Preparation of Certain 2-*N*-Alkylamino- and 2-*N*,*N*-Dialkylamino-10-methylphenothiazines *via* Phenothiazyne (1a)

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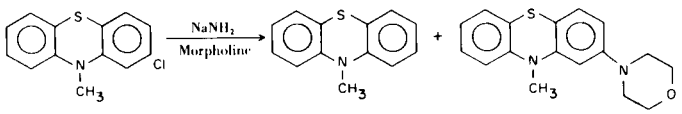
The treatment of 2-chloro-10-methylphenothiazine, **1**, with lithium alkylamide/alkylamine or lithium dialkylamide/dialkylamine yields the corresponding 2-*N*-alkylamino- or 2-*N*,*N*-dialkylaminophenothiazines in good yields *via* phenothiazyne. No significant reduction of **1** to 10-methylphenothiazine is observed. Yields of amines obtained by this method are considerably higher than those obtained by reacting **1** with sodamide in refluxing amine solvent. Attempts to introduce the $-CH_2CN$ moiety onto the phenothiazine nucleus by treating **1** with sodamide and acetonitrile in liquid ammonia produced only 2-amino-10-methylphenothiazine.

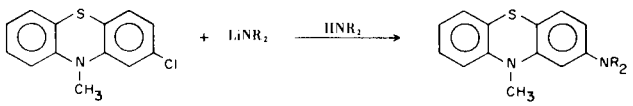
Recently, D. H. Jones (2) has reported that the action of sodamide on 2- or 3-chloro-10-methylphenothiazines in the presence of refluxing morpholine or morpholine derivatives produces the corresponding 2- or 3-morpholino-10-methylphenothiazine in yields ranging from 5 to 81%. The typical experiment described in that paper indicated that a significant amount of the reduced product, 10-methylphenothiazine, **2** (13%), was formed in addition to the aryne product, 2-morpholino-10-methylphenothiazine, **3** (35%).



1 2 3

This is consistent with Bunnett's (3) observation that a mixture of the somewhat similar base, piperidine, and sodamide can reductively dehalogenate certain haloaromatic compounds. We (4,5) have, however, demonstrated that high yields of *N*,*N*-dialkylanisidine can be obtained from the appropriate haloanisoles by using lithium dialkylamide in the presence of an excess (2-4 equivalents) of the corresponding free secondary dialkylamine. The use of a large excess of free amine allows the aryne intermediate to be essentially converted to typical aryne amine products while obviating reduction of aryne *via* hydride transfer from lithium dialkylamide. It was therefore of interest to determine if the use of lithium dialkylamide/dialkylamine also could convert halophenothiazines to the corresponding dialkylaminophenothiazine in good yields.

The results listed in Table I indicate that 2-*N*,*N*-dialkyl-



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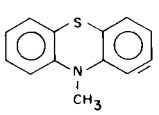
R = C_2H_5, *n*-C_3H_7, *iso*-C_3H_7, *n*-C_4H_9, *iso*-C_4H_9

amino-10-methylphenothiazine are obtained in good yields by the reaction of 1 equivalent of 2-chloro-10-methylphenothiazine, **1**, with 2 equivalents of various lithium dialkylamides in the presence of 2 equivalents of the corresponding dialkylamine. In general, maximum yields were obtained using a reaciton time of 2 hours, however, the butyl amines required overnight refluxing for maximum yields. Tlc chromatograms of the crude reaction products revealed that only trace amounts of 10-methylphenothiazine were obtained in all reactions. The assignment of location of the *N*,*N*-dialkylamino group on the phenothiazine nucleus was based upon the following. The aromatic region of the nmr spectrum of each amine contains a multiplet at 3.2 τ (5 H), a doublet (1 H, J = 2 Hz), at 3.82 τ and a partially resolved quartet (1 H) at 3.92 τ consistent with either 2- or 3-substitution. D. H. Jones (2) has previously shown that both 1- and 2-chlorophenothiazine gave the same 2-substituted-amino derivative. This indicates that these chlorophenothiazines yielded the same aryne intermediate, namely, 10-methyl-1,2-phenothiazyne, **5**, even though the 2-chloroisomer could also form 10-methyl-2,3-phenothia-



