1,2-Disubstituted Ethanes As Possible Precursors For The Synthesis of *Cannabis* Spirans

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Three possible methods for converting suitable 1,2-disubstituted ethanes into *Cannabis* spirans have been investigated. 4',5-Dihydroxy-3-methoxybibenzyl underwent intramolecular *o-p*- and *p-p*-coupling with ferricyanide in a chloroform–aqueous potassium carbonate system, but yields were low: certain other oxidants did not succeed or gave only traces of product. A method for making 1-hydroxy-1-(3,5-dimethoxyphenylethyl)cyclohexan-4-one ethylene acetal or thioacetal *via* a Birch reaction is described: despite favourable precedent, acid-catalysed cyclisation led to octahydrophenanthrenones rather than spiro-ketones, whilst *N,N*-dimethylformamide dineopentyl acetal gave two olefins. Jacquesy's super-acid method for making spirocyclohexenones from a methoxylated bibenzyl was not applicable to the 3,4',5-trimethoxy-case, which would have given cannabispirenone methyl ether, presumably because of protonation of both aromatic systems.

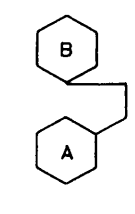
THE synthesis of cannabispirenone and the associated group of spirans, described in the preceding paper,[1] depends on the construction of the 6-membered B-ring on a pre-formed indan framework. This paper reports experiments directed to forming the spiran system by folding a suitable 1,2-substituted ethane (1)→(2). A biomimetic route to cannabispiradienone (4) [2] by intramolecular oxidative coupling of a suitably substituted bibenzyl (3) is attractive, though the formation of a five-membered ring is known to be distinctly more difficult than formation of a six- in cases where it has been attempted.[3] Using active manganese dioxide,[4] vanadium oxytrichloride,[5] or molybdenum oxytetrachloride [5] there was little evidence for the formation of appreciable amounts of spiro-dienone or a possible dihydrophenanthrene rearrangement product, *e.g.* (6).[2] With potassium ferricyanide in a biphasic system of chloroform and aqueous sodium carbonate,[5] however, the bibenzyl (3) was successfully oxidised to a mixture of two spirodienones (4) and (5) (*ca.* 2 : 1 respectively), but in low yield (3%). The two dienones represent the *o-p*- and *p-p*-modes of radical coupling and their biosynthetic significance has been discussed earlier.[2] These results are in agreement with a communication by El-Feraly *et al.*[6] who report failure with seven oxidants recommended in the literature, and success, in 2% yield, with ferricyanide system related to, but not the same as, the one we used: we have not however, been able to duplicate the preliminary claims [6] relating to molybdenum oxytetrachloride for which no detail is given. Until substantially improved yields can be attained, the one-electron transfer approach must remain of restricted synthetic value.

As a possible alternative for attaining the conversion (1)→(2) we have turned to carbenium ion processes. It has been known for many years that tertiary alcohols of type (7) can be cyclised under acid conditions to form octahydrophenanthrenes (9) and spirocyclohexanes (11).[7] The factors which lead to predominance of one or the other are, however, by no means fully understood. Our interest in the reaction was enhanced by a report by Carnmalm [8] that the dimethoxyalcohol (8), on treatment with sulphuric acid–acetic acid mixture, gave a crystalline spiran (12) in unstated yield in place of the desired (10). Since the only structural evidence for compound (12) was its failure to dehydrogenate, we have repeated Carnmalm's experiment and obtained his product (34%): its ^{13}C n.m.r. spectrum (especially the quaternary carbon at δ 49.2) confirmed his proposal. It was, therefore, decided to see if cannabispirone methyl ether could be made by such a route.

A better preparative method for making the intermediate bromide (16) than that involving the Arndt–Eistert procedure [8] seemed desirable, and we based this on the Birch reaction.[9] 3,5-Dimethoxybenzoic acid (13) was reduced with sodium in liquid ammonia and the anion was alkylated with the tetrahydropyranyl ether of 2-bromoethanol. Careful work-up gave the dihydrobenzoic acid (14) (94%). Oxidative decarboxylation (lead tetra-acetate) [9] gave the tetrahydropyranyl ether (15) (92%), which was converted into the desired bromide (16) (68%) by triphenylphosphine dibromide [10] (59% overall from 3,5-dimethoxybenzoic acid). Careful work-up was emphasised above since incautious acidification with hydrochloric acid leads to hydrolysis of the vinyl ethers and lactonisation forming the crystalline spiro-lactonic cyclohexane-1,3-dione (18) ($\nu_{max.}$ 1 763 cm^{-1}, $\lambda_{max.}$ 254 nm).

Yields of tertiary alcohols from the Grignard reagent (17) were poor, *e.g.* 28% with cyclohexanone. Two other products were isolated in the latter reaction: 3,5-dimethoxyethylbenzene (19) (45%) and 1,4-bis(3,5-dimethoxyphenyl)butane (20) (5%), so self-coupling and, more importantly, enolisation of the ketone, are unwanted side-reactions. The half-ethylene acetal of cyclohexane 1,4-dione [11] similarly gave (21a) (44%) and the half-ethylene thioacetal [12] gave (21c) (25%).

Cyclisation of compound (21a) using sulphuric acid–acetic acid gave the crystalline octahydrophenanthrenone (22b) (40%) as shown by ^1H n.m.r. and ^{13}C n.m.r. spectroscopy: in the latter there was no high-field O.R. singlet corresponding to a spirocarbon and instead two O.R. doublets at δ 35.5 and 32.7 corresponding to the ring junction carbons, along with five methylene triplets. Both boron trifluoride and polyphosphoric acid similarly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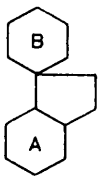
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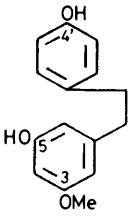
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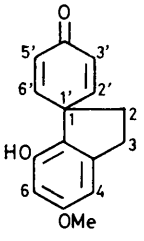
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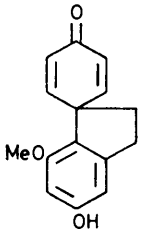
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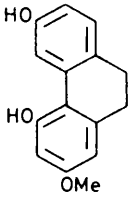
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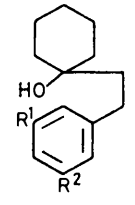
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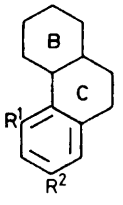
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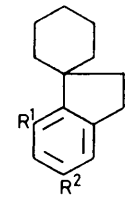
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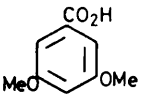
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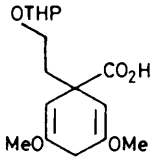
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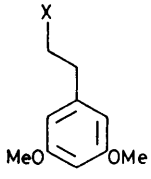
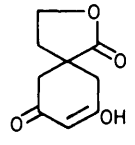
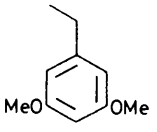

