whereupon refractive index and boiling point remained constant; b.p.$_{30}$ 43–44°, n_D^{30} 1.3912.

This fraction was shown to react with aniline under evolution of heat. If this reaction were carried out at 60°, a white solid was formed. Next it could be shown that this solid was not acetanilide, despite the literature statement that a mixture of aniline and acetic acid at room temperature within four months had formed acetanilide.[26]

Finally, by recrystallization from benzene, white needles were obtained which, through m.p. and mixed m.p. (143°) with authentic material, were identified as *N,N*-diphenylformamidine.[5] This result, along with the analytical data, suggests the conclusion that the fraction of n_D^{30} 1.3912 is an azeotropic mixture of the composition $7CH_3COOH.C_7H_9N_3$.

Anal. Calcd. for $7CH_3COOH.C_7H_9N_3$: C, 40.73; H, 6.23; N, 8.38. Found: C, 40.68; H, 6.25; N, 8.04.

Acknowledgment. The authors are very much indebted to the Olin Mathieson Chemical Corporation for their generous support of this work.

COLUMBUS, OHIO

(26) J. R. Pound and R. S. Russell, *J. Chem. Soc.*, 769 (1924).

[CONTRIBUTION FROM THE MEDICINAL CHEMICAL RESEARCH DEPARTMENT OF THE SCHERING CORPORATION]

3-Azaphenothiazine and Dialkylaminoalkyl Derivatives

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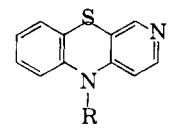
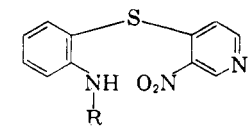
3-Azaphenothiazine has been synthesized and converted to 10-(3-dimethylaminopropyl)-3-azaphenothiazine. When 3-azaphenothiazine is alkylated with methyl iodide, or with the salts of aminoalkyl halides it forms novel quaternary salts which, upon treatment with aqueous alkali, liberate the corresponding anhydronium bases. The structures of these 3-alkyl derivatives of 3-azaphenothiazine are supported by their infrared and ultraviolet spectra as well as by *p*Ka measurements. The dipole moments of 3-azaphenothiazine and of 3-methyl-3-azaphenothiazine anhydronium base have been measured in dioxane solution. The pharmacology of the aminoalkyl derivatives of 3-azaphenothiazine is discussed.

The possibility that 10-(3-dimethylaminopropyl)-3-azaphenothiazine (I) might possess tranquilizing properties similar to those of the corresponding phenothiazine derivatives[1] led us to prepare and alkylate 3-azaphenothiazine (II).[2] Although in recent years many azaphenothiazines[3] and diazaphenothiazines[4] have been synthesized, the unsubstituted 3-azaphenothiazine[5] has not been described. We found that the Smiles rearrangement[6] of 2-acetamidophenyl 3-nitro-4-pyridyl sulfide (III) proceeded smoothly in acetone solution by the addition of powdered potassium hydroxide[7] to give a 62% yield of 3-azaphenothiazine (II). The preparation of the intermediate 2-aminophenyl 3-nitro-4-pyridyl sulfide (IV) in a number of steps starting from pyridine has been described.[3e]



I. R = $CH_2CH_2CH_2N(CH_3)_2$
II. R = H



III. R = $COCH_3$
IV. R = H

3-Azaphenothiazine (II) was alkylated with 3-dimethylaminopropyl chloride using sodium amide in refluxing toluene to give 10-(3-dimethylaminopropyl)-3-azaphenothiazine (I). The dihydrochloride of I was nearly inactive as a tranquilizing agent when injected intraperitoneally in mice and, in marked contrast to the corresponding 10-dialkylaminoalkyl-1-azaphenothiazines[8] had only slight sedative and antihistamine properties.

On the other hand, alkylation of 3-azaphenothiazine (II) with 3-dimethylaminopropyl chloride in the absence of a stronger base gave the novel 3-(3-dimethylaminopropyl)-3-azaphenothiazinium chloride (V chloride) which on treatment with

(1) For a review see D. G. Friend, *Clin. Pharmacol. Therap.*, 1, Adv. p. 5 (1960).

(2) For numbering of the phenothiazine nucleus see v. J. P. Bourguin *et al.*, *Helv. Chim. Acta*, 42, 2541 (1959).

(3) (a) V. A. Petrow and E. L. Rewald, *J. Chem. Soc.*, 591 (1945); (b) H. L. Yale and F. Sowinski, *J. Am. Chem. Soc.*, 80, 1651 (1958); (c) A. R. Gennaro, *J. Org. Chem.*, 24, 1156 (1959); (d) Y. Maki, *Chem. Abstr.*, 52, 1174 (1958); (e) A. J. Saggiomo, P. N. Craig, and M. Gordon, *J. Org. Chem.*, 23, 1906 (1958); (f) T. Takahashi and E. Yoshii, *Pharm. Bull.*, 2, 382 (1954).

(4) (a) J. Druey, *Angew. Chem.*, 70, 5 (1958); (b) T. Takahashi and Y. Maki, *Chem. Abstr.*, 52, 14622 (1958); (c) Y. Maki, *Chem. Abstr.*, 51, 14738 (1957); (d) T. Takahasi and Y. Maki, *Chem. Pharm. Bull.*, 6, 369 (1958).

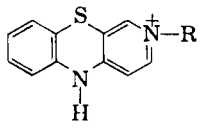
(5) 1-Nitro- and 1-amino-3-azaphenothiazines have been synthesized, and treatment of the latter compound with nitrous acid led to the formation of 3-azaphenothiazine-1,10-diazole.[3a] Attempts to prepare 3-azaphenothiazine by the fusion of 4-anilinopyridine with sulfur[3a] or by the Smiles rearrangement[6] of 2-formàmidophenyl 3-nitro-4-pyridyl sulfide[3e] were unsuccessful.

(6) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 151, 1263 (1935).

