(s, polymethylene). This material is isomeric with the hydroxyancepsenolide acetate reported earlier.[5g]

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.25; H, 9.24. Found: C, 68.39; H, 9.16.

Dehydration of 2a.—Phosphorous oxychloride–pyridine dehydration of 129 mg of **2a** in the manner described for hydroxyancepsenolide[5g] afforded 96 mg (78%) of ancepsenolide: mp 91.5–94.0° after recrystallization from chloroform–hexane, $[\alpha]^{27}_{589}$ +43.3° (2.98, $CHCl_3$); infrared and nmr spectra for this product were identical with those reported for ancepsenolide;[5f,g] mmp [with an authentic sample of ancepsenolide (mp 89.5–91.5°)] 89.5–92.0°.

Registry No.—**1**, 27261-77-4; **2a**, 27261-78-5; **2b**, 27261-79-6; **3**, 27261-80-9.

Acknowledgments.—We are pleased to acknowledge the use of the collecting facilities of the Port Royal Marine Laboratory of the University of the West Indies, Port Royal, Jamaica. We wish to thank Dr. W. Meyer and Mrs. P. Schroeder, University of Arkansas, and the NIH mass spectral center at Purdue University for providing us with mass spectra.

Notes

The Synthesis of (−)-$\Delta^{9(11)}$-*trans*-Tetrahydrocannabinol

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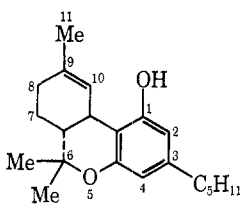
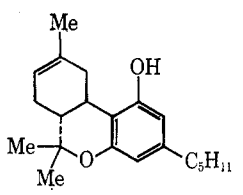
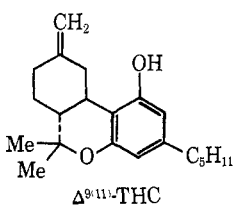
The growing interest in the chemistry and pharmacology of cannabinoids,[1] which include the active constituents of marijuana and hashish, has created a need for new methods of synthetically altering the basic dibenzopyran skeleton. We wish to describe the preparation and properties of $\Delta^{9(11)}$-*trans*-tetrahydrocannabinol ($\Delta^{9(11)}$-THC), which provides a key intermediate for the introduction of new functionalities at either C-9 or C-11.



Δ^9-THC



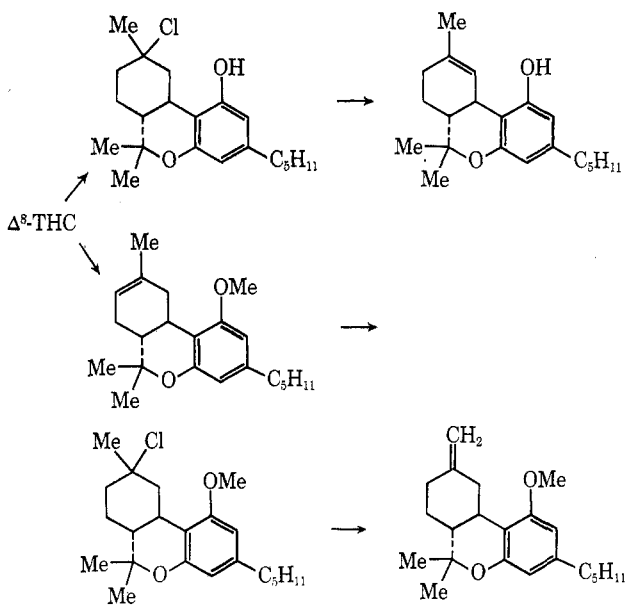
Δ^8-THC



$\Delta^{9(11)}$-THC

Although a total synthesis of racemic $\Delta^{9(11)}$-THC has been reported,[2] for biochemical studies it is desirable to have a ready source of the optically active isomer of the natural configuration. We therefore sought a method for the conversion of the readily available Δ^8 or Δ^9 isomers to $\Delta^{9(11)}$-THC. This contrathermodynamic conversion was accomplished by E2 elimination of the hydrogen chloride adduct of Δ^8- (or Δ^9-) THC (Scheme I), using the sterically hindered base potas-

SCHEME I



sium tricyclopentylcarbinolate, following the procedure recently described by Acharya and Brown.[3] It was first necessary, however, to protect the phenolic hydroxyl group, thus blocking any intramolecularly assisted elimination involving the phenolate anion (Scheme I. This intramolecular process has previously been ingeniously exploited in the conversion of Δ^8- to Δ^9-THC[2,4]).

