A Simple and Convenient Method for the Synthesis of Olivetols

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The alkylated olivetol derivatives were prepared for evaluation as analgesic agents. Olivetol derivatives were proven to have analgesic activity by the acetic acid-induced writhing test and tail-flick test. These compounds were prepared by condensation of appropriate olivetols with cyclic allylic alcohols in the presence of BF_3-etherate on alumina.

Introduction

In recent years an increasing number of articles has appeared describing the synthesis, properties, and biological activities of 5-alkyl-resorcinol derivatives. These compounds are 5-alkyl-2-(3-methyl-2-cyclohexen-1-yl)resorcinol analogues.

The goal of our research on developing simplified cyclohexenyl derivatives is the synthesis of new one having improved analgesic activity.

Previously, we have reported that simplified cannabidiol derivatives lacking the isopropenyl group (nor-isopropenyl cannabidiols) have anticonvulsant activity in rats. Nor-isopropenyl cannabidiols were found to be slightly more potent than cannabidiol[1].

In this report we describe a simple and convenient method for preparing alkylated olivetols from 1-methyl-2-cyclohexen-1-ol and olivetol derivatives and an evaluation of their analgesic activities.

Chemistry

We here report that when BF_3-etherate on alumina is used as a catalyst the reaction of 1-methyl-2-cyclohexen-ol (**1**) with olivetol (**2**) leads to the formation 2-(3-methyl-2-cyclohexen-1-yl)-olivetol (**3**) as the major product, in 34% yield as chromatographically pure oil.

No cyclization was observed vide infra and as the rest of the products was either much more polar (mainly compound (**4**), 20% yield) or much less polar compound (**5**) (6% yield) than compound (**3**), the last was separated with ease[2] (Scheme 1).

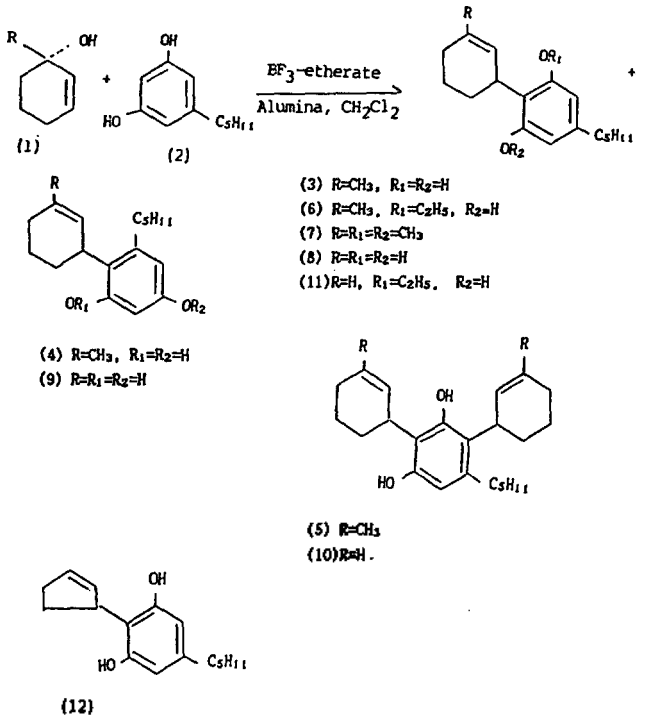
The acid-catalyzed condensation of 1-methyl-2-cyclohexen-1-ol with 3-ethylolivetol gave 2-(3-methyl-2-cyclohexen-1-yl)-3-ethylolivetol (**6**) in 18% yield.

The condensation described above takes place also when both phenolic groups of the olivetols are blocked as dimethyl ether (**7**) in *ca.* 40% yield.[1,2]

A second group of condensations which we investigated were these of 2-cyclohexen-1-ol with olivetol.

When 2-cyclohexen-1-ol was condensed with olivetol under the conditions of general procedure a mixture of three products was obtained which was separated by medium pressure liquid chromatography. The isomer (**9**) (35% yield) was the most polar component. The major product was 2-(2-cyclohexen-1-yl)-olivetol (**8**) in 37% yield, and the double condensation product (**10**) in 9% yield.

