Tetralone acids as intermediates for the synthesis of podophyllotoxin analogues

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Tetralone acids 6, 7 and 8 have been synthesised as intermediates for the synthesis of podophyllotoxin analogues 3, 4 and 5. The possible steric hindrance of cyclohexyl group on the intramolecular Friedel-Crafts acylation reaction of anhydrides 15 b,c to tetralone acids 7 and 8 is also discussed here.

Podophyllotoxin\(^1\) is a strong antimitotic agent which has been extracted from two important medicinal plants named *Podophyllum emodi* an Indian species and *Podophyllum peltatum*, a North American species\(^2\). It also occurs in many other plants of Podophyllum species. Podophyllotoxin and several of its analogues also showed other biological activities such as cathartic, cytotoxic anticancer, antitropical skin disease, antimalarial, anti HIV (AIDS) etc\(^3\).

\(\beta\)-Apopicropodophyllin 2, a dehydrated product of podophyllotoxin acts as a much stronger antimitotic agent\(^4\). With a view to study their structure antimitotic activity relationship\(^5\), it was decided to synthesise analogues 3, 4 and 5 by modifying methylenedioxy ring and pendant ring C in 1 and 2. Several synthetic routes\(^6\)\(^-\)\(^8\) have been reported for the synthesis of podophyllotoxin via the tetralone acids 6, 7 and 8. In the present paper, we have chosen Gensler’s\(^9\) method with some change in experimental procedure. The starting material for the synthesis of analogues 3, 4 and 5 are the ketones 11a-c which were prepared in high yield by stirring an equimolar solution of 1, 3-benzodioxole with phenyl acetyl chloride or cyclohexane carbonyl chloride and 1,4-benzodioxan with cyclohexane carbonyl chloride in the presence of stannic chloride in dichloromethane at 0°C. Itaconic acid half esters 12a-c were prepared as a mixture of cis and trans isomers by Stobbe condensation of ketones 11a-c with diethyl succinate using potassium tert-butoxide as a base in tert butanol at 90°C (Scheme I). Itaconic acids 13a-c were prepared by the saponification of etaconic acid half esters 12a-c. Benzhydryl succinic acids 14a-c were prepared by the reduction of itaconic acids 13a-c with 5% sodium amalgam in 5%aq sodium hydroxide solution\(^10\). Benzhydryl succinic anhydrides 15a-c were prepared by boiling benzhydryl succinic acids with acetyl chloride. Tetralone acids 6, 7, 8 were prepared by the intramolecular Friedel-Crafts acylation reaction of the benzhydryl succinic anhydrides 15a-c in the presence of Lewis acid anhydrous stannic chloride in dichloromethane. The products obtained were characterised by IR, \(^1\)H NMR and mass spectral data and also C.H. analysis.

Tetralone acid 6 was obtained in good yield (60%). The products 7 and 8 were formed in low yield.
(30-33%) and unreacted anhydrides 15b,c were recovered. We thought that the formation of low yield might be due to the steric hindrance effect of cyclohexyl group on the intramolecular acylation reaction of anhydrides 15b,c. W J Gensler suggested the stable conformation for anhydrides which undergo acylation easily to give tetralone acids (Figure 1). The cyclohexyl group is a nonaromatic molecule (non-planar) and it is projected below the plane of the molecule. This might cause steric hindrance on the intramolecular acylation reaction of anhydrides 15b,c. (Figure 2). The NMR spectrum of tetralone acid 6 exhibited a quartet at δ 3.9 ppm (J=6 Hz) for the dibenzylic proton C4-H. The large coupling constant (J) value indicated that C4-H and C3-H in 6 were diaxial. Hence the C3-carboxyl and C4-benzyl groups should be trans to each other, a configuration being thermodynamically more stable.

Experimental Section
Melting points were taken on open capillary and are uncorrected. IR spectra were recorded on a Perkin Elmer 399 spectrometer. 1H NMR spectra on Jeol 60 MHz NMR spectrometer using CDCl3 as solvent and TMS as internal reference (chemical shifts in δ, ppm) and mass spectra on Hitachi RMU-61 spectro
photometer and important fragments are given with the relative intensities in the bracket. The purity of the compounds was checked by TLC on silica gel plates.

