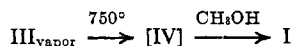
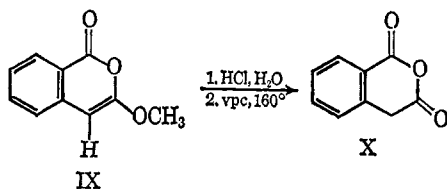
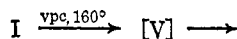


tigate the pyrolysis of III in the gas phase under conditions in which the keto ketene intermediate IV could be trapped by methanol. Indeed, pyrolysis of III vapor in a stream of nitrogen at 25 mm over a glowing Nichrome wire at *ca.* 750°, and introduction of a stream of methanol vapor directly above the Nichrome wire, gave I in 45–50% yield, mp 54–55° (*Anal.* Found: C, 68.10; H, 4.63); λ_{\max} (dioxane) 215 m μ (log ϵ 3.98), 242 (3.78), 285 (3.13), and 295 (3.08); ν_{\max} 1780 and 1735 cm⁻¹; δ 3.73 (singlet, 3 H), 5.07 (singlet, 1 H), and 7.50 ppm (multiplet, 4 H). The carbonyl absorption at 1780 cm⁻¹ and the ultraviolet spectrum are fully consistent with the corresponding values for other benzocyclobutenones.⁶ The mass spectrum of I included peaks with *m/e* 176 (molecular ion), 148, 133 (base peak), 105, 89, and 77, with metastable peaks for the transitions 176 → 148, 148 → 133, 133 → 105, and 105 → 77. Ultraviolet irradiation of I in methanol gave dimethyl homophthalate (VI). The spectroscopic data for I and its photochemical conversion to VI makes the structural assignment secure.



Attempted vpc of I on an SE-30 column at 160° gave an isomer, mp 56–61°; λ_{\max} (dioxane) 231 m μ (log ϵ 4.40), 240 (4.31), 270 (4.04), 280 (4.03), and 346 (3.52); ν_{\max} 1742 and 1645 cm⁻¹; δ 3.87 (singlet, 3 H), 5.53 (singlet, 1 H), 7.33 (multiplet, 3 H), and 8.10 ppm (multiplet, 1 H), considered to be 3-methoxyisocoumarin (IX), which probably arises *via* thermal cleavage of I to the *o*-quinodimethane (V). The mass spectrum of IX is identical with that of I, suggesting that I rearranges to IX in the mass spectrometer prior to fragmentation. Treatment of IX with dilute HCl gave, after preparative vpc,¹⁰ homophthalic anhydride (X).



No evidence for the existence of the enol tautomer II of I has been obtained. The nmr spectrum of I con-

(10) Under these vpc conditions (a 6 ft × 0.25 in. column of 2.5% SE-30 on Chromosorb W at 160°) homophthalic acid is dehydrated to homophthalic anhydride.

tains no low-field signal typical of a hydrogen-bonded enolic proton, and the ratio of aromatic signals to methine signal to methyl ester signal is 4:1:3, as required by the keto tautomer I. Furthermore, solutions of I give a negative ferric chloride test.

The synthesis of I from III is the first example of the formation of a strained ring system by an uncatalyzed thermal Wolff rearrangement, in contrast to the now widely employed photochemical Wolff rearrangement.¹¹ In addition, the fact that I cannot be prepared from III by irradiation suggests that the pyrolysis of diazo ketones in the vapor phase may prove to be of use in the synthesis of other strained but photochemically unstable systems.

Acknowledgment. This work was supported by Grant GP-4931 from the National Science Foundation.

(11) W. Kirmse, "Carbene Chemistry," Academic Press Inc., New York, N. Y., 1964, p 120.

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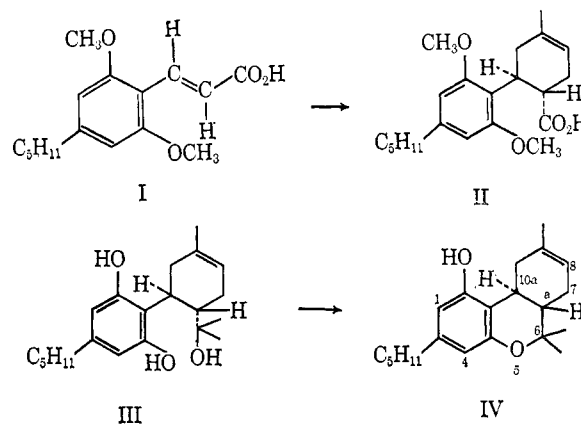
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Total Synthesis of Δ^8 -($\Delta^{1(6)}$)-Tetrahydrocannabinol, a Biologically Active Constituent of Hashish (Marijuana)

Sir:

