THE SYNTHESIS OF SUBSTITUTED AZAPHENOTHIAZINE DERIVATIVES

A Thesis

Presented to

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Master of Science

By

Wayne Keith Anderson

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ABSTRACT

1-Azaphenothiazine was prepared by direct thionation of 2-anilinopyridine while 2- and 4-azaphenothiazines were obtained by dehydrohalogenation of suitably substituted phenylthiopyridines. The 4-azaphenothiazine was obtained in small quantities only and no derivatives were prepared.

A series of 10-dialkylaminoalkyl derivatives were prepared from both 1- and 2-azaphenothiazines, using sodamide as the condensing agent with appropriate chloroamines.

Bis-quaternary salts of the 10-dialkylaminoalkyl-1-azaphenothiazines were then obtained by treating the 10-dialkylaminoalkyl-1-azaphenothiazines with $\alpha:\omega$-dibromoalkanes. Initial problems in purification of the bis-quaternary compounds were eventually overcome by using a modified mixing technique to ensure thorough mixing of the reactants.

The same bis-quaternary salts of the dialkylaminoalkyl-2-azaphenothiazines were attempted and these gave results similar to those obtained during early attempts to prepare the bis-quaternary salts from the dialkylaminoalkyl-1-azaphenothiazines. Some of the products analyzed well for the expected bis-quaternary salts, some analyzed well as mono-quaternary salts and some were obviously mixtures. The limited material available did not permit resynthesis of the entire group by the later used mixing modification. One member of

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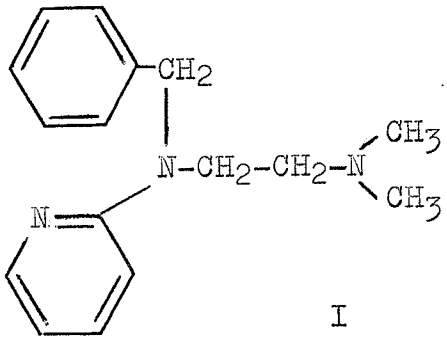
I. INTRODUCTION

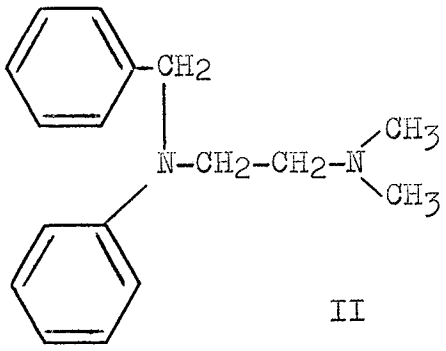
Since 1891, when methylene blue was first used, phenothiazine derivatives have gradually increased in importance. Today various phenothiazine drugs are valuable therapeutic agents in many areas of medicine. Their major uses are based upon either their tranquillizing, antihistaminic or antiemetic properties.

While the phenothiazines are valuable drugs, they are also potentially dangerous and have been known to cause side effects. It is for this reason that there is still a great need for better drugs.

There are several instances in medicinal chemistry where the substitution of a pyridine ring for a benzene ring has produced a more active compound. For example, it is well known that the increased effectiveness in Pyribenzamine(R) (I) is attained by exchanging the phenyl radicle in Antergan(R) (II) for a pyridyl radicle. Therefore by replacing one of the benzene rings in the phenothiazine nucleus with a pyridine

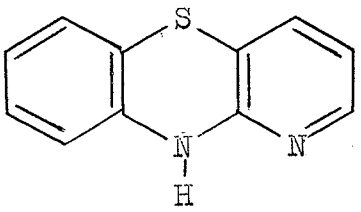


I



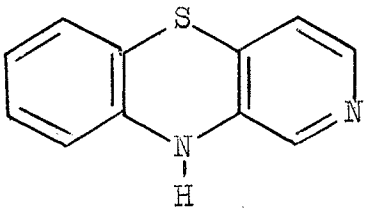
II

ring an attempt has been made to produce better drugs. Such compounds are based on one of the azaphenothiazine nuclei (III, IV, V and VI).



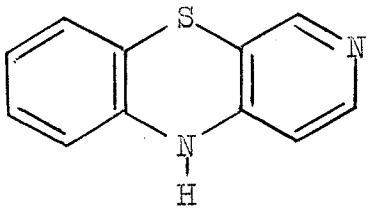
1-Azaphenothiazine

III



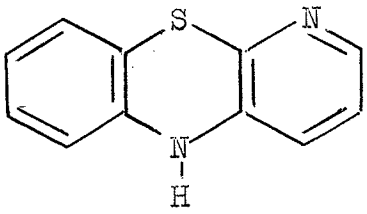
2-Azaphenothiazine

IV



3-Azaphenothiazine

V



4-Azaphenothiazine

VI

For a detailed discussion of the nomenclature of this type of compound, see Appendix I.

Comparisons of Phenothiazines with the Corresponding Azaphenothiazine Derivatives

Friend (1) has stated that three things should be considered in the development of new phenothiazine derivatives. These are:

1. Is its liver and blood toxicity lower than that which has been observed for potent phenothiazines such as perphenazine?

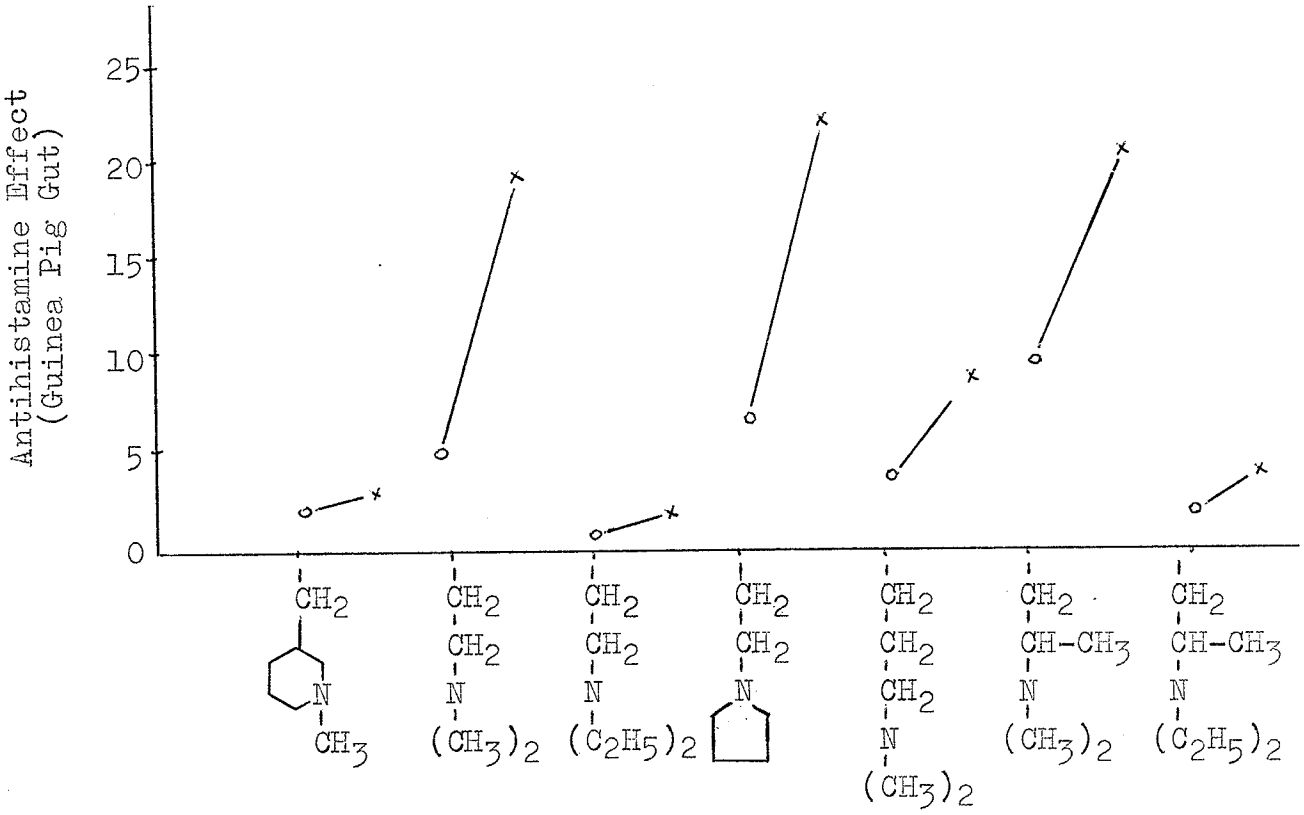
2. Is there less extrapyrimidal activity produced, even when the dose is raised to ten to twenty times that recommended?

3. Does the new phenothiazine have unique properties, such as tranquillizing action, alone or with antiemetic action, mainly antiemetic properties, a more selective antipruritic activity or a better antihistaminic action with less sedative effect?

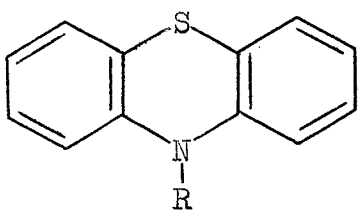
The structural change from phenothiazine to azaphenothiazine does not seem to be too considerable, but it results in a marked difference in the pharmacological properties of the two. Various azaphenothiazine derivatives have been shown to be superior to the corresponding phenothiazine compounds (2,3).

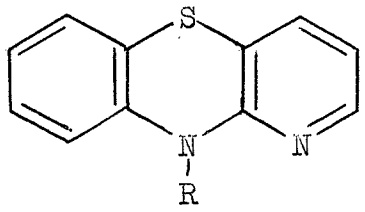
Figure I shows the increase in antihistaminic effect caused by substitution of the azaphenothiazine nucleus for

the phenothiazine nucleus (2). The effectiveness of Antazoline(R) is taken as unity. Twenty, therefore, denotes antihistaminic effectiveness twenty times as strong as that of Antazoline.



Phenothiazine derivatives - o; Azaphenothiazine derivatives - x

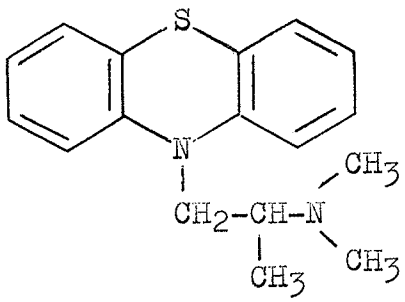




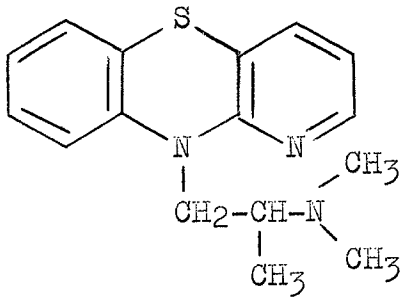
R = 10-Aminoalkyl Side Chain
(Chemical structure of Radical, R)

FIGURE I

The phenothiazine derivative promethazine (Phenergan$^{(R)}$) (VII) is a good antihistamine drug but it has marked central sedative action. On the other hand, the corresponding 1-aza-phenothiazine derivative, isothipendyl (Theruhistin$^{(R)}$) (VIII) is a very potent antihistamine drug and has very little central sedative effect (2,4,5,6,7).



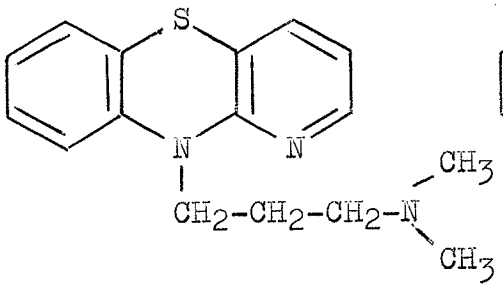
VII



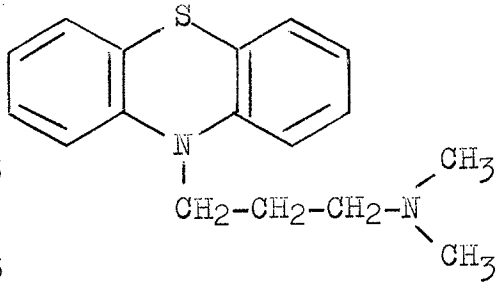
VIII

Isothipendyl has been reported to be devoid of any serious toxicities, acute or chronic, and is well tolerated by all age groups (6).

The drug prothipendyl (Dominal$^{(R)}$, Dominex$^{(R)}$) (IX) structurally resembles promazine (Sparine$^{(R)}$) (X); however, it is much more active.



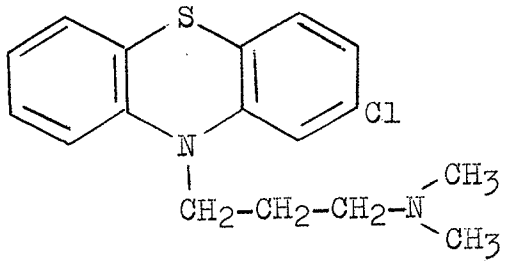
IX



X

Prothipendyl, in fact, constitutes an improvement over the phenothiazine derivative chlorpromazine (Largactil$^{(R)}$)

(XI) which is very much more potent than promazine (3, 8-23).



XI

While prothipendyl resembles chlorpromazine in activity, it is better tolerated, less toxic and more agreeable to the patients in its effects (8). The side effects produced by the phenothiazine compound are largely absent; there are no Parkinson-like effects, no signs of allergy (rash, urticaria, etc.), no jaundice, no detrimental effects on the blood, liver or kidney function and no orthostatic circulatory disturbances (8,9,10,11,12).

Prothipendyl also shows many advantages over chlorpromazine, which are listed below:

1. Prothipendyl shows a greater therapeutic margin than chlorpromazine and appears to be well tolerated (13).

2. It is relatively more active than chlorpromazine orally, presenting the advantage that oral treatment may be used in the beginning in moderately severe cases (14).

3. It is better tolerated parenterally (15).

4. It can be used in patients who are highly allergic to chlorpromazine (12).

5. The action of prothipendyl is fully maintained from

the onset of treatment, while the action of chlorpromazine tends to fall off after a few days, owing to habituation (14,15).

6. There is less initial sedation of patients with prothipendyl than with chlorpromazine (14).

7. The hypnotic effect of prothipendyl is described as much less pronounced and of shorter duration than that of chlorpromazine, thus leaving the vast majority of patients able to look after themselves, even with higher doses (15).

8. The hypotensive effect with prothipendyl is somewhat less than with chlorpromazine (16).

9. Prothipendyl is better tolerated than chlorpromazine for surgical premedication (17).

Structure Activity Relationships in Quaternary Ammonium Compounds

Since the phenothiazine nucleus occurs in a wide range of drugs with numerous uses, it would seem desirable to investigate the activities of phenothiazine and azaphenothiazine type drugs in various other areas of medicine. The synthesis of quaternary ammonium compounds would serve such a purpose, since these drugs, as a class, possess a wide spectrum of activity. Quaternary ammonium compounds are used as muscarinic and nicotinic stimulating and blocking agents, neuromuscular blocking, antihypertensive and antispasmodic

agents, as well as for other miscellaneous uses.

(a) Factors Influencing the Bonding of a Quaternary Ammonium Compound to an Anionic Site

There are a large number of factors which influence the bonding of a quaternary compound to an anionic site. However, only three of the more important ones will be discussed here. These are lipophilic balance, charge on the onium nitrogen and steric factors.

A high lipophilic balance will result in rapid passage of the ions through membranes and a greater loss at inactive sites. A low lipophilic balance will have the opposite results. Thus it is important for a quaternary ammonium compound to have a balance between the lipophilic and lipophobic portions of the molecule.

The higher the charge concentration on the quaternary nitrogen, the greater will be the strength of the electrostatic bond, active or inactive. The positive charge can be modified greatly by the substituents attached to it.

Substituents containing "pi" electrons close to the nitrogen will cause delocalization of the positive charge due to resonance. For example, a phenyl group attached to the quaternary nitrogen will tend to spread the positive charge. Therefore the further the ammonium group is away from the source of "pi" electrons, the less interaction there will be,

and consequently there will be a greater positive charge on the nitrogen.

A quaternary compound with small alkyl substituents on the onium nitrogen, such as tetramethylammonium, can approach close to the anionic site hence becoming relatively strongly bonded to the site. Bulkier groups around the ammonium nitrogen sterically hinder the nitrogen, preventing it from getting close to the anionic site. "Tying back" two alkyl groups as in pyrrolidine or piperidine will reduce steric hindrance and allow formation of a stronger bond. While the use of an unsaturated ring such as pyridine reduces the steric bulk, it also spreads the positive charge due to delocalization and any benefits obtained from the small steric size are greatly outweighed by the fact that the positive charge on the ammonium nitrogen is decreased (23).

The flexibility of the appendage structure also plays an important role in influencing activity. A molecule which is capable of flexing can exist in many different conformations and therefore will be capable of combining with a wider variety of receptors than a molecule of more rigidly fixed conformation. A more rigid structure would show less indiscriminate bonding to "inactive sites" and therefore would show an increase in potency. A rigid structure, on the other hand would be more greatly affected by small structural changes (23).

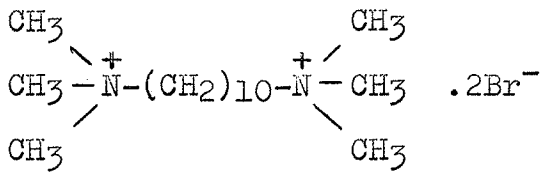
(b) Neuromuscular Blocking Agents

The primary requirement of a neuromuscular blocking agent is a strongly basic center capable of permanent existence as a positively charged center (24).

