Monatshefte für Chemie 128, 919–925 (1997)

Monatshefte für Chemie
Chemical Monthly

Printed in Austria

Reaction of π-Deficient Aromatic Heterocycles with Ammonium Polyhalides III [1]. Halogenation of Phenothiazin-5-oxide with Benzyltriethylammonium Polyhalides

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Summary. Halogenation of phenothiazin-5-oxide with benzyltriethylammonium polyhalides (*BTEA*) under mild conditions afforded chloro- and bromophenothiazines as well as a few unexpected products e.g. 1,3,7,9-tetrachloro-phenothiazin-5-oxide, 7,3′-dibromo-3, 10′-diphenothiazinyl tribromide, and 7,3′-dichloro-3,10′-diphenothiazinyl tetrachloroiodate. A new charge-transfer complex of phenothiazine-5-oxide with bromine is reported.

Keywords. Halogenation; Phenothiazines.

Reaktion elektronenarmer aromatischer Heterocyclen mit Ammoniumpolyhalogenverbindungen, 3. Mitt. [1]. **Halogenierung von Phenothiazin-5-oxid mit Benzyltriethylammoniumpolyhalogeniden**

Zusammenfassung. Halogenierung von Phenothiazin-5-oxid mit Benzyltriethylammoniumhalogeniden (*BTEA*) unter milden Bedingungen ergab neben Chlor- und Bromphenothiazinen einige unerwartete Reaktionsprodukte wir z.B. 1,3,7,9-Tetrachlorphenothiazin-5-oxid, 7,3′-Dibrom-3,10′-diphenothiazinylbromid und 7,3′-Dichlor-3,10′-diphenothiazinyltetrachloriodat. Außerdem wird über einen *charge-transfer*-Komplex von Phenothiazin-5-oxid mit Brom berichtet.

Introduction

Halogenation of aliphatic and aromatic compounds with quaternary ammonium polyhalides has been widely applied since 1987, very often leading to results superior to those achieved using classical methods [3]. However, halogenation of heterocyclic compounds with these reagents has not attracted much attention so far [2, 4].

After the successful halogenation of acridine and acridone with *BTEA* polyhalides [2], we have focussed our interest on phenothiazine derivatives, considering the practical importance of these compounds and the lack of knowledge with respect to their reactivity and the mechanisms involved in their chemical transformations.

In the presence of the corresponding molecular halogens or their hydracids, phenothiazin-5-oxide undergoes reductive chlorination [5–10] or bromination [5,6,10–12] yielding 1,3,7,9-tetrachloro-phenothiazine and 3,7,-di-, 1,3,7-tri-, or 1,3,7,9-tetrabromo-phenothiazine, respectively. There is no reference to the halogenation of phenothiazin-5-oxide proceeding without loss of oxygen (non-reductive halogenation) in the literature.

Results and Discussion

In the present paper, we report the halogenation of phenothiazin-5-oxide with benzyltriethylammonium tribromide (*BTEA*Br_3) and benzyltriethylammonium tetrachloride (*BTEA*ICl_4). The results of our experiments are summarized in Table 1. Besides the expected products of reductive halogenation, such as 1,3,7,9-tetrachloro- and 1,3,7,9-tetrabromo-phenothiazine, obtained in yields superior to any other previous method, we could isolate 3,7-dichloro-phenothiazine and 1,3,7,9-tetrachloro-phenothiazin-5-oxide which cannot be prepared by classical halogenation of phenothiazin-5-oxide. The formation of the latter compound apparently indicates a non-reductive pathway. It is the consequence of a hydrolysis of the phenazathionium cation, resulting from the oxidation of tetrachlorophenothiazine with an excess of *BTEA*ICl_4 under kinetically controlled conditions (Scheme 1) [10].

The same halogenation reagents allowed us to isolate two stable, well crystallized salts of the so-called "green products" ($\mathbf{G}^+$), the oxidized form of the 3,10′-diphenothiazine. The "green products" appear very often in processes involving phenothiazinyl or phenazathionium species [10], but only a few salts of $\mathbf{G}^+$ could be isolated as well defined compounds [13,14]. We succeeded in isolating a brominated (**a**) and a chlorinated (**e**) salt of $\mathbf{G}^+$ (Scheme 2).

