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Bromination of Methoxybiphenylenes

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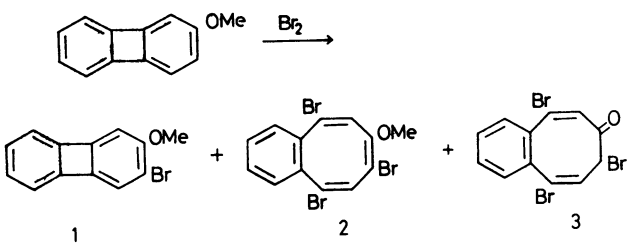
Bromination of 2-methoxybiphenylene derivatives did not give biphenyl derivatives but benzocyclooctene derivatives. 1-Methoxybiphenylene, on the other hand, was brominated to give the benzobicyclo[4.2.0]octadienone derivatives.

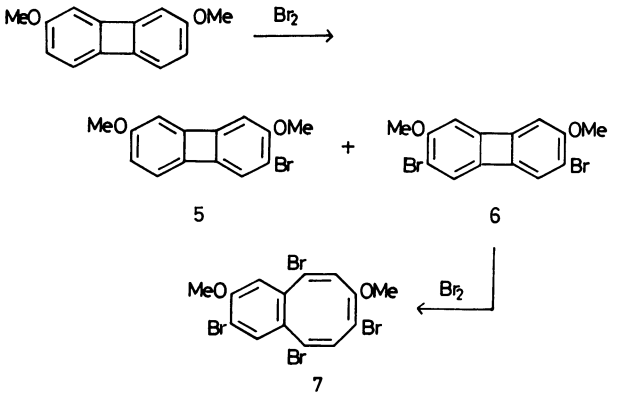
Biphenylene is a condensed ring aromatic hydrocarbon of special interest, because its central four-membered ring is expected to have contribution of an antiaromatic cyclobutadiene structure. According to expectation, biphenylene has been evidenced to have some specific reactivity in addition to the reactivity common to other condensed ring aromatics.[1] For example, biphenylene was brominated in the presence of pyridine to give a monobromobiphenylene (substitution product) in 49% yield,[2] and in the absence of the catalyst to give benzocyclooctene derivatives (benzene ring-opened products) as the main products.[3] Photobromination of biphenylene gave also a benzobicyclo[4.2.0]octadienone derivative (addition product) besides two products described above.[4] On the other hand, a 2-substituted biphenylene was brominated at the 3-position regioselectively to give a 2-substituted 3-bromobiphenylene,[1] which was reported to be brominated further with the C_{4a}–C_{4b} bond fission to give biphenyl derivatives (four-membered-ring-opened products).[5,6] We here report the systematic reexamination on bromination of methoxybiphenylenes.[7]

2-Methoxybiphenylene was treated with 1.6 molar equivalents of bromine in carbon tetrachloride at 40 °C to give 3-bromo-2-methoxybiphenylene (**1**), tribromo compound **2**, and tribromo ketone **3** in 30, 14, and 6% yields, respectively. The structure of **3** was first assigned as 5,8,10-tribromo-7,(8*H*)-benzocyclooctenone by the following spectral data. IR (KBr): 1680 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.81 (d, 1H, J=9.6 Hz, H-8), 6.73 (d, 1H, J=9.6 Hz, H-9), 7.18 (s, 1H, H-6), and 7.2—8.0 (m, 4H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 53.5 (C-8) and 185.2 (C-7). The isolation of **3** suggests an intermediate formation of 5,7,10-tribromo-8-methoxybenzocyclooctene (**2**) as its precursor. Monobromo compound **1** was further brominated in dichloromethane to give the same tribromo compound **2**, mp 118—119 °C in 70% yield. A tribromo compound having the same mp as that of **2** was previously prepared by bromination of **1** in acetic acid and assigned by McOmie and co-workers to 2′,4,6-tribromo-3-methoxybiphenyl (**4**) based on its IR and UV spectra.[5] We also reexamined the bromination of **1** under the same conditions described by the above authors[5] and obtained the same product as **2** in 43% yield, along with the starting biphenylene in 13% recovery. The ^1H NMR spectrum of **2** showed two olefinic doublets (J=1.2 Hz) at δ 6.53 and 6.66 in a similar magnetic field to the corresponding protons of 5,10-dibromobenzocyclooctene (δ 6.51, $J_{6,9}$=1.6 Hz).[3] The UV spectrum of **2** also resembles that of 5,10-dibromobenzocyclooctene rather than 2,2′-dibromobiphenyl (Fig. 1). In addition, **2** was converted with trifluoroacetic acid to tribromo ketone **3** in 63% yield, whose structure was conclusively determined by X-ray crystallographic analysis.[8] On the basis of these data the tribromo compound **2** should not be assigned to 2′,4,6-tribromo-3-methoxybiphenyl (**4**), but 5,7,10-tribromo-8-methoxybenzocyclooctene.



