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Spirolactones of Xanthene. IV.¹⁾ New Method of Xanthone Synthesis by Oxidation of Novel Spirolactones of Dibenzo[c, h]xanthene and Xanthenes

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Dibenzo[c,h]xanthone and halogen- and methyl-substituted xanthones have been synthesized by the oxidation of novel spirolactones of dibenzo[c,h]xanthene and xanthene, which were prepared by a new condensation reaction of 1-naphthol or phenol derivatives with oxalic acid in the presence of sulfuric acid. The oxidation was carried out by using potassium permanganate in the presence of aqueous potassium hydroxide. The dibenzo[c,h]xanthone and xanthones were identical with samples obtained by another synthetic route.

Keywords——spirolactone; dibenzo[c, h]xanthone; xanthone; l-naphthol; phenol; X-ray analysis

In previous papers,¹⁻⁵⁾ it has been reported that the reaction of 1-naphthol (1) with oxalic and sulfuric acids occurred with the loss of four molecules of water to give a novel spirolactone (2) of dibenzo[c, h]xanthene in excellent yield (70–75%). The molecular structure of 2 has been established by the X-ray diffraction method (Fig. 1). In the course of further investigation of this novel reaction, we found that the reaction proceeds when substituted phenols are used in place of 1-naphthol to give novel spirolactones (6, 10, 14 and 18) of xanthene as shown in Chart 1. The molecular structure of 14 was also determined by the X-ray diffraction method (Fig. 2).³⁾ Recently, we have found that these novel spirolactones give the dibenzo[c, h]xanthone (3) and xanthones (7, 11, 15 and 19) on potassium permanganate



Fig. 1. ORTEP Drawing of Compound $2^{1,2}$



Fig. 2. ORTEP Drawing of Compound 14³⁾

 $(KMnO_4)$ oxidation in the presence of aqueous potassium hydroxide. This reaction appears to have generality to form xanthone derivatives bearing various substituents, which can not be obtained easily by the other synthetic method, that is, the use of the Ullmann reaction⁴) followed by cyclization using sulfuric acid, polyphosphoric acid (PPA), or phosphoric acid. The structures of the resulting dibenzo[c,h]xanthone and xanthones were proved by confirming their identity with authentic samples obtained *via* another synthetic method, *i.e.*, the cyclization reaction of diphenyl ether derivatives obtained by the Ullmann reaction⁴) of 2chlorobenzoic acid and phenol derivatives by the use of PPA, phosphoric acid, or sulfuric acid.^{5,6}

Results and Discussion

The spirolactones (2, 6, 10, 14 and 18) prepared in this study are outlined in Charts 1, 2 and 3. The reactions were carried out by treating 1 mol of 1-naphthol (1) or substituted phenols (5, 9, 13 and 17) with 1 mol or less of oxalic acid in the presence of 1 mol of sulfuric acid at 130-145 °C for 3-5 h. The reactions were also successfully carried out by using mesitylene or xylene as solvents, but generally the use of no solvent led to a good yield of the desired spirolactone. The spirolactones were detected easily by thin-layer chromatography (TLC) after the reaction because of their high Rf values, as mentioned in the experimental section. The resulting reaction mixtures were purified by column chromatography on silica gel using chloroform or ethyl acetate as an eluent, or by preparative TLC (silica gel and chloroform eluate), and then recrystallized from xylene, toluene, benzene, chloroform or nitrobenzene. Regarding the formation of the spirolactones, the yields were high except for some cases involving sterically hindered substituents or halides on the phenol ring. A methyl group attached to the 3- or 4-position in the phenol ring (5 and 9) did not particularly affect the formation of the spirolactones. However, this reaction did not result in the formation of the desired spirolactone when the unsubstituted phenol was used, because the sulfonation reaction of phenol proceeded initially. In addition, a bulky substituent in the phenol ring, such as ethyl, propyl, tert-butyl, trimethylene, or phenyl, prevented the formation of the desired spirolactones.

