

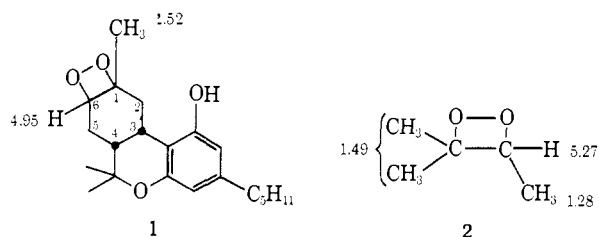
Hashish, a Novel Cannabinoid Containing a Cyclic Peroxide

Sir:

We wish to report the isolation of another compound from the pyridine-catalyzed reaction of citral with olivetol^{1,2} and propose that it is the novel cannabinoid **1** possessing a four-membered cyclic peroxide ring.

Recently Kopecky and Mumford³ have reported the synthesis of 3,3,4-trimethyl-1,2-dioxetane (**2**). This is the first example of isolation of a dioxetane, although the products from a number of reactions have been explained as occurring *via* such four-membered cyclic peroxides.⁴

We have found that further elution of the reaction mixture^{1a} with 12:88 and 15:85 ether-petroleum ether (bp 30–40°) gave a yellowish oil. This was rechromatographed on a thick silica gel plate to give a colorless resin in 5% yield, homogeneous on tlc; nmr (CDCl₃) δ 0.84 (3 H, t, ω-CH₃), 1.18, 1.28 (6 H, 2s), 1.52 (3 H, s), 2.12 (1 H, double doublet, *J* = 3 and 14 cps), 3.44 (1 H, m, *J* = 6 and 14 cps), 4.95 (1 H, d, *J* = 3 cps), 6.34 (1 H, d, *J* = 3 cps, aromatic H), 6.41 (1 H, d, *J* = 3 cps, aromatic H), 6.2 (1 H, broad, OH; D₂O exchangeable); λ_{max}^{EtoH} 280 (ε 2170) and 222 mμ sh (ε 8670); ir (cm⁻¹, CCl₄) 3610 (OH), 1130 (s, ether), 895 (m), and 850 (w).⁵ The mass spectrum indicates a molecular ion peak *m/e* 346 corresponding to C₂₁H₃₀O₄ and in addition shows (*inter alia*) peaks at *m/e* 231, 196 (base), 151, 139, and 123, which are explicable on the basis of structure **1**.^{6,6a} It gives a positive peroxide test.⁷



(1) (a) V. V. Kane and R. K. Razdan, *J. Am. Chem. Soc.*, **90**, 6551 (1968); (b) *Tetrahedron Letters*, 591 (1969).

(2) L. Crombie and R. Ponsford, *Chem. Commun.*, 894 (1968); *Tetrahedron Letters*, 4557 (1968).

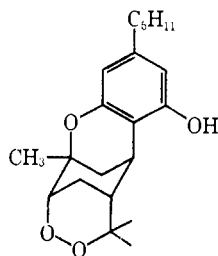
(3) K. R. Kopecky and C. Mumford, private communication. We wish to thank the authors for supplying us with spectral data. See also 51st Annual Conference of the Chemical Institute of Canada, Vancouver, British Columbia, June 1968, Abstracts, p 41; *Can. J. Chem.*, **47**, 709 (1969).

(4) See, for example, (a) D. Swern, J. E. Coleman, and H. B. Knight, *J. Am. Chem. Soc.*, **75**, 3135 (1953); (b) H. G. Aurich, *Tetrahedron Letters*, 657 (1964); (c) J. E. Huber, *ibid.*, 3271 (1968).

(5) We ascribe the bands at 895 and 850 cm⁻¹ to C₃C-O and O-O stretching, respectively: L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1958, p 121. Similar bands were observed in **2**.³

(6) A rationalization of the spectrum will be provided in our detailed paper.

(6a) NOTE ADDED IN PROOF. The alternative structure below was also considered for the peroxide but the nmr evidence supports structure **1**.