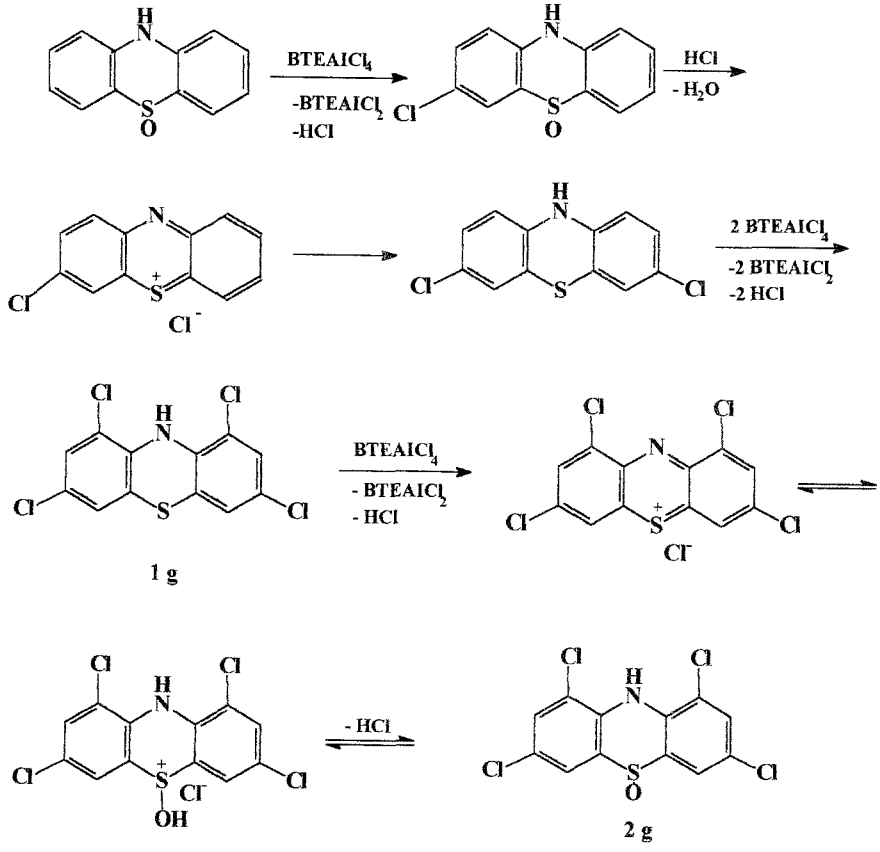
Structures **a** and **e** are supported by elemental analyses and by spectroscopic data: the absence of an ν-NH band in the IR spectrum, bands at 464 and 640 nm for **a** and at 468 and 650 nm for **e** characteristic for $\mathbf{G}^+$ in the UV/Vis spectrum [14–16], and a singlet with $g = 1.9945$, $DH = 19.56$ gauss for **a** as well as a singlet with $g = 1.9932$, $DH = 9.5$ gauss for **e**, respectively, in the ESR spectrum.

Moreover, the chemical behavior of $\mathbf{G}^+\mathbf{a}$ and $\mathbf{G}^+\mathbf{e}$ is consistent with the proposed structures. Upon the refluxing in acetic acid for a few minutes, 3-bromophenothiazine and 7-bromophenothiazone or the corresponding chlorinated derivatives could be detected by TLC analysis. This provided a very good method for the preparation of the rather elusive 3-bromo-phenothiazine (compound **b**, see Table 1 and Experimental).