(15) X = OTHP

(16) X = Br

(17) X = MgBr


(18)

gave (22b) whilst refluxing toluene-*p*-sulphonic acid in benzene gave the acetal (22a), identical with a specimen made from the ketone (22b). In an attempt to generate the carbenium ion under milder conditions, *N*,*N*-dimethylformamide dineopentyl acetal [13] was used, but this gave the olefins (23a) and (24a). The corresponding olefinic ketones could also be produced by phosphoryl chloride–pyridine treatment. No evidence for the formation of appreciable quantities of spiro-components was obtained in chromatographic work-up, nor in a g.l.c mass spectral examination of the cyclisation of (21a) using toluene-*p*-sulphonic acid or boron trifluoride–diethyl ether as catalysts. By treating the hydroxy-acetal (21a) with lithium diphenyl phosphide [14] it was found possible to mono-demethylate it, giving a mixture of mono-demethylated acetal [*cf.* (21a)] and mono-demethylated ketone [*cf.* (21b)]. Cyclisation of this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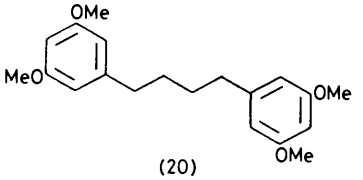
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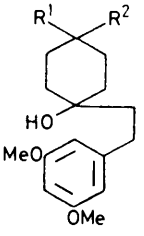
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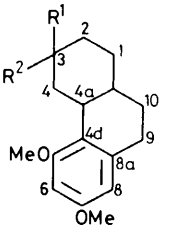
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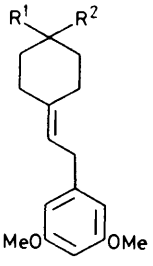
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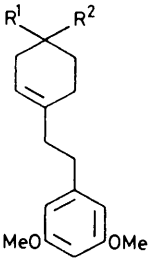
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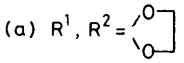
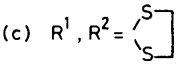
(a) $R^1, R^2 =$ 

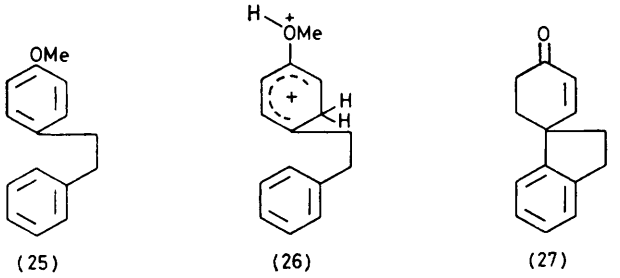
(b) $R^1, R^2 = O$

(c) $R^1, R^2 =$ 

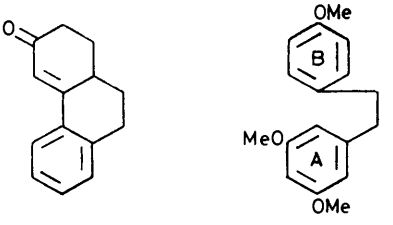
mixture (sulphuric–acetic acid) gave the two half-methyl ethers derived from the octahydrophenanthrenone (22b) and no cannabispirone was found. The two half-methyl ethers were made for reference, along with the bis-demethyl compound, by treating compound (22b) with magnesium iodide–diethyl ether.[15] Cyclisation of the thioacetal (21c) with toluene-*p*-sulphonic acid in benzene also gave an octahydrophenanthrenone derivative (22c). It was concluded that this type of route held little promise in connexion with cannabispirone synthesis.

Jacquesy and his colleagues [16] have pursued a different kind of carbenium-ion cyclisation to reach spiro-enones by the bond-forming process (1)—(2). They report that the bibenzyl (25) cyclises in super-acid medium (4.6M SbF_5 in HF at 0 °C for 50 min) to give a spirenone (27) (40%) and the hexahydrophenanthrenone (28) (32%): a bis-protonated intermediate (26) appears to be involved. Repetition of Jacquesy's experiment in our laboratory gave the spirenone (27) (32%), hexahydrophenanthrenone (28) (11%), and recovered compound (25) (13%): the spirenone was identical with the model compound prepared by a dif-

ferent route in the previous paper.[1] Attempts to apply these reaction conditions to the bibenzyl (29) in order to reach methyl cannabispirenone however, led only to recovered starting material. Presumably the doubly methoxylated ring-A of (29) is now itself heavily protonated and deactivated to attack by the protonated ring A and the synthesis, though attractive, has restricted generality.



