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SUBSTITUTED PYRIDINE AND QUINOLINE SULFIDES

by

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I. INTRODUCTION

The study of sulfur compounds represents a relatively neglected page of organic chemistry. In at least two directions its importance has, in the last few years, become felt more and more strongly - the field of industry and the field of pharmaceutical and biochemical research and chemotherapy.

The triumph of chemotherapy may be said to date back to 1910 when Erhlich discovered Salvarsan as a cure for syphilis. From 1910 on rapid strides were made in chemotherapy; but, until 1935, practically all of the successful chemical substances in use were remedies for tropical diseases caused by protozoa. It was not until 1935, with the use of sulfanilamide, that the first of a series of substances was used which was effective against bacteria - the bacteria which give rise to the commonest diseases. The synthesis of quinine itself, for years a stumbling block to organic chemists, was accomplished by Woodward and Doering in 1945.[1]

Chemists have for a very long time tried to find some definite relationship between chemical constitution and physiological activity so that they might use this knowledge in the preparation of new compounds that might have some value as therapeutic agents. In 1868 Crum Brown and

1. Woodward and Doering, J. Am. Chem. Soc., 67, 860 (1945).

Fraser[2] showed that by a slight and constant chemical change, tertiary bases of widely differing physiological activities could be converted to quaternary bases of almost uniform activity. This fact led people to believe that a chemotherapeutic millennium was at hand, and that by skillful prediction, the properties of a new therapeutic substance could be ascertained from an inspection of its chemical formula. Thirty years after (in 1901) Sir F. G. Hopkins[3] commented thus:

> Striking enough has been the increase in the number of important drugs since the researches referred to were carried out, and it cannot be denied that the search for these drugs has been greatly aided by the knowledge of the kind just discussed; but it is a matter for disappointment and perhaps for surprise that we should, today, after thirty years, be able to point to very few general relations bearing the stamp of such definiteness and simplicity as are found in the case brought to light by Crum Brown and Fraser; and even now the results obtained by these investigators may be quoted as the most satisfactory instance to hand of obvious relation between chemical constitution and physiological action.

After over one-third of a century these remarks still remain true, but nevertheless the search goes on.

With the outbreak of World War II there came an increased need of and a new impetus for the preparation of pharmaceuticals of all types, particularly those which

2. (a) Crum Brown and Fraser, Trans. Roy. Soc. Ed., 25, 707 (1868); (b) Crum Brown and Fraser, Proc. Roy. Soc. Ed., 6, 560 (1869).
3. Quoted in May and Dyson, "The Chemistry of Synthetic Drugs", Longmans, Green and Co., London, (1939), p. 4.

might be effective against malaria. The fight against malaria has been successful to a large measure and this dread disease seems destined to be checked due to the development of drugs such as atebrin, plasmoquin and paludrine and to the control of mosquitoes by better sanitation and new insecticides.

This investigation describes the preparation of quinoline and pyridine sulfides which might possess some physiological activity containing, in general, an alkylamino grouping. The approach followed was the introduction of alkylaminosulfur side chains into (a) molecular structures known to confer chemotherapeutic activity and into (b) molecular structures of the same types, but which were not known to possess any physiological activity. A group of miscellaneous compounds was also prepared, each containing sulfur and each based on some compound which has proved of some therapeutic value.

The preparation of compounds of these types seems of interest for several reasons: (1) the development of possible physiologically active compounds; (2) the development of intermediates or even final products that may prove to have some clinical or synthetic usefulness, and

(3) the purely theoretical interest that lies in the development of anything new.

II. HISTORICAL

A. Mercaptans

General

The most obvious approach in the synthesis of mercaptans is the substitution of an inorganic radical already present in an organic molecule by an -SH group from an inorganic source, such as hydrogen sulfide, a sulfide or a hydrosulfide. The simplest example of this type of synthesis is the formation of ethyl mercaptan from ethyl iodide and aqueous hydrogen sulfide.[4] This reaction takes place in an acid solution and is accelerated by the presence of precipitated sulfides or other absorbing agents. A very interesting example of the formation of a mercaptan from hydrogen sulfide is that of $SiCl_3SH$ which can be prepared by the reaction of hydrogen sulfide on silicon tetrachloride.[5]

Reactions with hydrosulfides have been carried out on many types of halogenated compounds even to the extent of

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4. Brown and Snyder, J. Am. Chem. Soc., 48, 1926 (1926).
5. Friedel and Landenburg, Ann., 145, 179 (1868).

determining the orientation of the entering -SH groups.[6] The hydrosulfide solution may be prepared by saturating alcoholic alkali or simply melted alkali with hydrogen sulfide. In most cases potassium or sodium sulfide is used. Other alkylating agents behave in a similar manner; sodium ethyl sulfate was the alkylating agent used in the first mercaptan synthesis.[7]

One further extension of this method of preparing mercaptans is that of replacing an $-NH_2$ group by an -SH group by diazotizing and treating with an alcoholic sulfide or hydrosulfide to liberate nitrogen. Better yields are obtained if the diazotized compound is first treated with a xanthate or a thiosulfate and then hydrolyzed.[8]

Mercaptans may be prepared by the addition of hydrogen sulfides to olefins, the addition taking place only at high pressures and temperatures. These reactions have been

6. (a) Kierzek, Bull. soc. chim., /4/ 41, 1299 (1927); (b) Albrecht, Ann., 161, 129 (1872); (c) Zencke, ibid., 400, 8 (1914); (d) Beilstein and Kurbatow, ibid., 197, 75 (1879); (e) Saizens, ibid., 139, 354 (1866); (f) Saizens, ibid., 144, 148 (1867); (g) Fasbender, Ber., 20, 460 (1887); (h) Bennett and Whincop, J. Chem. Soc., 119, 422 (1921); (i) Vorlander and Mittag, Ber., 46, 3450 (1913); (j) Carius, Ann., 124, 260 (1862); (k) Cahours and Hoffmann, ibid., 102, 292 (1857); (l) Meyer, Ber., 19, 3259 (1886); (m) Hagelberg, ibid., 23, 1083 (1890); (n) Fore and Bost, J. Am. Chem. Soc., 59, 2557 (1937); (o) Ellis and Reid, ibid., 54, 1686 (1932); (p) Hofmann and Cahours, J. Chem. Soc., 10, 320 (1858).

7. (a) Seise, Ann., 11, 1 (1834); (b) Liebig, ibid., 11, 14 (1834).

8. (a) Mauthner, Ber., 39, 1347 (1906); (b) Zencke and Dahm, ibid., 45, 3457 (1912); (c) Klason, ibid., 20, 2384 (1847); (d) Zencke and Jorg, ibid., 42, 3362 (1909).

catalyzed by clay,[9] metallic sulfides[10] and sulfur.[11]

There are a great many cases in which mercaptans are obtained by the hydrolysis of S-alkyl ethyl xanthates which are formed when reactive halogen compounds are treated with postassium ethyl xanthate.[12, 8b,d] Although the salt of any thioacid might be used in these reactions, the xanthates are the most readily available compounds of this type and are almost always employed in the laboratory. Sodium thiosulfate has been used but this compound reacts more slowly and requires care to avoid the formation of disulfides.

An important method for the preparation of mercaptans is that of reducing various compounds. Disulfides, if available, are perhaps the most convenient compounds to reduce. The most commonly used reducing agents are zinc and acetic acid,[13] potassium sulfide[14] and metallic sodium.[15] This latter agent is useful in the cleavage of disulfides, since in this method the sodium mercaptide is formed directly without isolating the mercaptan. Other compounds that are

9. United States Patent, 2,101,096 /C. A., 32, 954 (1938)/.
10. United States Patent, 2,052,268 /C. A., 30, 7122 (1936)/.
11. Jones and Reid, J. Am. Chem. Soc., 60, 2452 (1938).
12. (a) Debus, Ann., 72, (1849); ibid., 75, 121 (1850); (b) Salomon, J. prakt Chem., /2/ 6, 433 (1873); (c) Leuckart, ibid., /2/ 41, 179 (1890); (d) Billman, Ann., 339, 351 (1905); (e) Mauthner, Ber., 39, 1347 (1906); (f) Tschugaeff and Gasteff, ibid., 42, 4631 (1909).
13. Noller and Gordon, J. Am. Chem. Soc., 55, 1090 (1933).
14. Otto and Rössing, Ber., 19, 3129 (1886).
15. Stutz and Shriner, J. Am. Chem. Soc., 55, 1242 (1933).

reducible to mercaptans are sulfonic acids,[16] thiosulfonic acids and their esters,[16] sulfonamides,[17] sulfides,[18] sulfinic acids,[19] sulfenic acids,[20] alkyl hyposulfites[21] and thiocyanates,[22] sulfoxylates[23] and sulfanilides.[24]

It is possible to form mercaptans by reaction with sulfur. Among some of the most common examples of this type of synthesis are the reaction of benzene and sulfur in the presence of aluminum chloride to form benzenethiol,[25] the reaction of sulfur with phenylhydrazine,[26] the reaction of sulfur with diphenylamine[27] and the reaction of sulfur with aminodiphenylamine.[28] This latter reaction gives sulfides and polysulfides as well as mercaptans.

