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.

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(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).

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

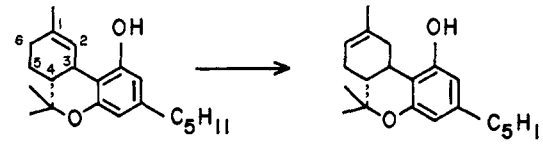
Sir:

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.

mined by measurement of the ultraviolet extinction coefficient at the 282-mμ maximum[1] and liquid scintillation counting[7] of an aliquot. A value of 1.44 Ci/mole was thus obtained, showing that an isotope effect had taken place during one or more of the steps in this conversion.

Experiments are now in progress in our laboratory to demonstrate the metabolic fate of (−)-$\Delta^{1(6)}$-THC in several laboratory animal species. Results thus far indicate that this method of labeling is satisfactory for such studies.

(7) The samples were counted in a Nuclear-Chicago Mark I counter; efficiencies were determined by the channels ratio method.

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Thallium in Organic Synthesis. I. Alkylation and Acylation of β-Dicarbonyl Compounds[1]

Sir:

Monoalkylation at carbon of β-dicarbonyl anions is a superficially prosaic process which, however, often competes with dialkylation at carbon, O-alkylation (formation of enol ethers), β-diketone cleavage, Claisen condensations, and coupling resulting from air oxidation of the enol salts of both the starting β-dicarbonyl compound and its monoalkylation product. As a consequence, careful fractional distillation of the resulting agglomerate (which may also contain unchanged starting material as well) is usually necessary for the isolation of the desired monoalkylation product.

We wish to describe a method for the monoalkylation of β-dicarbonyl compounds which gives the C-alkylated product in essentially quantitative yield under neutral conditions and which avoids *all* of the above-mentioned competitive reactions. The thallium(I) salt of the β-dicarbonyl compound is heated with an excess of an alkyl iodide, the thallium(I) iodide removed by filtration, and the product isolated by simple distillation.[2] Representative examples, reaction conditions, and yields are given in Table I. The products in all cases are vpc pure as isolated.[3]

The requisite thallium(I) salts are readily prepared in a number of ways, the simplest of which we have found to be the addition of thallium(I) ethoxide[4] to a solution of the β-dicarbonyl compound in an inert solvent such as benzene or petroleum ether. The thallium(I) salt crystallizes from the solution almost immediately and is collected by filtration and recrystallized, usually from ethanol. These salts are formed in quantitative yield and are beautifully crystalline, stable, nonhygroscopic, sharp melting solids which may be stored indefinitely. They may alternatively be prepared by the use of thallium(I) hydroxide in aqueous solution (*cf.* ref 3) or by direct exchange of thallium between the β-dicarbonyl compound and cyclopentadienylthallium(I);[5] the reaction is irreversible because of the formation of cyclopentadiene. Since this method avoids even traces of base, it is potentially suitable for the preparation of thallium(I) salts even from extremely base-sensitive substrates.

Table I. Mono-C-alkylation of Thallium(I) Salts of β-Dicarbonyl Compounds

Tl^+ salt of	Yield, % (hr), with CH_3I	CH_3CH_2I	$(CH_3)_2CHI$
Ethyl acetoacetate	100 (4)	100 (4)	91 (15)
Acetylacetone	100 (4)	93 (16)	90 (14)
2-Carbethoxycyclopentanone	100 (9)	100 (9)	96 (12)
Ethyl benzoylacetate	100 (4)	100 (4)	99 (22)
Ethyl 2-methylbenzoylacetate	100 (14)	92 (14)	93 (14)

The resulting monoalkylated β-dicarbonyl compounds may, in turn, be converted to their respective thallium(I) salts which may then be alkylated with a second alkyl halide. Both reactions are again quantitative. A representative example is given in Table I.

The thallium(I) salts of β-dicarbonyl compounds may be acylated as well as alkylated, and this reaction can be controlled to give O- or C-acylation. For example, the thallium(I) salt of acetylacetone upon treatment with acetyl chloride at −78° gives the enol acetate in >90% yield. However, treatment with acetyl fluoride at room temperature gives triacetylmethane in >95% yield. The latter compound may be converted in turn to its thallium(I) salt; alkylation with methyl iodide gives 1,1,1-triacetylethane in >95% yield. This compound may alternatively be prepared by acylation of the thallium(I) salt of 3-methylpentane-2,4-dione with acetyl fluoride.

The experimental conditions for acylations are essentially the same as for the alkylations cited above. The thallium(I) salt is suspended in ether and treated with the appropriate acylating agent. Thallium(I) halide is removed by filtration and the product isolated by simple distillation. Representative examples are given in Table II.

The crystal structure of a representative thallium(I) salt (acetylacetonatothallium(I)) has been determined.[6] It is a 1:1 complex; although one can pick out a discrete molecular unit in which a thallium atom is bonded to the two oxygen atoms of one acetylacetone ligand (Tl–O distances of 2.43 and 2.54 Å),[7] each thallium

(1) We gratefully acknowledge the financial support of this work by the Smith Kline and French Laboratories, Philadelphia, Pa.

(2) Alkyl bromides may also be used, but since they are less reactive than the iodides higher reaction temperatures and/or the use of a catalyst (*e.g.*, triethylamine) may be required, with a resulting small decrease in yield.

(3) Our attention was originally drawn to the possible synthetic potential of this reaction by an observation reported by R. C. Menzies and E. M. Wilkins (*J. Chem. Soc.*, 1151 (1924)) that the thallium(I) salt of ethyl acetonedicarboxylate was "readily soluble in cold ethyl or methyl iodide, thallous iodide being deposited on standing or on heating." Although Menzies later reported (C. M. Fear and R. C. Menzies, *J. Chem. Soc.*, 937 (1926)) apparent C-ethylation of the thallium(I) salt of ethyl acetoacetate in moderate yield, the structure of the product was not established, and the synthetic potential of the method was not recognized.

(4) G. Brauer, Ed., "Handbook of Preparative Inorganic Chemistry," Vol. 1, 2nd ed, Academic Press Inc., New York, N. Y., 1963, p 877.

(5) Methods available for the preparation of cyclopentadienylthallium(I) are summarized in A. N. Nesmeyanov and R. A. Sokolik, "Methods of Elemento-Organic Chemistry. Volume I. The Organic Compounds of Boron, Aluminum, Gallium, Indium and Thallium," The World Publishing Co., New York, N. Y., 1967.

(6) We are indebted to Dr. Ned C. Webb, The Procter and Gamble Co., Cincinnati, Ohio, for the X-ray determination. Full details on this structure will be published independently.

(7) Both ir and nmr spectra confirm O–Tl–O bonding. The complexes show no carbonyl band, but a C=C stretching band appears at 1630–1650 cm^{-1}. A single vinyl C–H signal is observed in all the complexes as a sharp singlet at about τ 4.5.