Notes

Boron Trifluoride Etherate on Alumina-A Modified Lewis Acid Reagent (VI). Synthesis of 2′-(1-Acetoxymethyl-1-cyclohexen-3-yl)-5′-alkylresorcinol Diacetate Derivatives

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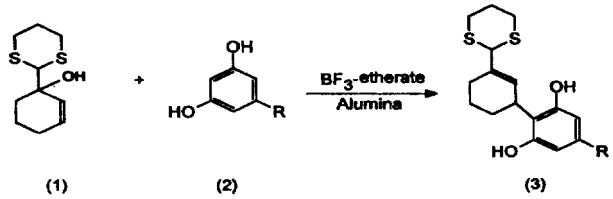
Recent work from our laboratories has resulted in a facile synthesis of 2′-(1-(1,3-dithian-2-yl)-cyclohexen-3-yl)-5′-alkylresorcinol derivatives (3) in good yield by reaction of cyclic allylic alcohol and 5-alkylresorcinol catalyzed by boron trifluoride etherate-on-alumina (Scheme 1)[1].

We reported that simplified cyclohexenyl derivatives (nor-ispropenyl cannabidiols) had anticonvulsant activity in rats. Nor-isopropenyl cannabidiols were slighly more potent than cannabidiol (CBD). A nor-isopropenyl CBD having a 1-acetoxy group (6) had potent anti-audiogenic seizure activity and a favorable protective index. In general compounds having a 1,1-dimethylheptyl side chain were more potent in both audiogenic seizure and rotorod neurotoxicity tests than *n*-amyl homologys[2]. Simplified analogs were obtained by condensing 1-thioxolanyl-2-cyclohexenol with 5-alkylresorcinol in the presence of boron trifluoride etherate-on-alumina (Scheme 1).

We report that the acid-catalyzed condensation between 1-thioxolanyl-2-cyclohexenol (1) and 5-alkylresorcinol (2) proceeds smoothly without intramolecular cyclization when BF_3-etherate-on-alumina is used as a catalyst[1]. However, intramolecular cyclization takes place in the absence of alumina[3].

Conversion of 2′-(1-(1,3-dithian-2-yl)-cyclohexen-3-yl)-5′-alkylresorcinols (3) into 2′-(1-acetoxymethyl-1-cyclohexen-3-yl)-5′-alkylresorcinol diacetates (6) was carried out as Sheme 2. After protecting two hydroxyl groups of (3) as its diacetate, the resulting dithiane-diacetate (4) was hydrolyzed to aldehyde (5) with mercuric chloride and red mercuric oxide in aqueous acetonitrile. Reduction of aldehyde (5)[4-6] with lithium aluminium hydride in dry ether and subsequent acetylation of alcoholic and phenolic group[7] with acetic anhydride gave 3-phenyl cyclohexenyl derivatives (6).

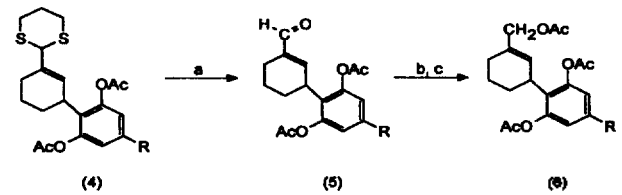
The IR spectra showed a strong carbonyl absorption at



(1) (2) (3)

R=H, CH_3, C_5H_{11}, $C(CH_3)_2C_6H_{13}$

Scheme 1.



(4) (5) (6)

(4a) R=H
b) R=CH_3
c) R=C_5H_{11}
d) R=$C(CH_3)_2C_6H_{13}$

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Ac=$-CO-CH_3$

Reagents: a) Red-HgO, $HgCl_2$, H_2O-CH_3CN
b) LAH, dry Ether
c) Ac_2O, Pyr.

Scheme 2.

1684 cm^{-1} (except at 1678 cm^{-1} for **5a**) and the ^{1}H-NMR spectra indicated the presence of aldehydic proton at 9.43 ppm (except at 9.44 ppm for **5a**).

The alkylated products (formula 6)[8,9] contain double bond and aromatic ring. As the ultraviolet spectra eliminate the possibility of conjugation with either the double bond or the aromatic ring, the cyclohexene double bond has to occupy the C-1 position. This position is supported on the basis of the chemical shift of the C-3 position, which indicated that it is deshieled by both the double bond and the aromatic ring. The NMR spectra show the presence of only one olefinic acetoxy group. Such an effect is possible only if the double bond occupies the C-1 position[10]. The two aromatic acetoxty protons are magnetically equivalent in the NMR spectrum. These findings are compatible with structure (6).

