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Some derivatives of phenothiazine

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NOTE TO USERS

SOME DERIVATIVES OF PHENOTHIAZINE

by

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I. INTRODUCTION

The earliest studies on the physiological action of the phenothiazine derivative methylene blue, by Guttmann and Ehrlich,[1] showed that this compound had a specific action in human malaria. Not until forty-three years later was it discovered, in connection with the investigation of the toxicity of organic sulfur compounds to mosquito larvae,[2] that phenothiazine possessed insecticidal properties. Additional research later revealed that phenothiazine itself is also useful as a larvicide, fungicide, bactericide, parasiticide, urinary antiseptic, anthelmintic agent and an antioxidant. In contrast to its high toxicity to lower forms of life, phenothiazine possesses a low toxicity to man and other higher forms of animal life. These discoveries, as well as its low cost of production, make phenothiazine a very useful compound.

Currently, considerable interest is shown in phenothiazine derivatives because of the discovery by Halpern,[3,4]

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[1] P. Guttmann and P. Ehrlich, Berlin. klin. Wochschr., 28, 593 (1891), /Chem. Zentr., 63, I, 221 (1892)/.

[2] F. L. Campbell, W. N. Sullivan, L. E. Smith and H. L. Haller, J. Econ. Entomol., 27, 1176 (1934).

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

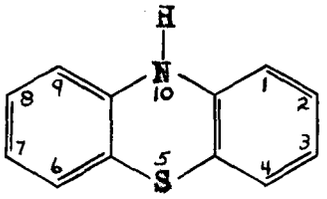
[4] B. N. Halpern, J. Allergy, 18, 263 (1947).

that certain 10-(dialkylaminoalkyl)phenothiazines are very active antihistaminic agents possessing a low degree of toxicity toward the host. A number of these derivatives also exhibit antianaphylactic, local anesthetic, anticonvulsant and antinicotinic action. A more detailed discussion of these properties will be given in a later section of this dissertation.

The purpose of this investigation has been: (1) to study further the metalation of phenothiazine derivatives with the view in mind to use this reaction as a means to introduce various substituents into the benzene nuclei; (2) to modify the structure of certain dialkylaminoalkyl derivatives and thereby compare the effect of changing the molecular structure on the physiological properties; (3) to extend the application of sodamide as a condensing agent in the preparation of 10-substituted phenothiazines; (4) to prepare various 10-acyl derivatives; and (5) to develop satisfactory methods to oxidize the sulfide linkage of the various derivatives to the sulfoxide and the sulfone, respectively.

II. HISTORICAL

A study of the chemistry of phenothiazine and its derivatives was initiated in 1883 by August Bernthsen[5] who suspected that the phenothiazine nucleus was present in methylene blue. In his series of experiments, he successfully determined the structure of both methylene blue and phenothiazine; the latter is given below with the numbering system in current use by Chemical Abstracts.



The synonym of phenothiazine, thiodiphenylamine, was used in the early papers on this compound and also appears occasionally in the current literature.

Meyer and Jacobson[6] in their "Lehrbuch" presented a summary of the chemistry of phenothiazine in respect to its

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

[6] V. Meyer and P. Jacobson, "Lehrbuch der organischen Chemie", Vol. 2, Part 3, Veit and Co., Leipzig, 1920, p. 1490.

connection with methylene blue. A review of the substitution reactions has been given by Van Ess.[7] Shirley[8] briefly summarized these substitution reactions and presented a review on the chemotherapy of phenothiazine and its derivatives. Two other reviews are given on the chemistry of phenothiazine; however, they are not readily accessible. The one periodical[9] is not received by the Iowa State College Library and the other[10] is at present missing from the Library files.

In the historical section of this dissertation, an attempt has been made to completely review the chemistry of phenothiazine and its derivatives since 1933 with the exception of the derivatives of methylene blue and benzophenothiazine. However, some of the earlier work will be included as well, in order to try to give a complete picture of the chemistry of phenothiazine up to the middle of 1951.

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[7]P. R. Van Ess, Doctoral Dissertation, Iowa State College (1936).

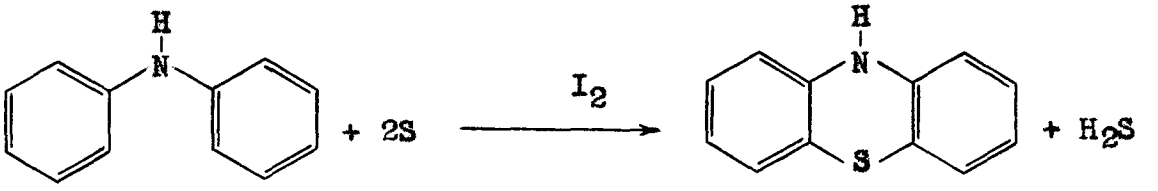
[8]D. A. Shirley, Doctoral Dissertation, Iowa State College (1943).

[9]E. C. Beeler, Bull. Natl. Formulary Comm., 10, 84 (1942), [C. A., 36, 5318 (1942)].

[10]R. L. Metcalf, Chem. Biol. Coordination Center, Natl. Research Council, Washington, D. C., Rev. No. 1, 84 pp. (1948), [C. A., 43, 5146 (1949)].

A. Ring Closure Reactions

Phenothiazine was first prepared in rather poor yield by Bernthsen,[5] by heating together sulfur and diphenylamine at 200-230°. This thionation reaction was greatly improved with the discovery[11,12] that the presence of 1% iodine gave an almost quantitative yield of phenothiazine, as well as reducing the temperature and time necessary for the reaction.



The application of iodine as a catalyst in the reaction was further demonstrated[12,13] by applying the method to the preparation of some benzophenothiazines.

A number of mono- and disubstituted phenothiazines have been prepared by fusing the appropriate diphenylamine with an equivalent amount of sulfur using iodine as a catalyst. Phenothiazone-3[14,15] was prepared by aeration of the

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

[12] E. Knoevenagel, J. prakt. Chem., 89 (2), 1 (1914).

[13] F. Kehrmann and J. H. Dardel, Ber., 55B, 2346 (1922).

[14] S.C.J. Olivier and W. P. Combe, Rec. trav. chem., 69, 526 (1950).

[15] D. F. Houston, E. B. Kester and F. DeEds, J. Am. Chem. Soc., 71, 3816 (1949).

resulting crude 3-hydroxyphenothiazine from the iodine catalyzed thionation of p-hydroxydiphenylamine. These two papers[14,15] also list references of earlier methods for preparing phenothiazone-3. p-Methoxydiphenylamine was cyclized to 3-methoxyphenothiazine,[16] using sulfur and iodine, in a higher yield than that reported by earlier workers.[17] A number of long chain alkyl ethers of 3-hydroxyphenothiazine were prepared in 80-84% yield by the action of sulfur on the corresponding 4-alkoxydiphenylamines[15,18] at 160-170° for forty-five minutes. 3-Methylphenothiazine[17] was prepared in quantitative yield by heating together p-methyldiphenylamine, sulfur and iodine at 280° for twenty minutes. The thionation[16] of p-anilinophenoxyacetic acid (with iodine as catalyst) giving 3-phenothiazinyloxyacetic acid was successful, but the methyl ester yielded no isolable product. Smith[19] reported the preparation of 3-fluoro- and 3,7-bis(1,1,3,3-tetramethylbutyl)phenothiazine in 39% and 31% respectively by heating together sulfur with the appropriate diphenylamine in the presence of iodine at 150-170° for about an hour.

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[16]R. Baltzly, H. Harfenist and F. J. Webb, ibid., 68, 2673 (1946).

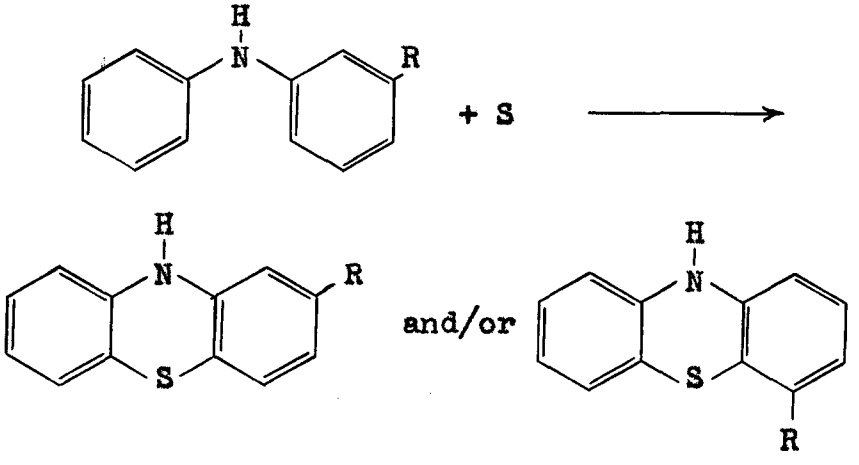
[17]H. Gilman and D. A. Shirley, ibid., 66, 888 (1944).

[18]D. F. Houston, U. S. Patent 2,505,772, May 2, 1950, /C. A., 44, 7068 (1950)/.

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

Fusion of sulfur, p,p'-dihydroxydiphenylamine and a small amount of iodine gave 3,7-dihydroxyphenothiazine[20] (leucothionol) which was readily oxidized to 7-hydroxyphenothiazone-3 (thionol). The attempts to prepare 1-carboxyphenothiazine[21] by thionation of o-carboxydiphenylamine or its ethyl ester were unsuccessful. A small amount of phenothiazine resulted from the latter reaction showing that pyrolysis had occurred as one of the steps of the reaction.

It is obvious that thionation of an ortho-substituted diphenylamine would produce a 1-substituted phenothiazine, while that of a para-substituted diphenylamine results in the 3-substituted phenothiazine, provided, of course, that no molecular rearrangement has taken place. On the other hand, thionation of a meta-substituted diphenylamine could



[20] D. F. Houston, E. B. Kester and F. DeEds, J. Am. Chem. Soc., 71, 3819 (1949).

[21] H. Gilman, D. A. Shirley and P. R. Van Ess, ibid., 66, 625 (1944).

conceivably result in the formation of either a 2- or 4-substituted phenothiazine or a mixture of the two. Work done by Smith[22] indicates that the reaction results in the formation of the 2-isomer on the basis of infra-red analysis. He prepared a trifluoromethylphenothiazine in 44% yield by the reaction of 3-trifluoromethyldiphenylamine, sulfur and iodine at 140-150° for one hour. An infra-red spectrum of the product showed a strong band at 12.17μ which was not present in the phenothiazine spectrum. Barnes[23] reported that vicinal-trisubstituted benzene derivatives produced a characteristic infra-red absorption band in the region from about 12.5 to 13.2μ, whereas unsymmetrical trisubstituted benzene compounds produced a band in the region of 12.0 to 12.5μ. Since the trifluoromethylphenothiazine had a band in the latter region, Smith provisionally assigned the trifluoromethyl group to position 2. The 4-isomer, which contains a vicinal-trisubstituted benzine ring, would be expected to have a strong band in the region of 12.5 to 13.2μ. Buu-Hoï and Lecocq[24] obtained from the thionation of m-tolyl-α-naphthylamine a methylbenzophenothiazine which they considered to be 8-methyl-1,2-benzophenothiazine in which

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

[23]R. B. Barnes, R. C. Gore, R. W. Stafford and V. Z. Williams, Anal. Chem., 20, 402 (1948).

[24]Ng. Ph. Buu-Hoï and J. Lecocq, Compt. rend., 218, 648 (1944).

the methyl group is para to the sulfur without giving any reason for their decision.

Some phenothiazine derivatives, for instance 3-hydroxyphenothiazine[25] and 3-hydroxy-7-methylphenothiazine[26], have been prepared by fusing together sulfur, hydroquinone and the appropriately para-substituted aniline.

A number of substituted phenothiazines have been prepared by the cyclization of some substituted diphenylsulfides or diphenylamines. Kehrmann[27], by reduction of bis-2-picramidodiphenyl disulfide, obtained 2-picramidothiophenol which, when treated with alkali, yielded 1,3-dinitrophenothiazine. Möhlau and his co-workers[28], wanting to prepare the isomeric 2,4-dinitro derivative, converted 2-benzamidothiophenol into 2-benzamidophenylpicryl sulfide by reaction with picryl chloride in the presence of sodium acetate. The sulfide yielded, on treatment with alkali, a 10-benzoyldinitrophenothiazine which on hydrolysis gave 1,3-dinitrophenothiazine. No satisfactory explanation could be given

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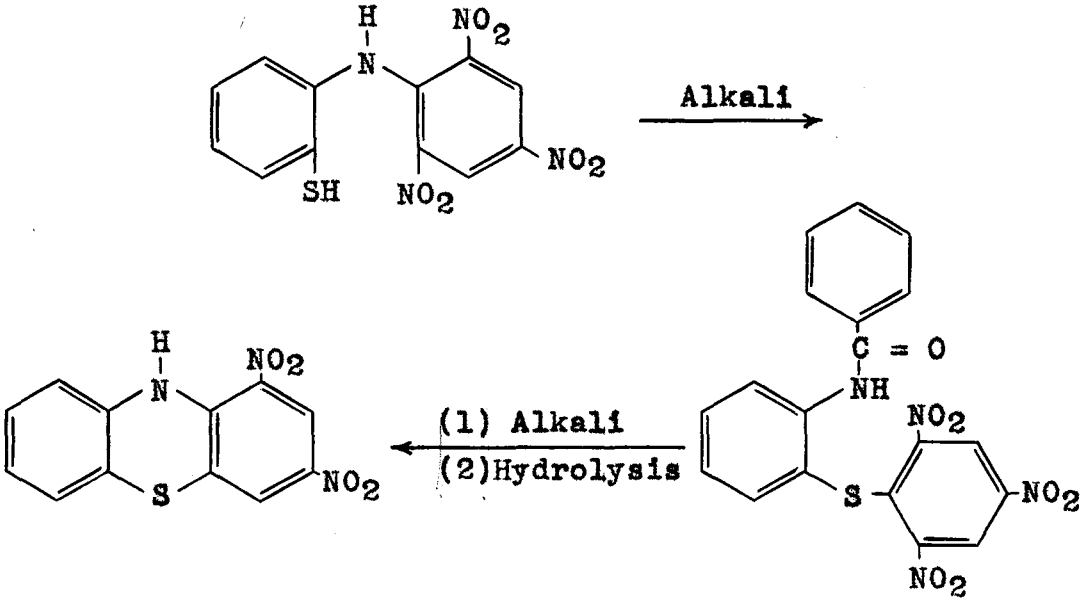
[25]Swiss patent 204,521, Aug. 1, 1939, [C.A., 35, 2337 (1941)].

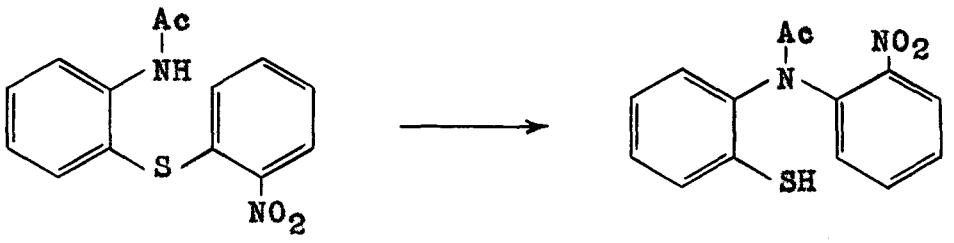
[26]Swiss patents 209,500, 209,501, 209,502, July 16, 1940, [C.A., 35, 4607 (1941)].

[27]F. Kehrmann and J. Steinberg, Ber., 44, 3011 (1911). See also F. Kehrmann and L. Schild, ibid., 32, 2605 (1899) and F. Kehrmann and F. Ringer, ibid., 46, 3014 (1913).

[28]R. Möhlau, H. Beyschlag and H. Kohres, ibid., 45, 131 (1912).



for this phenomenon until Smiles and co-workers[29,30] discovered that rearrangements of the type 2-nitro-2'-acylamidodiphenyl



sulfide to N-acyl-2-nitro-2'-mercaptodiphenylamine readily took place in alkaline media.

The rearrangement and cyclization of a substituted aminodiphenyl sulfide to give a phenothiazine derivative was

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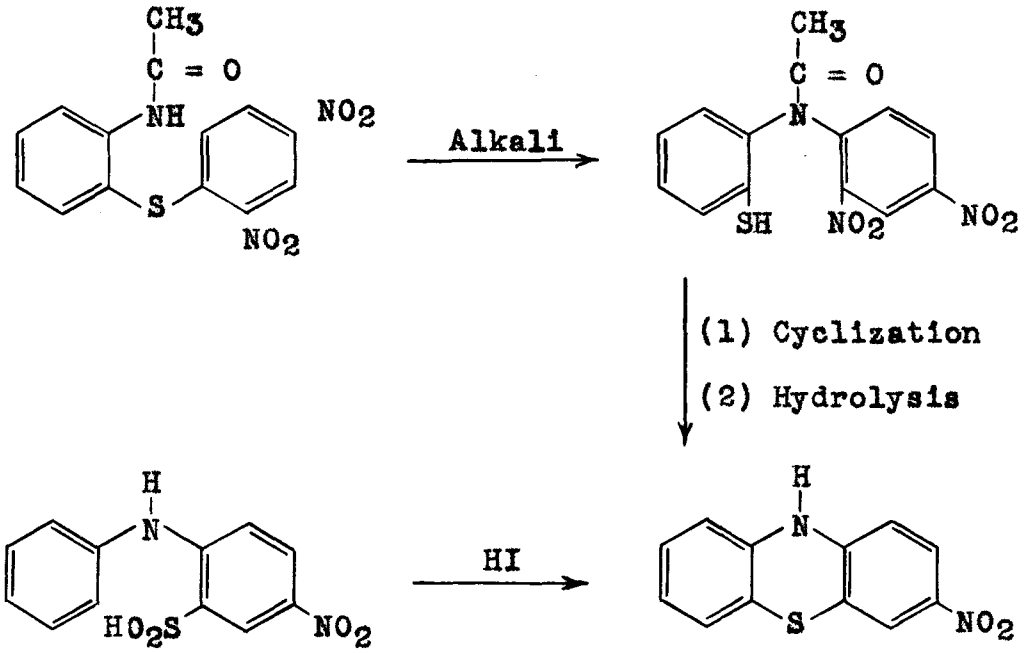
[29]W. J. Evans and S. Smiles, J. Chem. Soc., 181 (1935).

[30]C. F. Wight and S. Smiles, ibid., 340 (1935).

demonstrated by Smiles[31] in the following fashion. 2,4-Dinitro-2'-acetamidodiphenyl sulfide readily underwent rearrangement[25] in an acetone-alcohol solution containing sodium hydroxide to give N-acetyl-2,4-dinitro-2'-mercaptodiphenylamine. After boiling the solution one-half hour, 3-nitro-10-acetylphenothiazine was isolated. The acetyl group was removed by hydrolysis giving 3-nitrophenothiazine. The latter compound was also prepared by treating an aqueous solution of 4-nitrodiphenylamine-2-sulfinic acid, containing sulfurous acid, with hydriodic acid.



[31] W. J. Evans and S. Smiles, ibid., 1263 (1935).

Möhlau and co-workers[32] reported that 2,4-dibenzamido-5-tolylpicryl sulfide in alcohol containing sodium hydroxide cyclized to give a 90% yield of 2,4-dinitro-7-methyl-8-benzamido-10-benzoylphenothiazine, while in a boiling solution, containing somewhat more alkali, the sulfide cyclized to 2,4-dinitro-7-methyl-8-benzamidophenothiazine. It would seem obvious from Smiles' work that rearrangement would occur prior to cyclization and therefore, Möhlau obtained the 1,3-dinitro derivatives instead of the 2,4-isomers as he had concluded. sym-Tri(picrylmercapto)aniline in an alcoholic potassium hydroxide solution gave, upon warming, 1,3-dinitro-7,9-/di(picrylmercapto)/-phenothiazine.[33] In the same paper, it was reported that 4-chloro-2-aminothiophenol hydrochloride gave a picryl derivative and if, immediately upon adding the picryl chloride to the thiophenol, concentrated aqueous sodium acetate was added, 1,3-dinitro-8-chlorophenothiazine resulted. 2-Bromo-7-nitrophenothiazine was prepared in 64% yield by the rearrangement and cyclization of 2-acetamido-4-bromo-2', 4'-dinitrodiphenyl sulfide whereas 2-acetamido-4-bromo-2'-nitrodiphenyl sulfide failed to undergo the Smiles reaction to give a bromophenothiazine.[16] On the other hand,

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[32]R. Mitsugi, H. Beyschlag and R. Möhlau, Ber., 43, 927 (1910).

[33]J. Pollak, E. Riesz and Z. Kahane, Monatsh., 49, 213 (1928).

3-chlorophenothiazine[31] was obtained from the thiol formed by rearrangement of 4-chloro-2-nitro-2'-acetamidodiphenyl sulfide in boiling acetone solution containing sodium hydroxide. 3-Carboxyphenothiazine could not be formed by the cyclization of 2'-acetamido-4-carboxy-2-nitrodiphenyl sulfide.[16] In contrast to the latter failure, the action of alkali on 2,6-dinitro-4-carboxy-2'-mercaptodiphenylamine gave 1-nitro-3-carboxyphenothiazine.[34]

Thus, it is apparent from the foregoing reactions that a number of factors are involved in determining the success of this type of cyclization reaction. In one case, the replacement of the chlorine atom in 4-chloro-2-nitro-2'-acetamidodiphenyl sulfide by a carboxyl group, resulted in the failure of cyclization. However, beginning with the appropriate carboxydinitrodiphenylamine, 1-nitro-3-carboxyphenothiazine could be prepared. Hence, the carboxyl group, as well as the nitro group, has some influence on the success of the reaction. 2-Bromophenothiazine could not be prepared, but 2-bromo-7-nitrophenothiazine was prepared. Thus, these facts confirm Smiles' observation that cyclization occurs only if the one phenyl group contains sufficient nitro groups. In addition, the number of nitro groups necessary seems to be determined by the presence of other substituents

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[34]F. Ullmann, G. Engi, N. Wosnessensky, E. Kuhn and E. Herre, Ann., 366, 79 (1909).

in the molecule, e.g., chloro-, bromo- or the carboxyl group. Therefore it seems that the problem might be explored more fully to determine the factors governing this cyclization reaction.

Hodgson and co-workers[35] were unable to obtain any phenothiazine derivatives by the attempted cyclization of some diphenyl sulfides. The reduction of 2,2', 4,4'-tetranitrodiphenyl sulfide failed to give the corresponding tetramine with possible cyclization en route but resulted only in the formation of m-phenylenediamine. Attempts to condense 2,2'-dichloro-4,4'-dinitrodiphenyl sulfide with ammonia under high pressure or with potassium phthalimide, both at 200°, resulted only in unchanged starting material. 2,2'-Diamino-4,4'-dinitrodiphenyl sulfide, upon heating with various acids, could not be made to undergo ring closure. Heating 2-chloro-4,4'-dinitro-2'-acetamidodiphenyl sulfide in nitrobenzene with potassium carbonate and cuprous chloride resulted only in decomposition. Michels and Amstutz[36] found that 2,8-diiodophenothiazine could not be produced by cyclization of 2,2'-diamino-4,4'-diiododiphenyl sulfide either by heating its stannous chloride complex or its hydrochloride. However, they obtained 2,8-dinitrophenothiazine in 50% yield

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[35]H. H. Hodgson, D. P. Dodgson and E. W. Smith, J. Chem. Soc., 1104 (1948).