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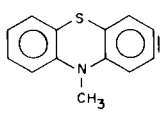

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TABLE I

Preparation of 2-*N*,*N*-Dialkylamino-10-methylphenothiazines

R_2NH R	Time Hours	Base	Yield %
Ethyl	1	$LiNEt_2$ (a)	72
	3	$LiNEt_2$ (a)	74
n-Propyl	24	KNH_2 (b)	7
	1	LiN(*n*-propyl)$_2$ (a)	75
Isopropyl	1	LiN(isopropyl)$_2$ (a)	48
n-Butyl	24	LiN(*n*-butyl)$_2$ (a)	62
Isobutyl	6	KNH_2 (b)	31
	24	LiN(isobutyl)$_2$ (a)	61

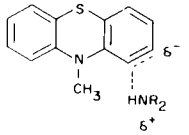
(a) One equivalent of **1**:2 equivalents of $LiNR_2$:2 equivalents of HNR_2. (b) One equivalent of **1**:3 equivalents of KNH_2 in liquid ammonia.

TABLE II

Preparation of 2-*N*-Alkylamino-10-methylphenothiazines

RNH_2 R	Time Hours	Base	TMEDA	Yield %
n-propyl	0.5	LiNH-*n*-propyl	---	42
	1	LiNH-*n*-propyl	---	43
	2	LiNH-*n*-propyl	---	52
	1	LiNH-*n*-propyl	0.01 mole	60
	2	LiNH-*n*-propyl	0.01 mole	75
Isopropyl	1	LiNH-isopropyl	---	45
	1	LiNH-siopropyl	0.01 mole	72
Isobutyl	2	LiNH-isobutyl	---	38
	2	LiNH-isobutyl	0.01 mole	59

zine, **6**. J. D. Roberts has shown that the influence of combined inductive and field effects, and not mesomeric effects, determine the direction of aryne formation (6) and of amine addition (7). Accordingly, the 10-nitrogen atom, a strong electron withdrawing group by induction (-I), increases the acidity of the 1-hydrogen atom of **1** to a much greater extent than that of the 3-hydrogen atom. Thus the preference for 1,2-aryne, **5**, from **1** is readily explained. In addition, comparison of the transition states for amine addition to the 1-position and to the 2-position of aryne, **5**, (**7** and **8**, respectively), indicates that the 10-nitrogen atom is closer to the developing negative charge in **8** than in **7**. Therefore, the strong electron withdrawing nitrogen atom is able to stabilize transition state **8** to a much greater extent than transition state **7**, resulting in sole formation of the 2-product. The 10-methyl group would



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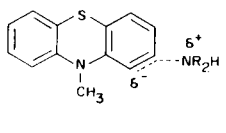

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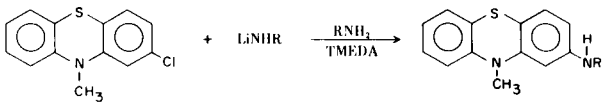
also offer some steric hindrance to amine addition to the 1-position. Since our system is similar to that employed by D. H. Jones, 2-substitution would also be expected on the basis of the previous arguments. Hence, 3-substitution is ruled out.

For comparison, *N*,*N*-di-*n*-propyl- and *N*,*N*-diisobutyl-10-methylphenothiazines (**4c** and **d**) were synthesized according to the method of Jones (2) in yields considerably lower (7% and 31%, **4c** and **d**, respectively) than those obtained in this study (75% and 61%, **4c** and **d**, respectively).

The preparation of 2-*N*-alkylamino-10-methylphenothiazine, **9**, by the action of lithium alkylamides in the presence of the corresponding primary alkylamine on **1** was also accomplished in this study in good yields.