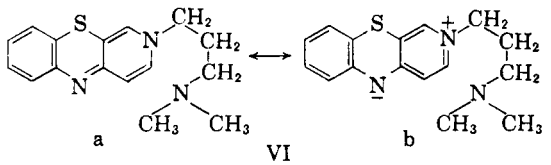
(7) The use of anhydrous potassium hydroxide in acetone as a medium for condensation reactions has been described, see K. A. Latif, M. M. Hossain, and M. A. Salam, *J. Ind. Chem. Soc.*, 35, 619 (1958). We found that when the alkali was added in alcoholic solution by the usual procedure the product was more difficult to isolate and the yield was lower.

(8) (a) Report of the Committee on New and Unused Therapeutics, *Ann. Allergy*, 16, 237 (1958); (b) A. Von Schlichtegroll, *Arz. Forsch.*, 7, 237 (1957); (c) *Arz. Forsch.*, 8, 489 (1958).

aqueous alkali gave reddish-brown crystals of the anhydronium base VI.[9] Although an *excess* of methanolic hydrogen chloride converted the anhydronium base VI to bright yellow crystals of the chloride hydrochloride of V, orange crystals of V chloride were generated with *one equivalent of* methanolic hydrogen chloride. A more convenient method of obtaining V chloride consisted in mixing methanolic solutions of equivalent weights of the anhydronium base VI and the chloride hydrochloride of V. The bromide hydrobromide and the dimaleate of V were also obtained.



V. R = $CH_2CH_2CH_2N(CH_3)_2$
VII. R = $CH_2CH_2CH_2NC_5H_{10}$
VIII. R = $CH_2CH_2NC_5H_{10}$
IX. R = $CH_2CH_2NH_2$
XII. R = CH_3



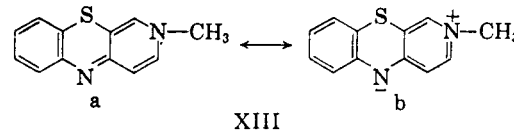
VI

The pharmacological evaluation of 3-(3-dimethylaminopropyl) - 3 - azaphenothiazinium chloride hydrochloride (V chloride hydrochloride) showed it to be a potent hypotensive agent. The intravenous injection of a dose of 2 mg./kg. caused a marked fall in the blood pressure of phenobarbital-anesthetized dogs which lasted for about one hour. In order to study further the hypotensive activity of this class of compounds a number of analogues were prepared. In VII, VIII, and IX the 3-dimethylaminopropyl substituent of V is replaced by 3-(*N*-piperidino)propyl, 2-(*N*-piperidino)ethyl, and 2-aminoethyl groups, respectively.

The chloride hydrochloride of VII was obtained as with V *via* the anhydronium base when 3-(*N*-piperidino)propyl chloride was substituted for 3-dimethylaminopropyl chloride. However, the product was obtained more conveniently by refluxing a solution of 3-azaphenothiazine (II) and 3-(*N*-piperidino)propyl chloride hydrochloride in absolute ethanol. The latter method also gave the halide hydrohalide salts of VIII and IX when 3-azaphenothiazine (II) was refluxed in alcoholic solution with 2-(*N*-piperidino)ethyl chloride hydrochloride and 2-aminoethyl bromide hydrobromide respectively. It is interesting that when 4-(*N*-piperidino)butyl chloride hydrochloride was treated with 3-azaphenothiazine in a similar manner, the 3-azaphenothiazine was recovered unchanged as its hydrochloride, probably because of selfquaternization of the 4-(N-piperidino)butyl chloride.

(9) (a) The anhydronium base VI may be considered to be a resonance hybrid of structures VIa and VIb. For the use of the term "anhydronium base" see B. Witkop, *J. Am. Chem. Soc.*, **75**, 3361 (1953); (b) For a critical discussion of the resonance hybrid structure of β-carboline anhydronium bases see I. D. Spenser, *J. Chem. Soc.*, 3659 (1956).

The halide hydrohalide salts of VII, VIII, and IX caused a fall in the blood pressure of normotensive dogs when given intravenously, but the effect was less marked and more transient than that of V chloride hydrochloride.



XIII

In accord with the structural assignments of the 3-aminoalkyl derivatives of 3-azaphenothiazine is the fact that, when 3-methyl-3-azaphenothiazinium iodide (XII iodide) (from 3-azaphenothiazine and methyl iodide) is converted to the corresponding anhydronium base XIII, the latter may again be alkylated with methyl iodide to form 3,10-dimethyl-3-azaphenothiazinium iodide (XIV iodide). The structure of the anhydronium base XIII may be represented as a resonance hybrid to which XIIIa and XIIIb make the major contributions, while XIVa and XIVb are the most important resonance structures of the quaternary cation XIV.

The infrared spectra of 3-azaphenothiazine (II), the anhydronium base XIII and the quaternary iodide XIV in Nujol mull provide an interesting confirmation of the structural assignments. Thus, while the spectrum of II has an intense band at 12.14 μ which may be attributed to the out of plane vibrations of two adjacent hydrogens on the pyridine ring,[10] this band is absent from the spectrum of XIII and is replaced in the spectrum of XIV by a weak, broad band at 12.02 μ. On the other hand, the spectrum of XIII has the characteristic intense band at 6.08 μ expected for conjugated ethylene and imine double bonds,[11] and, although this band is absent in the spectrum of II, it occurs in the spectrum of XIV as a band of medium intensity at 6.12 μ.

Some measure of the contribution of the dipolar amphion[12] XIIIb to the structure of the anhydronium base XIII was obtained by comparing the dipole moment of XIII with that of 3-azaphenothiazine (II). The dipole moments were measured[13] in dioxane solution and found to be 6.08 D and 4.65 D for XIII and II, respectively. These values indicate a considerable contribution of XIIIb to the structure of the anhydronium base XIII in dioxane solution.[14]

(10) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley, New York, N. Y., 2nd Ed. (1958), p. 280.