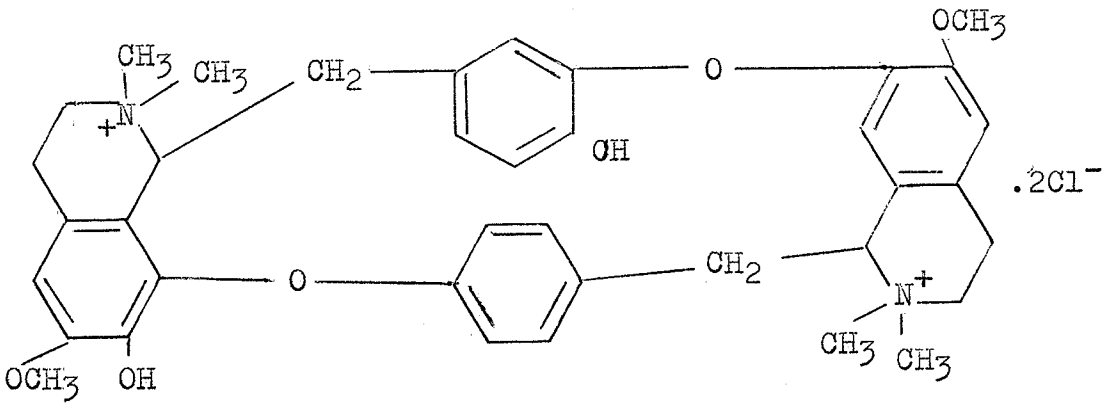
With few exceptions, the most active synthetic neuromuscular blocking agents are those compounds which contain two quaternary nitrogen atoms situated at a maximum distance apart of approximately fifteen angstrom units (23,24,25,26).

In the polymethylene-bis-trimethylammonium compounds (the "methonium" compounds), maximal neuromuscular blocking activity is obtained when the two onium heads are separated by a ten carbon methylene chain (23,27,28).

There are but few restrictions on the other substituents attached to the quaternary nitrogen, and these have been previously mentioned (charge on the ammonium nitrogen and steric factors). This is illustrated by the vast differences in two active compounds, decamethonium bromide (XII) and d-tubocurarine chloride (XIII).



XII



XIII

(c) Ganglionic Blocking Agents

In monoquaternary compounds, ganglionic blocking activity in general is greatly influenced by minor structural changes. Three or four substituents larger than methyl on the onium nitrogen usually provide ganglionic blocking characteristics.

Cavallito and Gray (23) have summarized as follows: "Sympathetic ganglionic blockade appears to be optimum among monoquaternaries having structures which provide a well distributed intermediate degree of steric hindrance to close approach of the onium nitrogen to the receptor. The intermediate degree of steric hindrance concerned appears to involve approximately a 'two carbon depth' around the nitrogen atom. The presence of n-propyl (or longer) substituents rather than isopropyl, ethyl or piperidinium provides relatively inactive compounds. It thus appears that if the monoquaternary nitrogen can approach to a receptor at a 'C-1'

distance, a stimulant response is induced; a 'C-2' depth of approach provides blocking action; a 'C-3' or greater distance probably reduces the electrostatic bonding force sufficiently to limit activity."

Ganglionic blocking agents of the bis-quaternary type fall into two general classes (29), those in which blocking activity depends upon the length of the chain connecting the two nitrogen atoms, and those in which activity is relatively independent of the length of the linking chain.

Compounds of the former type are generally those with small groups attached to the onium nitrogen such as the methonium compounds. Members of the latter class have a wide variety of larger substituents on the ammonium nitrogen.

Gill (29) suggested the following explanation of the differences between the compounds of the two classes: "It is suggested that acetylcholine acts on ganglia by combining reversibly with an anionic group in a protein constituent of the synaptic membrane, and that this combination interferes with the interaction of neighboring ionic groups in the protein so causing a reversible rearrangement of the secondary or tertiary protein structures which allow depolarization of the membrane to occur. Bis-quaternary compounds of the first type are assumed to combine similarly with an acetylcholine receptor, but the postulated protein rearrangement is prevented by the simultaneous combination of the drug with an adjacent anionic group, so that the protein is temporarily

'locked' in its resting configuration.

Compounds of class two, by virtue of their large quaternary groups are regarded as being unable to approach the acetylcholine receptor closely enough to cause the postulated protein rearrangement (although they hinder the close approach of acetylcholine), so that no 'locking' mechanism need be invoked and the activity is consequently independent of the linking chain."

In the methonium compounds, optimum blocking activity is obtained when the methylene chain separating the two onium heads is five to six carbon units long (30,31,32,33).

Unsymmetrical bis-quaternary compounds appear to be more selective ganglionic blocking agents than symmetrical compounds.

There are three factors which influence activity in the unsymmetrical bis-quaternary compounds, the small onium head, the linking chain and the large onium head. A two to three carbon linking chain appears to be the optimum for long duration of action (34). The small onium head should preferably be trimethyl ammonium or methyl pyrrolidinium. The criteria for the large onium head have not yet been established. However, it is known that it should preferably be planar (23).

The great specificity of the unsymmetrical compounds suggests, that the two receptors to which the bis-quaternary are attached, have different structural requirements (29).

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(d) Cholinergic Blocking Agents

A great many compounds have been prepared which possess parasympatholytic activity, but there still remains a lack of structure activity correlation.

In general a structure which contains an asymmetric carbon atom has a greater cholinergic blocking activity than an analogous symmetrical compound. A hydroxy group which is a fixed distance from the onium nitrogen is favorable for increased activity and also compounds with maximal activity usually contain at least one cyclic substitution (35).

When a compound can exist in more than one optically active form, one optical isomer is usually more active than the other. This difference may be a result of their combination, in one form or another, with another optically active substance to form diastereoisomers of different physical properties (36).

In the molecule of a parasympatholytic agent, Long et al.(35) have postulated four structural elements which serve as points of attachment to a receptor surface. These are, the cationic head (the onium head), the hydroxyl group (probably through hydrogen bonding), the "esteratic" group when present, and the cyclic substitutions.

Figure II shows the proposed receptor diagramatically, with a molecule of l-hyoscyamine attached (35). The numbered sites represent "pockets" in the receptor structure to

which the drug molecule is attached.

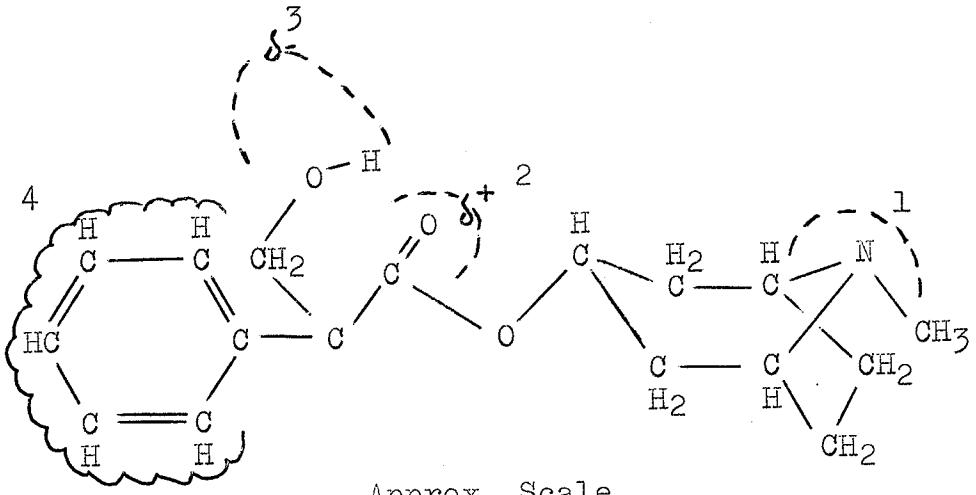


FIGURE II

Site 1 has a diameter of about two to three Angstrom units and the distance between sites 1 and 3 is about five to seven Angstrom units. The esteratic site (site 2) does not appear to be necessary for activity, although several active compounds contain the esteratic group. At least one cyclic structure is required. However, it has not been decided whether it should be saturated or unsaturated for optimum activity.

(e) Quaternary Ammonium Cholinesterase Inhibitors

It is generally believed that quaternary ammonium compounds inhibit acetylcholinesterase by competing with

acetylcholine for the anionic sites of the enzyme. Once the inhibitor is adsorbed on the enzyme, it prevents hydrolysis of acetylcholine by hindering its approach to the enzyme.

This hindering effect is accomplished by electrostatic repulsion between the positive charges of the inhibitor and acetylcholine, or by the bulk of the inhibitor covering the esteratic site (37,38,42).

In a bis-quaternary compound there is a gradual increase in anticholinesterase activity with increase in the length of the hydrocarbon chain separating the two onium heads (39,41). Activity appears to be optimum with rigid suitably situated structures approaching planar and dome shaped configurations (40).

The most important factor, however, appears to be the lipophilic nature of the terminal substituents (40,42). It seems that increased lipophilic character of the terminal group is associated with increased activity. The optimum lipophilic requirement has not been established as yet.

A strange feature about cholinesterase inhibitors is that the activity appears to be greater when the cationic charge on the nitrogen is more diffuse (or less concentrated).

(f) Quaternary Parasympathomimetic Agents

At least two methyl groups are required for acetylcholine-like activity of quaternary ammonium salts (43,44, 45). There are, however, a few minor exceptions (29,46).

Parasympathomimetic (acetylcholine-like) properties are generally favored by the presence of a sterically unhindered methylene "neck" linking the trimethylammonium group to the rest of the structure (23).

The parasympathetic nervous system is divided into two branches, muscarinic and nicotinic. The muscarinic part is that branch which is stimulated by a dose of muscarine. The nicotinic branch is stimulated by a dose of nicotine.

The relationships between structure and nicotinic activity are relatively obscure and are mainly concerned with alkyl compounds (47,48,49). In the case of muscarinic activity there is a little more structure activity correlation; this again involves mainly alkyl compounds (50,51,52,53).

As in the case of cholinergic blocking agents, a receptor theory has been developed for muscarinic agents (41, 54,55,56,57). This receptor theory is mainly based on evidence obtained from studies of acetyl-α-methylcholine, acetyl-β-methylcholine and muscarine (54,55,56). Diagrammatic representation of the receptor is shown im Figure III (41,54,57).

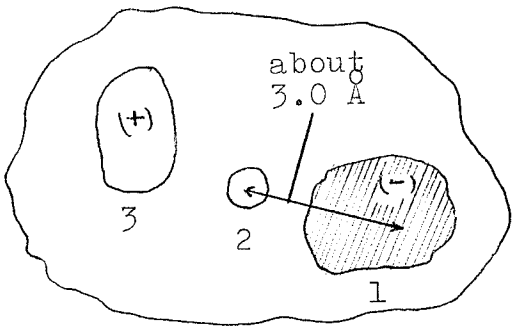


FIGURE III

Site 1 - Anionic cavity negatively charged to accommodate the quaternary nitrogen.

Site 2 - Positively charged point accommodating the ether linkage of muscarine or the ester linkage of acetylcholine and its homologues.

Site 3 - Positively charged area to accommodate the hydroxy group of muscarine, the carbonyl group of acetylcholine and its analogs or the double bond of furan derivatives of muscarine.

This receptor appears to be very highly specific and any slight modifications in the muscarine molecule greatly affect the activity of the compound (55).

Quaternary Phenothiazine and Azaphenothiazine Derivatives

(a) Structure Activity Relationships

The quaternization of physiologically active phenothiazines, all of which are tertiary amines, usually produces compounds with different pharmacological properties. Generally speaking, quaternization enhances the neurotropic antispasmodic effect, while the musculartropic effect is decreased. Antihistaminic action is also generally decreased (58).

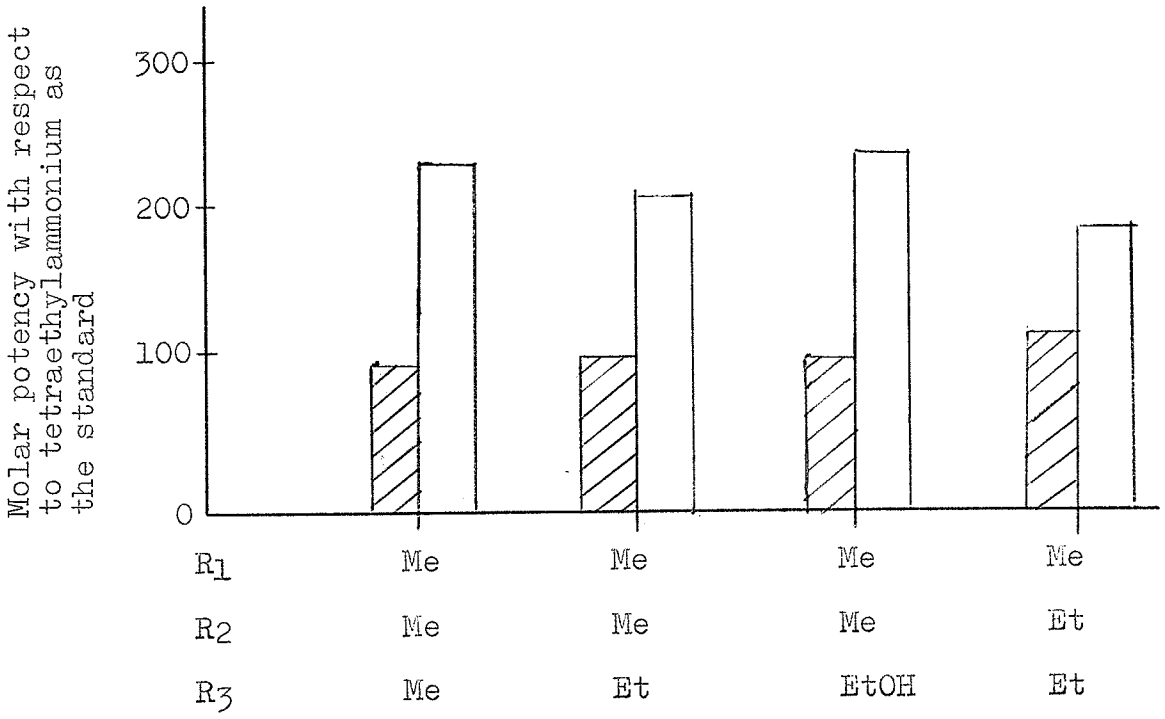
So far as it has been determined, simple structural modifications in the molecule do not influence ganglionic blocking activity to any great extent (59).

Alpha-methyl branching appears to enhance ganglionic blocking and parasympatholytic activity. Beta-methyl branching has little effect on ganglionic blocking activity but it reduces parasympatholytic activity (59,60). If the alpha branch is increased from methyl to ethyl, parasympatholytic activity is lost (60).

In the case of ganglionic blocking activity, the length of the chain connecting the phenothiazine moiety to the onium head does not seem to be too important. The nature of the free alkyl groups on the quaternary nitrogen does not appear to be as important in the phenothiazine series, as in the aliphatic series of ganglionic blocking agents (59).

With an unbranched alkyl chain separating the phenothiazine moiety and the onium head, ganglionic blocking activity is reduced with the introduction of a carbonyl group. In the alpha-methyl branched compounds, the activity is not greatly influenced.

Figure IV shows the effect of N-alkyl substituents and branching of the alkyl chain on ganglionic blocking activity (59).



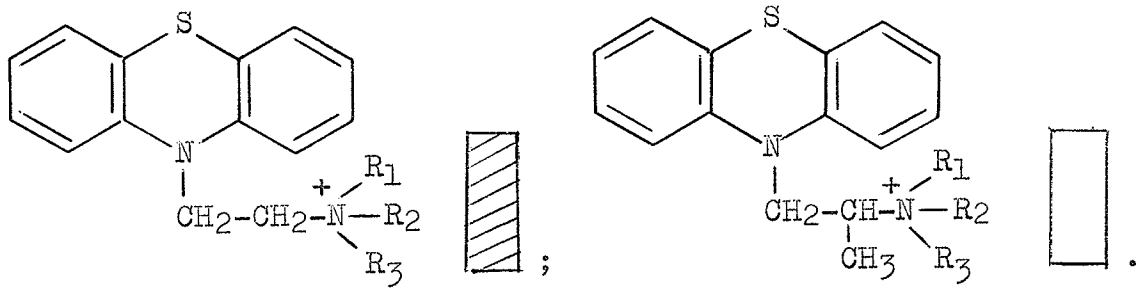


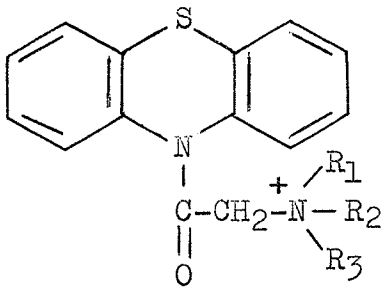
FIGURE IV

(b) Quaternary Phenothiazine Compounds

The general structure of quaternary phenothiazine derivatives which have been prepared are shown below with their

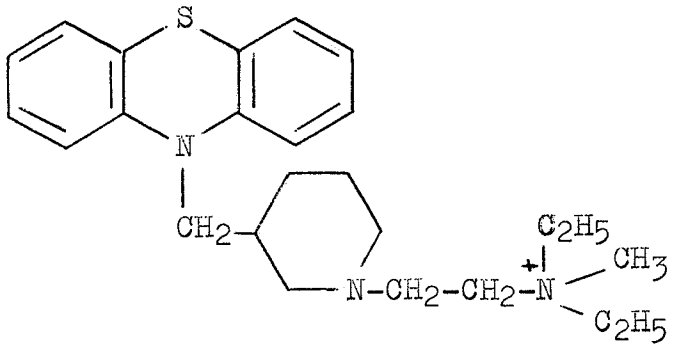
principal physiological action, where reported.

Compound 1 (58,60,61,62,63,66)



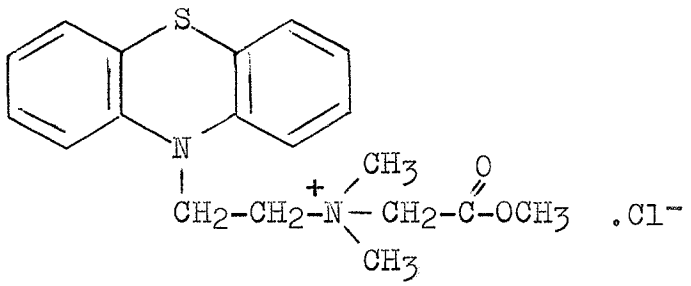
The nature of the quaternary nitrogen has been varied to a wide extent and both cyclic and straight chain substituents have been attached to the nitrogen. In general, this type of compound exhibits antispasmodic activity.

