Synthesis of 4-Arylisocoumarins (=4-Aryl-1*H*-2-benzopyran-1-ones) through Acidic Hydrolysis of (*Z*)-2-(1-Aryl-2-methoxyethenyl)benzaldehydes, Followed by Oxidation

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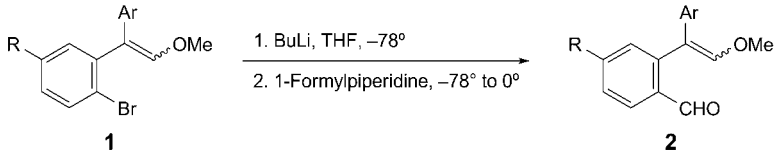
4-Arylisocoumarins (=4-aryl-1*H*-2-benzopyran-1-ones) **6** were prepared from 2-(1-aryl-2-methoxyethenyl)-1-bromobenzenes **1**. Successive treatment of these bromo styrenes with BuLi and 1-formylpiperidine gave a mixture of (*E*)- and (*Z*)-2-(1-aryl-2-methoxyethenyl)benzaldehydes **2**. Hydrolysis of (*Z*)-isomers with conc. HBr, followed by pyridinium chlorochromate (PCC) oxidation of the resulting 1*H*-2-benzopyran-1-ol derivatives **4** (and **5**), afforded the desired products.

Introduction. – Previously, we reported that 2-(1-aryl-2-methoxyethenyl)benzaldehydes **2**, easily prepared from 2-(1-aryl-2-methoxyethenyl)-1-bromobenzenes **1** (*Scheme 1*), were converted into 3-aryl-2-methoxyinden-1-one phenylhydrazones on treatment successively with $PhNHNH_2$ and conc. HBr [1]. We were interested in exploring the possibility of the transformation of these aldehydes into 4-arylisocoumarins (=4-aryl-1*H*-2-benzopyran-1-ones) **6** by acid hydrolysis, followed by oxidation of the resulting 1*H*-2-benzopyran-1-ols **4**. Herein, we report the results of our study, which provide a new procedure for the synthesis of 4-arylisocoumarins **6**. Isocoumarins have attracted much attention from organic as well as medicinal chemists[1]), because some of their derivatives have been shown to exhibit a variety of biological activities [3], and a number of biologically active compounds with the isocoumarin skeleton have been found in nature [4]. Therefore, several efficient methods for the preparation of isocoumarins have been recently reported [5]. However, there have been few reports on the synthesis of 4-substituted isocoumarins [6].

Scheme 1



1 **2**

Results and Discussion. – Our synthesis of 4-arylisocoumarins **6** from (*Z*)-2-(1-aryl-2-methoxyethenyl)benzaldehydes **2**, is outlined in *Scheme 2*. Successive treatment

[1]) For a recent excellent review, see [2].

of **1** with BuLi and 1-formylpiperidine under the conditions reported in [1] furnished **2** (*Table*). After chromatographic separation, compounds (*Z*)-**2** were treated with equiv. of conc. HBr at room temperature. The ^{1}H-NMR spectra of the mixtures after aqueous workup indicated that the products were mixtures of mainly cyclic hemiacetal derivatives, 4-aryl-1*H*-2-benzopyran-1-ols **4**, and cyclic methyl acetal derivatives, 4-aryl-1-methoxy-1*H*-2-benzopyrans **5**. The mixtures were subjected to the pyridinium chlorochromate (PCC) oxidation without any purification to give the desired products **6** in moderate yields from (*Z*)-**2** (*cf.* the *Table*). When the acid employed was conc. HI, rather complicated mixtures of products were formed, and the yields of the desired products after PCC oxidation considerably decreased (*ca.* 15%). The reactions using conc. HCl were found to give even more disappointing results. As they gave considerably complicated mixtures of products, we refrained from subjecting the mixture to the next oxidation step. It should be noted that, surprisingly, the formation of **6** from (*E*)-**2** could not be achieved, because hydrolysis of (*E*)-**2** gave results similar to those of hydrolysis of (*Z*)-**2** with conc. HCl.

