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CANNIZARRO REACTION IN THE PHENOTHIAZINE SERIES

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ABSTRACT. Cannizarro reaction in the phenothiazine series was extended with the aim at preparing the 10-alkyl-10*H*-phenothiazine-3-carboxylic acids and 10-alkyl-10*H*-phenothiazine-3-methanols.

INTRODUCTION

10-Alkylphenothiazines were used to enhance the reaction rate of different oxidative enzymes, such peroxidase [1,2]. To investigate the influence of different substituents upon these enzyme mediated reactions, various substituted phenothiazines were needed.

Starting from substituted diphenylamines, by cyclisation with sulfur, different C-1, C-2 and C-3 substituted phenothiazines can be prepared [3,4].

N-Alkylphenothiazines could be converted in the corresponding 3-substituted compounds, but in some cases the 3,7-disubstituted derivatives can also appeare [5].

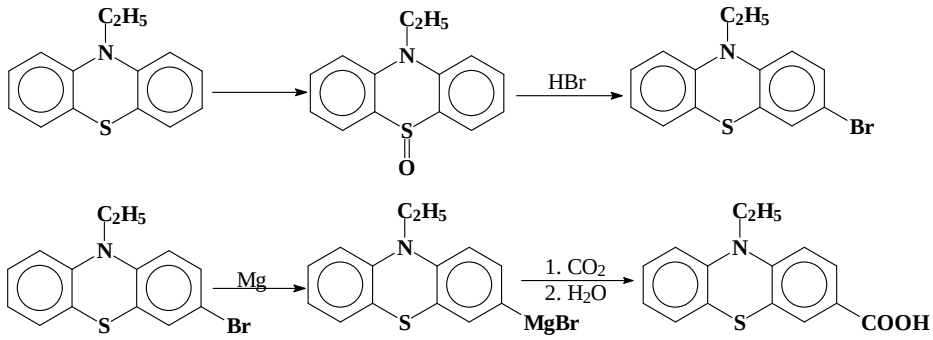
3-Bromophenothiazines were found to be authentic intermediates in order to access some phenothiazine derivatives, mostly *via* Grignard reaction [3] or *via* organolytic intermediates [7]; both methods were used for synthesis of N-alkylphenothiazine-3-carboxylic acids.

10-Ethylphenothiazine-3-carboxylic acid was firstly synthetised from 10-ethyl-phenothiazine by a five step procedure [6] (Scheme 1).

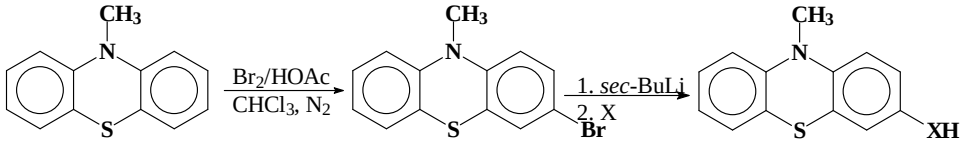
Gilman and Eisch [3] described the synthesis of the some 3-substituted compounds starting from 3-bromo-10-ethylphenothiazine *via* the Grignard reagent and subsequent carboxylation.

Recently, Ebdrup described the introduction of carboxy- and hydroxymethylene groups in position 3 of 10-methylphenothiazine by a bromine-lithium exchange reaction [7] with improved yields (Scheme 2).

10-Metyl-, respectively 10-ethyl-10*H*-phenothiazine-3-carboxylic acids were prepared starting from the corresponding 10-Alkyl-10*H*-phenothiazine-3-carbaldehyde by oxidation with alkaline hydroxides or silver oxide [4], or by Cannizarro reaction [8].



Scheme 1



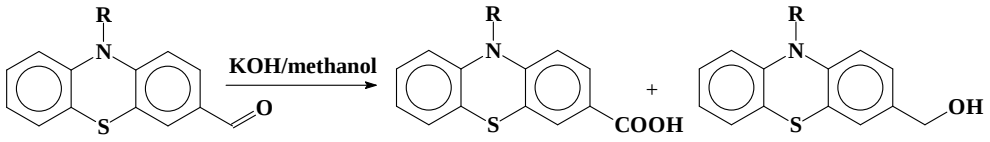
2,3 a

X	Comp.	Yield [%]
CO_2	**2 a**	85
$(CH_2O)_n$	**3 a**	38

Scheme 2

In alkaline media was performed the concomitant oxidation of the carbonyl group and of the sulfur bridge [9] with potassium permanganate to the corresponding S,S-dioxide compound.