(11) This band occurs in the spectrum of the naturally occurring anhydronium base, serpentine.[19b]

(12) See Ref. 9b for the use of this term.

(13) See Experimental.

(14) The dipole moment of the naturally occurring anhydronium base, sempervirine, in dioxane solution has been reported to be 8.5D: K. A. Jensen, *Acta Chem. Scand.*, **3**, 1447 (1949); see also R. Bentley and T. S. Stevens, *Nature*, **164**, 141 (1949); and B. Witkop, Ref. 9a.

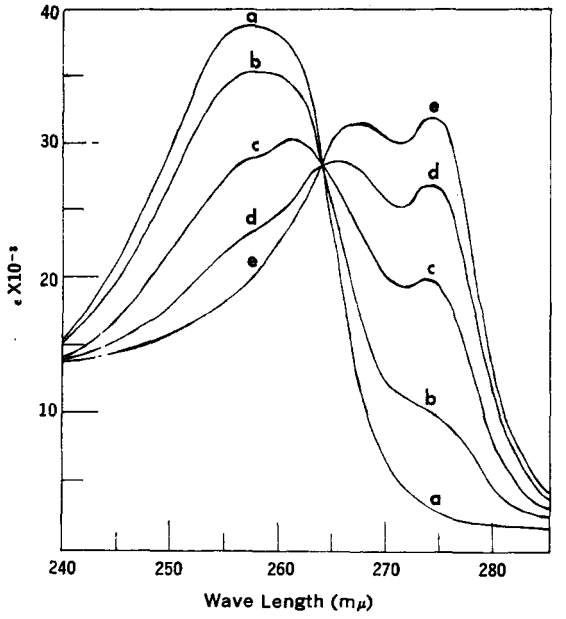
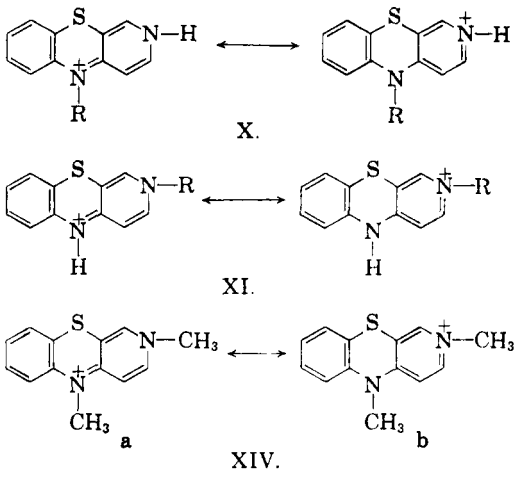


Fig. 1. Ultraviolet spectra of the hydrochloride of II in 50% ethanol: a, 0.1*N* in NaOH; b, at *p*H 6.36 (0.08*M* phosphate buffer); c, at *p*H 5.77 (0.08*M* phosphate buffer); d, at *p*H 4.87 (unbuffered); e, 0.1*N* in HCl

The ultraviolet spectra and base strengths of 3-azaphenothiazine and its 3- and 10-alkylated derivatives (Tables I and II) lend further support to the assigned structures. For instance the ultraviolet spectrum of 3-azaphenothiazine in 50% ethanol (or of its hydrochloride in alkaline solution, Fig. 1, a), has an intense maximum at 258 mμ which is replaced in acid solution by two maxima at 267 mμ and 274 mμ (Fig. 1, e). This bathochromic displacement is a consequence of increased resonance of the cation X (R = H).[15] As 3-azaphenothiazine is a weak base (pK_a = 5.9), its salts are partially dissociated in dilute solution so that the ultraviolet spectrum is a composite of the spectrum of the cation X (R = H) and the free base II. As may be seen in Fig. 1 the ultraviolet spectrum changes as the *p*H of the solution is varied and there is an isobestic point at 264 mμ, (*i.e.*, only one equilibrium is involved[16]). An alternate method for the determination of the pK_a is thus provided[17] (see Experimental) which may be applied in dilute aqueous solutions.[18]

The ultraviolet spectrum of 10-(3-dimethylaminopropyl)-3-azaphenothiazine dihydrochloride



(I dihydrochloride) in 50% ethanol is similar to that of 3-azaphenothiazine hydrochloride (II hydrochloride) in 50% ethanol (Table I). As anticipated, the spectrum of I dihydrochloride is similarly altered in acid and alkaline solution to give the spectrum of the cation X [R = $CH_2CH_2CH_2N^+H(CH_3)_2$] and of the free base I respectively. Furthermore the pK_a's of I dihydrochloride (5.2 and 8.2) indicate a weakly basic aromatic nitrogen and a typical tertiary aliphatic amine, respectively.

It should be noted that the structures of 3,10-dimethyl-3-azaphenothiazinium iodide (XIV iodide) and of the 3-alkyl-3-azaphenothiazinium salts (XI) closely resemble those of the cation X of 10-(3-dimethylaminopropyl)-3-azaphenothiazine, [R = $CH_2CH_2CH_2N^+H(CH_3)_2$], and of 3-azaphenothiazine itself (R = H). It is not surprising then that the spectra of X, XI and XIV are very similar in acid solution (Table I). The fact that the spectrum of the quaternary compound XIV remains unchanged in 50% ethanol and in alkaline solution is in accord with its structure.

It may be seen from Table I that the spectrum of 3-(3-dimethylaminopropyl)-3-azaphenothiazinium chloride hydrochloride (V chloride hydrochloride) remains unchanged in 50% ethanol and in acid solution, but gives a new shoulder at 285 mμ in alkaline solution. The spectra of the other 3-alkyl derivatives (VII, VIII, IX and XII) behave similarly. Furthermore the 3-alkyl derivatives all have pK_a values near 11.0 (Table II), as expected for the salts of anhydronium bases.[19] Because of the strongly basic nature of these compounds an alkaline solution is required to alter the spectra of the "quaternary salts" by removing a proton from the onium ions to form the corresponding anhydronium bases.[9b] This interpretation is supported in the present case by the fact that when the crystalline anhydronium bases are dissolved in chloroform the ultraviolet spectra of the solutions have the characteristic

(15) Similar bathochromic displacements have been observed when β-carboline and dihydro-β-carboline bases are converted to the corresponding salts.[9]

(16) A. E. Gillam and E. S. Stern, *Electronic Absorption Spectroscopy*, Edward Arnold (Publishers) Ltd., London, 2nd Ed. (1957), p. 289.

