occurring through the π-electrons of the nitrogen–nitrogen double bond.

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An Oxygen Insertion Reaction of Osuloses

Sir:

As a starting point for further synthetic work we were interested in preparing a suitably constituted 3-ketofuranose. To this end, both 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (I) and 5-carbomethoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (II) were subjected to several oxidizing conditions in an attempt to convert the free 3-hydroxyl to a keto function. However, none of the oxidizing agents, which included chromium trioxide in pyridine, acetone, and acetic acid, aluminum isopropoxide in acetone, potassium permanganate in acetone, and lead tetraacetate in benzene, gave a useful amount of the desired product. Either complex mixtures or unreacted starting materials were obtained. During the course of this work a new method for oxidizing hindered hydroxyl groups in carbohydrate derivatives using ruthenium tetroxide[1] was reported,[2] whereby 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose was converted into 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-3-hexulofuranose (III). Another group recently reported[3] that an oxidation of 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose (IV) with chromium trioxide in *t*-butyl alcohol gave 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*erythro*-3-pentulofuranose (V). We have applied the ruthenium tetroxide procedure to the oxidation of IV [λ_{max}^{Nujol} 2.8 (hydroxyl) and 5.82 μ (benzoate); τ^{CDCl_3} 4.03 (C-1 proton, doublet; $J_{1,2}$ = 3.5 c.p.s.), 5.42 (C-2 proton, doublet; $J_{2,1}$ = 3.5 c.p.s.), and 5.44 ± 0.42 p.p.m. (C-3, 4, 5 protons, multiplet)] and have also isolated V [λ_{max}^{Nujol} 5.62 (cyclic ketone) and 5.77 μ (benzoate); $\lambda_{max}^{CHCl_3}$ 5.62 (cyclic ketone) and 5.81 μ (benzoate); τ^{CDCl_3} 3.87 (C-1 proton, doublet; $J_{1,2}$ = 4.5 c.p.s.) and 5.44 ± 0.28 p.p.m. (C-2, 4, 5 protons, multiplet)]. The course of reaction was followed by t.l.c. (silica; $CHCl_3$–EtOAc, 4:1) and it was noted that, as the oxidation proceeded in the presence of excess ruthenium tetroxide, an increasing amount of an unexpected product was being formed. After 24 hr. this product, now the major product, was isolated and its elemental analysis and infrared and n.m.r. spectra indicated that it was the product of oxygen insertion, 1,2-*O*-isopropylidene-6-*O*-benzoyl-3-oxa-α-D-*erythro*-4-hexulopyranose (VI) [m.p. 111–112°; $[\alpha]_D$ +81° (*c* 1.03, $CHCl_3$); λ_{max}^{Nujol} 5.70 (lactone) and 5.80 μ (benzoate); τ^{CDCl_3} 4.08 (C-1 proton, doublet; $J_{1,2}$ = 3.8 c.p.s.), 4.32 (C-2 proton doublet; $J_{2,1}$ = 3.8 c.p.s.), and 5.23 ± 0.19 p.p.m. (C-5, 6 protons, multiplet)]. That the inserted oxygen is in the 3-position as in VI and not in the 4-position as in the isomeric VII is indicated by n.m.r. spectra. The position of the C-5 proton resonance in VI is essentially unchanged compared to that of the C-4 proton in V, whereas the C-2 proton resonance of VI shows a large downfield chemical shift compared to that of the C-2 proton in V.

Overend's[2] oxidation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (I) [τ^{CDCl_3} 4.07 (C-1 proton, doublet; $J_{1,2}$ = 3.8 c.p.s.), 5.48 (C-2 proton, doublet; $J_{2,1}$ = 3.8 c.p.s.), and 5.81 ± 0.26 p.p.m. (C-3, 4, 5, 6 protons, multiplet)] with ruthenium tetroxide was repeated. After a few hours the product III, as reported[2] previously, was produced, while after 48 hr. the product of oxygen insertion, 1,2:6,7-di-*O*-isopropylidene-3-oxa-α-D-*ribo*-4-heptulopyranose (VIII) [m.p. 62–64°; $[\alpha]_D$ +86° (*c* 0.5, $CHCl_3$); λ_{max}^{Nujol} 5.68 μ (lactone); τ^{CDCl_3} 4.12 (C-1 proton, doublet; $J_{1,2}$ = 3.7 c.p.s.), 4.29 (C-2 proton, doublet; $J_{2,1}$ = 3.7 c.p.s.), and 5.64 ± 0.34 p.p.m. (C-5, 6, 7 protons, multiplet)] was obtained.