R = *n*-C_3H_7, *iso*-C_3H_7 and *iso*-C_4H_9

9a = *n*-C_3H_7
b = *iso*-C_3H_7
c = *iso*-C_4H_9

Lithium alkylamides are generally insoluble in the reaction mixtures employed in this study. However, if they are prepared by the slow addition of *n*-butyllithium to the appropriate primary amine/ether solution, then the initially formed precipitate eventually will dissolve during the course of the reaction. The data listed in Table II indicates that the yields are enhanced by using an equimolar quantity of the lithium alkylamide and tetramethylethylenediamine (TMEDA). For example, the yield of **9b** was increased from 45 to 72% by the addition of TMEDA. Nucleophilic enhancement of certain nucleophiles by TMEDA is well established. This one-step synthesis, therefore, provides a very convenient method for preparing *N*-alkylaminophenothiazines free from *N*,*N*-dialkylamino isomer in good yields. Nmr analysis and the arguments previously presented for secondary amine addition indicate that the nucleophilic addition of primary amines to 10-methyl-1,2-phenothiazyne occurs at the 2-position.

Attempts to prepare cyanomethyl derivatives of 10-methylphenothiazines, **8a** and **8b**, by the action of lithium salt of acetonitrile or phenylacetonitrile failed due to the extreme insolubility of these salts in the reaction medium. Also, treatment of **1** with the sodium salt of acetonitrile or phenylacetonitrile in the presence of sodamide and ammonia afforded only 2-amino-10-methylphenothiazine in 60% yield. We (8) have shown that the reactivity of arynes is increased by substituents which inductively polarize the "triple bond" of the particular aryne intermediate. The polarized bond thus allows the more abundant but less reactive ammonia molecule to compete with the less abundant but more reactive carbon acid anion. For example, 3-methoxybenzyne undergoes four times more

addition with ammonia than with the anion of acetonitrile. Unfortunately, 1,2-phenothiazyne is apparently even more reactive than 3-methoxybenzyne in that no appreciable addition of the sodium salt of acetonitrile occurred. This factor may hinder the addition of other carbon acids to phenothiazynes.

EXPERIMENTAL

Materials.

The amines (Eastman Kodak) were dried over anhydrous potassium carbonate, distilled over anhydrous calcium hydride and stored over potassium carbonate. Purified potassium sodium (J. T. Baker Chemical Co.), sodium hydride (K and K Laboratories), *N*-butyllithium in hexane (Alfa Inorganics), and anhydrous ammonia (USS Agri-Chemical Division) were used as received. A generous supply of 2-chlorophenothiazine was donated by Smith, Kline and French Laboratories. 10-Methyl-2-chlorophenothiazine was prepared by methylating 2-chlorophenothiazine according to the method of Jones (2).

Preparation of 2-*N*,*N*-Dialkylaminophenothiazines.

a) Lithium Dialkylamide/dialkylamine Method.

The reactions were carried out under a nitrogen atmosphere and an oven dried 100-ml. flask equipped with an ice water cooled condenser, constant pressure addition funnel, and ground glass stopper.

To a stirred solution containing 30 ml. of anhydrous ether and 0.06 mole of the appropriate dialkylamine was added 0.02 mole of butyllithium (2.2 *M* in hexane) and the solution was refluxed for 10 minutes. 2-Chloro-10-methylphenothiazine (0.01 mole, 2.5 g.) was then added in portions during which time the solution became reddish brown. The reaction was refluxed for the period listed in Table I and then quenched by the slow addition of water until the darkly colored reaction mixture changed to cloudy white. The mixture was then washed with water and extracted with three 50-ml. portions of 10% hydrochloric acid. Addition of 10% sodium hydrogen solution to the combined acidic aqueous extracts afforded crude crystals or an oil of the appropriate *N*,*N*-dialkylamine products. After the crude product was collected, it was dried and then purified by column chromatography (2.5 x 20 cm alumina column using benzene as eluant) and recrystallized from 2-propanol.

2-*N*,*N*-Diethylamino-10-methyl phenothiazine.

This compound had m.p. 118-119°; nmr (carbon tetrachloride): m, 6.85 δ (Ar, 5 H), m 6.15 δ (Ar, 2H), Q 3.25 δ (CH_2CH_3, 4 H), S, 3.28 δ (N-CH_3, 3 H), t 1.1 δ (-CH_2CH_3, 6 H).

