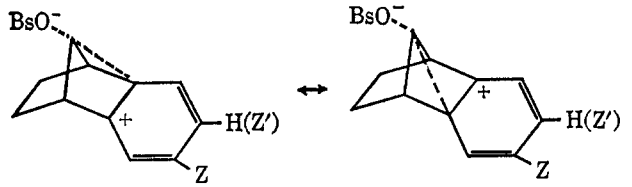
Table I. Acetolyses of *anti*-9-Benzonorbornenol Brosylates

Substituent	Temp, °C[a]	k_1, sec^{-1}	Rel rate at 77.6°
6,7-$(CH_3O)_2$	17.95	4.85×10^{-5}	
	38.00	6.45×10^{-5}	
	77.60	4.47×10^{-2} [b]	3000
6-CH_3O	77.60	8.08×10^{-4} [c]	54
6,7-$(CH_3)_2$	77.60	5.35×10^{-4}	36
6-CH_3	77.60	8.44×10^{-5} [c]	5.7
H	77.60	1.49×10^{-5} [c]	1

[a] Controlled to ±0.03°. [b] Calculated by Arrhenius plots. [c] Cited from ref 2a.

satisfactorily fitted by the relationship log $(k/k_0) = \rho(\sigma_p^+ + \sigma_m^+)/2$.[5]



Accordingly, the transition state in the solvolysis of *anti*-9-benzonorbornenyl derivatives is suggested to be symmetrical. As extensively investigated in a previous paper,[2a] the acetolysis of the sulfonates of this kind proceeds quantitatively to the formation of the *anti*-acetates with retention of configuration. However, in view of the fact that the solvolysis of 7-norbornenyl derivatives sometimes produces an unsymmetrical tricyclo[4.1.0.0^{3,7}]heptane derivative as a kinetic control product,[6] we prefer not on the basis of the present rate data alone to suggest a symmetrical structure for the cation intermediate formed subsequently to the transition state.[7] To help resolve this problem, the nmr studies on the cation produced from **8** under strong acidic conditions are currently under investigation.

(5) Although we employed the sum of σ^+ constants in previous papers,[2] the use of half of the sum seems to us to be more preferable. Because with only one substituent in an "intermediate" (half-*meta*, half-*para* type position), an average σ constant is justified, but not a sum. This change increases ρ to a value numerically twice as large as before (from −2.55 to −5.10). With two substituents, a sum of the *meta* and *para* values then can be used, in agreement with similar treatments with multiple substituents.

(6) H. Tanida, T. Tsuji, and T. Irie, *J. Am. Chem. Soc.*, **88**, 864 (1966), and references cited therein.

(7) M. Brookhart, A. Diaz, and S. Winstein [*ibid.*, **88**, 3135 (1966), footnote 12] have suggested that evidence for a symmetrical transition state in this case could also be evidence for a symmetrical intermediate.

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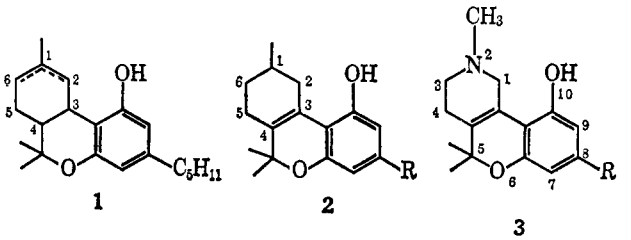
Physiologically Active Nitrogen Analogs of Tetrahydrocannabinols. Tetrahydrobenzopyrano[3,4-*d*]pyridines

Sir:

The recent interest in the isolation and synthesis of the various pharmacologically active constituents of hashish,[1] also known as bhang, charas, ganja, and marihuana depending on the country of origin and mode of preparation, prompts us to record our findings at this time.

We wish to report the successful synthesis of nitrogen analogs **3** (tetrahydrobenzopyrano[3,4-*d*]pyridines) of Adams's conjugated double-bond isomers **2** of natural tetrahydrocannabinol (**1**). The pharmacological activity of **3** closely resembles that of the carbocyclic analogs **1** and **2**.

Although it has been generally accepted that the active constituents in hashish are isomers of **1**, it is only recently that these isomers (*i.e.*, Δ^1-3,4-*trans* and Δ^6-3,4-*trans*) have been isolated and synthesized.[1]



During the study on natural tetrahydrocannabinols (THC) (**1**) Adams[2b] and his co-workers prepared **2**, which differed from natural THC in the position of the double bond in the alicyclic ring and in its optical activity. These compounds showed physiological activity similar to natural THC's (**1**).

Like the tetrahydrocannabinol constituents of marihuana (**1**) and the synthetic analogs (**2**), our nitrogen analogs (**3**, R = branched and straight chain) produce ataxia and motor deficits and generally act as central nervous system depressants in mice, cats, and monkeys when administered intravenously at comparable dose levels.[2] The synthesis and chemistry of one such nitrogen analog (**3**, R = n-C_5H_{11}) is described in this communication.

