September 22, 1958

To the Graduate Council:

I am submitting herewith a dissertation written by William Earl Tatum entitled "Synthesis of 7-(Dialkylaminoalkyl)-benzo[c]phenothiazines; The Metalation of 7H-Benzo[c]phenothiazine With n-Butyllithium." I recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

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SYNTHESIS OF 7-(DIALKYLAMINOALKYL)-BENZO [c] PHENOTHIAZINES; THE METALATION OF 7H-BENZO [c] PHENOTHIAZINE WITH n-BUTYLLITHIUM

A DISSERTATION

Submitted to
The Graduate Council
of
The University of Tennessee
in
Partial Fulfillment of the Requirements
for the Degree of
Doctor of Philosophy

---

by

William Earl Tatum

December, 1958

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To Pat, Judy, David, and Greg

422831

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The author wishes to express his sincerest gratitude to Dr. David A. Shirley for his encouragement and counsel during the course of the research. Thanks are due the National Institute of Mental Health and the Eli Lilly Company, not only for financial support of this investigation, but also for pharmacological evaluation of the new compounds produced. Appreciation is also expressed to Dr. W. H. Fletcher for instruction in operation of the infrared spectrophotometer.

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CHAPTER I

INTRODUCTION

Phenothiazine is one of the more widely investigated heterocyclic molecules known to modern chemistry. The founding of the synthetic dye industry in the latter part of the nineteenth century stimulated many new fields of organic research, one of which was phenothiazine chemistry. Bernthsen, known as the father of phenothiazine chemistry, first synthesized (1) this compound in 1883, after suspecting its presence in the nucleus of the methylene blue dyes.

Since that time phenothiazine and its derivatives have found uses as antioxidants (2), antihistamines (3), antiemetics (4), and in the treatment of Parkinson's disease (5). During the past decade, considerable attention has been given to N-(dialkylaminoalkyl)-phenothiazine types because of their excellent effect in suppressing nausea (4) and in the treatment of neuropsychiatric disorders (6). More recently, the tranquilizing activity of certain N-(dialkylaminoalkyl)-phenothiazine types has been reported (7). Thus, the pharmacological usefulness of phenothiazine derivatives is well-established.

On the other hand, the known chemistry of the benzophenothiazines is quite limited. Vast opportunity exists for chemotherapeutic investigations in this area, and only recently some penetration into this field of endeavor was begun. In 1942, it was (8) demonstrated that tumor growth inhibition occurred with some simple benzophenothiazine types. Talukdar and Shirley (9) recently prepared a series of 12-(dialkylamino-

alkyl)-benzo [a] phenothiazines for pharmacological evaluation, but the results of these tests are not yet available.

In view of such a wide spectrum of pharmacological application enjoyed by phenothiazine and its derivatives, and the opportunity for chemotherapeutic investigation in the field of benzophenothiazine chemistry, it is felt that benzophenothiazines structurally related to some of the more useful phenothiazine types should be synthesized and pharmacologically evaluated. This research is primarily concerned with the preparation of 7-(dialkylaminoalkyl)-benzo [c] phenothiazines, compounds similar in structure to the therapeutically useful phenothiazine types.

In connection with the synthesis of these N-alkylated benzophenothiazines, there was considerable interest in finding new and better methods of introducing substituents into the lesser accessible positions of the benzophenothiazine nucleus. In an effort to do this, a study of the metalation of 7H-benzo [c] phenothiazine with n-butyllithium was undertaken.

The compounds prepared in this investigation are currently being tested by the Eli Lilly Company of Indianapolis, Indiana, for central nervous system effects and by the National Cancer Institute for anticancer activity. It is hoped that the results of this research will in some way benefit the extensive program now being conducted for the development of new and more useful drugs.

CHAPTER II

HISTORICAL

A. Chemotherapeutic History of the Phenothiazines

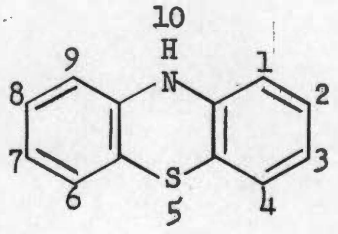
1. Introduction

One of the most interesting phases of scientific endeavor conducted during the past century has been the search for new and more useful drugs. In recent years, phenothiazine and its derivatives have made a large contribution to this effort since many important medical uses of this series of compounds have been discovered. It was the many pharmacological applications of compounds belonging to the phenothiazine series that stimulated the work described in this dissertation. However, it is not the purpose of the following discussion to present a detailed and complete review of the physiological properties of phenothiazine and its derivatives, but rather to provide a background of the more significant phenothiazine drugs which are structurally related to the type of compounds prepared in this investigation.

It is significant to note at this point that in 1944, Gilman and Shirley (10) prepared a series of N-(dialkylaminoalkyl)-phenothiazines for biological evaluation as antimalarials, but the compounds were found to be ineffective in this respect. In 1946, Halpern (3) tested these and similar N-alkylated derivatives and found them to be very good antihistamines. It was primarily this discovery that initiated extensive chemotherapeutic study of phenothiazine derivatives.

2. Phenothiazine

The numbering system for phenothiazine, as used by Chemical Abstracts, is shown in II-1. An excellent review on the chemistry



II-1

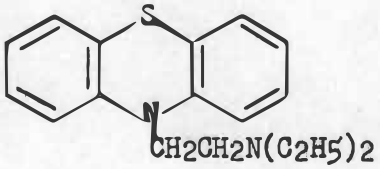
of phenothiazine has been given by Massie (11). Phenothiazine's role as the parent compound of the thiazine dyes has already been mentioned in Chapter I. It was not, however, until 1934 that phenothiazine was first employed biologically, when Campbell, Sullivan, Smith, and Haller (12) found that it had a lethal action on the larvae of culicine mosquitos. Findlay (13) has given an excellent review of the use of phenothiazine as an anthelmintic, both in animals and in man.

In 1942, DeEds, Stockton, and Thomas (14) introduced phenothiazine as a urinary antiseptic after clinical tests had proved successful. No undesirable effects were noted in the gastrointestinal tract, circulation, kidneys, or liver. Secondary anemia sometimes occurred in patients treated for a prolonged period.

Freedlander (15) has reported phenothiazine's usefulness as an antituberculostatic compound. Phenothiazine in dilution of 1:1,000,000 inhibited the growth of tubercle bacilli in vitro, but in the presence of serum the bacteriostatic effect was diminished. Oxidized forms of phenothiazine showed only moderate inhibition of growth.

3. Diparcol

Gilman and Shirley (10) originally synthesized 10-(2-diethylaminoethyl)-phenothiazine, or diparcol (II-2). In 1947, Bovet, Fournel,



II-2

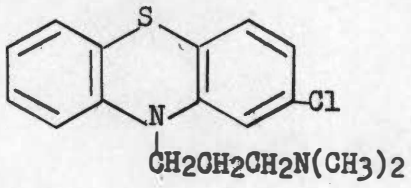
and Charpentier (16) investigated diparcol for use in the symptomatic treatment of Parkinson's disease. It is in the treatment of Parkinson's disease, where it has been shown to be clinically effective (5), that diparcol has found its most important use. In clinical treatment of 250 cases of Parkinsonism, Durel (17) reported that diparcol was effective (moderate to very good in action) in all but 6.1 per cent of the cases.

Schaepdryver (18) reported in 1950 that diparcol prevented or suppressed the bronchospasm produced in guinea pigs by acetylcholine, histamine, nicotine, and anaphylactic shock.

A more complete survey of the pharmacological properties of diparcol has been given by Heymans, Estable, and de Bonneveaux (19). Hopkins (20) has discussed diparcol in relation to its use in treatment of Parkinsonism.

4. Chloropromazine

By far the most useful member of the phenothiazine series of drugs is 2-chloro-10-(3-dimethylaminopropyl)-phenothiazine, or chloropromazine (II-3).



II-3

In 1955, Moyer, Kinross-Wright, and Finney (6) reported the excellent results of studies made on the use of chloropromazine in treatment of neuropsychiatric disorders. A group of 412 ambulatory and hospitalized patients having various types of mental disorders was given chloropromazine therapy and observed. Of this group, only 38 patients failed to respond to the drug. Excellent response was observed in 231 patients while the remainder displayed varying degrees of therapeutic response. Of particular importance was the observation that chloropromazine was quite effective in the treatment of schizophrenia. The patients observed encompassed almost all the clinical variants of this polymorphous disease, and the response observed was excellent.

Clinical investigations of Friend and Cummins (4) proved that chloropromazine had a powerful selective effect against nausea and vomiting caused by a variety of conditions. It was much more effective than diphenylhydramine and other well-known antiemetics, since it promptly proved effective in patients whose nausea and vomiting had not been relieved by these drugs. It is significant that the vomiting of pregnancy was successfully controlled.

Preliminary clinical investigations by Moyer, Kinross-Wright, and Finney (6) have also suggested possible use of chloropromazine for treatment of intractable hiccoughs.

5. The Relation of Structure to Physiological Activity

In view of the numerous physiological applications of the N-alkylated phenothiazines, some investigators have attempted to establish structural correlation between a given compound and a specific physiological use. Friebel, Flick, and Reichle (21) tested numerous phenothiazine derivatives with substituents on the nitrogen atom for antihistamine, antiacetylcholine, analgetic, and antiallergic action on mice. The substituents tested were: $Me_2NCH_2CH_2$-(I); $Et_2NCH_2CH_2$-(II); $Me_2NCH_2CH_2CH_2$-(III); 2-Cl-$Et_2NCHMeCH_2$-(IV); $Me_2NCHMeCH_2$-(V); $Et_2NCHMeCH_2$-(VI); $Me_3\overset{\oplus}{N}CHMeCH_2$-(VII). The antihistamine, antiacetylcholine, and broncholytic action of the dimethyl derivatives was stronger than that of the diethyl derivatives and most pronounced in I, II, V, VI, and VII. III and IV potentiated the analgetic and temperature-lowering effect of pyramidone (VIII). Quaternization of the nitrogen in VII increased the antihistamine and antiacetylcholine action as well as toxicity.

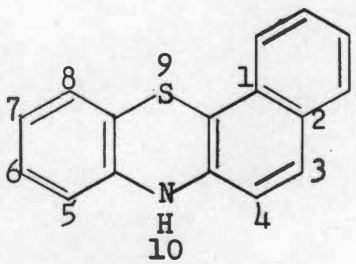
Certain observations have been made by Barlow (22) concerning the relative activity of the N-alkylated phenothiazines as antihistamines. In this group of drugs, members with branched chains are more potent than those with straight chains and the dimethylamino group can be replaced by pyrrole or pyrrolidine without much loss in activity. The introduction of a methoxy group para to the nitrogen reduces activity and replacement of sulfur by oxygen destroys it completely.

B. Chemistry of 7H-Benzo[c]phenothiazine

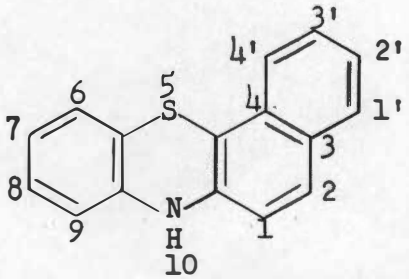
1. Nomenclature

Unfortunately, several different names for 7H-benzo[c]phenothiazine still appear in modern chemical literature. This compound was first prepared in 1890 by Kym (23) who called it thiophenyl-β-naphthylamine, probably because of its synthesis from sulfur and N-phenyl-β-naphthylamine. The name α,β-naphthophenothiazine for this compound first appeared in the literature (24) in 1921. More recently, Wahl and Ringeissen (25) called the compound benzonaphthothiazine.

Different ways of numbering the ring have also been used in the literature. Beilstein (26) conforms to a system of numbering shown in II-4. Buu-Hoï (27,28) has employed a different system (II-5) which is quite

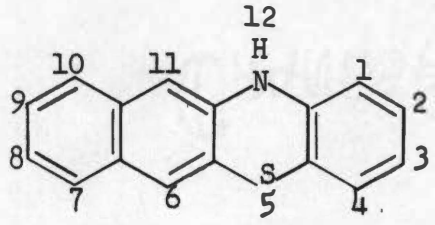


II-4

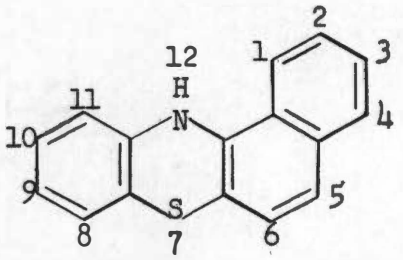


II-5

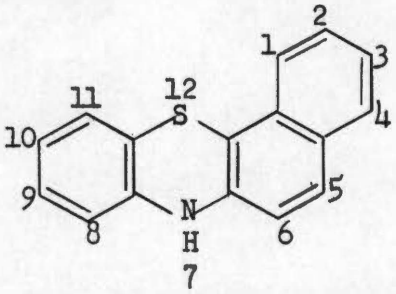
common in foreign publications although it is seldom found in domestic literature. However, a thorough literature survey revealed its presence in at least one very recent domestic publication (29). The currently accepted numbering and nomenclature for the isomeric benzophenothiazines, according to Chemical Abstracts and the Ring Index (30), is illustrated in II-6.



12H-benzo [b] phenothiazine



12H-benzo [a] phenothiazine



7H-benzo [c] phenothiazine

II-6

In view of the variety of nomenclature employed for 7H-benzo [c] phenothiazines, extreme care should be exercised when surveying the literature for this compound or its derivatives. All names in this dissertation are expressed in the manner recommended by Chemical Abstracts even though other nomenclature was employed in the original work.

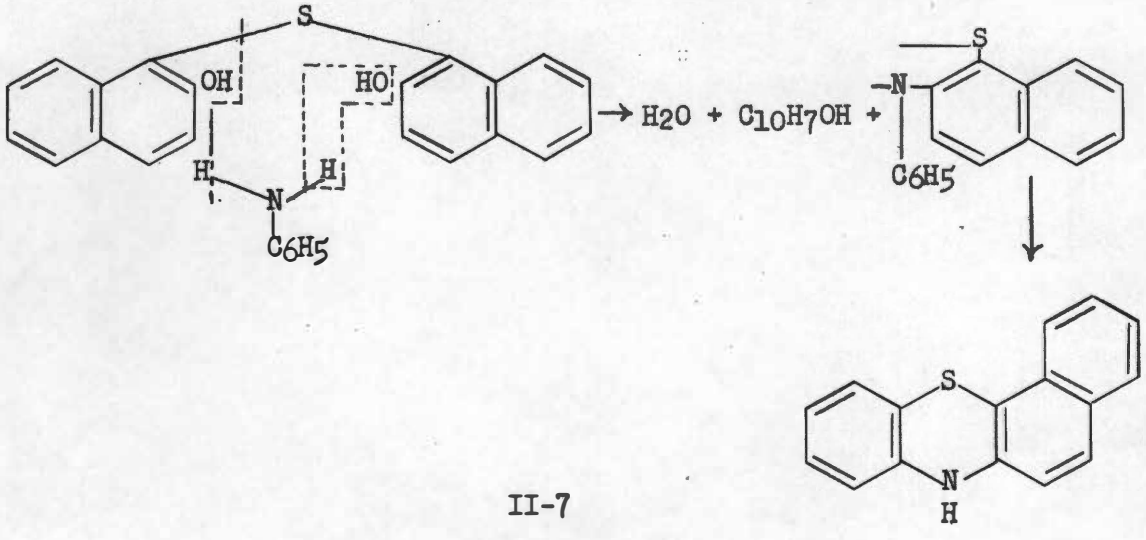
2. Methods of Preparation

a. From N-phenyl-2-naphthylamines. The first preparation of 7H-benzo [c] phenothiazine involved the reaction of N-phenyl-2-naphthylamine and sulfur at 200-240° for five hours (23). A poor yield of product was obtained. The conditions of this reaction have been greatly improved by the discovery (31) that the addition of catalytic amounts of

iodine shortened the reaction time, lowered the reaction temperature, and gave much better yields of product. This reaction, referred to as "thionation", has been used to prepare substituted 7H-benzo[c]-phenothiazines. Knoevenagel (32) used this method to prepare methyl- and chloro-substituted 7H-benzo[c]phenothiazines. Recently 9-fluoro-7H-benzo[c]phenothiazine was synthesized by thionation (29).

A preparation of 7H-benzo[c]phenothiazine by a modified thionation has been reported (33) in which a mixture of β-naphthol, aniline, sulfur, and iodine was heated and the product obtained directly from the crude reaction mixture.

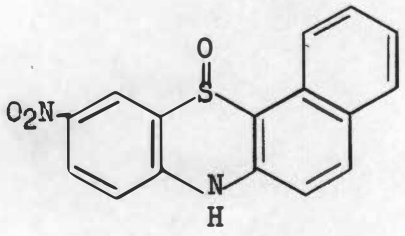
b. From sulfides. Wahl and Ringeissen (25) prepared 7H-benzo[c]phenothiazine, together with β-naphthol, by heating aniline and 2,2'-dihydroxy-1,1'-dinaphthylsulfide under reflux for six hours. A possible reaction path for this rather unexpected process was indicated by Wahl and Ringeissen to be as shown in II-7. Chemical evidence to indicate a probable mechanism was not cited.