The methyl ether was selected as a protecting group because of its stability to both the acidic and basic conditions employed in the reaction sequence and was readily obtained[5] in greater than 90% yield. Conversion of the methyl ether to the hydrogen chloride

(1) For a review, see R. Mechoulam and Y. Gaoni, *Fortschr. Chem. Org. Naturst.*, **25**, 175 (1967).

(2) K. E. Fahrenholtz, M. Lurie, and R. W. Kierstead, *J. Amer. Chem. Soc.*, **89**, 5934 (1967).

(3) S. P. Acharya and H. C. Brown, *Chem. Commun.*, 305 (1968).

(4) T. Petrzilka and C. Sikemeier, *Helv. Chim. Acta*, **50**, 1416 (1967).

(5) G. Brieger, D. Hachey, and T. Nestrick, *J. Chem. Eng. Data*, **13**, 581 (1968).

adduct with zinc chloride and hydrogen chloride in chloroform at 0°, followed by refluxing a toluene solution of this product with an excess of potassium tricyclopentylcarbinolate for 12 hr afforded a 65:35 mixture of the methyl ethers of $\Delta^{9(11)}$- and Δ^{8}-THC, plus a trace of the Δ^{9} isomer. Elution from silver nitrate–silica gel with a benzene–hexane mixture provided quantitative separation, the more strongly adsorbed $\Delta^{9(11)}$ isomer being isolated in approximately 45% overall yield.

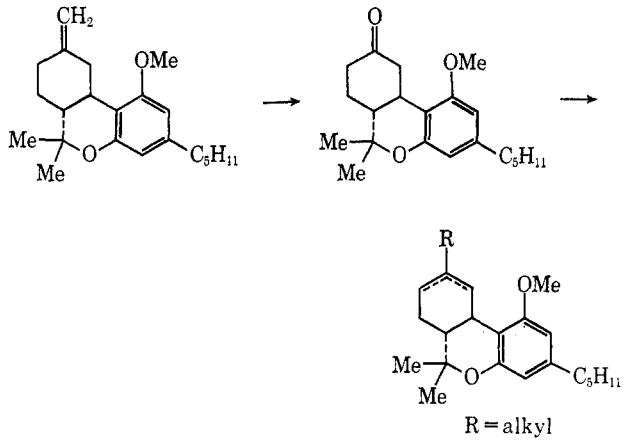
A number of reagents have been described which conceivably might be used for the final conversion of the methyl ether to the free phenol. Excluding acidic reagents (*e.g.*, boron tribromide) which would obviously cause double bond migration, lithium iodide,[6] pyridine hydrochloride,[7] methylmagnesium iodide,[8] and potassium hydroxide (in diethylene glycol) were examined. Surprisingly, with all of these reagents isomerization of the $\Delta^{9(11)}$ double bond to the Δ^{8} and Δ^{9} positions was competitive with demethylation. However, demethylation with only *ca.* 10% isomerization was successfully accomplished using potassium thiophenoxide in diethylene glycol. Thiophenoxide has commonly been used to affect dequaternization of amines,[9] but there is only one brief, unelaborated report[10] of its use with a phenol. Its successful use may be attributed to its high nucleophilicity and to the absence of any radical processes which are probably responsible for isomerization observed with reagents based on iodide nucleophilicity. Yields have varied between 75 and 100% in different experiments. Longer reaction times caused substantial isomerization of $\Delta^{9(11)}$-THC to the more stable Δ^{8} isomer.

Partial isomerization also occurred on bulb-to-bulb distillation at 200° and *p*-toluenesulfonic acid effected quantitative conversion to Δ^{8}-THC.

$\Delta^{9(11)}$-THC exhibits relatively weak psychotomimetic properties, showing approximately $^{1}/_{20}$th of the activity of Δ^{8}- and Δ^{9}-THC when administered intravenously to mice.[11] It has been recently demonstrated[12] that the major metabolic degradation of Δ^{8}- and Δ^{9}-THC involves hydroxylation of the vinylic 11-methyl group to produce physiologically active metabolites; this metabolic pathway is not available to the $\Delta^{9(11)}$ isomer.