16. Gutmann, Ber., 47, 635 (1914).
17. Fischer, E., ibid., 48, 93 (1915).
18. Hilditch, ibid., 44, 3583 (1911).
19. Otto and Rössing, ibid., 19, 1224 (1886).
20. Fries, ibid., 45, 2965 (1912).
21. Price and Twiss, J. Chem. Soc., 95, 1725 (1909).
22. Hoffman and Reid, J. Am. Chem. Soc., 45, 1931 (1923).
23. Bing, Röth and Walter, Ber., 57, 1398 (1924).
24. Fichter and Tamm, ibid., 43, 3032 (1910).
25. Glass and Reid, J. Am. Chem. Soc., 51, 3428 (1929).
26. Fischer, Ber., 10, 1334 (1877).
27. Bernthsen, Ann., 230, 73 (1885).
28. Gilman, "Organic Chemistry", John Wiley and Sons, Inc., New York, N. Y., (1944), Vol. I, p. 507.

β-Hydroxymercaptans[29] may be prepared by the action of hydrogen sulfide on cyclic oxides; β-aminomercaptans[30] by the action of hydrogen sulfide on cyclic amines; α-aminomercaptans[31] by the action of hydrogen sulfide on α-amino-alcohols; and β-ketomercaptans[32] by the action of hydrogen sulfide on β-keto unsaturated compounds.

A few cases are available in which thermal or similar decomposition by scission serves as a source of mercaptans. Mercaptides, sulfides, and disulfides are definite sources of mercaptans.[33]

A method of preparing mercaptans from alcohols has recently been described in the literature.[34] This method involves the formation of an isothiouronium salt by treating the alcohol with thiourea and a halogen acid and subsequently decomposing this salt with sodium hydroxide. A more detailed discussion of this method is given in the next section of this paper.

29. Nenitzescu and Scarlatescu, Ber., 68, 587 (1935).

30. Mills and Bogert, J. Am. Chem. Soc., 62, 1073 (1940).

31. Binz and Pence, ibid., 61, 3134 (1939).

32. (a) Fromm, Haas and Hubert, Ann., 394, 290 (1912).
(b) Nicolet, J. Am. Chem. Soc., 57, 1098 (1935).

33. (a) Lecher, Ber., 58, 417 (1925); (b) Faragher, Marrell and Comay, Ind. Eng. Chem., 20, 527 (1928).

34. Frank and Smith, J. Am. Chem. Soc., 68, 2103 (1946).

Tertiary alkylaminoalkyl mercaptans

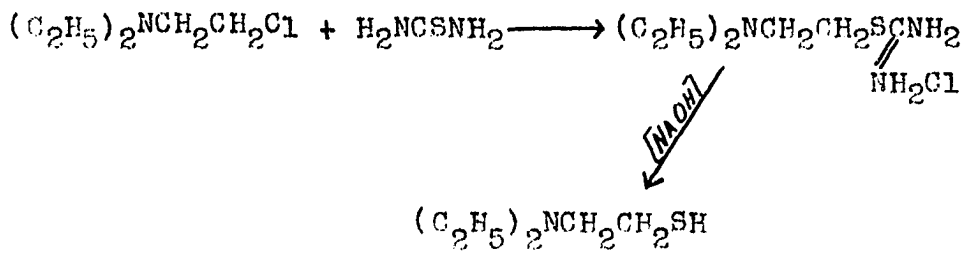
The methods for preparing tertiary alkylaminoalkyl mercaptans which have been reported in the literature correspond to those general methods for the preparation of mercaptans which have been given in the discussion above. The two tertiary alkylaminoalkyl mercaptans which were used particularly in these investigations are β-diethylaminoethyl mercaptan and γ-diethylaminopropyl mercaptan and, since the methods for their preparation are generally applicable, this section will be limited to a discussion of their preparation.

β-Diethylaminoethyl mercaptan has been prepared in 44% yield from lithium diethylamine and ethylene sulfide.[35] This method is long and involves the preparation of the organolithium compound from methyllithium and diethylamine. Gilman and co-workers[36] report the preparation of this mercaptan from β-diethylaminoethyl chloride and sodium hydrosulfide in yields varying from 25-57%. Albertson and Clinton[37] prepared the mercaptan in a 77.5% yield by the isothiouronium salt synthesis according to the following reactions:

35. Gilman and Woods, ibid., 67, 1843 (1945).

36. Gilman, Plunkett, Tolman, Fullhart and Broadbent, ibid., 67, 1845 (1945).

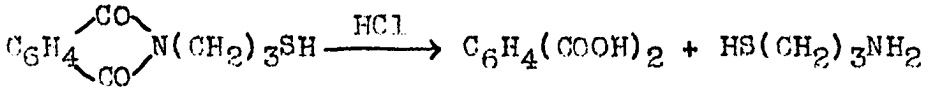
37. Albertson and Clinton, ibid., 67, 1222 (1945).



β-Diethylaminoethyl mercaptan has also been prepared by the reaction between diethylamine and ethylene sulfide in phenol.[35] No yield was reported on the preparation since the mercaptan was isolated as the bis-(β-diethylaminoethyl) disulfide.

γ-Diethylaminopropyl mercaptan has been prepared in 60% yield from γ-diethylaminopropyl chloride[36] and sodium hydrosulfide. Recently this mercaptan was prepared by the isothiouronium salt synthesis.[38]

One further method of preparing amino mercaptans should be mentioned. It is possible by means of a Gabriel reaction[39] to convert one mercaptan to another. This is illustrated by the case of the reaction of N-(γ-mercaptopropyl)-phthalimide with fuming hydrogen chloride in a bomb tube:



38. Fullhart, L., Doctoral Dissertation, Iowa State College, (1946).

39. Gabriel, Ber., 22, 1110 (1891).

Quinoline mercaptans

The most usual method for the preparation of quinolyl mercaptans is the reaction of the chloroquinoline with a solution of potassium or sodium hydrosulfide. John and Andraschko[40] prepared 6-methoxy-4-mercaptoquinoline by reacting 6-methoxy-4-chloroquinoline with an absolute ethanolic solution of potassium hydrosulfide in a sealed tube at 100° for fifteen hours. 2-Phenyl-4-mercaptoquinoline has been prepared[41] by the reaction between 2-phenyl-4-chloroquinoline and potassium hydrosulfide in absolute ethanol at 150-160° for eight hours.

Rosenhauer and co-workers[42] have prepared 2-mercaptoquinoline by means of the isothiouronium salt synthesis with subsequent decomposition of the complex with sodium carbonate. This preparation was carried out in yields of 90%. These workers prepared 2-mercapto-4-methylquinoline in this same manner. 2-Mercapto-4-methylquinoline is also reported by Roos[43] who prepared this compound by treating 2-hydroxy-4-methylquinoline with phosphorus pentasulfide. Roos[43] also prepared 2-mercaptoquinoline and 2-methyl-4-mercaptoquinoline

40. John and Andraschko, J. prakt. Chem., /2/ 128, 218 (1930).
41. John and Wünsche, ibid., 119, 43 (1928).
42. Rosenhauer, Ber., 62, 2733 (1929).
43. Roos, ibid., 21, 619 (1888).

by treating the corresponding hydroxy compounds with phosphorus pentasulfide. He reports no yields for these preparations.

8-Mercaptoquinoline has been reported by Edinger[44] who obtained it by hydrolyzing 8-benzoylmercaptoquinoline with hydrochloric acid. John and Wünsche[41] report 2-phenyl-4-mercaptoquinoline from 2-phenyl-4-chloroquinoline and potassium hydrosulfide.

Pyridine mercaptans

The only simple mercaptopyridine which is reported in the literature is 2-mercaptopyridine. Phillips and Shapiro[45] obtained this compound in 47% yield by treating 2-bromopyridine with thiourea and subsequently decomposing the isothiouronium complex with dilute alkali. Markwalk and co-workers[46] prepared this same compound from 2-chloropyridine and ethanolic potassium hydroxide and Gastel and Wibaut[47] prepared it from 2-iodopyridine and sodium hydrosulfide. 2-Mercaptopyridine was recently prepared by Thirtle[48] in 83% yield from potassium hydrosulfide and 2-bromopyridine.

Several substituted pyridine mercaptans have been prepared. Räth[49] obtained 2-mercapto-5-nitropyridine from

44. Edinger, A., ibid., 41, 937 (1908).
45. Phillips and Shapiro, J. Chem. Soc., 584 (1942).
46. Markwalk, Klemm and Trabert, Ber., 93, 1556 (1900).
47. Gastel and Wibaut, Rec. trav. chim., 53, 103 (1934).
48. Thirtle, J. Am. Chem. Soc., 68, 342 (1946).
49. Räth, C., Ann., 487, 105 (1931).

2-chloro-5-nitropyridine and methanolic potassium hydrosulfide; 2-mercapto-5-chloropyridine from 2,5-dichloropyridine and methanolic potassium hydrosulfide; 2-mercapto-5-bromopyridine from 2-chloro-5-bromopyridine and methanolic potassium hydrosulfide; 2-mercapto-5-iodopyridine from 2-chloro-5-iodopyridine and methanolic potassium hydrosulfide; 2-mercapto-5-iodopyridine from 2-hydroxy-5-iodopyridine and phosphorus pentasulfide; 2-mercapto-3-chloro-5-nitropyridine from 2,3-dichloro-5-nitropyridine and methanolic potassium hydrosulfide and in a similar manner 2-mercapto-3-bromo-5-nitropyridine and 2-mercapto-3-iodo-5-nitropyridine. Reduction of 2-mercapto-5-nitropyridine gave 2-mercapto-5-aminopyridine. Rath[49] also reports 2-mercaptopyridine-5-carboxylic acid from 2-chloropyridine-5-carboxylic acid and methanolic potassium hydrosulfide; 2-mercaptopyridine-5-thiocarboxamide from 2-chloro-5-cyanopyridine and methanolic potassium hydrosulfide; 2-mercapto-3-chloro-5-cyanopyridine from 2,3-dichloro-5-cyanopyridine and potassium hydrosulfide and in a similar manner 2-mercapto-3-bromo-5-cyanopyridine and 2-mercapto-3-iodo-5-cyanopyridine. Hydrolysis of 2-mercapto-3-chloro-5-cyanopyridine gave 2-mercapto-3-chloropyridine-5-carboxylic acid.

