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"Conjugate" Substitution of Hydrogen in the Methyl Group of Pentabromotoluene in the Presence of Strong Bases

V. N. Shishkin*, S. S. Vakaeva*, and K. P. Butin**

* *Ogarev Mordovian State University, Saransk, Mordovia, Russia*

** *Lomonosov Moscow State University, Moscow, Russia*

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Abstract — The reactions of pentabromotoluene with *i*-PrONa or *t*-BuONa in pyridine give *N*-(pentabromobenzyl)pyridinium bromide and a mixture of isomeric tetrabromotoluenes. In the presence of bromine or carbon tetrabromide, the reductive debromination is blocked, and the reactions involve exclusively substitution of hydrogen in the methyl group of pentabromotoluene by the pyridinium residue.

Previously we found that pentabromotoluene $C_6Br_5CH_3$ (I) reacts with MeONa in pyridine to form, along with tetrabromo(methoxy)toluenes, isomeric tetrabromotoluenes, as well as compounds in which the methoxy group substitutes both bromine in the aromatic nucleus and hydrogen in the methyl group [1]. This finding suggests concurrent protophilic attacks of the methoxide anion by the methyl group of substrate **I**, whose possibility is provided by the relatively high acidity of the methyl group (by polarographic estimates, pK_a ~16 [2]). Such transformation opens the way to the synthesis of functional derivatives containing a polybromoaromatic residue via "conjugate" substitution of hydrogen in the methyl group of polybromomethylbenzenes, by-passing intermediate synthesis of polybromobenzyl bromides.

The "conjugate" substitution of hydrogen in the methyl group of pentabromotoluene can be presented by the reaction sequence (1)–(4).

$$C_6Br_5CH_3 + B^- \rightleftharpoons C_6Br_5CH_2^- + BH, \quad (1)$$

$$C_6Br_5CH_2^- \xrightarrow{} C_6Br_5CH_2Br + [C_6Br_4CH_3]^- \xrightarrow{BH} C_6Br_4HCH_3, \quad (2)$$

$$C_6Br_5CH_2^- \xrightarrow{[Br^+]} \mathbf{II}, \quad (3)$$

$$C_6Br_5CH_2Br + Nu \longrightarrow C_6Br_5CH_2Nu^-Br^+. \quad (4)$$

Reaction (1) is an acid–base reaction that provides the pentabromobenzyl anion. The latter as a soft base abstracts bromine as a positively charged species from another pentabromotoluene molecule to form pentafluorobenzyl bromide (**II**) and dehydrobromination products [reaction (2)]. Presumably, with a more effective donor of [Br^+] than pentabromotoluene (**I**), reaction (2) will be blocked. In this case, the major reaction pathway will involve formation of pentabromobenzyl bromide (**II**) [reaction (3)] whose reaction with nucleophilic reagents will give α-bromine substitution products [reaction (4)].

To obtain evidence for his hypothesis, we have studied transformations of compound **I** in pyridine in the presence of *t*-BuONa, since in this case bromine substitution in the polybromoaromatic nucleus with such a sterically hindered nucleophile is unlikely [3]. The composition of the reaction products was determined by a combination of GLC, TLC, and preparative isolation of individual compounds, as well as, in certain cases, by ^{1}H and IR spectroscopy. The reaction conditions and product compositions are listed in the table.

As seen from the table, the conversion of compound **I** in its reaction with a double excess of *t*-BuONa in pyridine is 42% within 1 h (exp. no. 1).

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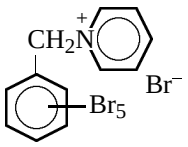
Reaction of pentabromotoluene (**I**) with sodium alkoxides RONa in pyridine (115°C, 1 h)

