Bromination of 2,6-Dimethyl-4-methoxybenzyl Alcohol Derivatives

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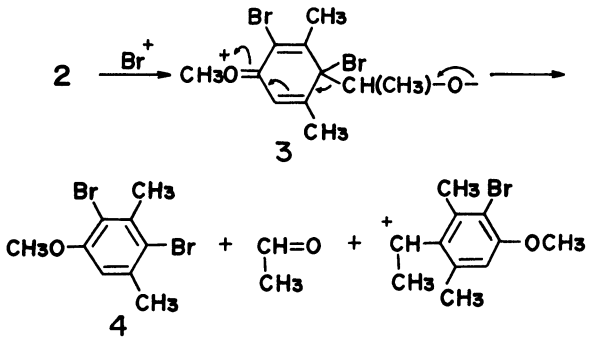
(Received August 26, 1983)

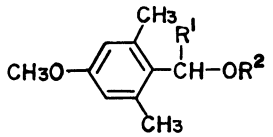
The reaction of 2,6-dimethyl-4-methoxybenzyl alcohols, ethyl ethers, and acetates, possessing electron-donating and -withdrawing groups at the benzylic position, with bromine water was studied at different temperatures. The reaction was strongly affected by the electronegativity of a benzyl substituent to afford bromination products of aromatic nuclei and 2,4-dibromo-3,5-dimethylmethoxybenzene along with 2,4,6-tribromo derivatives formed by the cleavage of C–C bond.

Bromination of bis[1-(2,6-dimethyl-4-methoxyphenyl)ethyl] ether (**1**) with bromine water in acetic acid has been reported to give acetaldehyde and 2,4-dibromo-3,5-dimethylmethoxybenzene (**4**) at 60 °C *via* bis[1-(3-bromo-2,6-dimethyl-4-methoxyphenyl)ethyl] ether (**2**).[1] A reaction mechanism involving the electrophilic displacement to **2** by bromine to give the oxonium intermediate **3**, which undergoes the cleavage of C–C bond to give the dibromide **4**, was proposed (Scheme 1). When the methoxyl group of **1** was displaced by



Scheme 1.

methyl group or hydrogen, the cleavage of C–C bond was not observed under the same conditions, whereas at room temperature, but not at 60 °C, 1-(2,6-dimethyl-4-methoxyphenyl)ethanol (**6a**) and 1-(2,4,6-trimethylphenyl)ethanol afforded **4** and 2,4-dibromo-1,3,5-trimethylbenzene along with acetaldehyde, respectively. These results supported that the cleavage reaction was influenced by the resonance effects of the methoxyl and methyl groups, and suggested that it should be further affected by the ease of formation of an aldehyde **5**. Similar cleavage of C–C bond have been observed in the bromination of some bromosalicylic acid and methylphenol derivatives.[2,3] We have devoted conciderable attention to the electrophilic reaction of bromine to 2,6-dimethyl-4-methoxybenzyl alcohols (**6**), ethyl ethers (**7**) and acetates (**8**), especially to the effects of R^1 and R^2 substituents (Fig. 1) on the cleavage of C–C bond. To compare the effect of substituent, a series of 2,6-dimethyl-4-methoxybenzyl alcohol derivatives, **6**, **7**, and **8**, possessing various electron-donating and -withdrawing substituents, CN, CO_2CH_3, $CONH_2$, CH_3, and H, at the benzylic position were synthesized from 3,5-xylenol *via* 2,6-dimethyl-4-methoxybenzaldehyde[4] and reaction with saturated bromine in water was studied in acetic acid at 10, 20, 30, 60 and 90 °C.



6a: R^1 = Me, R^2 = H
6b: R^1 = R^2 = H
6c: R^1 = $CONH_2$, R^2 = H
6d: R^1 = CO_2Me, R^2 = H
6e: R^1 = CN, R^2 = H

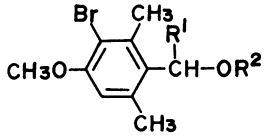
7a: R^1 = Me, R^2 = Et
7b: R^1 = H, R^2 = Et
7c: R^1 = $CONH_2$, R^2 = Et
7d: R^1 = CO_2Me, R^2 = Et
7e: R^1 = CN, R^2 = Et

8a: R^1 = Me, R^2 = Ac
8b: R^1 = H, R^2 = Ac
8c: R^1 = $CONH_2$, R^2 = Ac
8d: R^1 = CO_2Me, R^2 = Ac
8e: R^1 = CN, R^2 = Ac

Fig. 1.