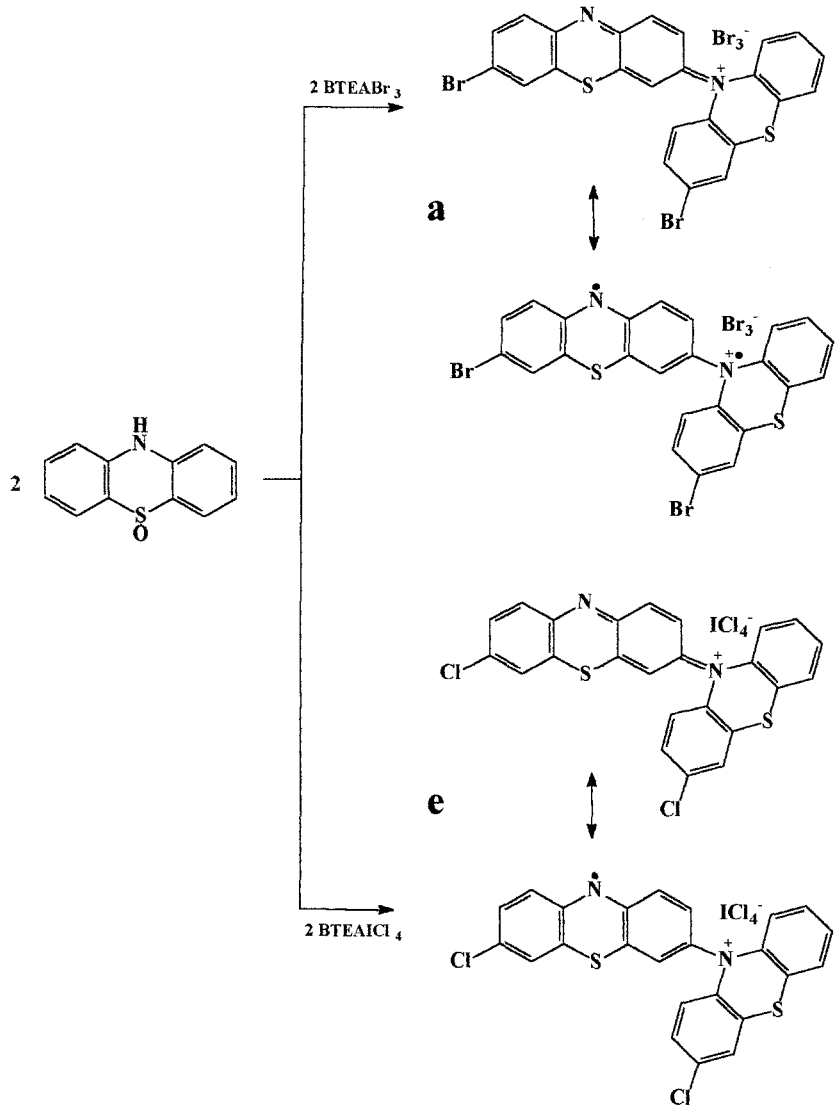
We also isolated a charge-transfer complex of 3-bromo-phenothiazin-5-oxide with bromine (compound **d**, Table 1) with a 2:1 molecular ratio of 3-bromo-phenothiazin-5-oxide:bromine, accurately reflected by elemental analysis. The IR spectrum clearly shows an intense band at 1051 cm^{-1}, corresponding to the SO stretching vibration, and a band at 3240 cm^{-1} generated by the NH group. The UV/Vis spectrum in *DMF* exhibits absorption maxima at 285, 315, and 344 nm, characteristic for phenothiazin-5-oxide [15] (taking into account the bathocromic shift induced by bromine [10]) and an absorption at 520 nm characteristic for the phenothiazinyl cation radical [15]. This fact, in combination with the intense ESR

Table 1. Halogenation products of phenothiazin-5-oxide (**1**) with *BTEA* polyhalides

	Molecular ratio (*BTEAY*:1), solvent	Reaction products	M.p. (lit. m.p.) (°C)	Yield (%)
BTEABr_3	1.5, acetic acid	7,3′-dibromo-3,10′-diphenothiazinyl tribromide (**a**)	151–153	50
–	–	3-bromo-phenothiazine (**b**)	180–181 ([21]: 181.5)	71
BTEABr_3	2, acetic acid	1,3,7,9-tetrabromo-phenothiazine (**c**)	270–271 ([22]: 272–273)	70
BTEABr_3	3, acetic acid	1,3,7,9-tetrabromo-phenothiazine (**c**)	270–271	94
BTEABr_3	2, methanol	(3-Bromo-phenothiazine-5-oxide)$_2$·Br_2 (**d**)	253–254	60
BTEAICl_4	1, methanol	7,3′-dichloro-3, 10′-diphenothiazinyl tetrachloroiodate (**e**)	134–135	41
BTEAICl_4	2, acetic acid	3,7-dichloro-phenothiazine (**1f**)	227–229 ([23]: 227)	30
		1,3,7,9-tetrachloro-phenothiazine (**2f**)	230–233 ([24]: 235)	53
BTEAICl_4	4, acetic acid	1,3,7,9-tetrachloro-phenothiazine (**1g**)	230–233	30
		1,3,7,9-tetrachloro-phenothiazine-5-oxide (**2g**)	180–181	28



