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Synthesis of New 10-Substituted Phenothiazine Derivatives

By M. M. El-Kerdawy, H. A. Moharram,

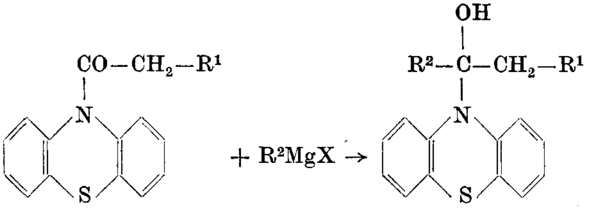
Department of Organic Chemistry, Drug Research and Control Centre, Giza, A. R. Egypt

and M. N. Tolba

Department of Medicinal Chemistry, National Research Centre, Dokki, Cairo, A. R. Egypt

The reaction of Grignard reagents, formed from alkyl or aryl halides, with 10-acetylphenothiazine **1a** [1] gave the corresponding hydroxy derivatives **2a–e**, in yields ranging from 15% to 55%. Similarly, Grignard reagents were added to the carbonyl group of 10-phenacetylphenothiazine **1b** [2] to furnish the corresponding hydroxy compounds **2f–j**.

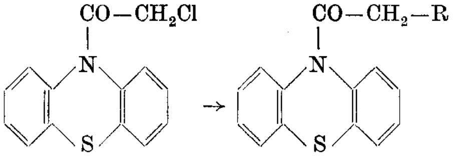
The IR spectra of compounds **2a–e** showed absorption bands at 3380–3385 cm⁻¹ (OH) [3]. The reaction of 10-chloroacetylphenothiazine **1c** [4] with different amines, in dry toluene, in the presence of KI as catalyst, gave the corresponding glycylphenothiazine derivatives **3a–f**.



1a, $R^1 = H$
1b, $R^1 = C_6H_5$

2

2	R^1	R^2
a	H	CH_3
b	H	C_2H_5
c	H	c-C_5H_9
d	H	c-C_6H_{11}
e	H	Ph
f	Ph	CH_3
g	Ph	C_2H_5
h	Ph	c-C_5H_9
i	Ph	c-C_6H_{11}
j	Ph	Ph



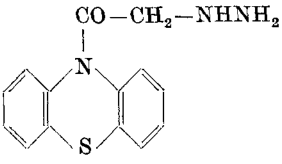
1c

3	R
a	piperidino
b	morpholino
c	3-piperidylamino
d	2-piperidylamino
e	4-piperidylamino
f	p-$CH_3OC_6H_4NH$

The structure of compounds **3a—f** has been established from their correct analytical data and by the consideration of their IR spectra (cf. Table 2).

10-Chloroacetylphenothiazine **1c** reacted with excess hydrazine hydrate to give 10-(hydrazinoacetyl)phenothiazine **4**. The IR spectrum of this compound showed absorption bands at 1700 cm^{-1} (C=O) and 3380 cm^{-1} (NH) [3].

Condensation of two moles of **1c** with one mole of hydrazine hydrate furnished, in 85% yield, 10,10′-[hydrazo-bis(methylenecarbonyl)]diphenothiazine **5**. This compound was also obtained from the condensation of compound **4** with equimolar amount of **1c**.



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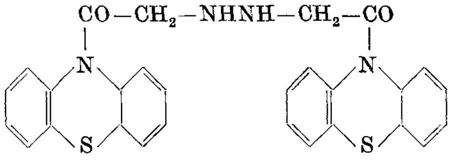

