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

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · APRIL 1964

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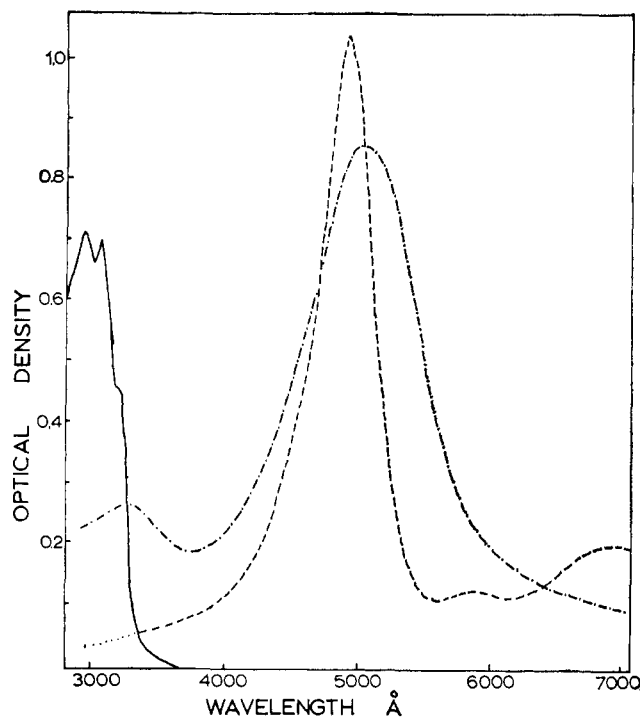


Fig. 1.—Visible and near-ultraviolet spectra of stilbene (—), stilbene⁻ (---), and stilbene⁻² (-·-·-). Cation and solvent effects on the spectra were small. The ratios of the heights of the various peaks attributed to stilbene⁻ were constant with changing temperature and exhibited only minor variations with solvent and metal ion. The following extinction coefficients were employed in the calculations: stilbene (3050 Å.), 2.95×10^4 ; stilbene⁻ (4800 Å.), 6.21×10^4 ; stilbene⁻ (5600 Å.), 0.80×10^4 ; stilbene⁻² (4800 Å.), 3.28×10^4 ; stilbene⁻² (5600 Å.), 1.49×10^4 . These values were obtained directly in experiments involving careful mass balancing and were reproducible with a variation of about $\pm 3\%$.

strongly solvated than triple ions,^{1b,5} 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 sensibly 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 $<10^{-3}$, of the order of 10, and $>10^3$, 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 monoalkali ad-

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

Acknowledgment.—This work was supported by funds provided through the Director of General Research of the University of Georgia.

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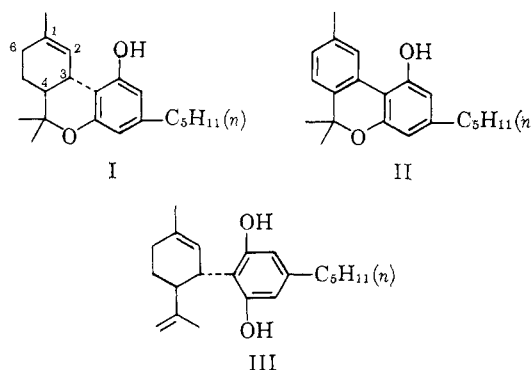
RECEIVED FEBRUARY 20, 1964

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^1 -3,4-*trans*-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)^{2a} and the tetrahydrocannabinol (I). Further purification of the latter was achieved by the preparation of the crystalline⁵ 3,5-dinitrophenylurethane of I [m.p. 115–116°, $[\alpha]_{\text{CHCl}_3}^D -14.0^\circ$; *Anal.* ($\text{C}_{28}\text{H}_{33}\text{O}_7\text{N}_3$). Found: C, 64.17; H, 6.54], followed by mild basic hydrolysis to the pure tetrahydrocannabinol (I) [b.p. 155–157° (0.05 mm.); $\lambda_{\text{max}}^{\text{EtOH}}$ 300 m μ (sh) (ϵ 840), 282 (ϵ 2075), 278 (ϵ 2040), $[\alpha]_{\text{CHCl}_3}^D -15.0^\circ$; *Anal.* ($\text{C}_{21}\text{H}_{30}\text{O}_2$). Found: C, 80.20; H, 9.55]. Purity was established by chromatoplate and by

