Synthesis of (±)-*O*-Methylcannabichromene and Some Homologues

M. de la Torre, F. García* and R. Cruz*

Instituto de Química (1), Universidad Nacional Autónoma de México, Circuito Exterior, Ciudad Universitária, México 20 D.F., Mexico

Received April 1, 1981

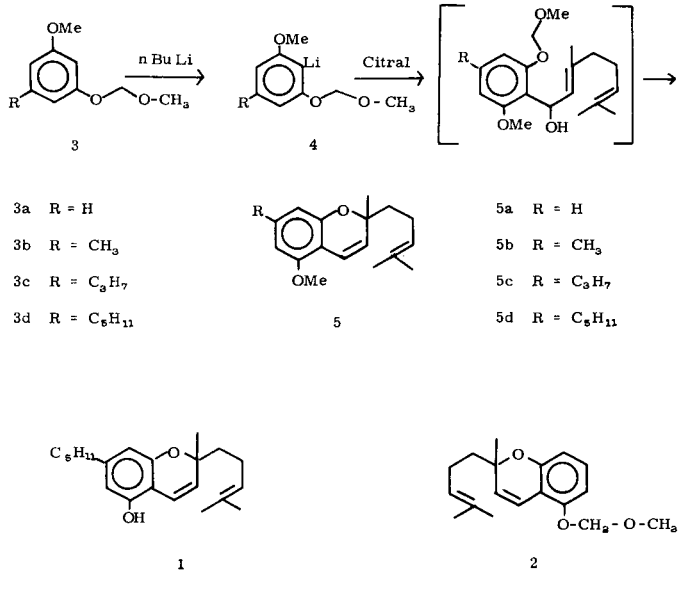
A facile novel synthesis of (±)-*O*-methylcannabichromene (**5d**) together with (±)-2-methyl-2-(4-methyl-3-pentenyl)-5-methoxy-2*H*-benzopyran (**5a**) and its 7-methyl (**5b**) and 7-propyl (**5c**) homologues, using organolithium salts is described.

J. Heterocyclic Chem., **18**, 1251 (1981).

Cannabichromene (**1**), one of the active principles in Hashish (Marihuana), was first isolated from *Cannabis sativa L.* and its structure determined by Gaoni and Mechoulam in 1966 (2). It has been previously synthesized by Kane and Razdan (3), Crombie and Ponsford (4) and Mechoulam (5), however yields are quite low and it has to be separated from a large number of by-products. More recently it has been reported (6) an improved procedure for the synthesis of cannabichromene. The presence of homologues of cannabinoids isolated from natural sources has been known for some time (7) but recent reports on the anti-inflammatory properties of cannabichromene (8) have made desirable alternative methods of synthesis for these compounds. Recently we reported (9) a one step synthesis of *d,l*-2-methyl-2-(4-methyl-3-pentenyl)-5-oxymethylenemethoxy-2*H*-benzopyran (**2**) condensing citral with 1,3-bis-(oxymethylenemethoxy)benzene-2-lithium derivative. We have now modified and extended this method for the synthesis of (±)-*O*-methylcannabichromene (**5d**) and some homologues. Starting with 1-methoxy-3-oxymethylenemethoxybenzene-2-lithium derivative (**4**) or the 5-methyl, 5-propyl and 5-pentyl homologues in a condensation reaction with citral we have been able to obtain (±)-*O*-methylcannabichromene (**5d**) and the corresponding homologues (**5a-c**). As previously observed, the intermediate condensation products reacted under the isolation procedure conditions (silica gel/chromatography) to yield the chromenes (Scheme). The reaction proceeded smoothly and yields were around 37% with large recovery of starting material. The required mixed ethers of 5-alkyl substituted resorcinols (**3a-d**) are easily prepared from the corresponding monomethyl ethers by treating its sodium salts with methyl chloromethyl ether. The corresponding phenols (R = H, R = CH_3 and R = C_5H_{11}) are commercially available and 5-propyl resorcinol was prepared by following Sutter's route (10) with some modifications.

