Synthesis and Characterization of New Hydroxy Tetralones as Intermediates for Podophyllotoxin Analogues.

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Abstract: In Berberidaceae plants such as podophyllum emodiwall, podophyllum peltatum linnaeus, podophyllum pleianthum the cytotoxin lignan lactone and /or antitumour activity producing compound podophyllotoxin is present. The rhizomes of podophyllum hexandrum are known to contain several lignans. Over the years, the lignans have been recognized as challenging targets for organic synthesis, particularly because of their unusual structures and interesting biological properties. Lignans are biosynthetically derived from the phenyl propanoid pathway.

Keywords: Synthesis of hydroxyl methylene tetralones, Synthesis of Podophyllotoxin Analogues.

I. Introduction

A number of methods have been devised for the construction of this class of molecules and several efforts have culminated in the total synthesis of podophyllotoxin their derivatives and related compounds. These efforts have lead to the development of the antitumor drugs etoposide and teniposide which are glucosides of epipodophyllotoxin. These semi-synthetic molecules are currently in use for treatment ofdifferenttypes of cancers, including small cell lung cancer, lymphoma, and kaposi's sarcoma, testicular cancer and malignant lymphoma.

II. Experimental

Materials and Methods

All the required reagents and chemicals were purchased from Sigma aldrich and Merck company. They were used without further purification. Melting points were taken in open capillary tubes and are uncorrected. Thin layer chromatography (TLC) is performed with E. Merck precoated silica gel plates (60F-254) with iodine as a developing agent to check the product purity. IR spectra in KBr were recorded on Perkin-Elmer model 683 spectrometers. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using tetramethyl silane (TMS) as an internal reference on Bruker spectrometer. Elemental analyses were performed on a Perkin-Elmer 2400. Mass spectra were obtained by Hitachi RMU-61 spectrophotometer. The products formed were purified by the repeated recrystallization and by column chromatography using silica gel mesh as an adsorbent.

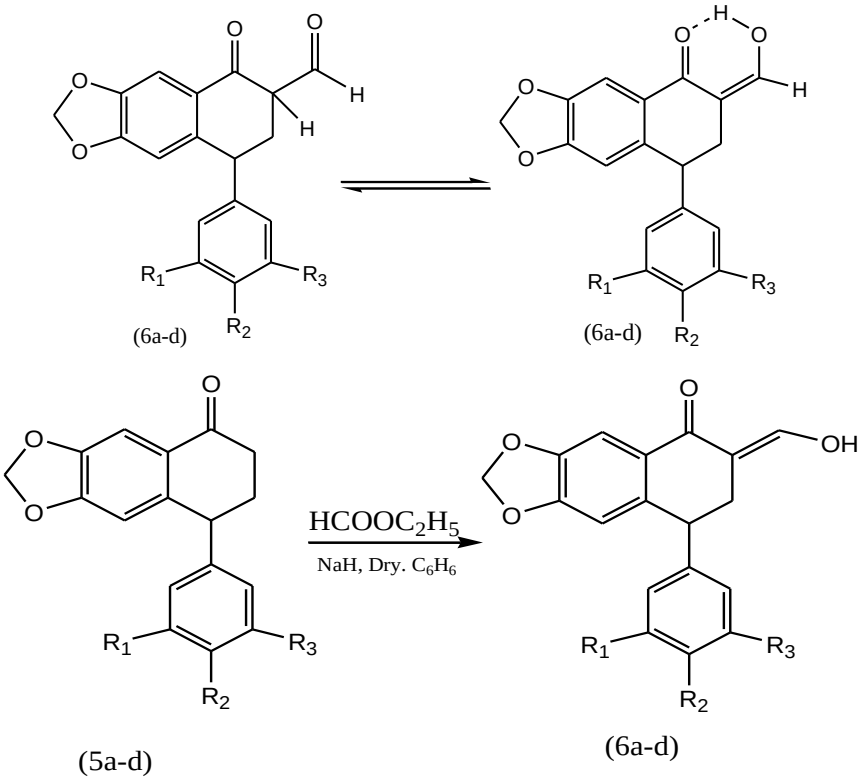
Reagents and conditions

Sodium Hydride, dry Benzene, Ethyl formate, Ethanol stirred at room temperature (29^{0} Centigrade) for an one hour.

III. General procedure for the Synthesis and Discussion of hydroxymethine tetralones. (6a-d).

The Sodium hydride is washed with pet ether to remove paraffin wax. Then the washed sodium hydride (1.1g) should added to the dry benzene (50ml) used as the solvent, to this 10ml of ethanol is added. The reaction mixture is stirred for one hour at room temperature (28^{o}C). Then about 8ml of ethyl formate is added with constant drop wise to the above reaction mixture and stirred for one hour at room temperature (28^{o}C) followed by constant dropwise addition of tetralones (6a-d) of 2 gms Hydroxy methine tetralones were prepared by Gensler and his co-workers by the reaction of tetralones with ethyl formate in the presence of sodium hydride in dry benzene. In the light of above studies the formylation of the tetralone was did by using ethyl formate and sodium hydride (which is used as a base) at room temperature to give hydroxyl methine tetralones (6a-d).

