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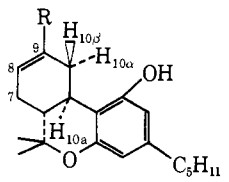
# *Communications to the Editor*

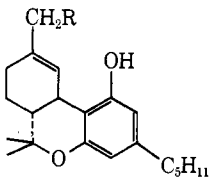
## 9-Nor-$\Delta^8$-tetrahydrocannabinol, a Cannabinoid of Metabolic Interest

*Sir:*

Both of the psychotomimetically active components of marihuana, $\Delta^8$-THC (**1a**) and $\Delta^9$-THC (**2a**),[1] are metabolized to the biologically active 11-hydroxy compounds, **1b** and **2b**, respectively,[1,2] and a number of other less active or inactive oxygenated compounds.[2e,3] In both mice[3] and monkeys,[4] the pharmacological effects of **1b** are comparable to the parent compound **1a**. 11-Hydroxy-$\Delta^9$-THC (**2b**) has been shown to parallel the activity of the parent compound **2a** in man[5] as well as in mice.[3] The greater potency of the 11-hydroxy metabolites over the parent compounds following intracerebral injection has led to speculation that these metabolites may be the active form of THC,[3] a postulate apparently supported by the observed delay in onset of certain behavioral effects of $\Delta^9$-THC[6] in rats after giving the known metabolic inhibitor of $\Delta^9$-THC,[7] SKF 525-A (2-dimethylaminoethyl-2,2-diphenylvalerate hydrochloride). An attempt to correlate behavioral effects in mice with brain concentration of $\Delta^9$-THC or 11-hydroxy-$\Delta^9$-THC was inconclusive when it was found that the levels of both substances paralleled the behavioral response.[8] The latter investigators also demonstrated that at 25 mg/kg of SKF-525a the brain levels of $\Delta^9$-THC were only slightly increased whereas the levels of 11-hydroxy-$\Delta^9$-THC were increased nearly threefold. This observation tends to cast doubt on the interpretations of some previous experiments employing SKF-525a and $\Delta^9$-THC. However, it was found that infusion of 11-hydroxy-$\Delta^9$-THC and $\Delta^9$-THC showed no significant difference in potency and time of onset of cardiac effects and subjective "high" in human subjects.[2e] This suggests that the parent compound may be active itself. Also, a number of synthetic cannabinoid analogs which cannot be converted to 11-hydroxy metabolites have been found to have some pharmacologic properties in common with $\Delta^8$- and $\Delta^9$-THC.[9,†]



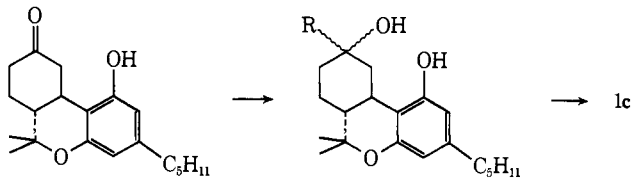
**1a**, R = $CH_3$
**b**, R = $CH_2OH$
**c**, R = H



**2a**, R = H
**b**, R = OH

The magnitude of the controversy over whether THC must first be metabolized at the 11 position to be active and the need for definitive evidence to resolve this controversy prompted us to synthesize 9-nor-$\Delta^8$-THC (**1c**). It was reasoned that if the parent $\Delta^8$-THC was active, then **1c** should be structurally similar enough to mimic its activity. However, if the bulk of the activity resided in **1b**, compound **1c** should be essentially inactive.

Thus, sodium borohydride reduction of 9-nor-9-oxohexahydrocannabinol (**3**)[10] gave a quantitative yield of 9-nor-9-hydroxyhexahydrocannabinol (**4a**) as a mixture of diastereomers.‡ Dehydration of **4a** (refluxing benzene, *p*-toluenesulfonic acid, 6 days) afforded an oily olefin§ (54% yield) purified by column chromatography on silica gel (5% ether in petroleum ether as eluent). By analogy to the dehydration of **4b** under similar conditions,[10] the thermodynamically more stable $\Delta^8$ olefin[11] would be expected.



**3**

**4a**, R = H
**b**, R = $CH_3$

Nmr spectra of this olefin confirm the structure as **1c**. The 60-MHz ($CDCl_3$) spectra of **1a** and **1c** are nearly identical except that **1c** lacks the vinyl methyl and there are two olefinic protons in **1c** of slightly different chemical shift from that of the single olefinic proton in **1a** ($\delta$ 5.78, multiplet for the two olefinic protons of **1c** *vs.* a broad absorption at $\delta$ 5.40 for **1a**).[10] This would appear to argue against the $\Delta^9$ position for the olefinic bond, because in $\Delta^9$-THC the olefinic proton lies in the deshielding region of the aromatic ring and absorbs at $\delta$ 6.32.[10] The close parallelism observed between the double-resonance studies of $\Delta^8$-THC at 220 MHz[12] and those of **1c** (at 100 MHz) further rules out the $\Delta^9$ (or $\Delta^7$) position of the double bond. The double-resonance results are summarized in Table I for $\Delta^8$-THC and **1c**. Two features of the 100-MHz nmr spectrum of **1c** are pertinent to the assignment of the position of the double bond.

First, the chemical shift of $H_{10\alpha}$ ($\delta$ 3.36) suggests that this proton is in an allylic position.[=] Secondly, $H_{10\alpha}$ is coupled to the $H_9$ olefinic proton,** thereby ruling out the $\Delta^7$ position for the double bond.

