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CANNABINOID BIS-HOMOLOGUES: MINIATURISED SYNTHESIS AND GLC STUDY

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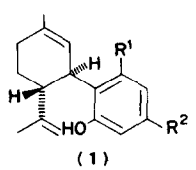
Key Word Index—Miniaturised syntheses; cannabidiol; Δ^1- and $\Delta^{1,6}$-tetrahydrocannabinol; cannabinol; cannabigerol; cannabichromen; cannabicyclol; cannabicitran; bis-homologues.

Abstract—Rapid miniaturised syntheses (1–20 mg.) of the cannabidiol, Δ^1- and $\Delta^{1,6}$-tetrahydrocannabinol, cannabinol, cannabigerol, cannabichromen, cannabicyclol and cannabicitran structures with Me, Pr^n, Am^n and $Hept^n$ side-chains have been carried out. This makes possible a GLC, and TLC, study of these 32 natural, or potentially natural, cannabinoids.

INTRODUCTION

The cannabinoids are meroterpenes found in fresh or dried *Cannabis sativa* [1–3]. Members of the class may be true natural products, or artefacts, and include the psychotomimetically active substances. Much of interest centres on the eight structure-types (**1–8**), although other cannabinoid types are known in *Cannabis* sources (e.g. methyl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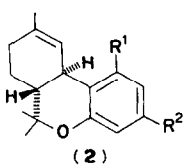
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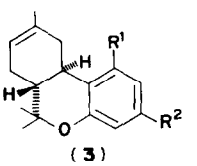
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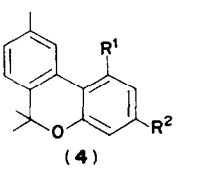
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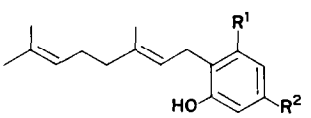
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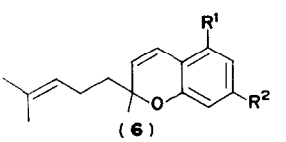
(a) R^1 = OH; R^2 = Me
(b) R^1 = OH; R^2 = Pr^n
(c) R^1 = OH; R^2 = Am^n
(d) R^1 = OH; R^2 = $Hept^n$
(e) R^1 = Me; R^2 = OH
(f) R^1 = Pr^n; R^2 = OH
(g) R^1 = Am^n; R^2 = OH
(h) R^1 = $Hept^n$; R^2 = OH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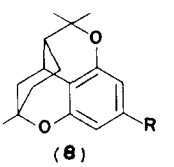
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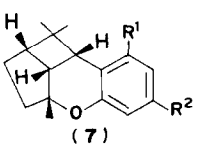
(a) R = Me
(b) R = Pr^n
(c) R = Am^n
(d) R = $Hept^n$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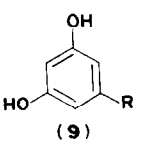
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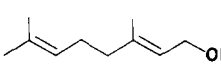
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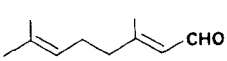
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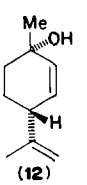
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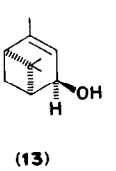
(13)

(A) R^1 = H; R^2 = CO_2H

(B) R^1 = CO_2H; R^2 = H

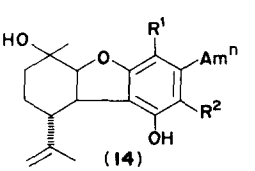
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Table 1. Chromatographic characteristics of synthetic cannabinoids

