



6, R = $C(=O)CH_3$
7, R = H

Scheme II



$(-)$-$\Delta^{9(11)}$-THC

8, R = Br
9, R = N_3
10, R = $NHC(=O)CH_3$

compounds in both the hot-plate and Nilsen tests. Because hydroxylation at the 11 position increases the potency of analgesia and most properties of the THC's (vide supra), the effects of other structural changes at the 11 position on the analgesic and behavioral properties of Δ^8-THC were examined. The 11-hydroxyl was replaced by such diverse groups as methyl, methoxy, amino, and acetamido to give compounds 1–4, respectively (Chart I). In addition, the isosteric oxime 5 was prepared in which the 11 carbon has been replaced by a nitrogen and the position of the double bond changed. Also, the hydroxyl in 5 is confined within the C-9,N-11 plane and can be syn or anti to the aromatic ring.

Chemistry. Compound 1 was prepared as the *racemic* form by the Grignard reaction of *racemic*[11] ketone to give 7, which was then dehydrated (Scheme I).

Compounds 2–4 were prepared from a common starting material, the optically active bromo compound 8, which was prepared from $(-)$-$\Delta^{9(11)}$-THC using the method of Weinhardt[12] et al. (Scheme II).

Refluxing 8 in methanolic HBr gave methoxy compound 2. Treatment of 8 with sodium azide in DMF gave 9, which upon reduction with $NaBH_4$ in refluxing 2-propanol gave amino compound 3. Acetylation of 3 gave 10 which, following base hydrolysis of the phenolic acetate, afforded acetamido compound 4.

The oxime 5 was prepared from ketone 11 using standard procedures.[13] TLC analysis of the analytical sample of 5 revealed two closely migrating spots of about equal intensity, presumably the syn and anti isomers.

Table I. Effect of Cannabinoids and Synthetic Compounds on Overt Behavior in Dogs[a]

dose, mg/kg	Δ^8-THC	11-OH-Δ^9-THC[b]	1[b]	2	3
0.01		2 (2)[b]			
0.05		4 (2)			
0.10	0 (1)	2+ (2)			
0.20	0 (1)		0 (1)		
0.40	2 (2)		0 (1)		
0.50					0 (1)
0.80			1– (1)		
1.00			1 (1)		0 (1)
2.00			2+ (2)	3+ (4)	1+ (2)
3.00			3+ (2)		
4.00				6 (3)	

[a] Semiquantitated by the dog ataxia rating scale (see Pharmacological Methods and ref 14). [b] These data were published previously (11-OH-Δ^9-THC (1) in ref 7 and 1 in ref 14) and are included here for purposes of comparison. [c] The mean score of all animals tested is presented with the number of animals tested in parentheses.

Table II. Analgesic Data

compd	hot-plate ED_{50}, mg/kg[a]
Δ^8-THC	8.8 (6.2-12.5)
11-OH-Δ^8-THC	1.9 (1.4-2.7)
1	NA[b]
2	8.2 (6.0-11.1)
3	NA[c]
4	NA[c]
5	NA[c]
morphine hydrochloride	1.2 (0.9-1.3)
codeine hydrochloride	7.5 (6.8-8.3)

[a] Ninety-five percent confidence limits are shown in parentheses. [b] Not active at 50 mg/kg. [c] Not active at 20 mg/kg.

Pharmacological Methods. Cannabinoids produce a very characteristic effect on the overt behavior of dogs, including static ataxia, hyperreflexia, and decreased spontaneous activity. The effects of the compounds reported in this paper were semiquantitated in dogs using the methodology and behavioral rating scale reported elsewhere.[14] Briefly, three independent observers noted the effect of the drug on each dog after IV administration using a scale of zero (no effect) to six (dog lies prostrate on floor), and the mean of their scores was recorded. The score reported is for the time of peak activity.

Analgesic testing was done (sc) in mice using the hot-plate test,[15] which we have used previously to screen a large number of cannabinoids, and establish structure–analgesic activity relationships in this series of compounds.[10]

All compounds were given as a suspension in Emulphor (EL-620), ethanol and saline.[16]

Results

Compounds 1–3 were examined in the dog static ataxia test, and the results are summarized in Table I along with those obtained with Δ^8-THC and 11-hydroxy-Δ^9-THC (11-hydroxy-Δ^8-THC was unavailable during this experiment) for comparison. All of the synthetic analogues were weaker than Δ^8-THC in this test. The methyl compound

1[17] and methoxy compound **2** were about equipotent; amino compound **3** was the least potent.

