$-260°$[11]. This may be described as a plain negative dispersion curve. The absolute configuration of (+)-dihydro coumarilic acid has been rigorously established by oxidative degradation to (+)-D malic acid[9]. (+)-5-Methoxy dihydro coumarilic acid **VIII** has a plain positive ORD curve in this area, ($[\Phi]_{350}+350°$; $[\Phi]_{325}+600°$; $[\Phi]_{311}+1200°$) and its (−)-enantiomer has a plain negative curve. (+)-5-Methoxy dihydro coumarilic acid (**VIII**) may therefore be presumed to have the same absolute configuration as (+)-dihydro coumarilic acid, i.e., the R-configuration. Nevertheless, a chirooptical comparison, where the chromophores are different, does not provide a rigorous proof of configuration, although this is often done[12]. It is preferable to either convert one chromophore to the other[13] or effect a chemical correlation.

The methoxy alcohol **IX** could be readily demethylated, but attempts to reductively remove the phenolic hydroxyl group by the usual methods were not successful. Instead, (+)-5-methoxy dihydro coumarilic acid (**VIII**) was ozonized in acetic acid (scheme 3) by essentially the same procedure as that described by Bonner[9] for (+)-dihydro coumarilic acid. No change in $[\alpha]_D$ was observed after the acid **VIII** had stood overnight at room temperature in acetic acid. Therefore, no racemization was anticipated as a consequence of the reaction conditions. (+)-5-Methoxy dihydro coumarilic acid (**VIII**) (500 mg) was dissolved in acetic acid (10 ml) and treated with ozonized air at room temperature for 24 h. The acetic acid solution was then treated with 30% H_2O_2, 10% Pd/C and concentrated to dryness. Oxalic acid was removed via its calcium salt as described by Bonner[9]. The residue was chromatographed on Dowex 50 resin (H^+ form). Elution with 50% aqueous acetic acid yielded the major fraction. This material was dissolved in methanol and treated with excess etheral diazomethane. The resulting yellow oil was chromatographed on alumina (neutral **III**). Elution by ether-methanol (1:1) gave a main fraction identified by tlc as slightly impure methyl D-(+)-malate (36% of theory). This oil was distilled in a hot box in vacuo. The distillate which had $[\alpha]_D + 10.1°$ (c = 1.00 acetone) (reported[9] $[\alpha]_D^{20} + 11.4°$ (c = 1.10 acetone)), was shown to be methyl D-(+)-malate by comparison [tlc (silica gel/ethyl acetate); NMR, IR] with an authentic sample prepared from the commercially available acid (Aldrich Chemical Co.). Thus, the absolute configuration of (+)-5-methoxy dihydro coumarilic acid (**VIII**) is rigorously established as the R-configuration, and in turn the absolute configuration of SU 23397 (**I**) as the R-configuration[14].

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A novel cannabinoid containing a 1,8-cineol moiety[1]

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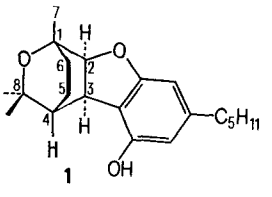
Sheehan Institute for Research Inc., 767B Concord Avenue, Cambridge, (Massachusetts 02138, USA),
3 November 1976

Summary. The synthesis of a novel cannabinoid containing a 1,8-cineol moiety (**1**) is described. It is much less biologically active than Δ^1-tetrahydrocannabinol.

We wish to report the synthesis of a novel cannabinoid **1** containing a 1,8-cineol residue. The formation of **1** was observed during our studies on cannabielsoin **2a**, which is a decarboxylation product of the naturally occurring constituent of hashish, cannabielsoic acid **2b**. In an earlier publication[2] we confirmed the gross structure of cannabielsoin[3] and revised the reported[4] configuration at C_1 to that shown in **2a** on the basis of a stereochemically unambiguous synthesis[2] of **2a** from **3**. Independently, Shani and Mechoulam[5] arrived at similar conclusions while working on the cannabielsoic acid series.



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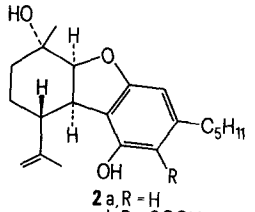
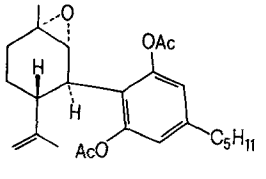


2 a, R = H
b, R = COOH



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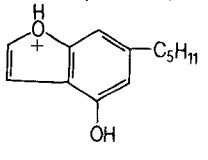

4

We have found that when cannabielsoin is refluxed in benzene in the presence of a catalytic amount of p-toluenesulphonic acid it undergoes an intramolecular cyclization in essentially quantitative yield. On the basis of NMR and mass spectral evidence, we can securely assign structure **1** to this novel cannabinoid: $[\alpha]_D^{25}$ − 21.2°C (c 1.55, ethanol); NMR (CCl_4) 6.07, 6.00 (2, aromatics), 5.30 (br, 1, OH), 4.50 (d, 1, J = 10 Hz, C_2-H), 3.97 (dd, 1, $J_{2,3}$ = 10 Hz, $J_{3,4}$ = 3 Hz, C_3-H), 2.02 (m, 1, C_4-H), 1.13 (s, 3, C_1-CH_3), 0.88 (t, 3, ω-CH_3). The positions of the C_1 and C_8 methyl groups agree with those reported for 1,8-cineol[6]; the magnitude of the coupling constant for protons at C_2 and C_3 is in accord with that