Cannabinoid		TLC Methods: Korte system[a] approx. R_f[c]	TLC Methods: $CHCl_3$ system[b] approx. R_f[d]	TLC Methods: Colour with fast blue salt B[e]	GLC Methods[h]: 1% Carbowax,[i] 220°, R_t (min)	GLC Methods[h]: Order of elution	GLC Methods[h]: Trimethylsilylated[f] compds. SCOT.OV225,190°[k] R_t (min)	GLC Methods[h]: Trimethylsilylated[f] compds. SCOT.OV225,190°[k] Order of elution
CD C_1	(1a)	0·0	0·5	brick red[g]	5·80	6	7·32	1
Δ^1-THC C_1	(2a)	0·15	0·4	crimson	6·84	8	14·64	5
$\Delta^{1,6}$-THC C_1	(3a)	0·15	0·4	crimson	6·16	7	12·84	4
CN C_1	(4a)	0·1	0·4	purple	12·50	14	22·60	10
CG C_1	(5a)	0·0	0·3	orange	14·90	17	12·76	4
CC C_1	(6a)	0·2	0·3	purple	5·76	6	11·68	3
CCY C_1	(7a)	0·2	0·6	pink	3·24	3	9·36	2
CCI C_1	(8a)	0·2	0·6	[j]	2·00	1	22·60	[j]
CD C_3	(1b)	0·0	0·6	brick red[g]	8·16	10	9·80	2
Δ^1-THC C_3	(2b)	0·25	0·55	crimson	9·84	13	21·64	9
$\Delta^{1,6}$-THC C_3	(3b)	0·3	0·6	crimson	8·84	12	18·56	8
CN C_3	(4b)	0·15	0·55	purple	18·25	20	35·00	15
CG C_3	(5b)	0·0	0·4	orange	22·32	21	17·88	7
CC C_3	(6b)	0·3	0·4	purple	8·16	10	17·48	7
CCY C_3	(7b)	0·3	0·7	pink	4·36	4	14·04	5
CCI C_3	(8b)	0·3	0·7	[j]	2·68	2	34·00	[j]
CD C_5	(1c)	0·1	0·7	brick red[g]	13·84	16	15·92	6
Δ^1-THC C_5	(2c)	0·5	0·6	crimson	16·96	19	38·20	16
$\Delta^{1,6}$-THC C_5	(3c)	0·6	0·65	crimson	15·56	18	33·08	14
CN C_5	(4c)	0·25	0·65	purple	31·40	25	63·96	21
CG C_5	(5c)	0·0	0·45	orange	39·04	26	30·36	13
CC C_5	(6c)	0·65	0·45	purple	13·80	16	30·20	13
CCY C_5	(7c)	0·65	0·75	pink	7·40	9	24·28	11
CCI C_5	(8c)	0·65	0·75	[j]	4·64	5	66·80	[j]
CD C_7	(1d)	0·1	0·75	brick red[g]	23·56	22	28·52	12
Δ^1-THC C_7	(2d)	0·75	0·7	crimson	29·20	24	70·84	22
$\Delta^{1,6}$-THC C_7	(3d)	0·85	0·7	crimson	26·72	23	61·24	20
CN C_7	(4d)	0·4	0·7	purple	56·80	27	115·20	23
CG C_7	(5d)	0·0	0·5	orange	66·40	28	53·80	18
CC C_7	(6d)	0·9	0·5	purple	23·70	22	54·30	19
CCY C_7	(7d)	0·9	0·8	pink	12·88	15	43·20	17
CCI C_7	(8d)	0·9	0·8	[j]	8·48	11	120·00	[j]

[a] Kieselgel G (0·5 mm) impregnated with $HCONMe_2$–CCl_4 (3:2), dried at 20°/15 min and eluted with cyclohexane (20 × 20 cm. plates) [27, 38]. Colours with Fast Blue Salt B reagent are less marked in this system.

[b] Kieselgel G (0·5 mm) eluted with $CHCl_3$ (20 × 20 cm plates).

[c] Relative to Δ^1-THC-C_5 standard = 0·5.

[d] Relative to Δ^1-THC-C_5 standard = 0·6.

[e] *o*-Dianisidine tetrazolium chloride (0·5%) in 0·1 N-aq. NaOH (nanogram sensitivity).

[f] Pale pink (non-phenolic); dark brown with I_2.

[g] Brick-red when concentrated, orange when dilute.

[h] Pye 104 instrument: flame ionisation detector at oven temp. Chart speed 2·6 cm/4 min.

[i] Carbowax 20 M (1%) on AW DMCS Chromosorb W (80/100 mesh) in glass columns (5 ft × 1/4 in.). On-column injection: oven temp. 220°, N_2 flow 60 ml/min. Injections 0·2–2·0 μl in hexane or Et_2O. Standards used: androst-4-ene-3.17-dione [39] (R_t 24·0 min) and dibenzyl phthalate (43·2 min).

[j] Sample treated with trisil before injection.

[k] SCOT OV225 (50 ft × 0·02 in., Perkin–Elmer) column: oven temp. 190°, injection 240°, N_2 flow 3 ml/min. Injections ≯0·5 μl direct or ≯2·0 μl using 3:1 splitter ratio. Standard used: docosane (retention time 8·0 min.)

[l] Cannabicitrans do not trimethylsilylate and form wide peaks. They have therefore been excluded from the elution order. Detection is feasible in a mixture if the latter is not too complex.

ethers [4, 5], cannabielsoic acids (**14**) [6], and a reported cannabidiolic acid-tetrahydrocannabitriol ester [7]); with intensive search among *C. sativa* races, it seems likely that new structures of related type may emerge. The eight structures (**1**–**8**) in themselves pose a problem in homology. Only eight members (**1c**–**8c**) with *n*-amyl side-chains were originally recognised, but from some varieties of *Cannabis* *n*-propyl compounds e.g. cannabidivarol (**1b**), Δ^1-tetrahydrocannabivarol (**2b**), cannabivarol (**4b**) have recently been isolated [7–10]. It is also known that representatives with methyl side chains e.g. cannabidiorcol (**1a**), Δ^1-tetrahydrocannabiorcol (**2b**), cannabiorcol (**4b**) are sometimes present in small amount [11], and with this downward bis-homologous extension it seems possible that the *n*-heptyl series may be found. This gives a problem in recognition and estimation of 32 closely related compounds.*

* Plant material also contains the salicylic acid structures corresponding to (**1**–**8**) in the orientations (a–d) [1–3]: these are readily decarboxylated to give members of the above set of 32 compounds and this simplifies recognition and estimation. Two members of a second, isomeric, series are reported [6, 13].