Compound 2 (64)



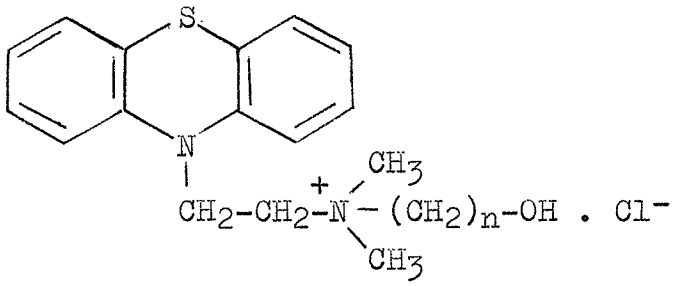
This compound has antispasmodic properties.

Compound 3 (65)



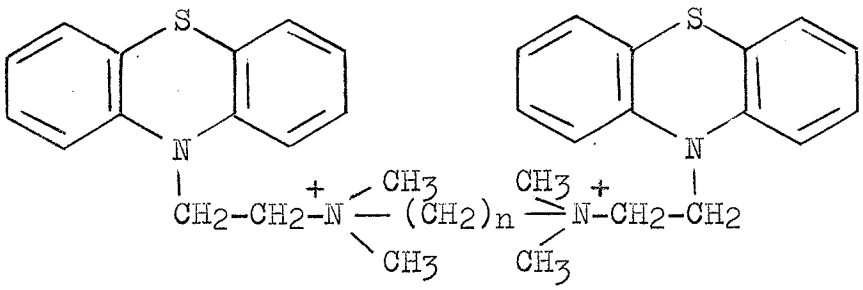
This type of compound exhibits antispasmodic and antihistaminic activity.

Compound 4 (67)



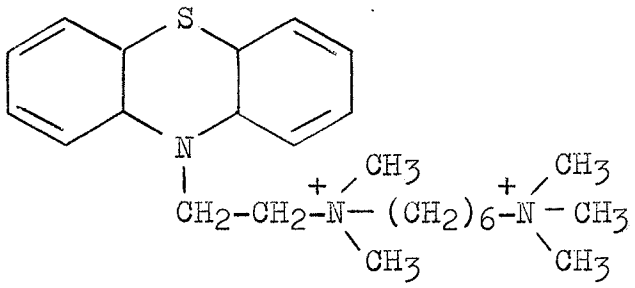
This type of compound has antihistaminic activity.

Compound 5 (68,69,70,71,72,73)



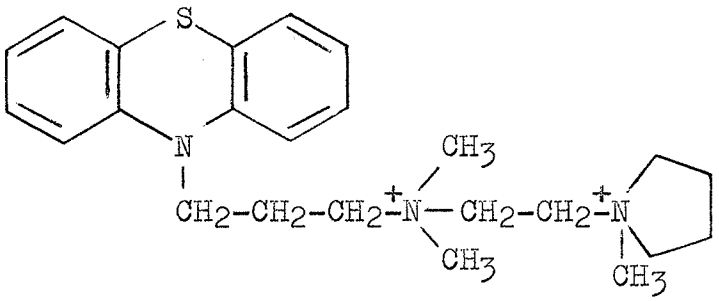
This general type of compound has been found to possess ganglionic blocking and neuromuscular blocking activity, depending on the size of "n".

Compound 6 (74)



This compound is a potent cholinesterase inhibitor, but it is too toxic for human use.

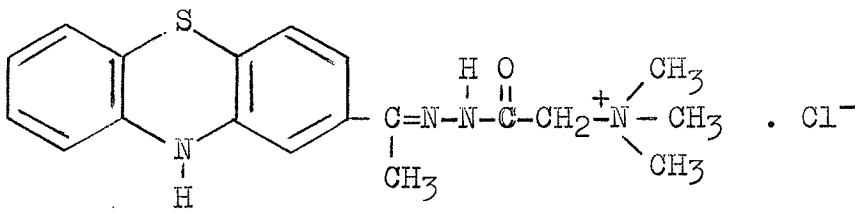
Compound 7 (77)



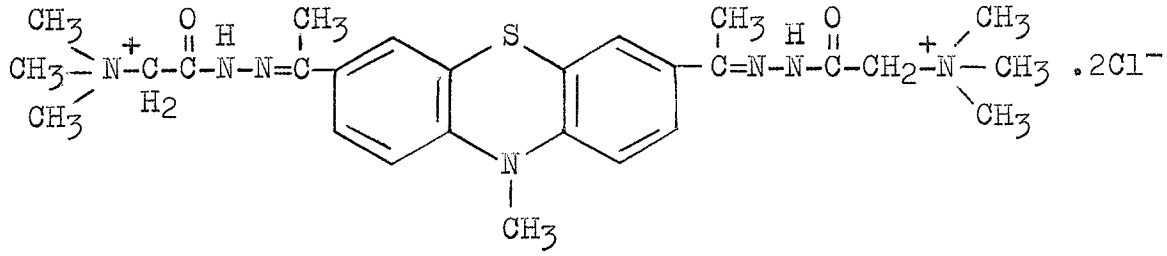
This type of compound has ganglionic blocking activity.

The following seven types of compounds have been prepared but there is no mention of their pharmacological activity.

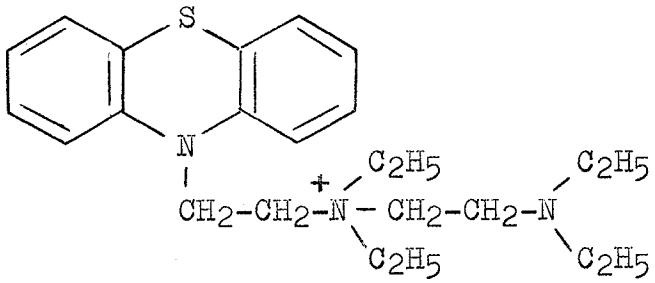
Compound 8 (75)



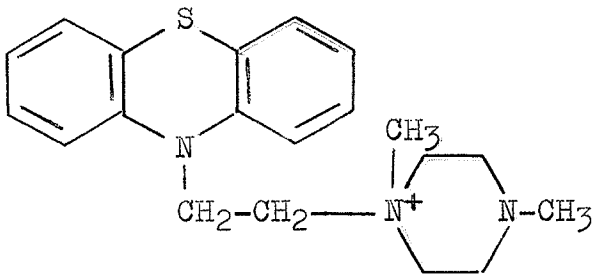
Compound 9 (75)



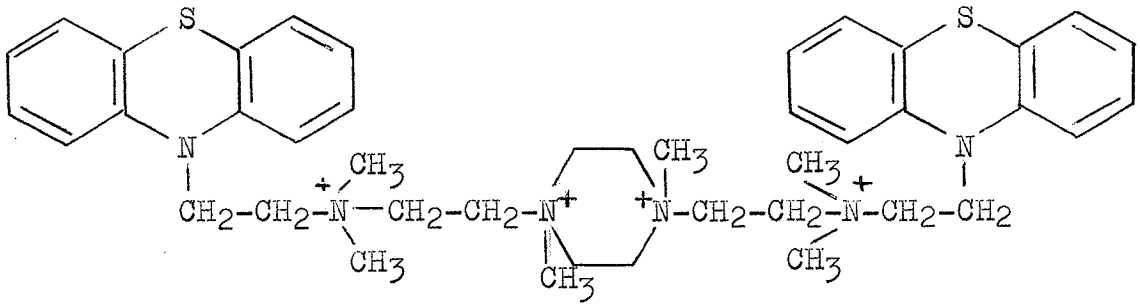
Compound 10 (76)



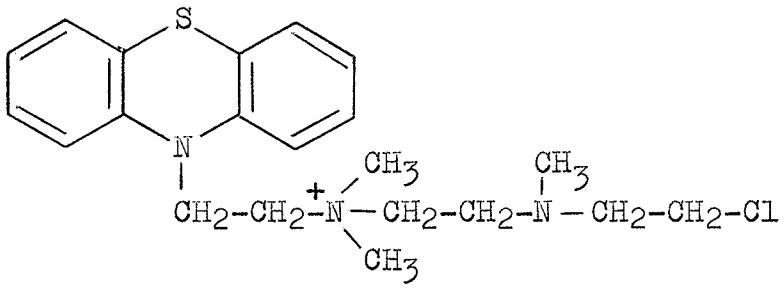
Compound 11 (76)



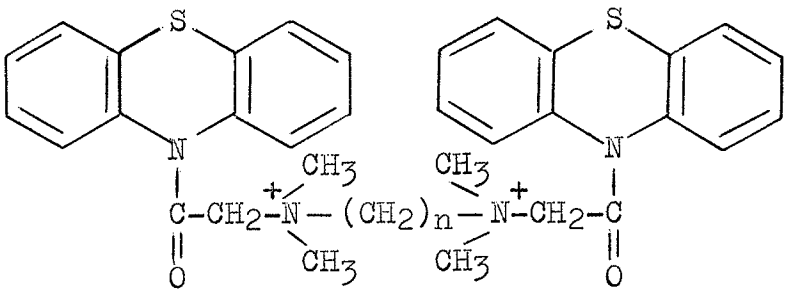
Compound 12 (78)



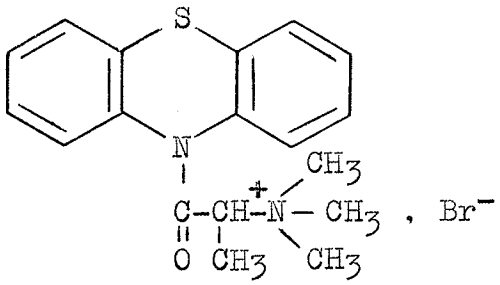
Compound 13 (78)



Compound 14 (79)



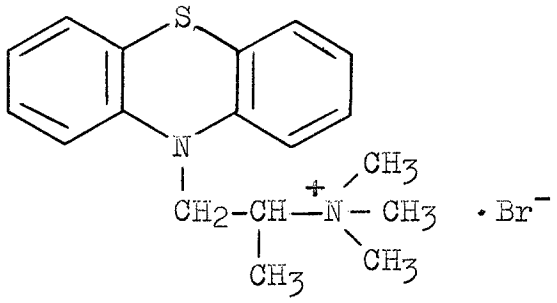
Only a few quaternary phenothiazines are used clinically and of these, Secergan(R) is the most important. Chemically Secergan is 10-(2-dimethylaminopropionyl)-phenothiazine methobromide (XIV).



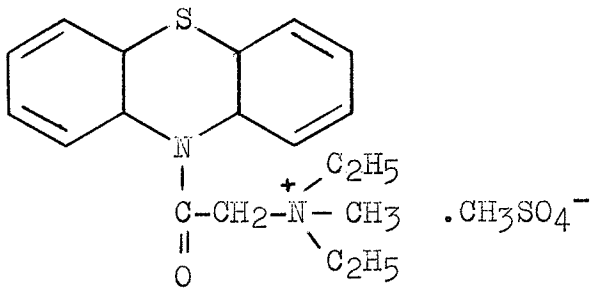
XIV

Secergan is a potent anticholinergic agent, having a marked affinity for the gastrointestinal tract (80,81,82,83, 84).

Two other quaternary phenothiazines used are thiazinamium (XV) and mephasine (XVI). Thiazinamium has anti-asthmatic and anti-tussive activity (85,86,87).



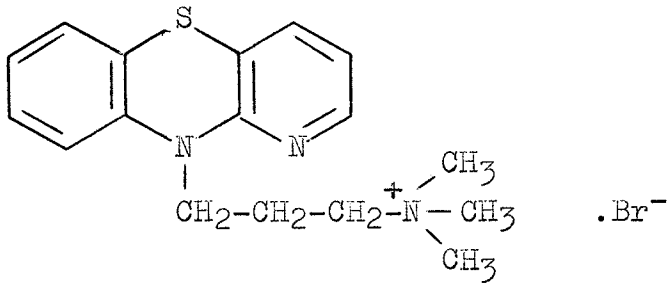
XV



XVI

(c) Quaternary Azaphenothiazine Compounds

Relatively few quaternary azaphenothiazine compounds have been prepared and all of these are simple salts of 10-aminoalkyl-1-azaphenothiazines, such as 10-(3-dimethylamino-propyl)-1-azaphenothiazine (XVII) (88).



XVII

Pharmacological studies on this type of compound have shown that quaternization of aminoalkyl-1-azaphenothiazine derivatives result in marked decrease of sedative, cataleptic, adrenolytic, noradrenolytic, acetylcholinic and vagolytic activity (3). It has been found that quaternization also reduces the antihistaminic activity of this series (2).

II. SYNTHESIS OF THE AZAPHENOTHIAZINE NUCLEI

Three general methods have been used to prepare the azaphenothiazine nuclei. These are

1. Thionation.
2. Ring closure (dehydrohalogenation).
3. Smiles Rearrangement.

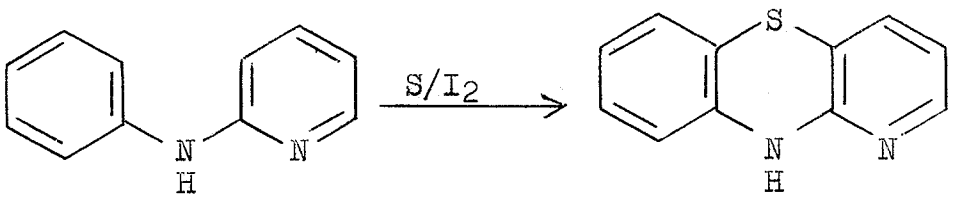
Direct Thionation

Since phenothiazine can be prepared by fusion of diphenylamine with sulphur (89,90), replacement of diphenylamine by a suitable phenylpyridylamine might be expected to produce the azaphenothiazine nucleus.

In 1945, Petrow and Rewald (91) unsuccessfully attempted to prepare 2-azaphenothiazine and 3-nitro-7-amino-1-azaphenothiazine from the corresponding phenylpyridylamines. They reported that they were unable to convert the diphenylamine analogs into azaphenothiazines by the known standard methods, such as fusion with sulphur in ortho-dichlorobenzene in the presence of iodine.

1-Azaphenothiazine (III) is the only azaphenothiazine which has been prepared by direct thionation. It is prepared from 2-anilino-pyridine (XVIII) and sulphur, using iodine as a catalyst (88,92,93,94). The addition of the iodine catalyst

lowers the temperature and time requirements and improves the yield (95). The iodine may be replaced by aluminium chloride. Both the iodine and sulphur may be replaced by sodium thiosulphate if the heating time is altered (93).



XVIII III

It has been reported that 2-anilinopyridine can be thionated using either sulphur dichloride or disulphur dichloride (93). However, in attempts to prepare 1-azaphenothiazine using sulphur dichloride, a black tarry mass was obtained which yielded only a very small amount of product.

Phenothiazine can be obtained in almost quantitative yield by the reaction of diphenylamine with the theoretical quantity of sulphur under the catalytic influence of iodine (89,90). In the synthesis of 1-azaphenothiazine from 2-anilinopyridine however, if a theoretical quantity of sulphur is used, a black mass is obtained from which only about 2 per cent of the product can be isolated by vacuum distillation. In addition it was noted that hydrogen sulphide evolution began at a temperature 100° higher than in the synthesis of phenothiazine (88).

By varying the reaction conditions, Schuler and Klebe (88) succeeded in isolating 1-azaphenothiazine in up to 60

per cent yield (based on unconverted 2-anilinopyridine). The most important changes involved the use of excess 2-anilinopyridine, careful regulation of the reaction temperature and isolation of the product as the hydrochloride (1-azaphenothiazine is a weaker base than 2-anilinopyridine).

Attempted synthesis of 1-azaphenothiazine using phenol, 2-aminopyridine, sulphur and iodine or aluminium chloride was unsuccessful (94).

Substituted 1-azaphenothiazines can also be prepared by direct thionation. 8-Methylthio-1-azaphenothiazine has been prepared from 2-(3-methylthiophenylamino)-pyridine (96).

In the early stages of the present study, numerous attempts were made to prepare 2-anilinopyridine as directed in the literature (97,98,99,100). However, at best, only small yields of impure product were obtained.

2-Aminopyridine and bromo- or iodobenzene were heated at various temperatures for varying lengths of time with sodium or potassium carbonate in the presence of copper. Various methods (crystallization, fractional distillation, sublimation and column chromatography) were employed in an effort to isolate the product from the reaction mixture. In all cases little or no 2-anilinopyridine was obtained. When the reaction time was increased to thirteen hours a fairly large amount of 2-diphenylaminopyridine was isolated.

The synthesis of 2-anilinopyridine by reacting the 2-aminopyridine with sodamide followed by the addition of

bromobenzene also proved unsuccessful.

In attempts to prepare 2-anilinopyridine by condensing phenol and 2-aminopyridine in the presence of zinc chloride, a black gummy tar resulted, from which no characterisable product could be isolated.

Finally, 2-aminopyridine was acetylated (101) and an attempt was made to condense 2-acetylaminopyridine with iodobenzene in the presence of potassium carbonate and copper to produce N-acetyl-2-anilinopyridine. No identifiable products could be isolated from the reaction mixture.

