9-Nor-9-hydroxyhexahydrocannabinols. Synthesis, Some Behavioral and Analgesic Properties, and Comparison with the Tetrahydrocannabinols[1,2]

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Received August 25, 1975

The racemic mixture and levo isomer of both 9-nor-9α-hydroxyhexahydrocannabinol and its 9β-hydroxy isomer were prepared. Both α- and β-hydroxy compounds were active in the dog ataxia test and depressed spontaneous activity in mice. However, only the β-hydroxy compound was an analgesic in mice with morphine-like potency. The behavioral and analgesic properties of these compounds may be mediated through different sites or mechanisms and may, therefore, be separable.

In an effort to find biologically active synthetic compounds based on the cannabinoid-type structure, we have prepared and tested the 9-nor-9-hydroxyhexahydrocannabinols (**9–12**, Scheme I). Whereas it is obvious that these compounds are structurally similar to the tetrahydrocannabinols (THC's) from marihuana (Chart I), they are intended to even more closely approximate the potent biologically active metabolites of the THC's, the 11-hydroxy-THC's.[3] Synthetic compounds **9–12** lack only the Δ^8 or Δ^9 double bond and the 11-methylene of the 11-hydroxy-THC's. In addition, by comparing axial vs. equatorial hydroxyls at the 9 position in these synthetic compounds, we have found that certain cannabinoid-like biological effects can be readily separated from other effects. The synthesis, analgesic properties in mice, some behavioral effects in dogs and mice, and comparison of these effects with the naturally occurring THC's are herein described.

Chemistry. We have previously described the synthesis of 9-nor-9-hydroxyhexahydrocannabinol both as the racemic mixture **7**[4] and as the levo mixture **8**[5] of diastereomers. Either **7** or **8** was obtained in essentially quantitative yield by sodium borohydride reduction respectively of the racemic **5**[4] or levo **6**[5] ketone, 9-nor-9-oxohexahydrocannabinol (Scheme I).

Gas chromatographic analysis of the products from the sodium borohydride reduction indicated that the ratio of equatorial hydroxy compound (**9** or **10**) to axial hydroxy compound (**11** or **12**) was about 93:7. The stereochemistry of the hydroxyl groups was assigned on the basis of the relative peak half-widths of the C-9 protons in the 100-MHz NMR spectra. In compounds **9** and **10** the peak half-width was twice as large as that observed in **11** and **12**, consistent with an axial C-9 proton in the former two compounds and an equatorial C-9 proton in the latter two. The reason for the specificity in this reduction is not readily apparent from examination of molecular models.

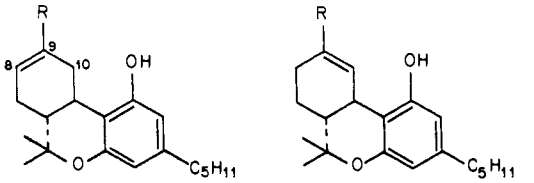
Potassium tri-*sec*-butyl borohydride has been reported to give nearly quantitative yields of axial alcohol resulting from equatorial attack on rigid cyclohexanones.[6] Reduction of **5** with this reagent was very selective, giving greater than 98% axial alcohol **11** and less than 2% equatorial alcohol **9** as determined by GC analysis. This provided selective syntheses of both the axial (**11** and **12**) and equatorial (**9** and **10**) alcohols. The racemic compounds, **9** and **11**, were readily purified by recrystallization, whereas the levo compounds, **10** and **12**, were glassy solids which required chromatographic purification.

Results

The effects of these compounds on the overt behavior of dogs are shown in Table I. As indicated, Δ^9-THC is more potent than Δ^8-THC and 11-hydroxy-Δ^9-THC is more potent than Δ^9-THC. The synthetic levo-9β-hydroxy compound **10** and the racemic mixture **9** were approximately equipotent with 11-hydroxy-Δ^9-THC. Based on the results from two dogs racemic 9α-hydroxy compound **11** appeared to be about one-fifth as potent as **9** and **10**.

