SELECTIVE OXIDATON METHODS FOR PREPARATION OF N-ALKYLPHENOTHIAZINE SULFOXIDES AND SULFONES

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Abstract: Efficient and selective oxidation methods for preparation of *N*-alkylphenothiazine sulfoxides **2a-h** and sulfones **3a-h** starting from *N*-alkylphenothiazines **1a-h** are described.

In the metabolism of the phenothiazine-based drugs often occuring metabolites are the corresponding sulfoxides, 7-hydroxylated derivatives or even sulfones (1-4).

Phenothiazines have been oxidized by various oxidizing agents. Most frequently H_2O_2 in various solvents has been used for *S*-oxidation (1). In ethanol (5) or in ethanol-acetone mixture (6), H_2O_2 produced phenothiazine-5-oxides. Sulfones were usually formed by H_2O_2/AcOH (7) which generates *in situ* peracetic acid. Similarly, oxidation with organic peracids, such as *m*-chloroperoxybenzoic acid (8), provided sulfones. Sulfone formation was also achieved with sodium perborate (9) or NaOCl (10). Sulfoxide formation by peracid systems was only reported for ammonium persulfate (11) or H_2O_2/oxalic acid (12). Transformation of phenothiazine derivatives into sulfoxides was achieved by several inorganic nitrogen oxides. Phenothiazines substituted with electron withdrawing groups were converted to sulfoxides by nitric acid (1). Sulfoxides were obtained by using nitrous acid generated *in situ* from $NaNO_2$ by acids like AcOH (13) or aqueous HCl (14). Phenothiazines were converted into sulfoxides by nitrogen dioxide/O_2 (15) or $NO^{(-)}BF_4^{(+)}/O_2$ (16). Heavy metal-based systems were also used for *S*-oxidation of phenothiazines. $KMnO_4/H_2O$ (17), $Et_3PhN^{(+)}MnO_4^{(-)}$ in organic

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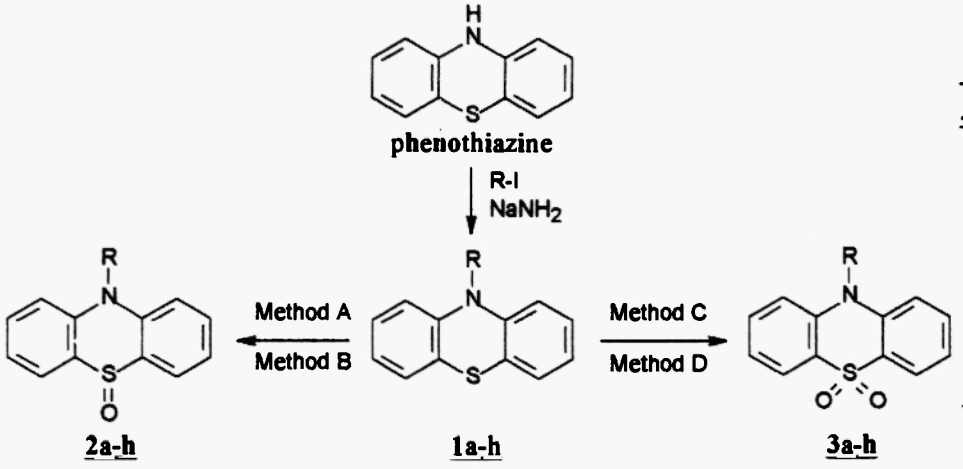
media (18), or OsO_4/*N*-methylmorpholine *N*-oxide (19) were applied for oxidation of phenothiazines into sulfones. On the contrary, the milder chromium based oxidizing agents like CrO_3/pyridine (20), resulted in sulfoxide formation. Ozone (21), electrochemical methods (22), tetramethyl oxirane (23) or perfluoroalkyl-oxaziridines (24) were also used for oxidizing phenothiazines to sulfoxides.