In this paper is described an improved procedure of Cannizarro reaction for the synthesis of 10-alkyl-10*H*-phenothiazine-3-carboxylic acids **2a-g** and the corresponding (10-alkyl-10*H*-phenothiazin-3-yl)methanols **3a-g** starting from the 3-formyl-derivatives **1a-g** in methanolic solutions (Scheme 3). Five new compounds **2c-g** were prepared in this way.



1a-g **2a-g** **3a-g**

Scheme 3

For comparison, the 10-alkyl-10*H*-phenothiazine-3-carboxylic acids **2a-g** were prepared by oxidation of 10-alkyl-10*H*-phenothiazine-3-carbaldehydes **1a-g** with silver oxide as described [4] and the (10-alkyl-10*H*-phenothiazine-3yl)methanols **3a-g** by reduction with sodium tetrahydroborate [10].

EXPERIMENTAL

Reagents and solvents were purchased from Aldrich or Fluka. The 10-alkyl-10*H*-phenothiazine-3-carbaldehydes **1a-g** were synthetized as previously described [10].

The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Gemini 300 spectrometer operating at 300 and 75 MHz, in $CDCl_3$. Chemical shifts are expressed in ppm values (TMS internal standard) on δ scale. The IR spectra were recorded on a FT-IR Nicolet 205 spectrofotometer, in KBr pellets. Wave numbers are expressed in cm^{-1}.

The elemental analysis for C, H, N and S were within +/- 0.2% of the theoretical values for all derivatives.

TLC was carried out using Merck Kieselgel 60 F_{254} alumina sheets. Spots were visualized by treatment with 5% ethanolic phosphomolybdendic acid solution and heating of the dried plates. Preparative chromatographic separations were performed using vacuum-chromatography on a Merck Kieselgel 60 (0.063-0.200 mm) silica-gel.

Melting points are uncorrected.

General procedure for synthesis of 10-alkyl-10*H*-phenothiazine-3-carboxylic acids 2a-g and (10-alkyl-10*H*-phenothiazine-3-yl)methanols 3a-g by Cannizarro reaction (Method A)

In a solution of KOH (10 g) in methanol (50 ml), a solution of 10-alkyl-10*H*-phenothiazine-3-carbaldehydes **1a-g** (20 mmol) in methanol (5 ml) was added and the reaction was kept 3-4 hours at reflux (TLC control). The solvent was distilled *in vacuo* and from the resulting mixture (alcohols **3a-g,** sodium salts of acid **2a-g**) the alcohols were separated by column chromatography using dichloromethane as eluent and recrystallized from ethanol. The silica gel was dried and sodium salts of acids were desorbed in boiling water (2x100 ml). The combined water solutions were treated with 32% hydrochloric acid, the precipitate filtered off and the desired products **2a-g** recrystallized from hexane. The yields and the melting points are given in Table 1.

General procedure for synthesis of 10-alkyl-10*H*-phenothiazine-3-carboxylic acids 2a-g by oxidation with silver oxide (Method B)

Silver nitrate (2.4 g, 0.014 mol) was dissolved in water (14 ml) and 10% NaOH solution (6 ml, cca 0.015 mol) was added. After five minutes the formed precipitate was filtered, washed with water and suspended in 10% NaOH solution (30 ml, cca 0.065 mol). The mixture was heated at 80 °C and the substrate **1a-g**

(0.01 mol) was added with stirring. The reaction was perfected at 80 °C 2-4 hours (TLC control). After cooling, the mixture was diluted with water (100 ml). The unsolved products were filtered off and washed with water (2x25 ml). From the filtrate, the desired products **2a-g** were precipitated with 32% hydrochloric acid, filtered, washed with water, dried and recrystallized from ethanol.