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

by heating, at 220-230° for thirty hours, a mixture of 2-amino-2'-iodo-4,4'-dinitrodiphenyl sulfide, cuprous iodide and sodium carbonate. This was the first reported preparation of a phenothiazine derivative by the direct ring closure of a diphenyl sulfide. They rule out the possibility of a Smiles rearrangement having occurred on the basis that: (1) such reactions take place in either aqueous or alcoholic alkaline solutions; (2) amino sulfides such as 2-amino-2'-nitrodiphenyl sulfide and various of its substitution derivatives do not undergo the rearrangement whereas the corresponding sulfones and/or N-acetyl derivatives do; (3) the diaminophenothiazine-5-dioxide obtained by the reduction and oxidation, under appropriate conditions, of the ring closure product was identical with the diamino compound obtained by means of the Friedel-Crafts and subsequent reactions.

Bis-(2-picramidophenyl) disulfide on reduction by sodium sulfide in an ethanol-benzene solution gave a poor yield of 1-nitrophenothiazine.[37] No ring closure product resulted upon treating 2,2'-diaminodiphenyl disulfide with 2-bromo-3-nitrobenzoic acid in ethanol containing sodium acetate or by heating a mixture the disulfide, potassium o-chlorobenzoate, sodium acetate and copper bronze in amyl alcohol.[21]

Treatment of 2-hydroxy-3-picryl-2,3-dihydrobenzothiazole with hot aqueous sodium carbonate for one hour gave a

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[37] F. Kehrmann and O. Nossenko, Ber., 46, 2809 (1913).

quantitative yield of 1,3-dinitro-10-formylphenothiazine.[38] The cleavage of the thiazole ring by alkali to give a salt of N-formyl-2-picramidothiophenol was demonstrated to be an intermediate step in the reaction.

The potassium salt of 1-nitrophenothiazine-3-sulfonic acid[34] was prepared by boiling a water solution of o-aminothiophenol hydrochloride and 4-chloro-3,5-dinitrobenzenesulfonic acid with sodium acetate followed by treatment with potassium hydroxide. Sodium 3-nitrophenothiazine-1-sulfonate[34] was also prepared in a similar manner by the reaction of o-aminothiophenol hydrochloride and 2-chloro-3,5-dinitrobenzenesulfonic acid. The action of sodium acetate and potassium hydroxide on a water solution of the potassium salts of 4-chloro-3,5-dinitrobenzenesulfonic acid and 3-amino-4-mercaptobenzene sulfonic acid gave the dipotassium salt of 1-nitrophenothiazine-3,8-disulfonic acid.[39]

The presence of a nitro group in either of the reactants is not always necessary for the production of phenothiazine derivatives from o-aminothiophenol. By refluxing a solution of cyclohexene oxide and o-aminothiophenol in alcoholic potassium hydroxide, 1,2,3,4,4a,10a-hexahydrophenothiazine[40] was

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[38] M. L. Tomlinson, J. Chem. Soc., 1607 (1936).

[39] J. Pollak and K. Deutscher, Monatsh., 56, 365 (1930).

[40] C.C.J. Culvenor, W. Davies and N. S. Heath, J. Chem. Soc., 278 (1949).

formed in 99% yield. A patent[41] described the preparation of 2-(1,1,3,3-tetramethylbutyl)phenothiazine by heating a mixture of o-aminothiophenol and 4-(1,1,3,3-tetramethylbutyl)-1,2-dihydroxybenzene at 260-280° for forty hours. No reason was given for assigning the alkyl group to position 2 of phenothiazine, the chance of its being in position 3 seems to be just as great. Desulfurization of the phenothiazine derivative would indicate whether the alkyl group occupied the 2- or 3-position.

When the blue solution, which was obtained by dissolving 4-nitrodiphenylamine-2-sulfinic acid in sulfuric acid, was immediately diluted with water, 3-nitrophenothiazine-5-oxide was obtained.[42] However, if the solution was allowed to stand one-half hour before dilution, then 3-nitrophenothiazine[43] was formed and sulfur dioxide was evolved. In hot acetic acid, N,4-dimethyl-2'-nitrodiphenylamine-2-sulfinic acid cyclized, with the liberation of oxides of nitrogen, to give 3,10-dimethylphenothiazine-5-dioxide, whereas, only a small amount of this compound was formed in alkaline media.[44]

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[41]J. B. Niederl, U. S. Patent 2,483,838, Oct. 4, 1949, [C.A., 44, 2036 (1950)].

[42]S. Krishua and M. S. Jain, Proc. 15th Indian Sci. Cong., 153 (1928), [C.A., 25, 3001 (1931)].

[43]See page 11 of this dissertation.

[44]L. A. Warren and S. Smiles, J. Chem. Soc., 2774 (1932).

The action of oleum on diphenylamine[45] at 50-80° resulted in the formation of a tetrasulfonic acid derivative of phenothiazine-5-dioxide. The sulfonic acid groups of the latter could be removed by hydrolysis with dilute mineral acids under suitable conditions. By starting with substituted diphenylamines, provided there was in each nucleus an unsubstituted position ortho to the imino group, various derivatives of phenothiazine-5-dioxide were prepared. (Contrast the action of sulfuric acid on phenothiazine itself.[46]) It is very likely that the diphenylamine derivative was first sulfonated and then the resultant product underwent cyclization, possibly by intramolecular sulfonation.

B. Nuclear Substitution Reactions

Since Van Ess[7] has given a complete review of the substitution reactions of phenothiazine up until 1932, only a brief summary of these reactions will be given in this dissertation. Nitration[5] of phenothiazine gave 3-nitrophenothiazine-5-oxide or, depending on the conditions, 3,7-dinitrophenothiazine-5-oxide and an unidentified isomeric dinitro-5-oxide. Likewise, nitration of 10-methyl-phenothiazine gave 3-nitro-

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[45] I. G. Farbenind, A.-G., German patent 582,268, Aug. 11, 1933, [C.A., 27, 5196 (1933)]; I. G. Farbenind, A.-G., British patent 420,444, Dec. 3, 1934, [C.A., 29, 3530 (1935)].

[46] See page 26 of this dissertation.

and 3,7-dinitro-10-methylphenothiazine-5-oxide.[47] 10-Acetylphenothiazine underwent nitration with nitric acid (d. 1.5) in acetic acid to give the 3,7-dinitro-5-oxide.[48] The 10-ethyl-, decyl- and phenyl-derivatives have been nitrated to give the corresponding 3-nitro-5-oxides.[17] More highly nitrated products of phenothiazine have been reported, but their structures have not been proven.[37,49, 50] It was assumed, on the basis of the directing influence of nitrogen, that the third and fourth nitro groups entered the positions ortho to the nitrogen. Direct chlorination of phenothiazine gave small yields of 3,7-dichlorophenothiazine and a tetrachlorophenothiazine whose structure was not determined.[51] The mercuration of 10-methyl- and 10-ethylphenothiazine gave the corresponding 3-acetoxymercuri- and 3,7-diacetoxymercuri-10-alkylphenothiazine.[52] These in turn were converted to the corresponding halo derivatives and arsonic acids by appropriate reactions.

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[47]F. Kehrmann and P. Zybs, Ber., 52B, 130 (1919).

[48]A. Bernthsen, Ann., 230, 122 (1885).

[49]E. DeB. Barnett and S. Smiles, J. Chem. Soc., 95, 1253 (1909).

[50]K. Pfaff, Reichsamt Wirtschaftsausbau Chem. Ber., PB52021, 1183 (1942), [C.A., 42, 9044 (1948)].

[51]O. Unger and K. A. Hofmann, Ber., 29, 1362 (1896).

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

The first Friedel-Crafts reaction involving phenothiazine was carried out by Scholl and Seer,[53] who reacted phenothiazine, phthalic anhydride and aluminum chloride in refluxing carbon disulfide. They obtained, in poor yield, a compound considered to be phenothiazine-3,7-diphthaloylic acid. This substance was cyclized by sulfuric acid to a bis-quinone which they regarded as linear. Under similar conditions, 10-methylphenothiazine gave a 25% yield of a diphthaloylic acid which in turn gave a linear bis-quinone. This acid was also considered to be the 3,7-derivative.

Baltzly, Harfenist and Webb,[16] and later, Michels and Amstutz[36] found that under Friedel-Crafts conditions in a reaction using an acyl compound and phenothiazine, orientation was due mainly to the sulfur rather than the nitrogen since the latter was deactivated by N-acylation. Baltzly and coworkers deduced by indirect evidence that acylation affected position 2 as shown by first hydrolyzing the 2,10-diacetylphenothiazine, resulting in 40-50% yield from the reaction of 10-acetylphenothiazine with acetyl chloride under appropriate conditions, to a monoacetylphenothiazine. The latter underwent the haloform reaction to give a carboxy acid which on cleavage with hydriodic acid or Raney nickel gave m-carboxydiphenylamine. Therefore, either the 2- or 4-position of

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[53] R. Scholl and C. Seer, Ber., 44, 1233 (1911).

phenothiazine had been substituted. The acid was ethylated and the resulting 10-ethyl derivative was shown to be different from the acid formed by carbonation, and subsequent acidification, of the metalation product from 10-ethylphenothiazine and n-butyllithium.[54] The latter acid was very likely the 4-carboxy derivative due to the stronger orienting influence of sulfur over nitrogen in metalation reactions. X-ray analysis and optical observations furnished additional evidence that the former was the 2-carboxy acid.

By increasing the ratio of 10-acetylphenothiazine and acetyl chloride, Michels and Amstutz[36] utilized the Friedel-Crafts reaction to prepare 2,8-diacetylphenothiazine, m.p. 249-251°. The structure of the latter was unambiguously proven in the following manner. The triacetylphenothiazine, formed in 30-55% yield by acylation, was oxidized by means of hydrogen peroxide to the dioxide which, in turn, was converted to 2,8-dicarboxyphenothiazine-5-dioxide using the haloform reaction. The acid was transformed into the azide going through the acid chloride. The azide, via the urethan, was converted into 2,8-diaminophenothiazine-5-dioxide which was shown to be identical with an authentic specimen[55] of

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

[55]See page 15 of this dissertation.

the diamine. Since the work done by Michels and Amstutz has definitely shown that the Friedel-Crafts reaction employing acetyl chloride involves the 2- and 8-positions of phenothiazine, then Baltzly's acid can be considered to be phenothiazine-2-carboxylic acid.

Massie[56] treated a mixture of phenothiazine and anhydrous aluminum chloride in carbon disulfide with excess acetic anhydride obtaining 10-acetylphenothiazine and a diacetyl compound which melted at 253-254°. Neither of the acetyl groups of the latter could be removed by hydrolysis. The structure of the compound was never determined but from the foregoing work it would appear to be the 2,8-derivative. Two ketonic products[57] were formed by the reaction of phenothiazine, stearoyl chloride and aluminium chloride in carbon disulfide. The one product melting at 78-79° was considered to be a monostearoyl compound and the second melting at 125-135°, a distearoyl derivative.

In the case of intramolecular condensations of the appropriate N-substituted phenothiazines, position 1 is involved in the Friedel-Crafts reaction. When 10-(2-carboxyphenyl)phenothiazine was treated with phosphorus pentachloride and stannic chloride, respectively, in xylene, a 60%

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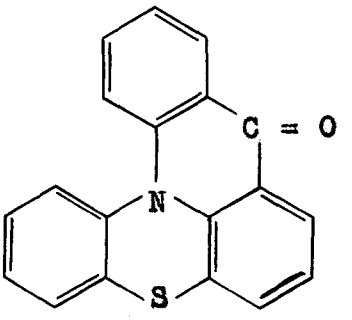
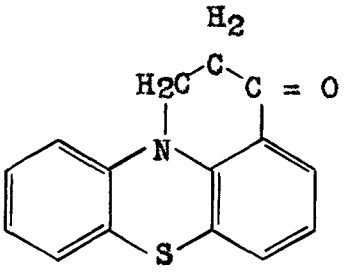
[56]S. P. Massie, Doctoral Dissertation, Iowa State College (1946) p. 103.

[57]M. R. McCorkle, unpublished studies.

yield of the carbonyl containing derivative, 9-quino[3,2,1-kl]phenothiazinone (I), resulted.[21] Smith[22] reported a



I



II

similar reaction. 2,3-Dihydro-3-keto-1H-pyrido[3,2,1-kl]-phenothiazine (II) was formed in 76% yield by the action of phosphorus pentoxide on β-(10-phenothiazyl)propionic acid in refluxing benzene solution.

In connection with the reaction of carbonyl compounds with phenothiazine, Buu-Hoï and Hoán[58] found that 10-methylphenothiazine readily underwent reaction with N-methylformanilide in the presence of phosphorus oxychloride and o-dichlorobenzene to give an 80% yield of 3-formyl-10-methylphenothiazine. Wolff-Kishner reduction of the latter gave 3,10-dimethylphenothiazine, which was identical with an authentic sample, thus showing that the aldehyde group had entered the 3-position exclusively. They concluded

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[58]Ng. Ph. Buu-Hoï and Ng. Hoán, J. Chem. Soc., 1834 (1951).

that the orientation was determined by the nitrogen since it had not been deactivated by acylation.

In view of the orienting influences of nitrogen and sulfur discussed by Buu-Hoï and Hoán and by Baltzly and co-workers, the phthaloylation of phenothiazine[53] very likely gave phenothiazine-2,8-diphthaloylic acid instead of the 3,7-isomer, as suggested by Scholl and Seer; whereas, the phthaloylation of 10-methylphenothiazine conceivably may have given the 3,7-diphthaloylic acid, as the workers had indicated. Thus, two types of substitution with the Friedel-Crafts reaction may be possible depending upon the substutient attached to the nitrogen of phenothiazine. Additional research is necessary to throw light on this interesting problem.

Metalation[21] of phenothiazine with n-butyllithium followed by carbonation, hydrolysis and acidification, gave a 52% yield of phenothiazine-1-carboxylic acid. The structure of the acid was proven by the following series of reactions. The methyl ester of the acid was refluxed with iodobenzene in the presence of potassium carbonate and copper bronze to give 1-carbomethoxy-10-phenylphenothiazine. This compound was hydrolyzed and the resulting free acid treated with phosphorus pentachloride and stannic chloride to give 9-quino[3,2,1-kl]phenothiazinone (I). Metalation[54] of 10-ethyl- and 10-phenylphenothiazine, respectively, with

n-butyllithium gave a monocarboxy-10-ethylphenothiazine and a monocarboxy-10-phenylphenothiazine. The former acid was cleaved with hydriodic acid to give m-carboxydiphenylamine, thus showing that metalation had occurred at either the 2- or 4-position. The latter was preferred because of the stronger orienting influence of sulfur over nitrogen in the case of metalation reactions.[59] The investigation of the Friedel-Crafts reaction in connection with phenothiazine had resulted in the preparation of 10-ethylphenothiazine-2-carboxylic acid which was different from the above acid. Thus, the only alternative was that metalation of 10-ethylphenothiazine with n-butyllithium in ether, and very likely the 10-phenyl derivative as well, involved position 4. 10-(γ-Diethylaminopropyl)phenothiazine was metalated with n-butyllithium in ether at room temperature and the metalation product was then reacted with benzonitrile.[60] An infra-red analysis of the resulting uncrystallizable oil indicated it to be 10-(γ-diethylaminopropyl)-4-benzoylphenothiazine. The reaction of 4-lithio-10-(γ-diethylaminopropyl)phenothiazine with triphenyltin chloride resulted in only the isolation of tetraphenyltin. The metalation product of 3-methoxyphenothiazine[16] upon carbonation gave,

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[59] H. Gilman and C. G. Stuckwisch, J. Am. Chem. Soc., 67, 877 (1945).

[60] T. N. Goreau, Master's Thesis, Iowa State College (1951).

following hydrolysis and acidification, a monocarboxy acid which was not identified. In view of the metalation of phenothiazine itself and the directing influence of oxygen, sulfur and nitrogen on metalation reactions,[59,61] it seems that, in the preceding case, each of positions 1, 2 or 4 of the phenothiazine derivative could have been susceptible to attack.

Magnesium reacted with 3-iodo-10-ethylphenothiazine in an ether-benzene solution to give the Grignard reagent.[54] Carbonation of the organometallic compound resulted in a 76% yield (on the basis of the iodo compound) of 10-ethylphenothiazine-3-carboxylic acid.

3,7-Dinitrophenothiazine was obtained as the chief product by means of the portionwise addition of powdered sodium nitrite to a suspension of phenothiazine in glacial acetic acid.[37] The addition of four moles of powdered sodium nitrite to a suspension of 1,3-dinitrophenothiazine in cold glacial acetic acid resulted in the formation of 1,3,7-trinitrophenothiazine.[27]

A reaction which cannot be classed as a substitution reaction, yet resulted in the production of a phenothiazine derivative containing nuclearly substituted functional groups, was the digestion of phenothiazine with sulfuric acid to

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[61]H. Gilman, M. W. Van Ess, H. B. Willis and C. G. Stuckwisch, J. Am. Chem. Soc., 62, 2606 (1940).

give 7-hydroxyphenothiazone-3.[62] The procedure was improved by Houston and co-workers[20,63] who obtained a 15% yield of 7-hydroxyphenothiazone-3 (as the lithium salt) by heating phenothiazine with 75-90% sulfuric acid at 160-165° for six hours. This compound was also formed by the oxidation of phenothiazine with 30% hydrogen peroxide and hydrochloric acid in aqueous ethanol.[64] However, in the latter reaction, the product was contaminated with compounds containing chlorine. Ferric chloride oxidation of phenothiazine in hot alcohol gave phenothiazone-3.[14,15,65] An attempted formation of 7-n-octyloxyphenothiazone-3[20] by ferric chloride oxidation of 3-n-octyloxyphenothiazine caused cleavage of the ether linkage and yielded chiefly phenothiazone-3. Traces of 7-hydroxyphenothiazone-3 were noted, but no octyloxy compound.

From a consideration of these reactions it is readily apparent that the four different nuclear positions of phenothiazine are susceptible to monosubstitution, the point of substitution depending, of course, upon the particular reaction involved. Nuclear disubstitution reactions produce

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[62]A. Bernthsen, Ann., 230, 187 (1885).

[63]See also S. Granick and L. Michaelis, J. Am. Chem. Soc., 69, 2982 (1947).

[64]F. DeEds and C. W. Eddy, ibid., 60, 1446 (1938).

[65]F. Kehrmann, Ann., 322, 54 (1902).

a symmetrical molecule, at least in the cases where the structure of the product was definitely established.

C. Reactions Involving the Imino Group

Phenothiazine was first alkylated[5] by heating it with an alkyl halide and the corresponding alkyl alcohol in a sealed tube at 100-110°. The 10-methyl and 10-ethyl derivatives were prepared in this fashion. Later these two compounds were prepared in 60% and 35% yield, respectively, by heating together the appropriate alcohol, a small amount of dry hydrogen chloride and phenothiazine in a sealed tube at 100°.[66] The higher molecular weight alcohols did not react at all under these conditions. Refluxing a methanol solution of phenothiazine and methyl iodide for several days gave the 10-methyl derivative.[66] 10-Allyl-, 10-(n-decyl)- and 10-(n-octadecyl)phenothiazine[17] were prepared in 62%, 9.4% and 20% yield, respectively, by heating together the alkyl bromide and phenothiazine in the presence of sodium carbonate and copper powder. The condensation of a γ-diethylaminopropyl halide or its hydrohalide with phenothiazine by direct heating was unsuccessful.[17]

A mixture of phenothiazine, ethyl bromoacetate, potassium carbonate and copper powder, heated at 150-160°,

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

gave ethyl 10-phenothiazylacetate.[67] In the same manner, ethyl β-(10-phenothiazyl)propionate was prepared using ethyl β-bromopropionate. These esters were saponified to the respective free acid. 10-Phenothiazylacetic acid lost carbon dioxide on boiling in acetic acid to give 10-methylphenothiazine; the propionic acid was stable under these conditions.

Phenothiazine was not alkylated by diethyl sulfate.[54] However, methylation of phenothiazine with dimethyl sulfate and sodium hydroxide in acetone was successful.[58]

The refluxing of a mixture of phenothiazine, ethanol, 40% aqueous formaldehyde and a small amount of primary sodium phosphate resulted in the formation of 10-ethoxymethylphenothiazine in 80% yield.[68] Besides ethanol, various alcohols up to and including hexadecyl alcohol were employed in preparing additional 10-alkoxymethylphenothiazine derivatives. Alicylic alcohols, with an alkoxy or other nonreactive substituent, were also used in the above type of reaction.

10-Lithiophenothiazine was prepared by the action of n-butyllithium on phenothiazine in ether; the former compound was then reacted with β-chloroethyl p-toluenesulfonate

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

[68]A. A. Levi, Imperial Chemical Industries Ltd., U. S. patent 2,415,252, Feb. 4, 1947, [C.A., 41, 2756 (1947)]; British patent 554,309, June 29, 1943, [C.A., 39, 311 (1945)].

giving 10-(β-chloroethyl)phenothiazine in 47% yield.[17] A 32% yield of 10(γ-chloropropyl)phenothiazine was obtained on using γ-chloropropyl p-toluenesulfonate as the alkylating agent. These halogen containing phenothiazine derivatives were treated with a number secondary amines to give the corresponding 10-(dialkylaminoalkyl)phenothiazines. 10-Benzylphenothiazine could not be isolated from the reaction of benzyl chloride and 10-lithiophenothiazine in ether.[69]

Alkylations[70] employing a 1-dialkylamino-2-chloropropane resulted in the formation of two isomeric products: the anticipated product (III) and the 2-alkylamino-1-propyl derivative (IV). The same result was obtained in alkylations using the isomeric 1-chloro-2-dialkylaminopropanes.[71] It has been proposed[70,72] and shown[73] that under the influence of alkaline condensing agents, alkylaminochloropropanes gave rise to a cyclic ethyleneimmonium ion, which then reacted with an anion R'^- to yield two isomeric compounds

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[69]I. Zarember, Master's Thesis, Iowa State College (1949).

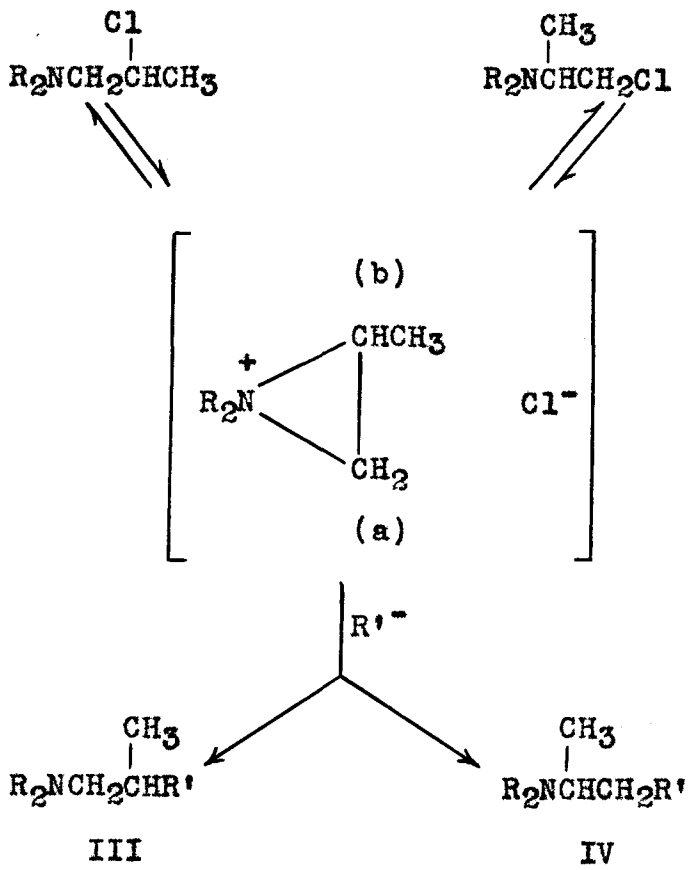
[70]E. M. Schultz, C. M. Robb and J. M. Sprague, J. Am. Chem. Soc., 69, 188 (1947); ibid., 69, 2454 (1947); W. R. Brode and M. W. Hill, ibid., 69, 724 (1947).

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

[72]J. F. Kerwin, G. E. Ullyot, R. C. Fuson and C. L. Zirkle, ibid., 69, 2961 (1947).