Results and Discussion

The results of the reaction with bromine water at 10, 20, 30, and 60 °C are summerized in Table 1. The alcohols, **6a—e**, mainly afforded the dibromide **4** at 20 °C derived from the cleavage of C–C bond, while at the same temperature, main products from the acetates, **8a—e**, possessing the electronegative acetyl group were 3-bromo derivatives, **11a—e**. On the other hand, in the reaction of the ethyl ethers at 20 °C, **7a** (R^1=Me) and **7b** (R^1=H) afforded **4**, but **7c** (R^1=$CONH_2$), **7d** (R^1=CO_2Me) and **7e** (R^1=CN) gave 3-bromo derivatives, **10c**, **10d**, and **10e**, as main products, respec-



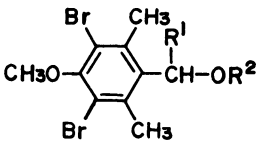
9c: R^1 = $CONH_2$, R^2 = H
9d: R^1 = CO_2Me, R^2 = H
9e: R^1 = CN, R^2 = H

10c: R^1 = $CONH_2$, R^2 = Et
10d: R^1 = CO_2Me, R^2 = Et
10e: R^1 = CN, R^2 = Et

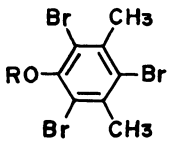
11a: R^1 = Me, R^2 = Ac
11b: R^1 = H, R^2 = Ac
11c: R^1 = $CONH_2$, R^2 = Ac
11d: R^1 = CO_2Me, R^2 = Ac
11e: R^1 = CN, R^2 = Ac

Table 1. Bromination of alcohols **6**, ethyl ethers **7**, and acetates **8** at 10, 20, 30, and 60 °C

Compound			Products (yield/%)								
	R^1	R^2	at 10 °C		at 20 °C		at 30 °C		at 60 °C		
6a	Me	H	**11a**(43)	**4**(45)	**11a**(81)	**4**(14)	**11a**(3)	**4**(95)	**4**(87)	**14**(7)	**15**(4)
6b	H	H	**4**(94)		**4**(96)		**4**(95)			—	
6c	$CONH_2$	H	**9c**(43)	**4**(39)	**4**(95)		**4**(92)			—	
6d	CO_2Me	H	**9d**(49)	**4**(44)	**4**(95)		**4**(98)			—	
6e	CN	H	**9e**(85)	**4**(10)	**9e**(18)	**4**(74)	**4**(96)		**4**(81)	**14**(6)	**15**(4)
7a	Me	Et	**4**(93)		**4**(95)		**4**(96)			—	
7b	H	Et	**4**(94)		**4**(97)		**4**(97)			—	
7c	$CONH_2$	Et	**10c**(92)		**10c**(90)	**4**(5)	**10c**(48)	**4**(29)	**12c**(23)		**4**(67)
							12c(20)		**14**(7)		**15**(3)
7d	CO_2Me	Et	**10d**(95)		**10d**(95)		**10d**(75)	**4**(7)	**12d**(43)		**4**(39)
							12d(15)		**14**(6)		**15**(4)
7e	CN	Et	**10e**(99)		**10e**(98)		**10e**(98)			**10e**(99)	
8a	Me	Ac	**11a**(90)	**4**(4)	**11a**(88)	**4**(12)	**11a**(40)	**4**(54)	**4**(87)	**14**(6)	**15**(2)
8b	H	Ac	**11b**(91)		**11b**(91)	**4**(4)	**11b**(84)	**4**(10)	**11b**(15)		**4**(66)
									14(7)		**15**(3)
8c	$CONH_2$	Ac	**11c**(92)		**11c**(90)		**11c**(94)		**11c**(73)	**13c**(13)	**4**(5)
8d	CO_2Me	Ac	**11d**(98)		**11d**(97)		**11d**(98)		**11d**(75)	**13d**(13)	**4**(5)
8e	CN	Ac	**11e**(45)	**8e**(44)	**11e**(55)	**8e**(37)	**11e**(60)	**8e**(32)	**11e**(93)		**4**(4)



12c: $R^1 = CONH_2$, R^2 = Et **13c**: $R^1 = CONH_2$, R^2 = Ac
12d: $R^1 = CO_2Me$, R^2 = Et **13d**: $R^1 = CO_2Me$, R^2 = Ac
12e: R^1 = CN, R^2 = Et **13e**: R^1 = CN, R^2 = Ac