(17) For detailed experimental procedure see H. C. Brown and X. R. Milm, *J. Am. Chem. Soc.*, **77**, 1723 (1955).

(18) The low solubility of the free base in water renders direct titration in aqueous solution impractical, although aqueous alcohol or aqueous dimethylformamide may be used.

(19) (a) A. P. Gray, *J. Am. Chem. Soc.*, **77**, 5930 (1955); (b) K. G. Krebs and N. Futscher, *Artz. Forsch.*, **10**, 75 (1960); (c) Ref. 9b.

TABLE I

ULTRAVIOLET SPECTRA OF THE 3-AZAPHENOTHIAZINE SERIES

Solution[a]		Wave Length Maxima, mμ (ε × 10^{-3})						
I[b]	A[c]	238 (11.4)		269[s] (22.4)	275 (24.6)		300 (2.9)	380 (2.5)
	B	235 (10.2)	258 (29.4)				308 (1.3)	
II[d]	A	237 (14.5)		267 (32.2)	274 (32.9)		308 (2.5)	405 (2.7)
	B	232 (10.4)	258 (38.8)				317 (1.8)	
V[e]	A	240 (14.5)		271 (32.5)	278 (34.0)		310 (3.0)	415 (3.6)
	B		260[s] (15.7)	270[s] (21.8)	276 (26.5)	285[s] (20.1)		444 (6.2)
VI[f]	C		260[s] (18.2)	270[s] (23.3)	277 (26.1)	284[s] (22.8)		425 (4.0)
VII[e]	A	240 (14.6)		271 (34.0)	279 (35.5)		310 (3.0)	415 (3.8)
	B		260[s] (16.1)	270[s] (22.9)	276 (27.8)	283[s] (21.2)		443 (6.5)
VIII[g]	A	240 (15.6)		271 (34.5)	279 (35.6)		310 (3.4)	420 (4.2)
	B		260[s] (16.6)	270[s] (23.5)	276 (29.0)	283[s] (22.5)		444 (6.9)
IX[h]	A	241 (15.6)		272 (34.1)	279 (35.2)		310 (3.4)	418 (4.0)
	B		260[s] (17.0)	270[s] (24.7)	276 (29.3)			443 (6.8)
XII[i]	A	240[s] (16.0)		270 (32.2)	277 (33.7)		305 (2.6)	410 (3.3)
	B		260[s] (15.3)	270[s] (22.1)	276 (26.4)	283[s] (19.7)		443 (5.9)
XIII[f]	C		260[s] (18.3)	270[s] (24.0)	277 (25.6)	285[s] (21.3)		440 (5.9)
XIV[i]	A[j]			270[s] (26.0)	276 (31.1)		300[s] (3.5)	390 (3.4)
	B[k]			270[s] (21.4)	278 (27.7)		300[s] (2.2)	390 (3.3)

[a] Approximately 4 × $10^{-5}M$ solutions in: A, 0.1N hydrochloric acid in 50% aqueous ethanol; B, 0.1N sodium hydroxide in 50% ethanol; C, chloroform. [b] Dihydrochloride. [c] Also 222 (15.5). [d] Hydrochloride. [e] Chloride hydrochloride. [f] Anhydronium base. [g] Chloride hydrochloride monohydrate. [h] Bromide hydrobromide. [i] Iodide. [j] Also 222 (30.7). [k] Also 222 (27.0). [s] Shoulder.

TABLE II

BASICITIES OF 3-AZAPHENOTHIAZINE SERIES

Compound	pK_a Values[a]	
I	5.2	8.2
II	5.3	
V	10.8	7.5
VII	10.8	7.7
VIII	10.8	5.7
IX	10.8	6.6
XII	11.0	

[a] Determined by titration of the corresponding salts in 66% dimethylformamide.

shoulder at 284–285 mμ (Table I, VI C and XIII C). On the other hand when the anhydronium bases are dissolved in 50% ethanol the spectra of the quaternary salts are obtained.[20]

The effect of N-aminoalkylation on the position of the long wave-length band (at 405 mμ) of 3-azaphenothiazine in acid solution is worth noting. For instance the 3-dimethylaminopropyl group in the 10-position causes a hypsochromic shift to 380 mμ while in the 3-position the same substituent causes a bathochromic displacement to 415 mμ (Table I, V A; note the same effect in VII A). The bathochromic effect of the aliphatic amine cation on the spectrum of the onium ion is even greater when the ions are separated by only two carbon atoms. Thus in VIII A and IX A of Table I the long wave-length bands are at 420 mμ and 418 mμ, respectively.

The pK_a data recorded in Table II indicate the extent to which the aromatic cation lowers the basicity of the alkyl amine. As anticipated, the alkyl amines are less basic when separated from the aromatic cation by only two carbon atoms.

(20) All known anhydronium bases exhibit this behavior.[9b]

EXPERIMENTAL[21]

2-Aminophenyl 3-nitro-4-pyridyl sulfide[22] (IV). To a stirred, ice cooled solution of 80.0 g. (1.42 moles) of potassium hydroxide in 500 ml. of water was added 100.0 g. (0.80 mole) of *o*-aminothiophenol, followed by 650 ml. of dioxane. 4-Chloro-3-nitropyridine hydrochloride[23] (122 g., 0.63 mole) was then added and the solution stirred with ice water cooling for 2 hr. Ice water (2 l.) was then added to the reaction mixture and the solid was collected and washed, first with cold dilute aqueous alkali and then with ice water. The crude product (m.p. 134–137°) was recrystallized from about 2 l. of 95% ethanol to give 105.0 g. (68%) of yellow crystals, m.p. 150–151° (reported[3e] m.p. 146–147°).