The structures of the spirolactones were supported by the results of infrared (IR), proton and carbon-13 nuclear magnetic resonance (¹H- and ¹³C-NMR) spectroscopy as well as mass (MS) spectrometry after isolation of the products. The IR spectra of the spirolactones showed the strong absorption (1790–1810 cm⁻¹) characteristic of the lactone moiety. In the ¹H-NMR spectra, the presence of sharp singlet signals in the range of $\delta 2.0-2.5$ confirmed the





Chart 2

presence of a methyl groups on a benzene ring. The ¹³C-NMR spectra contained three kinds of signals: the aromatic carbons appear at *ca*. δ 105—150, the spiro carbon (C-3) is observed at *ca*. δ 51, and the carbonyl carbon is observed at *ca*. δ 175. With regard to MS spectrometry, all the compounds exhibited a common fragmentation pattern corresponding to the molecular ion (M⁺), M⁺-CO, and M⁺-CO-OH, which assisted in confirming the structures. The elemental analyses and high-resolution mass (HR-MS) spectra of the spirolactones were in good agreement with the calculated values.

According to the molecular structure established by X-ray analysis, compound 2 possesses a ψ -like shape composed of three naphthalene rings fused by the spirolactone. The most interesting feature may be the dihedral angles of the naphthalene planes; 5.9° between rings A and B, 86.9° between rings A and C, and 81.4° between rings B and C. These dihedral angles may be compared with the corresponding values in the reported molecular structure of 2',5,7'-trichlorospiro[benzofuran-3(2H),9'-[9H]xanthen]-2-one (14)³: 22.8, 83.6, and 73.6°, respectively. The great difference in the butterfly angles of the benzoxanthene ring in 2 and 14 (5.9 and 22.8°) seems to be caused by the interaction between the carbonyl group of the lactone moiety and the oxygen atom of the xanthene ring, which is induced by the electron-withdrawing effects of the chloride atoms. Another reason may be the lesser steric hindrance of the phenyl ring of 14 in comparison with the bulky naphthalene ring of 2.

The preparation of dibenzo[c,h]xanthone (3) and xanthones (7, 11, 15, and 19) was successfully carried out by refluxing 1 mol of the spirolactone with 9 mol of potassium permanganate in aqueous potassium hydroxide solution for 15—20 h. The termination of the reaction could be checked by fading of the red color of potassium permanganate, or by



Chart 3

TLC (lower *Rf* values than the corresponding spirolactones). The structures of the desired xanthones (3, 7, 11, 15 and 19) were established by IR, ¹H-NMR, ¹³C-NMR and MS spectral investigation.

The molecular structure of **3** was proved by its identity with the unequivocal product obtained by cyclization⁷⁾ of 1-ethoxycarbonyloxynaphthalene (**4**), which was obtained from 1-naphthol (**1**) and ethyl chloroformate as shown in Chart 1. Spirolactone (**10**) was also oxidized to 3,6-dimethylxanthone (**11**), which was proved by reference to unequivocal product obtained by cyclization of 2-hydroxy-4-methylbenzoic acid (**12**) under reflux with acetic anhydride, as shown in Chart 2. On the other hand, spirolactones (**6**, **14** and **18**) of xanthenes formed by the condensation of the corresponding phenols (**5**, **13** and **17**) with oxalic and sulfuric acids gave the corresponding xanthones (**7**, **15** and **19**) by a similar procedure using *potassium permanganate oxidation in the presence of aqueous potassium hydroxide.* The structures of these xanthones were proved by reference to unequivocal materials obtained in high yields by cyclization of 2-chlorobenzoic acids with phenol derivatives.⁴ This cyclization to xanthones was carried out successfully by using PPA, sulfuric acid or phosphoric acid.

The main advantage of this route for the synthesis of dibenzo[c,h]xanthone and xanthones is the use of simple starting materials, such as phenol derivatives, and the ease of manipulation. This route is particularly suitable for the synthesis of symmetrically substituted xanthones, which are not obtainable in good yields by other synthetic methods, as described in the experimental sections. The present method should also be effective for obtaining symmetrical thioxanthones.