General procedure for the preparation of ketones 11a-c

A typical procedure is described for the preparation of 1,3-methylenedioxy- \( \alpha \)-phenyl-acetophenone 11a. 1,3-Benzodioxole 9a (8.95 g, 0.0732 mole) (prepared from catechol and dichloromethane in the presence of sodium hydroxide in dimethyl sulphoxide), and stannic chloride (23.9 g, 0.0917 mole) were taken in dichloromethane (75 mL). The reaction mixture was cooled to 0°C and protected from atmospheric moisture. The reaction mixture was stirred continuously for 30 min. A solution of phenyl acetyl chloride (12.2 g, 0.0789 mole) (prepared from phenyl acetic acid and thionyl chloride), in dichloromethane (75 mL) was added dropwise over a period of 1 hr to the above mixture. After 12 hr, the temperature of the reaction mixture had been allowed to come to 25°C, concentrated HCl (54 mL) was added dropwise over a period of 30 min. The reaction mixture was further stirred for 10 hr. During the addition of HCl and for sometime thereafter large amount of HCl gas evolved. The product was extracted into chloroform, washed with 10% aqueous KOH solution (2 x 100 mL) and then with 2% aqueous NaCl solution (2 x 75 mL). The solvent was removed by distillation. The product was purified by recrystallisation with methanol to give white crystalline compound in 80% yield (14.1 g), m.p. 83-84°C, IR (KBr), 1685 (C=O), 1590 cm\(^{-1}\) (aromatic C=C); \( ^1 \)H NMR (CDCl\(_3\)), \( \delta \) 6 (s, 2H, OCH\(_2\)), 4.2 (s, 2H, C\(_6\)H\(_5\)CH\(_2\)) 7.2 (bs, 5H, Ar-H), 7.3-7.7 (bm, C\(_5\)H and C\(_6\)H), 6.7-6.9 (d, J = 6.5 Hz, 1H, C\(_5\)H).

1,3-Methylenedioxy hexahydrobenzophenone 11b. It was obtained from 1,3-benzodioxole (13.4 g, 0.109 mole) and cyclohexane carbonyl chloride (17.36 g, 0.118 mole) as white crystalline solid in 73% yield (18.6 g), m.p. 104-05°C; IR (KBr), 1680 (C=O), 1590 cm\(^{-1}\) (aromatic C=C); \( ^1 \)H NMR (CDCl\(_3\)), \( \delta \) 6 (s, 2H, OCH\(_2\)), 1.2-2 (bm, 1H, cyclohexyl), 6.7-6.9 (d, J = 7 Hz, 1H, C\(_5\)H), 7.3-7.8 (bm, 2H, C\(_2\)H and C\(_3\)H).

1,4-Ethyleneedioxy-hexahydrobenzophenone 11c. It was prepared from 1,4-benzodioxan (14.96 g, 0.110 mole) and cyclohexane carbonyl chloride (17.36 g, 0.118 mole) as white crystalline substance in 75% yield (20.3 g), m.p. 81-82°C; IR (KBr) 1670 (C=O), 1580 cm\(^{-1}\) (aromatic C=C); \( ^1 \)H NMR (CDCl\(_3\)), \( \delta \) 4.2 (s, 4H, OCH\(_2\)CH\(_2\)), 1.2-2 (bm, 11H, cyclohexyl), 6.9-7.4 (bm, 3H, C\(_2\)H, C\(_3\)H and C\(_4\)H).

1,3-Methylenedioxyphenyl benzyl itaconic acids 13a. These were prepared by the Stobbe condensation of 1,3-methylenedioxyphenyl acetophenone 11a (10.26 g, 0.042 mole) with diethyl succinate (14.06 g, 0.080 mole) in presence of potassium t-butoxide (obtained from potassium 2.08 g, 0.053 atom and t-butyl alcohol) in tert butyl alcohol (100 mL) at reflux temperature for 10 hr. The cooled mixture was treated with 50% HCl (50 mL), was concentrated to 60 ml and diluted with water (75 mL). The itaconic acid half esters were extracted into ether (3 x 50 mL) and then into saturated sodium bicarbonate (3 x 50 mL) solution. The bicarbonate solution was acidified and extracted with ether and dried (anhyd. Na\(_2\)SO\(_4\)). The solvent was removed by distillation to give a brown semi solid in 85% yield (13.37 g). The itaconic acid half esters were saponified by refluxing in methanol (50 mL) and water (50 mL) mixture containing NaOH (6 g) for 8 hr. The reaction mixture was concentrated to 60 mL and then acidified with conc. HCl to give brown semisolid in 80% yield (9.88 g); IR (KBr) 3600-3100 (OH), 1700 (CH\(_2\)CO), 1690 (C=O), 1580 (aromatic C=C), 1600-1620 cm\(^{-1}\) (conjugated C=C); \( ^1 \)H NMR (CDCl\(_3\)), \( \delta \) 5.9 (s, 2H, OCH\(_2\)), 3.8-4.2 (m, 4H, C\(_6\)H\(_2\)CH\(_2\)) and CH\(_2\)CO, 6.8-7.1 (bs, 5H, Ar-H), 7.2-7.4 (m, 3H, C\(_2\)H, C\(_3\)H-C\(_4\)H), 9.8-10 (bs, 2H, COOH).