Analgesic data are shown in Table II along with some previously tested compounds for comparison. Only the methoxy compound **2** was active with an ED_{50} essentially equivalent to that of Δ^8-THC and codeine.

Discussion

Substitution of a hydrogen of the 11-methyl of Δ^8-THC with methyl, methoxy, or amino gave compounds that were not only less active than 11-hydroxy-Δ^9-THC in the dog static ataxia test but were less active than Δ^8-THC as well. We have previously reported[14] that 9-nor-Δ^8-THC, which lacks the 11-methyl of Δ^8-THC and therefore cannot be converted to an 11-hydroxy metabolite, was equipotent with Δ^8-THC in this test. This indicates that metabolism to an 11-hydroxy compound is not necessary for this activity in dogs. Therefore, whether or not any of these synthetic analogues (**1**, **2**, or **3**) is metabolized in vivo to an 11-hydroxy compound would be insufficient information to explain why their potencies are lower than Δ^8-THC. Apparently, they are less active due to unfavorable steric or physicochemical parameters.

Concerning the analgesic properties of the THC's, we have previously suggested[10] that the 11-hydroxy metabolites are responsible for a substantial part, if not all, of this activity in mice. Although it was unknown whether the 11-hydroxy increased analgesic activity by favorably affecting the distribution or through an improved interaction with a receptor(s), it was of interest to look at 11-substituted analogues with altered physical properties, especially altered hydrogen-bonding capacities. The amino group offered a potentially stronger hydrogen-bonding group, but, as indicated in Table II, amino compound **3** was inactive as an analgesic. In an attempt to restore activity, the amino group of **3** was converted to the acetamido group in **4** so that the N–H would more closely approximate the pK_a of an OH and avoid protonation or other factors causing **3** to be inactive. However, this also resulted in an inactive compound, possibly due to excess steric bulk in this case.

The methoxy compound **2** proved to be more interesting with analgesic potency equivalent to that of Δ^8-THC and codeine but less than 11-hydroxy-Δ^8-THC. A single-bonded oxygen on C-11 appears important for activity. We have previously reported that oxidation of the 11 position to a carboxyl or elimination of the 11-carbon both result in loss of analgesic activity.[14] However, it was also found that converting 11-hydroxy compounds to 8,11-dihydroxy compounds diminished analgesic potency.[10] The lower activity of the methoxy compared to the hydroxy compound could be due to steric factors or to the fact that the methoxy can only serve as a hydrogen-bond acceptor and not as a donor. Another interesting possibility is that **2**, like codeine,[18] could be demethylated in vivo to a more active analgesic (in this case 11-hydroxy-Δ^8-THC).

Substitution with the hydrophobic methyl group, compound **1**, gave an analgesically inactive compound. Metabolic 11-hydroxylation is presumably retarded in this compound due to steric hindrance, but even if it is not the potential hydroxylic product may be too hindered to interact with the proper receptors.

The mixture of *syn*- and *anti*-oximes **5** was also inactive in the hot-plate test and was therefore an unsuitable isostere of 11-hydroxy-Δ^8-THC.

In summary, replacement of the 11-hydroxyl in the potent 11-hydroxy-Δ^8-THC with methyl, methoxy, amino, and acetamido gave compounds less active in behavioral and analgesic tests. This may not necessarily be true for cannabinoids with other than *n*-pentyl side chains.[19]

Experimental Section

The assigned structures of all compounds were supported by their NMR, IR, and mass spectra. Spectral and elemental analyses were performed by the Section on Analytical Services and Instrumentation of this laboratory (NIH). NMR spectra were recorded on a Varian HA-100 or A-60. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected.

11-Methyl-9-hydroxyhexahydrocannabinol (7). To a refluxing solution of 3 M ethylmagnesium chloride in THF (0.03 mol) was added 1.2 g (0.0034 mol) of ketone **6**[11] in 10 mL of dry Et_2O. After refluxing for an additional 1 h, the mixture was cooled, 10 mL of H_2O was added cautiously, and the mixture was acidified with 10% HCl. The mixture was extracted with Et_2O, and the organic layer was washed with H_2O, 5% $NaHCO_3$, and H_2O, dried ($MgSO_4$), and evaporated to give 1.2 g (100%) of white solid. Recrystallization from ether–ligroin (bp 30–60 °C) gave the analytical sample as white crystals, mp 183–187 °C. Anal. ($C_{22}H_{34}O_3$) C, H.