Sucharda and Troszkiewicz[50] report the preparation of

50. Sucharda and Troszkiewicz, Roczniki chem., 12, 493 (1932) [C. A. 27, 5076 (1933)].

several mercaptopyridyl carboxylic acids from the chloro-compound and potassium hydrosulfide; 2-mercaptopyridine-3-carboxylic acid; 3-mercaptopyridine-2-carboxylic acid and 3-mercaptopyridine-4-carboxylic acid.

B. Sulfides

General

Broadbent[51] has reviewed the general methods of preparing dialkyl sulfides. The principal methods involve the reaction of mercaptides with alkylating agents such as alkyl halides, alkylsulfates, sodium alkyl sulfates or alkyl sulfonates. Symmetrical sulfides may be readily prepared by the action of alkylating agents on sodium or potassium sulfide. Thiophenols may be converted to sulfides in the presence of sulfuric acid, using tertiary alcohols or olefins as alkylating agents.[52] Sulfides may also be prepared from olefins by the addition of hydrogen sulfide, mercaptans and thiophenols;[53] from diazonium salts with sodium thiosulfate or sodium sulfide; by thermal decomposition of lead mercaptides;[54] by replacement of the $-SO_3Na$ group in some

51. Broadbent, S., Doctoral Dissertation, Iowa State College, (1946).

52. Ipatieff, Pines and Friedman, J. Am. Chem. Soc., 60, 2731 (1938).

53. Mayo and Walling, Chem. Rev., 27, 351 (1940).

54. Otto, Ber., 13, 1289 (1880).

aromatic sulfonates;[55] by introducing the RS- group into active methylene compounds by the use of thiolsulfonic esters[56] or sulfenyl chlorides;[57] catalytically from mercaptans in the presence of a metallic sulfide catalyst at high temperatures;[58] from aromatic hydrocarbons and chlorides of sulfur;[59] and from the reaction of ethylene oxide with hydrogen sulfide, mercaptans[60] or thiophenols.

Alkyl aminoalkyl sulfides

The literature records the preparation of only a few amines containing alkyl groups interrupted by sulfur. Gabriel and Colman[61] prepared 2-(2-aminoethylthio)-ethanol from 2-chloroethanol and 2-aminoethanethiol. Brighton and Reid[62] have prepared a number of 2-alkyl thioethylamines from sodium mercaptides and 2-bromoethylamine. Their compounds correspond to the formula $RSCH_2CH_2NH_2$ when R is n-butyl, n-amyl, iso-amyl, n-hexyl and n-heptyl. A British patent[63]

55. Reid, Mackall and Metter, J. Am. Chem. Soc., 43, 2104 (1921).

56. (a) Brooker and Smiles, J. Chem. Soc., 1723 (1926); (b) Gibson, ibid., 983 (1938).

57. (a) Zincke and Eismayer, Ber., 51, 751 (1918); (b) Zincke and Baeumer, Ann., 416, 86 (1918).

58. Sabatier and Mailhe, Compt. rend., 150, 1569 (1910).

59. Wood and Fieser, J. Am. Chem. Soc., 62, 2674 (1940).

60. Fromm and Jörg, Ber., 58, 304 (1925).

61. Gabriel and Colman, ibid., 45, 1645 (1912).

62. Brighton and Reid, J. Am. Chem. Soc., 65, 458 (1943).

63. British patent, 286,087 /C. A., 23, 241 (1929)/.

describes 2-(2-chloroethylthio)-triethylamine hydrochloride. United States patents list, but do not characterize 2-(2-diethylaminoethylthio)-ethylamine[64] and 3-(2-diethylaminoethylthio)-propylamine.[65] Several other alkylaminoalkanethiols are mentioned in the patent literature[66] but in general details of syntheses of these types are lacking.

Among the most recent work along these lines is that of Clinton and co-workers[67] who prepared some diethylaminoethylthioalkyl amines and their corresponding sulfones. They prepared 2-(2-diethylaminoethylthio)-ethylamine and 3-(2-diethylaminoethylthio)-1-propylamine in several different ways. The action of ammonia or of hexamethylenetetramine on the corresponding alkyl halide was not satisfactory. The reaction between ω-thiolalkylphthalimide and 2-chlorotriethylamine or between 2-diethylaminoethanethiol and an ω-bromoalkyl phthalimide gave low yields. However, an extension of the method of Snyder and Cannon[68] illustrated in the following equations gave from 84-91% yields:

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64. United States Patent, 2,082,171 /C. A., 31, 5112 (1937)/.

65. (a) United States Patent, 2,077,249 /C. A., 31, 4060 (1937)/. (b) United States Patent, 2,121,207 /C. A., 32, 6262 (1938)/.

66. United States Patent, 2,401,234 /C.A., 40, 5075 (1946)/.

67. Clinton, Suter, Laskowski, Jackman and Huber, J. Am. Chem. Soc., 67, 594 (1945).

68. Snyder and Cannon, ibid., 66, 511 (1944).

$$(C_2H_5)_2NCH_2CH_2Cl + H_2NCSNH_2 \longrightarrow (C_2H_5)_2CH_2CH_2SC(=NH_2Cl)NH_2$$

$$(C_2H_5)_2NCH_2CH_2SC(=NH_2Cl)NH_2 + \text{C}_6\text{H}_4(\text{CO})_2\text{N}(CH_2)_nBr \longrightarrow$$

$$\text{C}_6\text{H}_4(\text{CO})_2\text{N}(CH_2)_nSCH_2CH_2N(C_2H_5)_2$$

The amines were prepared from the phthalimido compounds by a modification of the procedure of Ing and Manske.[69]

Gilman and Woods[35] prepared a series of alkylamino alkylchloro sulfides by the action of thionyl chloride on the corresponding hydroxy compound. The hydroxy compounds were prepared in most cases from the sodium mercaptide and the alkyl chloride.

Quinoline sulfides

Relatively few quinoline compounds containing sulfur have been made and most of these were prepared during the last decade. Morton and Stubbs[70] report the preparation of a simple quinoline sulfide, 2-isopropylthio-4-methylquinoline, from 2-thiol-4-methylquinoline and isopropyl bromide.

69. Ing and Manske, J. Chem. Soc., 2348 (1926).

70. Morton and Stubbs, ibid., 1321 (1939).

Several bisquinoline sulfides have been reported. Rosenhauer[42] prepared bis-(2-methyl-4-quinolyl)sulfide; Roos[43] prepared bis-(2-quinolyl) sulfide; Surrey and Lindwall[71] report the preparation of bis-(8-nitro-5-quinolyl) sulfide, bis-(5-quinolyl) sulfide and bis-(5-nitro-8-quinolyl) sulfide. Winter and Reinhart[72] have prepared a series of quinolyl phenyl sulfides by condensing 5-nitro-8-chloroquinoline with thiophenol or its p-nitro derivative; these reactions were carried out in an alkaline medium. Compounds listed in this series are 5-nitro-8-quinolyl phenyl sulfide and 5-nitro-8-quinolyl p-nitrophenyl sulfide. In this same paper Winter and Reinhart[72] report the preparation of 5-amino-2-pyridyl 2-quinolyl sulfide and 5-diethylaminoethylamino-2-pyridyl 2-quinolyl sulfide.

No alkylaminoalkyl quinoline sulfides in which the sulfur atom is next to the quinoline nucleus have been described in the literature and there is little reference to any quinoline compounds containing an amino side chain interrupted by a sulfur atom. The patent literature describes 8-(2-diethylaminoethylmercaptoethylamino)-7-chloroquinoline.[74] This latter compound is also listed in a German patent,[75] No

71. Surrey and Lindwall, J. Am. Chem. Soc., 62, 173 (1940).

72. Winter and Reinhart, ibid., 62, 3508 (1940).

73. United States Patent, 1,938,047.

74. United States Patent, 2,233,970 /C.A., 35, 3771 (1941)/.

75. I. G. Farbenindustrie, German Patent, 683,692 (1939) /C. A., 36, 4973 (1942)/.

very great details of the method of synthesis or of the physical properties of these compounds are given.

Gilman and Woods[35] prepared a series of quinoline compounds having a basic side chain containing sulfur. These compounds were 6-methoxy-8-quinolylamino derivatives and were prepared from 6-methoxy-8-aminoquinoline and a chloro-compound containing sulfur. A typical preparation of this type is that of γ-(6-methoxy-8-quinolylamino)-propyl β-diethylaminoethyl sulfide from 6-methoxy-8-aminoquinoline and γ-chloropropyl β-diethylaminoethyl sulfide hydrochloride. Gilman and Tolman[76] prepared a similar series of 6-methoxy-8-quinolyamino compounds, a typical one of which is γ-(6-methoxy-8-quinolylamino)-propyl γ-diethylaminopropyl sulfide made from γ-diethylaminopropyl γ-chloropropyl sulfide and 6-methoxy-8-aminoquinoline.

Huber and co-workers[77] prepared a series of 6-methoxy-8-quinolylamino compounds containing sulfur side chains. These compounds were prepared by condensation of an excess of 6-methoxy-8-aminoquinoline with a diethylaminoethyl-thioalkyl chloride in the presence of water. Typical among the compounds which these workers prepared is 8-(2-(2-di-

76. Gilman and Tolman, J. Am. Chem. Soc., 67, 1847 (1945).

77. Huber, Blair, Boehme, Laskowski, Jackman and Clinton, ibid., 67, 1849 (1945).

ethylaminoethylthio)-ethylamino)-6-methoxyquinoline.