2-Acetamidophenyl 3-nitro-4-pyridyl sulfide (III). 2-Aminophenyl 3-nitro-4-pyridyl sulfide (105 g.) was covered with 300 ml. of acetic anhydride and the mixture heated on the steam bath for 15 min. during which time the solid completely dissolved. The hot solution was poured onto ice and 500 ml. of concentrated aqueous ammonia (28%) added. The yellow solid was collected, dried, and recrystallized from 300 ml. of 95% ethanol to give 110 g. (89%) of product, m.p. 123–124°. Further recrystallization from 95% ethanol did not raise the melting point.

Anal. Calcd. for $C_{13}H_{11}N_3O_3S$: C, 53.96; H, 3.83; N, 14.54. Found: C, 54.26; H, 3.77; N, 14.22.

3-Azaphenothiazine (II). To a stirred, refluxing solution of 32.5 g. (0.089 mole) of 2-acetamidophenyl 3-nitro-4-pyridyl sulfide in 2.5 l. of acetone under nitrogen was added 14.5 g. (0.26 mole) of powdered potassium hydroxide in small portions over a 30-min. period. The stirring and refluxing under nitrogen were continued for 1 hr. and then the acetone was distilled over 1.5 hr., vacuum being used at the end. Ice water (*ca.* 1 l.) was added to the residue, the mixture was stirred, and the solid collected, washed well with water, and dried to give 13.8 g. (62%) of 3-azaphenothiazine as a light yellow solid, m.p. 243–244° dec. Several recrystal-

(21) All melting points are corrected, but boiling points are uncorrected. Percent yields are enclosed in brackets.

(22) The preparation of this compound using the anhydrous sodium salt of *o*-aminothiophenol is described in Ref. 3e.

(23) T. Takahashi and K. Ueda, *Pharm. Bull.* (*Japan*), 2, 34 (1954).

lizations from ethanol or acetone raised the melting point to 246–248° dec.

Anal. Calcd. for $C_{11}H_8N_2S$: C, 65.97; H, 4.03; N, 13.99. Found: C, 65.95; H, 4.40; N, 13.63.

3-Azaphenothiazine hydrochloride was obtained as orange crystals upon addition of ethanolic hydrogen chloride to a solution of the base in acetone, m.p. 279–281° dec. (from ethanol).

Anal. Calcd. for $C_{11}H_8N_2S.HCl$: C, 55.81; H, 3.83; N, 11.84. Found: C, 55.83; H, 3.74; N, 11.52.

3-Azaphenothiazine hydrobromide formed yellow crystals from ethanolic hydrogen bromide and was recrystallized from aqueous ethanol for analysis, m.p. 263–265°, dec.

Anal. Calcd. for $C_{11}H_8N_2S.HBr$: C, 46.96; H, 3.23; N, 9.96. Found: C, 46.94; H, 3.40; N, 9.48.

10-(3-Dimethylaminopropyl)-3-azaphenothiazine (I). 3-Azaphenothiazine (29.2 g., 0.15 mole) and sodium hydride (7.2 g., 0.30 mole) (30 ml. of a 25% suspension in mineral oil) were added to 720 ml. of toluene and 180 ml. of anhydrous dioxane and the mixture refluxed with stirring. After 1 hr., 3-dimethylaminopropyl chloride (18.6 g., 0.15 mole) was added all at once followed by an additional 37.2 g. (0.30 mole) of the halide over a 4-hr. period. The reaction mixture first became green and then turned yellow and finally red as the halide was added. Refluxing and stirring were continued overnight and then the reaction mixture was cooled, excess sodium hydride decomposed with water, and the product extracted into 10% hydrochloric acid. The aqueous solution was made alkaline with ammonia and the product taken up in ether. The ether extract was dried over anhydrous sodium sulfate and distilled, first to remove ether, then under reduced pressure to remove unchanged halide and finally under high vacuum to give 33.5 g. (80.5%) of product as an orange oil, b.p. 200–210°/0.7 mm.; n^{25} 1.6347.

Anal. Calcd. for $C_{16}H_{19}N_3S$: C, 67.34; H, 6.71; S, 11.23. Found: C, 67.67; H, 6.92; S, 11.13.

The *dihydrochloride* formed yellow crystals from absolute ethanol-anhydrous ether, m.p. 262–264° dec.

Anal. Calcd. for $C_{16}H_{23}N_3S.2HCl$: C, 53.64; H, 5.91; N, 12.00. Found: C, 53.90; H, 6.00; N, 11.72.

When ethanol alone was used as a solvent the dihydrochloride separated as a monohydrate, m.p. 120–130° (with gas evolution) which solidified and remelted at 261–263° dec.

Anal. Calcd. for $C_{16}H_{19}N_3S.2HCl.H_2O$: N, 11.17. Found: N, 11.00.

The solvate was readily converted to the anhydrous salt when suspended in refluxing toluene or when recrystallized from absolute ethanol-anhydrous ether.

The *dihydrobromide* was recrystallized from absolute ethanol, m.p. 244–246° (dec.).

Anal. Calcd. for $C_{16}H_{19}N_3S.2HBr$: C, 42.97; H, 4.73; N, 9.40. Found: C, 43.08; H, 4.70; N, 9.62.

The *dimaleate* formed yellow crystals from 95% ethanol, m.p. 149–150° dec.

Anal. Calcd. for $C_{16}H_{19}N_3S.2C_4H_4O_4$: C, 55.70; H, 5.26; N, 8.12. Found: C, 55.35; H, 5.08; N, 8.17.

