A Novel Synthesis of 14-(Hydroxymethylalkyl) Derivatives of Dibenzoxanthenes and 3,3-Dimethyl-4-(2-hydroxy-1-naphthyl)benzo[*f*]chroman

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Several reactions of 2-naphthol with 2-alkyl-2-hydroxymethylaldehydes have been investigated. Novel synthesis of 14-(hydroxymethyl)alkyldibenzo[*a,j*]xanthenes and 3,3-dimethyl-4-(2-hydroxy-1-naphthyl)-benzo[*f*]chroman has been realized.

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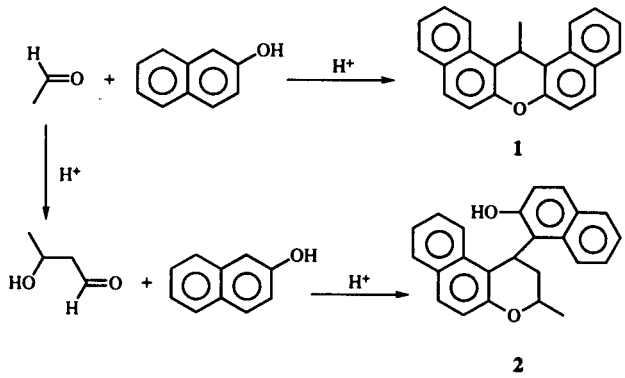
Whitesides and Claisen *et al.* reported the synthesis of 14-methyl-14*H*-dibenzo[*a,j*]xanthenes by using 2-naphthol and paraldehyde [1-2]. 14-Aryl-14*H*-dibenzo[*a*,j]-xanthenes which are widely used as anti-inflammatory agent in medicinal science have been produced from aromatic aldehydes and 2-naphthol [3-4]. We have recently reported on the synthesis and mechanistic data of 14-alkyl-14*H*-dibenzo[*a,j*]xanthenes [5] which may show anti-inflammatory effects as well as 14-aryl-14*H*-dibenzo[*a,j*]-xanthenes. However there seems to be no reports on the structural and mechanistic aspects of the synthesis of 14-functional substituted xanthenes in one step reaction in high yield. Therefore we extended our study to prepare 14-(hydroxymethylalkyl)-substituted dibenzo[*a,j*]xanthene compounds which might show better anti-inflammatory effect than the 14-aryldibenzo-[*a,j*]xanthenes.

14-Aryl-14*H*-dibenzoxanthene and 14-alkyl-14*H*-dibenzoxanthenes [5] have been produced by using one mole of aromatic or aliphatic aldehydes and two moles of 2-naphthol respectively. However, a mixture of 14-methyl-14*H*-dibenzo[*a,j*]xanthene (**1**) and 2-methyl-4-(2-hydroxy-1-naphthyl)benzo[*f*]chroman (**2**) has been produced when 2-naphthol/acetaldehyde ratio has been changed from 2:1 to 1:1. Only chroman **2** has been isolated when this ratio has been taken as 1:1.3. Formation of chroman **2** has been shown to be due to the reaction of 2-naphthol with 2-hydroxybutanal which occurred *in situ* by self aldol condensation of acetaldehyde (Scheme 1). The other aliphatic aldehydes gave only 14-alkylxanthene derivatives probably due to very low reaction rates of self aldol condensation.

2-Naphthol has been reacted with 2-hydroxymethyl-2-alkylaldehydes which had been synthesized with the method described earlier [6] and glyceraldehyde under similar experimental conditions used for the reaction between acetaldehyde and 2-naphthol. The reaction of 2,2-dimethyl-3-hydroxypropanal with 2-naphthol has given 3,3-dimethyl-4-(2-hydroxy-1-naphthyl)benzo[*f*]-

