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# Some reactions of phenothiazine and its derivatives

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# SOME REACTIONS OF PHENOTHIAZINE AND ITS DERIVATIVES

by

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# INTRODUCTION

For many years, phenothiazine and some of its derivatives have been useful as medicinal agents and have also found use in other fields. As examples, phenothiazine has been valuable as an anthelmintic,[1,2,3] tuberculostatic compound,[4] and insecticide.[5] β-Diethylaminoethyl 10-phenothiazinecarboxylate,[6] 10-(2-diethylaminoethyl)phenothiazine (Diparcol),[7] 2-chloro-10-(3-dimethylaminopropyl)phenothiazine (Chlorpromazine)[7] and 10-(2-diethylaminopropyl)phenothiazine[8] have been found to prevent nicotine-induced convulsions; while several, such as

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[1] H. A. Oelkers, Ärztl. Forsch., 5, II, 139 (1951) [C. A., 49, 12719 (1955)].

[2] S. D. Ul'yanov, Trudy Inst. Zool., Akad. Nauk Kazakh. S. S. R., 1, Parazitol, 200 (1953) [C. A., 49, 4172 (1955)].

[3] R. B. Griffiths, J. Pharm. and Pharmacol., 6, 921 (1954).

[4] B. L. Freelander, Proc. Soc. Exptl. Biol. Med., 57, 106 (1944).

[5] F. L. Campbell, W. N. Sullivan, L. E. Smith and H. L. Haller, J. Econ. Entomol., 27, 1176 (1937).

[6] R. Dahlbom, Acta Chem. Scand., 7, 879 (1953). See, R. Dahlbom, T. Edlund, T. Ekstrand and A. Katz, Arch. intern. pharmacodynamie, 90, 241 (1952).

[7] A. Balestrieri, Arch. intern. pharmacodynamie, 100, 361 (1955) [C. A., 49, 7736 (1955)].

[8] V. G. Longo and D. Bovet, Boll. soc. ital. biol. sper., 28, 612 (1952) [C. A., 49, 509 (1955)].

10-[(1-methyl-3-piperidyl)methyl]phenothiazine[9] and 10-(2-dimethylaminoethyl)phenothiazine (RP3015),[10] show good local anesthetic properties. The 10-(2-diethylaminoethyl)- and 10-(2-dimethylaminoethyl)phenothiazine are also used as fungistatic agents.[11] Both 10-(2-dimethylaminopropyl)phenothiazine (Promethazine)[12] and 10-[2(1-pyrrolidinyl)ethyl]phenothiazine (Pyrrolazote)[13] have shown good antihistaminic properties. The Chlorpromazine which has been mentioned above is perhaps best known for its use as a tranquilizing drug[14] and in the treatment of certain mental disorders.[15] Others, too numerous to mention, may be used for a variety of ailments, these falling into such catagories as urinary antiseptics, antispasmodics, circulatory agents, anti-shock agents, anti-inflammatory agents, and agents for the treatment of travel

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[9] O. Nieschulz, K. Popendiker and K. H. Sack, Arzneimittel-Forsch, 4, 232 (1954) [C. A., 49, 7746 (1955)].

[10] K. Teshima, Folia Pharmacol. Japon, 50, 565 (1954) [C. A., 49, 15065 (1955)].

[11] H. I. Chinn, R. B. Mitchell and A. C. Arnold, J. Invest. Dermatol., 20, 177 (1953).

[12] J. R. Leduc, Rev. can. biol., 8, 543 (1949).

[13] W. R. Reid, Jr., J. B. Wright, H. G. Kolloff and J. H. Hunter, J. Am. Chem. Soc., 70, 3100 (1948).

[14] E. L. Lear, A. E. Chiron and I. M. Pallin, J. Am. Med. Assoc., 163, 30 (1957); see also J. W. Dundee, Brit. J. Anaesth., 26, 357 (1954).

[15] C. P. Seager, Brit. Med. J., I, 882 (1955).

and motion sickness. An isotonic salt solution containing 10-(2-dimethylaminopropyl)phenothiazine has been used for storage of arterial transplantations.[16]

Aside from these medicinal aspects of phenothiazine and its derivatives, many of them find use as antioxidants in lubricating oils and greases. As examples, phenothiazine[17] has been used to stabilize a grease composed of a methylphenyl silicone polymer and lithium stearate; and 3-fluorophenothiazine was found to be an effective antioxidant for the synthetic lubricating oil, bis(2-ethylhexyl)sebacate.[18]

It should be emphasized that the phenothiazine derivatives that have been cited here as possessing favorable physiological activity or antioxidant properties are only a few of those which actually possess such activity. However, they should be sufficient to indicate the potential which new phenothiazine derivatives might have in these and in other fields.

The purpose of this study was to extend the chemistry of phenothiazine by the preparation of new derivatives for testing primarily as medicinal agents. Associated closely with this

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[16] A. Trapani, Patol. sper., 41, 105 (1953) [C. A., 49, 2555 (1955)].

[17] G. M. Hain and W. A. Zisman, U. S. Patent 2,693,449, November 2, 1954 [C. A., 49, 1320 (1955)].

[18] G. Cohen, C. M. Murphy, J. G. O'Rear, H. Ravner, and W. A. Zisman, Ind. Eng. Chem., 45, 1766 (1953).

was the proposed preparation of boron derivatives, particularly boronic acids, of phenothiazine. Such compounds should be quite interesting since other boronic acids have exhibited favorable physiological action on both plants and animals, benzeneboronic acid giving increased root elongation to seedlings when administered at the proper concentrations.[19] Benzeneboronic acid also acts as a larvicide[20] and enhances the efficiency of several hypnotics,[21] while the nitrobenzeneboronic acids[22] exert a bacteriostatic effect.

A more recent development in boron chemistry is the use of organoboronic acids and other boron compounds in the irradiation therapy of brain tumors.[23,24,25] This involves the bombardment of the tumor which has taken up the boron compound with slow neutrons, alpha particles being released as the

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[19] F. Caujolle and G. Bergal, Compt. rend., 238, 1516 (1949).

[20] H. W. A. Brown, D. B. W. Robinson, H. Hurtig, and B. J. Wenner, Can. J. Research, 26D, 177 (1948).

[21] F. Caujolle, P. Gayell, G. Roux, and C. Moscarela, Bul. Acad. Natl. Méd., 135, 314 (1951) [C. A., 46, 4129 (1952)].

[22] W. Seaman and J. R. Johnson, J. Am. Chem. Soc., 53, 711 (1931).

[23] P. G. Kruger, Proc. Nat. Acad. Sci., 26, 181 (1940).

[24] P. G. Kruger, Radiation Research, 3, 1 (1955).

[25] E. E. Stickley, Am. J. Roentgenol. Radium Therapy Nuclear Med., 75, 609 (1956).

result of the disintegration. This treatment tends to destroy the cancerous tissue. Azo dyes containing boron[26,27,28] are believed to be superior to other types of boron compounds because of selective take-up by the abnormal tissue over the normal tissue. They also show other advantages.[24] For these reasons phenothiazine derivatives containing both the azo group and boron were given consideration.

Due to the difficulty in preparing pure organoboron compounds and especially pure azo boronic acids, it was thought desirable to prepare several simple aromatic boronic acids and azo boronic acids in order to gain experience and techniques in handling such compounds. Thus, several compounds not containing the phenothiazine nucleus were made. These are included in the experimental section as a separate group.

Another purpose of this work was to prepare some phenothiazine derivatives for evaluation as possible liquid solution

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[26]H. R. Snyder and Clay Weaver, J. Am. Chem. Soc., 70, 232 (1948).

[27]H. R. Snyder and S. L. Meisel, J. Am. Chem. Soc., 70, 774 (1948).

[28]H. Gilman, L. Santucci, D. R. Swayampati and R. O. Ranck, J. Am. Chem. Soc., 79, 0000 (1957). See also this thesis.

scintillators.[29] A prediction as to the value of phenothiazine derivatives in this field is difficult to make since nitrogen containing heterocycles such as pyrrole and pyridine have been found to be good ring systems while the sulfur-containing heterocycle, thiophene, has been found to be a poor ring system for use in scintillators. Besides finding a good scintillator, the goal of the scintillator program is to attempt to correlate chemical constitution with scintillator activity.

A third purpose of this work was to investigate new techniques for N-substitution of phenothiazine and improve on old ones. It is true that the existing techniques are quite adequate for the preparation of many derivatives, while on others, they fail completely or give, at the very best, low yields.

Some study was also made on oxidation of phenothiazine derivatives to sulfoxides in an effort to get increased yields.

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[29]This refers to the problem of converting radioactive particle energy into visible and near ultraviolet photon energy which is converted to electrical energy by a photomultiplier tube so that radioactive emanations may be counted. Among other compounds, liquid organic solutions such as p-terphenyl dissolved in toluene may be used. For a more complete discussion on this see: H. Kallman and M. Furst, Nucleonics, 8, No. 3, 32 (1951); F. N. Hayes, L. C. King and D. E. Peterson, J. Am. Chem. Soc., 74, 1106 (1952); F. N. Hayes, U. S. Atomic Energy Unclassified Report LA-1639, 1953; and F. N. Hayes, D. G. Ott, V. N. Kerr and B. S. Rogers, Nucleonics, 13, No. 12, 38 (1955).

Since a large portion of this dissertation is concerned with substitution at the 10-position (nitrogen) of phenothiazine, a review of such substitutions as well as alteration of an N-substituent (reaction of an active group on the N-substituent) is presented for the years 1952 to the present time. This includes a table of all of the N-substituted compounds prepared during this time and supplements the reviews presented by Nelson[30] and Champaigne[31] covering this same type of material from the initiation of phenothiazine derivatives through 1951.

Brief discussions on oxidation and nuclear substitutions of phenothiazine are also included as is a brief resume of the history and preparation of organo boronic acids. These should give sufficient background for other portions of the thesis not directly related to N-substitution.

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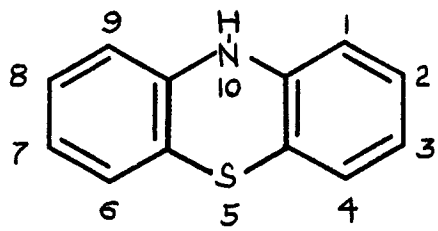
[30]R. D. Nelson, Doctoral Dissertation, Iowa State College (1951).

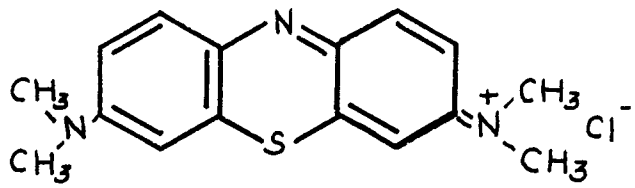
[31]J. F. Champaigne, M. S. Thesis, Iowa State College (1952).

# HISTORICAL

Phenothiazine (I) was first prepared by Bernthsen[32] in the year 1883 while attempting to prove the structure of methylene blue (II).




I




II

Other names such as thiodiphenylamine and 2,3,5,6-dibenzo-1,4-thiazine appear in the literature also, but phenothiazine is the name preferred by Patterson and Capell[33] and Chemical Abstracts. Chemisches Zentralblatt uses thiodiphenylamine. The preferred numbering system is that shown in I.

Several reviews have appeared on the chemistry and physiological action of phenothiazine and its derivatives during the past thirty-five years. The first of these appeared in

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[32]A. Bernthsen, Ber., 16, 2896 (1883); 17, 2854, 2857, 2860 (1884); Ann., 230, 73 (1885).

[33]A. M. Patterson and L. Capell, "The Ring Index," Reinhold Publishing Corp., New York, 1940.

a book by Meyer and Jacobsen[34] and concerns itself primarily with the chemistry of phenothiazine as related to methylene blue. The substitution reactions are reviewed by Van Ess,[35] Shirley[36] and Nelson.[30] Diehl[37] includes a table of nuclear substituted phenothiazines. Reactions of the imino nitrogen are covered adequately by both Nelson[30] and Champaigne[31] through the year 1951. The review by Champaigne[31] also includes a complete table of N-substituted phenothiazines through this same year. Reactions involving the sulfur atom, including oxidation, reduction, and cleavage, are discussed by both Nelson[30] and Diehl.[37] Nelson[30] also discusses ring closure reactions as methods of preparing phenothiazine and its derivatives.

The medicinal properties of phenothiazine and its derivatives and the physiological properties of 10-(dialkylaminoalkyl)phenothiazines have been presented by Shirley[36] and Nelson,[30] respectively. Two reviews on phenothiazine as an

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[34] V. Meyer and P. Jacobsen, "Lehrbuch der Organischen Chemie," Vol. 2, Part 3, Veit and Co., Leipzig, 1920, p. 1490.

[35] P. R. Van Ness, Doctoral Dissertation, Iowa State College (1936).

[36] D. A. Shirley, Doctoral Dissertation, Iowa State College (1943).

[37] J. W. Diehl, Master's Thesis, Iowa State College (1953).

anthelmintic are available[38,39] while Metcalf[40] presents a general review of the chemistry of phenothiazines. The most recent and truly excellent general review on phenothiazine from the year 1920 to 1954 has been published by Massie.[41]

Phenothiazine is prepared commercially by the ring closure of diphenylamine with sulfur using iodine as a catalyst. The first preparation by Bernthsen[32] did not utilize the iodine and yields were about 40%. With the discovery[42,43] that iodine aids the thionation reaction, yields as high as 100% of crude material melting at 180-181° were obtained. Commercial phenothiazine (N. F. purified) generally has a melting point of 185°.

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[38]E. C. Beeler, Bull. Natl. Formulary Comm., 10, 84 (1942).

[39]G. M. Findlay, "Recent Advances in Chemotherapy," 3rd. edition, Vol. I, The Blakiston Company, Philadelphia, Pa., 1950, p. 124.

[40]R. L. Metcalf, Chemistry Biology Coordination Center, National Research Council, Washington, D. C., Review No. 1, 84 pp. (1948).

[41]S. P. Massie, Chem. Revs., 54, 797 (1954).

[42]F. Ackermann, German patent 224,348, July 9, 1909 [C. A., 5, 210 (1911)].

[43]E. Knoevenagel, J. prakt. chem., 89, (2), 1 (1914).

## Reactions Involving the Imino Nitrogen or Involving a Substituent on the Nitrogen

Although the reactions of the imino group were reviewed through the year 1951 by both Nelson[30] and Champaigne,[31] such a vast amount of new work has been done since that time on N-substitution and alteration of an existing N-substituent that it seemed worthwhile to continue the review to the present time. Prior to this, however, a brief summary of the reviews mentioned above will be presented. In an attempt to obtain an orderly arrangement, the reactions involved will be classified according to the technique used to obtain the N-substitution. The first figure in the Appendix shows structures of several of the more complicated derivatives as an aid in nomenclature.

The earliest technique and one which is still used occasionally incorporates a sealed tube under moderate conditions of temperature and pressure. Bernthsen[32] prepared 10-methyl- and 10-ethylphenothiazine by heating phenothiazine and the appropriate alkyl alcohol and corresponding alkyl halide in a sealed tube at 100-110°. A slight modification of this, replacement of the alkyl halide with dry hydrogen chloride,[44]

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[44]H. I. Bernstein and L. R. Rothstein, J. Am. Chem. Soc., 66, 1886 (1944).

also gave the desired products. 10-Carboethoxyphenothiazine was prepared by heating ethyl chlorocarbonate, phenothiazine and ether in a closed tube at 120°.[45] Both 10-phenothiazinecarbonyl chloride and 10-10'-diphenothiazinylcarbonyl were prepared in a sealed tube containing phosgene, phenothiazine and toluene at 100°.[45,46]

The most widely used method of substituting in the 10-position is to reflux a mixture of phenothiazine, an organic halide (occasionally a sulfate) and a base in some solvent. A relatively large number of solvents has been utilized in this method. They include ethanol, acetone, dioxane, o-dichlorobenzene, benzene, xylene, toluene, ether and petroleum ether. Likewise, several different alkaline condensing agents have been employed. Some typical ones are sodium hydroxide, potassium hydroxide, trisodium phosphate, sodium amide, and in special cases, n-butyllithium. As examples of this method, 10-methylphenothiazine has been prepared by refluxing a mixture of methyl sulfate, sodium hydroxide and phenothiazine in acetone;[47] 10-[2-(4-morpholinyl)ethyl]phenothiazine from phenothiazine, sodium amide and 2-(4-morpholinyl)ethyl chloride

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[45] N. Fraenkel, Ber., 18, 1843 (1885).

[46] S. Paschkowezky, ibid., 24, 2905 (1891).

[47] Ng. Ph. Buu-Hoi and Ng. Hoan, J. Chem. Soc., 1834 (1951).

in toluene;[48] and 10-(p-methoxyphenyl)phenothiazine by refluxing a mixture of xylene, phenothiazine, p-methoxyiodobenzene, potassium carbonate and copper powder, which acts as a catalyst.[49] Others which differ slightly are also included in this catagory. For example, 10-(2-chloroethyl)phenothiazine and 10-(3-chloropropyl)phenothiazine were made by reacting 2-chloroethyl-p-toluenesulfonate and 3-chloropropyl-p-toluenesulfonate, respectively, with 10-lithiophenothiazine in ether solution. The 10-lithiophenothiazine was prepared prior to the addition of the halogen compound by adding phenothiazine to n-butyllithium in ether. The reactions were generally carried out at room temperature or below.[36]

In those instances where a particularly reactive halogen is used, the substitution may be accomplished without the alkaline condensing agent. 10-(Chloroacetyl)phenothiazine was prepared by refluxing a benzene or toluene solution of phenothiazine and chloroacetyl chloride[50] and 10-(β-bromopropionyl)phenothiazine was prepared from β-bromopropionyl bromide and phenothiazine in refluxing benzene.[51] If an

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[48] R. Dahlbom, Acta Chem. Scand., 3, 247 (1949).

[49] H. Gilman, P. R. Van Ess and D. A. Shirley, J. Am. Chem. Soc., 66, 1214 (1944).

[50] R. Dahlbom and T. Ekstrand, Acta Chem. Scand., 5, 102 (1951).

[51] T. Ekstrand, Acta Chem. Scand., 3, 302 (1949); T. Ekstrand, Swedish Patent 127,566 March 14, 1950 [C. A., 45, 188 (1951)].

excessively long reflux time is used, the base may be left out even though the halogen compound is not particularly reactive. 10-Methylphenothiazine has been prepared in satisfactory yields by refluxing a mixture of methyl iodide, methyl alcohol and phenothiazine for several days.[44] In contrast to this, if a basic solvent is used, the heating may be eliminated as was done in the preparation of 10-(benzenesulfonyl) phenothiazine from benzenesulfonyl chloride and phenothiazine in pyridine solution at room temperature.[52]

A very similar type of reaction to that just described involves the heating of a mixture of phenothiazine, alkyl or aryl halide (acid anhydrides are used in a few instances), base (usually sodium or potassium carbonate) and copper powder which acts as a catalyst. No solvent is employed. Gilman and Shirley[36,53] prepared 10-n-decylphenothiazine by heating a mixture of phenothiazine, n-decyl bromide, sodium carbonate and copper powder at 170-180° for 11 hours; 10-phenylphenothiazine was prepared by heating a mixture of phenothiazine, iodobenzene, sodium carbonate and copper powder at reflux for 12 hours;[49] and ethyl 10-phenothiazinylacetate was obtained by heating a mixture of phenothiazine, ethyl bromoacetate,

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[52]S. E. Hazlet and C. E. Roderuck, J. Am. Chem. Soc., 67, 495 (1945).

[53]H. Gilman and D. A. Shirley, J. Am. Chem. Soc., 66, 888 (1944).

potassium carbonate and copper powder at 150-160° for several hours.[54]

As is the case with the solvent-method described above, the basic condensing agent may also be eliminated in this technique if a particularly reactive compound is used for the substitution. Massie[55] prepared 10-acetylphenothiazine by merely heating a mixture of acetic anhydride and phenothiazine while 10-(o-carboxybenzoyl)phenothiazine was made by heating phenothiazine with succinic anhydride at 150° for a number of hours.[56] By heating long-chained acyl chlorides (palmityl, stearyl, etc.) with phenothiazine at 100-160°, Ford[57] obtained the corresponding 10-acylphenothiazine (10-palmitylphenothiazine, 10-stearylphenothiazine, etc.).

A method which has been very successful in the preparation of some N-substituted phenothiazines utilizes sodium amide in liquid ammonia.[58] Several 10-alkylphenothiazines including 10-ethylphenothiazine,[30,31] 10-allylphenothiazine[31] and

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[54]G. Cauquil and A. Cassadevall, Compt. rend., 225, 578 (1947).

[55]S. P. Massie, Doctoral Dissertation, Iowa State College (1946).

[56]P. S. Winnek and H. E. Faith, U. S. patent 2,461,460 February 8, 1949 [C. A., 43, 3853 (1949)].

[57]G. M. Ford, Doctoral Dissertation, Iowa State College (1937).

[58]T. H. Vaughn, P. R. Vogt and J. A. Nieuwland, J. Am. Chem. Soc., 56, 2120 (1934).

10-benzylphenothiazine[31] were prepared by adding phenothiazine to sodium amide in liquid ammonia followed by the addition of the appropriate alkyl halide (usually the bromide).

Although the preparation of N-substituted phenothiazine derivatives is primarily a substitution process, occasionally one may be prepared by an addition process. Using such a method, Smith[59] was able to prepare β-(10-phenothiazinyl)-propionitrile by the addition of phenothiazine to an excess of acrylonitrile in the presence of the strong base, benzyltrimethylammonium hydroxide.

Isomerization was found to occur in the reaction of either 1-chloro-2-dimethylaminopropane or 1-dimethylamino-2-chloropropane with phenothiazine in refluxing xylene using sodium amide as the condensing agent. Charpentier[60] obtained 10-(2-dimethylamino-1-propyl)phenothiazine using 1-dimethylamino-2-chloropropane as the starting material. Using 1-chloro-2-dimethylaminopropane, the same phenothiazine derivative was obtained.[60,61] Additional investigation indicated that two products, 10-(1-dialkylamino-2-propyl)phenothiazine and 10-(2-dialkylamino-1-propyl)phenothiazine, were formed

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[59] N. L. Smith, J. Org. Chem., 15, 1125 (1950).

[60] P. Charpentier, Compt. rend., 225, 306 (1947).

[61] P. Charpentier, U. S. patent 2,530,451, November 21, 1950 [C. A., 45, 3428 (1951)] ; Société des usines chimiques Rhône-Poulenc; British patent 649,150, January 17, 1951 [C. A., 45, 7156 (1951)] .

by the reaction of 1-dialkylamino-2-chloropropane (alkyl is methyl or ethyl) with phenothiazine in refluxing xylene using sodium amide as the condensing agent.[62] The latter phenothiazine derivative was formed in the greater amount. This isomerization has been attributed to the formation of a cyclic ethyleneimmonium ion by the dialkylaminochloropropanes in the presence of the strong base, sodium amide, giving two possible places of attack by the phenothiazinyl anion.[63-65]

In the early work, alteration of the N-substituent [reaction involving a functional group on the chain attached to the nitrogen such as the reaction of the chlorine on 10-(2-chloroethyl)phenothiazine] was also investigated to a marked degree. This enables the preparation of derivatives which might be impossible by other methods or which may be obtained in lower yields by other techniques. 10-(Ethylaminoacetyl)-phenothiazine was prepared by heating a mixture of 10-(chloroacetyl)phenothiazine, ethylamine, and benzene in a

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[62] P. Charpentier, P. Gailliot and J. Gaudechon, Compt. rend., 232, 2232 (1951); P. Charpentier and R. Ducrot, ibid., 232, 415 (1951); P. Charpentier, U. S. patent 2,526,118, October 17, 1950 [C. A., 45, 2511 (1951)].

[63] E. M. Schultz, C. M. Robb and J. M. Sprague, J. Am. Chem. Soc., 69, 188 (1947); ibid., 69, 2454 (1947); W. R. Brode and M. W. Hill, ibid., 69, 724 (1947); J. F. Kerwin, G. E. Ullyot, R. C. Fuson and C. L. Zirkle, ibid., 69, 2961 (1947).

[64] S. D. Ross, ibid., 69, 2982 (1947).

[65] E. M. Schultz and J. M. Sprague, ibid., 70, 48 (1948).

sealed bottle at 80° for 2 hours,[50] and 10-(cyclohexylaminoacetyl)phenothiazine was obtained by shaking 10-(chloroacetyl)-phenothiazine and cyclohexylamine in benzene solution for 10 hours at room temperature using a sealed bottle.[50] Cusic[66] converted 10-(2-chloroethyl)phenothiazine to 10-[2-(2-hydroxyethylmethylamino)ethyl] phenothiazine by refluxing it with (2-hydroxyethyl)methylamine in toluene for 72 hours, and Shirley[36] prepared 10-(2-diethylaminoethyl)phenothiazine by refluxing 10-(2-chloroethyl)phenothiazine with excess diethylamine for 60 hours in the presence of copper-bronze.

Although the preparation of quaternary salts of some phenothiazine derivatives [e.g. 10-(dialkylaminoalkyl)phenothiazines] was not extensively pursued in the years up through 1951, several were prepared. The method of preparation generally consisted of mixing the appropriate phenothiazine derivative with methyl chloride, methyl iodide, etc., using a solvent such as ethanol or methyl ethyl ketone. Examples of this type of compound are [2-(10-phenothiazinyl)ethyl]-(2-hydroxyethyl)dimethylammonium bromide[66] and [2-(10-phenothiazinyl)ethyl](2-hydroxyethyl)diethylammonium bromide.[66]

This concludes the summary of the work up to the beginning of 1952.

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[66] J. W. Cusic, U. S. patent 2,512,520, June 20, 1950 [C. A., 44, 8963 (1950)].

In very recent years even more emphasis has been placed on the preparation of N-substituted phenothiazines, due initially to the discovery by Halpern[67,68] that various 10-(dialkylaminoalkyl)phenothiazines are active antihistaminic agents possessing a low degree of toxicity to the host; but probably stimulated even more by the success of several phenothiazine drugs such as Phenergan, Diparcol, Chlorpromazine, Pyrrolazote, and RP3015, all of which contain an N-substituent with an amino nitrogen. More new N-substituted phenothiazines have appeared in the past 5 years than were made up to 1952.

Again, in this portion of the review, the reactions of the imino nitrogen are classified according to the technique employed to attain the substitution. The reactions involving alteration of the N-substituent are classified according to the type of compound formed: amine, ester, amide, etc. Generally much of the chemistry is the same as that which has been discussed. This will be covered lightly with new examples of derivatives prepared by these methods being included, while anything unusual or employing new techniques will be discussed more fully. Following the discussion is a table of the N-substituted phenothiazines that have appeared in the literature for the years 1952 through the year 1956. Some

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[67] B. N. Halpern and R. Ducrot, Compt. rend. soc. biol., 140, 361 (1946).

[68] B. N. Halpern, J. Allergy, 18, 263 (1947).

of these compounds are not new and will be found in the compilations prepared by Champaigne[31] and Massie.[41] They are listed only to supply the additional references. In order to be consistent in the nomenclature, some names as they appear in the literature have been changed. For example, one article may have used the name "10-(2-pyrrolidinoethyl)phenothiazine" while another may have used "10-[2-(1-pyrrolidinyl)ethyl]-phenothiazine". Both of these names refer to the same compound. In this thesis, the latter nomenclature has been used.

The sealed tube method was still employed for the preparation of a few N-substituted derivatives. 10-Phenothiazinecarbonyl chloride was again prepared by heating a mixture of phenothiazine and phosgene dissolved in toluene at 95-100° under a slight pressure for 2 hours.[69] Methyl 10-phenothiazinecarboxylate was prepared in a similar manner using phenothiazine and methyl chloroformate dissolved in toluene.[69]

The use of Grignard reagents, organolithium compounds, and sodium amide was quite extensive as a means of accomplishing the substitution. 10-(4-Chlorobutyl)phenothiazine was prepared by adding phenothiazine to phenyllithium in ether followed by the addition of an ether solution of 1,4-

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[69]R. Dahlbom, Acta Chem. Scand., 7, 879 (1953).

dichlorobutane and heating.[70] 10-(2,3-Epoxypropyl)phenothiazine was prepared in a similar manner using phenothiazine, phenyllithium and epichlorohydrin at 0° followed by a standing period at room temperature.[71]

Berg[72] reported the preparation of 10-(2-diethylaminoethyl)phenothiazine by the addition of a warm benzene solution of phenothiazine to a mixture of methyl iodide and magnesium in ether followed by the addition of 1-chloro-2-diethylaminoethane in benzene and a 1.5-hour reflux period. The 10-(2-dimethylamino-1-propyl) and 10-(1-dimethylamino-2-propyl) derivatives as well as other very similar ones were prepared using the same procedure. Berg also noted the isomerization which has been discussed previously (see pages 16 and 17 for a discussion) when using 1-dimethyl-2-chloropropane as the source of the N-substituent, both 10-(2-dimethylamino-1-propyl)- and 10-(1-dimethylamino-2-propyl)phenothiazine being obtained. These were separated by the fractional crystallization of their hydrochloride salts.

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[70] R. A. Robinson and J. W. Cusic, U. S. patent 2,590,125, March 25, 1952 [C. A., 47, 1195 (1953)].

[71] P. Charpentier, U. S. patent 2,595,215, May 6, 1952 [C. A., 47, 1194 (1953)].

[72] S. S. Berg and J. N. Ashley, U. S. patent 2,607,773 (1952) [C. A., 47, 6989 (1953)]; see also British patent 680,128, October 1, 1952 [C. A., 47, 10012 (1953)].

In an analogous fashion, the 10-acetyl-, 10-chloroacetyl-, 10-propionyl-, 10-butyryl- and 10-benzoylphenothiazines were prepared, phenothiazine being added to an alkylmagnesium halide in ether, followed by the addition of the appropriate acyl halide.[73]

10-(2-Hydroxyethyl)phenothiazine has been prepared by adding a toluene solution of ethylene oxide to sodiophenothiazine in toluene, prepared by refluxing a mixture of phenothiazine and sodium amide, and then continuing the heating for a period of one hour.[74] The 10-(2-dimethylaminoethyl) derivative and its diethylaminoethyl analog were prepared from 1-chloro-2-dimethyl-(or diethyl)-aminoethane and sodiophenothiazine (prepared in the usual manner from sodium amide and phenothiazine) in benzene at reflux.[75,76] By a similar procedure, 1-(1-piperidyl)-2-chloropropane hydrochloride reacted with sodiophenothiazine in refluxing toluene[77] to give 10-[1-(1-piperidyl)-2-propyl]phenothiazine.

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[73] G. Cauquil and A. Cassadevall, Compt. rend., 236, 1569 (1953).

[74] R. Dahlbom, Acta Chem. Scand., 6, 310 (1952).

[75] S. Nishijo and A. Nishimura, Japanese patent 1134, March 31, 1950 [C. A., 47, 2217 (1953)].

[76] C. J. Cavallito, A. P. Gray, and E. E. Spinner, J. Am. Chem. Soc., 76, 1862 (1954).

[77] J. R. Dahlbom and B. F. F. Sjögren, Swedish patent 134,621, February 26, 1952 [C. A., 48, 10783 (1954)].

A number of other bases, aside from the ones just discussed, have been employed for substitution reactions of the phenothiazine-nitrogen. Both 10-(2-dimethylaminoisobutyl)-phenothiazine and 10-[2-(2,6-dimethyl-1-piperidyl)ethyl]-phenothiazine were prepared from phenothiazine; 1-chloro-2-methyl-2-dimethylaminopropane hydrochloride and 1-(2-chloroethyl)-6-dimethylpiperidine, respectively; and sodium hydroxide in toluene at reflux.[70] A recent British patent[78] indicates the preparation of various 10-(dialkylaminoalkyl)-phenothiazines by the addition of a solution (benzene, toluene, or xylene) of a dialkylaminoalkyl halide to a mixture of phenothiazine and some basic compound (alkali metal; alkali-metal hydroxide, hydride or alkoxide; an aryl, alkyl, or aralkyl organometallic compound; or sodium amide) in the same solvent followed by a reflux period. The preparation of compounds such as 10-(1-diethylamino-2-propyl)phenothiazine, 10-(2-diethylaminopropyl)phenothiazine and other very similar ones are also discussed. This patent, which again indicates isomerization in the synthesis of branched-chain phenothiazines, appears to be a compilation of work published previously.