$\Delta^{9(11)}$-THC promises to be a useful synthetic intermediate in cannabinoid chemistry. For example, oxidation with potassium permanganate–periodate quantitatively affords the 9-ketone,[2] which may then be used to obtain tritium or ^{14}C-labeled Δ^{9}-THC[13] or, alternatively, higher homologs of the cannabinoids (Scheme II, R = alkyl, CT_3, or $^{14}CH_3$).

SCHEME II



R = alkyl

Experimental Section

Δ^{8}-THC 1-Methyl Ether.—A procedure described by Brieger, Hackey, and Nestrick[5] was employed. Anhydrous potassium carbonate (4.95 g) and methyl iodide (14.0 ml, 0.225 mol) were added to a solution of Δ^{8}-THC (4.84 g, 15.4 mmol) in dimethylformamide (24 ml), and the mixture was stirred and refluxed for 20 hr. At this time glc of an aliquot showed that the reaction was virtually complete. The mixture was poured into water (100 ml) and extracted with hexane (three 100-ml portions). The combined organic extracts were washed with Claisen's alkali[14] to remove unchanged Δ^{8}-THC and then with water and dried over magnesium sulfate. Removal of the solvent gave 5.04 g of the methyl ether as a brown oil, shown by glc to be 98% pure.

An analytial sample was prepared by silica gel thick layer chromatography. The nmr spectrum showed a singlet at τ 6.26 (3 H, OCH_3) in addition to the typical absorption observed for Δ^{8}-THC.[1]

Anal. Calcd *m/e* for $C_{22}H_{32}O_2$: 328.240. Found: 328.239.

$\Delta^{9(11)}$-THC 1-Methyl Ether.—To the methyl ether of Δ^{8}-THC (2.05 g) in chloroform (60 ml) was added fused zinc chloride (1.1 g), and anhydrous hydrogen chloride was then passed through the stirred mixture for 2 hr at 0°. The mixture was was then kept at room temperature overnight, before diluting with chloroform (40 ml) and washing with water (two 50-ml portions), aqueous sodium bicarbonate (25 ml), and water (10 ml). After drying over magnesium sulfate, the solvent was evaporated *in vacuo* to leave 2.25 g of the hydrogen chloride adduct as a light brown oil. The formation of this adduct was confirmed by mass spectroscopy (Calcd *m/e* for $C_{22}H_{33}ClO_2$: 364.217. Found: 364.218.) and nmr spectroscopy, which showed the absence of olefinic protons.

The hydrochloride adduct (3.94 g, 10.8 mmol) was dissolved in 65 ml (32.5 mmol) of 0.5 *M* potassium tricyclopentylcarbinolate in toluene, and the solution was refluxed under nitrogen for 23 hr. The mixture was washed with water (three 50 ml portions) and dried over magnesium sulfate. Concentration *in vacuo*, followed by elution of the crude product from 22% silver nitrate–silica gel with a solvent gradient of 10% benzene in hexane to 25% benzene in hexane, gave 1.67 g of $\Delta^{9(11)}$-THC 1-methyl ether of 97% purity, as well as 0.24 g of 73% purity: nmr τ ($CDCl_3$) 5.26 (2 H, s, $W_{1/2}$ = 8 Hz, C=CH_2), 9.22 (t, J = 7 Hz, CH_3-$(CH_2)_4$), 8.97, 8.61 (6 H, s, $C(CH_3)_2$), 7.50 (t, J = 7.5 Hz, Ar CH_2), 6.36 (1 H, d, J = 12 Hz, Ar CH), 6.21 (3 H, s, OCH_3), 3.77, 3.71 (2 H, s, Ar H); ir $\nu_{max}^{CCl_4}$ 890 cm^{-1}.

Anal. Calcd *m/e* for $C_{22}H_{32}O_2$: 328.240. Found: 328.240.

$\Delta^{9(11)}$-THC.—A (50:50) mixture of $\Delta^{9(11)}$-THC and Δ^{8}-THC 1-methyl ethers (3.10 g, 9.45 mmol), potassium thiophenoxide 15.8 g, 107 mmol), thiophenol (2.0 ml, 19.5 mmol), and diethylene glycol (160 ml) was refluxed under nitrogen for 30 min. The mixture was then diluted with water (200 ml) and extracted with hexane (two 200-ml portions). The combined organic extracts were washed with 3 *M* aqueous potassium hydroxide to

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(7) V. Prey, *Chem. Ber.*, **75**, 445 (1942).