1,3-Methylenedioxy-hexahydrodiphenyl itaconic acid 13b. It was prepared as brown gummy product in 78% yield (13.1 g) by the condensation of 1,3-methylenedioxy-hexahydrobenzophenone (11.74 g, 0.051 mole) with diethyl succinate (17.7 g, 0.1 mole) followed by saponification; IR (KBr) 3500-3100 (OH), 1680 (C=O), 1710 (CH\(_2\)CO), 1590 (aromatic C=C) and 1620 cm\(^{-1}\) (conjugated C=C); \( ^1 \)H NMR (CDCl\(_3\)), \( \delta \) 5.9 (s, 2H, OCH\(_2\)), 3.6 (s, 2H, CH\(_2\)CO), 1-2 (bm, 11H, cyclohexyl), 6.8-7.3 (bm, 3H, C\(_2\)H, C\(_3\)H and C\(_4\)H), 8.9 (bs, 2H, COOH).
1,4-Ethylene dioxy-hexahydrodiphenyl itaconic acid 13c. It was prepared from 1,4-ethylenedioxy-phenyl cyclohexyl ketone 11c (12.375 g, 0.0503 mole) and diethyl succinate (16.106 g, 0.0924 mole) followed by saponification as brown gummy product in 80% yield (13.92 g); IR (KBr), 3500-3100 (OH), 1750 (C=O), 1690 (α, β-unsaturated C=O), 1590 (aromatic C=C) and 1610 cm⁻¹ (conjugated C=C); ¹H NMR (CDCl₃) δ 4.1 (s, 4H, OCH₂CH₂O), 1-1.9 (bm, 11H, methyl), 3.1-3.3 (bs, 2H, CH₂-CO), 6.8-7.2 (m, 3H, C₂-H, C₃-H and C₆-H), 8.9 (bs, 2H, COOH).

1,3-Methylenedioxybenzhydyl succinic acid 14a. Powered 5% sodium-amalgam (200 g) was added to a solution of 13a (10g, 0.0294 mole) in 5%aq NaOH (200 mL) solution around 5°C. The reaction mixture was kept overnight at room temperature and filtered. The filtrate was acidified with 50% HCl to give white solid which on recrystallisation from ethanol gave white crystalline solid in 92% yield (9.045 g). m.p. 164°C; IR (KBr): 3500-3200 (OH), 1713 cm⁻¹ (C=O); ¹H NMR: δ 5.9 (s, 2H, OCH₂CH₂O), 2.8-3.8 (m, 1H, CH₃, 3.9-4.4 (d, J = 14 Hz, 1H, Ca-H), 5.3-5.5 (d, J = 6Hz, 2H,Cb-H), 3.1 (d, 2H, CH₃, CH₂), 6.8-7.4 (bs, 8H, Ar-H), 9.8-10 (bs, 2H, COOH).

1,3-Methylenedioxy-hexahydrobenzhydryl succinic acid 14b. It was obtained by the reduction of 1,3-methylenedioxyhexahydrodiphenyl itaconic acid 13b (9.6 g, 0.0289 mole) with 5% sodium-amalgam (200 g) as white crystalline solid in 88% yield (8.49 g). m.p. 132-34°C; IR (KBr): 3500-3200 (OH), 1750 cm⁻¹ (C=O); ¹H NMR (CDCl₃): δ 5.9 (s, 2H, OCH₂CH₂O), 3.1-3.5 (m, 3H, Ca-H, Cb-H, Cc-H), 1-2 (bm, 11H, cyclohexyl), 6.8-7.2 (bm, 3H, Ar-H), 9.9-9.3 (bs, 2H, COOH).

1,4-Ethylene dioxy hexahydro benzhydryl succinic acid 14c. The acid was prepared from 1,4-ethylenedioxyhexahydrodiphenyl itaconic acid 13c (12 g, 0.035 mole) and 5% sodium-amalgam (200 g) as white crystalline solid in 92% yield (11.1 g). m.p. 140-42°C; IR (KBr): 3500-3200 (OH), 1740 cm⁻¹ (C=O); ¹H NMR (CDCl₃): δ 4.3 (s, 4H, OCH₂CH₂O), 0.8-2 (bm, 11H, cyclohexyl), 8.5-9 (bs, 2H, COOH), 6.8-7.3 (m, 3H, Ar-H), 3.4-3.7 (m, 2H, Ca-H and Cb-H), 3.1 (d, J = 7Hz, 2H, Cc-H).