Preliminary biological testing of **1c** was performed in dogs utilizing a previously reported procedure.[14] In unanesthetized dogs **1c** produced a prance-like placement of the feet, static ataxia, hyperreflexia, and a decrease in

†See compounds 16 and 32. Also see compounds LII, LIII, LIV, LXI, and LI of ref 1b.

‡ Physical data for **4a**: ir ($CHCl_3$) 3590, 3420, 1622, and 1579 $cm^{-1}$; mass spectrum (70 eV) *m/e* 318 (parent), 300, 261, 257, 193; mp 178–179°. *Anal.* Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.37; H, 9.66.

§Physical data for **1c**: mass spectrum (70 eV) *m/e* 300 (parent), 257, 244, 231. *Anal.* Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.65; H, 9.42.

=$H_{10\alpha}$ in hexahydrocannabinol is at $\delta$ 2.89[12] and in $\Delta^7$-THC is at $\delta$ 2.95.[13]

**$J_{9,10\alpha}$ was not determined; however, irradiation of the olefinic absorption resulted in the absorption for $H_{10\alpha}$ collapsing from a doublet of multiplets into a resolved doublet of doublets. Similarly, irradiation of $H_{10\alpha}$ caused considerable sharpening of the olefinic absorption.

**Table I.** Nmr Data for **1a** and **1c**[a]

| Proton | Δ⁸-THC Chemical shift, δ | Δ⁸-THC Coupling constants, Hz | **1c** Chemical shift, δ | **1c** Coupling constants, Hz |
|---|---|---|---|---|
| $H_{10\alpha}$ | 3.22 | $J_{10\alpha,10\beta}$ = 17.0<br>$J_{10\alpha,10a}$ = 4.5 | 3.36 | $J_{10\alpha,10\beta}$ = 17<br>$J_{10\alpha,10a}$ = 5 |
| $H_{10a}$[b] | 2.70 | $J_{10a,10\beta}$ = 10.9<br>$J_{10a,10\alpha}$ = 4.5 | 2.73 | $J_{10a,10\alpha}$ = 5 |

[a] Nmr of **1a** is for 220 MHz and 100 MHz for **1c**. [b] $J_{10a,10\beta}$ was not determined for **1c**, although the signal for $H_{10a}$ collapsed from a complex multiplet to a broadened single peak when $H_{10\beta}$ was irradiated.

spontaneous activity. The same profile of behavior is seen after administration of Δ⁸- or Δ⁹-THC. These studies indicated that **1c** had the same intravenous minimal effective dose as Δ⁸-THC itself, that is, 0.2–0.4 mg/kg. In addition, **1c** was again as effective as Δ⁸-THC in producing bradycardia and hypotension in anesthetized dogs.

These results provide for the first time conclusive evidence that metabolism to the 11-hydroxymethyl is not a prerequisite for the above cited biological activities in the THC's. It is noteworthy that **1c** may be metabolized at other sites in the molecule similar to the natural THC's to give compounds that may have biological activity. However, the goal which was sought and obtained in this study was to establish the role of 11-hydroxylation in the activity of the THC's.

A detailed account of the pharmacological investigations of **1c** will be published at a later date.

**Acknowledgment.** The authors are indebted to Mr. Noel Whittaker for the 100-MHz double-irradiation studies and to Drs. Louis Harris and William L. Dewey and Mr. Billy Rae Martin, Department of Pharmacology, Medical College of Virginia, for the information on biological activity. The latter studies were supported by U. S. Public Health Service Grant MH-17001.

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# *Book Reviews*

**Studies in Organic Chemistry.** Paul G. Gassman, Executive Ed. **Vol. 1. Organoboranes in Organic Synthesis.** Gordon M. L. Cragg, Ed. Marcel Dekker, New York, N. Y. 1973. xii + 422 pp. 16 × 24 cm. $24.50.

This volume is a valuable compendium for the utilization of one of today's more versatile synthetic reagents, organoboranes. The material which is presented in this volume is not designed to be a substitute for that in Professor Brown's books on hydroboration, but rather to complement it by presenting in an organized fashion examples of the broad spectrum of the synthetic applications for organoboranes. The material is presented in ten chapters with numerous references at the end of each chapter and covers the literature through mid-1972. Therefore, the only significant advance in the field which is not discussed is the preparation and use of the various organohaloboranes which have recently appeared.

Chapter 1 constitutes an introduction to the remaining nine chapters by giving an overview to the numerous synthetic applications of organoboranes. Those nine chapters can be classified into two groups, chapters 2-7 concerning hydroboration and chapters 8-10 regarding the synthetic extension to functional groups.

Chapter 2 describes the syntheses and properties of the various classes of commonly used organoboranes while chapter 3 discusses the mechanism, stoichiometry, and stereochemistry of the hydroboration of alkenes. Chapter 4 presents in a few pages the various methods of oxidizing organoboranes to alcohols or ketones. The next three chapters detail successively with the hydroboration of functionalized alkenes, dienes and polyenes, and alkynes.

The remaining three chapters describe the use of organoboranes in functional group synthesis or transformation. Chapter 8 explores the various methods for chain extension by one, two, three, or more carbon atoms along with their mechanistic implications. Chapter 9 discusses the synthesis of alkyl halides, amines, sulfides, organomercury compounds, and other miscellaneous functional derivatives from organoboranes. The last chapter covers the reduction of a variety of functional groups with emphasis on the functional group selectivity and, in the cases of optically active organoboranes, stereoselectivity.

The book makes no pretensions about being detailed concerning reaction conditions since it contains literature references which should supply all the information necessary for the synthetic chemist. In that regard it should be an extremely valuable reference work for several years to come for any chemist involved in organic synthesis.

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