(25) (26) (27)



(28) (29)

EXPERIMENTAL

Intramolecular Oxidative Coupling of 4',5-Dihydroxy-3-methoxydihydrostilbene (3).—The dihydrostilbene (3) (200 mg) in chloroform (200 ml) was added to a solution of potassium ferricyanide (670 mg) and sodium carbonate (1.5 g) in water (50 ml) and the mixture was stirred vigorously for 5 h at 20 °C. The layers were separated and the aqueous layer was neutralised (HCl) and extracted with ether. The organic extracts were washed with water, dried ($MgSO_4$), and evaporated to an oil. When chromatographed on 20 × 20 cm silica plates, with ether–hexane (2 : 1) as eluant two bands corresponding to starting material (3) and cannabispiradienone (t.l.c. comparison) were separated. Both n.m.r. and mass spectral comparison confirmed the presence of the dienone (M^+, 242. $C_{15}H_{14}O_3$ requires M, 242) in the latter band (10 mg). It was further purified by h.p.l.c. using a reversed-phase C_{18} system, with methanol–water (9 : 1) as eluant. This gave the dienone product (6 mg, 3%). N.m.r. examination (250 MHz) showed: δ 7.00 (d, 2 H, J 10 Hz, 2',6'-H), 6.47 (m, 1 H, 4-H), 6.38 (d, 2 H, J 10 Hz, 3',5'-H), 6.22 (d, 1 H, J 2.4 Hz, 6-H), 3.77 (s, 3 H, OMe), 3.12 (t, 2 H, J 7.3 Hz, 3-H), and 2.31 (t, 2 H, J 7.3 Hz, 2-H). These data compare closely with those of natural cannabispiradienone-A (4). A second set of lines (about one half the intensity) correspond to cannabispiradienone-B (5): δ 6.89 (d, 2 H, J 10 Hz, 2'-6'-H), 6.27 (d, 2 H, J 10 Hz, 3',5'-H), 3.06 (t, 2 H, J 7.5 Hz, 3-H), and 2.25 (t, 2 H, J 7.5 Hz, 2-H).

A two-phase system of dihydrostilbene (3 mg) in chloroform (3 ml) and potassium ferricyanide (10 mg) in ammonia/ammonium acetate solution (1 ml) [from ammonium acetate (1 g), concentrated ammonia solution (1 ml) and water (10 ml)] gave little dienone detectable by t.l.c. (monitored over 1—20 h). Traces of spirodienone could be detected when the dihydrostilbene (3) (50 mg) was shaken with active manganese dioxide (500 mg) in dichloromethane, but amounts could not be increased in a series of experiments. A series of experiments with molybdenum oxytrichloride and vanadium oxytrichloride failed to produce detectable amounts of dienones.

Tetrahydropyranyl Ether of 1,4-Dihydro-1-(2-hydroxyethyl)-3,5-dimethoxybenzoic Acid (14).—3,5-Dimethoxybenzoic acid (13) (25 g, 0.137 mol) was dissolved in stirred liquid ammonia (1 l) under nitrogen, and sodium (8.1 g, 0.352 g-atom) was added in small pieces until the blue colour just remained. The mixture was then stirred until a yellow precipitate formed and the blue colour was discharged. 2-Bromoethanol tetrahydropyranyl ether (60 g, 0.286 mol) was then added dropwise when the precipitate dissolved gradually to give a colourless solution. Excess of ammonium chloride was added to the mixture and the ammonia allowed to evaporate overnight. The residue was dissolved in water and washed with ethyl acetate. These washings were discarded and the aqueous layer was acidified (2M-HCl) to pH4 (pH-meter) under a layer of ethyl acetate. Separation of the organic phase, further extraction with ethyl acetate, washing, drying, and evaporation gave the *dihydrobenzoic acid* (14) (40.2 g, 94%), m.p. 113—114 °C from ethyl acetate (Found: C, 61.25; H, 7.45%; M^+, 312.1591. $C_{16}H_{24}O_6$ requires C, 61.52; H, 7.7%; M^+, 312.1573), $\nu_{max.}$ (KBr) 1 692 cm^{-1}; ^1H n.m.r. (CD_3COCD_3) 2.06 (t, 2 H, J 7 Hz, CH_2CH_2OTHP) 2.71 (s, 2 H, C=C·CH_2C=C), 3.3—3.5 (m, 2 H, OCH_2), 3.58 (s, 6 H, 2 × OMe), 4.52 (q, 1 H, O·CH·O), 4.84 (s, 2 H, 2 × C=CH), and 7.75 (br s, 1 H, D_2O exchg., CO_2H).

Using too acidic a work-up, or direct treatment of the dihydrobenzoic acid (14) with acid gave the *spiro-lactone* (18), m.p. 162—164 °C, $\nu_{max.}$ (KBr) 1 763 (lactone) and 1 606 cm^{-1} (C=O of dimeric enol) $\nu_{max.}$ ($CHCl_3$) 1 770 (lactone) 1 672 (C=O of ketone), and 1 606 cm^{-1} (C=O of dimeric enol) (Found: C, 59.0; H, 5.65%; M^+, 182. $C_9H_{10}O_4$ requires C, 59.34; H, 5.53%; M, 182), ^1H n.m.r. (CD_3COCD_3): δ 2.2—2.4 (m, 2 H, CH_2CH_2O), 4.39 (m, 2 H, lactone CH_2O), 5.39 (s, 1 H, olefinic proton), and 7.0—7.7 (br, 1 H, D_2O exch., OH).

Tetrahydropyranyl Ether of 2-Bromoethanol.—2-Bromoethanol (149 g) was added dropwise to a stirred solution of dihydropyran (200 cm^3) containing phosphoryl chloride (1.6 cm^3), cooled in ice. After the mixture had been stirred at 20 °C overnight, dilute aqueous sodium hydroxide was added to it and the product extracted with ether. The extract was washed, dried, evaporated, and the residue distilled to give the *tetrahydropyranyl ether* (163.1 g, 65%), b.p. 62—64 °C/0.4 mmHg, n_D^{19} 1.4157 (M^+ −1, 207.0044. $C_7H_{13}BrO_2$ requires 208.0099, $C_7H_{13}O_2Br$ − 1 requires 207.0021); ^1H n.m.r.: δ 4.72 (br s, 1 H, O·CH·O).