Monoethyl olivetol undergoes condensation with 2-cyclohexen-1-ol leading to the expected product (**11**). The above condensation reaction also takes place with cyclopentenol.



Scheme 1.

Thus 2-cyclopenten-1-ol reacts easily with olivetol in the presence of BF_3-etherate on alumina to yield 12 in 47% yield (Scheme 1).

In the above described reactions, no intramolecular cyclization was not observed by the addition of one of the hydroxyl groups to a suitably placed double bond. This is undoubtedly due to the "mildness" of the BF_3-etherate on alumina reagent which catalyzes a Friedel-Crafts type reaction but apparently does not attack olefins (or attacks them at a low rate) to form a cationic center[4].

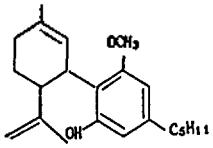
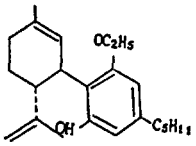
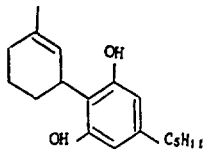
When the reactions delineated in Scheme 1 were performed in the absence of alumina the yields obtained were either low, or the desired products could not be isolated at all, due to cyclization reaction[1].

Analgesic Activity

The analgesic activity of the synthesized 2-(3-methyl-2-cyclohexen-1-yl)-olivetol was measured by the acetic acid-induced writhing test and tail-flick test.

Hence we have shown that in the cannabinoids, separation between psychotropic activity and analgesic activity can be achieved. This observation is of considerable importance as it opens the route to non-narcotic analgesics[3].

Table 1. Analgesic Activity of 2-(3-methyl-2-cyclohexen-1-yl)-olivetol, Cannabidiols and Morphine

Test compound	Acetic Acid-writhing P.O. mouse ED_{50} (mg/kg)	Tail-Flick P.O. mouse ED_{50} (mg/kg)
morphine	4.0	20.0
	10.0	40.0
	5.0	40.0
	20.0	80.0

We have to point out however that until wider analgesic testing is performed and until the addition liability of these compounds has been tested no conclusion can be made as regards the usefulness of this type of compounds. In addition more sophisticated tests for psychotropic activity have to undertaken, before we can state categorically that our compounds are not psychotropic.

The above described results do indicate that further research along the above lines may be of considerable pharmaceutical importance.

In summary we have developed a simple and convenient procedure for preparing the 2-alkylated 5-pentylresorcinols from cyclic allylic alcohol with olivetols. 2-alkylated derivaties have analgesic activities. This study will be continued for a development of new analgesic agent.

Experimetal

Unless Otherwise Stated the Following Applies

Mass spectra were recorded on a LKB 2091 Gas chromatograph-Mass Spectormeter at 70 eV. IR spectra were recoded as thin films (for oils) on a Perkin-Elmer grating infrared spectro-photometer, model 457. UV spectra were taken in ethanol solution on a Varian UV-Vis spectrophotometer, model 635. ^{1}H-NMR spectra were determined at 60 MHz on a Bruker W.P. 60 or at 300 MHz on a Bruker W.H. 300 instrument.

Column chormatography was performed by medium-pressure liquid chromatography (m.p.l.c) with an FMI pump on Merck Kieselgel 60, 230-400 mesh ASTM, with a mixed solvent of ethyl acetate and light petroleum (bp. 60-80℃) in the ratio 2 : 98 or 5 : 95.

General Procedure

BF_3-etherate (0.2 m*l*) was added under nitrogen to a stirred suspension of basiic aluminum oxide (Woelm, grade 1) (2 g) in dichloromethane (10 m*l*). Cyclic allylic alcohol (1 mmol) and olivetol (1 mmol) in dichloromethane (3 m*l*) were added to the solution *via* syringe and the mixture was stirred for 5 min at room temperature. The reaction was quenched with 10% aqueous solution of sodium bicarbonate (10 m*l*). Ether (50 m*l*) and an additional portion of sodium bicarbonate solution (50 m*l*) were added. The organic layer was washed with brine, dried and evaporated to dryness. The oil obtained was separated by medium pressure liquid chromatography.

