butadiene (two parts).[13] At 354° and higher conversion, the same products are formed in the ratios 7:4:2, while at 404° phenylbutadiene is no longer observed and naphthalene and 1,4-dihydronaphthalene appear at the expense of 9,10-dihydronaphthalene.

Since both molecules give rise to II, I and III may be placed on interconnected energy surfaces. Whether they are also interrelated through the attractive hypothetical common precursor, V, which can hypothetically lead to II by cleavage of carbon–carbon bonds 5,7 and 2,10, is not known.[14] Specifically, the thermal reorganization of I to II may involve VI (tricyclo-[5.3.0.0^{4,8}]deca-2,5,9-triene) as an intermediate. VI could suffer cleavage of carbon–carbon bonds 4,8 and 1,7 and thence proceed to II by way of cyclodecapentaene. VI might arise from I by a vinylcyclopropane type of rearrangement in analogy to

IV V VI

the thermal reorganization at 305° of homotropilidene to bicyclo[3.3.0]octa-2,6-diene.[15]

Ultraviolet irradiation of 9,10-dihydronaphthalene, reported by van Tamelen and Pappas[5] to lead "in ether to a distillable product mixture possessing only end absorption in the ultraviolet spectrum," leads under somewhat different conditions (irradiation in degassed pentane for 15 hr at 0° with a 2.5-w low-pressure mercury lamp) to a mixture of four products which were separated by glpc (2 m, 2.5% 20M Carbowax on 50/60 Anakrom column at 80°). The most striking product was identified by infrared spectrum as bullvalene. A second product is naphthalene. The other two are under investigation, but are not identical with the photoisomer of bullvalene isolated by Jones.[16] Coupled with the thermal rearrangement of Nenitzescu's hydrocarbon, III, this phototransformation of II represents the successful synthesis of bullvalene from III and a second path for the conversion of cyclooctatetraene to bullvalene.[3]

The theoretical considerations of Hoffmann and Woodward[17] permit the concerted photochemical transformation of 9,10-dihydronaphthalene to tetracyclo[4.4.0.0^{5,7}.0^{2,10}]deca-3,8-diene (V) which thus becomes an attractive focus of mechanistic speculation. We prefer to defer further discussion of the mechanisms of both the thermal and photochemical transformations until current experiments have been completed.

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(13) I. E. Muskat and M. Herrman, *J. Am. Chem. Soc.*, **53**, 252 (1931).

(14) This scheme has been proposed by Schröder as a partial rationalization of the formation of naphthalene from bullvalene and, in related form, as a rationalization of the conversion of cyclooctatetraene to the 76° dimer.[3]

(15) W. von E. Doering and W. R. Roth, *Tetrahedron*, **19**, 715 (1963).

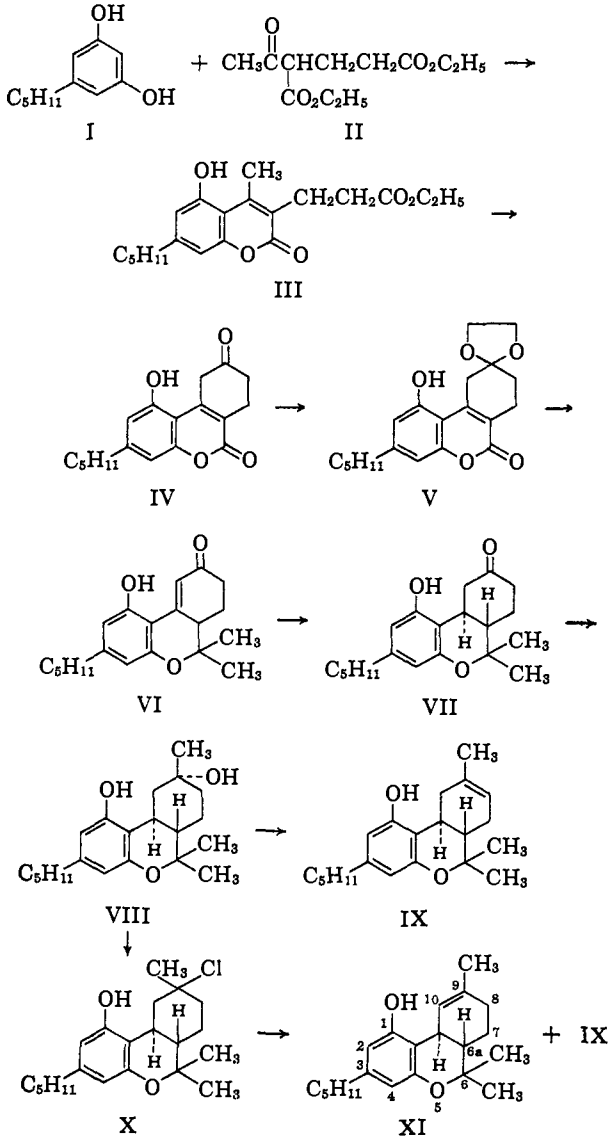
(16) M. Jones, Jr., private communication.