The requirements of investigations into the phytochemistry, pharmacology and forensic science of *Cannabis* make desirable ready access to individual small specimens of cannabinoids. (in isotopically labelled or unlabelled form). Cannabinoids are not readily isolated in pure form from plant sources [14]. Sometimes difficultly accessible plant races are required, or concentrations may be small, whilst in other cases the cannabinoid may not have been isolated from, or as yet discovered in, *Cannabis sativa*. A synthetic approach to the general problem of cannabinoid homology thus appeared of interest. The difficulty is the amount of time and effort involved. Normal-scale synthetic methods, developed in these and other laboratories, have made all members of the *n*-amyl series (**1c**–**8c**) available and we have now adapted such methods to a miniaturized scale employing 1–20 mg. of reactants. The small scale allows reactions and separations (by TLC) to be carried out rapidly and effectively. A search for suitable reaction conditions can also be effected with great economy of time and materials. From the four resorcinols (**9a**–d), which are available in radiolabelled and unlabelled form [15], and the three monoterpenes geraniol, citral and *p*-menthadienol, the 32 cannabinoids (**1a**–d to **8a**–d) can be made available and their chromatographic behaviour surveyed. This has given reference data for both known, and as yet potential, natural products of *Cannabis*. Such an approach may be useful in other phytochemical problems in which series of specimens of related or homologous natural products need to be obtained.

RESULTS

Initial investigations consisted of exploration of suitably miniaturized reactions for the production of the *n*-amyl series (**1c**–**8c**):* reference specimens of all the latter compounds were available from our earlier work. Conditions (60°/24 hr.) were established for the production of (−)-$\Delta^{1,6}$-tetrahydrocannabinol (**3c**) in 25% yield by boron trifluoride catalysed condensation of olivetol (**9c**) with (−)-*trans*-verbenol (**13**) [17] (Table 2). The acid catalysed condensation of olivetol with (+)-*p*-mentha-2,8-dien-1-ol (**12**) [18–20] proved particularly flexible (Table 3). At 60° (2 hr) in the presence of toluene-*p*-sulphonic acid in methylene chloride the (−)-$\Delta^{1,6}$-compound (**3c**) could be obtained in 68% yield, but at lower temperatures little $\Delta^{1,6}$-compound formed and mixtures of (−)-Δ^{1}-tetrahydrocannabinol (**2c**) and (−)-cannabidiol (**1c**) were obtained, from which two pure compounds were isolated. All three natural *para*-amyl terpenoid compounds are accompanied by the unnatural *ortho*-series (e.g. **1g**, **2g**) and separation was effected by TLC. Table 4 shows the boron-trifluoride catalysed [14] conversion of isolated (−)-cannabidiol first (5 min) into (−)-Δ^{1}-tetrahydrocanna-

Table 2. Acid catalysed condensation of olivetol (**9c**) with (−)-*trans*-verbenol (**13**)*

Reactants	Reagents	Products (%)
9c (3·2 mg) + **13**	A (200 μl)/20°/4 hr.	**3c** (24), **2c** (4), **9c** (77)†
9c (7·2 mg) + **13**	B (300 μl)/20°/1·5 hr.	**3c** (4), **2c** (2), **9c** (28)† Compd. A (36)† Compd. B (20)†
9c (3·8 mg) + **13**	B (200 μl)/60°/2 hr.	**3c** (13), **2c** (4) Compd. A (31) Compd. B (11)
9c (3·8 mg) + **13**	B (200 μl)/60°/24 hr.	**3c** (25) Compd. A (2)‡

* See ref. [40] for the preparation of (−)-*trans*-verbenol.

† Compound A is presumed to be the *p*-olivetyl pinene, and B the *o*-isomer described by Mechoulam [17].

‡ No compound B observed: product gummy and contains unidentified material.

[a] % Recovery.

Table 3. Acid catalysed condensation of olivetol (**9c**) with (+)-*p*-mentha-2,8-diene-1-ol (**12**)*

Reactants	Reagents	Products (%)
9c (7·0 mg) + **12**	B (200 μl)/5–10°/1 hr.	**1c** (16), **1g** (11), **3c** (1) **2c** (12), **2g** (5)†
9c (11·0 mg) + **12**	D (22 μl)/20°/3 days	**1c** (10), **1g** (16), **9c** (65)
9c (1·8 mg) + **12**	B (200 μl)/20°/2 hr.	**1c** (40), **1g** (29)‡
9c (1·2 mg) + **12**	B (100 μl)/60°/2 hr.	**3c** (68)
9c (1·5 mg) + **12**	B (400 μl)/80°/2 hr.	**3c** (61), **9c** (10)
9c (2·7 mg) + **12**	B (200 μl)/42°/4 hr.	**1c** (29), **1g** (11) **2c** (8), **3c** (<1)
9c (2·3 mg) + **12**	B (200 μl)/50°/1·5 hr.	**1c** (40), **1g** (24) **2c** (13), **2g** (4)

* *p*-Menthadienol added to **9c** + acid catalyst: products **1c** and **2c** can be separated on silica/$CHCl_3$ with care, but Korte method [27] sometimes required.