Mouse–activity–cage data are shown in Table II for both mice tested 10 min and those tested 90 min after injection. At 10 min both *levo*-9β-hydroxy compound **10** and *rac*-9α-hydroxy compound **11** significantly depressed spontaneous activity. Similar to the above results in dogs, **11** was approximately one-fourth as potent as **10** based on the relative doses to decrease spontaneous activity by one-half. At 90 min both Δ^8- and Δ^9-THC caused significant depression of spontaneous activity, in agreement with previous results.[7] Compound **10** was also tested at 90 min

Chart I



Scheme I

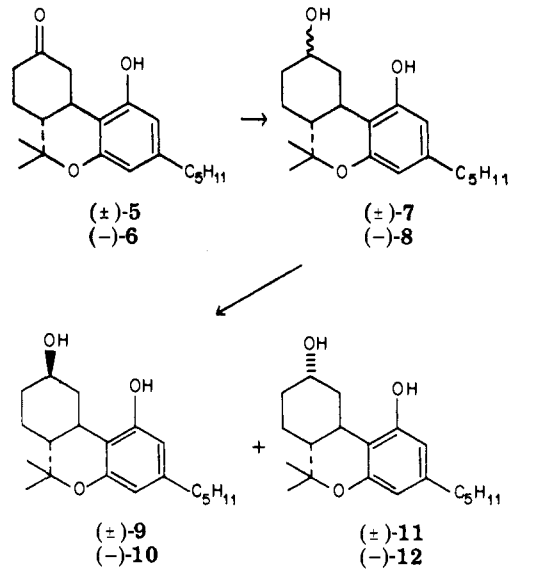


Table I. Effect of Cannabinoids and Synthetic Compounds on Overt Behavior in Dogs[a]

Dose, mg/kg	Δ^8-THC	Δ^9-THC	11-Hydroxy-Δ^9-THC	9	10	11
0.01			2 (2)			
0.05			4 (2)		1+ (3)	
0.10	0 (1)[b]	0 (1)	2+ (2)	3 (2)	3 (3)	
0.20	0 (1)	3+ (2)				
0.40	2 (2)	4 (2)				
0.50					5+ (2)	3- (2)
1.00	5+ (2)					

[a] Semiquantitated by the dog static-ataxia rating scale (see Pharmacological Methods and ref 7). [b] The mean score of all animals tested is presented with the number of animals tested in parentheses.

Table II. Effect of Cannabinoids and Synthetic Compounds on Spontaneous Activity of Mice[a]

	At 10 min postinjection[b]		At 90 min postinjection[c]		
Dose, mg/kg	10	11	Δ^8-THC	Δ^9-THC	10
0	104 ± 13	146 ± 17	121 ± 14	181 ± 22	94 ± 19
2.5	102 ± 27	139 ± 17	49 ± 13[d]	64 ± 19[d]	41 ± 14[e]
5.0	50 ± 12[d]	135 ± 17	84 ± 37	58 ± 20[f]	38 ± 11[e]
10.0	23 ± 5[f]	187 ± 23	28 ± 6[f]	87 ± 31[e]	50 ± 18
20.0	38 ± 8[f]	73 ± 10[d]	139 ± 56	84 ± 26[e]	15 ± 6[f]

[a] Number of interruptions of photocell (mean ± SE) per 15-min period beginning at designated time (see ref 7 for methodology). [b] Vehicle group had an n of 16; drug groups had an n of 8. [c] Vehicle group had an n of 12; drug groups had an n of 6. [d] Statistical difference from vehicle was determined by Student's t test ($p < 0.01$). [e] $p < 0.05$. [f] $p < 0.001$.

