SYNTHESIS AND CHARACTERIZATION OF A NOVEL 6-HETEROARYL-3,6-DIHYDRO-2H-PYRAN-2-ACETIC ACID

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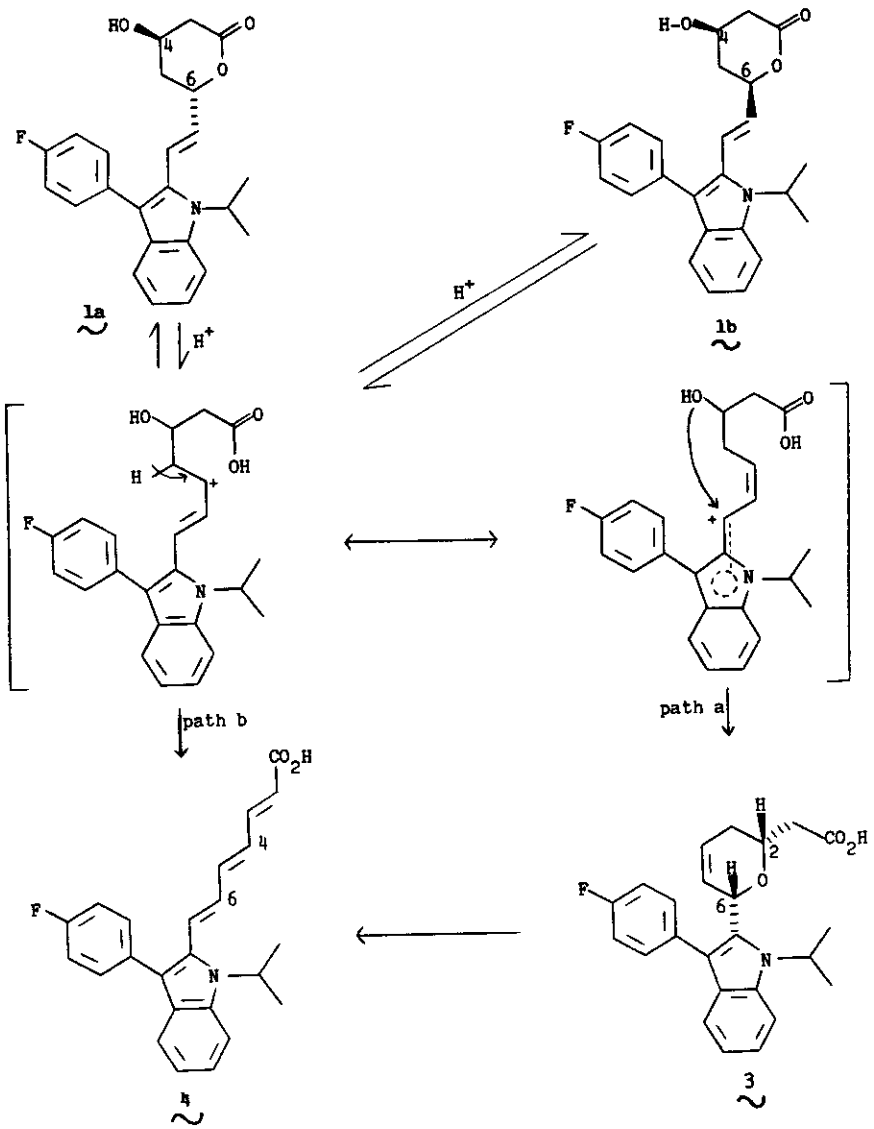
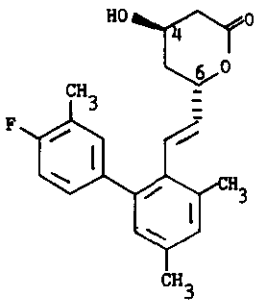
Abstract -Cis and trans-6-[2-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]ethenyl]-3,4,5,6-tetrahydro-4-hydroxy-2H-pyran-2-one (**1b** and **1a**) rearrange under mildly acidic conditions giving only cis-6-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,6-dihydro-2H-pyran-2-acetic acid (**3**). A mechanism is proposed for the acid catalyzed rearrangement.

