HETEROCYCLES, Vol 20, No 3, 1983

SYNTHESIS OF meta-SUBSTITUTED 9-PHENYLXANTHENES

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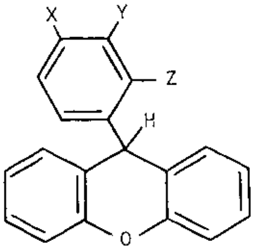
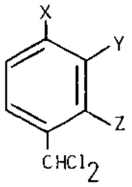
ABSTRACT— Construction of the dibenzopyran ring of 9-(3-methoxyphenyl)xanthene (**2**) by an aluminum chloride-catalyzed, geminal dialkylation reaction between 3-methoxybenzal chloride and phenyl ether was accomplished, but in poor yield; however, a satisfactory preparation of **2** was attained by the grignard reaction of 3-methoxyphenylmagnesium iodide with xanthone, and subsequent reduction; demethylation of **2** was effected by treatment with trimethylsilyl iodide in hot quinoline.

Identification of A274, a remarkably potent antioxidant that was originally[1] isolated in microscopic quantities from cultures of neuroblastoma cells subsequent to cytodifferentiation but afterwards shown[2] to be a contaminant widely distributed in commercial tissue culture medium preparations, was accomplished by the synthesis of two series of isomeric compounds for comparison by gas chromatography—mass spectrometry (GC-MS). It was thus shown[3] that 9-(4-methoxyphenyl)xanthene[4,5] (**1**) is isographic with and gives a mass spectrum superimposable upon that of the methyl ether prepared by diazomethylation of A274.

Kekule demonstrated[6] the formation of triphenylmethane in the reaction of benzal chloride with diphenyl mercury. Our initial syntheses[7] of 9-(4-, 3-, and 2-methoxyphenyl)xanthene (**1-3**, respectively) sought to extend the reaction of the isomeric methoxybenzal chlorides to cyclization by 2,2-disubstitution of phenyl ether under Friedel—Crafts conditions. Treatment of p-, m-, and o-anisaldehyde with thionyl chloride afforded the respective, isomeric methoxybenzal chlorides (**4-6**). The properties of **4**[8] and **6**[9] were consistent with reported descriptions, and



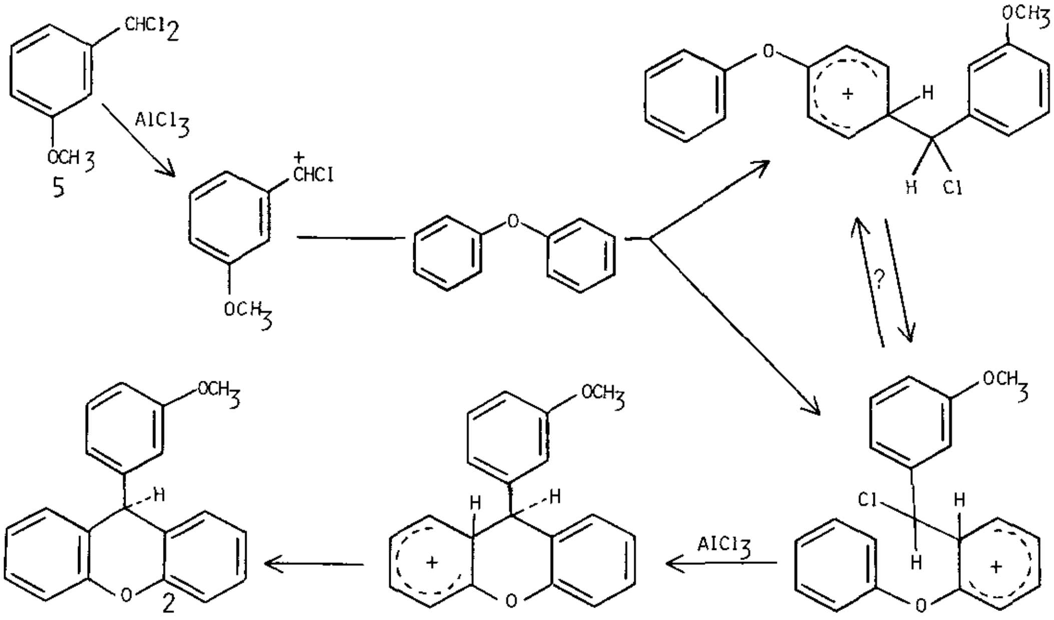
	X	Y	Z	
1	OCH_3	H	H	4
2	H	OCH_3	H	5
3	H	H	OCH_3	6



