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2-Substituted-10-carboxyphenothiazine hydrazides **3** were found to yield hydrazones **5** on reaction with aromatic aldehydes. However, a similar reaction of hydrazides **3** with aliphatic ketones in refluxing ethanol failed to give the expected hydrazones **6**. The corresponding phenothiazines **1** were isolated in this reaction, apparently through alcoholysis of the amide bond to the ring nitrogen atom in **3**.

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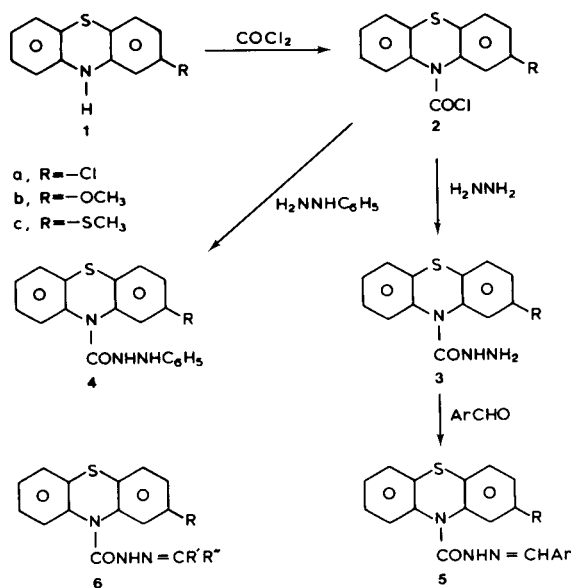
Besides the multiple pharmacological activity of compounds possessing the phenothiazine nucleus, the hydrazide of 10-carboxyphenothiazine has been shown [1] to display tuberculostatic activity. In order to study the pharmacological properties of derivatives of 2-substituted-10-carboxyphenothiazine hydrazides, the synthesis of compounds of the general formulae **5** and **6** has been undertaken. Compounds **5** and **6**, the hydrazones derived from the hydrazides **3**, might show increased tuberculostatic activity. We report herein the approach used for the synthesis of these compounds, which revealed an alcoholysis reaction of the $>N\text{-CONHNH}_2$ group of the hydrazides **3**.

hydrazides **4** were prepared by reaction of the acid chlorides **2** with phenylhydrazine in ethanol at room temperature.

The hydrazides **3a-3c** reacted easily with an equivalent of an aromatic aldehyde in a warm ethanolic solution to give the corresponding hydrazones **5**. These compounds were found to be highly insoluble and thus difficult to submit to a pharmacological screening.

The ir spectra proved useful [3] in confirming the structure of the insoluble compounds **5**. The acid chlorides **2** are characterized by a ν (C=O) band at 1730-1760 cm^{-1} and two bands, at 1590 and 1560 cm^{-1} , characteristic of the phenothiazine nucleus [4]. The hydrazides **3** are characterized by a broad ν (N-H) band at ~ 3300 cm^{-1} , a strong ν (C=O) amide band at 1660-1680 cm^{-1} , the two phenothiazine bands at 1590 and 1560 cm^{-1} , and a strong band at ~ 810 cm^{-1} , which is also characteristic of the 2,10-disubstituted phenothiazine nucleus - this band has been reported [4] to appear at a steady position, 785-800 cm^{-1} . The phenylhydrazides **4** are characterized by sharp ν (N-H) bands at 3300 and 3400 cm^{-1} , a strong ν (C=O) amide band at 1670 cm^{-1} and the two phenothiazine bands at 1590 and 1560 cm^{-1} . Finally, the hydrazones **5** are characterized by a sharp ν (N-H) band at 3200-3300 cm^{-1} , a strong ν (C=O) amide band at 1670-1680 cm^{-1} , a strong ν (C=N) band at 1520-1530 cm^{-1} and the phenothiazine strong bands at 1590, 1560 and ~ 810 cm^{-1} .