Preparation of Compounds (3), (4), and (5)

Under the conditions of general procedure we obtained three compounds. The first compound eluted was 2,4-bis-(3-methyl-2-cyclohexen-1-yl)-olivetol (**5**) (41 mg, 6%), an oil, UV_{max} (EtOH), 282 nm (ε 890); NMR δ ($CDCl_3$), 0.90 (3H, t, CH_3), 1.77 (2×3H, brs, CH_3), 2.49 (2H, t, benzylic H), 3.91 (2×1H, brs, C-3H), 5.61 (2H, brs, C-2H), 6.10 (1H, d, J=2.0 Hz, arom H); MS (20°), *m/e* 368(M^+, 100), 353(10), 340(10), 325(44); IR (film), 3400, 2910, 2840, 1615, 1574, 1426 cm^{-1}.

Methylation with methyliodide and potassium carbonate in DMF led to 2,4-bis-(3-methyl-2-cyclohexen-1-yl)-1,3-dimethylolivetol (**5a**), an oil, NMR δ ($CDCl_3$), 0.91 (3H, t, CH_3), 1.85 (2×3H, brs, CH_3), 2.55 (2H, brt, benzylic H), 3.62 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 5.40 (2×1H, brd, J=7 Hz, C-2H), 6.48 (1H, s, arom H); MS (20°), m/e 396(M^+, 100), 381(55), 368(13), 365(12), 353(11); IR (film), 2920, 2860, 1593, 1569, 1445 cm^{-1}. The second compound eluted was 2-(3-methyl-2-cyclohexen-1-yl)-olivetol (**3**) (187 mg, 34%), an oil, UV_{max} (EtOH), 273 (ε 2000), 280 nm (1910); NMR δ ($CDCl_3$), 0.88 (3H, t, CH_3), 1.78 (3H, brs, CH_3), 2.44 (2H, t, benzylic H), 3.89 (1H, br, C-3H), 5.64 (1H, brs, C-2H), 6.22 (2H, s, arom H); MS (20°), m/e 274(M^+, 68), 231(63), 218(100); IR (film), 3360, 1610, 1576, 1435 cm^{-1}.

The third compound eluted was 4-(3-methyl-2-cyclohexen-1-yl)-olivetol (**4**) (110 mg, 20%), an oil, UV_{max} (EtOH), 280 nm (ε 3820); NMR δ ($CDCl_3$), 0.89 (3H, t, CH_3), 1.78 (3H, s, CH_3), 2.44 (2H, t, benzylic H), 3.55 (1H, m, C-3H), 5.58 (1H, brs, C-2H), 6.13 (1H, s, arom H), 6.22 (1H, s, arom H): MS (20°), m/e 274(M^+, 100), 246(231), 231(83), 218(69), 203 (44); IR (film), 3440, 2940, 2895, 1600, 1455 cm^{-1}.

Preparation of 2-(3-methyl-2-cyclohexen-1-yl)-3-ethylolivetol (6)

Under the condition of general procedure we obtained (**6**) (110 mg, 18%), an oil, UV_{max} (EtOH), 202 (ε 29450), 216sh (14800), 280 nm (5270); NMR δ ($CDCl_3$), 0.87 (3H, t, CH_3), 1.35 (2H, t, J=6 Hz, CH_3), 1.75 (3H, brs, CH_3), 2.51 (2H, brt, benzylic H), 3.50 (1H, m, C-3H), 3.88 (2H, q, J=7 Hz, methylene H), 5.54 (1H, brs, C-2H), 6.06 (1H, s, arom H), 6.25 (1H, brs, arom H); MS (20°), m/e 302(M^+, 100), 259 (65); IR (film), 3460, 1620, 1586 cm^{-1}. Ethylation with ethyliodide and potassium carbonate in DMF led to 2-(3-methyl-2-cyclohexen-1-yl)-1,3-diethyl-olivetol (**6a**), an oil, NMR δ ($CDCl_3$), 0.89 (3H, t, CH_3), 1.39 (2×3H, t, J=5 Hz, CH_3), 1.66 (3H, brs, CH_3), 2.58 (2H, brt, benzylic H), 3.89 (2×2H, q, J=10 Hz, methlene H), 5.30 (1H, brs, C-2H), 6.29 (2H, s, arom H); MS (20°), m/e 330(M^+, 100); IR (film), 2910, 2860, 1581 cm^{-1}.