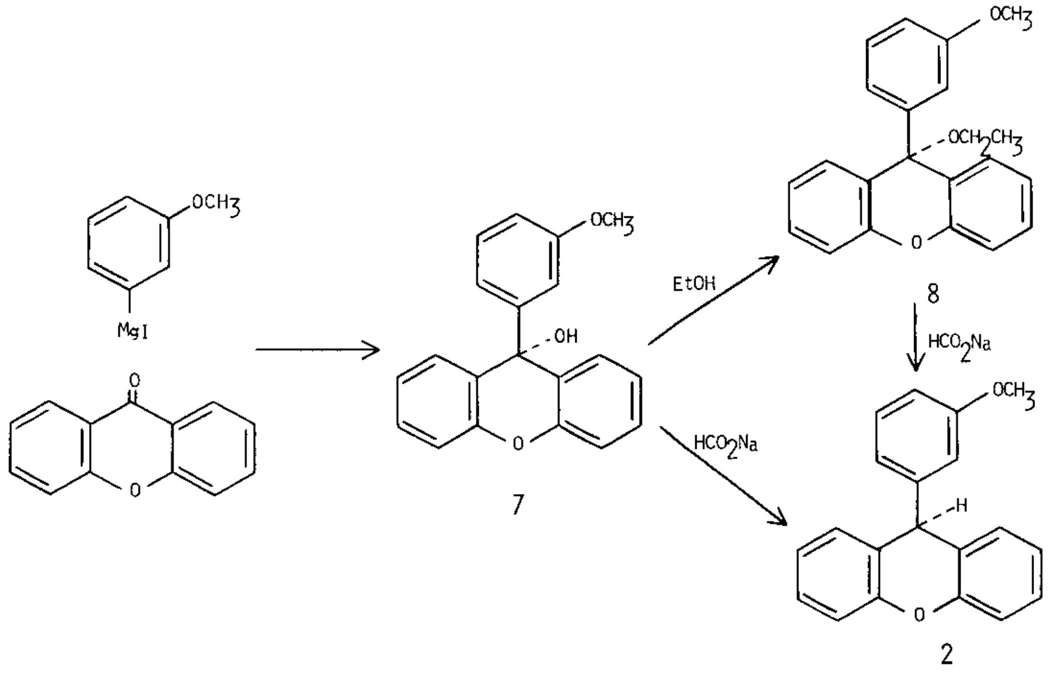
formation of **1**, **2** and **3** was clearly demonstrated[3] by comparative GC-MS, although the respective products were examined as components of the crude reaction mixtures and found to have been formed in amounts too minor (*ca.* 5%) to warrant isolation.

Because electrophilic substitution reactions readily afford 2- and 4-substituted phenylxanthenes, and because **2** and **5** are unreported compounds, the conversion of **5** into **2** was selected as the example of the cyclization reaction for which conditions were to be optimized. Thionyl chloride converted *m*-anisaldehyde into a water-white liquid, distillable at atmospheric pressure, that was shown by GC-MS to be more than 98% pure; nmr, IR, and mass-spectral data indicated the structure **5**, free of observable contaminants. In nitrogen-swept, flame-dried glassware, **5** was reacted overnight with phenyl ether in refluxing nitrobenzene in the presence of aluminum chloride. GC-MS of the dark, viscous, crude mixture revealed the formation of **2**, but in yields below 10%.