A series of diethylaminoethylthioalkyl derivatives of substituted 4-aminoquinolines was prepared by Huber and co-workers[78] along with a few corresponding sulfinyl and sulfonyl analogs. The compounds in this series were all 7-chloro-4-quinolyl derivatives.

A series of quinoline sulfides containing long-chained aliphatic groups has been prepared and discussed by Massie.[79]

Pyridine sulfides

All of the pyridine sulfides which have been described in the literature are simple bis-pyridyl sulfides or pyridyl compounds containing simple side chains. There are no aminopyridyl sulfides reported.

Surrey and Lindwall [71,80] report the preparation of bis-(5-nitro-2-pyridyl) sulfide, from 2-chloro-5-nitro-pyridine and sodium sulfide and later from 2-chloro-5-nitropyridine and thiourea. Using both of these methods these workers prepared some 2-pyridyl phenyl sulfides by condensing 2-chloro-5-nitropyridine with thiophenol or its

78. Huber, Blair, Laskowski, Jackman and Clinton, ibid., 68, 322 (1946).

79. Massie, S. P., Doctoral Dissertation, Iowa State College, (1946).

80. Surrey and Lindwall, J. Am. Chem. Soc., 62, 1697 (1940).

p-nitro derivative. In the case of the 2-chloro compounds and thiophenol no solvent or alkaline agent was required for reaction to take place at 135-150°. Winter and Reinhart[72] prepared 5-amino-2-pyridyl 2-quinolyl sulfide, 5-diethylaminoethylamino-2-pyridyl 2-quinolyl sulfide and a bis compound, 5-/bis-(diethylaminoethyl)-amino/-2-pyridyl phenyl sulfide. Bis-(2-pyridyl) sulfide is reported by Kolmer, Brown and Rauziss.[81]

Colonna[82] prepared a group of very interesting sulfur derivatives of pyridine. He reacted 2-mercapto-5-nitropyridine with chloroacetic acid and aqueous potassium hydroxide to obtain 5-nitropyridine-2-thiolglycolic acid. This compound was obtained in better yield by reacting 2-chloro-5-nitropyridine with thioglycolic acid and sodium bicarbonate. 5-Nitropyridine-2-thiopropionic acid was also prepared by these same methods. Colonna treated his products with dehydrating agents in order to finally obtain compounds in which the pyridine ring was condensed with rings containing sulfur.

A series of alkylpyridine sulfides along with the corresponding sulfoxides and sulfones is described by Courtot and Zwilling.[83]

81. Kolmer, Brown and Rauziss, J. Pharmacol., 61, 253 (1937).

82. Colonna, M., Gazz. chim. ital., 70, 154 (1940) /C. A. 24, 4737 (1940)/.

83. Courtot and Zwilling, Congr. chim. ind., Compt. rend. 18 me Congr., /C. A., 33, 6313 (1939)/.

Hydroxy sulfides

α-Bromoketones react with mercaptans to form keto sulfides which upon reduction yield secondary hydroxy sulfides.[84] The reaction of mercaptans with ethylene oxide is a well known one.[29] With excess ethylene oxide mercaptans yield alcohols of the type $R'-S-CH_2CH_2-(OCH_2CH_2)_n-OCH_2CH_2OH$ when n - 1 equals the number of excess moles of ethylene oxide.[85] The reaction of epichlorohydrin with mercaptans gives compounds of the type $R-S-CH_2CHOHCH_2Cl$ which are useful in various condensations. It has been found, however, that alkali mercaptides and epichlorohydrin at low temperatures give the mercapto oxide.[29,86]

C. Chemotherapeutic Substances Used As a Basis for These Investigations

Since very few references are made in the literature to quinoline and pyridine sulfides, there is likewise little reference as to any physiological action which any such compounds might have. Most of the compounds in this thesis contain both nitrogen and sulfur and certain compounds con-

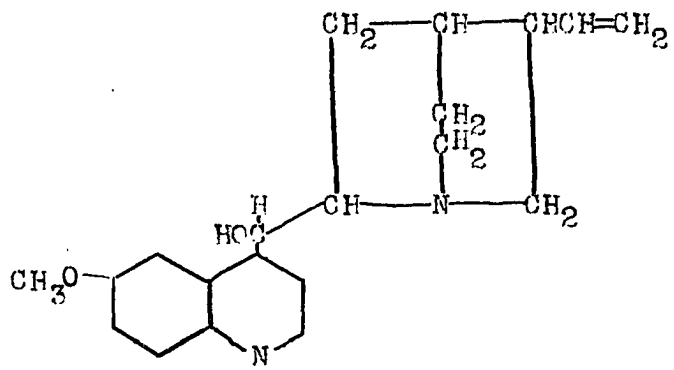
84. Prelog, Hahn, Brauchli and Beyerman, Helv. chim. acta., 27, 1209 (1944) /C. A., 40, 848 (1946)/.

85. English Patent, 437,590 (1934) /Chem. Zentr., I, 3019, (1936)/.

86. Gilman and Woods, J. Am. Chem. Soc., 67, 1864 (1945).

taining one or both of these elements which are active as therapeutic agents were used as a basis for the preparations.

Most of the alkaloids, known for many years to produce very marked and definite physiological effects, are derivatives either of quinoline or pyridine. The most outstanding quinoline derivative, as far as therapeutics is concerned, is quinine (I).



(I)

The therapeutic value of quinine arises chiefly from the fact that it has a specific action in malaria, apparently being far more poisonous to the protozoal parasites than to the cells of the host. The multiple action of quinine as a drug may be summarized as follows:

1. It is capable of slowing down the whole of the metabolic processes, including those of the intracellular enzymes. It is a strong antipyretic.

2. It shows a marked bactericidal action in addition to its action on the parasites of malaria.

3. It has a narcotic action exercised principally through the medullary centers.

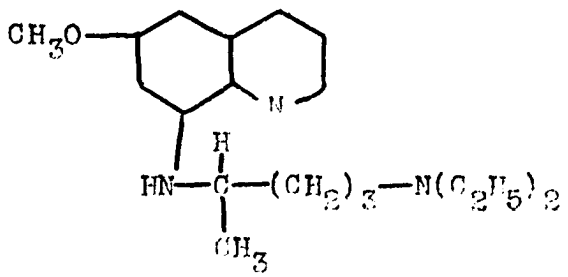
4. It shows a local anaesthetic action.

Quinine has several disadvantages as a drug. Poisoning by quinine may occur due to overdosage or to idiosyncrasy. When quinine is repeatedly administered in full doses cinchonism may result. This condition is characterized by impaired hearing and vision, nausea, headache, and gastro-intestinal and nervous disorders.

The total synthesis of quinine was not realized until 1945[1] and the synthesis is at the present time of little value from a commercial point of view since it involves many steps to produce only a small yield of material.

The difficulties in the synthesis of quinine which for a long time was the most important substance used in the treatment of malaria led to the study of other compounds which might be used as antimalarials. Plasmochin was synthesized by Schuleman, Schönhöfer and Wingler[87] on the basis of the fact that methylene blue showed plasmodicidal properties. Plasmoquin (II) is a quinoline derivative and has a tertiary amino side chain.

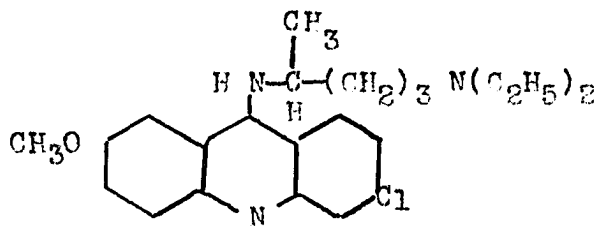
87. German Patent, 486,079, (1924) /C. A., 24, 1937 (1930)/.



(II)

Plasmochin is approximately sixty times as effective in avian malaria as quinine, its action being gametocidal.[88] The use of plasmochin in humans is limited due to the fact that the therapeutic dose often approaches the toxic dose. The most pronounced toxic effects produced by plasmochin are cyanosis and methemoglobin formation.

Atebrin (III) was introduced into malariatherapy by Schulemann (1930). It was synthesized by Mauun and Mietzch[89] on the basis of the clinical results obtained with plasmoquin.



(III)

88. Spatz, S. M., Doctoral Dissertation, Iowa State College, (1941) discusses generally the malarial cycle.

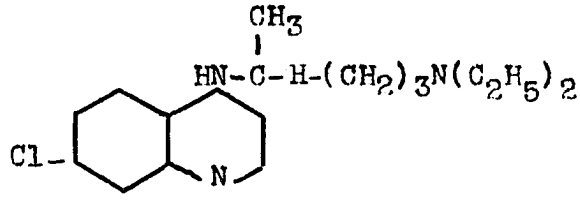
89. United States Patent, 2,077,249 /C. A., 31, 4060 (1937)/.

Atebrin, like quinine, is schizontal in action while plasmosquin is gametocidal. This drug has proved to be far superior to quinine and during World War II became the most important antimalarial. The toxicity of atebrin is relatively low, large doses causing gastro-intestinal disturbances, abdominal pains, headaches and anorexia.