(8) A. L. Wilds and W. B. McCormack, *J. Amer. Chem. Soc.*, **70**, 4127 (1948).

(9) M. Shamma, N. C. Deno, and J. F. Remar, *Tetrahedron Lett.*, 1375 (1966); J. McKenna, B. G. Hutley, and J. White, *J. Chem. Soc.*, 1729 (1965).

(10) G. K. Hughes and E. O. P. Thompson, *Nature*, **164**, 365 (1949).

(11) The evaluation of the activity of cannabinoids is based on the comprehensive procedure of S. Irwin, *Psychopharmacologia*, **13**, 222 (1968).

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(13) For a recent example of radiolabeling using the racemic ketone obtained by total synthesis, see J. L. G. Nilsson, I. M. Nilsson, and S. Agurell, *Acta Chem. Scand.*, **23**, 2209 (1969).

(14) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 153.

remove thiophenol and then extracted with Claisen's alkali (three 100-ml portions). The latter extracts were diluted with water, neutralized with carbon dioxide, and then extracted with hexane. The combined hexane extracts were dried and concentrated to give 2.68 g (91%) of a 43:57 mixture of $\Delta^{9(11)}$-THC and Δ^{8}-THC.

An analytically pure sample was obtained by elution from silver nitrate–silica gel: nmr τ ($CDCl_3$) 9.12 (t, J = 7 Hz, $CH_3(CH_2)_4$), 8.95, 8.82 (s, $C(CH_3)_2$), 7.56 (t, J = 7 Hz, Ar CH_2), 6.26 (d, J = 12 Hz, Ar CH), 5.22 (s, 2 H, $C{=}CH_2$), 3.92, 3.83 (s, 2 H, Ar H); ir $\nu_{max}^{CCl_4}$ 3600 (OH), 890 cm^{-1} ($C{=}CH_2$); $[\alpha]^{25}D$ −38.5° (*c* 1.03, 95% EtOH).

Anal. Calcd *m/e* for $C_{21}H_{30}O_2$: 314.225. Found: 314.225.

11-Nor-9-ketohexahydrocannabinol 1-Methyl Ether.—$\Delta^{9(11)}$-THC 1-methyl ether (1.48 g, 4.51 mmol) in *tert*-butyl alcohol (742 ml) was treated with potassium carbonate (1.88 g) in water (100 ml), potassium permanganate (0.233, g, 1.48 mmol) in water (100 ml), and sodium metaperiodate (7.74 g, 35.4 mmol) in water (150 ml). After stirring at room temperature for 75 min, the mixture was extracted with benzene (three 500-ml portions) and the combined organic extracts were washed with saturated aqueous sodium bicarbonate (250 ml) and water (250 ml). After drying and concentrating, there remained 1.36 g of the desired product as a pale yellow oil of 99% purity. This product crystallized with difficulty from hexane: mp 87–88.2° (capillary); ir $\nu_{max}^{CCl_4}$ 1715 cm^{-1}; nmr τ ($CDCl_3$) 9.12 (t, J = 7 Hz, $CH_3(CH_2)_4$), 8.92, 8.78 (s, $C(CH_3)_2$), 7.48 (t, J = 7 Hz, Ar CH_2), 6.24 (s, 3 H, OCH_3), 3.78, 3.69 (s, 2 H, Ar H).

Anal. Calcd *m/e* for $C_{21}H_{30}O_3$: 330.219. Found: 330.220.

Registry No.—*trans*-$\Delta^{9(11)}$-THC, 27179-28-8; *trans*-$\Delta^{9(11)}$-THC 1-methyl ether, 27179-29-9; 11-nor-9-ketohexahydrocannabinol 1-methyl ether, 27179-30-2.

Acknowledgments.—This work was carried out under Contract No. PH-43-68-1452 of the National Institute of Mental Health, National Institutes of Health. We are grateful to Dr. H. D. Christensen for determining the pharmacological properties of $\Delta^{9(11)}$-THC.