The lithium derivatives were prepared by reacting the corresponding mixed ethers with butyl lithium in anhydrous ether at room temperature for 24 hours and the metallation products used without further purification.

SCHEME



EXPERIMENTAL

The ir spectra were recorded on a Perkin Elmer 283 B spectrophotometer. ^{1}H-nmr spectra were recorded on Varian FT-80 or Varian HA-100 spectrometers using deuteriochloroform as solvent and tetramethylsilane as internal standard. Mass spectra were determined on Hitachi-Perkin Elmer RMU-7H or Hewlett Packard HP 5985 spectrometers. Elemental microanalysis were performed by Dr. F. Pasher's Laboratory, Bonn, Germany.

Starting Materials.

Sutter's method (10) was followed with some modifications for the synthesis of 3,5-dimethoxy-5-propylbenzene. The preparation of the acid chloride was effected with thionyl chloride in benzene under reflux instead of using phosphorus pentachloride in chloroform or carbon tetrachloride. In the Grignard reaction, the iodine derivative was used and for the Wolf-Kishner reduction, the Huang-Minlon modification was employed.

The preparation ot monomethyl ethers of 5-alkyl-substituted resorcinols and resorcinol was carried out starting with its corresponding dimethyl ethers and following the demethylation procedure described for orcinol (11).

Preparation of Mixed Ethers. General Procedure.

In a 500 ml round bottom flask with two ground joints and a nitrogen

0022-152X/81/061251-02$02.25

inlet fitted with a magnetic stirrer and drying tube, 5 g of sodium wire and 50 ml of anhydrous ethyl alcohol were placed and the system swept with nitrogen. The monomethyl ethers (0.054 mole) were added together with 0.08 moles of *N,N*-dimethylformamide and 300 ml of benzene *via* a separatory funnel. The solution turns to a light brown color. Immediately methyl chloromethyl ether (0.21 mole) was added dropwise during 2 hours. After this period, the solution turned brownish-yellow. The salts which separated as solids were filtered off through a buchner funnel and the filtrate washed with water until neutral. The benzene solution was dried over anhydrous sodium sulfate and distilled under *vacuo* yielding colorless oils. Yields are approximately 80%.

1-Oxymethylenemethoxy-3-methoxybenzene (**3a**).

This compound had bp 102°/0.5 mm Hg, yield 83%; ir (film): 3010, 2980, 2960, 1605, 1450, 1340, 1220, 1190, 1180, 1025 cm^{-1}; nmr: δ 3.50 (3H, s), 3.69 (3H, s), 5.1 (2H, s), 6.75 (4H, m); ms: m/e (relative intensities) 168 (30, M^+), 153 (7), 138 (12), 137 (19), 123 (21), 108 (18), 95 (27), 80 (25), 65 (27), 53 (17), 45 (100).

1-Oxymethylenemethoxy-3-methoxy-5-methylbenzene (**3b**).

This compound had bp 90°/0.5 mm Hg, yield 79%; ir (film): 3020, 2980, 2860, 1600, 1475, 1410, 1260, 1230, 1205, 1090 cm^{-1}; nmr: δ 2.25 (3H, s), 3.4 (3H, s), 3.7 (3H, s), 5.1 (2H, s), 6.35 (3H, m); ms: m/e (relative intensities) 182 (23, M^+), 167 (3), 152 (23), 137 (5), 123 (19), 109 (9), 91 (20), 97 (17), 78 (23), 75 (21), 45 (100).

1-Oxymethylenemethoxy-3-methoxy-5-propylbenzene (**3c**).

This compound had 85°/0.5 mm Hg, yield 77%; ir (film): 3020, 2980, 2960, 1610, 1460, 1340, 1290, 1220, 1190, 1150, 1180, 1030 cm^{-1}; nmr: δ 0.92 (3H, t, J = 7 Hz), 1.64 (2H, m), 2.65 (2H, t, J = 7 Hz), 3.45 (3H, s), 3.72 (3H, s), 5.12 (2H, s), 6.41 (3H, m); ms: m/e (relative intensities) 210 (13, M^+), 195 (3), 179 (8), 165 (17), 152 (12), 149 (10), 137 (7), 125 (5), 109 (8), 105 (12), 97 (6), 91 (9), 69 (25), 45 (100).

