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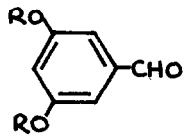
SYNTHESIS OF 4"-CARBOXYLATED CANNABINOIDS: STEREOSPECIFIC PROCESSES INVOLVING ETHYLIDENEMALONIC ESTER

Leslie Crombie, W.Mary L. Crombie, Geoffrey W. Kilbee
and Patoomratana Tuchinda.
Department of Chemistry, The University,
Nottingham, NG7 2RD.

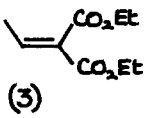
Summary: 4"-Carboxylated-cannabidiol,-Δ^1-and-$\Delta^{1,6}$-tetrahydrocannabinols and - cannabinol are synthesised. Condensation between aromatic aldehydes and ethylidenemalonic ester gives a 2E,4E-half ester stereospecifically, a reaction which can be used to make 2E,4E- or 2Z,4E-pentadienoates.

ω-Oxidation occurs in microbial transformation of the cannabinoids,[1] and is implicated in their mammalian metabolism.[2] 4"-Carboxylated cannabinoids are also of interest for spin-labelling purposes and as haptens for radio-immunoassay.[3] With this in mind we have undertaken the synthesis of 4"-carboxylated-cannabidiol, Δ^1-and-$\Delta^{1,6}$-tetrahydrocannabinols, and - cannabinol. In order to load the side-chain with four atoms of tritium or deuterium the synthesis was planned via a suitably substituted 5-arylpenta-2,4-dienoate, a convenient approach being condensation between ethylidenemalonic ester and an aromatic aldehyde:[4] the reaction was found to have useful stereochemical features.

Condensation between 3,5-dimethoxybenzaldehyde(1) and diethyl ethylidinemalonate(3) gave the diacid(6)(66%), m.p.223 - 224° when catalysed with methanolic KOH, but if methanolic benzyltrimethylammonium hydroxide was used the 2E,4E-half methyl ester(4), m.p.155 - 157°, was produced stereospecifically (66%). This is doubtless due to the operation of a Stobbe-type mechanism,[5] involving opening of lactonic intermediate(7a) as in (9,R=CO_2Me). A related base catalysed opening of hex-2-eno-δ-lactone has been studied.[6] Direct decarboxylation of (4) by heating with pyridine (48 h) led to the 2E,4E-ester (10a), (52%), identical with a specimen made by treating E-methyl 3-formylpropenoate with the Wittig reagent from 3,5-dimethoxybenzyltriphenylphosphonium bromide:the 2E,4E-acid had m.p.157 - 158°. On the other hand, when the diacid (6) was heated in quinoline, the 2Z,4E-acid(13a), m.p.143 - 144°, was formed stereospecifically in 74% yield. Apparently the lactonic acid (8a, or βγ-form), equilibrating with the diacid (6), is decarboxylated more rapidly than the latter, re-equilibration giving (13a). UV-irradiation of the 2Z,4E-acid (13a)



(1) R = Me
(2) R = CH_2Ph



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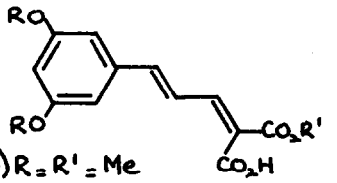
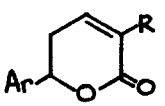
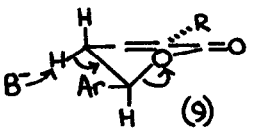


(4) R = R' = Me
(5) R = CH_2Ph, R' = Me
(6) R = Me, R' = H



(7) R = CO_2Me
(8) R = CO_2H



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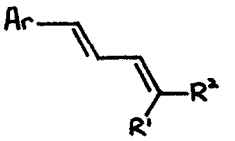
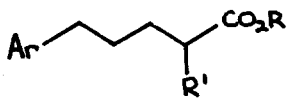


(10) R' = H, R^2 = CO_2Me
(11) R' = H, R^2 = CO_2H
(12) R' = CO_2Me, R^2 = H
(13) R' = CO_2H, R^2 = H

(a) Ar = 3,5-dimethoxyphenyl
(b) Ar = 3,5-dihydroxyphenyl
(c) Ar = 3,4-methylenedioxyphenyl



