# Halogenation Using Quaternary Ammonium Polyhalides. XI.[1] Bromination of Acetanilides by Use of Tetraalkylammonium Polyhalides

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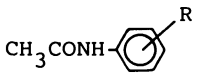
**Synopsis.** The reaction of acetanilides with tetraalkylammonium polyhalides, such as tetrabutylammonium tribromide, benzyltrimethylammonium tribromide, and benzyltrimethylammonium chlorobromate(1−), in dichloromethane-methanol at room temperature gave bromo-substituted acetanilides in good yields, respectively.

In general, bromo-substituted acetanilides (**2**) have been prepared from the acetylation of bromoanilines with acetyl chloride,[2] or acetic anhydride in acetic acid,[3] further, from the reaction of acetanilides (**1**) with bromine in acetic acid.[4] As a special brominating agent for **1**, *N,N*-dibromobenzenesulfonamide has also been used instead of bromine.[5]

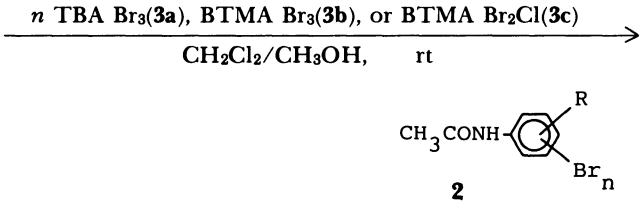
Recently, we have shown that benzyltrimethylammonium tribromide (BTMA $Br_3$) (**3b**) is a useful brominating agent to anilines.[6] In the present paper, we wish to report on the bromination of **1**, *N*-acetyl-protected anilines, by the use of tetraalkylammonium polyhalides, such as tetrabutylammonium tribromide (TBA $Br_3$) (**3a**), **3b** and benzyltrimethylammonium chlorobromate(1−) (BTMA $Br_2Cl$) (**3c**).

## Results and Discussion

The reaction of **1** with **3a**,[7] **3b**,[8] and **3c** in dichloromethane–methanol at room temperature gave **2** in good yields, respectively.



**1**






**2**

The results are summarized in Table 1. This table shows that **3c** is the strongest brominating agent to **1**, and that these brominations of **1**, except hydroxy- and amino-substituted acetanilides (e.g., **1h**, **1i**, and **1j**), have usually given predominantly the corresponding para-bromo derivatives.[15] The reaction of hydroxy- or amino-substituted acetanilides with these brominating agents gave mono-, di-, or tribromo-substituted derivatives which were products controlled mainly by the effect of the hydroxy or amino group on the orientation.

Recently, Berthelot et al.[16] reported that the bromination of **1a** with **3a** in chloroform at room temperature did not proceeded at all. However, as shown in the table, in the presence of methanol, the reaction of **1** with **3** in dichloromethane at room temperature easily gave **2** in good yields. In these cases, it can be presumed that the active species is probably the methyl hypobromite produced from the reaction of **3** with methanol.[17]

Since aminophenols and phenylenediamines are so sensitive for **3**, isolations of mono-, di-, or tribromo derivatives of these compounds are considerably difficult. However, the selective brominations of *N*-acetyl-protected anilines, such as 2-hydroxyacetoanilide (**1h**), 3-hydroxyacetanilide (**1i**), and 3-aminoacetanilide (**1j**), by use of **3** under mild conditions occured most readily, as shown in the table. Accordingly, bromo-substituted aminophenols and phenylenediamines should be obtained by the hydrolyses of these corresponding acetanilides.

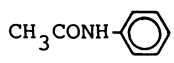
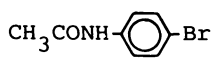
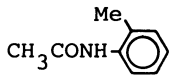
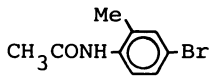
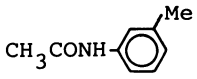
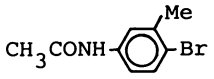
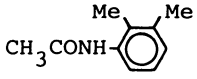
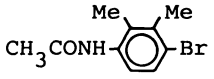
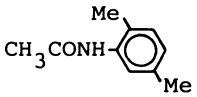
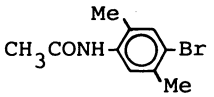
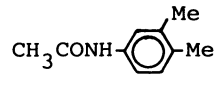
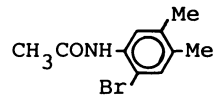
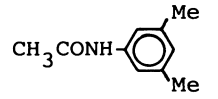
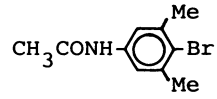
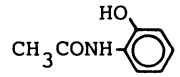
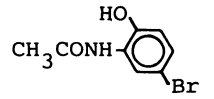
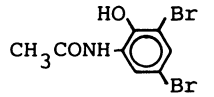
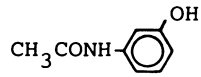
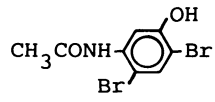
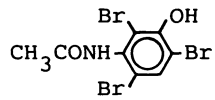
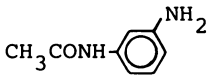
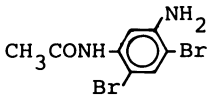
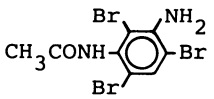
We believe that these tetraalkylammonium polyhalides such as TBA $Br_3$, BTMA $Br_3$, and BTMA $Br_2Cl$ are more useful brominating agents for **1** than bromine or *N,N*-dibromobenzenesulfonamide, because of their solid character, stability and nontoxicity.