† **9c** (17%) recovered; some *bis*- and other products formed.

‡ **9c** (6%) recovered; about 11% of *bis* compounds.

* *Nomenclature and abbreviations.* Existing names for the *n*-amyl series of natural origin are used and abbreviated [1] with a final descriptor [16] indicating the length of the *n*-alkyl side-chains: (**1c**) cannabidiol (CD–C_5); (**2c**) Δ^{1}-tetrahydrocannabinol (Δ^{1} THC–C_5); (**3c**) $\Delta^{1,6}$-tetrahydrocannabinol ($\Delta^{1,6}$–THC–C_5); (**4c**) cannabinol (CN–C_5); (**5c**) cannabigerol (CG–C_5), (**6c**) cannabichromen (CC–C_5); (**7c**) cannabicyclol (CCY–C_5); (**8c**) cannabicitran (citrylidenecannabis) CCI–C_5). In the natural compounds terpenic substitution is *p*- to the alkyl chain: the isomeric unnatural compounds are therefore designated as *ortho*-compounds e.g. (**1g**) *ortho*-cannabidiol (*o*-CD–C_5) etc. Compounds with side-chains other than C_5 are designated similarly e.g. (**2a**) Δ^{1}-tetrahydrocannabinol-C_1 (Δ^{1}–THC–C_1); (**5h**) *ortho*-cannabigerol-C_7 (*o*-CG–C_7).

binol (69%) and then into increasing amounts of the (−)-$\Delta^{1,6}$-compound (24 hr, 67%). The acid catalysed condensation of olivetol with citral (**11**) [17, 21, 22] was also examined (Table 5). (±)-*cis* and (±)-*trans*-Forms of Δ^1-tetrahydrocannabinol were accessible in small yield, along with (±)-(**1c**).

Table 4. Acid catalysed conversions of (−)-cannabidiol (**1c**) and (−)-Δ^1-tetrahydrocannabinol (**2c**)

Reactant	Reagents	Products (%)
1c (3·5 mg)	A (50 μl) 20 °, 5 min.	**2c** (48), **3c** (40)*
1c (3·5 mg)	A (50 μl) 20 °, 2 hr.	**2c** (49), **3c** (24)*
1c (3·5 mg)	A (50 μl) 20 °, 24 hr.	**2c** (14), **3c** (67)
1c (5·7 mg)	A (500 μl) 17 °, 5 min.	**2c** (69), **3c** (3)*
1c (5·7 mg)	A (500 μl) 17 °, 2 hr, 45 min.	**2c** (9c), **3c** (50)
1c (5·1 mg)	B (600 μl) 80 °, 45 min.	**2c** (45), **3c** (47), **9c** (2)
1c (5·1 mg)	B (600 μl) 80 °, 2 hr.	**2c** (7), **3c** (81)
2c (8·5 mg)	A (500 μl) 17 °, 5 min.	**2c** (85), **3c** (4)
2c (8·5 mg)	A (500 μl) 17 °, 45 min.	**2c** (59), **3c** (32)
2c (8·5 mg)	A (500 μl) 17 °, 2 hr, 45 min.	**2c** (16), **3c** (84)

* A third uncharacterised product present.

Pyridine-catalysed condensation of citral with olivetol (110°) [22, 23] (Table 6) was used to obtain specimens of cannabichromen (**6c**) together with the unnatural *ortho*-compound and some *bis*-chromenylated product. Reaction at 140°/4 hr improved the yield of cannabichromen (33%) and in addition gave cannabicitran (citrylidenecannabis, **8c**, 10%) together with small amounts of the two cannabicyclols (**7c** and **7g**). Cannabigerol (**5c**) was obtained by condensing geraniol with olivetol under acid-catalysed conditions [24–26]. A yield of 31% of (**5c**) was obtained, together with 39% of (**5g**) and small amounts of *cis*-2′-(**5c**) and -(**5g**) and *bis*-alkylated olivetol (Table 7).

Table 5. Acid catalysed condensation of olivetol (**9c**) with citral (**11**)*

Reactants	Reagents	Products (%)
9c (8·8 mg) + **11**	A (200 μl) 5 °, 4 hr.	**1c** (12), **1g** (9), **2c** (9) *cis*-**2c** (4)
9c (3·2 mg) + **11**	B (150 μl) 20 °, 24 hr.	**1c** (21), **1g** (27), **2c** (4) *cis*-**2c** (6), **2g** (8)†
9c (4·5 mg) + **11**	B (300 μl) 60 °, 2·5 hr.	**3c** (37), **2c** (2), *cis*-**2c** (4)‡

* Products (±): citral added to **9c** plus acid catalyst: use of 5×10^{-4} *N*-ethanolic hydrogen chloride gave a variety of other products.