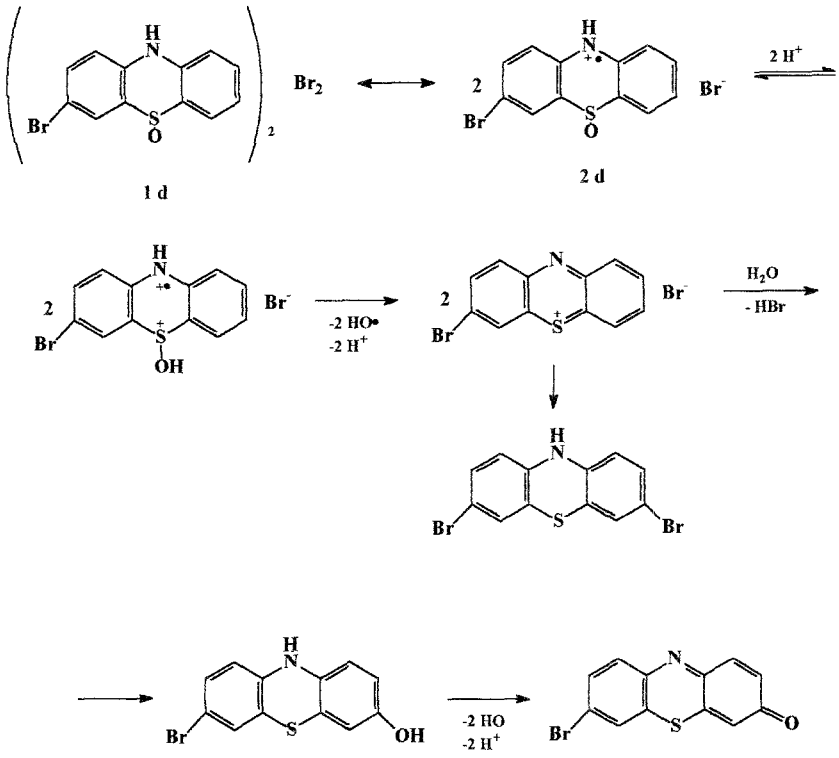
Scheme 1



Scheme 2

singlet signal ($g = 1.9995$, $DH = 15.6$ gauss), indicates a transfer of the electron from phenothiazin-5-oxide to bromine, confering a cation radical character to the complex (structure **2d**, Scheme 3). This is also reflected by its chemical behavior: 5 min reflux in acetic acid yields 3,7-dibromo-phenothiazine and 7-bromo-phenothiazone (detected by TLC), a reaction characteristic for phenothiazinyl species [10] (Scheme 3).

To our knowledge, this is the first charge-transfer complex of a phenothiazin-5-oxide derivative, only similar compounds derived from phenothiazine being reported in the literature. The important magnetical and electrical properties of this compound, considering the paramagnetic and semiconducting characteristics of the charge-transfer complexes of phenothiazines with bromine [17–20], will be reported elsewhere.



Scheme 3

Experimental

The elemental analyses for C, H, N, and halogen were within ±0.4% of the theoretical values for the new compounds **a, d, e,** and **2g**. Melting points are uncorrected. Mass spectra were recorded on a Varian MAT 311 instrument, ESR spectra on a Radiopan 253 SE/X spectrometer at a modulation frequency of 1000 kHz, IR spectra on a Unicam SP 200 G spectrometer, and UV/Vis spectra on a Carl Zeiss Specord instrument. The reactions were monitored by TLC using benzene:ether (4:1) as eluent; visualization was performed with iodine. *BTEA* polyhalides were prepared according to literature data [2].

7,3'-Dibromo-3,10'-diphenothiazinyl tribromide (**a**)

A mixture of phenothiazin-5-oxide (0.215 g, 0.1 mol), *BTEA*Br_3 (0.7 g, 1.5 mmol), and acetic acid (20 ml) was stirred magnetically at room temperature for 3 h. Then the reaction mixture was filtered and the precipitate was washed with hot water yielding 0.2 g (50%) of compound **a**, m.p.: 151–153°C.