The yields and the melting points are given in table 1.

General procedure for synthesis of (10-alkyl-10*H*-phenothiazine-3-yl)methanols 3a-g by chemical reduction (Method C)

The substrates **2a-g** (0.2 g) were dissolved in absolute methanol (5 ml) and $NaBH_4$ was added in small portions under stirring at room temperature; when the solution was decolorated, HCl soln. 2N was added dropwise, the resulting mixture was evaporated to dryness and the crude residue was extracted with water-toluene (1:2). The organic layer was dried over anhydrous magnezium sulfate and the solvent was removed. The residual crude (10-Alkyl-10*H*-phenothiazin-3-yl)methanols **3a-g** were purified by column chromatography on silica gel using toluene-acetone (9:1) as eluent.

10-Methyl-10*H*-phenothiazine-3-carboxylic acid 2a

^{1}H-NMR: 3.28 (3H, s), 6.67 (2H, m), 6.89 (1H, t), 7.01 (1H, dd), 7.08 (1H, m),7.49 (1H, d), 7.56 (1H, dd); *^{13}C-NMR:* 35.7, 113.6, 114.7, 122.4, 123.6, 125.8, 127.1, 127.6, 127.7, 130.3, 131.1, 143.9, 150.8, 171.5; *IR:* 3052, 2988, 2868, 1678, 1532, 1584, 1448, 1434, 1417, 1342, 1332, 1299, 1262, 1248, 1152, 1125, 1111; *Anal. Calc. for* $C_{14}H_{13}NO_2S$: C, 65.35, H, 4.31, N, 5.44, S, 12.46; *Found:*C, 65.32, H, 4.38, N, 5.41, S, 12.51

10-Ethyl-10*H*-phenothiazine-3-carboxylic acid 2b

^{1}H-NMR: 1.45 (3H, t), 3.98 (2H, q), 6.86 (2H, m), 6.96 (1H, t), 7.11-7.20 (2H, m), 7.78 (1H, d), 7.87 (1H, dd); *^{13}C-NMR:* 12.7, 42.4, 114.4, 115.8, 122.9, 123.5, 124.9, 127.3, 127.4, 127.6, 129.4, 130.3, 143.3, 150.5, 171.5; *IR*: 3060, 2983, 2860, 1671, 1598, 1574, 1443, 1424, 1407, 1399, 1328, 1297, 1267, 1252, 1162, 1135, 1109; *Anal. Calc. for* $C_{15}H_{13}NO_2S$: C, 66.40, H, 4.83, N, 5.16, S, 11.82; *Found:*C, 66.32, H, 4.78, N, 5.11, S, 11.91

10-Propyl-10*H*-phenothiazine-3-carboxylic acid 2c

^{1}H-NMR: 1.02 (3H, t), 1.84 (2H, m), 3.86 (2H, t), 6.85 (2Harom, m), 6.95 (1H, t), 7.14 (1H, d), 7.18 (1H, t), 7.81 (1H, d), 7.88 (1H, dd); *^{13}C-NMR:* 11.2, 20.1, 49.7, 114.5, 115.9, 122.9, 123.4, 124.8, 127.4, 127.5, 127.6, 129.3, 130.3, 143.2, 150.5, 171.6; *IR*: 3061, 2983, 2860, 1673, 1600, 1575, 1472, 1422, 1407, 1399, 1364, 1277, 1241, 1252, 1168, 1142, 1112; *Anal. Calc. for* $C_{16}H_{15}NO_2S$: C, 67.34, H, 5.30, N, 5.11, S, 11.91; *Found:*C, 67.32, H, 5.38, N, 5.21, S, 11.89;

10-Butyl-10*H*-phenothiazine-3-carboxylic acid 2d

^{1}H-NMR:0.96 (3H, t), 1.48 (2H, m), 1.79 (2H, m), 3.90 (2H, t), 6.86 (3H, m), 7.13(2H, m), 7.82 (1H, t), 7.86 (1H, dd); *^{13}C-NMR:* 13.8, 20.1, 28.7, 47.6, 114.5, 115.8, 122.9, 123.4, 124.8, 127.3, 127.4, 127.4, 129.3, 130.1, 143.3, 150.4, 171.5;

IR: 3060, 2932, 2872, 1687, 1601, 1574, 1470, 1420, 1407, 1399, 1328, 1297, 1270, 1214, 1159, 1140, 1112; *Anal. calculated for* $C_{17}H_{17}NO_2S$: C, 68.20, H, 5.72, N, 5.72, S, 10.71; *Found:*C, 68.32, H, 5.68, N, 5.81, S, 10.78.