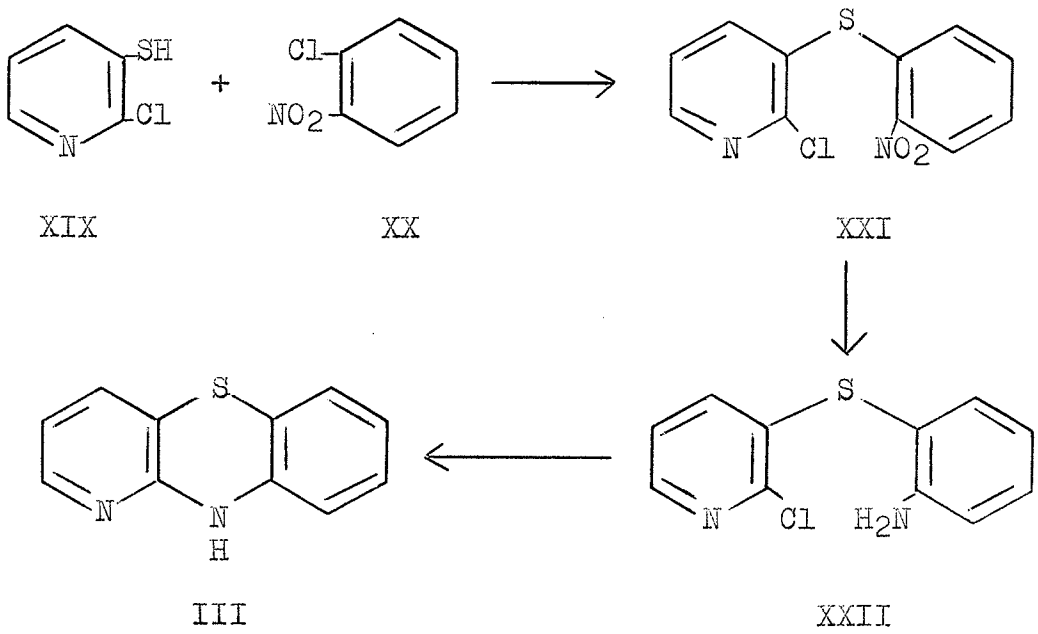
At this point it was learned that 2-anilinopyridine could be obtained from a custom manufacturer (Aldrich Chemical Co.) thus enabling the synthesis of 1-azaphenothiazine to be carried out by this method.

Ring Closure (Dehydrohalogenation)

1-, 2- and 4-azaphenothiazine have been prepared by cyclizing substituted phenylthiopyridines containing an amino and a bromo group ortho to the sulphur.

(a) Synthesis of 1-Azaphenothiazine

The preparation of 1-azaphenothiazine (III) follows the scheme shown in Figure V (102,103).



XIX XX XXI

XXII III

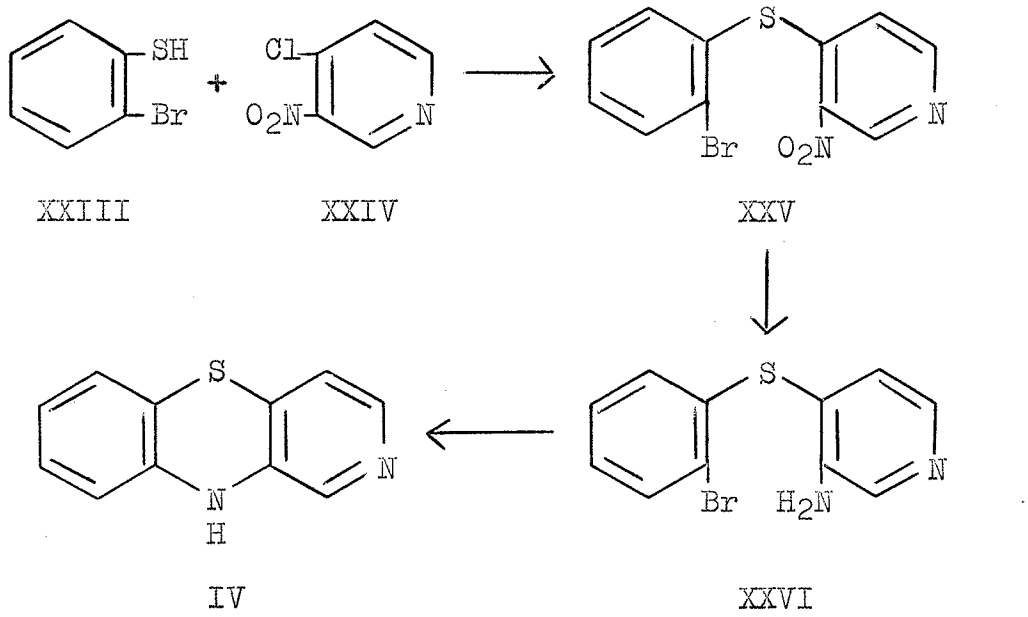
FIGURE V

The 2-chloro-3-mercaptopyridine (XIX) can be prepared by diazotization of 2-chloro-3-aminopyridine, conversion to the xanthate and hydrolysis. This is condensed with ortho-chloro-nitrobenzene (XX), in the presence of sodium hydroxide to 3-(2-nitrophenylthio)-2-chloropyridine (XXI), which is next reduced to the amine derivative (XXII) and cyclized to 1-azaphenothiazine (III) by the addition of sodium hydroxide to the reaction mixture.

8-Chloro-1-azaphenothiazine has also been prepared by this method using 2:5-dichloronitrobenzene (102,103).

(b) Synthesis of 2-Azaphenothiazine

The synthesis of 2-azaphenothiazine (IV) by this method follows the equations in Figure VI (102,104,105).



XXIII XXIV XXV

XXVI IV

FIGURE VI

The 2-bromothiophenol (XXIII) can be prepared by the diazotization of 2-bromoaniline, conversion to the xanthate and hydrolysis (105). The synthesis of 4-chloro-3-nitropyridine is a two step reaction (105,106,107,108). The first step is the nitration of 4-(1H)-pyridone to 4-hydroxy-3-nitropyridine. The second step involves the chlorination of 4-hydroxy-3-nitropyridine to produce 4-chloro-3-nitropyridine (XXIV). The chlorination is carried out using phosphorus pentachloride and phosphorus oxychloride and the

greatest difficulty encountered in the reaction is the removal of all the phosphorus pentachloride. If it is not completely removed before the final distillation, it then sublimes, plugging the distillation apparatus. As a result, the vacuum drops and the material being distilled superheats and decomposes. It has also been reported that small amounts of phosphorus oxychloride in the product retard the condensation with 2-bromothiophenol (105). 4-Chloro-3-nitropyridine is a lachrymator and a powerful skin irritant.

The condensation to form 4-(2-bromophenylthio)-3-nitropyridine (XXV) proceeds very rapidly and the product obtained is in a fairly pure form.

The 4-(2-bromophenylthio)-3-nitropyridine (XXV) is reduced with stannous chloride and hydrochloric acid to the amino derivative (XXVI). The amino derivative is cyclized with either copper bronze or cuprous iodide in N:N-dimethylformamide in the presence of sodium carbonate. An alternate method is to use acetamide in the absence of solvent (105). The amine, (XXVI), can also be cyclized with copper powder and potassium carbonate in N:N-dimethylformamide (102,104, 109).

Saggiomo et al (105) have reported that the cyclization to 2-azaphenothiazine (IV) proceeds best with no solvent and that higher yields and a purer product are obtained. They also reported that the cyclization to 8-chloro-2-azaphenothiazine proceeds better in N:N-dimethylformamide.

Saggiomo et al (105) used a large sublimation apparatus in which to carry out the reaction, subliming the product after cyclization was completed.

Another method used to isolate the product is to pour the reaction mixture into water, filter the precipitate and recrystallize several times. This method is slow and the yields are lower than in the case of the sublimation (102, 104,109). In this study the filtrate from the recrystallization was concentrated and the residue was distilled under vacuum to yield an orange oil, b.p. 208-212°C./0.09 mm. This oil solidified on standing, forming an orange solid with an indefinite melting range and only partially soluble in chloroform. The chloroform soluble portion was found to be 2-azaphenothiazine and the insoluble product was not identified. The insoluble residue was treated with charcoal and recrystallized from ethanol to yield orange platelets with an indefinite melting point above 220°C. This chloroform insoluble orange solid was probably some decomposition or rearrangement product formed during the distillation since the residue before distillation was totally soluble in chloroform.

10-Dialkylaminoalkyl derivatives of 2-azaphenothiazine have been prepared by attaching the dialkylamino chain to the amino group of the phenylthiopyridine before cyclizing with potassium carbonate and copper (109).

(c) Synthesis of 4-Azaphenothiazine

The synthesis of 4-azaphenothiazine by cyclization of the appropriately substituted phenylthiopyridine proceeds according to the equation in Figure VII (102,104).

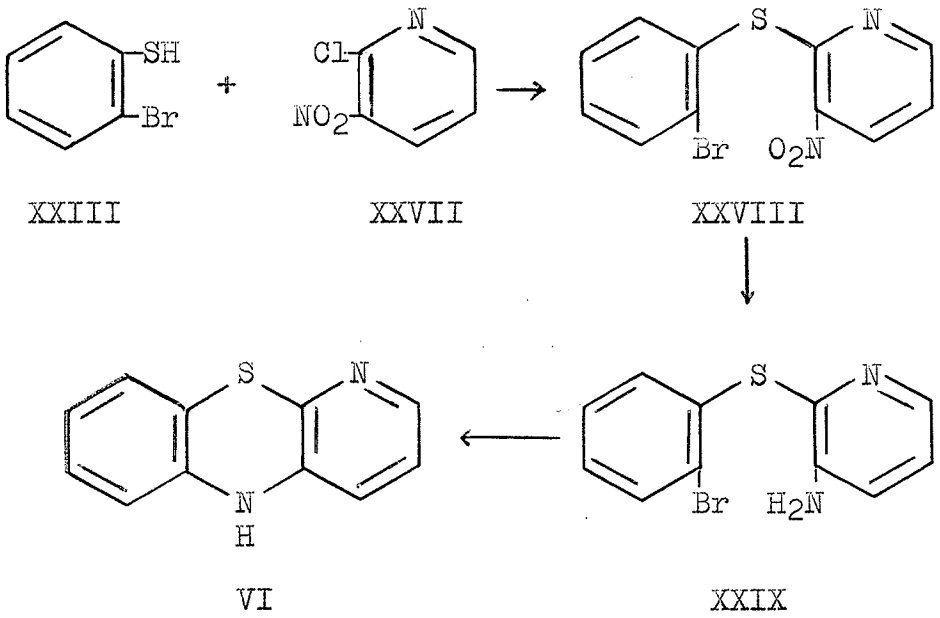


FIGURE VII

Attempts to synthesize 2-chloro-3-nitropyridine (XXVII) were unsuccessful. In the nitration of 2-(1H)-pyridone (110, 111,112) only a very small amount of the desired product, 2-hydroxy-3-nitropyridine, could be isolated. The main product formed was 2-hydroxy-3:5-dinitropyridine. It was learned that 2-chloro-3-nitropyridine could be purchased from an English chemical firm so this problem was eliminated.

The condensation of 2-chloro-3-nitropyridine with the

ortho-bromothiophenol proceeded quickly, as in the case of 2-azaphenothiazine, and the product obtained (XXVIII) was fairly pure.

In the reduction step with hydrochloric acid and stannous chloride, difficulties were encountered and a very impure product was obtained. Crystallization attempts and also column chromatography proved unsuccessful. Efforts to cyclize this impure product yielded only a black tar from which no 4-azaphenothiazine could be isolated.

A method whereby the amine could be partially purified was finally worked out. This involved fractional precipitation from a hot concentrated ethereal solution by the addition of petroleum ether. Cyclization of this partially purified amine (m.p. 85-91°C.) to 4-azaphenothiazine was successful.

Ring substituted 4-azaphenothiazines have also been prepared by this method (102,113,114).

Smiles Rearrangement

Figure VIII shows what is essentially a Smiles Rearrangement (115,116,117).

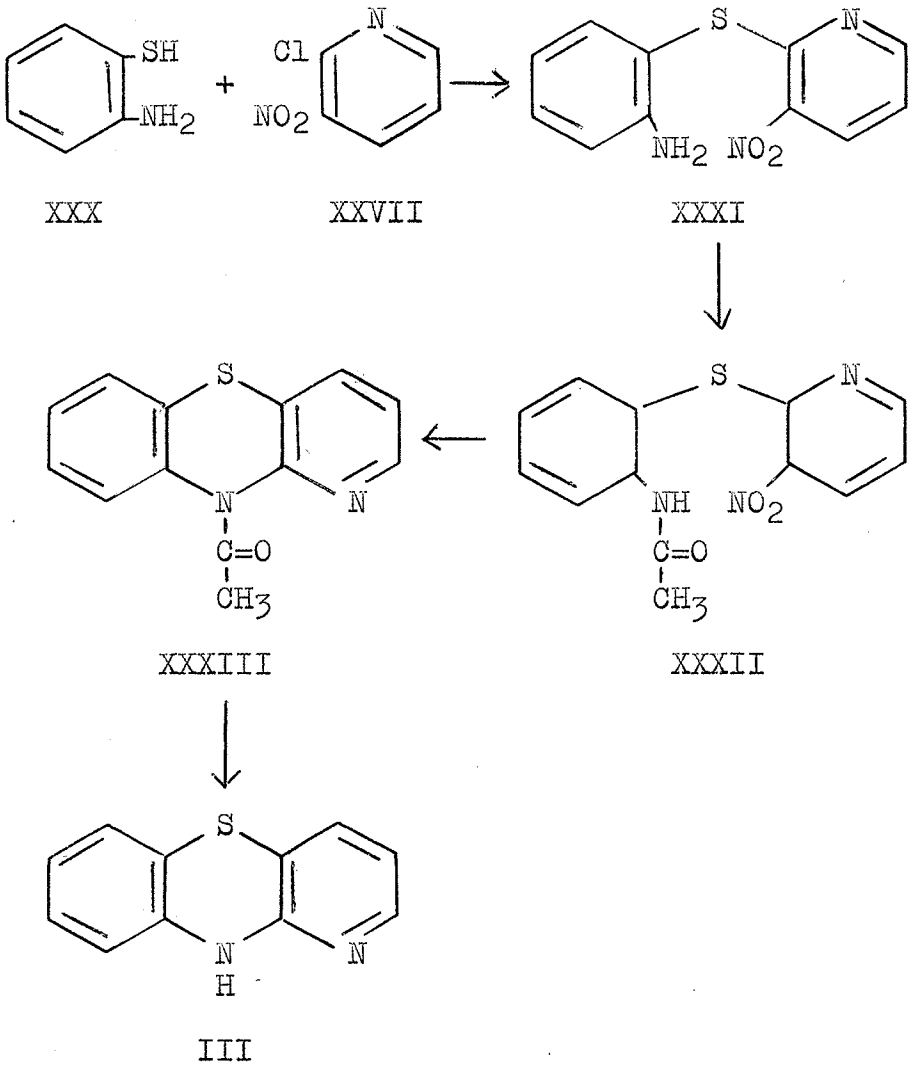


FIGURE VIII

In the above reaction the product formed is 1-azaphenothiazine (III). This is the only parent azaphenothiazine, as such, which has been prepared using this method. Some ring substituted 1-, 3- and 4-azaphenothiazines have been made in this way as well (91,96,115,116,117,118,119,120).

Very few Smiles rearrangements occur unless there is some kind of activation in the aromatic ring structure (121). In the case of 1-azaphenothiazine the activating groups are the nitro group and the pyridine nitrogen.

It was necessary to acetylate the amino group in 2-(2-aminophenylthio)-3-nitropyridine (XXXI) because sulphides do not rearrange with a primary amino group present; however, they do rearrange if an aminoacetyl group is present as in compound XXXII (121).

The actual rearrangement step is generally carried out in a nitrogen atmosphere using an alcoholic solution of potassium hydroxide (115,116,117).

3-Azaphenothiazine

The parent 3-azaphenothiazine nucleus has never been prepared using any of the above methods.

An unsuccessful attempt was made to prepare 3-azaphenothiazine via Smiles rearrangement (105). In this case 4-chloro-3-nitropyridine (XXIV) was condensed with ortho-aminothiophenol (XXX) to yield 4-(2-aminophenylthio)-3-nitropyridine. This was in turn converted to the formamido derivative and the rearrangement was attempted; however, no product was obtained. Only 1-nitro and 7-nitro-3-azaphenothiazine have been prepared using Smiles rearrangement (91,120).

Possibly the intermediate compound for 3-azaphenothiazine does not provide enough activation for the rearrangement to occur. The addition of the nitro group may give the molecule the necessary activation power.

3-Azaphenothiazine has not been prepared by dehydro-

halogenation and a possible explanation could be in the mechanism of its formation. Reactions of this type appear to fall in the class known as activated nucleophilic aromatic substitution. With this in mind, the following scheme can be shown for the synthesis of 2-azaphenothiazine.

