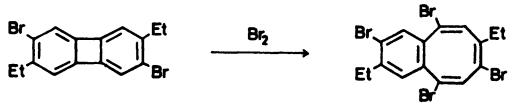
Bromination of Biphenylene Derivatives Having an Electron-releasing Substituent. A Preferential Formation of Benzocyclooctene Derivatives

Hiroto KIDOKORO, Yuko SAITO, Masaru SATO, Seiji EBINE,* Sadao SATO,†
Tadashi HATA,† and Chihiro TAMURA†
Department of Chemistry, Saitama University, Urawa, Saitama 338
†*Analytical and Metabolic Research Laboratories, Sankyo Co. Ltd., 1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140*
(Received September 25, 1982)

3-Substituted 2-bromobiphenylenes were brominated to give benzocyclooctene or 7(8*H*)-benzocyclooctenone derivatives, but not biphenyl derivatives. The structure of 5,8,10-tribromo-7(8*H*)-benzocyclooctenone was determined by X-ray diffraction analysis.

Biphenylene itself prefers an addition reaction to a substitution reaction on treatment with bromine,[1] probably because biphenylene has a partial anti-aromaticity in the central four-membered ring. On the other hand, biphenylene derivatives having an electron-releasing substituent at the 2-position undergo a predominant bromine-substitution reaction at the 3-position.[1] Further bromination of monobrominated biphenylene derivatives was previously reported to give biphenyl derivatives,[2,3] but the reaction product on bromination of 2-bromo-3-methoxybiphenylene was later corrected by us to be benzocyclooctene derivatives.[4] We now report a reexamination of bromination of 2,6-diethyl-, 2-acetoxy-, and 2-acetamidobiphenylenes.[5]

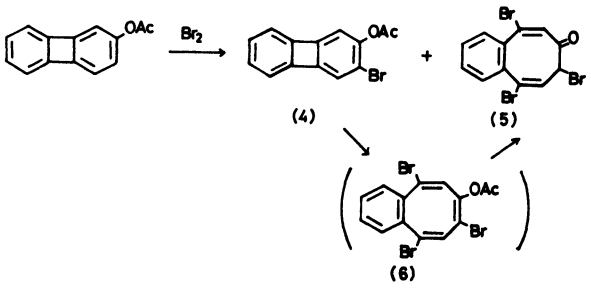
It was reported that the bromination of 2-ethylbiphenylene gave an inseparable mixture of mono- and dibrominated products.[6] On the other hand, 2,6-diethylbiphenylene was brominated in dichloromethane to give 3,7-dibromo-2,6-diethylbiphenylene (**1**) in moderate yield, which was further brominated with an excess of bromine to give 3,5,8,10-tetrabromo-2,7-diethylbenzocyclooctene (**2**) in 70% yield. The structure of **2** was assigned by electronic and ^{1}H-NMR spectral analogy to 5,8,10-tribromo-7-methoxybenzocyclooctene (**3**).[4,5] Thus, **2** showed a ^{1}H-NMR spectrum having two olefinic multiplets at δ=6.58 and 6.74.



(**1**) (**2**)

2-Acetoxybiphenylene was treated with 2 equivalents of bromine at room temperature to give a small amount of the monobrominated product **4** and tribromo ketone **5** in 34% yield. The structure of **4** was assigned to 2-acetoxy-3-bromobiphenylene by its ^{1}H-NMR spectrum: δ=2.32 (s, 3H, $OCOCH_3$), 6.48 (s, 1H, H-1), and 6.5—7.0 (m, 5H, H-4 and Ar–H). Tribromo ketone **5** was the same product with that obtained on bromination of 2-methoxybiphenylene,[4] and was probably formed by the action of a trace of acid on intermediately formed 7-acetoxy-5,8,10-tribromobenzocyclooctene (**6**). The result suggests that bromination of **4** gives **6** easily.

