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# CANNABINOID ACIDS AND ESTERS: MINIATURIZED SYNTHESIS AND CHROMATOGRAPHIC STUDY

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**Key Word Index**—Miniaturised synthesis; GLC; TLC; cannabidiolic acid; $\Delta^1$-tetrahydrocannabinolic acids -A and -B; $\Delta^{1,6}$-tetrahydrocannabinolic acids -A and -B; cannabigerolic acid; cannabichromenic acid; cannabicyclolic acid; cannabielsoic acid -A; methyl esters; *bis*-homologues.

**Abstract**—Rapid miniaturised synthesis of methyl cannabidiolate, $\Delta^1$- and $\Delta^{1,6}$-tetrahydrocannabinolates -A and -B, cannabigerolate and cannabichromenate are described. These, together with methyl cannabielsoate -A, cannabinolates -A and -B, cannabicyclolate, cannabidiolate monomethyl ether and cannabigerolate monomethyl ether, as well as selected side chain *bis*-homologues, all accessible by small-scale synthesis, are used in a GLC and TLC study.

## INTRODUCTION

In recent years there has been much interest in the uncarboxylated (so-called 'neutral') cannabinoids isolated from *Cannabis sativa**: numbered among these is the psychotomimetic $\Delta^1$-tetrahydrocannabinol (**1**) [1–3]. The primary products of biosynthesis are, however, the corresponding series of carboxylic acids [1–3]: recent biosynthetic work supports this view [7]. Cannabigerolic acid (**13b**) is the first formed cannabinoid and it is considered that other cannabinoid acids are then derived by oxidation and cyclisation processes. Fresh plant material contains predominantly the cannabinoid acids [8] but these are unstable, and on storage the proportion of decarboxylated cannabinoids increases [9]. Both Korte [8] and Shoyama [7, 10, 11] take the view that only certain cannabinoid acids should be classed as true natural products.

Cannabidiolic acid (**11b**) is the longest-known representative [12–15]: two isomeric $\Delta^1$-tetrahydrocannabinolic acids, -A (**2b**) and -B (**3b**) have also been isolated from *C. sativa* [10, 15–17] and a short-chain modification, $\Delta^1$-tetrahydrocannabivarolic acid -A, has *n*-amyl replaced by *n*-propyl [18]. Two isomeric cannabielsoic acids, designated -A (**25b**) and -B (**24b**), have been isolated from natural sources [19], but there is some discussion about their status as true natural products [11]. It is generally agreed however that the cannabinolic acid -A (**8b**) found in *Cannabis* preparations is an artefact resulting from dehydrogenation on storage [1]. $\Delta^{1,6}$-Tetrahydrocannabinolic acids -A (**5b**) or -B (**6b**) have not yet been reported from plant sources, though they have been made from cannabidiolic acid [20, 23] and the -A representative has found utility as a hapten in immunological studies [21]. Similarly, although cannabidiol monomethyl ether is known [22], a natural acid corresponding to this is still awaited.

The important position of cannabigerolic acid (**13b**) [7, 14] in biosynthesis (it occurs along with its monomethyl ether [23]) is referred to above. Cannabichromenic acid (**15b**) [24] occurs in mature *C. sativa* and is especially prominent in seedlings during the first week or two after germination [24]: thereafter cannabidiolic acid and $\Delta^1$-tetrahydrocannabinolic acids become the predominant acids of the cannabinoid mixture, the latter acid being especially associated with plant parts in active growth [25]. *C. sativa*, harvested in the vegetative phase, and stored, yields substantial amounts of cannabicyclolic acid (**18b**) [11], but the circumstances of its isolation suggest that it is probably an artefact of cannabichromenic acid.

The cannabinoid acids decarboxylate rather readily and for this reason are often handled as methyl esters, formed by treatment with diazomethane, or in trimethylsilylated form. Despite the phytochemical significance of the group, direct synthetic attention has been limited. Mechoulam [26] reported that cannabidiol and cannabigerol [7] could be successfully carboxylated with methyl magnesium carbonate, but with $\Delta^1$-tetrahydrocannabinol the process was unsatisfactory. The only reports of direct synthesis of cannabinoid acids (as esters) are Petrzilka's report of the condensation of *p*-menthadienol with ethyl olivetolate to give ethyl cannabidiolate [27] and Merlini's alkylation of ethyl olivetolate anion with geranyl bromide to form cannabigerolic ester [28]. In neither case was the acid itself successfully isolated. In a recent study, synthetic samples of the naturally occurring cannabinoid acids have become available as their more easily handled methyl esters [29]: these can be cleaved to the acids with lithium *n*-propylmercaptide [30], or in some cases by gentle base hydrolysis.

The aim of this paper, complementary to our similar study on the cannabinoids themselves [31], is to make available details of miniaturised synthetic methods (1–20 mg scale) and to present chromatographic results on the cannabinoid esters prepared. These miniaturised methods give rapidly, on demand, small specimens of cannabinoids of the olivetolic ester series, or its homo-

*Until recently *C. sativa* was regarded as a single species having a variety of ecotypes and cultivated strains giving rise to differing cannabinoid mixtures [4]. Lately, the case has been presented for recognition of three distinct species, *C. sativa*, *C. indica* and *C. ruderalis* [5, 6].

Table 1. Acid catalysed condensation of methyl olivetolate (31c) with (+)-*p*-menthadienol (32)

| Run | 01-Me ester (31c), mg | *p*-MD (32)μl | $CH_2Cl_2$ μl | Catalyst | Conditions | Recovered (31c)% | Products %† CD-Me Ester (11a) | *o*-CD Me Ester (36) | THC-Mixture* |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1.4 | 1.0 | 193‡ | 2.2 mg *p*-TSA | 65°/1.5 hr | 19 | 75 | 4 | 4 |
| 2 | 15.7 | 11.0 | 500‡ | 2.5 mg *p*-TSA | 40°/1.5 hr | 52 | 61 | 10 | 17 |
| 3 | 199.0 | 140.0 | $5 \times 10^3$‡ | 48.1 mg *p*-TSA | 50°/0.25 hr§ | 40 | 70 | 5 | trace |
| 4 | 640.0 | 450.0 | $5 \times 10^4$ | 290 mg *p*-TSA | 22°/1 hr | 64 | 89 | — | — |
| 5 | 2.0 | 1.4 | 400‡ | 2%$BF_3.Et_2O$‖ | −5°/1.5 hr | 10 | 38 | — | — |
| 6 | 20.4 | 14.2 | 515 | 3.7%$BF_3.Et_2O$‖ | −10°/1.5 hr | 25 | 41 | | 3 |
| 7 | 540.0 | 380.0 | $3.5 \times 10^4$ | 0.25%$BF_3.Et_2O$‖ | 0°/2.25 hr | 30 | 24 | 0.1 | 34 |
| 8 | 11.7 | 8.1 | 500‡ | 3.5%$BF_3.Et_2O$‖ | 0°/1.5 hr | 35 | 2 | — | 26 |

