lage wird immer wieder die genaue Kenntnis der molekularen Geometrie und der Bindungsverhältnisse angestrebt. Diese lässt sich heutzutage mittels Konformationsanalyse,«Valence Force Field»-Kalkulationen und insbesondere auch Röntgenanalyse in konsistenter Weise gewinnen. Bei der weiteren Diskussion der (photo)chemischen Prozesse zeigen sich 3 Faktoren zum Verständnis und zur Voraussicht des Ablaufs wichtig. Es ist die schon längst bekannte sterische Hinderung und zwei weitere, beim Studium der Reaktionen im Vitamin-D-Gebiet zuerst formulierte Faktoren: der Einfluss der Orbitalsymmetrie und (für Photoreaktionen) die Lage des Konformationsgleichgewichtes im Grundzustand. Insbesondere das letztgenannte Prinzip hat sich bei der Auffindung von bisher unbekannten Photoprodukten des Vitamins D als sehr wichtig erwiesen.

Auch in der Zukunft werden die von der Natur sorgfältig selektionierten Moleküle von Vitamin D und dessen Isomeren ein anregendes Beispiel und Untersuchungsobjekt beim Studium der detaillierten Mechanismen von Photoisomerisierungen und bei der Konformationsanalyse von Molekülen in aktiviertem Zustand darbieten.

SPECIALIA

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Δ^6-Tetrahydrocannabinol-7-oic Acid, a Urinary Δ^6-THC Metabolite: Isolation and Synthesis

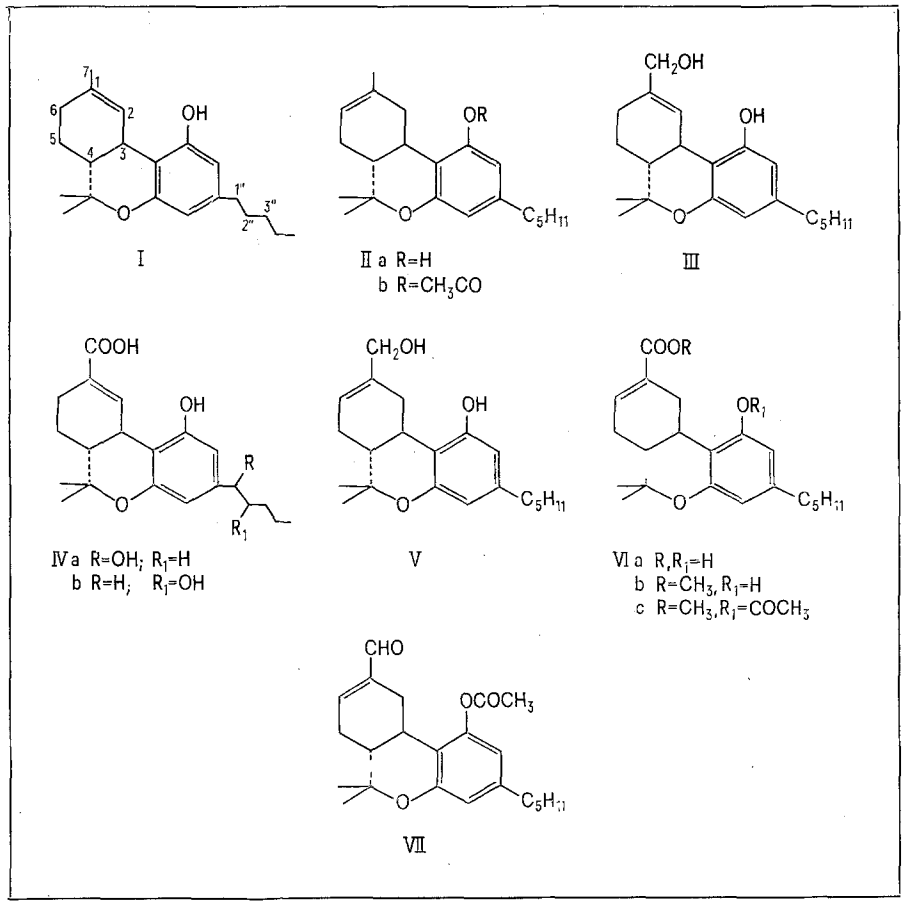
The metabolism of Δ^1-tetrahydrocannabinol (Δ^1-THC) (I) and Δ^6-THC (IIa) has been investigated by numerous groups in recent years[1,2]. The major primary metabolic process is considered to be mono-oxygenation, mostly on the C-7 position to give, in the case of Δ^1-THC, the biologically active 7-hydroxy-Δ^1-THC (III). Recently BURSTEIN et al.[3] reported the isolation from rabbit urine of 2 major acidic metabolites of Δ^1-THC. They were shown to possess structures IVa and IVb. The isolation of these acids poses two important questions: Are they formed from 7-hydroxy-Δ^1-THC (III)?; Are these acids, and/or their possible aldehydic precursors, also biologically active? Hence, it seemed of considerable importance and interest to synthesize and test the biological activity of these acids and the respective 7-aldehydo cannabinoids and to investigate the metabolism of 7-hydroxy-Δ^1-THC. However, practical methods for the preparation of Δ^1-THC derivatives oxygenated at C-7 have not yet been developed. As an alternative, we decided to synthesize the corresponding Δ^6-THC derivatives. Since the biological properties and usually also the chromatographic behaviour in the Δ^1 and Δ^6-THC series are closely parallel[4,5], we assume that results obtained in one of the series will also apply to the other. Concurrently we investigated the urinary metabolites of 7-hydroxy-Δ^6-THC (V), a major physiologically active metabolite of Δ^6-THC, for the possible presence of Δ^6-THC-7-oic acid (VIa).