(17) R. Hoffmann and R. B. Woodward, *J. Am. Chem. Soc.*, **87**, 2046 (1965).

Total Synthesis of *dl*-Δ^9-Tetrahydrocannabinol and of *dl*-Δ^8-Tetrahydrocannabinol, Racemates of Active Constituents of Marihuana

Sir:

The crude resin (marihuana, hashish) obtained from the female flowering tops of different *Cannabis sativa* L. varieties has long been known to possess psychotomimetic activity. The major active constituent of this resin has recently been shown to be *l*-Δ^9-tetrahydrocannabinol (XI),[1,2] and a total synthesis of *dl*-XI has



I II III IV V VI VII VIII IX X XI + IX

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

(2) Compound XI has been called Δ^1-tetrahydrocannabinol by other workers. However, we feel the numbering system used here is preferable, conforming to the *Chemical Abstracts* nomenclature of dibenzo[*b*,*d*]pyran compounds.

been reported.[3] Recently another physiologically active component of the resin has been isolated and shown to be *l*-Δ^8-tetrahydrocannabinol (IX)[4] and a total synthesis of the racemic modification of this material has also been reported.[5] These syntheses require a separation of isomers either by vapor phase chromatography[5] or repeated column chromatography.[3] This communication describes a convenient total synthesis and isolation of the racemic modification of these two active compounds.

Thus, the von Pechmann condensation of olivetol (I) and diethyl α-acetoglutarate (II) in the presence of phosphorus oxychloride gave the coumarin III, mp 123–124°,[6,7] in 74% yield. Cyclization of III with sodium hydride in dimethyl sulfoxide at 15–20° gave a 60% yield of IV, mp 205.5–207.5°. The latter compound was converted (94%) to the ketal V isolated as two polymorphs, mp 114.5–116° and 145–148°. Treatment of V with methylmagnesium iodide followed by acid hydrolysis gave VI, mp 198–199°, in 66% yield. Reduction of VI with lithium in liquid ammonia at Dry Ice temperature afforded a 59% yield of the *trans* ketone VII, also isolated as two polymorphs, mp 148–150° and 163–165°.[8] Conversion of VII to its tetrahydropyranyl ether followed by treatment with methylmagnesium iodide and subsequent removal of the protecting group gave a 37% yield of the carbinol VIII, mp 162–163°.[9] Dehydration of VIII with a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene gave a 90% yield of *dl*-Δ^8-tetrahydrocannabinol (IX) as a viscous oil. This material was a single isomer as shown by glpc, and its nmr spectrum[11] (olefinic H-8 proton signal in $CDCl_3$ at 5.40 and in CCl_4 at 5.33) was identical with that reported[5] for IX.