*Composition of THC mixture (OV225, GLC):

| Run | $\Delta^{1,6}$-THC-Me ester -A (5a) + *iso*-THC-Me ester -A and -B (29a and 30a) | $\Delta^1$-THC-Me ester -A (2a) + $\Delta^{1,6}$-THC-Me ester -B (6a) | $\Delta^1$-THC-Me ester -B (3a) |
|---|---|---|---|
| 1 | 1 | 1 | 2 |
| 2 | 2 | 4 | 11 |
| 7 | 14 | 10 | 10 |
| 8 | 10 | 8 | 8 |

†In this and other tables, unless indicated otherwise, product yields are corrected for recovered (31c). ‡Anhydrous $MgSO_4$ added. §Then 20°/0.75 hr. ‖ % of final soln.

logues, for comparison purposes. Only a limited number of reagents need be kept in stock. The TLC and GLC data given should assist rapid identification of new, or known, cannabinoid acids from plant sources.

The synthetic methods employed are based on those used in cannabinoid synthesis [1–3] and involve acid catalysed electrophilic terpenylation of methyl olivetolate (31c) (or homologues) using optically active terpenes, (+)-*p*-menthadienol (32) and (−)-*trans*-verbenol (33) to obtain the methyl $\Delta^1$-, and $\Delta^{1,6}$-tetrahydrocannabinolates of the -A and -B types in the natural stereochemical series. Similar reaction with geraniol (34) gives methyl cannabigerolate. Methyl cannabichromenate is obtained by pyridine catalysed condensation of citral (35) with methyl olivetolate—an aldol-like reaction followed by electrocyclization. The other cannabinoid esters mentioned earlier are derivable from these products. Methyl cannabichromenate as obtained here is (±), but natural cannabichromenic acid is reported as having a low rotation [24]: in view of continuing doubts as to the optical inactivity of natural cannabichromene itself, the stereochemical status of these compounds deserves review. Cannabicyclolic acid, synthetic and of natural origin is racemic [11].

†Nomenclature and abbreviations. The system used earlier [31] for cannabinoids of the natural '*para*'-series is expanded. Thus $\Delta^1$-tetrahydrocannabinolic acid -A (2b) becomes $\Delta^1$-THC-$C_5$-acid-A and methyl $\Delta^1$-tetrahydrocannabinolate-A (2a) is $\Delta^1$-THC-Me-ester-A. Basic abbreviations for uncarboxylated cannabinoids are shown under the formulae (e.g. $\Delta^{1,6}$-THC, CCY etc.) and the descriptor following indicates the length of the *n*-alkyl chain in the phenol portion i.e. -$C_5$ for the common natural series: -$C_1$, -$C_3$, and -$C_4$ representatives have also been found in *Cannabis*. If this descriptor is dropped, -$C_5$ is implied. The prefix '*ortho*' or '*o*', signifies the unnatural series with the terpenic substituent *ortho* to the *n*-amyl of the phenolic ring (compare natural '*para*'-methyl cannabidiolate (11a) with unnatural '*ortho*' (36)).

## RESULTS

Miniaturised synthesis of all the naturally derived cannabinoid esters of the -$C_5$ series, with the exception of methyl cannabielsoate-B, have been investigated, and a selection of experimental conditions and results are recorded in Tables 1–6 [32].† Further details of TLC work-up and GLC monitoring are given in the Experimental. Reference materials were available from a larger scale investigation [29] and in some cases materials isolated from natural sources were available. Where necessary, purity or identity can be checked spectroscopically by techniques adapted to sub-mg methods—MS, UV, IR and FT-NMR: spectral comparison data are available [29]. In addition, the esters prepared were hydrolysed and decarboxylated and the products compared (GLC and TLC) with authentic cannabinoid samples [31].

Condensation of (+)-*p*-menthadienol (32) with methyl olivetolate (31c) in the presence of toluene-*p*-sulphonic acid gave satisfactory yields of methyl cannabidiolate (Table 1). The '*ortho*' contaminant and any compounds of the methyl tetrahydrocannabinolate series can be readily removed on TLC. Boron trifluoride etherate was generally less satisfactory as a catalyst though there was little evidence of the '*ortho*' isomer or THC esters under restrained conditions: under less restraint, the latter form readily. Substantial recoveries of methyl olivetolate were encountered in this and other reactions reported: yields have been corrected for the material recovered, which can be re-processed. Nonetheless lower conversions are a disadvantage in this series, relative to our earlier work on the cannabinoids themselves [31].

Although a mixture of THC-esters of the -A and -B series can be obtained by adjusting conditions in the previous reaction, it is desirable to carry the reaction only to the methyl cannabidiolate stage, isolate, and then cyclise as in Table 2. Despite this, the product situation is still complex. Methyl $\Delta^1$-tetrahydrocannabinolates -A (2a) and -B (3a), together with their so-called *iso*-

Table 2. Acid catalysed transformation of methyl cannabidiolate (11a)

| CD-Me ester (11a) mg | $CH_2Cl_2$ µl | Catalyst | Conditions | Recovered (11a)% | THC-esters | Products % Composition of THC-esters: $\Delta^{1,6}$-THC-Me ester -A + *iso*-THC-Me esters -A + B* | $\Delta^1$-THC-Me ester -A + $\Delta^{1,6}$-THC-Me ester B* | $\Delta^1$-THC-Me ester -B* |
|---|---|---|---|---|---|---|---|---|
| 0.6 | 200 | 2.6 mg *p*-TSA | 28°/ 3 days | 0 | 84 | 11 | 68 | 5 |
| 3.1 | 300 | 2% $BF_3.Et_2O$¶ | 18°/24 hr | 7 | 45 | 18 | 19 | 8 |
| 0.6 | 400 | 0.5% $BF_3.Et_2O$ | 7°/ 1.5 hr | 0 | 42 | 25 | 17 | — |

| | | | | | | $\Delta^1$-THC-Me ester -A† | $\Delta^1$-THC-Me ester B† | $\Delta^{1,6}$-THC-Me ester -A (+ *iso*)† | $\Delta^{1,6}$-THC-Me ester -B (+ *iso*)† |
|---|---|---|---|---|---|---|---|---|---|
| 52.0 | $5 \times 10^3$ | 65 mg *p*-TSA¶ | 22°/15 min (+ 50°/1.5 hr) | 5 | 50 | 13 | 9 | 17‡ | 11§ |
| 470.0 | $5 \times 10^3$ | 380 mg *p*-TSA | 22°/48 hr | 2 | 50 | 14 | 20 | 5 | 11 |

