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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.
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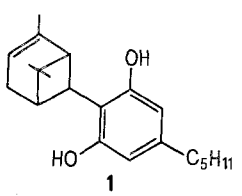
The direct synthesis of Δ^1-THC from chrysanthenol may have some biogenetic implications, especially since chrysanthenone and chrysanthenyl acetate[7] have been found to occur naturally. A biogenetic 'pinane route'[9] via **1** to Δ^1-THC and cannabichromene can be envisaged which does not require the 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,



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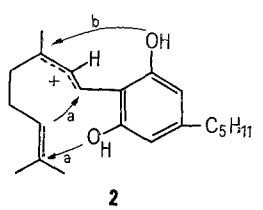

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this fact can be accommodated by a biogenetic scheme proceeding via intermediate[12] **2** to give Δ^1-THC (path a) or cannabichromene (path b)[13].

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

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Sheehan Institute and Sharps Associates (SISA), 767-B Concord Avenue, Cambridge (Massachusetts 02138, USA), 5 August 1974.

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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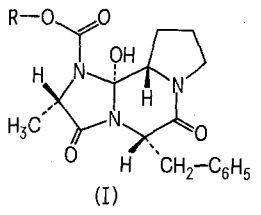
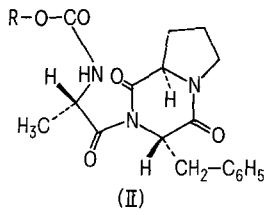
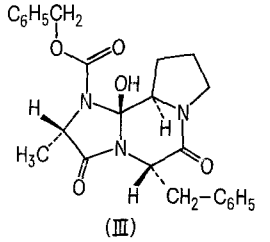
[3] This compound was obtained by acylation of Ala-Phe-Pro with allyloxycarbonyl chloride.
[4] All new compounds gave correct elemental analyses; NMR-spectra were recorded at 100 MHz in $CDCl_3$ with TMS as internal standard; mass spectra (MS) were recorded on an A.E.I. MS 12 (direct inlet system at 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–

Compound (Ia): Yield 45%; m.p. 98–100 °C; $[\alpha]_D^{20} = -18°$ (c 1 in $CHCl_3$); I.R. ν_{max} 3520–3400, 1720, 1640, 1445 cm^{-1} and no evidence of amide II band; NMR δ ppm 4.10 (1H, q, J = 6.5 Hz, Ala $C_\alpha H$), 4.84 (1H, 4 lines, X part of an ABX, Phe $C_\alpha H$), 3.7 (1H, m, Pro $C_\alpha H$ superimposed on Pro $C_\delta H_2$ multiplets), 4.90 (1H, bs, OH); MS *m/e* 399 (M^+, 19%), 381 ($M-H_2O$, 2%), 125[6] (3%), 70 (base peak). Hydrazinolysis[7] of (Ia) gave allyloxycarbonyl-Ala-$NHNH_2$ and cyclo (-Phe-Pro-).

Compound (IIa): Yield 15%; glassy oil; $[\alpha]_D^{20} = +114°$ (c 1 in $CHCl_3$); I.R. ν_{max} 3430 (carbamate NH), 1710, 1660, 1495 cm^{-1} (amide II); NMR δ ppm 5.38 (1H, q, J = 6.5 Hz Ala $C_\alpha H$), 2.35 (1H, m, Pro $C_\alpha H$), 5.20 (1H, m, Phe $C_\alpha H$), 5.45 (1H, unresolved, NH); MS *m/e* 399 (M^+, 10%), 381 ($M-H_2O$, less than 0.1%), 125[6] (26%), 128 (base peak). Hydrazinolysis[7] of (IIa) gave allyloxycarbonyl-Ala-$NHNH_2$ and cyclo(-Phe-D-Pro-).

It is known that N-hydroxyacyl-lactams and N-hydroxyacyl-diketopiperazines can give rise to oxacyclols[8–12]. In view of the probable existence of N-acyldiketopiperazines as reaction intermediates in the formation of cyclols from linear acyl-tripeptides *p*-nitrophenylesters, and because of the easy epimerization of the N-acyldiketopiperazines containing proline in polar medium[10], it seemed interesting to examine the reactivity of a cyclol in mild alkaline aqueous buffer. Azacyclol (Ib)[1] was then allowed to stand 1.5 h at room temperature in the buffer already cited[5]. Removal of dioxane and usual fractionation gave Z-Ala-Phe-D-Pro and Z-Ala in acidic fraction. From the neutral fraction, 4 main components could be isolated by TLC. Composition of the neutral fraction was as follows: starting azacyclol (Ib) (56%), cyclo(-Phe-D-Pro-) (17%), azacyclol (III) (10%) and acyl-diketopiperazine (IIb) (17%). Structure (IIb) and (III) were assigned on the basis of chemical and spectral properties.