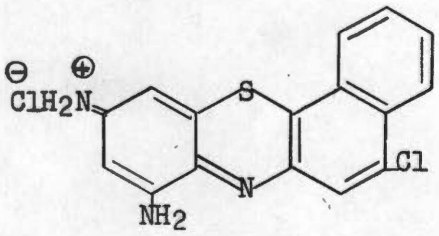
II-7

3. Nuclear Substitution Reactions

a. Nitration. In 1921, Ludwig-Semelic (24) reported the nitration of 7H-benzo[c]phenothiazine. At least two nitro derivatives resulted when 7H-benzo[c]phenothiazine was nitrated. One of these, a nitrosulfoxide (II-8), was crystallized directly from the crude nitration product. The other was a dinitro derivative, which was not isolated but reduced with stannous chloride and hydrochloric acid to a chlorodiamino-7H-benzo[c]phenothiazonium chloride (II-9).



II-8



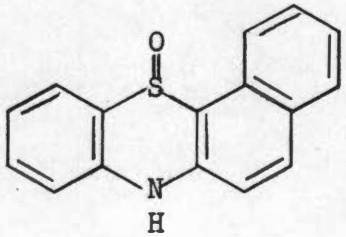
II-9

In the Chemical Abstracts reference cited for this work (24) no evidence for the structures of the nitration products was given. Experimental details, melting points, and other data were also unavailable. The original article appeared in a Yugoslavian journal which was apparently discontinued after only one publication, and further reference work could not be accomplished. (Chemical Abstracts indicated that the original article is not available in this country.)

b. Acylation via the Friedel-Crafts reaction. Burger and Clements (34) recently prepared 7-acetylbenzo[c]phenothiazine in 98 per cent yield and then subjected this compound to a Friedel-Crafts reaction with acetyl chloride. The N-acetyl group was subsequently removed by acid hydrolysis to yield an x-acetyl-7H-benzo[c]phenothiazine. The position

of the acetyl group was not established.

c. Oxidation. Kehrmann and Christopoulos (35) subjected 7H-benzo[c]phenothiazine to mild oxidation with sodium nitrite solution in acetic acid and obtained 7H-benzo[c]phenothiazine-12-oxide (II-10), m.p. 225° with decomposition.



II-10

4. Substitution of the Amino Hydrogen

a. Alkylation. Kym (23) in 1890 reported the first N-alkylation reaction of 7H-benzo[c]phenothiazine. He obtained 7-methylbenzo[c]phenothiazine as light yellow-green needles, m.p. 132-133°, by reaction of equimolar amounts of methyl iodide and 7H-benzo[c]phenothiazine in methanol at 150° for five hours.

Smith (36) recently reported the synthesis of 7-(2-cyanoethyl)-benzo[c]phenothiazine by reaction at room temperation of 7H-benzo[c]-phenothiazine with acrylonitrile, in the presence of a small amount of "Triton B". The product was isolated as yellow crystals melting at 215°.

b. Acylation. The N-acetyl derivative of 7H-benzo[c]phenothiazine was prepared by Kehrman and Christopoulos (35) in 1921 employing acetic anhydride and zinc chloride. The colorless crystals, from benzene, were

reported to melt at 126°. However, Burger and Clements (34) in a more recent synthesis of 7-acetylbenzo[c]phenothiazine reported its melting point as 134-135°.

5. Miscellaneous Derivatives of 7H-Benzo[c]phenothiazine

A few nuclearly substituted 7H-benzo[c]phenothiazines have been previously prepared by thionation of substituted N-phenyl-2-naphthylamines, and are listed in Table I.

C. Chemistry of Organolithium Compounds

1. Introduction

The metalation reaction, i. e., the replacement of hydrogen of an organic compound by a metallic atom to yield an organometallic compound, is of large importance in organic synthetic work. The combination of high-reactivity, relatively easy preparation, and solubility in inert solvents which is characteristic of organolithium compounds has made them of ever increasing value in chemical synthesis. A number of reactions which do not occur with Grignard reagents can be accomplished by use of organolithium compounds (38). Organolithium metalations of both aromatic and heterocyclic rings tend to occur in a position ortho to a hetero atom possessing an unshared electron pair. Thus, positions in ring compounds not readily substituted by ordinary electrophilic reagents are quite frequently made available by the metalation reaction. An outstanding example of the synthetic usefulness of this reaction is the metalation of resorcinol dimethyl ether, as shown in II-11, to yield, after reaction with carbon dioxide (carbonation), 2,6-dimethoxybenzoic acid (39) in 55 per

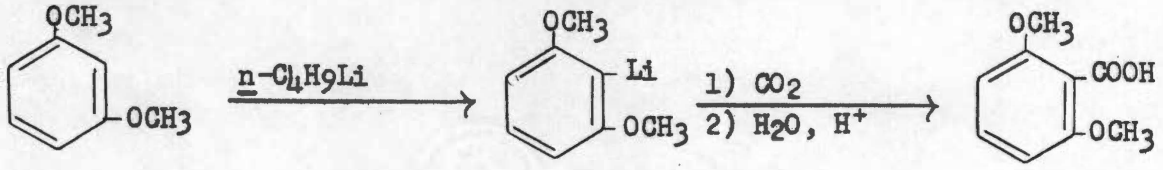
TABLE I

SUBSTITUTED 7H-BENZO [c] PHENOTHIAZINES

Substituent	2-Naphthylamine Used	Melting Point °C	Reference
9-Methyl	N-(m-tolyl)-	168-169	32
10-Methyl	N-(p-tolyl)-	182	31
9-Chloro	N-(m-chlorophenyl)-	163	32
8,11-Dimethyl	N-(2,5-dimethylphenyl)-	170	28
10-Hydroxy	N-(p-hydroxyphenyl)-	*	37
9-Fluoro	N-(m-fluorophenyl)-	159-160	29

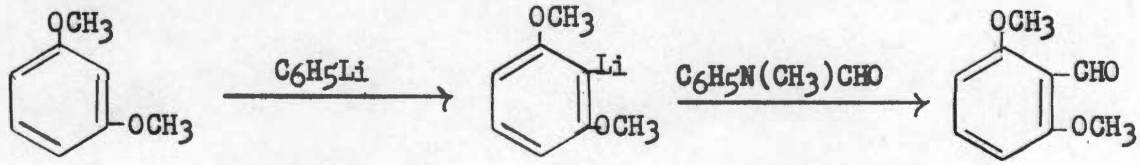
*Not reported.

cent yield. Metalation at this position provides the only clean-cut



II-11

means of entering the position between the two methoxy groups of resorcinol dimethyl ether. Further, phenyllithium metalates resorcinol dimethyl ether (40) to give a 55 per cent yield of the corresponding aldehyde after treatment of the reaction mixture with N-methylformanilide (II-12). Orientation of lithium at this position would seem to indicate



II-12

that the steric requirements for lithium substitution in the metalation reaction are not very pronounced.

The most frequently used metalating agent of the alkyllithium compounds is n-butyllithium, because of its ease of preparation, stability, and high degree of reactivity (40). The position of metalation can be identified in a number of ways, but this is most commonly done by converting the organolithium compound to its carboxylic acid by treatment with carbon dioxide. However, by appropriate treatment, the lithium atom may be replaced by hydroxyl (41), amino (42), halogen (43), formyl (44), acetyl (45), benzoyl (46), methyl (47), benzyl (48), benzhydryl (49), allyl (48), or substituted hydroxymethyl (50).

2. Methods of Preparation

Schlenk and Holtz (51) first prepared organolithium compounds by the action of lithium on dialkyl- and diarylmercury compounds (II-13). The preparative utility of this reaction depends largely upon

$$R_2Hg + 2Li \rightleftharpoons 2RLi + Hg$$

II-13

solubility differences between reactants and products. In some specific cases, it is still of synthetic value. At present, the most widely used method of preparation, introduced in 1930 by Ziegler and Colonius (52), involves the reaction of lithium with alkyl or aryl organic halides, as illustrated in II-14. Thus, n-butyllithium may be prepared in good

$$RX + 2Li \rightleftharpoons RLi + LiX$$

II-14

yield (53) by the reaction of an ethereal solution of n-butyl bromide with lithium metal. The metalation work described in this dissertation involves use of this reagent.

The metal-metal interconversion reaction (54) (II-15) is frequently used for preparation of specific organometallic reagents, and once again a reversible process is involved. There is a striking similarity between

$$RM + R'M' \rightleftharpoons R'M + RM'$$

II-15

these reactions and the classical ionic reactions of inorganic chemistry. The course of the metal-metal interconversion reaction is influenced by the insolubility of one of the products in the solvent used. Thus, methyllithium, which is insoluble in benzene, has been prepared utilizing

the exchange between ethyllithium and dimethylmercury in this solvent (55).

Various organolithium compounds, which are unavailable by direct reaction between a halide and the metal, are readily prepared by means of the halogen-metal exchange reaction (38), as shown in II-16. For example, 3-bromopyridine does not react satisfactorily with metallic

$$RLi + R'X = RX + R'Li$$

II-16

lithium but gives 3-pyridyllithium (38) with n-butyllithium in ether at -35° (II-17).



II-17

Several other preparative methods have been evolved throughout the years and include the addition of lithium (56) or organolithium compounds (57) to olefinic linkages and the cleavage of ethers with metallic lithium (58). Jones and Gilman (59) have summarized the methods of preparation of organometallic compounds.

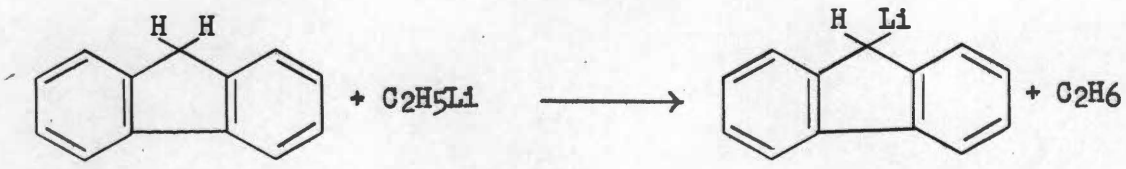
3. Structure

The chemical constitution of organolithium compounds is still quite obscure. Their solubility in non-polar solvents would strongly indicate that they are not salts. Further, fused ethyllithium does not conduct electricity, although it gives a conducting solution in diethylzinc. The latter is due to chemical interaction with the formation of a complex salt (38).

On the other hand, the non-volatility of these compounds would indicate that they are not simple monomeric covalent substances. Determination of molecular weights of these substances in ether and in benzene solution (60) indicates association (see Table II), and this, too, would point toward non-covalency of the compounds. Although a monomeric alkyllithium molecule would probably be somewhat polar, $R\overset{\delta-}{\leftarrow}\overset{\delta+}{Li}$, dipole interaction is unlikely to be solely responsible for the observed association and low volatility of organolithium compounds. It has been shown (38) that highly polar compounds are often more volatile, for example aluminum-chloride-diethylether, $Cl_3Al\text{-}O\text{-}Et_2$, whose dipole moment is 6.5 D., a value not likely to be exceeded by any alkyllithium, distils at 147°/11 mm. The corresponding bromide has an association factor of only 1.1-1.5 in benzene solution. The fact that lithium can attain a covalency of two or three was recently made apparent by synthesis of complexes such as $Na^{\oplus}\ Ph_2Li(OEt)_2^{\ominus}$ by Wittig, Ludwig, and Polster (61).

4. Typical Metalation Studies

The use of organolithium compounds as metalating agents dates from 1928, when it was discovered that ethyllithium reacted with fluorene to produce 9-fluorenyllithium, as shown in II-18, and with other hydro-



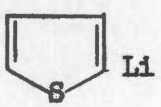
II-18

TABLE II

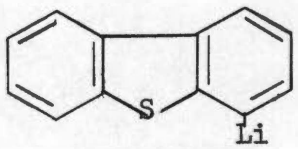
DEGREE OF ASSOCIATION OF ORGANOLITHIUM COMPOUNDS IN SOLUTION (60)

Compound	Approximate Degree of Association	Solvent
CH_3Li	3	Boiling Ether
C_2H_5Li	6	Freezing Benzene
n-C_4H_9Li	5	Boiling Ether
n-C_4H_9Li	7	Boiling Benzene
C_6H_5Li	2	Boiling Ether
$C_6H_5CH_2Li$	2	Boiling Ether

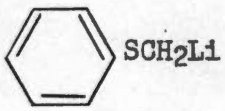
carbons in a similar manner (58). Since that time, numerous metalation reactions have been studied in an effort to learn more about orientation effects, mechanism, effect of varied reaction conditions, and types of compounds which are particularly susceptible to metalation. These studies soon pointed out the pronounced tendency of the entering lithium atom to replace a nuclear hydrogen atom ortho to the hetero atom, or a lateral hydrogen atom (i. e., one attached to a side chain) on a carbon adjacent to the hetero atom. Thus, n-butyllithium metalates thiophene in the 2-position (62), dibenzothiophene in the 4-position (63), and methyl phenyl sulfide on the methyl carbon atom (64), to give the organometallic compounds, II-19, II-20, and II-21, respectively. The tendency



II-19



II-20

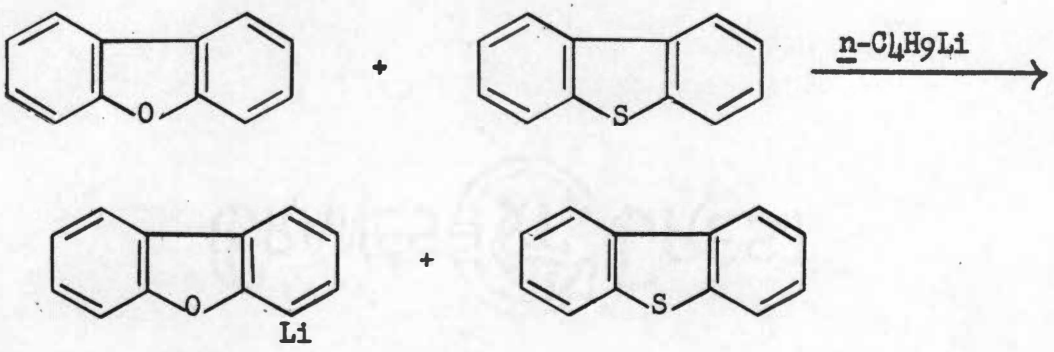


II-21

of the metalation reaction to produce ortho substitution, usually uncontaminated by para or other isomers, distinguishes it from the more familiar types of substitution and makes possible the preparation of many products not readily available through other routes.

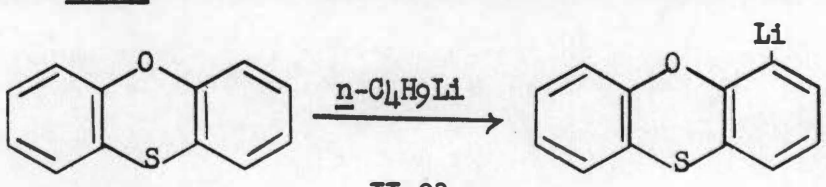
Different hetero atoms and groups show different activating powers in the metalation reaction. Some studies have been made to determine the relative activating influence of various hetero atoms in the metalation reaction. Competitive metalation (65), or metalation in which equimolar quantities of two (or more) compounds are allowed to compete for a common reactant present in insufficient amount for complete reaction, has been

employed for these studies. The observation that only dibenzofuran is metalated when a mixture of dibenzofuran and dibenzothiophene is allowed to react with an insufficient quantity of n-butyllithium (II-22) indicates that the ether linkage has a greater activating effect in



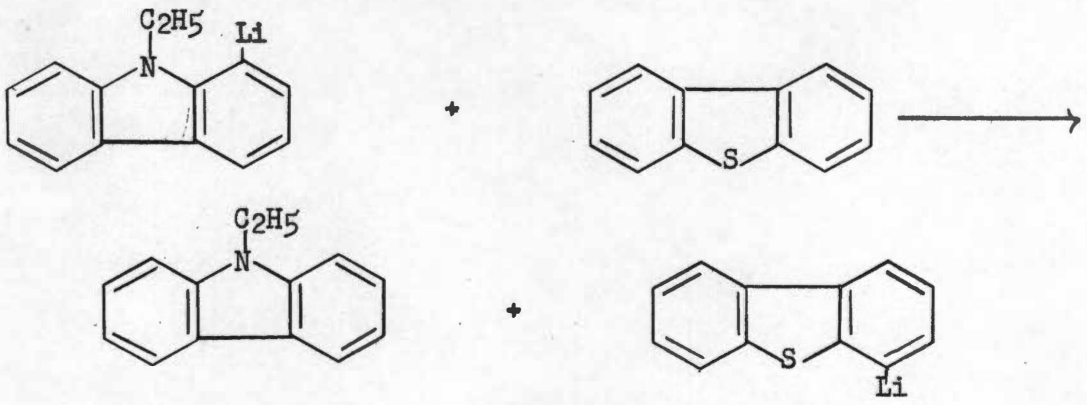
II-22

metalation than does the sulfide linkage (66). This observation was further exemplified by the metalation of phenoxathiin by n-butyllithium (II-23) which occurs ortho to the oxygen rather than to the sulfur atom (66).