*OV-225 GLC column. †OV17 GLC column after TLC separation. ‡From NMR: 26% *iso*-THC-Me ester -A + 74% $\Delta^{1,6}$-THC-Me ester -A. §From NMR: 33% *iso*-THC-Me ester -B + 67% $\Delta^{1,6}$-THC-Me ester-B. ‖By GLC (OV-17) 33% *iso*-THC-Me ester -B and 67% $\Delta^{1,6}$-THC-Me ester-B. ¶ $MgSO_4$ added.

Table 3. Acid-catalysed condensation of methyl olivetolate (31c) with verbenol (33)

| 01-Me ester (31c), mg | Verb. (33), µl | $CH_2Cl_2$ µl | Catalyst | Conditions | Recovered (31c)% | Products %: *p*-VB-Me ester (27) | *o*-VB-Me ester | $\Delta^{1,6}$-THC-ester-A (5a) | $\Delta^{1,6}$-THC-ester-B (6a) |
|---|---|---|---|---|---|---|---|---|---|
| 2.2 | 3.0 | 200 | 2.6 mg *p*-TSA | 18°/ 1.5 hr | 43 | 32 | <2 | — | — |
| 5.0 | 4.9 | 200 | 2.6 mg *p*-TSA | 18°/ 1.5 hr | 42 | 38 | <4 | — | — |
| 7.1 | 4.7 | 500 | 6.5 mg *p*-TSA | 29°/15 min | 56 | 20 | 1 | 4.5 | 4.5 |

Table 4. Acid catalysed transformation of methyl *p*-verbenylolivetolate (27)

| VB-Me ester (27) mg | $CH_2Cl_2$ ml | Catalyst $BF_3.Et_2O$ 50% (µl) | Conditions | Recovered (27)% | Products %: $\Delta^{1,6}$-THC Ester -A (5a) | $\Delta^{1,6}$-THC Ester -B (6a) |
|---|---|---|---|---|---|---|
| 5 | 3 | 15 | 20°/5 min | 2.5 | 39 | 14 |
| 5 | 3 | 10 | 20°/5 min | 6.3 | 27 | 48 |
| 5 | 3 | 1 | 20°/5 min | 0.6 | 12 | 47.5 |

Table 5. Acid catalysed condensation of methyl olivetolate (31c) with geraniol (34)

| Run | 01-Me ester (31c), mg | Geran. (34) µl | $CH_2Cl_2$ µl | Catalyst | Conditions | Recovered (31c) % | Products %: CG-Me ester (13a) | *o*-CG-Me ester |
|---|---|---|---|---|---|---|---|---|
| 1 | 1.4 | 4.8 | 500 | 6.5 mg *p*-TSA | 25°/1.75 hr | 76 | 35 | 19 |
| 2 | 1.6 | 3.0* | 500 | 6.5 mg *p*-TSA | 25°/3.5 hr | 62 | 32 | 32 |
| 3 | 1.6 | 8.0† | 500 | 6.5 mg *p*-TSA | 25°/2.5 hr | 58 | 50 | 40 |
| 4 | 2.2 | 1.7 | 500 | 6.5 mg *p*-TSA | 25°/2 hr | 83 | 21 | 16 |
| 5 | 1.6 | 1.0+‡ | 500 | 0.125% $BF_3.Et_2O$§ | 0–5°/24 hr | 83 | 45 | 37 |
| 6 | 1.6 | 3.0 | 500 | 0.5% $BF_3.Et_2O$ | 0–5°/4 hr | 49 | 34 | 11 |
| 7 | 1.4 | 12.0 | 500 | 0.5% $BF_3.Et_2O$ | 0°/5 min | 59 | 47 | 27 |
| 8 | 1.6 | 15.0 | 500 | 0.125% $BF_3.Et_2O$ | 0–5°/24 hr | 80 | 49 | 33 |

*Added at intervals. †Geraniol pre-treated with *p*-TSA (2 hr) and then (31c) added. ‡Extra geraniol added at intervals. §Magnesium sulphate added.

Table 6. Pyridine catalysed condensation of methyl olivetolate (31c) with citral (35)

| 01-Me ester (31c) mg | Citral µl | Pyridine µl | Conditions | Recovered (31c) % | Products % Olivetol | CC (14) | o-CC | CCI (20) | CC-Me ester (15a) |
|---|---|---|---|---|---|---|---|---|---|
| 130 | 93 | 66 | 145°/5 hr | 43 | 16 | 4 | 4 | 14 | 15 |
| 130 | 93 | 66 | 125°/5 hr | 52 | | traces | | | 8 |
| 130 | 93 | 66 | 165°/5 hr | 0 | 15 | — | 3 | 17 | 0 |

compounds (30a) and (29a), and methyl $\Delta^{1,6}$-tetrahydrocannabinolates -A (5a) and -B (6a), form. Conditions have not been established which avoid production of the latter two pairs and addition of anhydrous magnesium sulphate [33] appeared to have little influence on the formation of the $\Delta^{1,6}$-compounds. Nevertheless, using toluene-*p*-sulphonic acid, a yield of >80% of mixed THC-esters could be attained with complete utilisation of the starting material. Boron trifluoride etherate-catalysed reaction was less easy to control and produced more unwanted *iso*-THC's.

TLC of the THC-esters produced allowed separation of the -A group and collection of the mixed -B group. Thus methyl $\Delta^1$-tetrahydrocannabinolate -A (2a) could be isolated as well as a mixture of methyl $\Delta^{1,6}$-tetrahydrocannabinolate -A (5a) with methyl *iso*-tetrahydrocannabinolate -A (30a). By TLC of the -B groups, under different conditions, methyl $\Delta^1$-tetrahydrocannabinolate -B (3a) could be isolated but the mixture of the $\Delta^{1,6}$- and *iso*-compounds of the -B, (6a) and (29a), group again could not be separated. It is thus best to employ this reaction to obtain specimens of methyl $\Delta^1$-tetrahydrocannabinolates -A and -B and to use the following reaction to obtain the corresponding $\Delta^{1,6}$-compounds.