1 2 3

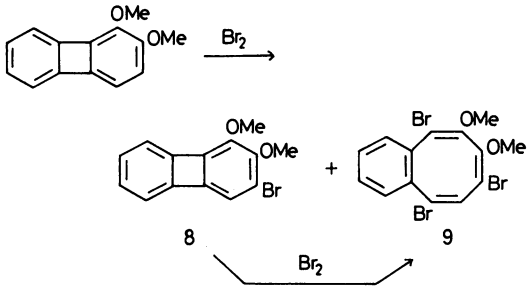
In order to generalize the fact that the further bromination of bromomethoxybiphenylenes gives brominated benzocyclooctenes, the bromination of other 2-methoxybiphenylenes was then examined. 2,7-Dimethoxybiphenylene was treated with 2 molar equivalents of bromine in dichloromethane to give 3-bromo-2,7-dimethoxybiphenylene (**5**) and 3,6-dibromo-2,7-dimethoxybiphenylene (**6**) in 30 and 20% yields, respectively, in partial agreement with McOmie *et al.*[6] who obtained only **6** in 46% yield under similar conditions. Compound **6** was further treated with 1.5 molar equivalents of bromine to give 2,5,8,10-tetrabromo-3,7-dimethoxybenzocyclooctene (**7**) in 89% yield. The ^1H NMR spectrum of **7**, like that of **2**, showed two olefinic doublets at δ 6.57 and 6.66 (J=1.2 Hz).



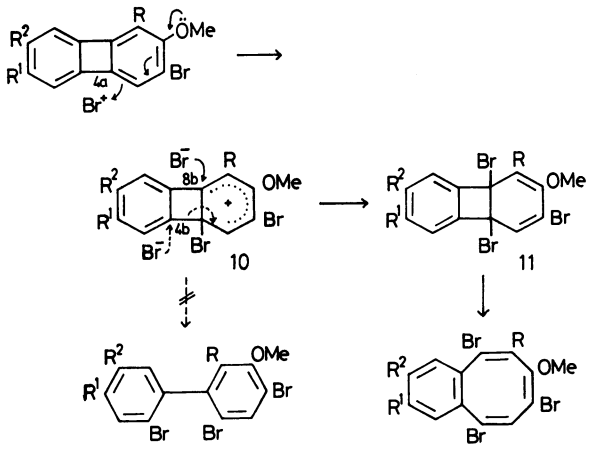
5 6 7

1,2-Dimethoxybiphenylene reacted with an excess of bromine to give 3-bromo-1,2-dimethoxybiphenylene (**8**) and 5,8,10-tribromo-6,7-dimethoxybenzocyclooctene (**9**) in 81 and 6% yields, respectively. Further bromina-

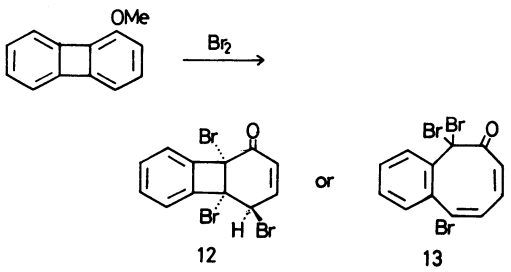
tion of **8** gave **9** in a low yield. The structure of **9** was assigned by the following ^{1}H NMR spectrum (CCl_4): δ 3.56 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 6.81 (s, 1H, H-9), and 7.44 (s, 4H, Ar–H). The UV spectra of **7** and **9** were closely similar to that of **2** (Fig. 2).



