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# *N*-(2,2,2-Trichloroethylidene)- and *N*-(1-Hydroxy-2,2,2-trichloroethyl)amides in C-Amidoalkylation Reaction of Functionally-substituted Aromatic Compounds

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**Abstract**—A reaction with phenol and pyrocatechol of *N*-(2,2,2-trichloroethylidene)arenesulfonyl-, ethoxycarbonylamides and 1-hydroxy-substituted *N*-(2,2,2-trichloroethyl)amides of arenesulfonic, carbamic, and acetic acids in the presence of oleum or in sulfuric acid provided the corresponding (1-amido-2,2,2-trichloroethyl)-substituted phenols. *N*-(2,2,2-Trichloroethylidene)-4-chlorobenzenesulfonamide reacted with salicylamide in the presence of oleum to afford 3-aminocarbonyl-4-[2,2,2-trichloro-1-(4-chlorobenzenesulfonamido)ethyl]benzene whereas the 1-hydroxy-2,2,2-trichloroethylamides of the acetic, carbamic, and arenesulfonic acids did not enter into such reactions.

The reactivity of N-sulfonyl-, acyl-, and alkoxycarbonylimines of chloral originates from the presence in their structure of strong electron-withdrawing substituents at the azomethine group [1]. Reactions of these imines with compounds containing hydroxy, amide, or amino groups as a rule results in products of the nucleophilic addition of OH [1, 2] or NH [1, 3] groups across the azomethine bond. We showed lately [4] that arenesulfonylimines of chloral in the presence of oleum take another reaction route with phenol, 2-halo- and 2-alkyl-substituted phenols. Instead of products of the nucleophilic addition we obtained compounds resulting from C-sulfonamidotrichloroethylation of the aromatic ring [4]. The same compounds were prepared by reaction of phenols with *N*-(1-hydroxy-2,2,2-trichloroethyl)amides of sulfonic acids in the presence of concn. sulfuric acid [4].

We continued systematic investigation on the C-amidoalkylating ability of polyhaloaldehyde imines and derivatives thereof [5–7] with respect to functionally-substituted arenes containing hydroxy groups or amide functions.

We were first to establish that *N*-(2,2,2-trichloroethylidene)ethoxyformamide (**I**) in the presence of oleum reacted as arenesulfonylimines with arenes and hetarenes [4, 7], in particular, with phenol and pyrocatechol, giving rise to ethoxycarbonylamino(trichloroethyl)-substituted arenes **IIIa–d** in 42–97% yield (Table 1).

4-Chlorobenzenesulfonic acid *N*-(2,2,2-trichloroethylidene)amide (**II**) in the presence of oleum also reacted regioselectively with pyrocatechol and salicylamide affording the corresponding C-aminotrichloroethylated products **IVa, b** in up to 90% yield (Table 1).

$$\underset{\textbf{I, II}}{RN{=}CHCCl_3} \xrightarrow{ArH,\ Oleum} \underset{\textbf{IIIa–d, IVa, b}}{RNHCH(Ar)CCl_3}$$

R = EtOC(O) (**I, III**), 4-$ClC_6H_4SO_2$ (**II, IV**); **III**, Ar = 4-$HOC_6H_4$ (**a**), 3,4-$(HO)_2C_6H_3$ (**b**), Ph (**c**), 4-$MeC_6H_4$ (**d**), **IV**, Ar = 3,4-$(HO)_2C_6H_3$ (**a**), 4-HO-3-$NH_2C(O)C_6H_3$ (**b**).

The reaction is carried out in the presence of oleum at room temperature and vigorous stirring of the reaction mixture in a medium of the aromatic hydrocarbon used as a substrate or in halogenated hydrocarbon. The optimal duration of the process 3–5 h. At the use of concn. sulfuric acid instead of oleum the reaction fails to proceed.

The heating and the use of large oleum amount reduces the yield of C-amidoalkylation products **III, IV** apparently due to side reaction of arene sulfonylation and to low stability of carbonyl and alkoxycarbonyl derivatives against strong mineral acids.

It is significant that in the presence of oleum the reaction of chloral ethoxycarbonylimine with arenes affords compounds **IIIa–d** without noticeable damage to the ethoxycarbonyl moiety.