Bromination of 2-acetamidobiphenylene was reported to give 2-acetamido-3-bromobiphenylene (**7**) in 65% yield, which was further brominated to give a biphenyl derivative.[3] We reexamined the reaction of 2-acetamidobiphenylene with an excess of bromine in acetic



acid, and obtained 5,8,10-tribromo-7(8*H*)-benzocyclooctenone (**5**) although in low yield, in addition to a tribromo compound (**A**) (mp 156—157 °C). (**A**) was previously assigned as 3-acetamido-2′,4,6-tribromobiphenyl (**9**) by Baker *et al.*, but the above result suggests that (**A**) is a benzocyclooctene derivative which transforms easily to **5** on acid hydrolysis. (**A**) was alternatively obtained on bromination of **6** in dichloromethane at room temperature in high yield and was converted on treatment with 48% hydrobromic acid in boiling ethanol to **5** in 80% yield. We reprepared (**A**) according to Baker and co-workers' direction,[3] and found it to have a ^{1}H-NMR having two olefinic doublets at δ=6.73 and 6.94 (J=1.3 Hz) and an electronic spectrum closely similar to those of **2** and **3** (Fig. 1), proving that (**A**) is 7-acetamido-5,8,10-tribromobenzocyclooctene (**8**).

We prepared **9** in the following manner. The reaction of *m*-nitrobenzenediazonium tetrafluoroborate with bromobenzene in the presence of 18-crown-6 gave a

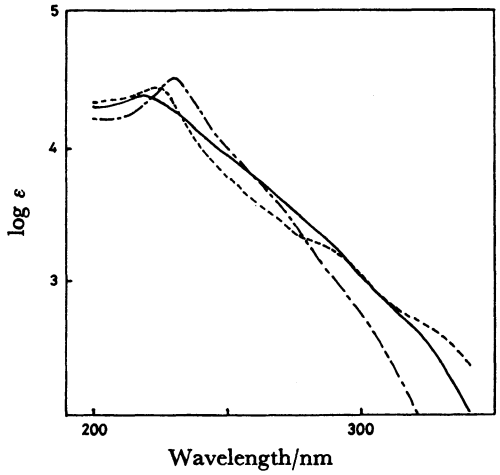
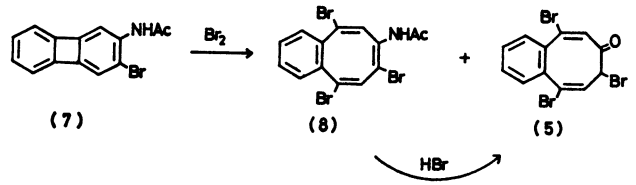


Fig. 1. Electronic spectra of **3** (------), **2** (·—·—·), and **8** (——).



mixture of 2′-bromo- and 4′-bromo-3-nitrobiphenyl in good yield. The former product (separated in 13% yield) was converted by reduction and successive acetylation to 3-acetamido-2′-bromobiphenyl, which was brominated, according to the procedure described by Baker *et al.*, to give **9**, colorless needles, mp 117—118 °C. The ^{1}H-NMR of **9** showed the following signals: δ=2.26 (s, 3H, $COCH_3$), 7.15—7.55 (m, 4H, H-3′—H-6′), 7.70 (broad s, 1H, NH), 7.97 (s, 1H, H-2), and 8.45 (s, 1H, H-5). **9** gave an IR spectrum different from that of **8**. Thus, **8** was unequivocally proved not to be **9**. Ultimately, the structure of **5** was determined by an X-ray crystallographic analysis (see below).