3-Bromo-phenothiazine (**b**)

0.2 g of compound **a** were refluxed in acetic acid (15 ml) for 15 min. Subsequently, the mixture was filtered and the precipitate was collected, dissolved in acetone, and chromatographed on silica gel with benzene as eluent. The second fraction was collected; removal of the solvent afforded 0.05 g (71%) of 3-bromo-phenothiazine; m.p. :180–181°C (Ref. [21]: 181.5°C), MS: $m/z = 277/279$ (M^+).

1,3,7,9-Tetrabromo-phenothiazine (**c**)

A mixture of phenothiazin-5-oxide (0.125 g, 1 mmol), *BTEA*Br_3 (1.35 g, 3 mmol), and acetic acid (20 ml) was stirred magnetically at room temperature for 6 h and then refluxed for 15 min. Subsequently it was cooled, filtered, and the precipitate was washed with acetone yielding 0.49 g (94%) of compound **c**. M.p.: 270–271°C (Ref. [21]: 272–273°C); MS: $m/z = 511/513/515/517/519$ (M^+).

(3-Bromo-phenothiazin-5-oxide)$_2$·Br_2 (**d**)

A mixture of phenothiazin-5-oxide (0.215 g, 1 mmol), *BTEA*Br_3 (0.9 g, 2 mmol), and methanol (15 ml) was stirred magnetically at room temperature for 6 h. Then the reaction mixture was filtered and the precipitate was washed with acetone affording 0.22 g (59%) of compound **d**, m.p.: 253–254°C.

7,3′-Dichloro-3,10′-diphenothiazinyl tetrachloroiodide (**e**)

A mixture of phenothiazin-5-oxide (0.215 g, 1 mmol), *BTEA*ICl_4 (0.46 g, 1 mmol), and acetic acid (20 ml) was stirred magnetically at room temperature for 7 h. Then the reaction mixture was filtered and the precipitate was washed with acetic acid yielding 0.15 g (41%) of compound **e**, m.p.:134–135°C.

3,7-Dichloro-phenothiazine (**1f**) and *1,3,7,9-Tetrachloro-phenothiazine* (**2f**)

A mixture of phenothiazin-5-oxide (0.215 g, 1 mmol), *BTEA*ICl_4 (0.9 g, 2 mmol), and acetic acid (20 ml) was stirred magnetically at room temperature for 2 h. Then the reaction mixture was filtered and the precipitate was washed with acetone yielding 0.19 g (53%) 1,3,7,9-tetrachloro-phenothiazine (**2f**); m.p.: 230–232°C (Ref. [24]: 235°C), MS: $m/z = 335/337/339/341/343$ (M^+). The filtrate was poured into water (20 ml), and the resulting precipitate was collected yielding 0.08 g (30%) of 3,7-dichlorophenthiazine (**1f**); m.p.: 227–229°C (Ref. [23]: 227°C), MS: $m/z = 267/269/271$ (M^+).

1,3,7,9-Tetrachloro-phenothiazine (**1g**) and *1,3,7,9-Tetrachloro-phenothiazin-5-oxide* (**2g**)

A mixture of phenothiazin-5-oxide (0.215 g, 1 mmol), *BTEA*ICl_4 (1.8 g, 4 mmol), and acetic acid (20 ml) was stirred magnetically at room temperature for 2 h. Subsequently the reaction mixture was filtered and the precipitate was washed with acetone affording 0.1 g (30%) 1,3,7,9-tetrachloro-phenothiazine (**1g**); m.p.: 230–232°C (Ref. [23]: 235°C), MS: $m/z = 335/337/339/341/343$ (M^+). The filtrate was poured into water (20 ml) and the resulting precipitate was collected yielding 0.1 g (28%) of 1,3,7,9-tetrachlorophenothiazin-5-oxide (**2g**); m.p.: 180–181°C, MS: $m/z = 351/353/355/357/359$ (M^+), IR: 1050 (ν_{so}), 3340 (ν_{NH})cm^{-1}.

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Received March 11, 1997. Accepted March 17, 1997