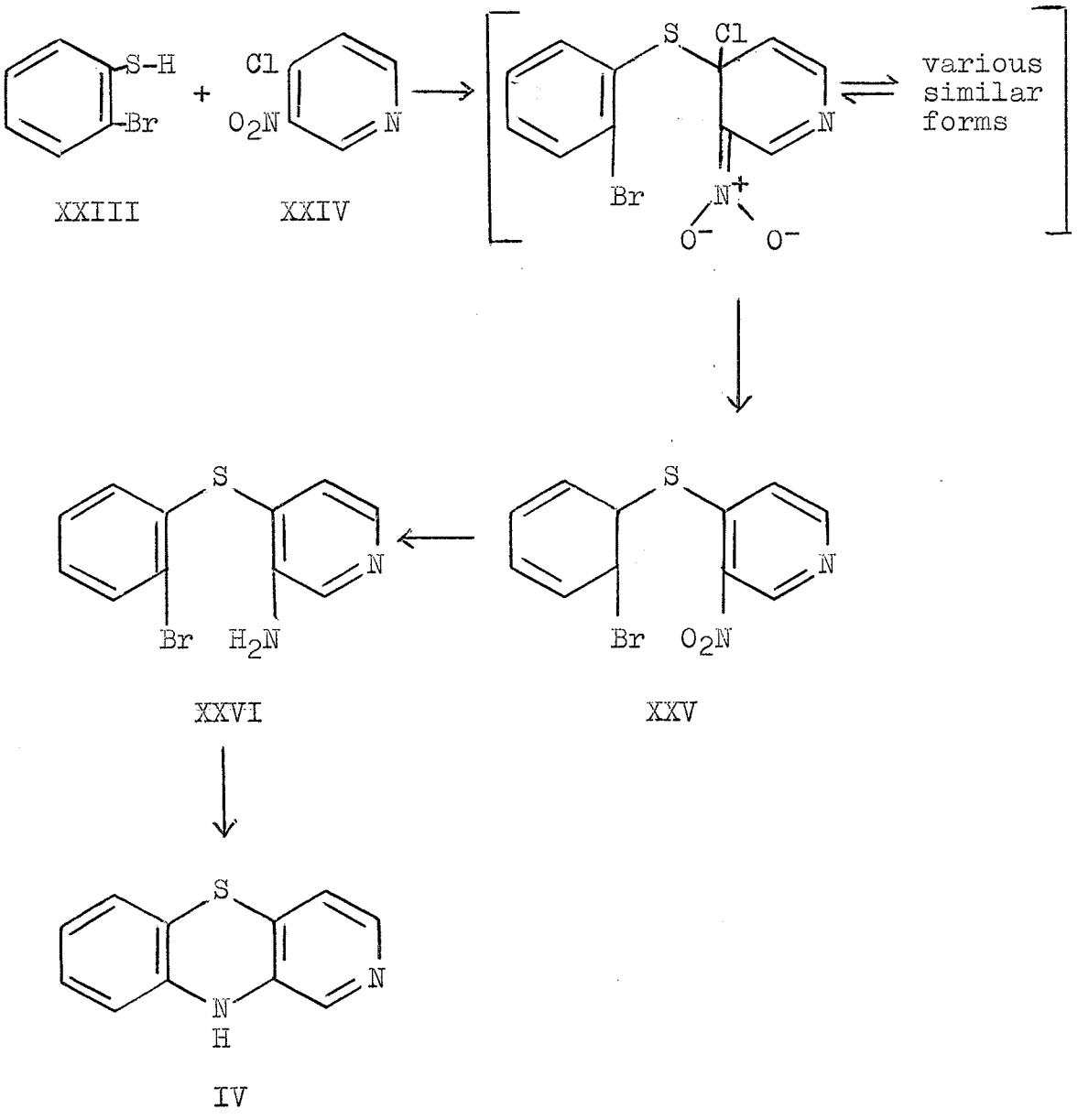
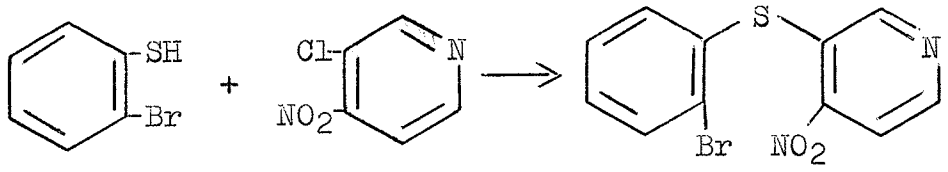


FIGURE IX

In this case, the 4-position in 4-chloro-3-nitropyridine (XXIV) is activated by the ortho-nitro group and a pyridine nitrogen in the para position. Both of these groups would activate position 4 for a nucleophilic substitution. A similar argument can be applied in the synthesis of 4-azaphenothiazine.

If 3-azaphenothiazine were to be prepared using this method, the first step in the reaction would require 2-bromothiophenol nucleophilically attacking 3-chloro-4-nitropyridine as shown in Figure X.



XXIII XXXIV XXXV

FIGURE X

This reaction has not been reported in the literature and was not attempted in this present study because the starting material, 3-chloro-4-nitropyridine (XXXIV) was not available. With this compound the 3-position is activated only by the ortho-nitro group and not by the pyridine nitrogen which is meta to the 3-position. Thus this compound presumably would not be activated enough to undergo a nucleophilic attack at position 3.

III. DISCUSSION

Probably the greatest obstacle during this study was the difficulty experienced in purifying many of the products described. Some of the intermediates required were prepared according to methods described in patents and the necessary purification data were usually brief or absent. As a direct result, synthesis of sufficient quantities of the various azaphenothiazine nuclei proved to be extremely time consuming.

Some of the new compounds prepared appeared to hold small amounts of impurity tenaciously and six or more recrystallizations were often required before these derivatives gave sharp melting points and good micro-analysis results. In a few cases, even ten or twelve recrystallizations still yielded products with analysis data which were barely acceptable, although there could be no doubt as to the true identity in each case. Attempts to purify products by other means (chromatography, fractional precipitation, zone refining, etc.) were usually less successful than repeated recrystallization. One of the likely reasons for this purification problem was that starting material and the expected products were often extremely similar in character and hence had similar solubilities, etc.

(a) 10-Dialkylaminoalkyl Azaphenothiazine Derivatives

The 10-dialkylaminoalkyl derivatives of 1- and 2-azaphenothiazine were prepared in good yield with sodamide as the condensing agent. With the exception of 10-(2-dimethylaminoethyl)-1-azaphenothiazine (XXXVI), all of the amines prepared in this series were oils, and it was necessary to prepare solid derivatives for identification purposes.

(b) Bis-Quaternary Salts of the 10-Dialkylaminoalkyl Azaphenothiazine Derivatives

Since there was a possibility that the pyridine nitrogen in the azaphenothiazine nuclei could quaternize with the $\alpha:\omega$-dibromo compound, preliminary experiments were carried out to determine whether or not this would occur. 1- and 2-azaphenothiazine were heated with the various dibromo compounds. No quaternization occurred and the starting materials were recovered.

In addition, ultraviolet spectral analysis of the bis-quaternary compounds indicates that the pyridine nitrogen did not react. When spectra of the bis-quaternary compound and the parent amine were compared, both were found to contain an absorption maximum at approximately 320 mμ. However, when 1- and 2-azaphenothiazine were compared with their methyl

iodide derivative, the peak in the region of 320 mμ was found to be absent in the quaternary compounds. This latter result indicates that the conjugation of the aromatic system has been affected by quaternization of the pyridine nitrogen in such a way that the absorption in the region of 320 mμ has been removed. Since, with the bis-quaternary compounds, the peak in the region of 320 mμ is still present, this would indicate that the pyridine nitrogen was not affected.

Attempts to prepare the bis-quaternary compounds in benzene solution were unsuccessful and it was found that the reaction proceeded best in the absence of solvent. When no solvent was present, the thorough mixing of the reactants became very important. If the reactants were not carefully mixed together, a mixture of products was obtained consisting of bis- and monoquaternary compounds. The mixing was best carried out by first dissolving the amine and the dibromo compound in chloroform and slowly allowing the chloroform to escape. The reaction mixture was then heated for an hour in the absence of solvent.

Another important point in the preparation of these compounds is the ratio of reactants. At first, a proportion of 2 moles of amine to 1 mole of dibromo compound was used; however this gave a mixture of mono- and bis-quarternary compounds. Thus, an excess of amine was necessary and a 3:1 ratio of amine to dibromoalkane proved to be satisfactory.

All the compounds in this series were very hygroscopic and all attempts at recrystallization were unsuccessful. In order to obtain pure products, it was necessary to have the reactants in a pure form. The product was thoroughly washed with dry ether to remove all traces of unreacted starting materials.

A number of attempts were made to purify the quaternary salts, by preparing salt derivatives of different acids (such as oxalic acid, citric acid, maleic acid, picric acid) but none of the preparations was successful. The only salt successfully prepared was the reineckate. After recrystallization from a mixture of ethanol, acetone and water, micro analytical results were poor and the compound appeared to be unstable.

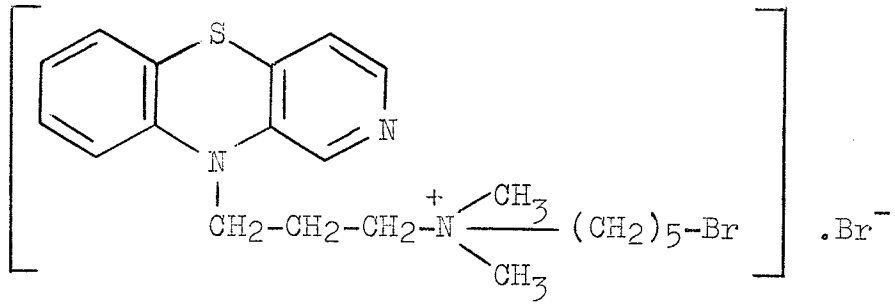
An alternative attempt to prepare the quaternary hydroxide by the use of moist silver oxide proved unsuccessful.

In order to characterize these compounds, a number of analyses were performed (equivalent weight determination and carbon-hydrogen-nitrogen analyses), producing confusing results with the original products.

Most of the bis-quaternary compounds of 10-(dialkylaminoalkyl)-1-azaphenothiazine were then remade using the modified mixing technique with chloroform, (with the exception of compounds LIII, LX, LXII and LXIII) and the analytical results were mainly satisfactory.

In the bis-quaternary compounds of the 2-azaphenothiazine series, compounds LXXIV, LXXV and LXXVII analyse as a

monoquaternary salt, typified by structure XXXVII shown below.



XXXVII

Compounds LXXVI*, LXXVIII, and LXXXI appear to be mixtures of mono- and bis-quaternary salts. The analysis for compounds LXXIX and LXXX show that these two compounds are bis-quaternary salts.

The variety of compounds obtained in the 2-azaphenothiazine series illustrate very well the importance of very thorough mixing of the reactants.

Compound LXXVI was remade using the new technique for mixing and good analytical results were obtained.

*The quantity of 2-azaphenothiazine available and the time factor made it impossible to remake this series of compounds.

(c) Synthesis of Substituted Aminoacetyl-1-Azaphenothiazine Derivatives

Many attempts were made to prepare 10-chloroacetyl-1-azaphenothiazine** (LXXXII) using chloroacetyl chloride, in a manner similar to the synthesis of 10-chloroacetylphenothiazine. The yields, using this method, were unpredictable and varied anywhere from 0 to 40 percent. The product obtained was very impure and purification was difficult.

A number of modifications of the standard method were unsuccessfully employed in an attempt to produce 10-chloroacetyl-1-azaphenothiazine in a pure form and in reasonable yields. These modifications were:

1. The proportion of chloroacetyl chloride was varied, along with the proportion of potassium carbonate.

2. Experiments were conducted using different solvents and different solvent:reactant ratios.

3. The reaction temperature and heating times were varied.

** The structure of the product from chloroacetylation of 1-azaphenothiazine is unknown. For convenience, it is referred to as "10-chloroacetyl-1-azaphenothiazine", since this was the expected product.

4. The added base was changed to sodium carbonate and sodium bicarbonate. Also, the reaction was attempted with no added alkali carbonates at all.

The best yield (40%) which could be obtained was by refluxing a stirred mixture of 1 mole of 1-azaphenothiazine, 2 moles of chloroacetyl chloride and potassium carbonate for three hours in dioxane. However the yield was unpredictable and the product obtained was very impure.

A possible explanation why this reaction did not work too well lies in the fact that α-halogen acids are converted into α-hydroxy acids (especially in the presence of alkali carbonates) on heating (122). Thus, if the condensation of chloroacetyl chloride with 1-azaphenothiazine proceeds at a slower rate than the conversion of the chloro acid to the hydroxy acid, then the hydroxy acid will form and react with the acyl halogen. Some of these polymers may condense with the azaphenothiazine and the result would be an impure product in low yield.

In addition to the above, unsuccessful attempts were made to prepare 10-chloroacetyl-1-azaphenothiazine using sodamide or aluminium chloride. In both cases a black tarry mass was obtained from which no 10-chloroacetyl-1-azaphenothiazine could be isolated.

Finally, the synthesis of "10-chloroacetyl-1-azaphenothiazine" was successfully carried out using chloroacetic acid anhydride and chloroacetic acid in dry dioxane. The

yields were fairly good, they were reproducible, and the product obtained was quite pure.

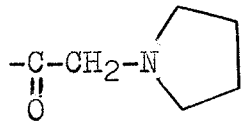
In the study which was carried out to verify the structure of the compound obtained from the chloroacetylation of 1-azaphenothiazine, the following information was obtained:

1. Elemental analysis for the chloroacetylation product fits an empirical formula of $C_{15}H_9O_2N_2SCl$. This differs from the analysis of the expected product, 10-chloroacetyl-1-azaphenothiazine ($C_{13}H_9ON_2SCl$) by C_2O.

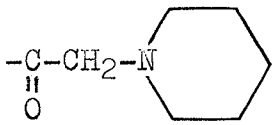
2. Acid hydrolysis of the chloroacetylation product did not give 1-azaphenothiazine which would have been the expected product from the hydrolysis of 10-chloroacetyl-1-azaphenothiazine. Instead, a new compound was obtained which contained no chlorine and whose elemental analysis differed from 1-azaphenothiazine by C_2O. In addition, infrared analysis of the hydrolysis product showed that a secondary amine group was not present, although the overall spectrum was very similar to that of 1-azaphenothiazine indicating the 1-azaphenothiazine nucleus was probably still intact.

3. Nuclear magnetic resonance spectra were run on compounds LXXXIX and LXXXIII which were originally thought to be 10-pyrrolidino- and 10-piperidinoacetyl-1-azaphenothiazine respectively. This revealed the presence of only five aromatic protons (peak at 6.8 ppm.) and also that position two was in some way substituted (shown by the absence of hydrogen on the carbon atom adjacent to the pyridine nitrogen), which

would be expected to give a quartet around 2.0 ppm). The N.M.R. spectra also confirmed the presence of the groupings



and

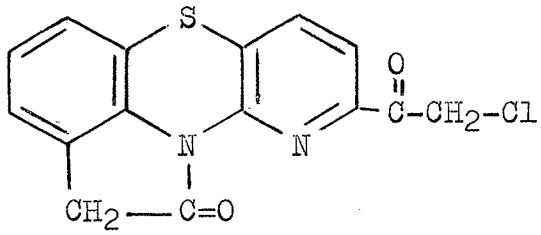


in the two respective compounds. The latter compound showed an unsplit singlet at 3.75 ppm. due to $-CH_2-$ not coupled to other magnetic nuclei, a peak at 2.6 ppm. due to the α-proton of piperidine and at 1.5 ppm. due to the β- and γ-protons of piperidine. Integration of the three sets of peaks yields a ratio of 2:3.9:6.4 which agrees well with the theoretical values of 2:4:6.

4. Non aqueous titration of compound LXXXIX gave an equivalent weight of 177.5.

There are several possible structures, therefore, for the chloroacetylation product and each one will be discussed individually.

The first structure which comes to mind and which fits most of the data is XXXVIII.



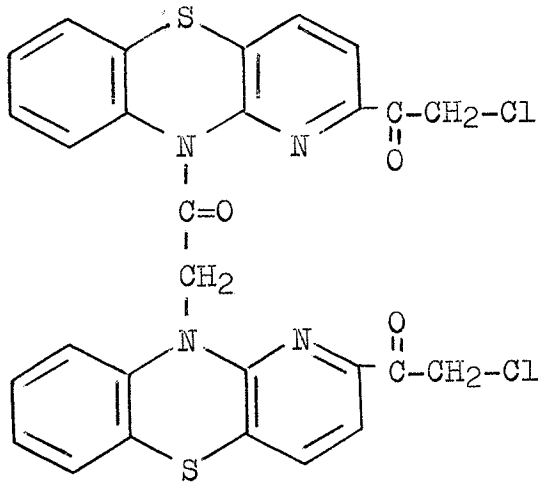
XXXVIII

This structure has five aromatic protons, position two in the 1-azaphenothiazine nucleus is substituted and the elemental analysis fits. In the case of the pyrrolidinoacetyl deriva-

tive (LXXXIX) the equivalent weight would be 175.5 which agrees well with the experimental value of 177.5 which was obtained. Also, acid hydrolysis of this ketone would be conceivably possible due to its position alpha to the pyridine nitrogen.

The infrared spectra do not support this structure, however. The infrared spectrum of the chloroacetylation product (KBr pellet) does not show a peak for a ring fused γ-lactam in the region from 1750 to 1700 cm.$^{-1}$ nor is there a peak for the aromatic ketone in the region of 1715 cm.$^{-1}$. The only carbonyl peak which does show up is one at 1650 cm.$^{-1}$ and this is strongly indicative of a tertiary amide.

Another structure which could be considered is XXXIX.

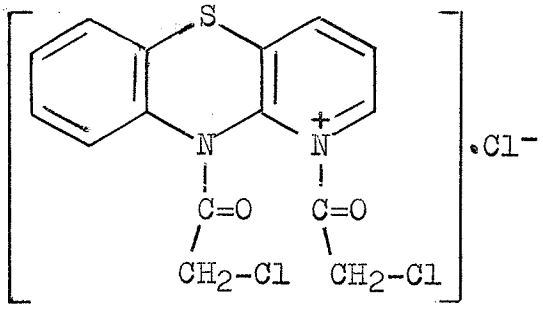


XXXIX

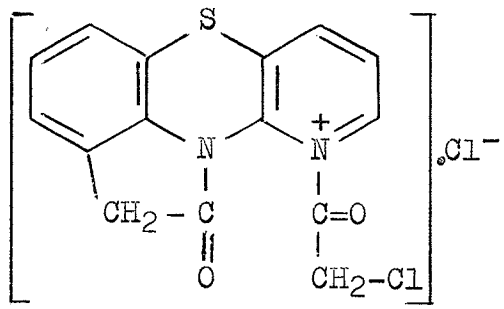
This compound is a tertiary amide and has position two in the azaphenothiazine nucleus substituted. The elemental analysis would also fit this structure. The main argument against structure XXXIX is the fact that it contains six aromatic

protons and also the argument used in the previous structure regarding the absence of the ketone carbonyl applies here.

Any quaternary compounds such as XL or XLI are very unlikely due to the presence of too many chlorine atoms to fit the analytical data and the spectral data.

