REACTION OF П-DEFICIENT AROMATIC HETEROCYCLES WITH AMMONIUM POLYHALIDES.

П[1].HALOGENATION OF PHENOTHIAZINE WITH BENZYLTRIETHYLAMMONIUM (BTEA) POLYHALIDES.

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ABSTRACT : The reactions of phenothiazine with benzyltriethylammonium polyhalides under mild, non-toxic conditions yield halogenophenothiazines and, for the first time to our knowledge, charge-transfer complexes with mixed halogenes of the type phenothiazine Cl_xI_y .

INTRODUCTION

Halogenation with quaternary ammonium polyhalides has been widely applied since 1987 in the class of aliphatic and aromatic compounds (2) but it was seldom used for heterocyclic compounds, except for thiophene (3) and acridine derivatives (1). Due to the fact that the results obtained by us (4) using BTEA in halogenation of acridine and acridone compounds were better, from a synthetic point of view, comparatively with classical methods, we extended our study to phenothiazines, in view of the practical importance of this class of substances.

So far, a great variety of reagents have been used for the halogenation of phenothiazines *e .g* . molecular chlorine (4-7), $CuCl_2$ (8,9), $NaNO_2$ and HCl (10), $SOCl_2$ (11), PCl_5 (12,13), HCl in the presence of either nitrous vapors (14) or H_2O_2 (15) for chlorination ; bromine (6,16,17) $NaNO_2$ and HBr (10) or $CuBr_2$ (18) for bromination. Iodination with molecular iodine leads only to charge-transfer complexes with paramagnetic and semiconducting properties (19-22). Similar compounds with bromine (23-25) or mixed halogens ($Br_x I_y$) (26) were also prepared.

EXPERIMENTAL

The elemental analyses for C, N and halogens were within ± 0.4 % of the theoretical values for the new compounds resulted from reaction e and g (see Table). M.p. were uncorrected. Mass spectra were recorded on a Varian MAT 311 instrument, ESR spectra on a Radiopan 253 SE/X instrument at a modulation of 100 kHz, IR spectra were recorded, in pellets, on an Unicam SP 200 G instrument and UV-VIS spectra, in CH_2Cl_2 solution, on a Carl Zeiss Specord spectrometer. The reactions were monitored by TLC using benzene:ether 4:1 as eluent and visualisation was done with iodine. BTEA polyhalides were prepared according to literature data (1).

3,7-Dibromophenothiazine

A mixture of phenothiazine (0.2 g, 1mmol), $BTEABr_3$ (0.9 g, 2 mmols) and methanol (15 mL) was refluxed for 6 hrs. The reaction mixture was cooled and the resulted precipitate was filtered and washed with CH_2Cl_2 yielding 0.2 g (56%) of 3,7-dibromophenothiazine, m.p.=198-199 ^{0}C [lit. ^{0}C 193 and 206 (6 a, 16)] MS: m/e M^+ 355/ 357/ 359.

1,3,7,9,-Tetrabromophenothiazine

A mixture of phenothiazine (0.2g, 1 mmol), $BTEABr_3$ (3.6 g, 8 mmols) and acetic acid (25 mL) was refluxed for 2 hrs. The reaction mixture was then cooled, the precipitate filtered and washed with acetone yielding 0.4 g (78%) of 1,3,7,9-tetrabromophenothiazine, m.p.=269-272 ^{0}C [lit. ^{0}C 272-273 (16)]. M.S. : m/e M^+ 511/ 513/ 515/ 517/ 519.

(3-Chlorophenothiazine)$_2$. ICl_3

A mixture of phenothiazine (0.2g, 1 mmol), $BTEAICl_4$ (0.92g, 2 mmols) and acetic acid (20 mL) was magnetically stirred at room temperature for 7 hrs. Subsequently the reaction mixture was filtered and the precipitate was washed with acetic acid yielding 0.2 g (57%) of compound (3-chlorophenothiazine)$_2$. ICl_3. M.p.= 136-137 ^{0}C.

1,3,7,9-Tetrachlorophenothiazine

A mixture of phenothiazine (0.2 g, 1 mmol), $BTEAICl_4$ (1.84 g, 4 mmols) and acetic acid (20 mL) was magnetically stirred at room temperature for 20 hrs, then it was filtered and the precipitate washed with acetone, yielding 0.25 g of crude product, m.p=222-226 ^{0}C. After recrystallization from nitrobenzene, 0.2 g of pure 1,3,7,9-tetrachlorophenothiazine were obtained, m.p.=230-231^0 C [lit.^{0} C 235(15)]. M. S. : m/e M^+ 335/ 337 / 339 / 341/ 343.