The basic solvent pyridine was used for the preparation of 10-(p-anisoyl)phenothiazine, p-anisoyl chloride being

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[78] Société des usines chimiques Rhône-Poulenc, British patent 701,741, December 30, 1953 [C. A., 49, 5534 (1955)].

added to a pyridine solution of phenothiazine followed by a short warming period.[79]

Again, in those instances where a very reactive halogen compound was used, the basic condensing agent was eliminated. 10-[(4-methyl-1-piperazinyl)carbonyl]phenothiazine was prepared by refluxing a mixture of phenothiazine and (4-methyl-1-piperazinecarbonyl chloride hydrochloride in chloroform;[80] 10-(α-bromobutyryl)phenothiazine, by refluxing a toluene solution of phenothiazine and α-bromobutyrylbromide for 4 hours;[81] 10-(β-chloropropionyl)phenothiazine, from phenothiazine and β-chloropropionyl chloride in refluxing benzene for 20 hours;[82] 2-chloroethyl 10-phenothiazinecarboxylate, by refluxing a benzene solution of phenothiazine and 2-chloroethyl chloroformate for 48 hours;[83] and 10-(6-chlorohexanoyl)phenothiazine was prepared by refluxing a toluene solution of

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[79] A. Mackie and A. Culter, J. Chem. Soc., 2577 (1954).

[80] H. G. Morren, British patent 666,457, February 13, 1952 [C. A., 47, 5458 (1953)].

[81] R. Dahlbom and T. Ekstrand, Acta Chem. Scand., 6, 1285 (1952).

[82] J. W. Cusic, U. S. patent 2,591,679, April 8, 1952 [C. A., 47, 4378 (1953)].

[83] J. W. Cusic, U. S. patent 2,650,919, September 1, 1953 [C. A., 48, 10783 (1954)].

phenothiazine and 6-chlorohexanoyl chloride for 15 hours.[84] A 2-hour reflux period was sufficient to prepare 10-(bromoacetyl)phenothiazine from phenothiazine and bromoacetyl bromide in benzene.[85]

According to a British patent[86] and a Swedish patent,[87] 10-(1-dimethylamino-2-propyl)phenothiazine, free of isomers, can be prepared by dropping a xylene solution of 1-dimethylamino-2-chloropropane on molten (200°) phenothiazine. No alkaline condensing agent was used.

A great many of the N-substituted compounds that have appeared in the past 5 years have been prepared by the reaction at an active center of a group already attached to the nitrogen of phenothiazine. A variety of salts have also been prepared from those compounds with an amino group attached to the nitrogen substituent. As has been mentioned previously, the reactions included in this portion of the discussion have been classified according to the new functional group formed; such as amine and amide.

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[84] J. W. Cusic, U. S. patent 2,694,705, November 6, 1954 [C. A., 49, 15980 (1955)].

[85] R. Dahlbom, Acta Chem. Scand., 7, 873 (1953).

[86] Aktiebolaget Recip., British patent 681,410, October 22, 1952 [C. A., 48, 743 (1954)].

[87] S. Carlssen, Swedish patent 150,469, June 28, 1955 [C. A., 50, 7152 (1956)].

Primary amines were prepared from nitrile groups by reduction with lithium aluminum hydride.[88] For example, 10-(2-cyanoethyl)phenothiazine was converted to 10-(3-aminopropyl)-phenothiazine using this reducing agent in acetic acid solution. This same patent also describes the formation of a primary amine by the treatment of 10-(2-phthalimidoethyl)phenothiazine with hydrazine hydrochloride, the first step in the reaction being the treatment of 10-(2-chloroethyl)phenothiazine with potassium phthalimide in dimethylformamide. The 10-(3-aminopropyl)phenothiazine was also prepared from the 10-(3-chloroethyl) derivative by heating with ammonia in ethanol at 100°.[88]

The general method of putting on amine groups, secondary and tertiary, is the reaction of a halogen substituent with an amine containing an active hydrogen. Several typical examples of this technique follow. 10-(α-Dimethylaminobutyryl)-phenothiazine was prepared from 10-(α-bromobutyryl)phenothiazine and dimethylamine by heating a benzene solution in a sealed bottle at 85° for several hours;[81] 2-dimethylaminoethyl 10-phenothiazinecarboxylate, by heating a mixture of 2-chloroethyl 10-phenothiazinecarboxylate, dimethylamine, methyl ethyl ketone and a small amount of potassium iodide for 4 days at

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[88]Société des usines chimiques Rhône-Poulenc, British patent 731,016, June 1, 1955 [C. A., 50, 12120 (1956)].

60-70°;[83] and 10-(γ-dimethylaminobutyryl)phenothiazine was prepared from the γ-chloro derivative by refluxing it with dimethylamine in acetone containing a small amount of potassium iodide.[84] Also described is the conversion of 10-(2-dimethylaminoethyl)phenothiazine to 10-(2-diethylaminoethyl)-phenothiazine by heating the former compound with diethylamine in methyl ethyl ketone containing potassium iodide.[84] Mackie and Misra[89] reported the preparation of 10-(2-diethylamino-ethylaminoacetyl)phenothiazine by refluxing 10-(chloroacetyl)-phenothiazine with 1-amino-2-diethylaminoethane in benzene for 12 hours. A propanolamine type of derivative, 10-(2-hydroxy-3-dimethylaminopropyl)phenothiazine was prepared by treating 10-(2,3-epoxypropyl)phenothiazine with dimethylamine in 90% methanol for 12 hours at 120° in a sealed tube.[90,91]

A number of derivatives have been prepared by reacting various piperidines, pyrrolidines, morpholines and similar compounds with a 10-(halogenalkyl)phenothiazine. Some of those prepared are the 10-[β-(1-piperidyl)propionyl]pheno-thiazine by refluxing the chloro compound with piperidine in

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[89] A. Mackie and A. L. Misra, J. Chem. Soc., 1281 (1955).

[90] J. W. Cusic, U. S. patent 2,629,719, February 24, 1953 [C. A., 48, 1444 (1954)].

[91] R. M. Jacobs, R. Horclois, R. Vaupre and M. Messer, Compt. rend., 243, 1637 (1956).

toluene for 6 hours;[82] the 10- [γ-(1-pyrrolidinyl)butyryl]-phenothiazine from pyrrolidine and the 10-(γ-bromobutyryl) derivative;[92] the 10- [α,β-bis(1-pyrrolidinyl)propionyl]-phenothiazine from pyrrolidine and 10-(α,β-dibromopropionyl)-phenothiazine;[92] and the 10- 2-(1-piperidyl)propyl phenothiazine was prepared from 10-(2-bromopropyl)phenothiazine by heating it with piperidine in the presence of copper powder.[93]

Substituents containing an alcohol group can be converted to halides with proper treatment. 10-(2-Hydroxypropyl)phenothiazine was changed to the 10-(2-bromopropyl)phenothiazine by treatment with phosphorus tribromide in chloroform.[93] This same hydroxy compound was changed to 10-(2-chloropropyl)-phenothiazine with thionyl chloride.[88] An exchange reaction was performed on 10-(chloroacetyl)phenothiazine, this being converted to 10-(iodoacetyl)phenothiazine by treatment with potassium iodide in acetone at reflux for 2 hours.[85]

Quite similar to reactions of the hydroxy group is the conversion of acids to acyl halides as is illustrated by the preparation of β-(10-phenothiazinyl)propionyl chloride by treating the corresponding acid with thionyl chloride in ether

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[92]J. R. Dahlbom and T. K. I. B. Ekstrand, U. S. patent 2,615,886, October 28, 1952 [C. A., 48, 1445 (1954)].

[93]J. R. Dahlbom, Swedish patent 134,622, February 26, 1952 [C. A., 48, 10783 (1954)].

containing a small amount of pyridine at -5°.[94]

A few reactions for obtaining the hydroxyl group are available. In one case, β-(10-phenothiazinyl)propionic acid was reduced to 10-(3-hydroxypropyl)phenothiazine by adding the acid to ether containing lithium aluminum hydride and refluxing for 30 minutes.[74] The formation of an aminohydroxy compound[90] has been pointed out previously.

A number of reactions can be used for converting an appropriate N-substituted phenothiazine to an ester. These make use of the well known methods of preparing this type of derivative; an acyl halide plus an alcohol, an acid and an alcohol, and a salt reacted with an alkyl halide. 1-Methyl-4-piperidyl 10-phenothiazinecarboxylate was prepared by refluxing a mixture of 10-phenothiazinecarbonyl chloride with 1-methyl-4-piperidinol in benzene for 15 hours;[83] 2-chloroethyl 10-phenothiazinecarboxylate was prepared by refluxing a mixture of 10-phenothiazinecarbonyl chloride and ethylene chlorohydrin for 12 hours;[69] 2-(dimethylamino)ethyl 10-phenothiazinecarboxylate was made by refluxing a toluene solution of the 10-phenothiazinecarbonyl chloride and 2-(dimethylamino)ethanol for 2 hours;[69] 2-(1-pyrrolidinyl)ethyl 10-phenothiazinecarboxylate was prepared similarly from the carbonyl chloride

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[94] R. Dahlbom and N. E. Willman, Acta Chem. Scand., 8, 1952 (1954).

derivative and 2-(1-pyrrolidinyl)ethanol;[69] and β'-dimethylaminoethyl β-(10-phenothiazinyl)propionate was prepared by a 2-hour reflux of a toluene solution of β-(10-phenothiazinyl)-propionyl chloride and 2-(dimethylamino)ethanol for 2 hours.[94]

Both 10-phenothiazinylcarbonylmethyl stearate[89] and methyl β-(10-phenothiazinyl)propionate[79] have been prepared from acid salts and alkyl halides, the former by refluxing a mixture of 10-(iodoacetyl)phenothiazine and sodium stearate in ethanol for 3 hours and the latter by refluxing the silver salt of β-(10-phenothiazinyl)propionic acid and methyl iodide in benzene for 2 hours.

Methyl 10-phenothiazinylpropionate was obtained by refluxing a methanolic solution of β-(10-phenothiazinyl)propionic acid containing some hydrochloric acid.[95]

The conversion of 10-phenothiazinylacyl halides, esters or anhydrides to amides was also accomplished. 10-Phenothiazinecarbonyl chloride reacted with 1-amino-2-dimethylaminoethane in methyl ethyl ketone for 12 hours at reflux produced N-(2-dimethylaminoethyl)-10-phenothiazinecarboxamide;[96] and N-(2-diethylaminoethyl)-N-methyl-10-phenothiazinecarboxamide was prepared by refluxing a benzene solution of 10-

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[95]Société des usines chimiques Rhône-Poulenc, French patent 986,718, August 3, 1951 [C. A., 50, 7880 (1956)].

[96]J. W. Cusic, U. S. patent 2,627,517, February 3, 1953 [C. A., 48, 744 (1954)].

phenothiazinecarbonyl chloride and 2-(diethylamino)ethylmethylamine.[97] The treatment of bis(10-phenothiazinyl)propionic anhydride with an ether solution of dimethylamine at -30° gave N,N-dimethyl-10-phenothiazinepropionamide[95] and ethyl 10-phenothiazinylacetate treated with a 10% methylamine in ethanol solution for 16 hours at 100° gave methyl-10-phenothiazinylacetamide.[98]

Because salt formation tends to alter the physiological properties of the free bases considerably, a great number of salts such as hydrochlorides, oxalates, gentisates, methochlorides, methobromides, methiodides, and theophyllinates have been formed from 10-substituted phenothiazines containing a nitrogen on the substituent. The method of preparation consists of mixing the appropriate phenothiazine with methyl iodide, oxalic acid, 7-theophylline acetic acid, etc. in a solvent such as acetone, ethanol, or nitrobenzene. The reaction generally takes place at room temperature although heating is required in some cases.

Dahlbom[99] prepared the methiodide of 10-(β-diethylaminopropionyl) phenothiazine [properly named as

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[97] A. W. Weston, R. W. DeNet, and R. J. Michaels, Jr., J. Am. Chem. Soc., 75, 4006 (1953).

[98] Société des usines chimiques Rhône-Poulenc, British patent 732,488, June 22, 1955 [C. A., 50, 7880 (1956)].

[99] J. E. Dahlbom, Swedish patent 136,720, July 29, 1952 [C. A., 47, 12427 (1953)].

10-(β-diethylmethylammoniumpropionyl)phenothiazine iodide by treating 10-(β-diethylaminopropionyl)phenothiazine with methyl iodide or by treating 10-(β-methylethylaminopropionyl)phenothiazine with ethyl iodide. By heating 10-(chloroacetyl)phenothiazine with triethylamine in nitrobenzene he was able to obtain 10-(triethylammoniumacetyl)phenothiazine chloride.[99] By dissolving the appropriate phenothiazine derivative in acetone or nitrobenzene and adding an excess of methyl or ethyl halide, Dahlbom[85] was able to obtain numerous salts including 10-(dimethylaminoacetyl)phenothiazine methobromide, methiodide and ethiodide; 10-(diethylaminoacetyl)phenothiazine methiodide, ethiodide and ethochloride; and several other similar ones.

A British patent[100] describes the formation of the oxalate salts of 1-dimethyl-2-propyl 10-phenothiazinecarboxylate, 2-(1-piperidyl)isopropyl 10-phenothiazinecarboxylate and 2-(4-morpholinyl)ethyl 10-phenothiazinecarboxylate. Schmalz and Burger[101] prepared the oxalate of 10-(3-diethylaminopropyl)phenothiazine. These were formed by mixing an ether solution of oxalic acid with an ether solution of the free base.

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[100] Aktiebolaget Astra Apotekarnes Kemiska Fabriker, British patent 708,896, May 12, 1954 [C. A., 49, 14039 (1955)].

[101] A. C. Schmalz and A. Burger, J. Am. Chem. Soc., 76, 5455 (1954).

Many salts were also prepared from 7-theophylline acetic acid. Such compounds as 10-(2-dimethylaminoethyl)phenothiazine theophylline acetate and 10-(2-diethylaminopropyl)phenothiazine theophylline acetate have been reported.[102,103] Salts also form between the appropriate phenothiazine derivative and 8-halotheophylline or 8-haloxanthine. Some examples of these are 10-[2-(2,5-dimethyl-1-piperidyl)ethyl]phenothiazine 8-chloroxanthine[104] and the 8-chlorotheophylline salt of 10-[2-(1-pyrrolidinyl)ethyl]phenothiazine.[104]

In this discussion no attempt has been made to indicate the yield obtained for a particular preparation. This was done to avoid unnecessary repetition of numbers which for close comparative purposes would be of little value since the yield reported in some of this work was for the crude material. However, in order to make this portion more complete, a general resume of the expected yield for a particular reaction will be given. Of course, the amount of product obtained is governed largely by the reactivity of the halogen, or other, compound employed for the N-substitution.

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[102] Société des usines chimiques Rhône-Poulenc, British patent 679,001, September 10, 1952 [C. A., 47, 12427 (1953)].

[103] R. J. Horclois, U. S. patent 2,595,853, May 6, 1952 [C. A., 47, 4378 (1953)].

[104] J. W. Cusic, British patent 677,798, August 20, 1952 [C. A., 48, 4010 (1954)].

The liquid ammonia procedure generally gives a 70 to 100% yield of product for those to which it can be applied. Unfortunately, its scope is limited and halogens of less than intermediate activity cannot be used.

The method in which no solvent is employed is generally quite successful for those reactions in which a halogen compound of even low activity is used. Yields of 50 to 75% can generally be expected for this procedure, unless the halogen is extremely active.

When a solvent is used, lower yields can be expected with a given halogen compound then for the no-solvent method. This is due mostly to the temperature which is governed by the boiling point of the solvent and which is generally much lower than that which can be obtained without solvent. Yields of 50% or less are usually obtained by this method.

The sealed tube reactions usually give a 50% yield although the 10-phenothiazinecarbonyl chloride was prepared in a yield of 80%.

The reactions used in the alteration of the N-substituent; amination, ester formation, etc. give variable yields, but generally fall in the range of 50 to 75%. In contrast to this the salt formations are much higher ranging from 80% to a nearly quantitative yield.

Table 1 of the N-substituted derivatives for the years 1952 through 1956 follows.

Table 1. N-Substituted phenothiazine compounds

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-Acetylphenothiazine | 198 | (73) |
| 10-(β-Allylaminopropionyl)-phenothiazine (See Figure 1a, Appendix.) | --- | |
| HCl salt | 165-166 | (84) |
| 10-Allylphenothiazine | b.p., 165-170/0.7 mm. | (105) |
| 3-[Allyl-(10-phenothiazinylcarbonylmethyl)amino]-1-propanol (See Figure 1b, Appendix.) | viscous oil | (84) |
| 10-(2-Aminoethyl)phenothiazine | --- | |
| HCl salt | 270-271 | (88) |
| Maleate | 181 | (88) |
| 10-(2-Aminopropyl)phenothiazine | 132-133 | (88) |
| HCl salt | 244-245 | (88) |
| 10-(3-Aminopropyl)phenothiazine | 191-192 | (88) |
| HCl salt | 228-230 | (88) |
| Maleate | 183-184 | (88) |
| n-Amyl β-(10-phenothiazinyl)-propionate (See Figure 1c, Appendix.) | 74-75 | (79) |

[105]This thesis.

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-(p-Anisoyl)phenothiazine | 173-174 | (79) |
| 10-Benzoylphenothiazine | 174<br>177-178 | (73)<br>(79) |
| 10-[3-(Benzyl-2-butenylamino)-butyryl]-phenothiazine (See Figure 1d, Appendix.) | viscous oil | (84) |
| N-Benzyl-N-(2-diethylaminoethyl)-10-phenothiazinecarboxamide (See Figure 1e, Appendix.) | --- | |
| HCl salt | 142-143 | (96) |
| Ethiodide | --- | (96) |
| 10-Benzylphenothiazine | 91-92<br>90.5-91.5 | (106)<br>(107) |
| N-Benzyl-10-phenothiazinecarboxanilide (See Figure 1f, Appendix.) | 112-113 | (96) |
| 10-(p-Biphenylyl)phenothiazine | 174-178 | (105) |
| 10-(Bromoacetyl)phenothiazine | 121-122 | (85) |

[106]H. Gilman, I. Zarember, and J. A. Beel, J. Am. Chem. Soc., 74, 3177 (1952).

[107]H. Gilman, R. D. Nelson and J. F. Champaigne, Jr., J. Am. Chem. Soc., 74, 4205 (1952).

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-(o-Bromobenzyl)phenothiazine | 90-92 | (105) |
| 10-(α-Bromobutyryl)phenothiazine | 120-121 | (81) |
| 10-(β-Bromobutyryl)phenothiazine | 167-168 | (81) |
| 10-(γ-Bromobutyryl)phenothiazine | 88-90 | (81) |
| 10-(β-Bromoisobutyryl)phenothiazine (See Figure 1g, Appendix.) | 110-111 | (81) |
| 10-(β-Bromopropionyl)phenothiazine | 144-145 | (85) |
| n-Butyl β-(10-phenothiazinyl)-propionate | 85-86 | (79) |
| sec-Butyl β-(10-phenothiazinyl)-propionate | 43-44 | (79) |
| tert-Butyl β-(10-phenothiazinyl)-propionate | 76 | (79) |
| 10-Butyrylphenothiazine | 94 | (73) |
| 10-(Chloroacetyl)phenothiazine | 112<br>---<br>110-112 | (73)<br>(79)<br>(84) |
| 10-(4-Chlorobutyl)phenothiazine | b.p., 205-210/1 mm. | (70) |
| 10-(β-Chlorobutyryl)phenothiazine | 158-160 | (82) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-(γ-Chlorobutyryl)phenothiazine | --- | (82) |
| | --- | (84) |
| | 95-96 | (85) |
| 3'-Chloro-N-(2-diethylaminoethyl)-10-phenothiazinecarboxanilide | creamy ppt. | (96) |
| 10-(2-Chloro-3-dimethylaminopropyl)phenothiazine | --- | (108) |
| 10-(2-Chloroethyl)phenothiazine | --- | (88) |
| | --- | (90) |
| Hexamethylenediamine salt | 183 | (109) |
| 2-Chloroethyl 10-phenothiazinecarboxylate | 146-148 | (69) |
| | 142-143 | (83) |
| 10-(6-Chlorohexanoyl)phenothiazine | --- | (84) |
| 10-(β-Chloropropionyl)phenothiazine | 135-136 | (82) |
| 10-(2-Chloropropyl)phenothiazine | 120-122 | (88) |
| 10-(3-Chloropropyl)phenothiazine | --- | (88) |

[108] R. M. Jacobs, R. Horclois, R. Vaupre and M. Messer, Compt. rend., 243, 1637 (1956).

[109] Société des usines chimiques Rhône-Poulenc, British patent 688,805, March 11, 1953 [C. A., 48, 2786 (1954)].

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-(2-Cyanoethyl)phenothiazine | 180-182 | (88) |
| 10-[2-(Cyclohexylamino)ethyl]-phenothiazine (See Figure 1h, Appendix.) | b.p., 199-201/0.7 mm. | (93) |
| 10-[β-(Cyclohexylamino)-propionyl]phenothiazine | b.p., 200/0.008 mm. | (110) |
| HCl salt | 206-207 dec. | (84) |
| N-Cyclohexyl-N-(2-diethylamino-ethyl)-10-phenothiazinecarboxamide | --- | (96) |
| 2-{Cyclohexyl[5-(10-phenothiazinyl-carbonyl)pentyl]amino}ethanol | viscous oil | (84) |
| 10-(n-Decyl)phenothiazine | b.p., 175-180/0.5 mm. | (105) |
| 10-(β-Diallylaminopropionyl)-phenothiazine HCl salt | 131-133 | (84) |
| 10-(α,β-Dibromopropionyl)-phenothiazine | viscous oil | (84) |
| 10-(β-Dibutylaminopropionyl)-phenothiazine | --- | (82) |

[110] Aktiebolaget Astra, Apotekarnes Kemiska Fabriker, British patent 662,903, December 12, 1951 [C. A., 46, 11250 (1952)].

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-(2,4-Dichlorobenzoyl)phenothiazine | 133-134 | (79) |
| 2',5'-Dichloro-N-(2-diethylamino-ethyl)-10-phenothiazinecarboxanilide | | |
| HCl salt | --- | (96) |
| 10-(Diethylaminoacetyl)phenothiazine | 58-59 | (110) |
| | b.p., 250/0.5 mm. | (110) |
| HCl salt | 208-209 | (84) |
| Ethochloride | 194-195 dec. | (85) |
| | 192-193 | (99) |
| Ethiodide | 198-199 dec. | (85) |
| Methiodide | 198-200 dec. | (85) |
| 10-(α-Diethylaminobutyryl)-phenothiazine | 64-66 | (81) |
| HCl salt | 202-203 dec. | (81) |
| 10-(β-Diethylaminobutyryl)-phenothiazine | 62-63 | (81) |
| HCl salt | --- | (81) |
| Methobromide | 199-200 | (84) |
| Methiodide | 215-216 | (84) |
| 10-(γ-Diethylaminobutyryl)-phenothiazine | --- | (81) |
| HCl salt | 151-153 | (81) |
| Oxalate | dec. | (81) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-(2-Diethylaminoethylamino-acetyl)phenothiazine | 79-80 | (89) |
| N-(2-Diethylaminoethyl)-N-methyl-10-phenothiazinecarboxamide | 69-71 | (97) |
| HBr salt | 160-161 | (97) |
| 10-(2-Diethylaminoethyl)-phenothiazine | b.p., 165-170/0.05 mm.<br>b.p., 195-197/1.5 mm.<br>b.p., 178-180/0.7 mm.<br>b.p., 165-175/0.05 mm.<br>--- | (72)<br>(75)<br>(76)<br>(111)<br>(78) |
| HCl salt | 184-186<br>186<br>184.5-186.5<br>186-187 | (72)<br>(75)<br>(76)<br>(111) |
| Ethobromide | 198 | (70) |
| Methochloride | 175 | (70) |
| Methiodide | 149-150 | (70) |
| 7-Theophylline acetate | 110<br>110 | (102)<br>(103) |
| Hexamethylenedi-bromide salt | 158-160 | (76) |
| Gentisate | 148-149 | (112) |

[111] J. N. Ashley and S. S. Berg, British patent 673,005, May 28, 1952 [C. A., 47, 6990 (1953)].

[112] Cassella Farbwerke Mainkur Akt-Ges., British patent 710,327, June 9, 1954 [C. A., 50, 1929 (1956)]; Walther Perach, U. S. patent 2,752,345, June 26, 1956 [C. A., 50, 12120 (1956)].

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| N-(2-Diethylaminoethyl)-10-phenothiazinecarboxamide | | |
| Citrate | 165-166 | (96) |
| Methobromide | 225-226 dec. | (97) |
| Methobromide·½$H_2O$ | 185-186 | (97) |
| Methiodide | --- | (96) |
| N-(2-Diethylaminoethyl)-10-phenothiazinecarboxanilide | | |
| HCl salt | 179-180 | (96) |
| 2-Diethylaminoethyl 10-phenothiazinecarboxylate (See Figure 11, Appendix.) | 54-56<br>54-55<br>52-53 | (69)<br>(97)<br>(100) |
| HCl salt | 163-164<br>159-160<br>165-166<br>163-164 | (69)<br>(83)<br>(97)<br>(100) |
| Ethobromide | 213-215 dec. | (69) |
| Methobromide | 220-221 dec. | (69) |
| Methiodide | 217-218 | (83) |
| 2-Diethylaminoethyl 10-phenothiazinethiocarboxylate | | |
| Methobromide | 228 dec. | (97) |
| Methiodide | 230-231 dec. | (97) |
| Oxalate | 158-160 dec. | (69) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| β'-Diethylaminoethyl β-(10-phenothiazinyl)propionate | | |
| Oxalate | 118-120 | (94) |
| β'-Diethylaminoethyl β-(10-phenothiazinyl)thiopropionate | | |
| Oxalate | 121-122 dec. | (94) |
| 10-(3-Diethylamino-2-hydroxypropyl)phenothiazine | 142-143 | (71) |
| HCl salt | 134 | (71) |
| 10-(2-Diethylamino-1-methylethyl)phenothiazine | b.p., 202-205/2 mm. | (72) |
| | --- | (78) |
| | b.p., 160-165/0.08 mm. | (111) |
| | --- | (113) |
| HCl salt | 166-168 | (72) |
| | 166-168 | (111) |
| Methochloride | 208 | (70) |
| 2-Diethylamino-1-methyl 10-phenothiazinecarboxylate | | |
| HCl salt | 180-182 | (97) |
| 10-(α-Diethylaminopropionyl)-phenothiazine | 99.5-100.5 | (110) |

[113] P. Charpentier, P. Gailliot and J. Gaudechon, Compt. rend., 232, 2232 (1951).

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-(β-Diethylaminopropionyl)-phenothiazine | b.p., 210-212/2 mm. | (82) |
| HCl salt | 163-164 | (82) |
| Methobromide | 202-204 | (84) |
| | 202-203 | (85) |
| Methiodide | 202-203 | (84) |
| | 183-184 | (85) |
| | 174-175 | (99) |
| N-(3-Diethylaminopropyl)-N-ethyl-10-phenothiazinecarboxamide | --- | (96) |
| 10-(2-Diethylaminopropyl)-phenothiazine | b.p., 202-205/2 mm. | (72) |
| | --- | (78) |
| | b.p., 160-165/0.08 mm. | (111) |
| | --- | (113) |
| HCl salt | 223-225 | (72) |
| | 223-225 | (111) |
| 7-Theophylline acetate | 131-132 | (102) |
| | 131-132 | (103) |
| 10-(3-Diethylaminopropyl)-phenothiazine | --- | (78) |
| Ethobromide | 152 | (70) |
| Methochloride | 200 | (70) |
| Oxalate | 176-177 | (101) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 2-Diethylaminopropyl 10-phenothiazinecarboxylate | 75-77 | (97) |
| HCl salt | 187-188 dec. | (97) |
| Methiodide | 194-195 | (83) |
| 3-Diethylaminopropyl 10-phenothiazinecarboxylate | | |
| Picrate | 93-95 | (100) |
| N,N-Diethyl-10-phenothiazinecarboxamide | 91-93 | (69) |
| 10-(Dimethylaminoacetyl)phenothiazine | 144-145 | (84) |
| HCl salt | 230-231 | (84) |
| Ethiodide | 216-218 dec. | (85) |
| Methobromide | 236-237 dec. | (85) |
| Methiodide | 234-235 dec. | (85) |
| 10-(2-Dimethylaminobutyl)-phenothiazine | | |
| Methochloride | 217 dec. | (70) |
| 10-(4-Dimethylaminobutyl)-phenothiazine | b.p., 195/1 mm. | (70) |
| Methochloride | 185 | (70) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-(α-Dimethylaminobutyryl)-phenothiazine | 98-99 | (81) |
| 10-(β-Dimethylaminobutyryl)-phenothiazine | 94-95 | (81) |
| | 90-91 | (82) |
| HCl salt | 136-138 | (82) |
| Ethobromide | 205-206 dec. | (85) |
| | 212-213 | (102) |
| Methochloride | 210-212 | (82) |
| Methobromide | 237 dec. | (102) |
| | 226-228 dec. | (103) |
| Benzyl chloride salt | --- | (82) |
| 10-(γ-Dimethylaminobutyryl)-phenothiazine | 93-95 | (81) |
| | 93-94 | (84) |
| HCl salt | 190-192 | (81) |
| | --- | (84) |
| Methiodide | 185-187 | (85) |
| 10-(2-Dimethylaminoethyl)-phenothiazine | b.p., 190-197/1.5 mm. | (75) |
| | 42-44.5 | (76) |
| | b.p., 171-175/1.7 mm. | (76) |
| | --- | (78) |
| | b.p., 160-165/0.2 mm. | (93) |
| | --- | (95) |
| HCl salt | 225 | (75) |
| Ethobromide | 140 | (70) |
| Methochloride | 230 | (70) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| Methiodide | 249-250 | (70) |
| 7-Theophylline acetate | 132<br>132 | (102)<br>(103) |
| 8-Chlorotheophylline salt | 168-169<br>168-169 | (104)<br>(114) |
| 8-Bromotheophylline salt | 167-168<br>167-168 | (104)<br>(114) |
| p-Aminosalicylate salt | 159-160 dec. | (115) |
| Hexamethylene dibromide salt | 229 (shrinks 190) | (76) |
| N-(2-Dimethylaminoethyl)-10-phenothiazinecarboxamide | 202-203 (with ½ mole $H_2O$) | (97) |
| HCl salt | 198-200 | (96) |
| Methiodide | 223-224 | (96) |
| N-(2-Dimethylaminoethyl)-10-phenothiazinecarboxanilide | | |
| HCl salt | 223-224 | (96) |

[114] J. W. Cusic, U. S. patent 2,534,237, December 19, 1950 [C. A., 46, 527 (1952)].

[115] M. Erlenbach and A. Sieglitz, British patent 689,835, April 8, 1953 [C. A., 47, 9575 (1953)].