Anal. Calcd. for $C_{17}H_{20}N_2S$: C, 71.77; H, 7.09; N, 9.86; S, 11.28. Found: C, 71.72; H, 7.13; N, 9.59; S, 10.98.

2-*N*,*N*-Di-*n*-propylamino-10-methylphenothiazine.

This compound had n.p. 77°; nmr (carbon tetrachloride): m 6.8 δ (Ar, 5 H), m 6.15 δ (Ar, 2 H), t 3.15 δ (CH_2-CH_2CH_3, 4 H), S 3.24 δ (N-CH_3, 3 H), sext 1.55 δ ($CH_2CH_2CH_3$, 4 H), t 0.85 δ ($CH_2CH_2CH_3$, 6 H).

Anal. Calcd. for $C_{19}H_{24}N_2S$: C, 73.03; H, 7.74; N, 8.97; S, 10.26. Found: C, 73.08; H, 7.85; N, 8.90; S, 10.05.

2-*N*,*N*-Diisobutylamino-10-methylphenothiazine.

This compound had m.p. 93-94°; nmr (carbon tetrachloride): m 6.82 δ (Ar, 5 H), m 6.12 δ (Ar, 2 H), d 3.06 δ (-CH_2-$\underset{\displaystyle CH_3}{\overset{|}{C}}H$-$CH_3$, 4 H), S 3.38 δ (N-$CH_3$, 3 H), sext 1.95 δ [-$CH_2$-$CH(CH_3)_2$, 2 H], d 0.88 δ [-$CH_2CH(CH_3)_2$, 6 H].

Anal. Calcd. for $C_{21}H_{28}N_2S$: C, 74.05; H, 8.29; N, 8.23; S, 9.42. Found: C, 74.00; H, 8.34; N, 7.85; S, 8.71.

Ir spectra were consistent with proposed structures.

b) Potassium Amide/dialkylamide Method.

Approximately 25-30 ml. of anhydrous ammonia was condensed into a 50-ml., oven dried reaction flask fitted with a dry ice condenser, drying tube (filled with anhydrous calcium chloride), slip seal stirrer and ground glass stopper. A few crystals of ferric nitrate hexahydrate were added to the ammonia. Purified potassium (1.18 g., 0.030 mole) was weighed, cut into small pieces in a beaker of mineral oil and rinsed in petroleum ether before it was added to the ammonia. The addition of potassium caused the ammonia to turn a dark blue color which rapidly changed to grey, indicating the formation of potassium amide. The remaining pieces were added, continuing in this manner until all the potassium was consumed. Then the dry ice condenser was replaced with a water condenser and the ammonia evaporated under nitrogen by means of a warm water bath. The appropriate dialkylamine solvent (50 ml.) was added and the mixture heated to reflux temperature with continuous stirring. At this point, 10-methyl-2-chlorophenothiazine (2.48 g., 0.010 mole) was added in portions. After the mixture was refluxed under nitrogen (6-24 hours) with stirring, the oil bath was removed and the reaction was quenched with ammonium chloride (2.0 g., 0.050 mole). The crude reaction mixture was then treated in the manner described in the previous method.

Preparation of 2-*N*-Alkylaminephenothiazines.

These amines were generally prepared according to the procedure described previously for the preparation of 2-*N*,*N*-dialkylaminophenothiazines. In certain reactions listed in Table II, TMEDA was added to the amine-ether solution prior to the addition of butyl lithium. The 2-*N*-alkylaminophenothiazines were isolated in the usual way and had the following physical properties.

2-*n*-Propylamino-10-methylphenothiazine.

This compound had m.p. 90-93°; nmr (carbon disulfide): m 6.8 (Ar, 5 H); m 5.95 δ (Ar, 2 H); S 3.5 δ (N - H, 1 H); Q 3.0 δ (N-$CH_2CH_2CH_3$, 2 H); S 3.12 δ (N-CH_3, 3 H); sext 1.55 δ (-$CH_2CH_2CH_3$, 2 H); t 0.95 δ ($CH_2CH_2CH_3$, 3 H).