Scheme 2

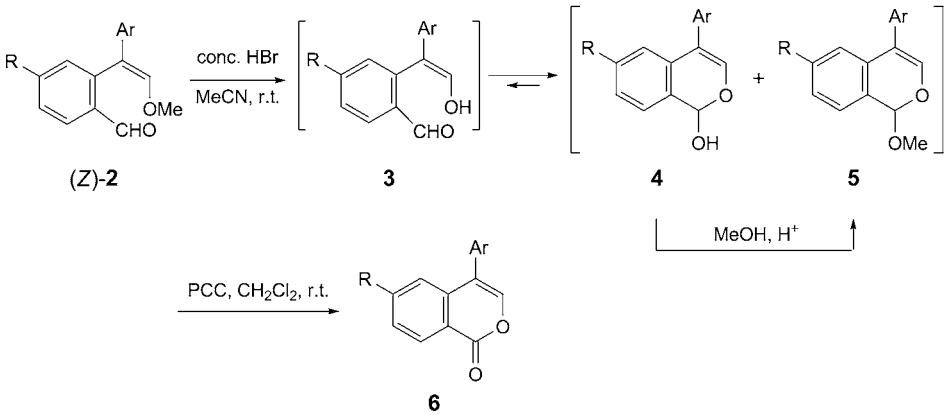


Table. *Preparation of 4-Arylisocoumarins* **6**

Entry	**1**	**2**	Yield[a])[b]) [%]	**6**	Yield[c]) [%]
1	**1a** (R = H, Ar = Ph)	**2a** [1]	79	**6a**	54
2	**1b** (R = H, Ar = 3-Me–C_6H_4)	**2b**	62	**6b**	48
3	**1c** (R = H, Ar = 4-Me–C_6H_4)	**2c** [1]	76	**6c**	49
4	**1d** (R = H, Ar = 4-Cl–C_6H_4)	**2d** [1]	79	**6d**	56
5	**1e** (R = Cl, Ar = Ph)	**2e** [1]	67	**6e**	61
6	**1f** (R = Cl, Ar = 4-Cl–C_6H_4)	**2f**	79	**6f**	58
7	**1g** (R = MeO, Ar = Ph)	**2g**	77	**6g**	32

[a]) Yields of isolated products. [b]) Each (*E*)/(*Z*) ratio is *ca.* 1 : 1. [c]) Yields of isolated products based on (*Z*)-**2**.

The formation of hemiacetal derivatives **4** only from (*Z*)-**2** may be rationalized by cyclization of (*Z*)-2-(1-aryl-2-hydroxyethenyl)benzaldehydes **3**, which were directly

and stereospecifically formed from (*Z*)-**2**. The initially formed hemiacetals **4** are partially converted into methyl acetal derivatives **5**. Both of **4** and **5** were oxidized with PCC to lead to isocoumarins **6** as depicted in *Scheme 2*.

In conclusion, we have demonstrated that 4-arylisocoumarins **6** can be prepared by a three-step sequence from 2-(1-aryl-2-methoxyethenyl)-1-bromobenzenes **1** *via* (*Z*)-2-(1-aryl-2-methoxyethenyl)benzaldehydes **2**. Although total yields of the desired products are not so high due to the inadequacy of the corresponding (*E*)-isomers for the present sequence, it may find some applications in organic synthesis because 4-arylisocoumarins are rather difficult to prepare by previous methods.

Experimental Part

General. All org. solvents were dried over appropriate drying agents and distilled prior to use. TLC: *Merck* silica gel *60 PF*$_{254}$. Column chromatography (CC): *Wako Gel* C-200E. M.p.: *Laboratory Devices MEL-TEMP II* melting point apparatus; uncorrected. IR Spectra: *Perkin–Elmer Spectrum65* FTIR spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: in $CDCl_3$ with TMS as an internal reference, with *JEOL ECP500* FT-NMR (^{1}H and ^{13}C) or *JEOL LA400* FT-NMR (^{1}H; spectrometer (at 500 or 400 (^{1}H), and 125 MHz (^{13}C)); δ in ppm, *J* in Hz. EI-MS (70 eV): with *JEOL JMS AX505 HA* spectrometer; *m*/*z* (rel. %).

2-(1-Aryl-2-methoxyethenyl)benzaldehydes **2a**, **2c**, **2d**, and **2e** were prepared from the corresponding 2-(1-aryl-2-methoxyethenyl)-1-bromobenzenes **1** [7] as described in [1]. BuLi was supplied by *Asia Lithium Corporation*. All other chemicals were commercially available.