The products VI and VIII[4] represent a new class of carbohydrate derivatives, and the oxygen insertion reaction is a new reaction[5] of ruthenium tetroxide.

(1) Prepared from ruthenium dioxide obtained from Englehard Industries, Newark, N. J. For other oxidations using ruthenium tetroxide see L. M. Berkowitz and P. N. Rylander, *J. Am. Chem. Soc.*, **80**, 6682 (1958).

(2) P. J. Beynon, P. M. Collins, and W. G. Overend, *Proc. Chem. Soc.*, 342 (1964).

(3) K. Oka and H. Wada, *Yakagaku Zasshi*, **83**, 890 (1963); *Chem. Abstr.*, 60, 1825 (1964).

(4) All compounds reported have given satisfactory elemental microanalyses.

(5) H. Nakata, *Tetrahedron*, **19**, 1959 (1963), has reported the conversion of β-cholestanol into 4-oxo-A-homo-5α-cholestan-3-one in acetic acid solution containing excess lead tetraacetate and catalytic amounts of ruthenium tetroxide. It seems likely that in this case, as Nakata suggested, the oxygen insertion results from a Baeyer–Villiger reaction involving peracetic acid.

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Received May 24, 1965

A Total Synthesis of *dl*-Δ^1-Tetrahydrocannabinol, the Active Constituent of Hashish[1]

Sir:

We wish to report that we have completed the first total synthesis[2] of *dl*-cannabidiol[3] (Ia) and *dl*-Δ^1-3,4-

(1) Hashish. VI. For Part V see H. Budzikiewicz, R. T. Aplin, D. A. Lightner, C. Djerassi, R. Mechoulam, and Y. Gaoni, *Tetrahedron*, in press.

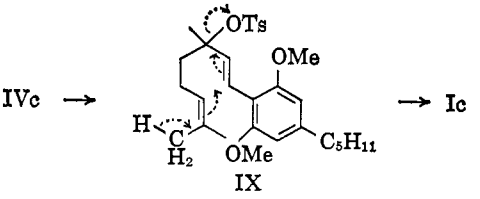
trans-tetrahydrocannabinol[4,5] (II), the psychotomimetically active constituent of hashish (marihuana).

Reaction of citral *a* (V) with the lithium derivative of olivetol dimethyl ether (VI)[9] at room temperature for 15 min. afforded a complicated mixture which presumably contained IVb as one of its components. The mixture was dissolved in pyridine containing *p*-toluenesulfonyl chloride and left for 24 hr. at room temperature. The reaction product was chromatographed on alumina and the fractions similar in polarity to that of cannabidiol dimethyl ether (Ic),[10] as shown by chromatoplate, were combined. Rechromatography of these fractions on 10% silver nitrate–alumina yielded *dl*-cannabidiol dimethyl ether (Ic) in a low yield. The infrared, n.m.r., and ultraviolet spectra were identical with those of Ic prepared from the natural product; λ_{max}^{EtOH} 271 (ϵ 1160) and 277 mμ (ϵ 1020), δ[11] 0.9 (t) (paraffinic methyl group), 1.48 and 1.58 (two olefinic methyl groups), 3.65 (s) (two OCH_3 groups), 4.28 (d) ($C{=}CH_2$), 5.1 (br) (C-2 proton), and 6.18 (s) (aromatic protons). Heating synthetic Ic with an excess of methylmagnesium iodide at 155–165° for 15 min. gave *dl*-cannabidiol (Ia) in an 80% yield.[12] Identity with natural cannabidiol was established by infrared and n.m.r. spectral comparisons. *dl*-Cannabidiol ditosylate melts at 138–140°; the ditosylate of natural cannabidiol melts at 81–83° Their infrared spectra in solution are identical.

Boiling *dl*-cannabidiol with 0.05% hydrogen chloride[4] in absolute ethanol for 2 hr. gave a mixture of the starting material and *dl*-Δ^1-3,4-*trans*-tetrahydrocannabinol (II). Identity with the natural material was established by infrared and n.m.r. spectral comparisons. The over-all yield of I was 2%.