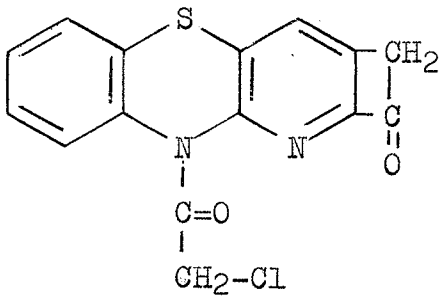


XL



XLI

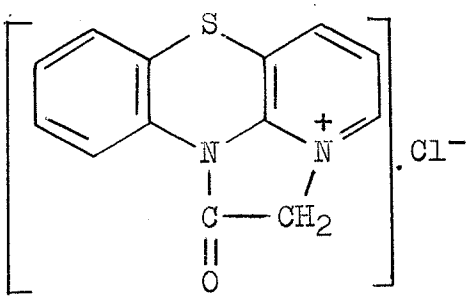
Structure XLII fits the N.M.R. data in that it has five aromatic protons and position two is substituted. The elemental analysis fits this compound and it would be expected to show a peak for a tertiary amide in the infrared spectrum.



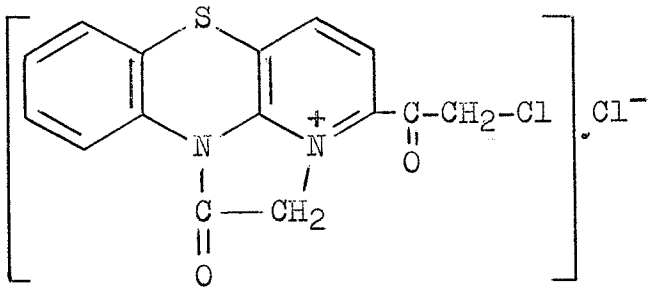
XLII

In addition there is a weak peak at 1780 cm.$^{-1}$ which is indicative of a four member ring ketone, however it appears to be much too weak for a carbonyl. Finally, the N.M.R. spectrum does not show the two protons alpha to the carbonyl in the four membered ring thus making this structure unlikely.

Structure XLIII is totally unacceptable because amino derivatives can be made and the chlorine must therefore be organically combined and not ionic in nature.



XLIII

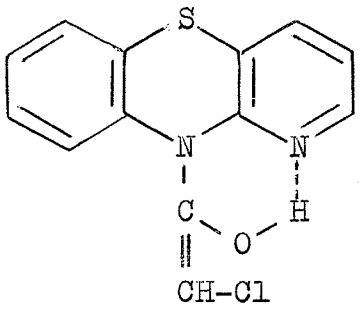


XLIV

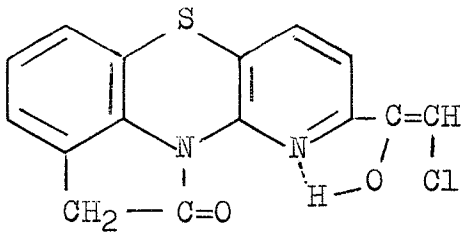
Both structures (XLIII and XLIV) can be eliminated on the basis that they contain seven and six protons respectively. Structure XLIV has a ketone group which is not shown on the infrared spectrum.

The formation of any of the structures proposed cannot be satisfactorily explained mechanistically and in the case of structures XXXVIII and XXXIX, no apparent driving force for the reaction can be determined and in fact the entropy factor would tend to disfavor formation of compounds such as these, very readily.

"10-chloroacetyl-1-azaphenothiazine" exhibits some puzzling properties which could only be explained on the basis of hydrogen bonded structures such as those shown below (XLV and XLVI).



XLV



XLVI

The evidence which points to such internal hydrogen bonding is as follows:

1. The compound is very insoluble in all solvents and is only very slightly soluble in hot dioxane, N:N-dimethylformamide, glacial acetic acid and trifluoroacetic acid.

2. The compound does not form a hydrochloride salt and in fact is insoluble in concentrated hydrochloric acid. This is in sharp contrast with all the other azaphenothiazine derivatives which readily form hydrochlorides.

3. It has an unexpectedly high melting point which is about 150° higher than the corresponding phenothiazine derivative. 10-Chloroacetylphenothiazine has m.p. 113.5-114.5°; 10-acetylphenothiazine m.p. 197-198° compared with 10-acetyl-1-azaphenothiazine m.p. 167-168°C.; 10-methylphenothiazine m.p. 99° compared with 10-methyl-1-azaphenothiazine m.p. 86°C.

4. It only reacts with secondary amines in polar solvents and at temperatures of about 100°C. or higher. This can be compared with 10-chloroacetylphenothiazine which reacts readily with secondary amines in benzene solution and

at low temperatures.

"10-chloroacetyl-1-azaphenothiazine" is too insoluble for an infrared solution spectrum or nuclear magnetic resonance spectra to be carried out.

"10-chloroacetyl-1-azaphenothiazine" would not condense with dimethylamine to form 10-(N:N-dimethylaminoacetyl)-1-azaphenothiazine presumably because the reaction had to be carried out in the cold. Dimethylamine was found to be too volatile for the standard condensation.

In the case of the reaction of "10-chloroacetyl-1-azaphenothiazine" with diethylamine, some product was formed but a very long heating time was required and the yield was low.

This relatively poor reactivity of "10-chloroacetyl-1-azaphenothiazine" can be explained on the basis of the hydrogen bonded structure. In this compound if the hydrogen bond existed, the chlorine would be attached to an sp^2 hybridized carbon atom whereas if the hydrogen bond did not exist the carbon would be sp^3 hybridized. The electronegativity of an sp^2 hybrid is greater than an sp^3 hybridized carbon, therefore in the hydrogen bonded structure the carbon chlorine bond would be a great deal stronger than it would normally be.

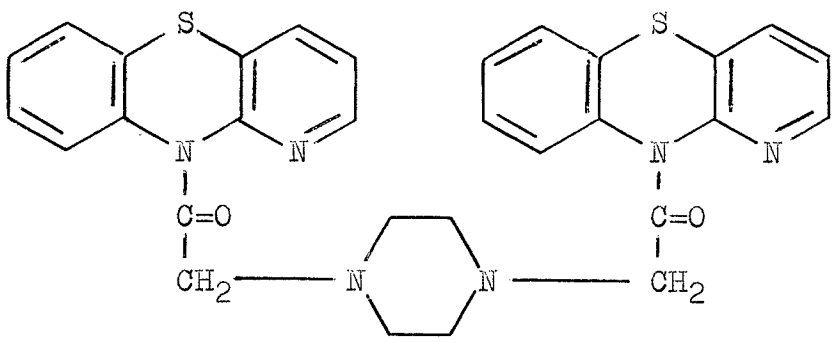
In the condensation of "10-chloroacetyl-1-azaphenothiazine" with the higher boiling secondary amines (dipropylamine, piperidine, pyrrolidine and N-methylpiperazine), the reaction worked quite well, although purification of the

products presented a problem.

In initial experiments, the reaction was carried out in N:N-dimethylformamide and when completed, the reaction mixture was poured into water. The product obtained was very impure and the purification was a long tedious process. However, the amount of solvent used was decreased and the reaction was completed, and allowed to stand overnight. The product which precipitated out of the reaction mixture, while obtained in a slightly lower yield, was then much purer than that obtained using the previous method. A number of recrystallizations were still required, however, in order to obtain a sample pure enough for the quaternization step which followed.

In preparing samples for micro-analysis, a large number of recrystallizations were required and the results which were obtained could not be improved upon with further recrystallization.

When "10-chloroacetyl-1-azaphenothiazine" was condensed with piperazine, only a small yield was obtained (about 25%) and the solubility properties of the compound were very different from the other substituted aminoacetyl-1-azaphenothiazine derivatives. When the filtrate from the reaction mixture was poured into water and basified with sodium carbonate, no precipitate formed, and no starting material was recovered.



XLVII

It was thought that structure XLVII might have been formed but it is fairly certain that the solubility of this structure would be very similar to that of the expected compound. The same compound was formed when a 3:1 ratio of piperazine to "10-chloroacetyl-1-azaphenothiazine", or when a 3:1 ratio of "10-chloroacetyl-1-azaphenothiazine" to piperazine was used. Both products melted in the range of 285-290°C. (decomposition) and gave a negative Beilstein test for halogen.

This product was insoluble and could not be recrystallized and hence micro-analytical data were not obtained.

(d) Bis-Quaternary Salts of the Substituted Aminoacetyl-1-Azaphenothiazines

In the synthesis of the bis-quaternary salts in this series the proportion of 3 moles of amine to one mole of α:ω-dibromo compound was used. Since the amines in this series were solids, the reactants could not be thoroughly

mixed in the absence of solvent and it was necessary to use solvent to ensure complete mixing and then remove the solvent to allow the reaction to proceed.

The bis-quaternary compounds in this series were only slightly hygroscopic and most of them could be recrystallized from 95 percent ethanol. Only the series with 10-(4-methyl-piperazinoacetyl)-1-azaphenothiazine (XC) could not be recrystallized. When ethanol was added to these compounds a sticky mass resulted.

(e) Chloroacetylation of 2-Azaphenothiazine

Several unsuccessful attempts were made to prepare 10-chloroacetyl-2-azaphenothiazine using chloroacetyl chloride. In most cases, the only product obtained was 2-azaphenothiazine hydrochloride.

The fact that this hydrochloride was isolated would serve to support the earlier theory advanced regarding the polymerization of chloroacetyl chloride (see page 49). When α-hydroxyacetyl chloride reacts with the chloroacetyl chloride, hydrogen chloride would be evolved.

An attempt was made to prepare 10-chloroacetyl-2-azaphenothiazine using chloroacetic anhydride and chloroacetic acid in dry dioxane. A dark brown solid, m.p. 135-153°C. (decomposition) was isolated from the reaction mixture. This compound was insoluble in water and only slightly sol-

uble in dilute hydrochloric acid. It gave a positive Beilstein test indicating the presence of halogen. Initial attempts to purify and identify this compound were unsuccessful and time did not permit further work with this compound.

(f) Formylation of 10-Methyl-1-Azaphenothiazine

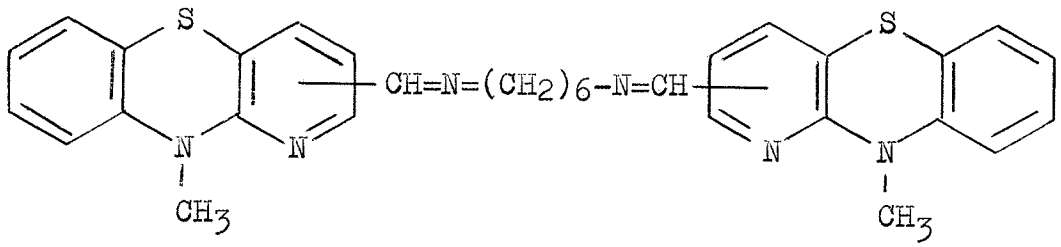
10-Methyl-1-azaphenothiazine (XLVIII) was prepared from 1-azaphenothiazine (III) by the standard sodamide condensation method.

10-Methyl-1-azaphenothiazine was then formylated with N-methylformanilide and phosphorus oxychloride in o-dichlorobenzene (123).

The product was difficult to purify and appeared to deformylate very readily; however, a sample was obtained which had a two degree melting range. Infrared analysis of the formylated 10-methyl-1-azaphenothiazine showed that the formyl group was probably in the 2-, 3- or 4-position of the pyridine ring in the 1-azaphenothiazine nucleus, since the disubstituted benzene pattern was clearly present (indicating the benzene ring was unsubstituted in the 1-azaphenothizzine nucleus). Furthermore, a 1:2:3:4-tetrasubstituted pattern present in the spectra would tend to point to substitution in either the 2- or 4-position of the pyridine ring.

The formyl derivative formed a precipitate with 2:4-dinitrophenylhydrazine and sodium bisulphite, but an oxime could not be obtained.

A preliminary experiment was conducted to form an imine of the type XLIX with hexane diamine; however no identifiable products were obtained.



XLIX

This aspect was not carried further due to a shortage of time.

IV. CONCLUSIONS

The compounds prepared during the course of this study are currently undergoing evaluation as potential therapeutic agents. In addition, similar compounds in the phenothiazine and hexahydrophenothiazine series have been prepared by other workers in this laboratory and it is hoped that some conclusions regarding structure-activity relationships can be drawn.

Several difficulties appeared during the course of this study and some of them have remained unresolved, thus producing some problems for future study.

Currently, further investigation is being carried out regarding the nature of the reaction involving the chloroacetylation of 1-azaphenothiazine in an effort to identify the product and determine a mechanism whereby it was formed.

V. EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Ultraviolet spectra were determined in the stated solvent with a Beckman DU spectrophotometer. Infrared spectra were determined with a Beckman IR-8 instrument, in carbon disulphide solution or in potassium bromide pellets.

Carbon and hydrogen microanalyses were carried out in the School of Pharmacy, using a Coleman Carbon/Hydrogen Analyzer. Carbon and hydrogen microanalyses on very hygroscopic substances and all nitrogen analyses were determined by either Drs. F. and E. Pascher, West Germany, or Geller Laboratories, U.S.A.

Equivalent weight determinations were carried out on a Metrohm E336 Potentiograph.

Refractive indices were determined with a Zeiss refractometer at the stated temperature.

In the purification of materials by column chromatography, aluminium oxide for chromatographic analysis (B.D.H.) was used.

1-Azaphenothiazine (III) (88)

340.5 g. (2.0 moles) of 2-anilinopyridine (XVIII), 80.2 g. (2.5 moles) of sulphur and 24.1 g. of iodine were mixed together and heated to 250°C. (hydrogen sulphide gas evolution began), then to 280°C. for 3 hours and finally for 1 hour at 325 to 330°C. The reaction mixture was distilled at a pressure of 15 to 20 mm. (the still contents heated to 410°C.) for 1 hour. The solid yellow distillate was treated with 140 ml. of concentrated hydrochloric acid in 690 ml. of water at 60°C., filtered hot and placed in the refrigerator overnight. The precipitate which formed was collected, dissolved in hot water and the stirred aqueous solution was slowly made alkaline with ammonium hydroxide. The yellow precipitate of 1-azaphenothiazine was collected, washed well with water and dried. The 1-azaphenothiazine was recrystallized twice from isopropyl alcohol (charcoal) to yield 130.0 g. (49 percent yield based on unconverted 2-anilinopyridine) of product as yellow needles, m.p. 115-116°C., $\epsilon(250.5)$ = 34,500; $\epsilon(334)$ = 5,000 (in 95 percent ethanol).

The acidic aqueous filtrate, from which the 1-azaphenothiazine hydrochloride precipitated, was made alkaline with ammonium hydroxide. The precipitate of 2-anilinopyridine was

collected and dried to yield 114.0 g. as a yellow solid.

10-Dialkylaminoalkyl-1-Azaphenothiazine Derivatives

15 g. (0.075 moles) of 1-azaphenothiazine (III) and 5.9 g. of sodamide were mixed together in 75 ml. of dry toluene. The mixture was warmed gently at first then refluxed, with constant stirring, for 1½ hours. The dark brown semi-solid mixture was cooled to 20 to 25°C. and a solution of 0.10 moles of an appropriate chloroamine in dry toluene (10 ml.) was added dropwise. After the addition was completed, the stirred mixture was allowed to stand at 20 to 25°C. for one-half hour, then heated at 60°C. for one-half hour and finally refluxed for 20 minutes. The reaction mixture was cooled, treated with a mixture of 15 ml. of concentrated hydrochloric acid and 15 ml. of water, made alkaline with sodium hydroxide solution and extracted with ether. The ethereal solution was dried over drierite, the ether and toluene were removed under vacuum and the residue was distilled under reduced pressure.

10-(3-Dimethylaminopropyl)-1-Azaphenothiazine (L) (124, 125, 126,127)

12.2 g. (0.10 moles) of 3-chloro-N:N-dimethyl-propylamine were used. 17.4 g. (84 percent yield) of a red

oil were obtained, b.p. 156-157°C./0.03 mm.; ϵ (252.5) = 24,000, ϵ (323) = 4,000 (in 95 percent ethanol).

A mono-oxalate salt of the amine was prepared by mixing ethereal solutions containing equimolar concentrations of the amine and anhydrous oxalic acid. The yellow precipitate obtained was recrystallized from methanol (charcoal) to yield shiny yellow platelets, m.p. 198.5-199°C. (frothing at the m.p. with decomposition). The melting point reported for this salt in the literature is 200°C.

10-(2-Dimethylaminopropyl)-1-Azaphenothiazine (LI) (124,125, 128,129)

12.2 g. (0.10 moles) of 2-chloro-N:N-dimethylpropylamine were used. 19.5 g. (91 percent yield) of a viscous golden-orange oil were obtained, b.p. 163-164°C./0.03 mm.; ϵ (252.5) = 25,000, ϵ (316) = 4,700 (in 95 percent ethanol).

A monohydrochloride salt was prepared by passing dry hydrogen chloride gas through an ethereal solution of the amine. The yellow precipitate was recrystallized from toluene (charcoal) to yield a white solid, m.p. 213.5-214°C. The melting point reported for this salt in the literature is 213-216°C.

10-(2-Dimethylaminoethyl)-1-Azaphenothiazine (XXXVI) (125,126, 128,129)

10.8 g. (0.10 moles) of 2-chloro-N:N-dimethylethylamine were used. 16.3 g. (80 percent yield) of an orange-red oil were obtained, b.p. 164-165°C./0.05 mm. This oil solidified and the orange solid was recrystallized from petroleum ether (charcoal) to yield yellow platelets, m.p. 67.5-68.5°C.; ϵ(252) = 28,900, ϵ(323) = 4,700 (in 95 percent ethanol).

A monohydrochloride salt was prepared and recrystallized from toluene (charcoal) to yield a cream colored solid, m.p. 196.5-197°C. The melting point reported in the literature for this compound is 195-198°C.

10-(2-Diethylaminoethyl)-1-Azaphenothiazine (LII) (124,125, 128,129)

13.6 g. (0.10 moles) of 2-chloro-N:N-diethylethylamine were used. 19.6 g. (91 percent yield) of a red oil were obtained, b.p. 167-168°C./0.04 mm.; ϵ(252.5) = 25,700, ϵ(323) = 4,300 (in 95 percent ethanol).

A monohydrochloride salt was prepared and recrystallized from benzene (charcoal) to yield a white solid, m.p. 183-184°C. The melting point reported in the literature for this compound is 182-184°C.