Preparation of 2-(3-methyl-2-cyclohexen-1-yl)-1,3-dimethylolivetol (7)

Under the conditions of general procedure we obtained (**7**) (240 mg, 40%), an oil, UV_{max} (EtOH), 212 (ε 1870), 230sh nm (8090): NMR δ ($CDCl_3$), 0.90 (3H, t, CH_3), 1.67 (3H, brs, CH_3), 2.55 (2H, t, benzylic H), 3.74 (3×3H, s, OCH_3), 5.24

(1H, brs, C-2H), 6.37 (2H, s, arom H); MS (20°), m/e 302 (M^+, 100), 287(31), 274(67); IR (film), 2910, 2840, 1604, 1575, 1436 cm^{-1}.

Preparation of Compounds (8), (9), and (10)

Under the conditions of general procedure we obtained three compounds. The frist compound eluted was 2,4-bis-(2-cyclohexen-1-yl)-olivetol (**10**) (30 mg, 9%), an oil, UV_{max} (EtOH), 275sh (ε 2060), 282 nm (2130); NMR δ ($CDCl_3$), 0.90 (3H, t, CH_3), 2.51 (2H, t, benzylic H), 3.72 (2×1H, m, C-3H), 6.00 (2×1H, brd, J=3 Hz, C-1H), 6.09 (2×1H, t, J=2 Hz, C-2H), 6.27 (1H, s, arom H); MS (20°), m/e 304(M^+, 100), 312(26), 297(29), 284(29); IR (film), 3470, 2930, 2870, 1616, 1580, 1430 cm^{-1}. Methylation with methyliodide and potassium carbonate in DMF led to 2,4-bis-(2-cyclohexen-1-yl)-1,3-diethylolivetol (**10a**), an oil, NMR δ ($CDCl_3$), 0.91 (3H, brd, CH_3), 2.66 (2H, brt, benzylic H), 3.65 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 5.63 (2×1H, brs, C_1-CH), 5.70 (2×1H, brs, C-2H), 6.49, 6.49 (1H, s, arom H); MS (20°), *m/e* 368 (M^+, 100), 353(40), 340(22), 325(8); IR (film), 3019, 2919, 2860, 1594, 1565, 1445 cm^{-1}. The second compound eluted was 2-(2-cyclohexen-1-yl)-olivetol (**8**) (95 mg, 37%), an oil, UV_{max} (EtOH), 273 (ε 1240), 282 nm (1220); NMR δ ($CDCl_3$), 0.89 (3H, brs, OH), 2.46 (2H, t, benzylic H), 3.94 (1H, m, C-3H), 5.55 (2H, brs, OH), 6.02 (1H, brd, J=2 Hz, C-1H), 6.10 (1H, brd, J=2 Hz, C-2H), 6.23 (2H, s, arom H); MS (20°), m/e 260(M^+, 53), 232(15), 217(24), 204(100); IR (film), 3340, 2930, 2866, 1625, 1584, 1440 cm^{-1}. The third compound eluted was 4-(2-cyclohexen-1-yl)-olivetol (**9**) (90 mg, 35%), an oil, UV_{max} (EtOH), 211 (ε 23080), 225sh (12940), 281 nm (2900); NMR δ ($CDCl_3$), 0.90 (3H, t, CH_3), 2.52 (2H, t, benzylic H), 3.57 (1H, br, C-3H), 5.94 (1H, brs, C-1H), 6.06 (1H, d, J=4 Hz, C-2H), 6.23 (2H, s, arom H); MS (20°), m/e 266(M^+, 100), 232(24), 217(39), 240; IR (film), 3440, 2935, 2885, 1595, 1443 cm^{-1}. Methlation with methyliodide and potassium carbonate in DMF led to 4-(2-cyclohexen-1-yl)-1,3-dimethylolivetol (**9a**), an oil, NMR δ ($CDCl_3$), 0.90 (3H, t, CH_3), 2.56 (2H, brt, benzylic H), 3.73 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 5.62 (2×1H, brs, C-1H and C-2H), 6.32 (2H, s, arom H); MS (20°), m/e 288(M^+, 100), 260(61), 245(29), 232(42); IR (film), 2928, 2860, 1587, 1455, 1433 cm^{-1}.