Scheme 1



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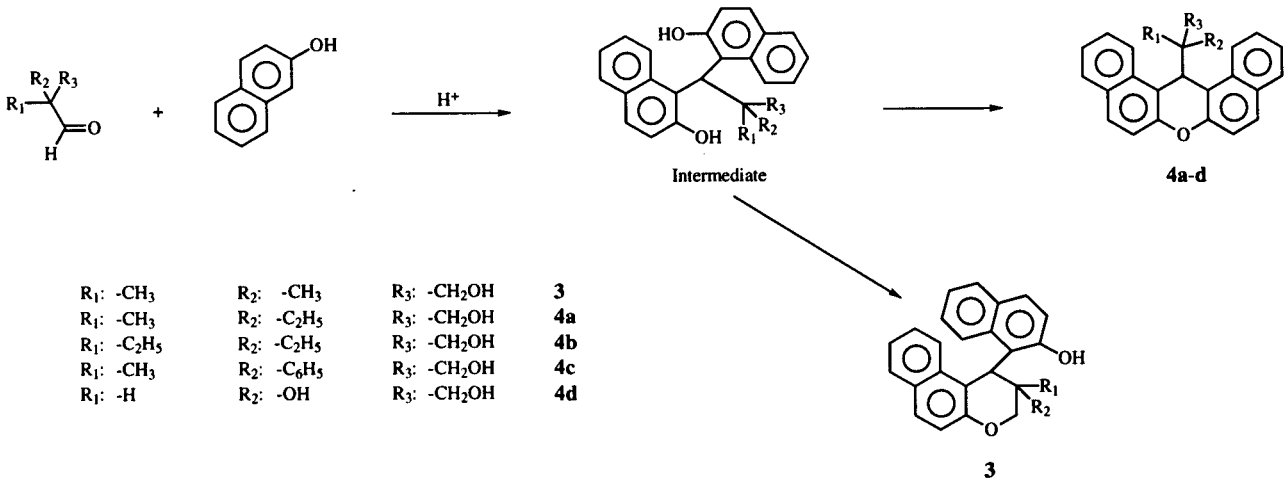
chroman (**3**) (Scheme 2). However, 2-hydroxymethyl-2-methylbutanal and glyceraldehyde have resulted the 14-(hydroxymethylalkyl)-14*H*-dibenzo[*a,j*]xanthene compounds **4a** and **4d**. The first step of the reaction is probably the condensation of aldehyde group with two moles of 2-naphthol to form an intermediate. In the second step, an intramolecular water elimination occurs either between the two naphthols to form xanthenes **4a-d** or from one naphthol and one methylol to form chroman **3**.

The preference of the elimination path is probably governed by steric effect of R_1 and R_2 as well as the mesomeric effect. If both R_1 and R_2 are methyl, the product is the chroman **3** compound. This mechanism is similar to the formation of chroman **2**. However, if R_1 and R_2 are higher alkyl groups, the reactions prefer the path to give dibenzoxanthenes **4**. Formation of chroman **3** was unique since the reaction of other 3-hydroxyaldehydes with 2-naphthol gave 14-hydroxyalkyl-substituted dibenzoxanthenes **4a-d**.

Chroman **3** and 14-(hydroxymethylalkyl)dibenzoxanthenes **4a-d** were characterized on the basis of their spectral data (^{1}H- and ^{13}C-nmr, ir (FT), hrms and gc-ms). In the ^{1}H-nmr spectrum of **3**, it was seen that the magnetic environments of methylene protons in the aliphatic portion of the spectrum are quite dissimilar and the large cou-