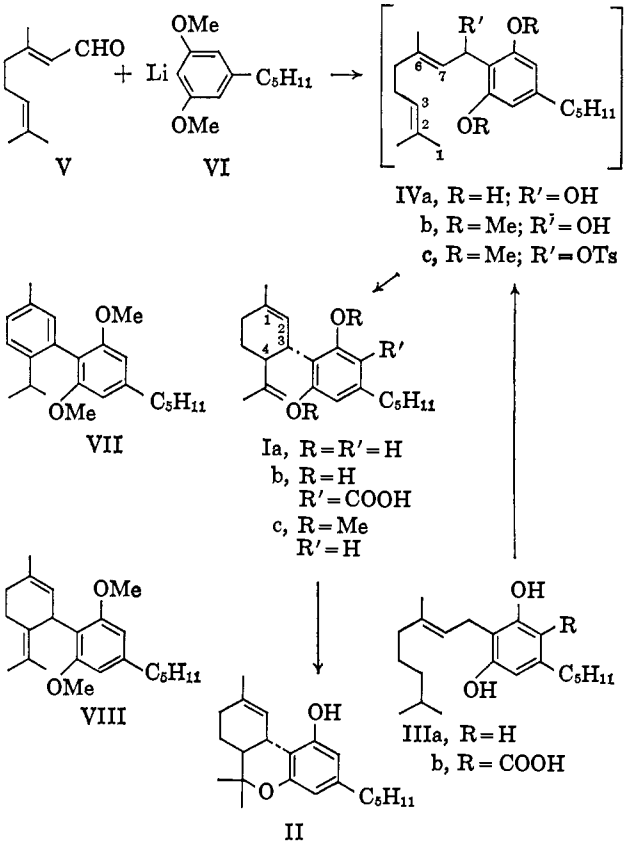
Three additional compounds were obtained with Ic in the silver nitrate–alumina chromatography: VII[2c]; VIII, m.p. 51–52°, mol. wt. 342 (mass spectrum), λ_{max}^{EtOH} 271 (ϵ 1110) and 278 mμ (sh) (ϵ 1020), δ 0.9 (t) (paraffinic methyl group), 1.35 and 1.65 (three olefinic methyl groups), 3.68 (s) (two OCH_3 groups), 4.55 (br) (C-3 proton), 5.05 (br) (C-2 proton), 6.18 (s) (aromatic protons), $C_{23}H_{34}O_2$ (*Anal.* Found: C, 80.76; H, 9.91); and *dl*-Ic (3,4-*cis* isomer), $C_{23}H_{34}O_2$ (*Anal.* Found: C, 80.72; H, 9.98). The ultraviolet spectrum of Ib *cis* is identical with that of the *trans* isomer; the infrared spectra are very similar but not superimposable. The n.m.r. spectra are also remarkably similar; however, in the *cis* isomer one of the olefinic methyl groups is at δ 1.42, the methoxy methyl groups are at 3.60, and the C-2 proton is at 5.2.

In the cyclization step (IV → I) of the synthetic route, and probably in the biogenetic one too, a *trans–cis* isomerization of the Δ^6-double bond in IV takes place, although formally this bond does not participate in the reaction. It seems possible that the geranyl derivative (IVc in the synthetic process) can isomerize through internal return[13] to the linalyl tosylate derivative (IX), which then can undergo cyclization. The



IX

formation of VIII, however, excludes the interesting possibility of a fully concerted reaction.[14]



Acknowledgments. We are indebted to Professors E. Wenkert and G. Ourisson for stimulating discussions

(2) A number of syntheses leading to isomers of these natural products have been reported: (a) R. Ghosh, A. R. Todd, and S. Wilkinson, *J. Chem. Soc.*, 1393 (1940); (b) R. Adams and B. R. Baker, *J. Am. Chem. Soc.*, 62, 2405 (1940); (c) F. Korte and H. Sieper, Abstracts of Papers, IUPAC Symposium on Natural Products, Kyoto, 1964, p. 292; *Ann.*, in press (private communication); see also (d) E. C. Taylor and E. J. Strojny, *J. Am. Chem. Soc.*, 82, 5198 (1960); (e) F. W. Hively, Thesis, University of Delaware, 1962.

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

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

(5) The route followed was patterned along a suggested biogenetic one. It is generally believed[6-8] that tetrahydrocannabinol (II) is formed in nature from geranyl pyrophosphate through cannabigerol[7] (IIIa) and cannabidiol (Ia). The cyclization of IIIa to Ia can be assumed to involve an intermediate in a state of oxidation higher than that of IIIa (for example, IVa). It is possible, however, that the biogenesis proceeds in a similar fashion through cannabigerolic acid (IIIb) and cannabidiolic acid (Ib) with decarboxylation: O. E. Schultz and G. Haffner, *Arch. Pharm.*, 293, 1 (1960); R. Mechoulam and Y. Gaoni, *Tetrahedron*, 21, 1223 (1965).