There seems to be a common trend on bromination of biphenylene derivatives having an electron-releasing substituent at the C_2 position. In these derivatives, bromination gives exclusively 3-substituted 2-bromobiphenylenes.[1] Further bromination of the 2-substituted 3-bromobiphenylenes takes place at the C_{4a}-position, forming an intermediate biphenylenium ion, similarly to the bromination of biphenylene itself, because the C_3-position is already occupied by the bromo substituent and the electron-releasing ability of the 2-substituent is cancelled by the electron-withdrawing bromo substituent. Successive addition of a bromide ion on the intermediate biphenylenium ion formed occurs exclusively at the C_{8b}-position, not at the C_{4b}-position. The resulting dibromo adducts undergo a spontaneous ring-opening to give benzocyclooctene derivatives. The bromide ion attack on the biphenylenium ion at the C_{4b}-position and subsequent C_{4a}–C_{4b} bond fission to biphenyl derivatives do not take place. An exceptional example that bromine attacked the unsubstituted benzene ring of 2-substituted biphenylene was presented in bromination of 2-ethylbiphenylene to 3,6- and 3,7-dibromo-2-ethylbiphenylenes.[6]

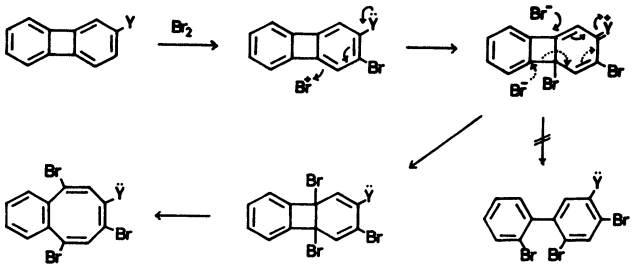


Table 1. Fractional atomic coordinates ($\times 10^4$), with estimated standard deviations in parentheses

Atom	x	y	z
C(1)	264(15)	1101(10)	4226(9)
C(2)	−672(14)	555(12)	3889(11)
C(3)	−269(16)	−143(11)	3517(11)
C(4)	1076(17)	−340(9)	3528(9)
C(5)	3570(16)	−106(8)	3916(9)
C(6)	4305(14)	195(9)	3682(10)
C(7)	5088(13)	972(8)	3268(7)
C(8)	3960(14)	1625(7)	3228(8)
C(9)	3611(15)	1899(8)	4053(8)
C(10)	2637(14)	1574(7)	4527(8)
C(4A)	2100(14)	195(7)	3858(8)
C(10A)	1660(13)	938(8)	4199(8)
O(7)	6302(10)	1087(8)	3031(7)
Br(5)	3636(2)	−1204(1)	4375(1)
Br(8)	4569(2)	2536(1)	2509(1)
Br(10)	2349(2)	1958(1)	5626(1)

Table 2. Bond lengths and angles with estimated standard deviations in parentheses

Bond length	l/Å		l/Å
C(1)–C(2)	1.378(23)	C(7)–C(8)	1.524(18)
C(1)–C(10A)	1.376(19)	C(7)–O(7)	1.248(16)
C(2)–C(3)	1.340(26)	C(8)–C(9)	1.430(18)
C(3)–C(4)	1.340(23)	C(8)–Br(8)	1.963(13)
C(4)–C(4A)	1.421(20)	C(9)–C(10)	1.318(19)
C(5)–C(6)	1.344(20)	C(10)–C(10A)	1.496(18)
C(5)–C(4A)	1.506(20)	C(10)–Br(10)	1.883(12)
C(5)–Br(5)	1.931(13)	C(4A)–C(10A)	1.391(18)
C(6)–C(7)	1.452(20)		
Bond angle	ϕ/°		ϕ/°
C(2)–C(1)–C(10A)	120.5(11)	C(7)–C(8)–Br(8)	109.6(7)
C(1)–C(2)–C(3)	121.9(16)	C(9)–C(8)–Br(8)	112.0(5)
C(2)–C(3)–C(4)	118.6(15)	C(8)–C(9)–C(10)	124.9(12)
C(3)–C(4)–C(4A)	122.3(11)	C(9)–C(10)–C(10A)	121.8(8)
C(6)–C(5)–C(4A)	134.6(11)	C(9)–C(10)–Br(10)	120.5(7)
C(6)–C(5)–Br(5)	114.5(8)	C(10A)–C(10)–Br(10)	117.5(7)
C(4A)–C(5)–Br(5)	110.9(7)	C(4)–C(4A)–C(5)	118.6(8)
C(5)–C(6)–C(7)	127.7(14)	C(5)–C(4A)–C(10A)	123.3(11)
C(6)–C(7)–C(8)	119.4(11)	C(4)–C(4A)–C(10A)	117.7(13)
C(6)–C(7)–O(7)	116.4(11)	C(1)–C(10A)–C(4A)	118.7(11)
C(8)–C(7)–O(7)	123.8(9)	C(1)–C(10A)–C(10)	118.4(8)
C(7)–C(8)–C(9)	110.3(7)	C(10)–C(10A)–C(4A)	122.9(14)