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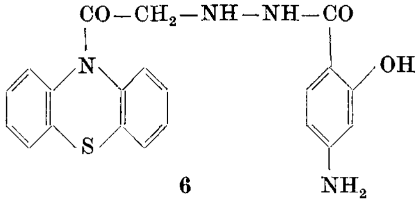
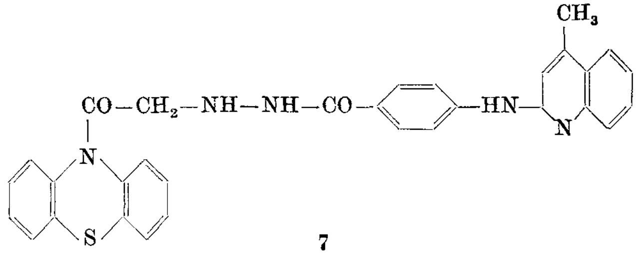
Compound **4** reacted smoothly with ethyl 4-amino-2-hydroxybenzoate and ethyl p-[(4-methyl-2-quinolyl)amino]benzoate to give 4-aminosalicylic acid 2-[(phenothiazin-10-ylcarbonyl)methyl]-hydrazide **6**, and p-[(4-methyl-2-quinolyl)amino]benzoic acid 2-(phenothiazin-10-ylcarbonyl)methylhydrazide **7**, respectively.



6



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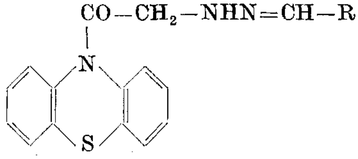
The IR spectrum of compound **6** showed absorption bands at 1680 cm^{-1} (C=O), 3280 cm^{-1} and 3405 cm^{-1} (NH) and 3505 cm^{-1} (OH), whereas, that of compound **7** showed bands at 1690 cm^{-1} (C=O) and 3380 cm^{-1} (NH) [3].

Condensation of **4** with aldehydes in glacial acetic acid gave the Schiff bases **8a—h**.



8	R
a	p-ClC_6H_4
b	o-$NO_2C_6H_4$
c	o-OHC_6H_4
d	p-$CH_3OC_6H_4$
e	2,4-$(OH)_2C_6H_3$
f	p-$(CH_3)_2NC_6H_4$
g	2,4-$(CH_3O)_2C_6H_3$
h	2-furfuryl.

The structure of these compounds was established from their correct analytical data and by the consideration of their IR spectra (cf. Table 3).

Experimental

All melting points are uncorrected. The IR absorption spectra were determined in potassium bromide pellets on Unicam SP. 200G infrared spectrophotometer.

Action of organomagnesium compounds on 10-acetylphenothiazine **1a**

To an ethereal solution of the organomagnesium bromide (prepared from 0.04 mole of magnesium, 0.03 mole of alkyl or aryl bromide, in 100 ml of dry ether and two crystals of iodine) was added a solution of 0.01 mole of **1a** in 50 ml dry ether. The reaction mixture was stirred, at room temperature, for two hours, then refluxed for 3 hours, set aside at room temperature overnight, then decomposed by saturated aqueous ammonium chloride solution. The organic layer was separated, dried over anhydrous sodium sulphate, then evaporated. The residue thus obtained was crystallized from the proper solvent to give **2a**–**e** as colourless crystals.

Similarly, 10-phenacetylphenothiazine **1b** reacted with organomagnesium bromide to give **2f**–**j** as colourless crystals.

Table 1 represents the physical and analytical data of compounds **2**.

Table 1 1,2-Substituted 1-(phenothiazin-10-yl)-ethanols

Compound	M.P. °C	Yield %	Molecular Formula	Molecular Weight	Analysis (Calcd./Found) C	H	N	S
2a	176[a])	50	$C_{15}H_{15}NOS$	257.3	70.09	5.89	5.45	12.47
					70.00	5.76	5.32	12.36
b	162[a])	25	$C_{16}H_{17}NOS$	271.4	70.91	6.34	5.17	11.82
					70.79	6.14	5.08	11.63
c	156[a])	55	$C_{19}H_{21}NOS$	311.4	73.36	6.82	4.50	10.30
					73.15	6.72	4.60	10.21
d	134[a])	32	$C_{20}H_{23}NOS$	325.5	73.90	7.14	4.31	9.86
					73.63	7.02	4.20	9.61
e	144[a])	15	$C_{20}H_{17}NOS$	319.4	75.30	5.28	4.39	10.04
					75.20	5.21	4.29	10.00
f	115[a])	43	$C_{21}H_{19}NOS$	333.4	75.73	5.76	4.21	9.62
					75.62	5.69	4.16	9.53
g	150[a])	49	$C_{22}H_{21}NOS$	347.5	76.17	6.11	4.04	9.23
					76.05	6.01	4.02	9.18
h	161[a])	52	$C_{25}H_{25}NOS$	387.5	77.58	6.52	3.62	8.28
					77.46	6.36	3.50	8.21
i	133[b])	37	$C_{26}H_{27}NOS$	401.6	77.69	6.78	3.49	7.97
					77.80	6.72	3.50	7.95
j	180[a])	44	$C_{26}H_{21}NOS$	395.5	79.06	5.37	3.55	8.11
					78.94	5.31	3.50	8.00

