day which became progressively severe in case of dose 0.4 mg developing into a heavy scab 3 days after the treatment. Scab had also formed on the other 4 rats. While the 0.4 mg dose left pinkish scars, the spots treated with the 2 lower doses developed small tufts of hair with time. On increasing the dose of the toxic oil (1 mg), the animals died within 5–6 days. The observed level of toxins (about 3–5 mcg/g of seeds) when consumed through the oral route may not be sufficient to cause symptoms of a mycotoxicosis immediately, but prolonged ingestion may be fatal[9] and is, therefore, cause for alarm.

Another important observation made during this study is the incidence of secondary infection of safflower seeds by contamination with the infected ones. Surface-sterilized (0.1% aq. $HgCl_2$) healthy seeds of safflower were kept on the fungal colony on a PDA medium. On the second day, the seeds were removed and divided into 2 parts. One part was kept with an equal number of healthy seeds in aseptic conditions, at 21 °C for 30 days. The spores and mycelia from the second part were removed by successive washing with mercuric chloride solution and sterile distilled water. These were then kept with an equal number of healthy seeds as described above. After incubation for 30 days, the seeds were transferred aseptically on sterilized PDA plates and the latter were incubated at 21 °C. Within 72 h, the fungus appeared on all seeds and formed colonies around them. The presence of the fungus inside and outside the seeds was also tested by the blotter technique[10]. These results would seem to indicate that the seeds which carry spores on their surface and those bearing mycelium on their parenchymatous tissues can both serve as sources of the inoculum. Consequently, the fungus is capable of infecting not only immature seeds in field conditions, it can also penetrate the hard core of mature seeds during harvest and storage. Fusarium, which was regarded as one among well-known 'field fungi'[11], has thus been found, for the first time, to invade seeds even during storage. In tropical countries, where warm and moist climates prevail, the incidence of secondary infection of seeds could be very high and, therefore, would involve high toxin risk in man and animals.

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The absolute configuration of SU 23397: A novel neuroleptic agent

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Summary. The absolute configuration of a novel chiral neuroleptic agent SU 23397 (**I**) was determined by ORD comparison of (+)-5-methoxy dihydro coumarilic acid (**VIII**), a synthetic precursor of SU 23397 (**I**), with (+)-dihydro coumarilic acid, whose absolute configuration is known[9]. This assignment was confirmed by oxidative degradation of (+)-5-methoxy dihydro coumarilic acid **VIII** to D-(+)-malic acid.

The antipsychotic activity of a novel chiral neuroleptic agent, SU 23397 (**I**) was recently described by 2 clinical groups[3,4]. It has been previously reported with other potent neuroleptic agents, e.g. octoclothepin[5] and butaclamol[6], that only one enantiomer of the racemic drug is active. SU 23397 (**I**) is the neuroleptically active (–)-enantiomer of such a racemic drug (**II**). We now describe the determination of the absolute configuration of SU 23397 (**I**) by both a chiro optical method and by degradation to a fragment of known absolute configuration.

SU 23397 (**I**) was originally prepared by Huebner by resolution via the N-acetyl-l-phenyl alanine salt of the racemate **II**[7]. The racemate **II** was prepared by alkylation of the commercially available (Aldrich Chemical Co.) triazaspirodecanone (**III**) with the bromo dihydro benzofuran **IV**[7] (scheme 1). The bromodihydro benzofuran **IV** was prepared by reaction of 2-allyl-4-methoxy phenol, obtained from a Claisen rearrangement, with bromine in the presence of a base. This compound **IV** is also available commercially (Alfred Bader Chemicals).

