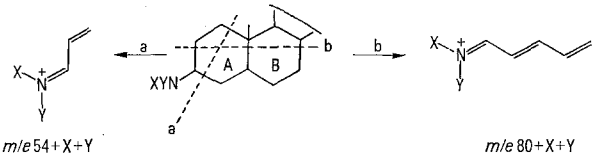
significent intensity), forms a diacetate, $C_{32}H_{50}N_2O_4$, m.p. 186–189°, ν_{max}^{ChF} 3440, 1720, 1660, 1510 and 1440 cm^{-1}, δ_{max}^{Chf} 1.95 (s), EIMS M^+ 526, when reacted with Ac_2O/pyridine for 18 h at 65°, followed by chromatography. When treated with sodium borohydride/formaldehyde in the modern version of the Eschweiler-Clark reaction[13], solacasine was converted to a tri-N-methyl dihydro analog **4**, $C_{31}H_{54}N_2O_2$, (EIMS[12], M^+ 486(5%), 471(12%), 454(M^+-CH_3OH, 53%), etc.) Reaction of solacasine with $NaBH_4$ alone led to a dihydro derivative **2**, $C_{28}H_{48}N_2O_2$, EIMS[12] M^+ 444(9%), 429(22%), 412(M^+-MeOH, 64%), 343(10%), 171(100%), 144(11%), 139(18%), 112(21%), 111(24%), 82(20%), 70(46%), 56(25%), etc., picrate salt, m.p. 178–182°. The common loss of methanol from the molecular ion in the mass spectra of these derivatives, coupled with an analogous loss of water by solanocapsine in its EIMS[12] (M^+ 430 (7%), 412 (M^+-HOH, 100%)) and CIMS[12] (*i*-BuH) MH^+ 431 (100%), 413 (MH^+-HOH 20%) no other significant peaks), the general similarity in spectra and properties suggested structure **3** as most likely for solacasine. Further support can be found in the fragmentation patterns. The mass spectra of steroidal alkamines are complex[14], but the presence or absence of certain fragments has diagnostic value. In particular cleavages a) and b) reveal a great deal about the structure of rings A and B. In this context, the presence of signi-



ficant ions at *m/e* 56 and 82 in the EIMS of **1**, **2** and **3**, and the lack of pairs of ions at *m/e* 70 and 96 in the same, argue that the 'extra' methyl group of **3** is unlikely to be attached to a carbon of either ring A or B and that the point of unsaturation must also be elsewhere. Ions *m/e* 84(55%) and 110(20%) in the EIMS of the Eschweiler-Clark product are consistent with that view as are their relative intensities (2:1)[14].

These inferences received strong support when solacasine and solanocapsine were converted to a common intermediate (**2**). Solanocapsine (**1**) was dissolved in cold, dry methanol and a slow stream of dry HCl gas was introduced intermittantly over 22 h at which time no more **1** was present upon TLC examination. Two main products were separated by sephadex LH-20 and silica gel chromatography. The more major of these two had identical TLC mobility in mixed spot experiments in 5 systems, an identical mass spectrum (EIMS), and formed an identical picrate salt (m.p. and IR-spectrum) when compared with **2** prepared by hydride reduction of **3**. The remaining point of uncertainly in the structure is the stereochemistry of the ketal moiety in **3**, but otherwise these experiments are rationalized by this formulation for solacasine.

The in vitro antimicrobial activity of these materials, using an agar-dilution streak assay[15], is as follows:

Microorganism	Compound 1	2	3	4
Staphylococcus aureus (6538P)[a]	100[b]	100	12.5	100
Mycobacterium smegmatis (607B)	100	100	5.0	100
Candida albicans (10231)	100	50	2.5	50

[a] American type culture collection number. [b] μg/ml.

The relatively small structural difference between **1** and **3** is nonetheless accompanied by a large difference in antibacterial potency. In vivo evaluation of **3** is in progress. The other agents are not potent enough to warrant further study.

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(−)-8β-Hydroxymethyl-Δ^1-Tetrahydrocannabinol: A Novel Physiologically Active Analog of Δ^1-Tetrahydrocannabinol[1]

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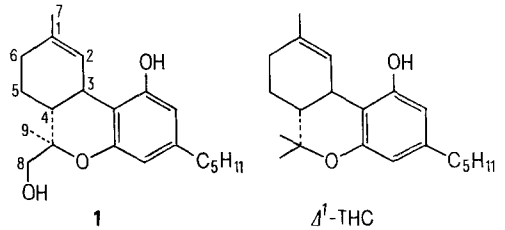
Summary. (−)-8β-Hydroxymethyl-Δ^1-tetrahydrocannabinol (THC) **1**, a novel analog of Δ^1, is shown to be as active as Δ^1-THC and twice as active as $\Delta^{1(6)}$-THC in the dog ataxia test.