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

(2) For a review of the early publications see: (a) A. R. Todd, *Experientia*, **2**, 55 (1946). For more recent work see: (b) F. Korte and H. Sieper, *Ann.*, **680**, 71 (1960); (c) R. S. de Ropp, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 756 (1960).

(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 undefined: cf. ref. 2a; also, E. C. Taylor and E. J. Strojny, *J. Am. Chem. Soc.*, **82**, 5198 (1960).

(5) G. Powel, M. Salmon, T. H. Bemby, and R. P. Walton [*Science*, **93**, 522 (1941)] have described the preparation of a crystalline 3,5-dinitrophenylurethane (m.p. 216°) of an active hashish constituent. This report has not been confirmed, and since then no other crystalline derivative seems to have been described. It is possible that Powel's compound was an impure sample of the 3,5-dinitrophenylurethane of cannabinol (m.p. 233–234°).

vapor phase chromatography. The tetrahydrocannabinol as obtained in the initial chromatography is not isomerized in the subsequent reactions. This was shown by the infrared and n.m.r. spectra, which remained unchanged during all purification steps, except for the disappearance of bands due to small impurities consisting mainly of cannabinol. Sulfur dehydrogenation of I gave cannabinol (II) in practically quantitative yield. This reaction defines the carbon skeleton of I.

The n.m.r. spectrum of I (see Table I) shows the presence of only one aliphatic methyl group and of

TABLE I^a
N.M.R. SPECTRUM OF TETRAHYDROCANNABINOL (I)

Group	Chemical shift, p.p.m.		
-CH ₃	0.88 (t) (3)		
-CH ₃ (olefinic and α to O)	1.08 (s)	1.38 (s)	1.65 (s)
	(9)		
C-3H	3.14 (br,d; $J = 10$ c.p.s.)		
C-2H	6.35 (br,s) (1)		
H (aromatic)	6.00 (d; $J = 2$ c.p.s.) (1)		
	6.18 (d; $J = 2$ c.p.s.) (1)		
-OH ^b	(1) ^b		

^a Determined on a Varian A-60 spectrometer in CCl₄; values are given in p.p.m. relative to (CH₃)₄Si as internal standard; letters in parentheses denote singlet (s), doublet (d), triplet (t), broad (br), coupling constant (J); numbers in parentheses denote number of protons determined by integration of areas.

^b Peak disappears on addition of D₂O.

three methyl groups which are either α to an oxygen or are olefinic. This observation places the double bond in the Δ^1 or $\Delta^{1(6)}$ position. It is of interest to compare the chemical shifts of the C-2 and C-3 protons in tetrahydrocannabinol (I) and in cannabidiol⁶ (III). The olefinic proton in I (δ 6.35) is unshielded as compared to that in III (δ 5.59), while the reverse relationship exists as regards the C-3 protons (I, δ 3.14; III, δ 3.85). This can be readily understood by examination of molecular models of these two compounds. In cannabidiol, the aromatic ring, which can rotate freely, is most probably in the same plane as the C-3 hydrogen, which is therefore unshielded.⁷ In tetrahydrocannabinol the additional ring tilts the aromatic ring, so that the latter is now in (or nearly in) the same plane as the olefinic proton, which is therefore unshielded. Such an effect is possible only if the double bond occupies the Δ^1 position and the protons on the two asymmetric carbons are *trans*, i.e., if tetrahydrocannabinol possesses structure I.