In the course of our studies on the synthesis and evaluation of 7-(3,5-disubstituted[1,1'-biphenyl]-2-yl)-3,5-dihydroxy-6-heptenoic acid lactones[1] (e.g., Compound **2**) as HMG-CoA reductase inhibitors, a patent describing indolyl lactone **1a** as a potent HMG-CoA reductase inhibitor was issued.[2] A sample of **1a** was prepared in order to compare its chemical and biological properties with those of compound **2**, one of our most potent biphenyl lactones. It readily became apparent that lactone **1a** was unstable to mildly acidic conditions.

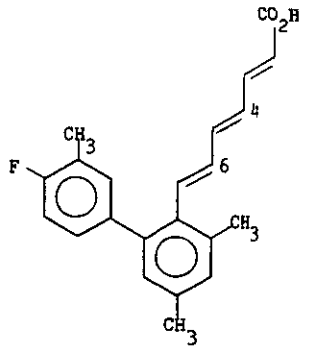
Biphenyl lactone **2**, as well as the other biphenyl lactones prepared in our previous study, undergo a rapid epimerization at C-6 when treated in toluene with a catalytic amount of p-toluenesulfonic acid or concentrated hydrochloric acid at 20 °C.[3] Indolyl lactone **1** (**a** or **b**), unexpectedly, rearranges (path a, Scheme I) concomitantly with or subsequently to a similar epimerization[4] at C-6 giving the novel pyran acetic acid **3** (the rapid epimerization of **1a** is detected by HPLC and, after 5 min., affords roughly a 2:1 mixture of **1a** and **1b**, which then rearranges more slowly to pyran acetic acid **3**).[5] Hence, the reaction conditions which led to **3** were investigated further. Replacement of toluene by acetonitrile or the use of concentrated hydrochloric acid or trifluoroacetic acid in toluene slows the reaction considerably (91% complete after 16 h, acetonitrile; 61% complete after 12 h, concentrated hydrochloric acid; 48% complete after 48 h at 5 °C, concentrated hydrochloric acid; 81% complete after 18 h, trifluoroacetic acid). Longer reaction time with concentrated hydrochloric acid in toluene leads to contamination of the product with increasing amounts of trienoic acid **4**. The trienoic acid is obtained almost exclusively when the concentrated hydrochloric acid reaction is heated at reflux (<2 h). The trienoic acid is the only product

SCHEME I





2



5

isolated when lactone 1 or pyran 3 is treated with concentrated hydrochloric acid in acetonitrile at 20 °C. To date we have been unable to induce a similar rearrangement of lactone 2 using any of the above reaction conditions. The corresponding trienoic acid, 5, is formed when lactone 2 is treated with concentrated hydrochloric acid in acetonitrile at 20 °C.

NMR spectroscopy confirms the structural assignments of acids 4 and 5. With the exception of the methyl and isopropyl groups, only aromatic and olefinic proton resonances are observed for the two compounds. The magnitudes of the olefinic coupling constants suggest that the compounds are all-trans isomers.[6] The formation of all trans trienoic acid 5 is consistent with similar results obtained in our laboratories upon vigorous acid treatment of other 6-substituted-4-hydroxy-2H-pyran-2-ones.

The structural assignment for pyran acetic acid 3 is based, in part, on carbon NMR data which show that the indolyl, fluorophenyl, and N-isopropyl groups are present and intact. Also present in the carbon spectrum are resonances for two olefinic carbons (128.9 and 124.5 ppm), two oxygenated methines (71.0 and 70.8 ppm), two methylenes (40.8 and 29.9 ppm), and a carboxylic acid carbon (176.5 ppm). The proton coupling sequence (COSY experiment) and chemical shifts provide evidence for a dihydropyran ring. The configuration of the ring substituents is clearly established as cis from NOE experiments. Irradiation of the C-2 proton produces a strong NOE in the C-6 proton resonance and vice versa. The infrared spectrum also indicates the presence of a CO_2H group (3500-2500 cm^{-1}) and acid carbonyl (1710 cm^{-1}) with the absence of absorbance for ester or lactone carbonyl at ~1735 cm^{-1}.