Treatment of an acetic acid solution of the alcohol VIII with Lucas reagent afforded a 60% yield of X, mp 87–90°.[12] Dehydrochlorination of X with sodium hydride in refluxing tetrahydrofuran gave in quantitative yield a mixture containing 74% of XI and 26% of IX as shown by glpc.[13] This mixture was treated with *m*-nitrobenzenesulfonyl chloride to give the *m*-nitrobenzenesulfonate of XI, mp 105.5–107.5°, in 23% yield. Mild basic hydrolysis of the latter compound then gave an 84% yield of *dl*-Δ^9-tetrahydrocannabinol (XI), mp (vac) 64.5–65.5°[14] (no detectable impurities by glpc), with spectra (nmr olefinic H-10 proton signal in $CDCl_3$ and in CCl_4 at 6.30) identical with those of natural *l*-Δ^9-tetrahydrocannabinol.[15]

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(3) R. Mechoulam and Y. Gaoni, *J. Am. Chem. Soc.*, 87, 3273 (1965).

(4) R. Hively, F. Hoffmann, and W. A. Mosher; see footnote 4 in ref 5.

(5) E. C. Taylor, K. Lenard, and Y. Shvo, *J. Am. Chem. Soc.*, 88, 367 (1966).

(6) All compounds prepared in the course of this work have satisfactory elemental analytical data, and have infrared, ultraviolet, and nmr spectra compatible with the assigned structures.

(7) The structure proof of III, which precludes the other possible coumarin or the two possible chromones, will be given in the full paper.

(8) The proof of *trans* ring fusion in VII will be given in the full paper.

(9) The axial configuration of the hydroxyl group in VIII is supported by the facile acidic dehydration to give IX. An equatorial hydroxyl group would be expected[10] to give the exocyclic olefin. We have prepared the exocyclic olefin by another method and have shown that it does not isomerize under the dehydration conditions.

(10) C. E. Cook, R. C. Corley, and M. E. Wall, *Tetrahedron Letters*, 891 (1965).

(11) Determined on a Varian A-60 spectrometer; values given in ppm relative to TMS as internal standard.

(12) The over-all yield of X from VII could be raised to 60% by allowing the Lucas reagent to react directly with the crude product of the reaction of VII with the Grignard reagent.

(13) Column, 0.5% NPGS and 0.5% PEG4000MS on Anakrom ABS 60/70 mesh; gas, nitrogen 100 ml/min; column temperature, 220°; retention time of XI, 20 min; retention time of IX, 18 min.

(14) Previously obtained as an oil.[3]

(15) We are indebted to Dr. Nathan B. Eddy of the Department of Health, Education and Welfare for a sample of *l*-Δ^9-tetrahydrocannabinol of natural origin.

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Book Reviews

Histones and Other Nuclear Proteins. By HARRIS BUSCH, Department of Pharmacology, Baylor University College of Medicine, Houston, Texas. Academic Press Inc., 111 Fifth Ave., New York, N. Y. 1965. 266 pp. 16 × 23.5 cm. $9.50.

The introductory chapter contains a number of rather poorly integrated topics including a classification of nuclear proteins, the role of proteins in control of the genome, history of the nuclear proteins, composition of spermatazoa, and material on protamines, histones, and acidic proteins and enzymes of the nucleus. From the standpoint of the reviewer, the historical presentation is not very comprehensive.

Chapter I on the protamines contains historical material, material on protamine isolation, something on analysis and structure of protamines, and finally a section on function of the protamines which, however, contains very little material pertaining directly to protamine function. This chapter seems weak in respect to factual material.

Chapters II through VII constitute the major part of the material on the histones and the best part of the book. Here the work appears to have been painstakingly and thoroughly done, and the reader can obtain an excellent picture of modern work on the histones, both from the standpoint of experimentation and the development of general ideas as to the role of the histones. The work on the nucleohistones edited by Bonner and Ts'o (Holden Day Inc., San Francisco, 1964) should, however, be consulted for certain more recent material not included in the book of Busch. The topics covered in Chapters II through VII include the following topics concerning the histones: composition and number, isolation, fractionation, the role in chromosomal structure, function, sequential amino acid analysis, and metabolism. Something on the isolation of cell nuclei is also included to serve as a basis for mate-