Table III. Analgesic Data

Compound	Analgesic ED_{50}, mg/kg[a]	
	Hot-plate	Nilsen
9	2.9 (2.3-3.6)	6.0 (4.4-8.3)
10	1.6 (1.3-1.8)	
12	N.A.[b]	
Morphine HCl	1.2 (0.9-1.3)	0.8 (0.6-1.2)
11-Hydroxy-Δ^8-THC	1.9 (1.4-2.7)	5.4 (3.2-8.9)

[a] 95% confidence limits are shown in parentheses. [b] Not active at 50 mg/kg.

and found to produce a significant decrease in spontaneous activity.

The results of analgesic testing of **9**, **10**, and **12** are shown in Table III along with previously tested 11-hydroxy-Δ^8-THC[5] and morphine. In the hot-plate test, **10** was approximately equipotent with morphine and 11-hydroxy-Δ^9-THC and about twice as potent as racemic compound **9**. Compound **9** and 11-hydroxy-Δ^9-THC were both slightly less active than morphine in the Nilsen test. Compound **12** was inactive in the hot-plate test at 50 mg/kg.

Discussion

The 9-nor-9-hydroxyhexahydrocannabinols have potent cannabinoid-like activity in both dogs and mice. In the dog, 9β-hydroxy compounds **9** and **10** were approximately equipotent with 11-hydroxy-Δ^9-THC. The quantitation of effect in this test is not sufficient to allow distinction between the activities of levo isomer **10** and racemic **9**. Generally the levo isomers of the THC's are much more active than their enantiomers.[5,8] Therefore, the levo isomers should be about twice as potent as their racemic counterparts and this appears to be true for the analgesic properties of **9** and **10** as well (vide infra). However, the dog ataxia test is qualitatively useful in predicting which agents have cannabinoid properties in man.

All of the synthetic and natural cannabinoids tested depressed the spontaneous activity of mice. The activity of the THC's at 10 min is not as definitive as that for the synthetic compounds. Previously we have reported a depression of activity by Δ^8-THC and little or no effect due to Δ^9-THC at 10 min.[7] However, on other occasions we have even observed a stimulation of activity produced by Δ^9-THC at 10 min. Because the response to the THC's is more consistent at 90 min, this would appear to be a more valid time interval during which to conduct the test.

Regarding the slightly greater potency of the β-hydroxy compound over the α-hydroxy isomer in these behavioral tests, a similar observation was made previously.[9] Mechoulam found that the 9β-methyl isomer of hexahydrocannabinol was more potent than the 9α isomer in behavioral tests in monkeys.[10] Therefore, based on these limited examples, it appears that for hexahydrocannabinols greater potency is achieved when a single-bonded 9-substituent lies essentially in the plane of the cyclohexane ring as opposed to being oriented below the ring.

The 9β-hydroxy compounds have good analgesic activity in mice in the two tests employed while the 9α-hydroxy compounds were inactive at considerably higher doses. The *levo*-9β-hydroxy isomer **10** was approximately twice as potent as the racemic mixture **9**, suggesting that only the levo isomer is active. Compound **10** was essentially equipotent with morphine and 11-hydroxy-Δ^9-THC in the hot-plate test and slightly less active than morphine in the Nilsen test. If these synthetic cannabinoids lack addiction liability, they may be useful as a novel class of potent analgesics.

A final point of interest is that the 9α- and 9β-hydroxy compounds produce similar behavioral effects in dogs and mice within about a four- or fivefold potency range, but only the 9β-hydroxy compounds are potent analgesics in mice. Therefore, it would appear that the analgesic and behavioral effects are produced through different sites or different mechanisms and these activities may be completely separable. A more thorough pharmacological evaluation of these compounds will be reported elsewhere.[11]

Experimental Section

The assigned structures of all compounds reported in this paper 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). 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. Gas chromatographic determinations were performed on a Beckman GC-55 at 230° using a 6-ft 5% XE-60 on Gas Chrom Q glass column. Potassium tri-*sec*-butyl borohydride was purchased as K Selectride (0.5 M in THF) from the Aldrich Chemical Co.