Acid catalysed verbenylation of methyl olivetolate allows the formation of methyl '*p*'-verbenylolivetolate (27) in around 40% yield with very little '*ortho*' impurity and no further reaction to give THC-esters (Table 3). On a preparative scale substantially higher yields have been obtained [29]. Brief treatment with boron trifluoride etherate then gave $\Delta^{1,6}$-tetrahydrocannabinolates -A (5a) and -B (6a), separable by TLC (Table 4). The ratio of the two esters was responsive to the acid catalyst concentration and, depending on requirements, the $\Delta^{1,6}$-A ester could be obtained in ~40%, and the $\Delta^{1,6}$-B ester in ~50%, yield.

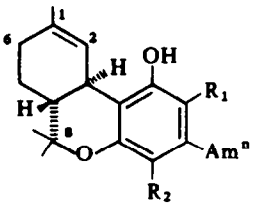
Acid catalysed geranylation of methyl olivetolate was examined on a miniaturized scale using both toluene-*p*-sulphonic acid and boron trifluoride etherate (Table 5). In all cases there was a large recovery of unused methyl olivetolate, even when excess geraniol was employed. Both methyl cannabigerolate (13a), and its '*ortho*'-isomer, were formed, and separated and purified by TLC. As discussed elsewhere [29], the reaction is complex as both geraniol (34) and cannabigerols are subject to further acid-catalysed transformations: addition of further geraniol during the reaction is sometimes beneficial.

Methyl cannabichromenate can be obtained, but only in modest yield, by chromenylating methyl olivetolate (31c) with citral (35) in the presence of pyridine at 145°. Table 6 illustrates the problem. At too low a temperature there is insufficient reaction to give an optimum yield of methyl cannabichromenate, but at too high a temperature there is extensive decarbomethoxylation and all the products belong to the uncarboxylated cannabinoid series. At a compromise temperature, compounds of the latter series are still formed—cannabichromen (14) cannabicyclol (17) and cannabicitran (20) along with

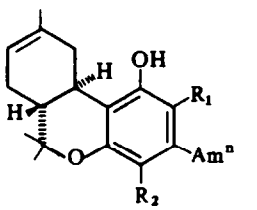
Table 7. TLC Chromatographic characteristics of synthetic cannabinoids

| Cannabinoid | | Colour with Fast Blue Salt B | Silica gel G systems* ($R_f$ Values) $Et_2O$–*n*-Hexane (1:19) | $CHCl_3$–*n*-Hexane (1:4) | $Et_2O$–*n*-Hexane (33:67) | $CHCl_3$ | $AgNO_3$/Silica gel G systems† ($R_f$ values) Korte system‡ | $Et_2O$–*n*-Hexane (1:19) | $Et_2O$–*n*-Hexane (33:67) |
|---|---|---|---|---|---|---|---|---|---|
| $\Delta^1$-THC-$C_5$-Me Ester -A | (2a) | Deep pink red | 0.45 | 0.27 | 0.90 | 0.89 | 0.98 | 0.41 | 0.80 |
| $\Delta^1$-THC-$C_5$-Me Ester -B | (3a) | Purple red | 0.02 | 0.01 | 0.40 | 0.42 | 0.23 | 0.00 | 0.31 |
| $\Delta^{1,6}$-THC-$C_5$-Me Ester -A | (5a) | Deep pink red | 0.51 | 0.29 | 0.92 | 0.95 | 0.98 | 0.46 | 0.82 |
| $\Delta^{1,6}$-THC-$C_5$-Me Ester -B | (6a) | Orange red | 0.02 | 0.01 | 0.42 | 0.44 | 0.29 | 0.00 | 0.35 |
| CN-$C_5$-Me Ester -A | (8a) | Purple blue | 0.45 | 0.27 | 0.85 | 0.89 | 0.96 | 0.50 | 0.79 |
| CN-$C_5$-Me Ester -B | (9a) | Brown purple | 0.02 | 0.00 | 0.34 | 0.42 | 0.11 | 0.00 | 0.38 |
| CD-$C_5$-Me Ester | (11a) | Pink orange | 0.34 | 0.27 | 0.80 | 0.90 | 0.54 | 0.02 | 0.38 |
| CG-$C_5$-Me Ester | (13a) | Pink orange | 0.14 | 0.11 | 0.60 | 0.83 | 0.65 | 0.00 | 0.43 |
| CC-$C_5$-Me Ester | (15a) | Red purple | 0.50 | 0.25 | 0.90 | 0.91 | 0.97 | 0.35 | 0.80 |
| CCY-$C_5$-Me Ester | (18a) | Pink | 0.57 | 0.31 | 0.93 | 0.93 | 0.98 | 0.65 | 0.90 |
| CE-$C_5$-Me Ester -A | (25a) | Purple red | 0.00 | 0.00 | 0.29 | 0.40 | 0.60 | 0.00 | 0.20 |
| CD-$C_5$-Me Ester monomethyl ether | | Very pale pink brown with $I_2$ | 0.48 | 0.30 | 0.80 | 0.96 | 0.99 | — § | — § |
| CG-$C_5$-Me Ester monomethyl ether | | Very pale pink brown with $I_2$ | 0.48 | 0.30 | 0.81 | 0.98 | 0.99 | — § | — § |
| VB-$C_5$-Me Ester | (27) | Salmon pink | 0.46 | 0.39 | 0.78 | 0.92 | 0.86 | 0.54 | 0.86 |
| CD-$C_1$-Me Ester | | Pink orange | 0.19 | 0.20 | 0.53 | 0.88 | 0.15 | 0.02 | 0.33 |
| CC-$C_1$-Me Ester | | Red purple | 0.41 | 0.25 | 0.82 | 0.89 | 0.92 | 0.30 | 0.81 |
| CCY-$C_1$-Me Ester | | Pink | 0.45 | 0.27 | 0.85 | 0.91 | 0.93 | 0.57 | 0.86 |
| $\Delta^{1,6}$-THC-$C_3$-Me Ester -A | | Deep pink red | 0.50 | 0.27 | 0.88 | 0.94 | 0.98 | 0.27 | 0.83 |
| $\Delta^{1,6}$-THC-$C_3$-Me Ester -B | | Orange red | 0.01 | 0.01 | 0.31 | 0.42 | 0.11 | 0.00 | 0.33 |
| VB-$C_3$-Me Ester | | Salmon pink | 0.42 | 0.34 | 0.75 | 0.93 | 0.74 | 0.45 | 0.81 |
| $\Delta^{1,6}$-$C_5$-THC‖ | (4) | Deep pink red | 0.12 | 0.07 | 0.67 | 0.73 | 0.67 | 0.09 | 0.70 |

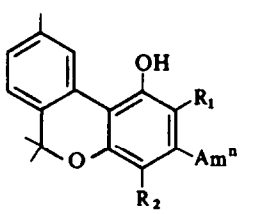
*Silica gel G 5 × 20 cm or 20 × 20 cm plates; thickness 0.5 mm. †Silica gel G: $AgNO_3$, 5:1 ratio, 20 × 20 cm plates; thickness 0.5 mm. ‡Silica gel G 20 × 20 cm plates; thickness 0.5 mm impregnated with $HCONMe_2$–$CCl_4$ (3:2), dried at 20°/15 min and eluted with cyclohexane. §Compounds difficult to detect. ‖Standard for comparison.



