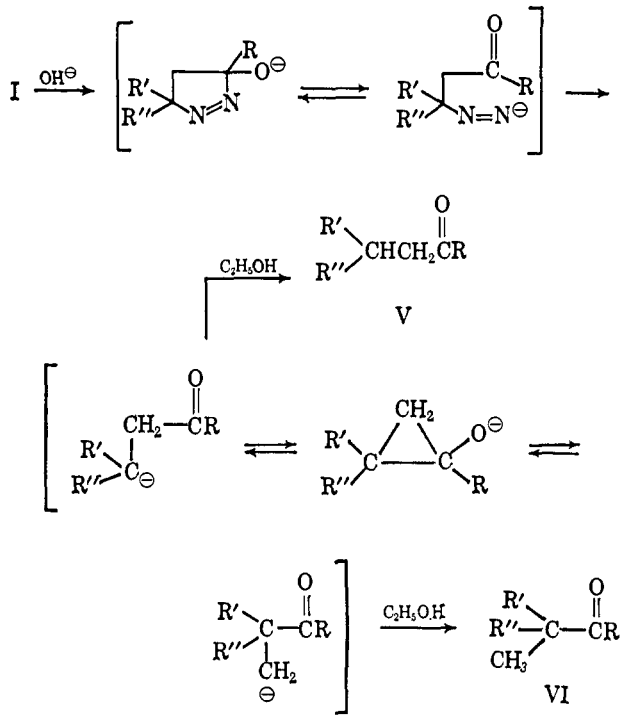
Scheme I



Recently it was reported that the Clemmenson reduction of α,β-unsaturated ketones involves a cyclopropanol intermediate.[7] The present examples may be viewed as analogous variations of the Wolff–Kishner reduction in that the over-all process is the saturation of an α,β-unsaturated ketone. It is planned to investigate the kinetics of this hydrolysis and the utility of this reaction for the preparation of otherwise difficultly accessible ketones.

(7) B. R. Davis and P. D. Woodgate, *Chem. Commun.*, 65 (1966).

(8) This research was supported in part by a grant from the Petroleum Research Fund.

(9) National Science Foundation Undergraduate Research Participant.

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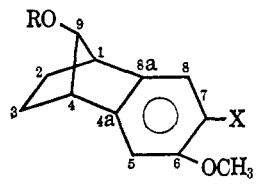
Acetolysis of 6,7-Dimethoxy-*anti*-9-benzonorbornenyl *p*-Bromobenzenesulfonate. Evidence for a Symmetrical Transition State[1]

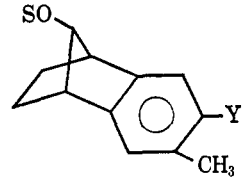
Sir:

In previous papers,[2] strikingly large substituent effects observed in the acetolysis of 6-substituted *anti*-9-benzonorbornenyl *p*-bromobenzenesulfonate (k_{OCH_3}/k_{NO_2} = 3.86 × 10^5 at 77.6°) were correlated by the modified Hammett relationship, $\log(k/k_0) = \rho(\sigma + \sigma^+)$ or $\rho(\sigma_p^+ + \sigma_m^+)$, and the implications of this alternative correlation have been discussed on the basis of the idea of internal aromatic substitution and/or of the simultaneous participation from the *meta* and *para* positions of the 6 substituents. For selection between these alternative possibilities and thereby for a better understanding of whether the solvolysis of *anti*-7-norbornenyl derivatives proceeds through the formation of a symmetrical or an unsymmetrical transition state, the synthesis and the study of the solvolytic behavior of symmetrically 6,7-disubstituted *anti*-9-benzonorbornenyl *p*-bromobenzenesulfonates are desirable.