All of these methods, however, required either expensive/unusual reagents, or afforded the desired products only in moderate yields *via* tedious purification. In this work, new methods applying convenient oxidizing agents, requiring mild conditions and simple work up and providing good yields for selective synthesis of phenothiazine-5-oxides **2a-h** or 5,5-dioxides **3a-h** from 10-alkylphenothiazines **1a-h** are reported (Scheme 1).



1, 2, 3	R
a	CH_3
b	C_2H_5
c	C_3H_7
d	C_4H_9
e	*iso*-C_4H_9
f	*iso*-C_5H_{11}
g	C_5H_{11}
h	C_7H_{15}

Scheme 1. Preparation and selective oxidations of 10-alkylphenothiazines **1a-h**

Experimental

Phenothiazine and reagents: Aldrich or Fluka. ^1H-/^{13}C-NMR: $CDCl_3$/TMS, Brucker DRX-500 equipment at 500/125 MHz, ppm (δ). IR: Specord 2000 spectrometer, KBr (cm^{-1}). TLC: Merck Kieselgel 60 F_{254} alumina sheets. Vacuum-chromatography: Merck Kieselgel 60 (0.063-0.200 μm). M.P.: uncorrected. Solvents: purified and dried by standard methods. All new compounds gave proper analysis data.

I. General procedure for alkylation of phenothiazine with alkyl iodides

Phenothiazine (20 g, 100 mmol) was suspended in 100 ml alkyl iodide and $NaNH_2$ (6 g, 150 mmol, 95 %) powder was added portionwise and the reaction was stirred at reflux temperature. After the reaction was completed (by TLC), the excess of alkyl iodide was distilled off in vacuo and unreacted $NaNH_2$ was quenched (water, 50 ml). Followed an extraction with toluene (50 ml, twice), drying ($MgSO_4$) and removal of solvent, the residual crude 10-alkylphenothiazines **1a-h** were purified by vacuum-distillation for **1c-h** and by recrystallization from ethanol for **1a-b** (Table 1).

Table 1. Preparation of 10-alkylphenothiazines **1a-h**

Compnd.	T [°C]	Time [h]	Yield [%]	M.p./lit. M.p. [°C]	B.p. /lit. B.p. [°C; mm Hg]
1a	43-44	12	91	100 /100 (25)	
1b	72-73	8	95	106 /103-4 (26)	
1c	102	7	96	50 /49-50 (26)	164;0.05 /162-5;0.02 (27)
1d	131	7	95		145;1 /143-6;0.1 (28)
1e	121	6	96	128 /127-9 (28)	156;1
1f	148	7	96	67 /66-8 (33)	169;0.5 /230-2;13 (33)
1g[1]	156	5	94		166;0.07
1h[2]	205	5	95		172;0.05

[1] **1g**: *^{1}H-NMR*: 0.96 (3H, t), 1.33-1.47 (m, 4H), 1.83 (2H, m), 3.86 (2H, t), 6.87-6.99 (4H, m), 7.15-7.20 (4H, m); *^{13}C-NMR*: 14.09, 22.41, 26.66, 29.22, 47.44, 115.42, 122.34, 124.93, 127.19, 127.44, 145.35; IR (CCl_4): 1592, 1460, 1336, 1288, 1256, 748; [2] **1h**: *^{1}H-NMR*: 0.89 (3H, t), 1.33 (4H, m), 1.45 (2H, m), 1.82 (2H, m), 3.85 (2H, t), 6.87- 6.94 (4H, m), 7.15-7.18 (4H, m); *^{13}C-NMR*: 14.10, 22.60, 26.97, 26.99, 28.98, 31.80, 47.47, 115.42, 122.33, 124.94, 127.19, 127.44, 145.37; *IR* (CCl_4): 1592, 1460, 1336, 1288, 1248, 748.