3,7-Dichlorophenothiazine.ICl_3

A mixture of phenothiazine (0.2 g, 1 mmol), $BTEAICl_2$ (1.6 g, 4 mmols) and acetic acid (20 mL) was magnetically stirred for 24 hrs., then it was filtered yielding 0.1 g of crude product. After recrystallization from benzene, 0.06 g (12%) of 3,7-dichlorophenothiazine.ICl_3 were obtained, m.p.=150-154 ^{0}C. M.S. : m/e M^+ 499/ 501/ 503/ 505/ 507 ; 367 (M^+ - 232).

RESULTS

Halogenation with BTEA polyhalides demonstrated that there still are some unexplored possibilities. The results of halogenation of phenothiazine with benzyltriethylammonium tribromide ($BTEABr_3$), dichloroiodate ($BTEAICl_2$) and tetrachloroiodate ($BTEAICl_4$) are summarized in Table.

Table. Halogenation of phenothiazine (1) with BTEA polyhalides in acetic acid (reaction a,c,d,e,f and g) or methanol (reaction b) .

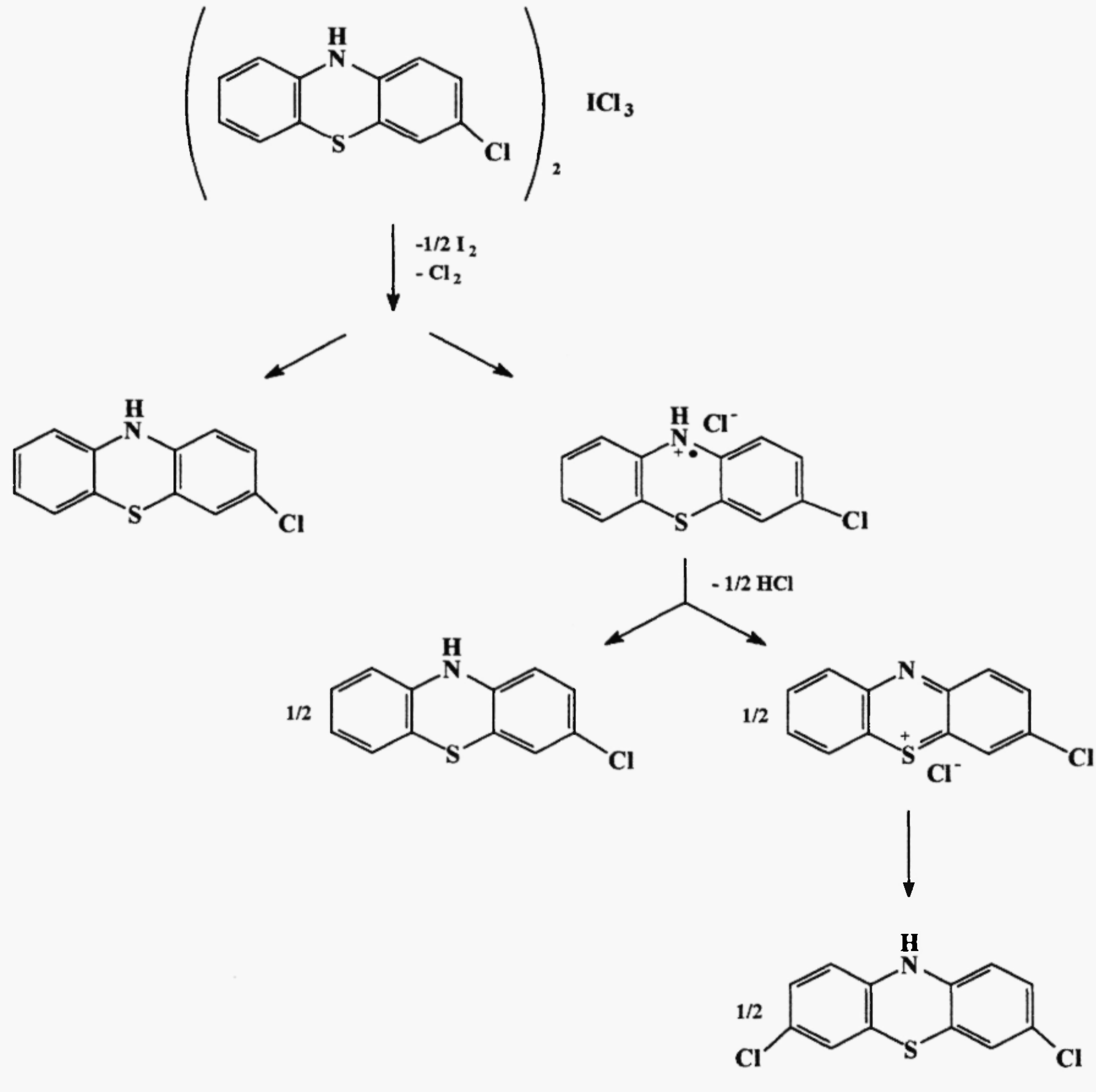
Reaction	BTEAY	Moelcular ratio BTEAY :1	Products	m.p. (lit. m.p.) °C	yield %
a	$BTEABr_3$	1	3-bromo-phenothiazine* 3,7-dibromo-phenothiazine*	___	___
b	$BTEABr_3$	2	3,7-dibromo-phenothiazine	198-199 (193 then 206) (6a,16)	56
c	$BTEABr_3$	8	1,3,7,9-tetrabromo-phenothiazine	269-272 (272-273) (16)	78
d	$BTEAICl_4$	1	3-chloro-phenothiazine* 3,7-dichloro-phenothiazine*	___	___
e	$BTEAICl_4$	2	(3-chloro-phenothiazine)$_2$. ICl_3	136-137	57
f	$BTEAICl_4$	4	1,3,7,9-tetrachlorophenothiazine	230-231 (235) (15)	59
g	$BTEAICl_2$	4	3,7-dichlorophenothiazine. ICl_3	150-154	12

