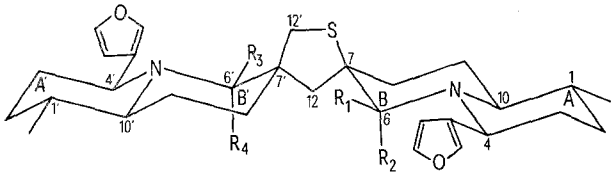
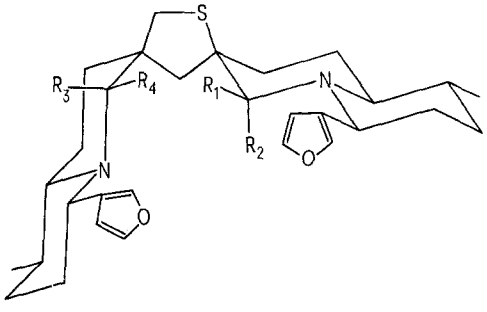


1, $R_1 + R_2 = H + OH$; $R_3 = R_4 = H$
2, $R_1 = R_2 = H$; $R_3 + R_4 = H + OH$
3, $R_1 = R_2 = R_3 = R_4 = H$
4, $R_1 + R_2 = H + D$; $R_3 = R_4 = H$
5, $R_1 = R_2 = H$; $R_3 + R_4 = H + D$



6, $R_1 + R_2 = H + OH$; $R_3 = R_4 = H$

alkaloids indicate incorporation of two regular sesquiterpenic units, of mevalonate origin[5], which are linked in a symmetrical fashion through carbon and a new heteroatom, sulfur. The key intermediate in the transition from C_{15} to C_{30} alkaloids would appear to be the conjugated immonium ion **9** which is formed from naturally abundant nupharidine **7** through the sequence: Polonovsky elimination by a natural anhydride (e.g. pyrophosphate) giving the enamine **8**; and allylic oxidation of the C-7 methyl giving the conjugated immonium ion **9**. Indeed, the transformation of N-oxide **7** to enamine **8** is facile in *vitro*[6].

Enamine immonium ion coupling giving dimeric structures is a well-known feature of enamine chemistry. In the present instance, such coupling involves a sulfur reagent which reacts first as a nucleophile with **9** giving **10**. In subsequent steps, enamine **10** couples with **9** giving **11** in which the newly formed enamine functions as a thiophile displacing leaving group X to give bisimmonium ion **12**. Specific reagents possessing the reactivity characteristics demanded of SX^- in this scheme can be reasonably postulated (e.g. thiosulfate). To complete the biogenesis, the bisimmonium ion **12** undergoes stepwise reduction and hydration to monohemiaminals and ultimately reduction to bisamines[7].

Résumé. Les structures des 6- et 6'-hydroxynéothiobinupharidine ont été déterminées par des études spectrales et la conversion en néothiobinupharidine-6- et 6'-d_1. Un schème de biogénèse des C_{30}, Nuphar monohémiaminals est proposé.

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Department of Chemistry, State University of New York, College of Environmental Science and Forestry, Syracuse (New York, 13210 USA), 29 August 1974.

[5] H. R. SCHÜTTE and J. LEHFELDT, Arch. Pharmak. *298*, 461 (1965).
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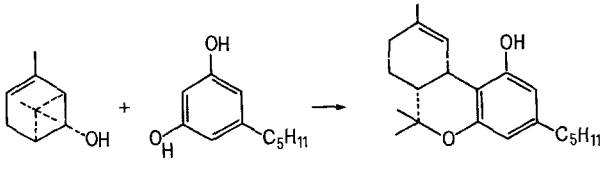
[7] Support of this work by the National Institutes of Health, U.S. Public Health Service (Grant No. AI 10188) is gratefully acknowledged.

A One-Step Synthesis of (−)-Δ^1- Tetrahydrocannabinol from Chrysanthenol

We have recently reported a simple one-step synthesis of (−)-Δ^1-tetrahydrocannabinol (THC) from *p*-mentha-2,8-dien-1-ol and olivetol[1]. The formation of Δ^1-THC by this method is in contrast to previously reported reaction of these reagents[2] which yielded $\Delta^{1(6)}$-THC as the major product. Two other syntheses of (−)-Δ^1-THC are from *trans*-(+)-2-carene oxide[3] and (−)-verbenol[4]. Although carene oxide is converted directly into Δ^1-THC, the route from verbenol, gives $\Delta^{1(6)}$-THC wich must be transformed to (−)-Δ^1-TCH by addition and elimination of hydrogen chloride. On mechanistic grounds, we reasoned that by virtue of the position of the double bond, verbenol can lead only to $\Delta^{1(6)}$-THC since the double bond has to migrate into that position during the ring opening of the cyclobutane ring. On the other hand, on the basis of similar arguments, we thought chrysanthenol should lead directly to Δ^1-THC. This was indeed found to be the case, albeit the yield was moderate.

Chrysanthenone[5,6] ($[\alpha]_D$ −36°) was reduced to the corresponding *cis*-chrysanthenol[5a,7] with lithium aluminum hydride in ether (0.5 h) and used without further purification in subsequent reaction. Equimolar quantities of chrysanthenol and olivetol were allowed to react in dry methylene chloride at 0° for 0.5 h in the presence of 0.1% boron trifluoride etherate. A resin containing



Chrysanthenol Olivetol Δ^1-THC

~25% (GLC)[8] Δ^1-THC was obtained and no $\Delta^{1(6)}$-THC was observed. The Δ^1-THC was separated by chromatography on thick silica gel plate (1:4 ethyl acetate/hexane) and was found to be identical to an authentic sample of (−)-Δ^1-THC (NMR, IR, TLC, GLC). The optical rotation corresponded to the % optical purity of the starting chrysanthenone. The identity of Δ^1-THC was further confirmed by its conversion to $\Delta^{1(6)}$-THC with *p*-toluenesulfonic acid in boiling benzene and comparison with an authentic sample.