Scheme 2

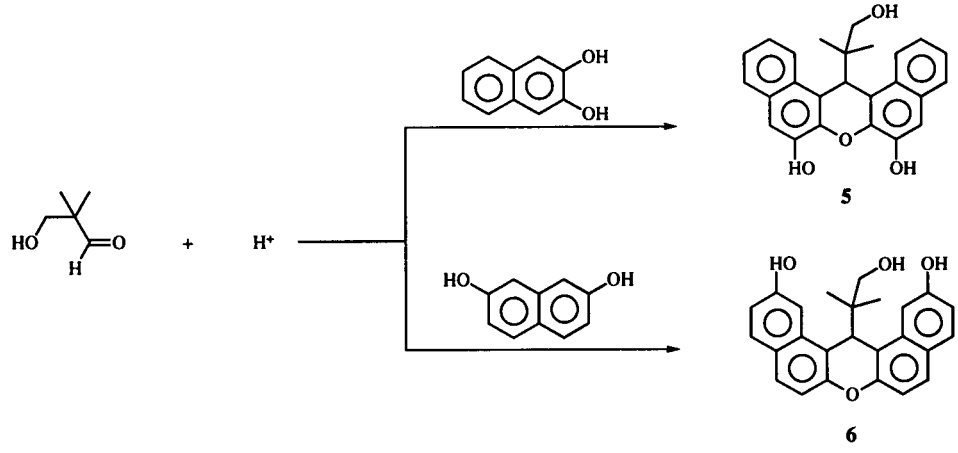


R_1: $-CH_3$	R_2: $-CH_3$	R_3: $-CH_2OH$	**3**
R_1: $-CH_3$	R_2: $-C_2H_5$	R_3: $-CH_2OH$	**4a**
R_1: $-C_2H_5$	R_2: $-C_2H_5$	R_3: $-CH_2OH$	**4b**
R_1: $-CH_3$	R_2: $-C_6H_5$	R_3: $-CH_2OH$	**4c**
R_1: -H	R_2: -OH	R_3: $-CH_2OH$	**4d**

pling constant between these two protons are more consistent with a rigid cyclic structure than a freely mobile side chain such as that in **4a-d**. The hydroxyl resonance appeared at 9.9 ppm, a chemical shift more consistent with a phenolic hydroxyl than with the primary alcohol. In the ^{13}C-nmr, 18 of the 20 possible aromatic resonance were observed, ruling out any structure with plane of symmetry. Additional resonance indicated the presence of four aliphatic carbon atoms and two aromatic C-O atoms. The molecular weight deduced from a strong parent ion ($M^+ = 354$) was likewise supported the proposed structure and also additional support for the assignment of the compound **3** were sought from its mass spectral fragmentation. Detailed spectral data were given into the experimental section. Compound **4a** and **4d** were consistent with the spectral data. The ^1H-nmr spectra of two compounds showed chemical shifts and coupling patterns uniquely define the acyclic structure. Also, spectra did not have any phenolic OH peaks at about 9 ppm. Combustion analysis were consistent with their elemental compositions and also the molecular weights were detected as 368 and 342 from hrms spectra respectively. In ^{13}C-nmr spectra, 19 of 20 possible aromatic resonance were observed due to the magnetic nonequivalency of the two naphthyl rings. This could be attributed to the chiral center in the side chain. The compounds **4b** and **4c** were only detected by gcms because of being obtained with very low yields. The proposed structure of **4b** and **4c** were confirmed by the mass spectral fragmentation patterns which are similar to compounds **4a** and **4d**.

Similar reactions have been carried out between 2,2-dimethyl-3-hydroxypropionaldehyde and dihydroxynaphthalenes such as 2,3- and 2,7-dihydroxynaphthalenes. Xanthene type products **5** and **6** have been formed. This different behavior of dihydroxynaphthalenes, is due to further activation of the naphthol rings by the second OH group which directs the reaction towards the intramolecular water elimination from the hydroxy groups of dihydroxynaphthalenes. Somehow, under the same experimental conditions, 2-hydroxymethyl-2-phenylpropionaldehyde gave polymeric products with 2,3- and 2,7-dihydroxynaphthalenes.

Scheme 3



EXPERIMENTAL

Melting points were determined on an Electrothermal 9100 capillary melting apparatus. Infrared spectra were obtained from films on sodium chloride plates for liquids or potassium bromide pellets for solids on a Jasco 5300 ir (FT) recording spectrophotometer. The ^{1}H- and ^{13}C-nmr spectra were recorded on a Bruker 200 MHz and are reported in δ units with tetramethylsilane as the internal standard. All column chromatography was performed on silica gel (60 mesh, Merck). Mass spectra (high and low resolution) were obtained by DS-55 model instrument at the University of East Anglia in England and Jeol 153 model instrument at the University of Strathclyde in Scotland. The gcms spectra were run on Hewlett Packard instrument. Elemental analysis were carried out at the University of Strathclyde, Glasgow, Scotland.

Synthesis of 2-Hydroxymethyl-2-alkylaldehydes.

A mixture of 1.5 moles of 2-alkylaldehydes, 0.8 mole of formaldehyde (37%) and 0.04 mole of triethylamine were placed in the flask and heated at reflux temperature for 3 hours. After cooling, triethylamine and unreacted formaldehyde were removed by distillation and the crude products were purified by vacuum distillation. Before reaction with naphthols, all 2-hydroxymethylaldehydes were redistilled and then used fresh in half an hour, in order to prevent an intermolecular acetalization reaction.

2,2-Dimethyl-3-hydroxypropionaldehyde [6].