Table 2. Yields and melting points for 10-alkylphenothiazine-5-oxides **2a-h**

No.	Method Yield [%] A	B	M.p./lit. M.p. [°C]	IR	NMR
2a	85	75	201-2/194-6 (29)	1584, 1480, 1456, 1356, 1264, 1048, 1020, 764	*^{1}H-*: 3.78 (3H, s), 7.29 (2H, t), 7.40 (2H, d), 7.64 (2H, t), 7.95 (2H, d)
2b	91	78	165-6/162-4 (30)	1584, 1488, 1456, 1376, 1256, 1056, 1024, 756	*^{1}H-*: 1.58 (3H, t), 4.36 (2H, q), 7.25 (2H, t), 7.46 (2H, d), 7.63 (2H, t), 7.94 (2H, d)
2c	82	78	121-2/138-40 (31)	1584, 1488, 1460, 1376, 1252, 1052, 1028, 752	*^{1}H-*: 1.12 (3H, t), 1.97 (2H, m), 4.18 (2H, t), 7.24 (2H, t), 7.41 (2H, t), 7.62 (2H, t), 7.95 (2H, d)
2d	88	76	130-1/-	1580, 1480, 1452, 1376, 1248, 1052, 1040, 1032, 768	*^{1}H-*: 1.08 (3H, t), 1.59 (2H, m), 1.95 (2H, m), 4.22 (2H, t), 7.24 (2H, t), 7.41 (2H, d), 7.62 (2H, t), 7.94 (2H, d)
2e	90	81	181-3/-	1584, 1460, 1360, 1248, 1040, 1024, 752	*^{1}H-*: 0.95 (6H, d), 2.33 (1H, m), 4.09 (2H, d), 7.20 (2H, t), 7.44 (2H, d), 7.55 (2H, t), 7.89 (2H, d); *^{13}C-*: 20.27, 27.07, 54.04, 116.80, 121.96, 125.88, 130.88, 132.44, 139.56
2f	91	80	116-8/-	1584, 1460, 1372, 1248, 1176, 1056, 1040, 1024, 768	*^{1}H-*: 1.08 (d, 6H), 1.87 (3H, m), 4.25 (2H, t), 7.23 (2H, t), 7.41 (2H, d), 7.62 (2H, t), 7.97 (2H, d); *^{13}C-*: 22.50, 26.61, 34.61, 46.70, 115.57, 121.63, 123.99, 131.71, 132.84, 138.27
2g	87	79	113-4/-	1580, 1480, 1376, 1248, 1160, 1056, 1040, 1032, 764	*^{1}H-*: 1.01 (3H, m), 1.47-1.57 (4H, m), 1.97 (2H, m), 4,23 (2H, t), 7.26 (2H, t), 7.43 (2H, d), 7.65 (2H, t), 7.96 (2H, d); *^{13}C-*: 14.07, 24.40, 25.92, 28.97, 48.19, 115.67, 121.67, 123.90, 131.74, 132.88, 138.33
2h	89	79	108-10/-	1584, 1456, 1376, 1252, 1160, 1060, 1044, 1032, 768	*^{1}H-*: 0.93 (3H, t), 1.33-1.38 (4H, m), 1.44 (2H, m), 1.53 (2H, m), 1.96 (2H, m), 4.21 (2H, t), 7.24 (2H, t), 7.40 (2H, d), 7.62 (2H, t), 7.93 (2H, d); *^{13}C-*: 14.19, 22.68, 26.35, 26.94, 31.07, 31.91, 48.34, 115.79, 121.78, 124.04, 131.83, 132.99, 138.45

Table 3. Yields and melting points for 10-alkylphenothiazine-5,5-dioxides **3a-h**