This structural determination is supported by a partial synthesis. A solution of cannabidiol (III) in absolute ethanol containing 0.05% hydrochloric acid on boiling for 2 hr. gives a mixture of the starting material and I. It can be assumed that these rather mild conditions cause no isomerization of the asymmetric centers or of the double bond.

Tetrahydrocannabinol (I) shows strong activity in the ataxia test⁸ in dogs. A full report will be submitted elsewhere by Dr. H. Edery.

Acknowledgments.—We are indebted to Prof. F. Sondheimer for his kind interest and encouragement, to Dr. Y. Shvo for the n.m.r. spectra, to Dr. H. Edery of the Israel Institute for Biological Research for the

biological tests, and to the Israeli Police for the supply of hashish.

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RECEIVED FEBRUARY 14, 1964

An Improved Method of Calculating Spin Properties from Spin-Polarized Wave Functions

Sir:

Amos and Hall¹ have given formulas for π -electron spin properties computed by the application of an annihilation operator to a single determinant wave function. They assumed that the annihilator could be taken as idempotent and that it commuted with the spin density operator. We would like to report π -electron spin properties, the spin density ρ , and the expectation value $\langle S^2 \rangle$, computed with new formulas which remove these assumptions and which correspond to integrations in which the annihilator operates upon the single determinant everywhere it appears in an integrand.

The single determinant we use is a spin-polarized open-shell (LCAO-MO-SCF)² function, i.e., one having different molecular orbitals for electrons with different spins. Let p electrons have α -spin and q β -spin (with $p > q$). The major spin component of the determinant will have multiplicity $2s + 1$ where $s = \frac{1}{2}(p - q)$ but there will also be spin states of higher multiplicities included in the wave function. Because of their presence, spin properties deduced from the single determinant will only approximate those of its major components. Considerable improvement might be expected if the most important cause of this, the spin state with multiplicity $2s + 3$, were removed from the wave function by applying the annihilator $[S^2 - (s + 1)(s + 2)]$ since the remainder of the spin components usually have negligible effect.¹

Spin densities and $\langle S^2 \rangle$ for a number of π -electron radicals when this is done accurately are shown in Tables I and II and subscripted (aa). The same properties computed using the approximate formulas of Amos and Hall are also given and subscripted (asa). For comparison we include the results deduced from the original determinant (sd) and from Hückel orbitals (h). The calculations were carried out on an I.B.M. 7090 computer with the Parr-Pariser³ integral approximations; all C-C bond lengths were assumed equal. Full details of the calculations and the lengthy new formulas will be given later as will a large number of applications.

As can be seen from the tables, the errors involved in the approximate formulas are small but so are some of the quantities to be calculated. In particular we note that $\langle S^2 \rangle_{asa}$ can sometimes fall below $s(s + 1)$, which is certainly wrong, whereas $\langle S^2 \rangle_{aa} > s(s + 1)$ as must be true. The annihilated single determinant must be very nearly the pure major spin component since $\langle S^2 \rangle_{aa}$ is very close to $s(s + 1)$ for the radicals considered here. For the single determinant we find $\langle S^2 \rangle_{sd}$ much larger than $s(s + 1)$. From Table I we see that negative spin densities occur in ρ_{aa} , ρ_{asa} , and ρ_{sd} at carbon atoms for which $\rho_h = 0$. At these atoms $\rho_{aa} \simeq$

(6) R. Mechoulam and Y. Shvo, *Tetrahedron*, **19**, 2073 (1963).

(7) L. M. Jackman, "N.M.R. Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 125.

(8) S. Loewe, *Arch. Exptl. Pathol. Pharmacol.*, **211**, 175 (1950).

(1) A. T. Amos and G. G. Hall, *Proc. Roy. Soc. (London)*, **A263**, 483 (1961).

(2) J. Pople and R. Nesbet, *J. Chem. Phys.*, **22**, 571 (1954).

(3) R. G. Parr and R. Pariser, *ibid.*, **23**, 711 (1955).