2-[2-Methoxy-1-(3-methylphenyl)ethenyl]benzaldehyde (**2b**). The title compound was prepared from *1-bromo-2-[2-methoxy-1-(3-methylphenyl)ethenyl]benzene* (**1b**) [7] as described in [1].

Data of (E)-**2b**. Yellow oil. R_f (AcOEt/hexane 1:10) 0.41. IR (neat): 2841, 2744, 1694, 1632. ^{1}H-NMR (500 MHz): 2.29 (*s*, 3 H); 3.82 (*s*, 3 H); 6.17 (*s*, 1 H); 7.00–7.02 (*m*, 1 H); 7.18–7.19 (*m*, 3 H); 7.32 (*ddd*, *J* = 7.8, 7.5, 0.9, 1 H); 7.43 (*td*, *J* = 7.5, 0.9, 1 H); 7.55 (*td*, *J* = 7.5, 1.4, 1 H); 7.95 (*dd*, *J* = 7.8, 1.4, 1 H); 10.09 (*s*, 1 H). Anal. calc. for $C_{17}H_{16}O_2$ (252.31): C 80.93, H 6.39; found: C 81.01, H 6.42.

Data of (Z)-**2b**. Yellow oil. R_f (AcOEt/hexane 1:10) 0.35. IR (neat): 2839, 2747, 1694, 1634. ^{1}H-NMR (500 MHz): 2.78 (*s*, 3 H); .3.67 (*s*, 3 H); 6.75 (*s*, 1 H); 6.94 (*d*, *J* = 7.4, 1 H); 6.97 (*s*, 1 H); 7.01 (*d*, *J* = 7.4, 1 H); 7.15 (*t*, *J* = 7.4, 1 H); 7.21 (*d*, *J* = 7.5, 1 H); 7.40 (*t*, *J* = 7.4, 1 H); 7.55 (*ddd*, *J* = 8.0, 7.4, 1.1, 1 H); 7.99 (*d*, *J* = 8.0, 1.1, 1 H); 10.07 (*s*, 1 H). Anal. calc. for $C_{17}H_{16}O_2$ (252.31): C 80.93, H 6.39; found: C 80.82, H 6.49.

4-Chloro-2-[1-(4-chlorophenyl)-2-methoxyethenyl]benzaldehyde (**2f**). The title compound was prepared from *1-bromo-4-chloro-2-[1-(4-chlorophenyl)-2-methoxyethenyl]benzene* (**1f**) as described in [1]. Compound **1f** was prepared from 2-bromo-5-chlorobenzaldehyde according to the procedure for the preparation of **1a** [7] *via* (2-bromo-5-chlorophenyl)(4-chlorophenyl)methanol and (2-bromo-5-chlorophenyl)(4-chlorophenyl)methanone.

(2-Bromo-5-chlorophenyl)(4-chlorophenyl)methanol. Yield: 96%. Colorless oil. R_f (AcOEt/hexane 1:10) 0.34. IR (neat): 3310. ^{1}H-NMR (500 MHz): 2.40 (*d*, *J* = 3.4, 1 H); 6.10 (*d*, *J* = 3.4, 1 H); 7.15 (*dd*, *J* = 8.6, 2.3, 1 H); 7.33 (*s*, 4 H); 7.46 (*d*, *J* = 8.6, 1 H); 7.60 (*d*, *J* = 2.3, 1 H). Anal. calc. for $C_{13}H_9BrCl_2O$ (332.02): C 47.03, H 2.73; found: C 47.04, H 2.73.

(2-Bromo-5-chlorophenyl)(4-chlorophenyl)methanone. Yield: 94%. White solid. M.p. 94–97° (hexane/CH_2Cl_2). IR (KBr): 1663. ^{1}H-NMR (500 MHz): 7.32 (*d*, *J* = 2.9, 1 H); 7.35 (*dd*, *J* = 8.6, 2.9, 1 H); 7.46 (*d*, *J* = 8.6, 2 H); 7.58 (*d*, *J* = 8.6, 1 H); 7.74 (*d*, *J* = 8.6, 2 H). Anal. calc. for $C_{13}H_7BrCl_2O$ (330.00): C 47.31, H 2.14; found: C 47.08, H 2.27.