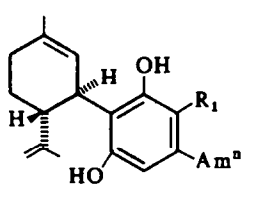
(1) $R_1 = R_2 =$ ($\Delta^1$-THC)
(2a) $R_1 = CO_2Me$, $R_2 = H$
(2b) $R_1 = CO_2H$, $R_2 = H$
(3a) $R_1 = H$, $R_2 = CO_2Me$
(3b) $R_1 = H$, $R_2 = CO_2H$



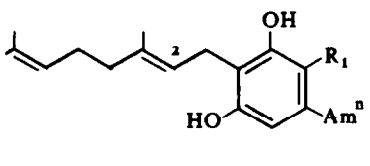
(4) $R_1 = R_2 = H$ ($\Delta^{1,6}$-THC)
(5a) $R_1 = CO_2Me$, $R_2 = H$
(5b) $R_1 = CO_2H$, $R_2 = H$
(6a) $R_1 = H$, $R_2 = CO_2Me$
(6b) $R_1 = H$, $R_2 = CO_2H$



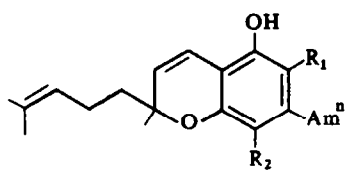
(7) $R_1 = R_2 = H$ (CN)
(8a) $R_1 = CO_2Me$, $R_2 = H$
(8b) $R_1 = CO_2H$, $R_2 = H$
(9a) $R_1 = H$, $R_2 = CO_2Me$
(9b) $R_1 = H$, $R_2 = CO_2H$



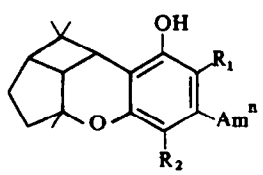
(10) $R_1 = H$ (CD)
(11a) $R_1 = CO_2Me$
(11b) $R_1 = CO_2H$



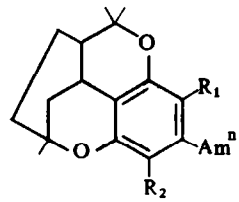
(12) $R_1 = H$ (CG)
(13a) $R_1 = CO_2Me$
(13b) $R_1 = CO_2H$



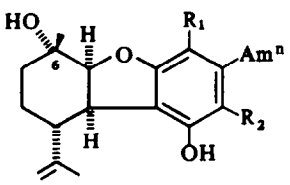
(14) $R_1 = R_2 = H$ (CC)
(15a) $R_1 = CO_2Me$, $R_2 = H$
(15b) $R_1 = CO_2H$, $R_2 = H$
(16a) $R_1 = H$, $R_2 = CO_2Me$
(16b) $R_1 = H$, $R_2 = CO_2H$



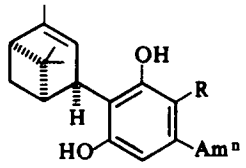
(17) $R_1 = R_2 = H$ (CCY)
(18a) $R_1 = CO_2Me$, $R_2 = H$
(18b) $R_1 = CO_2H$, $R_2 = H$
(19a) $R_1 = H$, $R_2 = CO_2Me$
(19b) $R_1 = H$, $R_2 = CO_2H$



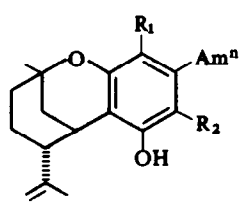
(20) $R_1 = R_2 = H$ (CCl)
(21a) $R_1 = CO_2Me$, $R_2 = H$
(21b) $R_1 = CO_2H$, $R_2 = H$
(22a) $R_1 = H$, $R_2 = CO_2Me$
(22b) $R_1 = H$, $R_2 = CO_2H$



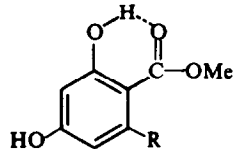
(23) $R_1 = R_2 = H$ (CE)
(24a) $R_1 = CO_2Me$, $R_2 = H$
(24b) $R_1 = CO_2H$, $R_2 = H$
(25a) $R_1 = H$, $R_2 = CO_2Me$
(25b) $R_1 = H$, $R_2 = CO_2H$



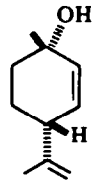
(26) R = H (VB)
(27) R = $CO_2Me$



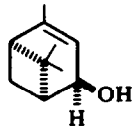
(28) $R_1 = R_2 = H$ (*iso*-$\Delta^8$-THC)
(29a) $R_1 = CO_2Me$, $R_2 = H$
(29b) $R_1 = CO_2H$, $R_2 = H$
(30a) $R_1 = H$, $R_2 = CO_2Me$
(30b) $R_1 = H$, $R_2 = CO_2H$



(31a) R = Me
(31b) R = $Pr^n$
(31c) R = $Am^n$ (OI Me-Ester)



(32) *p*-MD



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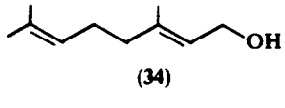
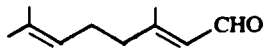


(34)



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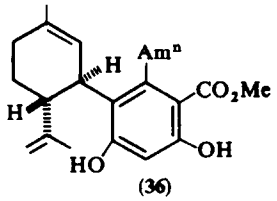

(36)

olivetol and the required methyl cannabichromenate (**15a**), but the latter is relatively easily isolated by TLC. Fortunately the chromenylation is regiospecific [34] and we have not detected B-type (**16a**) or '*ortho*' isomer. Cannabicitran esters (**21a**) and (**22a**) were also not found.