Anal. Calcd. for $C_{16}H_{18}N_2S$: C, 71.07; H, 6.71; N, 10.36; S, 11.86. Found: C, 70.80; H, 6.57; N, 10.07.

2-Isopropylamino-10-methylphenothiazine.

This compound had m.p. 114-116°; nmr (carbon disulfide): m 6.9 δ (Ar, 5 H); m 6.05 δ (Ar, 2 H); sept 3.57 δ [N-$CH(CH_3)_2$, 1 H]; S 3.35 δ (*N*-H, 1 H); S 3.23 δ (N-CH_3, 3 H); d 1.23 δ [N-$CH(CH_3)_2$, 6 H].

Anal. Calcd. for $C_{16}H_{18}N$ S: C, 71.07; H, 6.71; N, 10.36; S, 11.86. Found: C, 70.80; H, 6.66; N, 10.55.

2-*n*-Butylamine-10-methylphenothiazine.

This compound had m.p. 91-92°; nmr (carbon disulfide): m 6.75 δ (Ar, 5 H); m 5.95 δ (Ar, 2 H); S 3.39 δ (NH, 1 H); S 3.12 δ (N-CH_3, 3 H); t 2.98 δ [N-CH_2-$(CH_2)_2CH_3$, 2 H]; m 1.45 δ [N-$CH_2(CH_2)_2CH_3$, 4 H]; m 0.95 δ [$N(CH_2)_3CH_3$, 3 H].

Anal. Calcd. for $C_{17}H_{20}N_2S$: C, 71.84; H, 7.04; N, 9.86; S, 11.28. Found: C, 71.82; H, 7.34; N, 9.82.

2-Isobutylamino-10-methylphenothiazine.

This compound had m.p. 124-126°; nmr (carbon disulfide): m 6.95 δ (Ar, 5 H); m 6.1 δ (Ar, 2 H); S 3.55 δ (N-H, 1 H); S 3.35 δ (N-CH_3, 3 H); d 2.97 δ [N-CH_2CH(CH_3)$_2$, 2 H]; m 2.0 δ [N-CH_3CH(CH_3)$_2$, 1 H]; d 1.1 δ [N-CH_2CH(CH_3)$_2$, 6 H].

Anal. Calcd. for $C_{17}H_{20}N_2S$: C, 71.82; H, 7.04; N, 9.86; S, 11.28. Found: C, 71.22; H, 6.92; N, 9.24; S, 10.85.

2-Secbutylamino-10-methylphenothiazine.

This compound had m.p. 107-109°; nmr (carbon disulfide): m 6.77 δ (Ar, 5 H); m 5.95 δ (Ar, 2 H); complex m 3.3 δ [N-H, 1 H; N-CH(CH_2)(CH_3)$_2$, 1 H]; S 3.11 δ (N-CH_3, 3 H); complex m 1.1 δ [N-CH(CH_2CH)CH_3, 2 H; N-CH(CH_2CH_3)CH_3, 6H].

Anal. Calcd. for $C_{17}H_{20}N_2S$: C, 71.82; H, 7.04; N, 9.86; S, 11.28. Found: C, 71.84; H, 6.95; N, 9.93

Attempted Preparation of 2-Cyanomethyl-10-methylphenothiazine.

To a 500-ml. flask containing 0.04 mole of potassium amide (prepared *in situ* by the addition of 1.56 g., of potassium to 200 ml. of ammonia) was added 0.82 g. (0.02 mole) of acetonitrile. After stirring the resulting greenish solution for 10 minutes, 2.5 g. (0.011 mole) of acetonitrile was added and the reaction stirred for an additional 6 hours. At this time, the reaction mixture was quenched by the addition of 2.7 g. (0.05 mole) of ammonium chloride and the ammonia was evaporated to yield, after the usual processing, only 2-amino-10-methylphenothiazine (m.p. 161°, lit. (2) 161-162) in 60% yield.

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