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 2-Dimethylaminoethyl 10-phenothiazinecarboxylate | | |
| HCl salt | 212-213 dec.<br>214-215<br>215-216<br>211-212 dec. | (69)<br>(83)<br>(97)<br>(100) |
| Ethobromide | 233-234 dec. | (69) |
| Methochloride | 232 dec. | (83) |
| Methobromide | 248-249 dec. | (69) |
| Methiodide | 235-236 dec. | (69) |
| β'-Dimethylaminoethyl β-(10-phenothiazinyl)propionate | 81-83 | (94) |
| 10-(3-Dimethylamino-2-hydroxypropyl)phenothiazine | 84-85<br>--- | (71)<br>(108) |
| HCl salt | 131 | (71) |
| 10-(2-Dimethylaminoisobutyl)-phenothiazine | b.p., 175-180/1 mm. | (70) |
| Methochloride | 196 | (70) |
| 10-(β-Dimethylaminoisobutyryl)-phenothiazine | | |
| HCl salt | 251-252 dec. | (81) |
| Methobromide | 243-246 dec. | (85) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-(2-Dimethylamino-1-methylethyl)phenothiazine | 59-60 | (86) |
| | --- | (113) |
| | --- | (72) |
| | --- | (78) |
| HCl salt | 222 | (86) |
| | 222 | (87) |
| Methochloride | 227 dec. | (70) |
| 2-Dimethylamino-1-methylethyl 10-phenothiazinecarboxylate | | |
| Oxalate | 181-182 dec. | (69) |
| | 181-182 dec. | (100) |
| 10-(α-Dimethylaminopropionyl)-phenothiazine | | |
| Methiodide | 230-231 dec. | (85) |
| 10-(β-Dimethylaminopropionyl)-phenothiazine | 86-88 | (82) |
| Ethobromide | 209-210 | (85) |
| Ethiodide | 167-168 | (85) |
| Methobromide | 234-235 | (85) |
| Methiodide | 208 | (82) |
| | 198-200 | (85) |
| | 194-195 | (99) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-(2-Dimethylaminopropyl)-phenothiazine | 59-60 | (93) |
| | b.p., 158-160/0.2 mm. | (93) |
| | b.p., 145-155/0.08 mm. | (72) |
| | --- | (78) |
| | --- | (95) |
| | --- | (113) |
| HCl salt | 218-220 | (72) |
| Ethobromide | 188 | (70) |
| Methochloride | 205 | (70) |
| 7-Theophylline acetate | 134-135 | (102) |
| | 134-135 | (103) |
| 8-Chlorotheophylline salt | 152-153 | (104) |
| | 152-153 | (114) |
| 10-[2,3-Bis(dimethylamino)-propyl]phenothiazine | --- | (108) |
| N-(3-Dimethylaminopropyl)-10-phenothiazinecarboxamide | 82-83 | (96) |
| HCl salt | 193-194 dec. | (96) |
| 10-[β-(3,5-Dimethyl-4-morpholinyl)-propionyl]phenothiazine | | |
| HCl salt | 222-223 | (84) |
| N,N-Dimethyl-α-(10-phenothiazinyl)propionamide | 165-167 | (95) |
| N,N-Dimethyl-β-(10-phenothiazinyl)propionamide | 141-143 | (95) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-[2-(2,5-Dimethyl-1-piperidyl)-ethyl]phenothiazine | | |
| 8-Chloroxanthine salt | --- | (104) |
| 10-[2-(2,6-Dimethyl-1-piperidyl)-ethyl]phenothiazine (See Figure 1j, Appendix.) | b.p., 225/1 mm. | (70) |
| Methochloride | 232 dec. | (70) |
| Methiodide | 223 dec. | (70) |
| 8-Chloroxanthine salt | --- | (114) |
| 10-[$\alpha$,$\beta$-Di(4-morpholinyl)-propionyl]phenothiazine (See Figure 1k, Appendix.) | | |
| HCl salt | 229-230 | (84) |
| 10-(3,5-Dinitrobenzoyl)-phenothiazine | 265-266 | (79) |
| 10-($\beta$-Di-n-propylamino-propionyl)phenothiazine | 65-66 | (84) |
| 10-(2,3-Epoxypropyl)phenothiazine | ---<br>--- | (71)<br>(108) |
| 10-{6-[Ethyl-(1-methyl-2-butenyl)amino]hexanoyl}-phenothiazine | viscous oil | (84) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-Ethylphenothiazine | 103-104<br>102.5-103 | (105)<br>(107) |
| N-Ethyl-β-(10-phenothiazinyl)-propionamide | 120 | (95) |
| 10-Formylphenothiazine | 145<br>143-144.5 | (73)<br>(116) |
| n-Heptyl β-(10-phenothiazinyl)-propionate | 46-47 | (79) |
| 10-(n-Hexylaminoacetyl)phenothiazine | 172-173 | (89) |
| HCl salt | 204-205 dec. | (89) |
| 10-(β-n-Hexylaminopropionyl)-phenothiazine | | |
| HCl salt | 191-192 | (84) |
| n-Hexyl β-(10-phenothiazinyl)-propionate | 52-53 | (79) |
| 10-(N-2-Hydroxyethyl-N-methyl-β-alanyl)phenothiazine | --- | (117) |

[116] J. Cymerman-Craig, W. P. Rogers and G. P. Warwick, Australian J. Chem., 8, 252 (1955).

[117] J. W. Cusic, U. S. patent 2,576,106, November 27, 1951 [C. A., 46, 6152 (1952)].

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-{2-[(2-Hydroxyethyl)methylamino]ethyl}phenothiazine | | |
| 8-Chlorotheophylline salt | 135-140<br>135-140 | (104)<br>(114) |
| 2-[(2-Hydroxyethyl)methylamino]ethyl 10-phenothiazinecarboxylate | | |
| HCl salt | 172-173 | (83) |
| 10-{β-[(2-Hydroxyethyl)methylamino]propionyl}phenothiazine | ---<br>129-130 | (82)<br>(84) |
| 10-(2-Hydroxyethyl)phenothiazine | b.p., 210-213/0.3 mm. | (74) |
| 10-(2-Hydroxypropyl)phenothiazine | b.p., 190-195/0.35 mm. | (88) |
| 10-(3-Hydroxypropyl)phenothiazine | b.p., 160/0.01 mm. (bath temp.) | (74) |
| 10-(2-Imidazolin-2-ylmethyl)-phenothiazine | | |
| HCl salt | 241-243 | (118) |
| 10-(Iodoacetyl)phenothiazine | 129-131 | (85) |

[118] Ciba Ltd., British patent 670,580, April 23, 1952 [C. A., 46, 10209 (1952)].

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-(β-Isobutylaminopropionyl)-phenothiazine | | |
| HCl salt | 200-201 | (84) |
| Isobutyl β-(10-phenothiazinyl)-propionate | 73-74 | (79) |
| 10-(α-Isopropylaminobutyryl)-phenothiazine | --- | (110) |
| 10-(β-Isopropylaminopropionyl)-phenothiazine | | |
| HCl salt | 227 dec. | (84) |
| 10-(β-Isopropylaminovaleryl)-phenothiazine | --- | (82) |
| Isopropyl β-(10-phenothiazinyl)-propionate | 74-75 | (79) |
| 10-Methylphenothiazine | 99-100 | (119) |
| Methyl-10-phenothiazineacetamide | 228 | (95) |
| Methyl 10-phenothiazinecarboxylate | 118-120 | (69) |

[119]A. Burger and A. C. Schmalz, J. Org. Chem., 19, 1841 (1954).

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 2-{Methyl[2-(10-phenothiazinyl-carbonyl)ethyl]amino}ethanol | 120-130 | (84) |
| 1,1'-{[1-Methyl-2-(10-phenothiazinylcarbonyl)ethyl]-imino}-bis-[2-methyl-2-pentanol] | viscous oil | (84) |
| N-Methyl-β-(10-phenothiazinyl)-propionamide | 96 | (95) |
| Methyl β-(10-phenothiazinyl)-propionate | 64-65<br>68 | (79)<br>(95) |
| 10-[(4-Methyl-1-piperazinyl)carbonyl]-phenothiazine | 229-231 | (80) |
| 2-(4-Methyl-1-piperazinyl)-ethyl 10-phenothiazinecarboxylate | | |
| HCl salt | 258-260 | (83) |
| 10-[β-(4-Methyl-1-piperazinyl)-propionyl]phenothiazine | | |
| HCl salt | 206-207 | (84) |
| 10-[1-Methyl-2-(1-piperidyl)-ethyl]phenothiazine | b.p., 190-200/0.3-0.4 mm. | (77) |
| HCl salt | 256-257 | (77) |
| 1-Methyl-2-(1-piperidyl)ethyl 10-phenothiazinecarboxylate | | |
| Oxalate | 170-171 dec.<br>170-171 dec. | (69)<br>(100) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 1-Methyl-4-piperidyl 10-phenothiazinecarboxylate | | |
| Oxalate | 172-173 | (83) |
| 10-[β-(2-Methyl-1-piperidyl)-propionyl]phenothiazine | | |
| HCl salt | 190-191 | (84) |
| 10-[β-(4-Morpholinyl)butyryl]-phenothiazine | 133-134 | (84) |
| HCl salt | 188-189 | (84) |
| Methobromide | 211-212 | (84) |
| 10-[2-(4-Morpholinyl)ethyl]-phenothiazine | 74-75 | (77) |
| | 73-75 | (93) |
| | b.p., 187-190/0.1 mm. | (77) |
| | b.p., 188-190/0.1 mm. | (93) |
| N-[2-(4-Morpholinyl)ethyl]-10-phenothiazinecarboxamide | | |
| HCl salt | 214-215 | (96) |
| 2-(4-Morpholinyl)ethyl 10-phenothiazinecarboxylate | | |
| HCl salt | 213-214 | (97) |
| Oxalate | 111-114 dec. | (69) |
| | 109-111 dec. | (100) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-[β-(4-Morpholinyl)propionyl]phenothiazine | viscous oil | (82) |
| 10-(p-Nitrobenzoyl)phenothiazine | 225-226 | (79) |
| 4-Nitrobenzyl β-(10-phenothiazinyl)propionate | 160-161 | (79) |
| 10-(n-Octadecyl)phenothiazine | 53-54 | (105) |
| n-Octyl β-(10-phenothiazinyl)propionate | 38-39 | (79) |
| 10-Phenothiazinecarbonyl chloride | 172-173<br>---<br>---<br>--- | (69)<br>(96)<br>(97)<br>(100) |
| N-(10-Phenothiazinecarbonyl)-N',N'-diethylethylenediamine | | |
| HCl salt | 180-181 dec.<br>142-149 (with methanol of recrystallization) | (69) |
| p-Bis(10-Phenothiazinyl)benzene | 252-253 | (105) |
| p,p'-bis(10-Phenothiazinyl)biphenyl (See Figure 1, Appendix.) | 300-305 dec. | (105) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 2,2'-[2-(10-Phenothiazinylcarbonyl)ethyl]iminodiethanol | | |
| HCl salt | 177-178 | (84) |
| 10-Phenothiazinylcarbonylmethyl β-(10-phenothiazinyl)propionate | 179-180 | (79) |
| 10-Phenothiazinylcarbonylmethyl stearate | 73-74 | (89) |
| 3-[3-(10-Phenothiazinylcarbonyl)-propylamino]-1-propanol | viscous oil | (84) |
| [2-(10-Phenothiazinyl)ethyl]-trimethylammonium iodide | | |
| Theophylline hydrate salt | 175 | (70) |
| 8-Chlorotheophylline salt | 184 | (70) |
| β-(10-Phenothiazinylpropion)-p-bromo anilide | 193-194 | (79) |
| β-(10-Phenothiazinyl)propionic acid | --- | (120) |
| Sodium salt | 262-263 dec. | (79) |
| S-Benzylthiuronium salt | 160 | (79) |

[120] N. L. Smith, J. Org. Chem., 16, 415 (1951)

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 1-Phenylethyl-ammonium salt | 156-158 | (79) |
| Piperazonium salt | 190-191 | (79) |
| β-(10-Phenothiazinyl)propionitrile | 158-159 | (120) |
| β-(10-Phenothiazinylpropion)-p-toluidide | 140 | (79) |
| β-(10-Phenothiazinyl)propionyl chloride | 117 | (94) |
| N-[β-(10-Phenothiazinyl)propionyl]-N',N'-diethylethylenediamine | | |
| Oxalate | 130-131 | (94) |
| N-[β-(10-phenothiazinyl)propionyl]-piperidine | 127-128 | (94) |
| 10-(β-Phenylethyl)phenothiazine | 175-177 | (105) |
| 10-Phenylphenothiazine | 94.5-95.5 | (105) |
| | b.p., 170-175/0.05 mm. | (105) |
| 10-(γ-Phenylpropyl)phenothiazine | 172-174 | (105) |
| 10-(2-Phthalimidoethyl)phenothiazine | 173-174 | (88) |
| 10-(2-Phthalimidopropyl)phenothiazine | 172-174 | (88) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-[(1-Piperidyl)acetyl]phenothiazine | 163.5-164.5 | (110) |
| 10-[α-(1-Piperidyl)butyryl]-phenothiazine | 86-88 | (81) |
| HCl salt | 214-216 | (81) |
| 10-[γ-(1-Piperidyl)butyryl]-phenothiazine | 78-80 | (81) |
| HCl salt | --- | (81) |
| 10-[β-(1-Piperidyl)butyryl]-phenothiazine | | |
| HCl salt | 202-203 | (84) |
| Methobromide | 194.5 | (84) |
| 10-(1-Piperidyl)carbonylphenothiazine | 118-120 | (69) |
| 10-[2-(1-Piperidyl)ethyl]phenothiazine | 43-44 | (93) |
| | b.p., 240/0.3-0.4 mm. | (93) |
| | b.p., 220-230/0.3 mm. | (77) |
| HCl salt | 154-155 | (77) |
| Methochloride | 213 | (70) |
| 2-(1-Piperidyl)ethyl 10-phenothiazinecarboxylate | | |
| HCl salt | 122-124 | (83) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| N-[2-(1-Piperidyl)ethyl]-10-phenothiazinecarboxamide | | |
| HCl salt | --- | (96) |
| 10-[β-(1-Piperidyl)isobutyryl]-phenothiazine | 79-81 | (81) |
| HCl salt | --- | (81) |
| 10-[β-(1-Piperidylpropionyl]-phenothiazine | b.p., 220-230/3 mm. | (82) |
| HCl salt | 230-235 | (82) |
| Methobromide | 196-197 | (84) |
| 10-[2-(1-Piperidyl)propyl]-phenothiazine | 120-121 | (93) |
| HCl salt | 255-256 | (93) |
| Oxalate | 181-183 | (93) |
| 10-[3-(1-Piperidyl)propyl]-phenothiazine | b.p., 230-240/0.5 mm.<br>b.p., 245-248/0.5 mm. | (77)<br>(93) |
| 10-Propionylphenothiazine | 89 | (73) |
| n-Propyl β-(10-phenothiazinyl)-propionate | 34-35 | (79) |
| 10-[(1-pyridyl)acetyl]phenothiazine | | |
| HCl salt | 252-253 dec.<br>252-253 | (85)<br>(99) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-(2-Pyridyl)phenothiazine | 109-110 | (105) |
| 10-(2-Pyridyl)phenothiazine:Boron trifluoride complex | 305-310 dec. | (105) |
| 10-[α-(1-Pyridyl)propionyl]-phenothiazine | | |
| HI salt | 218-219 | (85) |
| 10-[β-(1-Pyridyl)propionyl]-phenothiazine | | |
| HCl salt | 216-217 dec.<br>214-215 | (85)<br>(99) |
| 10-[(1-Pyrrolidinyl)acetyl]-phenothiazine | 142-142.5 | (92) |
| 10-[α-(1-Pyrrolidinyl)butyryl]-phenothiazine | --- | |
| HCl salt | 206-208<br>206-208 | (81)<br>(92) |
| 10-[β-(1-Pyrrolidinyl)butyryl]-phenothiazine | 119-120 | (81) |
| HCl salt | --- | (81) |
| Methobromide | 171-173 | (84) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-[γ-(1-Pyrrolidinyl)butyryl]-phenothiazine | 106-107 | (92) |
| | 106-107 | (81) |
| (See Figure 1m, Appendix.) | --- | (82) |
| HCl salt | --- | (81) |
| Oxalate | 161-162 | (122) |
| 10-(1-Pyrrolidinyl)carbonyl-phenothiazine | 137-139 | (69) |
| 10-[2-(1-Pyrrolidinyl)ethyl]-phenothiazine | b.p., 142-146/0.1 mm. | (93) |
| HCl salt | 199-200 | (93) |
| 8-Chlorotheophyl-line salt | 166-167 | (104) |
| | 166-167 | (114) |
| 2-(1-Pyrrolidinyl)ethyl 10-phenothiazinecarboxylate | | |
| HCl salt | 215-217 dec. | (69) |
| | 220-221 dec. | (83) |
| | 215-216 | (97) |
| | 215-217 | (100) |
| Ethobromide | 215-216 | (83) |
| Methobromide | 200-201 | (83) |
| 10-[β-(1-Pyrrolidinyl)iso-butyryl]phenothiazine | | |
| HCl salt | 231-233 dec. | (81) |

Table 1. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 10-[α-(1-Pyrrolidinyl)propionyl]-phenothiazine | 94.5-95.5 | (92) |
| 10-[β-(1-Pyrrolidinyl)propionyl]-phenothiazine | 106-107<br>108-109 | (84)<br>(92) |
| 10-[α,β-Bis(1-pyrrolidinyl)-propionyl]phenothiazine | 102-104 | (92) |
| 10-[2-(1-Pyrrolidinyl)propyl]-phenothiazine | b.p., 155-160/0.1 mm. | (93) |
| HCl salt | 192-193 | (93) |
| 10-(2-Quinolyl)phenothiazine | 124-126 | (105) |
| 10-[2-(4-Thiamorpholinyl)iso-propyl]phenothiazine (See Figure 1n, Appendix.) | b.p., 165-170/0.05 mm. | (77) |
| 10-[2-(4-Thiamorpholinyl)propyl]-phenothiazine | b.p., 165-170/0.05 mm. | (99) |
| 10-(o-Tolyl)phenothiazine | 101-101.5 | (107) |
| 10-(p-Tolyl)phenothiazine | 135-136 | (107) |

## Oxidation Reactions

Both sulfoxides and sulfones can be formed by oxidation of phenothiazine and its derivatives. Whether the 5-oxide or the 5,5-dioxide is formed depends upon the oxidizing agent, the solvent, and other conditions such as the temperature and time of reaction. The best method for obtaining the monoxide is by the oxidation of the parent compound in refluxing ethanol using an excess of 30% hydrogen peroxide. However, some dioxide may also be formed if too great an excess of the oxidizing agent is used or if the time of reaction is extended for too long.

To obtain the sulfone, glacial acetic acid is used as the solvent, with hydrogen peroxide still being used as the oxidizing agent. Elevated temperatures, sometimes at reflux, are employed for these oxidations. Some examples of oxidations using hydrogen peroxide in either ethanol or glacial acetic acid are presented as part of the remainder of this section.

Phenothiazine-5-oxide was prepared by the addition of hydrogen peroxide to a refluxing ethanolic solution of phenothiazine containing a small amount of potassium hydroxide,[121] 3,7-dimethylphenothiazine-5-oxide was obtained by the

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[121] R. Pummerer and S. Gassner, Ber., 46, 2322 (1913).

addition of hydrogen peroxide to a refluxing ethanol solution of the parent compound; and both 10-benzylphenothiazine-5-oxide and 10-ethylphenothiazine-5-oxide were obtained by similar methods.[122] The 10-(2-chloroethyl)phenothiazine-5-oxide was prepared by the dropwise addition of 25% hydrogen peroxide to a warm ethanol solution of 10-(2-chloroethyl)-phenothiazine followed by a 2-day standing period.[90]

Using glacial acetic acid as the solvent and 15-30% hydrogen peroxide as the oxidizing agent a large number of dioxides, or sulfones, have been formed. The sulfone of a dichlorophenothiazine was formed by oxidation of the sulfoxide derivative with 17% hydrogen peroxide in 98% acetic acid at room temperature over a period of 2 weeks.[123] Others such as 2-nitro-10-ethylphenothiazine-5,5-dioxide and the corresponding methyl derivative were each prepared by using hydrogen peroxide in a refluxing glacial acetic acid solution of their monoxide form.[124] The 10-ethylphenothiazine-5,5-dioxide was prepared in a similar manner using 30% hydrogen

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[122]H. Gilman, R. K. Ingham, J. F. Champaigne, Jr., J. W. Diehl and R. O. Ranck, J. Org. Chem., 19, 560 (1954).

[123]D. S. Antonov, Bull. inst. chim. acad. bulgare sci., 2, 97 (1953) [C. A., 49, 6267 (1955)].

[124]D. S. Antonov and E. Karakasheva, Bull. inst. chim. acad. bulgare sci., 2, 113 (1953) [C. A., 49, 5442 (1955)].

peroxide in glacial acetic acid at 80° for 1.5 hours[125] while a 5-hour period in refluxing glacial acetic acid was used to convert 10-phenothiazinecarboxamide to the sulfone.[126] 3,7-Bis(1,1,3,3-tetramethylbutyl)phenothiazine-5,5-dioxide was prepared similarly using a reaction period of 1 hour.[127]

Other oxidizing agents may also be used to accomplish these oxidations although they are not used so extensively as hydrogen peroxide. Perhaps the next most useful is potassium permanganate which produces either the sulfoxide or sulfone depending also on the conditions (solvent, temperature and time) which are employed. Using acetone containing sulfuric acid and potassium permanganate at 15°, 10-methylphenothiazine was converted to the sulfoxide[128] while this oxidizing agent in boiling water converted 10-ethylphenothiazine to the sulfone.[44] 2-Chloro-10-methylphenothiazine was oxidized to the sulfone using a 2% aqueous solution of potassium permanganate.[124]

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[125] H. Gilman and R. D. Nelson, J. Am. Chem. Soc., 75, 5422 (1953).

[126] N. V. Savitskaya and M. N. Shchukina, Zhur. Obshcheĭ Khim., 24, 152 (1954) [C. A., 49, 3202 (1955)].

[127] N. L. Smith, U. S. patent 2,678,926, May 18, 1954 [C. A., 49, 6321 (1955)].

[128] E. DeB. Barnett and S. Smiles, J. Chem. Soc., 97, 188 (1910).

Nitric acid is also used to produce the sulfoxide, but this gives nuclear substitution as well and is discussed in the next section. Chromic acid, potassium hypochlorite and sodium nitrite have been used as oxidizing agents to a limited extent.

Although not considered a method of preparation, 10-methylphenothiazine-5-oxide was formed by the thermal oxidation of a bis(2-ethylhexyl)sebacate solution of its non-oxidized form.[129] This was encountered in the study of the antioxidant action of phenothiazine and its derivatives on various oils and greases.

In contrast to the amount of work that has been done on N-substitution, little has been done in the field of oxidation.

## Nuclear Substitution Reactions

Along with oxidation reactions, not much emphasis was placed on nuclear substitution reactions during the past 5 years. As a result, the general techniques such as chlorination, nitration, mercuration, acylation and metalation have not undergone any great change and few new techniques have been developed.

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[129] G. P. Brown, J. W. Cole, Jr. and T. I. Crowell, J. Org. Chem., 20, 1772 (1955).

Direct chlorination of phenothiazine is somewhat difficult to control and usually gives a mixture of the di-, tri- and tetrachloro derivatives. It has been established that the disubstituted compound is the 3,7- derivative,[130] but the structures of the more highly chlorinated derivatives have not been definitely confirmed.

The reductive halogenation of 10-substituted phenothiazine-5-oxides can be used for the introduction of a halogen into the 3-position. Gilman and Eisch[131] reported the preparation of 3-chloro- and 3-bromo-10-ethylphenothiazine with hydrochloric acid and hydrobromic acid, respectively. The reaction did not proceed with hydriodic acid. By a similar procedure, Schmalz and Burger[101] prepared 3-chloro-10-(3-dimethylaminopropyl)phenothiazine. When using this technique on the 3,7-dichloro-10-methylphenothiazine-5-oxide, a tetrachloro derivative of unknown structure resulted.[101]

Nitration of phenothiazine or its derivatives may also give a variety of products although the common ones are the 3-nitro-5-oxide and the 3,7-dinitro-5-oxide compounds. Bernthsen[32] prepared both 3-nitrophenothiazine-5-oxide and the 3,7-dinitro derivative while Gilman and Shirley[53]

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[130] O. Unger and K. Hoffman, Ber., 29, 1362 (1896).

[131] H. Gilman and J. Eisch, J. Am. Chem. Soc., 77, 3862 (1955).

obtained the 3-nitro-5-oxides of several N-substituted phenothiazines.

The preparation of 3-nitro-10-methylphenothiazine (not an oxide) by nitration of 10-methylphenothiazine has been reported.[101]

Mercuration of 10-methyl- and 10-ethylphenothiazine with mercuric acetate produced a mixture of the 3-acetoxymercuri- and 3,7-diacetoxymercuri derivatives which were separated by the selective solvent action of hot ethanol of the monosubstituted derivative.[35]

The Friedel-Crafts reaction has been used for the preparation of such derivatives as the 3,7-diacetylphenothiazine from phenothiazine, acetic anhydride and aluminum chloride in carbon disulfide[41] and 2,8,10-triacetylphenothiazine from 10-acetylphenothiazine, acetyl chloride and aluminum chloride in refluxing carbon disulfide.[132]

Massie and co-workers[133] have indicated the preparation of several 2-phenothiazinyl ketones from 10-acetylphenothiazine, an acid chloride and aluminum chloride in refluxing carbon disulfide. Among those prepared were the

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[132]J. G. Michels and E. D. Amstutz, J. Am. Chem. Soc., 72, 888 (1950).

[133]S. P. Massie, I. Cooke and W. A. Hills, J. Org. Chem., 21, 1006 (1956).

2-acetylphenothiazine, 2-(chloroacetyl)phenothiazine and 2-dodecanoylphenothiazine.

Metalation of phenothiazine with n-butyllithium followed by carbonation and hydrolysis produced a product which has been shown to be 1-phenothiazinecarboxylic acid.[134] The metalation and subsequent carbonation and hydrolysis of many N-substituted phenothiazines has produced the 4-carboxylic acid derivative. Compounds such as 10-ethylphenothiazine-4-carboxylic acid[49] and 10-phenylphenothiazine-4-carboxylic acid[49] have been reported. A recent article[135] indicates the formation of 10-methyl- and 10-ethylphenothiazine-1- and -4-carboxylic acids in equal amounts by the treatment of the lithio-10-alkyl phenothiazines with carbon dioxide. However, when these same lithio derivatives were treated with lithium salts such as lithium acetate or lithium benzoate the 3- and 4-acetyl or benzoyl derivatives were formed, the latter in the greater amount.

It has been found that metalation of the sulfoxide derivatives proceeds with reduction, an increased yield of the metalated product being formed as compared to the

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[134]H. Gilman, D. A. Shirley and P. R. Van Ess, J. Am. Chem. Soc., 66, 626 (1944).

[135]G. Cauquil, M. A. Casadevall and E. Casadevall, Compt. rend., 243, 590 (1956).

yield when the non-oxidized compound is used as the starting material.[30]

There are several miscellaneous reactions which do not fall into any of these categories. These include the preparation of Grignard reagents of halogen-substituted phenothiazines such as 3-iodo-10-ethylphenothiazine and conversion to the acid by carbonation;[49] reduction as in the formation of 3-amino-10-ethylphenothiazine from the 3-nitro-10-ethylphenothiazine-5-oxide with tin and hydrochloric acid,[131] and diazotization as in the formation of 2-chloro-10-methylphenothiazine-5,5-dioxide from the corresponding diazotized amine and cuprous chloride.[124] 3-Formyl-10-methylphenothiazine was prepared by refluxing 10-methylphenothiazine, N-methylformanilide and phosphorus oxychloride in o-dichlorobenzene.[47] This aldehyde proved useful for the synthesis of many other derivatives such as the 3,10-dimethylphenothiazine by reduction with hydrazine hydrate, 10-methyl-3-styrylphenothiazine by the addition of benzylmagnesium chloride followed by dehydration with formic acid and 10-methyl-2-(2,4,6-trinitrostyryl)phenothiazine by refluxing a mixture of 3-formyl-10-methylphenothiazine and 2,4,6-trinitrotoluene in ethanol containing a trace of piperidine.

## Preparation of Organoboronic Acids and Anhydrides

Organoboronic acids are those compounds which are characterized by the general formula $RB(OH)_2$ where R is an alkyl, alkenyl, aryl or heterocyclic group. The anhydrides, which in many cases exist as the trimer, would have the general formula $(RBO)_3$. A very recent review article by Lappert[136] on organoboron compounds includes a section on organoboronic acids and anhydrides giving a list of these compounds in the aliphatic and aromatic series as well as the few heterocyclic boronic acids which have appeared. Therefore, only brief mention will be made on a few of these compounds.

As was pointed out in the Introduction, azo boronic acids are of current interest and since Lappert did not include these in his review, except for brief mention of their preparation, those which have been prepared will be included here.

The general methods for preparing boronic acids are as follows:

(1) Oxidation of trialkylborons (controlled)

$$B(C_2H_5)_3 + O_2 \longrightarrow C_2H_5B(OC_2H_5)_2 \xrightarrow{2H_2O} C_2H_5B(OH)_2 + 2C_2H_5OH$$

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[136] M. F. Lappert, Chem. Revs., 56, 959 (1956).

(2) Metal alkyls or aryls on trialkyl borates

$$B(OR)_3 + ArMgBr \longrightarrow ArB(OR)_2 \xrightarrow{2H_2O} ArB(OH)_2 + 2ROH$$

R = $CH_3$-, $C_2H_5$-, $C_3H_7$-, $C_4H_9$-

$$B(OR)_3 + ArLi \longrightarrow ArB(OR)_2 \xrightarrow{2H_2O} ArB(OH)_2 + 2ROH$$

R = $CH_3$-, $C_2H_5$-, $C_3H_7$-, $C_4H_9$-

(3) Metal aryls on boron trichloride

$$Hg(C_6H_5)_2 + 2BCl_3 \longrightarrow 2C_6H_5BCl_2 + HgCl_2$$

$$\downarrow 2H_2O$$

$$2C_6H_5B(OH)_2 + 2HCl$$

Other special methods of introducing the boronic acid group have been used but will not be discussed here.

With arylboronic acids, additional substitutions may be made on the ring. The reactions to accomplish this include nitration, reduction of a nitro group, diazotization of an amine group, oxidation of an alkyl group to a carboxylic acid and esterification of the carboxylic acid group on a carboxyboronic acid.

The anhydride may usually be formed from the acid by merely heating or by using a desiccant such as sulfuric acid or phosphorus pentoxide. In some cases, this transformation is quite difficult while in others simple recrystallization from a non-hydroxylic solvent produces the anhydride. In special cases, anhydrides will form under other conditions.

The first organoboronic acid was prepared in 1859 by Frankland and Duppa[137] when they obtained ethylboronic acid by the controlled oxidation of triethylboron followed by hydrolysis. The first aromatic boronic acid, benzeneboronic acid, was not prepared until several years later. This was done by Michaelis and Becker[138] by the hydrolysis of a product resulting from the reaction between boron trichloride and diphenylmercury in a sealed tube at 180-200°. In the years following this, progress in the field of organoboron chemistry has been slow, relatively few compounds of this type having appeared in the past 75 years.

Little use was made of the controlled oxidation technique since besides the desired product, dialkyl boronites and trialkyl borates resulted.

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[137]E. Frankland and B. F. Duppa, Proc. Roy. Soc. (London), 10, 568 (1859); Ann., 115, 319 (1860); E. Frankland, J. Chem. Soc., 15, 363 (1862).

[138]A. Michaelis and P. Becker, Ber., 15, 180 (1882).

In addition to benzeneboronic acid, several others including m-toluneboronic acid[139] and 2-chlorovinylboronic acid[140] have been prepared from the mercury or mercurichloride compound.

The Grignard reaction has been employed most extensively. Gilman and Vernon[141] reported the preparation of benzeneboronic acid from phenylmagnesium bromide and trimethyl borate in refluxing ether. Both 4-dimethylamino-1-naphthaleneboronic acid and 4-methoxy-1-naphthaleneboronic acid were prepared from the corresponding Grignard reagents (obtained from the bromo compounds) and tri-n-butyl borate in ether solution at -15° and -60°, respectively.[142] The 2-thiopheneboronic acid was obtained by reacting its Grignard reagent with trimethyl borate at a low temperature[143] and 1-butaneboronic acid was obtained from the reaction of butylmagnesium bromide and trimethyl borate in ether solution at -70°.[144]

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[139] E. Khotinsky and M. Melamed, Ber., 42, 3090 (1909).

[140] A. E. Borisov, Izvest. Akad. Nauk S. S. S. R., Otdel. Khim. Nauk, 402 (1951) [C. A., 46, 2995 (1952)].

[141] H. Gilman and C. C. Vernon, J. Am. Chem. Soc., 48, 1063 (1926).

[142] H. R. Snyder and F. W. Wyman, J. Am. Chem. Soc., 70, 234 (1948).

[143] J. R. Johnson, M. G. Van Campen and O. Grummitt, J. Am. Chem. Soc., 60, 111 (1938).

[144] H. R. Snyder, J. A. Kuck and J. R. Johnson, J. Am. Chem. Soc., 60, 105 (1938).

The incorporation of organolithium compounds has been used recently in this Laboratory for the preparation of various organoboronic acids. Benzeneboronic acid was obtained in a high yield by the reaction of phenyllithium with tri-n-butyl borate in ether solution at a low temperature.[145] Others which have been prepared similarly are the o-, m- and p-hydroxybenzeneboronic acids or anhydrides,[105,146] 4-phenoxathiinboronic acid,[147] 1-[148] and 2-thianthreneboronic acid[147] and 4-dibenzothiopheneboronic acid.[149]

The nitration of benzeneboronic acid using concentrated nitric acid and concentrated sulfuric acid produced m-nitrobenzeneboronic acid[150] while the o-nitrobenzeneboronic acid was obtained when the nitration was carried out in acetic anhydride.[22]

Both o- and m-aminobenzeneboronic acid were obtained by reduction of the nitro compounds with ferrous hydroxide.[22]

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[145]J. J. Goodman, unpublished studies, Iowa State College (1955).

[146]H. Gilman, L. Santucci, D. R. Swayampati and R. O. Ranck, J. Am. Chem. Soc., 79, to be published (1957).

[147]L. Santucci and H. Gilman, J. Am. Chem. Soc., 79, to be published (1957).

[148]D. R. Swayampati, Doctoral Dissertation, Iowa State College (1955).