The Friedel–Crafts acylation (CH_3COCl–$AlCl_3$ in CS_2) of 6-methoxy-*anti*-9-benzonorbornenol acetate (**1**)[2a] afforded a mixture of 6-methoxy-7-acetyl-*anti*-9-benzonorbornenol acetate (**2**),[3] mp 112–113°, and its demethylated 6-methoxy-7-hydroxy-*anti*-9-benzonorbornenol acetate (**3**), mp 146–147°. The latter was converted into **2** by treatment with methyl iodide and silver oxide. The position of the acetyl group[4] was established by the nmr pattern of aromatic protons: aryl H_5 at τ 3.22 (singlet), aryl H_8 at τ 2.51 (singlet). The Baeyer–Villiger oxidation of **2** with *m*-chloroperbenzoic acid yielded the acetoxy derivative **4**, mp 138°, whose hydrolysis using lithium aluminum hydride followed by methylation of the phenolic hydroxyl group with dimethyl sulfate gave the desired 6,7-dimethoxy-*anti*-9-benzonorbornenol (**5**), mp 121–122°. The structure was confirmed by the nmr spectrum: two aryl H at τ 3.23 as a singlet, six methyl H at τ 6.16 as a singlet, one C_9 H at τ ~6.2 (overlapped with methyl H), two C_1,C_4 H at τ 6.95 as a multiplet, two C_2,C_3 *exo*-H around τ 7.8–8.1, and two C_2,C_3 *endo*-H around τ 8.7–9.0.



1, R = Ac; X = H
2, R = Ac; X = Ac
3, R = Ac; X = OH
4, R = Ac; X = AcO
5, R = H; X = OCH_3
6, R = Bs; X = OCH_3



7, S = Ac; Y = H
8, S = H; Y = CH_3
9, S = Bs; Y = CH_3

The chloromethylation ($HCHO$–HCl–CH_3COOH) of 6-methyl-*anti*-9-benzonorbornenyl acetate (**7**)[2a] followed by lithium aluminum hydride reduction afforded 6,7-dimethyl-*anti*-9-benzonorbornenol (**8**), mp 129.5–130.5°. The structure was established by the nmr spectrum: two aryl H at τ 3.18 as a singlet, one C_9 H at τ 6.30 as a multiplet, two C_1,C_4 H at τ 7.02 as a multiplet, six methyl H at τ 7.80 as a singlet, two C_2,C_3 *exo*-H around τ 7.8–8.1, and two C_2,C_3 *endo*-H around τ 8.8–9.1. The brosylates **6**, mp 147–148°, and **9**, mp 135.5–136°, were prepared from **5** and **8**, respectively, by a standard method.

The rates of acetolyses of **6** and **9** were carried out in glacial acetic acid containing 1 equiv of sodium acetate and are summarized in Table I, together with the rates of relevant compounds. It is clearly indicated that one CH_3O (or CH_3) substituent in the 6 position increases the rate by a factor of 54 (or 5.7) and two CH_3O (or CH_3) substituents in the symmetrical 6 or 7 positions increase the rate by a factor of 3000 (or 36), approximately the square of the value for the one substituent. Thus it was proved that, when $(\sigma_p^+ + \sigma_m^+)$ was used for the disubstituted compounds, all the rate data are

(1) The numbering used before[2] is replaced as shown in the formula, adapting the IUPAC rule.

(2) (a) H. Tanida, T. Tsuji, and H. Ishitobi, *J. Am. Chem. Soc.*, **86**, 4904 (1964); (b) H. Tanida, *ibid.*, **85**, 1703 (1963).

(3) Satisfactory analyses were obtained for all compounds described.

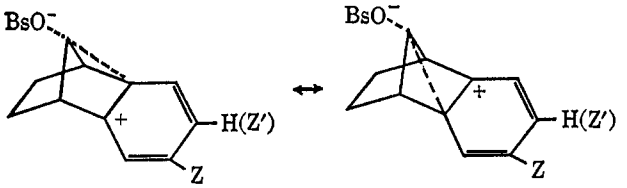
(4) Exclusive β orientation in the aromatic substitution of benzonorbornene derivatives was observed; see H. Tanida and R. Muneyuki, *J. Am. Chem. Soc.*, 87, 4794 (1965).

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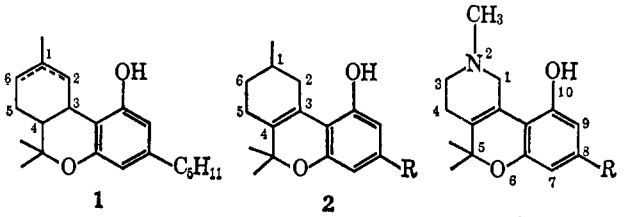
Physiologically Active Nitrogen Analogs of Tetrahydrocannabinols. Tetrahydrobenzopyrano[3,4-*d*]pyridines

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).