1-Bromo-4-chloro-2-[1-(4-chlorophenyl)-2-methoxyethenyl]benzene (**1f**). Yield: 89%. *Ca.* 1:1 mixture of stereoisomers. Anal. samples of each isomer was obtained by CC (SiO_2).

Data of (E)-**1f**. Colorless oil. R_f (THF/hexane 1:30) 0.47. IR (neat): 2837, 2747, 1690, 1629. ^{1}H-NMR (500 MHz): 3.83 (*s*, 3 H); 6.26 (*s*, 1 H); 7.17 (*dd*, *J* = 8.6, 2.3, 1 H); 7.22–7.35 (*m*, 5 H); 7.51 (*d*, *J* = 8.6, 1 H). Anal. calc. for $C_{15}H_{11}BrCl_2O$ (358.06): C 50.32, H 3.10; found: C 50.09, H 3.18.

Data of (Z)-**1f**. Colorless oil. R_f (THF/hexane, 1:30) 0.37. IR (neat): 2843, 2746, 1697, 1636. ^{1}H-NMR (500 MHz): 3.77 (*s*, 3 H); 6.66 (*s*, 1 H); 7.02 (*d*, *J* = 8.6, 2 H); 7.16 (*dd*, *J* = 8.6, 2.3, 1 H); 7.21 – 7.24 (*m*, 3 H); 7.56 (*d*, *J* = 8.6, 1 H). Anal. calc. for $C_{15}H_{11}BrCl_2O$ (358.06): C 50.32, H 3.10; found: C 50.23, H 3.26.

Data of (E)-**2f**. Yellow oil. R_f (AcOEt/hexane 1:15) 0.32. IR (neat): 2842, 2739, 1691, 1633. ^{1}H-NMR (500 MHz): 3.86 (*s*, 3 H); 6.25 (*s*, 1 H); 7.25 – 7.32 (*m*, 5 H); 7.42 (*dt*, *J* = 8.6, 1.1, 1 H); 7.89 (*d*, *J* = 8.6, 1 H); 9.97 (*s*, 1 H). Anal. calc. for $C_{16}H_{12}Cl_2O_2$ (307.17): C 62.56, H 3.94; found: C 62.53, H 4.11.

Data of (Z)-**2f**. Yellow oil. R_f (AcOEt/hexane 1:15) 0.25. IR (neat): 2840, 2742, 1691, 1629. ^{1}H-NMR (400 MHz): 3.76 (*s*, 3 H); 6.77 (*s*, 1 H); 7.06 (*d*, *J* = 8.8, 2 H); 7.18 (*d*, *J* = 2.0, 1 H); 7.26 (*d*, *J* = 8.8, 2 H); 7.40 (*dq*, *J* = 8.3, 1.0, 1 H); 7.93 (*d*, *J* = 8.3, 1 H); 9.96 (*s*, 1 H). Anal. calc. for $C_{16}H_{12}Cl_2O_2$ (307.17): C 62.56, H 3.94; found: C 62.31, H 3.96.

4-Methoxy-2-(2-methoxy-1-phenylethenyl)benzaldehyde (**2g**). The title compound was prepared from *1-bromo-4-methoxy-2-(2-methoxy-1-phenylethenyl)benzene* (**1g**) [8] as described reported in [1].

Data of (E)-**2g**. Yellow oil. R_f (AcOEt/hexane 1:10) 0.28. IR (neat): 2839, 2756, 1684, 1634. ^{1}H-NMR (500 MHz): 3.84 (*s*, 3 H); 3.86 (*s*, 3 H); 6.25 (*s*, 1 H); 6.80 (*d*, *J* = 2.3, 1 H); 6.96 (*dd*, *J* = 8.6, 2.3, 1 H); 7.19 (*tt*, *J* = 7.4, 1.1, 1 H); 7.29 (*dd*, *J* = 7.8, 7.4, 2 H); 7.41 (*dd*, *J* = 7.8, 1.1, 2 H); 7.96 (*d*, *J* = 8.6, 1 H); 9.96 (*s*, 1 H). Anal. calc. for $C_{17}H_{16}O_3$ (268.31): C 76.10, H 6.01; found: C 76.04, H 6.23.