10-(2-Methylpropyl)-10*H*-phenothiazine-3-carboxylic acid 2e

1H-NMR: 0.94 (6H, d); 2.14 (1H, m), 3.84 (2H, d), 6.82 (2H, m), 6.94 (1H, t), 7.09 (H, dd), 7.15 (H, m), 7.51 (H, d), 7.61 (H, dd); *13C-NMR:* 19.9, 25.6, 55.4, 115.8, 116.6, 123.4, 124.9, 125.9, 127.4, 127.4, 128.8, 129.3, 130.9, 143.2, 151.2, 171.6; *IR:* 3062, 2938, 2878, 1677, 1609, 1578, 1472, 1428, 1401, 1392, 1322, 1292, 1274, 1216, 1161, 1138, 1114; *Anal. calculated for* $C_{17}H_{17}NO_2S$: C, 68.20, H, 5.72, N, 5.72, S, 10.71; *Found:*C, 68.22, H, 5.66, N, 5.81, S, 10.72.

10-(3-Methylbuthyl)-10*H*-phenothiazine-3-carboxylic acid 2f

^{1}H-NMR: 0.96 (6H, d), 1.68-1.76 (2H, m), 1.78-1.83 (1H, m), 3.91 (2H, t), 6.87 (2H, m), 6.95 (1H, t), 7.11-7.19 (2H, m), 7.83 (1H, d), 7.89 (1H, dd); *^{13}C-NMR:* 22.6, 26.4, 35.6, 46.2, 114.5, 115.8, 122.9, 123.4, 124.9, 127.3, 127.4, 127.5, 129.3, 130.2, 143.3, 150.4, 171.6; *IR:* 3060, 2932, 2872, 1687, 1601, 1574, 1470, 1420, 1407, 1399, 1328, 1297, 1270, 1214, 1159, 1140, 1112; *Anal. calculated for* $C_{18}H_{19}NO_2S$: C, 68.98, H, 6.11, N, 4.47, S, 10.23; *Found:*C, 68.82, H, 6.18, N, 4.38, S, 10.27.

10-Pentyl-10*H*-phenothiazine-3-carboxylic acid 2g

^{1}H-NMR: 0.86 (3H, t), 1.25-1.42 (4H, m), 1.75 (2H, m), 3.78 (2H, t), 6.82 (H, d), 6.93 (H, t), 7.03 (H, d), 7.11 (H, t), 7.48 (H, d), 7.48 (H, dd); *^{13}C-NMR:* 13.9, 22.2, 26.3, 28.8, 47.7, 114.7, 115.9, 123.5, 123.6, 124.9, 127.4, 127.6, 128.3, 130.1, 130.9, 143.3, 171.6; *IR:* 3056, 2932, 2868, 1682, 1611, 1578, 1472, 1420, 1417, 1392, 1338, 1292, 1268, 1214, 1159, 1140, 1112; *Anal. calculated for* $C_{18}H_{19}NO_2S$: C, 68.98, H, 6.11, N, 4.47, S, 10.23; *Found:*C, 68.88, H, 6.28, N, 4.42, S, 10.22.