Synthesis of 7-Dimethylamino-6-demethyl-6-deoxytetracycline (Minocycline) *via* 9-Nitro-6-demethyl-6-deoxytetracycline

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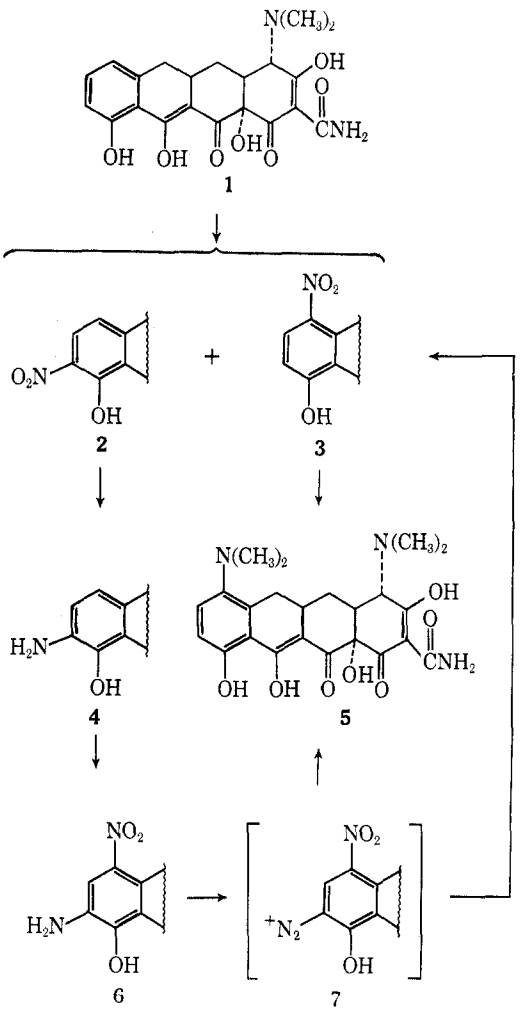
Recently it has been established that minocycline (7-dimethylamino-6-demethyl-6-deoxytetracycline, **5**) is a unique tetracycline derivative in that it is effective against tetracycline-resistant *staphylococci* in mice.[1,2] This important compound was originally prepared[1] by reductive methylation of 7-nitro-6-demethyl-6-deoxytetracycline (**3**) obtained by nitration of the accessible[3] 6-demethyl-6-deoxytetracycline (**1**). Unfortunately, the nitration of **1** affords a preponderance of the undesired 9-nitro isomer **2**, from which the 7-nitro isomer **3** must be separated.[4] Obviously, the efficiency of this process would be enhanced by the utilization of the 9-nitro isomer **2**.

The conversion of **2** to **5** has now been achieved *via* the previously reported[5] 9-amino-7-nitro intermediate **6**, obtained by catalytic reduction of **2** to the 9-amino derivative **4** followed by nitration.[6] The key feature of this sequence is the transformation of **6** to **5** by deamination at the 9 position *via* diazotization (butyl nitrite, sulfuric acid)[7] followed by reductive cleavage. Heating of the isolated diazonium salt **7** in ethanol affords the



7-nitro intermediate **3**,[8] convertible to the product **5** as previously described. This transformation, as well as reductive methylation, was accomplished in one operation by submitting **7**, prepared *in situ*, to hydrogenation with palladium catalyst in the presence of formaldehyde.[9]

(1) M. J. Martell and J. H. Boothe, *J. Med. Chem.*, **10**, 44 (1967).

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(5) J. L. Spencer, J. J. Hlavka, J. Petisi, H. M. Krazinski, and J. H. Boothe, *ibid.*, **6**, 405 (1963).

(6) A study of this reaction confirmed the reported conditions[5] as optimal. It may be noted that a twofold excess of nitrating agent resulted in much lower yields. Furthermore, nitration in liquid hydrogen fluoride gave apparently poorer results.

(7) J. J. Hlavka, A. Schneller, H. Krazinski, and J. H. Boothe, *J. Amer. Chem. Soc.*, **84**, 1426 (1962).

(8) For an earlier example of this reaction in the tetracycline series, see ref 7.

(9) The replacement of the diazonium group by hydrogen by this procedure is due either to hydrogenolysis or to reduction by formaldehyde. In either case it is unusual. Reduction of diazonium salts by formaldehyde is normally carried out in alkaline medium: R. Q. Brewster and J. A. Poje, *J. Amer. Chem. Soc.*, **61**, 2418 (1939). Hydrogenolysis of aromatic diazonium groups in the presence of palladium catalyst, a reaction first noted with another tetracycline by Dr. J. J. Hlavka of these laboratories, has no literature precedence of which we are aware.