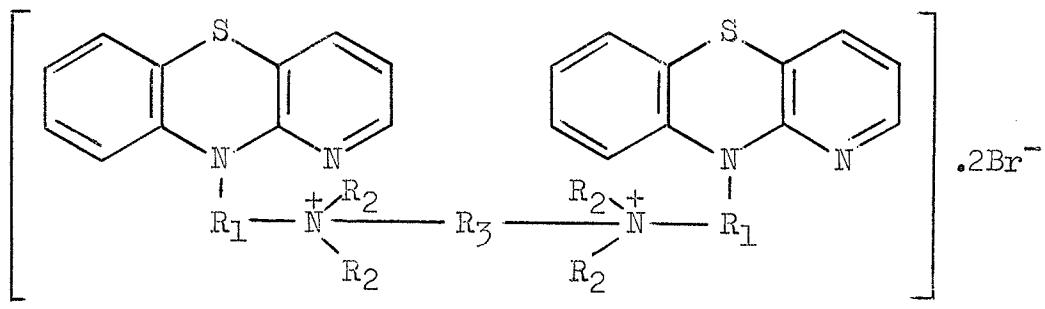
Bis-Quaternary Salts of the 10-Dialkylaminoalkyl-1-Azaphenothiazine Derivatives

A 3 mole proportion of the amine was heated with 1 mole of the α:ω-dibromo compound on a boiling water bath and swirled to ensure thorough mixing. The heating was continued for an hour. The mixture was then cooled, powdered and extracted with dry ether. The hygroscopic bis-quaternary compounds were dried and kept in a vacuum desiccator. Table I lists the physical properties and analysis data for the compounds prepared.

TABLE I

Physical Properties and Microanalysis Data for the

Bis-Quaternary Salts of 10-Dialkylaminoalkyl-1-azaphenothiazines



GENERAL STRUCTURE

Compound No.	R_1	R_2	R_3	Color	Sinter Point (°C.)	Melting Point (°C.)	Analysis Theoretical % C	% H	% N	Found % C	% H	% N
LIII	A	CH_3	a	Bright yellow	176	245-8	53.22	5.41	11.29			
LIV	A	CH_3	b	Bright yellow	72	130-3	54.41	5.74	10.88	53.70	5.26	10.12
LV	A	CH_3	c	Bright yellow	171	252-5	56.99	6.46	9.97	57.10	6.37	9.11
LVI	B	CH_3	a	Golden	67	98-100	54.41	5.74	10.88	54.05	5.41	10.45
LVII	B	CH_3	b	Bright yellow	66	105-7	55.50	6.04	10.50	53.33*	5.65	10.04
LVIII	B	CH_3	c	Orange-yellow	64	90-5	57.92	6.71	9.65	57.92	6.71	9.30
LIX	C	CH_3	a	Canary yellow	96	167-71	54.41	5.74	10.88	53.93	5.01	10.00
LX	C	CH_3	b	Bright yellow	80	124-6	55.50	6.04	10.50			
LXI	C	CH_3	c	Canary yellow	88	140-3	57.91	6.71	9.65	57.76	6.37	9.02
LXII	A	C_2H_5	a	Yellow	108	Inde-finite	55.49	6.04	10.50			
LXIII	A	C_2H_5	b	Yellow	120	Inde-finite	56.55	6.33	10.14			
LXIX	A	CH_3	d	Canary yellow	82	Inde-finite	52.78	5.60	12.68	52.43	5.95	11.97
LXX	B	CH_3	d	Orange yellow	67	Inde-finite	53.93	5.91	12.23	53.68	6.14	11.45
LXXI	C	CH_3	d	Yellow	81	Inde-finite	53.93	5.91	12.23	50.87*	6.18	11.75

* The low value cannot be accounted for.

A = $-CH_2-CH_2-$

B = $-CH_2-CH_2-CH_2-$

C = $-CH_2-\underset{\displaystyle CH_3}{\underset{|}{CH}}-$

a = $-(CH_2)_3-$

b = $-(CH_2)_5-$

c = $-(CH_2)_{10}-$

d = $-CH_2-CH_2-\underset{\displaystyle H}{\underset{|}{N}}-CH_2-CH_2-$

Nomenclature of the Bis-Quaternary Salts of 10-Dialkylaminoalkyl-1-Azaphenothiazine

LIII: Trimethylene bis[2-(1-azaphenothiazin-10-yl)ethyl] dimethylammonium bromide.

LIV: Pentamethylene bis[2-(1-azaphenothiazin-10-yl)ethyl] dimethylammonium bromide.

LV: Decamethylene bis[2-(1-azaphenothiazin-10-yl)ethyl] dimethylammonium bromide.

LVI: Trimethylene bis[3-(1-azaphenothiazin-10-yl)propyl] dimethylammonium bromide.

LVII: Pentamethylene bis[3-(1-azaphenothiazin-10-yl)propyl] dimethylammonium bromide.

LVIII: Decamethylene bis[3-(1-azaphenothiazin-10-yl)propyl] dimethylammonium bromide.

LIX: Trimethylene bis[2-(1-azaphenothiazin-10-yl)-1-methylethyl]dimethylammonium bromide.

LX: Pentamethylene bis[2-(1-azaphenothiazin-10-yl)-1-methylethyl]dimethylammonium bromide.

LXI: Decamethylene bis[2-(1-azaphenothiazin-10-yl)-1-methylethyl]dimethylammonium bromide.

LXII: Trimethylene bis[2-(1-azaphenothiazin-10-yl)ethyl] diethylammonium bromide.

LXIII: Pentamethylene bis[2-(1-azaphenothiazin-10-yl)ethyl] diethylammonium bromide.

LXIX: Diethylamine 2,2'-bis[2-(1-azaphenothiazin-10-yl) ethyl]dimethylammonium bromide.

LXX: Diethylamine 2,2'-bis[3-(1-azaphenothiazin-10-yl) propyl]dimethylammonium bromide.

LXXI: Diethylamine 2,2'-bis[2-(1-azaphenothiazin-10-yl)-1-methylethyl]dimethylammonium bromide.

o-Bromothiophenol (XXIII) (105)

150 g. (0.87 moles) of o-bromoaniline were added to a mixture of 155 ml. of concentrated hydrochloric acid in 550 ml. of water and the stirred suspension was diazotized at 0°C. by the dropwise addition of 62 g. (0.90 moles) of sodium nitrite in 220 ml. of water. The orange diazonium solution was then added carefully beneath the surface (by means of a long stemmed funnel) of a stirred solution of 240 g. of potassium xanthogenate (potassium ethyl xanthate) in 440 ml. of water at 70 to 80°C. Heating was continued for 1 hour after the addition was completed. The mixture was cooled and the red oil which separated was washed first with dilute sodium hydroxide solution then with water. The oil was added slowly to a refluxing mixture of 266 g. of potassium hydroxide in 200 ml. of water and 600 ml. of 95 percent ethanol. The mixture was refluxed for 21 hours, cooled, poured into ice water and made acidic with concentrated hydrochloric acid. The

brown oil which separated was collected, washed with water, dried over drierite and distilled under reduced pressure to yield 133.3 g. (81 percent) as a pale yellow oil, b.p. 114-116°C./18 mm., $n_D^{24.5} = 1.6319$.

A small sample of the o-bromothiophenol was fractionally distilled to yield a colorless oil, b.p. 112°C./17 mm., $n_D^{24.5} = 1.6328$. Saggiomo et al. (105) reported an 80 percent yield of a pale oil, $n_D^{28} = 1.6298$.

4-Hydroxy-3-nitropyridine (105,106,107)

100 g. (1.05 moles) of 4-(1H)pyridone were added slowly to a mixture of 341 g. of fuming nitric acid (96 percent) and 341 g. of fuming sulphuric acid (20 percent oleum) with stirring. The mixture was warmed gently at first, then boiled for 1 hour. The mixture was cooled, poured into 1250 ml. of water and partially neutralized with ammonium hydroxide solution. The yellow precipitate which formed was collected, washed with water and dried to yield 124 g. (84 percent) of 4-hydroxy-3-nitropyridine as a pale yellow solid, m.p. 278-280°C. (recrystallized from aqueous ethanol).

A small sample was recrystallized from toluene (charcoal) to yield fine white needles, m.p. 278.5-279°C. The melting point reported in the literature is 278-279°C. (106).

4-Chloro-3-nitropyridine (XXIV) (105,106,107)

An intimate mixture of 60 g. (0.43 moles) of 4-hydroxy-3-nitropyridine, 90 g. of phosphorus pentachloride and 6 g. of phosphorus oxychloride was heated for 3 hours at 130°C. to ensure gentle boiling. The temperature was then raised to 165°C. and maintained there for 1 hour under a rapid stream of nitrogen. The mixture was distilled under reduced pressure to yield 55.5 g. (84 percent yield) of 4-chloro-3-nitropyridine (XXIV) as a yellow oil, b.p. 121-123°C./16 mm. On cooling, a yellow solid, m.p. 42-45°C. was obtained. The melting point reported in the literature is 45°C. (106).

4-(2-Bromophenylthio)-3-nitropyridine (XXV) (102,104,105)

55 g. (0.35 moles) of 4-chloro-3-nitropyridine in 840 ml. of 95 percent ethanol were added to a stirred solution of 66 g. (0.35 moles) of o-bromothiophenol and 13.8 g. of sodium hydroxide in 400 ml. of water. The mixture was heated under reflux for 10 minutes and allowed to stand in the refrigerator overnight. The precipitate which formed was collected, washed with water and dried to yield 100 g. (92 percent) of product as golden needles, m.p. 96-99°C.

A small sample was recrystallized from 95 percent ethanol (charcoal) to yield shiny yellow needles, m.p.

100-101°C. The melting point reported in the literature is 101.5-102.5°C. (105).

4-(2-Bromophenylthio)-3-aminopyridine (XXVI) (102,104,105)

105 g. (0.34 moles) of 4-(2-bromophenylthio)-3-nitropyridine in 1700 ml. of 95 percent ethanol were refluxed for 4 hours with 354 g. of stannous chloride dihydrate and 1100 ml. of concentrated hydrochloric acid. The mixture was cooled slightly, slowly made alkaline with a concentrated solution of sodium hydroxide, cooled and extracted with ether. The ethereal solution was washed with a small quantity of water, dried over anhydrous sodium sulphate and evaporated to dryness under vacuum. The tan-colored solid residue was dried and recrystallized from aqueous ethanol (charcoal) to yield a solid, m.p. 94-96°C.

A small sample was recrystallized once more from aqueous ethanol (charcoal) to yield fine, light beige needles, m.p. 95-96°C. The melting point reported in the literature is 96-97°C. (105).

2-Azaphenothiazine (IV) (105,106,107)

84 g. (0.30 moles) of 4-(2-bromophenylthio)-3-aminopyridine were refluxed for 25 hours with 48 g. of anhydrous potassium carbonate and 8.4 g. of copper powder in 590 ml.

of N:N-dimethylformamide. The dark colored mixture was cooled, filtered to remove the copper powder and poured into 2 l. of cold water. The lime green precipitate was collected and dried to yield 55 g. of a solid. This solid was boiled with 150 ml. of benzene and filtered hot. The undissolved residue was recrystallized several times from benzene (charcoal) to yield 27 g. of 2-azaphenothiazine (IV) as shiny yellow platelets, m.p. 165-166°C., $\epsilon(262) = 34,600$, $\epsilon(323) = 4,200$ (in 95 percent ethanol).

The benzene was removed from the combined filtrates, leaving a black tarry mass. This mass was distilled under reduced pressure to yield 13 g. of a dark red oil, b.p. 208-215°C./0.09 mm., which solidified to form an orange solid. This solid was extracted with chloroform leaving a bright orange insoluble solid. The chloroform was removed from the extract and the solid residue was recrystallized from benzene (charcoal) to yield a further 6 g. of 2-azaphenothiazine (IV), m.p. 165-166°C. The total yield of pure 2-azaphenothiazine was 33 g. (55 percent).

2-Azaphenothiazine monohydrochloride

0.5 g. of 2-azaphenothiazine was dissolved in dilute hydrochloric acid to form a red solution. This solution was allowed to stand for 1 hour then the precipitated orange solid was collected, dried and washed well with benzene. The

salt had an indefinite melting point at approximately 268°C. (decomposition); ϵ(262) = 32,500, ϵ(321.5) = 4,100 (in 95 percent ethanol).

Calculated for $C_{11}H_9ClN_2S$: C, 55.81; H, 3.83.
Found: C, 55.94; H, 4.12.

2-Azaphenothiazine Methyl Iodide

2 g. of 2-azaphenothiazine were dissolved in 100 ml. of benzene and 2 g. of methyl iodide were added. The solution was allowed to stand for 2 days and the orange precipitate which formed was collected and washed with benzene. 2-Azaphenothiazine methyl iodide is a bright orange solid, m.p. 221-225°C. (decomposition); ϵ(243) = 21,500, ϵ(287) = 22,300.

Calculated for $C_{12}H_{11}IN_2S$: C, 42.11; H, 3.24
Found: C, 41.87; H, 3.47.

10-(3-Dimethylaminopropyl)-2-Azaphenothiazine (LXXII) (125, 130)

15 g. (0.075 moles) of 2-azaphenothiazine and 5.9 g. (0.15 moles) of sodamide were refluxed with constant stirring for 1½ hours in 75 ml. of dry toluene. The copper colored mixture was cooled to 20 to 25°C. and 12.2 g. (0.10 moles) of 3-chloro-N:N-dimethylpropylamine in 10 ml. of dry toluene

were added dropwise with constant stirring. The mixture was allowed to stand at 20 to 25°C. for one-half hour. It was then heated to 60°C. for a further half hour, and finally, refluxed for 20 minutes. The reaction mixture was cooled, treated with a mixture of 15 ml. of concentrated hydrochloric acid and 15 ml. of water, made alkaline with sodium hydroxide solution and extracted with ether. The ethereal solution was dried over drierite and the ether and toluene were removed under vacuum. The residue was fractionally distilled under reduced pressure to yield 15.8 g. (74 percent) of a yellow oil, b.p. 164-166°C./0.02 mm.

A mono-oxalate salt of the amine was prepared by mixing with an equimolar concentration of anhydrous oxalic acid in ether. The precipitate was collected, washed well with ether and dried to yield a yellow solid, m.p. 158-159°C. (decomposition). The melting point reported in the literature is 158-159°C.

10-(2-Dimethylaminopropyl)-2-Azaphenothiazine (LXXIII) (125, 130)

This compound was prepared exactly as described above for 10-(3-dimethylaminopropyl)-2-azaphenothiazine. 12.2 g. (0.10 moles) of 2-chloro-N:N-dimethylpropylamine were used and 15.25 g. (70 percent yield) of a very viscous yellow oil were obtained, b.p. 172-174°C./0.05 mm.

A cream colored mono-oxalate was prepared as before, m.p. 192.5-193°C. (decomposition) with frothing at the melting point. The monohydrochloride salt was also prepared but it was too hygroscopic for characterisation purposes.

A monopicrate derivative was prepared by mixing 0.5 g. of the amine dissolved in 95 percent ethanol with an equimolar concentration of picric acid in ethanol. The precipitate was collected and dried to yield a golden solid, m.p. 173-173.5°C. (decomposition). The melting point reported in the literature is 175°C.

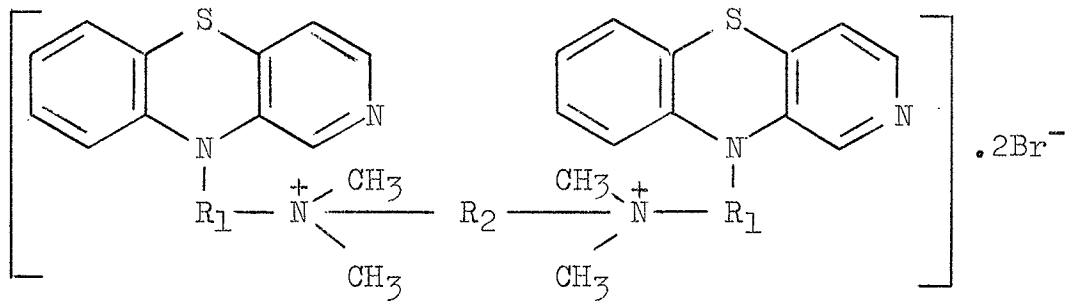
Bis-Quaternary Salts of the 10-Dialkylaminoalkyl-2-Azaphenothiazine Derivatives

1 g. (0.0035 moles) of the 10-dialkylaminoalkyl-2-azaphenothiazine derivative was mixed well with 0.0012 moles of an appropriate $\alpha:\omega$-dibromo compound. The mixture was heated on a boiling water bath for 1 hour, the solid orange mass was removed from the reaction flask, powdered and washed well with dry ether. Table II lists the compounds prepared in this way, with melting point and microanalyses data.

TABLE II

Physical Properties and Microanalysis Data for the

Bis-Quaternary Salts of 10-Dialkylaminoalkyl-2-azaphenothiazines



GENERAL STRUCTURE

Compound No.*	R_1	R_2	Sinter Point (°C.)**	Analysis Theoretical % C	% H	% N	Found % C	% H	% N
LXXIV	$-CH_2-CH_2-CH_2-$	a	115	54.39	5.74	10.88	47.46	5.52	8.76
LXXV	$-CH_2-CH_2-CH_2-$	b	111	55.49	6.04	10.50	49.29	6.15	8.13
LXXVI	$-CH_2-CH_2-CH_2-$	c	90	57.91	6.71	9.65	56.14 57.57	6.93 6.60	7.78 8.87***
LXXVII	$-CH_2-CH_2-CH_2-$	d	58	53.93	5.91	12.23	46.37	5.51	10.68
LXXVIII	$-CH_2-CH-$ CH_3	a	118	54.39	5.74	10.88	49.96	6.04	9.60
LXXIX	$-CH_2-CH-$ CH_3	b	97	55.49	6.04	10.50	55.80	6.35	10.49
LXXX	$-CH_2-CH-$ CH_3	c	86	57.91	6.71	9.65	58.77	6.96	10.64
LXXXI	$-CH_2-CH-$ CH_3	d	127	53.93	5.91	12.23	49.37	5.86	11.03

* All the compounds were orange in color.