(6) W. B. Whalley in "Chemistry of Natural Phenolic Compounds," W. D. Ollis, Ed., Pergamon Press, Inc., New York, N. Y., 1961, p. 39.

(7) Y. Gaoni and R. Mechoulam, *Proc. Chem. Soc.*, 82 (1964).

(8) J. H. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes and Acetogenins," W. A. Benjamin, Inc., New York, N. Y., 1964, p. 71.

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

(10) R. Adams, M. Hunt, and J. H. Clark, *ibid.*, 62, 196 (1940).

(11) Determined on a Varian A-60 spectrometer in CCl_4; values are given in p.p.m. relative to $(CH_3)_4Si$ as internal standard. Letters denote broad (br), singlet (s), triplet (t).

(12) For a review of this useful but neglected reaction see H. Meerwein in "Houben-Weyl, Methoden der Organische Chemie," Vol. VI, E. Müller, Ed., George Thieme Verlag, Stuttgart, 1964, p. 160. This reaction was brought to our attention by Professor G. Ourisson in whose laboratory dimethoxyresorcinol derivatives have been thus demethylated (private communication).

(13) W. G. Young, S. Winstein, and H. L. Goering, *J. Am. Chem. Soc.*, 73, 1958 (1951).

(14) *p*-Toluenesulfonyl chloride in pyridine does not isomerize Ic, or its 3,4-*cis* isomer, to VIII. This observation rules out the possibility of a concerted reaction followed by double bond migration.

and to Dr. N. Danieli for the mass spectra.

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Sativene, Parent of the Toxin from *Helminthosporium sativum*

Sir:

We have previously reported on the isolation and constitution of helminthosporal (**1**),[1,2] the toxin responsible for widespread destruction and losses of cereal crops.[3] In Western Canada this has amounted to 3–13% of the wheat crop over the last 25 years.[4] The suggestion was made that helminthosporal, itself not a direct farnesyl pyrophosphate cyclization product, might be derived by oxidative cleavage of a carbon–carbon bond in a hypothetical precursor, sativene (**2**), with an as yet unencountered carbon skeleton. Evidence was provided from labeling experiments to justify this.[5]

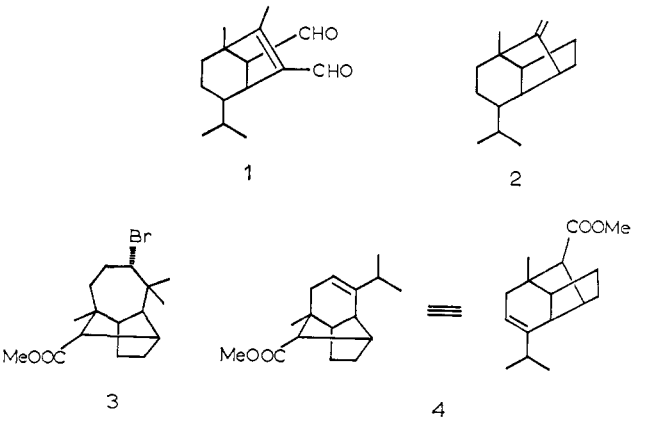
A search among the oxygenated compounds produced by the mold has not yet revealed the presence of any substance with an intact sativane skeleton, although more immediate precursors, such as prehelminthosporol, have been identified.[6] Attention was then given to the very small hydrocarbon fraction accompanying this oxygenated material.

Separation by gas–liquid chromatography gave a homogeneous substance in the yield of 0.5 mg./l. of culture fluid. This compound, $[\alpha]D$ $-186 \pm 3°$[7] (*Anal.* Found: C, 88.68; H, 11.67; mol. wt., 204[7]), showed absorption at 3060, 1660, and 885 $cm.^{-1}$ (CCl_4), compatible with an exocyclic methylene group. This interpretation was confirmed by the n.m.r. spectrum (τ 5.60 and 5.28; 2 H) which also showed signals at 9.13 (3 H, d, $J \sim 5$ c.p.s.), 9.10 (3 H, d, $J \sim 5$ c.p.s.), and 8.95 (3 H, s) These additional bands suggested the presence of a methyl attached to quaternary carbon, and of an isopropyl group. The derived diol (OsO_4), m.p. 63–64°, $[\alpha]D$ $-68°$ (*Anal.* Found: C, 74.88; H, 10.72; mol. wt. 238[7]), showed no absorption above 200 mμ in the ultraviolet, requiring the presence of but one double bond in the original hydrocarbon, and periodate cleavage of the diol gave material absorbing at 1740 $cm.^{-1}$.