Shortly after Pearl Harbor, when the United States was faced with the necessity of fighting a major war in some of the world's worst malaria countries, about 90% of the sources of the world supply of quinine fell into the hands of the Japanese. This condition made an intensive program for the development of alternate and improved antimalarials, and at the same time new drugs for other uses, a vital necessity. During the period of 1941-46 some 14,000 chemical compounds were screened for antimalarial activity under the auspices of the Committee on Medical Research of the office of Scientific Research and Development. Many of these compounds were tested for various other physiological properties. Among the 14,000 substances tested about 70 classes of organic compounds showed some antimalarial activity. The field has now been narrowed to four (possibly five) chemical groups, certain members of which appear to embody substantial improvements over existing drugs. The four groups are the 4-aminoquinolines, the 8-aminoquinolines, the quinolyl-4-α-piperidyl methanols and

the quinolyl-4-dialkylamino methanols. Certain 1,4-naphthoquinone derivatives should also be added to this list, although this group has not been as thoroughly tested on human subjects as have the other four groups.

One of the most promising of the 4-aminoquinolines is SN 7618[90] or 7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline (IV).



(IV)

SN 7618 was first synthesized by Anderson, Breitner and Jung[91] but its therapeutic potentialities were first realized by Surrey and Hammer.[92] This drug is at least four times as effective against avian malaria as is atebrin and twice as effective against the common human malarias. It is capable, moreover, of terminating a clinical attack of P. falciparum by oral administration while atebrin is usually given by intramuscular injection for this purpose. SN 7618 is an

90. This number refers to the survey number of the drugs listed in the files of the Survey of Antimalarial Drugs. Activities of drugs thus listed will be tabulated in a forthcoming monograph.

91. German Patent, 683,692 (1939) /C. A., 36, 4973 (1942)/.

92. Surrey and Hammer, J. Am. Chem. Soc., 68, 113 (1946).

effective suppressive, is well tolerated and does not color the skin.

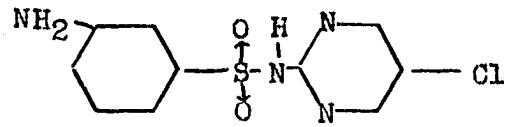
During the past few years a total of 248 derivatives of 4-aminoquinoline has been tested for antimalarial activity and toxicity. Of the drugs tested 64 represented side-chain variants of the 7-chloro-4-aminoquinoline nucleus, 63 represented derivatives of 7-chloro-4-anilinoquinoline, 35 represented derivatives of 6-methoxy-4-aminoquinoline and 86 represented nuclear variations of 4-(3-diethylaminopropylamino)-7-chloroquinoline (SN 9584).[90]

Of the new 8-aminoquinoline derivatives three hold definite promise of being superior to plasmochin as curative drugs. These are 6-methoxy-8-(5-isopropylaminopentylamino)-quinoline (SN 13,276),[90] 6-methoxy-8-(4-isopropylamino-1-methylbutylamino)-quinoline (SN 13,274)[90] and 4,6-dimethoxy-8-(4-isopropylamino-1-methylbutylamino)-quinoline (SN 9972).[90] Various other nuclear variants in the quinoline nucleus have been studied. Derivatives of 6-methoxy-8-aminolepidine have shown high activity against avian malaria but no definite evaluation can be made since little clinical testing of these compounds has been done.

In the field of quinoline carbinols a total of 204 4-quinoline methanols has been synthesized and in addition 32 quinoline methanols containing the side-chain in positions other than the 4-position have been synthesized. The most

active of these substances appear to be 6,8-dichloro-2-(p-chlorophenyl)-4-(-piperidyl)-carbinol drugs and dialkylaminocarbinols derived from 7-chloro-8-methyl-2-(p-chlorophenyl)-quinoline.

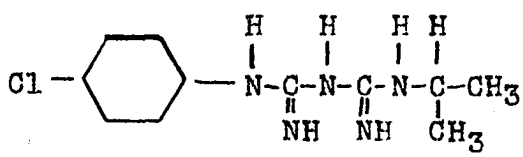
Among the important drugs recently announced, meta-chloridine[93] or 2-(m-aminobenzenesulfonylamino)-5-chloro-pyrimidine (V), is the first important antimalarial which contains sulfur.



(V)

A full report of the physiological properties of this compound has not yet been released but it is believed to be a superior suppressive agent.

A new compound recently developed by British workers[94] and known as paludrine, or N^1-p-chlorophenyl N^5-isopropyl biguanide (VI) is reported to be remarkably active in destroying malaria parasites and to be relatively non-toxic.

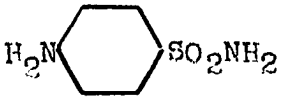


(VI)

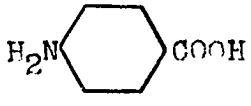
93. See, Volwiler and MacCorquodale, Chem. Eng. News, 24, 346 (1946).

94. Curd and Rose, Chem. and Ind., 75 (1946).

A consideration of important physiologically active compounds leads one to a discussion of the drugs which have proved promising in the treatment of tuberculosis. In recent years some of the most important work in the field of chemotherapy as applied to tuberculosis has been directed toward the preparation of drugs similar in chemical structure to the substances required by the bacteria for existence, yet antagonistic in their physiological action.[95] According to the theory of Woods, Fildes and McIlwain,[96] bacteria try to substitute structurally similar sulfanilamide in their metabolism for p-aminobenzoic acid, an essential growth factor for many bacteria.



Sulfanilamide



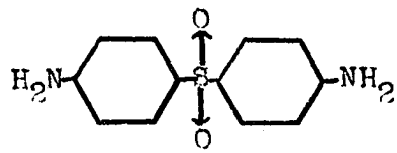
p-Aminobenzoic Acid

Sulfanilamide and drugs of this type cause bacteriostasis because they do not fulfill the requirements of the bacteria for growth and reproduction. Once rapid growth of bacteria is stopped, the normal body mechanisms can complete the task of coping with the infection.

95. Woods and Fildes, Chemistry & Industry, 18, 133 (1940).

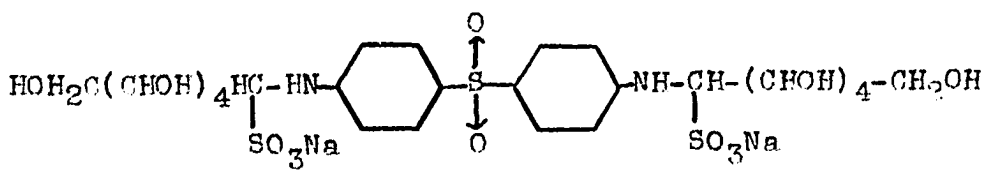
96. (a) Jenkins and Hartung, "The Chemistry of Organic Medicinal Products", John Wiley and Sons, Inc., New York, N. Y. (1943), p. 431; (b) Woods, Brit. J. Exptl. Path., 21, 74 (1940).

Many aminosubstituted aromatic sulfones which, according to their structure, should be metabolite antagonists to p-aminobenzoic acid have been prepared and tested for antituberculous activity. It has been in this group, the parent compound of which is 4,4'-diaminodiphenyl sulfone, that the most promising compounds have been found. 4,4'-Diaminodiphenyl sulfone (VII) has high antituberculous activity but is too toxic and too insoluble to be useful.



(VII)

Only three of the many compounds classed as metabolite antagonists tested for antituberculous activity were ever tested clinically: promin,[97] its bis(glucose sulfonate) (VIII), diasone,[98] its bis (N-methylene sodium sulfoxylate) (IX) and promizole, 4-aminophenyl-2'-aminothiazolyl-5'-sulfone[99] (X).

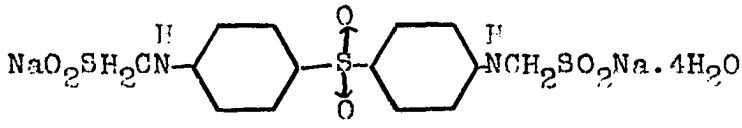


(VIII)

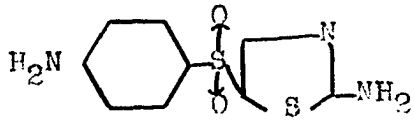
97. Feldman, Hinshaw and Moses, Proc. Staff Meetings Mayo Clinic, 15, 695 (1940).

98. Raiziss, Science, 98, 350 (1943).

99. Bambas; J. Am. Chem. Soc., 67, 671 (1945).



(IX)



(X)

Preliminary clinical tests were promising but they did not fulfill early hopes. Promin and diasone have recently found another use. Definite improvement in the clinical condition of a considerable series of cases of leprosy has been reported after treatment with promin. The drug acts slowly, however, and prolonged treatment is necessary for favorable results. Diasone offers two advantages over promin in that it can be given orally and unfavorable reactions are less frequent. Further clinical evaluation is necessary before these drugs may be regarded as leprostatic agents.

Pyridine itself, is found very widely distributed in nature and among these compounds are some of the most useful and important medicines and drugs. The physiological effects of pyridine compounds such as nicotinic acid, nicotinamide, cozymase and pyridine-β-carboxylic acid diethylamide are well known and need not be pointed out here further than to say that they do indicate that the pyridine

nucleus might have definite value as a basis for physiologically active compounds.

The drugs which have been mentioned in this section represent only a very minute portion of the field of chemotherapy. They do, however, serve to illustrate the several facts used as a basis for this research.

All of the compounds mentioned contain nitrogen, and most of them are heterocyclic in nature. In addition many are sulfur compounds. It seems, therefore, that the study of nitrogen and sulfur containing organic compounds is significant.