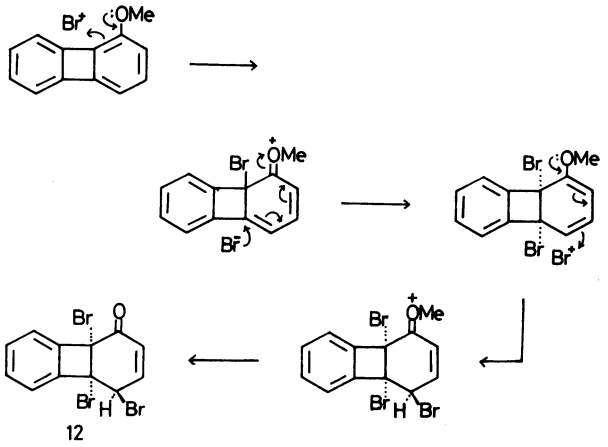
The bromination of biphenylene having one or two methoxyl groups at the 2- and other positions proceeds generally as follows. On treatment with bromine, biphenylene derivatives having an electron-releasing group at the 2-position give 3-substituted products predominantly.[1b] In agreement with this previous finding, 2-methoxy-, 1,2-dimethoxy- 2,7-dimethoxybiphenylenes undergo bromination at the 3- and 6-position to give 3-bromo and 3,6-dibromo derivatives **1**, **8**, and **6** respectively. On the other hand, biphenylene itself undergoes bromine addition followed by benzene ring-opening to give brominated benzocyclooctenes, because of latent antiaromatic character of the central four-membered ring. The above brominated methoxybiphenylenes (**1**, **6**, and **8**) are more electron-deficient than unbrominated methoxybiphenylenes and behave like biphenylene itself on further bromination: **1**, **6**, and **8** react with bromine to give first biphenylenium ions (**10**) and then dibromo adducts **11**, which undergo spontaneously ring-opening to give bromomethoxybenzocyclooctenes **2**, **7**, and **9** as shown in the following scheme. The bromide ion attacks **10** at the 4b-position and the subsequent C_{4a}–C_{4b} bond fission to **4** does not take place.



Bromination of 1-methoxybiphenylene proceeded in a somewhat different manner from that of 2-methoxybiphenylenes. Thus, 1-methoxybiphenylene was treated with an excess of bromine to give colorless crystals, mp



165—167 °C (decomp) in 25% yield, along with two kinds of unstable oils. The MS spectrum [M^+ *m/e* 404/406/408/410 (1.3/3.7/3.7/1.3%)] and IR spectrum (ν_{CO} 1683 cm^{-1}) suggest that the product is tribromo ketone **12** or **13**. The following ^{1}H NMR spectrum of the tribromo ketone is consistent with the structure **12**, rather than **13**: δ 5.35 (d, 1H, J=6.8 Hz), 5.93 (d, 1H, J=10.7 Hz), 6.98 (dd, J=10.7 and 6.5 Hz), and 7.1—7.8 (m, 4H, Ar–H). The ^{13}C NMR spectrum gave a further structual support showing the presence of three aliphatic carbon (47.7, 70.7, and 72.0 ppm) and two olefinic carbon signals (124.6 and 142.3 ppm). The stereochemistry of **12** was suggested by setting up the molecular model having a minimum steric strain. The formation of **12** on bromination of 1-methoxybiphenylene would be explained by the pathway described below.



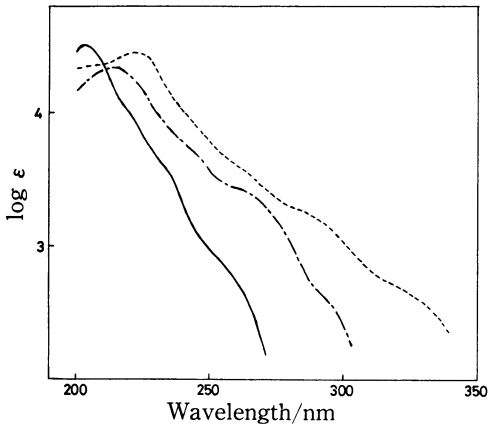


Fig. 1. UV spectra of 2,2′-dibromobiphenyl (——), 5,10-dibromobenzocyclooctene (– – –), and tribromo compound **2** (------).

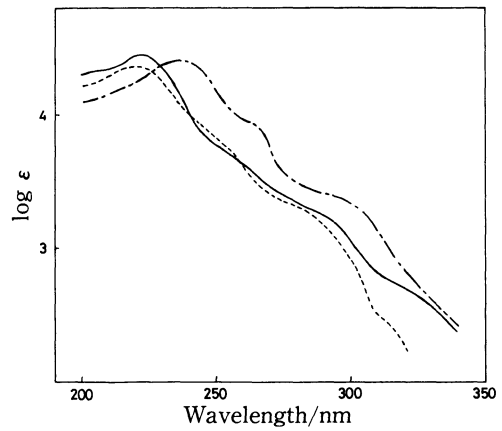


Fig. 2. UV spectra of **2** (——), **7** (– – –), and **9** (------).