No.	Method Yield [%] C	D	M.p./lit. M.p. [°C]	IR	NMR
3a	89	93	219-20/220-1 (32)	1592, 1480, 1468, 1380, 1280, 1248, 1168, 1156, 1144, 1088, 748, 576	^1H-: 3.73 (3H, s), 7.31 (4H, m), 7.64 (2H, t), 8.12 (2H, d)
3b	93	91	163-4/162-64 (32)	1592, 1480, 1468, 1380, 1280, 1248, 1168, 1156, 1144, 1088, 748, 576	^1H-: 1.58 (3H, t), 4.29 (2H, q), 7.29 (2H, t), 7.40 (2H, d), 7.65 (2H, t), 8.15 (2H, d)
3c	91	90	193-4/193-95 (32)	1592, 1464, 1372, 1288, 1248, 1168, 1152, 1140, 1080, 752, 572	^1H-: 1.09 (3H, t), 1.96 (2H, m), 4.13 (2H, t), 7.25 (2H, t), 7.35 (2H, d), 7.63(2H, t), 8.14 (2H, d)
3d	89	90	148-9/149-50 (33)	1592, 1480, 1468, 1372, 1288, 1248, 1168, 1152, 1140, 1080, 752, 572	^1H-: 1.06 (3H, t), 1.53 (2H, m), 1.92 (2H, m), 4.18 (2H, t), 7.28 (2H, t), 7.36(2H, d), 7.65 (2H, t), 8.13 (2H, d)
3e	93	92	138-9/143-44 (33)	1592, 1464, 1336, 1288, 1240, 1164, 1152, 1140, 1104, 1064, 760, 568	^1H-: 0.95 (6H, d), 2.26 (1H, m), 4.08 (2H, d), 7.27 (2H, t), 7.39 (2H, d), 7.62 (2H, t), 8.10 (2H, d); ^{13}C-: 20.38, 27.25, 55.05, 117.36, 122.32, 122.97, 125.97, 133.13, 142.36
3f	95	94	140/-	1592, 1576, 1464, 1372, 1280, 1248, 1168, 1152, 1140, 1080, 752, 572	^1H-: 1.05 (6H, d), 1.83 (3H, m), 4.19 (2H, t), 7.26 (2H, t), 7.37 (2H, d), 7.62 (2H, t), 8.11 (2H, d)
3g	92	91	95-6/-	1592, 1576, 1464, 1372, 1280, 1248, 1168, 1152, 1140, 1080, 752, 572	^1H-: 0.97 (3H, t), 1.45 (4H, m), 1.94 (2H, m), 4.16 (2H, t), 7.27 (2H, t), 7.35 (2H, d), 7.63 (2H, t), 8.13 (2H, d); ^{13}C-: 14.42, 22.73, 26.84, 29.22, 48.82, 116.35, 122.12, 124.02, 124.62, 133.51, 141.22
3h	92	92	75/-	1592, 1464, 1376, 1292, 1248, 1164, 1152, 1144, 1084, 756, 575	^1H-: 0.92 (3H, d), 1.34-1.50 (8H, m), 1.94 (2H, m), 4.16 (2H, t), 7.26 (2H, t), 7.35 (2H, d), 7.63 (2H, t), 8.13 (2H, d); ^{13}C-: 14.05, 22.54, 26.67, 26.76, 28.88, 31.73, 48.46, 115.96, 121.72, 123.62, 124.24, 133.11, 140.83

***II. Oxidation of 10-alkylphenothiazines* 1a-h *to sulfoxides* 2a-h**

***Method A*:** To a stirred solution of 10-alkylphenothiazine **1a-h** (5 mmol) in 25 ml of CH_2Cl_2, a solution of *m*-CPBA (5 mmol, ~1.23 g, ~70%, freshly titrated iodometrically) dissolved in 20 ml anhydrous CH_2Cl_2 was added dropwise (30 min, 0-5 °C). After the reaction was completed (checked by TLC, 2-4 h), the mixture was washed with 10% KOH solution (15 ml, twice), 5% HCl solution (10 ml), and satd. $NaHCO_3$ solution (10 ml) and dried ($MgSO_4$). The solvent was distilled off and residue was separated by column chromatography (CH_2Cl_2-acetone, 9:1). Finally, the products were recrystallized from hexane. Yields and melting points for the resulting sulfoxides **2a-h** are given in Table 2.

***Method B*:** To a cooled solution of 10-alkylphenothiazines **1a-h** (5 mmol) in 5 ml CCl_4, a mixture of 97% fuming nitric acid (5 mmol, 0.22 ml) and glacial acetic acid (0.1 ml) was added dropwise. After a few minutes, a white precipitate was formed which was removed by filtration, washed with saturated $NaHCO_3$ solution, dried and recrystallized from anhydrous DMF. Characteristics of sulfoxides **2a-h** obtained by this method, including the melting points, were identical to those obtained by Method A.