14: R = Me
15: R = H

tively. These results indicate that the C–C bond cleavage is strongly affected by the R^1 and R^2 substituents, as clarified below. Although **6a** and **6b** yielded **4** even at low temperature (10 °C), **6c**, **6d** and **6e** afforded 3-bromo derivatives, **9c**, **9d**, and **9e**, in yields of 43, 49, and 85%, respectively, along with **4**. The reaction of **6a** alone afforded a bromo acetate **11a** at low temperature and all of the alcohols, **6a**—**e**, gave mixtures of **4**, 2,4,6-tribromo-3,5-dimethylmethoxybenzene (**14**) and the corresponding phenol **15** at 60 and 90 °C. The resulting aldehydes from the C–C bond cleavage afforded their 2,4-dinitrophenylhydrazones, but the corresponding benzyl bromides presumed from bromination with generating hydrobromic acid in the reaction systems could not be isolated. The reaction of the ethyl ethers, **7a**—**e**, at 10 °C showed a similar result to that of **6a**—**e**, that is, **7a** and **7b** afforded **4** and **7c**—**e** yielded monobromides, **10c**—**e**. The ethers **7c**—**e**, however, afforded 3,5-dibromo derivatives, **12c** and **12d**, at 30 °C and **12e** at 90 °C by the second bromination on the benzene nucleus, while the first formation of **4** was recognized at 20, 30, and 90 °C, respectively. Apparently, the bromo substituent suppresses the bond cleavage reaction so that **7c** afforded 20% of **12c** at high temperature (90 °C). Both compounds having $CONH_2$ and CO_2Me groups afforded similar reaction products, but the proportions of products from **6c** and **6d** at 10 °C, and from **7c** and **7d** at 20, 30, and 60 °C revealed that the methoxycarbonyl group suppressed the C–C bond cleavage more than the carbamoyl group. Although the acetates, **8a** and **8b**, afforded the monobromides, **11a** and **11b**, at low temperature, they showed no formation of the corresponding dibromides at higher temperature. On the other hand, **8c**—**e** first showed the formation of dibromides, **13c**, **13d** and **13e**, at 60, 60, and 90 °C in 13, 13, and 7% yields along with **11c** (73%), **11d** (75%), and **11e** (49%), respectively. These acetates, **8c**—**e**, yielded **4** in 4—5% yields at 60 °C from hydrolysis of the acetate group.

Some potent points derived from our studies on the substituent effects are listed as follows: (i) The electrophilic substitution on the benzene nucleus of the alcohols **6** by bromonium ion, being accompanied by C–C bond cleavage, proceeds according to the mechanism proposed previously and the bond cleavage reaction is largely governed by the R^1 substituent. But in the reaction of the ethyl ethers, **7c**—**e**, and the acetates, **8c**—**e**, possessing electronegative carbamoyl, methoxycarbonyl and cyano groups, the bond cleavage reaction is in competition with the second bromination on benzene nucleus to give the dibromides, **12c**—**e** and **13c**—**e**. (ii) The cleavage reaction is also largely regulated by the R^2 substituent and occurred most readily in the reaction of the alcohols **6** by the easy formation of aldehydes. (iii) In each R^1 series, this reaction becomes difficult in the order of R^1=CN, CO_2Me, $CONH_2$, H, CH_3.

Experimental

All of the melting and the boiling points are uncorrected. The IR spectra were recorded with a Shimadzu IR-27C spectrophotometer. The ^1H NMR spectra were measured with JEOL JNM 60 and JNM 100 apparatus. The HPLC separation was done with Waters M45 system and Whatman

Partisil M9 Semi-prep column.

Preparation of ***6a, 7a, and 8a.*** To an ether soln of MeMgI prepared from MeI (8.0 g) and Mg (1.5 g), a soln of 2,6-dimethyl-4-methoxybenzaldehyde (5.0 g) was added with stirring. After refluxing for a 1/2 h, the resulting complex was decomposed with aq NH_4Cl and the ether layer was washed with aq $Na_2S_2O_3$, aq $NaHCO_3$, and water. The crude product was chromatographed over silica gel to give **6a** (4.7 g; 85%), $C_{11}H_{16}O_2$, mp 51—52 °C; IR ($CHCl_3$) 3240, 1605, 853, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.45 (3H, d, J=7.2), 1.84 (1H, s), 2.37 (6H, s), 3.71 (3H, s), 5.30 (1H, q, J=7.2), 6.52 (2H, s). Found: C, 73.56; H, 9.12%. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95%. The alcohol **6a** was refluxed with a catalytic amount of TsOH in abs EtOH for 12 h and after removal of EtOH, the crude product was purified by column chromatography to give the ethyl ether **7a** (95%), $C_{13}H_{20}O_2$, bp 92—93 °C/7 mmHg (1 mmHg≈133.322 Pa); IR ($CHCl_3$) 1605, 850, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.16 (3H, t, J=7.0), 1.44 (3H, d, J=7.0), 2.38 (6H, s), 3.28 (2H, q, J=7.0), 3.74 (3H, s), 4.88 (1H, q, J=7.0), 6.56 (2H, s). Found: C, 74.90; H, 9.58%. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68%. The alcohol **6a** was acetylated with Ac_2O in pyridine followed by treatment in the usual way to give the acetate **8a** (97%), $C_{13}H_{18}O_3$, bp 134—137 °C/10 mmHg; IR (liq film) 1750, 848, 827 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.51 (3H, d, J=7.0), 2.01 (3H, s), 2.41 (6H, s), 3.71 (3H, s), 6.25 (1H, q, J=7.0), 6.56 (2H, s). Found: C, 70.11; H, 8.09%. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16%.