† **9c** (26%) recovered, and other products formed.

‡ **9c** (19%) recovered, and other products formed.

With experience of the reaction, separation and analytical techniques gained in the *n*-amyl series, the syntheses of the full sets of homologues, mentioned above, was undertaken. The parallel behaviour, and characteristic colours of the reaction products with Fast Blue Salt B [27], allowed ready identification of the components separated by TLC. Identity of the isolated components was further confirmed by GLC analysis (Carbowax 20 M and, after trimethylsilylation, OV225) and, where necessary, GC–MS. Although the discrimination of the latter technique can be improved by variation of the electron beam energy and study of electron voltage/mass fragment intensity graphs [28], developments in pulsed Fourier transform ^{1}H-NMR are particularly suited to miniaturized synthetic work in the cannabinoid field when structural doubts exist. Satisfactory spectra are available at the <100 μg level, as shown in Fig. 1, and 20 μg in microtubes.

Table 6. Pyridine catalysed condensation of olivetol (**9c**) with citral (**11**)

Reactants	Reagents	Products (%)
9c (7·6 mg) + **11**	C (4 μl) 110 °, 5 hr.	**6c** (14), **6g** (14)*
9c (6·2 mg) + **11**	C (3·2 μl) 140 °, 4 hr.	**6c** (33), **6g** (26), **7c** + **7g** (3), **8c** (10)†

* **9c** (50%) recovered: traces of **7c** + **7g** and *bis*-material formed.

† **9c** (22%) recovered: small amounts of *bis*-condensation products.

Table 7. Acid catalysed condensation of olivetol (**9c**) with Geraniol (**10**)

Reactants	Reagents	Products (%)
9c (8·3 mg) + **10**	B (4 μl) 100 °, 2 hr.	**5c** (9), *cis*-2-**5c** (1), **5g** (14), *cis*-2-**5g** (2)*
9c (12·5 mg) + **10**	A (300 μl) 5 °, 4 hr.	**5c** (31), *cis*-2-**5c** (2), **5g** (39), *cis*-2-**5g** (2)†
9c (7·8 mg) + **10**	B (200 μl) 20 °, 2 hr.	**5c** (28), *cis*-2-**5c** (3) **5g** (22), *cis*-2-**5g** (3)†

* Solvent dioxan–H_2O (1:1): **9c** (70%) recovered and some *bis*-material formed.

† Small amounts of *bis*-material observed: unreacted **9c** still present.

Table 8 shows the synthesis of the cannabidiol series (**1a–d**) (32–45% yields) using 2·5–5·0 mg samples of the resorcinols. Tables 9 and 10 show reac-

Table 8. Synthesis of the cannabidiol series (**1a–d**)

Reactants	Reagents	Products (%)
9a (3·8 mg) + **12**	B (300 μl) 20 °, 2 hr.	**1a** (34), **1e** (64)
9b (4·7 mg) + **12**	B (400 μl) 20 °, 2 hr.	**1b** (32), **1f** (30)
9c (3·1 mg) + **12**	B (200 μl) 20 °, 2 hr.	**1c** (45), **1g** (50)
9d (2·5 mg) + **12**	B (200 μl) 20 °, 2 hr.	**1d** (37), **1h** (30)