D. Organosilicon Compounds

Nomenclature

For the convenience of the reader a list of some of the more common rules of nomenclature for organosilicon compounds follows. These rules are in accordance with those proposed by the Committee on Nomenclature, Spelling and Pronunciation of the American Chemical Society.[100]

1. The name of the compound SiH_4 is silane. The radical derived from it, H_3Si-, is silyl.

2. Compounds having the general formula

100. Crane, J. Chem. Eng. News, 24, 1233 (1946).

$H_3Si(SiH_2)_nSiH_3$ are called disilane, trisilane etc., according to the number of silicon atoms present. The radicals derived from these compounds are disilyl-, trisilyl-, etc.

3. Derivatives in which an OH is attached to silicon are named by adding the suffix ol, diol, triol, etc., to the parent compound. For example, H_3SiOH is silanol; $H_2Si(OH)_2$ is silanediol.

4. Compounds having the formula $H_3Si(OSiH_2)_nOSiH_3$ are called disiloxane, trisiloxane, etc., according to the number of silicon atoms present.

5. Compounds having the formula $H_3Si(NHSiH_2)_nNHSiH_3$ are called disilazane, trisilizane, etc., depending on the number of silicon atoms present.

A brief review of organosilicon chemistry

For some eighty years organic compounds of silicon have been the subject of much research, but it has been only recently that commercial and scientific interests in these compounds have widened and research in the field has been accelerated. So far probably less than two thousand organosilicon compounds have been investigated; but the infinite variability of the silicon molecule, the expanding literature on the subject, a standardized system of nomenclature and the development

of many synthetic methods make a great and expanding new chemistry built around silicon probable.

Silicon, the most abundant electropositive element on the earth's crust, is a hard, brittle, metallic-like substance which occurs chiefly as the oxide. Silicon is usually tetracovalent but, as would be expected from its position in the second short period of group four of the periodic table, it shows a maximum covalency of six.[101] In organic compounds silicon is tetravalent like carbon. Chemically it resembles boron and germanium as closely as carbon and it is impossible to predict the reactions of this element purely by analogy with those of carbon.[102]

There are two types of covalent compounds of silicon which are of particular interest to the work of this thesis and which are of general interest as starting materials in the best present methods for preparing organosilicon compounds. These are the halides and the esters.

The halides of silicon are prepared generally by the direct action of the respective halogen upon elementary

101. (a) Sidgwick, "The Electronic Theory of Valency" Oxford University Press, London, (1932), Chap. IX; (b) Sidgwick and Callow, J. Chem. Soc., 125, 532 (1924).

102. Rochow, "Chemistry of the Silicones", John Wiley and Sons Inc., New York, N. Y. (1946).

silicon or its alloys. As a group, the halides are volatile acid-smelling substances, their most characteristic reactions being the readiness with which they hydrolyze and their ability to form coördination compounds. For example, with ammonia silicon tetrachloride first forms a hexa-monate, $SiCl_4.6NH_3$ which upon heating passes through the stages $Si(NH_2)_4$, $Si(NH_2)_2NH$, $Si(NH)_2$ and finally to Si_3N_4. The reactions with water follow a similar course and ultimately give silica.

The tetra halides are the cheapest, most readily available compounds of silicon and are, for this reason, important as starting materials for the synthesis of many organosilicon compounds.

There are several reactions which should be noted in connection with the halides of silicon. The halogen atoms may be readily replaced stepwise by alkoxy and aroxy groups through reactions with the corresponding alcohol or phenol; hydrocarbon groups may be attached directly to the silicon by reaction with zinc aryls,[103] with mercury aryls,[104] with

103. (a) Friedel and Crafts, Ann., 136, 203 (1865); (b) Friedel and Ladenburg, ibid., 159, 259 (1871); (c) ibid., 203, 251, (1880).

104. Ladenburg, ibid., 173, 151 (1874).

sodium aryls and alkyls,[105] and with organomagnesium halides or Grignard reagents.[106] Recently the use of organolithium reagents in place of Grignard reagents to introduce alkyl or aryl radicals into the silane molecule has been demonstrated successfully.[107,133]

The halogen in silicon halides may be replaced by hydrogen with aluminum or some other metal as an absorber. Hurd[108] uses a mixture of hydrogen and the silicon halide vapor and passes this mixture over heated aluminum powder. A further interesting reaction of silicon halides is that with ethylene oxide to form a β-chloroethoxy or β-bromoethoxy group.[109]

$$-\overset{|}{\underset{|}{Si}}-Cl + CH_2 - CH_2 \longrightarrow -\overset{|}{\underset{|}{Si}} - OCH_2CH_2Cl$$
(O)

The organic esters of silicon are ordinarily referred to as organic orthosilicates, being considered esters of

105. (a) Polis, Ber., 18, 1540 (1885); (b) Kipping and Lloyd, J. Chem. Soc., 79, 449 (1901); (c) Schumb, Ackerman and Saffer, J. Am. Chem. Soc., 60, 2486 (1938); (d) Schumb and Saffer, ibid., 63, 93 (1941).

106. Kipping, Proc. Chem. Soc., 20, 15 (1904).

107. Fleming, United States Patent, 2,386,452 [C. A., 40, 603 (1946)].

108. Hurd, J. Am. Chem. Soc., 67, 1545 (1945).

109. (a) United States Patent, 2,381,137 [C.A., 39, 4888 (1945)]; (b) United States Patent, 2,381,138 [C. A., 39, 4890 (1945)]; (c) United States Patent, 2,381,139 [C. A., 39, 4890 (1945)].

the hypothetical orthosilicic acid $Si(OH)_4$. This view is based only on an analogy to the orthocarbonates for silicic acid is not acidic in the sense of furnishing hydrogen ions. Silicon esters are formed when the halides are reacted with alcohols, the products of such reactions being volatile colorless liquids of pleasant odor. Incomplete esterification gives volatile alkoxychlorosilanes or if water is present alkoxysiloxanes resulting from partial hydrolysis of the ester followed by intermolecular condensation of the silanols so formed.[102] The hydrolysis of silicon orthoesters is relatively slow and can be controlled. This fact makes the esters particularly useful in synthetic work. The silicic esters, like the halides, react with Grignard reagents to attach organic groups directly to the silicon atom in stepwise fashion.[110]

$$Si(OR)_4 + R'MgX \longrightarrow R'Si(OR)_3 + Mg(OR)X$$

$$R'Si(OR)_3 + R'MgX \longrightarrow R_2Si(OR)_2 + Mg(OR)X$$

Recently it has been shown that the esters react readily with organolithium compounds in a similar fashion.[107,133]

There are two general types of synthesis for organosilicon compounds: the substitution methods and the direct method. The substitution methods employ a silicon halide

110. United States Patent, 2,380,057.

or ester as starting material and the halogen atoms or ester groups are replaced successively by reactions with a suitable organometallic compound. The direct method uses a hydrocarbon halide to react directly with a copper silicon alloy in the liquid or vapor phase and in the presence of a metallic catalyst to produce a mixture of organosilicon halides. The methods employed in this thesis were substitution types.

This is only a very brief survey of a few of the most pertinent points about the organic compounds of silicon. A more complete review of organosilicon chemistry may be found in one of the excellent general reference works on the subject.[102,111]

111. (a) Friend, "A Text-Book of Inorganic Chemistry", Volume XI, Part I, Charles Griffin and Company, Ltd., London, 1928, p. 246; (b) Krause and Grosse, "Die Chemie der metall-organischen Verbindungen", Gebruder Borntraeger, Berlin, 1937, p. 263; (c) Grignard, Du Pont, and Locquin, "Traite de chimie organique. T. XIV. Composes azotes de l'acide carbonique. Composes organoarsenies, organophosphores ou organosilices", Masson and Cie, Paris, 1939; (d) Robindon, Sci. J. Roy. Coll. Sci., 15, 24 (1945); (e) Kipping, Proc. Roy. Soc. London, 159, 139 (1937); (f) Hausman, J. Chem. Ed. 23, 16 (1946); (g) Rochow and Norton, Colloid Chemistry, 6, 1092 (1946).

III. EXPERIMENTAL

β-Diethylaminoethyl Mercaptan

Method A[35]

To a solution of $(C_2H_5)_2NLi$, prepared from 88 g. (1.2 moles) of diethylamine and 1.2 moles of methyllithium in ether, cooled to -15° was added a solution of 78 g. (1.3 moles) of ethylene sulfide in 200 ml. of ether during two hours. The mixture was maintained below -5° for two hours and was allowed to warm up to room temperature during the next hour. The mixture was then cooled to -15° and 1.4 moles of hydrogen chloride in 303 ml. of anhydrous ether was added during fifteen minutes, followed by 100 ml. of water. From the dried ether layer was obtained 76 g. (48%) of product distilling at 66-68°/20 mm. Gilman and Woods[35] report yields of 48.1% and 44% for this preparation.

Method B[36]

Hydrogen sulfide was bubbled through 350 g. (1.4 moles) of melted sodium sulfide nonahydrate for several hours until it was saturated. To the resulting solution was added 90 g. (0.6 moles) of freshly distilled β-diethylaminoethyl chloride and the mixture was refluxed with stirring for one hour in an atmosphere of nitrogen. The reaction

mixture was cooled and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and distilled to give 44 g. (50%) of product boiling at 62-65°/21 mm. Yields from this preparation varied from 25-57%.

Method C[37]

To a refluxing solution of 99 g. (1.3 moles) of thiourea in 300 ml. of 95% ethanol a solution of 209 g. (1.16 moles) of β-diethylaminoethyl chloride hydrochloride in 600 ml. of 95% ethanol was added in a thin stream during one-half hour. The solution was left over night and the white isothiouronium complex precipitated out. The solid material was filtered and 268 g. (90%) of the complex melting at 193-194° was obtained.