The easy conversion of methoxybiphenylenes to methoxybenzocyclooctene derivatives stimulated the reexamination on bromination of 2,3-dimethoxybiphenylene, because the resulting bromodimethoxybenzocyclooctenes would be useful precursors to new benzocyclooctene-7,8-diones. It was previously reported that bromination of 2,3-dimethoxybiphenylene gave 1,4-dibromo-2,3-biphenylenedione.[6] The present reexamination on bromination of 2,3-dimethoxybiphenylene under various conditions, however, gave the same result as previously reported, no expected benzocyclooctene-7,8-dione being detected.

Experimental

Bromination of 2-Methoxybiphenylene in Carbon Tetrachloride. To a solution of 2-methoxybiphenylene (2.03 g, 11 mmol) in carbon tetrachloride (20 ml) was added a solution of bromine in carbon tetrachloride (37 g of 5% w/w solution, 11 mmol) under nitrogen. The mixture was stirred for 10 min at room-temperature and warmed at 40 °C for 50 min. A solution of bromine in carbon tetrachloride (10 g of 5% w/w solution, 6 mmol) was further added to the solution, whereupon the color of bromine was discharged almost instantaneously. The solution was washed with a saturated aq solution of sodium hydrogencarbonate and dried (anhyd $MgSO_4$). The yellow-brown oil which remained after evaporation was chromatographed on silica gel by elution with hexane–toluene (2 : 1). The following products were eluted successively. 3-Bromo-2-methoxybiphenylene (**1**) (860 mg, 30%): yellow needles, mp 100—101 °C (from cyclohexane–ethanol) (lit,[6] 102—103 °C). IR (KBr): 1420, 1254, 1233, and 746 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.92 (s, 3H, OCH_3), 6.3—6.9 (m, 6H). 5,7,10-Tribromo-8-methoxybenzocyclooctene (**2**) (538 mg, 14%): colorless needles, mp 118—119 °C (from ethanol–cyclohexane). Found: C, 37.01; H, 2.15%. Calcd for $C_{13}H_9Br_3O$: C, 37.09; H, 2.15%. UV (EtOH): 223 nm (log ε 4.46). IR (KBr): 1637, 1620, 1340, 1251, 1189, and 768 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.66 (s, 3H, OCH_3), 6.53 (d, 1H, J=1.2 Hz, H-6) 6.66 (d, 1H, $J_{6,9}$=1.2 Hz, H-9), 7.38 (s, 4H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 57.2 (q), 98.8 (s), 122.7 (s), 126.2 (s), 128.3 (d), 128.6 (d), 128.9 (d), 129.1 (d), 129.5 (d), 133.1 (d), 136.7 (s), 137.4 (s), and 149.8 (s). MS (70 ev): M^+ [*m/e* 418/420/422/424 (3.5/8/8/3.5%)], M^+-Br [*m/e* 339/341/343 (52/100/49%)]. 5,8,10-Tribromo-7,(8*H*)-benzocyclooctenone (**3**) (274 mg, 6%): yellow cubes, mp 138—139 °C (from hexane–acetone). Found: C, 35.42; H, 1.77%. Calcd for $C_{12}H_7Br_3O$: C, 35.42; H, 1.73%. UV (CH_3CN): 213 (log ε 4.24) and 225sh nm (4.20). IR (KBr): 1683, 1595, 1138, 965, 860, and 765 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.81 (d, 1H, J=9.5 Hz, H-8), 6.73 (d, 1H, J=9.5 Hz, H-9), 7.18 (s, 1H, H-6), and 7.2—8.0 (m, 4H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 53.6 (d, C-8), 120.7 (s), 128.3 (d), 129.6 (d), 130.3 (d), 131.0 (d), 132.5 (d), 133.5 (d), 134.3 (s), 137.0 (s), 137.9 (s), and 185.2 (s, C-7). MS (75 eV): M^+ [*m/e* 404/406/408/410 (0.02/0.04/0.04/0.02%)], M^+-2Br [*m/e* 246/248 (100/97%)].

5,7,10-Tribromo-8-methoxybenzocyclooctene (2). To a solution of **1** (0.25 g, 0.96 mmol) in dry dichloromethane (10 ml) was gradually added a solution of bromine (0.23 g, 2.8 mmol) in dry dichloromethane (7 ml) at 0 °C under nitrogen. The mixture was then kept for 1 h at a room-temperature. After evaporation, the residue was subjected to TLC on silica gel by elution with hexane–benzene. **2** (0.28 g, 70%) was obtained as colorless crystals, mp 118—120 °C.