Total syntheses^{1–3} have been reported of (\pm)- Δ^8 - and - Δ^9 -tetrahydrocannabinols,⁴ which occur in the corresponding enantiomorphic forms as psychotomimetically active constituents of hashish.⁵ Recently, (-)-cannabidiol, which is convertible to the naturally occurring (-)- Δ^8 - and - Δ^9 -tetrahydrocannabinols,^{6,7} has been synthesized from olivetol and (+)-*cis*- and -*trans*-*p*-mentha-2,8-dien-1-ols.⁸ We now report a total synthesis of (-)- Δ^8 -tetrahydrocannabinol which, since it involves the optical resolution of a racemic intermediate,



(1) R. Mechoulam and Y. Gaoni, *J. Am. Chem. Soc.*, **87**, 3273 (1965).
(2) E. C. Taylor, K. Lenard, and Y. Shvo, *ibid.*, **88**, 367 (1966).
(3) K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *ibid.*, **88**, 2079 (1966).

(4) Fahrenholtz³ has proposed, and we have adopted, the *Chemical Abstracts* nomenclature for these dibenzo[*b,d*]pyrans.

(5) U. Claussen and F. Korte, *Naturwissenschaften*, **53**, 541 (1966), have recently reviewed the chemistry and biological activity of hashish constituents.

(6) Y. Gaoni and R. Mechoulam, *J. Am. Chem. Soc.*, **86**, 1646 (1964).

(7) R. L. Hively, W. A. Mosher, and F. W. Hoffmann, *ibid.*, **88**, 1832 (1966).

(8) T. Petrzilka, W. Haefliger, C. Sikemeier, G. Ohloff, and A. Eschenmoser, *Helv. Chim. Acta*, **50**, 719 (1967).

also provides the first total synthesis of the corresponding unnatural (+) enantiomorph.

These syntheses depended initially on the observation that, since the cinnamic acid I,⁹ from its method of preparation by the Knoevenagel reaction of malonic acid with the corresponding aldehyde, should have the *anti* configuration, it may be predicted, from the rule governing the retention of configuration of the dienophile constituents in the Diels–Alder reaction (e.g., see ref 10), that the racemic adduct of I with isoprene⁹ should have the *trans* configuration II analogous to that found in Δ^8 - and Δ^9 -tetrahydrocannabinol.^{2,6,11} The *anti* configuration of I is confirmed by the pmr spectrum, in which the olefinic protons display a coupling constant, *J*, of 16.5 cps, in good agreement with the value of 17 cps observed for *anti*-styrenoid protons and quite distinct from the value of 10 cps found for corresponding *syn* protons.¹² The racemic adduct II, from I and isoprene, mp 114–116° (lit.⁹ 115–115.5°), was resolved by fractional crystallization of its diastereoisomeric (+)-1-1'-naphthylethylamine salts from hexane. Fusion of the resulting (–)-II,¹³ mp 137.5–138.5°, [α]^{24D} –63° (*c* 1.00, CHCl₃), with methylmagnesium iodide at 165°¹⁴ demethylated the dimethoxybenzene ring and converted the carboxyl to a 2-hydroxypropyl group giving what, from its infrared and pmr absorption spectra, is probably the crude triol III, and the latter, on distillation (bath temperature 200° (0.01 mm)) and filtration in benzene through neutral Al₂O₃, gave in 47% over-all yield from II a gum, [α]^{24D} –173° (*c* 1.20, C₂H₅OH),¹⁵ which was separated by preparative glpc¹⁶ into pure (–)- Δ^8 -tetrahydrocannabinol (IV) obtained as a gum [α]^{24D} –256° (*c* 0.99, C₂H₅OH) (lit. –266°,^{11b} –260°⁷). The 100-Mcps pmr spectrum¹⁷ displayed the following signals: three-proton triplet at δ 0.88, *J* = 6 cps (ω -CH₃); three-proton singlets at δ 1.09 and 1.36 (*gem*-CH₃); three-proton singlet at δ 1.70 (C₉ CH₃); two-proton triplet at δ 2.43 (benzylic CH₂); one-proton broad doublet at δ 3.18, half-band width 15 cps (C_{10a} H); one-proton broad multiplet at δ 5.42 (C₈ H); one-proton doublets at δ 6.08 and 6.26, *J* for both = 1.6 cps (C₂ and C₄ H), in excellent agreement with

the values given² for (±)-IV except for a 0.07-ppm discrepancy for the C_{10a} proton signal, which may be due to differences in estimating the center of this broad signal in the two spectra. The mass spectrum¹⁸ showed principal ions at *m/e* 314, 299, 271, 258, 246, 243, 231, and 193, in accord with the data presented for an authentic sample.¹⁹

The residual salts from the foregoing resolution were decomposed with 3 *N* hydrochloric acid and the resulting acid was resolved by fractional crystallization of its (–)-1-1'-naphthylethylamine salts from hexane to give the unnatural enantiomorph (+)-II, mp 137.5–138.5°, [α]^{24D} +63° (*c* 1.07, CHCl₃), which was converted, as for (–)-II, to (+)-IV, [α]^{24D} +250° (*c* 1.04, C₂H₅OH), which was chromatographically and spectrographically identical with (–)-IV.