11-Methyl-Δ^8-tetrahydrocannabinol (1). To 0.36 g (0.001 mol) of alcohol **7** in 35 mL of refluxing benzene was added 36 mg of *p*-toluenesulfonic acid. The H_2O was removed using a Dean–Stark trap during 20 min of refluxing. The mixture was concentrated and then chromatographed over silica gel using benzene as the eluent to give 0.329 g (96%) of a colorless oil: one spot by TLC and GC analysis; NMR ($CDCl_3$) δ 5.45 (1 H, br, olefinic), 3.24 (1 H, br d, J_{gem} = 17 Hz, $H_{10\alpha}$), 1.38, 1.15 (s, C-6 methyls), 1.02, 0.89 (br, C-11 and ω-methyls). Anal. ($C_{22}H_{32}O_2$) C, H.

11-Methoxy-Δ^8-tetrahydrocannabinol (2). To 2.0 g (0.0046 mol) of bromo compound **8**[12] in 50 mL of MeOH was added 0.25 mL of 33% HBr in AcOH. After heating to 80 °C for 3 h, the mixture was cooled and extracted with Et_2O–ligroin (bp 30–60 °C), 1:1. The organic layer was washed with H_2O and NaCl–H_2O, dried ($MgSO_4$), and evaporated to give 1.6 g of a tan oil. The oil was chromatographed over silica gel using Et_2O–petroleum ether to give 1.0 g (63%) of **2** as a light yellow oil: NMR ($CDCl_3$) δ 5.80 (1 H, br, olefinic), 3.91 (2 H, s, H-11), 3.37 (3 H, s, OCH_3); MS *m/e* calcd for $C_{22}H_{32}O_3$ 344.2351; found 344.2349.

11-Azido-Δ^8-tetrahydrocannabinol Acetate (9). To 11.5 g (0.026 mol) of bromo compound **8**[12] in 200 mL of dry DMF was added 2.1 g (0.032 mol) of NaN_3, and the mixture was stirred overnight at room temperature. The mixture was extracted with hexane–ether (2:1) which was then washed well with H_2O, dried ($MgSO_4$), and evaporated to give 9.5 g of light orange oil. Chromatography of the residue over silica gel using Et_2O–ligroin gave 4.1 g (40%) of nearly pure **9** as a golden oil: NMR ($CDCl_3$) δ 5.76 (br, 1 H, olefinic), 3.70 (br, 2 H, H_{11}), 2.29 (s, 3 H, acetate); IR (neat) 2090 (s), 1768 (s) cm^{-1}; mass spectrum (70 eV) *m/e* 397.

11-Amino-Δ^8-tetrahydrocannabinol (3). To 4.0 g (0.01 mol) of the azido compound **9** in 150 mL of *i*-PrOH was added 1.8 g of $NaBH_4$. The mixture was refluxed overnight under N_2. An additional 0.5 g of $NaBH_4$ was added and the mixture was refluxed overnight again under N_2. The mixture was then cooled and a solid separated, which was removed by filtration and discarded. The filtrate was concentrated to a semisolid and partitioned between Et_2O and H_2O. The Et_2O was washed with H_2O and NaCl–H_2O, dried (Na_2SO_4), and filtered through Celite. After concentrating the solution, ligroin (bp 30–60 °C) was added and the mixture cooled. This gave 0.714 g of white solid, mp 126–128 °C. The filtrate was concentrated and chromatographed over silica gel using $CHCl_3$–MeOH to give an additional 0.9 g (1.614 g total, 49%) as a light reddish glass which could be recrystallized to give additional white solid. Recrystallization of a sample from Et_2O–ligroin gave the analytical sample: mp 128–129 °C; NMR ($CDCl_3$) δ 5.60 (br, 1 H, olefinic), 3.95 (3 H, br, exchanged with D_2O, NH_2, and OH), 3.46 (br d, 1 H, J_{gem} = 17 Hz, $H_{10\alpha}$), 3.24 (s, 2 H, H_{11}). Anal. ($C_{21}H_{31}NO_2$) C, H, N.