Tetrahydropyranyl Ether of 1-(2-Hydroxyethyl)-3,5-dimethoxybenzene (15).—Lead tetra-acetate (42.6 g, 0.096 mol) was added in portions to a stirred solution of the dihydrobenzoic acid (14) (30 g, 0.096 mol) in dry benzene (800 ml); rapid evolution of carbon dioxide occurred. After being stirred overnight the mixture was shaken with dilute hydrochloric acid and the organic layer separated, washed with water, dried, and the solvent evaporated. The yellow oil was chromatographed (dry silica in nylon tube), with ether–hexane (3 : 7) as eluant to give the *tetrahydropyranyl ether* (15) (23.4 g, 92%) (Found: M^+, 266.1496. $C_{15}H_{22}O_4$ requires M, 266.1518), $\nu_{max.}$ (film) 1 600 cm^{-1}; $\lambda_{max.}$ (EtOH) 281 (ε 1 600), 273 (1 600), and 222 nm (7 000); ^1H n.m.r.: δ

1.4—1.7 (br m, 6 H, pyran methylenes), 2.9 (t, 2 H, *J* 7 Hz, ArC*H*$_2$), 3.4—4.1 (m, 4 H, 2 × OCH$_2$), 3.84 (s, 6 H, 2 × OMe), 4.67 (br t, 1 H, O·C*H*O), 6.42 (t, 1 H, *J* 2 Hz, aryl-H flanked by two methoxy-groups), 6.50 (d, 2 H, *J* 2 Hz, 2 × aryl-H).

3,5-Dimethoxyphenylethyl Bromide (16).—Bromine (36.8 g, 0.23 mol) was added dropwise to a stirred solution of triphenylphosphine (62.1 g, 0.24 mol) in dichloromethane (390 ml), the temperature being kept below 10 °C. The tetrahydropyranyl ether (15) (23.4 g, 0.088 mol) in dichloromethane (40 ml) was added dropwise and after being stirred at 20 °C (2 days) the green–brown solution was washed with water, dried, and the solvent removed to give a brown residue containing triphenylphosphine oxide. The latter was removed by repeated addition of ether and subsequent filtration. After removal of solvent, the product (37.9 g) was chromatographed on a composite column of alumina (170 g upper layer) and silica (250 g lower layer), with ether–n-hexane (1 : 1) as eluant to give 3,5-dimethoxyphenylethyl bromide (16) (14.6 g, 68%); ^{1}H n.m.r.: δ 3.09 (t, 2 H, *J* 8 Hz, CH$_2$), 3.56 (t, 2 H, *J* 8 Hz, CH$_2$), 3.82 (s, 6 H, 2 × OMe), and 6.40 (s, 3 H, 3 × ArH). It had b.p. 101—103 °C/0.25 mmHg (lit.,[8] b.p. 125—128 °C/1—2 mmHg) and was identical with a specimen made from 3,5-dimethoxybenzoic acid *via* homologation.

Acetalisation of Cyclohexane-1,4-dione.—(a) Dimethylformamide ethylene acetal (2.0 g, 0.17 mol) in dry dichloromethane (10 ml) was added dropwise to cyclohexane-1,4-dione (2 g, 0.018 mol) and glacial acetic acid (2 ml) in dichloromethane under nitrogen and stirred at 20 °C (30 h). The mixture was cooled in ice and poured into aqueous sodium hydroxide (10%; 40 ml). Extraction with dichloromethane and chromatography on silica, with ether–n-hexane (1 : 1) as eluant gave cyclohexane-1,4-dione monoethylene acetal (940 mg, 34%), m.p. 72—73 °C from hexane (lit.,[11] m.p. 71.5—72.5 °C) (Found: C, 61.35; H, 7.8. Calc. for $C_8H_{12}O_3$: C, 61.5; H, 7.4%), $\nu_{max.}$ (KBr) 1 705 cm^{-1}. *Cyclohexane-1,4-dione bisethylene acetal* (240 mg, 7%), was also isolated, m.p. 79.5—80.5 °C (Found: C, 59.85; H, 8.45. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.05%).

(b) Cyclohexane-1,4-dione (16.5 g, 0.15 mol), ethyleneglycol (8.25 ml, 0.15 mol), and toluene-*p*-sulphonic acid (300 mg) were refluxed with benzene (300 ml), and hexane (180 ml) in a Dean and Stark apparatus (18 h); water (2.7 ml) was collected. The product was washed with sodium hydrogen carbonate, dried, and evaporated and then chromatographed on dry silica with ether–n-hexane (1 : 1) as eluant to give cyclohexane-1,4-dione bisethylene acetal (7.37 g, 25%), m.p. 79—79.5 °C, followed by the monoethylene acetal (6.42 g, 28%), m.p. 72.5—73.5 °C. Cyclohexanedione (4.02 g, 24%) was recovered.

4-Benzoyloxycyclohexanone.—Cyclohexane-1,4-diol (25 g, 0.216 mol) was dissolved in chloroform (80 ml) and dry pyridine (60 ml) and benzoyl chloride (29.5 g, 0.0210 mol) in chloroform (60 ml) was added with stirring at 0—5 °C (5 h) to the mixture. After being kept overnight the chloroform solution was thoroughly washed with dilute sulphuric acid and water, dried, evaporated, and distilled to give 4-benzoyloxycyclohexanol as a viscous oil (28.6 g, 60.8%), b.p. 182—184 °C/2.5 mmHg (lit.,[12] b.p. 175—178 °C 0.2 mmHg). The distillation residue (6.8 g) crystallised from chloroform–light petroleum (b.p. 40—60 °C) to give the dibenzoyl derivative (4.5 g), m.p. 145—148 °C.

4-Benzoyloxycyclohexanol (28.6 g, 0.13 mol) in acetic acid (50 ml) was treated with chromium trioxide (13 g, 0.13 mol) in water containing acetic acid (50 ml) the temperature being kept below 35 °C; the mixture was then set aside overnight. The product was extracted with ether, and the extract washed successively with dilute aqueous sodium hydroxide and water. The extract was dried and solvent removed to leave a crystalline residue; this was recrystallised from ether–light petroleum (b.p. 40—60 °C) to give 4-benzoyloxycyclohexanone (23.3 g, 82%), m.p. 62—63.5 °C (lit.,[12] m.p. 63—64 °C).