3-(3-Dimethylaminopropyl)-3-azaphenothiazine anhydronium base (VI). A solution of 15.0 g. of 3-azaphenothiazine and 37 ml. of 3-dimethylaminopropyl chloride in 325 ml. of anhydrous dioxane was refluxed for 24 hr. and then the solvent was distilled. The residue was triturated with water and filtered and the filtrate was made strongly alkaline with 50% sodium hydroxide solution. The precipitate was extracted with methylene chloride, the extract was evaporated, and the residue was crystallized from anhydrous ether to give 6.2 g. (29%) of the anhydronium base as orange crystals, m.p. 84–91°. Several recrystallizations from ether raised the melting point to 95–96°. A small portion of the base was distilled in a collar flask at 0.005 mm. pressure (bath temperature 175–210°).

Anal. Calcd. for $C_{16}H_{19}N_3S$: C, 67.34; H, 6.71; N, 14.72. Found: C, 67.21; H, 6.51; N, 14.43.

3-(3-Dimethylaminopropyl)-3-azaphenothiazinium chloride hydrochloride (V *Chloride hydrochloride*). The chloride hydrochloride of V was prepared by treating an alcoholic solution of the anhydronium base VI with an excess of alcoholic hydrogen chloride. The yellow product was recrystallized from methanol-ethanol or methanol–ethyl acetate, m.p. 285–286° dec.

Anal. Calcd. for $C_{16}H_{20}N_3S.Cl.HCl$: C, 53.64; H, 5.91; N, 12.00. Found: C, 53.69; H, 5.99; N, 11.88.

V *Chloride* was obtained as orange crystals when 1 equivalent of anhydrous methanolic hydrogen chloride was added to a methanolic solution of the anhydronium base VI, the solution concentrated, and anhydrous ether added. Recrystallization from methanol–anhydrous ether gave an analytical sample, m.p. 170–172°.

Anal. Calcd. for $C_{16}H_{20}N_3S.Cl$: C, 59.71; H, 6.26; N, 13.05. Found: C, 59.90; H, 6.61; N, 13.51.

V Chloride was also obtained by dissolving molar equivalents of the anhydronium base VI and V chloride hydrochloride in methanol, then gradually displacing the methanol from the boiling solution with acetone and cooling.

V *Bromide hydrobromide* was obtained as yellow crystals from ethanol, m.p. 267–269° dec.

Anal. Calcd. for $C_{16}H_{20}N_3S.HBr$: C, 42.97; H, 4.73; N, 9.39. Found: C, 43.03; H, 5.00; N, 9.30.

When a hot solution of V bromide hydrobromide in 70% ethanol was allowed to cool slowly to room temperature the monohydrate was obtained as orange crystals which did not melt but lost water on heating to give the yellow anhydrous salt, m.p. 267–269° dec. The infrared spectrum of the monohydrate showed strong hydroxyl absorption at 2.95 mμ which was absent in the spectrum of the anhydrous salt.

Anal. Calcd. for $C_{16}H_{20}N_3S.Br.HBr.H_2O$: C, 41.30; H, 4.98; N, 9.03. Found: C, 41.51; H, 4.95; N, 9.11.

V *Dimaleate* formed yellow crystals from 95% ethanol, m.p. 186–187° dec.

Anal. Calcd. for $C_{16}H_{19}N_3S.2C_4H_4O_4$: C, 55.70; H, 5.26; N, 8.12. Found: C, 55.86; H, 5.58; N, 8.20.

3-(3-N-Piperidinopropyl)-3-azaphenothiazinium chloride hydrochloride (*VII Chloride hydrochloride*). A solution of 5.0 g. of 3-azaphenothiazine and 10 ml. of 3-(*N*-piperidino)-propyl chloride[24] in 80 ml. of dioxane was refluxed overnight and the solution decanted. The gum which had separated was dissolved in water, the solution made strongly alkaline with 50% aqueous sodium hydroxide and the precipitate taken up in methylene chloride. The extract was dried over anhydrous sodium sulfate and evaporated to give an oil which did not crystallize. Treatment with an excess of methanolic hydrogen chloride and dilution with ether gave 7.8 g. (79%) of VII chloride hydrochloride, m.p. 290–295° dec. Several recrystallizations from methanol–ethyl acetate gave yellow needles, m.p. 298–300° dec.

Anal. Calcd. for $C_{19}H_{24}N_3S.Cl.HCl$: C, 57.28; H, 6.33; N, 10.55. Found: C, 57.31; H, 6.33; N, 10.39.

Alternatively VII chloride hydrochloride was prepared by refluxing a solution of 1.0 g. of 3-azaphenothiazine and 2.0 of 3-(*N*-piperidino)propyl hydrochloride[25] in 50 ml. of absolute ethanol for 2 days, concentrating the solution and cooling to give 1.75 g. (90%) of yellow crystals, m.p. 295–300° dec., undepressed upon admixture with the product prepared as described above.

3-(2-N-Piperidinoethyl)-3-azaphenothiazinium chloride hydrochloride (*VIII Chloride hydrochloride*). 2-(*N*-Piperidino)-ethyl alcohol was obtained by allowing a solution of 11.0 g. of ethylene oxide and 21.2 g. of piperidine in 100 ml. of absolute ethanol to stand overnight and then distilling at atmospheric pressure to give 21.8 g. (67.7%) of an oil,

(24) A. Marxer, *Helv. Chim. Acta*, 24, E209 (1941).

(25) P. Ofner, *J. Chem. Soc.*, 1800 (1951), reports m.p. 213–214° for the hydrochloride and m.p. 111–112° for the picrate. We found melting points of 225–226° and 116–117° for the hydrochloride and picrate, respectively.

b.p. 204–208° (reported,[26] b.p. 200–202°/742 mm.). Treatment of the alcohol with thionyl chloride in chloroform in the usual manner followed by recrystallization from absolute ethanol gave 2-(*N*-piperidino)ethyl chloride hydrochloride, m.p. 233–236° (reported[27] m.p. 234°).