## Experimental

**Benzyltrimethylammonium Chlorobromate(1−) (BTMA $Br_2Cl$) (3c).** To a solution of bromine (15.98 g, 0.1 mol) in dichloromethane (100 ml) was added dropwise a solution of benzyltrimethylammonium chloride (18.57 g, 0.1 mol) in water (100 ml) under stirring at room temperature. After the mixture was stirred for 30 min, the dichloromethane layer was separated and dried with magnesium sulfate, and then evaporated in vacuo to give a residue which was recrystallized from dichloromethane–ether (10:1) affording BTMA $Br_2Cl$ as stable orange crystals; yield 24.50 g (71%); mp 101—102 °C. Found: C, 34.88; H, 4.63; N, 4.01; $Br_2Cl$, 56.31%. Calcd for $C_{10}H_{16}NBr_2Cl$: C, 34.76; H, 4.67; N, 4.05; $Br_2Cl$, 56.51%.

**4-Bromoacetanilide (2a); Typical Procedure:** To a solution of acetanilide (**1a**) (0.50 g, 3.70 mmol) in dichloromethane (50 ml)–methanol (20 ml) was added **3c** (1.41 g, 4.08 mmol) at room temperature. The mixture was stirred for 20 min until a decoloration of the orange color took place. The solvent was distilled and to the obtained residue was added water (20 ml). The mixture was extracted with ether (40 ml×4). The ether layer was then dried with

Table 1. Bromination of Acetanilides by Use of Tetraalkylammonium Polyhalides

| | Substrate 1 | Product 2 | Molar ratio 3/1 | 3 used | Reaction time | Yield[a]/% | Mp $\theta_m$/°C Found | Mp $\theta_m$/°C Reported |
|---|---|---|---|---|---|---|---|---|
| a |  |  | 1.1 | **3a** | 12 h | 95 | | |
| | | | | **3b** | 2 h | 97 | 163—164 | 168.8[9] |
| | | | | **3c** | 20 min | 97 | | |
| b |  |  | 1.1 | **3a** | 36 h | 91 | | |
| | | | | **3b** | 27 h | 87 | 160 | 158—159[10] |
| | | | | **3c** | 10 h | 99 | | |
| c |  |  | 1.1 | **3a** | 1 h | 98 | | |
| | | | | **3b** | 3 h | 96 | 103—104 | 103—104[11] |
| | | | | **3c** | 15 min | 99 | | |
| d |  |  | 1.1 | **3a** | 12 h | 95 | | |
| | | | | **3b** | 2 h | 96 | 159—160 | 161—162[3] |
| | | | | **3c** | 2 h | 89 | | |
| e |  |  | 1.1 | **3a** | 12 h | 96 | | |
| | | | | **3b** | 2 h | 95 | 188 | 187[4] |
| | | | | **3c** | 20 min | 93 | | |
| f |  |  | 1.1 | **3a** | 12 h | 91 | | |
| | | | | **3b** | 16 h | 92 | 163—164 | 164[12] |
| | | | | **3c** | 15 min | 91 | | |
| g |  |  | 1.1 | **3a** | 10 min | 97 | | |
| | | | | **3b** | 2 min | 96 | 180—181 | — |
| | | | | **3c** | 1 min | 96 | | |
| h-1 |  |  | 1.0 | **3a** | 15 min | 97 | | |
| | | | | **3b** | 2 min | 99 | 175—176 | 175—175.5[13] |
| | | | | **3c** | 1 min | 96 | | |
| h-2 | |  | 2.1 | **3a** | | —[b] | | |
| | | | | **3b** | | —[b] | 174 | 174—175[14] |
| | | | | **3c** | 2 h | 89 | | |
| i-1 |  |  | 2.0 | **3a** | 1 h | 93 | | |
| | | | | **3b** | 1 h | 92 | 237—238 | — |
| | | | | **3c** | 2 min | 88 | | |
| i-2 | |  | 3.1 | **3a** | | —[c] | | |
| | | | | **3b** | 24 h | 69 | 205 | — |
| | | | | **3c** | 14 h | 93 | | |
| j-1 |  |  | 2.0 | **3a** | 10 min | 96 | | |
| | | | | **3b** | 3 min | 91 | 162—163 | — |
| | | | | **3c** | —[d] | 96 | | |
| j-2 | |  | 3.1 | **3a** | | —[c] | | |
| | | | | **3b** | 21 h | 57 | 218—218.5 | — |
| | | | | **3c** | 3 h | 98 | | |

a) Yield of isolated product. b) A mixture of mono- and dibromo compounds was obtained. c) A mixture of di- and tribromo compounds was obtained. d) Product **2j-1** precipitated almost immediately as soon as the solution of **3c** was added into the solution of **1j**.