Preparation of ***6b, 7b, and 8b.*** The reduction of 2,6-dimethyl-4-methoxybenzaldehyde with $LiAlH_4$ followed by the treatment with aq NaOH gave **6b** (92%), $C_{10}H_{14}O_2$, mp 70—71 °C; IR (Nujol) 3350, 1603, 853, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.61 (1H, s), 2.37 (6H, s), 3.73 (3H, s), 4.60 (2H, s), 6.55 (2H, s). Found: C, 72.30; H, 8.50%. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49%. The treatment of **6b** with a catalytic amount of TsOH in abs EtOH under reflux afforded **7b** (93%), $C_{12}H_{18}O_2$, bp 117—119 °C/7 mmHg; IR ($CHCl_3$) 1605, 850, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.23 (3H, t, J=6.8), 2.36 (6H, s), 3.54 (2H, q, J=6.8), 3.76 (3H, s), 4.45 (2H, s), 6.56 (2H, s). Found: C, 74.30; H, 9.29%. Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34%. The acetylation of **6b** with Ac_2O in pyridine afforded **8b** (92%), $C_{12}H_{16}O_3$, mp 59—60 °C; IR ($CHCl_3$) 1745, 1603, 877, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 2.00 (3H, s), 2.34 (6H, s), 3.73 (3H, s), 5.15 (2H, s), 6.55 (2H, s). Found: C, 69.20; H, 7.71%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%.

Preparation of ***6e, 7e, and 8e.*** A mixture of 2,6-dimethyl-4-methoxybenzaldehyde (2 g) and anhydrous HCN (2 ml) was kept with CaO (400 mg) in a sealed tube at 50 °C for 2 h. The reaction mixture was acidified with dil H_2SO_4 followed by extraction with ether to give the cyanohydrin **6e**[5] (1.8 g; 77%), $C_{11}H_{13}NO_2$, mp 122—123 °C; IR ($CHCl_3$) 3470, 2280, 1610, 850, 834 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.47 (6H, s), 3.04 (1H, d, J=4.0), 3.77 (3H, s), 5.83 (1H, d, J= 4.0), 6.60 (2H, s). Found: C, 69.23; H, 6.91; N, 7.30%. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33%. The treatment of **6e** with a catalytic amount of TsOH in abs EtOH under reflux afforded **7e** (90%), $C_{13}H_{17}NO_2$, mp 49—59 °C; IR ($CHCl_3$) 1608, 850, 830 cm^{-1}; ^1H NMR($CDCl_3$) δ=1.41 (3H, t, J=7.0), 2.45 (6H, s), 3.67 (2H, m), 3.74 (3H, s), 5.46 (1H, s), 6.60 (2H, s). Found: C, 71.04; H, 7.90; N, 6.39%. Calcd for $C_{13}H_{17}NO_2$: C, 71.20, H, 7.82; N, 6.39%. The acetylation of **6e** with Ac_2O in pyridine afforded **8e** (98%), $C_{13}H_{15}NO_3$, mp 54—55 °C; IR (Nujol) 1770, 1610, 860, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.08 (3H, s), 2.48 (6H, s), 3.73 (3H, s), 6.60 (2H, s), 6.80 (1H, s). Found: C, 66.91; H, 6.45; N, 6.11%. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.84; N, 6.01%.