** These compounds sinter, gradually go gummy and slowly melt with frothing and decomposition.

*** After remaking by the modified mixing technique.

a = $-(CH_2)_3-$

b = $-(CH_2)_5-$

c = $-(CH_2)_{10}-$

d = $-CH_2-CH_2-\underset{H}{N}-CH_2-CH_2-$

The calculated values for the monoquaternary derivatives are as follows:

Compounds LXXIV and LXXVIII: C, 46.83; H, 5.17; N, 8.62.

Compounds LXXV and LXXIX: C, 48.93; H, 5.67; N, 8.15.

Compounds LXXVI and LXXX: C, 53.33; H, 6.71; N, 7.18.

Compounds LXXVII and LXXXI: C, 46.51; H, 5.46; N, 10.85.

Nomenclature of the bis-quaternary salts of 10-dialkylaminoalkyl-2-azaphenothiazines

LXXIV: Trimethylene bis[2-(2-azaphenothiazin-10-yl) ethyl]dimethylammonium bromide.

LXXV: Pentamethylene bis[2-(2-azaphenothiazin-10-yl) ethyl]dimethylammonium bromide.

LXXVI: Decamethylene bis[2-(2-azaphenothiazin-10-yl) ethyl]dimethylammonium bromide.

LXXVII: Diethylamine 2,2'-bis[3-(2-azaphenothiazin-10-yl) propyl]dimethylammonium bromide.

LXXVIII: Trimethylene bis[2-(2-azaphenothiazin-10-yl)-1-methylethyl]dimethylammonium bromide.

LXXIX: Pentamethylene bis[2-(2-azaphenothiazin-10-yl)-1-methylethyl]dimethylammonium bromide.

LXXX: Decamethylene bis[2-(2-azaphenothiazin-10-yl)-1-methylethyl]dimethylammonium bromide.

LXXXI: Diethylamine 2,2'-bis[2-(2-azaphenothiazin-10-yl) -1-methylethyl]dimethylammonium bromide.

"10-Chloroacetyl-1-azaphenothiazine" (LXXXII)

50 g. (0.25 moles) of 1-azaphenothiazine, 54 g. (0.32 moles) of chloroacetic anhydride and 75 g. (0.79 moles) of chloroacetic acid were refluxed for 1 hour, with constant

stirring, in 250 ml. of dry dioxane. The hot mixture was poured into 1 l. of hot water and filtered. The precipitate was washed with hot ethanol until the washings were colorless then dried to yield 43 g. (63 percent) of a fine fluffy yellow-green solid, m.p. 275-277°C. (decomposition).

A small sample was prepared for analysis by recrystallization several times from glacial acetic acid (charcoal) to yield fine pale yellow fluffy needles, m.p. 276-277°C. (with decomposition - gradually darkening before the melting point).

Calculated for $C_{15}H_9ClN_2O_2S$:	C, 56.87;	H, 2.86;	N, 8.85.
Calculated for $C_{13}H_9ClN_2OS$:	C, 56.42;	H, 3.28;	N, 10.12.
Found:	C, 56.99;	H, 3.18;	N, 8.60.

Hydrolysis of "10-Chloroacetyl-1-azaphenothiazine"

2 g. of "10-chloroacetyl-1-azaphenothiazine" were added to a mixture of 5 ml. concentrated hydrochloric acid and 15 ml. glacial acetic acid and refluxed for fifteen minutes. The reaction mixture was basified and the precipitated solid was filtered off. Recrystallization from alcohol yielded a buff colored solid, m.p. 198-199°C. The average yield was approximately 50 percent.

Calculated for $C_{13}H_8N_2OS$:	C, 64.97;	H, 3.35;	N, 11.65.
Found:	C, 64.71;	H, 3.62;	N, 11.05.

"10-(Piperidinoacetyl)-1-azaphenothiazine" (LXXXIII)

20 g. (0.072 moles) of "10-chloroacetyl-1-azaphenothiazine" and 18.8 g. (0.22 moles) of piperidine were heated, with constant stirring, on a boiling water bath for 1 hour in 200 ml. of N:N-dimethylformamide. The dark brown mixture was cooled overnight in the refrigerator and filtered. The precipitate was washed with water and the filtrate was poured into 1 l. of water, basified with sodium carbonate and filtered. The solid collected was recrystallized several times from isopropyl alcohol (charcoal) to yield 18 g. (77 percent) of small yellow needles, m.p. 177-179°C. (decomposition). See Table III for analysis data.

"10-(Piperidinoacetyl)-1-azaphenothiazine" mono-oxalate (LXXXIV)

0.5 g. of the amine was dissolved in 150 ml. of hot dry benzene and an equimolar concentration of anhydrous oxalic acid in dry benzene was added. The solution was allowed to cool and the salt precipitated out as a yellow solid, m.p. 232.5-233°C. (decomposition) with frothing at the melting point.

Calculated for $C_{22}H_{21}O_6N_3S$:	C, 58.00;	H, 4.65.
Found:	C, 57.57;	H, 4.95.

"10-(Piperidinoacetyl)-1-azaphenothiazine" methyl iodide (LXXXV)

0.5 g. of the amine was dissolved in 150 ml. of dry benzene, an equimolar concentration of methyl iodide was added and the mixture was allowed to stand overnight. The precipitate which formed was collected and dried to yield a yellow solid, m.p. 229.5-230°C. (decomposition).

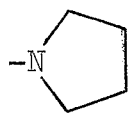
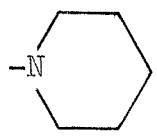
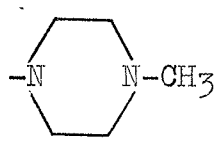
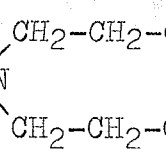
"10-(Piperidinoacetyl)-1-azaphenothiazine" monohydrochloride (LXXXVI)

Dry hydrogen chloride gas was passed through a benzene solution of the amine. The precipitate was washed with hot isopropyl alcohol and dried to yield a buff colored solid of indefinite melting point. No suitable solvent was found for recrystallization. The salt was also slightly hygroscopic and it was not therefore suitable for analysis.

Four more similar aminoacetyl derivatives were prepared using the above method. These are listed in Table III along with details of the preparation and the analysis results.

TABLE III

"10-Substitutedaminoacetyl-1-azaphenothiazines"

Compound No.	R	m.p. (°C.)	% Yield	Reaction Temp. (°C.)	Heating Time (Hrs.)	Recrystallization Solvents	Analysis** Theoretical % C	% H	% N	Found % C	% H	% N
LXXXVIII	-Cl	276-7*	63	153	1	Glacial acetic acid	56.89	2.86	8.85	56.99	3.18	8.60
LXXXIX		173-5*	72	100	1	Isopropyl alcohol	64.94	4.88	11.96	65.00	5.48	11.85
LXXXIII		177-9*	77	100	1	Isopropyl alcohol	65.73	5.24	11.50	65.57	5.54	10.91
XC		228-30*	70	125	2	N,N-Dimethylformamide	63.14	5.30	14.73	63.11	5.55	14.40
XCI		127-9*	15	100	40	Ether/ Ether	64.57	5.42	11.90	64.72	5.67	10.91
XCII		132-4*	67	100	1	Isopropyl alcohol	66.10	6.08	11.02	64.89	5.92	10.83

* Decomposition.

** All the calculated values are based on the expected formula plus C_2O (see page 50).

Compound No.	LXXXIX	LXXXIII	XC	XCI	XCII
m.p. of monooxalate derivative (°C.)	225-225.5° (decomposition) frothing at m.p.	232.5-233° (decomposition) frothing at m.p.		212-212.5° (decomposition) frothing at m.p.	215-215.5° (decomposition) frothing at m.p.
m.p. of methyl iodide derivative	222.5-230° (decomposition)	212-212.5° (decomposition)	230-230.5° (decomposition)		192.5-193° (decomposition)

All the methyl iodides were formed by dissolving 0.5 g. of the tertriary amine in 200 ml. of benzene, adding a molar equivalent of methyl iodide and allowing the mixture to stand overnight. The yellow precipitates were collected, washed with benzene and dried. All the methyl iodide derivatives gradually darkened before the melting point.

Bis-quaternary salts of the "10-substitutedaminoacetyl-1-azaphenothiazine" derivatives

3 moles of the substitutedaminoacetyl derivative were mixed with 1 mole of α:ω-dibromoalkane in 25 ml. of chloroform. The mixture was refluxed for one hour then the chloroform was slowly removed by evaporation. The residue was heated on a water bath under reduced pressure to remove the last traces of solvent and the solid residue was powdered and extracted with hot benzene.

The compounds prepared in this manner are listed in Table IV.

TABLE IV

Bisquaternary Salts of "10-Substitutedaminoacetyl-1-azaphenothiazines"

Compound No.	Starting Compound	Dibromo-alkane	Sintering Point (°C.)*	Melting Point (°C.)	Analysis Theoretical** % C	% H	% N	Found % C	% H	% N
XCIII	LXXXIX	a	215	217-9(d.)	54.42	4.46	9.29	53.56	4.51	8.94
XCIV	LXXXIX	b	224	236-7(d.)	55.36	4.75	9.01	54.27	5.20	9.20
XCV	LXXXIX	c	207	210-12(d.)	57.48	5.43	8.38	57.23	5.98	8.24
XCVI	LXXXIX	d	234	indefinite	54.02	4.64	10.50	52.63	4.34	
XCVII	LXXXIII	a	206	213-6(d.)	55.36	4.75	9.01	53.82	4.60	
XCVIII	LXXXIII	b	207	210-12(d.)	56.25	5.04	8.75			
XCIX	LXXXIII	c	193	205-8(d.)	58.24	5.67	8.15	57.48	5.09	
C	LXXXIII	d	245	indefinite	54.94	4.93	10.20	53.56	4.52	9.27
CI	XC	a	207	210-13(d.)	53.64	4.82	11.64			
CII	XC	b	197	204-6(d.)	54.54	5.09	11.31	54.16	5.23	
CIII	XC	c	203	217-20(d.)	56.60	5.70	10.56	54.37	5.80	
CIV	XC	d	195	indefinite	53.28	4.98	12.71	50.42	4.89	

* All compounds gradually darken in color before sintering, slowly turn black and froth at the melting point.

** All the calculated analysis figures are based on the expected structure (CV) below plus C_2O on each azaphenothiazine unit.

LXXXIX = "10-Pyrrolidinoacetyl-1-azaphenothiazine"

LXXXIII = "10-Piperidinoacetyl-1-azaphenothiazine"

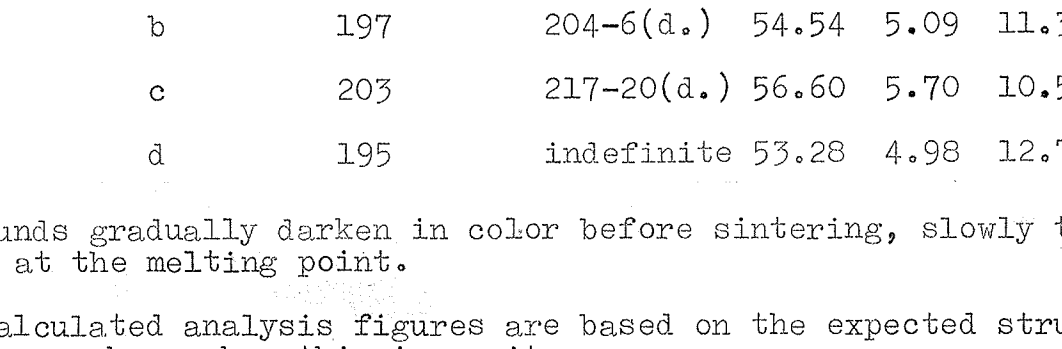
XC = "10-(4-methylpiperazinoacetyl)-1-azaphenothiazine"

a = 1,3-Dibromopropane

b = 1,5-Dibromopentane

c = 1,10-Dibromodecane

d = 2,2'-Dibromodiethylamine



EXPECTED GENERAL STRUCTURE CV

Q = Pyrrolidine, piperidine, N-methylpiperazine

R = $-(CH_2)_3-$, $-(CH_2)_5-$, $-(CH_2)_{10}-$, $-CH_2CH_2NHCH_2CH_2-$

2-(2-Bromophenylthio)-3-nitropyridine (102,104)

100 g. (0.63 moles) of 2-chloro-3-nitropyridine in 1500 ml. of 95 percent ethanol were added to a stirred solution of 120 g. (0.64 moles) of o-bromothiophenol and 25 g. of sodium hydroxide in 700 ml. of water. The mixture was refluxed for 10 minutes and allowed to stand overnight in the refrigerator. The yellow precipitate which formed was collected and dried to yield 186.5 g. (95 percent) of small golden platelets, m.p. 115-116°C.

A small sample was recrystallized from 95 percent ethanol (charcoal) to yield small yellow platelets, m.p. 115.5-116°C. The melting point reported in the literature is 116°C. (102).

2-(2-Bromophenylthio)-3-aminopyridine (102,104)

93 g. (0.30 moles) of 2-(2-bromophenylthio)-3-nitropyridine and 305 g. of stannous chloride dihydrate were refluxed for 4 hours in a mixture of 1450 ml. of 95 percent ethanol and 1 l. of concentrated hydrochloric acid. The mixture was cooled slightly and slowly made alkaline with a concentrated solution of sodium hydroxide. The alkaline solution was cooled and extracted with ether. The ethereal solution was washed with a small amount of water, dried over anhydrous sodium sulphate and evaporated to dryness under reduced

pressure. The tan solid residue was powdered and dried to yield 80 g. (95 percent) of 2-(2-bromophenylthio)-3-amino-pyridine, m.p. 68-78°C. The solid was dissolved in the minimum amount of hot ether, treated with charcoal and filtered. Petroleum ether was added to the cloud point and the solution was then allowed to stand overnight in the refrigerator. The precipitate was collected and dried to yield a light brown solid, m.p. 80-87°C.

A small sample was recrystallized several times from an ether/petroleum ether mixture (charcoal) to yield a pale yellow solid, m.p. 87-91°C. The melting point reported in the literature is 93°C. (102).

4-Azaphenothiazine (102,104)

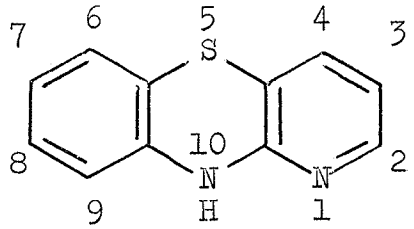
94 g. (0.33 moles) of 2-(2-bromophenylthio)-3-amino-pyridine, 96 g. of anhydrous potassium carbonate and 10 g. of copper powder were refluxed for 18 hours with constant stirring in 700 ml. of N,N-dimethylformamide. The black mixture was cooled, filtered (to remove the copper powder) and poured into 2 liters of water. The precipitate which formed was collected, extracted with small amounts of hot benzene to remove the bulk of the impurity and the undissolved residue was recrystallized several times from chlorobenzene (charcoal) to yield 1.5 g. of 4-azaphenothiazine as a yellow solid, m.p. 241-242°C.

APPENDIX I

NOMENCLATURE

There are four possible monoazaphenothiazines and they are called 1-, 2-, 3- and 4-azaphenothiazine depending upon the manner of fusion of the pyridine ring to the benzothiazine nucleus.

There is some confusion in the literature as to the numbering of the azaphenothiazine nucleus and thus 1-azaphenothiazine is sometimes called 4-azaphenothiazine and vice versa; there is similar confusion with 2- and 3-azaphenothiazine. The numbering system which will be used throughout this paper is shown below (105):

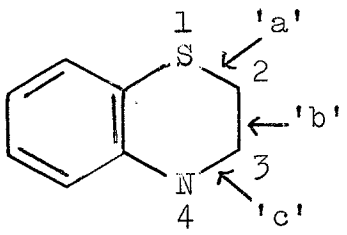


This numbering is identical with that of phenothiazine and permits ready comparison of the two series.

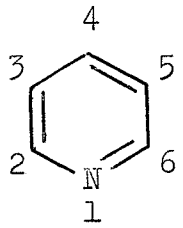
Systematically, the azaphenothiazines are named as pyrido derivatives of benzothiazine.

The Butterworth's publication on the international union of pure and applied chemistry nomenclature rules states that (131):

"Isomers are distinguished by lettering the peripheral sides of the base component, a, b, c, etc., beginning with 'a' for the side '1,2', 'b' for the side '2,3', and lettering every side around the periphery. To the letter, as early in the alphabet as possible, denoting the side where fusion occurs are prefixed, if necessary, the numbers of the position of attachment of the other component. These letters are chosen to be as low as consistent with the numbering of the component, and their order conforms to the direction of lettering of the base component. The numbers and letters are enclosed in square brackets and placed immediately after the designation of the attached component. This expression merely defines the manner of fusion of the components."



Benzothiazine



Pyridine

The systematic name for 1-azaphenothiazine is 10H-pyrido-[3,2-b][1,4]-benzothiazine.

The systematic name for 2-azaphenothiazine is 10H-pyrido-[4,3-b][1,4]-benzothiazine.

The systematic name for 3-azaphenothiazine is 5H-pyrido-[3,4-b][1,4]-benzothiazine.

The systematic name for 4-azaphenothiazine is 5H-pyrido-[2,3-b][1,4]-benzothiazine.

The Butterworth's publication (132) also states that, "when a name applies equally to two or more isomeric condensed parent ring systems with the maximum number of noncumulative double bonds and when a name can be made specific by indicating the position of one or more atoms in the structure, this is accomplished by modifying the name of a locant, followed by italic capital 'H' for each of these hydrogen atoms. Such symbols ordinarily precede the name. The said atom or atoms are called 'indicated hydrogen'."

Another method by which these compounds can be named is the I.U.P.A.C. "a" nomenclature (or replacement nomenclature). Thus, 1-azaphenothiazine could be named 10-thia-1:9-diaza-anthracene.

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