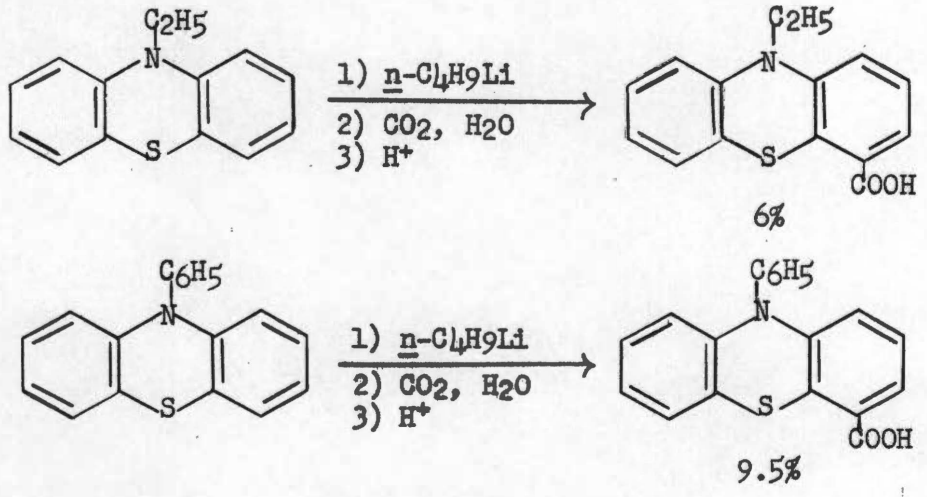
II-23

Results from several investigations seem to indicate that the sulfide linkage activates an ortho position toward metalation more strongly than a tertiary amino linkage. Gilman and Stuckwisch (67) found that only dibenzothiophene was metalated when equimolar quantities of dibenzothiophene and 9-ethylcarbazole were allowed to compete for an insufficient quantity of n-butyllithium. Further, they observed that 1-(9-ethylcarbazoyl) lithium metalated dibenzothiophene in the 4-position, as shown in II-24, whereas 4-dibenzothienyllithium had no effect on 9-ethylcarbazole.



II-24

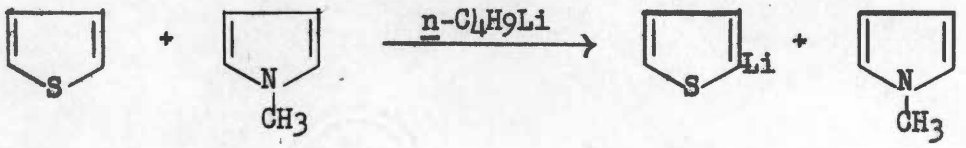
Gilman, Van Ess and Shirley (68) studied the metalation of 10-ethyl- and 10-phenylphenothiazine with n-butyllithium and observed that metalation occurred (II-25) in both cases in the 4-position, but in poor yield.



II-25

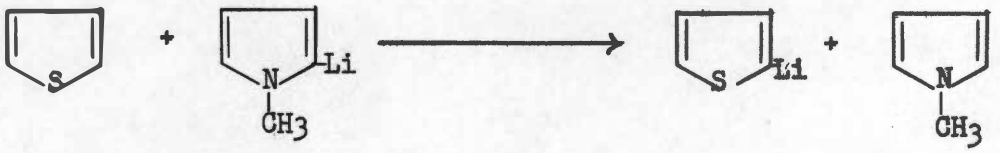
Shirley and Goan (69) recently investigated a series of competitive metalations in order to substantiate previous observations that the sulfide linkage has a stronger activating power toward ortho metalation than does a tertiary amino linkage. Only thiophene was metalated when an equimolar mixture of thiophene and N-methylpyrrole was allowed to compete for an in-

sufficient amount of n-butyllithium (II-26). It was further shown that



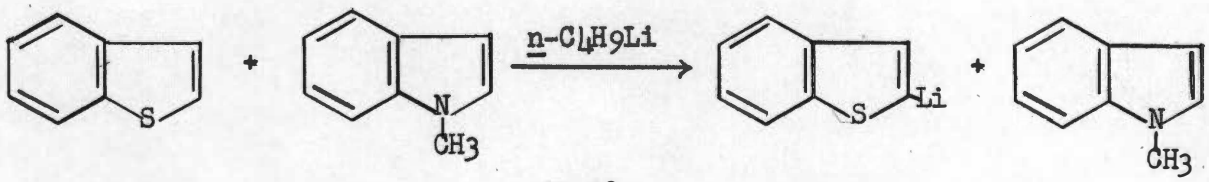
II-26

thiophene could be metalated by 2-lithio-1-methylpyrrole (II-27), but the



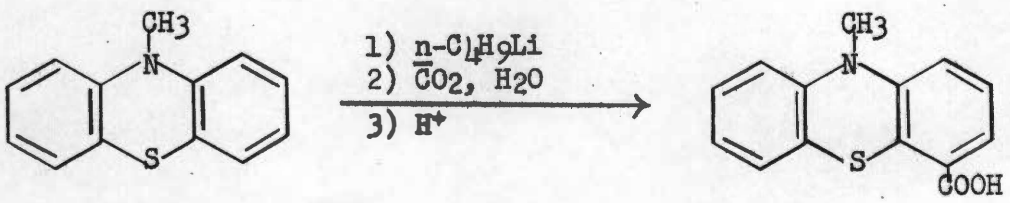
II-27

reverse reaction did not occur. In a similar manner, it was shown that only thianaphthene was metalated when a mixture of thianaphthene and N-methylindole was reacted with an insufficient quantity of n-butyllithium, as illustrated in II-28. In connection with these studies, N-methylpheno-



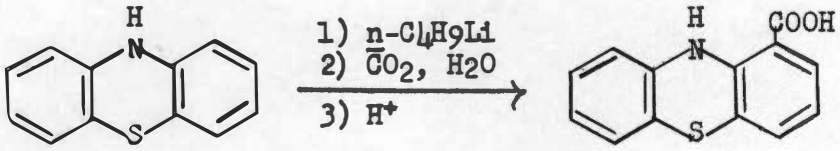
II-28

thiazine was metalated with n-butyllithium, and again the site of metalation, as in the cases of N-ethyl and N-phenylphenothiazine, was adjacent to sulfur, or in the 4-position, as is shown in II-29.



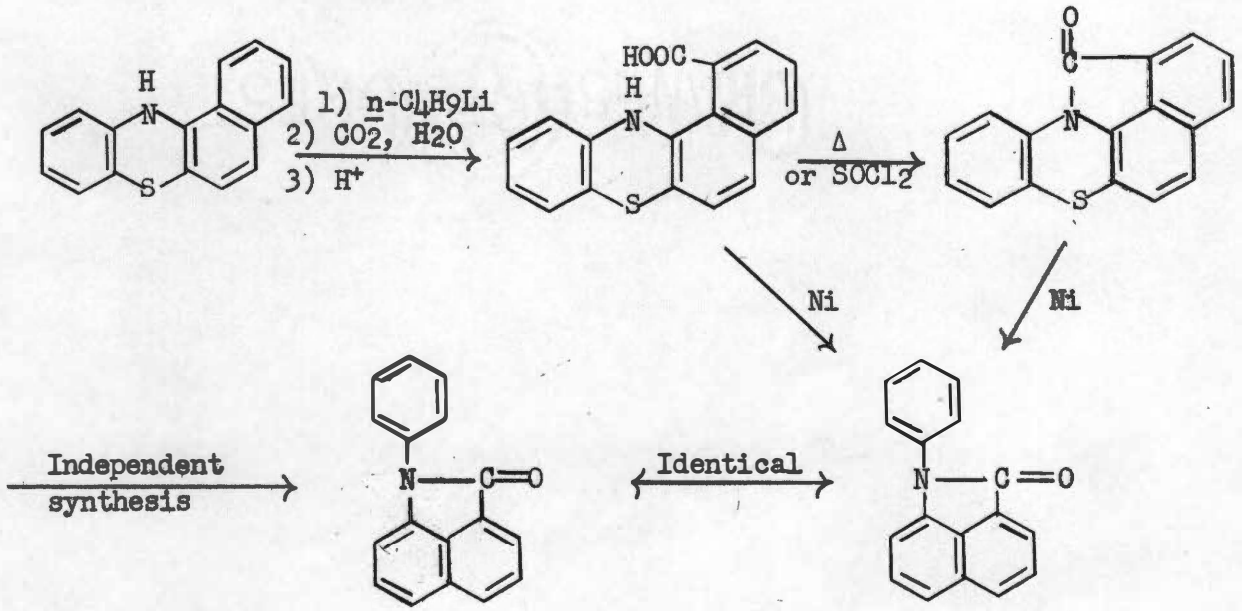
II-29

On the other hand, the rule of precedence of sulfur over nitrogen in determining position of metalation does not hold for secondary amines, because phenothiazine itself has been shown to undergo metalation (70) in the 1-position to give, on carbonation, a 52 per cent yield of phenothiazine-1-carboxylic acid (II-30).



II-30

Further evidence for this type of orientation with secondary amines was recently observed by Shirley (71) in studying the metalation of 12H-benzo[a]phenothiazine. It was shown by a series of reactions outlined in II-31 that metalation of this compound with n-butyllithium occurred in the 1-position.



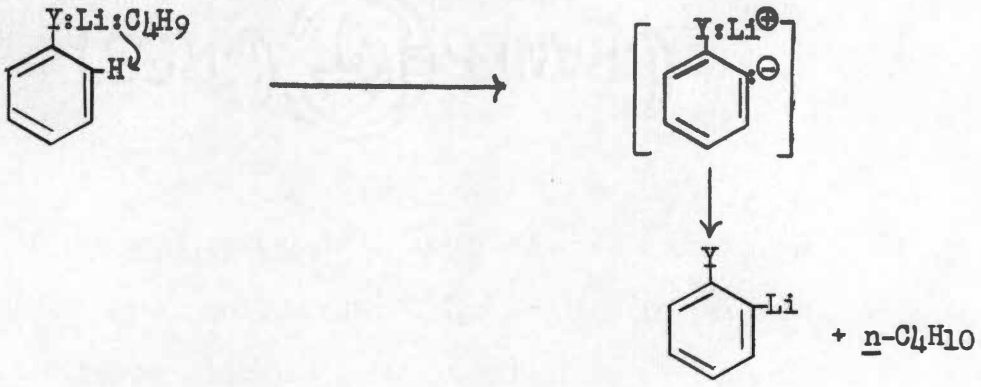
II-31

5. Theoretical Considerations

A single mechanism capable of explaining the numerous metalation reactions already accomplished has not yet been proposed. Several conflicting mechanisms have been set forth, but no single one is consistent with the results observed in all metalations. Morton (72) has proposed an "electrophilic" mechanism which placed emphasis on the electrophilic character of the cation of the metalating compound. This mechanism has met with considerable opposition because of its inability to interpret a very large percentage of metalation results available.

In 1946, Roberts and Curtin (73) proposed a "nucleophilic" mechanism which, contrary to Morton's postulation, emphasized the role of the carbanion of the metalating agent in determining the course of the reaction. As the basis for their mechanism, Roberts and Curtin metalated trifluoromethylbenzene with n-butyllithium. The trifluoromethyl group, known to be a strong meta director toward electrophilic substitution, should cause metalation to occur in the meta position if the electrophilic mechanism of Morton were correct. However, carbonation of the reaction mixture yielded a mixture of o- and m-trifluoromethylbenzoic acids in an approximate ratio of five to one, respectively. This result, coupled with previous observations that highly negative substituent groups tended to cause metalation in a position ortho to the substituent, led Roberts and Curtin to the proposal of the "nucleophilic mechanism." This mechanism postulates an initial coordination of the metallic atom of the metalating agent with an unshared electron pair on the substituent group, followed by the removal of an o-hydrogen by the anion of the metalating

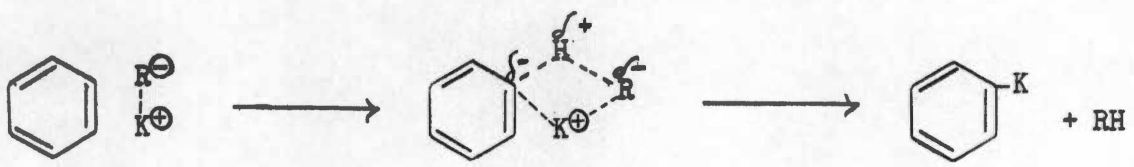
agent, as outlined in II-32. The coordination step of this mechanism



II-32

would be expected to aid the reaction by increasing the polarization of the carbon-metal bond of the metalating agent and by enhancing the polarization of an adjacent carbon-hydrogen bond on the molecule undergoing metalation in a manner to facilitate removal of the proton.

However, the "nucleophilic" mechanism does not satisfactorily explain a number of apparently contradictory observations. For example, tert.-butylbenzene undergoes metalation primarily in the para position (74) and this observation is not satisfactorily interpreted on the basis of the above mechanism. Bryce-Smith (75) has modified the "nucleophilic" mechanism set forth by Roberts and Curtin in an effort to explain this type of metalation reaction. This mechanism retains the idea of inductive polarization of the carbon to hydrogen bonds of the ring by substituent groups, but postulates formation of an intermediate four-membered ring transition state as shown in II-33. Thus, the electron-releasing



II-33

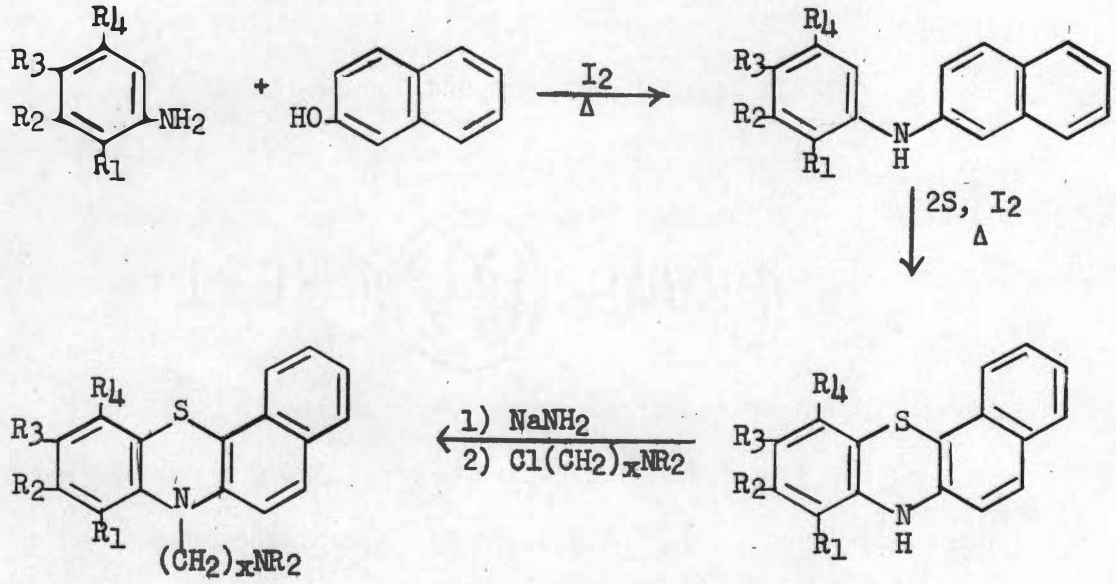
effect of the tert.-butyl group would tend to decrease the acidity of all the ring hydrogens, but the hydrogen atom in the position para to the tert-butyl group would be least affected, thus promoting metalation at that position. This mechanism, which combines the ideas of Roberts and Curtin with those of Bryce-Smith, has received wide acceptance.

CHAPTER III

DISCUSSION

A. Synthetic Methods

The series of reactions illustrated schematically in III-1 was used for the synthesis of all 7-(dialkylaminoalkyl)-benzo[c]-phenothiazines prepared in this investigation.



III-1

1. N-Phenyl-2-naphthylamines

All of the N-phenyl-2-naphthylamines prepared as intermediates in this work have been previously reported. Since the synthetic procedures reported in the literature for preparation of the different amines varied considerably, it was the initial objective of this investigation to find a satisfactory, general method for synthesis of all

the desired N-phenyl-2-naphthylamines. Knoevenagel (32) first employed iodine as catalyst in preparation of amines of this type, and reported much higher yields of product amine than when iodine was not used. Knoevenagel's procedure involved condensation of a substituted aniline with β-naphthol, and this general procedure was found to be quite satisfactory in work reported in this dissertation.

After a thorough investigation of reaction variables in synthesis of the desired N-phenyl-2-naphthylamines, the following procedure was found to give optimum yields. A mixture of 1.0 mole of β-naphthol, approximately 1.3 moles of the appropriately substituted aniline, and a catalytic amount of iodine was heated under reflux for fifteen to forty hours. The dark reaction mixture obtained was then fractionated by distillation in vacuo and the product crystallized from an appropriate solvent.

One method of isolating the substituted N-phenyl-2-naphthylamines after the appropriate heating period has been described by Buu-Hoï (28, 76) in current chemical publications. It consists of extracting the dark reaction product with benzene, washing with aqueous sodium hydroxide, and drying the benzene extracts over sodium sulfate. After removal of the solvent, the residue is fractionated by distillation under vacuum. In the work reported in this dissertation, it was found more convenient to fractionate directly the dark reaction mixture, thus avoiding emulsions which were encountered while using the above procedure.