A solution of 3.8 g. of 3-azaphenothiazine and 5.4 g. of 2-(*N*-piperidino)ethyl chloride hydrochloride in 75 ml. of absolute ethanol was refluxed overnight and then concentrated and cooled to give 5.6 g. (75%) of VIII chloride hydrochloride as yellow crystals, m.p. 284–291° dec. The salt was recrystallized several times from methanol–anhydrous ether for analysis, m.p. 290–293° dec. The analytical results and the presence of an hydroxyl band at 3.0 mμ in the infrared spectrum indicate 1 mole of methanol of crystallization.

Anal. Calcd. for $C_{18}H_{22}N_2S.Cl.HCl.CH_4O$: C, 54.80; H, 6.54; N, 10.09. Found: C, 54.32; H, 6.34; N, 9.76.

3-(2-Aminoethyl)-3-azaphenothiazinium bromide hydrobromide (IX Bromide hydrobromide). A solution of 3.8 g. of 3-azaphenothiazine and 6.2 g. of 2-aminoethyl bromide hydrobromide in 100 ml. of absolute ethanol was refluxed overnight, cooled, and filtered to give 3.5 g. (45%) of IX bromide hydrobromide, m.p. 288–293° dec. The salt was recrystallized several times from aqueous ethanol for analysis, m.p. 296–298° dec.

Anal. Calcd. for $C_{13}H_{14}N_2S.Br.HBr$: C, 38.53; H, 3.73; N, 10.37. Found: C, 38.33; H, 3.63; N, 10.43.

The reaction of 3-azaphenothiazine with 4-(N-piperidino)-butyl chloride hydrochloride. 4-(*N*-Piperidino)butyl alcohol was obtained in low yield when piperidine and 4-chlorobutyl alcohol were refluxed overnight in dioxane solution and the reaction worked up in the usual manner to give a colorless oil, b.p. 131–133°/19 mm. (reported[28] b.p. 133–134°/20 mm.). Treatment of the alcohol with thionyl chloride in chloroform solution followed by distillation of the solvent and excess thionyl chloride gave 4-(*N*-piperidino)butyl chloride hydrochloride, m.p. 162–163° (from 2-propanol-ether) (reported[29] m.p. 162°).

A solution of 2.83 g. of 3-azaphenothiazine and 3.46 g. of *N*-(4-chlorobutyl)piperidine hydrochloride in 50 ml. of absolute ethanol was refluxed overnight, then concentrated, cooled, and filtered to give 3.4 g. of yellow solid, m.p. 265–278°. Two recrystallizations, first from methanol–ethyl acetate, then from methanol-2-propanol raised the melting point to 279–281° (undepressed upon admixture with 3-azaphenothiazine hydrochloride). The infrared and ultraviolet spectra were superimposable upon those of 3-azaphenothiazine hydrochloride.

Anal. Calcd. for $C_{11}H_8N_2S.HCl$: N, 11.84. Found: N, 11.81.

3-Methyl-3-azaphenothiazinium iodide (XII Iodide). A solution of 2.0 g. of 3-azaphenothiazine and 10 g. of methyl iodide in 100 ml. of acetone was refluxed for 1 hr., cooled, and filtered to give 2.7 g. (78%) of XII iodide as a deep yellow solid, m.p. 228–231°. Several recrystallizations from water gave a sample for analysis, m.p. 231–232°.

Anal. Calcd. for $C_{12}H_{11}N_2S.I$: C, 42.12; H, 3.24; N, 8.19. Found: C, 42.55; H, 3.44; N, 7.69.

XII Maleate was obtained by treating the anhydronium base XIII (see below) with maleic acid in methanol solution. Recrystallization from methanol gave yellow crystals, m.p. 233–234°.

Anal. Calcd. for $C_{12}H_{11}N_2S.C_4H_4O_4$: C, 58.17; H, 4.27; N, 8.48. Found: C, 58.10; H, 4.47; N, 8.62.

3-Methyl-3-azaphenothiazine anhydronium base (XIII). To a stirred mixture of 50 ml. of benzene and 30 ml. of 20% aqueous sodium hydroxide was added 1.8 g. of XII iodide. After a short time the benzene solution was separated, dried over anhydrous sodium sulfate, concentrated, and diluted with pentane to give 0.8 g. (71%) of the anhydronium base as a vermilion solid, m.p. 162–166°. One recrystallization from benzene-pentane raised the melting point to 166–167°, which was unchanged on further recrystallization.

Anal. Calcd. for $C_{12}H_{10}N_2S$: C, 67.26; H, 4.70; N, 13.08. Found: C, 67.65; H, 4.47; N, 13.01.

3,10-Dimethyl-3-azaphenothiazinium iodide (XIV Iodide). A solution of 0.5 g. of 3-methyl-3-azaphenothiazine anhydronium base and 5 ml. of methyl iodide in 30 ml. of acetone was concentrated and cooled to give 0.65 g. (78%) of XIV iodide as a bright yellow solid, m.p. 189–192°. The melting point was unchanged after recrystallization from methanol. The sample was dried at 80° in high vacuum for analysis.

Anal. Calcd. for $C_{13}H_{12}N_2S.I$: C, 43.83; H, 3.68; N, 7.87. Found: 43.60; H, 4.07; N, 7.59.

Determination of the pK_a of 3-azaphenothiazine hydrochloride from ultraviolet spectra. Solutions of 3-azaphenothiazine hydrochloride ($4.27 \times 10^{-5}M$) were prepared in 50% ethanol as follows: a, 0.1*N* in hydrochloric acid; b, 0.1*N* in sodium hydroxide; c, d, e, 0.08*M* in phosphate buffer. The *p*H of solutions c, d, and e were measured on a Beckman *p*H Meter and the molar extinction coefficients (ϵ) of all of the solutions were determined at 274 mμ on a Beckman DU Spectrophotometer. pK_a values were calculated using the expression: $pK_a = pH - \log[(\epsilon_a - \epsilon)/(\epsilon - \epsilon_b)]$, in which *p*H is the measured *p*H of the solution, ϵ_a is the molar extinction coefficient in acid, ϵ_b is the value in alkali and ϵ is the value at the measured *p*H.[30] The results recorded in Table III are in good agreement with the mean value of 5.9 determined by titration of the salt in 50% aqueous ethanol.

