yellow "zero-valent" complex **2**, R = allyl, in a trap cooled by liquid nitrogen.[3] Even higher yields (>80%) of this product can be obtained by the addition in portions of triethylenetetramine to the solutions of **1** and nickel bromide during the disproportionation reaction. Confirmation of the bis(π-allyl) structure **2** for the volatile substance was obtained from the mass spectrum[4] and from the comparison of its nmr[5,6] spectrum with that of **2** derived from the reaction of allylmagnesium halide with nickel(II) halide.[1] The yellow "zero-valent" complex **2**, R = methallyl, was similarly obtained from **1**, R = methallyl, and identified by its mass[7] and nmr[6,8] spectra and also by its chemical properties, including (1) conversion to methallyl iodide with excess I_2, (2) reaction with nickel bromide to form **1**, R = methallyl, and (3) reaction with allyl bromide in dimethylformamide to give a mixture of biallyl, allylmethallyl, and bimethallyl by allylic coupling.[2]

The extension of this technique for the conversion of π-allylnickel(I) complexes of type **1** to bis(π-allyl)nickel(0) complexes is clearly limited by the requirement that the latter possess substantial volatility and therefore low molecular weight. The medium used is also critical. For example, only small amounts of **2**, R = allyl or methallyl, can be distilled from solutions of **1** in tetraglyme, presumably because the equilibrium is less favorable to disproportionation in that medium.[9] The transformation **1** → **2** can be achieved much more generally by the use of a suitable reducing agent, *e.g.*, zinc–copper couple. The allyl and methallyl complexes **2** can be obtained in >90% yield by reaction with an excess of zinc–copper couple[10] (granules) at 25° in hexamethylphosphoric amide or dimethylformamide at 0.01 mm by collection of the volatile product in a liquid nitrogen cooled trap. The nonvolatile bis(π-allyl)nickel complexes **3–5** have been obtained (in yields of 60–80%) simply by reduction of the corresponding π-allylnickel(I) complexes using zinc–copper couple under 1 atm of argon and isolation by extraction with pentane after addition of a small amount of water.[11]

The complexes **3–5** were characterized by their chemical properties, including protonation to R–H with *p*-toluenesulfonic acid and allylic coupling *via* R–I to R–R using 1 equiv of I_2, and by their reaction with CO which produced R–R from **3** and mixtures of R–R and RCOR from **4** and **5**.

π-R_2Ni

3, R = $CH_2{=}C(COOC_2H_5){-}CH_2$

4, R = $(CH_3)_2C{=}CH{-}CH_2$

5, R = 

The formation of nickel(0) complexes by reduction of π-allylnickel(I) halide complexes with zinc is apparently the result of the direct interaction of zinc with the nickel(I) complexes rather than the displacement of equilibrium 1 by reduction of nickel bromide by zinc. We have been able to demonstrate that nickel bromide is not reduced by zinc–copper couple in dimethylformamide under the conditions which allow the conversion of nickel(I) to nickel(0) complexes.

The synthetic route to bis(π-allyl)nickel derivatives by the reduction of π-allylnickel(I) halide complexes is more convenient than the method[1] based on the reaction of an allylic Grignard reagent with a nickel halide and also allows the synthesis of complexes such as **3** which contain functional groups that would interfere with the Grignard synthesis. The intermediate π-allylnickel(I) complexes are easily obtained in high yield from the reaction of nickel carbonyl with an allylic halide.[12–14]

(3) Some solvent codistils with **2**, the amount being smallest with hexamethylphosphoric amide, the least volatile of these solvents. Solvent-free **2** can be obtained by a redistillation of the product obtained using hexamethylphosphoric amide.

(4) See G. Wilke and B. Bogdanović, *Angew. Chem.*, 73, 756 (1961).

(5) J. K. Becconsall, B. E. Job, and S. O'Brien, *J. Chem. Soc.*, 423 (1967).

(6) H. Bönnemann, B. Bogdanović, and G. Wilke, *Angew. Chem. Intern. Ed. Engl.*, 6, 804 (1967), report that solutions of bis(π-allyl)nickel contain two geometrical isomers in the ratio 3:1. In the present work a 2.5:1 ratio of these forms was found by nmr analysis in benzene as solvent.