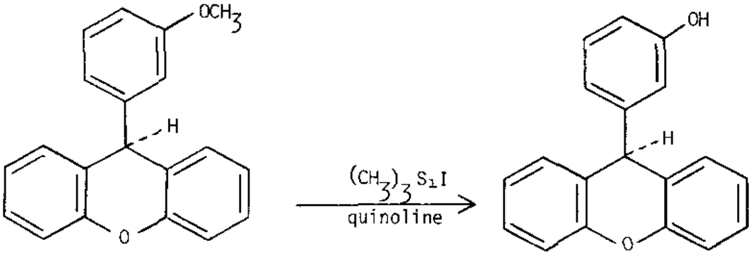
That the major course of the reaction did not follow the scheme illustrated below may indicate that the *ortho* and *para* monoadducts are not interconverting, that the cyclization reaction provides a driving force insufficient to induce the initial *para* adduct to rearrange, or that the methoxybenzal chloride reacts competitively as an aromatic substrate. As the yield did not improve significantly, we turned to a more conventional[4,10] synthetic approach to **2**.



Reaction of 3-iodoanisole with magnesium in dry tetrahydrofuran and thence with a solution of xanthone in benzene—tetrahydrofuran afforded a mixture containing varying amounts of **2** and a compound presumed to be the initial adduct (**7**). Crystallization of the latter product from ethanol afforded a crystalline solid, spectroscopic characterization of which indicated the structure 9-ethoxy-9-(3-methoxyphenyl)-xanthene (**8**). Triaryl carbinols were early recognized to be labile both to hydrogenolysis [4,11-14] and to mild, acid-catalyzed conversion[15] into ethers, and the presence of unreacted magnesium after the reaction and of traces of acid in the crude solid should be sufficient to cause the subsequent conversions of **7** into **2** and **8**, respectively. Many of the reagents used to reduce triphenylmethanols are strongly acidic, and concern about the possible lability of the methyl ether group caused us to select formic acid[4,14] partially buffered with sodium carbonate[16] for the hydrogenolysis step. The reagent smoothly converted **8** into **2**, and in subsequent preparations the crude product from the Grignard reaction was reduced to **2** without purification; two recrystallizations gave a homogeneous, crystalline solid, whose nmr, IR, and mass spectra were in accord with the structure assigned.



Attempted demethylation of **2** by extended treatment with refluxing 57% hydriodic acid resulted only in gradual decomposition of the starting material, and a solution of **2** and trimethylsilyl iodide (TMSI) in deuteriochloroform was unchanged after 2 days at room temperature. Treatment of **2** with TMSI in freshly purified quinoline for 1 h at reflux produced[17] a 35% yield of a colorless, crystalline solid, whose nmr and IR spectra were consistent with the expected structure, 9-(3-hydroxyphenyl)xanthene (**9**), and whose mass spectrum was qualitatively identical with those of A274[1] and 9-(4-hydroxyphenyl)xanthene.[5]



2

9

EXPERIMENTAL

Proton nmr spectra were recorded using a Varian EM-390 or JEOL FX-90Q (90 MHz) or JEOL FX-270 (270 MHz) spectrometer; ^{13}C-nmr spectra were recorded using a JEOL FX-90Q or FX-270 spectrometer. SiMe$_4$ was used as an internal standard. IR spectra were measured with a Perkin—Elmer 257 spectrometer, UV spectra were measured with a Perkin—Elmer 297 spectrometer, and GC-MS was performed on a Finnigan 4023 quadrupole GC-MS-DS package fitted with 2-m x 2-mm (i.d.) glass column packed with 3% OV-1 on 100-120 mesh Gas-Chrom Q. Injector, separator, and source temperatures were 250°C, the column temperature was programmed from 60-240°C at a rate of increase of 20°C per minute, and the flow rate of the carrier gas (He) was 23 cm^3 per minute.

3-Methoxybenzal chloride (*5*)

A mixture of m-anisaldehyde (4.2 ml; 31 mmol) and thionyl chloride (5 ml; 42 mmol; freshly distilled, first from quinoline and again from linseed oil) was refluxed for 24 h. Fractional distillation at atmospheric pressure afforded 8.3 g (88% yield) of **5** boiling from 238 to 240^{o}C; pmr (270 MHz; CD$_3$COCD$_3$-CCl$_4$): δ3.77 (3H, s, -OCH$_3$), 6.88 (1H, -CHCl$_2$), 7.13 (3H, m, Aryl), 7.26 (1H, m, Aryl); cmr (67 MHz): δ_c 55.15 (-OCH$_3$), 71.72 (-CHCl$_2$), 111.72 (C-4), 115.50 (C-2), 118.16 (C-6), 129.73 (C-5), 141.63 (C-1), 159.78 (C-3); IR (film): 3100, 2910 (CH), 2820 (OCH$_3$), 1580 and 1475 (aryl C=C), 1250 and 1020 (C-O), 900, 760 (*m*-disubst.), 730 cm^{-1} (C-Cl); UV (EtOH): λ_{max} 225nm (ε 8800), 282 (ε 3700), mass spectrum: 193.96 (4.3%; calc. 193.99), 191.96 (18.5; calc. 191.99), 189.96 (28.5, $M^{+\cdot}$ calc. 189.99), 157.02 (38.7, calc. 157.02), 155.08 (100, $M^{+\cdot}$-Cl; calc. 155.03).