Experimental

Spectroscopy—The ¹H-NMR, totally decoupled and off-resonance decoupled ¹³C-NMR spectra were measured in CDCl₃ solution in 5 mm tubes on a JEOL FX-200 spectrometer. Chemical shifts are relative to tetramethylsilane. The IR spectra were measured on a JASCO A-3 spectrometer. The electron impact (EI) MS spectra were obtained on a Hitachi RMU-7M mass spectrometer.

Chromatography—The TLC was performed on Merck Kieselgel 60 F_{254} strips, 9.5×3.5 cm, and thickness, 0.25 mm with CHCl₃ or ethyl acetate (EtOAc). The preparative TLC was carried out on Merck Kieselgel 60 F_{254} plate, 20×20 cm, and thickness 2 mm with CHCl₃ as an eluent.

Melting Points——The melting points were measured with a Yanagimoto micro-melting point apparatus and are uncorrected.

Spiro[7*H*-dibenzo[*c*,*h*]xanthen-7,3'(2'*H*)-naphtho[1,2-*b*]furan]-2'-one (2)—The reported method^{1,2}) was used to obtain 2 from 7 g of 1-naphthol (0.049 mol), 3.5 g of oxalic acid (0.039 mol) and 4.4 g of conc. sulfuric acid (0.046 g).

2',5,7'-Trimethylspiro[benzofuran-3(2H),9'-[9H]xanthen-2-one (6)——The reported method^{1,2)} was used to obtain 6 from 11 g of 4-methylphenol (0.1 mol), 8 g of oxalic acid (0.09 mol), and 8 g of conc. sulfuric acid (0.08 mol).

3',6,6'-Trimethylspiro[benzofuran-3(2*H***),9'-[9***H***]xanthen]-2-one (10)** Compound **10** (23.3 g; 65% yield) was synthesized from 11 g of 3-methylphenol (0.1 mol) and 8 g of oxalic acid (0.09 mol) with 8 g of conc. sulfuric acid (0.08 mol) by the same procedure as above except that the product was isolated by preparative TLC with CHCl₃ as the developer. mp 205—208 °C. IR (KBr): 2920, 1810 (C=O), 1620, 1600, 1500 cm⁻¹. ¹H-NMR (CDCl₃) δ : 2.31 (s, 6H), 2.42 (s, 3H), 6.50 (d, 2H), 6.72 (d, 2H), 6.84—7.40 (m, 5H). ¹³C-NMR (CDCl₃) δ : 21.09, 21.75, 51.13 (C-3), 108.17, 111.26, 117.20, 117.68, 117.76, 124.59, 124.71, 125.05, 126.15, 126.68, 126.83, 127.20, 129.73, 140.01, 140.11, 140.43, 150.89, 153.86, 176.55 (C=O). MS *m/z* (relative intensity, %): 342 (35, M⁺), 314 (97, M⁺ – CO), 299 (100), 269 (5). HR-MS *m/z*: Calcd for C₂₃H₁₈O₃ 342.1241. Found: 342.1254. TLC (CHCl₃) *Rf*=0.72.

3',6,6'-Trichlorospiro[benzofuran-3(2H),9'[9H]xanthen]-2-one (18) Compound **18** (7.9 g: 23% yield) was synthesized from 11 g of 3-chlorophenol (0.17 mol) and 8 g of oxalic acid (0.09 mol) with 8 g of sulfuric acid (0.08 mol) by the same procedure as above. mp 233–235 °C. IR (KBr): 1810, 1610, 1590, 1470, 1400 cm⁻¹. ¹H-NMR (CDCl₃) δ : 6.29 (d, 1H), 6.48 (d, 1H), 6.49 (d, 1H), 7.08–7.20 (m, 6H for aromatic ring protons). ¹³C-NMR (CDCl₃) δ : 50.74 (C-3), 112.11, 117.64, 118.00, 124.71, 126.25, 126.34, 128.34, 129.87, 135,83, 136.17, 151.08, 154.05, 174.48 (C=O). MS *m/z* (relative intensity, %): 402 (10, M⁺), 374 (50, M⁺–CO), 339 (100, M⁺–CO–OH–H₂O), 276 (15), 162 (23), 106 (25). TLC (CHCl₃) *Rf*=0.60. *Anal*. Calcd for C₂₀H₉Cl₃O₃: C, 59.51; H, 2.25; Cl, 26.35. Found: C, 59.30; H, 2.40; Cl, 26.13.