1 Acknowledgment. This work was supported by NIDA (grant No. DA-00574-01).
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expected[4,5] for a cis-fused ring junction; and the observed coupling constant for protons at C_3 and C_4 corresponds[7] to the measured value from the Dreiding model (approx. 50°). The mass spectrum (70 eV) shows a molecular ion (M+) at m/e 330 and major fragment ions at 205 (base peak, **4**), 204, 148 and 147 consistent with the assigned structure.

Transannular ring formation to give compound **1** requires a cis-orientation of the hydroxyl- and isopropenyl-substituents in **2a** and serves as confirmatory evidence for the stereochemical assignment of the C_1-hydroxyl group as α (axial). Compound **1**, tested in mice for overt symptomatology, produced mild catatonia at 10 mg/kg (i.v.). In the same test Δ^1-tetrahydrocannabinol is active at 0.5 mg/kg[8].

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Correlation of anthothecol and hirtin

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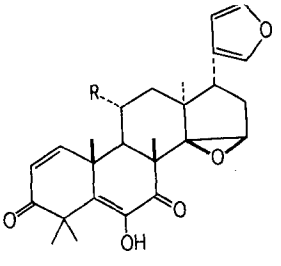
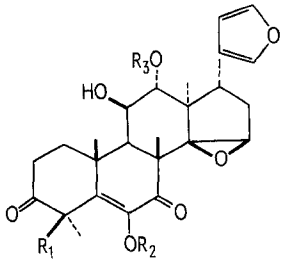
Summary. Hirtin (**3**) and anthothecol (**2**) have been correlated by conversion of each to the derivative (**10**).

A large number of furanoid tetranortriterpenes (limonoids) have been isolated from members of the Meliaceae and Rutaceae[1]. These show a great variety and complexity of structure but are related biogenetically and can be further classified on the basis of skeletal modifications into subgroups. The simplest of these are tetracarbocyclic and 4 of this group, cedrelone (**1**)[2,3], anthothecol (**2**)[4–7], hirtin (**3**) and desacetylhirtin (**4**)[7,8], are further characterized by the presence of a diosphenol in ring B. The structure of cedrelone (**1**) has been defined by X-ray analysis and recently the complete stereochemistry of hirtin (**3**) and desacetylhirtin (**4**) has been assigned from chemical[9] and X-ray[10] data. We now report a correlation of hirtin (**3**) with anthothecol (**2**).

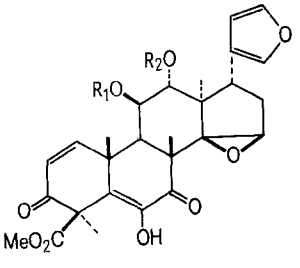
Treatment of the diol (**5**)[7] in dimethylformamide with lithium iodide under conditions of halolysis[11,12] led to a mixture (44%; 1:1) of **6** $C_{27}H_{34}O_7$ (M^+ 470), m.p. 197 to 199 °C, and **7** $C_{26}H_{32}O_7$ (M^+ 456), m.p. 213.5 °C. The spectral characteristics of **6** UV[λ_{max} (EtOH) 210, 264 nm, ε_{max} 7160, 8710]; IR[ν 3413, 1709, 1675, 1590, 1495 and 877 cm^{-1}]; NMR($CDCl_3$) [δ 0.72, 1.33 (2), 1.43, 1.48 (singlets, C-methyls), 4.07 (2H, broad singlet, H-11, H-12), 3.93 (1H, singlet, H-15), 3.69 (3H, singlet, O-methyl) and 6.30, 7.39, and 7.43 (each 1H, narrow multiplets, furan protons)] are in agreement with the structure. The spectra of **7** differed significantly only in the absence of the methoxy signal in the NMR and the characteristic reversible base shift for the diosphenol in the UV. The



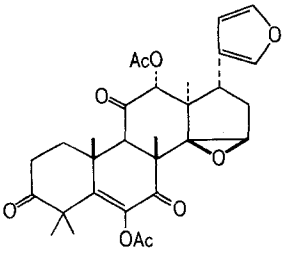
1 R = H
2 R = OAc



5 $R_1 = CO_2Me$; $R_2 = Me$; $R_3 = H$
6 $R_1 = R_2 = Me$; $R_3 = H$
7 $R_1 = Me$; $R_2 = R_3 = H$
8 $R_1 = Me$; $R_2 = R_3 = Ac$



3 $R_1 = Ac$; $R_2 = COEt$
4 $R_1 = H$; $R_2 = COEt$



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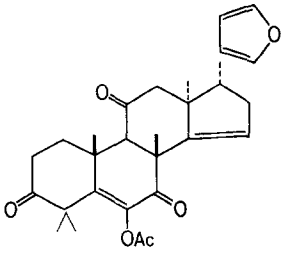

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