9-(3-Methoxyphenyl)xanthene (**2**) from 3-methoxybenzal chloride (**5**).

Anhydrous aluminum chloride (5.8g, 44 mmol) was added slowly under nitrogen to a mechanically stirred solution of **5** (2.0 g, 10.86 mmol) and freshly distilled phenyl ether (1.8 g, 11.25 mmol) in dried nitrobenzene (25 ml) at room temperature. After 30 min, the reaction mixture was heated to reflux for 14 h, cooled to room temperature, and shaken with a mixture of 10 ml of conc. HCl, 25 g of ice, and 50 ml of ether. The water layer was washed thrice with 50-ml portions of ether, and the combined ethereal extracts were washed with 75-ml portions of saturated aqueous NaHCO$_3$ and of water, dried, and concentrated *in vacuo* to a brown syrup that was shown by GC-MS to contain *ca*. 8% of the xanthene **2**, plus similar amounts of nearly a dozen other products, none of which exhibited mass-spectral fragments in common with **2**.

9-(3-Methoxyphenyl)xanthene(**2**) from xanthone

A solution of 5.0 g (21 mmol) of *m*-iodoanisole in 20 ml of dry tetrahydrofuran was added dropwise with efficient stirring under nitrogen into 25 ml of dry tetrahydrofuran covering 0.6 g (25 mmol) of magnesium turnings. Addition of an iodine crystal after 10 min produced spontaneous exothermicity, and a reaction temperature of 50-60°C was maintained for a total of 60 min by intermittent immersion in a bath of hot water. The mixture was then allowed to cool to room temperature, and a solution of xanthone (1.16 g, 21.0 mmol) in 20 ml of dry benzene and 10 ml of dry tetrahydrofuran was added during 30 min, whereupon the mixture was refluxed for 48 h, cooled to room temperature, and poured into 60 ml each of ether and water. The mixture was filtered, acidified with dilute HCl, and separated. The water layer was extracted thrice with 30-ml portions of ether, and the combined ether layers were dried, concentrated *in vacuo*, and passed through a 1-g bed of silica gel in ether. Concentration of the orange eluate gave a greenish solid, which was recrystallized from 95% ethanol to give 3.6 g (56% yield) of yellow solid **8**, mp 84-85°C, pmr (90 MHz, CDCl$_3$): δ1.12 (3H, t, *J* 7Hz, (OCH$_2$)CH$_3$), 2.98 (2H, q,

$OCH_2(CH_3)$), 3.74 (3H, s, CH_3), 6.98-7.24 (12H, m, Aryl); cmr (22.5 MHz): δ_c 15.39 (CCH_3), 55.15 (OCH_3), 58.83 (OCH_2), 96.16 (C-9), 111.22 (C-4'), 112.63 (C-2'), 116.05 (x2, C-4), 119.40 (C-6'), 123.30 (x2, C-2), 123.84 (x2, C-8a), 128.83 (x2, C-1 or -3), 129.37 (x2, C-3 or -1), 129.69 (C-5'), 149.68 (C-1'), 151.26 (x2, C-4a), 159.16 (C-3'); IR(KBr): 3030, 2960 (CH), 2840 (OCH_3), 1595, 1580, 1485 (Aryl C=C), 1250, 1230, and 1060 (C-O), 780 (_m_-disubst.), 750 cm^{-1} (_o_-disubst.); UV (EtOH): λ_{max} 218 nm (ϵ 16,600), 280 (ϵ 7,600); mass spectrum: 332 (4%, $M^{+\cdot}$), 289 (4), 288 (29), 287 (100, $M^{+\cdot}$-OEt), 271 (9), 255 (6), 242 (4), 225 (9), 197 (14, $M^{+\cdot}$-C_6H_4OMe), 181 (7), 92 (4), 77 (4).