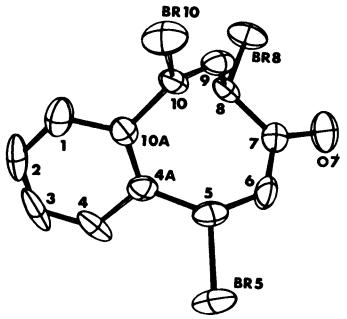


Fig. 2. Molecular conformation and atomic labelling.

TABLE 3. TORSION ANGLES OF THE EIGHT-MEMBERED RING

Torsion angle	ϕ/°	
	This study	Boat form of cyclooctane
C(4a)–C(5)–C(6)–C(7)	−0.2	0.0
C(5)–C(6)–C(7)–C(8)	13.6	73.5
C(6)–C(7)–C(8)–C(9)	63.6	0.0
C(7)–C(8)–C(9)–C(10)	−90.7	−73.5
C(8)–C(9)–C(10)–C(10a)	−7.8	0.0
C(9)–C(10)–C(4b)–C(4a)	57.6	73.5
C(10)–C(10a)–C(4a)–C(5)	10.6	0.0
C(10a)–C(4a)–C(5)–C(6)	−57.2	−73.5

Crystal and Molecular Structures of ***5***. The geometrical aspects of the molecule and the atomic numbering are shown in Fig. 2. Bond lengths and angles, and torsion angles are given in Tables 2 and 3, respectively.

The conformation of the eight-membered ring can be described as an approximation to the boat form, although there are some significant deviations. A comparison of the torsion angles found in this study with those calculated for the boat conformation of cyclooctane by Hendrickson,[9] shows that the major difference is at the C(7)–C(6) and C(7)–C(8) bonds attached to the carbonyl group. This may be due to the conjugating effect between the carbonyl group and adjacent double bonds, and these related four atoms, C(5), C(6), C(7), and O(7), are almost planar with a maximum deviation of 0.077 Å at C(6). Thus, the *endo*-cyclic bond angles of the eight-membered ring range from 134.6° (C(4a)–C(5)–C(6)) to 110.3° (C(7)–C(8)–C(9)), corresponding to regular octahedral and tetrahedral angles, respectively. The Br(8) atom is located at the equatrial position of the eight-membered ring.

Experimental

*3,7-Dibromo-2,6-diethylbiphenylene (**1**).* To a solution of 2,6-diethylbiphenylene[6] (0.20 g, 0.96 mmol) in dichloromethane (20 ml) was added a solution of bromine (19.7 ml of 0.5% v/v solution, 1.9 mmol) in dichloromethane under ice-cooling. The solution was stirred for 1 h at room temperature, then poured into water and extracted with dichloromethane. After drying over anhyd sodium sulfate the extract was evaporated. The crystalline residue was recrystallized from acetone–hexane. The title compound (128 mg, 36%) was obtained as yellow needles, mp 165—166 °C. Found: C, 52.72; H, 3.91%. Calcd for $C_{16}H_{14}Br_2$: C, 52.49; H, 3.85%. UV (EtOH): 210.2 (log ε 3.91), 252 (4.61), 261 (5.00), and 372 nm (3.82). IR (KBr): 2950, 1555, 1417, and 880 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ=1.15 (t, 6H, J=7.5 Hz, CH_3), 2.62 (q, 4H, J=8 Hz, CH_2), 6.58 (s, 2H, H-1 and H-5), and 6.84 (s, 2H, H-4 and H-8). MS (70 eV): *m/e* 364 (M^+, 84%), 349 (M^+ +2, 100%).