Olivetol (**4**) was allowed to react with 4-carbethoxy-N-methyl-3-piperidone hydrochloride[3] (**5**) in the presence of concentrated sulfuric acid and phosphorus oxychloride[4] at room temperature for 16 hr, and the reaction mixture was neutralized with sodium bicarbonate. A solid was obtained which was filtered, washed, and recrystallized from acetonitrile to give the intermediate coumarin (**6**), mp 146–147.5°, in 23% yield. *Anal.* Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.61; H, 7.64; N, 4.45. λ_{max}^{EtOH} 305 mμ (ε 13,100) and 255 mμ (ε 9880). The nmr spectrum of **6** agreed with the assigned structure.

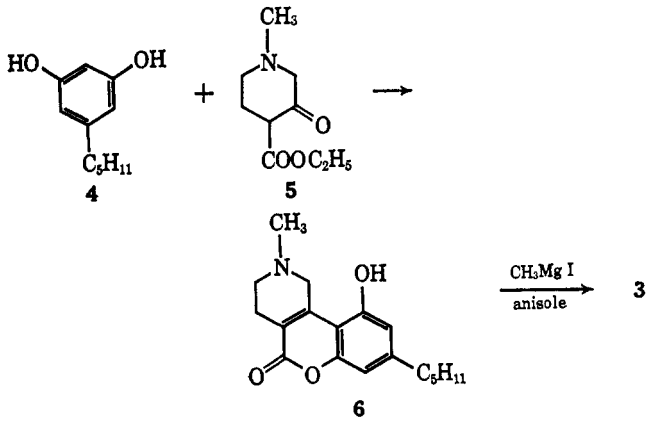
Treating a solution of **6** in pyridine with excess methylmagnesium iodide in anisole solution at 50°, followed

(1) (a) R. Mechoulam and Y. Shvo, *Tetrahedron*, **19**, 2073 (1963); (b) Y. Gaoni and R. Mechoulam, *J. Am. Chem. Soc.*, **86**, 1646 (1964); (c) R. Mechoulam and Y. Gaoni, *ibid.*, **87**, 3273 (1965); (d) E. C. Taylor, K. Lenard, and Y. Shvo, *ibid.*, **88**, 367 (1966); (e) R. L. Hively, W. A. Mosher, and F. W. Hoffmann, *ibid.*, **88**, 1832 (1966); (f) K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *ibid.*, **88**, 2079 (1966). (g) Another active constituent of biogenetic importance, cannabichromene, was recently reported by Y. Gaoni and R. Mechoulam, *Chem. Commun.*, 20 (1966).

(2) For the pharmacology of marihuana and synthetic tetrahydrocannabinols, see (a) S. Garattini in "Hashish: Its Chemistry and Pharmacology," G. E. W. Wolstenholme, Ed., Little, Brown and Co., Boston, Mass., 1965, p 70; (b) R. Adams, M. Harfenist, and S. Loewe, *J. Am. Chem. Soc.*, **71**, 1624 (1949); (c) R. Dagirmanjian and E. S. Boyd, *J. Pharmacol. Exptl. Therap.*, **135**, 25 (1962); (d) E. S. Boyd, E. D. Hatchinson, L. C. Gardner, and D. A. Meritt, *Arch. Intern. Pharmacodyn.*, **144**, 533 (1963); (e) E. S. Boyd and D. A. Meritt, *ibid.*, **153**, 1 (1965); (f) *J. Pharmacol. Exptl. Therap.*, **149**, 138 (1965).

(3) S. M. McElvain and J. F. Vozza, *J. Am. Chem. Soc.*, **71**, 896 (1949).

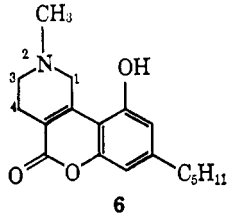
(4) R. M. Anker and A. H. Cook, *J. Chem. Soc.*, 58 (1946).



by decomposition of the reaction mixture with sulfuric acid and neutralization of the product with sodium bicarbonate, gave **3** in 47% yield. Recrystallization from acetonitrile gave an analytically pure sample, mp 187–188°. *Anal.* Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 75.83; H, 9.24; N, 4.45. λ_{max}^{EtOH} 225 mμ (ε 20,700), 280 mμ (ε 9880).

The nmr spectra of **3** and **6** are summarized in Table I. The use of trifluoroacetic acid as the solvent for **3** caused general downfield shift of absorption for **3** relative to **6** and consequently a protonation splitting of the N-methyl absorption to a doublet.