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

(III)and IV), depending on whether the reagent R'^- attacked the ethyleneimmonium ion at (a) or (b). Since the position (a) was least substituted, it seemed probable that it was the favored point of attack, the main product thus being the one represented by structure IV.



The reaction of phenothiazine with 1-dimethylamino-2-chloropropane in the presence of sodamide gave a compound which was reported to be 10-(1-dimethylamino-2-propyl)-phenothiazine.[3] The foregoing results of the alkylations involving a 1-dialkylamino-2-chloropropane led Charpentier[74]

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

to investigate the structure of the compound believed to be 10-(1-dimethylamino-2-propyl)phenothiazine. He found the product, from the alkylation of phenothiazine with 1-dimethylamino-2-chloropropane in the presence of sodamide, to be instead 10-(2-dimethylamino-1-propyl)phenothiazine by means of the following reactions. Exhaustive methylation of the phenothiazine derivative gave 10-(1-propenyl-1)phenothiazine which was identified by: (1) potassium permanganate oxidation in cold acetone to 10-formylphenothiazine; and (2) hydrolysis by boiling normal sulfuric acid to give phenothiazine and propanal. 10-(2-Dimethylamino-1-propyl)-phenothiazine was also prepared from phenothiazine and 1-chloro-2-dimethylaminopropane.[74,75] Additional investigation of the reaction[76] of phenothiazine, sodamide and 1-dialkylamino-2-chloropropane (the alkyl groups were either methyl or ethyl groups) in refluxing xylene resulted in the isolation of two products: 10-(1-dialkylamino-2-propyl)-phenothiazine and 10-(2-dialkylamino-1-propyl)phenothiazine. The latter was formed in the larger amount. The structures of these compounds were proven by cleavage with hydrobromic

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[75]P. Charpentier, U. S. patent 2,530,451, Nov. 21, 1950, [C.A., 45, 3428 (1951)]; Société des usines chimiques Rhône-Poulenc, British patent, 649,150, Jan. 7, 1951, [C.A., 45, 7156 (1951)].

[76]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, Oct. 17, 1950, [C.A., 45, 2511 (1951)].

acid of the dialkylaminoalkyl group of the two phenothiazine derivatives, respectively, giving the 1-dialkylamino-2-bromopropane and the 1-bromo-2-dialkylaminopropane. The picrates of the last two compounds were prepared and compared with the respective authentic specimens. They were found to be identical.

Some 1-piperidyl- and 4-morpholinylalkyl derivatives of phenothiazine[77] were prepared by condensing the hydrochlorides of β-(1-piperidyl)ethylchloride,[78] 1-(1-piperidyl)-2-chloropropane and 1-(4-morpholinyl)-2-chloropropane with phenothiazine in the presence of two equivalents of sodamide. Only one reaction product was isolated from the reaction between phenothiazine and 1-(1-piperidyl)-2-chloropropane or 1-(4-morpholinyl)-2-chloropropane. It was shown that rearrangement had occurred in both cases and the compounds obtained were 10-[2-(1-piperidyl)-1-propyl]phenothiazine and 10-[2-(4-morpholinyl)-1-propyl]phenothiazine, respectively. This was performed by preparing these two compounds by a different method. Phenothiazine reacted smoothly with propylene oxide in the presence of sodamide to give

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

[78]See also Société des usines chimiques Rhône-Poulenc, British patent 632,277, Nov. 18, 1949, [C.A., 44, 5399 (1950)].

10-(2-hydroxy-1-propyl)phenothiazine.[79] On treating this compound with phosphorus tribromide, 10-(2-bromo-1-propyl)-phenothiazine was formed. The structure of the hydroxypropyl and bromopropyl derivatives was established by hydrogenation of the latter, which yielded a compound identical with 10-propylphenothiazine prepared by the hydrogenation of 10-allylphenothiazine. On treating 10-(2-bromo-1-propyl)-phenothiazine with piperidine and morpholine, respectively, 10-[2-(1-piperidyl)-1-propyl]- and 10-[2-(4-morpholinyl)-1-propyl]phenothiazine were obtained.

Various other 10-dialkylaminoalkylphenothiazines[80] have been prepared in good yields from 10-sodiophenothiazine (formed by reaction of phenothiazine with sodamide) and a dialkylaminoalkyl halide in an organic solvent such as xylene at an elevated temperature. The reaction was also successful in cases where the benzene nuclei of phenothiazine contained substituted alkyl or alkoxy groups. Lithium amide, as well as sodamide, was used in the preparation of a series

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[79] See also R. Dahlbom, Swedish patent 129,843, Oct. 24, 1950, [C.A., 45, 5193 (1951)]. Phenothiazine and some of its derivatives were reacted with propylene oxide or ethylene oxide in the presence of an alkaline condensing agent, such as an alkali amide, sodium phenoxide or lithium propionate, to give the corresponding 10-(2-hydroxyalkyl)phenothiazine.

[80] Société des usines chimiques Rhône-Poulenc, British patent 608,208, Sept. 10, 1948, [C.A., 43, 2647 (1949)]; P. Charpentier, U. S. patent 2,519,886, Aug. 22, 1950, [C.A., 45, 673 (1951)].

of dialkylaminoalkyl derivatives of phenothiazine.[81] The yields varied from poor to good for the different compounds. A study of the relationship between antihistaminic activity and variation of structure was made on these compounds.

The alkylation of phenothiazine with various N-pyrrolidylethyl chlorides in the presence of sodamide proceeded smoothly giving from 36 to 61% yields of the respective products.[82] The 1-(1-pyrrolidyl)-2-chloropropanes were considered to give the 10-[2-(1-pyrrolidyl)-1-propyl]phenothiazines, in yields of 29-88%, on the basis that rearrangement occurs in this type of reaction. No attempt was made to prove the structures of these products.

A number of 10-alkylphenothiazines have been prepared by the reaction of phenothiazine, sodamide and an alkyl halide in liquid ammonia.[83] 10-Propyl-, 10-(p-methoxybenzyl)- and 10-isopropylphenothiazine were prepared in 83%, 91% and 67%, respectively, by this procedure. tert.-Butyl chloride did not undergo reaction with 10-sodiophenothiazine in liquid ammonia.

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[81] J. B. Wright, E. H. Lincoln, R. V. Heinzelmann and J. H. Hunter, J. Am. Chem. Soc., 72, 3536 (1950).

[82] W. B. Reid, Jr., J. B. Wright, H. G. Kolloff and J. H. Hunter, ibid., 70, 3100 (1948); J. H. Hunter and W. B. Reid, Jr., U. S. patent 2,483,998, Oct. 4, 1949, [C.A., 44, 2573 (1950)].

[83] J. F. Champaigne, unpublished studies.

Phenothiazine and 2-(chloromethyl)imidazoline hydrochloride, upon refluxing in o-dichlorobenzene, gave 10-(2-imidazolin-2-ylmethyl)phenothiazine hydrochloride.[84] 10-(2-Imidazolin-2-ylmethyl)-3-methoxyphenothiazine hydrochloride was prepared by the same method.

Phenothiazine reacted with aryl iodides under appropriate conditions. The heating of a mixture of phenothiazine, iodobenzene, potassium carbonate, copper iodide and bromobenzene resulted in the formation of 10-phenylphenothiazine.[85] The procedure for the preparation of 10-phenylphenothiazine was improved by Gilman, Van Ess and Shirley.[54] A variety of 10-phenylphenothiazines were prepared in which the 10-phenyl group was substituted with the carbomethoxy, chloro, methoxy, methyl or nitro group.[17,21,54] These derivatives were prepared by heating phenothiazine, the aryl iodide, potassium carbonate and copper bronze in a solvent such as xylene or petroleum ether (b.p. 200-230°).

Phenothiazine was acylated by acetic anhydride to give 10-acetylphenothiazine.[5] 10-Carboethoxyphenothiazine was prepared by heating phenothiazine with ethyl chlorocarbonate in ether in a tube at 120°.[86] Phosgene reacted with

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[84]K. Miescher and A. Morxer, U. S. patent 2,485,212, Oct. 18, 1949, [C.A., 44, 2572 (1950)]. See also reference 81.

[85]E. DeB. Barnett and S. Smiles, J. Chem. Soc., 97, 364 (1910).

[86]N. Fraenkel, Ber., 18, 1845 (1885).

phenothiazine to give 10-chlorocarboxyphenothiazine, as well as 10,10'-diphenothiazylcarbonyl.[5] A number of 10-acyl derivatives of phenothiazine were prepared by heating together equivalent amounts of the long-chain fatty acid chloride and phenothiazine.[87] 10-Benzoyl-3-nitrophenothiazine-5-oxide[88] was prepared by the reaction of benzoyl chloride and the phenothiazine derivative in pyridine. Phenothiazine reacted with phthalic anhydride at 150° to give 10-(o-carboxybenzoyl)-phenothiazine.[89] The abstract of the patent stated that other 10-carboxyacylphenothiazines had been prepared by this procedure but did not list them.

Phenothiazine, and some of its nuclearly substituted derivatives, reacted readily with various haloacyl halides when heated under reflux in benzene or toluene until hydrogen halide was no longer evolved. Thus, the corresponding 10-haloacylphenothiazines were formed in good yields.[90,91] The acyl halides used were chloroacetyl chloride, α-bromopropionyl bromide, β-chloropropionyl chloride,

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

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

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

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

[91]T. Ekstrand, ibid., 3, 302 (1949); T. Ekstrand, Swedish patent 127,566, Mar. 14, 1950, [C.A., 45, 188 (1951)].

α,β-dibromopropionyl chloride, α-bromobutyryl chloride and α,α-dimethyl-β-bromopropionyl chloride. These haloacylphenothiazines were treated with a number of primary and secondary amines, for example, diethylamine, ethylamine, piperidine, morpholine and pyrrolidine, giving the desired 10-aminoacylphenothiazines.[90] Attempts to prepare a number of 10-(hydroxyalkylaminoacetyl)phenothiazines resulted in only the isolation of phenothiazine. Some 10-hydroxyalkylaminoalkyl)phenothiazines which have been described[92] were stable compounds. The reaction between α,β-dibromopropionylphenothiazine and the various amines invariably yielded the bisamino compounds, even when the halo compound was used in excess.[90]

The reaction of benzenesulfonyl chloride with phenothiazine and 3,7-dinitrophenothiazine in pyridine gave the corresponding sulfonyl derivatives.[88] Likewise, 10-(p-acetamidobenzenesulfonyl)-, 10-(p-nitrobenzenesulfonyl)- and 10-(p-toluenesulfonyl)phenothiazine were prepared by the same procedure.[66,93]

The addition of a 40% solution of benzyltrimethylammonium hydroxide to a mixture of phenothiazine and an excess of

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

[93]See also K. A. Jensen, B. Possing and K. Schmith, Dansk Tids. Farm., 15, 191 (1941), [C.A., 38, 1482 (1944)].

acrylonitrile gave β-(10-phenothiazyl)propionitrile in 73% yield.[22] The cyanoethylation reaction involving 2-trifluoromethylphenothiazine resulted in the formation of the propionitrile in 67% yield.[19] The boiling of phenothiazine and mercuric acetylamide in ethanol for several hours gave 10, 10'-bisphenothiazyl.[94] Phenothiazine in dry diethyl ether reacted with phenylisocyanate to give 10-anilidocarbonylphenothiazine.[95]

The action of hot hydriodic acid on 10-methylphenothiazine-5-dioxide[96] and the sulfone of β-(10-phenothiazyl)-propionic acid[19] resulted in the cleavage of the alkyl group to give phenothiazine-5-dioxide. In the case of a 10-ethylphenothiazine carboxylic acid, hydriodic acid removed both the alkyl group and the sulfur to give m-carboxydiphenylamine.[16,54] Some 10-(dialkylaminopropyl)phenothiazines were cleaved by hot hydrobromic acid to give the corresponding bromodialkylaminopropane and phenothiazine.[43] The sulfone of 10-phenothiazylpropionitrile reacted readily with alcoholic sodium hydroxide to give phenothiazine-5-dioxide.[19] In the

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[94]L. Pesci, Gazz. chim. ital., 46, I, 103 (1916), [C.A., 10, 2885 (1916)].

[95]R. A. Henry and W. M. Dehn, J. Am. Chem. Soc., 71, 2297 (1949). See also S. Paschkowezky, Ber., 24, 2910 (1891).

[96]A. Bernthsen, Ber., 39, 1807 (1906).

attempts to reduce some 10-aminoacylphenothiazines to the corresponding 10-aminoalkyl derivatives, it was found that the acyl compounds were instantly split into phenothiazine and the aminoalcohol by the action of lithium aluminum hydride in ether at room temperature.[90]

A number of quaternary ammonium salts of some of the 10-(dialkylaminoalkyl)phenothiazines have been prepared.[92,97]

D. Reactions Involving the Sulfur Atom

A variety of oxidizing agents has been used to oxidize the sulfur of a number of phenothiazine derivatives to the sulfoxide or the sulfone.

Both 10-methyl-[5] and 10-ethylphenothiazine[66] were oxidized to the respective sulfones in yields of about 57% by potassium permanganate in boiling water. The oxidation of 10-methylphenothiazine by potassium permanganate in an acetone solution at 15°, containing excess sulfuric acid, gave a 45% yield of the sulfoxide.[98] A small amount of sulfone was also isolated from the reaction mixture. 10-Benzylphenothiazine-5-dioxide[99] was formed under similar

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[97]Société des usines chimiques Rhône-Poulenc, French patent 942,366, Feb. 7, 1949, [C.A., 45, 3427 (1951)].

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

[99]R. D. Desai, J. Indian Inst. Sci., 7, 235 (1924), [C.A., 19, 2645 (1925)].

conditions starting with 10-benzylphenothiazine and using acetic acid instead of sulfuric acid. In contrast to these reactions, 10-(1-propenyl-1)phenothiazine reacted with potassium permanganate in cold acetone to give 10-formylphenothiazine.[74] No mention was made of the possible formation of any sulfoxide or sulfone. 10-Phenylphenothiazine in chloroform was oxidized with aqueous permanganate giving the dioxide.[54] The oxidation of 10-(p-toluenesulfonyl)phenothiazine with permanganate in boiling water gave a 74% yield of the monoxide.[66] Under these conditions the 10-(p-acetamidobenzenesulfonyl) derivative did not react at all. 10-Carboethoxyphenothiazine was readily converted to its sulfone in 83% yield by permanganate in a 75% acetic acid solution.[66] The action of potassium permanganate on 10-acetylphenothiazine in boiling water brought about decomposition as shown by the liberation of acetic acid; no sulfoxide or sulfone was isolated.[5]

Phenothiazine-5-oxide was prepared in 55% yield by allowing a solution of phenothiazine, hydrogen peroxide[100] and a small amount of sodium ethoxide in acetone to stand at room temperature for ten days.[49] Pummerer and Gassner[101] were unable to prepare phenothiazine-5-oxide by this

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[100]The concentration of hydrogen peroxide in this and subsequent reactions was 30% unless otherwise specified.

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

procedure. Only small quantities of 10-methylphenothiazine-5-oxide were obtained in attempts to prepare the sulfoxide by allowing a solution of 10-methylphenothiazine and hydrogen peroxide in acetone to stand for three weeks.[98] Neither the p-tolylsulfonyl or the p-acetamidobenzenesulfonyl derivative of phenothiazine could be oxidized by hydrogen peroxide in acetone.[66]

Phenothiazine-5-oxide was prepared in 75% yield by the oxidation of phenothiazine with hydrogen peroxide in boiling ethanol containing a small amount of potassium hydroxide.[101] 3,7-Dimethylphenothiazine was oxidized to the sulfoxide by hydrogen peroxide in refluxing alcohol.[102] A number of phenothiazine derivatives were oxidized to the respective monoxide in fair yield by hydrogen peroxide in ethanol at room temperature. The solutions were usually allowed to stand for a few days and then the product was isolated. The compounds oxidized by this procedure were 3-methoxyphenothiazine,[102] and the 10-(β-chloroethyl)-, octadecyl- and phenyl- derivatives of phenothiazine.[17] The reaction of 3-octyloxyphenothiazine with alcoholic solutions of hydrogen peroxide containing potassium hydroxide oxidized the sulfur atom yielding the monoxide.[20]

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[102] F. Kehrmann and L. Diserens, ibid., 48, 318 (1915).

Oxidation, and hydrolysis, of 2,8,10-triacetylphenothiazine to 2,8-diacetylphenothiazine-5-dioxide proceeded smoothly, in yields of 85-95%, by using hydrogen peroxide in hot glacial acetic acid.[36] Attempted oxidations of 2,8-diacetamido-10-acetylphenothiazine and of 2,8-dinitrophenothiazine with hydrogen peroxide led in both cases to compounds believed to be in an intermediate stage of oxidation.[36] A number of nuclearly and 10-substituted phenothiazine derivatives were readily converted in good yields to the corresponding sulfone by the action of hydrogen peroxide in refluxing glacial acetic acid solutions.[19] However, under similar conditions, a tetrachlorophenothiazine was only oxidized to the sulfoxide.[103]

The action of concentrated nitric acid on phenothiazine or its derivatives brought about oxidation of the sulfur, as well as nitration when the latter reaction was possible through the availability of unsubstituted positions. A cold suspension of phenothiazine in glacial acetic acid reacted with nitric acid to give 3-nitrophenothiazine-5-oxide.[5] Tetrachlorophenothiazine-5-oxide was prepared, although evidently in an impure condition, by the action of nitric acid on the sulfide.[104] The nitration of a number of 10-substituted

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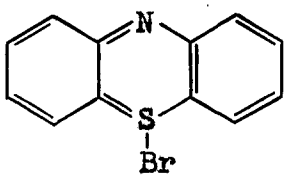
[103] O. L. Brady and S. Smiles, J. Chem. Soc., 97, 1559 (1910).

[104] O. Unger and K. A. Hofmann, Ber., 29, 1362 (1896).

derivatives of phenothiazine also resulted in the oxidation of the sulfur to the sulfoxide.[17,47] Barnett and Smiles[49] found that a tetranitrophenazothionium hydroxide was readily attacked by concentrated nitric acid and was thereby oxidized to the sulfone.

Hypochlorous acid reportedly oxidized 2,8-diacetamido-10-acetylphenothiazine in acetic acid at 80° to give a small amount of the dioxide.[36] An alcoholic solution of bromine acted on phenothiazine in cold alcohol to give phenazothionium bromide (V).[101,105] The oxidation of phenothiazine



V

with saturated bromine water gave a compound which was thought to be 3,7-dihydroxyphenazothionium bromide.[106] 3,7-Dinitrophenothiazine-5-oxide in acetic acid at 60-70° was

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[105]F. Kehrmann, ibid., 34, 4170 (1901).

[106]C. W. Eddy and F. DeEds, Food Research, 2, 305 (1937).

oxidized with chromic anhydride giving the dioxide.[107] The oxidation of a tetrachlorophenothiazine with either chromic acid or potassium persulfate in concentrated sulfuric acid gave a product which was thought to be a mixture composed of equal molecular proportions of the sulfide and the azothionium hydroxide.[103] The treatment of a concentrated acetic acid solution of 3-acetamido-10-methylphenothiazine with aqueous sodium nitrite[108] resulted in the formation of the monoxide.[47] 3,7-Diacetamido-10-methylphenothiazine was also oxidized to the monoxide by this procedure.

An isomorphous mixture of a mono- and a dichlorophenothiazine was obtained upon boiling a hydrochloric acid solution of phenothiazine-5-oxide. 10-Methylphenothiazine-5-oxide was converted by concentrated hydrochloric acid to the phenazothionium chloride which upon heating with excess acid gave a chloro-10-methylphenothiazine. No dichloro compound was isolated from this reaction. The addition of hydrogen peroxide to a concentrated solution of phenothiazine in ethanol at 0° saturated with hydrogen chloride resulted in a 75% yield of a tetrachlorophenothiazine.[109] In some cases, a trichlorophenothiazine-5-oxide resulted from the

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[107]B. Ciocca and L. Canonica, Boll. ist. sieroterap. milanese, 23, 81 (1944), [C.A., 40, 3119 (1946)].

[108]See page 26 of this dissertation.

[109]H. J. Page and S. Smiles, J. Chem. Soc., 97, 1112 (1910). See also T. P. Hilditch and S. Smiles, ibid., 101, 2294 (1912).

action of hydrogen peroxide and hydrogen chloride on phenothiazine in an alcohol solution.[103] 3,7-Dinitrophenothiazine was obtained, mixed with a tetrachloro compound, when the dinitro sulfoxide was warmed in acetic acid or alcohol with concentrated hydrochloric acid.[37] Likewise, hydrochloric acid reacted with an alcohol solution of 3-nitrophenothiazine-5-oxide to give a chloro-7-nitrophenothiazine. This very likely was the 3-chloro derivative. 3-Nitrophenothiazine-5-oxide was also reduced by alcohol and 30% sulfuric acid to 3-nitrophenothiazine.

3-Nitro- and 3,7-dinitrophenothiazine-5-oxide suspended in alcohol were reduced by stannous chloride and hydrochloric acid to the corresponding aminophenothiazines.[47] Thus, the sulfoxide as well as the nitro group was reduced. On the other hand, only the nitro groups of 3,7-dinitrophenothiazine-5-dioxide were reduced by stannous chloride and hydrochloric acid, or by ammonium sulfide in ammonia solution, to give 3,7-diaminophenothiazine-5-dioxide.[107]

Various reactions have been carried out in which the sulfur has been removed from the phenothiazine nucleus. Bernthsen[5] obtained N-phenylacridine by heating phenothiazine with benzoic acid and zinc chloride. The heating of a mixture of phenothiazine[110] and freshly reduced copper in the presence of illuminating gas, resulted in the formation

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[110]E. Holzmann, Ber., 21, 2069 (1888).

of acridine. Phenothiazine and hydrogen in the presence of molybdenum oxide reacted with extreme ease to give a mixture of diphenylamine, aniline and benzene.[111] The reaction of hydrogen with phenothiazine in dioxane, at 250° and high pressure using cobalt sulfide as calalyst, yielded a mixture of o-mercaptodiphenylamine and diphenylamine.[112] The treatment of phenothiazine in alcohol with Raney nickel gave diphenylamine.[113] The sulfur of 10-ethyl- and 10-phenylphenothiazine-4-carboxylic acid was removed by hot hydriodic acid to give m-carboxydiphenylamine and m-carboxytriphenylamine respectively.[54]

A refluxing, dioxane solution of phenothiazine reacted with lithium, in an atmosphere of nitrogen, to give a 29% yield of o-mercaptodiphenylamine and a 4.4% yield of diphenylamine following hydrolysis.[114] Thirty-six per cent of the phenothiazine was recovered. In another case, the reaction mixture was carbonated prior to hydrolysis and acidification, with the result that the same products were formed in approximately corresponding amounts. The reaction

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[111] N. A. Orlow, ibid., 64B, 2631 (1931).

[112] F. K. Signaigo, U. S. patent 2,402,686, June 25, 1946, [C.A., 40, 5767 (1946)].

[113] K. H. Shah, B. D. Tilak and K. Venkataraman, Proc. Indian Acad. Sci., 28A, 142 (1948), [C.A., 44, 3958 (1950)].

[114] R. K. Ingham, unpublished studies.

of lithium and 10-ethylphenothiazine under similar conditions, following carbonation and acidification, resulted in the production of an alkali-soluble, bicarbonate-insoluble oil.

E. Physiological Properties of the 10-(Dialkylaminoalkyl)phenothiazine Derivatives

A number of 10-(dialkylaminoalkyl)phenothiazines were first prepared by Gilman and Shirley in 1944.[17] These compounds, at that time, were tested only for their antimalarial activity and found to be ineffective. The strong antihistaminic action of this class of phenothiazine derivatives was discovered by Halpern,[3,4] who reported that 10-(β-dimethylaminoethyl)phenothiazine (RP3015) and 10-(β-dimethylaminoisopropyl)phenothiazine (phenergan[115] or RP3277) were considerably more active than antergan as antihistaminic agents. In addition, the toxicity[116] of these compounds was lower than that of any previously described

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[115] Phenergan, as used in most experiments, was found to be a mixture of 10-(2-dimethylamino-1-propyl)- and 10-(1-dimethylamino-2-propyl)phenothiazine, the former being present in the larger amount. P. Charpentier and R. Ducrot, Compt. rend., 232, 415 (1951).