This product was obtained in a yield of 91% as a white cloudy oil, bp 85-88°/10 mm Hg; ir: ν_{max}/cm^{-1} (film), 3400-2980, 1720, 1480, 1050; ms: m/z 102 (M$^+$), 101, 88, 73, 55; ^{1}H-nmr, (deuteriochloroform): 9.73 (s, 1H, CHO), 3.8 (s, 2H, CH_2), 3.6 (s, 1H, OH), 1.1 (s, 6H, CH_3).

Anal. Calcd. for $C_5H_{10}O_2$: C, 58.82; H, 9.80. Found: C, 58.64; H, 10.11.

2-Hydroxymethyl-2-methylbutyraldehyde.

This product was obtained in a yield of 65% as a pale white oil, bp 98-99°/9 mm Hg; ir: ν_{max}/cm^{-1} (film), 3400, 2950, 1720, 1480, 1050; ^{1}H-nmr, (deuteriochloroform): 9.5 (s, 1H, CHO), 4.5 (s, 2H, CH_2OH), 3.5 (s, 1H, OH), 1.2 (m, 2H, CH_2), 0.9 (s, 3H, CH_3), 0.8 (t, 3H, CH_3).

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.06; H, 10.34. Found: C, 62.56; H, 10.68.

2-Hydroxymethyl-2-ethylbutyraldehyde.

This compound was obtained in a yield of 68% as a pale white oil, bp 100-102°/12 mm Hg; ir: ν_{max}/cm^{-1} (film), 3400, 2950, 1720, 1480, 1050; ^{1}H-nmr, (deuteriochloroform): 9.6 (s, 1H, CHO), 4.5 (s, 2H, CH_2OH), 3.5 (s, 1H, OH), 1.5 (q, 4H, CH_2), 0.8 (t, 6H, CH_3).

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.61; H, 10.76. Found: C, 64.97; H, 10.97.

2-Hydroxymethyl-2-phenylpropionaldehyde.

This compound was obtained in a yield of 79% as a white oil, bp 145-150°/15 mm Hg; ir: ν_{max}/cm^{-1} (film), 3400, 3100, 2980, 1720, 1480, 1050; ^{1}H-nmr, (deuteriochloroform): 9.7 (s, 1H, CHO), 7.8 (m, 5H, Ar), 3.6 (m, 2H, CH_2), 3.05 (s, 1H, OH), 1.5 (s, 3H, CH_3).

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.17; H, 7.31. Found: C, 73.65; H, 7.20.

General Method for the Reaction of 2-Hydroxymethyl-2-alkylaldehydes with Naphthols.

Naphthol (2.5 moles) was dissolved in acetic acid and heated to 50-60°; 0.15 mole of concentrated hydrochloric acid and 1 mole of 2-hydroxymethyl-2-alkylaldehyde, freshly prepared and freshly distilled, were added slowly and stirred for 4 hours at this temperature. The mixture was cooled and the crude product was precipitated. If precipitation was not observed after cooling, the reaction mixture was poured into cold water to precipitate the crude product. The product was crystallized with toluene or glacial acetic acid.

3,3-Dimethyl-4-(2-hydroxy-1-naphthyl)benzo[*f*]chroman (**3**).

This compound was obtained in a yield of 95% as a white needle crystalline, mp 195-196°; ir ν_{max}/cm^{-1} (potassium bromide): 3350, 3000, 2950, 1620, 1580, 1260; ms: m/z 354 (M$^+$), 281, 239, 144, 128; ^{1}H-nmr (deuteriochloroform): 9.9 (s, 1H, OH), 7.8-6.8 (m, 12H, Ar), 5.1 (d, 1H, j = 1.27 benzylic), 4.32 (d, 1H, j = 10.9, CH_2), 3.74 (dd, 1H, j = 10.9, j = 1.7, CH_2), 0.7 (s, 3H, CH_3); ^{13}C-nmr (deuteriochloroform): 22.3 (CH_3), 29.7 (q-C), 38.6 (-CH), 65.6 (OCH_2), 18 peaks between 116.8-132 (aromatic C), 153 (=C-O), 151.1 (C-OH).

Anal. Calcd. for $C_{25}H_{22}O_2$: C, 84.74; H, 6.21. Found: C, 85.02; H, 6.40.