(7) The mass spectra of the complexes **2**, R = allyl, and **2**, R = methallyl, show molecular ion peaks corresponding to ^{58}Ni and ^{60}Ni isotopes in a ratio 2.5:1 as well as fragments corresponding to RNi^+, $RNiH^+$, and $(RR - H)^+$.

(8) Two isomeric forms of **2**, R = methallyl, in the ratio 2.1:1 (in C_6H_6) were indicated by the nmr spectrum (*cf.* previously reported[6] ratio of 2.3:1).

(9) The most critical solvent interaction in controlling the position of equilibrium 1 is likely the coordination and solvation of nickel(II) bromide.

(10) E. Le Goff, *J. Org. Chem.*, 29, 2048 (1964).

(11) Because of the extreme sensitivity of the bis(π-allyl)nickel complexes to oxygen, air must be rigorously excluded during these experimental operations.

(12) E. J. Corey and M. F. Semmelhack, *J. Am. Chem. Soc.*, 89, 2755 (1967).

(13) In connection with the role of bis(π-allyl)nickel compounds in allylic coupling reactions it has been observed that, although facile coupling occurs with allylic halides,[2] the reaction with *nonallylic* halides[12] such as iodobenzene or cyclohexyl iodide is much slower with the zero-valent complexes **2** than with the nickel(I) complexes **1**.

(14) This work was supported by the National Science Foundation and the National Institutes of Health.

E. J. Corey, L. S. Hegedus, M. F. Semmelhack
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138
Received December 20, 1967

Stereoelectronic Factor in the Chloranil Dehydrogenation of Cannabinoids. Total Synthesis of *dl*-Cannabichromene[1,2]

Sir:

We wish to present evidence suggesting that the dehydrogenation of hydroaromatic compounds by chloranil can be added to the list of reactions in which stereoelectronic factors have been found to influence the course, stereochemistry, and rate. Among these are enolization, protonation and bromination of enols,[4] bimolecular eliminations,[5] oxidation of allylic alcohols by manganese dioxide,[6] dichlorodicyanoquinone,[7] and

(1) Hashish. XII. For part XI see R. Mechoulam, P. Braun, and Y. Gaoni, *J. Am. Chem. Soc.*, 89, 4552 (1967).

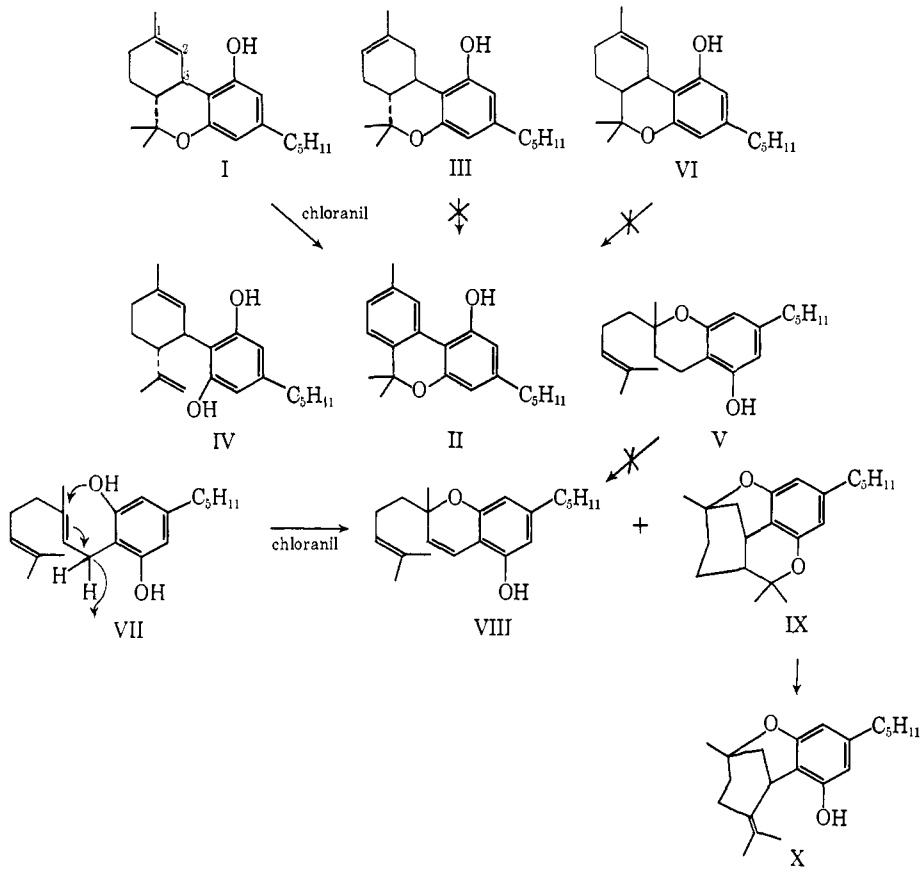
(2) The term *cannabinoids* has been proposed[3] for the group of C_{21} compounds typical of and present in *Cannabis sativa* L., as well as for their analogs and transformation products.