The presence of only one exchangeable proton in the nmr and the absence of infrared absorption bands in the 3560-cm⁻¹ (nonbonded, typical of hydroperoxides) region rule out the presence of a hydroperoxide structure. The position of the C-1 methyl singlet at 1.52 ppm and the C-6 proton at 4.95 ppm is in excellent agreement with the dioxetane **2**.³

The multiplet at δ 2.12 is assigned to one of the C-5 protons on the basis of collapse of the 3-cps coupling during irradiation of C-6 at δ 4.95. The double resonance experiments (100 Mcps) suggest that the 14-cps portion of the C-5 multiplet may be due either to geminal coupling at C-5 or to coupling with the C-4 proton. Furthermore, the benzylic C-3 proton (δ 3.44) appears to be coupled to one of the C-2 protons with a coupling constant 14 cps. The remaining 6-cps coupling constant may be either with the C-4 or the remaining C-2 proton. In addition the irradiation experiments indicate a small long-range coupling⁸ between the benzylic proton and the C-5 proton at δ 2.12, but unfortunately our spectra were not sufficiently resolved to allow us to confirm this last indication. We were unable to determine the coupling constant for the C-3-C-4 interaction. However, the position of the benzylic C-3 proton in **1** indicates a *cis* stereochemistry at the ring fusion, as it is more in agreement with *cis* rather than *trans* compounds in cannabinoids.⁹

When **1** was passed through a vpc column (10% SE-31 on 80–100 mesh Chromosorb W; gas, helium; oven temperature, 220°), a single peak was observed.¹⁰ Its mass spectrum showed a molecular ion peak at *m/e* 314 (different from **1**; *i.e.*, less 32) and in addition included peaks at 299 (M⁺ - CH₃), 271 (M⁺ - C₃H₇), 258 (M⁺ - C₄H₉), 246, 231 (base), and 193, which are characteristic of tetrahydrocannabinols.¹¹

Treatment of **1** in the presence of hydrogen–10% palladium on charcoal in methanol for 16 hr afforded a crystalline compound, mp 94–95°, to which we assign structure **3**;¹² nmr (CDCl₃) δ 0.88 (3 H, t, ω-CH₃), 1.11, 1.25 (6 H, 2s, *gem*-dimethyl), 1.41 (3 H, s), 2.5 (1 H, m), 3.55 (3 H, s, OCH₃), 4.84 (1 H, d, *J* = 7 cps, hemiacetal), 4.0, 5.94 (2 H, broad, D₂O exchangeable), 6.18 (1 H, d, *J* = 3 cps, aromatic H), 6.31 (1 H, d, *J* = 3 cps, aromatic H); ir (cm⁻¹, KBr) 3430, 3200 (OH), and 1190 (m), 1130 (s), 1075 (m), 1035 (m) (C-O-C-O-C bands). The mass spectrum confirms the molecular composition C₂₂H₃₄O₅ (*m/e* calcd for C₂₂H₃₄O₅ 378.2406; found

(7) F. Feigl, "Spot Tests in Organic Analysis," Elsevier Publishing Co., New York, N. Y., 1956, p 474.

(8) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. II, Pergamon Press, London, 1965, pp 683, 815.

(9) (a) R. Mechoulam and Y. Gaoni, *Fortschr. Chem. Org. Naturstoffe*, **25**, 186 (1967); (b) Y. Gaoni and R. Mechoulam, *Israel J. Chem.*, **6**, 679 (1968).

(10) We attempted to carry out the vpc analysis on a preparative scale; after a few runs the peak could not be reproduced. However, the column behaved exactly as above when used after ~1 month. This is taken as evidence that there is something in the column which removes the peroxide but is deactivated on prolonged use. This method could not therefore be used in a preparative sense to characterize the material. Since the product obtained from vpc gave the molecular ion and fragmentation pattern of a tetrahydrocannabinol, it is assumed that this material was the hitherto unknown Δ⁶-3,4-*cis*-tetrahydrocannabinol.