In contrast to the easy conversion of the hydrazides **3** to the hydrazones **5**, the analogous reaction of **3** with aliphatic ketones R'COR'' failed to yield the corresponding hydrazones **6**. Aliphatic ketones, *i.e.* methyl ethyl ketone and diethyl ketone, have been reported [5] to give the expected hydrazones on reaction with the hydrazides of 2- and 3-methylphenothiazine-10-propionic acids in ethanolic solution. Under these conditions and heating the reaction mixture for several hours, the hydrazides **3a-3c** were found to yield the parent phenothiazines **1**. The



The 2-substituted phenothiazines **1a-1c** were converted to the acid chlorides **2** by reaction with phosgene in chloroform or toluene [2] and these were then converted to the corresponding hydrazides **3** by reaction with hydrazine hydrate in ethanol. In a similar manner, the phenyl-

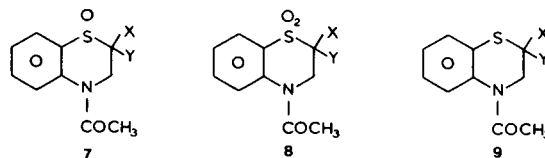
Table 1
Physical Data of Compounds 3-5

Compound	Ar	Mp (yield)	Molecular Formula	Analytical Data				
				Calcd./Found				
				C	H	Cl	N	S
3b	-----	160-161° (71 %)	C ₁₄ H ₁₃ N ₃ O ₂ S	58.52	4.56		14.62	11.16
				58.42	4.49		14.45	11.24
4a	-----	134° (75%)	C ₁₉ H ₁₄ ClN ₃ OS	62.03	3.84	9.64	11.42	8.72
				61.81	3.85	10.04	11.70	8.41
4b	-----	180-181° (57%)	C ₂₀ H ₁₇ N ₃ O ₂ S	66.09	4.71		11.56	8.82
				65.93	4.78		11.43	8.57
4c	-----	158-159° (57%)	C ₂₀ H ₁₇ N ₃ OS ₂	63.30	4.52		11.07	16.90
				63.16	4.57		11.04	17.03
5a	-C ₆ H ₅	169-171° dec (87%)	C ₂₀ H ₁₄ ClN ₃ OS	63.24	3.71	9.33	11.06	8.44
"	-C ₆ H ₄ -OH-2	178-180° (63%)	C ₂₀ H ₁₄ ClN ₃ O ₂ S	60.68	3.56	8.96	10.61	8.10
"	-C ₆ H ₄ -OCH ₃ -4	150-153° dec (70%)	C ₂₁ H ₁₆ ClN ₃ O ₂ S	61.53	3.93	8.65	10.25	7.82
"	-C ₆ H ₃ (OCH ₃)(OH)-3,4	178-180° dec (75%)	C ₂₁ H ₁₆ ClN ₃ O ₃ S	59.22	3.79	8.32	9.86	7.53
"	-CH=CH-C ₆ H ₅	161-164° dec (92%)	C ₂₂ H ₁₆ ClN ₃ OS	65.10	3.97	8.73	10.35	7.90
"				64.80	3.96	8.85	10.29	8.22
5b	-C ₆ H ₅	182-184° dec (97%)	C ₂₁ H ₁₇ N ₃ O ₂ S	67.18	4.56		11.20	8.54
"	-C ₆ H ₄ -OH-2	184-186° dec (96%)	C ₂₁ H ₁₇ N ₃ O ₃ S	64.43	4.38		10.74	8.19
"	-C ₆ H ₄ -OCH ₃ -4	182-183° dec (48%)	C ₂₂ H ₁₉ N ₃ O ₃ S	65.16	4.72		10.37	7.91
"				64.89	4.71		10.23	7.84
"	-C ₆ H ₃ (OCH ₃)(OH)-3,4	188-190° dec (82%)	C ₂₂ H ₁₉ N ₃ O ₄ S	62.70	4.54		9.97	7.61
"				62.60	4.70		10.02	7.63
"	-CH=CH-C ₆ H ₅	157-160° dec (85%)	C ₂₃ H ₁₉ N ₃ O ₂ S	68.80	4.77		10.47	7.99
"				68.54	4.81		10.44	7.78
5c	-C ₆ H ₅	170-172° dec (84%)	C ₂₁ H ₁₇ N ₃ OS ₂	64.42	4.38		10.73	16.38
"	-C ₆ H ₄ -OH-2	160-163° (83%)	C ₂₁ H ₁₇ N ₃ O ₂ S ₂	64.19	4.54		10.77	16.66
"				61.89	4.20		10.31	15.74
"				61.98	4.29		10.24	15.67
"	-C ₆ H ₄ -OCH ₃ -4	144-147° dec (81%)	C ₂₂ H ₁₉ N ₃ O ₂ S ₂	62.68	4.54		9.97	15.21
"				62.58	4.57		10.05	15.37
"	-C ₆ H ₃ (OCH ₃)(OH)-3,4	159-161° dec (70%)	C ₂₂ H ₁₉ N ₃ O ₃ S ₂	60.39	4.37		9.60	14.66
"				59.97	4.39		9.71	14.81
"	-CH=CH-C ₆ H ₅	142-144° dec (70%)	C ₂₃ H ₁₉ N ₃ OS ₂	66.16	4.59		10.06	15.36
"				66.05	4.87		10.09	15.28