5,8,10-Tribromo-7(8H)-benzocyclooctenone (3). To a solution of **2** (28 mg) in a small amount of chloroform-*d*, was added trifluoroacetic acid (0.5 ml). The solution was then warmed to 70—80 °C. After evaporation, the crystalline residue was recrystallized from hexane–acetone giving the tribromo ketone **3** (17 mg, 63%).

Bromination of 2,7-Dimethoxybiphenylene. To a solution of 2,7-dimethoxybiphenylene (0.25 g, 1.2 mmol) in dry dichloromethane (10 ml) was added a solution of bromine in dichloromethane (20 ml of 0.3% v/v solution, 1.2 mmol) at −50 °C under nitrogen. The solution was then stirred for 1 h at a room-temperature. After evaporation, the residue was passed through a short column packed with alumina in order to remove a tar. The yellow crystals obtained were purified by TLC on silica gel by elution with benzene, affording the following products, the unreacted starting material (28 mg, 11%) and 3-bromo-2,7-diemthoxybiphenylene (**5**) (102 mg, 30%), colorless crystals, mp 100—101 °C (from hexane–acetone). Found: C, 57.66; H, 3.72%. Calcd for $C_{14}H_{11}BrO_2$: C, 57.75; H, 3.82%. UV (CH_3CN): 250 (log ε 4.56), 258 (4.85), and 369 nm (3.67). IR (KBr): 1615, 1575, 1473, 1456, 1418, 1280, 1270, 1224, 1029, 1013, and 800 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.73 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.0—6.6 (m, 3H), 6.45 (s, 1H, H-8), and 6.72 (s, 1H, H-1). MS (70 eV): M^+ [*m/e* 290/292 (100/98%)], M^+-CH_3 [*m/e* 275/277 (70/68%)], and M^+-CH_3-CO [*m/e* 247/249 (44/43%)]. 3,6-Dibromo-2,7-dimethoxybiphenylene (**6**) (86 mg, 20%), colorless leaflets, mp 166—168 °C (lit,[6] 170—171 °C). ^1H NMR ($CDCl_3$): δ 3.84 (s, 6H, OCH_3), 6.47 (s, 2H, H-1,8), and 6.73 (s, 2H, H-4,5).

2,5,8,10-Tetrabromo-3,7-dimethoxybenzocyclooctene (7). To a solution of **6** (86 mg, 0.23 mmol) in dry dichloromethane (10 ml) was added a solution of bromine in dichloromethane (6 ml of 0.5% v/v solution, 0.58 mmol). The solution was stirred for 1 h at a room-temperature, then washed with water, and dried (anhyd $MgSO_4$). After evaporation, the residue was purified through TLC on silica gel by elution with toluene–hexane (1 : 1). The title compound (109 mg, 89%) was obtained as yellow cubes, mp 200—203 °C (decomp). Found: C, 31.96; H, 1.97%. Calcd for $C_{14}H_{10}Br_4O_2$: C, 31.73; H, 1.90%. UV (CH_3CN): 220sh (log ε 4.15) and 266 nm (4.41). IR (KBr): 2950, 1638 (w), 1620 (w), 1592, 1497, 1355, 1248, and 1049 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.65 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.57 (d, 1H, J=1.3 Hz, H-6), 6.66 (d, 1H, J=1.3 Hz, H-9), 6.80 (s, 1H, H-4), and 7.64 (s, 1H, H-1). MS (75 eV): M^+ [*m/e* 526/528/530/532/534 (0.8/3.0/5.5/3.0/0.8%)] and M^+-Br [*m/e* 447/449/451/453 (35/100/95/35%)].