***III. Oxidation of 10-Alkylphenothiazines* 1a-h *to 10-alkylphenothiazine-5,5-dioxides* 3a-h**

***Method C*:** To a solution of 10-alkylphenothiazine **1a-h** (5 mmol) in 25 ml of $CHCl_3$, aqueous solution (50 ml) of $KMnO_4$ (7.5 mmol) and $C_{16}H_{35}N(CH_3)_3^{(+)}$ $Cl^{(-)}$ (0.5 g) were added and the resulting mixture was vigorously stirred at R.T. for 4-6 h. Then the reaction mixture was filtered on white quartz sand. The organic layer was separated, washed with water (15 ml, four times), dried ($MgSO_4$) and concentrated in vacuum. The residue was purified by column chromatography (eluent CH_2Cl_2) and recrystallized from dry ethanol. Yields and melting points for the resulting sulfones **3a-h** are given in Table 3.

Method D: To a stirred solution of **1a-h** (5 mmol) in CH_2Cl_2 (20 ml) *m*-CPBA (0,01 mmol, ~2.5 g, 70%) was added in small portions at room temperature and the resulting mixture was stirred at R.T. for 2 h. Further work up was carried out as described for Method A, except that ethanol was used for recrystallization. Characteristics of sulfones **3a-h** obtained by this method were identical to those obtained by using Method C.

Results and Discussion

10-Alkylphenothiazines **1a-h** were obtained from phenothiazine by reaction with the corresponding alkyl iodides in the presence of $NaNH_2$ without using solvent (Scheme 1, Table 1).

10-Alkylphenothiazine-5-oxides **2a-h** were prepared from the appropriate 10-alkylphenothiazines **1a-h** by two alternative methods (Scheme 1, Table 2). Sulfoxide formation was carried out by dropwise addition of *m*-CPBA acid dissolved in anhydrous CH_2Cl_2 into a solution of the *N*-alkylphenothiazines **1a-h** in CH_2Cl_2 at 0 °C (Method A). The same 10-alkylphenothiazine-5-oxides **2a-h** were obtained by addition of glacial AcOH solution of fuming HNO_3 into a solution of *N*-alkylphenothiazines **1a-h** in CCl_4 (Method B), also at 0 °C. Similarly, two alternative methods were elaborated for oxidation of 10-alkylphenothiazines **1a-h** into the corresponding 10-alkylphenothiazine-5,5-dioxides **3a-h** (Scheme 1, Table 3). The 10-alkylphenothiazines **1a-h** were transformed into their sulfones **3a-h** at R.T. by $KMnO_4$ in a water-chloroform two-phase system using cetyltrimethylammonium chloride phase-transfer catalyst (Method C). Alternatively, portionwise addition of solid *m*-CPBA acid into CH_2Cl_2 solution of 10-alkylphenothiazines **1a-h** at R.T. resulted in smooth formation of the 10-alkylphenothiazine-5,5-sulfones **3a-h** (Method D). Selective formation of 10-alkylphenothiazine-5-oxides **2a-h** (Method A) was achieved at low temperature (0 °C) in highly diluted system by using exact equivalency of precisely titrated *m*-CPBA. Twofold amount of *m*-CPBA at R.T., however, resulted in the formation of 10-alkylphenothiazine-5,5-dioxides **3a-h** (Method D). Since sulfoxides **2a-h** are poorly soluble in CCl_4, they precipitated in the case of Method B and no formation of nitro-compounds were detected. These results confirm that *S*-oxidation of *N*-alkylphenothiazines by nitric acid precedes nitration in formation of nitrophenothiazine sulfoxides (34). Efficiency of the $KMnO_4$ oxidation was enhanced by using phase-transfer catalysis (Method C). By this modification, oxidation of the *N*-alkylphenothiazines **1a-h** to the corresponding sulfones **3a-h** could be performed at R.T. within 2 h in good yields.

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