phenothiazines **1** were also isolated after refluxing an ethanolic solution of the hydrazides **3a-3c** (see Experimental). The observed transformation of the hydrazides **3** to the corresponding phenothiazines **1** should then be ascribed to an alcoholysis reaction of the amide bond to the ring nitrogen atom in compounds **3**.

Apparently, the phenothiazinyl group assists in the nucleophilic attack on the amide carbonyl of the hydrazides **3**, by stabilizing the negative charge on the ring nitrogen atom. The closely related benzothiazine derivatives **7** (X

= -H, Y = -Cl; X = Y = -Cl) and **8** (X = Y = -H; X = -H, Y = -Cl; X = Y = -Cl) have been reported



[6] to undergo a facile deacetylation reaction, simply by refluxing in dry methanol, though the acetyl derivatives **9** ($X = Y = -H$; $X = -H$, $Y = -Cl$; $X = Y = -Cl$) could not be deacetylated except under rather severe conditions. On the other hand, phenothiazine was isolated from the reaction of 10-chloroacetylphenothiazine with thiourea in refluxing ethanol [7]. It would thus seem that the phenothiazine nucleus might behave as a good leaving group and this fact should not be overlooked under suitable reaction conditions.

EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. The ir spectra were obtained with a Perkin Elmer 137 spectrometer as nujol mulls. The tlc were performed on silica gel G plates; the eluent was in general a mixture of benzene-ether 7:1 and the spots were observed by exposure to iodine vapors.

Physical characteristics and analytical data for all new compounds are reported in Table 1.

Acid Chlorides **2**.

Reaction of the phenothiazines **1a-1c** with phosgene [2] afforded the corresponding acid chlorides: **2a**, mp 98-100°, lit [2] mp 100-101°; **2b**, mp 89-91°, lit [2] mp 94-95°; **2c**, mp 120-122°, lit [8] mp 122-124°.

Hydrazides **3**.

A mixture of 5 g of the acid chloride **2b**, 10 ml of hydrazine hydrate and 100 ml of ethanol was refluxed for 20 minutes. After cooling, the corresponding hydrazide **3b** separated as a crystalline solid (3.2 g, 71%), mp 160-161°. A recrystallization from ethanol did not improve its mp.

In a similar manner were prepared the hydrazides: **3a**, mp 170-171°, lit [1] mp 174°; **3c**, mp 135-137°, lit [9] mp 136-138°.

Phenylhydrazides **4**.

A mixture of the acid chloride **2** (3.3 mmoles) and phenylhydrazine (5 mmoles) in 8 ml of ethanol was stirred at room temperature for 2 hours. The solid which precipitated was filtered and recrystallized from benzene to give the phenylhydrazide **4**.

Hydrazones **5**.

The hydrazide **3** (7 mmoles) in 40 ml of ethanol was refluxed for 10 minutes and the aromatic aldehyde ArCHO (7 mmoles) was then added in the hot solution. The hydrazone **5** which precipitated immediately was filtered and recrystallized from acetone or ethanol. In most cases, the highly insoluble compound was purified by a short treatment with acetone at reflux.

Reaction of the Hydrazides **3** with Aliphatic Ketones.

The mixture of hydrazide **3** (7 mmoles) and a ketone (7 mmoles), such as methyl ethyl ketone, diethyl ketone or acetophenone, in 40 ml of ethanol was refluxed for 4 to 7 hours. The product which precipitated after cooling the reaction mixture or after concentration of the solution was found to be identical (tlc, mixed mp and ir spectra) to the parent phenothiazine **1**.

The same product **1** was obtained after refluxing an ethanolic solution of the hydrazide **3**.

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