The sum of the available evidence was thus compatible, but merely compatible, with structure **2**. Too little material remained for further, degradative, studies to be considered.

Recently the conversion of longifolene into the bromo ester **3** was reported, together with its ring contraction, under the influence of silver ion to isopropyl derivatives including **4**.[8,9] We have prepared **3**: on distillation from iron powder at 180° (0.2 mm.) **4** is obtained (45%). Hydrogenation gave the saturated methyl ester reduced with lithium aluminum hydride to the alcohol, $[\alpha]D$ $+77°$ (*Anal.* Found: C, 81.49; H, 11.28); α-naphthylurethan, m.p. 105–106° (*Anal.* Found: C, 80.38; H, 8.63; N, 4.26). The alcohol was acetylated and pyrolyzed in the vapor phase at 550°[11] to give (+)-sativene, $[\alpha]D$ $+191 \pm 3°$, identical in infrared spectrum (CCl_4) and n.m.r. spectrum with the natural hydrocarbon. It was converted into the diol, m.p. 63–64°, $[\alpha]D$ $+68°$, enantiomeric with the diol from the naturally occurring hydrocarbon.

This partial synthesis[12] establishes unequivocally the nature of the natural hydrocarbon isolated from the culture fluid. Its production by the mold adds significant credibility to the biosynthetic scheme suggested for these substances,[5] though it does not require that the specific hydrocarbon itself be the progenitor of the toxins.[16]



(1) Terpenoids: Part XI.
(2) P. de Mayo, E. Y. Spencer, and R. W. White, *Can. J. Chem.*, **39**, 1608 (1961); **41**, 2996 (1963).
(3) R. A. Ludwig, *Can. J. Botany*, **35**, 291 (1957).
(4) B. J. Sallans, *Can. Plant Disease Survey*, **38**, 11 (1958).
(5) P. de Mayo, R. Robinson, E. Y. Spencer, and R. W. White, *Experientia*, **18**, 359 (1962).
(6) P. de Mayo, E. Y. Spencer, and R. E. Williams, *Can. J. Chem.*, **43**, 1357 (1965).
(7) Rotations were determined in chloroform. Molecular weights (mass spectrum) were determined by N. S. McIntyre and R. Ryhage.
(8) G. Ourisson, Simonsen Lecture, *Proc. Chem. Soc.*, 274 (1964).
(9) We wish to express our most sincere thanks to Professor Ourisson (Strasbourg) for making experimental data[10] available to us prior to publication, and for his generous scientific good will.
(10) D. Helmlinger, Thesis, University of Strasbourg, 1964.
(11) See, for example, D. H. R. Barton and P. de Mayo, *J. Chem. Soc.*, 887 (1953).
(12) Formally, in view of the synthesis of longifolene,[13] this represents the final stages of a total synthesis. Also, since the absolute stereochemistry of longifolene is known,[14] this confirms the absolute stereochemistry of helminthosporal (**1**), established by Corey and Nozoe.[15]
(13) E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *J. Am. Chem. Soc.*, **86**, 478 (1964).
(14) G. Ourisson, *Bull. soc. chim. France*, **22**, 895 (1955).
(15) E. J. Corey and S. Nozoe, *J. Am. Chem. Soc.*, **85**, 3527 (1963).
(16) The authors are glad to acknowledge support for this work under Grant No. EF-00419-01 from the National Institutes of Health.
(17) Holder of a National Research Council of Canada Scholarship.

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Received May 24, 1965

Organic Syntheses by Means of Noble Metal Compounds. XII.[1] Reaction of the Cyclooctadiene–Palladium Chloride Complex with Ethyl Malonate

Sir:

It is known that a nucleophilic attack of a hydroxide anion on the ethylene–palladium chloride complex gives acetaldehyde.[2] The reactions of other nucleo-

(1) Part XI: J. Tsuji and S. Hosaka, *J. Polymer Sci.*, in press.
(2) J. Smidt, *Angew. Chem.*, **74**, 93 (1962).