Biological testing is currently underway with (±)-IV and will be extended to both of the constituent enantiomorphs. The authors hope to report the results in a later full communication.

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(18) Measured on the Atlas CH-4 mass spectrometer.

(19) U. Claussen, H.-W. Fehlhaber, and F. Korte, *Tetrahedron*, **22**, 3535 (1966).

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A Stereospecific Synthesis of (–)- Δ^1 - and (–)- $\Delta^{1(6)}$ -Tetrahydrocannabinols¹

Sir:

A number of total syntheses of racemic Δ^1 -tetrahydrocannabinol (Δ^1 -THC) (I) and $\Delta^{1(6)}$ -THC (II) have been published recently.² No resolution has been reported so far, and hence these syntheses are of limited value in psychobiological research for which compounds with the natural modification are required.³

We report now a facile, stereospecific synthesis leading to (–)- $\Delta^{1(6)}$ -THC and thence to (–)- Δ^1 -THC. A pinane derivative was chosen as a starting material for the following reasons: (i) its bulky dimethyl-

(1) Hashish. XI. For part X see R. Mechoulam and Y. Gaoni, *Tetrahedron Letters*, 1109 (1967).

(2) (a) R. Mechoulam and Y. Gaoni, *J. Am. Chem. Soc.*, **87**, 3273 (1965); (b) E. C. Taylor, K. Lenard, and Y. Shvo, *ibid.*, **88**, 367 (1966); (c) K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *ibid.*, **88**, 2079 (1966).

(3) The isolation from natural sources of both (–)- Δ^1 -THC,⁴ the major active constituent of hashish, and (–)- $\Delta^{1(6)}$ -THC,⁵ a minor active component in some marijuana samples, is rather tedious and not practical. Semisynthetic preparations from the more abundant cannabidiol (III) have, however, been described.^{4–6} The structures of I, II, and III as written in this paper correspond to the absolute configuration of the naturally occurring (–) modifications.^{1,7}

(4) Y. Gaoni and R. Mechoulam, *J. Am. Chem. Soc.*, **86**, 1646 (1964).

(5) R. L. Hively, W. A. Mosher, and F. W. Hoffmann, *ibid.*, **88**, 1832 (1966).

(6) Y. Gaoni and R. Mechoulam, *Tetrahedron*, **22**, 1481 (1966).

(7) T. Petržilka, W. Haefliger, C. Sikemeier, G. Ohloff, and A. Eschenmoser, *Helv. Chim. Acta*, **50**, 719 (1967).

(9) R. Adams and R. B. Carlin, *J. Am. Chem. Soc.*, **65**, 360 (1943).

(10) J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).

(11) (a) R. Mechoulam and Y. Shvo, *Tetrahedron*, **19**, 2073 (1963);

(b) Y. Gaoni and R. Mechoulam, *ibid.*, **22**, 1481 (1966).

(12) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p 238.

(13) This substance, its enantiomorph, and (+)- and (–)-IV gave satisfactory elemental analyses.

(14) V. Grignard and J. Ritz, *Bull. Soc. Chim. France*, **3**, 1181 (1936); W. Salzer, *Z. Physiol. Chem.*, **274**, 39 (1942); A. L. Wilds and W. B. McCormack, *J. Am. Chem. Soc.*, **70**, 4127 (1948).

(15) Optical rotations were measured on a Carl Zeiss photoelectric precision polarimeter, accurate to 0.005°.

(16) Using N₂ as the carrier gas in a Varian Aerograph Autoprep Model 705 gas chromatograph having a 10-ft column (0.375 in. o.d.) at 280° packed with 45–60 mesh Gas Chrom P containing 20% (w/w) SE-30; 20-mg samples were injected in 0.2 ml of CH₂Cl₂. The crude material had previously been shown to be 70–75% pure by glpc using He at a flow rate of 40 cc/min as the carrier gas in a Perkin-Elmer Model 881 chromatograph having a 6-ft column (0.25 in. o.d.) packed with 80–100 mesh AW DMCS Chrom G maintained isothermally at 150° for 1 min and thereafter programmed at 4°/min to 250°, the sample being injected in CH₂Cl₂ at 250°. Under these conditions IV had a retention time of 24 min, the main impurity had a retention time of 22 min, and trace impurities appeared at retention times of 20, 21, 24.7, and 25 min.

(17) Measured on the Varian HA-100 spectrometer using 2–3% solutions in CDCl₃ containing tetramethylsilane as the internal reference standard. Chemical shifts are given in δ units as parts per million measured downfield from the reference, and coupling constants are given in cycles per second.