*3,5,8,10-Tetrabromo-2,7-diethylbenzocyclooctene (**2**).* To a solution of **1** (0.12 g, 0.33 mmol) in dry dichloromethane (10 ml) was added a solution of bromine (8.4 ml of 0.5% v/v solution, 0.81 mmol) in dichloromethane. The solution was stirred for 4 h at room temperature. The color of bromine did not disappear. The solution was washed with aq sodium hydrogencarbonate and dried over anhyd sodium sulfate. After evaporation, the crude crystalline residue was recrystallized from acetone–hexane. The title compound (116 mg, 70%) was obtained as pale yellow cubics, mp 133—135 °C. Found: C, 36.29; H, 2.39%. Calcd for $C_{16}H_{11}Br_4$: C, 36.54; H, 2.68%. UV (EtOH): 230 nm (log ε 4.62). IR (KBr): 2950, 1610, 1330, 950, and 640 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ=0.88 (t, 3H, J=8.0 Hz, CH_3), 1.26 (t, 3H, J=7.0 Hz, CH_3), 1.9—2.5 (m, 2H, CH_2), 2.77 (q, 2H, J=7.3 Hz, CH_2), 6.58 (m, 1H, H-4), 6.74 (m, 1H, H-7), 7.30 (s, 1H, H-6′), and 7.58 (s, 1H, H-3′). ^{13}C-NMR ($CDCl_3$): δ=11.4 (q), 13.7 (q), (29.0 (t), 29.1 (t), 115.5 (s), 119.2 (s), 121.9 (s), 125.1 (s), 129.7 (d), 132.8 (d), 134.8 (d), 135.8 (s), 136.4 (s), 142.4 (s), and 144.2 (s). MS (70 eV): *m/e* 522 (M^+, 0.01%), 442 (M^+ −Br, 5.4%), 362 (M^+ −2Br, 13.5%), and 29 (Et^+, 100%).

Bromination of 2-Acetoxybiphenylene. To a solution of 2-acetoxybiphenylene[7] (0.20 g, 0.95 mmol) in dichloromethane (20 ml) was added a solution of bromine (0.30 mg, 1.9 mmol) in dichloromethane (19.5 ml) under ice-cooling. The solution was stirred for 1.5 h, then washed with aq sodium hydrogencarbonate, and dried over anhyd sodium sulfate. After evaporation, the oily residue was subjected to TLC on silica gel by elution with benzene–ethyl acetate. 5,8,10-Tribromo-7(8*H*)-benzocyclooctenone (**5**) (132 mg, 35%)[4] was obtained, along with an oily mixture. The latter oil was treated three times with methanol to form a small amount of 2-acetoxy-3-bromobiphenylene as yellow needles, mp 125—126 °C. Found: C, 58.39; H, 3.04%. Calcd for $C_{14}H_9BrO_2$: C, 58.15; H. 3.13%. UV (EtOH): 245 (log ε 4.60), 254 (4.97), 345 (3.47), and 365 nm (3.67). IR (KBr): 1765, 1420, 1200, and 745 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ=2.32 (s, 3H, $COCH_3$), 6.48 (s, 1H, H-1), and 6.5—7.0 (m, 5H). MS (70 eV): *m/e* 288 (M^+, 2.3%), 246 (M^+ −CH_2CO, 34%), 139 (M^+−Br−CH_2CO−CO, 100%) and 138 (M^+ −Br−CH_3CO−CO).