* Unseparated products, detected by mass spectrometry and TLC

DISCUSSION

Due to the high reactivity of phenothiazine toward electrophilic reagents, selective halogenation leading to 3-chloro or 3-bromo derivatives was not possible (see Table reaction **a** and **d**). However, these reagents allowed us to obtain 3,7-dibromo- (see Table reaction **b**), 1,3,7,9-tetrabromo- (see Table reaction **c**) or 1,3,7,9-tetrachlorophenothiazine (see Table reaction **f**) with yields comparable with classical methods but under milder and non-toxic conditions. Besides, the same reagents led to the two new compounds (see Table reaction e and **g**). So we isolated two charge-transfer complexes of phenothiazine with ICl_3. Elemental analysis suggested a (3-chloro-phenothiazine)$_2$.ICl_3 structure for compound resulted from reaction e. The same structure is also consistent with IR spectra ($\nu_{NH} = 3260$ cm^{-1}) and its chemical behavior; thus refluxing in acetic acid for 5 minutes a mixture of 3-chloro- and 3,7-dichlorophenothiazine was detected by TLC (see Scheme).

The visible spectra in CH_2Cl_2 exhibits absorptions at 468 and 565 nm characteristic for the phenothiazinyl cation radicals (27). This fact, correlated with the intense ESR signal in solid state (singlet, g = 1.990, DH = 13.8 Gauss) points out an advanced transfer of the electrons from the phenothiazine to ICl_3 . On standing a few hours in CH_2Cl_2 , the above mentioned compound was converted into the so-called "green product" with visible absorptions at 468 and 640 nm, reaction which is also specific for cation radicals of phenothiazine (27).



Elemental analysis for compound obtained from reaction g agrees with the formula phenothiazine.ICl_3. The mass spectra shows the molecular peak at m/e 499 and another peak at m/e 267 (M^{+}- 232) indicating the dichlorophenothiazinyl fragment. The spectral data also support this assumption; ν_{NH} = 3260 cm^{-1} in IR, in pellet; λ_{max} = 296, 364, 448, 660 nm, in UV- VIS spectra , in CH_2Cl_2 ; singlet, g = 1.989, DH = 20.2 Gauss, in ESR spectra in solid state.

Unfortunately we did not succeed to prepare, with good yields, mixed halogenophenothiazine using these reagents. Thus, after 30 hours of refluxing in methanol of 2-chlorophenothiazine with $BTEABr_3$ (1:1 molar ratio), 80% of starting material was recovered.

CONCLUSION

The reaction of phenothiazine with BTEA polyhalides, which take place under mild and non-toxic condition, allowing to obtain halogenophenothiazine derivatives with yields comparable with those of classical methods. Further, is it to be noted that with these reagents was possible to obtain, for the first time, charge-transfer complexes with mixed halogenes of the type phenothiazine . $Cl_x I_y$.

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