(10-Methyl-10*H*-ph*enothiazine-3-yl)methanol 3a

^{1}H-NMR: 3.33 (3H, s), 4.54 (2H, s), 6.73-6.78 (2H, m), 6.90 (1H, t), 7.11-7.15 (4H, m) ; *^{13}C-NMR*: 35.4, 64.7, 113.9, 114.1, 122.5, 123.3, 126.1, 126.4, 127.2, 127.5, 127.5, 135.3, 145.8, 145.4; *IR*: 3432, 2984, 1464, 1332, 1288, 1260, 1200, 1144, 1076, 1048,760; *MS:* 245, 244, 243, 242, 232, 231, 230, 229, 226, 214, 212, 211, 201, 200, 199; *Anal. Calc.for* $C_{14}H_{13}NOS$: C, 69.11, H, 5.39, N, 5.76, S, 13.18; *Found*: C, 69.14, H, 5.31, N, 5.77, S, 13.23

(10-Ethyl-10*H*-ph*enothiazine-3-yl)methanol 3b

^{1}H-NMR: 1.38 (3H, t), 3.88 (2H, q), 4.51 (2H, s), 6.78-6.83 (2H, m), 6.87 (1H, t), 7.09-7.13 (4H, m); *^{13}C-NMR*: 13.1, 41.9, 64.6, 114.9, 115.1, 122.4, 124.3, 124.8, 126.2, 127.2, 127.3, 127.4, 135.1, 144.5, 144.5; *IR*: 3320, 2984, 1464, 1328, 1288, 1240, 1216, 1132, 1120, 1112, 1064, 1040, 1024, 1008, 756; *MS:* 259, 258, 257, 256, 242, 240, 231, 230, 229, 228, 213, 212, 211, 200, 199; *Anal. Calc. for* $C_{15}H_{15}NOS$: C, 70.01, H, 5.87, N, 5.44, S, 12.46; *Found*: C, 69.97, H, 5.81, N, 5.47, S, 13.43.

(10-Propyl-10*H*-phenothiazine-3-yl)methanol 3c

^{1}H-NMR: 0.95 (3H, t), 1.76 (2H, m), 3.74 (2H, t), 4.45 (2H, s), 6.74 (1H, d), 6.79 (1H, d), 6.86 (1H, t), 7.02-7.16 (4H, m); *^{13}C-NMR*: 11.3, 20.1, 49.1, 64.4, 115.2, 115.2, 115.4, 122.3, 124.6, 124.9, 127.1, 127.2, 127.4, 132.2, 134.9, 144.7, 145.2; *IR*: 3352, 2960, 1496, 1468, 1336, 1288, 1248, 1232, 1136, 1120, 1112, 1092, 1040, 1028, 1008, 748; *MS:* 273, 272, 271, 270, 255, 254, 244, 243, 242, 231, 230, 229, 228, 213, 212, 210; *Anal. Calc. for* $C_{16}H_{17}NOS$: C, 70.82, H, 6.31, N, 5.16, S, 11.81; *Found*: C, 70.84, H, 6.37, N, 5.25, S, 11.73.

(10-Butyl-10*H*-phenothiazine-3-yl)methanol 3d
^{1}*H-NMR*: 0.91 (3H, t), 1.45 (2H, m), 1.74 (2H, m), 3.80 (2H, t), 4.48 (2H, s), 6.78 (1H, d), 6.82 (1H, d), 6.87 (1H, m), 7.09-7.13 (4H, m); ^{13}*C-NMR*: 13.8, 20.2, 28.9, 47.1, 64.5, 115.2, 115.3, 115.4, 122.4, 124.6, 125.1, 126.2, 126.3, 127.1, 127.2, 127.4, 134.9; *IR*: 3352, 2960, 1496, 1468, 1332, 1288, 1244, 1216, 1136, 1120, 1108, 1084, 1040, 748; *MS*: 287, 286, 285, 284, 269, 268, 244, 243, 242, 231, 230, 229, 228, 213, 212, 210, 200, 199; *Anal. Calc. for:* $C_{17}H_{19}NOS$: C, 71.54, H, 6.71, N, 4.91, S, 11.23; *Found*: C, 71.64, H, 6.77, N, 4.85, S, 11.32.