Preparation of ***6c, 7c, and 8c.*** Into a soln of the cyanohydrin **6e** in abs EtOH, dry HCl gas was passed at 50 °C for 3 h. After removal of the solvent, the crude product was purified by column chromatography to give the glycolamide **6c** (76%), $C_{11}H_{15}NO_3$, mp 145.5—146 °C; IR (Nujol) 3500, 3350, 1670, 1585, 853, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.33 (6H, s), 3.56 (1H, d, J=2.0), 3.74 (3H, s), 5.45 (1H, br), 5.75 (2H, br), 6.60 (2H, s). Found: C, 63.03; H, 7.03; N, 6.82%. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69%. The treatment of **6c** with a catalytic amount of TsOH in abs EtOH under reflux afforded **7c** (87%), $C_{13}H_{19}NO_3$, mp 121—122 °C; IR (Nujol) 3500, 3150, 1700, 1605, 875, 846, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.18 (3H, t, J=6.8), 2.37 (6H, s), 3.40 (2H, q, 6.8), 3.77 (3H, s), 5.25 (1H, s), 6.20 (1H, br), 6.68 (2H, s), 6.93 (1H, br). Found: C, 65.93; H, 8.09; N, 5.89%. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90%. The acetylation of **6c** with Ac_2O in pyridine at room temperature afforded **8c** (78%), $C_{13}H_{17}NO_4$, mp 145 °C; IR (Nujol) 3490, 3200, 1755, 1700, 860, 845 cm^{-1}: ^1H NMR ($CDCl_3$) δ=2.17 (3H, s), 2.47 (6H, s), 3.80 (3H, s), 6.50—5.60 (2H), 6.60 (2H+1H, s). Found: C, 62.32; H, 6.97; N, 5.52%. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57%.

Preparation of ***6d, 7d, and 8d.*** The amide **6c** was hydrolyzed with 30% aq KOH and methylated with diazomethane to give the methyl glycolate **6d** (82%), $C_{12}H_{16}O_4$, mp 149—150 °C; IR (Nujol) 3480, 1750, 1605, 855, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.34 (6H, s), 3.27 (1H, br s), 3.71 (6H, s), 5.46 (1H, br s), 6.56 (2H, s). Found: C, 64.26; H, 7.16%. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19%. The treatment of **6d** with a catalytic amount of TsOH in abs EtOH under reflux afforded **7d** (92%), $C_{14}H_{20}O_4$, bp 109—111 °C/7 mmHg; IR ($CHCl_3$) 1765, 1610, 845, 830 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.21 (3H, t, J=6.8), 2.41 (6H, s), 3.48 (2H, d quint, J=2.0, 6.8),[6] 3.65 (3H, s), 3.72 (3H, s), 5.29 (1H, s), 6.55 (2H, s). Found: C, 66.38; H, 8.14%. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99%. The acetylation of **7d** with Ac_2O in pyridine afforded **8d** (95%), $C_{14}H_{18}O_5$, mp 66—66.5 °C; IR (Nujol) 1750, 1735, 865, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.12 (3H, s), 2.35 (6H, s), 3.66 (3H, s), 3.72 (3H, s), 6.61 (2H+1H, s). Found: C, 63.09; H, 6.77%. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81%.

Reaction of the Alcohols ***6****, the Ethyl Ethers* ***7****, and the Acetates* ***8*** *with Bromine Water.* To a soln of a material (100 mg) in acetic acid (15 ml), saturated bromine in water (10 ml) containing KBr (0.8 g) was added with stirring until a red colour persisted and the soln was stirred for 1 h, in which to keep the red colour, additional bromine water was sometimes added. After addition of aq $Na_2S_2O_3$, the reaction products at 10, 20, and 30 °C from **7** and **8** except for **7c** and **8c** were directly extracted with hexane from the resulting mixture, and the others were extracted with ether after neutralization with aq $NaHCO_3$. The crude product was chromatographed over silica gel and difficult congeners (**10** and **12**, and **11** and **13**) were separated by a use of HPLC with 1—2% MeOH in CH_2Cl_2.

2,4-Dinitrophenylhydrazones of Aldehydes from ***6a*** *and* ***6b.*** The reactions of **6a** and **6b** with bromine water were carried out under a N_2 stream at 90 °C and the each resulting vapour was bubbled through a soln of 2,4-dinitrophenylhydrazine in aq HCl. The precipitate was collected by filtration and recrystallized from EtOH. 2,4-Dinitrophenylhydrazone of acetaldehyde; mp 146—147 °C. 2,4-Dinitrophenylhydrazone of formaldehyde; mp 165—166 °C. They were identified by direct comparison with authentic samples.