A few other experimental observations recorded during a study of the conditions of this condensation reaction are worthy of mention. The

amount of iodine employed as catalyst did not have an observable effect on the yields of N-phenyl-2-naphthylamines obtained. On the other hand, the effect of the ratio of concentrations of substituted aniline and β-naphthol on the yield of secondary amine was quite pronounced. For example, when a mixture of equimolar amounts of 2,5-dimethylaniline and β-naphthol was heated under reflux for either eighteen or thirty-five hours (using iodine catalyst), a 21 per cent yield of N-(2,5-dimethylphenyl)-2-naphthylamine was obtained. However, reflux of a mixture of 2,5-dimethylaniline and β-naphthol, in a molar ratio of approximately 1.3 to 1.0 for twenty-four hours, gave a 50 per cent yield of product.

Periods of reflux, ranging from fifteen to forty hours, were employed. The optimum heating period for a specific amine was determined by "trial and error" although this particular reaction variable was much less important than the reactant concentrations employed. It was found desirable to allow escape of water vapor formed during the reaction. This was accomplished by use of an air condenser.

2. 7H-Benzo[c]phenothiazines

The reaction of N-phenyl-2-naphthylamines with sulfur using iodine catalyst, referred to as thionation, is a reaction quite sensitive to varied experimental conditions. The effects of variations in temperature, reaction time, method of product isolation, etc. are quite pronounced. Roe, Montgomery, Yarnall, and Hoyle (29) recently reported the experimental conditions for preparation of 9-fluoro-7H-benzo[c]-phenothiazine, and indicated that several other runs under slightly

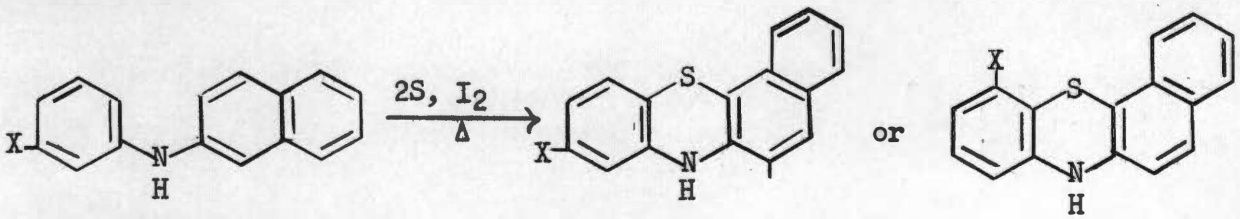
different conditions gave none of the desired product.

Each substituted 7H-benzo[c]phenothiazine prepared in this work, even if previously reported in the literature, required several preparative attempts in order to select the most satisfactory set of experimental conditions. The effects of temperature and reaction time are illustrated for each substituted 7H-benzo[c]phenothiazine by data appearing in Chapter IV (for example, see Tables III and V). The use of chromatography over "Florisil" adsorbent aided in purification of some of the substituted 7H-benzo[c]phenothiazines. However, this purification technique was somewhat limited in usefulness since only a few grams could be conveniently chromatographed in one operation, and larger quantities of the purified 7H-benzo[c]phenothiazines were necessary for subsequent reactions.

In thionation reactions, an important question is the proper length of the heating period. An initial, vigorous evolution of hydrogen sulfide followed by a steady (and much slower) evolution is characteristic of the reaction. After a certain length of time, usually only a few minutes, the evolution of hydrogen sulfide (bubbling of the reaction mixture) ceases, and it is at this point that the reaction should be stopped. Further heating seems to promote tar formation, resulting in a considerable loss of product. On the other hand, an insufficient heating period results in incomplete conversion of reactants to product, and separation of unchanged starting materials from product may be quite tedious.

For preparation of several of the desired 7-(dialkylaminoalkyl)-benzo[c]phenothiazines, a large supply of 7H-benzo[c]phenothiazine was necessary. Kym (23) first reported the preparation of this compound by heating a mixture of sulfur and N-phenyl-2-naphthylamine, but iodine was not utilized as catalyst and consequently a heating period of five hours was necessary. Kehrmann and Dardel (77) prepared this compound by heating a mixture of sulfur, N-phenyl-2-naphthylamine, and iodine *in vacuo*. A modification of this procedure was found most desirable in this work, since attempts to carry out this preparation *in vacuo*, as described by Kehrmann and Dardel, were not completely satisfactory. For example, the solid reactants, when heated *in vacuo*, tended to sublime from the reaction mixture and caused considerable "clogging" of the rubber tubing connected to the apparatus. It was found most satisfactory simply to heat the reactants (under the hood) in a round-bottom flask, using a Wood's metal bath for accurate temperature control.

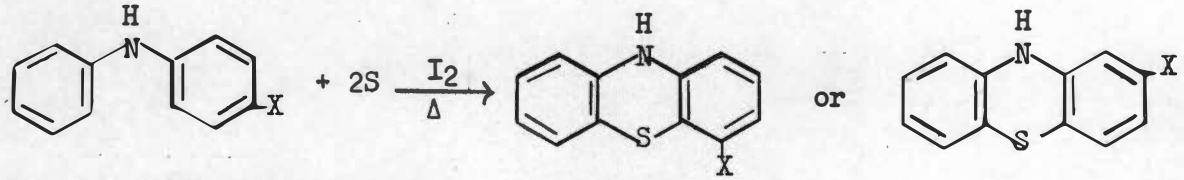
Thionation of N-phenyl-2-naphthylamines substituted in the *meta* position of the phenyl group can lead to two products, since ring-closure can occur *ortho* or *para* to the substituent (III-2). Earlier workers in



X = substituent

III-2

the phenothiazine series have carefully examined situations in which thionation could lead to two isomeric products, and this work clearly demonstrated (7,78,79,80) that thionation occurred predominately para to the substituent (III-3). The application of infrared spectra in



X = substituent

4-isomer

2-isomer
(major product)

III-3

assignment of the particular structure has proved rather successful. For example, the isomer showing a band at about 12.2 microns was concluded to be the 2-isomer since 1,2,4-trisubstituted benzenes show a characteristic deep band in the region 12.0-12.5 microns (7,78,79). On the other hand, the isomer showing a band at about 12.7 microns was assigned a structure corresponding to the 4-isomer, since 1,2,3-trisubstituted benzenes exhibit a characteristic deep band in the region 12.5-13.15 microns (7,78,79).

The structure of each substituted 7H-benzo[c]phenothiazine reported in this dissertation is indicated by its method of preparation with the exception of 9-chloro-7H-benzo[c]phenothiazine. Thionation of N-(m-chlorophenyl)-2-naphthylamine could lead to two isomeric products, but Knoevenagel (32) reported that only one product was obtained. Thionation of N-(m-chlorophenyl)-2-naphthylamine in this investigation gave the same product reported by Knoevenagel, as indicated by identical melting points, and this product was the only one isolated from the reaction.

Application of infrared spectra to the structural problem involved in thionation of N-(m-chlorophenyl)-2-naphthylamine unfortunately did not provide an unequivocal answer to the problem. 7H-Benzo[c]-phenothiazine itself shows a sharp band at 12.4 microns (attributed to β-naphthalene (81) substitution), and this band simply broadens in the chloro-substituted compound with no new bands appearing in the 12-13 micron region. Thus, evidence from infrared spectra for the structure of the proposed 9-chloro-7H-benzo[c]phenothiazine cannot be presented, and the structure indicated should be regarded as tentative. However, in view of the evidence presented for preferential para ring closure in similar thionation reactions in the phenothiazine series (7,78,79, 80), assignment of the structure corresponding to 9-chloro-7H-benzo[c]-phenothiazine seems quite logical.

3. 7-(Dialkylaminoalkyl)-benzo[c]phenothiazines

The desired 7-(dialkylaminoalkyl)-benzo[c]phenothiazines were prepared by conventional condensation methods (9) in yields ranging from 40 to 63 per cent. These condensations involved reaction of substituted 7H-benzo[c]phenothiazines with various dialkylaminoalkyl chlorides in xylene or toluene in the presence of freshly-prepared sodamide. All of the N-alkylated benzo[c]phenothiazines reported in this dissertation were highly viscous yellow or yellow-orange oils with a characteristic green fluorescence.

Several N-alkylation reactions on 7H-benzo[c]phenothiazine were carried out employing modified reaction conditions before a satisfactory

procedure was found. Use of a large excess of dialkylaminoalkyl chloride in this reaction greatly improved the yields of 7-(dialkylaminoalkyl)-benzo[c]phenothiazines. Further improvement of yields resulted from use of a short Vigreux column in distillation of the products. Usually, a single distillation of the crude product through the Vigreux column was sufficient for purification of the N-alkylated materials, whereas two or three distillations were necessary when this column was not employed.

One of the most critical factors in the condensation reaction involved the time of reflux required for complete formation of the N-sodio salt of the 7H-benzo[c]phenothiazine. If complete formation of the N-sodio salt is not allowed, competition occurs between the 7H-benzo[c]-phenothiazine and the dialkylaminoalkyl chloride for the sodamide present, resulting in reduced yields of 7-(dialkylaminoalkyl)-benzo[c]phenothiazines. About one hour was usually required for complete formation of the N-sodio salt, but this time varied some depending upon the particular substituted 7H-benzo[c]phenothiazine used. The formation of this salt was conveniently followed by observation of the ammonia evolved in the process.

The role of the reaction solvent should also be noted. Mixed xylenes (b.p. about 138°) seemed to be quite satisfactory for all condensations except those involving use of 2-dimethylaminoethyl chloride. The boiling point of this particular chloride (b.p. 108-109°) made it desirable to employ toluene (b.p. 111°) as solvent medium rather than the higher-boiling xylene. The effect of reaction solvent on the yield

of 7-(2-dimethylaminoethyl)-benzo [c] phenothiazine is illustrated in Table IV of this dissertation (see page 51).

Picrate derivatives or quaternary salts with methyl iodide were prepared for further characterization the 7-(dialkylaminoalkyl)-benzo-[c] phenothiazines.

B. A Study of the Metalation of 7H-Benzo [c] phenothiazine With n-Butyllithium

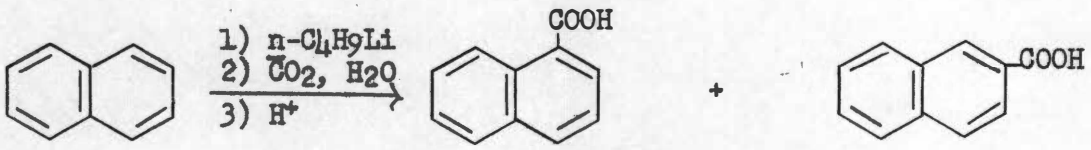
1. Significance

The synthetic usefulness of the metalation reaction has already been discussed in Chapter II. During the course of this research, it became of interest to metalate 7H-benzo [c] phenothiazine with n-butyllithium in order to determine the potential synthetic utility of the metalation reaction toward future synthesis of substituted 7H-benzo [c]-phenothiazines.

As indicated in Chapter II, metalation has been observed to occur ortho to nitrogen rather than to sulfur in a heterocyclic system containing both the sulfide and secondary amine linkages (70,71). The metalation of 7H-benzo [c] phenothiazine was of some further interest since it would provide additional information as to the relative activating effects of heterocyclic sulfur and nitrogen atoms in systems of this type. It would also be of interest to observe whether the benzene ring or the naphthalene ring became the primary site of metalation.

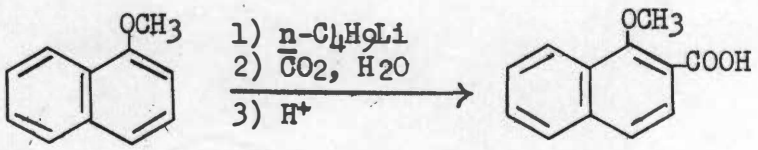
Most of the substitution reactions of naphthalene (82) occur in the more active 1-position, i. e., halogenation, nitration, etc. Con-

trolled sulfonation provides the principal method for introducing a functional group into the less-active 2-position. However, metalation of naphthalene (63) with n-butyllithium gave a 20 per cent yield of a mixture of 1- and 2-naphthoic acids (III-4). The 1-naphthoic acid was



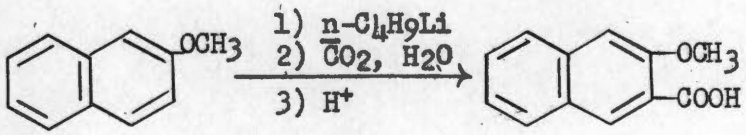
III-4

present in the larger amount. Metalation of 1-methoxynaphthalene (83) gave a 20-25 per cent yield of 1-methoxy-2-naphthoic acid (III-5).



III-5

Metalation in the 2-position is not surprising since metalation might be expected to occur next to the methoxy group. However, when 2-methoxynaphthalene was metalated (83), the position of attack was in the 3-position rather than in the 1-position (III-6), giving a 50 per cent



III-6

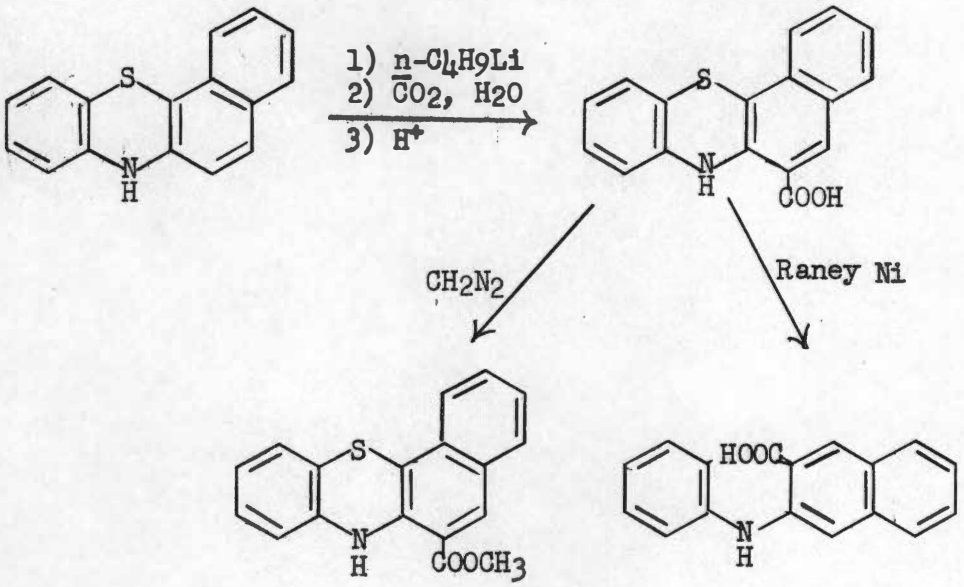
yield of 2-methoxy-3-naphthoic acid. Thus, reaction of 7H-benzo[c]-phenothiazine with n-butyllithium would afford an opportunity for meta-

lation to occur in either an α- or β-position of the napthalene ring. It would be of interest to compare the result of this metalation with those obtained from metalation of naphthalene and its 1- and 2-methoxy derivatives.

2. Experimental Results

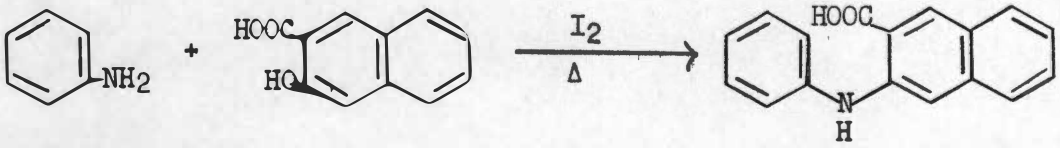
The metalation of 7H-benzo [c] phenothiazine was accomplished with an excess of n-butyllithium. Carbonation of the reaction mixture gave an orange-brown acidic material having a neutralization equivalent of approximately 304. The neutralization equivalent calculated for a monocarboxy-7H-benzo [c] phenothiazine is 293.3. Purification of this crude acidic material gave a 41 per cent yield of orange-red needles melting at 292-295° with decomposition. Subsequent recrystallizations with considerable loss raised the melting point to 300-301° with decomposition. The neutralization equivalent of the product was 296. Elemental analytical values for this acid agreed with the empirical formula $C_{17}H_{11}NO_2S$, which corresponds to a monocarboxy-7H-benzo [c] phenothiazine. A methyl ester which melted at 150-151° was prepared (III-7) from the acid and diazomethane in almost quantitative yield. The elemental analytical values for this ester agreed with the empirical formula $C_{18}H_{13}NO_2S$, which corresponds to a monocarbomethoxy-7H-benzo [c] phenothiazine.

The position of metalation in the benzophenothiazine nucleus was established by desulfurization (84) of the acid (m.p. 292-295° with decomposition) with Raney nickel (III-7). The melting point and infrared spectrum of the product obtained from the desulfurization reaction were



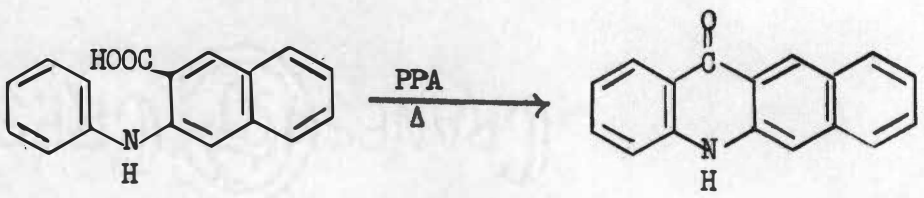
III-7

identical with the melting point and infrared spectrum of a synthetic sample of N-phenyl-3-amino-2-naphthoic acid, prepared according to a modification of the procedure (III-8) of Schöpff (85).