magnesium sulfate and evaporated in vacuo to give a residue which was recrystallized from ethanol–water (1:3) affording **2a** as colorless crystals; yield 0.77 g (97%); mp 163—164 °C (lit,[9] mp 168.8 °C).

**4-Bromo-3,5-dimethylacetanilide (2g).** Compound **2g** was prepared from the reaction of 3,5-dimethylacetanilide (**1g**) with equimolecular amount of **3** by a similar procedure to that discribed above: colorless crystals; mp 180—181 °C (ethanol–water (1:3)): IR (KBr) 1670 $cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$) $\delta$=2.05 (3H, s, $COCH_3$), 2.34 (6H, s, 3 and 5-$CH_3$), 7.34 (2H, s, 2 and 6-H), 9.63 (1H, br. s, NH). Found: C, 49.58; H, 4.92; N, 5.74%. Calcd for $C_{10}H_{12}NOBr$: C, 49.61; H, 4.99; N, 5.79%.

**2,4-Dibromo-5-hydroxyacetanilide (2i-1).** Compound **2i-1** was prepared from 3-hydroxyacetanilide (**1i**) and 2 equiv of **3** by a similar procedure to that discribed above: colorless

crystals; mp 237—238 °C (ethanol–water (1:3)); IR (KBr) 1680 $cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$) $\delta$=2.17 (3H, s, $CH_3$), 7.55 (1H, s, 6-H), 7.75 (1H, s, 3-H), 8.38 (1H, br. s, OH), 10.08 (1H, br. s, NH). Found: C, 30.98; H, 2.19; N, 4.49%. Calcd for $C_8H_7NO_2Br_2$: C, 31.10; H, 2.29; N, 4.53%.

**3-Hydroxy-2,4,6-tribromoacetanilide (2i-2).** Compound **2i-2** was prepared similary from **1i** and 3 equiv of **3b** or **3c**: colorless crystals, mp 205 °C (ethanol–water (1:3)); IR (KBr) 1675 $cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$) $\delta$=2.08 (3H, s, $CH_3$), 3.50 (1H, br. s, OH), 7.73 (1H, s, 5-H), 9.69 (1H, br. s, NH). Found: C, 24.81; H, 1.60; N, 3.60%. Calcd for $C_8H_6NO_2Br_3$: C, 24.77; H, 1.56; N, 3.61%.

**5-Amino-2,4-dibromoacetanilide (2j-1).** Compound **2j-1** was prepared similary from **1j** and 2 equiv of **3**: colorless crystals, mp 162—163 °C (ethanol–water (1:3)); IR (KBr) 1655 $cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$) $\delta$=2.12 (3H, s, $CH_3$), 4.25 (2H, br. s, $NH_2$), 7.38 (1H, s, 6-H), 7.45 (1H, s, 3-H), 8.67 (1H, br. s, NH). Found: C, 30.97; H, 2.52; N, 8.90%. Calcd for $C_8H_8N_2OBr_2$: C, 31.20; H, 2.62; N, 9.10%.

**3-Amino-2,4,6-tribromoacetanilide (2j-2).** Compound **2j-2** was prepared similary from **1j** and 3 equiv of **3b** or **3c**: colorless crystals, mp 218—218.5 °C (ethanol–water (1:3)); IR (KBr) 1675 $cm^{-1}$ (CO); $^1H$ NMR ($CDCl_3$) $\delta$=2.10 (3H, s, $CH_3$), 4.28 (2H, br. s, $NH_2$), 7.62 (1H, s, 5-H),9.48 (1H, br. s, NH). Found: C, 24.97; H, 1.79; N, 6.98%. Calcd for $C_8H_7N_2OBr_3$: C, 24.84; H, 1.82; N, 7.24%.

We wish to thank Dr. Mamoru Nakai and Mr. Katsumasa Harada, Ube Laboratory, Ube Industries, Ltd., for elemental analysis.

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14) L. C. Raiford, *J. Am. Chem. Soc.*, **41**, 2076 (1919).
15) Exceptionally, the brominations of 3,4-dimethylacetanilide (**1f**), in which the para-position was occupied by methyl group, with **3** gave orthobromo derivative, 2-bromo-4,5-dimethylacetanilide (**2f**), respectively.
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