Data of (Z)-**2g**. Yellow oil. R_f (AcOEt/hexane 1:10) 0.20. IR (neat): 2839, 2757, 1682, 1641. ^{1}H-NMR (500 MHz): 3.72 (*s*, 3 H); 3.82 (*s*, 3 H); 6.69 (*d*, *J* = 2.9, 1 H); 6.77 (*s*, 1 H); 6.95 (*dd*, *J* = 9.2, 2.9, 1 H); 7.15 (*dd*, *J* = 7.8, 1.1, 2 H); 7.20 (*tt*, *J* = 7.4, 1.1, 1 H); 7.27 (*dd*, *J* = 7.8, 7.4, 2 H); 7.99 (*d*, *J* = 9.2, 1 H); 9.93 (*s*, 1 H). Anal. calc. for $C_{17}H_{16}O_3$ (268.31): C 76.10, H 6.01; found: C 76.04, H 6.03.

4-Phenylisocoumarin (= *4-Phenyl-1*H-*2-benzopyran-1-one*; **6a**). *Representative Procedure.* To a stirred soln. of *2-[(Z)-2-methoxy-1-phenylethenyl]benzaldehyde* ((*Z*)-**2a**; 0.24 g, 1.0 mmol) in MeCN (8 ml) at 0° was added conc. HBr (0.17 g, 1.0 mmol). After stirring at r.t. for 4 h, sat. aq. $NaHCO_3$ (15 ml) was added, and org. materials were extracted with AcOEt (3 × 10 ml). The combined extract was dried (Na_2SO_4) and concentrated by evaporation. The residue was dissolved in CH_2Cl_2 (8 ml) and *Celite* (0.80 g), and pyridinium chlorochromate (PCC; 1.0 g, 2.0 mmol) was added under stirring at r.t. After stirring for 30 min at the same temp., the mixture was filtered by suction and the filtrate was concentrated by evaporation. The residue was purified by prep. layer chromatography (PLC; SiO_2; R_f (AcOEt/hexane 1:10) 0.30) to give **6a** (0.12 g, 54%). White solid. M.p. 95 – 98° (hexane/CH_2Cl_2) ([6]: 94 – 95°). IR (KBr): 1759, 1740, 1628, 1603. ^{1}H-NMR (500 MHz): 7.39 – 7.41 (*m*, 3 H); 7.46 – 7.51 (*m*, 4 H); 7.56 (*ddd*, *J* = 8.0, 7.4, 1.1, 1 H); 7.69 (*ddd*, *J* = 8.0, 7.4, 1.1, 1 H); 8.40 (*dd*, *J* = 8.0, 1.1, 1 H). MS: 222 (100, M^+).

4-(3-Methylphenyl)isocoumarin (= *4-(3-Methylphenyl)-1*H-*2-benzopyran-1-one*; **6b**). Yellow viscous oil. R_f (AcOEt/hexane 1:15) 0.37. IR (neat): 1732, 1630. ^{1}H-NMR (400 MHz): 2.43 (*s*, 3 H); 7.19 – 7.38 (*m*, 4 H); 7.38 (*t*, *J* = 7.8, 1 H); 7.42 (*d*, *J* = 8.3, 1 H); 7.56 (*ddd*, *J* = 8.3, 7.3, 1.5, 1 H); 7.69 (*ddd*, *J* = 8.3, 7.3, 1.5, 1 H); 8.39 (*dd*, *J* = 8.3, 1.4, 1 H). ^{13}C-NMR: 21.4; 120.7; 121.3; 124.6; 126.8; 128.4; 128.7; 129.1; 129.9; 130.4; 132.9; 134.6; 136.8; 138.6; 142.1; 162.0. MS: 236 (100, M^+). Anal. calc. for $C_{16}H_{12}O_2$ (236.27): C 81.34, H 5.12; found: C 81.20, H 5.36.

4-(4-Methylphenyl)isocoumarin (= *4-(4-Methylphenyl)-1*H-*2-benzopyran-1-one*; **6c**) [6a]. Pale-yellow solid. M.p. 98° (hexane/Et_2O). IR (KBr): 1728, 1631. ^{1}H-NMR (500 MHz): 2.44 (*s*, 3 H); 7.24 (*s*, 1 H); 7.29 (*s*, 4 H); 7.41 (*d*, *J* = 8.0, 1 H); 7.55 (*dd*, *J* = 8.0, 7.4, 1 H); 7.68 (*ddd*, *J* = 8.0, 7.4, 1.1, 1 H); 8.39 (*dd*, *J* = 8.0, 1.1, 1 H). ^{13}C-NMR: 21.2; 120.5; 121.4; 124.7; 126.4; 128.4; 129.5; 129.7; 130.0; 134.6; 137.0; 138.3; 141.1; 162.1. MS: 236 (100, M^+). Anal. calc. for $C_{16}H_{12}O_2$ (236.27): C 81.34, H 5.12; found: C 81.11, H 5.15.

