Acylations of 1,10-Dilithiophenothiazine. A New Synthesis of 1-Formylphenothiazine

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The synthesis of 1-formyl-, 1-benzoyl-, 1-anisoyl-, and 1-nicotinyl-phenothiazines (**1-4**) resulting from the reaction of the corresponding amids with 1,10-dilithiophenothiazine (**5**) is reported. The site of attachment on 1,10-dilithiophenothiazine, based on the nature of some different acylating reagents, is also discussed.

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The dilithiation of phenothiazine and subsequent reaction with solid carbon dioxide to give 1-carboxyphenothiazine (**6**) has been known in the literature for some time (2). An extensive study of the scope and limitations of the lithiation concerning the introduction of different electrophiles has been reported by French workers (3). Attempted preparation of the 1-carboxaldehyde (**1**), however, failed. Later, **1** was prepared *via* lithium aluminum hydride reduction of 2-ethyl-2-dimethylamino-1,3-diekto-2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazine (**7**) (4). In 1965 Driscoll and Neeley reported on improved synthesis of **1** *via* Rosenmund reduction of the acid chloride of 1-carboxyphenothiazine (**6**) (5).

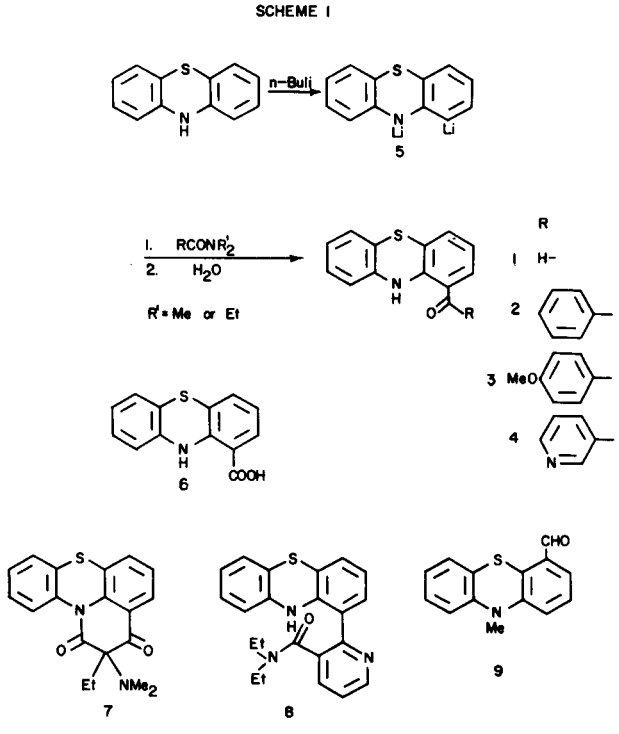
As part of our program leading to the synthesis of phenothiazine derivatives related to promazine with restricted sidechain rotation, 1-phenothiazines are important precursers. We therefore undertook a reinvestigation of the lithiation of phenothiazine and here report the reaction of 1,10-dilithiophenothiazine (**5**) with four different dialkylamides to give **1**, **2**, **3** and **4**.

Results and Disscussion.

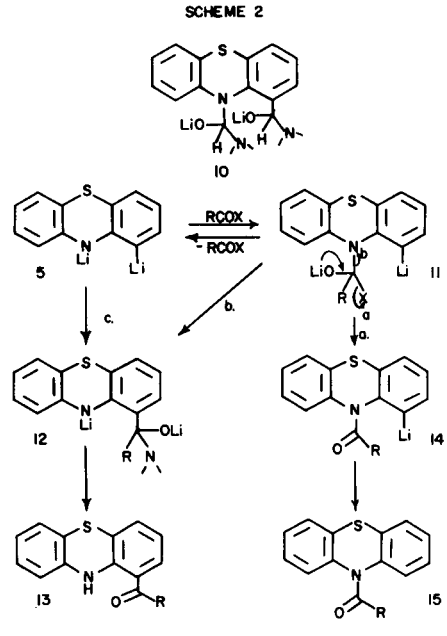
We found that *N,N*-dimethylformamide, *N,N*-dimethylbenzamide and *N,N*-dimethyl-4-methoxybenzamide each reacted smoothly with 1,10-dilithiophenothiazine. The same reaction conditions applied to the slightly more steric requiring *N,N*-diethylnicotinamide gave **4**, but in lower yield. Competition between addition over the carbonyl function and addition to the 1,2-azomethine bond in the pyridine nucleus contributed in part to the low yield in this case to give the 2-substituted pyridine derivative **8**. The reaction of various 3-substituted pyridine derivatives with aryllithium has been reported (4). The structure of **8** was determined with decoupling experiments at 250 MHz. The double doublet at lowest field, 8.15 ppm, was assigned the 5-proton in the pyridine ring, and the signals at 7.84 ppm and 7.40 ppm correspond to the 3- and 4-protons respectively. The coupling constants and low field NH signal, 8.83 ppm, support the proposed structure.