Synthesis. Δ^6-THC acetate (IIb) was oxidized with selenium dioxide in ethanol for 24 h. On chromatography yields of 27–33% of Δ^6-THC-7-al acetate (VII) were obtained. This oily compound, $[\alpha]_D$ (in ethanol)-271°, was identified on the basis of its IR-spectrum (peaks at 1690 and 1775 cm^{-1} for the aldehydic and acetate groups respectively); its UV-spectrum (peaks at 281 nm, ε, 2680; 274 nm, ε, 2620; shoulder at 220 nm, ε, 15200), and its NMR-spectrum (δ, in $CDCl_3$, 0.90, 1.20, 1.42, methyl groups; 2.26, s, acetate methyl group; 6.46, 6.55, d, aromatic protons; 6.80, m, vinylic proton; 10.22, s, aldehydic proton).

The aldehyde VII, was oxidized in a 59–63% yield to Δ^6-THC-oic acid methyl ester (VIb) by reaction with manganese dioxide and sodium cyanide in methanol for 12 h[6,7]. The oily VIb, $[\alpha]_D$ (in ethanol) −302°, was identified by its IR-spectrum (peak at 1695 cm^{-1} of the carbomethoxyl group), and its NMR-spectrum (δ, in $CDCl_3$, 0.88, 1.10 and 1.38, methyl groups; 3.73, s, carbomethoxyl group; 6.15 and 6.20, aromatic protons; 7.02, m, olefinic proton). On hydrolysis, Δ^6-THC-7-oic acid (VIa) was obtained, $[\alpha]_D$ (in ethanol) −287°; IR-spectrum, peak at 1690 cm^{-1}, and typical wide carboxylic acid band in the 3000 cm^{-1} region; UV-spectrum, peaks at 274 nm, ε, 1454; 281 nm, ε, 1454 and shoulder at 230 nm, ε, 10530; molecular weight (mass spectrum) 344; NMR-spectrum, δ (in CCl_4), 0.95, 1.25 and 1.30 (methyl groups); 3.65 (C-2 proton); 5.90, 6.07 (aromatic protons), 7.05 (olefinic proton). The methyl ester acetate of Δ^6-THC-7-oic acid (VIc) was prepared by acetylation of VIb.

Biological tests. The free acid (VIa), its methyl ester acetate (VIc), and the aldehyde (VII) were tested in rhesus monkeys as described before[4]. Neither VIa, nor VIc showed any activity in doses up to 10 mg/kg. These observations contrast sharply with the activity recorded

[1] W. D. M. PATON and J. CROWN, *Cannabis and its Derivatives* (Oxford University Press, London 1972).
[2] R. MECHOULAM, *Marijuana. Chemistry, Pharmacology, Metabolism and Clinical Effects* (Academic Press, New York 1973).
[3] S. BURSTEIN, J. ROSENFELD and T. WITTSTRUCK, Science *176*, 422 (1972).
[4] H. EDERY, Y. GRUNFELD, Z. BEN-ZVI and R. MECHOULAM, Ann N.Y. Acad. Sci. *191*, 40 (1971).
[5] M. E. WALL, Ann. N.Y. Acad. Sci. *191*, 23 (1971).
[6] E. J. COREY, N. W. GILMAN and B. E. GANEM, J. Am. chem. Soc. *90*, 5616 (1968).
[7] J. L. G. NILSSON, I. M. NILSSON, S. AGURELL, Z. BEN-ZVI and R. MECHOULAM, Acta pharmac. Suecica *9*, 215 (1972).



in the same, or other, tests for Δ^6-THC (IIa) 7-hydroxy-Δ^1-THC (III) and 7-hydroxy-Δ^6-THC (V) at 20–200 times lower doses[4,5]. The aldehyde VII showed activity (drowsiness, decreased motor activity, occasional partial ptosis, occasional head drop) at 1 mg/kg. The synthesis and biological testing of Δ^6-THC-7-oic acid were first reported by us at a symposium held at the Ciba Foundation in London[1]. Recently a further synthesis of this compound was published[8].