Bromination of 2-Acetamidobiphenylene. To a solution of 2-acetamidobiphenylene[8] (0.33 g, 1.6 mmol) in acetic acid (30 ml) was added a solution of bromine (2 ml of 10% v/v solution, 3.8 mmol) in the same solvent. The solution was stirred for 2 h at 80 °C, then poured into water (150 ml), and extracted three times with ether. The extract was dried over anhyd magnesium sulfate. After evaporation, the residue was chromatographed on silica gel by elution with benzene–ethyl acetate. One of the products obtained was **5** (64 mg, 10%) (mp 138—139 °C).[4] The other was **8** (colorless crystals, mp 155—156 °C) (177 mg, 25%). Found: C, 37.54; H, 2.23; N, 3.03%. Calcd for $C_{14}H_{10}Br_3NO$: C, 37.54; H, 2.25; N, 3.13%. IR (KBr): 1655, 1620, 1292, and 940 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ=2.03 (s, 3H, $COCH_3$), 6.73 (d, 1H, J=1.3 Hz, H-4), 6.94 (d, 1H, J=1.3 Hz, H-7), 7.3 (broad s, 1H, NH), and 7.44 (s, 4H, Ar–H). ^{13}C-NMR ($CDCl_3$): δ=29.4 (q), 122.2 (s), 125.9 (s), 129.1 (d), 129.5 (d), 129.6 (d), 130.3 (d), 132.3 (d), 133.9 (s), 136.6 (s) 138.3 (s), 139.7 (s), and 145.2 (s), MS (70 eV): *m/e* 445 (M^+, 0.8%), 366 (M^+ −Br, 16%), 323 (M^+−Br−CH_3CO, 38%), and 246 (M^+−2Br−CH_2CO,

100%).

5,8,10-Tribromo-7(8H)-benzocyclooctenone (5). To a solution of 2-acetamido-3-bromobiphenylene (58 mg, 0.2 mmol) in dry dichloromethane (7 ml) was added a solution of bromine (4 ml of 0.5% v/v solution, 0.38 mmol) under ice-cooling. The solution was stirred for 2 h at room temperature. After the usual work-up, the residue obtained was purified by TLC on silica gel by elution with benzene–dichloromethane. The title compound (85 mg, 94%) was obtained.

A solution of **8** (53 mg, 0.12 mmol) in ethanol (2 ml) and 48% hydrobromic acid (0.5 ml) was refluxed for 2 h. After usual work-up, the product obtained was recrystallized from hexane–acetone to give the title compound (35 mg, 80%).

2'-Bromo- and 4'-Bromo-3-nitrobiphenyl. To a suspension of 3-nitrobenzenediazonium tetrafluoroborate, prepared from *m*-nitroaniline (6.7 g, 0.05 mol), in dry bromobenzene, were added 18-crown-6 (0.5 g) and potassium acetate (7.54 g, 0.077 mol). The mixture was stirred for 1.5 h under water-cooling and then filtered. The filtrate was washed with a saturated aq solution of sodium chloride, and dried over anhyd magnesium sulfate. After evaporation, the red oily residue was chromatographed on alumina using benzene–hexane as eluent to give a colorless oil (10.1 g), from which 2'-bromo-3-nitrobiphenyl (1.82 g, 13%) and 4'-bromo-3-nitrobiphenyl (1.1 g, 8%) were obtained by fractional recrystallization from ether. 2'-Bromo-3-nitrobiphenyl, colorless plates, mp 76—78 °C (lit,[3] 77—78 °C). IR (KBr): 1535, 1352, 763, 739, and 687 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ=7.1—7.6 (m, 3H), 7.6—8.1 (m, 3H), 8.2—8.5 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ=122.1 (s), 122.4 (d), 124.3 (d), 127.6 (d), 128.8 (d), 129.6 (d), 130.9 (d), 133.2 (d), 135.4 (d), 139.9 (s), 142.3 (s), and 147.8 (s). 4'-Bromo-3-nitrobiphenyl, colorless crystals, mp 84—85 °C. IR (KBr): 1535, 1359, 877, 824, 796, 763, 738, and 675 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ=7.3—8.1 (m, 6H) and 8.15—8.6 (m, 2H).