1-Oxymethylenemethoxy-3-methoxy-5-pentylbenzene (**3d**).

This compound had 115°/0.5 mm Hg, yield 79%; ir (film): 3010, 2960, 2935, 2890, 1595, 1460, 1445, 1405, 1340, 1315, 1215, 1195, 1145, 1180, 1025; nmr: δ 0.88 (3H, t, J = 7 Hz), 1.3 (6H, m), 2.5 (2H, t, J = 7 Hz), 3.42 (3H, s), 3.78 (3H, s), 5.15 (2H, s), 6.45 (3H, m); ms: m/e (relative intensities) 238 (5, M^+), 223 (3), 207 (3), 193 (6), 182 (9), 167 (7), 137 (12), 121 (9), 109 (8), 91 (10), 79 (15), 65 (17), 45 (100).

Preparation of Lithium Salts. General Procedure.

In a 500 ml round bottom flask with two ground joints and gas inlet, 250 ml of anhydrous ether were placed together with 0.033 mole of the corresponding mixed ethers. The flask was fitted with a reflux condenser and a rubber stopper, the system was filled up with nitrogen and after 10 minutes 0.047 mole of *n*-butyllithium in hexane (1.4 *M*) was added *via* a hypodermic syringe. The solution turned from pale yellow to orange and became turbid. It was let with stirring during 24 hours and reacted with citral after this period.

Preparation of *O*-Methylcannabichromene and Homologues. General Procedure.

Citral (0.033 mole) was added to the same flask at −70° and that temperature was kept for 4 hours, after which the mixture was stirred for 4 hours more at room temperature. At the end of this reaction period 50 ml of a saturated ammonium chloride solution was added. The phases were separated and the aqueous layer washed several times with ether. Finally the ether layer was dried over anhydrous sodium sulfate, the solvent evaporated and the product separated by column chromatography on silica gel (70-230 mesh) eluting with a 8:2 benzene/hexane mixture. The product was further purified by tlc and distillation.

2-Methyl-2-(4-methyl-3-pentyl)-5-methoxy-2*H*-benzopyran (**5a**).

This compound had 110°/0.1 mm Hg, yield 42%; ir (film): 3100, 2900, 2840, 1665, 1600, 1465, 1380, 1280, 1100 cm^{-1}; nmr: δ 1.4 (3H, s), 1.55 (3H, broad), 1.65 (3H, broad), 1.7 (2H, m), 2.2 (2H, m), 3.7 (3H, s), 5.1 (1H, m), 5.52 (1H, d, J = 8 Hz), 6.5 (3H, m), 6.7 (1H, d, J = 8 Hz); ms: m/e (relative intensities) 258 (7, M^+), 243 (9), 228 (6), 175 (100), 160 (22), 144 (17), 132 (43), 129 (31).

Anal. Calcd. for $C_{17}H_{22}O_2$: C, 79.03; H, 8.58; O, 12.39. Found: C, 78.94; H, 8.63; O, 12.52.

2-Methyl-2-(4-methyl-3-pentyl)-5-methoxy-7-methyl-2*H*-benzopyran (**5b**).

This compound had 117°/0.5 mm Hg yield 37%; ir (film): 3065, 2990, 2870, 1630, 1575, 1465, 1385, 1260, 1240, 1230, 1150 cm^{-1}; nmr: δ 1.35 (3H, s), 1.55 (3H, broad), 1.65 (3H, broad), 1.75 (2H, m), 2.1 (2H, m), 2.2 (3H, s), 3.75 (3H, s), 5.1 (1H, m), 5.4 (1H, d, J = 9 Hz), 6.15 (1H, s), 6.25 (1H, s), 6.6 (1H, s, J = 9 Hz); ms: m/e (relative intensities) 272 (17, M^+), 257 (9), 229 (4), 215 (5), 189 (100), 174 (15), 151 (5), 148 (7), 128 (3), 115 (5), 91 (5).