Cyclohexane-1,4-dione Monoethylene Thioacetal.—4-Benzoyloxycyclohexanone (7 g, 0.032 mol), ethane-1,2-dithiol (3 g, 0.032 mol), toluene-*p*-sulphonic acid (20 mg), and benzene (60 ml) were refluxed in a Dean and Stark apparatus (20 h, water collected 0.55 ml). Removal of the benzene gave a solid which was crystallised from benzene–light petroleum (b.p. 40—60 °C) to give 4-benzoyloxycyclohexanone ethylene thioacetal (8.7 g, 92%), m.p. 73—75 °C (lit.,[12] m.p. 73—76 °C), $\nu_{max.}$ (KBr) 1 700 cm^{-1}. The thioacetal (8 g, 0.0272 mol) and sodium methoxide solution (Na 85 mg and methanol 30 ml) were heated under reflux for 15 h after which methanol was distilled off and the residue extracted twice with acetone. Evaporation and distillation of the extract removed methyl benzoate (31 °C/0.25 mmHg): the pot residue was crystallised from benzene–light petroleum (b.p. 40—60 °C) to give 4-hydroxycyclohexanone ethylene thioacetal (4.31 g, 83%), m.p. 84—85 °C (lit.,[12] m.p. 83.5—85 °C).

Chromium trioxide (4.1 g, 0.041 mol) was cautiously added to pyridine (45 ml) followed by the above thioacetal (3 g, 0.016 mol) in pyridine (15 ml). The mixture was stirred for 3 days and then diluted with ether (70 ml) and filtered. The ethereal filtrate was washed with 2M-sulphuric acid and water, dried, evaporated, and chromatographed on dry silica in a nylon tube with ether–n-hexane (1 : 1) as eluant to give cyclohexane-1,4-dione monoethylene thioacetal[12] (1.02 g, 34%) as an oil, $\nu_{max.}$ 1 710 cm^{-1}; ^{1}H n.m.r.: δ 2.3—2.5 (dd, 4 H, *J* 11 and 4 Hz), 2.5—2.7 (dd, 4 H, *J* 11 and 4 Hz), and 3.44 (s, 4 H, SCH$_2$CH$_2$S).

3,5-Dimethoxyphenylethylcyclohexanol (8).—A Grignard reagent was formed from 3,5-dimethoxyphenylethyl bromide (3 g, 0.0122 mol) and magnesium (307 mg, 0.0126 g-atom) in rigorously dried tetrahydrofuran (60 ml), with stirring and refluxing (5 h). The reagent was cooled to 0 °C and cyclohexanone (1.196 g, 0.0122 mol) in dry tetrahydrofuran (20 ml) was added slowly with stirring. After a period under reflux (1 h) the product was worked up with aqueous ammonium chloride to give an oil which was chromatographed on a silica column using gradient elution with ether–n-hexane (1 : 4)→(4 : 1). Products isolated were: (*a*) 3,5-dimethoxyethylbenzene (19) (oil, 920 mg, 45%), ^{1}H n.m.r.: δ 1.24 (t, 3 H, *J* 8 Hz, CH$_2$C*H*$_3$), 2.48—2.76 (q, 2 H, *J* 8 Hz, C*H*$_2$CH$_3$), 3.85 (s, 6 H, 2 × OMe), 6.32 (s, 1 H, 4-ArH), 6.42 (s, 2 H, 2- and 6- ArH); (*b*) 1,4-bis(3,5-dimethoxyphenyl)butane (20) (182 mg, 5%), m.p. 101—102 °C (*M*$^+$, 330), ^{1}H n.m.r.: δ 1.58—1.78 (m, 4 H, ArCH$_2$C*H*$_2$-C*H*$_2$CH$_2$Ar), 2.42—2.68 (m, 4 H, ArC*H*$_2$CH$_2$CH$_2$C*H*$_2$Ar), 3.83 (s, 12 H, 4 × OMe), and 6.39 (s, 6 H, 6 × ArH): (*c*) 3,5-Dimethoxyphenylethylcyclohexanol (8)[8] (910 mg, 28% (*M*$^+$, 264), ^{1}H n.m.r.: δ 6.46 (d, 2 H, *J* 2 Hz, 2 × ArH *o*-to side-chain), 6.38 (t, 1 H, *J* 2 Hz, ArH *p*-to side-chain), 3.86 (s, 6 H, 2 × OMe), 2.80—2.57 (m, 2 H, ArC*H*$_2$CH$_2$) 1.88—1.68 (m, 2 H, ArCH$_2$C*H*$_2$), 1.56 (br, s, 10 H, 5 × cyclohexane CH$_2$), and 1.41 (br s, 1 H, D$_2$O exch., OH).

Cyclisation of Dimethoxyphenylethylcyclohexanol (8) *to 5,7-Dimethoxyindan-1-spirocyclohexane* (12).—The cyclohexanol

(8) (220 mg, 0.83 mmol) in acetic acid (2 ml) was treated with concentrated sulphuric acid (0.2 ml) at 20 °C and was then heated at 100 °C for 30 min. The mixture was poured into hydrogen carbonate solution and extracted with ether. Evaporation of the ether extract gave a semi-solid which crystallised from hexane to give the spiran (12) (69 mg, 34%), m.p. 95—96 °C, (lit.,[8] m.p. 95—96 °C) (Found: M^+, 246.1636. $C_{16}H_{22}O_2$ requires M, 246.1620), ^{1}H n.m.r. 1.17—1.78 (m, 10 H, 5 × cyclohexane CH_2), 2.00 (t, 2 H, J 8 Hz, $ArCH_2CH_2$), 2.84 (t, 2 H, J 8 Hz, $ArCH_2CH_2$), 3.82 (s, 6 H, 2 × OMe), 6.32 (s, 1 H, 6-H), and 6.38 (s, 1 H, 4-H): ^{13}C n.m.r. δ 23.6, 26.0, 31.1, 34.6, 35.2 (all t, 5 × cyclohexane methylene carbons), 49.2 (s, spiro-C-1), 55.0 55.3 (each q, OMe), 97.2, 100.7 (each d, 2 × arom. CH), and 131.1, 145.6, 157.5, and 160.0 (all s, 4 × substituted aromatic carbons).