The photochemical cyclization of methyl cannabichromenate proceeded in excellent yield to give methyl cannabicyclolate (**18a**) [11]. Dehydrogenation of methyl $\Delta^{1,6}$-tetrahydrocannabinolates -A and -B was adaptable to small-scale work to give methyl cannabinolates -A (**8a**) and -B (**9a**) [29]. Methyl cannabielsoate -A (**25a**) [35], methyl cannabigerolate monomethyl ether, and methyl cannabidiolate monomethyl ether were also prepared by adaption of methods suitable for larger scale work. Samples of cannabinoid acids were prepared by the methods mentioned earlier.

TLC data for the cannabinoid methyl esters are shown in Table 7. The most useful general system is ether–hexane–silica G, using ether–hexane (1:19) for compounds of high $R_f$ such as methyl cannabidiolate (**11a**), methyl $\Delta^1$- and $\Delta^{1,6}$-tetrahydrocannabinolate -A (**2a**) and (**5a**) methyl cannabichromenate (**15a**), methyl cannabinolate -A (**8a**) and methyl cannabicyclolate (**18a**). For compounds of low $R_f$ such as methyl $\Delta^1$- and $\Delta^{1,6}$-tetrahydrocannabinolate -B (**3a**) and (**6a**) and methyl cannabinolate -B (**9a**) ether–hexane (33:67) was used, and this was also used for decarboxylated cannabinoids. Methyl cannabigerolate is best run in ether–hexane

containing 10–20% of the former. Although mixtures of cannabinoid esters can be separated successfully in many cases, such separations are generally less easy than in the case of uncarboxylated cannabinoids e.g. the separation of methyl $\Delta^1$-tetrahydrocannabinolate -A from methyl cannabinolate -A or from methyl cannabichromenate. The corresponding -B esters are similarly difficult to separate. However, these pairs are resolved by GLC. A particularly useful feature of TLC methods is the very ready separation of esters of the -A series from those of the -B series.

The Korte system, valuable for the uncarboxylated cannabinoids [4], is less useful with these esters. Silver nitrate systems are also less effective but do improve certain difficult separations such as the resolution of methyl $\Delta^1$-tetrahydrocannabinolate -A from methyl cannabichromenate -A or methyl cannabinolate. For the cannabinoid acids, Mechoulam's mixture (benzene–methanol–acetic acid) [17] is useful, though separations are not easy. However the acids are readily decarboxylated and separated in that form [31].

There is a broad similarity between the Fast Blue Salt B colours given by cannabinoid esters and the decarbomethoxylated counterparts [31] i.e. methyl cannabidiolate and methyl cannabigerolate, orangey tones; methyl cannabichromenate and methyl cannabinolate, purple tones; methyl cannabicyclolate, pink. Compounds of the -A and -B series show different colours, e.g. methyl $\Delta^1$- and $\Delta^{1,6}$-tetrahydrocannabinolate -A (like $\Delta^1$- and $\Delta^{1,6}$-tetrahydrocannabinols), crimson–red, whilst methyl $\Delta^1$-tetrahydrocannabinolate -B gives a purplish–red and methyl $\Delta^{1,6}$-tetrahydrocannabinolate an orangey–red. Similarly methyl cannabinolate -A gives, like cannabinol, a bluish–purple whilst the -B isomer gives a brownish–purple. These differing responses provide a valuable guide in dealing with mixtures and reaction products.

In GLC work the un-trimethylsilylated methyl esters of the cannabinoid acids give rather poor separations and require rather high temperature (OV-17 column). For this reason most of our work has been done on trimethylsilylated (BSTFA) compounds. Best separations were obtained by using SCOT OV225 columns (215°, or programmed runs), though where fine separations were not required in examining reaction products we have also used the less efficient OV17 (274 cm column, 230°). Data are summarized in Table 8. Retention orders on these two phases may differ, e.g. on the OV17 system the -B esters emerge just before the corresponding -A esters and do not separate satisfactorily, whereas on the OV225 system the order is reversed and separations complete. Comparison of OV17 and OV225 phases, both as SCOT columns, showed that separations among the cannabinoid methyl esters are poorer with the former.