[149]G. Wilder, Doctoral Dissertation, Iowa State College (1955).

[150]A. D. Ainly and F. Challenger, J. Chem. Soc., 2171 (1930).

Hydrogenation with a platinum catalyst produced the amines also.[151]

The m-aminobenzeneboronic acid was diazotized and then hydrolyzed to give the m-hydroxybenzeneboronic acid.[22,26] The diazotized compound was also coupled with the m-hydroxybenzeneboronic acid to give an azo dye.[26] Compounds of this type will be discussed in somewhat more detail later on in this section.

Oxidation of o- and p-toluneboronic acids with potassium permanganate produced the corresponding carboxybenzeneboronic acids.[152] The ethyl esters of m- and p-carboxybenzeneboronic acid were produced by the reaction of the acid with ethanol using sulfuric acid as the catalyst, the water being removed by the addition of benzene which formed a ternary azeotrope.[153]

Azo dyes containing boron have been prepared by coupling a diazotized aminobenzeneboronic acid with an active coupling agent such as a phenol or aniline derivative; or by coupling a hydroxyarylboronic acid with a diazotized amine derivative such as o-nitrobenzenediazonium chloride.

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[151] F. R. Bean and J. R. Johnson, J. Am. Chem. Soc., 54, 4415 (1932).

[152] W. König and W. Scharrnbeck, J. prakt. Chem., 128, 153 (1930).

[153] H. G. Kuivila and A. R. Hendrickson, J. Am. Chem. Soc., 74, 5068 (1952).

Snyder and Weaver[26] and Snyder and Meisel[27] prepared several of these from m-hydroxybenzeneboronic acid. Coupled with diazotized p-aminobenzoic acid, 2-(p-carboxybenzeneazo)-5-hydroxybenzeneboronic acid was formed while tetrazotized benzidine gave 4,4'-bis(2-borono-4-hydroxybenzeneazo)biphenyl. Tetrazotized benzidinediboronic acid was coupled with H acid (1-amino-8-naphthol-3,6-disulfonic acid) to give a dye also. In this Laboratory several dyes such as 2-hydroxy-5-(p-bromophenylazo)benzeneboronic acid anhydride were formed from o-hydroxybenzeneboronic acid anhydride;[28] this particular one originating from diazotized p-bromoaniline. Table 2 lists the azo boron dyes which have been prepared. Some of the nomenclature has been changed to conform to Chemical Abstracts.

Despite the generally rigid conditions employed in the techniques of nitration, oxidation, and reduction as has been discussed previously, the boronic acid group tends to remain undisturbed. Nevertheless, deboronation is considered to be a facile process since the deboronation of arylboronic acids can be accomplished by simply heating in water at an elevated temperature, or for some of the more stable ones, by heating in the presence of a little acid or base. The alkyl boronic acids are more stable to deboronation but are much more unstable to oxidation than those of the aromatic series. Chemical reagents such as hydrogen peroxide, halogens,

Table 2. Azo boronic acids

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| 2,2'-(4,4'-Biphenylenebisazo)bis-(5-hydroxybenzeneboronic acid) (See Figure 2a, Appendix.) | >300 dec. | (26) |
| 4,4'-Bis(8-amino-1-hydroxy-3,6-disulfo-2-naphthylazo)-2,2'-biphenyldiboronic acid, tetra-sodium salt | >340 | (27) |
| 4,4'-Bis(8-amino-1-hydroxy-5,7-disulfo-2-naphthylazo)-2,2'-biphenyldiboronic acid, tetra-sodium salt (See Figure 2b, Appendix.) | >340 | (27) |
| 4,4'-Bis(hydroxynaphthylazo)-2,2'-biphenyldiboronic acid (See Figure 2c, Appendix.) | 240 dec. | (27) |
| 4,4'-Bis(2-borono-4-hydroxyphenylazo)-diphenic acid | >300 dec. | (26) |
| p-(2-Borono-4-diethylaminophenylazo)-benzoic acid | 248-250 | (26) |
| p-(2-Borono-4-hydroxyphenylazo)-benzoic acid | 254-256 | (26) |

Table 2. (Continued)

| Name of Compound | M.P., °C | Ref. |
|---|---|---|
| Dye from acetoacetanilide and tetrazotized 4,4'-diamino-2,2'-biphenyldiboronic acid | 174-175 dec. resolidified and melted at 270-280 | (27) |
| 5-Hydroxy-2,3'-azodibenzeneboronic acid | > 350 dec. | (26) |
| 2-Hydroxy-5-(p-bromophenylazo)-benzeneboronic acid anhydride (See Figure 2d, Appendix.) | 350-355 | (28) (105) |
| 2-Hydroxy-5-(o-nitrophenylazo)-benzeneboronic acid anhydride | 236-238 | (28) (105) |
| 2-Hydroxy-5-(m-nitrophenylazo)-benzeneboronic acid anhydride | 221-222 | (28) |
| 2-Hydroxy-5-(p-nitrophenylazo)-benzeneboronic acid anhydride | 242-242.2 | (28) |
| 2-Hydroxy-5-(phenylazo)benzene-boronic acid anhydride | 236-238 | (28) (105) |

cupric chloride and mercuric chloride have been used for the cleavage of the boronic acid group.

# EXPERIMENTAL

## Phenothiazine Derivatives

### General

Chemicals. Phenothiazine NF, Purified, having a melting point of 184-185°, obtained from the Eastman Kodak Co. or furnished by the Dow Chemical Co., was used in all experiments.

Matheson, Coleman and Bell anhydrous liquid ammonia having a purity of 99.9% or better was used for the experiments requiring liquid ammonia. The sodium used in the liquid ammonia experiments was J. T. Baker purified lump sodium cut into approximately ½ inch cubes for laboratory use.

The tetrahydrofuran which was used was Eastman Kodak Co. White Label quality further purified and dried by refluxing over sodium for approximately 24 hours followed by distillation over sodium. This operation was usually carried out just prior to using the material. Other solvents such as ether or benzene which were used for reactions were of the best commercial quality available and were dried with sodium wire before using.

The halogen compounds used for the N-substitutions were also Eastman White Label or of equal quality. Many of these

were obtained from the Columbia Chemical Company. If only lower quality material was available, it was distilled or recrystallized from a suitable solvent before use.

The lithium which was used was in wire form about 1/8 inch in diameter and was obtained from the Lithium Corporation of America. This was cut into pieces 1/8 to 1/4 inch long for use in the experiments.

The activated alumina used for chromatographic purifications was 80-200 mesh and was obtained from either the Chicago Apparatus Company or Wilkens-Anderson Company.

Other miscellaneous chemicals such as anhydrous sodium carbonate, copper powder, etc. were of at least reagent grade quality. The solvents used for recrystallizations ranged in quality from technical for such chemicals as petroleum ether to pure for such chemicals as absolute methanol or ethanol.

Apparatus. All of the reactions not utilizing anhydrous liquid ammonia were carried out in regular standard-taper flasks equipped with agitator and the other necessary fittings such as a reflux condenser and thermometer when such were required. Agitation, except where otherwise indicated, was provided by a Trubore stirrer run at approximately 400 to 600 rpm. For a majority of those reactions in which liquid ammonia was employed, a 500-ml. cylindrical flask, previously calibrated, was used. This enabled a reasonably accurate measurement of the liquid ammonia directly into the flask

from the storage tank. Besides the usual fittings, this flask was equipped with a Dewar-type Dry Ice condenser which served as the only means of keeping the liquid ammonia condensed in the flask. This was preferred to the use of a Dry Ice-acetone bath since the temperature of the reaction mixture would always be at -33°, the reflux temperature of liquid ammonia.

In a few experiments, special equipment was used and is discussed under the section where it was applied.

Inert atmosphere. In any reaction requiring a dry, inert atmosphere the equipment which was to be used for the reaction was dried overnight in an oven at 120-130°, was assembled and while still hot was swept with dry, oxygen-free nitrogen. The contents of the flask were then kept under a slight positive nitrogen pressure throughout the remainder of the reaction. Commercial, oil-pumped (99.9% pure) nitrogen passed through a de-oxygenating agent (sodium anthraquinone-β-sulfonate)[154] and drying agents (concentrated sulfuric acid and Drierite) was used.

Sodium amide and sodiophenothiazine. For the preparation of some N-substituted phenothiazines, sodiophenothiazine was reacted with a halogen compound in liquid ammonia. For a 0.1 mole run, 0.11 mole of sodium amide in liquid ammonia was first prepared by the addition of 2.6 g. (0.11 mole) of sodium

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[154] L. J. Brady, Anal. Chem., 20, 1033 (1948).

to the liquid ammonia. Following the addition of the first pieces of sodium, a crystal of ferric nitrate was added as a catalyst. After stirring for about 1 hour or after the gray color of the sodium amide was very evident, 20 g. (0.1 mole) of phenothiazine was added and agitation was continued for another hour before reacting the sodiophenothiazine, which had formed, with the halogen compound.

Sodiophenothiazine in tetrahydrofuran. Many reactions were run or at least attempted by reacting a halogen compound with sodiophenothiazine in tetrahydrofuran. For this, the sodiophenothiazine was prepared in liquid ammonia as described above. For a 0.1 mole run, 150 ml. of tetrahydrofuran was then added and the ammonia was permitted to evaporate, the contents of the flask being put under nitrogen before all of the ammonia had escaped. When the reaction mass had warmed to room temperature, the halogen compound was added and stirring was continued for several hours at room temperature or at reflux, still in an inert atmosphere.

n-Butyllithium. This reagent was prepared using essentially the procedure of Gilman and co-workers,[155] but utilizing a variation described by Oita.[156] A few drops of a solution

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[155] H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn and L. S. Miller, J. Am. Chem. Soc., 71, 1499 (1949).

[156] K. Oita, Doctoral Dissertation, Iowa State College (1955).

composed of 172 g. (1.25 moles) of n-butyl bromide in 300 ml. of anhydrous ether was added to a suspension of 20 g. (2.87 moles) of cut lithium wire in 400 ml. of anhydrous ether at room temperature and under an inert atmosphere. The contents of the flask were cooled to -30° and the remainder of the n-butyl bromide solution was added over a period of 1.5 to 2 hours, the temperature being maintained at -30 ± 5°. After the addition was complete, agitation was continued for 2 hours at -30° and then for 2 more hours at -10° to 0°. The n-butyllithium solution was then poured through a glass-wool plug into a liquid-addition funnel where it was stored under refrigeration until used. The yield which was usually between 85% and 95% was determined by the double titration method.[157]

Miscellaneous. Several of the compounds whose preparations are described are known and were made to provide starting material for other derivatives. In some of these, however, some small variation was made in the published procedure sometimes leading to a better yield of, or better quality material.

The structures of new compounds were based upon the method of preparation, quantitative elemental analysis and information which could be obtained from the infrared spectra.

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[157] H. Gilman and A. H. Haubein, J. Am. Chem. Soc., 66, 1515 (1944).

These spectra were obtained as Nujol mulls by use of the Baird Double Beam Infrared Spectrophotometer of the Institute for Atomic Research, Iowa State College. Appreciation is expressed to Drs. M. Margoshes, R. M. Hedges and R. D. Kross and to Messrs. R. McCord and E. M. Layton, Jr. for the determination of the spectra. These spectra are on file.

The melting points, which are uncorrected, were all obtained using a previously unheated bath.

The compounds are not listed in the order of preparation but are listed in groups such as N-substituted phenothiazines, N-substituted phenothiazine-5-oxides, etc. Under each of these groups, the compounds are listed alphabetically.

N-Substituted phenothiazine derivatives

10-Allylphenothiazine.[31,36,53] This compound was prepared according to the procedure of Champaigne[31] except that a greater concentration (3.5 times as great) of sodiophenothiazine in liquid ammonia was used. One-half mole of sodiophenothiazine was prepared by the standard procedure by the addition of 100 g. (0.5 mole) of phenothiazine to 0.55 mole of sodium amide in 1000 ml. of liquid ammonia. Fifty-seven grams (0.75 mole) of allyl chloride was then added over a period of 1 hour. The ammonia was permitted to evaporate and the remaining residue was extracted with benzene which was

chromatographed on a column of activated alumina. The column was eluted with additional benzene. Evaporation of the benzene from the eluate left 126.5 g. of a yellow oil which represents a 106% yield of impure material. Vacuum distillation produced 110 g. (92%) of material having a boiling range of 165-170°/0.7 mm. Shirley[36,53] reported a 62% yield of material having a boiling range of 187-195° (1 mm.). This was made in refluxing benzene using sodium carbonate as the condensing agent and copper powder as a catalyst. Champaigne[31] reported a crude yield of 95.5%.

10-(p-Biphenylyl)phenothiazine. Twenty grams (0.1 mole) of phenothiazine, 35 g. (0.15 mole) of p-bromobiphenyl, 12 g. (0.113 mole) of anhydrous sodium carbonate and 1 g. of copper powder were stirred at 150-160° for 16 hours. This seemed to be the maximum temperature which could be used without excessive sublimation of the p-bromobiphenyl during the early stages of the reaction. After the 16-hour heating period, the temperature was raised to 200-210° where it was maintained for an additional 4 hours.

The unreacted p-bromobiphenyl was removed by steam distillation, 15 g. (0.065 mole) being recovered. The solid remaining in the steam distillation flask was recovered by filtration and was dissolved in benzene. This was filtered to remove the copper powder and was chromatographed on a column of activated alumina, the column being eluted with

additional benzene. Evaporation of the eluate left 29 g. of a hard resinous material having a melting point range of 140-170° and representing an 83% yield of crude material. Two recrystallizations of this material from an acetone-water system gave 20 g. (57.5%) of material having a melting point range of 174-178°. Further recrystallizations failed to improve the melting point. The infrared spectrum showed no absorption band for N-H and did show absorption bands characteristic of ortho and para disubstitution.

Anal. Calcd. for $C_{24}H_{17}NS$: S, 9.12. Found: S, 9.24, 9.37.

Other preparations of this compound using the same procedure gave material of the same yield and quality.

p-Bis(10-phenothiazinyl)benzene. Twenty-four grams (0.12 mole) of phenothiazine, 16.5 g. (0.05 mole) of p-diiodobenzene, 12 g. (0.11 mole) of anhydrous sodium carbonate and 1 g. of copper powder were stirred at 200° for 12 hours. During the heating period it was necessary to scrape the sides of the reaction vessel to re-introduce the sublimed p-diiodobenzene back into the reaction mass. After cooling to room temperature, the hardened product was extracted with 1 liter (in several small portions) of benzene. This was filtered to remove the insoluble inorganic material. The benzene was stripped from the filtrate and the remaining residue was extracted with three, 20-ml. portions of absolute ethanol to

remove any unreacted phenothiazine and p-diiodobenzene. Twenty-one grams (89%) of material melting over the range of 234-238° remained. This was dissolved in benzene and chromatographed on a column of activated alumina, the column being eluted with additional benzene. Removal of the solvent from the eluate left 18 g. of material melting at 248-250°. Recrystallization of this from benzene gave 16.5 g. (70%) of material melting at 253-255°. Another recrystallization of this from an ethanol-benzene system failed to improve the melting point. The infrared spectrum showed absorption bands characteristic of ortho and para disubstitution, respectively, and showed no characteristic N-H absorption band.

Anal. Calcd. for $C_{30}H_{20}N_2S_2$: S, 13.57. Found: S, 13.70, 13.70.

In another experiment a 55% yield of material having a melting point of 252-253° was obtained. This was finished by extracting the crude material with benzene, filtering and reducing the volume of the solvent which caused the crystallization of product. This was removed by filtration. Evaporation of the benzene extract to dryness left a black residue which was washed with absolute ethanol, redissolved in benzene and chromatographed on a column of activated alumina. The column was eluted with additional benzene. Evaporation of the eluate left a viscous residue which was combined with the

solid portion isolated from the original benzene extract and recrystallized again from benzene.

p,p'-Bis(10-phenothiazinyl)biphenyl. (See Figure 1 , Appendix.) Twenty four grams (0.12 mole) of phenothiazine, 15.6 g. (0.05 mole) of p,p'-dibromobiphenyl, 12 g. (0.113 mole) of anhydrous sodium carbonate and 1 g. of copper powder were stirred at a temperature of 150-210° for a period of 24 hours. An early low temperature (150°) was used to prevent excessive sublimation of the halogen compound. The temperature was gradually raised as the reaction progressed. After cooling to room temperature, the reaction mass was extracted with benzene. This was filtered to remove the inorganic material and was then reduced in volume. Twelve and one-half grams of material having a melting point range of 200-300° separated. This was recrystallized again from benzene to give 5 g. (18%) of material having a melting point range of 295-300°, with decomposition. The material could not be purified further and gave a low sulfur analysis. The infrared spectrum did support the structure, however, showing characteristic ortho and para disubstitution bands and no absorption band characteristic of N-H.

Anal. Calcd. for $C_{36}H_{24}N_2S_2$: S, 11.69. Found: S, 9.27, 9.09.

10-(o-Bromobenzyl)phenothiazine. One-tenth mole of sodiophenothiazine was prepared by the usual method by adding 20 g.

(0.1 mole) of phenothiazine to 0.11 mole of sodium amide in 100 ml. of liquid ammonia. The ammonia was then replaced with 150 ml. of tetrahydrofuran. A solution of 27 g. (0.132 mole) of o-bromobenzyl chloride in 150 ml. of tetrahydrofuran was added at room temperature over a period of 15 minutes after which stirring was continued for 6 hours. The reaction mass was filtered and the solvent was removed by distillation leaving 36 g. (97.5%) of brown resinous material.

Attempted chromatographic purification by passing a benzene solution of the crude material through a column of activated alumina followed by elution with benzene and evaporation of the solvent from the eluate left a viscous oil which failed to solidify. Recrystallization of a portion of this from an ethanol-water system gave material having a melting point range of 91-93° but the crystal formation was poor.

Further purification of the chromatographed material by vacuum distillation was also inadequate since a large portion of the material tended to pyrolyze. Material boiling at 190-200°/0.005 mm. was collected. This was also resinous in nature and crystallized with difficulty from an ethanol-water system. Two recrystallizations from this solvent system gave a product melting at 90-92°. The infrared spectrum showed an absorption band characteristic of ortho disubstitution and had no absorption band in the region characteristic of N-H.

Anal. Calcd. for $C_{19}H_{15}BrNS$: S, 8.71. Found: S, 8.99, 9.01.

10-[4-(7-Chloroquinolyl)] phenothiazine (attempted). Twenty grams (0.1 mole) of phenothiazine, 30 g. (0.15 mole) of 4,7-dichloroquinoline, 12 g. (0.113 mole) of anhydrous sodium carbonate and 1 g. of copper powder were heated at reflux for several hours. Due to the excessive sublimation of the 4,7-dichloroquinoline this technique was inadequate and no product was obtained. No other attempts using other techniques were tried.

10-(n-Decyl)phenothiazine.[31,36,53] Material of this type was prepared previously in 9.4% yield by Shirley[36,53] by heating a mixture of phenothiazine, n-decyl bromide, sodium carbonate and copper powder at 170-180° for 11 hours. Champaigne[31] prepared this compound using the liquid ammonia procedure and obtained an 86.7% yield of crude material which he was unable to purify. In this new experimental work, several reactions were carried out in an effort to get a high yield of pure material.

In liquid ammonia. One-tenth mole of sodiophenothiazine was prepared by the standard procedure in 200 ml. of liquid ammonia. Thirty-three grams (0.15 mole) of n-decyl bromide was added and agitation was continued for 6 hours. The ammonia was evaporated and the residue was extracted with benzene. The benzene extract was chromatographed on a column

of activated alumina and the column was eluted with additional benzene. The benzene was stripped from the eluate and the remaining material was vacuum distilled to give 20.4 g. (60%) of product boiling at 175-180°/0.5 mm. This was still contaminated with a red component and unreacted phenothiazine.

When the concentration of sodiophenothiazine in liquid ammonia was increased to 1.5 and 2 times that used above, and with the same finishing procedure being used, yields of 80% and 68%, respectively, of material contaminated with phenothiazine and the red component were obtained.

Extraction with petroleum ether (b.p., 60-70°) instead of benzene followed by chromatographic purification (using petroleum ether as the eluent also) and distillation gave an 84% yield of product free of any unreacted phenothiazine and the red component. A concentration of 0.1 mole of sodiophenothiazine in 150 ml. of ammonia was used in this experiment.

Use of high-speed counter-rotating agitation with a shorter reaction time (45 minutes) gave a 74% yield of pure product. Petroleum ether (b.p., 60-70°) was employed in the finishing step of this experiment.

Using ether as a solvent for the halogen compound. One-tenth mole of sodiophenothiazine in 150 ml. of liquid ammonia was prepared in the usual way. A solution of 33 g. (0.15 mole) of n-decyl bromide in 100 ml. of ether was added and agitation was continued for 6 hours. The solvents were

then evaporated, and the residue was extracted with petroleum ether (b.p., 60-70°). This extract was chromatographed on a column of activated alumina, the column being eluted with additional petroleum ether (b.p., 60-70°). The solvent was stripped from the eluate and the remaining material was vacuum distilled to give 28.5 g. (84%) of pure product boiling at 175-180°/0.5 mm.

Using the same procedure but with high-speed counter-rotating agitation and shorter reaction times (1, 2, and 3 hours) yields of about 75% were obtained.

In tetrahydrofuran. One-tenth mole of sodiophenothiazine was prepared in 150 ml. of liquid ammonia by the standard procedure. The ammonia was then replaced with 150 ml. of tetrahydrofuran and a solution of 33 g. (0.15 mole) of n-decyl bromide in 150 ml. of tetrahydrofuran was added slowly. Agitation was continued for 12 hours at room temperature. The tetrahydrofuran was removed by distillation, the residue was extracted with benzene, the benzene was stripped off and the material remaining was vacuum distilled. Twenty-nine and one-half grams (86.5%) of material boiling at 175-180°/0.5 mm., $n_D^{25}$ 1.5853, $d_{25}^{25}$ 1.0442 was obtained. This was free of any unreacted phenothiazine or red component. Shirley[36,53] reported a boiling point of 183-185°/0.5 mm.

Anal. Calcd. for $C_{22}H_{29}NS$: $MR_D$, 110.84. Found: $MR_D$, 111.57.

10-Ethylphenothiazine.[30,31,32,37,44,49,107,122] This compound was prepared previously in good yield by several workers.[30,31,37,107,122] using the liquid ammonia procedure. In the first preparations of this compound[30,31] using the liquid ammonia technique a low concentration of sodiophenothiazine in ammonia (0.15-0.19 mole/liter) was used and the time cycle used to complete the reaction was quite long (8 to 12 hours). In a series of experiments which were run the concentration of sodiophenothiazine was increased in regular intervals until a concentration of 1 mole/liter was reached. The overall size of the reaction (more liquid ammonia) was also increased and the time cycle was shortened to about one-third of the original. Consistently higher yields (98-99%) were obtained at the higher concentrations than at the lower concentrations (92-98%) and the material was characterized by having a melting point 1 to 2° higher. The higher concentrations made the additions of phenothiazine to the sodium amide and ethyl bromide to the sodiophenothiazine a little more troublesome but these could be handled without incident if the additions were made at a slow enough rate. The best procedure for the preparation of 10-ethylphenothiazine follows.

Sodiophenothiazine (4.33 mole) was prepared by the addition of 865 g. (4.33 mole) of phenothiazine to 4.76 moles of sodium amide in 4360 ml. of liquid ammonia using the standard procedure. Seven hundred and ten grams (6.5 moles) of ethyl

bromide was added slowly over a period of 1 hour. The liquid ammonia was permitted to evaporate and the residue was extracted with hot benzene, 1.5 to 2 liters, added in several portions, being required. This benzene extract was chromatographed on a column of 900 g. of activated alumina. The column was eluted with additional benzene. Removal of the benzene from the eluate left 980 g. (99%) of 10-ethylphenothiazine having a melting point of 102.5-104°.

Some experiments were run in which the chromatographic purification was eliminated. This led to a quantitative yield of material generally having a melting point of 99-101°.

10-(p-Nitrobenzyl)phenothiazine. (attempted). One-tenth mole of sodiophenothiazine was prepared by the addition of 20 g. (0.1 mole) of phenothiazine to 0.11 mole of sodium amide in 120 ml. of liquid ammonia. The ammonia was then replaced with 150 ml. of tetrahydrofuran. When the reaction had reached room temperature, a solution composed of 24 g. (0.11 mole) of p-nitrobenzyl bromide in 150 ml. of tetrahydrofuran was added over a 10-minute period. Stirring was then continued for 24 hours at 20°. The mass was filtered to remove the inorganic material and the tetrahydrofuran was distilled from the filtrate leaving 32 g. of black solid. This was dissolved in benzene and was chromatographed on a column of activated alumina, the column being eluted with additional benzene. The first eluent contained a large amount of unreacted phenothiazine,

identified by melting point and mixture melting point, and another fraction which contained 2.5 g. of material melting at 178-179°. Recrystallization of this from a benzene-petroleum ether (b.p., 77-115°) system gave 2.3 g. of material melting at 181-182°. Additional recrystallizations failed to raise the melting point further. A mixture melting point with an authentic sample of phenothiazine (185°) melted over the range of 150-170°. The qualitative analysis indicated nitrogen but gave no test for sulfur. A quantitative nitrogen analysis did not agree with the calculated value for 10-(p-nitrobenzyl)phenothiazine.

Anal. Calcd. for $C_{19}H_{14}N_2O_2S$: N, 8.38. Found: N, 9.30, 9.46.

Since the compound contained no sulfur, it was thought that the product might be p-nitrobenzyldiphenylamine which has a calculated nitrogen value of 9.21%. However, the reported melting point for this compound is 92-94°.[158] Coupling of the p-nitrobenzyl bromide may also have occurred leading to p,p'-dinitrodibenzyl. This has a calculated nitrogen content of 10.29% and a melting point of 180.5.[159] Another possibility that exists is 9-(p-nitrobenzyl)carbazole which has a nitrogen

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[158] S. Forrest, S. H. Tucker and M. Whalley, J. Chem. Soc., 303 (1951).

[159] I. Heilbron, "Dictionary of Organic Compounds," Vol. II, Oxford University Press, New York, N. Y., 1953, p. 371.

content of 9.27%. This compound is not reported in the literature. The infrared spectrum showed no characteristic N-H absorption band, but did indicate the nitro group. It also showed a sharp absorption band at 11.7μ and other less pronounced absorption bands at 12.7μ, 12.9μ, 13.3μ, 13.8μ, and 14.4μ. The material was not identified definitely.

In another experiment in which a 36-hour reaction time was used with an excess of p-nitrobenzyl bromide (32.5 g./0.15 mole), 4.75 g. of yellow needles melting at 180-181° were obtained.

10-(o-Nitrophenyl)phenothiazine (attempted).[36,53] One-tenth mole of sodiophenothiazine was prepared by the standard procedure in 120 ml. of liquid ammonia. The ammonia was replaced with 150 ml. of tetrahydrofuran and a solution of 36.6 g. (0.15 mole) of o-iodonitrobenzene in 150 ml. of tetrahydrofuran was added over a 10-minute period. Agitation was continued for 15 hours at room temperature. The reaction mass was filtered and the tetrahydrofuran was distilled from the filtrate. The residue which remained was dissolved in benzene and chromatographed of a column of activated alumina, the column being eluted with additional benzene. Several fractions were collected but none of the material recovered from these resembled 10-(o-nitrophenyl)phenothiazine (m.p., 156-157°).[36,53]

10-(p-Nitrophenyl)phenothiazine (attempted).[36,53] Fifty-five hundredths mole of sodiophenothiazine in 75 ml. of liquid ammonia was prepared in the usual way. The ammonia was replaced with 75 ml. of tetrahydrofuran after which a solution composed of 18.5 g. (0.075 mole) of p-nitroiodobenzene in 150 ml. of tetrahydrofuran was added over a 30-minute period. Stirring was continued for 24 hours at room temperature. The mass was filtered and the tetrahydrofuran was removed from the filtrate by distillation. The residue was examined but none of the desired product was isolated.

10-(n-Octadecyl)phenothiazine.[31,36,53] This compound has been prepared previously in a low yield by Shirley[36,53] by heating a mixture of phenothiazine, n-octadecyl bromide, anhydrous sodium carbonate and copper powder for several hours. An unsuccessful attempt was made by Champaigne[31] in which a toluene solution of n-octadecyl bromide was added to a mixture of sodiophenothiazine in anhydrous liquid ammonia. Several experiments, some of which are described below, were run in this current series in an effort to get a high yield of product.

In liquid ammonia using high-speed agitation. One-tenth mole of sodiophenothiazine was prepared by the standard procedure by the addition of 20 g. (0.1 mole) of phenothiazine to 0.11 mole of sodium amide in 150 ml. of anhydrous liquid ammonia. Fifty grams (0.15 mole) of molten n-octadecyl bromide

was added and stirring with a high-speed counter-rotating agitator was continued for 3 hours. The ammonia was evaporated and the residue was extracted with petroleum ether (b.p., 60-70°). This was filtered and then chromatographed on a column of activated alumina, the column being eluted with additional petroleum ether (b.p., 60-70°). Evaporation of the eluate left 7.5 g. (17%) of crude product melting at 42-44°. Recrystallization of this from an ethanol-water system gave 5.8 g. (12.9%) of material having a melting point of 52-52.5° and which showed no depression in melting point when mixed with an authentic sample (53°).[36]

A few variations were made in this procedure which did not give as good yields. These included the addition of sodiophenothiazine in liquid ammonia to a dispersion of n-octadecyl bromide in liquid ammonia (5% crude yield), sodiophenothiazine in liquid ammonia added to molten (40-50°) n-octadecyl bromide (10% crude yield), and ground (28 mesh) n-octadecyl bromide added to sodiophenothiazine in liquid ammonia (5% crude yield).

Using various solvents for the halogen compound.

One-tenth mole of sodiophenothiazine was prepared as above in 150 ml. of anhydrous liquid ammonia. A solution of 50 g. (0.15 mole) of n-octadecyl bromide in 150 ml. of ether was added and agitation was continued for 7 hours. A 4-bladed propellor-type agitator run at about 1200 rpm was used for

this. Evaporation of the solvents left 25 g. (55%) of crude material which on recrystallization from an ethanol-water system gave 11.5 g. (25%) of material melting at 42-43°.

Using 100 ml. of ammonia for the sodiophenothiazine and 200 ml. of ether for the halogen compound gave 32.8 g. (72.5%) of crude material melting at 40-43° which on recrystallization gave a 40% yield of pure (53°) material. Using these same amounts of ammonia and ether but with inverse addition, a 53% yield of material melting at 53.5° was obtained. Using a higher ratio of ether to ammonia did not show any advantages.

When the sodiophenothiazine was added to an n-pentane solution of n-octadecyl bromide a 6% crude yield of product was obtained. Using this inverse addition with tetrahydrofuran as a solvent for the halogen compound, 36% of pure material was produced and with ethylene glycol dimethyl ether with the inverse addition a 49% yield of pure material resulted. Using normal addition, with ethylene glycol dimethyl ether a 54% yield of material melting at 53-54° was obtained.

Using tetrahydrofuran or ether for the halogen compound and replacing the ammonia with the same solvent. One-tenth mole of sodiophenothiazine was prepared by the standard procedure by the addition of 20 g. (0.1 mole) of phenothiazine to 0.11 mole of sodium amide in 150 ml. of liquid ammonia. The ammonia was then replaced with 150 ml. of tetrahydrofuran. A solution of 50 g. (0.15 mole) of n-octadecyl bromide in 150

ml. of tetrahydrofuran was added over a period of 2 hours and agitation was continued at room temperature for 32 hours. The tetrahydrofuran was removed by distillation, and the residue was extracted with benzene. This extract was filtered, the benzene was stripped off and the excess n-octadecyl bromide was removed by vacuum distillation. The remaining undistilled portion weighed 47 g. (104%) and had a melting point of 44-45°. Recrystallization of this from an ethanol-water system gave 40.5 g. (90%) of material having a melting point of 53-54°. A repeat of this experiment gave the same results.

Refluxing the tetrahydrofuran solution of the reactants showed no advantages.

When ether was substituted for tetrahydrofuran as a solvent for both the halogen compound and the sodiophenothiazine a much cruder product was formed. This was not purified.

Phenothiazine:boron trifluoride complex.

In ether (attempted). Seven and two-tenths grams (0.036 mole) of phenothiazine was dissolved in 180 ml. of ether at reflux under a nitrogen atmosphere. Heating was discontinued and 4.5 ml. (0.036 mole) of boron fluoride ethyl ether was added over a 5-minute period. Agitation was continued for 3 hours at 30°. Some of the ether was removed. When the volume was reduced sufficiently, a solid melting at 182-183° separated. This was removed by filtration and

identified as phenothiazine by melting point and mixed melting point.