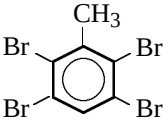
Exp. no.	RONa, additive	**I** : RONa : additive ratio	Conversion of substrate **I**, %	Identified reaction products[a]
1	*t*-BuONa	1 : 2	42	**IV** + **V** + **VI** (0.31), **III** (0.14), **VII** (traces)
2	*t*-BuONa	1 : 4	89	**IV** + **V** + **VI** (0.46), **III** (0.02), **VII** (traces)
3	*i*-PrONa	1 : 2	67	**IV** + **V** + **VI** (0.49), **III** (0.31), **VII** (traces)
4	*i*-PrONa	1 : 4	100	**IV** + **V** + **VI** (0.5), **III** (0.06), **VII** (traces)
5	*i*-PrONa, Br_2	1 : 4 : 2	44	**IV** + **V** + **VI** (0.37), **III** (0.22)
6	*i*-PrONa, Br_2	1 : 8 : 6	26	**IV** + **V** + **VI** (0.19), **III** (0.74)
7	*i*-PrONa, Br_2	1 : 10 : 6	17	**IV** + **V** + **VI** (traces), **III** (0.97)
8	*i*-PrONa, CBr_4	1 : 2 : 2	35	**III** (0.94), **VII** (traces)

[a] The yield, mol, per 1 mol of reacted compound **I**.

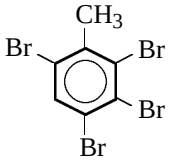
As reaction products we identified (2,3,4,5,6-pentabromobenzylpyridinium) bromide (**III**) and a mixture of isomeric tetrabromotoluenes, that comprises, by ^1H NMR data, 2,3,5,6-tetrabromotoluene (**IV**) (73.5%), 2,3,4,6-tetrabromotoluene (**V**) (24.5%), and 2,3,4,5-tetrabromotoluene (**VI**) (2%).



III



IV



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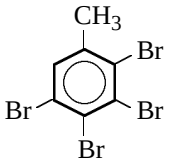
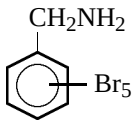


VI



VII

As seen from the composition of tetrabromotoluenes, pentabromotoluene is primarily dehydrobrominated *para* to the methyl group, which corresponds to the combined polar effect of the substituents in the benzene ring of the substrate. In addition, unidentified compounds and traces of pentabromobenzylamine (**VII**) are formed.

Increased excess of *t*-BuONa increases the conversion of compound **I**, but the fraction of pyridinium salt **III** in the reaction products sharply decreases compared with tetrabromotoluenes (exp. no. 2). Moreover, the fraction of unidentified products, too, increases. This result can be explained by further transformations of salt **III**. The heteroring cleavage in pyridinium derivatives under the action of nucleophiles, forming polymethines, is well known [4, 5]. In this connection we can suggest that in the reaction in hand, too, the pyridinium ring in salt **III** is cleaved under the action of excess *t*-BuONa. Evidence for this suggestion comes from the presence of trace amounts of pentabromobenzylamine (**VII**) among the reaction products. Amine **VII** was formed by decomposition of pentabromobenzylpyridinium bromide in the presence of *t*-BuONa or *i*-PrONa.

Note that in exp. nos. 1 and 2 we recovered unreacted compound **I**, which is probably associated with substantial steric hindrances to reaction of the polybromoaromatic compound to *t*-BuONa. Therefore, we took for the base the less sterically congested *i*-PrONa. Actually, the latter faster reacted in the same conditions (exp. no. 3). However, here, too, ca. 30% of unreacted pentabromotoluene (**I**) was obtained. With a greater excess of *i*-PrONa (1 : 4), the conversion of substrate **I** was near 100%.

In should be noted that in exp. no. 4, like in exp. no. 2, the fraction of salt **III** in the reaction products decreases compared with tetrabromotoluenes, on account of decomposition of the salt in the presence of excess base.

The formation of tetrabromotoluenes and pentabromobenzylpyridinium bromide (**III**) suggests that this process includes reactions (1), (2), and (4), and the role of nucleophile here is played by the pyridine

itself [reaction (4)]. In no one experiment we detected pentabromobenzyl isopropyl ether and bis(pentabromobenzyl) ether (the latter can be formed by reaction of pentabromobenzyl bromide with *t*-BuONa [6]). About 0.5 mol of a mixture of tetrabromotoluenes is formed per 1 mol of reacted compound **I** (exp. nos. 2–4), which corresponds to the theoretical yield by Eqs. (1) and (2).