Experimental

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Mass spectra were recorded on a LKB 2091 Gas Chromatograph-Mass Spectrometer at 70 eV. IR spectra were recorded as thin films (for oils) on a Perkin-Elmer grating infrared spectrophotometer, model 457. 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 chromatography was performed by medium-pressure liquid chromatography (m.p.l.c) with an FMI pump on Merck Kieselgel 60, 230-400 mesh ASTM, with admixed solvent of diethyl ether and light petroleum (b.p. 60-80℃). Microanalysis was done in house.

2′-(1-Oxo-cyclohexen-3-yl)-resorcinol diacetate (5a)[6]. Red mercuric oxide (69 mg, 0.32 mmol), boron trifluoride etherate (0.04 m*l*, 0.32 mmol), and 15% aqueous tetrahydrofuran (10 m*l*) were stirred vigorously under nitrogen. Compound (**4a**) was dissolved in the minimum of THF and was added *via* a syringe in reaction mixture. The reaction mixture required 1.5 hrs at reflux to complete the reaction. Ethyl ether (30 m*l*) was then added, the precipitated salt were

filtered and the ether layer was washed with saturated sodium carbonate and saturated sodium chloride. After drying over magnesium sulfate, the ether was evaparated under *vacuo*. The resulting oil was chromatographed on preparative TLC plates (eluent 20% ethyl acetate in petroleum ether b.p. 60-80°) to yield (**5a**) (25 mg, 52%), an oil, UV_{max} (EtOH), 302 nm (ε 580); NMR δ ($CDCl_3$), 2.21 (2×3H, s, $COCH_3$), 3.84 (1H, br, C-3H), 6.68 (1H, brs, C-2H), 6.90 (1H, d, J=2 Hz, arom H), 7.30 (1H, brs, arom H), 7.25 (1H, d, J=6 Hz, arom H), 9.44 (1H, s, C-7H); MS (20°), m/e 302 (M^+, 20), 260 (94), 218 (100); IR (film), 1765, 1680, 1645 cm^{-1}.

2'-(1-Oxo-cyclohexen-3-yl)-5'-methylresorcinol diacetate (5b)[6]. Under the condition of procedure (**5a**) compound (**5b**) was obtained in 65% (35 mg) yield, mp. 130℃; UV_{max} (EtOH), 233 nm (ε 16170); NMR δ ($CDCl_3$), 2.19 (2×3 H, s, $COCH_3$), 2.23 (3H, s, CH_3), 3.70 (1H, br, C-3H), 6.65 (1H, brs, C-2H), 6.78 (2H, br, arom H), 9.43 (1H, s, C-7H); MS (140°), m/e 316 (M^+, 54), 274 (100); IR (KBr), 1765, 1685, 1645, 1576 cm^{-1}; Anal. Calcd: $C_{18}H_{20}O_5$, C, 68.35; H, 6.33: Found; C, 68.24; H, 6.27.

2'-(1-Oxo-cyclohexen-3-yl)-5'-pentylresorcinol diacetate (5c). A solution of the compound (**4c**) (46.1 mg, 0.1 mmol) in aqueous 80% acetonitrile (10 m*l*), unless otherwise state was added at 25℃ to an efficiently stirring solution of mercuric chloride (0.22 mmol) in the same solvent mixture (5 m*l*). Mercuric oxide (0.11 mmol) was added to buffer the reaction mixture near pH 7. The dithiane-mercuric chloride complex usually separated as a flocculent white precipitate. The mixture was stirred and heated at reflux under nitrogen for 1 hr, cooled, and filtered, the filter cake was washed thoroughly with 1 : 1 hexane-dichloromethane. The organic phase of the filterate was washed with 5 M aqueous ammonium acetate, water, and brine, dried, and freed solvent. The pure product was obtained after preparative TLC with 30 : 70 ethyl acetate-petroleum (23 mg, 62% yield), an oil, UV_{max} (EtOH), 272 (ε 3460), 281 nm (3370); NMR δ ($CDCl_3$), 0.89 (3H, t, CH_3), 2.19 (2×3H, s, $COCH_3$), 2.49 (2H, t, benzylic H), 3.62 (1H, br, C-3H), 6.67 (1H, brs, C-2H), 6.77 (2H, s, arom H), 9.43 (1H, s, C-7H); MS (20°), m/e 372 (M^+, 45), 330 (84), 288 (100); IR (film), 1740, 1685 cm^{-1}.