III-8

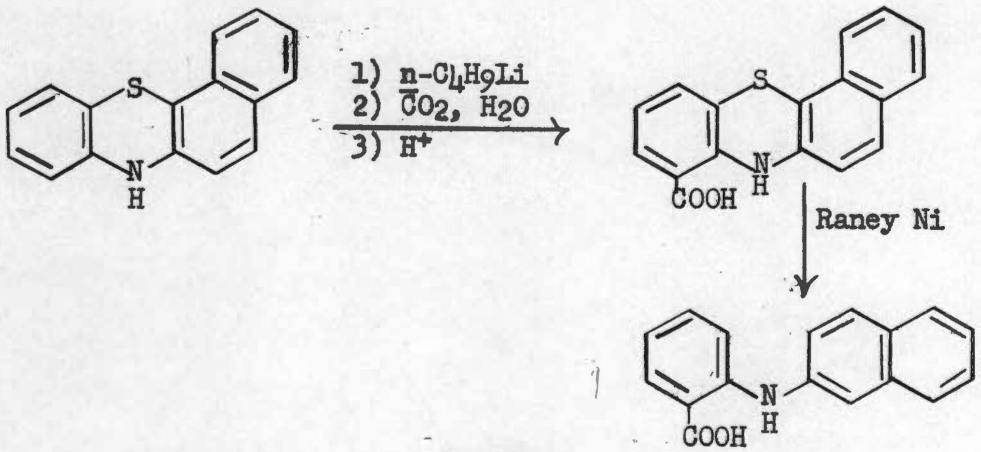
A sample of N-phenyl-3-amino-2-naphthoic acid obtained from the desulfurization of 6-carboxy-7H-benzo [c] phenothiazine was heated with an excess of polyphosphoric acid to give (III-9) a 90 per cent yield of benz [b] acridone, m.p. 304-305°. Benz [b] acridone, m.p. 304-305°, was



III-9

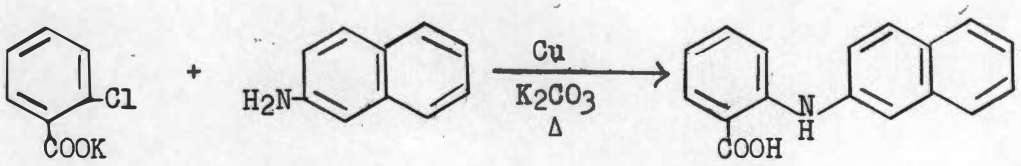
also obtained (III-9) by reaction of polyphosphoric acid with a sample of N-phenyl-3-amino-2-naphthoic acid synthesized from aniline and 3-hydroxy-2-naphthoic acid. Infrared spectra of both samples of benz [b]-acridone obtained from the different samples of N-phenyl-3-amino-2-naphthoic acid (synthetic and desulfurization product) were identical. Albert, Brown, and Duewell (86) reported the melting point of benz [b]-acridone as 303°.

Had 7H-benzo [c] phenothiazine been metalated in the 8-position (the position ortho to nitrogen in the benzene ring) in any detectable amount, then N-(o-carboxyphenyl)-2-naphthylamine should also have been isolated as a product of the Raney nickel desulfurization reaction, as shown in III-10. A synthetic sample of N-(o-carboxyphenyl)-2-naphthyl-



III-10

amine was prepared (III-11) according to the procedure of Ullmann and

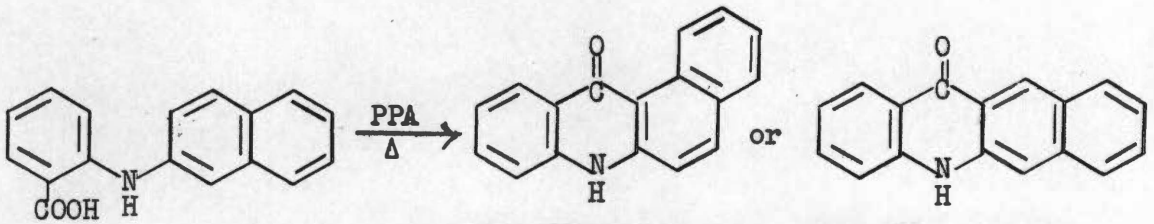


III-11

Rasetti (87). The product (white needles) melted at 210-211°, whereas Ullmann and Rasetti reported the melting point as 212°. The infrared spectrum (and melting point) of this acid were not identical with the melting point and infrared spectrum of the N-phenyl-3-amino-2-naphthoic acid obtained from a Raney nickel desulfurization of the 7H-benzo [c] - phenothiazine metalation acid.

As only one product, N-phenyl-3-amino-2-naphthoic acid, was isolated each time the Raney nickel desulfurization reaction was carried out, it was concluded that metalation of 7H-benzo [c] phenothiazine occurred primarily in the 6-position. In one case, a Raney nickel desulfurization of the crude metalation acid (obtained directly from carbonation of 7H-benzo [c] phenothiazine) was carried out, and also yielded only N-phenyl-3-amino-2-naphthoic acid, but in very poor yield. The poor yields (24 per cent or less) are partially attributed to adsorption of product (or reactant) on the surface of the rather large amount of Raney nickel present in the reaction mixture.

It is of interest at this point to note that treatment of N-(o-carboxyphenyl)-2-naphthylamine with polyphosphoric acid could lead to both benz [a] acridone and benz [b] acridone (III-12). Ullmann and Rasetti



benz [a] acridone benz [b] acridone

III-12

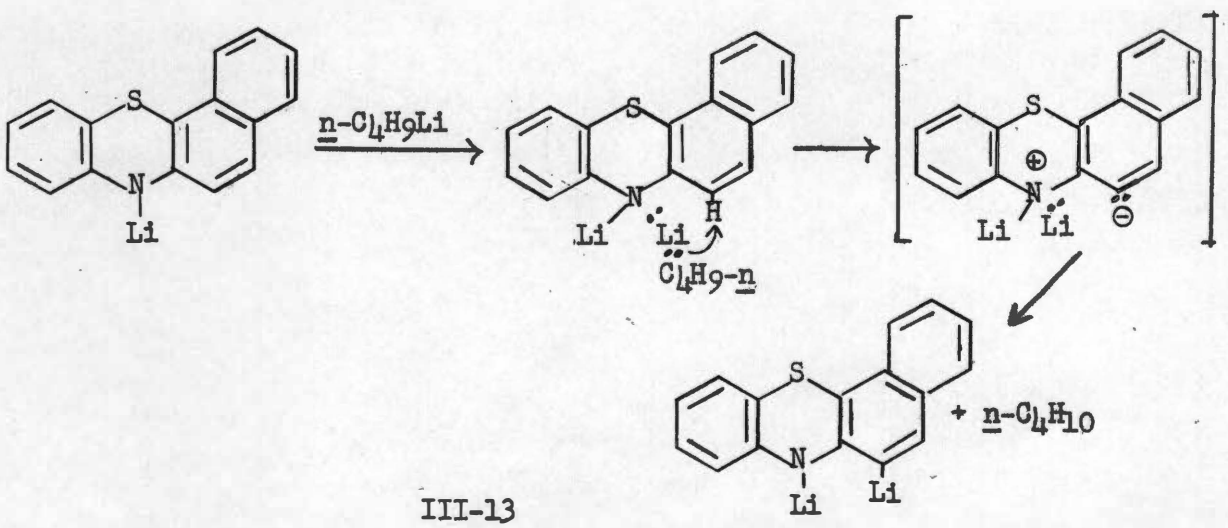
(87) reported that only benz [a] acridone, m.p. >360°, was obtained when N-(o-carboxyphenyl)-2-naphthylamine was heated with phosphorous pentachloride and aluminum chloride. Evidence for assignment of the structure benz [a] acridone to the product was based on reduction of the compound to benz [a] acridine and comparison of physical properties with those given previously by Ullmann and Baezner (88) for benz [a] acridine. In work reported in this dissertation, treatment of N-(o-carboxyphenyl)-2-naphthylamine with polyphosphoric acid gave an 89 per cent yield of benz [a] acridone, m.p. > 360°.

3. Interpretation of Results

The results of metalation of 7H-benzo [c] phenothiazine with n-butyllithium were highly satisfactory in terms of the potential synthetic utility of this reaction. Since metalation occurred in the 6-position, which is a β-position of the naphthalene ring, this reaction will afford a method of introducing several different substituents at this position. The 6-position of 7H-benzo [c] phenothiazine would certainly be difficult to reach by use of other chemical reagents.

The results of metalation of 7H-benzo [c] phenothiazine with n-butyllithium afford further evidence that the rule of precedence of sulfur over nitrogen (40) in determining the position of metalation apparently does not hold for secondary amines. Thus, 7H-benzo [c] - phenothiazine, like phenothiazine (70) and 12H-benzo [a] phenothiazine (71), was metalated in a position ortho to nitrogen rather than ortho to sulfur.

The nucleophilic mechanism set forth by Roberts and Curtin (see pages 25-26 of this dissertation) appears to explain satisfactorily the results of metalation of 7H-benzo [c] phenothiazine with n-butyllithium. However, it should be pointed out that in metalation of aromatic secondary amines, such as 7H-benzo [c] phenothiazine, the first equivalent of n-butyllithium is consumed in replacing the active hydrogen atom of the nitrogen with lithium. Thus, in these cases, the species actually metalated is the N-lithio salt of the compound. Application of the mechanism of metalation proposed by Roberts and Curtin to the case of 7H-benzo [c] phenothiazine is shown in III-13. The postulation of forma-



III-13

tion of the six-membered-ring transition state is particularly attractive since it places the anion in a favorable position to remove the ortho hydrogen.

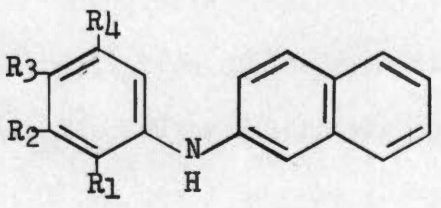
A satisfactory explanation for metalation in the 6-position of 7H-benzo[c]phenothiazine rather than in the 8-position, which is also ortho to nitrogen, cannot be given. It appears that the six-membered-ring transition state shown in III-13 could be formed just as easily by utilizing the 8-position.

CHAPTER IV

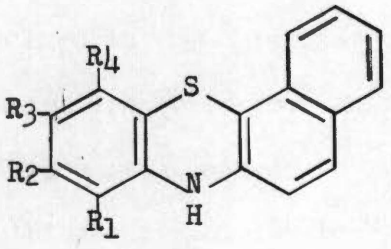
EXPERIMENTAL*

A. Synthesis of 7-(Dialkylaminoalkyl)-benzo[c]phenothiazines and Reaction Intermediates

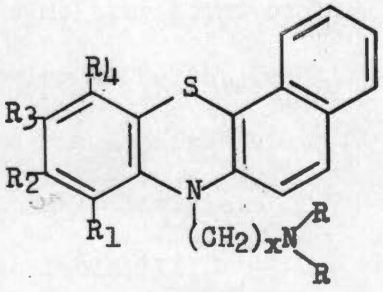
The following abbreviated structural formulas represent types of compounds synthesized in this investigation. Frequent reference will be made to these structures as an aid in clarification of chemical nomenclature.



I



II



III

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*The melting and boiling points are not corrected.

Melting points were determined with a Kofler micro hot stage apparatus, unless indicated otherwise.

Elemental microanalyses were performed by the Weiler and Strauss Microanalytical Laboratory, Oxford, England.

1. 7H-Benzo[c]phenothiazine (Structure II: $R_1=R_2=R_3=R_4=H$)

A modification of the procedure of Kehrmann and Dardel (77) was used in preparing this compound. A mixture of 21.9 g. (0.1 mole) of N-phenyl-2-naphthylamine*, 6.42 g. (0.2 mole) of sulfur, and 0.25 g. of iodine was heated at 175-180° for twenty minutes in a Wood's metal bath. The warm mass was then dissolved in the minimum quantity of boiling acetone. The acetone extract was filtered and then concentrated to a volume of about 40-50 ml. on a steam bath. Approximately 150 ml. of benzene was added to the acetone solution after which the remainder of the acetone was removed by evaporation. The benzene extract was then concentrated to a volume of approximately 70 ml. and placed in the cold room to allow crystallization of the product. The crude yellow solid thus obtained was collected by filtration and recrystallized from benzene to yield 14.9 g. (61 per cent) of pure 7H-benzo[c]phenothiazine, m.p. 180-181°. Kehrmann and Dardel (77) report a melting point of 178° for this compound.

Other runs employing different reaction conditions gave yields of 7H-benzo[c]phenothiazine ranging from 46 to 60 per cent. The effect of varied reaction conditions on the yield of 7H-benzo[c]phenothiazine obtained is illustrated in Table III.

2. N,N-Dialkylaminoalkyl Chlorides

All of the dialkylaminoalkyl chloride hydrochlorides used were obtained commercially except 2-diethylaminoethyl chloride hydrochloride

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*Eastman White Label Grade, m.p. 108-109°, was used.

TABLE III

EFFECT OF VARIED REACTION CONDITIONS ON THE YIELD OF 7H-BENZO [c] PHENOTHIAZINE

Reaction Temperature (°C)	Reaction Time (Mins.)	Solvent Used to Extract Crude Product	No. of Recrystallizations Required on Extracted Product	Solvent for Recrystallization	Melting Point of Product (°C)	Yield (Per Cent)
180	35	Benzene	1	Acetone-Ligroin (b.p. 60-75°)	178-179	46
180-190	40	95 Per Cent Ethanol*	1	Benzene	177-179	48
178-182	15	Acetone	1	Benzene	180-181	55
180-190	60	95 Per Cent Ethanol	1	Benzene	178-179.5	55
170-173	20	95 Per Cent Ethanol	2	Benzene	178-179	55
178-182	20	Acetone	1	Benzene	179-180	57
180	25	Acetone-95 Per Cent Ethanol	1	Benzene	180-181	60

*When 95 per cent ethanol was used to extract the crude product, the subsequent step always involved the addition of water to precipitate the crude 7H-benzo [c] phenothiazine.

which was prepared by the procedure of Slotta and Behnisch (89). The free bases were prepared from the hydrochlorides by the procedure of Gilman and Shirley (10).

a. 2-Diethylaminoethyl chloride hydrochloride. To a chilled (ice bath) solution of 156 g. (1.32 moles) of 2-diethylaminoethyl alcohol in 1500 ml. of benzene was added a solution of 321 g. (2.7 moles) of thionyl chloride in 300 ml. of benzene. The mixture was stirred rapidly throughout the addition period. The contents of the flask were refluxed for two hours on a water bath, cooled and filtered. There was obtained 213 g. (95 per cent) of the white hydrochloride.

b. 2-Diethylaminoethyl chloride. One hundred grams (0.58 mole) of the above hydrochloride was dissolved in the minimum amount of boiling water and then treated with 150 ml. of 40 per cent aqueous sodium hydroxide. The liberated chloride was extracted with 500 ml. of ether. The ethereal extract was dried with anhydrous sodium sulfate and distilled. The material boiling at 146-147° was collected, diluted with 50 ml. of dry xylene* and stored in the cold room. The yield of colorless liquid product was 55 g. (70 per cent).

Other dialkylaminoalkyl chlorides used were obtained from the corresponding hydrochlorides by this same procedure.

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*All of the dialkylaminoalkyl chlorides employed in this investigation tended to dimerize on standing. To minimize this reaction, the free bases were diluted with dry xylene and stored in the cold room.

3. Sodamide

A modification of Vogel's suggested procedure (90) was used to prepare all sodamide employed in this investigation. In a 500-ml., three-necked flask having ground joints and equipped with a removable glass stopper, a ball-joint stirrer and a "Dry-Ice" condenser, was placed approximately 100 ml. of liquid ammonia. Sufficient sodium to produce a permanent blue color was added, then one very small crystal of ferric nitrate was added followed by the remainder of the 0.9 g. of sodium (thirty minutes). Following the addition of the last piece of sodium, stirring was continued until the mixture turned into a grey suspension. The ammonia was then evaporated by means of a water bath, during which sufficient anhydrous xylene (or toluene) was added through a dropping funnel in order that the volume of liquid remained at about 100 ml. After complete removal of the ammonia, the sodamide suspension was stirred and warmed on the steam bath for five minutes, and then cooled to room temperature. The sodamide thus prepared was used immediately in subsequent reactions. A theoretical yield may be assumed in the sodamide preparation (90).