3-Acetamido-2',6-dibromobiphenyl. According to the direction described by Baker *et al.*,[3] 3-acetamido-2'-bromobiphenyl, prepared by reduction and subsequent acetylation of 2'-bromo-3-nitrobiphenyl, was brominated to give the title compound in 72% yield, but 3-acetamido-2',4,6,-tribromobiphenyl was not isolated.

5-Acetamido-2',4,6-tribromobiphenyl. 2',6-Dibromobiphenyl (365 mg, 1 mmol) and anhydrous sodium acetate (621 mg) were dissolved in boiling acetic acid (9.5 ml) and acetic anhydride (0.8 ml). To the mixture was added a solution of bromine (0.50 g, 3.1 mmol) in acetic acid (5 ml). The solution was refluxed for 1 h and poured into ice-water. The crystals were collected by suction, then washed with water, and dried. The products were chromatographed on silica gel by elution with benzene–ethyl acetate to give a colorless oil (227 mg, 50.6%) and colorless crystals (156 mg, 42.7%). The latter was recovered starting material. Crystallization and recrystallization of the former oil from ether gave the title compound as colorless crystals, mp 117—118 °C.

X-Ray Crystallography of 5. A crystal of dimensions 0.4 $\times$0.4$\times$0.2 mm obtained from hexane–acetone, was used for the intensity measurements. Intensity data were obtained on a Rigaku four-circle automatic diffractometer, equipped with graphite-monochromated Cu $K\alpha$ radiation, and using the θ-2θ scan technique ($2\theta \leq 127°$). 1554 independent reflecions ($F_o \geq 2.5\,\sigma F_o$) were corrected for Lorentz and polarization factors but not for absorption.

Crystal Data. $C_{12}H_7OBr_3$, orthorhombic, Pbca, z=8, a=9.667(2), b=16.261(3), c=15.957(3) Å, D_{calcd}=2.08 g/cm^3. The structure was solved by heavy atom methods. The positional and thermal parameters were refined by block diagonal least-squares methods. The positions of all hydrogen atoms were located from a difference Fourier synthesis. The final discrepancy index R is 0.079. The positional parameters for nonhydrogen atoms are listed in Table 1. Thermal parameters for nonhydrogen atoms, fractional coordinates and isotropic thermal hydrogen atoms, and observed and calculated structure factors are kept at the Chemical Society of Japan (Document No. 8313).

References

1) M. P. Cava and M. J. Mitchel, "*Cyclobutadiene and Related Compounds*," Academic Press, New York and London (1965), p. 255; J. W. Barton, "*Nonbenzenoid Aromatics*" ed by J. P. Snyder, Academic Press, New York and London, (1969), p. 32.

2) J. M. Blatchly, D. V. Gardner, J. F. W. McOmie, and M. L. Watts, *J. Chem. Soc., C*, **1968**, 1545.

3) W. Baker, J. F. W. McOmie, D. R. Preston, and V. Rogers, *J. Chem. Soc.*, **1958**, 414.

4) H. Kidokoro, M. Sato, and S. Ebine, *Bull. Chem. Soc. Jpn.*, **55**, 3204 (1982).

5) A part of this work was published in a preliminary report: H. Kidokoro, M. Sato, and S. Ebine, *Chem. Lett.*, **1981**, 1269.

6) D. V. Gardner and J. F. W. McOmie, *J. Chem. Soc., C*, **1968**, 2420.

7) J. M. Blatchly, D. V. Gardner, and J. F. W. McOmie, *J. Chem. Soc., C*, **1967**, 272.

8) W. Baker, J. F. W. McOmie, *J. Chem. Soc.*, **1958**, 2666.

9) J. B. Hendrickson, *J. Am. Chem. Soc.*, **89**, 7036 (1967).