1-(3,5-*Dimethoxyphenylethyl*)-4-*oxocyclohexanol Ethylene Acetal* (21a).—3,5-Dimethoxyphenylethyl bromide (5 g, 0.02 mol) in dry tetrahydrofuran (30 ml) was added slowly (during 3 h) to magnesium (600 mg, 0.025 g-atom) in refluxing tetrahydrofuran, stirred under nitrogen (initiated with iodine). The Grignard reagent was refluxed for a further 6 h and cyclohexane-1,4-dione monethylene acetal (3.2 g, 0.02 mol) in dry tetrahydrofuran (30 ml) was added: the mixture was stirred and refluxed for 18 h. Work-up with aqueous ammonium chloride gave an oil which was chromatographed on a dry silica column (nylon tube) with ether–n-hexane (4 : 1) as eluant until the solvent front reached the bottom of the column. Dissection of the column, guided by t.l.c., gave the *acetal* (21a) (2.90 g, 44%), an oil (M^+, 322.1776. $C_{18}H_{26}O_5$ requires M, 322.1780). It had $\lambda_{max.}$ (EtOH) 204 (ε 35 000), 222 (6 300), 273 (1 400), and 279 nm (1 400); ^{1}H n.m.r.: δ 6.38 (d, 2 H, J 2 Hz, *o*-ArH), 6.34 (t, 1 H, J 2 Hz, *p*-ArH), 3.98 (s, 4 H,; OCH_2CH_2O), 3.78 (s, 6 H, 2 × OMe), 2.67 (m, 2 H, $ArCH_2$), 1.5—1.9 (m, 10 H, 5 × CH_2), and 1.38 (s, 1 H, D_2O exch., OH).

Cyclisation of the Acetal (21a) *using Sulphuric–Acetic Acid.*—The acetal (2.5 g) was stirred in a mixture of concentrated sulphuric acid (2.5 ml) and glacial acetic acid (25 ml) at 100 °C for 30 min. The mixture was then poured into aqueous sodium hydrogen carbonate and the product extracted with ether (1.73 g). Crystallisations from ether–n-hexane gave the *octahydrophenanthrenone* (22b) (700 mg, 35%) as pale yellow prisms, m.p. 136.5—137.5 °C (Found: M^+, 260.1407. $C_{16}H_{20}O_3$ requires M, 260.1412), $\lambda_{max.}$ (EtOH) 223 (ε 9 000), 277 (2 000), and 283 nm (2 000); $\nu_{max.}$ (KBr) 1 695 cm^{-1}; ^{1}H n.m.r.: δ 6.26 (s, 2 H, 2 × ArH), 3.78 (s, 6 H, 2 × OMe), 3.37 (d, of t, 1 H, J 12 and 4 Hz, $ArCH$·), 2.88—2.96 (m, 2 H, $ArCH_2$), 2.08—2.48 (m, 8 H, 4 × CH_2), and 1.61—1.80 (m, 1 H, CH); ^{13}C n.m.r.: δ 211.8 (C=O), 158.8, 157.8, 137.2, 120.9) (all s, 4 × substituted aromatic carbons), 104.5, 96.1 (both d, 2 × unsubstituted aromatic CH), 55.1 (q, 2 C, 2 × OMe), 43.8, 37.2 (t, 2 × methylene CH_2), 35.1 and 32.7 (both d, 2 × ring junction CH), and 31.3, 30.3, and 22.7 (all t, 3 × methylene).

Octahydrophenanthrenone Ethylene Acetal (22a).—The octahydrophenanthrenone (22b) (250 mg) was refluxed in a Dean and Stark apparatus for 24 h with ethylene glycol (0.2 ml) and toluene-*p*-sulphonic acid (10 mg) in dry benzene (30 ml). Work-up and chromatography (dry silica column, elution ether–n-hexane 1 : 1) gave the *ethylene acetal* (22a) (15 mg), m.p. 117—119 °C from ether–n-hexane (Found: M^+, 304.1673. $C_{18}H_{24}O_4$ requires M, 304.1674). The acetal OCH_2CH_2O was represented in the ^{1}H n.m.r. spectrum at 3.99 (br t, 4 H).

Cyclisation of the Acetal (21a) *Using Toluene*-p-*sulphonic Acid.*—The acetal (21a) (100 mg) was refluxed with toluene-*p*-sulphonic acid (10 mg) in benzene for 16 h. After work-up and p.l.c. on silica with chloroform–methanol (99.5 : 0.5) as eluant, the above octahydrophenanthrenone ethylene acetal (22a) (m.p. and mixed m.p. 115—116 °C, and comparison of ^{1}H n.m.r. and mass spectrum) was the only product characterised.

Cyclisation of the Acetal (21a) *Using Boron Trifluoride.*—Boron trifluoride–diethyl ether (10 μl; 50% solution in ether) was added to compound (21a) (30 mg) in dry dichloromethane (2 ml). After 10 min, t.l.c. indicated that reaction was complete: water was added to the mixture and the product extracted with ether. After p.l.c. as above, the octahydrophenanthrenone (22b) was isolated (m.p. and mixed m.p. 133 °C and i.r. comparison).

Reaction of the Acetal (21a) *with* N,N-*Dimethylformamide Dineopentyl Acetal.*—The acetal (21a) (480 mg) and the dineopentyl acetal (1 ml) in benzene (15 ml) were refluxed with stirring for 6 days, the reaction being monitored at intervals by t.l.c. The mixture was washed with water, dried, evaporated, and the product chromatographed on silica with chloroform–methanol (99.5 : 0.5) as eluant to give a yellow oil (100 mg). The latter was chromatographed on a silica plate with benzene as eluant (triple elution) to yield two products with closely similar R_F values. The first (least polar) was the *exocyclic olefin* (23a) (10 mg) (M^+, 304.1679. $C_{18}H_{24}O_4$ requires M, 304.1674), ^{1}H n.m.r.: δ 6.33 (s, 3 H, 3 × Ar*H*), 5.33 (t, 1 H, J 8 Hz, =CH), 3.97 (s, 4 H, O·CH_2-CH_2O), 3.77 (s, 6 H, 2 × OMe), 3.30 (d, 2 H, J 8 Hz, Ar-CH_2CH=), 2.21—2.41 (m, 4 H, 2 × CH_2C=CH·), and 1.70 (t, 4 H, J 7 Hz, 2 × $OCCH_2$). The *endocyclic olefin* (24a) (12 mg) (M^+, 304.1685) had ^{1}H n.m.r.: δ 6.33 (s, 3 H, 3 × ArH), 5.35 (br s, 1 H, CH_2CH=C), 3.98 (s, 4 H, OCH_2-CH_2O), 3.77 (s, 6 H, 2 × OMe), 2.6—2.8 (m, 2 H, $ArCH_2$), 2.25 (br t, 4 H, 2 × CH_2), and 1.5—1.8 (m, 4 H, 2 × CH_2).