(3) R. Mechoulam and Y. Gaoni, *Fortschr. Chem. Organ. Naturstoffe*, 25, 175 (1967).

(4) For example, E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, 78, 6269 (1956), and earlier papers; R. Villotti, H. J. Ringold, and C. Djerassi, *ibid.*, 82, 5693 (1960); S. K. Malhotra and H. J. Ringold, *ibid.*, 86, 1997 (1964); *cf.* G. Stork and S. D. Darling, *ibid.*, 86, 1761 (1964).

(5) For a recent summary see E. L. Eliel, N. L. Allinger, S. T. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, Inc., New York, N. Y., 1965, p 291.

(6) A. Nickon and J. F. Bagli, *J. Am. Chem. Soc.*, 83, 1498 (1961); G. Stork, *Alkaloids*, 6, 223 (1960).



chromic acid,[8] dichlorodicyanoquinone dehydrogenation of ketones,[9] etc.

Δ^1-3,4-*trans*-Tetrahydrocannabinol (Δ^1-THC) (I)[10] is converted into cannabinol (II) in 90% yield on boiling with chloranil in benzene for 2 hr while $\Delta^{1(6)}$-THC (III)[11] and Δ^1-3,4-*cis*-THC (VI)[12a] remain almost unchanged under identical experimental conditions for up to 20 hr. The same applies also to cannabidiol (IV),[13] which does not yield the corresponding biphenyl derivative, and to the chroman V,[14] which is not converted into VIII.[15]

Braude, Linstead, and Jackman have shown that quinone dehydrogenation of hydroaromatic compounds is a two-step reaction proceeding through a cationic intermediate.[16] On this basis we assume that the difference in reactivity between Δ^1-THC (I), $\Delta^{1(6)}$-THC (III), and V is due to the absence of allylic activation on the benzylic hydrogens in III and V. The difference among I, IV, and VI is more subtle. In I, the pseudo-axial C_3–H is essentially perpendicular to the planes of both the aromatic ring and the double bond, while in IV it is nearly perpendicular to the plane of the double bond only and is nearly parallel to the plane of the aromatic ring. These conformations have been deduced from nmr analysis.[10,13] In I, the C_3–H, during abstraction as hydride, will remain in constant overlap with the π electrons of both unsaturated systems, thus lowering the energy of the transition state. In IV, overlap is possible with the π electrons of the double bond only. The same factors are probably involved in the nonreactivity of VI. The C_2–H in the preferred[17a,c] conformation of VI is at a dihedral angle of *ca.* 35° with the C_3–H[17] and hence σ–π overlap in the transition state is limited to the phenolic ring only, with which C_3–H forms an angle of *ca.* 80°.[17a,c] The observed differences in reactivity are not due to steric hindrance. Cannabigerol (VII) is dehydrogenated with chloranil in benzene at a lower rate than is I,[18] though in any reasonable conformation at least one of the two allylic-benzylic hydrogens in VII is subject to less hindrance than the C_3–H in I. The lower rate is probably due to the tendency of the double bond to be slightly out of the plane of the aromatic ring.[17a] This leads to less overlap with the leaving hydride during the dehydrogenation.

The products of the dehydrogenation of VII are *dl*-cannabichromene (VIII)[19] (in 45% yield) and the

(7) S. H. Burstein and H. J. Ringold, *J. Am. Chem. Soc.*, **86**, 4952 (1964).