2,4-Dinitrophenylhydrazones of Aldehydes from ***6c, 6d*** *and* ***6e.*** Into reaction mixtures of **6c**, **6d**, and **6e** with bromine water at 60 °C, a soln of 2,4-dinitrophenylhydrazine was added and the solutions were left overnight. Each ether extract was purified by chromatography and recrystallization. 2,4-Dinitrophenylhydrazone of glyoxylamide; $C_9H_8O_6N_4$, mp 241.5—243.5 °C (decomp); IR (Nujol) 3400, 3250, 3150, 3070, 1675, 1615, 1590 cm^{-1}; MS, m/z (rel intensity) 253 (M^+, 65), 181 (28), 152 (29), 74 (100). 2,4-Dinitrophenylhydrazone of

methyl glyoxylate; $C_9H_8O_6N_4$, mp 200—202.5 °C (decomp); IR (Nujol) 3300, 3090, 1730, 1620, 1590 cm^{-1}; MS, *m/z* (rel intensity) 268 (M^+, 100), 237 (12), 180 (44), 181 (12), 152 (13). 2,4-Dinitrophenylhydrazone from **6e**; mp 126—127 °C; IR (Nujol) 3300, 1620, 1570 cm^{-1}; MS, *m/z* (rel intensity) 238 (M^+, 100), 181 (24), 152 (21).