Analysis of the results of the French work together with our findings indicates that the site of acylation is essentially dependent on the leaving group involved in the addition. Acetylchloride was found to give *N*-acylation while the lithium salt of acetic acid or benzoic acid gave *C*-acylation (3). We reason that the reported failure in the reaction of *N*-methylformanilide to give the 1-carboxaldehyde (**1**) hardly could be due to steric interactions in the 1,2 addition to the carbonyl function since 4-formyl-10-methylphenothiazine (**9**) was isolated after lithiation of 10-methylphenothiazine followed by trapping with *N*-methylformanilide (3). The different reaction course using *N*-methylacetanilide compared to *N,N*-dimethylformamide probably results from the capability of the arylamide to delocalize the negative charge which, in turn, can compete with the phenothiazine anion as leaving group and consequently favor the irreversible route *a* as outlined in the scheme. 1-Formylphenothiazine is easily hydrolyzed in the workup to give phenothiazine.

SCHEME I



SCHEME 2



Leaving group(X)	Reaction Path	Substitution position
$Cl^{\ominus}$	a	10
$PhN^{\ominus}Me$	a	10
$MeN^{\ominus}Me$	b,c	1
$LiO^{\ominus}$	b,c	1

The failure to form 1-formylphenothiazine starting from *N*-methylformanilide indicates that the amides must first be attached to the nitrogen anion. Involvement of the diacylated species **10** on the reaction coordinate to explain the formation of 1-formylphenothiazine when the less steric requiring *N,N*-dimethylformamide is employed can be ruled out, since only one equivalent of amide is required to give a high yield of the 1-carboxaldehyde (**1**). We prefer to interpret this result with the assumption that **11** is either rearranged to **12** in an irreversible step, route *b*, or *via* an equilibrium with the dilithio compound (**5**) which eventually can be trapped with the acylation reagent *via* the route *c*. The same ganeral discussion based on leaving group dependence explains the reaction course when lithium salts of carboxylic acids or acid chlorides are used as acylation reagents as in the French work (3).

EXPERIMENTAL

All ir spectra were in accordance with proposed structures and were obtained on a Beckman IR-33 spectrophotometer. The nmr spectra were recorded on a Varian EM 360 L spectrometer or on a Bruker WM-250 MHz spectrometer with tetramethyl silane as an internal standard. The mass spectra were recorded on a Varian MAT 311 A double focusing mass spectrometer. The elemental analyses were preformed at the University Analytical Center, Tucson, Arizona.

1-Formylphenothiazine (**1**).

To a solution of 1.99 g (10 mmoles) of phenothiazine in 80 ml of dry ether, 15.6 ml (25 mmoles) of *N*-butyllithium in hexane was added with stirring and under an argon atmosphere at room temperature. After 24 hours, the reaction mixture was cooled to -70 and 0.73 g (10 mmoles) of freshly distilled dimethylformamide was added dropwise. After it was stirred one hour at room temperature, the reaction mixture was hydrolyzed with ice cold aqueous 0.5 *N* hydrogen chloride. The mixture was shaken vigorously and the organic layer was then separated. The aqueous phase was extracted three times with ether and the combined organic phases were washed with water and dryed (magnesium sulfate). After evaporation of the solvent (aspitator) the red residue was chromatographed (silica gel, hexane/ethylacetate, 10/1) to give 1.61 g (71%) of 1-formylphenothiazine, mp 81-83° [lit (4) mp 80-81°]; nmr (deuteriochloroform): δ 10.1 (s, 1H, NH), 9.8 (s, 1H, CHO), 7.4-6.5 (m, 7H, arom).