(8) S. H. Burstein and H. J. Ringold, *ibid.*, **89**, 4722 (1967).

(9) H. J. Ringold and A. Turner, *Chem. Ind.* (London), 211 (1962); H. J. Ringold, M. Gut, M. Hayano, and A. Turner, *Tetrahedron Letters*, 835 (1962).

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

(11) Y. Gaoni and R. Mechoulam, *Tetrahedron*, **22**, 1481 (1966); R. L. Hively, W. A. Mosher, and F. W. Hoffmann, *J. Am. Chem. Soc.*, **88**, 1832 (1966).

(12) (a) E. C. Taylor, K. Lenard, and Y. Shvo, *ibid.*, **88**, 367 (1966); (b) Y. Gaoni and R. Mechoulam, *ibid.*, **88**, 5673 (1966).

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

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

(15) In all cases 5–10% of unidentified products which seem to be due to phenolic oxidation were formed.

(16) L. M. Jackman, *Advan. Org. Chem.*, **2**, 329 (1960); E. A. Braude, L. M. Jackman, R. P. Linstead, and G. Lowe, *J. Chem. Soc.*, 3133 (1960); R. F. Brown and L. M. Jackman, *ibid.*, 3144 (1960), and earlier references therein.

(17) (a) By empirical measurements from Dreiding models. *Cf.* also (b) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, 77, 2505 (1955), for a vector analysis of cyclohexene, leading to $\theta = 37°$ for the corresponding angle. (c) F. Johnson and S. K. Malhotra, *ibid.*, **87**, 5492 (1965).

(18) The period of half-life of I in this reaction is 30 min, while that of VII is 8 hr.

(19) (a) Y. Gaoni and R. Mechoulam, *Chem. Commun.*, 20 (1966); (b) U. Claussen, F. V. Spulak, and F. Korte, *Tetrahedron*, **22**, 1477

tetracyclic diether IX (in 15% yield). This represents the first total synthesis of cannabichromene (in its racemic form). *dl*-Cannabichromene thus obtained is, except for optical rotation, identical with the natural product:[20] it has the same infrared, nmr, and mass spectra, the same R_f (on thin layer chromatography), and the same retention time on vapor phase chromatography. It gives a 3,5-dinitrophenylurethan, mp 106–107°, which does not depress the melting point of the same derivative of natural cannabichromene, mp 106–107°.

Structure IX for the compound formed together with cannabichromene is put forward on the following grounds: (a) mol wt 314 (by mass spectrum); (b) four methyl groups (by nmr), one of which is the terminal methyl group on the side chain, while the others (at δ 0.94, 1.30, and 1.40) are in the region normally associated in this series with methyls on a saturated carbon atom or α to an oxygen atom, but not on a double bond; (c) no olefinic protons; two aromatic protons (at δ 6.13) which appear essentially as a singlet, indicating a similarity in the environment of the aromatic protons; (d) no hydroxylic bands in the infrared, strong etheric bands at 1060 and 1120 cm^{-1}; (e) conversion into $\Delta^{4(8)}$-isotetrahydrocannabinol (X)[12] on boiling with *p*-toluenesulfonic acid in benzene.

Acknowledgments. We are grateful to the National Institutes of Health (Grant MH-13180) for partial support of this work. We thank Dr. A. Pohland of Ely Lilly Research Laboratories, Indianapolis, Ind., for a helpful suggestion, Drs. H. Edery and Y. Grunfeld of the Institute for Biological Research, Ness Ziona, Israel, for the biological tests, and Miss Ilana Ramati for skillful technical help.

(1966); (c) I. M. Campbell, C. H. Calzadilla, and N. J. McCorkindale, *Tetrahedron Letters*, 5107 (1966).

(20) Synthetic *dl*-cannabichromene shows no activity in the dog ataxia or monkey behavioral tests in doses up to 10 mg/kg. These observations are in accord with the negative results reported for natural cannabichromene in humans.[21] The positive dog ataxia test previously observed by us[19a] was probably due to impurities in the natural material, which was available in minute amounts.

(21) H. Isbel, C. W. Gorodetzsky, D. Yasinsky, U. Claussen, F. von Spulak, and F. Korte, *Psychopharmacologia*, 11, 184 (1967).