Bromination of 1,2-Dimethoxybiphenylene. To a solution of 1,2-dimethoxybiphenylene (0.25 g, 1.2 mmol) in dry dichloromethane (40 ml) was slowly added a solution of

bromine in dichloromethane (27 ml of 0.5% v/v solution, 2.7 mmol) under ice-cooling. After being stirred for 1 h, the solution was washed with water and dried (anhyd $MgSO_4$). The solvent was evaporated and the resulting yellow oil was purified through TLC on silica gel by elution with hexane–benzene. 3-Bromo-1,2-dimethoxybiphenylene (**8**) (0.25 g, 81%), colorless crystals, mp 67—68 °C (from hexane–acetone). Found: C, 57.66; H, 3.72% . Calcd for $C_{14}H_{11}BrO_2$: C, 57.75; H, 3.81%. UV (CH_3CN): 257 (log ε 4.56), and 282 nm (4.09). IR (KBr): 2970, 1587, 1475, 1396, 1248, 1028, and 746 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.81 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 6.55 (s, 1H, H-4), and 7.44 (s, 4H, Ar–H). MS (75 eV): M^+ [*m/e* 290/292 (100/100%)] and M^+-CH_3 [*m/e* 275/277 (47/44%)]. 5,7,10-Tribromo-8,9-dimethoxybenzocyclooctene (**9**) (29 mg, 6%), yellow leaflets, mp 116—117 °C (from hexane–acetone). Found: C, 37.33; H, 2.51%. Calcd for $C_{14}H_{11}Br_3O_2$: C, 37.28; H, 2.46%. UV (EtOH): 220 nm (log ε 4.37). IR (KBr): 2970, 1307, 1294, and 1009 cm^{-1}. ^1H NMR (CCl_4): δ 3.59 (s, 3H, OCH_3), 3.71 (OCH_3), 6.81 (s, 1H, H-9), and 7.44 (s, 4H, Ar–H). MS (70 eV): M^+ [*m/e* 448/450/452/454 (3.2/9.2/9.2/3.2%)], M^+-Br [*m/e* 367/369/371 (37/76/38%)] and M^+-2Br [*m/e* 290/292 (96/100%)].

*5,7,10-Tribromo-8,9-dimethoxybenzocyclooctene (**9**).* To a solution of 3-bromo-1,2-dimethoxybiphenylene (30 mg, 0.1 mmol) was added a solution of bromine (25 mg, 0.16 mmol) in dichloromethane (1.6 ml) under stirring. The solution was stirred for 3 h at a room-temperature. After the usual work-up, followed by TLC on silica gel by elution with benzene–hexane, the oily product was separated into the title compound (9 mg, 19%) and the starting material (14 mg, 47%).

*4,4a,8b-Tribromo-1,4,4a,8b-tetrahydrobiphenylen-1-one (**12**).* To a solution of 1-methoxybiphenylene (0.10 g, 0.55 mmol) in dichloromethane (5 ml) was added under stirring a solution of bromine in dichloromethane (0.5%v/v solution) at 0 °C under nitrogen until the bromine-color of the reaction mixture remained unchanged (27 ml, 2.6 mmol). The solution was then stirred for 2 h at a room-temperature. After the usual work-up, an orange oil obtained was purified by measn of TLC by elution with toluene. In addition to an unstable red oil (55 mg) and an unstable orange oil (44 mg) [IR (Neat): 1697, 1668, and 757 cm^{-1}, ^1H NMR ($CDCl_3$): δ 6.34 (d, 1H, J= 10.3 Hz), 7.01 (d, 1H, J=10.4 Hz), 7.59 (s, 4H), and 7.1—7.6 (m)], the title compound (55 mg, 25%) was obtained as colorless crystals, mp 165—167 °C (decomp) from hexane). Found: C, 35.31; H, 1.77%. Calcd for $C_{12}H_7Br_3O$: C, 35.42; H, 1.74%. UV (CH_3CN): 257 (log ε 4.56) and 282 nm (4.09). IR (KBr): 1683, 1611, 1467, 800, and 750 cm^{-1}. ^1H NMR ($CDCl_3$): δ 5.35 (d, 1H, J=6.8 Hz, H-5), 5.93 (d, 1H, J= 10.7 Hz, H-3), 6.98 (dd, 1H, J=10.7 and 6.8 Hz, H-4), and 7.1—7.8 (m, 4H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 47.7 (d), 70.7 (s), 72.0 (s), 121.3 (d), 123.0 (d), 124.6 (d), 131.9 (d), 132.0 (d), 141.6 (s), 142.3 (d), 143.3 (s), and 186.9 (s). MS (70 eV): M^+ [*m/e* 404/406/408/410 (0.4/1.0/1.0/0.4%)], M^+-Br [*m/e* 325/327/329 (18/38/18%)], $M^+-Br-CO$ [*m/e* 297/299/301 (13/26/13%)], and M^+-2Br [*m/e* 246/248 (40/38%)], and $M^+-3Br-CO$ [*m/e* 139 (100%)].

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8) The details of the X-ray analysis of **3** will be published in the subsequent paper in this series.