[116] B. N. Halpern, Compt. rend. soc. biol., 140, 363 (1946); P. Vallery-Radot, J. Hamburger and B. N. Halpern, Presse méd., 55, 661 (1947), [C.A., 43, 3525 (1949)]; D. Bovet, J. Fournel and P. Charpentier, Thérapie (Paris), 2, 115 (1947), [C.A., 42, 5116 (1948)].

antihistamine. These reports initiated a study of the physiological properties, as a whole, of the 10-(dialkylaminoalkyl)phenothiazines.

Halpern[117] reported that RP3015 and 10-(2-dimethylamino-1-propyl)phenothiazine (promethazine) protected guinea pigs against four hundred and fifteen hundred lethal doses of histamine, respectively, whereas antergan protected them against sixty lethal doses.[4] In an earlier paper,[118] Halpern stated that RP3015 did not prevent the production of stomach ulcers in guinea pigs caused by three hundred lethal doses of histamine injected at one time. These ulcers were fatal within twenty-four hours. However, the phenothiazine derivative did protect the animals against the other effects of histamine. The bronchospasm produced in guinea pigs by histamine and acetylchloline and by nicotine was prevented or suppressed by 10-(β-diethylaminoethyl)phenothiazine (diparcol).[119] On the other hand, this

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[117]B. N. Halpern, Arch. intern. pharmacodynamie, 74, 314 (1947), [C.A., 42, 2348 (1948)]. See also B. N. Halpern and D. Wood, Compt. rend., 230, 138 (1950), and R. Cattaneo and S. Rosso, Minerva med., 40, I, 623 (1949). [C.A., 43, 6722 (1949)].

[118]B. N. Halpern and J. Martin, Compt. rend. soc. biol., 140, 830 (1946).

[119]A. de Schaepdryver, Arch. intern. pharmacodynamie, 82, 207 (1950), [C.A., 44, 7983 (1950)].

compound did not inhibit the effect of histamine on the heart.[120]

The antihistaminic activity of 10-(2-dimethylamino-1-propyl)phenothiazine was found to be from three to ten times that of the 1-dimethylamino-2-propyl isomer.[115] 10-(3-Dimethylamino-2,2-dimethylpropyl)phenothiazine had no antihistaminic activity,[121] even though it is very similar in structure to the previous compounds. 10-(3-Dimethylaminopropyl)phenothiazine had a very weak antihistaminic action.[122] The compound, 10-[β-(1-pyrrolidyl)ethyl]-phenothiazine, was found to be a potent antagonist of many of the effects of histamine.[123] It had a low degree of toxicity compared to pyribenzamine.

The reaction of diparcol or RP3015 with halo- or dihaloalkanes gave various quaternary ammonium salts which were therapeutically useful compounds.[124] The product[125]

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[120] I. T. Beck, E. Frommel, M. Favre and F. Vallette, ibid., 78, 613 (1949), [C.A., 43, 7129 (1949)].

[121] D. R. Wood, Brit. J. Pharmacol., 5, 195 (1950), [C.A., 44, 8534 (1950)].

[122] B. N. Halpern, G. Perrin and P. Dews, Compt. rend. soc. biol., 141, 1125 (1947).

[123] M. J. Vander Brook, K. J. Olson, M. T. Richard and M. H. Kuizenga, J. Pharmacol. Exptl. Therap., 94, 197 (1948).

[124] P. Charpentier, U. S. patent 2,480,355, Aug. 30, 1949, [C.A., 44, 1145 (1950)]; Sociétés des usines chimiques Rhône-Poulenc, British patent 641,452, Aug. 9, 1950, [C.A., 45, 2511 (1951)].

[125] R. Ducrot and P. Decourt, Compt. rend. soc. biol., 144, 908 (1950).

from the reaction of pentamethylene bromide with RP3015 was more potent as an antihistaminic agent than the parent compound itself. 10-(2-Dimethylamino-1-propyl)phenothiazine reacted with a methyl halide to give a quaternary ammonium salt whose antihistaminic activity was twice that of phenergan.[126]

The local anesthetic action of RP3015 was about double that of cocaine[122] and more than five times as great as that of procaine.[127] In contrast to this, Beck and co-workers[120] reported that diparcol was inferior to procaine as a local anesthetic. Phenergan, 10-(3-dimethylaminopropyl)- and 10-(3-dimethylamino-2,2-dimethylpropyl)phenothiazine, respectively, had a local anesthetic action of two, three and four to six times that of cocaine.[122]

The action of large doses of nicotine on the heart, arterial pressure, respiratory and motor centers and muscles of various animals was reduced considerably by diparcol.[128,129]

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[126]P. Decourt, Bull. acad. natl. méd., 114, 632 (1950), [C.A., 45, 3942 (1951)].

[127]R. Hazard, E. Corteggiani and A. Cornec, Compt. rend. soc. biol., 143, 908 (1949).

[128]C. Heymans, J. J. Estable and S. C. de Bonneveaux, Arch. soc. biol. Montevideo, 16, 1 (1949), [C.A., 44, 10150 (1950)]; Arch. intern. pharmacodynamie, 79, 185 (1949), [C.A., 43, 7130 (1949)]; C. Heymans and J. J. Estable, Science, 109, 122 (1949); J. Tripod, Brit. J. Pharmacol., 4, 323 (1949), [C.A. 44, 3616 (1950)].

[129]V. G. Longo and D. Bovet, Farm. sci. e tec. (Pavia), 4, 515 (1949), [C.A., 44, 1611 (1950)].

10-(2-Diethylamino-1-propyl)phenothiazine was more active than phenergan as an antinicotinic agent, whereas, RP3015 was inactive.[129]

In Parkinson's disease and hyperthyroidism, diparcol[130] brought about a marked reduction of the basal metabolic rate. The higher the initial rate, the greater was the reduction. The metabolic rate after exercise could also be reduced by diparcol. This compound was clinically effective in relieving some of the symptoms of parkinsonism in human patients, whereas, RP3015 and the ethiodide of diparcol had little or no such activity.[131]

Diparcol was found to exert a selective inhibiting action on pseudocholinesterase,[132] similar to that of diisopropyl fluorophosphate, without exerting an appreciable effect on cholinesterase. On the other hand, diparcol completely antagonized the effects of diisopropyl fluorophosphate.[133]

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[130]J. Mahaux and K. Kowaleski, Arch. intern. pharmacodynamie, 80, 464 (1949), [C.A., 44, 1605 (1950)].

[131]D. Bovet, P. Durel and V. Longo, Compt. rend. soc. biol., 144, 514 (1950).

[132]J. J. Gordon, Nature, 162, 146 (1948); R. D. Hawkins and B. Mendel, Biochem. J., 44, 260 (1949); H. Casier, Arch. intern. pharmacodynamie, 82, 155, (1950), [C.A., 44, 7983 (1950)].

[133]C. Heymans, ibid., 81, 230 (1950), [C.A., 44, 7428 (1950)].

A "central analgesic" action of diparcol was shown by corneal anesthesia of rabbits.[134]

Diparcol did not inhibit the effect of adrenaline on the heart in experiments on guinea pigs.[120] However, in dogs, chloroform-adrenaline ventricullar fibrillation could be prevented by diparcol.[135] The administration of 10-(2-dimethylamino-1-propyl)phenothiazine, before adrenalin injection, protected rabbits against the edematous effects of adrenaline but did not prevent the blood pressure effects.[136] Contrary to the previous results, reports stated that phenergan failed to protect guinea pigs[137] or rabbits[138] against pulmonary edema induced by adrenaline. Phenergan was effective in the prevention of acute edema of the lungs, caused by chloropicrin, of rabbits.[139]

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[134]A. Hardt and R. Hotovy, Arch. Exptl. Path. Pharmakol. 209, 264 (1950), [C.A., 44, 8519 (1950)].

[135]G. C. Meirsman-Roobroeck, Arch. intern. pharmacodynamie, 83, 353 (1950), [C.A., 44, 10140 (1950)].

[136]B. N. Halpern, J. Hamberger and S. Cruchard, Acta Allergol., 1, 97 (1948), [C.A., 43, 320 (1949)]; B. N. Halpern and S. Cruchard, Experientia, 3, 34 (1948), [C.A., 42, 4277 (1948)]; J. J. Reuse, Compt. rend. soc. biol., 142, 638 (1948).

[137]C. A. Winter, Proc. Soc. Exptl. Biol. Med., 72, 122 (1949).

[138]C. A. Stone and E. R. Loew, ibid., 71, 122 (1949).

[139]B. N. Halpern and S. Cruchard, Compt. rend., 225, 1194 (1947).

Increase in the permeability of the capillaries of the kidneys and the hemato-ocular barrier, produced by histamine or other conditions, was prevented by phenergan.[140] This compound produced a significant decrease in the body temperature of intact rats.[141] The injection of anesthetized cats with phenergan caused an immediate fall in blood pressure; the fall was proportional to the amount injected.[142] Phenergan had a preservative action, lasting for at least two months, on the heart, skeletal muscle, skin, intestine, brain, lung, liver, pancreas and spleen.[143] It had a more pronounced antibiotic action than any other antihistaminic on staphylococcus.[143] It was suggested that the antibiotic action may have been due to the phenothiazine portion of the molecule. Phenergan partially inhibited the action of trypsin and papain on gelatin, but had no effect on the action of pepsin.[144] Administration

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[140] B. N. Halpern, L. G. Guillaumat and S. Cruchard, Acta Allergol., 1, 376 (1948), [C.A., 43, 3526 (1949)]; Compt. rend. soc. biol., 142, 622 (1948); J. Hamburger, B. N. Halpern and J. Neel, ibid., 142, 183 (1948).

[141] B. N. Halpern and M. Briot, ibid., 143, 633 (1949).

[142] S. Glanzmann and J. A. Salva Miquel, Acta Allergol., 2, 26 (1949), [C.A., 43, 7584 (1949)].

[143] J. R. Leduc, Rev. can. biol., 8, 543 (1949); ibid., 8, 439 (1949).

[144] R. Maral, M. Carraz and A. Blandin, Compt. rend. soc. biol., 144, 136 (1950).

of the foregoing phenothiazine derivative suppressed the characteristic local abcess provoked by the subcutaneous injection of a suspension of Salmonella typhimurium;[145] however, it accelerated the spread throughout the body of the bacteria inoculated subcutaneously in rabbits, and increased the mortality as well.[146] The injection of phenergan also caused inoculated vaccine virus to spread rapidly throughout the bodies of rabbits.[147] Phenergan exerted considerable protective action against the ill effects of second-degree burns produced experimentally in rats and guinea pigs.[148]

Side effects noted in some patients treated with phenergan were drowsiness, lassitude, light-headedness and aching limbs.[149] Phenergan prolonged the sleep-producing effect of the barbitrate, evipal, in mice.[150]

The pharmacological properties of diparcol were discussed

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[145] B. N. Halpern and H. Reber, ibid., 143, 257 (1949).

[146] B. N. Halpern, J. Dumas and H. Reber, ibid., 143, 1563 (1949); M. Ducrot, ibid., 143, 1577 (1949).

[147] G. Barski, ibid., 143, 1568 (1949).

[148] J. Pellerat and M. Murat, ibid., 143, 1082 (1949).

[149] W. A. Bain, F. F. Hellier and R. P. Warin, Lancet, 255, 964 (1948).

[150] C. A. Winter, J. Pharmacol. Exptl. Therap., 94, 7 (1948).

in two papers, one by Heymans et al.[151] and the other by Bovet et al.[116] In dogs, diparcol caused a transient fall of blood pressure and peripheral vasodilation. Small doses of the compound suppressed the cardioinhibitory reflexes from the corotid sinus and large ones also depressed the vasomotor reflexes. It blocked the cardioinhibitory action of the vagus but did not affect cardiac inhibition produced by acetylcholine. Diparcol stimulated respiration and had a spasmolytic effect on the intestines and bladder. It counteracted the toxic effects of acetylcholine, diisopropyl fluorophosphate, pilocarpine and nicotine and diminished the convulsions caused by strychnine, metrazole and chloralosan.

A study[152] of the rate of excretion of RP3015 in urine showed that intramuscular injection of the drug resulted in a constant rate of elimination. Oral administration of the compound resulted in irregular excretion for the first few hours. These results suggested that in the latter case, absorption of the drug was not complete in the earlier hours after treatment. The urines of men and rabbits given

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[151] C. Heymans, J. J. Estable and S. C. de Bonneveaux, Arch. intern. pharmacodynamie, 79, 123 (1949), [C.A., 43, 7129 (1949)].

[152] T. Kawakita, Igaku to Seibutsugaku (Med. & Biol.), 18, 170 (1951), [C.A., 45, 5821 (1951)].

phenergan were found to have insignificant antihistaminic activity.[153]

F. Dimetalation of Heterocyclic Compounds

Very few dimetalation reactions of heterocyclic compounds have been reported in the literature. In 1920, Weissgerber and Kruber[154] obtained an amorphous yellow substance from the reaction of thionaphthene with sodamide in xylene at 120°. Treatment of the yellow product with carbon dioxide, water and acid resulted in the production of an acidic material. The crude acid was converted to the methyl ester. From the latter, both methyl thionaphthene-2-carboxylate and dimethyl thionaphthene-2,3-dicarboxylate were isolated. Thus, sodamide must have metalated thionaphthene to give both the mono- and dimetalation product. Thieno[3,2-b]thiophene was dimetalated[155] with excess ethylmagnesium bromide in dimethylaniline at 200°. The isolation of a dicarboxylic acid, following carbonation and subsequent reactions, resulted. By analogy with the metalation of thiophene, the product was probably the 2,5-dicarboxy acid.

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[153] G. Romano, Farm. sci. e tec. (Pavia), 4, 25 (1948), [C.A., 43, 4774 (1949)].

[154] R. Weissgerber and O. Kruber, Ber., 53B, 1551 (1920).

[155] F. Challenger and G. M. Gibson, J. Chem. Soc., 305 (1940).

The oxygen containing heterocycle, dibenzofuran, readily underwent reaction with n-butylsodium in refluxing ether to give, following carbonation and acidification, a 77% yield of the dibasic acid, 4,6-dicarboxydibenzofuran.[156] Treatment of the dimetalated product with dimethyl sulfate gave a 90% yield of crude 4,6-dimethyldibenzofuran. Dibenzofuran was also dimetalated with ethylsodium and ethylpotassium.[157] The metalation of dibenzo-p-dioxin with two and one-half equivalents of n-butyllithium in refluxing ether resulted in the formation of two different dibasic acids, subsequent to carbonation and acidification.[158] The reaction of phenylcalcium iodide with phenoxathiin in refluxing ether gave, following the conventional procedures of carbonation and acidification, a small amount of acid, m.p. 260-262°, which was shown to be dissimilar to phenoxathiin-2-carboxylic acid, m.p. 260-262°.[61] No analytical values were reported for the acid. Later studies showed that phenoxathiin was dimetalated with an equivalent amount of n-butyllithium in refluxing ether.[159] Carbonation and acidification of the reaction mixture gave a dicarboxy acid which was shown to be the same

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[156]H. Gilman and R. V. Young, J. Am. Chem. Soc., 57, 1121 (1935).

[157]H. Gilman and R. V. Young, J. Org. Chem., 1, 324 (1936).

[158]H. Gilman and C. G. Stuckwisch, J. Am. Chem. Soc. 65, 1461 (1943).

[159]S. Avakian, unpublished studies.

as the foregoing unidentified acid. Phenylcalcium iodide reacted with 2,8-dibromodibenzofuran in refluxing ether-benzene (2:1) to give, following carbonation and acidification, a 9.3% yield of 2,8-dibromo-4,6-dicarboxydibenzofuran.[160] This work was repeated later;[161] however, a smaller amount of the acid was isolated. Only unidentifiable products resulted on using phenylsodium or benzylsodium as the metalating agent.[160]

A mixture of mono- and dibasic acids was obtained by the metalation of thianthrene with n-butyllithium (under conditions similar to the metalation of dibenzo-p-dioxin) and subsequent necessary reactions.[158] The dibasic acid was not purified or identified. The reaction of phenylisopropylpotassium with 1,4-dihydrodibenzothiophene gave some dibenzothiophene together with what appeared to be a mixture of mono- and dicarboxydibenzothiophenes following carbonation and acidification.[162] No definite compounds were identified in the acid fraction. Dibenzothiophene-5-dioxide was metalated with varying amounts of n-butyllithium in ether at $-20° \pm 5°$.[163] The metalation product was carbonated and the

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[160] R. E. Dickey, unpublished studies.

[161] D. L. Esmay, unpublished studies.

[162] H. Gilman and A. L. Jacoby, J. Org. Chem., 3, 108 (1938).

[163] D. L. Esmay, Doctoral Dissertation, Iowa State College (1951).

resulting mixture acidified. By using one equivalent of the organometallic compound, an 18% yield of 4-carboxydibenzothiophene-5-dioxide was obtained; with two equivalents of the alkyllithium compound, a 20% yield of the 4-carboxy acid and a 4% yield of 4,6-dicarboxydibenzothiophene-5-dioxide were isolated; and with three equivalents of n-butyllithium, a 20.4% yield of the dicarboxy acid was obtained.

III. EXPERIMENTAL

A. Metalation of Some Derivatives with n-Butyllithium Followed by Reaction with Benzophenone

1. Of phenothiazine[21] to give 1-diphenylhydroxymethylphenothiazine

A solution of 0.113 mole of n-butyllithium[164] in 110 ml. of ether was added in a nitrogen atmosphere to a solution of 7.5 g. (0.0377 mole) of phenothiazine in 200 ml. of anhydrous ether. The solution refluxed spontaneously during the addition of the first 40 ml. of the organometallic compound. The color of the solution changed from amber to dark brown and then to a lighter brown. Refluxing with stirring was continued for twenty-three hours. After twenty hours, Color Test I[165] was strongly positive and Color Test II[166] was indefinite. A solution of 13.7 g. (0.075 mole) of benzophenone in 70 ml. of ether was added at such a rate so as to

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[164]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).

[165]H. Gilman and F. Schulze, ibid., 47, 2002 (1925).

[166]H. Gilman and J. Swiss, ibid., 62, 1847 (1940).

maintain reflux. The color of the solution became very dark. Following hydrolysis, the yellow ether extract was concentrated with the result that 11.8 g. (82%) of fine yellow crystals, m.p. 203-208° (decomp.), separated. Recrystallization from benzene raised the melting point to 213-213.5° (decomp.). The yield of pure product was 10 g. (70%).

Anal. Calcd. for $C_{25}H_{19}NOS$: N, 3.68; active hydrogen, 2.00. Found: N, 3.73; active hydrogen, 1.90 and 1.86.

An infra-red analysis[167] of the compound indicated the presence of the imino, hydroxyl, phenyl and o-phenylene groups.

2. Of 10-ethylphenothiazine[54] to give 4-diphenylhydroxymethyl-10-ethylphenothiazine

A solution of 0.124 mole of n-butyllithium[164] (prepared from butyl bromide and lithium in 76% yield) in 100 ml. of ether was added rapidly with stirring to a mixture of 22.7 g. (0.1 mole) of 10-ethylphenothiazine and 350 ml. of anhydrous ether. The apparatus had previously been dried and swept out with dry nitrogen. The addition of the first portion of the organometallic compound caused the color of the mixture to turn from light green to light yellow. The mixture was stirred with refluxing in a nitrogen atmosphere

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[167]The analysis and interpretation thereof were made by Dr. V. A. Fassel and Mr. M. Margoshes.

for twenty-three hours. After eighteen hours, both Color Test I[165] and Color Test II[166] were positive. A solution of 22.7 g. (0.124 mole) of benzophenone in 50 ml. of ether was added with external cooling by immersing the reaction flask in a cold water bath. During the addition of the benzophenone the color of the solution underwent a series of changes: light orange, dark green, orange and finally dark brown. The reaction mixture was stirred for a few minutes longer and then hydrolyzed with 200 ml. of water. The color of the ether layer still remained dark. The ether layer was separated and dried with anhydrous sodium sulfate. The warm residual oil, after removal of the ether, was immediately dissolved in 500 ml. of hot petroleum ether (b.p. 60-70°). On cooling 5.7 g. of brown oil separated from the solution. The mother liquor was chromatographed on a 48 x 212 mm. column of alumina.[168] From the eluate there were obtained 8.0 g. (35% recovery) of ethylphenothiazine, a small amount of benzophenone and 16.2 g. of white crystals, m.p. 170-175°. A solution of the foregoing 5.7 g. of brown oil in 120 ml. of benzene was chromatographed on a 19 x 155 mm. column of alumina[168] giving 4.2 g. of white crystals, m.p. 160-170°. The total yield of the crude carbinol was 20.4 g. (77% yield on the basis of the 10-ethylphenothiazine recovered). The carbinol was purified by recrystallization

[168]Alcoa Activated Alumina, Grade: F-20.

from acetone giving 14.5 g. (55%) of coarse crystals, m.p. 180-181°.

Anal. Calcd. for $C_{27}H_{23}NOS$: N, 3.42; active hydrogen, 1.00. Found: N, 3.47; active hydrogen, 0.94.

Little information was obtained from the complex infrared spectrum[167] of the product. One of the bands indicated the presence of the hydroxy group in the molecule.

3. Of 10-(γ-diethylaminopropyl)phenothiazine to give 4-diphenylhydroxymethyl-10-(γ-diethylaminopropyl)phenothiazine

One hundred and twenty-five milliliters of 1.16M n-butyllithium[164] (0.145 mole) in ether was added to a solution of 31.3 g. (0.1 mole) of 10-(γ-diethylaminopropyl)-phenothiazine in 150 ml. of anhydrous ether. The solution was stirred, in an atmosphere of nitrogen, at reflux temperature for twenty-two hours and at room temperature for fifteen hours. Color Test I[165] of the red-brown solution was positive. A solution of 30 g. (0.165 mole) of benzophenone in 50 ml. of dry ether was added over a period of a few minutes. An ice bath prevented refluxing of the solution. Following hydrolysis, the ether layer was extracted with 200 ml. of 1.6N hydrochloric acid. A dilute acid and ether insoluble oil, brown in color, separated. The acidic solution and oil were made alkaline with sodium hydroxide and the mixture was extracted with ether. The ether solution

was dried with sodium carbonate. A residue of 41.3 g. of dark brown oil remained after removal of the ether. This weight of product was an increase of 10 g. over that of the phenothiazine derivative used in the reaction. The 10 g. increase thus represented the reaction of 0.055 mole of benzophenone or 55% monometalation. The crude product dissolved, with the exception of 1.5 g. of gum, in 700 ml. of petroleum ether (b.p. 60-70°). The solution was chromatographed on a column of about 500 g. of alumina.[169] The column was eluted with petroleum ether (b.p. 60-70°), benzene and chloroform, in the order named. The only crystallizable portion of the product was obtained from the benzene eluate. The crude monocarbinol, m.p. 136-139°, weighed 5 g. (10%). Recrystallization from benzene gave 4 g. (8%) of white, cubic crystals, m.p. 140-140.5°.

Anal. Calcd. for $C_{32}H_{34}N_2OS$: N, 5.66; active hydrogen, 1.00. Found: N, 5.56; active hydrogen, 1.07 and 0.94.

The chloroform eluted a brown oil which gave an intense green color with concentrated hydrochloric acid. Treatment of the product, m.p. 140-140.5°, in a similar fashion with the acid gave only a light reddish colored material. The oil set to a glass; however, all attempts to crystallize it failed. An infra-red analysis[167] showed that the compound had a hydroxyl group. Because of the complex nature of the

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[169]Fisher Scientific Co., A-541/2, 80-200 mesh.

infra-red curve, little other evidence concerning the structure of the compound could be obtained.