TABLE III

pK_a VALUES FROM ULTRAVIOLET SPECTRA

No.	*p*H	$\epsilon \times 10^{-3}$	$\log \frac{\epsilon_a - \epsilon}{\epsilon - \epsilon_b}$	pK_a
a	Acid	32.1		
b	Base	1.09		
c	6.36	10.3	+0.48	5.88
d	6.00	15.4	+0.13	5.87
e	5.77	19.9	−0.11	5.88

Measurement of dipole moments. Dipole moments were calculated according to the method of Halverstadt and Kumler.[31] Dielectric constants were determined with a Sargent Chemical Oscillometer, Model V. Specific volume measurements were made with a pycnometer. The molar refractions (R_D) were calculated from bond refractions.[32] The molar orientation polarization P_μ° was calculated from the equation: $P_\mu^\circ = p_2^\circ M - R_D$ and the dipole moment μ from the equation $\mu = 0.0127(P_\mu^\circ T)^{1/2}$. In Tables IV and V values are given for 3-azaphenothiazine (II) and the anhydronium base XII, respectively, in dioxane solution at 25°. The symbols have the same significance as in the paper by Halverstadt and Kumler.[31]

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(31) I. F. Halverstadt and W. D. Kumler, *J. Am. Chem. Soc.*, 64, 2988 (1942).

(32) A. I. Vogel, W. T. Cresswell, G. H. Jefferey, and J. Leicester, *J. Chem. Soc.*, 514 (1952).

TABLE IV

w_2	ϵ_{12}	v_{12}			
0.00168	2.238	0.97593	$\epsilon_1 = 2.212$	$\beta = 0.48$	$R_D = 53.8$
0.00331	2.260	0.97520	$v_1 = 0.9768$	$p_2^0 = 2.5105$	$P_\mu^0 = 448.9$
0.00561	2.292	0.97412	$\alpha = 14.33$	M = 200.3	$\mu = 4.65$ D

TABLE V

w_2	ϵ_{12}	v_{12}			
0.00150	2.246	0.97636	$\epsilon_1 = 2.212$	$\beta = 0.29$	$R_D = 54.5$
0.00281	2.281	0.97596	$v_1 = 0.9768$	$p_2^0 = 3.8381$	$P_\mu^0 = 768.0$
0.00488	2.324	0.97537	$\alpha = 22.04$	M = 214.3	$\mu = 6.08$ D

physical measurements carried out in the course of this work. In particular we wish to thank Mr. E. Townley for the ultraviolet spectra, Mr. J. McGlotten for the *p*Ka and dipole moment data, Mr. R. Wayne for the determination and interpretation of infrared spectra, and Mr. E. Connor for microanalyses. Microanalyses were also performed by Galbraith Laboratories, Knoxville, Tennessee.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

The Cyclization of *N*-Alkenylthionamides to Thiazolines and Dihydrothiazines

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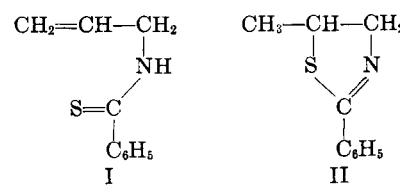
A group of *N*-alkenylbenzthionamides and acetthionamides have been prepared from the corresponding isothiocyanates and Grignard reagents. Allylic *N*-alkenylthionamides cyclize when treated with acidic catalysts such as aluminum chloride, but not with benzoyl peroxide. The position of cyclization follows the Markovnikov rule with an apparent slight preference for thiazolines over dihydrothiazines when other factors are equal.

In the course of the wartime penicillin project, one of us found that *N*-allyldicarboethoxyacetthionamide could be cyclized to a thiazoline ring.[2] It was the object of the present work to learn something of the nature of the reaction and to determine whether the cyclization of allylthionamides might have any generality. If so, an efficient synthetic route might become available, since allylic isothiocyanates are readily available, and thionamides can be prepared by the addition of Grignard reagents to them.[3]

N-Allylbenzthionamide (I) was chosen as an uncomplicated model. Cyclization to 2-phenyl-5-methyl-2-thiazoline (II) was effected by a variety of acidic catalytic agents, such as zinc chloride, boron fluoride, and sulfuric acid; aluminum chloride in nitrobenzene was the most effective, giving II in 47% yield. In contrast, benzoyl peroxide did not produce detectable cyclization. The assignment of structure II to the cyclization product, instead of the isomeric dihydrothiazine structure, is supported by the agreement of the melting point of its picrate with that reported for 2-phenyl-5-methyl-2-thiazoline picrate prepared in a different way, but more direct proof that cyclization had taken place at the β-rather than the γ-carbon was obtained by hydrolyzing II to 1-aminopropan-2-thiol, isolated and identified as the hydrochloride of the corresponding disulfide.



I II

This cyclization is stoichiometrically identical to the intermolecular addition of mercaptans to olefins, and is readily conceived as a reaction of the enethiol tautomer of the thionamide. The

(1) From the doctoral thesis of J. M. S., Union Carbide Summer Fellow, 1957. Presented at the National Meeting, American Chemical Society, New York, September, 1960.

(2) *The Chemistry of Penicillin*, ed. by H. T. Clarke, Princeton University Press, Princeton, 1949, p. 470. [A similar reaction had been postulated previously, but not experimentally established as an intermediate stage in the acid-catalyzed condensation of phenols with allyl isothiocyanate: J. B. Niederl, W. F. Hart, and J. V. Scudi, *J. Am. Chem. Soc.*, **58**, 707 (1936); J. C. Crawhall and D. F. Elliott, *J. Chem. Soc.*, 3094 (1952)].

(3) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., New York, 1954, p. 1200.