4. 7-(2-Dimethylaminoethyl)-benzo[c]phenothiazine (Structure III: $x=2$; $R=CH_3$; $R_1=R_2=R_3=R_4=H$)

This compound was prepared according to the procedure of Talukdar and Shirley (9) employing only minor modifications. Freshly prepared sodamide (0.09 mole), contained in a 500-ml., three-necked flask equipped with a ball-joint stirrer and dropping funnel, was covered with 80 ml. of dry toluene. To this warm suspension was added 20 g. (0.08 mole) of

powdered 7H-benzo[c]phenothiazine. A wine color developed immediately upon addition of the benzophenothiazine, and the resulting mixture was refluxed with stirring for 1.25 hours (no more ammonia evolution detected), after which 11.8 g. (0.11 mole) of dimethylaminoethyl chloride in 10 ml. of dry toluene was added over a period of forty minutes. During addition of the chloride solution, the wine color of the suspension gradually disappeared and was replaced by a yellow-green color. After one further hour of reflux, the solution was cooled in an ice bath, and an excess of 10 per cent acetic acid solution was added. The resulting layers were separated, and the toluene layer extracted twice more with 10 per cent acetic acid solution. The combined acid extracts were washed once with toluene and then basified with 40 per cent aqueous sodium hydroxide solution. The dark oil which separated was extracted several times with ether. The ether extracts were combined and dried with anhydrous sodium sulfate. After removal of the ether on a steam bath, the dark oily residue was distilled *in vacuo*, yielding 15.0 g. of crude, viscous oil, b.p. 235-240°/0.5 mm. Redistillation of this crude oil yielded 11.0 g. (43 per cent) of highly viscous, yellow-orange oil, b.p. 212-214°/0.2 mm.

Anal. Calcd. for $C_{20}H_{20}N_2S$: C, 74.96; H, 6.29; N, 8.74.

Found: C, 75.09; H, 6.10; N, 8.80.

Several modifications of this procedure gave yields ranging from 23 to 39 per cent. Pertinent experimental details for these other runs are listed in Table IV.

TABLE IV

EFFECT OF VARIED REACTION CONDITIONS ON THE YIELD OF 7-(2-DIMETHYLAMINOETHYL)-BENZO [c] PHENOTHIAZINE

Moles of Benzo [c] phenothiazine Used	Moles of Chloride Used	Moles of Sodamide Used	Reflux Time* for N-sodio Salt Formation (Mins.)	Reflux Time Required After Chloride Addition (Hrs.)	Reaction Solvent	Acid Used in Work-Up of Product	B.P. of Product (°C)	Yield (Per Cent)
0.035	0.037	0.038	15	2.5	Xylene	5 per cent hydrochloric acid	220-230 at 0.3-0.5 mm.	23
0.036	0.102	0.042	30	4	Xylene	5 per cent hydrochloric acid	212-214 at 0.2 mm.	25
0.041	0.050	0.043	90	2.5	Xylene	5 per cent hydrochloric acid	212-214 at 0.2 mm.	34
0.040	0.055	0.045	75	0.5	Toluene	10 per cent acetic acid	212-214 at 0.2 mm.	39

*This represents the time of reflux from addition of benzophenothiazine up to the beginning of chloride addition.

5. 7-(2-Dimethylaminoethyl)-benzo[c]phenothiazine Methiodide

The procedure followed was similar to that given by Shriner and Fuson (91). An excess of methyl iodide was added to an ethereal solution of 7-(2-dimethylaminoethyl)-benzo[c]phenothiazine. The solution was then warmed on a steam bath and placed in the cold room. The white solid which precipitated was collected by filtration and melted at 220.5-224°. The crude methiodide was recrystallized from a hot 95 per cent ethanol solution by adding sufficient ether to produce slight cloudiness and chilling the solution. The faint yellow glassy crystals obtained melted at 231-233°. A subsequent recrystallization from the same solvent mixture did not alter the melting point.

Anal. Calcd. for $C_{21}H_{23}IN_2S$: C, 54.54; H, 5.01; N, 6.06.

Found: C, 54.50, 54.49; H, 4.84, 5.23; N, 5.95, 5.70.

6. 7-(2-Dimethylaminoethyl)-benzo[c]phenothiazine Picrate

The procedure is that of Shriner and Fuson (91). A saturated solution of 0.5 g. of 7-(2-dimethylaminoethyl)-benzo[c]phenothiazine in 95 per cent ethanol was prepared and filtered. The filtrate was added to 10 ml. of a saturated solution of picric acid in 95 per cent ethanol, and the resulting solution was heated to boiling. The solution was allowed to cool slowly. The crude orange solid thus obtained was recrystallized twice from 95 per cent ethanol, yielding yellow crystals of the picrate, m.p. 222-224°.

Anal. Calcd. for $C_{26}H_{23}N_5O_7S$: N, 12.74.

Found: N, 12.60 and 12.95.

7. 7-(3-Dimethylaminopropyl)-benzo[c]phenothiazine (Structure III: x=3; R=CH_3; R_1=R_2=R_3=R_4=H)

A suspension of freshly prepared sodamide (0.115 mole) in xylene (9) was heated under reflux and stirred during addition of 27.4 g. (0.11 mole) of powdered 7H-benzo[c]phenothiazine. Immediately the characteristic red N-sodio salt formation was observed. The red suspension was refluxed with stirring for 1.5 hours, after which the 3-dimethylaminopropyl chloride in 15 ml. of dry xylene was added over a period of forty-five minutes. The mixture was then further refluxed with continued stirring for ten hours. The reaction mixture was cooled in an ice bath and then extracted 3 times with 5 per cent aqueous hydrochloric acid solution. The acid extracts were combined, washed with ether, and then basified with sodium hydroxide pellets. The basic solution was extracted with ether during which an emulsion was encountered. The emulsion was broken with benzene. The ether-benzene extracts were dried over anhydrous sodium sulfate and then both solvents were removed on a steam bath. Distillation in vacuo of the residual oil yielded 16.7 g. of yellow oil, b.p. 235-244°/0.35 mm., largely at 240-244°/0.35 mm. The crude oil was redistilled to give a viscous yellow oil, b.p. 219-221°/0.2 mm., of which 14.7 g. (40 per cent) was obtained.

Anal. Calcd. for $C_{21}H_{22}N_2S$: C, 75.41; H, 8.38; N, 6.63.

Found: C, 75.53; H, 8.30; N, 6.61.

8. 7-(3-Dimethylaminopropyl)-benzo[c]phenothiazine Methiodide

This derivative was prepared in the usual manner (91). Two recrystallizations of the crude material from a 95 per cent ethanol and ether

solvent mixture gave faint yellow crystals, m.p. 238.5-240°.

Anal. Calcd. for $C_{22}H_{25}IN_2S$: C, 55.46; H, 5.29; N, 5.88.
Found: C, 55.31; H, 5.66; N, 5.61.

9. 7-(3-Dimethylaminopropyl)-benzo[c]phenothiazine Picrate

This picrate was prepared in 95 per cent ethanol solution as previously described (91). After recrystallization from 95 per cent ethanol, the yellow picrate melted at 177-178°.

Anal. Calcd. for $C_{27}H_{25}N_5O_7S$: N, 12.43. Found: N, 12.35, 12.60.

10. 7-(2-Diethylaminoethyl)-benzo[c]phenothiazine (Structure III: x=2; R=C_2H_5; $R_1=R_2=R_3=R_4=H$)

To a refluxing and stirred suspension of 0.15 mole of freshly prepared sodamide in xylene (9) was added 30.0 g. (0.12 mole) of 7H-benzo[c]-phenothiazine. The suspension was refluxed for one hour, after which 30.0 g. (0.22 mole) of 2-diethylaminoethyl chloride in 30 ml. of xylene was added over a period of forty-five minutes. The reaction mixture was then refluxed with stirring for 0.5 hour, and then stirred (without reflux) for another 2.5 hours. After cooling the reaction mixture, 10 per cent acetic acid was added and the resulting layers were separated. The xylene layer was extracted twice more with 10 per cent acetic acid. The acid extracts were combined and then basified with 40 per cent sodium hydroxide solution. The basic solution was extracted 3 times with ether. The ethereal extracts were combined and washed 5 times with water. After removal of the ether, the oily residue was distilled in vacuo and the product collected at 208-214°/0.08 mm., the main portion coming over at 210-212°/0.08 mm. The

crude product was redistilled to yield 25.1 g. (60 per cent) of yellow-orange oil, b.p. 210-212°/0.08 mm.

Anal. Calcd. for $C_{22}H_{24}N_2S$: C, 75.82; H, 6.94; N, 8.04.

Found: C, 75.88, 75.49; H, 6.56, 6.46; N, 7.85, 7.61.

11. 7-(2-Diethylaminoethyl)-benzo[c]phenothiazine Picrate

A picrate derivative of the above compound was prepared (91) in 95 per cent ethanol. Recrystallization of the crude compound from 95 per cent ethanol gave a golden yellow solid, m.p. 152.5-153.5°.

Anal. Calcd. for $C_{28}H_{27}N_5O_7S$: N, 12.13. Found: N, 12.05, 12.20.

12. N-(p-Tolyl)-2-naphthylamine (Structure I: $R_1=R_2=R_4=H$; $R_3=CH_3$)

The general procedure followed was that given by Knoevenagel (32). Thus, a mixture of 160.7 g. (1.5 mole) of p-toluidine, 144.2 g. (1.0 mole) of β-naphthol, and 3.0 g. of iodine was heated under reflux for forty-two hours. Upon cooling, the reaction mixture solidified into a hard, solid mass. This mixture was fractionated *in vacuo* to yield 122.8 g. of amine, b.p. 218-219°/3.5-3.7 mm. The crude amine was then recrystallized from 95 per cent ethanol to yield 106.7 g. (46 per cent) of faint yellow solid, m.p. 102-103°. Merz and Weith (92) report m.p. 102-103°.

Several other runs employing different reaction conditions gave lower yields of the desired product.

13. 10-Methyl-7H-benzo[c]phenothiazine (Structure II: $R_1=R_2=R_4=H$; $R_3=CH_3$)

a. Run 1. The procedure of Ackermann (31) was employed. A mixture of 10 g. (0.043 mole) of p-tolyl-2-naphthylamine (m.p. 103-104°), 2.8 g. (0.087 mole) of sulfur and a small iodine crystal was heated at 175-180°

in a 100-ml., round-bottom flask for twenty minutes. The reaction mixture was cooled to about 110° and at this temperature sufficient toluene was added to dissolve the reaction mixture. As the toluene solution cooled, the product crystallized and was removed by filtration. After washing with cold petroleum ether (b.p. 30-60°), the yellow product melted at 188-190°, and was sufficiently pure for subsequent reactions. The yield was 6.8 g. (60 per cent). Subsequent recrystallizations from chlorobenzene and toluene raised the melting point to 192-193°. Ackermann reports the melting point to be 182° (31).

Anal. Calcd. for $C_{17}H_{13}NS$: C, 77.55; H, 4.98; N, 5.32.

Found: C, 77.20, 77.26; H, 4.81, 5.11; N, 5.08, 5.12.

b. Run 2. A procedure involving heating the reactants at 175-180° for thirty minutes with the same work-up as in (a) gave a yield of 53 per cent.

c. Run 3. Reaction at 175° for fifteen minutes with the same work-up as in (a) gave a yield of 54 per cent.

d. Run 4. Identical procedure as in (a) was followed except the work-up was modified. The crude product was extracted with a benzene and acetone mixture. After removal of the acetone on a steam bath, the residual benzene solution was treated with "Norit-A" decolorizing carbon, filtered, and the filtrate was placed in the cold room to allow crystallization of the product. The 24.0 g. of crude product obtained was recrystallized from benzene to give 20.0 g. (48 per cent) of yellow solid, m.p. 188-190°.

14. 10-Methyl-7-(3-dimethylaminopropyl)-benzo[c]phenothiazine

(Structure III: x=3; R=CH_3; R_1=R_2=R_4=H; R_3=CH_3)

To a stirred suspension of 0.075 mole of sodamide in 60 ml. of dry xylene was added (9) 16.43 g. (0.07 mole) of 10-methyl-7H-benzo[c]-phenothiazine, followed by 15 ml. of additional dry xylene to wash in the benzophenothiazine. The characteristic wine color of the N-sodio salt was again observed. The suspension was refluxed and stirred for one hour, after which approximately 11.0 g. (0.09 mole) of 3-dimethylamino-propyl chloride in 15 ml. of xylene was added over a period of forty-five minutes. The solution was then refluxed with continued stirring for 1.5 hours. The cooled solution was extracted 3 times with 10 per cent acetic acid and once more with 5 per cent hydrochloric acid. The combined acid extracts were washed once with xylene and then basified with sodium hydroxide pellets. The product (a dark green oil which separated to the top) was extracted 3 times with ether. The combined ethereal extracts were dried over anhydrous magnesium sulfate. The ether and other low-boiling constituents were removed on a steam bath and under water pump vacuum. The residue was then distilled *in vacuo* using a Claisen head (Vigreux modification) and the yellow oil which distilled at 248-250°/1.75 mm. was collected. The yield was 15.3 g. (63 per cent).

Anal. Calcd. for $C_{22}H_{24}N_2S$: C, 75.82; H, 6.94; N, 8.04.

Found: C, 75.65, 76.02; H, 6.93, 7.04; N, 8.08, 8.20.

15. 10-Methyl-7-(3-dimethylaminopropyl)-benzo[c]phenothiazine Methiodide

The methiodide of 10-methyl-7-(3-dimethylaminopropyl)-benzo[c]-phenothiazine was prepared by the dropwise addition of methyl iodide to

an ether solution of the compound (91). Recrystallization of the crude methiodide from 95 per cent ethanol and ether gave a pale yellow solid which melted at 243-244°.

Anal. Calcd. for $C_{23}H_{27}IN_2S$: C, 56.32; H, 5.55; N, 5.71.

Found: C, 56.24, 56.21; H, 5.26, 5.56; N, 5.60, 5.50.

16. N-(2,5-Dimethylphenyl)-2-naphthylamine (Structure I: $R_1=R_4=CH_3$; $R_2=R_3=H$)

A modification of Buu-Hoi's procedure was used (76). A mixture of 35 g. (0.289 mole) of 2,5-dimethylaniline, 28.0 g. (0.194 mole) of β-naphthol, and 0.15 g. of iodine was heated for twenty-four hours in a 200-ml., round-bottom flask equipped with an air condenser. The reaction mixture was then distilled in vacuo and the material distilling at 195-200°/1.5-2.0 mm. was collected. This crude amine was redistilled at 194-195°/1.5 mm. to yield 24.2 g. (50 per cent) of a yellow viscous oil which reddened rapidly in the air. This amine was obtained as a yellow solid, m.p. 39-40°, by dissolving in petroleum ether (ligroin, b.p. 30-60°) the oil obtained from the distillation and allowing the mixture to stand in the cold room for a few hours. Buu-Hoi (76) reports an 84 per cent yield of this amine, m.p. approximately 40°.

Several modifications of the above procedure gave lower yields of the desired product.

17. 8,11-Dimethyl-7H-benzo[c]phenothiazine (Structure II: $R_1=R_4=CH_3$; $R_2=R_3=H$)

a. Run 1. A mixture of 10.0 g. (0.041 mole) of N-(2,5-dimethylphenyl)-2-naphthylamine, 2.92 g. (0.091 mole) of sulfur, and 2 small iodine

crystals was heated at 180° for twenty minutes (28). The cooled reaction mixture was extracted with benzene, treated with "Norit-A" decolorizing carbon, filtered, and placed in the cold room to allow crystallization of the product. There was obtained 8.6 g. (77 per cent) of golden yellow solid, m.p. 180-182°. Subsequent recrystallizations of the compound from benzene, toluene, and carbon tetrachloride brought the melting point to 181-183°. Chromatography of this material in benzene solution on a 2 x 50 cm. column of "Florisil" adsorbent (60/100 mesh) followed by elution with benzene, gave golden yellow needles, m.p. 180-181°. Buu-Hoï (28) reported the melting point of this compound as 170°.

Anal. Calcd. for $C_{18}H_{15}NS$: C, 77.94; H, 5.45; N, 5.05.

Found: C, 77.85, 77.99; H, 5.51, 5.22; N, 4.74, 4.86.

b. Run 2. A mixture of 10.0 g. (0.041 mole) of N-(2,5-dimethylphenyl)-2-naphthylamine, 2.92 g. (0.091 mole) of sulfur, and 2 small iodine crystals was heated at 185-195° for twenty minutes. The crude product was extracted from the reaction mixture with toluene and then recrystallized twice from benzene and once from toluene. A 45 per cent yield of product melting at 181-182.5° was obtained.

c. Run 3. The same quantities of reactants, as in (b), were heated first at 160-170° for twelve minutes and then at 170-180° for ten minutes. The cooled reaction mixture was extracted with benzene and the benzene extracts were treated with "Norit-A" decolorizing carbon and then filtered. Upon cooling the filtrate, the product crystallized and was removed by filtration. Recrystallization of this material first from carbon tetrachloride and then from benzene, yielded the yellow crystalline product, m.p. 181-182.5°, in 52 per cent yield.

d. Run 4. A mixture of 34.6 g. (0.14 mole) of N-(2,5-dimethylphenyl)-2-naphthylamine, 8.98 g. (0.28 mole) of sulfur, and 0.3 g. of iodine was heated at 180° for twenty-five minutes. The reaction mixture was cooled, extracted with carbon tetrachloride, treated with "Norit-A", filtered, and placed in the cold room. The yellow powder thus obtained was recrystallized twice from benzene to yield 26.0 g. (67 per cent) of yellow product, m.p. 177-179°.