In order to provide a more efficient synthesis of SU 23397 (**I**), it was necessary to introduce the chirality earlier in the synthetic scheme and via an intermediate which could be epimerized and thus be recycled. (±)-5-methoxy dihydro coumarilic acid **VII** was such an intermediate. Dihydro coumarilic acid had been resolved via its amphetamine salts[8] and the absolute configuration of the enantiomers determined[9]. (±)-5-Methoxy coumarilic acid (**VI**), m.p. 211–213 °C, was synthesized by the procedure of Tanaka[10] and reduced in 91% yield by sodium amalgam in dilute aqueous base[8] to the previously undescribed (±)-5-methoxy dihydro coumarilic acid (**VII**), m.p. 99–102 °C (ex benzene). This acid **VII** was resolved via its amphetamine salts as was done for the unsubstituted acid[8]. The salt obtained with l-amphetamine, m.p. 159–162 °C (ex acetone), yielded the (+)-5-methoxy dihydro coumarilic acid (**VIII**) [m.p. 81–83 °C (ex benzene/pet ether); $[\alpha]_D^{25}$ + 37° ($CHCl_3$)] on treatment with cold 6N HCl. This acid **VIII** was reduced, by 1 h reflux in THF with excess $LiAlH_4$, to the carbinol **IX**

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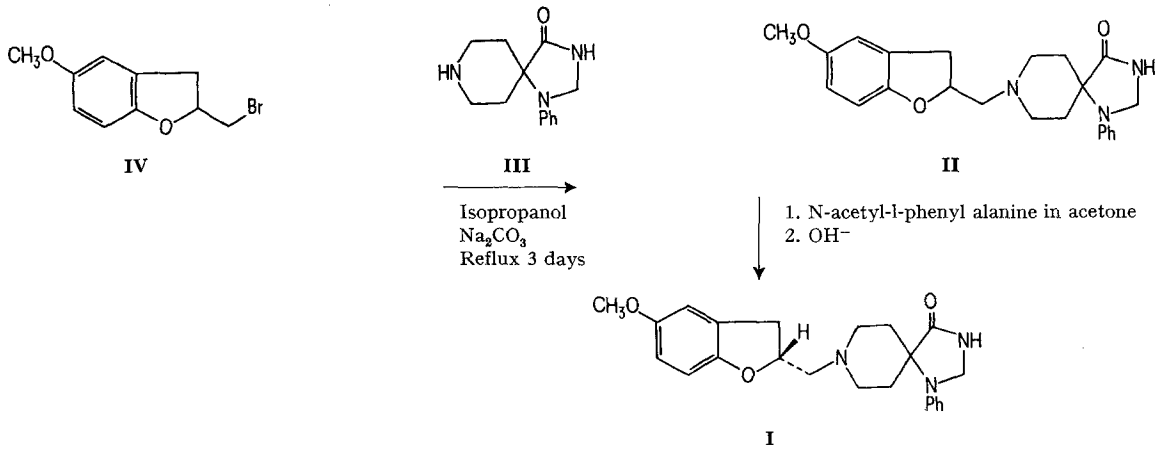
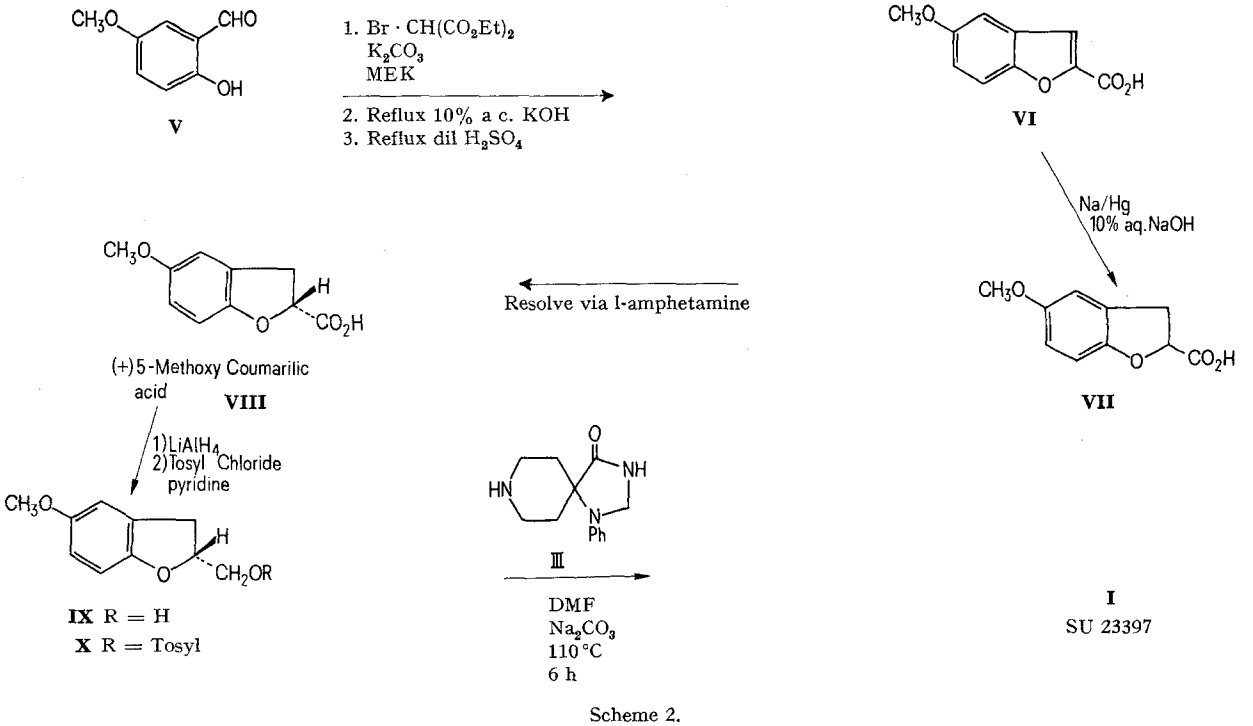
($[\alpha]_D^{25}$ – 49° ($CHCl_3$)), which was not characterized but used directly. The carbinol **IX** was dissolved in pyridine and reacted with p-toluene sulfonyl chloride. The tosylate **X** [m.p. 80–81 °C (ex. ether) $[\alpha]_D^{25}$ – 69.5° ($CHCl_3$)] was reacted in DMF with the triazaspirodecanone **III** and Na_2CO_3 as a catalyst to give in 56% yield, SU 23397 (**I**). The SU 23397 (**I**) obtained by this procedure (scheme 2) was identical in all respects with that obtained by resolution of the racemate **II** (scheme 1). Therefore, the determination of the absolute configuration of SU 23397 (**I**) can be accomplished by establishing the absolute configuration of (+)-5-methoxy dihydro coumarilic acid (**VIII**).