In extension of systematic investigation on C-amidoalkylating properties of 1-functionally-sub-

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stituted polyhaloethylamides we studied the reaction between *N*-(1-hydroxy-2,2,2-trichloroethyl)ethoxyformamide and *N*-(1-hydroxy-2,2,2-trichloroethyl)-amides of arenesulfonic and acetic acids **Va–c** with phenol, pyrocatechol, and salicylamide in the presence of sulfuric acid. It was established that amides **Va–c** in the presence of concn. sulfuric acid also reacted regioselectively with phenol, pyrocatechol, benzene, and toluene to afford the products of C-amidotrichloroethylation of the latter, amides **IIIa–d, IVa, VIa–d.**

$$\underset{\textbf{Va–c}}{RNHCH(OH)CCl_3} \xrightarrow{ArH,\ H_2SO_4} \underset{\textbf{IIIa–d, IVa, VIa–d}}{RNHCH(Ar)CCl_3}$$

R = EtOC(O) (**IIIa–d, Va**), 4-$ClC_6H_4SO_2$ (**Vb, IVa**), MeC(O) (**Vc, VIa–d**); **VI**, Ar = 4-$HOC_6H_4$ (**a**), **3,4-$(HO)_2C_6H_3$** (**b**), Ph (**c**), 4-$MeC_6H_4$ (**d**).

The reaction was carried out in the same way as above for 3–8 h in the presence of 6–10-fold excess of sulfuric acid. The heating and the use of larger amounts of sulfuric acid did not increase the yield of compounds **III, IV, VI,** apparently due to the reasons discussed before. The yield is increased in the presence of excess aromatic compound and at cooling at the beginning of the reaction.

We failed to C-amidoalkylate the salicylamide with hydroxytrichlroethylamides **Va–c** under any conditions.

The C-amidoalkylating activity of amides **Va–c** was formerly investigated with respect to benzene, its alkyl and halo derivatives [8–10]. It was reported that arene C-amidoalkylation with alkoxycarbonyl- and acylamides required long time (up to 100 h) and great excess (~10 to 100-fold) of sulfuric acid [9, 10]. Yield of reaction products did not exceed 49% for ethoxy derivatives [9] and 86% for acetyl derivatives [10]. The structure of compounds formed was confirmed by chemical reactions [9, 10].

The composition of synthesized amidotrichloroethyl-substituted arenes **III, IV, VI** is confirmed by elemental analyses (Table 1), and the structure was proved by spectral methods (Table 2).

In the IR spectra of amides **III, IV, VI** are present absorption bands from vibrations of the NH, C=C arom C–H bonds of alkyl groups. The IR

**Table 2.** IR and $^1$H NMR spectra of compounds $RNHCHArCCl_3$ **III, IV, VI**

| Compd. no. | IR spectrum, $\nu$, $cm^{-1}$ | | | $^1$H NMR spectrum, $\delta$, ppm ( $J_{NHCH}$, Hz)[a] | | | | |
|---|---|---|---|---|---|---|---|---|
| | NH | CO | other absorption bands | solvent | CH | NH | Ar | R |
| **IIIa** | 3290 | 1670 | 2950–2970 (C–H aliph) | $(CH_3)_2CO$-$d_6$ | 5.58 | 6.78 | 6.86, 7.54 (*AA'BB'*) | 1.17 t, 4.07 q |
| **IIIb** | 3240 | 1680 | 2900–2970 (C–H aliph), 3420 (OH) | DMSO-$d_6$ | 5.49 d (10.0) | 7.40 d | 6.82 d, 7.04 d, 7.20 s | 1.16 t, 4.07 q |
| **IIIc** | 3280 | 1680 | 2930–2960 (C–H aliph), 3050 (C–H arom) | $CDCl_3$ | 5.61 d (9.2) | 5.96 d | 7.34, 7.47 m | 1.22 t, 4.12 q |
| **IIId** | 3380 | 1680 | 2930–2980 (C–H aliph) | $CDCl^3$ | 6.01 d (10.4) | 5.58 d | 7.14, 7.36 (*AA'BB'*) 2.32 (Me) | 1.19 t, 4.12 q |
| **IVa** | 3250 | – | 3420, 3470 (OH), 1160, 1320 ($SO_2$) | $(CH_3)_2CO$-$d_6$ | 5.06 | 8.71 | 6.64 d, 6.82 d, 6.97 s | 7.32, 7.62 (*AA'BB'*) |
| **IVb** | 3200, 3250 | 1670 | 3480 (OH), 1170, 1350 ($SO_2$) | DMSO-$d_6$ | 5.02 d (10.6) | 8.23 d | 6.64 d, 7.28 d, 7.86 s | 7.18, 7.55 (*AA'BB'*) |
| **VIa** | 3280 | 1650 | 3400 (OH), 2870–2890 (C–H aliph) | DMSO-$d_6$ | 5.95 d (9.7) | 7.58 d | 6.86, 7.25 (*AA'BB'*) | 2.11 |
| **VIb** | 3280 | 1660 | 3390 (OH) | DMSO-$d_6$ | 5.89 d (9.7) | 7.62 d | 6.82 d, 6.93 d, 7.20 s [3,4-$(OH)_2C_6H_3$)] | 2.03 |
| **VIc** | 3260 | 1680 | 2930–2950 (C–H aliph), 3050 (C–H arom) | $CDCl_3$ | 5.87 d (9.7) | 6.54 d | 7.23, 7.35 m | 1.98 |
| **VId** | 3240 | 1650 | 2920, 2950 (C–H aliph), 3020 (C–H arom) | DMSO-$d_6$ | 5.91 d (9.8) | 6.56 d | 7.16, 7.38 (*AA'BB'*) 2.34 (Me) | 2.07 |