18. 8,11-Dimethyl-7-(3-dimethylaminopropyl)-benzo [c] phenothiazine

(Structure III: x=3; R=CH_3; R_1=R_4=CH_3; R_2=R_3=H)

The N-alkylation reaction was carried out in the usual manner (9). Freshly prepared sodamide (0.65 mole) was covered with 75 ml. of dry xylene. To this solution was added 16.85 g. (0.606 mole) of 8,11-dimethyl-7H-benzo [c] phenothiazine. The resulting suspension was refluxed and stirred for one hour. Approximately 12.2 g. (0.1 mole) of 3-dimethylaminopropyl chloride in 15 ml. of dry xylene was then added dropwise over a period of one hour. The solution was then refluxed and stirred for two more hours. The reaction mixture was cooled in an ice bath, extracted several times with 10 per cent acetic acid, and the acid extracts were combined. The xylene layer was then extracted twice with 6 per cent hydrochloric acid solution. All the acid extracts were combined, washed once with xylene, and then basified with sodium hydroxide pellets. The dark oil which separated was extracted 4 times with ether. The ethereal extracts were combined and dried with anhydrous magnesium sulfate. The ether was then removed and the residue distilled in vacuo, using a Claisen

head (Vigreux modification) for distillation. The yellow oil, distilling at 236-238°/1.25 mm., was collected. There was obtained 12.1 g. (55 per cent) of pure product.

Anal. Calcd. for $C_{23}H_{26}N_2S$: C, 76.20; H, 7.23; N, 7.73.
Found: C, 75.81, 75.70; H, 6.99, 6.84; N, 8.07, 8.24.

19. 8,11-Dimethyl-7-(3-dimethylaminopropyl)-benzo[c]phenothiazine Methiodide

This methiodide was prepared in the usual manner (91). Two recrystallizations of the crude methiodide from a 95 per cent ethanol and ether mixture gave faint yellow crystals, m.p. 251-252.5°.

Anal. Calcd. for $C_{24}H_{29}IN_2S$: C, 57.14; H, 5.79; N, 5.55.
Found: C, 57.78; H, 5.95; N, 5.19.

20. N-(p-Methoxyphenyl)-2-naphthylamine (Structure I: $R_1=R_2=R_4=H$; $R_3=OCH_3$)

Following the general procedure described by Knoevenagel (32) for preparation of secondary amines of this type, a mixture of 28.8 g. (0.2 mole) of β-naphthol, 30.8 g. (0.25 mole) of p-anisidine, and 0.5 g. of iodine was heated for twenty-four hours under reflux using an air condenser. The desired amine was obtained by distillation of the reaction mixture in vacuo followed by recrystallization of the crude product from 95 per cent ethanol solution. There was obtained 24.5 g. (49 per cent) of faint pink crystalline product, m.p. 104-104.5°. The melting point reported for N-(p-methoxyphenyl)-2-naphthylamine by Bucherer and Seyde (93) was 104°.

21. 10-Methoxy-7H-benzo[c]phenothiazine (Structure II: $R_1=R_2=R_4=H$; $R_3=OCH_3$)

After investigating numerous conditions for the preparation of 10-methoxy-7H-benzo[c]phenothiazine, the following procedure was found to be superior. A mixture of 6.25 g. (0.025 mole) of N-(p-methoxyphenyl)-2-naphthylamine, 1.6 g. (0.05 mole) of sulfur, and two small iodine crystals was heated at 180-185° for eight minutes. After allowing the reaction mixture to cool, the product was extracted with benzene. The benzene solution was filtered, placed on a 2 x 50 cm. column of "Florisil" adsorbent (60/100 mesh), and then eluted with benzene. The chromatographed product, after recrystallization from benzene using a "Norit-A" decolorizing carbon treatment, appeared as golden yellow needles and melted at 167-167.5°. The yield obtained was 3.61 g. (52 per cent). Subsequent recrystallizations from benzene and toluene did not alter the melting point.

Anal. Calcd. for $C_{17}H_{13}NOS$: C, 73.09; H, 4.69; N, 5.01.

Found: C, 73.01, 72.30; H, 4.72, 4.86; N, 5.01, 4.69.

Other runs employing modifications of the above procedure gave lower yields of product. These modifications are tabulated in Table V in order to illustrate the effect of a change in reaction variables on the yield of 10-methoxy-7H-benzo[c]phenothiazine.

22. 10-Methoxy-7-(3-dimethylaminopropyl)-benzo[c]phenothiazine (Structure III: $x=3$; $R=CH_3$; $R_1=R_2=R_4=H$; $R_3=OCH_3$)

This compound was prepared in the usual manner (9). To a refluxing and stirred suspension of freshly prepared sodamide (0.065 mole) in 80 ml. of dry xylene was added 16.0 g. (0.057 mole) of 10-methoxy-7H-benzo[c]-

TABLE V

EFFECT OF REACTION PROCEDURE MODIFICATIONS ON THE YIELD OF 10-METHOXY-7H-BENZO[c] PHENOTHIAZINE

Reaction Temperature (°C)	Reaction Time (Mins.)	Solvent Used to Extract Crude Product	No. of Recrystallizations Required on Extracted Product	Solvent for Recrystallization	Melting Point of Product (°C)	Yield (Per Cent)
180	10	Toluene	2	Benzene	167	47
175-185	12	Benzene	2	1) Toluene 2) Benzene	165-167	45
180-185	15	Benzene	1	Benzene	167	43
180-185	20	Benzene	2	Benzene	166-167	41

phenothiazine. The resulting red mixture was refluxed and stirred for forty-five minutes. The 3-dimethylaminopropyl chloride (0.075 mole) in 15 ml. of xylene was then added over a period of forty-five minutes, during which the red color of the solution was replaced by a greenish color. Following addition of the chloride, the solution was refluxed for five hours and then allowed to cool to room temperature. The product was extracted several times with 5 per cent hydrochloric acid solution. The acid extracts were combined and washed with xylene. The acidic solution was basified with sodium hydroxide pellets and the dark oil thus liberated was extracted several times with ether. The ether extracts were combined and dried with anhydrous sodium sulfate. After removal of the ether, the residue was distilled *in vacuo* (using a modified Claisen head) to yield 10.1 g. of yellow-orange oil, b.p. 260-266°/1.3-1.4 mm. This oil was redistilled at 245-247°/1.45 mm., yielding 8.4 g. (43 per cent) of highly viscous yellow-orange oil.

Anal. Calcd. for $C_{22}H_{24}N_2OS$: C, 72.49; H, 6.64; N, 7.69.

Found: C, 72.72, 72.27; H, 6.49, 6.51; N, 7.20, 7.42.

Other attempts to improve the yield in this reaction were unsuccessful.

A satisfactory derivative of the above compound could not be prepared. The compound formed both a methiodide and picrate, but neither could be satisfactorily purified.

23. N-(m-Chlorophenyl)-2-naphthylamine (Structure I: $R_1=R_3=R_4=H$; $R_2=Cl$)

This amine was prepared (32) by refluxing a mixture of 95.7 g. (0.75 mole) of m-chloroaniline, 72.1 g. (0.5 mole) of β-naphthol, and 1.0 g. of iodine for forty-five hours. The product was obtained by distillation in vacuo of the crude reaction mixture. The amine was collected at 218-221°/2.5 mm. and then recrystallized from 95 per cent ethanol. The yield was 92.0 g. (73 per cent) of faint pink crystalline amine, which melted at 100-101°. Knoevenagel (32) reports N-(m-chlorophenyl)-2-naphthylamine, b.p. 250-253°/11 mm., to melt at 101°.

24. 9-Chloro-7H-benzo[c]phenothiazine (Structure II: $R_1=R_3=R_4=H$; $R_2=Cl$)

A mixture of 15 g. (0.059 mole) of N-(m-chlorophenyl)-2-naphthylamine, 3.75 g. (0.117 mole) of sulfur, and 0.2 g. of iodine was heated at 180° for exactly nine minutes. After cooling the reaction mixture to about 110°, the product was extracted with hot toluene. The toluene extract was filtered and placed in the cold room to permit crystallization of the product. The crude product thus obtained was recrystallized from toluene using "Norit-A" to yield 9.4 g. (56 per cent) of yellow crystals, m.p. 163-163.5°. The yield reported by Knoevenagel (32) for the preparation of this compound according to the above procedure was 70 per cent.

Anal. Calcd. for $C_{16}H_{10}ClNS$: C, 67.72; H, 3.55; N, 4.94.

Found: C, 68.15, 68.53; H, 3.75, 3.93; N, 4.95, 5.02.

Other preparations of this compound, carried out in a similar manner, resulted in yields ranging from 41 to 55 per cent.

25. 9-Chloro-7-(3-dimethylaminopropyl)-benzo[c]phenothiazine (Structure III: x=3; R=CH_3; R_1=R_3=R_4=H; R_2=Cl)

The procedure followed was similar to that used in previous N-alkylation reactions (9). Freshly prepared sodamide (0.085 mole) was covered with 75 ml. of dry xylene. To this was added 21.3 g. (0.075 mole) of 9-chloro-7H-benzo[c]phenothiazine, and the resulting red suspension was refluxed and stirred for forty-five minutes. The 3-dimethylaminopropyl chloride (approximately 0.10 mole) was added dropwise with continued stirring and reflux over a period of forty-five minutes. After one further hour of refluxing and stirring, the solution was stirred at 100° for six hours and then cooled in an ice bath. The mixture was extracted twice with 8 per cent acetic acid and then once with 4 per cent hydrochloric acid solution. The acid extracts were combined, washed once with xylene, and basified with sodium hydroxide pellets. The product separated to the top as a dark, viscous oil which was extracted 4 times with ether. The combined ethereal extracts were dried over anhydrous sodium sulfate. After removal of the ether and other low-boiling constituents, the oily residue was distilled *in vacuo* to yield 15.3 g. of crude product boiling at 250-260°/1.3 mm. Redistillation of the crude oil yielded 12.1 g. (44 per cent) of yellow, viscous oil, b.p. 253-256°/1.3 mm.

Anal. Calcd. for $C_{21}H_{21}ClN_2S$: C, 68.37; H, 5.74; N, 7.59.

Found: C, 68.27, 68.76; H, 5.53, 5.43; N, 7.32, 7.36.

26. 9-Chloro-7-(3-dimethylaminopropyl)-benzo[c]phenothiazine Methiodide

The methiodide of 9-chloro-7-(3-dimethylaminopropyl)-benzo[c]-phenothiazine was prepared (91) in ether solution. Two recrystallizations

of the crude material from 95 per cent ethanol and ether gave a faint yellow methiodide melting at 217-218.5°.

Anal. Calcd. for $C_{22}H_{24}ClIN_2S$: C, 51.72; H, 4.74; N, 5.48.

Found: C, 51.87, 51.58; H, 4.81, 4.61; N, 5.46, 5.54.

B. A Study of the Metalation of 7H-Benzo [c] phenothiazine With n-Butyllithium*

1. Preparation of n-Butyllithium

The procedure is essentially that of Gilman, Beel, Brannen, Bullock, Dunn, and Miller (53). A 1-l., three-necked flask was equipped with a reflux condenser, mechanical stirrer, and a graduated dropping funnel. The apparatus was swept out thoroughly with dry nitrogen. A mixture of 17.2 g. (2.48 g. atoms) of lithium (cut into small pieces) and 400 ml. of sodium-dried ether was placed in the flask. About 30 drops of a solution of 137.0 g. (1.0 mole) of reagent grade n-butyl bromide in 100 ml. of dry ether was then added to initiate reaction. After the reaction had commenced (as was evidenced by a steady ether reflux and the appearance of shiny lithium surface), the reaction mixture was cooled to -10° in a bath of acetone and crushed solid carbon dioxide. The temperature of the reaction mixture was maintained at -10° while the remainder of the n-butyl bromide-ether solution was added dropwise over a period of one hour. After the addition was complete, the mixture was allowed to warm to 0-10° over

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*Several of the acids synthesized in this metalation work tended to sublime before melting. It was therefore desirable to determine the melting points of all acids prepared in this investigation by use of sealed capillary tubes.

a period of two hours. The mixture was then decanted into a graduated dropping funnel through a narrow glass tube plugged with glass wool. The transfer was made under an atmosphere of dry nitrogen. The yields of n-butyllithium thus obtained were determined by the double-titration method of Gilman and Haubein (94), and ranged between 60 and 75 per cent.

2. Metalation of 7H-Benzo [c] phenothiazine With n-Butyllithium

a. Run 1. A 500-ml., three-necked flask having ground joints was equipped with a dropping funnel, reflux condenser, and magnetic stirrer. The system was flushed with dry nitrogen and maintained under an atmosphere of nitrogen. Finely pulverized 7H-benzo [c] phenothiazine (12.5 g., 0.05 mole) melting at 180-181° was placed in the flask and covered with 200 ml. of dry ether. A solution of 0.141 mole of n-butyllithium in 125 ml. of ether was added with stirring over a period of twenty minutes. The mixture was allowed to stir under reflux for twenty-six hours. After cooling in a Dry Ice-acetone bath, the mixture was carbonated by addition of small pieces of Dry Ice to the flask. As soon as the mixture warmed to room temperature, it was hydrolyzed with 150 ml. of distilled water. The two layers were separated, and the ether layer was extracted 3 times with 5 per cent aqueous sodium hydroxide solution. The aqueous extracts were combined with the initial water layer and then washed twice with ether. Evaporation of the ethereal layer from the metalation reaction mixture and subsequent recrystallization of the crude solid thus obtained yielded 0.5 g. of yellow crystalline solid, m.p. 179-181°. A mixture of this solid and a sample of 7H-benzo [c] phenothiazine, m.p. 180-181°, melted at 180-181°. Acidification of the cooled (ice bath) aqueous solu-

tion from above with 50 per cent hydrochloric acid solution yielded an orange-brown solid which was collected by filtration. After drying in a vacuum oven, the crude acidic material weighed 14.1 g. A neutralization equivalent of this material was determined in an ethanol-benzene solvent mixture and gave a value of approximately 304. The value calculated for a monocarboxybenzo[c]phenothiazine is 293.3. The acidic material melted at 248-257° with decomposition. Fractional crystallization of this crude material initially from a benzene and ligroin (b.p. 60-75°) solvent mixture and then from an acetone and ligroin (b.p. 60-75°) mixture yielded about 0.8 g. of a red-orange solid melting at 300-301° with decomposition and approximately 50 mg. of an orange material, m.p. 264-266° with decomposition. A yield is not reported here due to considerable mechanical loss.

(1) 6-Carboxy-7H-benzo[c]phenothiazine. Subsequent physical and chemical evidence obtained from degradation reactions, infrared analyses, etc. indicated that the red-orange solid melting at 300-301° with decomposition was 6-carboxy-7H-benzo[c]phenothiazine. Two further recrystallizations of the compound from a tetrahydrofuran-ligroin (b.p. 90-120°) mixture failed to alter the melting point of the acid. The acid was insoluble in warm 5 per cent sodium bicarbonate solution, moderately soluble in cold acetone and benzene, and very soluble in tetrahydrofuran. An infrared spectrum* of the compound was determined. A very pronounced

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*All infrared spectra were determined using a Perkin-Elmer, Model 21, double beam infrared spectrophotometer employing the potassium bromide disc technique. Concentrations of approximately 1 mg. of sample in 250-300 mg. of potassium bromide were employed, and a sodium chloride prism was used. All spectra determined in this work are on file in the Department of Chemistry, University of Tennessee.

band at 5.97 microns (carbonyl band (81) of the carboxylic acid group) was observed which did not appear in the spectrum of 7H-benzo[c]phenothiazine.

The neutralization equivalent of this acid was measured in a solvent mixture consisting of 80 per cent absolute ethanol and 20 per cent benzene. Titration was made with standard sodium hydroxide solution, employing phenolphthalein as indicator. After correcting for the solvent blank, a value of 295.8 was found, and this is in reasonable agreement with the calculated value of 293.3.

Anal. Calcd. for $C_{17}H_{11}NO_2S$: C, 69.60; H, 3.78; N, 4.80.

Found: C, 69.38, 69.25; H, 3.80, 3.87; N, 4.68, 5.11.

(2) Unknown metalation acid. The orange solid melting at 264-266° with decomposition and some prior darkening, was recrystallized from an acetone and ligroin (b.p. 60-75°) solvent mixture, but the decomposition point was unchanged. The solid was insoluble in warm, 5 per cent sodium bicarbonate solution, moderately soluble in cold acetone and benzene, and very soluble in tetrahydrofuran. The acidic material gave a neutralization equivalent of 294.1 as compared to the calculated value of 293.3 for a monocarboxy-7H-benzo[c]phenothiazine.

Anal. Calcd. for $C_{17}H_{11}NO_2S$: C, 69.60; H, 3.78, N, 4.80.

Found: C, 69.47, 69.57; H, 3.80, 3.85; N, 4.86, 4.54.

The pronounced similarity of the infrared spectrum of this material with that of the other metalation acid, m.p. 300-301° with decomposition, seems to indicate that this solid may possibly be an impure sample of the higher melting acid.