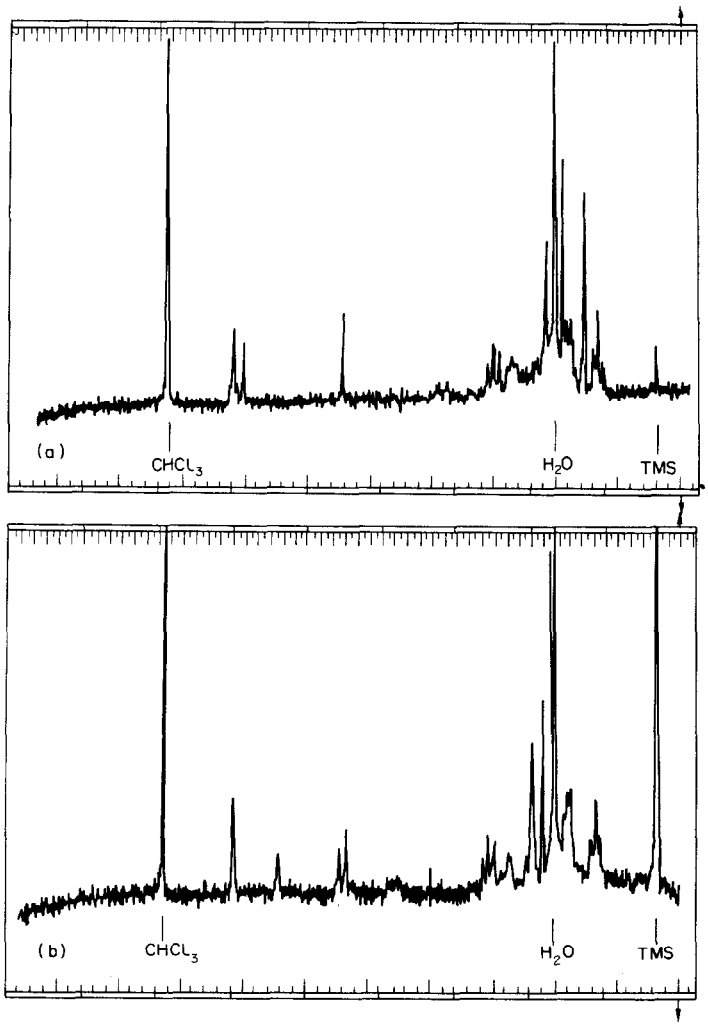

Fig. 1. NMR spectra at 100 MHz of Δ^1-tetrahydrocannabinol (a) (0·08 mg) and cannabidiol (b) (0·08 mg). Pulsed Fourier Transform NMR with automatic block averaging using a Jeol JNM-PS-100S spectrometer and Nicolet 108E computer (20K), 8K data points, 11K scans, pulse width 10 μ sec, repetition 5·0 sec, frequency range 1000 Hz.

tions, on a similar scale, used to isolate the Δ^1-tetrahydrocannabinols (**2**a–d) (13–26%) and the $\Delta^{1,6}$-tetrahydrocannabinols (**3**a–d). All of these syntheses involve (+)-*p*-mentha-2,8-dien-1-ol-olivetol condensations catalysed by toluene *p*-sulphonic acid, conditions being varied to favour the different products required. Compounds of the cannabinol (**4**a–d) series were isolated by dehydrogenation of the specimens of (**3**a–d) using sulphur at 200° [29].

The four cannabigerols (**5**a–d) were obtained by

Table 9. Synthesis of the Δ^1-tetrahydrocannabinol series (**2**a–d)

Reactants	Reagents	Products (%)
9a (3·2 mg) + **12**	B (300 μl)/56°/1 hr.	**1**a (4), **1**e (1), **2**a (20) **2**e (26), **3**a (14)
9b (1·7 mg) + **12**	B (200 μl)/48°/2 hr.	**1**b (31), **1**f (6), **2**b (26) **2**f (4), **3**b (4)
9c (2·3 mg) + **12**	B (200 μl)/56°/2 hr.	**1**c (40), **1**g (24), **2**c (13), **2**g (4), **3**c (0)
9d (4·2 mg) + **12**	B (350 μl)/56°/2 hr.	**1**d (29), **1**h (12), **2**d (14)

Table 10. Synthesis of the $\Delta^{1,6}$-tetrahydrocannabinol series (**3**a–d)

Reactants	Reagents	Products (%)
9a (4·2 mg) + **12**	B (300 μl)/77°/2 hr.	**3**a (60)
9b (4·3 mg) + **12**	B (300 μl)/77°/2 hr.	**3**b (31)
9c (5·1 mg) + **12**	B (400 μl)/77°/2 hr.	**3**c (64)
9d (9·4 mg) + **12**	B (600 μl)/77°/2 hr.	**3**d (52)

Table 11. Synthesis of the cannabigerol series (**5**a–d)*

Reactants	Reagents	Products (%)
9a (2·1 mg) + **10**	B (200 μl); 20°; 2 hr.	5a (24); 5c (24)
9b (2·1 mg) + **10**	B (200 μl); 20°; 2 hr.	5b (18); 5f (18)
9c (2·3 mg) + **10**	B (200 μl); 20°; 2 hr.	5c (26); 5g (21)
9d (2·0 mg) + **10**	B (200 μl); 20°; 2 hr.	5d (7); 5b (5)

* Traces of *cis*-2′-isomers were formed throughout.

geranylation of the alkyl resorcinols as mentioned above (Table 11). Similarly the homologous cannabichromens (**6**a–d) and cannabicitrans (**8**a–d) were obtained by the pyridine catalysed condensation of citral with the alkylresorcinols (Table 12). Small specimens of each of the cyclols (**9**a–d) were made photochemically [30] from the chromens (**8**a–d).

Table 12. Synthesis of the cannabichromen series (**6**a–d) and the cannabicitran (citrylidene-cannabis) series (**8**a–d)

Reactants	Reagents	Products (%)
9a (9·8 mg) + **11**	C (6·4 μl); 140°; 5 hr.	6a (10); 6e (17)
9b (10·8 mg) + **11**	C (5·7 μl); 140°; 5 hr.	6b (11); 6f (10)
9c (2·4 mg) + **11**	C (1·2 μl); 140°; 5 hr.	6c (19); 6g (11)
9d (12·1 mg) + **11**	C (4·7 μl); 140°; 5 hr.	6d (11); 6h (9)
9a (15·9 mg) + **11**	C*; 140°; 10 hr.	6a (3); 6e (15); 8a (6)
9b (19·8 mg) + **11**	C*; 140°; 10 hr.	6b (10); 6f (7); 8b (6)
9c (15·3 mg) + **11**	C*; 140°; 10 hr.	6c (5); 6g (7); 8c (2)
9d (16·8 mg) + **11**	C*; 140°; 10 hr.	6d (4); 6g (4); 8d (1)

* 1 mol. proportion.