Reaction of the Acetal (21a) *with Phosphoryl Chloride–Pyridine.*—The acetal (21a) was stirred at 20 °C with phosphoryl chloride (100 mg) in pyridine (5 ml) for 16 h. The mixture was poured into dilute hydrochloric acid and extracted with ethyl acetate. The extract was worked up and subjected to p.l.c. on silica, with ether–n-hexane (1 : 4) as eluant, to give the *deprotected exocyclic olefin* (23b) (M^+, 260.1422. $C_{16}H_{20}O_3$ requires M, 260.1412), ^{1}H n.m.r.: δ 6.33 (s, 3 H, 3 × ArH), 5.47 (br s, 1 H, =CH), 3.78 (s, 6 H, 2 × OMe), 3.34 (d, 2 H, J 7 Hz, $ArCH_2CH$=), and 2.35—2.90 (complex, 8 H, 4 × CH_2): $\nu_{max.}$ 1 705 cm^{-1}.

Cyclisation of the Acetal (21a) *with Polyphosphoric Acid.*—The acetal (21a) (500 mg) was stirred in phosphoric acid (2.5 ml, 88%), for 1 h and phosphorus pentoxide (2.2 g) was added in four portions at 20 min intervals: the mixture was then stirred at 80 °C for 1 h. The cooled mixture was then poured onto ice and extracted with ether; the extract was worked up and chromatographed on a dry silica column (nylon tube) with ether–n-hexane (1 : 1) as eluant to give the octahydrophenanthrenone (22b) (80 mg), m.p. and mixed m.p. with the sample above 134—135 °C.

G.l.c.–Mass Spectral Investigation of the Cyclisation of Compound (21a).—The hydroxyacetal (21a) (10 mg) was heated at 80 °C in benzene (1 ml) with toluene-*p*-sulphonic acid for 18 h; g.l.c. analysis (1% OV-17 glass 5 ft × ¼ in column at 230 °C, N_2 15 ml/min) showed a mixture of the acetal and ketone products. The reaction was then carried out in butan-2-one (1 ml) to exchange substantially the acetal; the products formed were (24b) (rel. area 20%); (23b) (14%),

(22b) (31%), (22a) (12%), (21b) (21%), identified by R_t, together with an unidentified product (2%) which was not the required spiro-compound. The R_t values of the standard compounds under the above g.l.c. conditions were (24b), 3.6; (23b), 4.0; (22b), 4.7; (24a), 5.6; (23a), 5.8; (22a), 6.2; (21b), 8.0; and (21a) 11.2 min.

A similar experiment at 80 °C using compound (21a) (5 mg), butan-2-one (1 ml), and BF_3–diethyl ether (0.05 ml) was carried out. After 15 min t.l.c. indicated that deprotection of the ketone was almost complete, but no cyclisation had occurred. Heating at 170 °C in a sealed container for 5 min caused rapid cyclisation and g.l.c./m.s. examination showed the presence of (24b), (23b), and mainly (22b) but no positive evidence for the formation of methyl cannabispirone was obtained.

Demethylation of Compound (21a) *with Lithium Diphenyl Phosphide*.—The Hydroxyacetal (21a) (273 mg, 0.85 mmol) in dry tetrahydrofuran (1 ml) was added to the red solution formed by adding n-butyl-lithium (2.2 ml of 1.4M solution, 2.51 mmol) to diphenylphosphine (0.4 ml, 2.31 mmol) [14] at −10 °C and the mixture was stirred at 20 °C (3½ h). The product was poured into water and extracted with ether; the ether extracts contained 52 mg of an oil, containing some recovered compound (21a). The aqueous solution was acidified (HCl) to pH 3 and extracted with ether to give a semi-solid (110 mg). P.l.c. on 20 × 20 cm HF 254 silica plates (elution with ether) gave two main bands giving positive phenolic colours with Fast Blue Salt B (FBSB). The faster eluting band (M^+, 308) corresponded to mono-demethylated ketone [*cf.* (21b)].

Cyclisation of Mono-demethylated Compounds of (21a) *and* (21b).—The crude mixture of mono-demethylated compounds [*cf.* (21a)] and [*cf.* (21b)] (100 mg) was heated with glacial acetic acid (100 μl) and concentrated sulphuric acid (10 μl) at 100 °C for 30 min. The mixture was then poured into water and extracted with chloroform. The extract was washed, dried and worked up to give a product which was chromatographed on a 20 × 20 cm silica plate with chloroform–methanol (99.5 : 0.5) and then chloroform–ether (4 : 1) as eluants. Seven bands could be recognised, three being phenolic (FBSB). Band 5 (*ca.* 5 mg) had m.p. 206—207 °C (M^+, 246), R_t as trimethylsilyl derivative 15.7 min (5% OV.17, 230 °C) and was identical (mixed m.p.) with mono-demethylated octahydrophenanthrenone-A (below). It gave a dull-red FBSB colour and R_F values in ether or chloroform–methanol (95 : 5) also corresponded. Band 6 (*ca.* 5 mg) had m.p. 191—193 °C (FBSB colour purple), M^+, 246.1265 ($C_{15}H_{18}O_3$ requires M, 246.1256) R_t (as above) 18.7 min. It was identical with mono-demethylated octahydrophenanthrenone-B (below) (mixed m.p., t.l.c., and g.l.c.) comparison. No identification of a compound corresponding to cannabispirone-A or -B could be made.