We have recently reported[3] the synthesis of (−)-8β-hydroxymethyl-Δ^1-tetrahydrocannabinol (THC) (**1**), a novel analog of Δ^1-THC. In that paper, we stated that compound **1** exhibited THC-like overt central nervous systems (CNS) symptomatology in rodents at 1.0 mg/kg (i.v.). In the present communication, we confirm these results and compare the activity of **1** with Δ^1- and $\Delta^{1(6)}$-THC's in mice and dogs, and show that, in the latter, compound **1** is at least as active as Δ^1-THC and twice as active as $\Delta^{1(6)}$-THC. This is the first example of a modification in the geminal methyl part of the molecule of Δ^1-THC, although a few examples have been reported in the $\Delta^{3,4}$-THC series. The activity of **1** is noteworthy, since in the $\Delta^{3,4}$-THC's it has been shown that the geminal methyl group affords optimum activity[4–6]. However, no similar hydroxymethyl derivative is known in the $\Delta^{3,4}$- series for a direct comparison with **1**.

Δ^1-THC and other cannabinoids produce a characteristic effect in dogs, which includes static and dynamic ataxia, hyperflexia and decreased activity. This dog

ataxia test is well documented[7,8] and is known to provide the best correlation with activity in man[7]. This test has been further refined and semiquantitated by one of us[9]. After drug administration (i.v. in ethanol and Emulphor) independent observers rate the effect of each dose on



1 Δ^1-THC

every dog using a behavioral rating scale of zero (no effect) to 6 (dog lies prostrate on the floor) and the mean of their scores at peak activity is calculated. A comparison of compound **1** with Δ^1- and $\Delta^{1(6)}$-THC's[9b] in this test is shown below. The mean scores are given with the number of dogs tested in parenthesis. In addition, compound **1** showed a minimum effective dose (MED) for ataxia and 'popcorn effect'[10] at 1.0 mg/kg (i.v.) in mice. In the same tests Δ^1- and $\Delta^{1(6)}$-THC's were active at 0.5 mg/kg. In the spontaneous motor activity test in mice at 10 mg/kg (i.p.), the activity was decreased 36.6 $\pm$ 4.5%[11] by compound **1**, 41.2%[11] by Δ^1-THC and 69.3%[11] by $\Delta^{1(6)}$-THC. Compound **1** was inactive in the hot-plate procedure upto 10 mg/kg (i.p.). These pharmacological tests were carried out according to procedures described by us earlier[10].

It is thus clearly seen that the substitution of a methyl by a hydroxymethyl group in the 8β-position in Δ^1-THC results in a compound as active as Δ^1-THC.

Relative effect on the overt behavior of dogs

Dose (mg/kg)	Compound **1**	Δ^1-THC	$\Delta^{1(6)}$-THC
0.1	1 + (2)	0 (1)	0 (1)
0.2	3 (2)	3 + (2)	0 (1)
0.4	4 (1)	4 (2)	2 (2)

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Direct Fluorination of Carcinogenic Polycyclic Aromatic Hydrocarbons. 6-Fluorobenzo[a]pyrene[1]

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Summary. Xenon difluoride reacts with benzo[a]pyrene(BaP) in dichloromethane solution in an open system to give 6-fluorobenzo[a]pyrene. This method constitutes a direct route to fluorine substituted carcinogenic polycyclic aromatic hydrocarbons.

Polycyclic aromatic hydrocarbons (PAH) are present in tobacco smoke and are common contaminants of the urban environment. They are suspected of contributing to the increasing incidence of cancer of the human respiratory tract. One of the most intriguing problems in cancer research concerns the mechanism by which the relatively inert PAH initiate tumors[2]. Fluorine substituted carcinogenic PAH have been prominent in the study of structure-activity relationships of chemical carcinogens in this series[3–5]. Hitherto, the syntheses of such fluorine derivatives were based on the following 2 general methods: a) A 'tailormade' sequence analogous to the one applied in a well-established synthesis of the corresponding polycyclic hydrocarbon but with a fluorine-substituted starting material (e.g., the synthesis of 3-fluorobenzo[rst]pentaphene[6]). b) A direct electrophilic substitution of the PAH followed by appropriate transformations of the substituent to fluorine. Neither method is satisfactory, especially in the higher members of the PAH series. We report a straightforward synthesis of 6-fluorobenzo[a]pyrene (I) by a direct fluorination of benzo[a]pyrene (BaP) with xenon difluoride. The notorious BaP has played a leading role in this area of cancer research and still ranks among the most powerful all around carcinogenic substances[3–7].

The reaction of xenon difluoride and BaP was carried out in dichloromethane solution in a Kel-F tube in an open system, under anhydrous conditions. Initiation was

[1] Acknowledgment. This work was financed in part by a grant from The Israel Commission for Basic Research.
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