β-Diethylaminoethyl isothiouronium chloride hydrochloride (268 g.) was suspended in 400 ml. of water and a hot solution of 81.2 g. of sodium hydroxide in 300 ml. of water was added. The mixture was saturated with salt and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and distilled to give 85 g. (60%) of product boiling at 63-65°/20 mm.

γ-Diethylaminopropyl Mercaptan

Method A[36]

Hydrogen sulfide was bubbled through 240 g. (1 mole)

of melted sodium sulfide nonahydrate for several hours until it was saturated. To the resulting solution was added 78 g. (0.52 mole) of freshly distilled γ-diethylaminopropyl chloride[112] and the reaction mixture was refluxed with stirring for three hours. The reaction mixture was cooled and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and distilled to give 45 g. (60%) of product boiling at 73-76°/20 mm.

In another preparation using 6 moles of γ-diethylaminopropyl chloride the ether extract was treated with 20% sodium hydroxide solution in order to obtain product that was free of γ-diethylaminopropyl chloride (b. p., 75-76°/20 mm.). Hydrochloric acid was added with stirring to the alkaline solution. The two layers which formed were separated. The slightly alkaline solution was made acidic and ammonium hydroxide was added until it was alkaline. The alkaline solution was extracted with ether and the extracts were combined with those from the first extract and dried over anhydrous sodium sulfate. After removal of the ether, a yield of 47 g. (20%) of product boiling at 83-85°/20 mm. was obtained.

Method B[38]

To a refluxing solution of 152 g. (2 moles) of thiourea

112. Gilman and Shirley, J. Am. Chem. Soc., 66, 888 (1944).

in 350 ml. of 95% ethanol a solution of 1.53 moles of γ-diethylaminopropyl chloride hydrochloride was added in a thin stream during one-half hour. The resulting clear solution was refluxed for six hours. Upon removal of some of the solvent the isothiouronium complex separated out. The solid material was filtered and 86% of product melting at 128-130° was obtained.

γ-Diethylaminopropylisothiouronium chloride hydrochloride (50 g.) was suspended in 150 ml. of water and a hot solution of 154 g. of sodium hydroxide in 100 ml. of water was added. The mixture was saturated with salt and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and distilled to give 50% of product boiling at 68-70°/20 mm.

2-Quinolyl β-Diethylaminoethyl Sulfide Hydrochloride

A solution of 19.9 g. (0.15 mole) of β-diethylaminoethyl mercaptan in 50 ml. of absolute ethanol was added to a stirred and gently refluxing solution of sodium ethoxide prepared from 0.15 g. atom of sodium in 50 ml. of absolute ethanol. After refluxing for thirty minutes, there was added to the sodium mercaptide a solution of 20 g. (0.12 mole) of 2-chloroquinoline in absolute ethanol and the resulting mixture was refluxed for four hours in an atmosphere of nitrogen. After removal of the ethanol, the residue was

treated with a mixture of ether and water. The ether layer was separated, dried over anhydrous sodium sulfate and treated with hydrogen chloride. Recrystallization of the hydrochloride from absolute ethanol gave 22.7 g. (65%) of product melting at 192-193°.

Anal. Calcd. for $C_{15}H_{21}N_2ClS$: N, 9.46; Cl, 11.82; S, 10.81. Found: N, 9.28; Cl, 11.45 and 11.52; S, 10.66 and 10.45.

2-Quinolyl γ-Diethylaminopropyl Sulfide Hydrochloride

A solution of 16.1 g. (0.11 mole) of γ-diethylaminopropyl mercaptan in 50 ml. of absolute ethanol was added to a stirred and gently refluxing solution of sodium ethoxide prepared from 0.11 g. atom of sodium in 60 ml. of absolute ethanol. After refluxing for thirty minutes, there was added to the sodium mercaptide a solution of 14.7 g. (0.09 mole) of 2-chloroquinoline in absolute ethanol and the resulting mixture was refluxed for five hours in an atmosphere of nitrogen. The ethanol was removed and the residue was treated with a mixture of ether and water. The ether layer was separated, dried over anhydrous sodium sulfate and treated with hydrogen chloride. Recrystallization of the hydrochloride from absolute ethanol gave 14 g. (50%) of product melting at 141-142°.

Anal. Calcd. for $C_{16}H_{23}N_2ClS$: N, 9.03; Cl, 11.29.

Found: N, 9.10 and 9.41; Cl, 11.34 and 11.22.

4-Methyl-2-quinolyl β-Diethylaminoethyl Sulfide Dihydrochloride

A solution of 11.9 g. (0.09 mole) of β-diethylaminoethyl mercaptan in 50 ml. of absolute ethanol was added to a refluxing solution of 0.09 g. atom of sodium in absolute ethanol and the mixture was stirred for thirty minutes. Then a solution of 12.3 g. (0.07 mole) of 2-chloro-4-methylquinoline in absolute ethanol was added and the reaction mixture was refluxed for three hours in an inert atmosphere. The solvent was removed and the residue was treated with ether and water. The ether layer was separated, dried over anhydrous sodium sulfate and treated with ethereal hydrogen chloride. Recrystallization of the dihydrochloride from absolute ethanol gave a yield of 43% of product melting at 216-217°.

Anal. Calcd. for $C_{16}H_{24}N_2Cl_2S$: N, 8.09; Cl, 20.23; S, 9.24. Found: N. 7.80 and 8.10; Cl, 20.00 and 20.22; S. 9.40.

4-Methyl-2-quinolyl γ-Diethylaminopropyl Sulfide Dihydrochloride

To a stirred and gently refluxing solution of 0.09 g. atom of sodium in absolute ethanol was added a solution of 12 g. (0.09 mole) of γ-diethylaminopropyl mercaptan in 50 ml. of absolute ethanol and the mixture was refluxed for

thirty minutes. Then a solution of 12.3 g. (0.07 mole) of 2-chloro-4-methylquinoline in absolute ethanol was added and the reaction mixture was refluxed for four hours in an atmosphere of nitrogen. The solvent was removed and the residue was taken up in ether and washed with water. The ether solution was dried over anhydrous sodium sulfate and treated with ethereal hydrogen chloride. Recrystallization of the dihydrochloride from an absolute ethanol-ethyl acetate mixture gave 60% of product melting at 199-200°.

Anal. Calcd. for $C_{17}H_{26}N_2Cl_2S$: N, 7.77. Found: N, 7.90 and 7.80.

6-Methoxy-2-quinolyl β-Diethylaminoethyl Sulfide Dihydrochloride

Method A

A solution of 10.6 g. (0.08 mole) of β-diethylaminoethyl mercaptan in 50 ml. of absolute ethanol was added to a stirred and gently refluxing solution of sodium ethoxide prepared from 0.08 g. atom of sodium in 60 ml. of absolute ethanol. After refluxing for thirty minutes there was added to the sodium mercaptide a solution of 10. g. (0.05 mole) of 2-chloro-6-methoxyquinoline in absolute ethanol and the resulting mixture was refluxed for nine hours in an atmosphere of nitrogen. The ethanol was removed under reduced pressure and the residue was dissolved in ether and washed

with water. The ether solution was dried over anhydrous sodium sulfate and treated with ethereal hydrogen chloride. Recrystallization of the dihydrochloride from absolute ethanol gave 33% of product melting at 168-170°.

Anal. Calcd. for $C_{16}H_{24}ON_2Cl_2S$: N, 7.73; Cl, 19.33; S, 8.84. Found: N, 7.94; Cl, 19.00; S, 8.78 and 8.53.

2-Chloro-6-methoxyquinoline was prepared in 55% yield from 6-methoxyquinoline-N-oxide hydrochloride and phosphorus oxychloride.[113] The 4-isomer was obtained in 33% yield in the same reaction. The 6-methoxyquinoline-N-oxide hydrochloride was prepared in 88% yield by oxidizing 6-methoxyquinoline with perbenzoic acid.[113]

Method B

6-Methoxy-2-quinolyl β-diethylaminoethyl sulfide dihydrochloride was also prepared in 30% yield by refluxing for four hours a mixture of a solution of 5 g. (0.04 mole) of β-diethylaminoethyl chloride and 0.02 mole of the sodium salt of 2-mercapto-6-methoxyquinoline in absolute ethanol. After removal of the solvent the residue was taken up in ether, dried over anhydrous sodium sulfate and treated with ethereal hydrogen chloride. The dihydrochloride which melted at 168-170° was identified by a mixed melting point with the

113. Magidson and Rubstov, J. Gen. Chem. (U.S.S.R.), 7, 1896, (1937) [C. A., 32, 564 (1938)].

dihydrochloride from the first preparation.

2-Mercapto-6-methoxyquinoline

This compound was prepared, with some modification, according to the directions of John[40] for the preparation of 4-mercapto-6-methoxyquinoline.

A mixture of 14 g. (0.09 mole) of 2-chloro-6-methoxyquinoline, 11 g. of potassium hydrosulfide and 46 ml. of absolute ethanol was heated at reflux temperature for fifteen hours. The solid material which formed was washed well with water and neutralized with acetic acid. After recrystallization from absolute ethanol 5 g. (33%) of product melting at 185-187° was obtained.

Anal. Calcd. for $C_{10}H_9ONS$: N, 7.33. Found: N, 7.40.