In benzene. Seven and two-tenths grams (0.036 mole) of phenothiazine was dissolved in 250 ml. of benzene at 25° in an atmosphere of nitrogen. Four and one-half millliliters (0.036 mole) of boron fluoride ethyl ether was added over a 2-minute period. This caused a change in color from a light yellow to a dark red and the separation of a solid material. Slow evaporation of the solvent caused the separation of needle crystals having a melting point of 158-160°. Some other solid also separated. The needle crystals gave a positive test for boron, but attempts to purify the material further failed because of its instability.

10-(β-Phenylethyl)phenothiazine (attempted). One-tenth mole of sodiophenothiazine was prepared by the usual procedure in 100 ml. of liquid ammonia. Five and one-half grams (0.11 mole) of β-phenylchloroethane was added and stirring was continued for 4 hours. The ammonia was permitted to evaporate and the remaining residue was extracted with benzene giving a red solution. This was chromatographed on a column of activated alumina, the column being eluted with additional benzene. Evaporation of the solvent from the eluate left 21 g. (70%) of material melting at 174-175°. Recrystallization of this from an ethanol-water system failed to increase the melting point. The material was green in color and was considered

to be impure. No further attempts at purification were made.

10-Phenylphenothiazine.[36,49,128,160]

In tetrahydrofuran (attempted). One-tenth mole of sodiophenothiazine was prepared in 150 ml. of liquid ammonia by the standard procedure. The ammonia was then replaced with 150 ml. of tetrahydrofuran. A solution composed of 30.6 g. (0.15 mole) of iodobenzene in 150 ml. of tetrahydrofuran was added and stirring was continued for 32 hours at room temperature. The reaction mass was filtered and the tetrahydrofuran was removed by distillation. Examination of the residue which remained indicated that no 10-phenylphenothiazine had formed.

When a similar reaction was run for 32 hours at reflux (65°) no product was isolated either.

Using the no-solvent method. The procedure used by Shirley[36,49] was used with some variation being made in the finishing procedure. One hundred grams (0.5 mole) of phenothiazine, 153 g. (0.75 mole) of iodobenzene, 60 g. (0.57 mole) of anhydrous sodium carbonate and 5 g. of copper powder were stirred at reflux for 15 hours. The excess iodobenzene was removed by steam distillation. The solid remaining in the flask was recovered by filtration. This had a melting point range of 84-90° and weighed 140 g. (98%).

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[160] C. Finzi, Gazz. chim. ital., 62, 175 (1932) [C. A., 26, 4338 (1932)].

One fourth (35 g.) of the crude material was recrystallized from glacial acetic acid to give 14 g. (10%) of material melting at 94.5-96° (literature value, 94.5°)[49]. The material was contaminated with a greenish-blue color which originated from the copper powder.

The remaining amount of crude material was vacuum distilled. Ninety-one grams (66%) of material melting at 87-90° (b.p., 170-175/0.05 mm.) was obtained. This material was recrystallized from glacial acetic acid to give 80 g. (58%) of material melting at 94.5-95.5°.

It was also found that purification by chromatographic techniques using benzene or petroleum ether (b.p., 60-70°) on activated alumina might also be possible.

10-(γ-Phenylpropyl)phenothiazine (attempted). One-tenth mole of sodiophenothiazine was prepared in 100 ml. of liquid ammonia by the standard procedure. Seventeen grams (0.11 mole) of γ-phenylchloropropane was added and agitation was continued for 4 hours. The ammonia was permitted to evaporate and the residue was extracted with benzene. This was chromatographed on a column of activated alumina, the column being eluted with additional benzene. Evaporation of the solvent from the eluate left 23 g. (72%) of material melting at 150-151°. Recrystallization of this from ethanol-water gave material having a melting point of 172-174°. This material

was green in color indicating that it was still impure. No further purification was done.

10-(2-Pyridyl)phenothiazine.

In liquid ammonia (attempted). Five hundredths of a mole of sodiophenothiazine was prepared in the usual manner in 150 ml. of liquid ammonia. Eight and one-half grams (0.075 mole) of 2-chloropyridine was added and agitation was continued for 6 hours. The ammonia was permitted to evaporate and the residue was extracted with benzene. This was filtered to remove any inorganic salts and the filtrate was chromatographed on a column of activated alumina, the column being eluted with additional benzene. Evaporation of the solvent from the eluate left a semi-solid material which was extracted with ethanol. An insoluble solid (1.6 g.) having a melting point range of 160-200° remained. This could not be purified further. No worthwhile material could be recovered from the ethanol extract.

In tetrahydrofuran (attempted). Five hundredths of a mole of sodiophenothiazine was prepared in 150 ml. of liquid ammonia by the standard procedure. The ammonia was then replaced with 75 ml. of tetrahydrofuran. When the reaction mass had reached room temperature a solution of 8.5 g. (0.075 mole) of 2-chloropyridine in 75 ml. of tetrahydrofuran was added during a period of 15 minutes. Agitation was continued for 18 hours at room temperature after which the solvent was removed by

distillation. The residue was extracted with benzene which was filtered to remove the inorganic material. Removal of the benzene left 14.5 g. of material having a melting point of 149-150°. Recrystallization of this from an acetone-water system gave 4.5 g. of material melting at 177-179° and 4.5 g. melting at 165-170°. This latter material was subjected to vacuum sublimation to give a product having a melting point of 182-183°. This material showed no melting point depression when mixed with an authentic sample of phenothiazine (m.p., 185°).

In another attempt to prepare this compound in tetrahydrofuran, 2-bromopyridine was used and stirring was carried out for 50 hours at room temperature. This also was unsuccessful.

Using kerosene as a solvent (attempted). Twenty grams (0.1 mole) of phenothiazine, 23.7 g. (0.15 mole) of 2-bromopyridine, 20.7 g. (0.15 mole) of anhydrous potassium carbonate, 1 g. of copper-bronze powder and 250 ml. of kerosene (b.p., 190-215°) were stirred at reflux (203°) for 50 hours. The kerosene and the unreacted 2-bromopyridine were then removed by steam distillation. The remaining solid was recovered by filtration and was extracted with acetone. This acetone extract was filtered and the filtrate was evaporated leaving 37 g. of a black semisolid material having a melting point range of

100-150°. This material was subjected to vacuum distillation but no product could be isolated.

Using the no-solvent method. Twenty grams (0.1 mole) of phenothiazine, 13.7 g. (0.15 mole) of 2-bromopyridine, 12.5 g. (0.109 mole) of anhydrous sodium carbonate and 1 g. of copper powder were stirred at reflux for 15 hours. After cooling to room temperature, the reaction mass was extracted with hot water to remove the soluble salts and was then aspirated to remove any water and unreacted 2-bromopyridine. The remaining solid was subjected to vacuum distillation. A portion of the material distilled at 170-175°/0.03 mm. to give a viscous product which gradually solidified on standing. This material was recrystallized from an ethanol-water system to give 7.5 g. (27.1%) of material melting at 109-110°.

The undistilled portion was dissolved in benzene and chromatographed on a column of activated alumina, the column being eluted with additional benzene. Evaporation of the solvent from the eluent left 19 g. (68.9%) of material having a melting point of 90-93°. This was recrystallized from an ethanol-water system to give 7.0 g. (26%) of material melting at 107-108°.

The infrared spectrum confirmed the structure showing characteristic absorption bands for C = N and o-disubstitution. The N-H absorption band was absent.

Anal. Calcd. for $C_{17}H_{12}N_2S$: S, 11.59. Found: S, 11.66, 11.48.

In another experiment starting with 0.3 mole of phenothiazine, 59 g. (71%) of material having a melting point of 107-108° was obtained by vacuum distillation of the crude material. Recrystallization of this from an ethanol-water system gave 51 g. (62%) of material melting at 108-109°.

10-(2-Pyridyl)phenothiazine:boron trifluoride complex. Five and one-half grams (0.02 mole) of 10-(2-pyridyl)phenothiazine was dissolved in 100 ml. of benzene under an atmosphere of nitrogen. Five milliliters (0.04 mole) of boron fluoride ethyl ether was added at room temperature over a period of 1 minute. Immediately upon the addition of the boron compound a yellow solid precipitated. Agitation was continued for 3 hours after which the solid was removed by filtration and dried. When the material became dry, the yellow color was lost, the material then appearing white. Seven and one-half grams of product having a melting point range of 278-300° was obtained. The material was recrystallized from ethanol to give 4.4 g. (60% based on the nitrogen analysis) of material melting at 305-310° with preliminary softening at 295°. Another recrystallization from ethanol failed to increase the melting point. Evaporation of the recrystallizing liquors to dryness left material having a melting point of 307-308° with preliminary

softening at 240°. The infrared spectrum showed the characteristic absorption bands for ortho disubstitution.

Anal. Calcd. for $(C_{17}H_{12}N_2S)_2:(BF_3)_3$: N, 7.31. Found: N, 7.47.

Note that the analysis corresponds to two moles of 10-(2-pyridyl)phenothiazine to three moles of boron trifluoride.

Some of the compound was suspended in water at room temperature to determine the ease of hydrolysis. After being in contact for 12 hours, the solid was filtered off and examined. The material melted at 108-110° and showed no depression in melting point when mixed with an authentic sample of 10-(2-pyridyl)phenothiazine. Shorter periods of hydrolysis were not investigated.

10-(2-Quinolyl)phenothiazine.

In tetrahydrofuran (attempted). Five hundredths of a mole of sodiophenothiazine was prepared in 100 ml. of liquid ammonia by the standard procedure. The ammonia was then replaced with 130 ml. of tetrahydrofuran. When the material had warmed to room temperature a solution composed of 14.25 g. (0.075 mole) of 2-chloroquinoline in 160 ml. of tetrahydrofuran was added over a 15-minute period. Stirring was continued for 12 hours at room temperature. During this time the color changed from a black to a light yellow and an insoluble substance formed indicating that some reaction had possibly occurred. However, a work up of the reaction mixture

by filtration followed by distillation of the solvent and recrystallization of the residue from ethanol, or sublimation, gave only phenothiazine, identified by melting point and mixed melting point.

No-solvent method. Twenty grams (0.10 mole) of phenothiazine, 24.5 g. (0.15 mole) of 2-chloroquinoline, 12 g. (0.113 mole) of anhydrous sodium carbonate, and 1 g. of copper powder was stirred at reflux for 15 hours. After cooling to room temperature the crude mass was extracted several times with hot water to remove any soluble material. An effort was made to distill the residue under vacuum, but this was unsuccessful. The material could not be recrystallized successfully from ethanol, petroleum ether (b.p., 60-70°), acetone-water or acetic acid.

Another run was prepared as above except that the mixture was stirred at reflux (220-230°) for 48 hours. After cooling to room temperature, the mass was extracted with hot benzene. The benzene was stripped off and the remaining residue was subjected to vacuum distillation. Four grams of 2-chloroquinoline was recovered. The undistilled portion was redissolved in benzene and chromatographed on a column of activated alumina, the column being eluted with additional benzene. Eight fractions, all of which gave a viscous yellow oil after evaporation of the solvent, were collected. These were combined and recrystallized from an ethanol water system to give

14 g. (43%) of material having a melting point of 126-128°. The material was still quite colored (yellow) and believed to be somewhat impure. However, repeated recrystallizations failed to raise the melting point. The infrared spectrum supported the structure showing characteristic absorption bands for 1,2,4 trisubstitution, ortho disubstitution and the C = N. There was no N-H absorption band present.

Anal. Calcd. for $C_{21}H_{15}N_2S$: S, 9.79. Found: S, 10.35, 10.19.

10-(Triphenylmethyl)phenothiazine (attempted).

In tetrahydrofuran. One-tenth mole of sodiophenothiazine was prepared by the standard method. The ammonia was then replaced with 150 ml. of tetrahydrofuran. After the mass had reached room temperature, a solution of 42 g. (0.15 mole) of triphenylmethyl chloride in 150 ml. of tetrahydrofuran was added slowly over a 2-hour period. Stirring was continued for 32 hours at room temperature. The tetrahydrofuran was then removed by distillation and the residue was extracted with benzene. This was chromatographed on a column of activated alumina, the column being eluted with additional benzene. Removal of the benzene left a solid which was extracted with acetone. The insoluble portion had a melting point of 225-230° after first showing signs of decomposition at 190-195°. Attempts were made to recrystallize this from both toluene and

glacial acetic acid, but without success. Other methods of purification also failed.

In another similar experiment, the excess triphenylmethyl chloride was removed by vacuum distillation leaving a solid material having a melting point range of 140-160°. Efforts to purify this also failed.

In liquid ammonia. One tenth mole of sodiophenothiazine was prepared in the usual manner in 150 ml. of liquid ammonia. Forty-two grams (0.15 mole) of triphenylmethyl chloride was added and agitation was continued for 4 hours. After the ammonia had evaporated, the remaining residue was extracted with benzene and filtered. No method was found to purify the material.

10-(γ-Triphenylsilylpropyl)phenothiazine (attempted). Three and eight tenths grams (0.016 mole) of 10-allylphenothiazine, 26 g. (0.1 mole) of triphenylsilane, 0.32 g. (0.0013 mole) of benzoyl peroxide and 35 ml. of hexane were stirred at reflux for 14 hours. The hexane was then removed by distillation and the unreacted triphenylsilane by vacuum distillation. None of the desired product was isolated.

Another reaction which was carried out between 75 and 80° for 14 hours also failed to give any product.

Additions of triphenylsilane to a double bond have been reported.[161]

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[161] H. Merten and H. Gilman, J. Am. Chem. Soc., 76, 5798 (1954).

N-Substituted phenothiazine-5-oxide derivatives

10-(n-Decyl)phenothiazine-5-oxide. Ten grams (0.0295 mole) of 10-(n-decyl)phenothiazine was dissolved in 600 ml. of refluxing absolute ethanol. Twenty-five milliliters (0.24 mole) of 30% hydrogen peroxide was added and stirring at reflux was continued for 6 hours. Three hundred and fifty milliliters of the solution was removed by distillation and the remainder was poured into 1250 ml. of water and refrigerated overnight. Ten and one-tenth grams of material having a melting point of 93.5-95° crystallized from the solution. This represents a yield of 93%. Recrystallization of the material from an ethanol-water system gave 9.2 g. (90%) of material melting at 97-98°. Another recrystallization failed to raise the melting point.

The infrared spectrum showed the characteristic sulfoxide absorption band.

Anal. Calcd. for $C_{22}H_{29}NOS$: S, 9.02. Found: S, 8.87, 9.00.

In another experiment in which a greater concentration of reactants was employed (102 g. of 10-(n-decyl)phenothiazine in 2250 ml. of absolute ethanol oxidized with 93 ml. of 30% hydrogen peroxide followed by removal of 1500 ml. of solvent and pouring into 3700 ml. of water previously heated to 75°) 99 g. (93%) of material melting at 97-98° and 5 g. (5%) of

material melting at 91-92° were obtained, this last portion after concentration of the filtrate.

10-Ethylphenothiazine-5-oxide.[30,31,37,122,125] This compound has been prepared previously by a number of workers. The preparation described here was run at conditions of higher concentration. Three hundred and ninety grams (1.72 mole) of 10-ethylphenothiazine was dissolved in 4300 ml. of refluxing absolute ethanol. Five hundred and forty milliliters (5.25 moles) of 30% hydrogen peroxide was added and stirring was continued for 5 hours at reflux. Thirty-one hundred milliliters of the solvent was removed by distillation and the remaining undistilled portion was poured into 21 liters of water previously heated to 80°. Upon cooling, 405 g. (97%) of material melting at 161-162° crystallized from the solution. The reported melting point for this compound is 162-163°.[125]

Other experiments, in which the same concentration of reactants was used, consistently gave yields above 95%. This is approximately 10% greater than the amount of material which could be obtained using lower concentrations (0.572 mole of 10-ethylphenothiazine in 4300 ml. of absolute ethanol). This lower yield at the lower concentrations was also experienced by Diehl[37] and Champaigne.[31]

Other oxidations of 10-ethylphenothiazine using unpurified material (99-101°) and recovered solvent were run without affecting the yield or quality of the final product adversely.

Diehl[162] indicated that if the oxidation were run under an atmosphere of nitrogen the final product consistently would come out white instead of a light pink which usually persists when an air atmosphere is used. This was tried in several experiments and substantiates this technique.

10-(n-Octadecyl)phenothiazine-5-oxide.[36,53] This compound was prepared using essentially the same procedure as Shirley[36,53] except that a greater concentration of reactants was used. Ninety grams (0.2 mole) of 10-(n-octadecyl)phenothiazine was dissolved in 2000 ml. of refluxing absolute ethanol. Sixty milliliters (0.59 mole) of 30% hydrogen peroxide was added and stirring was continued at reflux for 5 hours. Fifteen hundred milliliters of the solvent was removed by distillation and the remaining undistilled portion was poured into 2500 ml. of water previously heated to 80°. Upon cooling to room temperature, 92 g. (98%) of material having a melting point range of 90-95° separated. Recrystallization of this from an ethanol-water system gave 90 g. (96%) of material melting at 95-96°. Additional recrystallizations failed to raise the melting point further. A mixture point with an authentic specimen (98°)[36,53] showed no depression. Shirley[36,53] reported a 53% yield of this material.

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[162] J. W. Diehl, private communication, Iowa State College (1953).

10-Phenylphenothiazine-5-oxide.[36,53] This compound was prepared in a manner similar to that described by Shirley[36,53] except that a smaller concentration of hydrogen peroxide was used. Twenty-one and one-half grams (0.075 mole) of 10-phenylphenothiazine was dissolved in 500 ml. of refluxing absolute ethanol in an atmosphere of nitrogen. Twenty-five millliliters (0.245 mole) of 30% hydrogen peroxide was added and stirring was continued at reflux for 5 hours. Three hundred milliliters of the solvent was then removed by distillation and the remaining undistilled portion was poured into 925 ml. of water which had been heated previously to 80°. Upon cooling to room temperature, 21.8 g. (100%) of material melting at 172-173° crystallized. Recrystallization of this from an ethanol-water system failed to raise the melting point. Shirley[36,53] reported a 71% yield of material having a melting point of 170-171°.

10-(2-Pyridyl)phenothiazine-5-oxide. Thirteen and eight-tenths grams (0.05 mole) of 10-(2-pyridyl)phenothiazine was dissolved in 333 ml. of refluxing absolute ethanol. The solution was covered with a nitrogen atmosphere and 17 ml. (0.167 mole) of 30% hydrogen peroxide was added after which the reaction was stirred at reflux for 5 hours. Two hundred millliliters of the solvent was removed by distillation and the remaining portion was poured into 620 ml. of water which had been heated previously to 80°. Upon cooling, 10.3 g. of

white needles having a melting point range of 129-133° and 3.4 g. of solidified oil drops melting over the range of 121-126° separated. These combined weights represent a crude yield of 94%. The crude was recrystallized from an ethanol-water system to give two fractions of material, the first weighing 5.5 g. (38%) and melting at 156-157° and the second weighing 4.5 g. (31%) and melting over the range of 125-132°. Another recrystallization of the second fraction from an ethanol-water system failed to increase the melting point. Recrystallization of the first fraction from this same solvent system gave material now melting over the range of 120-158°.

It was observed that the lower melting material crystallized in needles while the higher melting form crystallized in prisms. Both forms had identical infrared spectra.

Anal. Calcd. for $C_{17}H_{12}N_2OS$: S, 10.97. Found: S (needle form), 10.47, 10.52; S (prism form) 10.59, 10.72.

Both forms of material were combined and recrystallized from benzene to give a product melting at 157-158° after showing decomposition between 120-157°. Another recrystallization from a benzene-petroleum ether (b.p., 60-70°) system raised the melting point to 158.5-159.5° and still another one failed to change it.

The infrared spectrum of the compound indicated the presence of the sulfoxide group.

Anal. Calcd. for $C_{17}H_{12}N_2OS$: S, 10.97. Found: S, 10.62, 10.81.

N-Substituted phenothiazine-5,5-dioxide derivatives

10-(n-Decyl)phenothiazine-5,5-dioxide. Seventeen grams (0.05 mole) of 10-(n-decyl)phenothiazine was dissolved in 290 ml. of glacial acetic acid at 70°. Sixteen milliliters (0.154 mole) of 30% hydrogen peroxide was added causing the formation of a deep red color. Stirring was continued for 1.5 hours at 80° after which an additional 5 ml. (0.48 mole) of 30% hydrogen peroxide was added. This caused no apparent change in the reaction. One hundred and ninety milliliters of the solvent was removed by distillation. Upon cooling, 13.5 g. (73%) of pink-brown material having a melting point of 93-95.5° separated. Recrystallization of this from an ethanol-water system produced 12.1 g. (67%) of material having a melting point of 95.5-96.5°. Additional recrystallization did not raise the melting point.

Anal. Calcd. for $C_{22}H_{29}NO_2S$: S, 8.65. Found: S, 8.49, 8.50.

An additional 4.7 g. of a brown semi-solid material was recovered by dilution of the acetic acid filtrate from the reaction mixture with water. No effort was made to purify this.

10-Ethylphenothiazine-5,5-dioxide.[30,31,37,44] This was prepared following the method described by Champaigne.[31] One hundred and sixty-two grams (0.714 mole) of 10-ethylphenothiazine was dissolved in 4130 ml. of glacial acetic acid at 70°. Two hundred and twenty milliliters (2.18 moles) of 30% hydrogen peroxide was added and stirring was continued for 1.5 hours at 80°. An additional 66 ml. (0.65 mole) of 30% hydrogen peroxide was added with no apparent change. Three thousand milliliters of the solvent was removed by distillation and after the undistilled portion had cooled, 121 g. (65%) of material having a melting point of 161-162° separated. Dilution of the acetic acid filtrate with water gave an additional 37 g. (20%) of material having a melting point of 153-154°. Recrystallization of this from glacial acetic acid gave 28 g. (15%) of material melting at 161-162°. Champaigne[31] reported 82 to 95% yields of material having a melting point of 161-163°.

Another experiment was carried out in which unchromatographed 10-ethylphenothiazine was used as the starting material (m.p., 100-102°). From 0.714 mole of 10-ethylphenothiazine, 126 g. (68.2%) of product having a melting point of 159-161° crystallized from the acetic acid solution. Dilution of the acetic acid filtrate with water gave an additional 30 g. (16.2%) of material having a melting point of 152-155°.

Recrystallization of this from glacial acetic acid resulted in 21 g. (11.3%) of material with a melting point of 160-161°.

10-(n-Octadecyl)phenothiazine-5,5-dioxide. Twenty-two and one-half grams (0.05 mole) of 10-(n-octadecyl)phenothiazine was dissolved in 300 ml. of glacial acetic acid at 80°. Fifteen milliliters (0.147 mole) of 30% hydrogen peroxide was added and the reaction was stirred for 1.5 hours, the temperature being maintained at 80°. An additional 10 ml. (0.098 mole) of 30% hydrogen peroxide was added causing no change in the reaction. Upon cooling to room temperature, 22 g. (91.5%) of material melting at 93-93.5° separated. Recrystallization of this from absolute ethanol failed to increase the melting point. The infrared spectrum showed an absorption band characteristic of the sulfone.

Anal. Calcd. for $C_{30}H_{45}NO_2S$: S, 6.63. Found: S, 6.64, 6.71.

10-Phenylphenothiazine-5,5-dioxide.[160] Twenty and one-half grams (0.075 mole) of 10-phenylphenothiazine was dissolved in 440 ml. of glacial acetic acid at 80° to give a green solution. Twenty-three milliliters (0.225 mole) of 30% hydrogen peroxide was added causing a change in color to red. The reaction was stirred at 80° for 1.5 hours during which time the color changed to a light orange. Two hundred and fifty milliliters of solvent was removed by distillation under a partial vacuum provided by a water aspirator. The solution

became dark red during this time. When the solution had cooled to room temperature, 19 g. (83%) of orange crystals melting over the range of 205-208° separated. An additional 2 g. (8.7%) of material having a melting point range of 190-200° was obtained upon dilution of the acetic acid filtrate with water. These two amounts were combined and recrystallized from absolute ethanol to give 20 g. (87%) of material melting sharply at 211-211.5°. Finzi[160] reported a melting point of 204-205°.

The infrared spectrum showed the characteristic absorption band for the sulfone group.

Anal. Calcd. for $C_{18}H_{13}NO_2S$: S, 10.43. Found: S, 10.36, 10.81.

10-(2-Pyridyl)phenothiazine-5,5-dioxide. Two and three tenths grams (0.007 mole) of 10-(2-pyridyl)phenothiazine-1', 5,5-trioxide, 2.2 g. (0.04 g. atom) of iron powder, and 30 ml. of glacial acetic acid were stirred at 100° for 1 hour. The hot solution was filtered and was then diluted with water. Neutralization of the solution with sodium hydroxide caused the separation of a solid which was removed by filtration. This solid was extracted with ethanol which was diluted with water and allowed to evaporate. This caused the crystallization of 1.25 g. (57% of material melting at 180-181°. The infrared spectrum showed the characteristic absorption band

for the sulfone, but a band at 12$\mu$, present in the trioxide was absent.

Anal. Calcd. for $C_{17}H_{12}N_2O_2S$: S, 10.40. Found: S, 10.23, 10.40.

10-(2-Pyridyl)phenothiazine-1',5,5-trioxide. Thirteen and eight-tenths grams (0.05 mole) of 10-(2-pyridyl)phenothiazine was dissolved in 292 ml. of glacial acetic acid at 80° to give a deep yellow solution following the procedure of Ochiai[163] for the preparation of pyridine-1-oxide. Thirty-one milliliters (0.3 mole) of 30% hydrogen peroxide was added and stirring was continued for 15 hours at 80°. During this time the solution became nearly colorless and then near the end of the heating time assumed a deep orange color. One hundred and eighty five milliliters of the solvent was removed by distillation under the partial vacuum provided by a water aspirator. Refrigeration of the remaining acetic acid solution gave 16 g. (99%) of material melting over the range of 220-226°. Dilution of the filtrate with water gave an additional 2 g. (12.3%) of material melting at 225-227°. The two portions of material were combined and recrystallized from absolute ethanol to give 13 g. (80%) of material melting at 232.5-234°. Another recrystallization from absolute ethanol failed to raise the melting point. The infrared spectrum

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[163]E. Ochiai, J. Org. Chem., 18, 534 (1953).

supported the expected structure, the characteristic sulfone bond being present as well as a band at 12$\mu$ which was not present in the spectra of the unoxidized compound or its monoxide.

Anal. Calcd. for $C_{17}H_{12}N_2O_3S$: S, 9.88. Found: S, 9.88, 10.02.

In another preparation carried out in the same manner an 86% yield of product was obtained.

N-Substituted phenothiazines with nuclear substitution

3-Bromo-10-ethylphenothiazine.[37,131] The procedure used for this preparation was essentially that used by Eisch.[131] Forty-nine grams (0.2 mole) of 10-ethylphenothiazine-5-oxide was suspended in a mixture of 100 ml. of water and 100 ml. of 48% hydrobromic acid (0.89 mole). Stirring was carried out at room temperature for 30 minutes and then at reflux for 30 minutes. A quantitative yield (56 g.) of crude material having a melting point range of 95-106° resulted.

Three recrystallizations of this material from absolute ethanol gave 24.5 g. (44%) of material melting at 120-121°. Another recrystallization raised the melting point to 122-123°. Concentration of the recrystallizing liquors gave an additional 9 g. (16%) of impure material which was also

recrystallized from ethanol several times to give material melting at 122-123°.

Chromatographic purification of this material using benzene as the solvent and eluent and activated alumina as the adsorbent failed to increase the melting point further.

However, vacuum sublimation of material melting at 122-123° gave a lower melting (115-118°) and a higher melting (124-125°) fraction.

In another experiment employing 50 g. (0.2 mole) of 10-ethylphenothiazine-5-oxide, 100 ml. of water, and 150 g. (0.93 mole) of concentrated (48%) hydrobromic acid with a 30-minute stirring period at room temperature and a 1-hour stirring period at reflux gave 50 g. (89%) of creamy-white material melting at 121-122°. This was isolated by extracting the reaction mass with ether, the ether extract being washed with a 10% sodium carbonate solution and then evaporating. Recrystallization of the material from absolute ethanol gave 45 g. (80%) of material having a melting point of 123-124°.

When 48% hydrobromic acid was used without dilution with water, no product was isolated.

3-Chloro-10-(n-decyl)phenothiazine. Following the procedure[131] for the preparation of 3-chloro-10-ethylphenothiazine thirty-five and one-half grams (0.1 mole) of 10-(n-decyl)-phenothiazine-5-oxide and 100 ml. (0.6 mole) of 6 N hydrochloric acid were refluxed for 1 hour. The reaction mass was

made alkaline with the addition of 10% sodium hydroxide and was extracted several times with ether. Evaporation of the ether left a dark semisolid material which was subjected to vacuum distillation. Two fractions were collected. The first of these weighed 1 g. and had a boiling point of 43°/0.04 mm. while the second weighed 4 g. and had a boiling range of 185-190°/0.04 mm. Recrystallization of this second fraction from petroleum ether (b.p., 60-70°) gave 2 g. of a non-crystalline solid melting over the range of 153-163°. Concentration of the mother liquors from the recrystallization failed to produce any additional material. Repeated recrystallizations of the compound failed to increase the melting point.

The infrared spectrum indicated ortho disubstitution and 1,2,4 trisubstitution but no sulfoxide group showing that the material was possibly the desired product. However, the wide melting point range indicated an impure product. This was substantiated by a quantitative sulfur analysis.

Anal. Calcd. for $C_{22}H_{28}ClNS$: S, 8.57. Found: S, 9.49, 9.66.

3-Chloro-10-ethylphenothiazine.[37,101,131] Forty-nine grams (0.2 mole) of 10-ethylphenothiazine-5-oxide, 100 ml. of concentrated hydrochloric acid, and 100 ml. of water were refluxed for a period of 1 hour. After cooling to room temperature, the solid was removed by filtration and recrystallized twice from absolute ethanol to give 42 g. (81%) of material

melting at 116-117°. This procedure is essentially that used by Eisch[131] who reported a 77% yield of material melting at 116-117.5°.

10-(n-Decyl)phenothiazine-4-carboxylic acid. Seventeen and one-quarter grams (0.05 mole) of 10-(n-decyl)phenothiazine-5-oxide was suspended in 250 ml. of anhydrous ether under an atmosphere of nitrogen. The suspension was cooled to -20° by means of a Dry Ice-acetone bath and 0.05 mole of n-butyllithium[155] in 45 ml. of ether was added at such a rate as to maintain the temperature at -20°. After stirring for 2 hours at -20° another 0.1 mole of n-butyllithium in 90 ml. of ether was added and the mixture was permitted to warm to 0° where it was maintained for 4 hours. The reaction mass was then poured jet-wise into a Dry Ice-ether slurry. After this mixture had warmed to room temperature the ether was extracted with 100 ml. of 10% sodium hydroxide in several portions. Acidification of this basic extract with hydrochloric acid caused the precipitation of a yellow oil which gradually solidified on standing. This weighed 7 g. (36%) and had a melting point of 124-125°. Recrystallization of this from glacial acetic acid gave 6.2 g. (32%) of material melting at 128-129°. Additional recrystallizations failed to raise the melting point. The infrared spectrum showed characteristic absorption bands for the carbonyl group and 1,2,3 trisubstitution.

Anal. Calcd. for $C_{23}H_{29}NO_2S$: S, 8.36. Found: 8.21, 8.33.

The sodium salt was prepared by adding an excess of 10-(n-decyl)phenothiazine-4-carboxylic acid to a solution of sodium hydroxide. When the maximum amount of material had dissolved, the solution was filtered and the filtrate was allowed to evaporate slowly. Yellow plate-like crystals having a melting point of 253-254° formed. A flame test indicated the presence of sodium.

10-Ethylphenothiazine-3-boronic acid (attempted). A halogen-metal interconversion was carried out on 3-bromo-10-ethylphenothiazine using the same conditions that were used for 3-bromodibenzothiophene.[164] Fifteen and three-tenths grams (0.05 mole) of 3-bromo-10-ethylphenothiazine was partially dissolved in 250 ml. of ether under an atmosphere of nitrogen. The mixture was cooled to 5° and 0.055 mole of n-butyllithium[155] in 44 ml. of ether was added over a period of 5 minutes. Complete solution was attained by the time this addition was finished. Stirring was continued for 10 minutes at 5°. Color Test I[165] gave a blue color while Color Test II[166] gave a violet color.

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[164]G. Illuminati, J. F. Nobis and H. Gilman, J. Am. Chem. Soc., 73, 5887 (1951).

[165]H. Gilman and J. A. Schulze, J. Am. Chem. Soc., 47, 2002 (1925).