The rearrangement of 1 can be envisioned to consist of an initial protonation of the lactone followed by ring opening to a carbonium ion which is resonance stabilized by the indole. The ease with which the lactone ring of 1 opens is presumed to reflect the greater stability of its carbonium ion relative to that in the carbocyclic series. The oxygen at C-4 of the lactone ring then traps the carbonium ion giving the thermodynamically more stable cis pyran (path a). Alternatively, deprotonation of the carbonium ion (path b), and subsequent dehydration, accounts for formation of the trienoic acid 4. The reason for the dichotomy of reaction pathways is not immediately apparent.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR spectra were recorded in $CDCl_3$ on a NT-360 spectrometer. ^{13}C NMR spectra were recorded in $CDCl_3$ on an XL-300 spectrometer at 75.43 MHz. Chemical shifts are reported in parts per million relative to Me_4Si as the internal standard. Elemental analyses for carbon, hydrogen, and nitrogen were determined using a Perkin-Elmer Model 240 elemental analyzer and are within $\pm$0.4% of theory. Analytical thin layer chromatography (TLC) was conducted on Whatman MK6F precoated silica gel plates with 19:1 $CHCl_3/CH_3OH$ as solvent. Analytical high pressure liquid chromatography (HPLC) was done on a Whatman

Partisil 5 RAC column using 4:1 hexane/iPrOH as the eluting solvent at 4 ml/min. Infrared (IR) spectra were run on a Perkin-Elmer 297 spectrometer. Ultraviolet (UV) spectra were recorded in MeOH with a Beckman ACTA MVI spectrophotometer.

cis-6-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,6-dihydro-2H-pyran-2-acetic Acid (3). Compound **1a**[2] (500 mg, 1.27 mmol) was dissolved in toluene (50 mL) and treated with pTSA (15 mg). After stirring at 20 °C for 3 h (HPLC indicated the reaction was 90% complete after 1 h, 96% complete after 2 h and 97% complete after 3 h) the solution was diluted with Et_2O (100 mL), washed with H_2O (3 x 100 mL), dried ($MgSO_4$), filtered and evaporated. Chromatography of the residue on silica gel with 5:1 $CHCl_3$/acetone afforded 400 mg (80%) of **3** as a pale amber glass: TLC [R_f of **3** 0.28 vs. 0.53 for **1a** and 0.47 for **1b**]; HPLC [elution time of 8.08 min]; IR (KBr) 3500-2500 (br m, COOH), 1710 (s, CO), cm^{-1}; UVλ_{max} 228.5 nm (38,320 $M^{-1}cm^{-1}$), 278 nm (12,040 $M^{-1}cm^{-1}$) [vs. 230 nm (24,600 $M^{-1}cm^{-1}$), 306 nm (12,800 $M^{-1}cm^{-1}$) for **1a**]; ^1H NMR δ 7.58 (indole C_4H, dd, 7.6, ~ 1 Hz), 7.57 (indole C_7H, d, 8.3), 7.41 (F-C-C-C-H, dd, 8.7 5.5, 2H), 7.20 (indole C_6H, ddd, 8.3, 7.0, 1.2), 7.14 (F-C-C-H, dd, 8.8, 8.7 2H), 7.08 (indole C_5H, dd, 7.6, 7.0), 5.94 (pyran C_4H, dddd, 10.2, 4.9, ~ 2.5, ~ 2.5), 5.83 (pyran C_5H, dddd, 10.2, ~ 2, ~ 2, ~ 2), 5.57 (pyran C_6H, m), 5.09 ($NCH(CH_3)_2$, septet, 7.0), 4.21 (pyran C_2H, m), 2.72 ($CH-CO_2H$, dd, J = 16.1, 9.1), 2.59 ($CH-CO_2H$, dd, J = 16.1, 3.7), 2.21 (pyran C_3H, m, 2H), 1.62 ($CH(CH_3)_2$, d, 7.0, 6 H). ^{13}C NMR (proton decoupled) δ 176.5 (CO_2H), 161.8 (C-F, d, 245 Hz), 134.8 (C), 133.2 (C), 131.9 (C-C-C-F, d, 7.5), 130.8 (C-C-C-C-F, d, 3.0), 128.9 (pyran C_5), 127.9 (indole C_{3a}), 124.5 (pyran C_4), 121.9 (indole C_6), 119.9 (indole C_4), 119.4 (indole C_5), 116.0 (indole C_3), 115.3 (C-C-F, d, 21.2), 112.5 (indole C_7), 71.0 (pyran C_2), 70.8 (pyran C_6), 48.1 (NCH), 40.8 (CH_2-CO_2H), 29.9 (pyran C_3), 21.2 (CH_3), 21.0 (CH_3). Anal. calcd for $C_{24}H_{24}FNO_3$: C, 73.26; H, 6.15; N, 3.56. Found: C, 73.62; H, 6.39; N, 3.47.