Demethylation of Octahydrophenanthrenone (22b).—Magnesium iodide–diethyl ether [15] reagent was made by adding iodine crystals (8 g, 0.31 mol) in portions to magnesium turnings (1.6 g, 0.067 g-atom) in dry ether (10 ml) and dry benzene (20 ml) with stirring and cooling. The solution (25 ml, 0.027 mol) was added to the dimethoxyketone (22b) (740 mg, 2.8 mmol) in dry benzene (80 ml) containing tetrabutylammonium iodide; the mixture was then stirred and refluxed overnight. Work-up with dilute hydrochloric acid followed by p.l.c. on silica with ether–n-hexane (4 : 1) as eluant gave: (*a*) recovered (22b) (200 mg), and, in order of increasing polarity, (*b*) mono-demethyl-(22b)-A (30 mg), m.p. 206—207 °C from ethyl acetate (M^+, 246), (*c*) mono-demethyl-(22b)-B (50 mg), m.p. 190—191 °C from ethyl acetate (M^+, 246), and (*d*) bis-demethyl-(22b) (20 mg), m.p. 214—216 °C from ether (M^+, 232). The 5- or 7-orientation of the two mono-methyl ethers has not been determined.

1-(3,5-*Dimethoxyphenylethyl*)-4-*oxocyclohexanol Ethylene Thioacetal* (21c).—Cyclohexane-1,4-dione monothioacetal (996 mg, 0.0053 mol) in dry tetrahydrofuran (10 ml) was added slowly with stirring, to a Grignard reagent at 0 °C, made from 3,5-dimethoxyphenylethyl bromide (1.17 g, 0.0048 mol) and magnesium (120 mg, 0.005 g-atom) in dry tetrahydrofuran (70 ml). The mixture was refluxed (1 h). Work-up with aqueous ammonium chloride, followed by chromatography of the product on a silica column with gradient elution with ether–n-hexane (1 : 4) ⟶ (4 : 1) gave (*a*) 3,5-dimethoxyethylbenzene (19) (230 mg, 29%), (*b*) 1,4-bis(3,5-dimethoxyphenyl)butane (20) (62 mg, 4%), m.p. 101—102 °C, and (*c*) the title *thioacetal* (21c) (422 mg, 25%) (M^+, 354. $C_{18}H_{26}O_3S_2$ requires M, 354), ^{1}H n.m.r.: δ 1.4—2.4 (m, 10 H, $ArCH_2CH_2$ plus 8 methylene protons of cyclohexane), 2.5—2.8 (m, 2 H, $ArCH_2CH_2$), 3.32 (s, 4 H, SCH_2CH_2S), 3.80 (s, 6 H, 2 × OMe), and 6.24—6.44 (m, 3 H, Ar*H*).

Cyclisation of Compound (21c) *Using Toluene*-p-*sulphonic Acid*.—The thioacetal (21c) (200 mg) and toluene-*p*-sulphonic acid (20 mg) were refluxed in benzene (20 ml) for 16 h. Removal of the solvent and p.l.c. on silica plates with ether–n-hexane (1 : 1) as eluant gave the *octahydrophenanthrenone thioacetal* (22c) (37 mg, 19%), m.p. 107—109 °C from n-hexane (Found: M^+, 336.1222. $C_{18}H_{24}O_2S_2$ requires 336.1218), $\lambda_{max.}$ (EtOH): 227 (13 100), 274 (3 350), and 281 nm (3 380); ^{1}H n.m.r.: δ 1.6—2.3 (m, 10 H, $ArCH_2CH_2$ + 8 methylene and methine protons), 2.7—2.9 (m, 2 H, $ArCH_2CH_2$), 3.32 (s, 4 H, SCH_2CH_2S), 3.79, 3.82 (each s, 3 H, 2 × OMe), and 6.2—6.4 (m, 2 H, Ar*H*); ^{13}C n.m.r.: δ 22.76, 30.52, 31.82, 37.31, and 43.31 (five t, 5 methylenes), 32.32, 34.55 (two d, 2 × ring junction CH), 37.78, 38.52 (two t, SCH_2CH_2S), 55.25, 55.43 (two q, 2 × OMe), 68.98 (s, CH_2SCSCH_2), 96.39, 104.62 (two d, 2 × unsubs. aromatic C), and 122.17, 137.76, 158.22, and 158.66 p.p.m. (four s, 4 × subs. aromatic C).

Cyclisation of 1-(4-*Methoxyphenyl*)-2-*phenylethane* (25) *in* SbF_5–HF.—1-(4-Methoxyphenyl)-2-phenylethane (m.p. 60.5—62 °C) [16] (1.18 g, 0.0056 mol) was dissolved in a solution of antimony pentafluoride (14.1 g) in hydrofluoric acid (9.07 g) at 0 °C and the reaction was stirred at 0 °C for 50 min. The homogeneous solution was poured into ice and neutralised with sodium carbonate. The mixture was extracted with ether and worked up; p.l.c. of the product on a 40 × 40 cm silica plate with ether–light petroleum (b.p. 40—60 °C) (1 : 1) as eluant gave: (*a*) recovered starting material (144 mg, 12%), (*b*) the spiro-compound (27) (360 mg, 33%), m.p. 47—48 °C (lit.,[16] m.p. 41 °C) identical (mixed m.p. and spectral comparison) with the specimen synthesised by a different route in the preceding paper,[1] (*c*) hexahydrophenanthrenone (28) (121 mg, 11%), m.p. 76.5—77 °C (lit.,[16] m.p. 78 °C) (M^+, 198.1059. Calc. for $C_{14}H_{14}O$: M, 198.1045), $\nu_{max.}$ KBr 1 658 cm^{-1}; $\lambda_{max.}$ (EtOH) 227 (8 550), 233 (5 950), and 298 nm (15 800).

Treated under the same conditions, 4.46M-SbF_5–HF at 0 °C) trimethoxylated dihydrostilbene (29) was recovered unchanged. A second experiment using 2.5M SbF_5–HF at 0 °C gave the same result. The dihydrostilbene (29) was prepared by a Wittig reaction using 3,5-dimethoxybenzyltriphenylphosphonium bromide and 4-methoxy-

benzaldehyde which gave the expected *cis,trans*-stilbene (79%), hydrogenated to 1-(3,5-dimethoxyphenyl)-2-(4-methoxyphenyl)ethane (29) (94%), an oil (Found: M^+, 272.1427. $C_{17}H_{20}O_3$ requires M, 272.1412). For details of similar preparations see ref. 17.

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