[166]H. Gilman and J. Swiss, J. Am. Chem. Soc., 62, 1847 (1940).

This solution of 3-lithio-10-ethylphenothiazine was then added over a 45-minute period to a solution of 29 g. (0.125 mole) of tri-n-butyl borate in 167 ml. of ether in a nitrogen atmosphere, cooled to -70° by means of a Dry Ice-acetone bath. Color Test I was negative immediately upon completion of this addition. One hundred and sixty-seven milliliters (0.18 mole) of 10% sulfuric acid was added and the mass was allowed to warm to 5°. The aqueous layer was separated from the ether layer and washed twice with small portions of fresh ether which were combined with the main ether layer. The ether solution was extracted with three portions of 10% potassium hydroxide amounting to 133 ml. (0.25 mole). This basic extract was washed with ether and was then acidified by the addition of 10% sulfuric acid. A large amount of viscous brown oil separated which could not be purified successfully.

10-Ethylphenothiazine-4-boronic acid (attempted). Twelve and two-tenths grams (0.05 mole) of 10-ethylphenothiazine-5-oxide was suspended in 500 ml. of ether under an atmosphere of nitrogen. This suspension was cooled to -20° and 0.05 mole of n-butyllithium[155] in 40 ml. of anhydrous ether was added over a period of 5 minutes, the temperature being maintained at -20°. Stirring was continued for 3 hours at -20° after which another 0.1 mole of n-butyllithium in 80 ml. of ether was added over a 10-minute period. The temperature was permitted to rise to 0° and stirring was continued for 4 hours

at this temperature. At the end of this time, Color Test I[165] was a deep blue and Color Test II[166] was just slightly positive.

This ether solution of 4-lithio-10-ethylphenothiazine was then added over a 1.5-hour period to a solution composed of 35 g. (0.152 mole) of tri-n-butyl borate and 200 ml. of ether in a nitrogen atmosphere, cooled to -70° by means of a Dry Ice-acetone bath. Color Test I was negative immediately upon completion of the addition. The reaction was permitted to warm to 0° and 85 ml. (0.093 mole) of 10% sulfuric acid and 100 ml. of water were added to adjust the pH to 7. A white, gummy solid separated which was insoluble in the aqueous layer and only sparingly soluble in the ether layer. An additional 500 ml. of water was added in an attempt to dissolve the solid. The aqueous layer was separated from the ether layer and washed twice with 150-ml. portions of fresh ether which were combined with the main portion.

Evaporation of the ether layer to dryness followed by vacuum drying at room temperature left a viscous oil which was insoluble in 10% sodium hydroxide. Efforts to purify this by recrystallization failed.

The ether insoluble-water insoluble material was then examined. This material was slightly soluble in base and reprecipitated on addition of acid. It had a melting point range of 100-200°. This was recrystallized twice from an

ethanol-water system to give material having a melting point of 100-101°. This material showed no melting point depression when mixed with an authentic specimen of 10-ethylphenothiazine. The infrared spectrum also confirmed the identity. It should be pointed out here that the original crude material must have been something other than 10-ethylphenothiazine due to its ether insolubility. Decomposition possibly resulted during the purification. Attempts to recrystallize this material from other solvents also failed.

Several unsuccessful attempts to prepare this compound prior to the experiment described above were also made. These employed several minor variations such as attempted isolation of the product from the ether layer by extraction with potassium hydroxide and the use of trimethyl borate as a source of the boron. All of these experiments gave the same insoluble material as was isolated above.

10-Ethylphenothiazine-4-carboxylic acid.[30,31,37]

From 10-ethylphenothiazine-5-oxide. This compound was prepared following the method used by Diehl.[37] Twenty-four and three-tenths grams (0.1 mole) of 10-ethylphenothiazine-5-oxide was suspended in 500 ml. of ether in an atmosphere of nitrogen. After cooling to -20°, 0.1 mole of n-butyllithium[155] was added, the temperature being maintained at -20° during the addition and for 2 hours thereafter. Another 0.2 mole of n-butyllithium was then added and the temperature was

raised to 0° where it was kept for 4 hours. At the end of this time the reaction mass was poured jet-wise into a slurry of Dry Ice and ether. After warming to room temperature, the ether was extracted with 10% sodium hydroxide in several portions. Acidification of this basic extract produced a gummy solid which was redissolved in 10% sodium hydroxide and reprecipitated with acid to give 22 g. of material melting over the range of 155-165°. This material was recrystallized from glacial acetic acid to give 15 g. (55%) of material melting at 180.5-181.5°. Diehl[37] reported a 54.8% yield of material melting at 179.5-181°.

From 10-ethylphenothiazine using n-butyl alcohol as a catalyst (attempted). Eleven and four-tenths grams (0.05 mole) of 10-ethylphenothiazine was dissolved in 250 ml. of ether in a nitrogen atmosphere and cooled to -20°. Three and seven-tenths grams (0.05 mole) of n-butyl alcohol was added followed by the addition of 0.15 mole of n-butyllithium[155] in 110 ml. of ether. The reaction was stirred at -20° for 2 hours and then at 0° for 4 hours. The mass was carbonated by pouring it jet-wise into a Dry Ice-ether slurry. After the mixture had warmed to room temperature the ether was extracted with several small portions of 10% sodium hydroxide. Acidification of this basic extract failed to produce any of the desired product.

A control run in which no n-butyl alcohol was used also failed to produce any product. In each experiment, 92% of the starting material was recovered from the ether layer.

3-Triphenylsilyl-10-ethylphenothiazine (attempted). The ether suspension of triphenylsilylpotassium (prepared by treating 8 g. (0.0154 mole) of hexaphenyldisilane with excess sodium-potassium alloy) was added to a stirred suspension of 9.5 g. (0.0361 mole) of 3-bromo-10-ethylphenothiazine in 150 ml. of ether in a nitrogen atmosphere at room temperature. Following completion of the addition, stirring was continued for 2 hours at room temperature and then at reflux for 3 hours. Color Test I[165] was still slightly positive at the end of this time. The reaction mass was hydrolyzed by the addition of 150 ml. of water. The mass was filtered and the two layers were separated, the aqueous layer being washed twice with additional ether which was combined with the main ether portion. The ether layer was dried with anhydrous sodium sulfate and then concentrated on the steam plate. This caused the separation of 0.8 g. of hexaphenyldisilane, identified by melting point and mixed melting point. Complete removal of the ether left a residue which on recrystallization from benzene gave 1.6 g. of hexaphenyldisiloxane, also identified by melting point and mixed melting point.

The benzene solution from which the hexaphenyldisiloxane was removed was passed through a column of activated alumina,

the column being eluted with additional benzene. Evaporation of the eluate left a semicrystalline product which was dissolved in carbon tetrachloride and again chromatographed on activated alumina, carbon tetrachloride also being used as the eluent. An amorphous material having a melting point of 178-180° remained. This could not be purified any further and remained unidentified.

4-Triphenylsilyl-10-ethylphenothiazine (attempted). 4-Lithio-10-ethylphenothiazine was prepared by treating 22.7 g. (0.1 mole) of 10-ethylphenothiazine-5-oxide suspended in 1 liter of ether under a nitrogen atmosphere with 0.1 mole of n-butyllithium[155] in 75 ml. of ether at -20° for 2 hours and then with an additional 0.2 mole of n-butyllithium in 150 ml. of ether for 4 hours at 0°. This was separated into two equal portions. One portion was added to a solution of 29.5 g. (0.1 mole) of triphenylchlorosilane in 150 ml. of ether at room temperature. In a second experiment, the reverse addition was made. In each case, stirring was continued for 2 hours at room temperature following completion of the addition and then hydrolyzed by the addition of 200 ml. of water. The ether layer was separated from the aqueous layer, this being washed with additional ether which was combined with the main ether portion. The ether layer was dried with magnesium sulfate and was then evaporated to dryness. Material

melting over the range of 100-200° was recovered from each experiment.

Attempts were made to purify these crudes chromatographically using benzene on activated alumina, but the only known material which could be isolated from either experiment was hexaphenyldisiloxane, identified by the method of melting point and mixed melting point.

## Boronic Acid Derivatives

### General

Chemicals. All chemicals used in this section of the experimental were Eastman White Label or of equal quality. Some of these, such as the 6-bromo-2-naphthol and o-bromodimethylaniline, were custom made by Reaction Products of Painesville, Ohio. Several of the borate esters were furnished free of charge by the American Potash and Chemical Corporation. They also kindly furnished some benzeneboronic acid. Some of the tri-n-butyl borate and trimethyl borate was prepared in This Laboratory.

The ethylene chloride which was used for several of the recrystallizations was pure and was dried before use by distilling over phosphorus pentoxide. The material, used for the purifications was recovered by distillation and then redried

by distilling again over phosphorus pentoxide. This drying was carried out as a precautionary measure since some aromatic boronic acids are known to deboronate by heating in water. Any technical grade ethylene chloride which was employed was washed with sulfuric acid, water, and then distilled over phosphorus pentoxide before use.

The diatomaceous earth used in the chromatographic purification experiments was Johns-Manville Analytical Celite and the silicic acid used also for chromatography was Mallinckrodt Analytical Reagent Grade. Generally a 1:2 mixture of Celite and silicic acid was used. This was prepared by shaking thoroughly 1 pound of silicic acid with 1/2 pound of Celite in a gallon jar. The chromatographic column was packed with a slurry of the adsorbent and the solvent (usually reagent grade chloroform) which was to be used for the chromatographic purification. Even packing of the column was difficult but this was accomplished with a reasonable amount of success by constant stirring of the column with a rod while solvent was being passed through.

Apparatus. The usual standard-taper glassware with appropriate fittings was used for all reactions. The formation of boronic acids was carried out at -70°. This temperature was obtained by use of a Dry Ice-acetone bath. For some reactions, a special 1-liter cylindrical flask designed to fit a 2-quart wide-mouth Dewar flask was used. This enabled

the maintenance of a -70° temperature overnight if it was necessary.

All of the diazotizations and couplings were carried out in open flasks at 0-5°. This temperature was provided by means of an ice-salt bath.

Titration of boronic acids. The neutralization equivalents of the boronic acids or anhydrides were determined by complexing the material with D-mannitol and then titrating with standard sodium hydroxide. Approximately 50 to 100 mg. of the sample was dissolved in 30 to 50 ml. of 50% ethanol. Two grams of D-mannitol was added and the titration was carried out with 0.05 N sodium hydroxide, the endpoint being detected with phenolphthalein in the case of the colorless compounds or with a Beckman Model G pH meter using a glass-calomel electrode system for the azo boronic acids.

In some instances, water was sufficient to dissolve the compound while in others it was necessary to use a mixture of acetone and water.

Preparation of tri-n-butyl borate. This intermediate was prepared following the procedure of Johnson and Tompkins.[167] Three hundred and seventy-two grams (6 moles) of boric acid and 2000 g. (27 moles) of n-butyl alcohol were heated in a

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[167] J. R. Johnson and S. W. Tompkins, Organic Syntheses, 13, 16 (1933).

5-liter flask equipped with a Vigreux column with a take-off leading through a condenser to a receiver. The amount of heat applied was such that the solution distilled at the rate of 100 ml./hour. This distillate consisted of a mixture of n-butyl alcohol and water and distilled at 91°. After several hours, the n-butyl alcohol in the distillate was separated from the water, was dried with anhydrous potassium carbonate and was returned to the reaction flask through a dropping funnel. This same procedure was repeated several times until the temperature of the distillate reached 111°. This indicated completion of the reaction.

The excess n-butyl alcohol was removed by distillation under the partial vacuum supplied by a water aspirator, this boiling at 43°/18 mm. The tri-n-butyl borate was also distilled at reduced pressure. A 92% yield (1273 g.) of product boiling at 116°/18 mm. was collected.

Trimethyl borate. The preparation was made following the procedure of Schlesinger and co-workers.[168] Three hundred and seventy-two grams (6 moles) of boric acid and 1536 g. (48 moles) of methyl alcohol were heated at reflux for 1 hour. Material distilling up to 70° was then removed. Enough lithium chloride was added to the distillate to cause the separation

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[168] H. I. Schlesinger, H. C. Brown, D. L. Mayfield and J. R. Galbreath, J. Am. Chem. Soc., 75, 213 (1953).

of two layers. The upper layer was separated and fractionated. Fifty-nine grams of a forerun boiling over the range of 54-66° was collected followed by 68 g. (11%) of trimethyl borate boiling at 66-68°.

In another experiment 210 g. (3 moles) of boric oxide and 384 g. (12 moles) of methyl alcohol were used. This was treated as in the experiment above. Ninety-nine grams of a forerun boiling over the range of 54-65° was collected followed by 119 g. (28%) of trimethyl borate boiling at 65-68°.

Neither of these experiments approached the 90% yield claimed by the originators of the process.

Miscellaneous. The discussion in the phenothiazine section on inert atmospheres, preparation of n-butyllithium[155] and determination of infrared spectra also applies to this section. All reactions involving organometallic compounds were carried out in a nitrogen atmosphere. Most of the compounds discussed in this section are new. A few, however, are known compounds and new methods of preparation have been employed here. The compounds have been arranged into two groups, the first consisting of the simple boronic acids and the second of the azo boronic acids. The compounds are arranged alphabetically within each group. Some cleavage reactions of simple boronic acids are described in the last section.

All melting points were obtained using a previously unheated bath.

The quantitative elemental analyses were carried out by the Schwarzkopf Microanalytical Laboratory.

## Simple boronic acids

Benzeneboronic acid. This material was not prepared but some material obtained from the American Potash and Chemical Corporation having a neutralization equivalent of 125.55 and a melting point of 210-213° was purified for analytical purposes and testing. One sample was recrystallized from toluene and another from water. In each case, the benzeneboronic acid was dissolved in the hot solvent, Norit-A was added, the mixture was filtered and the filtrate was cooled to room temperature. The material which crystallized was recovered by filtration and dried in air under a heat lamp. The material which was recrystallized from toluene had a neutralization equivalent of 106.5 and a melting point of 212-214° while the material which was recrystallized from water had a neutralization equivalent of 122.1 and a melting point of 217-218°. The theoretical neutralization equivalent for benzeneboronic acid is 121.94 and for the anhydride, 103.92. The material which was recrystallized from toluene must be mostly anhydride, and that from water, the acid. The acid was submitted for boron and molecular weight analyses.

Anal. Calcd. for $C_6H_7BO_2$: B, 8.92; M.W., 121.94. Found: B, 9.02, 9.08; M.W., 127.

In later experiments, some of the acid was converted to the anhydride by recrystallization from ethylene chloride, by heating at 75° for 24 hours in the vacuum oven and by heating the material above its melting point in a stream of nitrogen.

1-Butaneboronic acid.[144]

From n-butyllithium (attempted). n-Butyllithium[155] was prepared in the usual way. Two-tenths of a mole of n-butyllithium in 200 ml. of ether was added to a mixture of 21 g. (0.2 mole) of trimethyl borate and 60 ml. of ether cooled to -70°. Color Test I[165] was negative immediately upon completion of the addition. After the reaction had warmed to 0° it was hydrolyzed by the addition of a mixture of 12 ml. (0.21 mole) of concentrated sulfuric acid and 120 ml. of water. The ether layer was separated from the aqueous layer and was washed twice with 80-ml. portions of ether which were combined with the main portion. The ether layer was concentrated and 10 ml. of water was added. Evaporation was continued until all of the volatile material was gone. At this point two layers were present; water and some other material believed to be a form of 1-butaneboronic acid. This was placed in a nitrogen-filled desiccator containing 65% sulfuric acid but crystallization failed to occur over a period of time.

From n-butylmagnesium bromide. The procedure used was that employed by Snyder, Kuck and Johnson.[144] The butylmagnesium bromide was prepared following the method of Dreger.[169] Twelve and one-half grams (0.514 g. atom) of magnesium turnings and a crystal of iodine were treated with 8 ml. of a solution of 68.5 g. (0.5 mole) of n-butyl bromide in 167 ml. of ether. After the reaction was initiated the remainder of the n-butyl bromide solution was added over a period of 45 minutes. The rate was such as to maintain a gentle reflux. Stirring was continued until refluxing ceased. The titration of an aliquot indicated a 96% yield of n-butylmagnesium bromide.

This n-butylmagnesium bromide solution was then added over a period of 6 hours to a solution composed of 55 g. (0.53 mole) of trimethyl borate and 150 ml. of ether previously cooled to -70°. Stirring was continued for 14 hours following completion of the addition, the temperature being maintained at -70°. Color Test I[165] was negative at this time. After the reaction had warmed to -10° it was hydrolyzed by the addition of 30 ml. (0.525 mole) of concentrated sulfuric acid in 300 ml. of water. The aqueous layer was separated from the ether layer and washed with 100 ml. of ether which was combined

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[169]E. E. Dreger, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 306.

with the main ether portion. The ether solution was concentrated on the steam plate, 20 ml. of water was added and evaporation was continued until all of the volatile material had escaped. Upon cooling, solid material separated which was removed by filtration. This was bottled while still wet and stored in a nitrogen-filled desiccator containing 65% sulfuric acid. A portion of the material was dried and the melting point obtained. The material melted at 84-86°. The literature value[144] is 92-94°. On the basis of the dried portion the yield of crude was estimated at 60%. Recrystallization of another portion of the material from toluene gave a product having a melting point range of 86-90°.

o-Dimethylaminobenzeneboronic acid/or anhydride (attempted). A solution of 40 g. (0.20 mole) of o-bromodimethylaniline in 60 ml. of ether was added over a 1-hour period to a suspension of 3.36 g. (0.485 g. atom) of cut lithium wire in 60 ml. of ether. The rate was such as to maintain a gentle reflux. Stirring was continued for 15 minutes following completion of the addition. The o-dimethylaminophenyllithium-ether solution was then poured through a glass-wool plug into a liquid-addition funnel and an aliquot was removed and titrated. A yield of 100% was indicated. This was then added over a 15-minute period to a solution of 48 g. (0.207 mole) of tri-n-butyl borate in 60 ml. of ether previously cooled to -70°. Color Test I[165] was negative immediately upon completion of

the addition. The reaction was permitted to warm to 0° and was hydrolyzed by the addition of 75 ml. (0.082 mole) of 10% sulfuric acid and 75 ml. of water. This lowered the pH to 7. The aqueous layer was washed twice with 100-ml. portions of ether which were combined with the main portion. The ether was evaporated and the remaining residue was placed in the vacuum oven for 24 hours at room temperature. Twenty-nine grams of a viscous brown oil resulted. This represents an 88% yield of crude material. Three recrystallizations from ethylene chloride gave 22 g. (67%) of material melting at 85-87°.

Anal. Calcd. for $C_8H_{12}BNO_2$ (the acid): B, 6.56. Calcd. for $C_8H_{10}BNO$ (the anhydride): B, 7.36. Found: B, 5.94, 6.01.

The analysis does not check with either the acid or the anhydride. Attempts to get a neutralization equivalent on this material by the standard procedure failed, the sample consuming no base. This was attributed to failure of the D-mannitol to complex. Therefore, a mixture of the sample and D-mannitol was refluxed in water for a period of 8 hours before titrating. This sample consumed some base and gave a neutralization equivalent of 215. Several repetitions of this gave neutralization equivalents approximating 220. This does not agree with either the acid (165) or the anhydride (147). The infrared spectrum showed absorption bands at 8.5$\mu$, 8.9$\mu$,

9.7$\mu$ and 10.8$\mu$ as well as the characteristic -OH band. There was no ortho disubstitution band.

Continued heating of the sample above the melting point caused resolidification at 197°, followed by slow decomposition between 350 and 500°. The neutralization equivalent of this material obtained by the standard procedure (no refluxing required) was 108. The infrared spectrum of this resolidified material was very similar to that of the unheated material except that the absorption bands at 8.5$\mu$, 9.7$\mu$ and 10.8$\mu$ were much less pronounced.

Recrystallization of the material from other solvents was also tried without too much success. The material did recrystallize from petroleum ether (b.p., 60-70°) with difficulty to give a product also melting at 85-87°. Another recrystallization from petroleum ether gave a product melting over the range of 114-120°.

The material was also characterized by its good solubility in any solvent, ranging from water to petroleum ether (b.p., 60-70°), in which it was tried.

The compound is quite possibly a complex formed between dimethylaniline and boric acid. This would fit the data quite well including the boron analysis, the complex having a calculated boron content of 5.93%.

p-Dimethylaminobenzeneboronic acid anhydride.[170] This material was prepared following the procedure of Abbott[170] except that a change was made in the finishing procedure. A solution of 60 g. (0.3 mole) of p-bromodimethylaniline in 90 ml. of ether was added over a 1-hour period to a suspension of 5.07 g. (0.72 g. atom) of cut lithium wire in 90 ml. of ether. Agitation was continued for 15 minutes following completion of the addition and the reaction mass was poured through a glass-wool plug into a liquid-addition funnel. The titration of an aliquot indicated a 100% yield of p-dimethylaminophenyllithium. This organometallic compound was added over a 20-minute period to a solution composed of 72 g. (0.312 mole) of tri-n-butyl borate in 90 ml. of ether previously cooled to -70°. Color Test I[165] was slightly positive immediately upon completion of the addition but became completely negative within a few minutes. After the mixture had warmed to 0° it was hydrolyzed by the addition of 117 ml. (0.126 mole) of 10% sulfuric acid and 120 ml. of water to bring the pH to 7. The aqueous layer was separated from the ether and washed twice with 100-ml. portions of ether which were combined with that from the reaction. The ether was dried with anhydrous sodium sulfate and then removed by distillation.

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[170] R. K. Abbott, Doctoral Dissertation, Iowa State College (1944).

The residue was subjected to vacuum distillation to remove the n-butyl alcohol, unreacted p-bromodimethylaniline and any other volatile material. The undistilled portion was extracted with 100 ml. of absolute ethanol and the insoluble portion was recovered by filtration and dried in the vacuum oven at room temperature to give 15.9 g. (32.2%) of product. This was recrystallized from ethylene chloride to give 13.4 g. of white crystals having a melting point range of 230-275°. This represents a yield of 27%. Reduction in volume of the ethanol recrystallizing liquors gave material which on recrystallization from ethylene chloride had the same melting point as the main fraction and amounted to an additional 3% yield. All of the material was combined and recrystallized again from ethylene chloride without any change in melting point.

Using the standard procedure, a neutralization equivalent of 167 (theoretical for the acid is 165) was obtained, although this was based on a very indefinite endpoint using both phenolphthalein and the pH meter to detect the endpoint. The infrared spectrum showed the characteristic absorption bands for C-N and p-disubstitution but did not show any -OH absorption band. This indicated that the compound was more than likely the anhydride (neutralization equivalent, 147). When the neutralization equivalent was obtained using a reflux period before the titration, values of 144.2 and 145.4 were obtained

on duplicate samples. The quantitative boron analysis also confirmed the anhydride.

Anal. Calcd. for $C_8H_{10}BNO$: B, 7.36. Found: B, 7.41, 7.65.

Attempts to isolate the product following the procedure of Abbott[170] were not successful, the product always coming out as a brown to black oily solid which decomposed more on standing. This procedure consisted of distillation of the ether layer after hydrolysis of the reaction mass, addition of a potassium hydroxide solution followed by distillation of the n-butyl alcohol, and neutralization of the undistilled aqueous layer.

Many other recrystallizing solvents were used in an attempt to purify the product but none proved adequate.

o-Hydroxybenzeneboronic acid anhydride.

With isolation by extraction with 10% sodium hydroxide. To 91 g. (0.525 mole) of o-bromophenol dissolved in 200 ml. of ether cooled to 5° was added 1.08 mole of n-butyllithium[155] in 800 ml. of ether. This addition was made over a period of 75 minutes and stirring was continued for 3 hours at 20-25° after which time Color Test II[166] was negative. The procedure used for this halogen-metal interconversion has

been reported previously.[171,172] This ether solution of lithium o-lithiophenoxide was then added over a period of 1 hour to a solution composed of 248 g. (1.08 mole) of tri-n-butyl borate and 200 ml. of ether previously cooled to -70°. Color Test I[165] was negative immediately upon completion of the addition. After warming to 0° the reaction mass was hydrolyzed by the addition of 360 ml. (1.045 moles) of 10% hydrochloric acid. The aqueous layer was separated from the ether and was washed twice with 200-ml. portions which were combined with the main ether layer. This ether solution was extracted with 800 ml. (2.1 moles) of 10% sodium hydroxide in three portions. The basic extract was washed once with ether, and was then warmed on the steam plate to expel any residual ether. Acidification with 10% hydrochloric acid caused the precipitation of 76 g. of crude material having a melting point range of 130-150°. This crude was recrystallized twice from toluene to give 35 g. (55.5%) of product melting over the range of 170-175°.

In other experiments a number of other solvents were found to be useful in recrystallizing this compound. These include benzene, acetone-benzene, ethylene chloride, water,

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[171] H. Gilman, C. E. Arntzen and F. J. Webb, J. Org. Chem., 10, 374 (1945).

[172] H. Gilman and C. E. Arntzen, J. Am. Chem. Soc., 69, 1537 (1947).

and acetone-water. The analytical sample was recrystallized from an acetone-water system and had a melting point range of 180-183°. The infrared spectrum indicated characteristic absorption bands for ortho disubstitution and the hydroxy group.

Anal. Calcd. for $C_6H_5BO_2$: C, 60.09; H, 4.20; B, 9.02; neut. equiv., 119.94. Found: C, 60.24, 60.30; H, 4.12, 4.18; B, 9.12, 9.21; neut. equiv., 120.0.

Chromatographic purification was tried on some crude material and found to be somewhat useful although not as adequate as the recrystallization techniques. Five grams of crude material (m.p., 154-160°) was dissolved in 200 ml. of chloroform and chromatographed on 200 grams of 1:2 Celite-silicic acid, the column being eluted with additional chloroform. Material having a melting point range of 179-187° and a neutralization equivalent of 115 was recovered from the eluate.

With isolation by evaporation of the ether layer.

Starting with 98.5 g. (0.57 mole) of o-bromophenol and using tri-n-butyl borate as the source of the boron, 91 g. of crude material was isolated by evaporation of the ether layer following the acid hydrolysis of the reaction mass. The crude melted over the range of 130-148°. This was washed with 400 ml. of water leaving 47 g. of material having a melting point range of 165-170°. Recrystallization of the washed material

from ethylene chloride gave 37 g. (55%) of product having a melting point range of 175-180°.

When trimethyl borate was used in place of tri-n-butyl borate, a 47% yield of material melting over the range of 180-185° was obtained.

m-Hydroxybenzeneboronic acid anhydride.[26,151]

From m-bromophenol. Thirty-four and six-tenths grams (0.2 mole) of m-bromophenol was dissolved in 90 ml. of ether under a nitrogen atmosphere. To this stirred solution was added 0.44 mole of n-butyllithium in 332 ml. of ether over a period of 50 minutes, the temperature being maintained at 20°. Agitation was continued for 4 hours at 20° at which time Color Test II[166] was negative.[173] This ether solution of lithium m-lithiophenoxide was then added over a 30-minute period to a solution of 140 g. (0.6 mole) of tri-n-butyl borate in 220 ml. of ether cooled previously to -70°. During this time the reaction mass became very viscous. When the addition was complete, the reaction was permitted to warm to 0°. Color Test I[165] was negative. The reaction mixture was hydrolyzed by the addition of 250 ml. of saturated ammonium chloride solution, 150 ml. of 10% hydrochloric acid and 100

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[173]The conditions used for this halogen-metal interconversion were found to be the optimum conditions as determined by a series of experiments run in this Laboratory in which the metalated product was converted to the carboxylic acid by carbonation. These conditions gave a 33.3% yield of the carboxylic acid.

ml. of water to get the pH below 7. The aqueous layer was separated from the ether and was washed twice with 100-ml. portions of ether which were combined with the main ether solution. This ether solution was extracted ten times with 60-ml. portions of 10% sodium carbonate which were poured into a mixture of 400 ml. of ether and 500 ml. of saturated ammonium chloride solution. Four hundred milliliters of 10% hydrochloric acid was also added to get the pH to 6. The aqueous layer was separated from the ether and was extracted several times with additional ether which was combined with the main portion. Evaporation of this ether extract to dryness left a solid material which upon crystallization from ethylene chloride gave 6 g. (25%) of material having a melting point range of 208-212°.

The initial ether layer was evaporated to about one-fourth its original volume and the same process was repeated. This gave an additional 1.1 g. (4.5%) of material melting over the range of 208-212°. The two final acid layers were combined and evaporated to one-fourth volume. This was extracted several times with ether to give 0.9 g. (3.8%) of material with a melting range of 215-230°. All of the crude was combined and recrystallized from ethylene chloride to give 7.3 g. (30.4%) of material having a melting point range of 215-225°, dec. The analytical sample was recrystallized an additional time from ethylene chloride without any change in the melting

point. The infrared spectrum showed the characteristic absorption bands for meta disubstitution and the hydroxy group.

Anal. Calcd. for $C_6H_5BO_2$: B, 9.02; neut. equiv., 119.94. Found: B, 9.22, 9.28; neut. equiv., 117, 122.4.

From 2-(m-bromophenoxy)tetrahydropyran (attempted). The 2-(m-bromophenoxy)tetrahydropyran was prepared using a procedure similar to that used for the ortho[174] and para[175] isomers. To a stirred mixture of 33.6 g. (0.4 mole) of freshly distilled dihydropyran and 4 drops of concentrated hydrochloric acid previously heated to 60° was added 34.6 g. (0.2 mole) of m-bromophenol over a period of 30 minutes. The rate was such as to keep the temperature below 70°. Stirring was continued for 2 hours following completion of the addition, the temperature being permitted to drop to that of the room. Eighty milliliters of ether was added to the reaction mass which was then extracted three times with 20-ml. portions of 10% sodium hydroxide. These basic aqueous layers were combined and extracted three times with 50-ml. portions of ether. An additional 100 ml. of water was added to dissolve an orange-colored solid which separated during this operation. The ether

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[174] B. F. Hofferth, Doctoral Dissertation, Iowa State College (1950).

[175] W. E. Parham and E. L. Anderson, J. Am. Chem. Soc., 70, 4187 (1948).

extracts were combined and dried with anhydrous sodium sulfate. The ether and excess dihydropyran were removed by distillation at atmospheric pressure after which the remaining material was subjected to vacuum distillation. The material boiled over the range of 98-105°/2 mm. This material was distilled a second time, two fractions being collected. The first fraction weighed 5 g. and distilled at 119-120°/1 mm. while the second fraction distilled at 115°/0.4 mm., $n_D^{20}$ 1.5504, $d_{20}^{20}$ 1.3952, and weighed 38.5 g. (75%).

Anal. Calcd. for $C_{11}H_{13}BrO_2$: Br, 31.08; $MR_D$, 58.12. Found: Br, 30.60, 30.55; $MR_D$, 58.75.

One-tenth mole of n-butyllithium in 100 ml. of ether was added to a solution of 25.7 g. (0.1 mole) of the material prepared above and 100 ml. of ether, the temperature being maintained between 10 and 20°. Stirring was continued for 1 hour following completion of the addition at this same temperature. Color Test II[166] was only slightly positive at this time. The solution was then added over a period of 30 minutes to a mixture of 34.5 g. (0.15 mole) of tri-n-butyl borate and 100 ml. of ether previously cooled to -70°. Color Test I[165] was negative immediately upon completion of the addition. After the reaction had warmed to about 0°, 90 ml. (0.25 mole) of 10% hydrochloric acid was added. The ether layer was separated from the aqueous layer which was then washed with two small portions of ether. These were combined with the main ether

solution. The ether solution was extracted four times with 35-ml. portions (0.35 mole) of 10% sodium hydroxide which were combined and heated on the steam plate to expel any residual ether. Acidification of this with 10% hydrochloric acid caused the precipitation of a gummy product which solidified on standing. Efforts to purify this, even by recrystallization from ethylene chloride, were unsuccessful.

2-Hydroxy-6-naphthaleneboronic acid. Using a described procedure,[176] 11.15 (0.05 mole) of 6-bromo-2-naphthol in 125 ml. of ether was treated with 0.1 mole of n-butyllithium in 98 ml. of ether over a period of 15 minutes at 20°. One-half hour after the completion of the addition, Color Test II[166] was negative. This solution was then added over a 20-minute period to 24 g. (0.105 mole) of tri-n-butyl borate dissolved in 100 ml. of ether previously cooled to -70°. Color Test I[165] was negative immediately upon completion of the addition. After warming to 0°, the reaction mass was hydrolyzed by the addition of 50 ml. (0.145 mole) of 10% hydrochloric acid. The aqueous layer was separated from the ether and washed twice with 100-ml. portions of ether which were combined with the main ether solution. This ether solution was extracted with 100 ml. (0.263 mole) of 10% sodium hydroxide in three portions.

