

Isolation, Structure, and Partial Synthesis of an Active Constituent of Hashish

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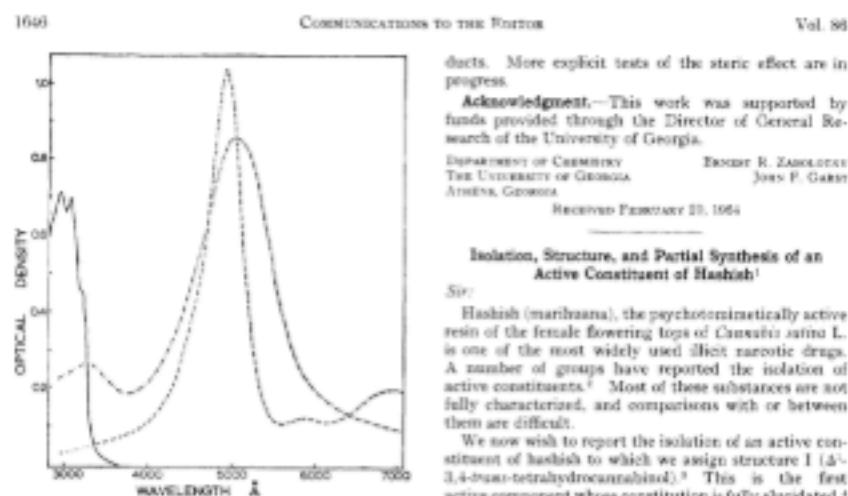


Fig. 1.—Visible and near-ultraviolet spectra of stilbene (—), stilbene⁺ (---), and stilbene⁻² (-·-·-). Cation and solvent effects on the spectra were small. The ratios of the heights of the various peaks attributed to stilbene⁺ were constant with changing temperature and exhibited only minor variations with solvent and metal ion. The following extinction coefficients were employed in the calculations: stilbene (3000 Å), 2.95 × 10⁴; stilbene⁺ (4800 Å), 4.25 × 10⁴; stilbene⁻² (3600 Å), 0.90 × 10⁴; stilbene⁻² (4800 Å), 3.28 × 10⁴; stilbene⁻² (5600 Å), 1.44 × 10⁴. These values were obtained directly in experiments involving careful state balancing and were reproducible with a variation of about ±3%.

strongly solvated than triple ions,¹⁰ the difference being greater for cations of smaller radii, leading to a trend to smaller *K* with decreasing cationic radii. Both effects, in opposite directions, should operate in solution. The directions of the effects can be similarly rationalized if ionic association is incomplete, but the arguments are slightly more complex.

The quantitative measurements were spectrophotometric. Figure 1 gives the forms of the spectra of stilbene, stilbene⁺, and stilbene⁻² in tetrahydrofuran, 2-methyltetrahydrofuran, and 1,2-dimethoxyethane. By suitable choices of solvent, metal ion, and amount of metal allowed to react with the stilbene, extinction coefficients for all three species could be directly determined. These appeared to be rather insensitive to solvent variation. *K* was calculated directly from the equilibrium expression and was usually constant for a given solvent and metal ion. The concentrations of hydrocarbons and ions employed in these experiments ranged about 10⁻⁴ M. All experiments were done at room temperature.

Corresponding equilibria for triphenylethylene have been observed in 1,2-dimethoxyethane, tetrahydrofuran, and dioxane, with the disproportionation constants (sodium cation) being <10⁻⁴, of the order of 10, and >10³, respectively. In general the value of *K* for triphenylethylene appears to be intermediate between that for stilbene and that for tetraphenylethylene, a trend which is consistent with the operation of a steric effect favoring disproportionation of the monoalkyl ad-

ducts. More explicit tests of the steric effect are in progress.

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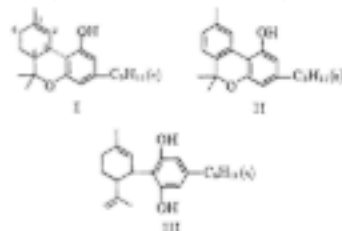
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Isolation, Structure, and Partial Synthesis of an Active Constituent of Hashish¹

Sir:

Hashish (marihuana), the psychotomimetically active resin of the female flowering tops of *Cannabis sativa* L. is one of the most widely used illicit narcotic drugs. A number of groups have reported the isolation of active constituents.² Most of these substances are not fully characterized, and comparisons with or between them are difficult.

We now wish to report the isolation of an active constituent of hashish to which we assign structure I (Δ^8 -3,4-dihydro-tetrahydrocannabinol).³ This is the first active component whose constitution is fully elucidated.⁴



Chromatography of a hexane extract of hashish on Florisil yielded an active fraction, which on repeated chromatography on alumina could be separated into the inactive cannabinol (II)⁵ and the tetrahydrocannabinol (I). Further purification of the latter was achieved by the preparation of the crystalline⁶ 3,5-dinitrophenylurethane of I (m.p. 115-120°, $[\alpha]_D^{25} -140^\circ$; *Anal.* (C₂₀H₂₈O₂N₂). Found: C, 64.17; H, 6.54; N, 19.29). Hydrolysis of I yielded the pure tetrahydrocannabinol (I) [m.p. 155-157° (0.05 mm.); $[\alpha]_D^{25} -300$ (neat) (c 0.840), 282 (c 2075), 278 (c 2040), $[\alpha]_D^{25} -120^\circ$; *Anal.* (C₂₀H₂₈O₂). Found: C, 80.20; H, 9.55]. Purity was established by chromatography and by

(1) Hashish, Part III. See part II, see Y. Gaoni and R. Mechoulam, *Proc. Chem. Soc.*, in press.

(2) For a review of the early publications see: (a) A. S. Todd, *Experiments*, 4, 55 (1948). For more recent work see: (b) F. Korte and H. Singer, *Ann.*, 486, 71 (1931); (c) R. S. de Sopp, *J. Am. Pharm. Assoc. Sci. Ed.*, 48, 758 (1959).

(3) The hashish investigated by us contains a single tetrahydrocannabinol. Most previous reports suggest the presence of mixtures of isomers.

(4) It has been generally accepted that the active constituents are isomers of I, the position of the double bond and the stereochemistry of the asymmetric centers remaining unchanged; cf. ref. 2b; also, E. C. Taylor and K. J. Haney, *J. Am. Chem. Soc.*, 80, 5196 (1958).

(5) G. Bacci, M. Salomon, F. M. Sordani, and R. P. Walsh [*Ann. N.Y. Acad. Sci.* (1941)] have described the preparation of a crystalline 3,5-dinitrophenylurethane (m.p. 210°) of an active hashish constituent. This material has not been confirmed, and since then no other crystalline tetrahydrocannabinol has been described. It is possible that Todd's compound was an impure sample of the 3,5-dinitrophenylurethane of cannabinol (m.p. 210-212°).