A solution of **8** (1.2 g, 3.6 mmol) and anhydrous sodium carbonate (1.25 g) in 90% formic acid (14.4 ml) was refluxed for 2 h and placed in an ice—water bath. The green gum that settled out was recrystalized two times from 95% ethanol to give 0.68 g (66% yield) of **2** (>99% pure by GC-MS), mp 65-66°C, pmr (270 MHz, $CDCl_3$): δ 3.79, 3.80 (3H, 2xs, OCH_3), 5.3 (1H, br S, H-9), 6.80-7.60 (12H, m, Aryl); cmr (22.5 MHz): δ_c 44.48 (C-9), 55.12 (OCH_3), 111.73 (C-4'), 114.52 (C-2'), 116.54 (x2, C-4), 120.8 (C-6'), 123.17 (x2, C-2), 124.28 (x2, C-8a), 127.89 (x2, C-1 or -3), 129.64 (x3, C-5' and C-3 or -1), 147.95 (C-1'), 151.1 (x2, C-4a), 159.9 (C-3'), IR(KBr): 3080-2930 (CH), 2840 (OCH_3), 1600, 1585, and 1490 (Aryl C=C), 1250 and 1040 (C-O), 770 (_m_-disubst.), 740 cm^{-1} (_o_-disubst.); UV(EtOH): λ_{max} 225 nm (ϵ 16,700), 225 (ϵ 10,000), 284 (ϵ 5,200); mass spectrum: 288.12 (20.2%, $M^{+\cdot}$; calc 288.12), 257 (4), 181.10 (100, $M^{+\cdot}$-C_6H_4OMe; calc. 181.07), 152 (15.4), 151 (6), 77 (5.8), 51 (2.8).

Demethylation of 9-(3-methoxyphenyl)xanthene (2)

A mixture containing **2** (500 mg, 1.73 mmol), trimethylsilyl iodide (0.369 ml, 2.6 mmol), and freshly purified quinoline (5 ml) was heated to 180°C for 1 h, cooled, poured into 10 ml of 5% HCl, and extracted with 20 ml of ether. The ether layer was washed with 10% NaOH, which was back extracted thrice with 20-ml portions of ether. The combined ether layers were dried and concentrated _in vacuo_ to deposit an off-white solid. Recrystallization from ethanol gave 150 mg (35% yield) of amorphous, pale-yellow, 9-(3-hydroxyphenyl)xanthene (**9**), homogeneous by GC-MS, mp 170-178°C, pmr (90 MHz, $CDCl_3$): δ 1.40 (1H, br, OH), 5.21 (1H, s, H-9), 6.61-7.24 (12H, m, Aryl); cmr (22.5) MHz: δ_c 44.31 (C-9) 113.82 (C-4'), 115.39 (C-2'), 116.64 (x2, C-4), 120.86 (C-6'), 123.25 (x2, C-2), 124.22 (x2, C-8a), 127.96 (x2, C-1 or -3), 129.75 (x3, C-5' and C-3 or -1), 148.33 (C-1'), 151.15 (x2, C-4a), 155.97 (C-3'); IR (KBr): 3450 (OH), 3050-2900 (CH), 1595, 1580, and 1485 (Aryl C=C), 1240 (C-O), 770 (m-disubst.), 740 cm^{-1} (o-disubst.); UV (EtOH): λ_{max} 220 nm (ϵ 14,000), 245 (ϵ 7,200), 282 (ϵ 3,800); mass spectrum: 274.10 (18%, $M^{+\cdot}$; calc. 274.10), 181.08 (100, $M^{+\cdot}-C_6H_4OH$; calc. 181.07), 152 (15), 127 (4), 93 (4), 77 (5), 65 (17), 51 (6).

ACKNOWLEDGEMENTS

Mass spectra were recorded by Courtney Pape; some of the nmr spectra were recorded by Mike Bockman and Jan Ruzicka; valuable suggestions were made by Courtney Pape and Carlos Ramirez.

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Received, 1st November, 1982