14-(2-Hydroxymethylbut-2-yl)-14*H*-dibenzo[*a,j*]xanthene (**4a**).

This compound was obtained in a yield of 70% as a white needle crystalline, mp 163-165°; ir: ν_{max}/cm^{-1} (potassium bromide): 3400, 3100, 2950, 1600, 1200; ms: m/z 368 (M$^+$), 281, 141, 126; ^{1}H-nmr (deuteriochloroform): 8.3-7.2 (m, 12H, Ar), 5.5 (s, 1H, benzylic), 3.8 (s, 2H, CH_2), 1.4 (s, 3H, CH_3), 1.1 (m, 2H, CH_2), 0.9 (t, 3H, CH_3); ^{13}C-nmr (deuteriochloroform): 9.4 (CH_3CH_2-), 20.9 (CH_3-), 32.9 (CH_3CH_2-), 38.1 (q-C), 47.8 (benzylic-C) 69.6 (CH_2OH), 109.2-152.6 (aromatic C).

Anal. Calcd. for $C_{26}H_{24}O_2$: C, 84.78; H, 6.52. Found: C, 85.10; H, 6.41.

14-(3-Hydroxymethylpent-3-yl)-14*H*-dibenzo[*a,j*]xanthene (**4b**).

This compound was only detected by gcms analysis; m/z 364 (M$^+$), 282, 141, 61. The formation ratio was about 6%.

14-(1-Hydroxy-2-phenylprop-2-yl)-14*H*-dibenzo[*a,j*]xanthene (**4c**).

This compound was only detected by gcms analysis; m/z 415 (M$^+$), 387, 282, 257, 141, 61. The formation ratio was about 9%.

14-(1,2-Dihydroxyethyl)-14*H*-dibenzo[*a,j*]xanthene (**4d**).

This compound was obtained in a yield of 55% as a white needle crystalline, mp 192-193°; ir: ν_{max}/cm^{-1} (potassium bromide): 3500, 3100, 2950, 1620, 1600, 1260, 800; ms: m/z 342 (M$^+$), 325, 181, 157, 128, 110, 98; ^{1}H-nmr (deuteriochloroform): 8.1-7.2 (m, 12H, Ar), 5.28 (s, 1H, OH), 4.38 (s, 1H, benzylic), 3.8 (m, 1H, CH), 1.59 (d, 2H, CH_2); ^{13}C-nmr (deuteriochloroform): 44.6 (benzylic-C), 66.5 (CH_2OH), 75.7 (CHOH), 111.2-156.1 (aromatic C).

Anal. Calcd. for $C_{23}H_{18}O_3$: C, 80.70; H, 5.26. Found: C, 81.20; H, 5.68.

6,8-Dihydroxy-14-(2-hydroxymethylprop-2-yl)-14*H*-dibenzo[*a,j*]xanthene (**5**).

This compound was obtained in a yield of 52%; ν_{max}/cm^{-1} (potassium bromide): 3300, 1620, 1210, 1140; ms: m/z 386 (M^+), 315, 287, 227, 161, 143, 85, 61; ^{1}H-nmr, (deuteriochloroform): 8.1-7.1 (m, 10H, Ar), 6.74 (s, 2H, phenolic OH), 4.41 (s, 1H, benzylic), 2.18 (s, 2H, CH_2), 1.3 (s, 6H, $2CH_3$).

Anal. Calcd. for $C_{25}H_{22}O_4$: C, 77.72; H, 5.69. Found: C, 77.44; H, 5.31.

2,12-Dihydroxy-14-(2-hydroxymethylprop-2-yl)-14*H*-dibenzo[*a,j*]xanthene (**6**).

This compound was obtained in a yield of 72%; ν_{max}/cm^{-1} (potassium bromide) 3300, 1620, 1140, 820; m/z 386 (M^+), 369, 315, 229, 213, 161; ^{1}H-nmr, (deuteriochloroform): 7.94 (s, 2H, phenolic OH), 7.8-7.0 (m, 10H, Ar), 4.41 (s, 1H, benzylic), 2.18 (s, 2H, CH_2), 1.3 (s, 6H, $2CH_3$).

Anal. Calcd. for $C_{25}H_{22}O_4$: C, 77.72; H, 5.69. Found: C, 77.39; H, 5.34.

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