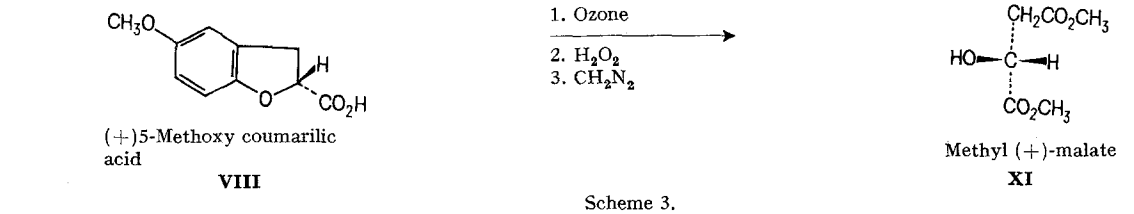
The ORD curve, to limits of experimental capability at that time, i.e. ~ 300 mμ, of (–)-dihydro coumarilic acid, had been published, i.e., $[\Phi]_{589}$ –30°; $[\Phi]_{400}$ –110°; $[\Phi]_{320}$



Scheme 1.



Scheme 2.



Scheme 3.

$-260°$[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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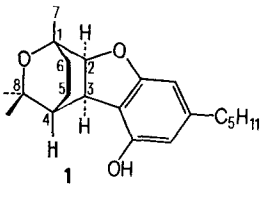
Summary. The synthesis of a novel cannabinoid containing a 1,8-cineol moiety (**1**) is described. It is much less biologically active than Δ^1-tetrahydrocannabinol.

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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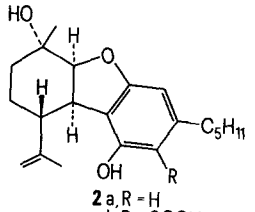
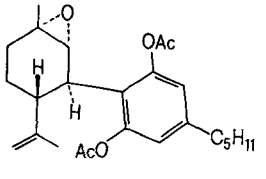


2 a, R = H
b, R = COOH



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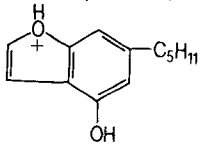

4

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

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