4. Of 10-[β-(1-pyrrolidyl)ethyl]phenothiazine to give 4-diphenylhydroxymethyl-10-[β-(1-pyrrolidyl)ethyl]phenothiazine and 4,6(?)-bis(diphenylhydroxymethyl)-10-[β-(1-pyrrolidyl)ethyl]phenothiazine

One hundred and forty-five thousands mole of n-butyllithium[164] in 120 ml. of ether was added to a solution of 29.6 g. (0.1 mole) of 10-[β-(1-pyrrolidyl)ethyl]phenothiazine[170] in 250 ml. of anhydrous ether. The mixture was stirred under reflux in an atmosphere of nitrogen for twenty-two hours. The color of the solution remained yellow throughout the course of the metalation reaction. Color Test II[166] gave a dark green color and therefore indefinite evidence concerning the presence of any butyllithium. Color Test I[165] was positive. A solution of 26.4 g. (0.145 mole) of benzophenone in 60 ml. of ether was added. The color of the mixture gradually changed from yellow to very dark green and then brown. The mixture was hydrolyzed, a yellow ether layer resulted. The latter was separated. On standing, 11 g. (16.7%) of white solid, m.p. 192-194°, crystallized from the ether solution. This compound was slightly soluble

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[170] The free base was obtained from a generous sample of pyrrolazote hydrochloride kindly supplied by Dr. J. A. Hogg of The Upjohn Company, Kalamazoo, Mich.

in the common organic solvents. Two recrystallizations of the product from dioxane gave 8.1 g. (12.3%) of fine white crystals, m.p. 199-200°. Recrystallization of a portion from petroleum ether (b.p. 60-70°) did not change the melting point.

Anal. Calcd. for $C_{44}H_{40}N_2O_2S$: N, 4.24; S, 4.85; active hydrogen, 2.00. Found: N, 4.12 and 4.10; S, 4.44 and 4.41; active hydrogen, 1.95 and 2.00.

The infra-red spectrum[167] of this compound showed the presence of a hydroxyl group in the molecule as well as a vicinal trisubstituted benzene ring.

The ethereal mother liquor was extracted with dilute hydrochloric acid. An insoluble red oil separated. The oil was treated with dilute sodium hydroxide to liberate the free base and the mixture extracted with ether. After drying the ether solution with sodium carbonate, the ether was removed leaving 24.4 g. of oil which changed to a sticky glass on standing. This material was refluxed with about 600 ml. of petroleum ether (b.p. 60-70°) giving a yellow solution and leaving an insoluble oil. The solution was chromatographed on a column of 250 g. of alumina[168]. The column was eluted with petroleum ether (b.p. 60-70°), benzene and chloroform, respectively. The benzene eluted 1.3 g. (2.7%) of material, m.p. 203-204°. Recrystallization from 100 ml. of acetone gave white crystals, m.p. 204-205°. The

mixed melting point with the other product, m.p. 199-200°, was depressed to 183-193°.

Anal. Calcd. for $C_{31}H_{30}N_2OS$: N, 5.86; active hydrogen, 1.00. Found: N, 5.90; active hydrogen, 0.89 and 0.94.

B. Metalation of Some Derivatives with n-Butyllithium Followed by Carbonation

1. Of 10-(γ-diethylaminopropyl)phenothiazine

A solution of 71.8 g. (0.23 mole) of 10-(γ-diethylaminopropyl)phenothiazine[80] and 0.267 mole of n-butyllithium[164] in 600 ml. of ether was stirred at room temperature in an atmosphere of nitrogen for twenty hours. The color of the solution changed from light yellow to light orange. At the end of this time Color Test II[166] gave a red brown color and Color Test I[165] was positive. The solution was poured jet-wise into a stirred Dry Ice-ether slurry. The mixture was hydrolyzed with the result that an emulsion formed. The addition of sodium hydroxide did not break the emulsion, thus it had to be filtered. The alkaline layer, after separation from the ether, was made slightly acid with hydrochloric acid giving 29 g. of gum which did not solidify. This gum dissolved readily in concentrated hydrochloric acid but separated again on dilution of the acid solution. Solution of the gum was effected by treatment

with dilute sodium hydroxide. Adjustment of the pH of the solution to 5 precipitated an oil. Further attempts to crystallize the acidic material, or its sodium salt, by treatment with ethanol were unsuccessful.

2. Of 10-ethylphenothiazine-5-oxide[171] to give 10-ethylphenothiazine-4-carboxylic acid

(a) At 0°. A solution of 0.025 mole of n-butyllithium[164] in 26 ml. of ether was added, in an atmosphere of nitrogen, to a stirred suspension of 6.1 g. (0.025 mole) of 10-ethylphenothiazine-5-oxide in 250 ml. of ether at -20 ± 5°. After an hour, Color Test II[166] was still positive. The color of the ether solution had immediately become yellow. After three hours there was no visible change in the mixture, therefore an additional amount of n-butyllithium (0.05 mole) was added; the temperature was allowed to increase to 0° and maintained at that point for four hours. The metalation reaction was terminated by pouring the solution jet-wise, through a glass-wool plug, into a Dry Ice-ether slurry. The monoxide never completely dissolved during the course of the reaction, thus 1.4 g. (23%) of undissolved 10-ethylphenothiazine-5-oxide was recovered. The carbonation mixture

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[171] Compare the reaction of n-butyllithium with dibenzothiophene-5-oxide, H. Gilman and D. L. Esmay, J. Am. Chem. Soc., in press.

was extracted with very dilute sodium hydroxide. The ether layer, after separation, was dried with potassium carbonate. Removal of the ether left a small amount of oil which was not investigated further. Acidification of the alkaline layer precipitated 4.0 g. (76% on the basis of the oxide that underwent reaction) of yellow acidic material, m.p. 171-175°. Recrystallization of this product from acetic acid gave 2.8 g. (53%) of yellow, cubic crystals, m.p. 178-179°. The mixed melting point with the acid which Van Ess[54] had prepared by the metalation of 10-ethylphenothiazine, and appropriate reactions, was undepressed. The latter acid itself melted at 178-179° and was shown to be 10-ethylphenothiazine-4-carboxylic acid by an indirect method.[16] No 10-ethylphenothiazine was isolated from this reaction.

(b) <u>At -20°</u>. The amount of reagents and the conditions of the reaction were the same as in the previous case with the exception that the temperature was maintained at -20 ± 5° for six and one-half hours. The solution was carbonated and worked up in a similar fashion as well. Seven-tenths gram (11.5%) of 10-ethylphenothiazine-5-oxide was recovered which had never dissolved during the course of the reaction. The reason that a smaller amount of oxide was recovered in this reaction could be explained by its having been in a finer state of subdivision. One and eight-tenths grams (36% on the basis that 5.4 g. of the oxide

underwent reaction) of 10-ethylphenothiazine was isolated from the ether extract. Acidification of the alkaline solution precipitated 2.9 g. (48%) of yellow solid, m.p. 166-171°. Purification of the acidic material was effected by recrystallization from acetic acid thereby giving 1.5 g. (25%) of the pure acid, m.p. 178-179°. The mixed melting point with an authentic sample of the acid was undepressed.

C. Preparation of 10-Substituted Phenothiazine Derivatives

1. 10-(γ-Diethylaminopropyl)phenothiazine[80]

The phenothiazine used in this and subsequent reactions was purified in the following fashion. Sixty to seventy grams of the crude material was dissolved in approximately 600 ml. of hot toluene and the resulting solution treated with Norit and filtered. Upon cooling, a yellow solid crystallized from the filtrate. The solid was filtered off. The filter cake was suspended in about 400 ml. of petroleum ether (b.p. 60-70°). The mixture was refluxed for a few minutes and then filtered while still hot. The purified material weighed 40-50 g. and melted at 181-182°.

Eighty-five grams (0.427 mole) of phenothiazine was added, with stirring, to 0.435 mole of sodamide[172] (prepared

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

from 10.0 g. of sodium and liquid ammonia) in 450 ml. of liquid ammonia in a one-liter, three-neck flask equipped with a stirrer and protected from the moisture in the atmosphere by drying tubes. After stirring for one hour, 340 ml. of xylene was carefully added and the ammonia allowed to evaporate. The mixture was heated to reflux and 68.2 g. (0.455 mole) of γ-diethylaminopropyl chloride was added over a period of two hours. The mixture was then refluxed with stirring for another hour. After cooling, the mixture was extracted with 800 ml. of 1.25N hydrochloric acid and the acidic solution was in turn extracted with one liter of ether. The aqueous solution was made alkaline with about 70 g. of sodium hydroxide. The alkaline solution was extracted with ether and the ether solution dried over anhydrous sodium sulfate. The ether was removed by distillation. The residue was distilled under reduced pressure giving 113 g. (84.5%) of yellow oil, b.p. 147-153° (0.03-0.04 mm.).

Various attempts to prepare the crystalline picrate of this compound[8] failed; only an oil resulted.

2. 10-Methylphenothiazine[58]

Fifteen millliliters of dimethyl sulfate (Eastman practical grade) was added with stirring to a mixture of 10 g. (0.05 mole) of phenothiazine, dissolved in 100 ml. of dioxane, and 50 g. of anhydrous potassium carbonate. The

color of the mixture immediately turned brown and soon after heating to a reflux temperature, the color became yellow. After three and one-half hours of refluxing with stirring, another 10 ml. of dimethyl sulfate was added. The mixture was refluxed with stirring for a total of twenty-four hours. It was carefully poured into about 400 ml. of warm water, and after standing overnight, 10.5 g. of tan solid, m.p. 75-80°, was filtered off. After extracting this solid with hot ethanol, a tar remained. From the ethanol extract there crystallized 4.3 g. (40%) of light yellow needles, m.p. 91-94°. Four and four-tenths grams of solid, m.p. 120-150°, was obtained from the mother liquor. This compound was not investigated further since its melting point was considerably higher than that of 10-methylphenothiazine. The solid, m.p. 91-94°, was recrystallized from 95% ethanol giving 2.8 g. (26%) of yellow needles, m.p. 99-100°.

3. 10-Ethylphenothiazine[54,66]

(a) In benzene. Nineteen and nine-tenths grams (0.1 mole) of phenothiazine was added with mechanical stirring to 0.113 mole of sodamide[172] (prepared from 2.6 g. of sodium and 200 ml. of liquid ammonia) in liquid ammonia. After fifteen minutes, 120 ml. of dry benzene was slowly added; the mixture partially solidified. Following the evaporation of the ammonia, the mass again became fluid. The mixture

was gently refluxed for three hours and then a solution of 24.0 g. (0.154 mole) of ethyl iodide in 35 ml. of dry benzene was added dropwise over a period of two and one-half hours. The refluxing with stirring was continued for an additional hour. The hot mixture was then filtered and the residue washed with warm benzene; the total volume of the solution was about 350 ml. The cold solution was chromatographed on a column of 180 g. of alumina[168] giving 16 g. (70%) of crude 10-ethylphenothiazine and some phenothiazine (identified by the mixed melting point method). Two recrystallizations of the crude product gave 8.1 g. (36%) of yellow needle-like prisms, m.p. 102.5-103°.

(b) In liquid ammonia. Forty-seven grams (0.236 mole) of phenothiazine was added with stirring to a suspension of 0.26 mole of sodamide[172] in 1600 ml. of liquid ammonia giving a dark red mixture. The stirring was continued for two and one-half hours and then 39 g. (0.354 mole) of ethyl bromide was added dropwise over a period of forty-five minutes. During the addition of the ethyl bromide, the color of the mixture gradually became lighter and a grey-brown solid separated. The ammonia was allowed to evaporate and the residue was refluxed with 500 ml. of petroleum ether (b.p. 60-70°) and benzene (1:2). The inorganic material was filtered off and washed with three small portions of hot benzene. The golden brown filtrate was concentrated to 150 ml.

On standing, 19.6 g. of light green cubic crystals, m.p. 103-104°, separated. The mother liquor was chromatographed on a column of 180 g. of alumina[169] giving 32.2 g. of light green crystals, m.p. 102-103°. The total yield of pure 10-ethylphenothiazine was 51.8 g. (97%).

In a second preparation of 10-ethylphenothiazine, 19.9 g. (0.1 mole) of phenothiazine was added to 0.11 mole of sodamide[172] in 650 ml. of liquid ammonia. The resulting mixture was treated with 16.5 g. (0.15 mole) of ethyl bromide in the same manner as in the preceding reaction. After evaporation of the ammonia, the residue was extracted with a solution of benzene and petroleum ether (b.p. 60-70°) (4:1). The solution was chromatographed on a column of 200 g. of alumina[169] to give 21 g. (92%) of the desired product, m.p. 103-104°, and 0.3 g. (1.5%) of phenothiazine (mixed melting point).

4. 10-Benzylphenothiazine[52,69,99]

Nineteen and nine-tenths grams (0.1 mole) of phenothiazine was added with mechanical stirring to a suspension of 0.12 mole of sodamide[172] (prepared from 2.96 g. of sodium and liquid ammonia) in 80 ml. of dry xylene. The brown mixture was refluxed for forty minutes and then a solution of 19 g. (0.15 mole) of benzyl chloride in 20 ml. of xylene was added dropwise over a period of two and one-half hours. The

mixture was refluxed for another half-hour. The color changed from brown to black. The mixture was filtered while hot to remove the inorganic material. The solvent was removed and the residue distilled giving 10 g. of yellow oil, b.p. 195-205° (0.02-0.03 mm.) with the heating bath at 270-290°. The oil was dissolved in benzene and the solution chromatographed on a column of alumina.[169] From the eluate there were obtained 4.5 g. (15.5%) of white crystals, m.p. 88.5-90°. This solid was recrystallized from ethanol giving small white platelets, m.p. 90-90.5°. Zarember[69] obtained a compound from the cleavage of 2-benzyloxyquinoline with phenothiazine which melted at 91-92° and analyzed for 10-benzylphenothiazine. The mixed melting point of his phenothiazine derivative with the foregoing 10-benzylphenothiazine was undepressed.

5. 10-Phenylphenothiazine[54] (attempted)

(a) In xylene. Nineteen and nine-tenths grams (0.1 mole) of phenothiazine was added to a suspension of 0.12 mole of sodamide[172] (prepared from 2.76 g. of sodium and liquid ammonia) in 80 ml. of dry xylene and the mixture heated, with mechanical stirring, at reflux temperature for two hours. A solution of 30.6 g. (0.15 mole) of iodobenzene in 20 ml. of dry xylene was added with stirring over a period of two and one-half hours to the refluxing mixture. The

mixture was refluxed for an additional thirty-five hours. The color of the suspension remained a light brown during the period of reflux. Ten milliliters of ethanol was added to destroy any excess sodamide or 10-sodiophenothiazine. The color of the mixture became almost black. The mixture was filtered while hot to remove the inorganic materials. Twelve grams (60%) of phenothiazine (mixed melting point) crystallized from the filtrate on cooling. There was no evidence indicating the formation or presence of 10-phenylphenothiazine.

(b) In liquid ammonia. 10-Sodiophenothiazine was prepared by adding 10 g. (0.05 mole) of phenothiazine to 0.055 mole of sodamide[172] (prepared from 1.26 g. of sodium) in 400 ml. of liquid ammonia. The dark red mixture was stirred for two and one-half hours and then 15.3 g. (0.075 mole) of iodobenzene was added over a period of one-half hour. The appearance of the mixture did not seem to change. The mixture was stirred for nineteen hours and then an additional 30.6 g. (0.15 mole) of iodobenzene was added. Liquid ammonia was added occasionally to maintain the volume of the mixture at about 400 ml. The mixture was stirred for a total of forty-two hours and then the remaining ammonia was allowed to evaporate. Ten milliliters of ethanol was added to the residue to destroy any active sodium compounds, if such were present. The mixture was extracted with hot benzene to

remove the inorganic material. The benzene solution was concentrated to about 150 ml. An equal volume of petroleum ether (b.p. 60-70°) was added and the dark solution was chromatographed on a 48 x 160 mm. column of alumina.[169] From the eluzte, 42.3 g. (92%) of the iodobenzene (identified by the boiling point) and 8.5 g. (85%) of the phenothiazine (mixed melting point) were recovered. There was no evidence for the formation of 10-phenylphenothiazine.

6. 10-(p-Tolyl)phenothiazine

A mixture of 10.9 g. (0.05 mole) of p-iodotoluene, 10 g. (0.05 mole) of phenothiazine, 0.2 g. of copper bronze powder, 75. g. of anhydrous potassium carbonate, 10 ml. of xylene and 50 ml. of nitrobenzene was heated at 155-165° (internal temperature) with stirring for seventeen hours. The mixture was filtered while still hot and the residue was washed with about 40 ml. of hot xylene. The solvent was removed under reduced pressure; the dark red liquid, which remained, solidified on cooling. The crude product was dissolved in 350 ml. of benzene and the solution chromatographed on a column of 150 g. of alumina[169] giving 4.6 g. (32%) of light yellow solid, m.p. 128-134°. The product was recrystallized from petroleum ether (b.p. 60-70°) to give 2.2 g. (15%) of yellow, coarse, flat, translucent crystals, mp. 135-136°.

Anal. Calcd. for $C_{19}H_{15}NS$: N, 4.85. Found: N, 4.76.

7. 10-(o-Tolyl)phenothiazine

A mixture of 16.4 g. (0.075 mole) of o-iodotoluene, 10 g. (0.05 mole) of phenothiazine, 0.2 g. of copper bronze powder, 7.5 g. of anhydrous potassium carbonate, 50 ml. of nitrobenzene and 5 ml. of xylene was heated at 165-175° (internal temperature) with stirring for twenty-three hours. The inorganic material was removed by filtration of the hot mixture and washed with hot xylene. The solvent was then removed by distillation under reduced pressure. The dark red residue dissolved in 350 ml. of benzene and the resulting solution was chromatographed on a 38 x 185 mm. column of alumina.[169] The eluate was collected in approximately 125 ml. portions. Removal of the solvent left residues totaling 12.4 g. (86%) and melting at 80-95°. The crude material was purified by recrystallization from petroleum ether (b.p. 60-70°) and methanol, respectively, giving 7.5 g. (52%) of light brown, short, coarse needles, m.p. 101-101.5°.

Anal. Calcd. for $C_{19}H_{15}NS$: N, 4.85. Found: N, 4.77.

8. 10-Acetylphenothiazine[5]

(a) Using acetyl chloride. Two and four-tenths grams (0.03 mole) of acetyl chloride in 20 ml. of dioxane was slowly added with stirring to a solution of 2 g. (0.01 mole) of phenothiazine in 40 ml. of dioxane in which was suspended

4 g. of anhydrous sodium carbonate. The mixture was stirred at room temperature for a few minutes and then slowly heated to a gentle reflux. The heating was continued for forty minutes. Immediately upon adding some of the acetyl chloride, the color of the solution changed from blackish brown to dark green. After refluxing for awhile, the color of the solution became light brown. The solution was poured into very dilute hydrochloric acid; 2.2 g. (91%) of yellow solid, m.p. 184-188°, was filtered off. This was recrystallized from ethanol to give 1.9 g. (79%) of light yellow crystals, m.p. 197-198°.

(b) Using acetic anhydride. A solution of 19.9 g. (0.1 mole) of phenothiazine in 50 ml. of acetic anhydride (90-95%) was refluxed for three hours. On cooling the solution in an ice-bath, 23.8 g. (99%) of solid, m.p. 198-199°, crystallized. The mixed melting point with the compound from the previous reaction was undepressed.

9. 10-Chloroacetylphenothiazine[90]

A solution of 5.7 g. (0.05 mole) of chloroacetyl chloride in 10 ml. of dioxane was added with stirring to a mixture of 8 g. (0.04 mole) of phenothiazine, dissolved in 45 ml. of dioxane, and 7 g. of anhydrous sodium carbonate. The mixture was heated on a water-bath at 45-60° with stirring for eighty minutes and then poured into a very dilute

sodium carbonate solution. A green solid separated immediately and on standing overnight, some white needles crystallized. The crude product weighed 11.1 g. (100%) and melted at 95-100°. The product was recrystallized from 95% ethanol to give 8 g. (72%) of greenish needles, m.p. 113-115°. If the solution were too concentrated, the product would oil out. The solid was purified by recrystallization from a benzene-petroleum ether (b.p. 60-70°) solution to give 5 g. (45%) of brownish,translucent needles of square cross-sectional area, m.p. 113.5-114.5°.

10. 10-Dichloroacetylphenothiazine

(a) Using dichloroacetic acid anhydride. Fourteen and four-tenths grams (0.06 mole) of dichoroacetic acid anhydride was added to a solution of 8 g. (0.04 mole) of phenothiazine in 25 ml. of dioxane. The mixture was heated with stirring at 70-75° for two hours and then allowed to stand an additional three hours at room temperature. The mixture was poured into water. An oil separated which promptly solidified to give 12.5 g. (100%) of green solid, m.p. 123-131°. This was recrystallized from ethanol to give 10 g. of green crystals, m.p. 136-140°. Further recrystallization from either ethanol or glacial acetic acid did not further raise the melting point. Therefore, a dilute benzene solution of the crude product was chromatographed on a column

of 150 g. of alumina.[169] The eluate was concentrated and 5 g. of very light green solid, m.p. 152-155°, crystallized. This was recrystallized from ethanol to give 4 g. (32%) of light green crystals, m.p. 154-155°.

Anal. Calcd. for $C_{14}H_9Cl_2NOS$: N, 4.52; Cl, 22.86. Found: N, 4.87 and 4.66; Cl, 22.32, 22.42 and 22.42.

(b) Using dichloroacetyl chloride. Four grams (0.027 mole) of dichloroacetyl chloride in 20 ml. of dioxane was added with stirring to 2 g. (0.01 mole) of phenothiazine in 40 ml. of dioxane containing 4 g. of anhydrous sodium carbonate. The color of the mixture first turned green and then brownish black. The mixture was heated at a gentle reflux temperature for forty minutes. The solution was poured into water from which a tar separated. The tar was dissolved in a mixture of 95% ethanol and acetone. The concentration of the solution resulted in, first, the deposition of a tar, and then crystals. These crystals were dissolved in 95% ethanol and addition of water to this solution caused the precipitation of 1 g. (33%) of solid, m.p. 105-115°. This solid was recrystallized from petroleum ether (b.p. 60-70°) containing a small amount of ethanol to give 0.7 g. (23%) of light green crystals, m.p. 138-142°. Further recrystallizations yielded a small amount of solid, m.p. 149-151°. The mixed melting point with 10-dichlorophenothiazine prepared by the first procedure was undepressed.

(c) An attempted preparation. A solution of 4 g. (0.02 mole) of phenothiazine and 25 ml. of ethyl dichloroacetate was heated on a hot water-bath for two hours.[173] On cooling a greenish solid, m.p. 177-179° (decomp.), crystallized from the solution. The mixed melting point with phenothiazine was undepressed. The mother liquor was refluxed for two hours and on cooling in an ice-bath a solid, m.p. 170-175°, crystallized out. This was shown to be crude phenothiazine. A total of 2.1 g. of phenothiazine was recovered. There was no evidence for the presence of the desired product.

(d) A second attempted preparation. Three and five-tenths grams (0.024 mole) of dichloroacetyl chloride was added with stirring to an ice-cold solution of 3 g. (0.016 mole) of phenothiazine in 35 ml. of pyridine. The solution darkened immediately. It was allowed to stand at 40° for forty minutes and then refluxed for thirty minutes. The cooled solution was poured into dilute hydrochloric acid. A dark brown solid, m.p. 175-178°, precipitated. This was shown to be phenothiazine by the mixed melting point method. None of the desired acyl compound was isolated.

Repetition of the experiment gave the same results.