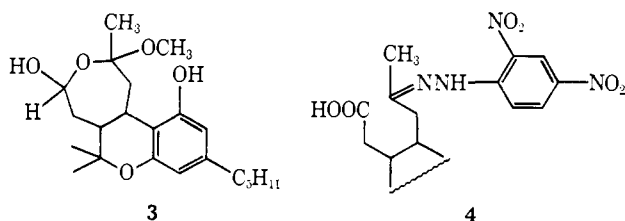
(11) H. Budzikiewicz, R. T. Alpin, D. A. Lightner, C. Djerassi, R. Mechoulam, and Y. Gaoni, *Tetrahedron*, **21**, 1881 (1965); U. Claussen, H. W. Fehlhaber, and F. Korte, *ibid.*, **22**, 3535 (1966).

(12) We prefer structure **3** to the alternative structure, where the methoxyl and hydroxyl groups are interchanged, on mechanistic grounds.

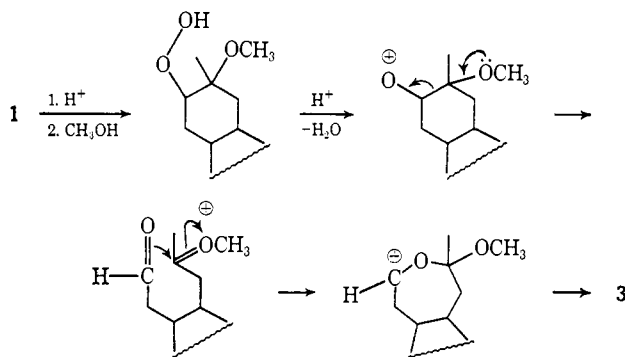
378.2402), and in addition included peaks at 360 ($M^+ - H_2O$), 346 ($M^+ - CH_3OH$), 331, and 288 (base) which are completely explicable on the basis of structure **3**.

The methyl singlet at 1.41 ppm and the hemiacetal proton at 4.84 ppm are in agreement with literature values in similar compounds.¹³ Similarly, the slight shift in the position of *gem*-dimethyl groups in **3** is in accordance with that reported by Gaoni and Mechoulam in the case of 1-methoxyhexahydrocannabinol.^{9b}

3 gives a positive test with Tollens reagent. This is taken as confirmation of the presence of a hemiacetal function in **3**. Moreover, it furnished a resinous 2,4-dinitrophenylhydrazone of the acid¹⁴ **4** ($C_{27}H_{34}N_2O_8$; *m/e* 542) which was purified by chromatography on thick



silica gel plates. We submit that the most reasonable interpretation of the mechanism of formation of **3** is



Similar rearrangements of hydroperoxides are known in the literature.¹⁵ In confirmation of this proposed mechanistic scheme, **3** was also formed when **1** was treated with a catalytic amount of *p*-toluenesulfonic acid in methanol for 16 hr.

Isolation of similar compounds in the Δ^1 - and Δ^8 -*trans*-tetrahydrocannabinol series is in progress.

Acknowledgment. The authors wish to thank Drs. R. Lyle and P. Dowd for helpful discussions, Dr. P. Levins for nmr and mass spectral data, and JEOLCO, Inc., for decoupling experiments. We also wish to acknowledge the financial support of Arthur D. Little, Inc.

(13) L. J. Dolby, C. A. Elliger, S. Esfandiori, and K. S. Marshall, *J. Org. Chem.*, **33**, 4508 (1968); N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution NMR Spectra Catalog," Vol. I, Varian Associates, Palo Alto, Calif., 1962, p 143.

(14) We believe this is formed by oxidation of **3** to the corresponding lactone followed by ring opening. Oxidative properties of 2,4-dinitrophenylhydrazine are known; see, e.g., D. Welti and D. Whittaker, *Chem. Ind.* (London), 968 (1962).