Such overlaps as do occur in the GLC work can

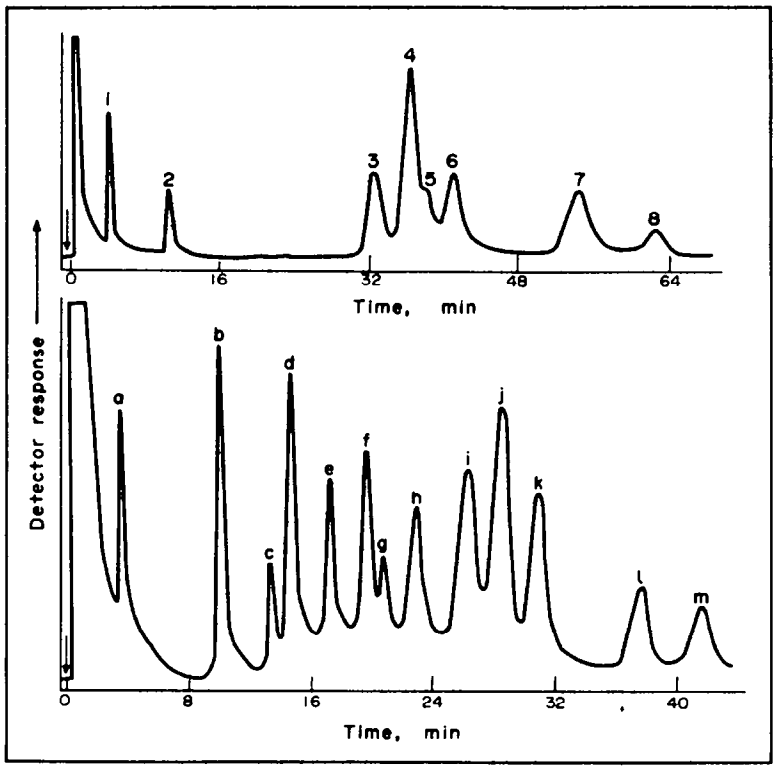


Fig. 1. GLC of trimethylsilylated (BSTFA + 1% TMCS) cannabinoid methyl ester mixtures (4 μl), OV225 SCOT column (15 m × 0.05 cm), $N_2$ 5 ml/min, FID at oven temp. Upper block: unprogrammed, temp. 214°. Lower block: programme 3 min at 205°, then 2°/min until 225°. 1. 01-Me ester; 2. $\Delta^{1,6}$-THC-$C_5$; 3. $\Delta^{1,6}$-THC-$C_5$-Me ester -A; 4. $\Delta^1$-THC-$C_5$-Me ester -A + $\Delta^{1,6}$-THC-$C_5$-Me ester -B; 5. CG-$C_5$-Me ester monomethyl ether; 6. $\Delta^1$-THC-$C_5$-Me ester -B; 7. CN-$C_5$-Me ester -A + CE-$C_5$-Me ester -A; 8. CN-$C_5$-Me ester -B; a. Docosane; b. CD-$C_1$-Me ester; c, CCY-$C_1$-Me ester; d, CD-$C_5$-Me ester; e. CC-$C_1$-Me ester; f. $\Delta^{1,6}$-THC-$C_3$-Me-ester -A + CCY-$C_5$-Me ester; g. $\Delta^{1,6}$-THC-$C_3$-Me ester -B; h. CG-$C_5$-Me ester; i. CC-$C_5$-Me ester + $\Delta^{1,6}$-THC-$C_5$-Me ester -A; j. $\Delta^{1,6}$-THC-$C_5$-Me ester -B + $\Delta^1$-THC-$C_5$-Me ester -A; k. $\Delta^1$-THC-$C_5$-Me ester -B; l. CN-$C_5$-Me ester -A; m. CN-$C_5$-Me ester -B.

Table 8. GLC characteristics of silylated synthetic cannabinoids*

| Cannabinoid | | Retention time, mins OV 17† | OV 225 SCOT‡ |
|---|---|---|---|
| 01-Me ester | (31c) | 4.36 | 2.84 |
| 01-Acid | | 5.16 | 2.76 |
| CD-$C_1$-Me ester | | 9.84 | 5.60 |
| CC-$C_1$-Me ester | | 16.00 | 11.80 |
| CC-$C_1$-Acid | | 18.04 | 11.16 |
| CCY-$C_1$-Me ester | | 12.28 | 8.24 |
| CCY-$C_1$-Acid | | 13.24 | 7.40 |
| VB-$C_3$-Me ester | | 21.08 | 11.68 |
| $\Delta^{1,6}$-THC-$C_3$-Me ester -A | | 22.00 | 14.24 |
| $\Delta^{1,6}$-THC-$C_3$-Me ester -B | | 21.08 | 15.32 |
| CD-$C_5$-Me ester | (11a) | 17.96 | 8.40 |
| CD-$C_5$-Acid | (11b) | 18.48 | 7.60 |
| *o*-CD-$C_5$-Me ester | (36) | 22.44 | 11.24 |
| CD-$C_5$-Me ester monomethyl ester | | 21.20 | 10.76 |
| CE-$C_5$-Me ester -A | (25a) | 39.96 | 35.28 |
| *iso*-CE-$C_5$-Me ester -A | | 37.84 | 31.00 |
| CC-$C_5$-Me ester | (15a) | 32.92 | 20.64 |
| CC-$C_5$-Acid | (15b) | 35.28 | 18.52 |
| CCY-$C_5$-Me ester | (18a) | 24.52 | 13.52 |
| CCY-$C_5$-Acid | (18b) | 24.44 | 11.72 |
| CG-$C_5$-Me ester | (13a) | 33.00 | 17.24 |
| CG-$C_5$-Acid | (13b) | 32.80 | 15.24 |
| *o*:CG:$C_5$-Me ester | | 34.40 | 19.35 |
| CG-$C_5$-Me ester monomethyl ether | | 41.88 | 24.36 |
| VB-$C_5$-Me ester | (27) | 32.80 | 16.96 |
| $\Delta^1$-THC-$C_5$-Me ester -A | (2a) | 37.56 | 23.12 |
| $\Delta^1$-THC-$C_5$-Acid-A | (2b) | 37.24 | 20.16 |
| $\Delta^1$-THC-$C_5$-Me ester B | (3a) | 36.76 | 26.04 |
| $\Delta^{1,6}$-THC-$C_5$-Me ester -A | (5a) | 35.92 | 21.64 |
| $\Delta^{1,6}$-THC-$C_5$-Acid -A | (5b) | 36.04 | 18.36 |
| $\Delta^{1,6}$-THC-$C_5$-Me ester -B | (6a) | 33.52 | 23.28 |
| $\Delta^{1,6}$-THC-$C_5$-Acid -B | (6b) | 36.76 | 21.68 |
| *iso*-THC-$C_5$-Me ester -B | (29a) | 30.92 | 20.88 |
| CN-$C_5$-Me ester -A | (8a) | 49.04 | 33.40 |
| CN-$C_5$-Me ester -B | (9a) | 47.60 | 38.52 |
| $\Delta^{1,6}$-THC-$C_4$ | (4) | 14.00 | 6.88 |

*Cannabinoids silylated by treatment with BSTFA containing 1% TMCS and heating at 85° for 15 mins.

†Conditions: glass column 2.74 × 0.006 m packed with 3% OV 17 on diatomite C AWDMCS (100/120). $N_2$ 100 ml/min. Oven temp. 233°. 1–2 μl injected directly onto column. Flame ionization detector. Retention times of standards: docosane 5.16, $\Delta^4$-androsten-3,17-dione 63.60, dibenzylphthalate 95.60 min.

‡Conditions: SCOT stainless steel OV 225 column 15.25 × 0.0005 m (Perkin–Elmer). $N_2$ 7 ml/min. Oven temp. 215°. Injection temp. 280°. Flame ionization detector. Retention times of standards: docosane 2.00, tetracosane 3.12, octacosane 9.76 min.

generally be avoided by prior TLC separation into the -A and -B groups of esters e.g. this circumvents the overlap between methyl $\Delta^{1,6}$-tetrahydrocannabinolate-B and methyl $\Delta^1$-tetrahydrocannabinolate -A. Typical GLC separations are shown in Fig. 1. The upper diagram illustrates the behaviour of methyl esters of various cannabinoids of the -$C_5$ group (methyl olivetolate and $\Delta^{1,6}$-tetrahydrocannabinol are included for reference), whilst the lower temperature-programmed run also includes various representatives of the -$C_1$ and -$C_3$ series.