Dibenzo[*c*,*h*]xanthone (3)—A solution of 10 g (0.063 mol) of potassium permanganate in 200 ml of water was added dropwise at 100 °C to a mixture of 3 g (0.007 mol) of spiro[7*H*-dibenzo[*c*,*h*]xanthen-7,3'(2'*H*)-naphtho[1,2-*b*]-furan]-2'-one (2) and 3 g (0.053 mol) of potassium hydroxide in 50 ml of water, and the whole was refluxed for 13 h. The reaction mixture was then allowed to cool to room temperature, and 50 ml of ethanol was added to the reaction mixture. The precipitates were collected, washed with water, and extracted with 100 ml of ethanol. The filtrate was kept at room temperature for a further 5 h, and the precipitates that appeared were collected to obtain 3. The ethanol extract was concentrated to obtain the residual products, including 3. The combined crude 3 was recrystallized from ethanol to obtain pure crystals of 3, 0.66 g (31%). The melting point was 248—250 °C alone and on admixture with unequivocal material obtained from 1-ethoxycarbonyloxynaphthalene (4) by Bender's method.⁷¹ (lit.⁷¹, mp 245 °C; 17% in yield). They showed identical IR, ¹H-NMR, ¹³C-NMR, and MS spectra as follows. IR (KBr): 3050, 1650, 1630, 1620, 1500, 1460 cm⁻¹. ¹H-NMR (CDCl₃) δ : 7.48—7.60 (m, 6H), 7.7 (q, 2H), 8.12 (d, 2H), 8.46 (q, 2H). ¹³C-NMR (CDCl₃) δ : 118.20 (C-6a), 121.31, 122.40, 124.06 (C-2a), 124.30, 126.83, 127.97, 129.21, 136.12 (C-1a), 152.66 (C-14a), 176.23 (C = O). MS *m/z*: 296 (100, M⁺), 268 (10, M⁺ – CO), 267 (8, M⁺ – CHO).

2,7-Dimethylxanthone (7)—Compound 7 (1.79 g; 34.7% yield) was synthesized from 8 g of 2',5,7'-trimethylspiro[benzofuran-3(2H),9'-[9H]xanthen]-2-one (6) (0.023 mol) and 10 g (0.0179 mol) of potassium hydroxide in 160 ml of water, and 35.2 g (0.223 mol) of potassium permanganate in 670 ml of water, by the same procedure as described above. The melting point was 150—151 °C alone and on admixture with an authentic sample obtained by the cyclization of 2-carboxy-4,4'-dimethyldiphenyl ether (8) with sulfuric acid according to Granoth and Pownall⁸ (lit.⁸), mp 141 °C; 65% yield). They showed identical IR, ¹H-NMR, ¹³C-NMR and MS spectrometry as follows. IR (KBr): 1660, 1620, 1610, 1480 cm⁻¹. ¹H-NMR (CDCl₃) δ : 2.42 (6H, s, 2 × CH₃), 7.30 (2H, d, J=9 Hz, H-4, H-5), 7.45 (2H, dd, J=9, 2 Hz, H-3, H-6), 8.08 (2H, d, J=2 Hz, H-1, H-8). ¹³C-NMR (CDCl₃) δ : 20.77 (CH₃), 117.68, 121.43 (C-2), 125.98, 133.37 (C-1a), 135.81, 154.39 (C-4a), 177.21 (C-9). MS m/z (relative intensity, %): 224 (M⁺), 195 (23, M⁺ – CHO), 181 (13, M⁺ – CO – CH₃).