Reaction products at 10, 20, 30, and 60 °C. **4**,[1] $C_9H_{10}OBr_2$, mp 107—110 °C; ^1H NMR ($CDCl_3$) δ=2.36 (3H, s), 2.58 (3H, s), 3.82 (3H, s), 6.61 (1H, s). **9c**, $C_{11}H_{14}NO_3Br$, mp 144—145 °C; IR (Nujol) 3470, 3230, 1690, 1640, 825 cm^{-1}; ^1H NMR (acetone-d_6) δ=2.37 (3H, s), 2.43 (3H, s), 3.82 (3H, s), 4.93 (1H, d, *J*=3.8), 5.48 (1H, d, *J*=3.8), 6.45—7.04 (2H), 6.77 (1H, s). Found: C,45.51; H, 4.99; N, 4.77%. Calcd for $C_{11}H_{14}NO_3Br$: C, 45.85; H, 4.90; N, 4.86%. **9d**, $C_{12}H_{15}O_4Br$, mp 119—120 °C; IR (Nujol) 3450, 1734, 1723, 1580, 836 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.37 (3H, s), 2.45 (3H, s), 3.19 (1H, d, *J*=3.0), 3.76 (3H, s), 3.86 (3H, s), 5.42 (1H, d, *J*=3.0), 6.58 (1H, s). Found: C, 47.76; H, 4.90%. Calcd for $C_{12}H_{15}O_4Br$: C, 47.54; H, 4.99%. **9e**, $C_{11}H_{12}NO_2Br$, mp 122—123 °C; IR (Nujol) 3600, 828 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.41 (3H, s), 2.58 (3H, s), 3.55 (1H, br), 3.83 (3H, s), 5.85 (1H, s), 6.58 (1H, s). Found: C, 48.65; H, 4.52; N, 5.01%. Calcd for $C_{11}H_{12}NO_2Br$: C, 48.91; H, 4.48; N, 5.18%. **10c**, $C_{13}H_{18}NO_3Br$, mp 140—141.5 °C; IR (Nujol) 3540, 3160, 1700, 1590, 833 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.17 (3H, t, *J*=7.0), 2.36 (3H, s), 2.45 (3H, s), 3.37 (2H, q, *J*=7.0), 3.82 (3H, s), 5.19 (1H, s), 6.58 (1H, s), 6.77 (2H, br). Found: C, 49.50; H, 5.51; N, 4.40%. Calcd for $C_{13}H_{18}NO_3Br$: C, 49.38; H, 5.74; N, 4.43%. **10d**, $C_{14}H_{19}O_4Br$, mp 88.5—89.5 °C; IR ($CHCl_3$) 1765, 1595, 828 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.19 (3H, t, *J*=7.0), 2.36 (3H, s), 2.46 (3H, s), 3.47 (2H, br quint, *J*=7.0), 3.65 (3H, s), 3.81 (3H, s), 5.26 (1H, s), 6.59 (1H, s). Found: C, 50.69; H, 5.82%. Calcd for $C_{14}H_{19}O_4Br$: C, 50.77; H, 5.78%. **10e**, $C_{13}H_{16}NO_2Br$, mp 65—65.5 °C; IR ($CHCl_3$) 2300, 1585, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.26 (3H, t, *J*=7.2), 2.44 (3H, s), 2.60 (3H, s), 3.68 (2H, m), 3.85 (3H, s), 5.48 (1H, s), 6.60 (1H, s). Found:C, 52.35; H, 5.40; N, 4.61%. Calcd for $C_{13}H_{16}NO_2Br$: C, 52.36; H, 5.41; N, 4.70%. **11a**, $C_{13}H_{17}O_3Br$, mp 94—95 °C; IR ($CHCl_3$) 1745, 1585, 825 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.54 (3H, d, *J*=6.8), 2.04 (3H, s), 2.42 (3H, s), 2.57 (3H, s), 3.85 (3H, s), 6.27 (1H, q, *J*=6.8), 6.56 (1H, s). Found: C, 52.11, H, 5.48%. Calcd for $C_{13}H_{17}O_3Br$: C, 51.84; H, 5.69%. **11b**, $C_{12}H_{15}O_3Br$, mp 67—68 °C; IR ($CHCl_3$) 1740, 1593, 832 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.04 (3H, s), 2.37 (3H, s), 2.48 (3H, s), 3.86 (3H, s), 5.17 (2H, s), 6.62 (1H, s). Found: C, 50.20; H, 5.22%. Calcd for $C_{12}H_{15}O_3Br$: C, 50.19; H, 5.27%. **11c**, $C_{13}H_{16}NO_4Br$, mp 170—172 °C; IR (Nujol) 3450, 3120, 1690, 1585, 835 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.13 (3H, s), 2.46 (3H, s), 2.51 (3H, s), 3.70 (3H, s), 5.83 (2H, br), 6.59 (1H, s), 6.63 (1H, s). Found: C, 47.13; H, 4.95; N, 4.40%. Calcd for $C_{13}H_{16}NO_4Br$: C, 47.29; H, 4.89; N, 4.24%. **11d**, $C_{14}H_{17}O_5Br$, mp 77.5—79 °C; IR (Nujol) 1760, 1735, 1580, 833 cm^{-1};^1H NMR ($CDCl_3$) δ=2.08 (3H, s), 2.36 (3H, s), 2.43 (3H, s), 3.66 (3H, s), 3.80 (3H, s), 6.60 (1H, s), 6.65 (1H, s). Found: C, 48.83; H, 4.92%. Calcd for $C_{14}H_{17}O_5Br$: C, 48.71; H, 4.97%. **11e**, $C_{13}H_{14}NO_3Br$, mp 87 °C; IR (liq film) 1775, 1590, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.10 (3H, s), 2.49 (3H, s), 2.63 (3H, s), 3.85 (3H, s), 6.59 (1H, s), 6.87 (1H, s). Found: C, 50.07; H, 4.53; N, 4.44%. Calcd for $C_{13}H_{14}NO_3Br$: C, 50.02; H, 4.52; N, 4.48%. **12c**, $C_{13}H_{17}NO_3Br_2$; IR (Nujol) 3470—3150, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.16 (3H, t, *J*=6.9), 2.49 (6H, s), 3.37 (2H, q, *J*=6.9), 3.83 (3H, s), 5.33 (1H, s), 5.82 (1H, br), 6.85 (1H, br). Found: C, 39.34; H, 4.60; N, 3.32%. Calcd for $C_{13}H_{17}NO_3Br_2$: C, 39.52; H, 4.34; N, 3.54%. **12d**, $C_{14}H_{18}O_4Br_2$; IR (Nujol) 1765, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.21 (3H, t, *J*=6.8), 2.47 (6H, s), 3.52 (2H, quint, *J*=6.8), 3.67 (3H, s), 3.82 (3H, s), 5.37 (1H, s). Found: C, 40.75; H, 4.27%. Calcd for $C_{14}H_{18}O_4Br_2$: C, 41.00; H, 4.42%. **13c**, $C_{13}H_{15}NO_4Br_2$, mp 178.5—179.5 °C; IR (Nujol) 3450—3100, 1740, 1690, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.12 (3H, s), 2.54 (6H, s), 3.82 (3H, s), 5.60—5.85 (2H), 6.70 (1H, s). Found: C, 38.32; H, 3.77; N, 3.35%. Calcd for $C_{13}H_{15}NO_4Br_2$: C, 38.17; H, 3.70; N, 3.42%. **13d**, $C_{14}H_{16}O_5Br_2$, mp 81.5—82.5 °C; IR (Nujol) 1730 cm^{-1}: ^1H NMR ($CDCl_3$) δ=2.15 (3H, s), 2.50 (6H, s), 3.71 (3H, s), 3.85 (3H, s), 6.78 (1H, s). Found: C, 39.70; H, 3.79%. Calcd for $C_{14}H_{16}O_5Br_2$: C, 39.65; H, 3.80%. **14**, $C_9H_9OBr_3$, mp 116.5 °C; ^1H NMR ($CDCl_3$) δ=2.59 (6H, s), 3.82 (3H, s). **15**, $C_8H_7OBr_3$, mp 165—167 °C; IR (Nujol) 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.57 (6H, s), 6.00 (1H, br). Found: C, 26.75; H, 1.97%. Calcd for $C_8H_7OBr_3$: C, 26.77; H, 1.97%.