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88; O, 11.75. Found: C, 79.05; H, 9.00; O, 11.80.

2-Methyl-2-(4-methyl-3-pentenyl)-5-methoxy-7-propyl-2*H*-benzopyran (**5c**).

This compound had 165-167°/0.5 mm Hg, yield 35%; ir (film): 3065, 2990, 1630, 1620, 1575, 1430, 1395, 1385, 1260, 1240, 1150 cm^{-1}; nmr: δ 0.9 (3H, t, J = 8 Hz), 1.35 (3H, s), 1.50 (3H, broad), 1.62 (3H, broad), 1.7 (4H, m), 2.1 (2H, m), 2.48 (2H, t, J = 8 Hz), 3.75 (3H, s), 5.10 (1H, m), 5.40 (1H, d, J = 10 Hz), 6.15 (1H, s), 6.25 (1H, s), 6.65 (1H, d, J = 10 Hz); ms: m/e (relative intensities), 300 (5, M^+), 285 (7), 257 (4), 243 (5), 217 (100), 188 (23), 179 (21), 161 (19), 145 (12), 91 (17), 69 (15).

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39; O, 10.65. Found: C, 79.83; H, 9.45; O, 10.85.

2-Methyl-2-(4-Methyl-3-pentenyl)-5-methoxy-7-pentenyl-2*H*-benzopyran (**5d**).

This compound had 155-157°/0.5 mm Hg yield 37%; ir (film): 3065, 2990, 2870, 1630, 1620, 1575, 1465, 1430, 1385, 1360, 1150 cm^{-1}; nmr: δ 0.9 (3H, t, J = 8 Hz), 1.40 (3H, s), 1.60 (3H, broad), 1.67 (3H, broad), 1.70 (6H, m), 1.72 (2H, m), 2.15 (2H, m), 2.50 (2H, t, J = 9 Hz), 3.75 (3H, s), 5.1 (1H, m), 5.4 (1H, d, J = 10 Hz), 6.15 (1H, s), 6.25 (1H, s), 6.6 (1H, J = 10 Hz); ms: m/e (relative intensities) 328 (9, M^+), 313 (9), 285 (7), 271 (5), 259 (5), 245 (100), 234 (65), 192 (80), 178 (85), 135 (72), 122 (75), 105 (20), 91 (32), 77 (29).

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83; O, 9.74. Found: C, 80.57; H, 9.92; O, 9.83.

REFERENCES AND NOTES

(1) Contribution No. 000 from Instituto de Química, U. N. A. M.

(2) Y. Gaoni and R. Mechoulam, *J. Chem. Soc., Chem. Commun.*, 20 (1966).

(3) V. V. Kane and R. K. Razdan, *J. Am. Chem. Soc.*, **90**, 6551 (1968).

(4) L. Crombie and R. Ponsford, *J. Chem. Soc., Chem. Commun.*, 894 (1968).

(5) R. Mechoulam and B. Yagen, *Tetrahedron Letters*, 5349 (1969).

(6) M. A. Elsohly, E. G. Boeren and C. E. Turner, *J. Heterocyclic Chem.*, **15**, 699 (1978).

(7) T. B. Vree, D. D. Breimer, C. A. M. van Ginneken and J. M. van Rossum, *J. Chromatogr.*, **74**, 124 (1972).

(8) P. W. Wirth, E. S. Watson, M. Elsohly, C. E. Turner and J. C. Murphy, *Life Sci.*, **26**, 1991 (1980).

(9) F. García, R. Laureles and R. Cruz, *Org. Prep. Proced. Int.*, **12**, 230 (1980).

(10) C. M. Sutter and A. W. Weston, *J. Am. Chem. Soc.*, **61**, 232 (1939).

(11) R. N. Mirrington and G. I. Feutrill, *Org. Synth.*, **53**, 90 (1973).