[a]) Crystallization from benzene.

[b]) Crystallization from toluene.

Reaction of 10-chloroacetylphenothiazine **1c** with amines

A mixture of 2 g (0.01 mole) of **1c** and 0.03 mole of the appropriate amine in 20 ml of dry toluene was refluxed for 3 hours. The amine hydrochloride was filtered off, the organic layer was extracted with 1N HCl (3×20 ml), and the acidic extract neutralized with sodium carbonate solution. The precipitated solid was collected, washed with sodium carbonate solution and then crystallized from the proper solvent to give **3a—f** as colourless crystals.

Table 2 represents the physical and analytical data of compounds **3a—f**.

10-(Hydrazinoacetyl)phenothiazine **4**

A mixture of 2.8 g (0.01 mole) of **1c**, 2 g (0.05 mole) of hydrazine hydrate (99—100%) and 15 ml of ethanol was refluxed for 3 hours. The reaction mixture was left to cool and diluted with water. The precipitated solid was filtered off, washed with water and then crystallized from ethanol-water to give 2.2 g (80%) of **4** as colourless needles that melted at 175 °C.

$C_{14}H_{13}N_3OS$ (271.3) Calcd. C 61.95 H 4.77 N 15.48 S 11.79
Foind C 61.99 H 4.79 N 15.49 S 11.81.

10,10′-[Hydrazo-bis(methylenecarbonyl)]diphenothiazine **5**

A mixture of 5.5 g (0.02 mole) of **1c**, 0.4 g (0.01 mole) of hydrazine hydrate and 20 ml of ethanol was refluxed for 3 hours. The reaction mixture was cooled, diluted with water and the precipitated solid was collected, washed with cold water and then crystallized from ethanol to give 3.3 g (76%) of **5** as colourless crystallized from ethanol to give 3.3 g (76%) of **5** was colourless crystals, m.p. 207 °C.

$C_{28}H_{22}N_4O_2S_2$ (510.6) Calcd. C 65.81 H 4.35 N 10.98 S 12.54
Found C 65.74 H 4.27 N 10.90 S 12.44.

4-Aminosalicylic acid 2-[(phenothiazin-10-ylcarbonyl)-methyl]hydrazide **6**

A mixture of 2.7 g (0.01 mole) of **4**, 1.8 g (0.01 mole) of ethyl 4-amino-2-hydroxybenzoate and 20 ml of ethanol, was refluxed for 3 hours. The reaction mixture was cooled and diluted with water. The separated white solid was collected, washed with cold water and then crystallized from ethanol to give **6** as colourless crystals that melted at 105 °C.

$C_{21}H_{18}N_4O_3S$ (405.5) Calcd. C 62.12 H 4.48 N 13.80 S 7.89
Found C 62.06 H 4.32 N 13.72 S 7.52.

In a similar manner, p-[(4-methyl-2-quinolyl)amino]benzoic acid 2-[(phenothiazin10-ylcarbonyl)methyl]hydrazide **7** was prepared from **4** (2.7 g; 0.01 mole) and ethyl p-[(4-methyl-2-quinolyl)amino]benzoate (3.1 g; 0.01 mole), as colourless crystals, m.p. 147 °C (yield 85%).