(14) R = H, R' = H
(15) R = Me, R' = H
(16) R = Me, R' = CO_2H

(benzene, trace of iodine) gives the 2E,4E-acid (11a). These reactions are generally useful in the stereospecific synthesis of 2Z-4E-and 2E,4E-stereomers of 5-arylpenta-2,4-dienoates.[7]

Although the dimethoxypentanoate (15a), obtained by hydrogenating (10a) or (12a), can be demethylated by refluxing HI, yields of (14b) are poor, and demethylation with BBr_3 at 20° gave mainly the cyclised product, 7,9-dihydroxy-benzsuberone. For 4"-carboxylated cannabinoid synthesis, the best approach was condensation of the dibenzylated aldehyde (2) with diethyl ethylidene-malonate (3) in methanolic benzyltrimethylammonium hydroxide to give (5)(68%), hydrogenated and hydrogenolysed to the half-ester (16b)(95%). The latter was decarboxylated in hot pyridine to give methyl 5-(3,5-dihydroxyphenyl)-pentan-oate (15b)(94%).

Condensation of (15b)(0.31 mmol) with (+)-p-menthadienol (PMD)[8] (0.36 mmol), catalysed by toluene-p-sulphonic acid (PTSA)(0.06 mmol) in benzene/ether for 2½h at 24° gave, after plc, 4"-carbomethoxylated o-(18,R=Me)(34%), $[\alpha]_D^{24}$($CHCl_3$) -75.4°, and p-(17,R=Me)(27%), $[\alpha]_D^{25}$($CHCl_3$)-75.5°, cannabidiol types. A similar reaction using (14b) gave acid (17,R=H)(27%), $[\alpha]_D^{23}$($CDCl_3$)-58.2°, also obtained by hydrolysis of (17,R=Me). Under stronger acid conditions (PTSA

0.028 mmol, benzene, 3h, 60 - 70°), PMD(0.10 mmol) and ester (15b)(0.08 mmol) gave the $\Delta^{1,6}$-THC relative (19,R=Me)(35%), $[\alpha]_D^{23}(CHCl_3)$-156°, $(M^+-15)/M^+$ < 0.1; a similar preparation has been reported by Lotz et al.[9]

Whilst (17,R=Me) and (19,R=Me) are readily formed and separated, conditions for the important Δ^1-THC type (20,R=Me) are more exacting. The following is typical of a number of experiments. Ester (15b)(3.7 mmol) was stirred in CH_2Cl_2(21 ml) with PMD(4.5 mmol) and PTSA(1.8 mmol) for 6 h at 19°, tlc monitoring showing reaction had proceeded to the cannabidiol stage. Further PTSA(1.8 mmol) was added and the mixture heated to 40°(2 h) : reaction was stopped whilst some cannabidiol still remained. Plc (40 × 40 cm plates, silica G HF254), eluting with methylene chloride (97)/n-hexane (2.85)/methanol (0.15%), gave the Δ^1-THC-type (20,R=Me)(10%. range 8 - 15%), almost pure as a single band. An adjacent mixed band (22%, range 14 - 22%) [containing (17)(19) and (20), all R=Me], was separated by hplc using a C_{18}-reversed phase Corasil column [elutant: methanol (2)/water (1)] to give a further 5% of (20,R=Me). The latter had $[\alpha]_D^{25}(CHCl_3)$-125°, M^+ 358.2163, $(M^+-15)/M^+$ 0.50, ν_{max}(film) 1725 cm^{-1}, λ_{max}(EtOH)210(ε 30,400), 230i(9.700), 278.5(1,950) and 285(1,950)nm and the corresponding acid (20,R=H) had $[\alpha]_D^{25}(CHCl_3)$-97.8°, $(M^+-15)/M^+$ 0.60. On dehydrogenation (S/190°/45 min), a mixed fraction containing (17),(19) and (20), all R=Me, gave the 4"-carbomethoxylated cannabinol type (21)(21%), hydrolysed to the corresponding acid.[10]

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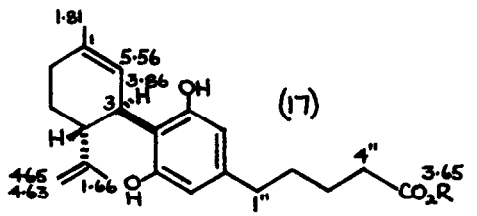