3,6-Dimethylxanthone (11)—Compound **11** (0.3 g; 35.2% yield) was synthesized from 1.8 g of 3',6,6'-trimethylspiro[benzofuran-3(2H),9'-[9H]xanthen]-2-one (**10**) (0.005 mol) and 2.2 g (0.039 mol) of potassium hydroxide in 36 ml of water, and 7.8 g (0.049 mol) of potassium permanganate in 150 ml of water, by the same procedure as described above. The melting point was 169—171 °C alone and in admixture with unequivocal materials obtained from 2-hydroxy-4-methylbenzoic acid (**12**)⁹⁾ by Weber's method (lit.⁹⁾ mp 166 °C; 4% yield). Both are also identified

by means of IR, ¹H-NMR, ¹³C-NMR and MS spectrometry as follows. IR (KBr): 1650, 1620, 1610, 1420 cm⁻¹. ¹H-NMR (CDCl₃) δ : 2.44 (6H, s, 2 × CH₃), 7.18 (2H, dd, *J*=9, 1.5 Hz, H-2 and H-7), 7.26 (2H, d, *J*=1.5 Hz, H-4 and H-5), 8.12 (2H, d, *J*=9 Hz, H-1 and H-8). ¹³C-NMR (CDCl₃) δ : 21.87, 117.61, 119.58 (C-3), 125.18, 126.32, 145.88 (C-1a), 156.12 (C-4a), 176.62 (C-9). TLC (benzene) *Rf*=0.19.

2,7-Dichloroxanthone (15)—Compound **15** (0.7 g; 24.8% yield) was synthesized from 5 g of 2',5,7'trichlorospiro[benzofuran-3(2*H*),9'-[9*H*]xanthen]-2-one (**14**)³¹ (0.012 mol) and 5.1 g (0.091 mol) of potassium hydroxide in 85 ml of water, and 17 g (0.11 mol) of potassium permanganate in 340 ml of water, by the same procedure as described above. The melting point was 228—230 °C alone and in admixture with an authentic sample obtained by the cyclization of 4,4'-dichlorodiphenyl ether according to Granoth and Pownall⁸ (lit.⁸) mp 219 °C; 45% yield). Both were identified by means of IR, ¹H-NMR, ¹³C-NMR and MS spectrometry as follows. IR (KBr): 3080, 1670, 1610, 1600, 1460 cm⁻¹. ¹H-NMR (CDCl₃) δ : 7.42 (2H, d, J = 9 Hz, H-4 and H-5), 7.65 ((2H, dd, J = 9, 2 Hz, H-3 and H-6), 8.24 (2H, d, J = 2 Hz, H-1 and H-8). ¹³C-NMR (CDCl₃) δ : 119.78, 122.31 (C-2), 126.08, 130.19 (C-1a), 135.28, 154.34 (C-4a), 174.95 (C-9). TLC (benzene) Rf=0.48.

3,6-Dichloroxanthone (19)—Compound **19** (0.84 g; 26.3% yield) was synthesized from 5 g of 3',6,6'trichlorospiro[benzofuran-3(2*H*),9'-[9*H*]xanthen]-2-one (**18**) (0.012 mol) and 5.1 g (0.09 mol) of potassium hydroxide in 85 ml of water, and 17 g (0.11 mol) of potassium permanganate in 340 ml of water, by the same procedure as described above. The melting point was 190—191 °C alone and in admixture with unequivocal material obtained from 3,3'-dichloro-6-carboxydiphenyl ether according to Goldberg and Wragg⁶ (lit.⁶) mp 184—186 °C; 21% yield). Both were also identified by means of IR, ¹H-NMR, ¹³C-NMR and MS spectrometry as follows. IR (KBr): 3100, 1670, 1610, 1600, 1420 cm⁻¹. ¹H-NMR (CDCl₃) δ : 7.33 (2H, dd, J=9, 2 Hz, H-2 and H-7), 7.44 (2H, d, J=2 Hz, H-4 and H-5), 8.20 (2H, d, J=9 Hz, H-1 and H-8). ¹³C-NMR (CDCl₃) δ : 118.00, 120.32 (C-3), 125.20, 128.10, 141.16 (C-1a), 156.12 (C-4a), 175.29 (C-9). TLC (benzene) Rf=0.41.

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