(15) E. G. E. Hawkins, "Organic Peroxides," D. Van Nostrand Co., Inc., Princeton, N. J., 1961, p 54.

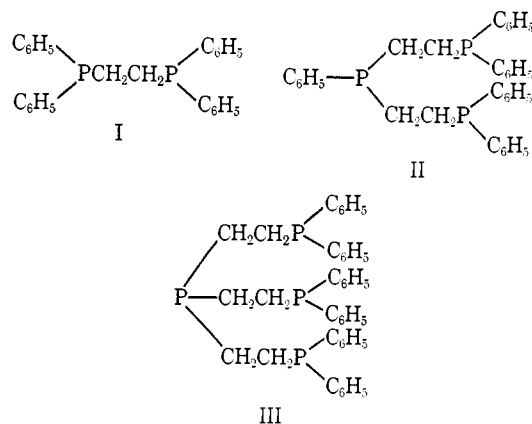
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Received April 2, 1969

A New Synthesis of Polytertiary Phosphines and Arsines

Sir:

The base-catalyzed addition of phosphorus-hydrogen bonds to carbon-carbon multiple bonds is an important reaction in organophosphorus chemistry.¹ This communication reports an extension of this reaction to the preparation of novel polytertiary phosphines by the base-catalyzed addition of phosphorus-hydrogen bonds to vinylphosphines and ethynylphosphines. Many of the new polytertiary phosphines prepared by this synthetic method are useful multidentate ligands in coordination chemistry.

A commonly used chelating ditertiary phosphine is 1,2-bis(diphenylphosphino)ethane, $(C_6H_5)_2PCH_2CH_2P(C_6H_5)_2$ (I), previously² prepared by reaction of an alkali metal diphenylphosphide with 1,2-dichloroethane. The reaction between stoichiometric quantities of diphenylphosphine and diphenylvinylphosphine in boiling benzene for 20 hr in the presence of 5–10% phenyllithium catalyst gives an 80% yield of $(C_6H_5)_2PCH_2CH_2P(C_6H_5)_2$ (I), mp 139–140° (lit.² mp 140–142°). The infrared spectrum of I prepared from diphenylphosphine and diphenylvinylphosphine was identical with that of material prepared from lithium diphenylphosphide and 1,2-dichloroethane.



This new preparative method is particularly useful for the preparation of novel tridentate and tetradentate chelate polytertiary phosphines with $-CH_2-CH_2-$ bridges between the phosphorus atoms. The chelating tritertiary phosphine³ $C_6H_5P[CH_2CH_2P(C_6H_5)_2]_2$ (II), mp 129–130° (lit.² mp 131–132°), can be obtained in 50–90% yields either from $C_6H_5PH_2$ and $(C_6H_5)_2PCH=CH_2$ or from $(C_6H_5)_2PH$ and $C_6H_5P(CH=CH_2)_2$ in boiling benzene using a phenyllithium or, preferably, a potassium *t*-butoxide catalyst; these new methods for preparing II are much more efficient than its previously² reported preparation from sodium diphenylphosphide and phenylbis(2-bromoethyl)phosphine. Similarly the new chelating tetratertiary phosphine³ $P[CH_2CH_2P(C_6H_5)_2]_3$ (III),³ mp 129–130°, can be prepared in 60–75% yields from $(C_6H_5)_2PH$ and $(CH_2=CH)P$ or in lower yields from PH_3 and $(C_6H_5)_2PCH=CH_2$; in the latter case the reaction is carried out using phenyllithium catalyst in a sealed stainless steel cylinder at 100° for 36 hr. A chelating tetratertiary phosphine

(1) K. Sasse in "Methoden der Organischen Chemie," Houben-Weyl, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1963, pp 25–28.

(2) W. Hewertson and H. R. Watson, *J. Chem. Soc.*, 1490 (1962).

(3) The new compounds gave satisfactory analyses for all elements. The ³¹P nmr spectra were consistent with the proposed structures.