Preparation of 2-(2-cyclohexen-1-yl)-3-ethylolivetol (11)

Under the conditions of general procedure we obtained (**11**) (45 mg, 16%), an oil, UV_{max} (EtOH), 283 nm (ε 2950); NMR δ ($CDCl_3$), 0.90 (3H, t, CH_3), 1.37 (3H, t, J=7 Hz, CH_3), 2.54 (2H, t, benzylic H), 3.80 (1H, m, C-3H), 4.03 (2H, q, J=7 Hz, methylene H), 5.99 (1H, brs, C-1H), 6.06 (1H, d, J=3 Hz, C-2H), 6.29 (1H, d, J=2 Hz, arom H), 6.39 (1H, d, J=2 Hz, arom H); MS (20°), m/e 288(M^+, 100), 260(37), 245(31), 232(52); IR (film), 3480, 2930, 2870, 1630, 1584, 1440 cm^{-1}. Ethylation with ethyliodide and potassium carbonate in DMF led to 2-(2-cyclohexen-1-yl)-1, 3-diethylolivetol (**11a**) an oil, NMR δ ($CDCl_3$), 0.85 (3H, t, CH_3), 1.34 (3H, t, J=10 Hz, CH_3), 1.36 (3H, t, J=10 Hz, CH_3), 2.85 (2H, m, benzylic H), 4.00 (2×2H, q, J=7 Hz, methylene H), 5.60 (2×1H, brs, C-1H and C-2H), 6.27 (2H, s, arom H); MS (90°), m/e 316 (M^+, 100), 288(14), 273(15), 260(22); IR (film), 2920, 2872, 1600, 1580, 1460, 1430 cm^{-1}.

Preparation of 2-(2-cyclopenten-1-yl)-olivetol (12)

Under the conditions of general procedure we obtained (**12**) (115 mg, 47%), an oil, 273 (ε 4120), 280 nm (3890); NMR δ ($CDCl_3$), 0.89 (3H, t, CH_3), 2.57 (2H, t, benzylic H), 4.56 (1H, m, C-3H), 6.02 (1H, d, J=2 Hz, C-1H), 6.13 (1H, d, J=2 Hz, C-2H), 6.23 (2H, s, arom H); MS (20°), m/e 246(M^+, 65), 231(54), 217(10), 240(12), 190(100); IR (film), 3460, 2938, 2865, 1630, 1585, 1445 cm^{-1}.

Acetylation with acetic anhydride in pyridine led to 2-(2-cyclopenten-1-yl)-olivetol diacetate (**12a**), an oil, NMR δ ($CDCl_3$), 0.88 (3H, t, CH_3), 2.41 (2×3H, s, $COCH_3$), 2.55 (2H, t, benzylic H), 3.95 (1H, brs, C-3H), 5.66 (1H, brs, C-1H), 5.74 (1H, brs, C-2H), 6.70 (2H, s, arom H); MS (20°), m/e 330(M^+, 9), 287(100), 271(71), 246(68), 228(51); IR (film), 2930, 2858, 1625, 1572, 1425 cm^{-1}.

Analgesic Tests

All compounds were administered as fresh suspension (0.1-0.2 m*l*) orally to mice. The test compound was dissolved in propylene glycol and a solution of 2% gun accacia was gradually added to from the suspension. The final concentration of propylene glycol was never above 5%. The tests were carried out at least on 3 dose levels in order to calculate the dose response lines.

Acetic Acid-induced Writhing Test. Six mice per dose level were examined. Thirty minutes after administration of the drug, 0.6% acetic acid (0.25 m*l*) was injected i.p. The number of abdominal contractions per animal was counted for 25 minutes.

Tail-flick Test. Ten mice per dose level was examined. The mouse was held in the standard receptacle. The tail was immersed into water at 58℃ and immediately withdrawn on jerk. After a 5 sec. rest the procedure was repeated for a total of 10 times.

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