Isolation. 7-Hydroxy-Δ^6-THC (V) was tritiated by acid catalyzed proton exchange[9] (23.1 mCi/mmol) and administered i.v. to rabbits (0.2–0.4 mg/kg). Approximately 45% of the administered compound was eliminated as metabolites in the urine during the first 24 h. Less than 1% of the eliminated radioactivity consisted of unchanged 7-hydroxy-Δ^6-THC. After prior purification on an Amberlite XAD-2 column, 50–70% of the excreted radioactivity was extracted with diethyl ether at pH 3.0. This fraction was found not to contain any detectable (0.1%) amount of compound VIa. The aqueous phase after removal of the extractable acids was hydrolyzed with β-glucoronidase. The liberated acids were extracted and the acid fraction was further purified by reextraction into 5% aqueous sodium bicarbonate and after acidification again extracted into diethyl ether[7]. Acids were converted to their methyl esters with diazomethane and separated by column chromatography on Sephadex LH-20[10]. The fraction corresponding to the elution volume of Δ^6-THC-7-oic acid methyl ester (VIb) was collected. The purified fraction was compared by TLC with the reference compound VIb on silica gel G plates using ether-light petroleum (1:1) as solvent. About 22% of the radioactivity coincided with VIb. The isolated material was also compared with the reference VIb on alumina plates (developed 3 times with 3% methanol in chloroform). The fraction isolated from Sephadex LH-20 was further compared by GLC with VIb and found to contain, among a number of not completely resolved peaks, a compound with identical retention time.

The identity of Δ^6-THC-7-oic acid isolated from hydrolyzed rabbit urine and synthetic VIa was verified by gas chromatography-mass spectrometry of the methyl esters using the mass spectrometer as a specific ion detector[11]. The spectrometer was adjusted to record exclusively the intensity of 3 fragments, m/e 358 (M^+), 326 and 302 in the mass spectrum of VIb. A compound with the same retention time (8.6 min, 3% OV-17/GasChromQ, 250°) and having the same 3 fragments in a similar ratio as in the reference compound was present in the purified extract from hydrolyzed rabbit urine. Based on this evidence, we conclude that Δ^6-THC-7-oic acid in conjugated form is excreted as a metabolite of 7-hydroxy-Δ^6-THC- and hence also of Δ^6-THC- in the urine of the rabbit. The bound acid VIa constituted only a minor part (0.4%) of the excreted metabolites.

[8] C. G. PITT, F. HAUSER, R. L. HAWKS, S. SATHE and M. E. WALL, J. Am. chem. Soc. *94*, 8578 (1972).
[9] S. AGURELL, in *The Botany and Chemistry of Cannabis* (Ed. C. R. B. JOYCE and S. H. CURRY; J. and A. Churchill, London 1970).
[10] E. ÄNGGÅRD and H. BERGKVIST, J. Chromat. *48*, 542 (1970).
[11] C. G. HAMMAR and R. HESSLING, Analyt. Chem. *43*, 298 (1971).

The present results are in agreement with previous findings where no detectable amounts of free Δ^1-THC-7-oic acids could be found after administration of Δ^1-THC[7]. To be eliminated, it appears that the free acids need further hydroxylation (IVa, b) and/or conjugation.

The results presented in this paper in conjunction with those in the literature, particularly the recent observations by BURSTEIN et al.[3], make possible a tentative partial delineation of the overall THC metabolism. In the case of Δ^1-THC, the initial conversion[1,2] is oxygenation, mainly at C-7, but also at C-6, and as an epoxide[12,13] on C-1, C-2. With Δ^6-THC, oxygenation takes place on C-7, on C-5[12,13] and on the side chain (1'' and 3''-hydroxy-Δ^6-THC). Some of the mono oxygenated THC's are biologically active and may represent the actual active species in the body[1,2,14]. Others, such as 1''hydroxy-Δ^6-THC and 6-keto-Δ^1-THC, show no activity (rhesus monkey). It should be pointed out that the various metabolites have been isolated in studies with different animal species or animal organ homogenates and may not all be relevant to human metabolism. However, 7-OH-Δ^1-THC, 6β and 6α-hydroxy-Δ^1-THC have been identified as metabolites of Δ^1-THC in man[15,16]. The THC-7-oic acids, on the basis of the present report, are formed by further metabolism of the respective 7-hydroxy-THC's. The 7-aldehydo compounds are possible intermediates[17]. The acids are excreted mainly as water-soluble 'conjugates', the nature of which is as yet unknown. All the THC-7-oic acids, including those hydroxylated on the side chain, on the basis of the present report, are probably inactive and represent the final, or one of the final, detoxification stages. Very little, if any, unchanged THC's, or mono oxygenated THC's are excreted as such[18].