With structures (**1**–**8**) in side-chain variants (a–d) available. TLC data using two systems were obtained and data are recorded in Table 1. For GLC purposes, a variety of stationary phases on Chromosorb W in glass (5 ft × 1/4 in.) systems, or surface coated open tube systems (50 ft × 0·02 in.), using intact and trimethylsilylated samples, was examined. These included, in order of increasing polarity, SE30 [31], OV1 [32], OV17 [33], OV25, OV210, XE60 [34], OV225 and Carbowax 20 M [35]. A mixed neopentylglycoladipate/trimer acid (12/1) column was also investigated [36]. As a result of this survey, two systems were selected-Carbowax 20 M (5 ft × 1/4 in.) for intact cannabinoids, and OV225 (SCOT 50 ft × 0·02 in.) for trimethylsilylated cannabinoids. Retention time data are listed in Table 1 for the 32 cannabinoids. Fig. 2A, B and C shows the alkyl chain-lengths vs. log retention time plots from the two column types: approximate linearity is followed after the deviant first term of each series. A similar deviation has recently been noted in a group of $\Delta^{1,6}$-THC cannabinoid structures [37].

Figure 4 shows the separation achieved with mixtures of 28 cannabinoids run as a single sample mixture. Four of the cannabinoids, the citrans (**8**a–d), have not been included since they do not silylate and thus give broad slow moving peaks on the OV225 system (see Table 1). By using the two columns, compounds with coincident retention

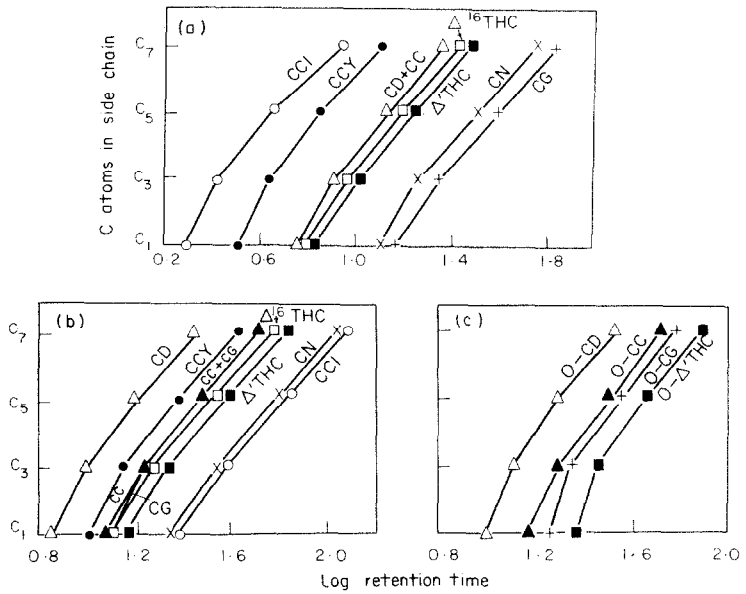

Fig. 2. Relationship between alkyl chain length and GLC log retention time of cannabinoids. A. Carbowax 20 M (1%) column 220°; B and C. OV 225 SCOT 50′ column 190°. Cannabinoids injected after treatment with Trisil.

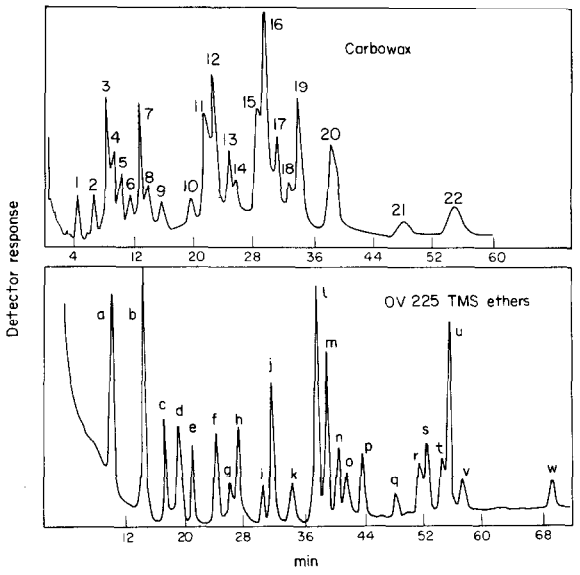

Fig. 3. GLC of cannabinoid mixtures. 1. Carbowax 20 M 1% on DMCS Chromosorb W 80/100 mesh. Glass column 5 ft × 1/4 in. Temperature programme: 15 min at 207° increasing to 230° at 2°/min; N_2, 60 ml/min. F.I.D. at oven temp. 1 μl. Injected directly onto column. 2. OV 225 SCOT column 50 ft × 0·02 in. Cannabinoids injected after silylation with Trisil. Temperature programme, 20 min at 182° increasing to 220° at 1°/min; N_2, 3 ml/min. F.I.D. at oven temperature. Injection at 240°, 0·5 μl.