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[6] It was prepared from (–)-verbenone $[\alpha]_D$ -242° by irradiation in cyclohexane according to the procedure of ERMAN[5b]. The optical purity of chrysanthenone was 33% on the basis of $[\alpha]_D$ -108° for pure material[5b].
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[8] Percentage yield based on GLC assay. The compounds were identified on the basis of relative retention times of authentic samples (silylated and unsilylated) and by addition of authentic samples to the reaction mixture with subsequent GLC. A Varian Aerograph Model 1400 equipped with a 6 ft. × 1/8-inch ss. column packed with 5% OV-101 on 100–200 mesh GasChrom Q and a flame ionization detector was used for GLC analysis.
[9] See for example L. RUZICKA, Pure appl. Chem. *6*, 493 (1963).
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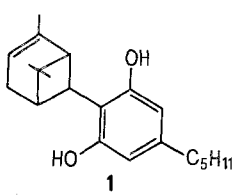
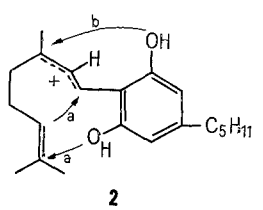
[11] C. E. TURNER and K. HADLEY, J. Pharm. Sci. *62*, 251 (1973) and references cited therein.
[12] L. RUZICKA, *Perspectives in Organic Chemistry* (Ed. A. R. TODD; Interscience Publishers Inc. ,New York, N.Y. 1956), p. 282.
[13] Acknowledgment. This work was supported by NIDA (Grant No. DA-00574-01). We are grateful to Glidden and Co. and The Proctor and Gamble Co. for a gift of (–)-verbenone.

The direct synthesis of Δ^1-THC from chrysanthenol may have some biogenetic implications, especially since chrysanthenone and chrysanthenyl acetate[7] have been found to occur naturally. A biogenetic 'pinane route'[9] via **1** to Δ^1-THC and cannabichromene can be envisaged which does not require the intermediacy of cannabidiol. This is of interest since cannabidiol, which is considered an intermediate in the proposed scheme[10] for the biosynthesis of Δ^1-THC, has been reported to be absent from several Cannabis and hashish samples[11]. Alternatively,



1



2

this fact can be accommodated by a biogenetic scheme proceeding via intermediate[12] **2** to give Δ^1-THC (path a) or cannabichromene (path b)[13].

Zusammenfassung. Eine Einschritt-Synthese von (–)-Δ^1-Tetrahydrocannabinol (THC) ausgehend von Chrysanthenol mit möglichen biogenetischen Folgerungen wird beschrieben.

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Evidence for a Base Catalyzed Interconversion of Azacyclols Derived from N-(Acylalanyl)-Phenylalanyl-Prolin-Lactams

We have recently[1,2] reported on the possibility of obtaining cyclol peptides (I) starting from linear N-benzyloxycarbonyltripeptides *p*-nitrophenylesters. In one of the proposed routes for the azacyclol formation, we postulated the intermediacy of an acylalanyl-diketopiperazine. In this paper we wish to report further results obtained in this field.

During an investigation concerning the influence of structural factors on azacyclols formation, we have found that two main compounds were formed by treating the *p*-nitrophenylester of N-allyloxycarbonyl-Ala-Phe-Pro[3,4] with an aqueous mild alkaline buffer under the conditions already described[5]. In fact preparative TLC on silica gel of the reaction mixture gave, in addition to the expected azacyclol (Ia), a further cyclic tripeptide, which resulted to be acyl-*trans*-diketopiperazine (IIa).

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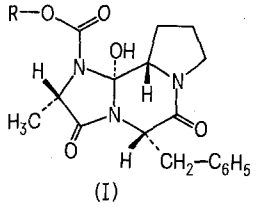
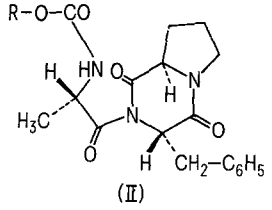
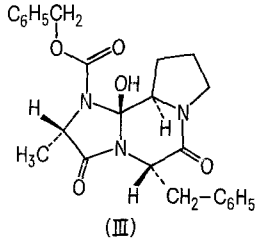
[2] G. LUCENTE, A. ROMEO and G. ZANOTTI, Gazz. chim. ital. *102*, 941 (1972).
[3] This compound was obtained by acylation of Ala-Phe-Pro with allyloxycarbonyl chloride.
[4] All new compounds gave correct elemental analyses; NMR-spectra were recorded at 100 MHz in $CDCl_3$ with TMS as internal standard; mass spectra (MS) were recorded on an A.E.I. MS 12 (direct inlet system at 150 °C and 70 eV). Abbreviations in accordance with IUPAC-IUB Commission on Biochemical Nomenclature, Arch. Biochem. Biophys. *150*, 1 (1972).
[5] One h at room temperature in a dioxane-aqueous buffer solution (0.1 *M* $NaHCO_3$: 0.1 *M* Na_2CO_3: dioxane-1:1:2).



(I)



(II)



(III)

a) R = CH_2=CH–CH_2–
b) R = C_6H_5–CH_2–