Reaction of 6a with Bromine Water at 90 °C. The alcohol **6a** (100 mg) was stirred with saturated bromine water in acetic acid (15 ml) at 90 °C for 1 h. The crude product was isolated in the usual way to give **4** (87 mg; 66%), **14** (31 mg; 15%), and **15** (24 mg; 12%).

Reaction of 7c with Bromine Water at 90 °C. The ethyl ether **7c** (100 mg) was treated in a manner similar to the one descrived for **6a** at 90 °C and the crude product afforded **4** (46 mg; 37%), **12c** (33 mg; 20%), **14** (34 mg; 22%) and **15** (25 mg; 17%).

Reaction of 7e with Bromine Water at 90 °C. The ethyl ether **7e** (100 mg) was treated in a similar manner as above at 90 °C and the crude product afforded **4** (5 mg; 4%), **10e** (19 mg; 14%), **12e** (110 mg; 64%), **14** (3 mg; 2%) and **15** (2 mg; 2%). **12e**, $C_{13}H_{15}NO_2Br_2$, mp 101—102 °C; ^1H NMR ($CDCl_3$) δ=1.26 (3H, t, *J*=6.8). 2.55 (6H, s), 3.72 (2H, m), 3.83 (3H, s), 5.83 (1H, s). Found: C, 41.38; H, 4.06; N, 3.66%. Calcd for $C_{13}H_{15}NO_2Br_2$: C, 41.41; H, 4.01; N, 3.71%.

Reaction of 8e with Bromine Water at 90 °C. The acetate **8e** (100 mg) was worked up in a similar manner as above at 90 °C to give **4** (34 mg; 27%), **11e** (66 mg; 49%), **13e** (12 mg; 7%), **14** (11 mg; 7%) and **15** (9 mg; 6%). **13e**, $C_{13}H_{13}NO_3Br_2$, mp 137.5 °C; IR ($CHCl_3$) 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ= 2.14 (3H, s), 2.63 (6H, s), 3.87 (3H, s), 7.03 (1H,s). Found: C, 40.06; H, 3.45; N, 3.51%. Calcd for $C_{13}H_{13}NO_3Br_2$: C, 39.92; H, 3.35; N, 3.58%.

2,4-Dinitrophenylhydrazones of Aldehydes from 8d. Into a reaction mixture of **8d** (100 mg) with bromine water at 90 °C, a soln of 2,4-dinitrophenylhydrazine was added and the reaction vessel was left overnight at room temperature. Ether extract of the reaction mixture was purified by chromatography and recrystallization to give 2,4-dinitrophenylhydrazones of methyl glyoxylate and glyoxylic acid; 18 mg and 23 mg. 2,4-Dinitrophenylhydrazone of glyoxylic acid, mp 185—188 °C; IR (Nujol) 3500—2500, 3280, 1705, 1618, 1577 cm^{-1}, afforded a methyl ester by methylation with diazomethane, which was identical with the 2,4-dinitrophenylhydrazone of methyl glyoxylate.

We wish to express our sincere gratitude to Dr. Shibata of Osaka City University for the elemental analysis.

References

1) T. Kamikawa, M. Nakatani, and T. Kubota, *Tetrahedron*, **24**, 2091 (1968).

2) E. Grovenstein, Jr. and U. V. Henderson, Jr., *J. Am. Chem. Soc.*, **78**, 569 (1956); E. Grovenstein, Jr., and G. A. Ropp, *ibid.*, **78**, 2560 (1956); I. P. Beletskaya, Kh. Vill, and D. A. Reutov, *Zh. Org. Khim.*, **3**, 615 (1967).

3) A. P. Krysin and V. A. Koptyug, *Izv. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, **1975**, 73.

4) C. T. Davis and T. A. Geissmann, *J. Am. Chem. Soc.*, **76**, 3507 (1954).

5) M. Nakatani and T. Hase, *Bull. Chem. Soc. Jpn.*, **52**, 462 (1979).

6) Similar observation that methylene protons of alkoxyl group attached to an asymmetric carbon display one AB-type signal in ^1H NMR spectrum, has been reported. G. M. Whitesides, D. Holtz, and J. D. Roberts, *J. Am. Chem. Soc.*, **86**, 2628 (1964). As noted in the experimental section, the methylene protons of ethoxyl group of the following compounds were observed as a quartet in the case of R=H, CH_3 and $CONH_2$, but they displayed double quintet-type or multiplet spectra in the case of R=CO_2Me or CN, respectively.