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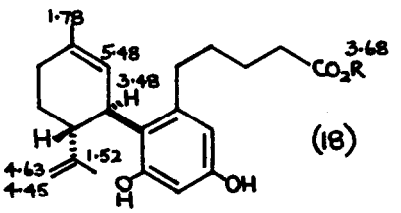

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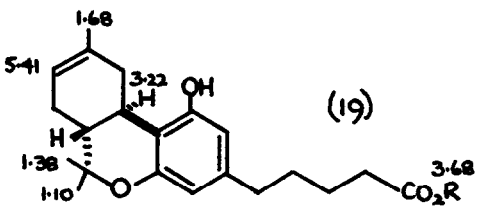

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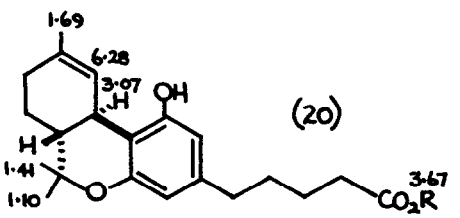

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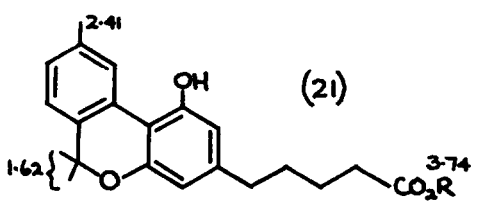

(21)

N.m.r. data given (δ) for Me esters

References and Footnotes

1. L.W. Robertson, S.-W. Koh, S.R. Huff, R.K. Malhotra and A. Ghosh, Experientia, 1978, 34, 1020. L.W. Robertson, S.R. Huff, A. Ghosh and R. Malhotra, Lloydia, 1978, 41, 659.

2. B.R. Martin, D.J. Harvey and W.D.M. Paton, J.Pharm.Pharmac., 1976, 28, 773.

3. C.E. Cook, M.L. Hawes, E.W. Amerson, C.G. Pitt and D. Williams in "Cannabinoid Assays in Humans", Ed. R. Willette. Res.Monograph Ser.Natl. Inst., Drug Abuse U.S., 1976, 7, 15.

4. P.D. Gardner, W.J. Horton, G. Thomson and R.R. Twelves, J.Amer.Chem.Soc., 1952, 74, 5527.

5. Recently a Stobbe mechanism has been proposed for a related reaction; see S. Rebuffat, M. Giraud and D. Molho, Bull.Soc.Chim.Fr., 1978, II, 457.

6. U. Eisner, J.A. Elvidge and R.P. Linstead, J.Chem.Soc., 1953, 1372. J.A. Elvidge and P.D. Ralph, J.Chem.Soc.(B), 1966, 243.

7. Earlier in our laboratories (J.C. Williams, Ph.D. Thesis, Univ.of London, 1961) 2Z,4E-piperic acid(13c) m.p.144 - 145° was prepared in this way via ethylidenemalonic ester, identical with a specimen made by partial hydrogenation of 5-(3,4-methylenedioxyphenyl)pent-4-en-2-ynoic acid.E.Ott and F.Eichler, Ber, 1922, 55, 2653 observed that (6), having a (c) type ring, prepared in a different way, could be decarboxylated to (13c).

8. T. Petrzilka, W. Haefliger and C. Sikemeier, Helv.Chim.Acta, 1969, 52, 1102; (+)-trans-p-mentha-2,8-dien-1-ol was employed.

9. F. Lotz, U. Kraatz and F. Korte, Annalen, 1977, 1132.

10. All the 4"-carbomethoxylated cannabinoids were characterised by accurate M^+, uv, ir and nmr spectra, together with R_f data for two silica and two reverse-phase systems. Fast Blue Salt B colours: (17) orange, (18) blue purple, (19) crimson, (20) crimson, (21) purple. R_t (silylated) for OV225 and OV17 SCOT columns (50 ft, temp.220° and 240° respectively): (17) 8.8, 9.0; (18) 10.4, 10.3; (19) 19.0, 15.9; (20) 21.4, 17.7; (21) 34.0, 21.6. mins.

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