An attempt to prepare the methyl ester of this acid with diazomethane was unsuccessful, i.e., the ester obtained could not be satisfactorily purified. This, too, would strongly indicate that the acid was impure. Insufficient material prevented further study of this acid.

b. Run 2. The procedure followed here was similar to Run 1, except that 25 g. (0.1 mole) of 7H-benzo[c]phenothiazine in 300 ml. of ether was metalated with 0.24 mole of freshly prepared n-butyllithium in 200 ml. of ether. Carbonation, hydrolysis, and extraction of the water layer were performed as previously described in (a). Acidification of the aqueous layer yielded 23.6 g. of tan acidic solid. Reprecipitation of this acid through the sodium salt gave 21.1 g. of acidic material. Purification of this solid was accomplished by dissolving it in the minimum amount of tetrahydrofuran, treating the solution with "Norit-A" decolorizing carbon, and filtering. The filtrate was then heated to boiling, ligroin (b.p. 60-75°) was added, and the remainder of the tetrahydrofuran was removed. The ligroin solution was then placed in the cold room to allow crystallization of the product. There was obtained 12.1 g. (41 per cent) of red-orange needles melting at 292-295° with decomposition. This material was sufficiently pure for subsequent reactions.

Other metalation runs were made, but the procedure and work-up employed were similar to that of Run 2 and therefore will not be described.

3. Preparation of 6-Carbomethoxy-7H-benzo[c]phenothiazine

A solution of approximately 0.1 mole of diazomethane in 150 ml. of ether was prepared from N-methyl-N-nitroso-p-toluenesulfonamide according to the procedure of DeBoer and Backer (95). To this cooled (ice bath) solu-

tion was added 0.1 g. (0.0034 mole) of acid in ether. An evolution of gas from the solution was observed. The solution was allowed to remain overnight under a hood to permit evaporation of the ether. There was obtained 96 mg. (92 per cent) of red-orange crystals melting at 149-150°. Recrystallizations from petroleum ether and then from methanol raised the melting point to 150-151°. An infrared spectrum of this ester exhibited a pronounced band at 5.90 microns, which is characteristic of the carbonyl of an ester group (81).

Anal. Calcd. for $C_{18}H_{13}NO_2S$: C, 70.33; H, 4.26; N, 4.56.

Found: C, 70.40, 70.42; H, 4.25, 4.30; N, 4.67, 4.90.

4. Activation of Raney Nickel

Following the procedure of Covert and Adkins (96), 100 g. of commercial nickel-aluminum alloy was added during two hours to a solution of 100 g. of sodium hydroxide in 400 ml. of distilled water, contained in a 2-l. beaker surrounded by ice. The mixture was then heated on a hot plate for 2.5 hours, with occasional stirring, at 115-125°. A further 133 ml. of a 19 per cent solution of sodium hydroxide was added and the mixture held at 115-120° for two more hours. The suspension was then diluted to a volume of one liter. The solution of sodium aluminate was decanted and the nickel washed by decantation about 20 times (or until the wash solution was neutral to litmus). The nickel was then washed 4 times with 95 per cent ethanol and then stored in the cold room under absolute ethanol in glass-stoppered bottles.

5. Raney Nickel Desulfurization Reactions (84)

a. Desulfurization of crude 7H-benzo[c]phenothiazine metalation acid. Five grams (0.017 mole) of crude acidic material obtained directly from acid precipitation of the aqueous solution resulting from metalation of 7H-benzo[c]phenothiazine with n-butyllithium, was subjected to a Raney nickel desulfurization reaction. The acid was placed in a 1-l., three-necked flask containing 250 ml. of 95 per cent ethanol. Only a portion of the acidic material dissolved. To this suspension was added approximately 50 g. of activated Raney nickel in about 100 ml. of absolute ethanol. Sufficient 95 per cent ethanol to bring the total volume of the solution to 450 ml. was added. The mixture, reddish-brown in color, was refluxed and stirred (magnetic stirrer) for 4.5 hours after which time the solution was light yellow in color. The solution was cooled and the catalyst was removed by filtration. The filtrate was concentrated on a hot plate to a very small volume and placed in the cold room. The crude yellow-green solid thus obtained was recrystallized from benzene, using "Norit-A" decolorizing carbon treatment to yield 0.110 g. of yellow needles, m.p. 235-237°. The structure corresponding to N-phenyl-3-amino-2-naphthoic acid was assigned to this compound, since its melting point and infrared spectrum were identical with the melting point and infrared spectrum of an authentic synthetic sample of N-phenyl-3-amino-2-naphthoic acid (see page 75). Both samples of N-phenyl-3-amino-2-naphthoic acid above were observed to sublime readily below the melting point. Thus, sealed capillary tubes were used to determine the melting points. On the other hand, the infrared spectra and melting points of

this acid, m.p. 235-237°, (obtained from the desulfurization reaction) and a synthetic sample of N-(o-carboxyphenyl)-2-naphthylamine (see page 78) were not identical.

The poor yield of N-phenyl-3-amino-2-naphthoic acid probably resulted from loss of material due to adsorption of product (or reactant) on the large surface of Raney nickel available in the reaction mixture, rather than from mechanical losses.

b. Desulfurization of purified 6-carboxy-7H-benzo[c]phenothiazine. Seven grams (0.024 mole) of 6-carboxy-7H-benzo[c]phenothiazine melting at 292-295° with decomposition was placed in a 1-l., three-necked flask equipped with a reflux condenser and magnetic stirrer. The acid was covered with about 300 ml. of 95 per cent ethanol. To this solution was added about 80 g. of freshly activated Raney nickel in 150 ml. of absolute ethanol. After stirring and refluxing the red suspension for thirty minutes, the color of the solution changed to a light yellow, but refluxing and stirring was continued for another 1.5 hours. The reaction mixture was cooled in an ice bath and the catalyst removed by filtration. The yellow filtrate was concentrated to a volume of 150 ml., treated with "Norit-A" decolorizing carbon, and filtered. This filtrate was concentrated to a volume of approximately 20 ml. and a few drops of 5 per cent hydrochloric acid solution were added to the hot solution to produce cloudiness. Cooling precipitated a yellow solid which was removed by filtration. There was obtained 1.6 g. (25 per cent) of yellow solid melting at 233-236°. Recrystallization of the material from benzene gave 1.4 g. of yellow needles, m.p. 235-237°. The melting point and infrared

spectrum of this material were also identical with the melting point and infrared spectrum of the synthetic sample of N-phenyl-3-amino-2-naphthoic acid.

6. Preparation of Benz[b]acridone

To a 100-ml., round-bottom flask was added 200 mg. of N-phenyl-3-amino-2-naphthoic acid, m.p. 235-237°, which was obtained from a Raney nickel desulfurization of 6-carboxy-7H-benzo[c]phenothiazine. This acid was covered with an excess (perhaps 30-40 ml.) of polyphosphoric acid. As the solution was warmed on a steam bath and stirred, a deep red color developed. The contents of the flask were heated at 85-90° for ten minutes, cooled, and an excess of water was added to precipitate the yellow-orange product. Recrystallization of the crude benz[b]acridone from 95 per cent ethanol yielded 167 mg. (90 per cent) of yellow-orange leaflets, m.p. 304-305°. The ethanol solution of this compound showed a strong green fluorescence. The structure corresponding to benz[b]acridone was assigned to this compound since its melting point and infrared spectrum were identical with the melting point and infrared spectrum of an authentic, synthetic sample of benz[b]acridone (see page 77).

7. Synthesis of N-Phenyl-3-amino-2-naphthoic Acid

The procedure of Schöpff (85) was followed with minor modifications. A mixture of 65.2 g. (0.7 mole) of aniline, 94.1 g. (0.5 mole) of 3-hydroxy-2-naphthoic acid, and 1.0 g. of iodine was placed in a 500-ml., round-bottom flask equipped with reflux condenser and magnetic stirrer. The reaction mixture was refluxed with stirring for 8.25 hours and while the mix-

ture was still hot and in the liquid form, it was poured into 200-250 ml. of 5 per cent hydrochloric acid solution. This dissolved unreacted aniline. The residue was treated with hot, 95 per cent ethanol, whereby 9.3 g. (7.1 per cent) of the anilide of 3-hydroxy-2-naphthoic acid, m.p. 243-244°, remained undissolved. Schöpff (85) reports m.p. 243-244°. The alcoholic filtrate was then precipitated with water to yield a greenish-yellow solid. This crude solid was treated with about 300-400 ml. of 7 per cent sodium carbonate solution in order to dissolve the N-phenyl-3-amino-2-naphthoic acid. The undissolved solid, after recrystallization from glacial acetic acid, melted at 168-170°. Schöpff (85) reports m.p. 168-169.5° for the anilide of N-phenyl-3-amino-2-naphthoic acid. The yield was 2.1 g. (1.2 per cent). The sodium carbonate filtrate contained both unchanged 3-hydroxy-2-naphthoic acid and N-phenyl-3-amino-2-naphthoic acid. A crude separation of the two acids was obtained by fractional precipitation from basic solution by addition of concentrated hydrochloric acid. This gradual neutralization caused the gold-yellow N-phenyl-3-amino-2-naphthoic acid to precipitate first. The first appearance of unchanged 3-hydroxy-2-naphthoic acid was detectable since it appeared as a very light yellow (almost white) precipitate. However, the recovery of unchanged 3-hydroxy-2-naphthoic acid was not made. Then the crude yellow N-phenyl-3-amino-2-naphthoic acid thus obtained was collected by filtration and allowed to air dry. Recrystallization of the crude material from benzene using "Norit-A" decolorizing carbon, gave 12.2 g. (10 per cent) of golden yellow needles, m.p. 235-237°. Schöpff (85) did not report a yield in this preparation but indicated the melting point

of N-phenyl-3-amino-2-naphthoic acid to be 235-237°. Albert, Brown and Duewell reported a 14 per cent yield of N-phenyl-3-amino-2-naphthoic acid, m.p. 229°, from a similar synthesis (86).

Benz [b] acridone was prepared in 91 per cent yield from the N-phenyl-3-amino-2-naphthoic acid synthesized above using polyphosphoric acid and following exactly the procedure previously given for its preparation. The benz [b] acridone thus obtained melted at 304-305°. Albert, Brown, and Duewell (86) report the melting point of benz [b] acridone to be 303°.

8. Attempted Preparation of the Anilide of N-Phenyl-3-amino-2-naphthoic Acid

Approximately 0.5 g. of the N-phenyl-3-amino-2-naphthoic acid, m.p. 235-237°, synthesized from 3-hydroxy-2-naphthoic acid, aniline, and iodine, was placed in a 50-ml., round-bottom flask equipped with a condenser and magnetic stirrer. To this was added 3 ml. of thionyl chloride, after which the mixture was warmed on a steam bath for fifteen minutes. The solution was brown-black in color. After removal of the condenser, the excess thionyl chloride was boiled off and the flask then cooled to room temperature in an ice bath. Addition of a solution of 3 ml. of aniline in 30 ml. of benzene and warming of the mixture for about two minutes on a steam bath precipitated a crude green solid which was removed by filtration, washed with water, 5 per cent hydrochloric acid solution, 5 per cent sodium hydroxide solution, and finally again with water. All attempts to purify this crude material were unsuccessful. Thionyl chloride used in this reaction may have promoted cyclization of the N-phenyl-3-amino-2-naphthoic acid to benz [b] acridone. No further attempts were

made to prepare the anilide of N-phenyl-3-amino-2-naphthoic acid by this method.

9. Synthesis of N-(o-Carboxyphenyl)-2-naphthylamine

The procedure is similar to that of Ullmann (87). A mixture of 25 g. (0.175 mole) of β-naphthylamine and 25 g. (0.129 mole) of potassium-o-chlorobenzoate was placed in a 500-ml., round-bottom flask equipped with a magnetic stirrer and reflux condenser. The mixture was covered with 85 ml. of n-amyl alcohol and the suspension was heated to the boiling point to give a homogeneous system. While the solution was at the boiling point, 6.5 g. of anhydrous potassium carbonate and 0.7 g. of copper bronze catalyst were added. The mixture was refluxed and stirred for twelve hours and then cooled to room temperature. The insoluble solid (unchanged β-naphthylamine) was removed from the cooled solution by filtration. The filtrate was placed in a 500-ml. flask and steam-distilled to remove the amyl alcohol. The residual aqueous solution was acidified with concentrated hydrochloric acid to precipitate a crude, purple solid. Three recrystallizations of this material from 95 per cent ethanol, using "Norit-A" decolorizing carbon, yielded 2.2 g. (7 per cent) of white needles, m.p. 210-211°. Ullmann (87) did not report a yield in this preparation, but indicated the melting point of N-(o-carboxyphenyl)-2-naphthylamine to be 212°.

10. Preparation of Benz[a]acridone

To a 100-ml., round-bottom flask was added 0.5 g. (0.0019 mole) of N-(o-carboxyphenyl)-2-naphthylamine, m.p. 210-211°. About 30-40 ml. of polyphosphoric acid was added and the resulting mixture was stirred and

warmed on a steam bath to 90°. As the solution was warmed a red color developed. The contents of the flask were heated at 90° for 1.25 hours, cooled, and water was added to precipitate the crude product. The yellow solid thus obtained was removed by filtration and recrystallized from pyridine to yield yellow needles which melted above 360°. Ullmann and Rasetti (87) report benz [a] acridone to melt above 360°.

C. Physiological Testing

The compounds synthesized in this investigation are currently being tested by the Eli Lilly Company for central nervous system effects and other miscellaneous biological properties and by the National Cancer Institute for anticancer activity. Although testing of these materials is still incomplete, physiological results from a few of the compounds have been obtained.

1. Anticancer Effects

The compounds examined in the routine anticancer screen tests are observed for activity against three mouse tumors. The selection of these particular tumors was made because all clinically-tested compounds of value are effective against at least one of these mouse tumors. Thus, all three mouse tumors are necessary for detection of new positive compounds. The three tumor systems employed are Sarcoma (S-180), Adenocarcinoma (Ca-755), and Leukemia (L-1210).

Preliminary testing of four 7-(dialkylaminoalkyl)-benzo [c] - phenothiazines on the Sarcoma (S-180) tumors has indicated a fair degree

of toxicity in these compounds, but detectable inhibition of tumor growth has not yet been observed. Anticancer tests of the benzo[c]-phenothiazine derivatives synthesized in this work are quite incomplete at this time.

2. Central Nervous System Effects

In these tests, conducted on mice, the compounds are examined for several physiological properties. Irritability, respiration, salivation, skin color, tail erection, analgesia, and numerous other effects are examined. Preliminary reports indicated that 9-chloro-7-(3-dimethylaminopropyl)-benzo[c]phenothiazine may be a central nervous system depressant, whereas the pattern of activity observed with 7-(3-dimethylaminopropyl)-benzo[c]phenothiazine suggested that it might have mixed central nervous system stimulant and depressant properties.

3. Antimicrobial Effects

The compounds prepared in this investigation are also being examined by the Eli Lilly Co. for antimicrobial activity toward numerous pathogenic bacteria and fungal plant pathogens. It has been observed that 8,11-dimethyl-7-(3-dimethylaminopropyl)-benzo[c]phenothiazine and 7-(2-dimethylaminoethyl)-benzo[c]phenothiazine exhibit inhibitory properties toward a long series of test organisms and fungal plant pathogens. However, conclusions on potential uses of these compounds as antimicrobial agents cannot be known at this time.

CHAPTER V

SUMMARY

In view of the pharmacological importance of phenothiazine and its derivatives, this investigation was undertaken to synthesize a series of 7-(dialkylaminoalkyl)-benzo [c] phenothiazines, compounds structurally related to the more important phenothiazine types. In connection with preparation of these compounds, the metalation of 7H-benzo [c] phenothiazine was studied in an effort to find a synthetic route for introduction of substituents into a position of the benzophenothiazine nucleus not readily accessible by other preparative techniques. Metalation of this compound was found to occur in the 6-position in yields up to 41 per cent.

The following compounds which were prepared during the course of this work, have not been previously reported.

10-Methoxy-7H-benzo [c] phenothiazine

10-Methoxy-7-(3-dimethylaminopropyl)-benzo [c] phenothiazine

7-(2-Dimethylaminoethyl)-benzo [c] phenothiazine

7-(2-Dimethylaminoethyl)-benzo [c] phenothiazine methiodide

7-(2-Dimethylaminoethyl)-benzo [c] phenothiazine picrate

7-(3-Dimethylaminopropyl)-benzo [c] phenothiazine

7-(3-Dimethylaminopropyl)-benzo [c] phenothiazine methiodide

7-(3-Dimethylaminopropyl)-benzo [c] phenothiazine picrate

7-(2-Diethylaminoethyl)-benzo [c] phenothiazine

7-(2-Diethylaminoethyl)-benzo [c] phenothiazine picrate

10-Methyl-7-(3-dimethylaminopropyl)-benzo [c] phenothiazine

10-Methyl-7-(3-dimethylaminopropyl)-benzo [c] phenothiazine methiodide

8,11-Dimethyl-7-(3-dimethylaminopropyl)-benzo [c] phenothiazine

8,11-Dimethyl-7-(3-dimethylaminopropyl)-benzo [c] phenothiazine methiodide

9-Chloro-7-(3-dimethylaminopropyl)-benzo [c] phenothiazine

9-Chloro-7-(3-dimethylaminopropyl)-benzo [c] phenothiazine methiodide

6-Carboxy-7H-benzo [c] phenothiazine

6-Carbomethoxy-7H-benzo [c] phenothiazine

Pharmacological evaluation of the compounds prepared during this research is being conducted by the Eli Lilly Company and by the National Cancer Institute.

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