3-Carboxy-4-benzyl-6,7-methylenedioxy-1-tetra­tone 6. A solution of 1,3-methylenedioxybenzhydryl succinic acid 14a (9g, 0.0263 mole) in acetyl chloride (30 mL) was refluxed for 3 hr. The excess acetyl chloride was distilled off and the residue after dissolving in benzene (70 mL) was washed with 5% sodium bi-carbonate solution (2×30 mL) and then with cold water. The organic layer after drying (anhyd Na₂SO₄) was concentrated to give a brown semisolid anhydride 15a in 96% yield (8.2 g) (IR: 1785 and 1870 cm⁻¹ for cyclic anhydride).

A solution of anhydride 15a (8.2 g, 0.025 mole) in dichloromethane (60 mL) was added over a period of 20 min to a magnetically stirred solution of stannic chloride (13.36 g, 0.0513 mole) in dichloromethane (60 mL) at 0°C. The reaction mixture was further stirred at 0°C for 6 hr. After the reaction, the mixture was treated with cold 50% HCl, the organic layer separated was extracted into chloroform (2×50 mL) and washed thoroughly with 50% HCl (2×40 mL) and then with water (2×50 mL). The acidic compound was extracted into the saturated sodium bicarbonate solution (3×50 mL) and neutralised with conc. HCl (50 mL) and crushed ice (200 mL) to give a white solid in 60% yield (4.9 g). It was recrystallised from ethanol, m.p. 160-62°C; IR (KBr): 3600-3200 (OH), 1705 (Carboxylic C=O), 1670 cm⁻¹ (tetralone C=O); ¹H NMR (CDCl₃): δ 5.9 (s, 2H, OCH₂CH₂O), 2.7 (d, J = 7Hz, 2H, C₂-H), 2.8-3.8 (m, 4H, C₃-H, C₄-H, C₅-H, C₆-H), 6.5 (s, 1H, C₇-H), 7.1-7.3 (s, 5H, Ar-H), 8.6-9 (bs, 1H, COOH), Mass (m/z, Rel. Int.), 324 (M⁺, 506.3), 233 (940), 91 (560), Anal. Calcd. for C₁₆H₁₄O₄: C, 70.4; H, 4.9. Found. C, 70.3; H, 5.0%.

3-Carboxy-4-cyclohexyl-6,7-methylenedioxy-1-tetralone 7. It was prepared from the cyclisation of 1,3-methylenedioxy-hexahydrobenzhydryl succinic anhydride 15b (7.5 g, 0.024 mole) in presence of stannic chloride (14 g, 0.0537 mole) in dichloromethane (60 mL) as a solid in 30% yield (2.27 g), m.p. 127-29°C.

Compound 15b was obtained from 1,3-methylenedioxyhexahydro benzhydryl succinic acid 14b (8g, 0.024 mole); IR (KBr): 3600-3200 (OH), 1710 (carboxyl C=O), 1680 cm⁻¹ (tetralone C=O); ¹H NMR (CDCl₃): δ 5.9 (s, 2H, OCH₂CH₂O), 0.8-2 (bm, 11H, cyclohexyl), 2.2-3.3 (m, 4H, C₃-H, C₄-H and C₅-H), 7.3 (s, 1H, C₆-H), 6.8 (s, 1H, C₇-H), 9.5 (bs, 1H, COOH); Mass (m/z, Rel. Int.), 316 (M⁺, 520), 188 (930), 83 (160), Anal. Calcd. for C₁₅H₁₂O₃: C, 68.3; H, 6.3. Found. C, 68.3; H, 6.2%.

3-Carboxy-4-cyclohexyl-6,7-methylenedioxy-1-tetralone 8. It was obtained from 1,4-ethylenedioxyhexahydrobenzhydryl succinic anhydride 15c (6.2 g, 0.0187 mole) and stannic chloride (12 g, 0.046 mole)
as a white solid in 33% yield (2.04 g), m.p. 185-87°C and starting material was recovered.

Compound 15e was prepared from 1,4-ethylene-dioxyhexahydrobenzhydryl succinic acid 14c (7g, 0.02 mole); IR (KBr): 3600-3200 (OH), 1710 (carboxyl C=O), 1675 cm⁻¹ (tetralone C=O); ¹H NMR (CDCl₃): 4.2 (s, 4H, OCH₂CH₂0), 0.9-1.9 (bm, 11H, cyclohexyl), 6.9 (s, 1H, C₅-H), 7.4 (s, 1H, C₆-H), 2.6-3.5 (m, 4H, C₂-H, C₃-H and C₄-H), 9.7-10 (bs 1H, COOH), Mass (m/z, Rel. Int.): 330 (M⁺, 190), 286 (200), 203 (800). Anal. Calcd for C₁₉H₂₂O₅: C, 69.1; H, 6.6. Found, C, 69; H, 6.7%.

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