$C_{31}H_{25}N_5O_2S$ (531.6) Calcd. C 70.11 H 4.75 N 13.19 S 6.33
Found C 69.67 H 4.53 N 13.35 S 6.49.

Reaction of 10-(hydrazinoacetyl)phenothiazine **4** with aldehydes

A solution of 2.7 g (0.01 mole) of **4**, 0.01 mole of the appropriate aldehyde and 50 ml of glacial acetic acid, was refluxed for 2—3 hours. The reaction mixture was cooled, poured onto crushed ice and the formed precipitate was collected washed several times with cold water and then crystallized from the proper solvent to give **8a—h** as colourless crystals.

Table 3 represents the physical and analytical data of compounds **8a—h**.

Table 2 N-Substituted 10-glycyl-phenothiazine derivatives

Compound	M.P. °C[a])	Yield %	Reaction time hrs.	IR cm^{-1}	Molecular Formula	Molecular Weight	Analysis (Calcd./Found) C	H	N	S
3a	161	72	5	1695	$C_{19}H_{20}N_2OS$	324.4	70.42	6.23	8.65	9.88
							70.35	6.16	8.74	9.84
b	133	59	10	1700	$C_{18}H_{18}N_2O_2S$	326.4	66.30	5.57	8.59	9.82
							66.24	5.50	8.55	9.80
c	310	54	3	1695, 3340	$C_{19}H_{15}N_3OS$	333.4	68.86	4.55	12.62	9.62
							68.62	4.48	12.60	9.60
d	211	73	4	1695, 3380	$C_{19}H_{15}N_3OS$	333.4	68.86	4.55	12.62	9.62
							68.43	4.45	12.57	9.56
e	179	80	4	1695, 3300	$C_{19}H_{15}N_3OS$	333.4	68.86	4,55	12.62	9.62
							68.45	4.48	12.60	9.58
f	108	64	4	1695	$C_{21}H_{18}N_2O_2S$	362.4	69.66	5.02	7.74	8.85
							69.58	4.94	7.70	8.82

[a]) Crystallization from ethanol-water.

Table 3 Hydrazones from 10-(hydrazinoacetyl)phenothiazine 4 and aromatic aldehydes[a])

Compound	M.P. °C[b])	Yield %	Molecular Formula	Molecular Weight	Analysis (Calcd./Found) C	H	N	S
8a	157	79	$C_{21}H_{16}ClN_3OS$	393.4	64.18	4.11	10.69	8.15
					64.00	4.01	10.39	8.12
b	163	59	$C_{21}H_{16}N_4O_3S$	404.4	62.42	4.00	13.87	7.93
					62.22	3.70	13.52	7.59
c	170	59	$C_{21}H_{17}N_3O_2S$	375.4	67.26	4.58	11.21	8.54
					67.20	4.51	11.17	8.38
d	175	77	$C_{22}H_{19}N_3O_3S$	389.5	67.93	4.93	10.81	8.24
					67.72	4.69	10.53	8.16
e	179	62	$C_{21}H_{17}N_3O_3S$	391.5	64.51	5.42	10.75	8.20
					64.27	5.52	10.65	8.12
f	169	57	$C_{23}H_{22}N_4OS$	402.5	68.72	5.52	13.94	7.97
					68.20	5.19	13.70	7.87
g	184	60	$C_{23}H_{21}N_4OS$	419.5	65.93	5.16	10.03	7.65
					65.67	5.00	9.87	7.45
h	167	42	$C_{19}H_{15}N_3O_2S$	349.4	65.37	4.34	12.04	9.18
					65.20	4.16	11.93	9.08

[a]) IR spectra of all compounds showed an absorption band at 1620 cm^{-1} (C=N].
[b]) Crystallization from ethanol.

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Anschr. d. Verf.: Dr. M. N. TOLBA, Department of Medicinal Chemistry, National Research Centre, Dokki, Cairo, A. R. Egypt;
Dr. M. M. EL-KERDAWY, H. A. MOHARRAM, Department of Organic Chemistry, Drug Research and Control Centre, Giza, Cairo, A. R. Egypt