1, CCY–C_1; 2, CCY–C_3; 3, CD–C_1 + CC–C_1; 4, $\Delta^{1,6}$ THC–C_1; 5, Δ^1–THC–C_1; 6, CCY–C_5; 7, CD–C_3 + CC–C_3; 8, $\Delta^{1,6}$–THC–C_3; 9, Δ^1–THC–C_3; 10, CN–C_1 + CCY–C_7; 11, CD–C_5 + CC–C_5; 12, $\Delta^{1,6}$–THC–C_5 + CG–C_1; 13, Δ^1–THC–C_5; 14, CN–C_3; 15, CG–C_3; 16, CD–C_7 + CC–C_7; 17, $\Delta^{1,6}$–THC–C_7; 18, Δ^1–THC–C_7; 19, CN–C_5; 20, CG–C_5; 21, CN–C_7; 22, CG–C_7.

a, CD–C_1; b, CD–C_3 + CCY–C_1; c, CC–C_1; d, CG–C_1 + $\Delta^{1,6}$–THC–C_1; e, Δ^1–THC–C_1 + CCY–C_3; f, CD–C_5; g, CC–C_3 + CG–C_3; h, $\Delta^{1,6}$–THC–C_3; i, Δ^1–THC–C_3; j, CN–C_1; k, CCY–C_5; l, CD–C_7; m, CC–C_5 + CG–C_5; n, $\Delta^{1,6}$–THC–C_5; o, CN–C_3; p, Δ^1–THC–C_5; q, CCY–C_7; r, CG–C_7; s, CC–C_7; t, $\Delta^{1,6}$–THC–C_7; u, CN–C_5; v, Δ^1–THC–C_7; w, CN–C_7.

times on one column can be separated on the other, although new overlaps may occur. With curve resolution an accurate analysis of the 28 natural, and potentially natural, cannabinoids can be achieved.

EXPERIMENTAL

Reactions were usually carried out in Reactivials (Pierce Chemicals) of 0·6 ml total capacity using 1–20 mg. of alkyl resorcinol (**9**). Unless stated otherwise all reactants are in 1:1 mol proportions. Yields of products were determined by GLC methods using an added standard, frequently docosane. Products were usually chromatographed on Silica-G (20 × 20 cm, 0·5 mm thickness) in $CHCl_3$. Band positions were located by (a) inspection in UV light, (b) strip spraying with Fast-Blue Salt B. The cannabinoids were recovered by CH_2Cl_2 extraction and their purity determined after trimethylsilylation (Trisil, 15 min.) by GLC using a 50′ - SCOT OV225 column. GLC on Carbowax 20 M (5 ft) and TLC using the Korte system provided additional checks. The following cannabinoids, available from previous work in our laboratory, were used for comparison purposes: cannabidiol, Δ^1-tetrahydrocannabinol, $\Delta^{1,6}$-tetrahydrocannabinol, cannabicyclol, cannabichromen, cannabicitran, *cis*-Δ^1-tetrahydrocannabinol, *ortho*-cannabicyclol, *ortho*-cannabichromen, *bis*-cannabicyclol, *bis*-cannabichromen, cannabigerol and cannabinol. Samples of olivetol, divarinol and *n*-heptylresorcinol were prepared by Mr. R. Forbes [15].

In the tables, the reagents are abbreviated as follows:

A = 0·5% BF_3 etherate in CH_2Cl_2.

B = Saturated solution of toluene-*p*-sulphonic acid in reagent grade CH_2Cl_2 previously dried over Na_2SO_4.

C = Pyridine.

D = *N*,*N*-Dimethylformamidedineopentyl acetal.

E = 98–100% Formic acid.

Synthesis of the cannabinol series (**4**a–d). Compounds of the $\Delta^{1,6}$-tetrahydrocannabinol series (**3**a–d) (Table 10) were heated, in mg. quantities, with sulphur (0·2–1 mg.) at 200°/1 hr, in a sublimation apparatus. Cannabinols (**4**a–d) were formed (22–23% yield) and were purified by TLC on silica gel G in $CHCl_3$.

Synthesis of the Cannabicyclol Series (**7**a–d). Compounds of the chromen series (**6**a–d) (Table 12) were dissolved (mg. amounts) in acetone cyclohexane (1:1) and irradiated with a medium quartz lamp (Pyrex filter) for 5–7 1/2 hr [30]. The cyclols were purified from residual chromen by TLC on silica gel G in $CHCl_3$.

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