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.[7] Briefly, three independent observers rated the effect of each dose of the drug on each dog 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 at the time of peak activity is reported.

Effects on spontaneous activity in albino mice (Swiss–Webster, 20–25 g) were determined for these compounds using a procedure described previously.[7] Drugs were given ip and then the mice were placed in a photocell activity chamber. Interruptions of the photocell were recorded for 15 min at 10 and 90 min after injection.

Analgesic properties were determined in mice by the hot-plate[12] and Nilsen[13] tests using the methodology described in the references.

All compounds were given as a suspension in Emulphor (EL-620), ethanol, and saline.[14]

(±)-9-Nor-9β-hydroxyhexahydrocannabinol (9). To 0.6 g (0.002 mol) of ketone **5** in 20 ml of MeOH was carefully added 0.288 g (0.008 mol) of $NaBH_4$. After stirring for 30 min 10 ml of H_2O was added and the mixture evaporated to dryness. The residue was taken up in Et_2O–H_2O and the Et_2O layer washed with 5% HCl and brine and dried (Na_2SO_4). Evaporation gave a white solid, 0.6 g (100%). Examination of this solid by GC indicated that the mixture was about 95% of **9** and 8% of **11**. Recrystallization of the solid from Et_2O–ligroine gave pure **9**, mp 178–179°. In the 100-MHz NMR spectrum (acetone-d_6) the peak half-width of the C-9 proton (3.70 ppm) was 18.0 Hz, indicative of an axial proton.[15] Anal. ($C_{20}H_{30}O_3$) C, H.

(±)-9-Nor-9α-hydroxyhexahydrocannabinol (11). To 0.03 g (0.0001 mol) of ketone **5** in 5 ml of dry THF under N_2 at −78° was added 1 ml of 0.5 M potassium tri-*sec*-butyl borohydride (0.0005 mol) from a syringe through a rubber septum. After stirring for 2 h at −78° a small amount of H_2O was cautiously added. The aqueous layer was acidified with HCl and extracted with Et_2O. The Et_2O was washed with 5% $NaHCO_3$, H_2O, and brine and then dried ($MgSO_4$). Evaporation gave a colorless, viscous liquid which was found by GC analysis to contain 98% of **11** and 2% or less of **9**. Crystallization[16] from Et_2O–ligroine gave 14 mg (47% yield) of white, crystalline **11**, mp 138–140°. In the 100-MHz NMR spectrum ($CDCl_3$) the peak half-width of the C-9 proton (4.25 ppm) was 8.0 Hz, indicative of an equatorial proton.[15] Anal. ($C_{20}H_{30}O_3$) C, H.

(−)-9-Nor-9β-hydroxyhexahydrocannabinol (10) and **(−)-9-Nor-9α-hydroxyhexahydrocannabinol (12).** Using the same procedure as for **9** above, 2.0 g of ketone **6** gave approximately 2.0 g of a mixture of **10** and **12**. Column chromatography over silica gel using acetone–ligroine gave initially 0.088 g of pure **12** (4.4% yield), followed by a mixture of **10** and **12**, and then 0.4 g (20% yield) of pure **10**. Both **10** and **12** were glassy substances which resisted attempts at crystallization. Also, the spectral and chromatographic properties of **10** and **12** were identical with their racemic counterparts **9** and **11**, respectively.

Acknowledgment. The authors are indebted to Mrs. Louise Atwell for the analgesic testing.

References and Notes

(1) Presented in part at the 168th National Meeting of the American Chemical Society, Atlantic City, N.J., 1974.
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(16) Crystallization of the product from larger runs using up to 2.0 g of starting material was impeded by an oily by-product. This oil could be removed by distillation using a bath at 60° and high vacuum into a receptacle cooled in dry ice–Me_2CO. Following chromatography of the residue over silica gel using ligroine (bp 30–60°)–Me_2CO, pure **11** was obtained.