Compound (IIb): Colourless foam; $[\alpha]_D^{20} = +82°$ (c 2 in $CHCl_3$); I.R. ν_{max} 3430, 1710, 1655, 1495 cm^{-1}; NMR δ ppm 5.47 (1H, q, J = 7.0 Hz, Ala $C_\alpha H$), 2.40 (1H, m, Pro $C_\alpha H$), 5.27 (1H, t, J = 5.0 Hz, Phe $C_\alpha H$), 5.78 (1H, d, J = 8.5 Hz, NH); MS *m/e* 449 (M^+, 4.5%), 431 ($M-H_2O$, 0.4%), 125[6] (32%), 91 (base peak). Hydrazinolysis[7] of (IIb) gave cyclo(-Phe-D-Pro-) and Z-Ala-$NHNH_2$. Compound (IIb) could be synthesized in high yield by treating Z-Ala-Phe-Pro with excess Ac_2O-AcONa at 100 °C for 1 h.

Compound (III): Colourless foam; soluble in 1 *N* NaOH from which can be reprecipitated on acidification. $[\alpha]_D^{20} = +71°$ (c 1 in EtOH); I.R. ν_{max} 3500–3300, 1715, 1645, 1440 cm^{-1}; NMR δ ppm 4.30 (1H, q, J = 7.0 Hz, Ala $C_\alpha H$), 4.40 (1H, m, Pro $C_\alpha H$), 4.15 (1H, unresolved m, X part of an ABX, Phe $C_\alpha H$), 6.30 (1H, bs, OH); MS *m/e* 449 (M^+, 30%), 431 ($M-H_2O$, 2.5%), 125[6] (17%), 91 (base peak). Hydrazinolysis[7] of (III) gave cyclo(-Phe-D-Pro-) and Z-Ala-$NHNH_2$.

When the same treatment with the alkaline buffer was applied to N-acyldiketopiperazine (IIb), a reaction mixture containing the same components as for azacyclol (Ib) was obtained. In this case the composition of the neutral fraction was as follows: starting material (IIb) (35%), cyclo(-Phe-D-Pro-) (40%), azacyclol (Ib) (8%), azacyclol (III) (18%).

The above results seem to indicate that in the mild alkaline medium an equilibrium can be established between acyl-*trans*-diketopiperazine (IIb) and its *cis*-isomer. Each isomer can in turn equilibrate with the corresponding azacyclol. The *cis* -isomer of (IIb) could not be detected, and this fact can be ascribed to the already known instability of these *cis*-isomers[10] and to a higher tendency to isomerize into the corresponding azacyclol (Ib). The different reactivity between acyl-*trans*-diketopiperazine (IIb) and the corresponding *cis*-isomer can be reasonably related to the already known different conformations between DL and LL isomers of cyclic dipeptides[13,14]. Such different conformation should influence the reactivity of the amide carbonyl; in the *cis*-isomer the amide bond is in fact forced into a slightly non-planar arrangement. When the synthesis of the *cis*-isomer of (IIb) was attempted by reacting Z-Ala-Cl with the N-trimethylsilyl derivative of cyclo(-Phe-Pro-), only azacyclol (Ib) was obtained.

The base catalyzed interconversion, observed by us in the case of the described azacyclols, was not found in the case of oxacyclols containing the same diketopiperazine system. Such different behaviour could possibly derive either from a higher instability of the corresponding hydroxyacyl-diketopiperazines or from a greater stability of the oxacyclols.

Riassunto. È stata studiata la reattività in ambiente acquoso blandamente alcalino dei cicloli tripeptidici. Si è messo in evidenza un equilibrio tra i sistemi azaciclolici attraverso le corrispondenti acil-alanil-dichetopiperazine.

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22 July 1974.

[6] Peak at *m/e* 125 is the base peak in the MS of cyclo(-Phe-Pro-).

[7] Hydrazine hydrate (2 moles) was added to 1% methanolic solution of the compound (1 mole). The mixture was left 18 h at room temperature. By this treatment N-propionyl-cyclo(-Phe-Pro-) gave cyclo(-Phe-Pro-). For this procedure see: A. HOFMANN, H. OTT, R. GRIOT, P. A. STADLER and R. J. FREY, Helv. chim. Acta *46*, 2306 (1963).

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Vinca Alkaloids XXXV.[1] Desacetoxyvinblastine a New Minor Alkaloid from *Vinca rosea* L. (*Catharanthus roseus* G. Don)

In the process of purifying larger quantities of VLB[2] (vincaleukoblastine (I)), we have noticed the presence of a new dimeric indole-indoline alkaloid. Physical and chemical data clearly indicated that the new compound is desacetoxyvinblastine (II).

The UV and IR spectra of VLB and desacetoxy VLB are quite similar. The nature of the difference between the 2 alkaloids is immediately apparent from the NMR and mass spectral data. Thus, the signal of the acetyl methyl of VLB (s, δ = 2.10 ppm)[3] is missing in the NMR-