2'-(1-Oxo-cyclohexen-3-yl)-5'-(1,1-dimethylheptyl) resorcinol daicetate (5d). Under the condition of procedure (**5c**) compound (**5d**) was obtained in 65% (28 mg) yield, an oil, UV_{max} (EtOH), 207 (ε 13380), 226 nm (1650); NMR δ ($CDCl_3$), 0.88 (3H, t, CH_3), 1.26 (2×3H, s, CH_3), 2.19 (2×3 H, s, $COCH_3$), 3.73 (1H, br, C-3H), 6.70 (1H, brs, C-2H), 6.89 (2H, s, arom H), 9.43 (1H, s, C-7H); MS (50°), m/e 428 (M^+, 62), 386 (100); IR (film), 1770, 1685, 1645, 1625 cm^{-1}.

2'-(1-Acetoxymethyl-1-cyclohexen-3-yl)-resorcinol diacetate (6a). Compound (**5a**) (20 mg, 0.066 mmol) in dry ether (2 m*l*) was added, during 15 min, to a suspension of lithium aluminium hydride (50 mg) in ether (5 m*l*). The mixture was stirred for 1 hr at room temperature. The excess of reagent was destroyed with a saturated solution of sodium sulphate, and hydrochloric acid (N), and the mixture was worked up in the usual way. The oil obtained was dissolved in pyridine (3 m*l*) and acetic anhydride (1.5 m*l*) and was left at room temperature overnight. The mixture was worked up in the usual way. Chromatography on silica (elution with 2.5% ethyl acetate in petroleum ether b.p. 60-80°) yield (**6a**) (9 mg, 39%), an oil, UV_{max} (EtOH), 210 (ε 16360), 263 nm (1880); NMR δ ($CDCl_3$), 2.04 (3H, s, $COCH_3$), 2.22 (2×3H, s, $COCH_3$), 3.74 (1H, br, C-3H), 4.45 (2H, q, J=12 Hz, C-7H), 5.52 (1H, d, J=6 Hz, C-2H), 6.89 (2H, d, J=9 Hz, arom H), 7.11 (1H, d, J=6 Hz, arom H); MS (230°), m/e 364 (M^+, 10), 329 (55), 286 (100); IR (film), 1750, 1620, 1586 cm^{-1}.

2'-(1-Acetoxymethyl-1-cyclohexen-3-yl)-5'-methylresorcinol diacetate (6b). Under the condition of procedure (**6a**) compound (**6b**) was obtained in 46% (31 mg) yield, an oil, UV_{max} (EtOH), 262 (ε 360), 271 nm (340); NMR δ ($CDCl_3$), 2.05 (3H, brs, $COCH_3$), 2.22 (2×3H, brs, $COCH_3$), 2.31 (3H, brs, CH_3), 3.51 (1H, br, C-3H), 4.47 (2H, brs, C-7H), 5.58 (1H, br, C-2H), 6.74 (2H, brs, arom H); MS (20°), m/e 344 (M^+, −16, 35), 300 (57), 257 (100); IR (film), 1745, 1630, 1580 cm^{-1}.

2'-(1-Acetoxymethyl-1-cyclohexen-3-yl)-5'-pentylresorcinol diacetate (6c). Under the condition of procedure (**6a**) compound (**6c**) was obtained in 55% (30 mg) yield, an oil, UV_{max} (EtOH), 262 (ε 380), 270 sh nm (300); NMR δ ($CDCl_3$), 0.89 (3H, t, CH_3), 2.06 (3H, s, $COCH_3$), 2.23 (2×3H, s, $COCH_3$), 2.58 (2H, t, benzylic H), 3.53 (1H, br, C-3H), 4.46 (2H, brs, C-7H), 5.60 (1H, brs, C-2H), 6.74 (2H, s, arom H); M/S (20°), m/e 356 (M^+, −60, 89), 296 (14), 271 (100); IR (film), 1746, 1625, 1576 cm^{-1}.

2'-(1-Acetoxymethyl-1-cyclohexen-3-yl)-5-(1,1-dimethylheptyl)resorcinol diacetate (6d). Under the condition of procedure (**6a**) compound (**6d**) was obtained in 52% (42 mg) yield, an oil, UV_{max} (EtOH), 263 nm (ε 300); NMR δ ($CDCl_3$), 0.87 (3H, t, CH_3), 1.24 (2×3H, s, CH_3), 2.07 (3H, s, $COCH_3$), 2.24 (2×3H, s, $COCH_3$), 3.54 (1H, br, C-3H), 4.49 (2H, brs, C-7H), 5.67 (1H, brs, C-2H), 6.84 (2H, s, arom H); MS (20°), m/e 412 (M^+, −60, 100), 370 (76); IR (film), 1625, 1570 cm^{-1}.

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