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[176] S. V. Sunthanker and H. Gilman, J. Org. Chem., 16, 8 (1951).

This extract was heated on the steam plate to expel any residual ether and was then acidified by the addition of 10% hydrochloric acid. This caused the precipitation of a tan solid which after drying in the vacuum oven at room temperature weighed 7.75 g. (82.5%) and had a melting point range of 200-204°.

Attempts to recrystallize this material from an ethanol-water system failed, but needle-like crystals having a melting point range of 225-250° resulted by slow evaporation of a benzene-acetone system. Another recrystallization from acetone-benzene failed to increase the melting point or narrow the melting point range. Four and one-tenth grams (44%) of pure material was obtained. The infrared spectrum showed characteristic absorption bands for $\beta$ substitution and the hydroxy group.

Anal. Calcd. for $C_{10}H_9BO_3$: B, 5.76; neut. equiv., 188. Found: B, 6.16, 5.82; neut. equiv., 190, 190.5.

Other preparations of this material that were made gave essentially the same yield and quality of material.

Recrystallization from ethylene chloride was also tried and found to be satisfactory although the material is not appreciably soluble in the hot solvent. Continued heating in the refluxing solvent tended to cause decomposition, as did prolonged standing in air.

Chromatographic purification using a chloroform solvent and eluent on Celite-silicic acid was unsuccessful.

Azo boronic acids

p-(3-Borono-4-hydroxyphenylazo)benzenesulfonic acid. The procedure described by Feiser[177] for the preparation of Orange II (coupling between diazotized sulfanilic acid and β-naphthol) was used in this experiment. Nine and six-tenths grams (0.05 mole) of sulfanilic acid monohydrate was dissolved in a solution of 2.65 g. (0.025 mole) of anhydrous sodium carbonate in 100 ml. of water at 60°. After cooling to 20°, 3.7 g. (0.0535 mole) of sodium nitrite (97%) was added. The resulting mixture was then poured into 10 ml. (0.12 mole) of concentrated hydrochloric acid containing 50 g. of ice. The suspension of diazobenzene sulfonate was added slowly to a solution of 6 g. (0.05 mole) of 2-hydroxybenzeneboronic acid anhydride and 12 g. (0.3 mole) of sodium hydroxide in 60 ml. of water cooled to 5°. Following completion of the addition, agitation was continued for 90 minutes. The mass was acidified by the addition of hydrochloric acid but no solid precipitated. After an extended period of refrigeration, 27 g.

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[177]L. F. Feiser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, p. 208.

of material contaminated with a large amount of sodium chloride and having no melting point under 400°, separated.

The material was insoluble in the common organic solvents, but was quite soluble in hot water and only moderately soluble in cold water. Four recrystallizations from water gave a product which appeared to be pure but whose physical constants did not agree with the theoretical values. The infrared spectrum, however, supported the expected structure.

Anal. Calcd. for $C_{12}H_{11}BN_2O_6S$: S, 9.94; neut. equiv., 322. Found: S, 8.57, 8.43; neut. equiv., 398, 409.

The material could not be purified further.

2-Hydroxy-5-(p-bromophenylazo)benzeneboronic acid. (See Figure 2d, Appendix.) Eight and six-tenths grams (0.05 mole) of p-bromoaniline in 11.5 ml. (0.133 mole) of concentrated hydrochloric acid and 73 ml. of water was diazotized with a solution of 3.55 g. (0.05 mole) of sodium nitrite (97%) in 8 ml. of water according to the procedure of Gomberg and Bachmann.[178] This p-bromobenzenediazonium chloride solution was then added over a 10-minute period to a solution composed of 5.5 g. (0.135 mole) of sodium hydroxide, 6.0 g. (0.05 mole) of 2-hydroxybenzeneboronic acid anhydride, 50 ml. of water and 50 g. of ice cooled also with an ice-salt bath. Stirring

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[178] M. Gomberg and W. E. Bachmann, Organic Syntheses, 8, 42 (1928).

was continued for 9 hours following completion of the addition, the temperature being maintained at 0-5°. The reaction mixture was filtered and the filter cake was suspended in 500 ml. of water at 40°. The suspension was acidified by the addition of 10% hydrochloric acid. The precipitated solid was removed by filtration and dried at 45° in the vacuum oven. The dried material weighed 14.3 g. (89%) and had a melting point range of 170-190°. Acidification of the filtrate from the reaction mass gave a small amount of additional, but very impure, material.

The brown crude solid material was washed with 200 ml. of ethylene chloride, a process which removed a large portion of the impurities, and the washed material was recrystallized three times from ethylene chloride to give 3 g. of bright yellow and rather fibrous material having a melting point range of 350-355°. This weight represents a 20% yield of pure material. The infrared spectrum showed characteristic absorption bands for 1,2,4 trisubstitution and <u>para</u> disubstitution as well as an absorption band for the hydroxy group.

<u>Anal.</u> Calcd. for $C_{12}H_8BBrN_2O_2$: B, 3.57; Br, 26.38; neut. equiv., 302.9. Found: B, 3.95, 3.70; Br, 25.65, 25.44; neut. equiv., 308.

Another similar experiment was run using 43 g. (0.25 mole) of <u>p</u>-bromoaniline. This gave a 99% crude yield of material having a melting point range of 194-206°. This was

recrystallized from ethylene chloride to give 16.8 g. (22%) of material melting over the range of 348-355°.

In an experiment where a 30-minute coupling time was used, an 86% yield of crude material having a melting point range of 130-141° was obtained.

In the attempted chromatographic purification of this compound, 12 g. of crude (m.p. range 180-200°) was partially dissolved in benzene and was chromatographed on a column of 450 g. of Celite-silicic acid. The purest material which could be obtained on elution with additional benzene had a melting point range of 210-220° which is very inferior to the recrystallized material. Poorer separations were obtained when chloroform was substituted for benzene as the solvent and eluent. A mixture of chloroform and carbon tetrachloride (1:1) was superior to chloroform alone.

p-(3-Borono-4-hydroxyphenylazo)benzoic acid. Six and eight-tenths grams (0.05 mole) of p-aminobenzoic acid was added to a solution of 3.75 g. (0.0527 mole) of sodium nitrite (97%) in 14 ml. of water. This was stirred to a uniform paste and poured into a mixture of 13.5 ml. (0.135 mole) of concentrated hydrochloric acid and 15 g. of ice cooled also with an ice-salt bath. The p-carboxybenzenediazonium chloride was added to a solution of 6 g. (0.05 mole) of o-hydroxybenzeneboronic acid anhydride, 10 g. (0.25 mole) of sodium hydroxide and 50 ml. of water cooled to 0-5°. Immediately before the

addition, 50 g. of ice was added to the basic solution. Stirring was continued for 8 hours at 0-5° and then the reaction mass was filtered. The filtrate was acidified by the addition of 10% sulfuric acid. This caused the precipitation of a solid which after drying weighed 21 g. and had a melting point range of 205-400°.

Recrystallization of a portion of this from ethylene chloride gave material having a melting point range of 200-300° with decomposition. The material was not soluble enough in the hot solvent to permit the recrystallization of any suitable amount.

Trichloroethylene was investigated as a possible solvent for recrystallization, but the dye was even more insoluble in this than it was in ethylene chloride.

Recrystallization from 1,1,2,2-tetrachloroethane gave material having a melting point range of 247-253° and a neutralization equivalent of 211.5 which does not agree very well with the theoretical value of 268.

The material could not be purified further.

2-Hydroxy-5-(o-nitrophenylazo)benzeneboronic acid. Twenty-eight grams (0.2 mole) of o-nitroaniline in 45 ml. (0.53 mole) of concentrated hydrochloric acid and 80 ml. of water was diazotized with a solution of 14.5 g. (0.204 mole) of sodium nitrite (97%) in 50 ml. of water according to the procedure

of Smith and Boyer.[179] This o-nitrobenzenediazonium chloride solution was filtered and added over a period of 30 minutes to a solution of 24 g. (0.2 mole) of o-hydroxybenzeneboronic acid anhydride, 22 g. (0.55 mole) of sodium hydroxide and 200 ml. of water cooled to 0-5°. Stirring was continued for 8 hours following completion of the addition, the temperature being maintained below 5°. The reaction mass was filtered. The filter cake was suspended in 2000 ml. of water at 40° and acidified by the addition of 10% hydrochloric acid. The solid was removed by filtration. After drying in air under a heat lamp, the material weighed 42 g. (68%) and had a melting point range of 150-180°. Acidification of the filtrate from the reaction mass with 10% hydrochloric acid gave an additional 7 g. (13%) of crude material having a melting point range of 130-180°. The crudes were combined and washed with 4.5 liters of refluxing ethylene chloride. Eleven grams (20.5%) of material having a melting point range of 220-230° was filtered from the hot solution. An additional 3.1 g. (5.8%) of material having this same melting point range separated from the filtrate upon cooling. Concentration of the filtrate did not yield any additional material. The two portions of partially purified material were combined and

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[179] P. A. S. Smith and J. H. Boyer, Organic Syntheses, 31, 14 (1951).

recrystallized again from ethylene chloride to give 10.5 g. (19.5%) of material melting at 228-230°.

The infrared spectrum showed characteristic absorption bands for 1,2,4 trisubstitution and ortho disubstitution as well as the usual -OH and $-NO_2$ absorption bands.

Anal. Calcd. for $C_{12}H_8BN_3O_4$: B, 4.02; N, 15.61; neut. equiv., 269. Found: B, 4.46, 4.37; N, 15.15, 15.43; neut. equiv., 280.

In earlier experiments to produce this compound, benzene was used as a recrystallizing solvent. The maximum melting point that could be obtained on material recrystallized from this solvent was 213-214°. The quantitative elemental analysis and the neutralization equivalent indicated that the material was not as pure as that which could be obtained from ethylene chloride.

Anal. Calcd. for $C_{12}H_8BN_3O_4$: N, 15.61; neut. equiv., 269. Found: N, 15.18, 15.24; neut. equiv., 290.3.

2-Hydroxy-5-(phenylazo)benzeneboronic acid anhydride. The diazotization of 18.6 g. (0.2 mole) of aniline in a mixture of 45 ml. (0.54 mole) of concentrated hydrochloric acid, 290 ml. of water and 280 g. of ice with a solution of 14.2 g. (0.23 mole) of sodium nitrite (97%) in 32 ml. of water was carried out according to German dyestuff information.[180]

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[180] I. G. Farbenindustrie, British Intelligence Objectives Subcommittee, Report No. 1548, p. 65 (PB85593).

This benzenediazonium chloride solution was then added over a period of 30 minutes to a stirred solution composed of 22 g. (0.55 mole) of sodium hydroxide, 24 g. (0.2 mole) of 2-hydroxybenzeneboronic acid anhydride and 200 ml. of water previously cooled to 0-5°. Immediately before the addition was started, 200 g. of ice was added to the reaction flask. Stirring was continued for 11 hours at 0-5° following completion of the addition. The reaction mass was filtered; the filter cake was suspended in 2000 ml. of water at 40° and acidified by the addition of 10% hydrochloric acid. After cooling to room temperature, the precipitated solid was removed by filtration and was dried in a vacuum oven at 45°. Forty-five grams (100%) of crude reddish-brown material having a melting point range of 178-188° was obtained. Acidification of the filtrate from the reaction mass gave less than 1 g. of additional crude material which was combined with the bulk of the crude.

The crude material was washed with approximately 500 ml. of ethylene chloride. This removed a large portion of the impurities, the washed material now having a melting point range of 210-220°. This material was recrystallized three times from ethylene chloride to give 14 g. (31%) of bright yellow fibrous material melting at 236-238°. After each recrystallization the volume of the filtrate was reduced in order to recover the maximum amount of material. The infrared spectrum showed the characteristic absorption bands for

the hydroxy group, monosubstitution and 1,2,4 trisubstitution.

Anal. Calcd. for $C_{12}H_9BN_2O_2$: B, 4.84; neut. equiv., 224. Found: B, 5.08, 4.96; neut. equiv., 226, 227.

In an experiment where a 3-hour coupling time was employed, the crude yield was 100% and the material had a melting point range of 150-185°.

A 9-hour coupling time gave a 94% yield of material isolated in two portions; the first of these had a melting point range of 170-180° and represents a yield of 21.3% while the second portion had a melting point range of 188-192° and represents a yield of 72.7%.

Chromatographic purification of this dye was studied to a reasonable extent without any outstanding success being attained. In one experiment, 2.25 g. of crude dye (m.p. range, 188-197°) was dissolved in 500 ml. of chloroform and was chromatographed on a column composed of a 1:2 mixture of Celite and silicic acid. The column was eluted with additional chloroform. Nine fractions were collected. Material from fractions 1 through 3 were semi-solids and represented 20% of the original weight. No melting point was obtained on this portion of material. The solid from fraction 4 which represented 11% of the original weight had a melting point range of 140-150°. Fractions 5 through 8 gave material all with melting points higher than the crude, fraction 6 having the

maximum range 204-209°. This series of fractions represents 49% of the starting material. The product from fraction 9 was again a semisolid, no melting point being obtained, and was 4.5% of the original weight. Fraction 6 had a neutralization equivalent of 234 which indicates material of fair purity. The calculated value for the neutralization equivalent for the anhydride is 224.

The use of a 1:1 solution of chloroform and carbon tetrachloride as the solvent and eluent was superior in one respect to chloroform alone in that sharper separations could be made, but was inferior in another in that the solubility of the compound was lower.

A 1:1 mixture of Celite and silicic acid showed no advantage.

Cleavage reactions with n-butyllithium

Cleavage of benzeneboronic acid with five equivalents of n-butyllithium at reflux for 1.5 hours. One-half mole of n-butyllithium[155] in 365 ml. of ether was added to a mixture of 12.2 g. (0.1 mole) of benzeneboronic acid in 130 ml. of ether under an atmosphere of nitrogen over a period of 22 minutes. Stirring was continued at reflux for 1.5 hours after which the reaction mass was poured jet-wise into an agitated slurry of Dry Ice and ether. When the carbonate mass was warmed to room

temperature, it was acidified by the addition of 200 ml. (0.58 mole) of 10% hydrochloric acid. The acid layer was washed twice with 100-ml. portions of ether which were combined with the main ether layer. This ether solution was extracted four times with 50-ml. portions (0.2 mole) of 8% sodium bicarbonate and then four times with 50-ml. portions (0.525 mole) of 5% sodium hydroxide. Acidification of each of these extracts with 10% hydrochloric acid produced no precipitate. These acidified extracts were evaporated to dryness and extracted with ether. Evaporation of each of the ether layers left 0.1 g. of unidentified material melting over the range of 100-150°.

The original ether layer from the reaction was then examined. The ether was removed by distillation and the remaining higher boiling material was fractionated. This gave 10.7 g. of material identified by refractive index as di-*n*-butyl ketone. The boiling point and infrared spectrum also confirmed the identity. Some *n*-octane was also thought to be present based on the refractive index and infrared spectrum.

The presence of valeric acid was indicated by odor.

No benzoic acid, benzene or 1-butaneboronic acid were isolated in this experiment.

Cleavage of benzeneboronic acid with three equivalents of n-butyllithium.

At room temperature for 20 minutes. A solution of 0.225 mole of n-butyllithium[155] in 200 ml. of ether was added to a mixture of 10.38 g. (0.085 mole) of benzeneboronic acid in 220 ml. of ether over a period of 10-15 minutes at room temperature. Stirring was continued at room temperature for 20 minutes after which the mass was carbonated by pouring into a Dry Ice-ether slurry. The mixture was acidified to a pH of 4-5 with 10% hydrochloric acid and the ether layer was extracted with 100 ml. (0.1 mole) of 8% sodium bicarbonate in four portions and 100 ml. (0.262 mole) of 5% sodium hydroxide, also in four portions. Acidification of the sodium bicarbonate extract with 10% hydrochloric acid produced no solid, but acidification of the sodium hydroxide extract gave, after recrystallization from toluene, 2.5 g. (29%) of 1-butaneboronic acid identified by melting point (90-92°), mixed melting point and infrared spectrum.

The ether was distilled from the original ether layer and the higher boiling materials were fractionated. An unmeasured amount of benzene derivatized as the m-dinitro compound was isolated as well as some n-octane, and di-n-butylketone.

Some valeric acid, indicated by odor, also resulted from this experiment.

At reflux temperature for 20 minutes. This experiment was run exactly as the one described above but a reflux temperature was used. Two and fifteen-hundredths grams (25%) of 1-butaneboronic acid as well as valeric acid, n-octane, di-n-butyl ketone and a small amount of benzene were isolated. No benzoic acid was obtained.

At -60 to -50° for 25 minutes. Twelve and two-tenths grams of benzeneboronic acid in 250 ml. of ether under nitrogen was treated with 0.3 mole of n-butyllithium[155] in 218 ml. of ether added over a 20-minute period. The temperature was kept at -50 to -60° during the addition and for 25 minutes following. At this time Color Test I[165] was positive and Color Test II[166] was negative. The mixture was carbonated in the usual manner, acidified by the addition of 100 ml. (0.29 mole) of 10% hydrochloric acid and the ether layer extracted four times with 25-ml. portions (0.1 mole) of 8% sodium bicarbonate and four times with 25-ml. portions (0.262 mole) of 5% sodium hydroxide.

Acidification of the sodium bicarbonate layer gave 0.75 g. (6.2%) of benzoic acid identified by melting point and mixed melting point as well as the infrared spectrum. Acidification of the sodium hydroxide extract caused the formation of white needles which did not melt under 350°. No 1-butaneboronic acid was isolated.

The original ether layer also contained a large amount of insoluble material melting between 160-200° which could not be purified.

Cleavage of o-hydroxybenzeneboronic acid anhydride. Eight grams (0.067 mole) of o-hydroxybenzeneboronic acid anhydride in 250 ml. of ether was treated with 0.134 mole of n-butyllithium[155] in 97 ml. of ether at room temperature. This addition required 10 minutes. Color Test II[166] was negative immediately upon completion of the addition so another 0.67 mole of n-butyllithium in 49 ml. was added. Color Test II was also negative after this addition. Stirring was continued for 20 minutes at room temperature after which the reaction was carbonated in the usual way. The mass was hydrolyzed by the addition of 100 ml. (0.29 mole) of 10% hydrochloric acid and then the ether layer was extracted four times with 25-ml. portions (0.1 mole) of 8% sodium bicarbonate and four times with 25-ml. portions (0.262 mole) of 5% sodium hydroxide. Acidification of the sodium bicarbonate extract with 10% hydrochloric acid gave 1.65 g. (18%) of material melting at 151-155° which was identified as salicylic acid (159°) by the infrared spectrum.

Acidification of the sodium hydroxide extract gave 1.3 g. of material melting over the range of 155-165°. This decomposed before positive identification could be made.

No 1-butaneboronic acid was isolated.

# DISCUSSION

## Phenothiazine Derivatives

### N-Substitution reactions

N-Substitution reactions were carried out using three of the four techniques that were presented in the Historical: reactions between sodiophenothiazine and an organic halide in liquid ammonia, reactions between sodiophenothiazine with an organic halide in some solvent other than liquid ammonia or between phenothiazine and an organic halide in a hydrocarbon solvent using some alkaline condensing agent, and the reaction between phenothiazine and an organic halide in the presence of an alkaline condensing agent and a copper powder catalyst using no solvent. No sealed tube reactions were employed.

It was found that the no-solvent technique was consistently the most successful, this being useful in the preparation of many derivatives such as the 10-(2-pyridyl)- and 10-(2-quinolyl)- which could not be made by the liquid ammonia procedure or by the solvent method using tetrahydrofuran. The preparation of such compounds as 10-(p-biphenylyl)phenothiazine, p-bis(10-phenothiazinyl)benzene and p,p'-bis(10-phenothiazinyl)-biphenyl were not attempted in liquid ammonia or tetrahydrofuran

due to the failure of 10-phenylphenothiazine to be prepared in these media.

The use of a higher concentration of sodiophenothiazine in liquid ammonia (four times that used by Champaigne[31,107]) was found to be advantageous in the preparation of 10-ethylphenothiazine giving a slightly higher yield of product and better quality material than could be obtained at the lower concentration. Even the unpurified material had a melting point only 3 or 4° lower than the pure product.

The only disadvantage of using this higher concentration was the extra care necessary in making the additions of phenothiazine to the sodium amide and the halogen compound to the sodiophenothiazine. It was thought that the reaction might become too vigorous at this high concentration but the heat of vaporization of liquid ammonia (327 cal./g.) is high enough that the system always remained under control if the additions were made at a slow enough rate.

Using a concentration 3.5 times that used by Champaigne,[31] 10-allylphenothiazine was prepared pure in a yield of 92% which is possibly better than the yield of pure material which could have been obtained from the 95.5% crude yield obtained by him.

The higher concentration of sodiophenothiazine in liquid ammonia was also tried as a means of getting increased yields of good quality 10-(n-decyl)phenothiazine and 10-(n-octadecyl)-phenothiazine. Champaigne[31] used a concentration of 0.143

mole/liter of sodiophenothiazine in liquid ammonia for the preparation of 10-(n-decyl)phenothiazine and reported an 86.7% crude yield. Using concentrations of 0.5 mole/liter, 0.75 mole/liter and 1 mole/liter, yields of 60%, 80%, and 68% respectively of slightly impure material were obtained. Even though these are lower than that reported by Champaigne (crude yield) it is believed that the higher concentration is advantageous.

In the preparation of 10-(n-octadecyl)phenothiazine in liquid ammonia a concentration of 0.75 mole/liter of sodiophenothiazine was used. This gave a 12.9% yield of pure product. No experiments have ever been attempted at lower concentrations so no comparison is possible. Champaigne[31] used either toluene or xylene as a supplementary solvent for the n-octadecyl bromide in the liquid ammonia experiments which he conducted and obtained no yield of product. Again it is quite possible that this high concentration was advantageous in obtaining this small yield of product.

Whether the increased concentration of sodiophenothiazine in liquid ammonia was useful or not in these latter two preparations became of secondary interest following the preparation of both compounds in high yield using tetrahydrofuran as the solvent. 10-(n-Decyl)phenothiazine was prepared pure in a yield of 86.5% and the 10-(n-octadecyl)phenothiazine was obtained pure in a yield of 90%. In these experiments,

sodiophenothiazine was reacted with the appropriate bromo compound in tetrahydrofuran at room temperature.

With this success, a number of others whose preparations had failed or did not seem feasible in liquid ammonia were attempted in tetrahydrofuran at room temperature and in some instances at reflux. These include 10-phenyl-, 10-(o-nitrophenyl)-, 10-(p-nitrophenyl)-, 10-(p-nitrobenzyl)-, 10-(triphenylmethyl)-, 10-(o-bromobenzyl)-, 10-(2-pyridyl)- and 10-(2-quinolyl)phenothiazine. Only one of these, the preparation of 10-(o-bromobenzyl)phenothiazine, was successful using this technique. This was apparently produced in a good yield although the material was difficult to purify.

It is not too surprising that the 10-phenylphenothiazine failed to form in tetrahydrofuran since the halogen of iodobenzene is quite unreactive. However, it was believed that an activated halogen such as is present in o-iodo- or p-iodonitrobenzene and 2-bromopyridine would undergo displacement if this solvent had any large effect on the leaving group.

Apparently the greatest value of tetrahydrofuran lies in its ability to dissolve the reactants. Unlike ethyl bromide which remains molten in liquid ammonia and which gives a quantitative yield of 10-ethylphenothiazine, n-decylbromide and n-octadecylbromide are solids in this medium. Most of the reaction that takes place between the sodiophenothiazine and these halogen compounds must occur before solidification

takes place. This is borne out by the experiments in which ground (28 mesh) solid n-octadecyl bromide was added to sodiophenothiazine in liquid ammonia giving 4-6% of crude yield compared to a 17% crude or 12.9% pure yield when molten n-octadecyl bromide was added. If these halogen compounds, which are comparable in reactivity to ethyl bromide, were liquid in liquid ammonia a nearly quantitative yield of product would be predicted. Tetrahydrofuran shows excellent solvent action on both sodiophenothiazine and the n-decyl and n-octadecyl bromides enabling the reaction to take place readily.

Only one other solvent which was used for the solution of both the halogen compound and sodiophenothiazine was investigated. This was ether in the preparation of 10-(n-octadecyl)-phenothiazine. A much poorer crude product was obtained in this experiment than was obtained with tetrahydrofuran. The material was never purified but it is estimated that a 50-60% yield of pure material would have resulted. Sodiophenothiazine appears to have a lower solubility in ether than in tetrahydrofuran.

Using solvent combinations; liquid ammonia for the sodiophenothiazine and n-pentane, ether, tetrahydrofuran, or ethylene glycol dimethyl ether for the n-octadecyl bromide, some product was obtained, the pentane-ammonia system showing

the lowest yield (6% crude) with the others giving approximately equal yields (40-50%).

Combinations of ether or tetrahydrofuran with ammonia gave high yields (60-80%) of the 10-(n-decyl)phenothiazine.

The superiority of these somewhat polar solvents over n-pentane may again be partially explained by the better solubility of the sodiophenothiazine in them.

N-Substituted phenothiazine-5-oxides

Several of the N-substituted phenothiazines that were prepared were oxidized to the monoxide with 30% hydrogen peroxide using a higher concentration of phenothiazine derivative in ethanol than had been used previously[30,31,125] giving higher yields. In some cases the concentration of hydrogen peroxide was also higher although in some of the previous work a higher ratio of hydrogen peroxide to unoxidized phenothiazine compound was used to no advantage.

Using a concentration (0.4 mole/liter) of 10-ethylphenothiazine three times that used by Champaigne[31] with a corresponding increase in the concentration of hydrogen peroxide (1.23 moles/liter), the sulfoxide was prepared consistently in yields above 95%. At the lower concentration, the yields were generally 85-90%. When using a concentration of 2.5 moles of hydrogen peroxide/liter with 0.11 mole/liter of

10-ethylphenothiazine, Nelson[30,125] obtained a mixture of the dioxide (15.5%) and the monoxide (62%) which were separated chromatographically using activated alumina.

All of these preparations were run at reflux.

10-(n-Octadecyl)phenothiazine-5-oxide was obtained in a 96% yield using a concentration of 0.1 mole/liter of 10-(n-octadecyl)phenothiazine with 0.3 mole/liter of hydrogen peroxide. Shirley,[36,53] in obtaining a 53% yield, used a concentration of 0.0183 mole/liter for the parent compound and 0.49 mole/liter for the hydrogen peroxide. However, this may not be a fair comparison since Shirley used a short reflux period followed by a 2-day standing period for this preparation, whereas the higher yield was obtained by the usual 5-hour reflux period.

10-Phenylphenothiazine-5-oxide was prepared in a quantitative yield using 0.15 mole/liter of 10-phenylphenothiazine and 0.49 mole/liter of hydrogen peroxide added as a 30% solution. A 71% yield of product was obtained by Shirley[36,53] using this same concentration of unoxidized compound but using twice the concentration of hydrogen peroxide. Again the conditions which he used were different, the reaction being carried out at reflux for a few minutes followed by a 2-day standing period instead of a 5-hour reflux period.

The other two monoxides that were prepared are new and were produced in high yield. The 10-(2-pyridyl)phenothiazine-

5-oxide was prepared in 93% crude yield using a concentration of 0.15 mole/liter of 10-(2-pyridyl)phenothiazine and 0.5 mole/liter of hydrogen peroxide while 10-(n-decyl)phenothiazine-5-oxide was obtained in a 90% yield using a concentration of 0.05 mole/liter and 0.41 mole/liter for the unoxidized compound and hydrogen peroxide, respectively. When 10-(n-decyl)-phenothiazine-5-oxide was prepared using three times these concentrations of reactants, a yield of 93-98% was obtained.

Using the older technique it was customary to pour the reaction mass into excess cold water as a method of isolation. It was found that a better crystal form and purer crude product could be obtained by previously heating the water to 80° before carrying out this operation.

N-Substituted phenothiazine-5,5-dioxides

Most of the sulfones were prepared using the procedure for the preparation of 10-ethylphenothiazine-5,5-dioxide established by Nelson[30] in which a concentration of 0.172 mole/liter of unoxidized compound in glacial acetic acid was treated with 0.52 mole/liter of hydrogen peroxide, added as a 30% solution, at 80° for 1.5 hours followed by an additional 0.157 mole/liter (usually) of hydrogen peroxide, reduction in volume of the solvent and cooling to isolate the product. The 10-ethyl-, 10-phenyl-, 10-(n-decyl)- and 10-(n-octadecyl)-

phenothiazine-5,5-dioxides were prepared in yields of 70%, 87%, 65-73% and 91% in that order.

The 10-(2-pyridyl)phenothiazine was oxidized under the conditions employed by Ochiai[163] for the preparation of pyridine-1-oxide. The infrared spectrum indicated the sulfone group and also had a sharp band at 12 which was believed to be due to the N-oxide since this band was not present in the spectra of 10-(2-pyridyl)phenothiazine or its sulfoxide. The sulfur analysis substantiated the trioxide structure. When this trioxide was treated with iron in hot (100°) glacial acetic acid a new compound was formed which still retained the sulfone group as determined by the infrared spectrum but which no longer had the band at 12 . This compound was thus believed to be 10-(2-pyridyl)phenothiazine-5,5-dioxide. The quantitative sulfur analysis matched the calculated value for this structure.

N-Substituted phenothiazines with nuclear substituents

The reductive halogenation of 10-ethylphenothiazine using either hydrochloric acid or hydrobromic acid was carried out by an established procedure[131] with comparable results being obtained. This technique was extended to the preparation of 3-chloro-10-(n-decyl)phenothiazine from 10-(n-decyl)phenothiazine-5-oxide. The success achieved in this synthesis was

rather limited with difficulty being experienced in the purification of the compound. However, the fact that reduction had occurred with halogenation was established by qualitative analysis and the infrared spectrum. The purification trouble probably is not too surprising considering that the simpler molecule, 3-bromo-10-ethylphenothiazine, is also somewhat difficult to get in the pure form.

10-Ethylphenothiazine-4-carboxylic acid was prepared by a known procedure[37,122] with the material being obtained in yield and quality equal to that which has been reported. This same procedure was utilized in the preparation of 10-(n-decyl)-phenothiazine-4-carboxylic acid using 10-(n-decyl)phenothiazine-5-oxide as the starting material. The yield of acid which was produced was somewhat lower than the yield of the 10-ethyl acid (36% vs. 55%). However, since only one experiment was run it is uncertain whether this lower yield is the maximum for the reaction or not.

Metalation of 10-ethylphenothiazine-5-oxide proceeds to the extent of 50-60% as determined by carbonation and hydrolysis to the acid. This metalation is carried out at -20° to 0°. In contrast to this, metalation of 10-ethylphenothiazine at the temperature of refluxing ether proceeds to the extent of only 10-20% as also determined by carbonation to the acid.[31] When using the monoxide as the starting material it has been noted that reduction possibly takes place prior to metalation

this being based on a negative reaction of Color Test I[165] after the first equivalent of n-butyllithium[155] has been added. If this is the case, metalation of 10-ethylphenothiazine may actually be taking place in the presence of some material such as lithium butoxide which could form during the reduction. The use of n-butyl alcohol which would form lithium butoxide in the presence of n-butyllithium was investigated as a catalyst in the metalation of 10-ethylphenothiazine using the conditions that are normally used for the metalation of the oxide. A control experiment was carried out at the same time but neither attempt gave any acid upon carbonation. Evidently some complex intermediate structure accounts for the high metalation yield of 10-ethylphenothiazine-5-oxide.

Despite the good yield of carboxylic acid that can be obtained from the 4-lithio-10-ethylphenothiazine, the attempted conversion to the corresponding boronic acid derivative by reaction with tri-n-butyl borate at -70° was unsuccessful. Starting with 3-lithio-10-ethylphenothiazine, prepared by a halogen-metal interconversion of the 3-bromo derivative, no boronic acid was formed either. Other sulfur- or oxygen-containing heterocyclic compounds have had boronic acid derivatives prepared of them in good yields. These compounds also appear to be quite stable. Both 2-thiopheneboronic

acid[143,181] and 2-furanboronic acid[143] were prepared from the corresponding Grignard reagent and trimethyl borate while 1-thianthreneboronic acid,[148] 2-thianthrene boronic acid,[147] 4-dibenzothiopheneboronic acid,[149] 4-dibenzofuranboronic acid[156] and dibenzo-p-dioxin-1-boronic acid[182] have all been prepared in good yields from the corresponding lithium compound and tri-n-butyl borate. In contrast to this are the nitrogen-containing heterocyclic compounds which do not seem to form stable boronic acid derivatives easily. Only one of these, the 9-ethylcarbazole-3-boronic acid, has been reported.[183] This was prepared in a yield of less than 5%. The preparation of 9-ethylcarbazole-1-boronic acid was also attempted[183] but no boronic acid was obtained.