7-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-2,4,6-heptatrienoic Acid (4). Compound **1a** (500 mg, 1.27 mmol) was dissolved in acetonitrile (5 mL) and treated with conc. HCl (100 μL). The trienoic acid started to separate as tiny orange needles after about 3/4 h at 20 °C. After standing an additional h at ambient temperature the flask was cooled to -20 °C and the solid was collected by filtration (300 mg, 63%), mp 191-192 °C. A small sample was recrystallized from acetonitrile for elemental analysis, mp 193-193.5 °C; TLC (R_f of **4** 0.26 vs. 0.28 for **3**]; HPLC [elution time 9.34 min]; IR (KBr) ~ 3300-2100 (br m, COOH), 1660 (s, CO) cm^{-1}; UVλ_{max} 230 nm (17,320 $M^{-1}cm^{-1}$), 283 nm (22,361 $M^{-1}cm^{-1}$), 383 nm (25,997 $M^{-1}cm^{-1}$); ^1H NMR δ 7.55 (indole, ddd, 8.4, 0.8, <1 Hz), 7.51 (indole, ddd, 7.7, 1.2 <1), 7.41 (fluorophenyl, dd, 8.9, 5.5, 2 H), 7.40 (C_3H, ddd, 15.1, 11.1, 0.4), 7.22 (indole, ddd, 8.3, 7.0, 1.2), 7.15 (fluorophenyl, dd, 8.9, 8.7, 2H), 7.09 (indole, dd, 7.8, 7.2, 0.8), 6.81 (C_7H, d, 15.7), 6.68 (C_5H, ddd, 14.8, 11.1, 0.4), 6.37 (C_6H, dd, 15.5, 11.1), 6.25 (C_4H, dd, 14.7, 11.1), 5.87 (C_2H, d, 15.1), 4.90 ($CH(CH_3)_2$, septet, 7.0), 1.70 ($CH(CH_3)_2$, d, 7.0, 6H). ^{13}C NMR (proton decoupled) δ 172.4 (CO_2H), 161.7 (C-F, d, 245.8 Hz),

146.4 (CH), 141.7 (CH), 136.1 (C), 133.0 (C), 132.5 (CH), 131.9 (C-C-C-F, d, 7.5), 131.1 (C-C-C-C-F, d, 3.0), 130.1 (CH), 128.6 (C), 126.0 (CH), 122.7 (CH), 120.0 (CH), 120.0 (CH), 119.9 (CH), 117.3 (C), 115.6 (C-C-F, d, 21.7), 111.9 (CH), 47.8 ($\underline{C}H(CH_3)_2$), 21.8 ($CH(\underline{C}H_3)_2$). Anal. Calcd for $C_{24}H_{22}FNO_2$: C, 76.78; H, 5.90; N, 3.73. Found: C, 77.11; H, 6.03; N, 3.70.

7-(4'-Fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl)-2,4,6-heptatrienoic Acid (5).

Lactone **2** (350 mg, 1 mmol) was converted, using the conditions described above for the preparation of **4**, into **5** in 71% yield, mp 173-175°. An analytical sample was prepared by crystallization from toluene-hexane, mp 174-175°; IR (KBr) ~3300-2100 (br s, COOH), 1680 (s, CO) cm^{-1}; UV λ_{max} 278 nm (15,615 $M^{-1}cm^{-1}$), 343 nm (34,061 $M^{-1}cm^{-1}$); ^1H NMR δ 7.37 (C_3H, ddd, 15.1, 11.4, 0.5 Hz), 7.15-6.9 (aryl, complex, 5H), 6.64 (C_7H, d, 16), 6.58 (C_5H, ddd, 14.6, 10.7, 0.5), 6.21 (C_4H, ddd, 14.7, 11.3, 0.5), 6.18 (C_6H, dd, 15.6, 10.9), 5.84 (C_2H, d, 15.1), 2.41 (CH_3, s, 3H), 2.34 (CH_3, s, 3H), 2.29 (CH_3, d, 1.8, 3H). Anal. Calcd for $C_{22}H_{21}FO_2$: C, 78.55; H, 6.29. Found: C, 78.30; H, 6.57.

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