Table I. Summation of Nmr Spectra of **3** and **6**[a]



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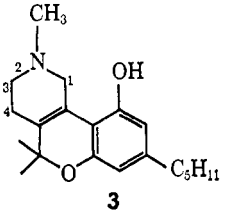
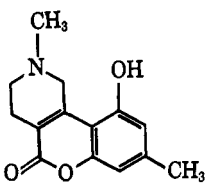


3

Type of proton	δ	Rel area	δ	Rel area
Aromatic	6.78 (m)	(1)	6.47 (m)	(2)
	6.86 (m)	(1)		
C-1	4.22 (s)	(2)	4.52 (m)	(2)
C-3	2.80 (m)	(4)	3.73 (br, m)	(2)
C-4	2.80 (m)		2.64 (br, m)	(2)
N-CH_3	2.41 (s)	(3)	3.19 (d)	(3)
gem-di-CH_3	...	...	1.43 (s)	(3)
			1.51 (s)	(3)
ω-CH_3	0.82 (m)	(3)	0.91 (t)	(3)

[a] The spectrum of **6** was determined in pyridine solution, and that of **3** in trifluoroacetic acid. Values are given in parts per million relative to TMS as an internal standard: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad.

We have similarly prepared analogs of **3** where the C_5H_{11} side chain in the aromatic ring was replaced by CH_3, $CH(CH_3)(CH_2)_4CH_3$, $CH(CH_3)(CH_2)_{11}CH_3$, and $CH(CH_3)$-*c*-C_6H_{11}. Satisfactory analytical and spectral data were obtained for all of these compounds. When the side chain was CH_3, two coumarins **7** and **8** were isolated from the Pechmann condensation. The only differences in the nmr spectra in trifluoroacetic acid of **7** and **8** are in the absorption positions of the aromatic methyl and aromatic protons. The absorptions in **7** are at 2.37 ppm (aromatic methyl) and a splitting of the aromatic protons at 6.71 and 6.8 ppm, whereas in **8** they are at 2.74 and 6.97 ppm, respectively.



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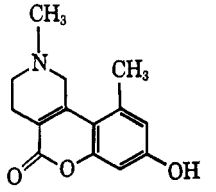

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The investigation of these and other analogs of the tetrahydrocannabinols is being continued, and the detailed results of our biological and chemical findings will be reported elsewhere.

Acknowledgment. We are indebted to Dr. A. T. Shulgin of the Dow Chemical Co. for drawing our attention to the synthesis of these nitrogen analogs and to Dr. F. W. Hoffmann of the Research Laboratories, U. S. Army Edgewood Arsenal, for his encouragement of this work.[5]

(5) Carried out for the U. S. Army Edgewood Arsenal in collaboration with the Sterling-Winthrop Research Institute, Rensselaer, N. Y., under Contract No. DA18-108-AMC-103(A). In conducting the research reported herein, the investigators adhered to the "Principles of Laboratory Animal Care" as established by the National Society for Medical Research.

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Conjugated Dienes as Quenchers for Excited Singlet States of Aromatic Hydrocarbons[1]

Sir:

In recent study of photosensitized reactions of conjugated dienes, we have noted marked discrepancies between predicted and measured quantum yields when aromatic hydrocarbons are used as sensitizers.[2] Furthermore, the isomerization of piperylene (1,3-pentadiene) sensitized by benzene is accompanied by formation of a number of photoadducts of the diene to benzene. The reactions are probably related to other photoaddition reactions of benzene reported recently.[3]

These observations were disturbing because we have used piperylene to measure the efficiency of intersystem crossing of similar hydrocarbons.[4] We now find that the deviations are due to interactions (including reactions) between excited singlet states of the aromatic hydrocarbons and the dienes in their ground states. The processes are easily monitored by observing quenching of fluorescence of the sensitizer molecules. We present results of experiments using systems in which little or no chemical reaction occurs between the

(1) Mechanisms of Photochemical Reactions in Solution. XLII. For part XLI see A. J. Fry, R. S. H. Liu, and G. S. Hammond, *J. Am. Chem. Soc.*, in press.

(2) Unpublished results from this laboratory.

(3) R. Srinivasan and K. A. Hill, *J. Am. Chem. Soc.*, **87**, 4653 (1965); G. Koltzenburg and K. Kraft, *Tetrahedron Letters*, 389 (1965); *Angew. Chem. Intern. Ed. Engl.*, **4**, 981 (1965); J. G. Atkinson, D. E. Ayer, G. Büchi, and E. W. Robb, *J. Am. Chem. Soc.*, **85**, 2257 (1963); D. Bryce-Smith and J. E. Lodge, *J. Chem. Soc.*, 695 (1963); K. E. Wilzbach and L. Kaplan, *J. Am. Chem. Soc.*, **88**, 2066 (1966).

(4) A. A. Lamola and G. S. Hammond, *J. Chem. Phys.*, **43**, 2129 (1965).