To trap the pentabromobenzyl anion formed we used bromine. The reaction in the presence of Br_2 provides more salt **III** and less tetrabromotoluenes (exp. nos. 5–7), implying blocking of reaction (2), that enhances with increasing amount of Br_2 and gets complete when the $\mathbf{I}:RONa:Br_2$ ratio is 1:10:6. Evidence for this conclusion comes from the absence among the reaction products of tetrabromotoluene and the formation of ca. 1 mol of salt **III** per 1 mol of reacted substrate **I** (exp. no. 7), which corresponds to the theoretical yield of salt **III** in the reaction sequence (1), (3), and (4).

In his case, the source of $[Br^+]$ can be both the bromine itself and isopropyl hypobromite *i*-PrOBr formed by bromine reaction with *i*-PrONa [7]. Noteworthy is the great amount of unreacted pentabromotoluene (**I**), which may be associated with a deficit of the base. Probably, the *i*-PrOBr formed under the reaction conditions reacts with excess *i*-PrONa to form propene oxide and other compounds [7].

For the donor of $[Br^+]$ we also used CBr_4 [8]. In this case, at $C_6Br_5CH_3:CBr_4 = 1:2$ in the same conditions we isolated no other products than salt **III** and traces of amine **VII** (exp. no. 8). The absence in the reaction products of tetrabromotoluenes suggests complete blocking of reaction (2). However, with CBr_4 as the source of $[Br^+]$, the substrate conversion, too, is rather low (35%).

It is interesting to note that in dioxane or CCl_4 as solvents and in the presence of a phase-transfer catalyst no deprotonation of pentabromotoluene was observed.

EXPERIMENTAL

The IR spectra were obtained on an InfraLYUM FT-02 instrument. The ^1H NMR spectra were obtained on Bruker AM-300 (300 MHz) and Bruker DPX-400 (400 MHz) instruments in $CDCl_3$ and DMSO-d_6, internal reference HMDS.

Gas chromatography was performed on a Chrom-42 chromatograph, thermoionic detector, glass column (3000 × 3.5 mm, stationary phase Chromaton N-Super (0.16–0.20 mm) + 3% OV-17, oven temperature 220–260°C, carrier gas nitrogen.

Isomeric tetrabromotoluenes [2], pentabromotoluene [9], pentabromobenzyl bromide [9], pentabromobenzyl isopropyl ether [6], and bis(pentabromobenzyl) ether [6] were synthesized by described procedures.

(2,3,4,5,6-Pentabromobenzyl)pyridinium bromide (III). A mixture of 50 ml of pyridine and 5 g of pentabromobenzyl bromide (**II**) was heated under reflux for 4 h. The precipitate was filtered off, washed with dioxane, dried, and recrystallized from water. Yield 90%, decomp. point 264–265°C. IR spectrum (KBr), ν, cm^{-1}: 3050 w, 3029 w, 2998 m, 2990 m, 2952 w, 2836 w, 1624 s, 1512 w, 1497 m, 1476 v.s, 1429 m, 1346 w, 1321 m, 1304 w, 1287 w, 1229 w, 1186 m, 1156 m, 1148 m, 1063 w, 938 w, 777 m, 735 w, 685 w, 675 w, 480 w. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 6.36 s (2H, $CH_2C_6Br_5$), 8.12–8.31 m (2H, $H^{2,6}$), 8.62–8.77 m (1H, H^4), 8.94–9.16 m (2H, $H^{3,5}$).

Reaction of pentabromotoluene (I) with bases in pyridine (see table). A mixture of 200 ml of pyridine and 0.02 mol of compound **I** was heated until the latter dissolved completely, after which required amounts of bases and additives were added. The resulting mixtures were heated under reflux for 1 h, treated with water, and neutralized with HCl. The precipitate was filtered off, washed with water, and dried. Reaction products were extracted with hot dioxane, the extract was evaporated, and the residue was analyzed by TLC, GLC, and ^1H NMR. The residue undissolved in hot dioxane was salt **III** (by IR spectroscopy).

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