Based on the negative Color Test I[165] taken immediately after reacting the 3-lithio- or 4-lithio-10-ethylphenothiazine with tri-n-butyl borate, both reactions took place. However, all that was isolated in either experiment was a gummy product which was insoluble in ether and acid. This was assumed to be something other than 10-ethylphenothiazine based on its poor ether solubility, but material isolated from the purification

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[181]E. Krause and G. Renwanz, Ber., 65, 777 (1932).

[182]J. J. Dietrich, unpublished studies, Iowa State College (1957).

[183]J. B. Honeycutt, Doctoral Dissertation, Iowa State College (1956).

of the gum from the attempted preparation of the 4-boronic acid was identified as 10-ethylphenothiazine. This could have resulted from decomposition of the gummy material.

The basic character of the nitrogen must affect the formation of phenothiazineboronic acids adversely.

In the attempted formation of the 3- and 4-triphenylsilyl-10-ethyl phenothiazines, none of the desired products were isolated. Based on Color Test I[165], which became negative, it is believed that the reactions occur and that an adequate purification technique is all that is needed to obtain these compounds. In both attempts, hexaphenyldisiloxane was isolated. Where triphenylsilylpotassium was used, the method of formation of the disiloxane is rather difficult to interpret although its presence is not unusual, being a common by-product of reactions utilizing triphenylsilylpotassium. Triphenylsilane may first form by hydrolysis followed by a nucleophilic attack on the silicon by hydroxide ion to form triphenylsilanol. This would then, by intermolecular dehydration, form hexaphenyldisiloxane. When using triphenylchlorosilane, the formation of hexaphenyldisiloxane is more reasonable, nucleophilic attack of the silicon forming the silanol which by the same intermolecular dehydration would give the hexaphenyldisiloxane.

Phenothiazine derivatives as scintillators

Several of the phenothiazine derivatives that were prepared have been tested[184] as liquid solution scintillator[29] against a solution of 3.0 g./liter of 2,5-diphenyloxazole in toluene which has been assigned an arbitrary value of 1.00 (pulse height). The following phenothiazine derivatives all gave a value of less than 0.12 which is the minimum that can be measured: 10-(o-tolyl)-,[30,107] 10-phenyl-, 10-allyl-, 10-(2-pyridyl)phenothiazine and p-bis(10-phenothiazinyl)benzene; 10-phenylphenothiazine-5-oxide and -5,5-dioxide; and 10-(2-pyridyl)phenothiazine-5-oxide, -5,5-dioxide and -1',5,5-trioxide. Other similar structures that can be compared with these are the corresponding derivatives of carbazole, phenoxazine and possibly fluorene. In the carbazole series, the following results were obtained: 9-phenyl- (0.24), 9-(p-biphenylyl)- (0.35), 9-(2-pyridyl)- (0.20), and 9-(2-quinolyl)carbazole (0.14); p-bis(9-carbazolyl)benzene (0.27) and p,p'-bis(9-carbazolyl)biphenyl (0.93). Both 10-phenyl phenoxazine and p-bis(10-phenoxazyl)benzene showed values of less than 0.12 while 9-phenylfluorene and 9,9-diphenylfluorene had values of 0.18 and 0.14, respectively. The 10-(2-quinolyl)- and

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[184]Evaluation of the compounds for this purpose were made by Drs. Wright R. Langham, F. N. Hayes and D. G. Ott of the Los Alamos Laboratories.

10-(p-biphenylyl)phenothiazine and p,p'-bis(10-phenothiazinyl)-biphenyl have not been tested as yet. The unsubstituted compounds in this series all show values of 0.12 or less.

Studies to date[29] show that the better scintillators are made up of aromatic rings linked in a linear fashion to allow continuous conjugation throughout the molecule with some heterocyclic systems such as furan, oxazole, pyridine, pyrrole, indole and benzoxazole being beneficial and thiophene, thiazole and benzothiazole generally being of little value. The best scintillator found to date using a concentration of 3 g./liter is 2-phenyl-5-(4-biphenylyl)-1,3,4-oxadiazole with a value of 1.20. However, other compounds run at higher concentrations may show values greater than this.

Honeycutt[183] has discussed some of the relative values of phenothiazine, carbazole and fluorene as possible scintillators. From the results that are listed above it appears that N-substituted carbazoles have some potential while the other ring systems, including phenothiazine, have little possibilities.

An increase in scintillation activity in the carbazole series was noted in going from 9-phenyl- (0.24) to the 9-(p-biphenylyl)- (0.35) with the p-bis(9-carbazolyl)benzene being intermediate at 0.27. A big jump was noted in the p,p'-bis-(9-carbazolyl)biphenyl which had a value of 0.93. Whether such an increase will be noted in the phenothiazine and phen-

oxazine series awaits the testing of some of these compounds in the two series. Since there was little difference between the phenyl derivatives and p-bis(heterocycle)benzenes in each of the three series there is some possibility that p,p'-bis-(10-phenothiazinyl)biphenyl and p,p'-bis(10-phenoxazyl)biphenyl will show fair scintillation activity.

On the basis that sulfur-containing rings affect scintillation activity adversely and oxygen- and nitrogen-containing rings are beneficial, it was predicted[183] that 10-phenylphenoxazine would be a better scintillator than 10-phenylphenothiazine. However, this was not the case, both showing the minimum activity. The prediction[183] that it would not be as good as 9-phenylcarbazole was correct, this being attributed to the intact biphenylyl structure in 9-phenylcarbazole which is absent in 10-phenylphenoxazine.

From this it can be seen that still only general correlations can be made in predicting scintillation activity from structure and that a more specific structure-scintillation activity correlation awaits the testing of additional compounds.

## Boron Derivatives

### Simple boronic acids

All of the boronic acid derivatives, except the 1-butaneboronic acid, were prepared by treating the corresponding

lithium compound with tri-n-butyl borate at -70°. This low temperature is used to prevent, or keep to a minimum, the formation of any borinic acid, a compound in which two -OH groups of boric acid have been replaced with organic radicals. The technique of using organolithium compounds for this type of preparation is quite new being extensively investigated for the first time by Goodman[145] for the preparation of benzeneboronic acid. Abbott[170] has prepared p-dimethylaminobenzeneboronic acid previously from p-dimethylaminophenyllithium. This technique makes possible the preparation of compounds such as the hydroxybenzeneboronic acid isomers that would not be feasible by the usual Grignard method. In other instances it provides an easier method to obtain the desired product.

The attempt to make 1-butaneboronic acid by treating n-butyllithium[155] with trimethyl borate was unsuccessful probably due mainly to insufficient technique used in the isolation. Aliphatic boronic acids are much more unstable to atmospheric conditions than aromatic boronic acids and decomposition may have resulted in this case. It should be possible to prepare 1-butaneboronic acid from the lithium compound. The preparation using the Grignard reagent was as successful as that reported in the literature.[144]

o-Hydroxybenzeneboronic acid anhydride was first prepared by Swayampati[146,148] from o-bromophenol using two equivalents of n-butyllithium[155] and subsequent reaction with tri-n-butyl

borate. He obtained the product in a yield of 55%. When the hydroxy group of o-bromophenol was protected with dihydropyran to give 2-(o-bromophenoxy)tetrahydropyran and this treated with one equivalent of n-butyllithium[155] and tri-n-butyl borate in the usual way, a comparable yield was obtained. The product was isolated in each of these experiments by extraction with base followed by acidification of the extract.

m-Hydroxybenzeneboronic acid was made previously[26,151] by a different method. This involved the formation of m-nitrobenzeneboronic acid by nitration of benzeneboronic acid, reduction to the amino compound, diazotization and finally hydrolysis. The yield in this last step was 34%. Starting with m-bromophenol, and using the standard n-butyllithium treatment followed by reaction with tri-n-butyl borate, a 33% yield of m-hydroxybenzene boronic acid anhydride was obtained. This compound could not be isolated by acidification of a basic extract because of its high water solubility. Isolation was accomplished by evaporation of the ether layer to dryness after a series of extractions to remove a large portion of the boric acid and n-butyl alcohol. The attempt to prepare the compound using 2-(m-bromophenoxy)tetrahydropyran as the starting material failed.

The para isomer has also been prepared in a yield of 40% starting with p-bromophenol using the same procedure as was used for the other isomers.[146] It was also necessary to

isolate this by concentration of an ether extract because of the high water solubility of the compound.

When using 2-(p-bromophenoxy)tetrahydropyran as the starting material and treating it with n-butyllithium, 2-hydroxy-5-bromobenzeneboronic acid was isolated.[147]

In this series, the ortho isomer exists only as the anhydride, coming out in this form even upon recrystallization from water, whereas the para isomer crystallized as the acid from an acetone-water system and resisted complete conversion to the anhydride even upon prolonged heating in a vacuum oven at 75°. The meta isomer crystallized as the anhydride from ethylene chloride. Its stability as an acid was not investigated.

p-Dimethylaminobenzeneboronic acid anhydride was prepared in a yield lower than that reported by Abbott[170] (30% vs. 62%) and having a different melting point (235-270° vs. 243-245°). Also the material crystallized as the anhydride from ethylene chloride while the material prepared by Abbott was isolated from an aqueous medium and was reported as the acid.

A few dialkylamino aromatic boronic acids have been reported[26,142] and difficulty has been experienced by other workers in obtaining or purifying them. For example, Snyder and Weaver[26] reported their inability to find a satisfactory solvent or solvent mixture for m-diethylaminobenzeneboronic acid. Snyder and Wyman[142] reported the preparation of

4-dimethylamino-1-naphthaleneboronic acid which they stored as the crude hydrochloride and purified by two reprecipitations from water by the dropwise addition of base. They noted the ease of deboronation of this compound.

König and Scharrnbeck[152] attempted the preparation of o-dimethylaminobenzeneboronic acid but the only products which they were able to isolate were dimethylaniline and boric acid which would result from the hydrolysis of the compound which they expected. This attempted preparation was done by treating the Grignard reagent with a borate ester.

In the experiment reported in this thesis for the preparation of o-dimethylaminobenzeneboronic acid, the lithium compound was treated with tri-n-butyl borate with apparent reaction as judged by the negative Color Test I[165]. However, the resulting compound also seems to have decomposed on hydrolysis, the only compound which was isolated being identified tentatively as a complex between boric acid and dimethylaniline. Such a complex is quite possible considering the method of isolation which was used for the compound.

The preparation of 2-hydroxy-6-naphthaleneboronic acid was carried out without incident, but the purification difficulties followed closely those of other naphthaleneboronic acids. Decomposition seems to occur during recrystallization and it was never possible to get a pure white product.

Yabroff, Branch, and Bettman[185] noted the decomposition of α- and β-naphthaleneboronic acid in hot water while Soddy[186] had some difficulty in purifying 1-hydroxy-5-naphthaleneboronic acid, never being able to get a white product.

It has been observed in this work on boronic acids as well as by other workers[147] that melting points are generally characterized by wide ranges, and occasionally by poor reproducibility. This was quite evident in the p-dimethylaminobenzeneboronic acid anhydride and especially in the o-hydroxybenzeneboronic acid anhydride which had melting points varying from a range of 170-175° to a sharp melting point of 193-194°. The melting point which was obtained depended largely upon the solvent used for recrystallization. Despite the differences in melting point all of the material was of the same purity as judged by the neutralization equivalent.

Azo boronic acids

The azo boronic acids were prepared by coupling o-hydroxybenzeneboronic acid anhydride with a suitable diazonium salt using procedures similar to those used for non-boron containing

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[185] D. L. Yabroff, G. E. K. Branch and B. Bettman, J. Am. Chem. Soc., 56, 1850 (1934).

[186] T. S. Soddy, unpublished studies, Iowa State College (1956).

compounds. In contrast to the high yield (90-100%) generally obtained with the non-boron analogs, low yields (20-30%) were obtained on the boron compounds. This may be attributed partially to the deactivating influence of the boronic acid group making o-hydroxybenzeneboronic acid anhydride a poorer coupling entity than phenol.

Another reason for the low yields may be attributed to decomposition during purification. Purification was difficult, very few solvents being suitable for recrystallization and chromatographic purification being considered inadequate as far as it was studied. Only partial purification could be attained using an ethanol-water system for recrystallization, a solvent combination which was used somewhat successfully in dyes prepared from m-aminobenzeneboronic acid and m-hydroxybenzeneboronic acid.[26] Benzene was only partially successful as a recrystallizing solvent also. Even though ethylene chloride cannot be considered a good recrystallizing solvent for this type of compound based on the differential solubility between the hot and the cold solvent, it did give pure compounds. Solubilities of the dyes which were purified using this solvent ranged from 0.75 to 1.5 g./liter making it possible to crystallize only a small amount of material from a large volume of solvent.

Although the infrared spectra were used as a partial means of identification of these azo boronic acids as well

as the simple boronic acids, little is known about absorption bands which may be attributed to the boronic acid group. In a study made of several aromatic boronic acids it was observed that a band at 9.1-9.2$\mu$ may be indicative of the C-B bond.

Cleavage reactions of aromatic boronic acids with n-butyllithium

The first cleavage of an aromatic boronic acid with n-butyllithium was accomplished by Santucci.[147] In an attempt to perform a halogen metal interconversion on 2-hydroxy-5-bromobenzeneboronic acid he obtained 5-bromosalicylic acid, and 1-butaneboronic acid on carbonation of a mixture that was refluxed in ether for 18 minutes using 5 equivalents of n-butyllithium[155] for each equivalent of boronic acid. When a 1.5 hour reflux period was used, the products which were isolated were 5-bromosalicylic acid, p-hydroxybenzoic acid and 1-butaneboronic acid. No mechanism was postulated for this because of insufficient data.

In order to gain additional information on the cleavage of aromatic boronic acids with n-butyllithium, the cleavage of benzeneboronic acid and o-hydroxybenzeneboronic acid anhydride were studied to a small extent, carbonation being carried out to terminate the reactions. In the cleavage of benzeneboronic

acid at reflux temperature for a period of 1.5 hours using five equivalents of n-butyllithium no products other than those originating from n-butyllithium such as valeric acid and di-n-butyl ketone could be isolated. When run at either reflux or room temperature for a period of 20 minutes with three equivalents of n-butyllithium, 1-butaneboronic acid was isolated as well as benzene. These products would correspond to the p-hydroxybenzoic acid and 1-butaneboronic acid isolated by Santucci using a 1.5 hour reflux time. When the benzeneboronic acid was treated with n-butyllithium at -60° for a period of 25 minutes and then carbonated, benzoic acid was isolated as well as a high melting unidentified material. No 1-butaneboronic acid was isolated. This experiment would correspond to Santucci's 18-minute experiment in which he isolated 5-bromosalicylic acid.

From this it appears that cleavage of benzeneboronic acid is more easily accomplished than cleavage of 2-hydroxy-5-bromobenzeneboronic acid since comparable products were obtained at a lower temperature with benzeneboronic acid than with the 2-hydroxy-5-bromobenzeneboronic acid. This latter compound gave products after 1.5 hours at reflux, whereas the former gave nothing resembling benzene, benzoic acid or 1-butaneboronic acid under similar conditions, possibly indicating complete decomposition. These experiments also show that under the milder conditions, a lithium atom presumably

replaces the boronic acid group which gives the carboxylic acid on carbonation, while under more severe conditions the boronic acid group is replaced with a hydrogen. However, this could result from hydrolysis of the lithium compound prior to carbonation.

In the single experiment that was carried out with o-hydroxybenzene boronic acid anhydride, salicylic acid, but no 1-butaneboronic acid was obtained. This was carried out at room temperature using 3 equivalents of n-butyllithium. On the basis of the experiments discussed above it is predicted that if this reaction were run at a higher temperature, phenol and 1-butaneboronic acid would be isolated.

Although there seems to be some correlation between these experiments there is still insufficient data to postulate a mechanism. It appears, however, that different mechanisms may exist at different temperatures. It is possible though that in each case the boronic acid group is being replaced with a hydrogen and that any carboxylic acid that results upon carbonation arises from the metalation of the position ortho to the hydroxy group or meta to the boronic acid group in the case of 2-hydroxy-5-bromobenzeneboronic acid and o-hydroxybenzeneboronic acid anhydride. This would not, however, account for the formation of benzoic acid from benzeneboronic acid, since this molecule would not likely metalate in any position.

Organoboron compounds in brain tumor therapy

The use of organoboron compounds in brain tumor therapy is relatively new, having been initiated in 1940 by Kruger.[23,24] This therapy is of a nuclear disintegration type in which boron (atomic weight 10) contained in a compound such as borax or a boronic acid is bombarded with slow neutrons giving off alpha particles according to the following equation.

$$_5B^{10} + {}_0n^1 \longrightarrow {}_3Li^7 + {}_2He^4 + 2.79 \text{ mev.}$$

This treatment tends to destroy any tissue, normal or abnormal, into which the boron compound has been injected. Any surrounding tissue which does not contain boron remains unaffected since the disintegration products have short ranges, 4$\mu$ to 7$\mu$.

Borax containing the boron isotope 10 has been studied the most extensively but this compound has certain disadvantages in that the differential uptake of the compound between cancerous and healthy tissue is low, being of the order of 2, and also the compound is not retained very long by the tissue. The few dyes[26,27] that have been tested show certain advantages over borax in that the takeup is more rapid, they are retained for a much longer period of time and are taken up preferentially by the cancerous tissue soon after injection,

the differential uptake between the cancerous and normal tissue being of the order of 100. Unfortunately, the dyes have certain disadvantages in that they eventually tend to color the whole body and may be taken up later by the heart, liver, kidneys, etc. This color is gradually excreted, however. Some non-boron azo dyes are also known to be carcinogenic to the liver[187] and it is not yet known how these azo boron dyes will behave in this respect. However, there are certain groups such as the bromo, hydroxy, nitro and trifluoromethyl which are known to reduce the carcinogenic activity of azo dyes.

Even though boron-containing azo dyes seems to show advantages over borax and possibly other boron containing compounds, the investigation of these other boron compounds has not been eliminated. These would have an advantage over the dyes in that they would not color the whole system. Several of the boronic acids and azo boronic acids that were prepared have been submitted for testing[188] but no results are available as yet.

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[187] J. P. Greenstein, "Biochemistry of Cancer," 2nd Ed., Academic Press, New York, N. Y., 1954.

[188] This testing is being carried out by the Brookhaven National Laboratory. The results will be reported by Dr. Otho D. Easterday of the Medical Department, Physiology Division.

There is some question as to whether the boron trifluoride complexes that were prepared would be suitable for testing in this work. Due to the rapid hydrolysis of the complex formed between 10-ethylphenothiazine and boron trifluoride it would probably be unsuitable. However, the complex formed between 10-(2-pyridyl)phenothiazine and boron trifluoride was stable enough to be recrystallized from ethanol and appears to have undergone hydrolysis at a slow enough rate in water making consideration of this compound worthwhile. Even if hydrolysis did occur after injection it could possibly prove useful.

## Suggestions for Future Research

Since two of the primary purposes or considerations of this work were the preparation of a phenothiazineboronic acid and a phenothiazine derivative containing both boron and an azo group, further effort should be expended toward this goal. For the preparation of a boronic acid derivative of phenothiazine, an approach could be through an N-phenyl or N-benzyl derivative such as 10-(p-bromophenyl)phenothiazine or 10-(o-bromobenzyl)phenothiazine. In such molecules as this, the boronic acid group would be attached to a single benzene ring instead of the heterocyclic nucleus, and would quite possibly

be more stable than a nuclear substituted boronic acid derivative of phenothiazine.

For the preparation of azo boronic acids, a somewhat similar approach could be used. Derivatives like 10-(p-nitrophenyl)phenothiazine and 10-(p-nitrobenzyl)phenothiazine could be reduced, diazotized and coupled with o-hydroxybenzeneboronic acid anhydride. The use of 3-amino-10-ethylphenothiazine has been considered as a possible approach to the desired compound, but this starting material is quite unstable and difficult to prepare.

Additional organoboron compounds and azo boronic acids should be synthesized with some emphasis being placed on the more water soluble compounds so that some comparison can be obtained concerning the relative value of these with the more insoluble compounds in brain tumor therapy. A majority of the simple boronic acids and all of the dyes that have been submitted for testing are water insoluble or at the most, slightly soluble. The p-(3-borono-4-hydroxyphenylazo)benzenesulfonic acid is a compound of the water soluble type but it apparently could not be obtained in a pure form, unless the material has crystallized as a hydrate. Hydrates have been postulated on other dyes[27] but this was based only on the analysis. The actual existence of such compounds could be studied.

In the synthesis of other azo boron dyes, the groups which are known to decrease the carcinogenic activity of the compound should be incorporated for complete study. A true course of research in this brain tumor therapy study, however, awaits the results of some of the compounds which are currently being tested.

The cleavage study of aromatic boronic acids remains to be completed since the data collected from the reactions that have been run does not seem to be sufficient to postulate a course for the reaction. This may involve quite an extensive study as the products which are formed seem to be dependent on the temperature of the reaction. They could also be dependent on the time of the reaction and to the additional groups attached to the ring. Cleavages in solvents other than ether, both a more polar and a less polar, might be of interest.

# SUMMARY

A history of the N-substitution reactions of phenothiazine has been presented with special emphasis being placed on the 5-year period from 1952 through 1956. A table of the N-substituted compounds prepared during this time has been included.

A brief history of the chemistry of organoboronic acids has also been presented.

Several new N-substituted phenothiazines, their sulfoxides and sulfones, were prepared for testing as liquid solution scintillators and for general physiological screening. The results of the scintillator testing has indicated that derivatives containing the phenothiazine nucleus will probably have low scintillation activity.

In the preparation of these compounds it was found that tetrahydrofuran is a good solvent for some N-alkylations.

N-alkylations run in liquid ammonia at high concentrations were found to be superior to those run at lower concentrations, a higher yield of material generally being obtained.

The use of increased concentration for the preparation of several N-substituted phenothiazine-5-oxides was found to give a superior yield to preparations made at lower concentrations.

Several new aromatic boronic acids and azo boronic acids were synthesized for study in brain tumor therapy. The results of the biological activity of these compounds are not yet available.

ACKNOWLEDGEMENTS

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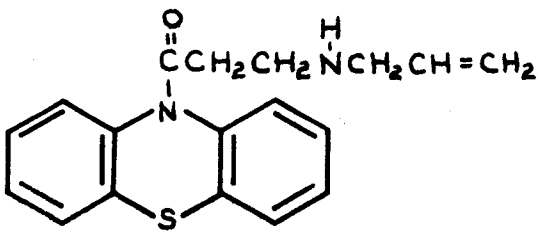
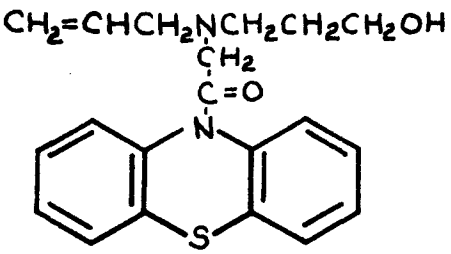
Thanks are also due to the Division of Biology and Medicine of the United States Atomic Energy Commission whose financial assistance has made some of this work possible.

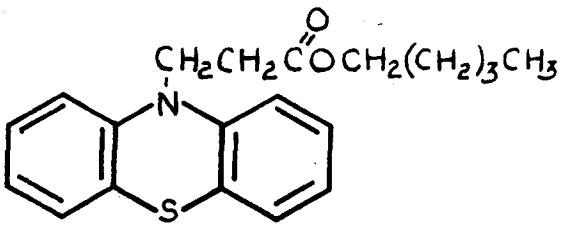
# APPENDIX



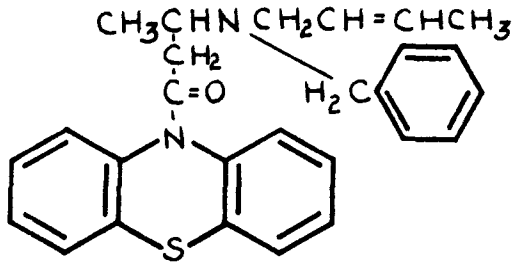
a. 10-(β-Allylaminopropionyl)phenothiazine



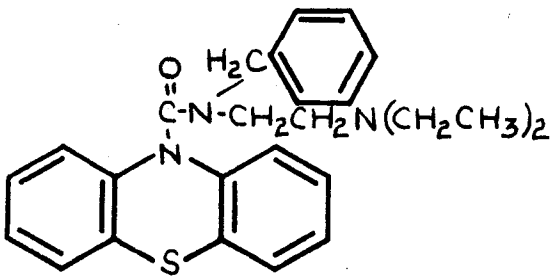
b. 3-[Allyl-(10-phenothiazinylcarbonylmethyl)-amino]-1-propanol



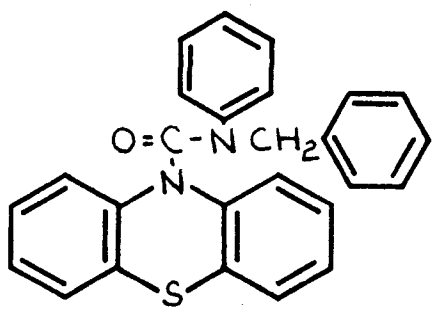
c. n-Amyl β-(10-phenothiazinyl)propionate



d. 10-[β-(Benzyl-2-butenyl-amino)butyryl]phenothiazine

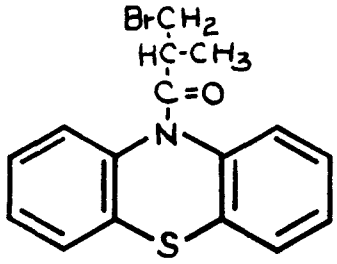


e. N-Benzyl-N-(2-diethylaminoethyl)-10-phenothiazinecarboxamide

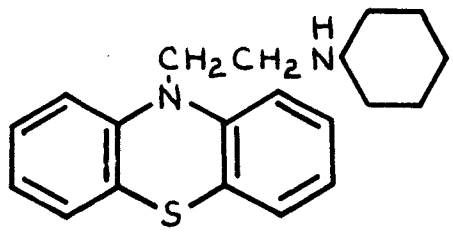


f. N-Benzyl-10-phenothiazinecarboxanilide

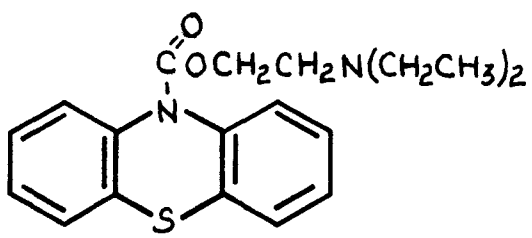
Figure 1. Some N-substituted phenothiazine derivatives



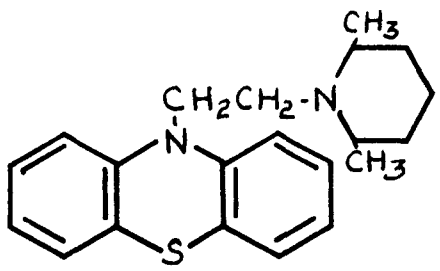
g. 10-(β-Bromoisobutyryl)-phenothiazine



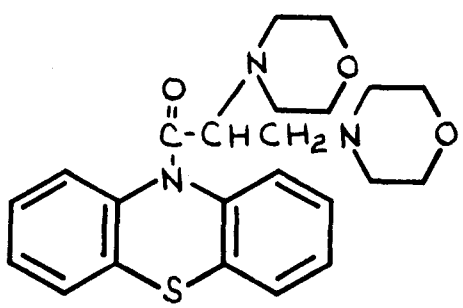
h. 10-[2-(Cyclohexylamino)-ethyl]phenothiazine



i. 2-Diethylaminoethyl 10-phenothiazine-carboxylate

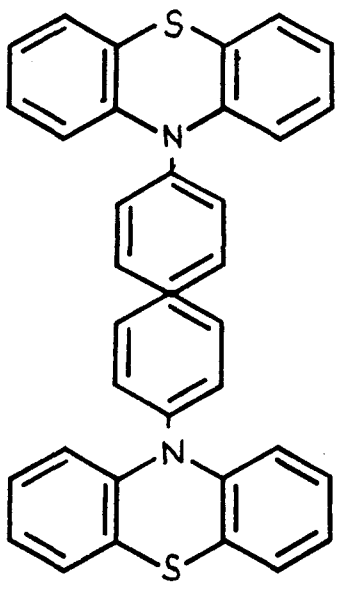


J. 10-[2-(2,6-Dimethyl-1-piperidyl)ethyl] phenothiazine

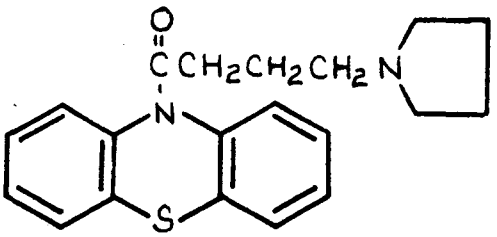


K. 10-[α,β-Di(4-morpholinyl)-propionyl]phenothiazine

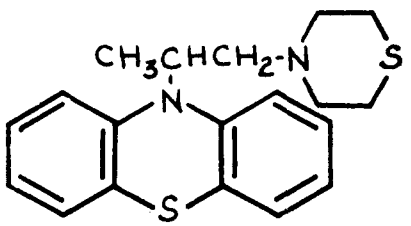
Figure 1. (Continued)



l. p,p'-Bis(10-phenothiazinyl)biphenyl

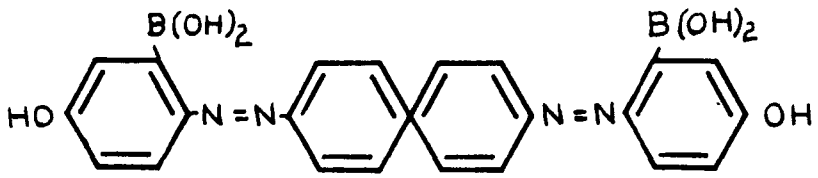


m. 10-[γ-(1-Pyrrolidinyl)-butyryl]phenothiazine

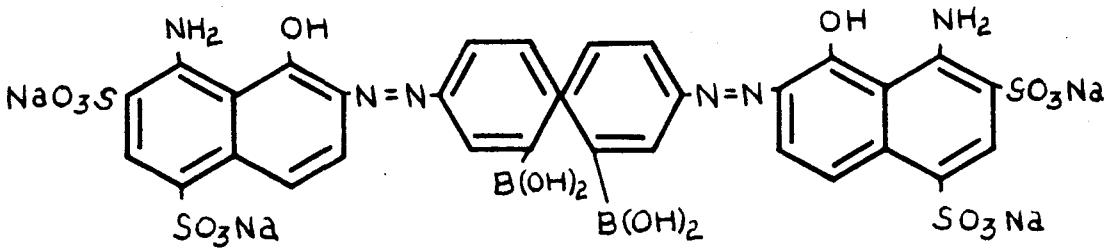


n. 10-[2-(4-Thiamorpholinyl)isopropyl]-phenothiazine

Figure 1. (Continued)

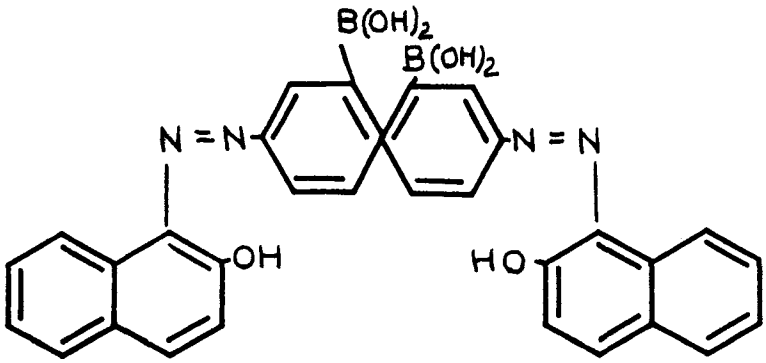



a. 2,2'-(4,4'-Biphenylenebisazo)bis(5-hydroxybenzeneboronic acid

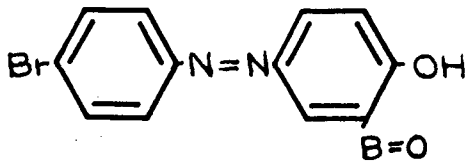



b. 4,4'-Bis(8-amino-1-hydroxy-5,7-disulfo-2-naphthylazo-2,2'-biphenyldiboronic acid, Tetra-Sodium Salt

**Figure 2. Some azo boronic acids**




c. 4,4'-Bis(2-hydroxy-1-naphthylazo)-2,2'-biphenyldiboronic acid




d. 2-Hydroxy-5-(p-bromophenylazo)benzeneboronic acid anhydride

Figure 2. (Continued)