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[173]The procedure followed for this reaction was that described for the preparation of dl-N-dichloroacetyl-1-p-nitrophenyl-2-amino-1, 3-propanediol from the free amine. J. Controulis, M. C. Rebstock, and H. M. Crooks, Jr., J. Am. Chem. Soc., 71, 2463 (1949).

11. 10-Phenacetylphenothiazine

A solution of 20 g. (0.13 mole) of phenacetylchloride in 30 ml. of dioxane was added to a mixture of 19.9 g. (0.10 mole) of phenothiazine, dissolved in 80 ml. of dioxane, and 11 g. of anhydrous sodium carbonate. The mixture was heated with stirring at about 50° for two and one-half hours. The color of the solution turned green, then black and finally green again. The mixture was poured into water and 31.9 g. (100%) of solid, m.p. 139-145°, separated. This was recrystallized twice from benzene to give 21 g. (66%) of white cubic crystals, m.p. 152-155°.

Anal. Calcd. for $C_{20}H_{15}NOS$: N, 4.46. Found: N, 4.43.

12. 10-(3-Carboxy-4-hydroxyphenyl)phenothiazine (attempted)

A mixture of 8.6 g. (0.043 mole) of phenothiazine, 10 g. (0.043 mole) of methyl 5-bromosalicylate, 7 g. of potassium carbonate, 2 g. of copper bronze powder and 7 ml. of xylene was heated, with stirring, in an oil-bath at 155-170° for twenty-four hours. The contents of the flask were extracted with hot benzene. Six and six-tenths grams (77%) of phenothiazine (mixed melting point) crystallized from the benzene extract. Boiling water was added to the residue and the mixture filtered while hot. Acidification of the aqueous filtrate resulted in the precipitation of 7.5 g. (80%) of 5-bromosalicylic acid. The latter was identified by the

mixed melting point method. None of the desired product was isolated.

13. 10-(3-Carboxy-4-nitrophenyl)phenothiazine (attempted)

(a) Using methyl 2-nitro-5-bromobenzoate. A mixture of 26 g. (0.1 mole) of the ester, 19.9 g. (0.1 mole) of phenothiazine, 15 g. of potassium carbonate, 2 g. of copper bronze powder and 100 ml. of toluene was refluxed with stirring for twenty hours. The refluxing was continued for an additional sixteen hours after adding 30 ml. of xylene. The hot mixture was then filtered. Fifteen grams (75%) of phenothiazine and 12 g. (46%) of methyl 2-nitro-5-bromobenzoate were recovered. These compounds were identified by the mixed melting point method. There was no evidence for the presence of the desired condensation product.

(b) Using 2-nitro-5-bromobenzoic acid. A solution of 7.3 g. (0.03 mole) of 2-nitro-5-bromobenzoic acid and 6 g. (0.03 mole) of phenothiazine in 25 ml. of pyridine was refluxed for twenty-four hours. There was no evidence for the desired reaction taking place by testing aliquotes of the reaction mixture for the presence of bromide ion. One-half gram of copper bronze powder was added and the refluxing continued for another twenty-four hours. The solution was then diluted with benzene and extracted with 7% potassium hydroxide. Acidification of the alkaline extract yielded

no organic acid. The benzene layer was extracted with dilute hydrochloric acid and on standing 3 g. (50%) of phenothiazine (mixed melting point) crystallized from the benzene. A nitrobenzene-like odor was detected in the benzene extract. None of the desired product could be isolated.

14. p-(10-Phenothiazyl)benzenesulfonamide (attempted)

(a) Using p-bromobenzenesulfonamide. A mixture of 19.9 g. (0.1 mole) of phenothiazine, 33.9 g. (0.15 mole) of p-bromobenzenesulfonamide, 13 g. of anhydrous potassium carbonate and 2 g. of copper bronze powder was heated at 200-205°, with stirring, for four and one-half hours. Five milliliters of xylene was added to make the melt more fluid and to wash down the phenothiazine that had sublimed to the upper part of the flask. The temperature of the oil-bath dropped to 180°. The reaction was continued for twenty-one hours. The hot mixture was extracted with toluene. On cooling, 16 g. (80%) of phenothiazine (mixed melting point) crystallized. No condensation product was isolated.

(b) Using p-iodobenzenesulfonamide. Twenty-five grams (0.126 mole) of phenothiazine, 28.3 g. (0.1 mole) of the amide, 30 ml. of xylene, 10 g. of anhydrous potassium carbonate and 2 g. of copper bronze powder were heated, with stirring, in an oil-bath at 160° for sixteen hours. The reaction mixture was worked up in a manner similar to the

preceding experiment. Twenty grams (80%) of p-iodobenzenesulfonamide and 23 g. (92%) of phenothiazine were recovered. Both compounds were identified by the mixed melting point method. There was no evidence for the formation of the desired product.

D. Preparation of Some Monoxides and Dioxides

1. Phenothiazine-5-oxide[101]

A solution of 24.5 g. (0.123 mole) of phenothiazine, 800 ml. of ethanol, 8 ml. of 10% alcoholic potassium hydroxide and 24 ml. of 30% hydrogen peroxide was heated with stirring on a steam-bath for three hours.[101] A small amount of solid was filtered off. Very little solid crystallized from the mother liquor, even after it had stood for ten days. Therefore, the solution was poured into 3 l. of water; 24.1 g. of solid, m.p. 160-163° (decomp.), which had precipitated, was filtered off. Barnett and Smiles[49] reported that phenothiazine-5-oxide melted at about 250° (decomp.). Apparently the reaction did not go to completion under the conditions described. Therefore, the solid, m.p. 160-163° (decomp.), was redissolved in 750 ml. of ethanol and 35 ml. of 30% hydrogen peroxide was added to the refluxing solution. The solution was refluxed for four hours. Most of the solvent was removed by distillation and the remaining solution was poured into

water; 25.4 g. (96%) of yellow solid, m.p. 242-242.5° (decomp.), which had precipitated, was filtered off. Recrystallization of the solid from ethanol did not change its melting point. The mixed melting point with an authentic sample of phenothiazine-5-oxide was undepressed.

2. 10-Methylphenothiazine-5-dioxide[5]

(a) Using potassium permanganate. One hundred and fifty milliliters of 3% potassium permanganate solution was added to a hot solution of 3 g. (0.014 mole) of 10-methylphenothiazine in 40 ml. of dioxane. The solution was refluxed with stirring for one and one-half hours. From time to time solid potassium permanganate was added, the first portions causing a vigorous reaction. The hot mixture was filtered and the manganese dioxide extracted with three portions of dioxane. The dioxane solution was poured into water precipitating 2.8 g. (81%) of white solid, m.p. 217-220°. Recrystallization of this product from ethanol-dioxane (1:1) gave 2.2 g. (64%) of white crystals, m.p. 221-223°.

(b) Using hydrogen peroxide. Three milliliters of 30% hydrogen peroxide was added to a solution of 1.4 g. (0.0066 mole) of 10-methylphenothiazine in 20 ml. of glacial acetic acid. After one-half hour of reflux, about 10 ml. of solvent was removed by distillation. During the course of the reaction, the color of the solution changed from dark brown to red. On cooling, 1.0 g. (62%) of orange platelets, m.p.

218-219° (decomp.), crystallized from the residual solution. This product was recrystallized from ethanol to give 0.7 g. (44%) of brown crystals, m.p. 220-221° (decomp.). The mixed melting point with 10-methylphenothiazine-5-dioxide prepared by the first method was undepressed.

3. 10-Ethylphenothiazine-5-oxide

Three hundred milliliters of 30% hydrogen peroxide was added to a hot solution of 29.5 g. (0.13 mole) of 10-ethylphenothiazine in 1200 ml. of absolute ethanol. The mixture was refluxed for a total of eight hours. After five hours, more hydrogen peroxide (100 ml.) was added. The solution stood for fifteen hours and was then concentrated by distilling off 700 ml. of solvent. The remaining solution was poured into 2 l. of ice water, thus precipitating 25.5 g. of white solid, m.p. 146-149°. Recrystallization of the product from 125 ml. of absolute ethanol gave fine white crystals, m.p. 145-150°. Since this one recrystallization from ethanol did not seem to purify the product, the total amount of crude material was dissolved in 800 ml. of benzene and the solution chromatographed on a 38 x 196 mm. column of alumina.[168] The column was eluted with benzene and finally absolute ethanol, the eluate being collected in 125 ml. portions. This procedure resulted in the isolation of 5.2 g. (15.5%) of 10-ethylphenothiazine-5-dioxide, m.p. 161-163°,

and 19.7 g. (62%) of the monoxide, m.p. 162-163°. The mixed melting point of the two products was depressed to 138-141°.

Anal. Calcd. for $C_{14}H_{13}NOS$: N, 5.76. Found: N, 5.85.

4. 10-Ethylphenothiazine-5-dioxide[66]

A solution of 29.5 g. (0.13 mole) of 10-ethylphenothiazine and 40 ml. of 30% hydrogen peroxide in 750 ml. of glacial acetic acid was heated at about 70° with stirring for one and one-half hours. The color of the solution changed from dark green to dark brown and then to amber. More hydrogen peroxide (12 ml.) was added and the solution stood for three hours at room temperature. Five hundred and fifty milliliters of solvent was removed by distillation under the reduced pressure produced by a water aspirator. From the residual solution, there crystallized 26.5 g. (78.5%) of buff colored platelets, m.p. 162-164°. The mother liquor was poured into one liter of water thereby precipitating 7.1 g. (21%) of brown solid, m.p. 157-159°. Recrystallization of the latter portion from 75 ml. of ethanol gave 5.6 g. (16.5%) of long, brown crystals, m.p. 161-163°. The total yield of pure product was 32.1 g. (95%). The mixed melting point with the dioxide obtained from the previous reaction was undepressed.

5. 10-Acetylphenothiazine-5-oxide

(a) Using nitric acid. Five milliliters of concentrated nitric acid (d. 1.42) was slowly added to a solution of 5 g. (0.021 mole) of 10-acetylphenothiazine in 105 ml. of glacial acetic acid cooled in an ice-bath. After twenty minutes an additional milliliter of nitric acid was added. The reaction mixture was stirred occasionally while standing in the ice-bath for thirty minutes and then poured into 400 ml. of water. After a few minutes a dark red solid began to separate, this was filtered off and shown to be 3-nitrophenothiazine-5-oxide by the mixed melting point method. The filtrate was poured over ice and 2.5 g. (46%) of light brown powder, m.p. 156-159°, was filtered off. The product was purified by five recrystallizations from ethanol to give 1 g. (19%) of flat white needles, m.p. 169.5-170°.

Anal. Calcd. for $C_{14}H_{11}NO_2S$: N, 5.45. Found: N, 5.47.

Further attempts to prepare this compound by nitric acid oxidation beginning with 10 g. (0.042 mole) of 10-acetylphenothiazine resulted in very low yields of even the crude monoxide.

(b) Using hydrogen peroxide. A solution of 5 g. (0.021 mole) of 10-acetylphenothiazine, 500 ml. of ethanol and 60 ml. of 30% hydrogen peroxide was refluxed for five hours. Another 20 ml. of hydrogen peroxide was added and the refluxing continued for thirty minutes. The solution stood at

room temperature for about sixty hours. Approximately 450 ml. of the solvent was removed by distillation and still no solid crystallized out. Water was added and 4.7 g. (88%) of white solid, m.p. 169-170°, separated. The mixed melting point with 10-acetylphenothiazine-5-oxide prepared by the first method was undepressed.

6. 10-Acetylphenothiazine-5-dioxide

(a) From 10-acetylphenothiazine. Five milliliters of 30% hydrogen peroxide was added with stirring to a solution of 5 g. (0.021 mole) of 10-acetylphenothiazine in 150 ml. of glacial acetic acid at room temperature. A solid began to separate out after a few minutes (this solid was shown to be unreacted started material). After fifteen minutes another 3 ml. of hydrogen peroxide was added. The mixture was heated to about 60° and after some time the solid went back into solution. The solution was maintained at 60° for one and one-half hours with stirring. After standing overnight, 120 ml. of solvent was removed by distillation under reduced pressure. Four and three-tenths grams (80%) of white solid, m.p. 200-216° (decomp.), crystallized from the cooled solution. Recrystallization of the product from ethanol gave 3.9 g. (68%) of small, flat, white crystals, m.p. 216-217°.

Anal. Calcd. for $C_{14}H_{11}NO_3S$: N, 5.13. Found: N, 5.18.

(b) From 10-acetylphenothiazine-5-oxide. Six-tenths milliliter of 30% hydrogen peroxide was added with stirring to a solution of 0.36 g. (0.0014 mole) of 10-acetylphenothiazine-5-oxide in 16 ml. glacial acetic acid at about 60°. The color of the solution turned from brown to red. After twenty minutes another 0.3 ml. of hydrogen peroxide was added. The solution was heated at about 60° with stirring for a total time of one hour and then poured into about 125 ml. of water. The pink solid, which was filtered off, weighed 0.17 g. (45%) and melted at 200-203° with darkening beginning at 195°. Two recrystallizations of the product from ethanol gave white platelets, m.p. 214-216°. The mixed melting point with a sample of 10-acetylphenothiazine-5-dioxide prepared by the previous method was undepressed.

7. 10-Chloroacetylphenothiazine-5-oxide

Two and three-tenths milliliters of concentrated nitric acid (d. 1.42) was added dropwise with stirring to an ice-cooled solution of 3.2 g. (0.012 mole) of 10-chloroacetylphenothiazine in 35 ml. of glacial acetic acid. After fifteen minutes, an additional 0.7 ml. of nitric acid was added. The solution was stirred for an over-all period of twenty-five minutes while being cooled in an ice-bath. Water was added to the solution and an oil immediately separated. On standing, this oil solidified; this was followed by the

deposition of a cream-colored powder. Three and two-tenths grams (95%) of cream solid, m.p. 175-180° (decomp.), was obtained. The product was purified by recrystallization from ethanol to give 2.9 g. (86%) of light brown platelets, m.p. 186-187° (decomp.).

Anal. Calcd. for $C_{14}H_{10}ClNO_2S$: N, 4.80; Cl, 12.15. Found: N, 4.72; Cl, 12.36 and 12.08.

In a less successful experiment, concentrated nitric acid was added to a cold suspension of 3 g. (0.011 mole) of 10-chloroacetylphenothiazine in glacial acetic acid until all of the solid had dissolved. The solution was allowed to stand at room temperature for four hours. An orange solid, m.p. 276-281°, crystallized. This was shown to be 3-nitrophenothiazine-5-oxide by the mixed melting point method. The mother liquor was poured into water. The brown solid which precipitated was extracted with hot ethanol. From the ethanol there was obtained a small amount of 10-chloroacetylphenothiazine-5-oxide (mixed melting point).

8. 10-Chloroacetylphenothiazine-5-dioxide

One milliliter of 30% hydrogen peroxide was added with stirring to a solution of 1.00 g. (0.0036 mole) of 10-chloroacetylphenothiazine in 30 ml. of glacial acetic acid. The color of the solution immediately became a dark green. Another 0.6 ml. of hydrogen peroxide was added after heating

the solution at about 70° for fifteen minutes. The color became almost black and then pink. The solution was heated at 60-70° with stirring for one and one-half hours. About half the solvent was removed by distillation under reduced pressure. The solid which crystallized out weighed 0.80 g. (72%) and melted at 208-209°. Purification of the product by recrystallization from ethanol (in which it was slightly soluble) gave 0.57 g. (51%) of light brown needles, m.p. 211° (decomp.).

Anal. Calcd. for $C_{14}H_{10}ClNO_3S$: N, 4.56. Found: N, 4.60.

9. 10-Dichloroacetylphenothiazine-5-dioxide

One milliliter of 30% hydrogen peroxide was added with stirring to a solution of 0.98 g. (0.0032 mole) of 10-dichloroacetylphenothiazine in 15 ml. of warm glacial acetic acid. The color of the solution immediately became a dark green. After fifteen minutes, another 0.6 ml. of hydrogen peroxide was added and the color of the solution became almost black. The solution was heated at about 60° with stirring for a total of two hours. A solid crystallized during this time. The light green product, m.p. 211-212° (decomp.), weighed 0.86 g. (80%). This solid was recrystallized from about 125 ml. of ethanol to give 0.75 g. (70%) of very light green platelets, m.p. 211-212° (decomp.). Eleven-hundreths gram

of solid, m.p. 197-201° (decomp.), was obtained by pouring the acetic acid mother liquor into water. This solid was recrystallized from ethanol to give 0.08 g. of brown crystals, m.p. 202-204° (decomp.).

Anal. Calcd. for $C_{14}H_9Cl_2NO_3S$: N, 4.09. Found, N, 4.12.

10. The attempted nitric acid oxidation of 10-dichloroacetylphenothiazine

One and five-tenths grams (0.0049 mole) of 10-dichloroacetylphenothiazine was dissolved in 35 ml. of glacial acetic acid. On cooling in an ice-bath a brown solid crystallized from the solution. This solid was redissolved by warming. Again the solution was cooled; however, 2 ml. of concentrated nitric acid (d. 1.42) was added before any of the solid recrystallized. After a short while tan needles began to separate. After twenty minutes this solid, m.p. 155-156°, was filtered off and washed with acetic acid. The mixed melting point with starting material was undepressed. The mother liquor was poured into water and a tan colored solid, m.p. 145-148°, separated. After recrystallization from ethanol the melting point was raised to 154-145°. This was also shown to be starting material. None of the desired monoxide could be isolated.

A second attempt to prepare the oxide by this method also failed.

11. 10-Phenacetylphenothiazine-5-oxide

(a) Using nitric acid. Five and two-tenths milliliters of concentrated nitric acid (d. 1.42) was added dropwise to a solution of 5 g. (0.016 mole) of 10-phenacetylphenothiazine in 110 ml. of glacial acetic acid cooled in an ice-bath. The color of the solution became almost black. After fifteen minutes an additional milliliter of nitric acid was added. The reaction was allowed to continue for a total of thirty minutes and then the solution was poured into water. A brown oil separated and on standing it solidified. This solid, m.p. 130-135°, weighed 4.8 g. (92%) after drying. Two recrystallizations of the solid from ethanol raised the melting point to 135-140°. Recrystallization from benzene gave 3.4 g. of crystals, m.p. 133-140°. Thus, since it was apparent that recrystallization alone would not purify the compound satisfactorily, the compound was purified by chromatography. A solution of the crude product was chromatographed on a column of 45 g. of alumina.[169] From the eluate, there was obtained 2.6 g. (50%) of product, m.p. 140-141°. Recrystallization from ethanol raised the melting point of the fine, white crystals to 141-141.5°.

Anal. Calcd. for $C_{20}H_{15}NO_2S$: N, 4.20. Found: N, 4.39.

(b) Using hydrogen peroxide. Sixty milliliters of 30% hydrogen peroxide was added to a refluxing solution of 8.2 g.

(0.026 mole) of 10-phenacetylphenothiazine in 400 ml. of ethanol. The solution was refluxed for two hours and an additional 15 ml. of hydrogen peroxide was added. The color of the solution was originally a light yellow, it became pink on the addition of hydrogen peroxide and gradually became colorless during the reflux period. The solution was refluxed for a total of nine hours and then allowed to stand at room temperature for ten hours. About 350 ml. of solvent was distilled off and water poured into the residue. Eight and one-tenth grams (94%) of solid, m.p. 135-137°, separated. This was recrystallized from ethanol to give 6 g. (70%) of irregular white platelets, m.p. 138-140°. The mixed melting point with the product made by the previous method was undepressed. This compound was not further purified by chromatography.

12. 10-Phenacetylphenothiazine-5-dioxide

(a) From 10-phenacetylphenothiazine. Five milliliters of 30% hydrogen peroxide was added with stirring to a solution of 5 g. (0.016 mole) of 10-phenacetylphenothiazine in 150 ml. of glacial acetic acid at room temperature. The color of the solution turned a light blue. The solution was stirred at room temperature for twenty minutes and then another 3 ml. of hydrogen peroxide was added. The solution was heated to about 60° and stirred at this temperature for one

hour. During this time the color of the solution changed from light blue to almost colorless and then pink. After standing over night, 120 ml. of solvent was removed by distillation under reduced pressure. A solid separated shortly after the distillation was started. Three and eight-tenths grams (70%) of solid, m.p. 215-216° (decomp.), was filtered off. The mother liquor was poured into water and 1.6 g. of solid, m.p. 150-154° (decomp.), precipitated. The first portion of solid was found to be only slightly soluble in ethanol and it was therefore recrystallized from xylene. Two recrystallizations from xylene gave 2.6 g. (48%) of white needles, m.p. 215-216° (decomp.), with softening beginning at 210°.

Anal. Calcd. for $C_{20}H_{15}NO_3S$: N, 4.01. Found: N, 4.22.

(b) From 10-phenacetylphenothiazine-5-oxide. Four milliliters of 30% hydrogen peroxide was added to a solution of 3.7 g. (0.011 mole) of 10-phenacetylphenothiazine-5-oxide in 100 ml. of glacial acetic acid at about 60°. The solution was kept at this temperature for two and one-half hours with occasional shaking. After fifteen minutes another 2 ml. of hydrogen peroxide was added. On standing, 3.2 g. (83%) of almost white, coarse needles, m.p. 212-216° (decomp.), crystallized from the pink solution. This solid was recrystallized from 125 ml. of glacial acetic acid giving 3.1 g. of irregular needles, m.p. 212° (decomp.). These crystals

were recrystallized from 400 ml. of ethanol giving 3.0 g. (77%) of needles, m.p. 212-213° (decomp.). The mixed melting point with 10-phenacetylphenothiazine-5-dioxide prepared by the preceding procedure was undepressed.

E. Miscellaneous Reactions

1. Preparation of γ-diethylaminopropyl chloride[8]

The method of preparation followed was that described by Gilman and Shirley[17] except that a longer reflux period was used. The compound was also prepared, according to a similar method, in 79%[174] yield and in 87%[175] yield, respectively. However, few details were given concerning these preparations.

A solution of 197 g. (1.5 moles) of γ-diethylaminopropanol in 200 ml. of chloroform was added over a period of forty-five minutes to a solution of 358 g. (3.0 moles) of thionyl chloride in 1200 ml. of chloroform cooled in an ice-salt bath. The solution was then refluxed in a steam-bath for twelve hours. During this time the color of the solution changed from yellow to light brown. The chloroform and excess thionyl chloride were distilled off, the last portions

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[174] O. Gawron and P. E. Spoerri, J. Am. Chem. Soc., 67, 514 (1945).

[175] J. Walker, J. Chem. Soc., 630 (1945).

being removed under reduced pressure. The residue was cooled in an ice-bath and 375 ml. of 40% sodium hydroxide was added carefully with stirring. The alkaline solution was extracted with three portions of ether totaling 1000 ml. The ether extract was dried over anhydrous sodium sulfate. Following removal of the ether, the residual liquid was distilled to give 197 g. (88%) of γ-diethylaminopropyl chloride, b.p. 65-69° (16 mm.) with the heating bath at 82-85°. On standing, the chloride became cloudy after a few days, even at 5°, due very likely to the formation of quaternary ammonium salts.

2. Hydriodic acid cleavage of the crude carbonation product from 10-(γ-diethylaminopropyl)phenothiazine[176] to give m-carboxydiphenylamine

Three grams of the crude amphoteric carbonation product and 25 ml. of concentrated hydriodic acid (d. 1.50) were refluxed for twenty hours. The gum was only partially soluble in the acid forming an orange solid; this solid dissolved almost completely during the course of the reaction. During this period hydrogen sulfide was evolved. On cooling after the addition of some water, an oil separated which partially solidified on standing. This semi-solid material dissolved almost completely in 10% sodium hydroxide solution and the mixture was filtered. Acidification of the filtrate with

[176]See page 68 of this dissertation.

hydrochloric acid precipitated a solid, m.p. 124-127°. This solid was dissolved in benzene, the solution filtered and then petroleum ether (b.p. 80-115°) was added. A green tar separated. The supernatant solution was decanted and more petroleum ether was added. After standing a few days, 0.8 g. of fine, light tan crystals, m.p. 139-140°, separated. The mixed melting point with an authentic specimen of m-carboxydiphenylamine[8,54] was undepressed.