IV. Structural Synthesis



Here, a= R_1=H, R_2=H, R_3=H.

b= R_1=OCH_3, R_2=H, R_3=H.

c= R_1=OCH_3, R_2=OCH_3, R_3=H.

d= R_1=OCH_3, R_2=OCH_3, R_3=OCH_3.

Abbrevations:

KBr= Potassium Bromide

MHz= mega hertz

gms= grams

ml= milli litre

m= multiplet

s= singlet

cm^{-1}= wave number

δ= delta

Ar= aromatic

%= percentage

d= doublet

ESI= electrospray ionization

m/z=mass/atomic number

H^+=hydrogen

g= gram

NMR= nuclear magnetic resonance spectroscopy.

Compound 6a: **(E)-7, 8 dihydro-6-(hydroxymethylene)-8-phenyl naphtho [2, 3-d] [1, 3] dioxol-5(6H) one.**

Molecular formula: $C_{18}H_{14}O_4$. Molecular weight: 294.301. Colour: Dark brown solid. Melting point: 134-136ºC. IR(KBr) (υ/cm-^{1}): 1667.31 (C=O), 2853.23(C-H), 1609.64 (ArC=C).^{1}H NMR ($CDCl_3$, 400MHz) δ: 5.967(s, 2H, -O-CH_2-O), 3.921(t, 1H, -CH), 2.286 (d, 2H , -CH_2) , 5.803 (s ,1H, OH vinyl), 6.721-7.725 (m ,7H, Ar-H). MS (ESI,m/z): 295.283(M+1). Elemental analysis: Calculated (in %): C=73.46, H=4.79. Found (in %): C=73.21, H=4.47.

Compound 6b: (E)-7, 8 dihydro-6-(hydroxymethylene)-8-phenyl naphtho [2,3-d] [1,3] dioxol-5(6H) one.

Molecular formula: $C_{19}H_{16}O_5$. Molecular weight: 324.325. Physical state: Dark brown solid. Melting point: 148-149ºC. IR (KBr)(υ/cm-^{1}): 1667.41(C=O), 2925.16 (C-H), 1604.36 (ArC=C). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 5.873(s, 2H, -O-CH_2-O), 4.211(t, 1H, -CH), 2.126 (d, 2H , -CH_2) , 5.313 (s ,1H, OH vinyl), 6.784-7.353 (m ,6H, Ar-H). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 159.921, 153.132, 149.125, 145.756, 2MS (ESI, m/z): 325.316(M+1). Elemental analysis: Calculated (in %): C=70.36, H=4.97. Found (in %): C=70.33, H=4.99.

Compound 6c: (E)-7, 8 dihydro-6-(hydroxymethylene)-8-phenyl naphtho [2, 3-d] [1,3] dioxol-5(6H) one.

Molecular formula: $C_{20}H_{18}O_6$. Molecular weight: 354.35. Colour: Dark brown solid. Melting point: 152-154ºC. IR (KBr) (υ/cm-^{1}): 1672.31(C=O), 2927.53(C-H), 1603.06 (ArC=C). ^{1}H NMR ($CDCl_3$, 400MHz) δ: 5.921(s, 2H, -O-CH_2-O), 4.781(t, 1H, -CH), 2.134 (d, 2H , -CH_2) , 6.203 (s ,1H, OH vinyl), 6.484-7.153 (m ,5H, Ar-H). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 153.783, 149.851, 148.329, 145.397, 145.318, 137.782, 136.382, 129.222, 121.421, MS (ESI, m/z): 355.342(M+1). Elemental analysis: Calculated (in %): C=67.79, H=5.12. Found (in %): C=67.80, H=5.08.

Compound 6d: (E)-7, 8 dihydro-6-(hydroxymethylene)-8-phenyl naphtha [2, 3-d] [1,3] dioxol-5(6H) one.

Molecular formula: $C_{21}H_{20}O_7$. Molecular weight: 384.379. Physical state: Dark brown solid. Melting point: 159-161ºC. IR(KBr) (υ/cm-^{1}): 1681.51(C=O), 2924.63(C-H), 1601.93 (ArC=C).^{1}H NMR ($CDCl_3$, 400MHz) δ: 5.931(s, 2H, -O-CH_2-O), 4.011(t, 1H, -CH), 2.186 (d, 2H , -CH_2) , 6.003 (s ,1H, OH vinyl), 6.484-7.153 (m ,4H, ArH). ^{13}C NMR ($CDCl_3$, 100MHz) δ: 153.643, 149.971, 149.622, 149.242, 145.744, 137.931, 137.216, 130.783, 129.799, 116.392, 115.087. MS (ESI, m/z): 385.365(M+1). Elemental analysis: Calculated (in %): C=65.62, H=5.24. Found (in %): C=65.60, H=5.28.

V. Conclusions

In this summary, a convenient synthesis of hydroxy tetralones as intermediates for podophyllotoxin analogues has been developed. The chalcone method gave good yields of tetralones. We have used environmental friendly chemicals and conditions. They are very useful for the synthesis of analogues of podophyllotoxin.

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