Zusammenfassung. 7-Hydroxy-Δ^6-tetrahydrocannabinol (7-hydroxy-Δ^6-THC), ein psychotomimetisch aktiver Metabolit des Δ^6-THC, wird von Kaninchen in inaktive Δ^6-THC-7 Säure metabolisiert. Die Synthese dieser Säure wird beschrieben.

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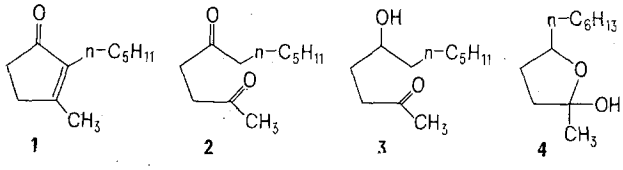
Israel Insitute for Biological Research, Medical School, Tel-Aviv University, Ness-Ziona (Israel), 17 April 1973.

[12] O. GURNY, D. E. MAYNARD, R. G. PITCHER and R. W. KIERSTEAD, J. Am. chem. Soc. *94*, 7928 (1972).
[13] R. MECHOULAM, H. VARCONI, Z. BEN-ZVI, H. EDERY and Y. GRUNFELD, J. Am. chem. Soc. *94*, 7930 (1972).
[14] E. W. GILL, G. JONES and D. K. LAWRENCE, Biochem. pharmac. *22*, 175 (1973).
[15] L. LEMBERGER, J. AXELROD and I. J. KOPIN, Ann. N.Y. Acad. Sci. *191*, 142 (1971).
[16] M. E. WALL, D. R. BRINE, C. G. PITT and M. PEREZ-REYES, J. Am. chem. Soc. *94*, 8579 (1972).
[17] S. BURSTEIN and J. ROSENFELD, Acta pharmac. Suecica *8*, 699 (1971).
[18] The work in Jerusalem was supported by the US National Institute of Mental Health and in Stockholm by the Swedish Medical Research Council.

A Facile Approach to Dihydrojasmone

Our continued interest[1] in the fragrant components of *Jasminum grandifolum* and related species has led to the development of a simple synthesis of dihydrojasmone (**1**). The present approach involves, as in our previous syntheses and a number of others, undecan-2,5-dione (**2**) as the penultimate precursor.



The HAUSER method[2] is a convenient procedure for the synthesis of methyl alkyl ketones. However, its extension to building up the γ-ketol system via alkylation of an oxirane or a derivative thereof was hitherto unexplored. An analysis of various synthetic possibilities toward dihydrojasmone prompted us to investigate such a reaction, since upon procurement of 5-hydroxyundecan-2-one (**3**) by a simple alkylation, one is assured of a three-step synthesis of the target molecule from readily accessible and inexpensive materials.

Alkylation of pentan-2,4-dione with 1,2-epoxyoctane in refluxing absolute ethanol in the presence of sodium iodide and anhydrous potassium carbonate for 20 h followed by distillation off most of the solvent, dissolution of the residue in water and extraction into ether and final isolation by Girard T separation[3], furnished in 28% yield. (Bp. 81° (oven temp.)/0.75 Torr; Anal. Found: C, 71.11; H, 11.84; ν (CH_2Cl_2) 3605, 1710 cm^{-1}). Judging from the spectral characteristics, especially the methyl ketone absorption region in the PMR-spectrum, this alkylation product exists in a dynamic equilibrium between the ketol **3** and the hemiacetal **4** forms.

JONES[4] oxidation was then carried out by dropwise introduction of chromic acid to a stirred acetone solution of the **3**, **4** mixture until an orange-brown tinge persisted. Water was added and the diketone **2** was obtained by ether extraction and distillation (74% yield).

Since **2** has been previously converted to dihydrojasmone, our synthesis is completed. The success of producing **3** indicates a rapid and general way for the synthesis of γ-ketols.

Résumé. La dihydrojasmone a été synthétisée en trois étapes à partir du pentanedione-2,4.

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[1] H. C. HO, T. L. HO and C. M. WONG, Can. J. Chem. *50*, 2718 (1972); T. L. HO, H. C. HO and C. M. WONG, Can. J. Chem. *51*, 153 (1973).
[2] S. BOATMAN, T. M. HARRIS and C. R. HAUSER, J. org. Chem. *30*, 3321 (1965).
[3] A. I. VOGEL, *A Textbook of Practical Organic Chemistry*, 3rd edn, (Longman-Green, London 1962), p. 976.
[4] K. BOWDEN, I. M. HEILBRON, E. R. H. JONES and B. C. L. WEEDON, J. chem. Soc., *39* (1946).
[5] This research was supported by NRCC, Ottawa.