(10-(2-Methylpropyl)-10*H*-phenothiazine-3-yl)methanol 3e
^{1}*H-NMR*: 0.97 (6H, d), 2.16 (1H, m), 3.65 (2H, d), 4.78 (2H, s), 6.78 (1H, d), 6.82 (1H, d), 6.87 (1H, m), 7.11-7.13 (4H, m); ^{13}*C-NMR*: 20.2, 45.9, 55.3, 64.6, 115.7, 115.9, 122.5, 122.7, 125.3, 125.9, 126.2, 126.8, 126.9, 127.2, 127.5, 127.8; *IR:* 3400, 2952, 1496, 1464, 1336, 1288, 1244, 1232, 1144, 1116, 1104, 1068, 1012, 736; *Anal. Calc. for* $C_{17}H_{19}NOS$: C, 71.54, H, 6.71, N, 4.91, S, 11.23; *Found*: C, 71.61, H, 6.74,N, 4.89, S, 11.29

(10-(2-Methylbutyl)-10*H*-phenothiazine-3-yl)methanol 3f
^{1}*H-NMR*: 0.94 (6H, d), 1.68 (2H, m), 1.72 (1H, m), 3.84 (2H, t), 4.52 (2H, s), 6.85 (3H, t), 7.11 (4H, m); ^{13}*C-NMR*: 22.6, 26.4, 35.9, 45.9, 64.8, 115.4, 115.4, 115.5, 122.4, 124.9, 125.5, 126.2, 126.4, 127.3, 127.5, 127.7, 135.1; *IR*: 3344, 2952, 1488, 1468, 1328, 1288, 1248, 1216, 1136, 1116, 1104, 1084, 1040, 748; *Anal. Calc. pt.* $C_{18}H_{21}NOS$: C, 72.20, H, 7.07, N, 4.68, S, 10.71; *Determinat*: C, 72.28, H, 7.11, N, 4.62, S, 10.67

(10-Pentyl-10*H*-phenothiazine-3-yl)methanol 3g
^{1}*H-NMR*: 0.87 (3H, t), 1.27-1.40 (4H, m), 1.77 (2H, m), 3.79 (2H, t), 4.37 (2H, s), 6.77-6.82 (2H, m), 6.86 (1H, t), 7.09-7.12 (4H, m); ^{13}*C-NMR*: 14.1, 22.4, 29.2, 4.5, 49.2, 64.5, 115.2, 122.3, 124.8, 125.1, 126.2, 126.6, 126.9, 127.2, 127.6, 132.4, 144.9, 145.4; *IR:*3400, 2952, 1488, 1468, 1316, 1288, 1252, 1220, 1136, 1124,1104, 984, 748. *Anal. Calc. for* $C_{18}H_{21}NOS$: C, 72.20, H, 7.07, N, 4.68, S, 10.71; *Found*: C, 72.28, H, 7.04, N, 4.69, S, 10.69.

RESULTS AND DISCUSSION

The IR and NMR spectra and the elementhal analysis confirmed the structures of compounds **1a-g** and **3a-g**.

The yields and melting points of synthetized derivatives **2a-g** and **3a-g** were given in Table 1, in comparison with those described in literature in the case of methyl- and ethyl derivatives.

Sodium salts of **2a-g** had better solubility in organic solvents that in water. For this reason the work up of the reaction mass from Cannizarro reaction could not be performed by selective extraction in water-organic heterogenous system. This property of the carboxylates **2a-g** made them potential phase transfer catalysts.

Methanol as solvent in Cannizarro reaction rise the yields in comparison with the method when the reaction was performed in thawing system, however the reaction time was longer.

Table 1.

Yields and melting points

Compd.	Yield [%]		m.p.(lit.) [°C]
	Method A	Method B	
2a	39	58	245(240-244[7])
2b	32	55	204(200[3])
2c	30	55	179
2d	29	56	143
2e	31	58	124
2f	28	52	188
2g	29	54	167
3a	48	82	132(133[7])
3b	42	68	99(98[9])
3c	39	72	-
3d	44	75	-
3e	31	78	-
3f	33	73	-
3g	34	71	-

CONCLUSIONS

Cannizarro reaction performed in methanol as solvent is a convenient method for concomitant synthesis of (10-alkyl-phenothiazine)-3-carboxylic acids **2a-g** and (10-alkyl-phenothiazine-3-yl)methanols **3a-g**. Structures of **2a-g** and **3a-g** were confirmed by elemental analysis and spectral data and were the same with those obtained with silver oxide (for acids) and with sodium tetrahydroborate (for alcohols).

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