11-Acetamido-Δ^8-tetrahydrocannabinol Acetate (10). To 0.2 g (0.0006 mol) of amine **3** in 5 mL of dry pyridine was added 2 mL of Ac_2O. The mixture was stirred for 2 h at room temperature and then for 1 h at 50 °C. The solvents were evaporated

in vacuo (bath temperature 70 °C), and the residue was partitioned between Et_2O–ligroin (2:1) and H_2O. The organic layer was washed well with H_2O and then with NaCl–H_2O, dried ($MgSO_4$), and evaporated to give 0.25 g of nearly colorless, glassy material: one spot on TLC; NMR ($CDCl_3$) δ 6.10 (br t, J = 5.5 Hz, NH), 5.65 (1 H, br, olefinic), 3.79 (d, 2 H, J = 5.5 Hz, 11-H), 2.30 (s, 3 H, $COCH_3$), 1.98 (s, 3H, $-COCH_3$); IR (CCl_4) 1775, 1692 cm^{-1}; mass spectrum (70 ev) m/e 413.

11-Acetamido-Δ^8-tetrahydrocannabinol (4). To 0.23 g (0.00056 mol) of acetate **10** in 15 mL of MeOH under N_2 was added 3 drops of 10% NaOH. The mixture was stirred at room temperature for 1.5 h. Then, 3 drops of 10% HCl was added and the mixture partitioned between Et_2O and H_2O. The Et_2O was washed with H_2O and NaCl–H_2O, dried ($MgSO_4$), and evaporated to give 0.2 g of light-brown oil. Chromatography of this oil over silica gel using Me_2CO–ligroin (bp 30–60 °C) gave 0.11 g (53%) of **4** as a cream-colored glass: IR (CCl_4) 1669 cm^{-1}; MS m/e calcd for $C_{23}H_{33}NO_3$ 371.2460; found 371.2460.

9-Nor-9-oxohexahydrocannabinol Oxime (5). To 0.5 g (0.0016 mol) of ketone **11**[10] in 2.5 mL of dry pyridine and 2.5 mL of absolute EtOH was added 0.5 g of H_2NOH·HCl, and the mixture was heated to reflux for 2 h. Then the solvents were removed in vacuo and the residue was triturated in 2.5 mL of cold H_2O. After discarding the H_2O wash, the residue was taken up in a small amount of Et_2O and chromatographed over silica gel using Et_2O–ligroin (bp 30–60 °C). This gave 0.5 g (94%) of **5** as a white glass, mp 65–75 °C. On TLC (silica gel, ligroin–acetone–Et_2O, 7:2:1) this material gave two closely running spots; presumably syn and anti isomers. Recrystallization from ether–ligroin gave 0.3 g of cream-colored crystals, mp 114–117 °C; mass spectrum (70 ev) m/e 331. Anal. ($C_{20}H_{29}NO_3$) C, H, N.

Acknowledgment. The authors are indebted to Mrs. Louise Atwell for the analgesic testing, Mr. William Landis (NIH) for the high-resolution mass spectra, and Dr. Robert Willette (NIDA) for a generous supply of (−)-$\Delta^{9(11)}$-THC. The authors especially wish to thank Dr. E. L. May (MCV) for many helpful discussions. Supported in part by USPHS Grant DA-00490.

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2′,3′-Bis(2-chloroethyl)aminophosphoryl-3′-amino-3′-deoxyadenosine: A Cyclic Nucleotide with Antitumor Activity

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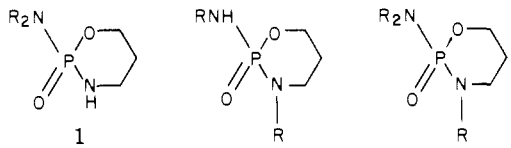
The synthesis of the title compound from 3′-amino-3′-deoxyadenosine in 40% yield is reported. 3′-Amino-3′-deoxyadenosine was made by an improved synthesis in 12 steps from inexpensive D-xylose in 15% overall yield. Both isomers of the title compound, separated by column chromatography, possess confirmed activity against KB tumor cell cultures.

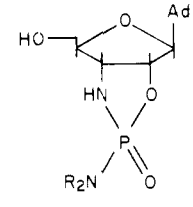
Cyclophosphamide (1) is effective against more varieties



1 2, R = $ClCH_2CH_2$ 3

of human cancer than any of the approximately 50 compounds shown to have clinically detectable antitumor activity.[2] It therefore becomes of interest to synthesize modifications of this drug and its highly promising analogues isophosphamide (2) and triphosphamide (3), which may enhance selectivity in tumor cell destruction.

In this note, we describe the synthesis of the cyclic nucleotides **4a,b** which are isomeric at phosphorus and the



4a,b

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