3. Hydrolysis of 10-acetylphenothiazine-5-oxide

A solution of 1.0 g. (0.0039 mole) of 10-acetylphenothiazine-5-oxide in 15 ml. of ethanol and 2 ml. of 10% sodium hydroxide was refluxed for a few minutes. The color of the solution immediately became brown. After a short time colorless platelets crystallized. The solution was cooled and 0.6 g. (72%) of solid, m.p. 250-251° (decomp.), filtered off. The mixed melting point with an authentic specimen of phenothiazine-5-oxide[101] was undepressed.

The other 10-acylphenothiazine-5-oxides were hydrolyzed, by a similar procedure, to give phenothiazine-5-oxide.

4. Hydrolysis of 10-acetylphenothiazine-5-dioxide

One and one-half milliliters of 10% sodium hydroxide was added to a hot solution of 0.50 g. (0.0018 mole) of 10-acetylphenothiazine-5-dioxide in 30 ml. of absolute ethanol.

The color of the solution immediately became yellow. After a few minutes, part of the solvent was removed by distillation. The addition of water to the residual solution precipitated 0.42 g. (100%) of yellow solid, m.p. 255-257° (decomp.). Recrystallization from absolute ethanol raised the melting point to 256-257°. The mixed melting point with an authentic sample of phenothiazine-5-dioxide, prepared by the hydriodic acid cleavage of 10-methylphenothiazine-5-dioxide,[96] was undepressed.

The other 10-acylphenothiazine-5-dioxides were hydrolyzed, in a similar fashion, to give phenothiazine-5-dioxide.

5. Attempted nitration of ethyl m-iodobenzoate

Into a one-liter round-bottom flask, equipped with a mechanical stirrer, were placed 175 ml. of concentrated sulfuric acid (d. 1.87) and 88 g. (0.32 mole) of ethyl m-iodobenzoate. The ethyl m-iodobenzoate was prepared by the following sequence of reactions: diazotization[177] of m-aminobenzoic acid, treatment of the diazonium salt with potassium iodide,[177] esterification of the crude m-iodobenzoic acid by dissolving the acid in a solution of dry hydrogen chloride in absolute ethanol and heating the solution at a gentle

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[177] L. Gattermann, "Laboratory Methods of Organic Chemistry," MacMillan and Co., Ltd., London, 1943, p. 283; F. B. Dains and F. Eberly in A. H. Blatt's "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 355.

reflux, and finally, purification of the ethyl ester by distillation,[178] b.p. 101-108° (0.1-0.5 mm.). The mixture was cooled to 5° in an ice-bath. A solution of 27 ml. (0.41 mole) of concentrated nitric acid (d. 1.42) in 30 ml. of concentrated sulfuric acid was added over a period of seventy minutes with the temperature of the mixture being maintained at about 5°. The addition of the nitrating mixture immediately caused, in the solution, the formation of a purplish-black color which disappeared after stirring for a few minutes. This phenomenon recurred until about half of the nitric acid had been added; after this point, the color of the solution remained an orange-yellow. Following the addition of the nitrating mixture, the solution was stirred for an additional twenty minutes with gradual warming, and then poured over ice. A sticky, orange material separated. The water layer was poured off and ether added to the residue. Stirring in the presence of ether brought about crystallization of the residue. The solid was washed with four portions of ether to remove any of the relatively soluble material. Seventy-one grams of solid material remained, m.p. 185-190° (decomp.). This solid was recrystallized twice from absolute ethanol with the result that the melting point was raised to 193.5-194.5° (decomp.) with the first recrystallization, and to 196-196.5° (decomp.) with the second.

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[178] J. B. Cohen and H. S. Raper, J. Chem. Soc., 85, 1271 (1904).

Anal. Found: I, 38.02 and 38.09. The compound contained no nitrogen (Dumas analysis). The lead acetate qualitative test for sulfur, following sodium fusion, was positive.

The compound was quite insoluble in ether, benzene, dioxane, chloroform and p-dichlorobenzene. It was very soluble in glacial acetic acid and moderately soluble in ethanol. The compound was insoluble in 3% sodium hydroxide.

The product of this attempted nitration seemed to dissolve in nitrobenzene and consequently this solvent was chosen as the one for the molecular weight determination by the cryoscopic method. The values found were 3120 and 2480. The compound crystallized from the nitrobenzene after the solution had stood for a few days, as shown by a mixed melting point of this crystalline product with the original. Thus, the compound probably was not sufficiently soluble in nitrobenzene to give satisfactory results in the molecular weight determination.

An infra-red analysis[167] of the compound gave absorption bands indicating the presence of the sulfone and the carbonyl groups in the molecule. The absorption spectrum did not compare at all with that of m-iodobenzoic acid.

6. Treatment of the product from the attempted nitration of ethyl m-iodobenzoate with sodium hydroxide

Seven and one-half grams of the compound, m.p. 196-196.5° (decomp.), was gently warmed in 60 ml. of 10% sodium hydroxide. The solid dissolved almost completely after warming for about three or four minutes to give a yellow solution. Then a light yellow solid separated to give a very thick suspension. The suspension was boiled gently for a few more minutes and the solid redissolved to give a dark red solution. A test for the iodide ion on an aliquote of this solution was negative. A portion of the solution was distilled. The distillate gave a positive iodoform test, thus, indicating that ethyl alcohol was obtained during the course of the hydrolysis. The alkaline solution was acidified with hydrochloric acid, resulting in the precipitation of 5 g. of red brown solid, m.p. 142-143°. This solid was extracted with petroleum ether (b.p. 60-70°) leaving an orange residue. Two and four-tenths grams of white solid, m.p. 173-176°, crystallized from the petroleum ether extract. Purification of this material by recrystallization from acetone gave white crystals, m.p. 183-184°. The mixed melting point with m-iodobenzoic acid was undepressed.

7. Attempted nitration of m-iodobenzoic acid

Seventy-four grams (0.3 mole) of m-iodobenzoic acid,

m.p. 183-184°,[179] (prepared by the hydrolysis of the ester, described in the previous experiment, with 10% sodium hydroxide and acidification of the hydrolyzate to give the m-iodobenzoic acid) was dissolved in 275 ml. of warm concentrated sulfuric acid. Upon cooling the solution to 5°, m-iodobenzoic acid crystallized out unchanged as shown by the mixed melting point method. To this suspension was added 30 ml. (0.47 mole) of nitric acid (l. 1.42), dissolved in 30 ml. of concentrated sulfuric acid, over a period of three and one-half hours, during which time the reaction mixture warmed up to room temperature. The portionwise addition of the nitrating mixture caused the formation of a dark violet color in the suspension. Stirring for a few minutes after each addition resulted in the disappearance of the cark color. This behavior continued until approximately an equivalent amount of nitric acid had been added, after which point the color remained yellow. The solid dissolved during the course of the reaction. The reaction mixture was poured over ice; a brown, sticky solid separated. On standing overnight, a small amount of crystals separated from the solution. The solid was filtered off and dissolved in 3% sodium hydroxide. Very fine needle-like crystals slowly separated from the

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[179]The mixed melting point with Eastman's White Label m-iodobenzoic acid (m.p. 183.5-184.5°) was undepressed. See R. L. Datta and N. R. Chatterjee, J. Am. Chem. Soc., 41, 294 (1919).

alkaline solution. This sodium salt was decomposed by hydrochloric acid giving 34 g. of white solid, m.p. 246-247° (decomp.).

Anal. Found: I, 48.35 and 48.15. The neutral equivalent, determined in an ethanol solution using phenophthalein as the indicator, was found to be 476 and 481. The compound contains neither nitrogen (the ferrocyanide test) nor sulfur (the lead acetate test). The qualitative tests were made on the sodium-fusion product of a portion of the compound.

The acidic compound was more soluble in 3% sodium hydroxide than in 10% sodium hydroxide. The compound was quite insoluble in all the common organic solvents as well as iodobenzene and p-dichlorobenzene with the result that no suitable solvent was found in which the molecular weight of the unknown compound could be determined by the freezing point method.

An infra-red analysis[167] of the compound indicated the presence of the carboxyl and carbonyl groups in the molecule. The spectrum did not compare with that of m-iodobenzoic acid, or that of the product from the attempted nitration of ethyl m-iodobenzoate. There was no band indicating the presence of the sulfone group.

8. Dehalogenation[180] of the product from the attempted nitration of m-iodobenzoic acid

Five grams of the compound was dissolved in 150 ml. of hot (90°) 10% sodium hydroxide. Fifteen grams of nickel-aluminum alloy was added in small portions to the solution over a period of twenty minutes with stirring and heating on the steam bath. The stirring and heating were continued for another hour. The filtered solution was poured into 5N nitric acid. Aluminum salts precipitated immediately, but dissolved upon stirring this suspension for a few minutes. The acid solution was extracted with ether and the ether solution was dried with calcium chloride. Three and two-tenths gram of residue, m.p. 110-125°, remained after the removal of the ether. Treatment of this residue with petroleum ether (b.p. 60-70°) separated it into two acidic fractions, which on purification were found to be benzoic and m-hydroxybenzoic acid, respectively, by the mixed melting point method. Because of the difficulty in separating and purifying these acids no molar ratio of the two was obtained.

9. Hydrolysis of the product from the action of nitric and sulfuric acids on m-iodobenzoic acid

Four grams of the solid, m.p. 246-247° (decomp.), was

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[180] E. Schwenk, D. Papa and H. Ginsberg, Ind. Eng. Chem., Anal. Ed., 15, 576 (1943).

dissolved in 120 ml. of 10% sodium hydroxide by heating on a steam bath. The heating, with stirring, was continued for two hours. The solution was acidified with hydrochloric acid and extracted with six portions of ether, the total volume of ether being about 350 ml. This ether solution was washed with water and dried with calcium chloride. A solid, m.p. 158-180°, remained after removal of the ether. Small amounts of two acids were isolated, by means of fractional recrystallization, from this material. The one acid melted at 180.5-181.5°, and the second melted at 224-225°. The first contained iodine and gave a strong violet color with ferric chloride indicating the presence of a phenolic hydroxyl group. Its neutral equivalent was found to be 238 and 239. The second acid contained iodine but gave no color with ferric chloride. Its neutral equivalent was found to be 185 and 188. The mixed melting point of the acid, m.p. 180.5-181.5°, with m-iodobenzoic acid, m.p. 183.5-184.5°, was undepressed. The neutral equivalent for m-iodobenzoic acid is 248.0. The infra-red spectrum[167] for the acid, m.p. 224-225°, showed the presence of the phenolic hydroxyl and the carbonyl groups and indicated the presence of the carboxyl group. However, some acids do give a weak band for the carboxyl group; for example, salicylic acid.

IV. DISCUSSION

A. Metalation Reactions of Phenothiazine and Some of Its Derivatives

The metalation of phenothiazine[8,21] with an organometallic compound was successfully accomplished by stirring, at room temperature, a mixture of approximately two equivalents of n-butyllithium with one equivalent of phenothiazine in ether for twenty hours. The fact that monometalation had occurred was established by the isolation of a pure monocarboxyphenothiazine, in 52% yield, following carbonation and acidification of the reaction mixture. The acid was shown to be phenothiazine-1-carboxylic acid by a method discussed in an earlier section of this dissertation.[181] Thus, the position ortho to the nitrogen in the heterocyclic compound phenothiazine was involved. There was no evidence for dimetalation of phenothiazine in this reaction.

The reaction of approximately one equivalent of n-butyllithium with 10-ethylphenothiazine in refluxing ether for twenty hours resulted in the isolation of a monocarboxy-10-ethylphenothiazine in 6% pure yield[7,54] subsequent to carbonation. Cleavage of this product with hydriodic acid gave m-carboxydiphenylamine. Consequently, the substitution

[181] See pages 22 and 24 of this dissertation.

reaction must have involved a position meta to the nitrogen which could have been the 2- or 4-position of phenothiazine. Because of the tendency for substitution ortho to the hetero element of a heterocyclic compound in metalation reactions, the favored position was that one ortho to the sulfur, position 4. Later, indirect evidence[16,36] showed that the foregoing reactions did give 10-ethylphenothiazine-4-carboxylic acid.[182]

From the above investigations one sees that phenothiazine was metalated by n-butyllithium at position 1 and that 10-ethylphenothiazine was metalated at position 4. Shirley[8] mentioned the possibility that steric effects might have been involved in causing the reaction to take a different course in the two cases. Another factor, which may affect the reaction, is that phenothiazine itself is not involved, but 10-lithiophenothiazine. (10-Ethylphenothiazine has no active hydrogen which can undergo reaction.) The replacement of the active hydrogen by lithium very likely increases the formal negative charge on the nitrogen and thus electronic, as well as steric effects, may influence the course of the reaction.

The metalation of 10-(γ-diethylaminopropyl)phenothiazine with slightly more than one equivalent of n-butyllithium, at room temperature for twenty hours, resulted in the

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[182]See pages 21 and 22 of this dissertation.

formation of a crude amphoteric substance after carbonation. This product resisted all attempts of purification. However, a portion of the crude material was cleaved with boiling hydriodic acid to give m-carboxydiphenylamine (identified by the mixed melting point method). Thus, either position 2 or 4 of the phenothiazine derivative was involved. By considering the foregoing reactions of 10-ethylphenothiazine, the crude product must have contained some 10-(γ-diethylaminopropyl)phenothiazine-4-carboxylic acid. In a second reaction involving 10-(γ-diethylaminopropyl)-phenothiazine and one and four-tenths equivalents of n-butyllithium in refluxing ether, the intermediate organometallic compound was treated with benzophenone. Following hydrolysis, a diphenylhydroxymethyl-10-(γ-diethylaminopropyl)phenothiazine was isolated in 8% yield. The infrared spectrum[167] of this compound showed a strong band for the hydroxyl group and one for a vicinal trisubstituted benzene nucleus. There was no band indicating unsymmetrical trisubstitution in a benzene ring. The conclusion drawn from the infra-red analysis and from the previous cleavage reaction is that metalation affected the 4-position. Thus, the above carbinol is very likely the 4-diphenylhydroxymethyl derivative. A glass, which could not be purified, also was obtained from the reaction. A band for the hydroxyl group was present in the infra-red spectrum[167] of the material.

This may have been due to the presence of the foregoing carbinol, or possibly a second carbinol was formed in the reaction. One is led to speculate on the latter idea since treatment of the glass with concentrated hydrochloric acid produced an intensely green colored substance (possibly a halochromic salt), whereas, treatment of the pure carbinol with acid under the same conditions gave a light reddish colored material. It would be interesting to investigate this reaction more fully to determine if a second carbinol actually was formed.

10-[β-(1-Pyrrolidyl)ethyl]phenothiazine was metalated using approximately one and one-half equivalents of n-butyllithium by refluxing the reactants in ether for twenty-two hours. Benzophenone, instead of carbon dioxide, was used to tag the resulting organometallic compound. The metalation reaction took an unexpected course as evidenced by the isolation, after hydrolysis, of a diphenylhydroxymethyl- and a bis(diphenylhydroxymethyl)-10-[β-(1-pyrrolidyl)ethyl]-phenothiazine in a 2.7% and a 12.3% yield, respectively. The monocarbinol is considered to be the 4-diphenylhydroxymethyl derivative on the basis of the previous reactions involving a 10-alkylphenothiazine. The infra-red analysis[167] of the dicarbinol gave a spectrum which showed bands for the hydroxyl group and a vicinal trisubstituted benzene ring. There was no band indicating the presence of an unsymmetrical

trisubstituted benzene nucleus. Thus, the dimetalation reaction affected the two carbon atoms ortho to the sulfur, or less likely, the carbons ortho to the nitrogen. Other possibilities would be the formation of a 1,6-dilithio or a 1,4-dilithio derivative. The latter ideas are ruled out on the basis that (1) no known metalation reaction of a 10-alkylphenothiazine has involved the 1-position, (2) unsymmetrical disubstitution seems to be less likely, and (3) no dimetalation reaction has been reported to affect just the one benzene ring of a tricyclic heterocycle.[183] Consequently, the most reasonable structure for the dicarbinol seems to be the one in which the two diphenylhydroxymethyl groups are assigned to positions 4 and 6 of 10-[β-(1-pyrrolidyl)ethyl]phenothiazine.

The previous reaction is the first one known from which a definite product has been isolated as the result of dimetalation of a tricyclic heterocycle containing the sulfide linkage. At about the same time that the above work was completed, it was observed[163] that dibenzothiophene-5-dioxide underwent dimetalation by the action of three equivalents n-butyllithium in ether at -20°. The intermediate organometallic compound gave, following carbonation and acidification, a 20.4% yield of 4,6-dicarboxydibenzothiophene-5-dioxide.

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[183]If a substituent such as the methoxy group were present in one of the two benzene nuclei, then that nucleus might undergo dimetalation with n-butyllithium using the proper conditions.

This was the first reported dimetalation of a tricyclic heterocycle containing the sulfone group.

Phenothiazine and 10-ethylphenothiazine were reacted with n-butyllithium to see if these compounds might also undergo dimetalation.

A solution of phenothiazine and three equivalents of n-butyllithium was refluxed in ether for twenty-three hours. A 70% yield of pure 1-diphenylhydroxymethylphenothiazine was isolated following treatment of the reaction mixture with benzophenone and water. There was no evidence that dimetalation had occurred. No phenothiazine was recovered. Shirley[21] obtained a 52% yield of pure phenothiazine-1-carboxylic acid as a result of the metalation of phenothiazine. His lower yield of product probably was due to his using a smaller excess of n-butyllithium and carrying out the reaction at room temperature instead of at ether reflux temperature.

10-Ethylphenothiazine was metalated with n-butyllithium (approximately 20% excess) in refluxing ether for twenty-three hours. After treatment of the reaction mixture with benzophenone and water, a 55% yield of pure 4-diphenylhydroxymethyl-10-ethylphenothiazine was obtained. There was no evidence that dimetalation had occurred in this reaction. Van Ess[54] metalated 10-ethylphenothiazine with the result that a 6% yield of pure 10-ethylphenothiazine-4-carboxylic

acid was obtained subsequent to carbonation and acidification. The lower yield of metalation product in his case probably was due to the smaller excess of n-butyllithium used.

The reaction of dibenzothiophene-5-oxide with three and two-tenths equivalents of n-butyllithium[171] in ether at -10°, resulted in the formation of a 35.7% yield of 4-dibenzothiophenecarboxylic acid and a 10.8% yield of dibenzothiophene following carbonation and acidification. This reaction was extended to see if it would apply to 10-ethylphenothiazine-5-oxide as well. A suspension of the phenothiazine derivative was treated with three equivalents of n-butyllithium in ether at -20° for three hours. Since no visible change seemed to take place, the temperature of the mixture was increased to 0° and maintained at that point for four hours. Following carbonation and acidification, a 53% yield of pure 10-ethylphenothiazine-4-carboxylic acid (mixed melting point) was obtained. No 10-ethylphenothiazine was isolated from the reaction. In a second experiment involving the same amount of reactants and the same conditions, except that the reaction mixture was maintained at -20° for six and one-half hours, a 25% yield of pure 10-ethylphenothiazine-4-carboxylic acid and 36% of 10-ethylphenothiazine were obtained. Thus, reduction and metalation occur in the case of 10-ethylphenothiazine-5-oxide as well as in that of

dibenzothiophene-5-oxide. Gilman and Esmay[171] discuss a possible mechanism for the reaction. The above results indicate that the higher reaction temperature (0°) favors the reduction-metalation reaction, whereas, lower temperatures (-20° and -10°[171]) favor the reduction reaction.

B. Preparation of Some 10-Substituted Phenothiazines

The reactions of various dialkylaminoalkyl halides with phenothiazine and the condensing agent sodamide, in an inert solvent such as xylene, have been highly successful.[184]

The need of 10-ethylphenothiazine arose during the course of this investigation. Since the methods described for the preparation of this compound required the use of high pressure equipment,[5,66] the suggestion was made to use the sodamide-condensation type of reaction for the preparation. Consequently, ethyl iodide was reacted with phenothiazine and sodamide in refluxing benzene to give a 36% yield of the desired, pure product. The question was raised concerning the possibility of carrying out the condensation reaction in liquid ammonia. Phenothiazine was added to a suspension of sodamide in liquid ammonia and then after about two hours, ethyl bromide was added. A reaction started immediately as evidenced by the change in color of the

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[184]See Part C of the historical section of this dissertation.

reaction mixture from very dark red to dark brown. Pure 10-ethylphenothiazine was isolated in a yield of 97%. In a second experiment, 92% of the 10-ethyl derivative and 1.5% of phenothiazine were obtained. Thus, the reaction for preparation of this particular phenothiazine derivative proceeds exceptionally well in liquid ammonia and far surpasses the methods of preparation described previously.

Phenothiazine was found to be slightly soluble in liquid ammonia giving a green solution.[185] However, the addition of the compound to sodamide in liquid ammonia produced a dark red mixture. The red color was probably due to the 10-sodiophenothiazine dissolved in liquid ammonia. Because of the intensity of the color, it was difficult to determine by visual inspection alone whether or not the phenothiazine derivative was completely in solution; however, it appeared to be so.

The attempt to prepare 10-phenylphenothiazine in xylene, or in liquid ammonia, by the reaction of iodobenzene and phenothiazine with sodamide as the condensing agent was unsuccessful. Apparently the halogen of iodobenzene is not sufficiently reactive to undergo reaction with 10-sodiophenothiazine.

Zarember[69] found that the reaction of 2-benzyloxyquinoline with phenothiazine, in refluxing cumene, gave a

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[185] F. de Carli, Gazz. chim. ital., 57, 347 (1927), [C.A., 21, 3047 (1927)].

90% yield of 2-hydroxyquinoline and a 34% yield of a product melting at 91-92°, which analyzed for 10-benzylphenothiazine. There is a disagreement in the literature concerning the melting point of the latter compound. Desai[99] reported that 10-benzylphenothiazine, m.p. 90.5-91°, was formed in 25% yield by heating a mixture of benzyldiphenylamine and sulfur at 220° for eight hours. Finzi[52] stated that the compound was obtained by heating phenothiazine and benzyl chloride at 140-145° for two hours. However, his product melted at 130°. Zarember was unable to repeat Desai's work. A repetition of Finzi's preparation yielded a small amount of crystals, m.p. 132-134°. The mixed melting point with the compound, m.p. 91-92°, was 80-105°, thus showing that the two products were different substances rather than different crystalline forms of the same compound. Therefore, Zarember attempted to prepare the compound by the following procedure. A mixture of benzyl chloride (0.03 mole) and 10-lithiophenothiazine (prepared from 0.025 mole of phenothiazine and 0.11 mole of phenyllithium) in benzene-ether solution was stirred for one day at room temperature and then one hour at reflux temperature. The reaction was carried out in an atmosphere of nitrogen. No pure product was isolated. It seems that the failure of the reaction probably may have been due to the fact that a rather large excess of phenyllithium was used. The amount of phenyllithium used was

more than enough to react with both the phenothiazine and benzyl chloride. Thus, the benzyl chloride possibly reacted with the excess phenyllithium instead of with the 10-lithiophenothiazine.

The reaction of benzyl chloride and 10-sodiophenothiazine (prepared from phenothiazine and sodamide) in refluxing xylene gave a 15.5% yield of product which melted at 90-90.5°. The mixed melting point with Zarember's compound, m.p. 91-92°, was undepressed. This indicates that the two compounds are identical. Since, the latter compound analyzed for a benzylphenothiazine, both products are considered to be 10-benzylphenothiazine. Later, this compound was prepared in 66% yield by reacting benzyl chloride (50% excess) with 10-sodiophenothiazine in liquid ammonia.[83] Thus, liquid ammonia is the more satisfactory solvent for this reaction, as well as in the case of the preparation of 10-ethylphenothiazine from 10-sodiophenothiazine.