1-Benzoylphenothiazine (**2**).

The same metallation procedure as above was followed; thus, 1.49 (10 mmoles) of *N,N*-dimethylbenzamide in 5 ml of ether was added at -70°. After one hour stirring at room temperature, the reaction mixture was worked up as before to give, after chromatography (silica gel, hexane/ethyl acetate, 10/1) 1.94 g (64%) of 1 benzoylphenothiazine, mp 90-91° [lit (3) 91°]; nmr (deuteriochloroform): δ 10.3 (s, 1H, NH), 7.7-6.4 (m, 12H, arom).

1-*p*-Anisoylphenothiazine (**3**).

Using the same metallation procedure as above, 1.79 (10 mmoles) of *N,N*-dimethyl-4-methoxybenzamide in 5 ml of ether was added at -70°. After one hour of stirring at room temperature, the reaction mixture was worked up as before to give after chromatography (silica gel, toluene) 2.06 g (62%) of 1-*p*-anisoylphenothiazine as a red oil; nmr (deuteriochloroform): δ 10.0 (s, 1H, NH), 7.7-7.6 (m, 11H, arom), 3.8 (s, 3H, OCH_3); ms: m/e 333.

Anal. Calcd. for $C_{20}H_{15}NO_2S$: C, 72.05; H, 4.53; N, 4.20. Found: C, 72.21; H, 4.58; N, 4.53.

1-Nicotinoylphenothiazine (**4**) and *N,N*-Diethyl-2-(1-phenothiazinyl)-nicotinamide (**8**).

The same metallation procedure as above 1.78 g (10 mmoles) of *N,N*-diethylnicotineamide in 5.0 ml of ether was added at -70°. After one hour stirring at room temperature, the reaction mixture was hydrolyzed with ice-cold water (aqueous hydrogen chloride gave tars) and worked up as above. The crude product was chromatographed (silica) using toluene as eluent to remove unreacted phenothiazine. The eluent was then changed to ether and **4** followed by **8** were separated and isolated.

1-Nicotinoylphenothiazine (**4**).

This compound was obtained in a yield of 20§ (0.60 g) red Crystals, mp 94-96°; nmr (deuteriochloroform): δ 10.4 (s, 1H, NH), 8.9-6.4 (m, 11H, arom); ms: m/e 304.

Anal. Calcd. for $C_{18}H_{12}N_2OS$: C, 71.03; H, 3.97; N, 9.20. Found: C, 70.96; H, 4.20; N, 9.34.

N,N-Diethyl-2-(1-phenothiazinyl)nicotinamide (**8**).

This compound was obtained in a yield of 3% (0.12 g), amorphous red solid; 250 MHz nmr (deuteriochloroform): δ 8.83 (s, 1H, NH), 8.75 (dd, 1H, pyridine-6H), $J_{6H,5H}$ = 4.8 Hz, $J_{6H,4H}$ = 1.8 Hz, 7.84 (dd, 1H, pyridine-4H, $J_{4H,5H}$ = 7.7 Hz, $J_{4H,6H}$ = 1.8 Hz), 7.40 (dd, 1H, pyridine-5H, $J_{5H,4H}$ = 7.7 Hz, $J_{5H,6H}$ = 4.8 Hz), 7.27-6.47 (m, 7H, phenothiazine-H), 3.80-2.60 (m, 4H, CH_2), 0.99 (t, 3H, CH_3, $J_{CH_3CH_2}$ = 7.2 Hz), 0.72 (t, 3H, CH_3, $J_{CH_3CH_2}$ = 7.2 Hz); ms: m/e 375.

Anal Calcd. for $C_{22}H_{21}N_3OS$: C, 70.37; H, 5.64; N, 11.19. Found: C, 70.01; H, 5.70; N, 11.30.

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REFERENCES AND NOTES

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