Raphael Mechoulam, Boris Yagnitinsky
Laboratory of Natural Products, School of Pharmacy
Hebrew University, Jerusalem, Israel

Yehiel Gaoni
Department of Chemistry
The Weizmann Institute of Science
Rehovoth, Israel

Received January 26, 1968

Stereospecifically Labeled $\Delta^{1(6)}$-Tetrahydrocannabinol

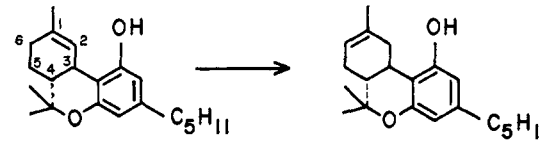
Sir:

The widespread use of marijuana as a psychotomimetic agent has prompted us to undertake a study of the metabolism of the active principles of this drug. (−)-Δ^1-Tetrahydrocannabinol [(−)-Δ^1-THC] (I) and its isomer (−)-$\Delta^{1(6)}$-THC (II) are believed to be the compounds responsible for both the psychotomimetic and analgetic properties of *Cannabis* resin.[1] We therefore sought a method for introducing a radioisotope into either of these compounds to permit a metabolic study to be made.

Work done by our group[2] and others[3] has shown that I can be readily isomerized to II in the presence of *p*-toluenesulfonic acid in nearly quantitative yield. It was thought that, if catalyst in which the acidic proton had been exchanged with tritium were used, the introduction of isotopic hydrogen at the 2 position could be accomplished.

In order to test the feasibility of this procedure, an isomerization with deuterium-exchanged *p*-toluenesulfonic acid was carried out. A sample of (−)-Δ^1-THC (I, 18 mg) in which the phenolic hydrogen had been exchanged by exposure to excess 99.8% D_2O, was dissolved in dry benzene (50 ml), and deuterated acid (10 mg) was added. The mixture was refluxed for 2 hr, at which time the solution was extracted with 2% Na_2CO_3 solution and the product isolated from the neutral fraction as a red oil. Thin layer chromatography on silica gel in a hexane–acetone system (9:1) yielded 15 mg of (−)-$\Delta^{1(6)}$-THC (II) as a pale yellow oil.

The nmr spectrum[4] of the product showed that the isomerization had taken place under these conditions and that approximately one atom of deuterium had been introduced at position 2. Evidence for the isomerization was observed in the shift of the signal for the olefinic proton from 378 cps in I to 322 cps in II, as



I II

reported previously.[1] The position and stereochemistry of the deuterium was demonstrated by the nature of the signal from the hydrogen at position 3. In the undeuterated compound this appeared as a broad doublet centered at 190 cps. The deuterated sample gave a quartet centered at 193 cps with coupling constants of about 16 and 4.5 cps. The larger coupling constant is assigned to the coupling between the C-3 and C-4 protons which are diaxial. The smaller constant is due to the coupling between C 3 and an equatorial proton at C-2. Therefore, there must be deuterium at the C-2 axial position. This is the expected orientation since the protonation of the double bonds usually proceeds by axial addition.[5]

The isomerization was repeated exactly as above except that tritiated water[6] (specific activity 1.80 Ci/mole) was used instead of deuterated water. The product was again purified by thin layer chromatography and the radiochemical purity demonstrated by paper chromatography on a "Bush A" system. The specific activity of the (−)-$\Delta^{1(6)}$-THC-2-axial-^{3}H thus obtained was deter-

(1) R. Mechoulam and Y. Gaoni, *Fortschr. Chem. Organ. Naturstoffe*, 25, 175 (1967).

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

(3) (a) E. C. Taylor, K. Lenard, and Y. Shvo, *J. Am. Chem. Soc.*, 88, 367 (1966); (b) R. Hively, W. A. Mosher, and F. Hoffman, *ibid.*, 88, 1832 (1966).

(4) The spectra were run on a Varian DP/DA-60 instrument in CCl_4 with $(CH_3)_4Si$ as an internal standard. The authors wish to thank Thomas Wittstruck of the Worcester Foundation for Experimental Biology for aid in interpretation of the spectra.

(5) For a recent example see S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, 87, 3228 (1965).

(6) Purchased from New England Nuclear Corp., Boston, Mass.