4-(4-Chlorophenyl)isocoumarin (= *4-(4-Chlorophenyl)-1*H-*2-benzopyran-1-one*; **6d**) [6a]. White solid. M.p. 164 – 165° (hexane/CH_2Cl_2) ([6]: 165 – 166°). IR (KBr): 1745, 1628. ^{1}H-NMR (500 MHz): 7.25 (*d*, *J* = 8.0, 2 H); 7.33 – 7.35 (*m*, 2 H); 7.47 (*d*, *J* = 8.0, 2 H); 7.57 (*dd*, *J* = 8.0, 6.9, 1 H); 7.70 (*ddd*, *J* = 8.0, 6.9, 1.7, 1 H); 8.40 (*d*, *J* = 8.0, 1 H).

6-Chloro-4-phenylisocoumarin (= *6-Chloro-4-phenyl-1*H-*2-benzopyran-1-one*; **6e**). White solid. M.p. 126 – 128° (hexane/Et_2O). IR (KBr): 1742, 1630. ^{1}H-NMR (500 MHz): 7.30 (*d*, *J* = 8.0, 1 H); 7.39 – 7.42 (*m*, 3 H); 7.50 – 7.56 (*m*, 4 H); 8.36 (*d*, *J* = 8.0, 1 H). ^{13}C-NMR (125 MHz): 119.6; 119.9; 124.4; 128.8; 129.1; 129.1; 129.8; 131.8; 132.3; 138.3; 141.7; 143.4; 161.2. MS: 256 (100, M^+). Anal. calc. for $C_{15}H_9ClO_2$ (256.68): C 70.19, H 3.53; found: C 70.12, H 3.47.

6-Chloro-4-(4-chlorophenyl)isocoumarin (=*6-Chloro-4-(4-chlorophenyl)-1*H*-2-benzopyran-1-one*; **6f**). White solid. M.p. 200–202° (hexane/Et_2O). IR (KBr): 1745, 1630. ^{1}H-NMR (500 MHz): 7.26 (*s*, 1 H); 7.30 (*d*, *J* = 1.7, 1 H); 7.32 (*d*, *J* = 8.6, 2 H); 7.49 (*d*, *J* = 8.6, 2 H); 7.52 (*dd*, *J* = 8.6, 1.7, 1 H); 8.32 (*d*, *J* = 8.6, 1 H). ^{13}C-NMR: 118.9; 119.6; 124.1; 129.3; 129.4; 130.8; 131.0; 131.9; 135.0; 137.9; 141.9; 143.5; 161.0. MS: 290 (100, M^+). Anal. calc. for $C_{15}H_8Cl_2O_2$ (291.13): C 61.88, H 2.77; found: C 61.83, H 2.71.

6-Methoxy-4-phenylisocoumarin (=*6-Methoxy-4-phenyl-1*H*-2-benzopyran-1-one*; **6g**). Pale-yellow solid. M.p. 139–141° (hexane/CH_2Cl_2). IR (KBr): 1724, 1636, 1605. ^{1}H-NMR (500 MHz): 3.80 (*s*, 3 H); 6.78 (*dd*, *J* = 2.5, 1 H); 7.08 (*dd*, *J* = 8.8, 2.5, 1 H); 7.23 (*s*, 1 H); 7.39–7.41 (*m*, 2 H); 7.43–7.50 (*m*, 3 H); 8.32 (*dd*, *J* = 8.8, 1 H). ^{13}C-NMR: 55.6; 107.8; 114.5; 116.1; 120.5; 128.5; 128.9; 129.8; 132.4; 133.2; 139.1; 142.9; 161.8; 164.7. MS: 252 (100, M^+). Anal. calc. for $C_{16}H_{12}O_3$ (252.26): C 76.18, H 4.79; found: C 76.03, H 4.92.

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