Abnormal rearrangements have been noted in the reaction of benzylmagnesium chloride with certain carbonyl compounds, such as formaldehyde, ethyl formate, acid chlorides and anhydrides. o-Tolyl and p-tolyl derivatives were isolated. Carbon dioxide, ketones and esters gave rise to the expected products. These observations[186] suggested the

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[186]H. Gilman and J. E. Kirby, J. Am. Chem. Soc., 54, 345 (1932); H. Gilman and J. F. Nelson, ibid., 61, 741 (1939); P. R. Austin and J. R. Johnson, ibid., 54, 647 (1932); J. R. Johnson, ibid., 55, 3029 (1933); W. G. Young and S. Siegl, ibid., 66, 354 (1944).

possibility that rearrangement may have occurred in the reaction of benzyl chloride with 10-sodiophenothiazine. Consequently, 10-(p-tolyl)- and 10-(o-tolyl)phenothiazine were prepared in order to compare them with 10-benzylphenothiazine.

Equal molar quantities of phenothiazine and p-iodotoluene were heated at 155-165° in the presence of copper bronze, potassium carbonate, xylene and nitrobenzene. A 15% yield of 10-(p-tolyl)phenothiazine, m.p. 135-136°, was obtained. The 10-(o-tolyl) derivative, m.p. 101-101.5°, was prepared in 52% yield by a similar procedure except that a 50% excess of o-iodotoluene was used. The latter fact probably accounts for the higher yield of the desired product in the case of the o-tolyl derivative. The melting points show that these compounds are different from the 10-benzyl derivative. In addition, the mixed melting point of 10-(o-tolyl)- and 10-benzylphenothiazine was depressed to 70-72°.

Since various derivatives of sulfanilamide are active chemotherapeutic agents, the preparation of p-(10-phenothiazyl)benzenesulfonamide was attempted. The reaction employing p-bromobenzenesulfonamide and phenothiazine was unsuccessful. The p-iodo derivative was next tried thinking that the halogen would be sufficiently reactive to give a successful condensation reaction, especially since the halogen

would probably be activated by the sulfonyl group. No condensation product could be isolated from this reaction either.

p-Aminosalicylic acid is known to possess bacteriostatic action against tubercle bacilli.[187] Substitution on the amino group by the methyl or stearoyl group or on the carboxyl by the methyl or ethyl radical changed the activity only slightly.[188] The bacteriostatic action was completely absent if the amino group was in the 3- or 5-position. Consequently, the desire was to investigate the possibility of preparing p-(10-phenothiazyl)salicylic acid to see if this compound would have a combination of the desirable physiological properties of both phenothiazine and p-aminosalicylic acid.

Because of the difficulty in obtaining a p-halosalicylic acid, the condensation of phenothiazine and methyl 5-bromosalicylate was attempted by heating the reactants in the presence of potassium carbonate, copper bronze and xylene. The reaction was unsuccessful. It was thought that if a halobenzoic acid, which possessed a nitro group para to the halogen, were used, the reaction might be successful because

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[187]J. Lehmann, Svenska Läkartidn., 43, 2029 (1946), [C.A., 41, 1334 (1947)]. The tuberculostatic activity of other substituted benzoic acids is listed by A. A. Goldberg, H. S. Jeffries, H. S. Turner and D. M. Besly, Quart. J. Pharm. Pharmacol., 19, 483 (1946).

[188]J. Lehmann, Lancet, 250, 15 (1946).

of the activating influence of the nitro group on a para-substituted halogen. The reaction of methyl 2-nitro-5-bromobenzoate with phenothiazine did not give the desired product. The preparation of various 10-(carboxyhydroxyphenyl)phenothiazines was not investigated further because of other problems which arose.

A number of 10-acylphenothiazines were prepared, in poor to good yields, by reacting the appropriate acyl chloride with phenothiazine, dissolved in dioxane, in the presence of anhydrous sodium carbonate. Phenothiazine, or some of its derivatives, readily reacted with an acyl halide in pyridine to give the 10-acyl derivative.[88] Attempts to prepare 10-dichloroacetylphenothiazine by this method failed. Either a tar resulted or phenothiazine was recovered.

C. Oxidation Reactions

Pummerer and Gassner[101] reported the formation of phenothiazine-5-oxide in 75% yield by the oxidizing action of 30% hydrogen peroxide on phenothiazine dissolved in hot ethanol containing some potassium hydroxide. The oxidation reaction was carried out by following their directions but was found to be unsuccessful. Instead of phenothiazine-5-oxide, m.p. 250° (decomp.), a solid which melted at 160-163° was isolated. Consequently, the latter material was

redissolved in ethanol and the solution refluxed after the addition of hydrogen peroxide. No potassium hydroxide was used in this second reaction. An almost quantitative yield of the oxide resulted. The alkali, in the first attempt, catalyzed the decomposition of the peroxide and thus, the decomposition reaction probably was complete before much of the phenothiazine had been oxidized.

A number of 10-acylphenothiazine-5-oxides were prepared, in good yields, by the action of excess 30% hydrogen peroxide on the acyl derivative in refluxing ethanol. There was no indication that any dioxide had been formed as well. Alkali could not have been used to catalyze the foregoing reactions as evidenced by the rapid hydrolysis of the acyl group upon the addition of 10% sodium hydroxide to a hot ethanolic solution of the 10-acyl-phenothiazine-5-oxide. This reaction was used as supplementary proof to show that the phenothiazine portion of the derivative had been oxidized to the monoxide. The resulting phenothiazine-5-oxide was identified by the mixed melting point method.

An exception to the above reactions was the oxidation of 10-ethylphenothiazine by hydrogen peroxide in refluxing ethanol. Two products were isolated from the reactions: the monoxide in 62% yield and the dioxide in 15.5% yield. The rather large excess of hydrogen peroxide used may account for the fact that the dioxide was formed. However, there

was not sufficient time to investigate the reaction more fully to learn if the monoxide alone would result under milder conditions.

Early reports[189] stated that the oxidation of sulfides by excess 30% hydrogen peroxide in acetone or aqueous solutions at ordinary temperatures gave only the sulfoxides. These conditions are not strictly comparable to those used for the production of sulfoxides in this investigation. Thus, the observations of Smiles and Hinsberg do not preclude the formation of small amounts of dioxide by carrying out the oxidation reaction in a refluxing ethanol solution.

10-Methyl- and 10-ethylphenothiazine, as well as various 10-acyl derivatives, were oxidized to the corresponding dioxides, in fair to excellent yields, by means of excess 30% hydrogen peroxide in glacial acetic acid solution. In addition, a number of the monoxide derivatives were oxidized to the respective dioxides by this same procedure. One method of forming peracetic acid[190] is the heating of a mixture of 30% hydrogen peroxide and glacial acetic acid. Since hydrogen peroxide in ethanol oxidized the sulfur of the phenothiazine derivatives to the sulfoxide, and the use of hydrogen peroxide in acetic acid resulted in the oxidation

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[189] M. Gazdar and S. Smiles, J. Chem. Soc., 93, 1833 (1908); O. Hinsberg, Ber., 41, 2836 (1908).

[190] D. Swern, Chem. Rev., 45, 1 (1949).

of the sulfur to the sulfone, it seems possible that in the latter reaction peracetic acid would be formed *in situ* and thus it would behave as the oxidizing agent. This very likely would account for the difference in the degree of oxidation upon using ethanol or glacial acetic acid as the solvent.

The fact that oxidation of the 10-acylphenothiazines in acetic acid gave the corresponding dioxides was shown (in addition to quantitative analysis) by hydrolyzing the particular product with alcoholic alkali to give phenothiazine-5-dioxide. The latter was identified by the mixed melting point method.

The attempt to prepare 3-nitro-10-chloroacetylphenothiazine-5-oxide by the reaction of concentrated nitric acid with the acyl derivative in glacial acetic acid quite unexpectedly gave 3-nitrophenothiazine-5-oxide and 10-chloroacetylphenothiazine-5-oxide. It seems obvious that the acyl derivative was first oxidized to give the monoxide and that this reaction then was followed by hydrolysis and nitration, or nitration and hydrolysis, to give 3-nitrophenothiazine-5-oxide. The order in which last two steps occurred could not be determined by considering the products of the reaction alone. Previous reactions using nitric acid and phenothiazine, or some of its derivatives, gave the corresponding nitromonoxides.[5,17,47] One exception involved a

tetrachlorophenothiazine.[104] In that case, only oxidation of the sulfur was observed, doubtless because the chlorine atoms occupied the positions normally affected by nitration reactions. The nitric acid oxidation reaction was extended to other 10-acylphenothiazines. In a second experiment, 10-chloroacetylphenothiazine gave an 86% yield of the monoxide and very little, if any, 3-nitrophenothiazine-5-oxide. Under similar conditions, 10-phenacetylphenothiazine gave 50% of the oxide; 10-acetylphenothiazine gave 19% of the oxide, as well as the product of hydrolysis and nitration; the 10-dichloroacetyl derivative gave no oxidation product and very little, if any, 3-nitrophenothiazine-5-oxide. Thus, it is apparent that the group attached to the nitrogen affects the success of the oxidation reaction. This observation is also noted by Bernstein and Rothstein.[66] They found that 10-ethylphenothiazine was converted to the sulfone and that 10-(p-toluenesulfonyl)phenothiazine was readily oxidized to the monoxide by potassium permanganate in boiling water, whereas, the p-acetamidobenzenesulfonyl derivative did not undergo reaction. Neither of the latter two derivatives was oxidized by hydrogen peroxide in acetone.

D. Attempted Nitration Reactions

The nitration of ethyl m-iodobenzoate was attempted with the purpose in mind to prepare an ethyl nitro-m-

iodobenzoate. The latter compound then would have been reacted with phenothiazine in the presence of potassium carbonate and copper bronze powder in anticipation of the occurrence of a condensation reaction to give a 10-(3-carboethoxynitrophenyl)phenothiazine. The nitro group of the latter compound could possibly be reduced. Subsequent diazotization and replacement of the diazonium group with the hydroxyl group would give rise to a (10-phenothiazyl)-hydroxybenzoic acid. The tuberculostatic properties of the latter could be compared with those of p-aminosalicylic acid.[184] However, these hopes were cut short by the isolation of a nitrogen-free product, m.p. 196-196.5°, from the action of nitric and sulfuric acids on ethyl m-iodobenzoate.

Alkaline hydrolysis of the unexpected product resulted in the isolation of ethanol, m-iodobenzoic acid and an unidentified solid. A qualitative sulfur test on the material, m.p. 196-196.5°, (following sodium fusion) was positive. The infra-red spectrum showed the presence of the sulfone group in the compound. These analyses indicate that sulfonation occurred as one of the steps of the reaction giving rise to a sulfone. However, it appears that not all of the ethyl m-iodobenzoate was sulfonated, inasmuch as alkaline hydrolysis of the product yielded m-iodobenzoic acid. Some more complex reaction may have taken place, one which involved sulfonation, as well as some other type of condensation. No sulfonation reaction of an iodobenzoic acid was

found to be recorded in the literature. Because of the oxidizing properties of nitric acid, it seems possible that in the course of the reaction the iodine might have been oxidized to an iodoso or iodoxy group. The halogens give no strong, characteristic band in an infra-red spectrum. Therefore, no information concerning the iodine was gained from the infra-red analysis.

Since the nitration of ethyl m-iodobenzoate failed, the nitration of m-iodobenzoic acid was tried. Again, an unexpected product was formed. The reaction of nitric and sulfuric acids with m-iodobenzoic acid yielded an acidic material, m.p. 246-247°. The qualitative nitrogen and sulfur tests were negative on a portion of the solution resulting from the sodium-fusion product of the unknown material. Treatment of the compound, m.p. 246-247°, with nickel-aluminum alloy in sodium hydroxide, resulted in the production of benzoic and m-hydroxybenzoic acid following acidification. m-Iodobenzoic acid and another iodine containing acid, m.p. 224-225°, (neutral equivalent, 185 and 188) were isolated upon acidification of the alkaline hydrolyzate of the unknown compound. The acid, m.p. 224-225°, did not give a positive test for the phenolic hydroxyl group using ferric chloride, however, the infra-red spectrum showed the group to be present. It seems from the above results that this latter acid is probably a m-hydroxyiodobenzoic acid, since m-hydroxybenzoic

acid was formed as a result of the dehalogenation reaction in an alkaline solution.

The foregoing evidence suggests that m-iodobenzoic acid and ethyl m-iodobenzoate, respectively, underwent different reactions with the nitric and sulfuric acid mixture. The violet color produced temporarily by the portionwise addition of nitric acid to the iodo compound in concentrated sulfuric acid was possibly due to the liberation of free iodine. The disappearance of the color might be a result of the iodination of some molecule present in the reaction mixture.

Attention is drawn to a paper by Twiss and Heinzelmann[191] since they treated various iodophthalic and iodobenzoic acids, respectively, in concentrated sulfuric acid with concentrated nitric acid under conditions similar to those described in this dissertation for the attempted nitration of m-iodobenzoic acid. Their conditions were the dropwise addition of concentrated nitric acid, with stirring but without cooling, to a suspension of the iodo derivative in concentrated sulfuric acid, warming of the mixture on a steam-bath until all of the solid had gone into solution and then pouring the resulting solution over ice. The conditions used in this investigation were the slow addition of a

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[191] D. Twiss and R. V. Heinzelmann, J. Org. Chem., 15, 496 (1950).

mixture of concentrated nitric and sulfuric acids with stirring to a cooled suspension of m-iodobenzoic acid in sulfuric acid, warming of the mixture to room temperature until the solid dissolved, then pouring the solution over ice. In the latter reaction a transient violet color resulted upon the dropwise addition of the nitric-sulfuric acid mixture, whereas, in the experiments of Twiss and Heinzelmann, a brown color developed upon adding nitric acid. They observed in a number of cases that the iodine of the iodo compound was oxidized to the iodoso or iodoxy group. However, they found that m-iodobenzoic acid was not oxidized, instead, it was partially nitrated. No analysis, yield or melting point was given for the nitration product. They made no mention of an anomalous reaction having occurred in the latter reaction. A similar acid, 2,3-diiodobenzoic acid, was observed to take up two active oxygen atoms by their nitric-sulfuric acid oxidation. Meyer and Wachter[192] treated the three isomeric monoiodobenzoic acids with boiling concentrated nitric acid and found that only the iodine atom ortho to the carboxyl group could thus be oxidized to form an iodoso group, while the iodine in the meta and para isomers remained unchanged. The presence of ortho-substituents apparently influences the oxidation of the iodine. These foregoing observations suggest that the unexpected product

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[192]V. Meyer and W. Wachter, Ber., 25, 2632 (1892).

from the action of nitric and sulfuric acids on m-iodobenzoic acid might contain an iodoso or iodoxy group.

The results of the degradation reactions of this investigation indicate that the product from the attempted nitration of m-iodobenzoic acid may be an ester of an iodobenzoic acid and a m-hydroxyiodobenzoic acid. Considering the possibility of oxidation of the iodine to an iodoso group and the value of the iodine analysis (found: I, 48.35 and 48.15) the compound, m.p. 246-247° (decomp.), may be an ester of a m-iodosobenzoic acid and a m-hydroxyiodosobenzoic acid. This compound would have a molecular weight of 526 and an iodine content of 48.3%. However, the values of the neutral equivalents in the two cases do not correspond. The values found, 476 and 481, for the neutral equivalent of the product from the attempted nitration of m-iodobenzoic acid might be held in question since the compound was quite insoluble in ethanol, thus making the end-point of the titration uncertain.

Iodoso compounds are, with few exceptions, yellow, amorphous substances, and iodoxy compounds are colorless crystalline substances which explode on heating.[193] Since the products from the attempted nitration reactions are colorless, crystalline substances which decomposed at the

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[193]H. Meyer, "Lehrbuch der Organisch-Chemischen Methodik," Verlag von Julius Springer, Berlin, 1922, p. 1087.

melting point, the compound from the attempted nitration of m-iodobenzoic acid might be an ester of an iodobenzoic and an hydroxyiodoxybenzoic acid, or one of an iodoxybenzoic acid and an hydroxyiodobenzoic acid instead of an ester containing two iodoso groups. The iodine content and neutral equivalent would still be the same as that for the hypothetical ester proposed in the preceding paragraph.

The melting points of the following acids are included here in order to compare them with the unidentified acid (m.p. 224-225°) obtained by the alkaline hydrolysis of the compound, m.p. 246-247°. m-Hydroxy-p-iodobenzoic acid[194] melts at 225-227°; p-iodosalicylic acid[195] melts at 228° with decomposition; m-iodoxybenzoic acid[196] explodes at 243°. An hydroxyiodoso- or hydroxyiodoxybenzoic acid was not found to be reported in the literature.

The problem of identification could be attacked further by the following methods: acid hydrolysis of the two unexpected products (assuming each to be an ester) with the subsequent identification of the resulting compounds; reduction, using lithium aluminum hydride,[197] of each of the

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[194] H. R. Frank, P. E. Fanta and D. S. Tarbell, J. Am. Chem. Soc., 70, 2314 (1948).

[195] P. Brenans and C. Prost, Compt. rend., 178, 1010 (1924)

[196] C. Willgerodt, Ber., 27, 2328 (1894).

[197] R. F. Nystrom and W. G. Brown, J. Am. Chem. Soc., 69, 2548 (1947).

compounds from these attempted nitration reactions and identification of the alcohols formed; the quantitative analysis of various derivatives such as the p-nitrobenzyl ester and the p-bromophenacyl ester; and identification of the one acid, m.p. 224-225°, from the alkaline hydrolysis of the compound, m.p. 246-247°, by means of quantitative analysis and the preparation of various derivatives. In view of the slight solubility of the products from the attempted nitration reactions, the molecular weights of the two compounds could be determined by the X-ray diffraction method.

E. Research Suggestions

Since a dimetalation reaction of 10-[β-(1-pyrrolidyl)-ethyl]phenothiazine was observed in the course of this investigation, it would be well to try to extend this reaction to other phenothiazine derivatives. A more active metalating agent may be necessary for a successful reaction in the other cases, considering the fact that phenothiazine and 10-ethylphenothiazine were not observed to undergo dimetalation by using n-butyllithium. Other reactions which also might be carried out are: metalation of phenothiazine-5-oxide, phenothiazine-5-dioxide and various 10-substituted phenothiazine-5-oxides and -dioxides. Since the sulfoxide group is involved in the proposed mechanism for the reduction-metalation reaction of dibenzothiophene-5-oxide,[171]

phenothiazine-5-oxide may be metalated at position 4, whereas, phenothiazine is metalated at position 1.

Phenothiazine[12,32,49] and 10-acylphenothiazines[12] have been observed to undergo the Friedel-Crafts reaction. No reactions of this kind have been reported using a 10-alkylphenothiazine. Therefore, this type of reaction might be carried out to determine which nuclear position of the 10-alkylphenothiazine is involved.[198] Massie[56] prepared a diacetylphenothiazine, m.p. 253-254°, by the reaction of phenothiazine and acetic anhydride under conditions of the Friedel-Crafts reaction. This compound should be investigated further to determine if it is the 2,8-diacetyl derivative.

The attempted condensation of p-iodobenzenesulfonamide with phenothiazine was unsuccessful. However, if 10-sodiophenothiazine (prepared from sodamide and phenothiazine) were used, the condensation reaction might be possible. The amido hydrogens of the sulfonyl compound are reactive, therefore, sufficient sodamide must be present to react with them, as well as with the phenothiazine. Another factor to consider is the possible cleavage of the sulfonamide by the sodamide.

It would be well to investigate the preparation of various 10-(carboxyhydroxyphenyl)phenothiazines since

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[198]See page 24 of this dissertation.

p-aminosalicylic acid is known to show antituberculous activity.[184]

Inasmuch as 10-ethylphenothiazine gave rise to both the sulfoxide and the sulfone by the action of hydrogen peroxide in refluxing ethanol, the reaction should be investigated more fully to learn if the dioxide was formed only as a result of the large excess of the oxidizing agent employed.

Vivian and co-workers[199] report that heating 4-chloro-3'-ethoxy-2-nitrodiphenylamine at 265-270° with hydrated ferrous oxalate and granular lead yielded two isomeric substituted phenazines, namely, 2-chloro-7-ethoxy- and 8-chloro-1-ethoxyphenazine. A number of other phenazine derivatives were prepared by the same procedure. The thought arose that this reaction might possibly be applied to the synthesis of some phenothiazine derivatives by starting with an appropriately substituted diphenyl sulfide. This sulfide could be heated in the presence of ferrous oxalate and lead to see if a phenothiazine compound would result.

"Open models" of atabrine have been prepared.[200] This suggested the idea that attempts might be made to prepare "open models" of some of the dialkylaminoalkylphenothiazines. Inasmuch as the latter type of compounds show very

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[199]D. L. Vivian, G. Y. Greenberg and J. L. Hartwell, J. Org. Chem., 16, 1 (1951).

[200]H. Gilman and S. M. Spatz, J. Am. Chem. Soc., 66, 621 (1944).

favorable physiological properties, the "open model" series might exhibit similar desirable properties to a greater degree. Culvenor and co-workers[201] have prepared 2-phenyl-2, 3-dihydro-1,4,4H-benzothiazine and some other benzothiazines. The phenyl compound, with the exception of being a dihydro derivative, represents an "open model" of phenothiazine. As a starting point, the phenyl derivative might be condensed with various dialkylaminoalkyl halides in the presence of sodamide to give the corresponding N-(dialkylaminoalkyl) derivatives. Attempts could be made to prepare other derivatives having the phenyl group attached to the 3-carbon of the above benzothiazine.

Another molecule patterned after a 10-dialkyaminoalkyl-phenothiazine is an N-(dialkylaminoalkyl)-o-(phenylamino) phenylalkyl sulfide. These compounds could probably be prepared by means of the lithium-cleavage reaction of the phenothiazine derivatives followed by reaction with an alkyl halide to give the desired sulfides.

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[201] C.C.J. Culvenor, W. Davies and N. S. Heath, J. Chem. Soc., 278 (1949).

V. SUMMARY

A survey of the chemistry of phenothiazine has been presented, as well as a summary of the physiological properties of the 10-(dialkylaminoalkyl) derivatives. The dimetalation reactions of heterocylic compounds have been presented.

It has been found that 10-[β-(1-pyrrolidyl)ethyl]-phenothiazine underwent dimetalation by the action of n-butyllithium in refluxing ether. The intermediate organometallic compound was reacted with benzophenone. Phenothiazine, 10-ethyl- and 10-(γ-diethylaminopropyl)phenothiazine were observed to undergo only monometalation under similar conditions. The metalation very likely occurred ortho to the sulfur.

It has been found that 10-ethylphenothiazine-5-oxide was reduced and metalated by n-butyllithium at 0° to give 10-ethylphenothiazine-4-carboxylic acid following carbonation and acidification. 10-Ethylphenothiazine also resulted when the reaction was carried out at -20°.

An authentic sample of 10-benzylphenothiazine was prepared.

10-Ethylphenothiazine was prepared in almost quantitative yield by the reaction of ethyl bromide and 10-sodiophenothiazine in liquid ammonia. 10-Phenylphenothiazine

could not be prepared by the reaction of iodobenzene with 10-sodiophenothiazine.

The attempted condensation of p-bromo- or p-iodobenzenesulfonamide with phenothiazine was unsuccessful.

A number of 10-acylphenothiazines were prepared.

The action of hydrogen peroxide on various 10-substituted phenothiazines in refluxing ethanol oxidized the sulfur to the sulfoxide. In warm glacial acetic acid, the sulfur was oxidized to the sulfone.

Nitric acid in glacial acetic acid oxidized some 10-acylphenothiazines to the corresponding monoxides.

The action of nitric and sulfuric acids on ethyl m-iodobenzoate and m-iodobenzoic acid, respectively, gave anomalous results. The products isolated were not completely identified.