[a] No splitting of NHCH signal was observed in the $^1$H NMR spectrum recorded in acetone.

spectra of ethoxycarbonylamides **III** and acetamides **VI** contain besides the absorption bands of C=O groups, the IR spectra of sulfonamide derivatives **IV** contain the absorption band of $SO_2$ group. In the IR spectra of the derivatives of substituted phenols appear strong absorption bands of the hydroxy groups (Table 2). In the IR spectrum of compound **IVb** the absorption bands of C=O, NH, and OH groups are unlike those of the initial salicylamide by frequency and form.

In the $^1$H NMR spectra of compounds **III, IV, VI** appear a characteristic doublet of the NHCH fragment (*J* 9–10 Hz), signals of aromatic protons, and of protons from acetyl or ethoxycarbonyl group. The relative integral intensities in the spectra correspond to the assumed structures of compounds **III, IV, VI**.

The comparison of the published data [8–10] and those obtained in the present study on the optimal duration of reactions and on the yields of C-amidoalkylation products permits a conclusion that the most active in the C-amidoalkylation among the *N*-(1-hydroxy-2,2,2-trichloroethyl)amides are the sulfonamide derivatives. Less active are the alkoxycarbonylamides, and the amides of carboxylic acids are the least active. It is apparently caused by different ability of the lone electron pair of the amide nitrogen to stabilize the amido-substituted carbocations that are generated under the action of proton-donor reagents from trichloroethylamides containing a nucleofugal group in the α-position to the nitrogen.

In the alkoxycarbonyl- and acylamides the lone electron pair of the amide nitrogen is capable to conjugation with a carbonyl group and therefore it less stabilizes the carbocation that results in increased duration of the reaction and decreased yield of C-amidoalkylated products.

The synthesized amidotrichloroethyl-substituted arenes **III, IV, VI** are colorless or lightly colored crystalline substances with slight specific odor; they are well soluble in organic solvents and insoluble in water.

## EXPERIMENTAL

$^1$H NMR spectra were recorded on spectrometer Bruker DPX-400 (400 MHz), internal reference HMDS. IR spectra were registered on spectrophotometer Specord 75IR from samples pelleted with KBr.

Trichloroethylideneamides **I, II** were obtained by procedures [11] and [4] respectively.

In reactions was used 3–20% oleum.

***N*-[1-(4-Hydroxyphenyl)-2,2,2-trichloroethyl]-ethoxycarbonylamine (IIIa).** (a) A solution of 0.01 mol of amide **I** in 10 ml of chloroform, 1 ml of oleum, and 0.01 mol of phenol were vigorously stirred at room temperature for 5 h. The reaction mixture was diluted with 15–20 ml of cold water and with water solution of sodium carbonate. The insoluble reaction product was filtered off, dried in a vacuum desiccator over $P_2O_5$, and recrystallized from acetone–chloroform mixture, 1:1. (b) A solution of 0.01 mol of amide **Va** in 10–15 ml of chloroform, 2 ml of concn. sulfuric acid, and 0.01 mol of phenol were vigorously stirred at room temperature for 5 h. The workup of the reaction mixture was carried out as in procedure *a*.

Amides **IIIb–d, IVa** were prepared similarly along procedures a, b. Compounds **VIa–d** were obtained by method b.

***N*-[1-(3-Aminocarbonyl-4-hydroxyphenyl)-1,1,2-trichloroethyl]-4-chlorobenzenesulfonamide (IVb).** A solution of 0.01 mol of amide **II** in 10 ml of anhydrous chloroform and 0.01 mol salicylamide were stirred in the presence of 0.5 ml of oleum for 5 h at room temperature. The solvent was distilled off in a vacuum. The residue was washed with water (10 ml), then with 5–7% aqueous ammonia (20 ml), and again with water till neutral washings. Then the insoluble product was dried in a vacuum desiccator over $P_2O_5$, and recrystallized from acetone–chloroform mixture, 1:1.

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