This study has shown that using miniaturised reactions, GLC for monitoring, and TLC for isolation, it is feasible to quickly obtain specimens of almost all the known cannabinoid acids as their methyl esters, even though there are greater difficulties than in the uncarboxylated cannabinoid series studied earlier [11]. The methods are generally applicable, with minor modification, to other known, or as yet unknown, cannabinoid ester series of natural origin e.g. with resorcinol side chains of Me, *n*-Pr, *n*-Bu. Only a small stock of a relatively few, stable, starting materials is required. This type of approach is applicable to other groups of natural products where homology and the existence of related sets of compounds leads to difficulties in obtaining specific reference specimens.

## EXPERIMENTAL

Reactions were usually carried out in Reactivials (Pierce Chemicals) of 0.6 ml total capacity. Yields of products were determined by GLC using an added standard, frequently docosane. Products were chromatographed on Silica-G (20 × 20 cm., 0.5 mm thickness) using solvent systems indicated below. Band positions were located by (a) inspection in UV light, (b) strip-spraying with Fast-Blue Salt B. The cannabinoid esters were recovered by $Et_2O$ extraction, and their purity determined by trimethylsilylation (bistrimethylsilyl-trifluoroacetamide + 1% trimethylchlorosilane, 85°, 15 min) and GLC using a 1.5.4 m SCOT OV225 column. TLC provided a further check. The various reaction products were isolated and monitored as follows:

*Methyl cannabidiolate* (**11a**). TLC (5% $Et_2O$ in hexane) sepd high $R_f$ CD-Me ester from small amounts of '*ortho*'-isomer and methyl olivetolate which remained at the base of the plate. If a specimen of '*ortho*'-CD-Me ester is required, careful TLC (33% $Et_2O$ in hexane) will separate it from methyl olivetolate. Any traces of THC-methyl esters -B separate easily from CD-Me ester, but make it difficult to purify '*ortho*'-CD-Me ester. Monitoring: GLC (OV225) separates all the components.

*Methyl $\Delta^1$-tetrahydrocannabinolate -A* (**2a**) *and -B* (**3a**) *prepared from methyl cannabidiolate.* TLC (5% $Et_2O$ in hexane) separates CD-Me ester, $\Delta^1$-THC Me ester -A, $\Delta^{1,6}$-THC Me ester -A + *iso*-THC Me ester -A, and the ester -B group of compounds. Further TLC of the low $R_f$ ester -B group (33% $Et_2O$ in hexane, double elution) separates $\Delta^1$-THC-Me ester -B from $\Delta^{1,6}$-THC-Me ester -B + *iso*-THC-Me ester -B. It is difficult to separate the latter pair and we have only done this by direct crystallization on larger samples. The best approach is to stop the reaction before excessive amounts of $\Delta^{1,6}$-THC-methyl ester forms and to employ the reaction for making the $\Delta^1$-series. Monitoring: GLC (OV225) separates CD-Me ester, $\Delta^{1,6}$-THC-Me ester -A, $\Delta^{1,6}$-THC-Me ester -B + $\Delta^1$-THC-Me ester -A, and $\Delta^1$-THC-Me ester -B. GLC after TLC separation of the ester -A and ester -B groups, allows resolution of the $\Delta^{1,6}$-THC-Me ester B/$\Delta^1$-THC-Me ester -A ester overlap. Similarly *iso*-THC-Me ester -B can be resolved from $\Delta^{1,6}$-THC-Me ester -B.

*Methyl $\Delta^{1,6}$-tetrahydrocannabinolate -A* (**5a**) *and -B* (**6a**) *by the verbenol route.* (a) *Formation of the verbenyl intermediate* (**27**). TLC (5% $Et_2O$ in hexane) easily sepd the '*para*' intermediate (**27**) from unchanged methyl olivetolate and any small amount of '*ortho*' isomer could also be removed. Monitoring; GLC (OV225) separation complete. (b) *Formation of* (**5a**) *and* (**6a**). TLC (5% $Et_2O$ in hexane) separated $\Delta^{1,6}$-THC-Me ester -A from both the starting material and $\Delta^{1,6}$-THC-Me ester -B. Monitoring: GLC (OV225), separations complete.

*Methyl cannabinolate -A* (**8a**) *and -B* (**9a**). As formed by miniaturized sulphur dehydrogenation of $\Delta^{1,6}$-THC methyl ester -A, CN-Me ester -A could be separated by TLC (5% $Et_2O$ in hexane, double elution). The -B series was similar but sulphur impurities were difficult to remove. Monitoring: GLC (OV225) separations complete.

*Methyl cannabigerolate* (**13a**). CG-Me ester separated completely from methyl olivetolate on TLC (10 or 20% $Et_2O$ in hexane). '*ortho*'-CG-Me ester has a low $R_f$ and can be separated

from methyl olivetolate by further TLC (33% $Et_2O$ in hexane). Monitoring: GLC (OV225), separations complete.

*Methyl cannabichromenate* (**15a**). CC-Me ester separates easily from the reaction products by TLC (5% $Et_2O$ in hexane) even though decarboxylation and further reaction to produce cannabichromen, cannabicitran and cannabicyclol have occurred Monitoring GLC (OV225), separations complete.

*Methyl cannabicyclolate* (**18a**) Photochemical transformation of methyl cannabichromenate [11, 29] is successful on a very small scale and TLC (5% $Et_2O$ in hexane) gave complete purification. Monitoring: GLC (OV225), separations complete.

*Methyl cannabielsoate -A* (**25a**). Products from Mechoulam's photochemical reaction [19] were separated by TLC (20% $Et_2O$ in hexane). There is complete separation of methyl cannabielsoate -A from methyl *iso*-cannabielsoate -A and CD-Me ester. Monitoring: GLC (OV225), separations complete.

*Monomethyl ether of methyl cannabidiolate* (**11a**, *with unchelated hydroxyl methylated*). This was formed by protracted diazomethane treatment and purified by TLC (5% $Et_2O$ in in hexane) which removed remaining CD-Me ester. Monitoring: GLC (OV225), separations complete.

*Monomethyl ether of methyl cannabigerolate* (**13a**, *with unchelated hydroxyl methylated*). Formed as above, TLC (10% $Et_2O$ in hexane) separated it completely from unchanged CG-Me ester. Monitoring: GLC (OV225), separations complete.

*Cannabinoid acids.* When prepared from the corresponding esters either by lithium *n*-propylmercaptide reagent or gentle alkaline hydrolysis, TLC ($C_6H_6$–MeOH–HOAc (44:5:1) [17] was used to separate the acid from unchanged ester or decarboxylated cannabinoid. Methanolic alkaline hydrolysis is suitable only if the acid is not decarboxylated too readily e.g. CC-Acid, CD-acid.

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