4-Methyl-2-quinolyl β-(N-Piperidyl)ethyl Sulfide

A solution of 16 g. (0.1 mole) of 2-mercapto-4-methylquinoline in a mixture of equal parts of ethylene glycol and methyl cellosolve was added to sodium ethoxide prepared from 0.1 g. atom of sodium in 50 ml. of absolute ethanol and the mixture was refluxed for twenty minutes. A solution of 16 g. (0.1 mole) of N-β-chloroethylpiperidine in absolute ethanol was added and the reaction mixture was refluxed for six hours. After removal of the ethanol the residue was treated with water and ether. The ether layer was

separated and upon standing crystals settled out. Recrystallization from absolute ethanol gave 11 g. (40% of product melting at 75-76°.

Anal. Calcd. for $C_{17}H_{22}N_2S$: N, 9.79; S, 11.18. Found: N, 9.74; S, 11.03 and 11.00.

The 2-mercapto-4- methylquinoline[42] was prepared in 88% yield from thiourea and 2-chloro-4-methylquinoline. The N-β-chloroethylpiperidine[114] was obtained in 60% yield from N-β-hydroxyethylpiperidine and thionyl chloride in chloroform; and the N-β-hydroxyethylpiperidine[115] was prepared in 80% yield from the reaction of piperidine with ethylene chlorohydrin in acetone.

4-Methyl-2-quinolyl β-(N-Morpholino)ethyl Sulfide

A solution of 15.9 g. (0.1 mole) of 2-mercapto-4-methylquinoline in a mixture of equal parts of ethylene glycol and methyl cellosolve was added to sodium ethoxide prepared from 0.1 g. atom of sodium in 50 ml. of absolute ethanol and the mixture was refluxed for twenty minutes. A solution of 16 g. (0.1 mole) of N-β-chloroethylmorpholine was added and the reaction mixture was refluxed for six hours. After removal of the ethanol, the residue was treated with water and ether. The ether layer was separated and upon standing crystals of product settled out. Recrystallization

114. I. G. Farbenindustrie, French patent 802,416 (1946) [Chem. Zentr., II, 4255 (1936)].
115. v. Braun, Brainsdorf and Räth, Ber., 55, 1666 (1922).

from absolute ethanol gave 10 g. (40%) of material melting at 85-85.5°.

Anal. Calcd. for $C_{16}H_{20}ON_2S$: N, 9.72: S, 11.11. Found: N, 9.79; S, 11.03 and 11.00.

The N-β-chloroethylmorpholine[35] was prepared in 65% yield from N-β-hydroxyethylmorpholine and thionyl chloride in chloroform. The N-β-hydroxyethylmorpholine[116] was prepared in 91% yield from the reaction of morpholine with ethylene chlorohydrin in acetone.

6-Methoxy-4-methyl-2-quinolyl γ-Diethylaminopropyl Sulfide Hydrochloride

Method A

To a solution of sodium γ-diethylaminopropyl mercaptide in absolute ethanol (prepared from 0.06 mole of γ-diethylaminopropyl mercaptan and 0.06 g. atom of sodium) was added 12.4 g. (0.06 mole) of 2-chloro-4-methyl-6-methoxyquinoline[117] in 75 ml. of methyl cellosolve. The mixture was refluxed for seven hours in an inert atmosphere. The ethanol was removed under reduced pressure and the residue was shaken with ether and water. The ether layer was dried over anhydrous sodium sulfate and treated with ethereal hydrogen chloride to give

116. Mason and Block, J. Am. Chem. Soc., 62, 1443 (1940).

117. Kindly furnished by S. P. Massie.

a solid product. Recrystallization from absolute ethanol gave 10.5 g. (50%) of the hydrochloride melting at 200-201°.

Anal. Calcd. for $C_{18}H_{27}ON_2ClS$: N, 7.91. Found N, 8.09.

Method B

To a solution of 7.8 g. (0.03 mole) of γ-diethylaminopropylisothiouronium chloride hydrochloride in 50 ml. of methyl cellosolve was added 6.2 g. (0.03 mole) of 2-chloro-4-methyl-6-methoxyquinoline dissolved in a minimum of methyl cellosolve. The mixture was heated under reflux with stirring and treated with a solution of 3.2 g. (0.15 g. atom) of sodium in absolute ethanol, added in a thin stream over a period of one hour. The reaction mixture was refluxed for seven hours, filtered and freed from solvent by distillation under reduced pressure. The residue was dissolved in ether, washed with water and dried over anhydrous sodium sulfate. Treatment with ethereal hydrogen chloride gave 46% of product which, after recrystallization from absolute ethanol, melted at 200-201°.

4-Carboxy-2-quinolyl β-Diethylaminoethyl Sulfide Hydrochloride

A solution of 6.6 g. (0.05 mole) of β-diethylamino-

ethyl mercaptan in 20 ml. of absolute ethanol was added to a stirred and gently refluxing solution of sodium ethoxide prepared from 0.05 g. atom of sodium in 50 ml. of absolute ethanol. After refluxing for thirty minutes, there was added to the sodium mercaptide a solution of 8.8 g. (0.04 mole) of 2-chlorocinchoninic acid in absolute ethanol and the resulting mixture was refluxed for nine hours. After removal of the ethanol, the residue was taken up in ether and treated with 30% sodium hydroxide. The solution was made acid and the ether layer was separated and dried over anhydrous sodium sulfate. Treatment with ethereal hydrogen chloride gave a solid which, after recrystallization from absolute ethanol, gave 9 g. (70%) of product melting at 240-242°.

Anal. Calcd. for $C_{16}H_{21}O_2NClS$: N, 8.23. Found N, 8.25.

N-Acetylisatin[118]

Seventy-five grams (0.51 mole) of isatin was heated at reflux temperature for thirty minutes with 150 g. of acetic anhydride. The solution was cooled and 73 g. (75%) of N-acetylisatin m. p. 151° separated out of solution.

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118. Camp, Arch. Pharm., 237, 687 (1899).

2-Hydroxycinchoninic Acid[119]

N-Acetylisatin (56 g.) was boiled for one hour under reflux with 30 g. of sodium hydroxide in 1800 ml. of water. The solution was cooled, neutralized to congo paper and the precipitate which formed was collected and washed with water. The precipitate was treated with sodium bicarbonate solution and the unreacted isatin was filtered off. The filtrate was acidified and a yield of 85% of product melting at 341° was obtained.

2-Chlorocinchoninic Acid[119]

2-Hydroxycinchoninic acid (18 g., 0.1 mole) was heated with 45 g. of phosphorus oxychloride for thirty minutes in an oil bath at 130-140°. The dark brown liquid was cooled, poured into water, and, after two hours, the solid material was collected. Purification was effected by dissolving the material in sodium bicarbonate solution and reprecipitating it with dilute acid. A yield of 16 g. (82%) of product which effervesced at 200° was melted at 244-246° was obtained. Kondo and Nozol[120] report a melting point of 244° and Ainley and King[120] report a melting point of 233-235° for this compound.

119. Ainley and King, Proc. Roy. Soc. (London), 125B, 69 (1938).

120. Kondo and Nozol, J. Pharm. Soc. Japan, 56, 10 (1936) /C. A., 30, 3432 (1936)/.

6-Methoxy-4-quinolyl β-Diethylaminoethyl Sulfide Dihydrochloride

A solution of 7 g. (0.05 mole) of β-diethylaminoethyl mercaptan in absolute ethanol was added to a refluxing solution of 0.05 mole of sodium ethoxide. After refluxing for thirty minutes, there was added to the sodium mercaptide a solution of 7.5 g. (0.03 mole) of 4-chloro-6-methoxyquinoline[113] in absolute ethanol and the resulting mixture was refluxed for nine hours in an atmosphere of nitrogen. After removal of the ethanol, the residue was treated with water and ether. The ether layer was separated, dried over anhydrous sodium sulfate and distilled to give 2 g. (23%) of product boiling at 195-200°/1.5 mm. Addition of hydrogen chloride to an ether solution of this material precipitated the dihydrochloride which upon recrystallization from absolute ethanol melted at 219-220°.

Anal. Calcd. for $C_{16}H_{24}ON_2ClS$: N, 7.73; Cl, 19.33; S. 8.84. Found: N, 7.75; Cl, 19.03; S, 8.78.

7-Chloro-4-quinolyl β-Diethylaminoethyl Sulfide Dihydrochloride

A solution of 19 g. (0.1 mole) of 4,7-dichloroquinoline in absolute ethanol was added slowly and with stirring to 0.1 mole of sodium β-diethylaminoethyl mercaptide and the reaction mixture was refluxed for ten hours in an atmosphere

of nitrogen. The solvent was removed under reduced pressure and the residue was taken up in ether, washed with 30% sodium hydroxide solution and dried over anhydrous sodium sulfate. Treatment of the ether solution with ethereal hydrogen chloride gave 23 g. (75%) of the dihydrochloride which, after recrystallization from absolute ethanol, melted at 234-235°.

Anal. Calcd. for $C_{15}H_{19}N_2Cl_2S.2HCl$: N, 7.65; Cl, 19.12; S, 8.74. Found: N, 8.00; Cl, 18.99 and 18.99; S, 8.47 and 8.50.

2-Quinolyl β-Hydroxy-γ-morpholinopropyl Sulfide

To a stirred solution of sodium 2-quinolyl mercaptide in absolute ethanol (prepared from 0.18 mole of 2-thiolquinoline and 0.18 g. atom of sodium) was added approximately 0.3 mole of 1-morpholino-2,3-epoxypropane in absolute ethanol. An exothermic reaction set in and salt precipitated out. The reaction mixture was refluxed for six hours in an atmosphere of nitrogen. The solution was filtered from the salt which had formed and the ethanol was removed under reduced pressure. A yield of 43 g. (80%) of crude product remained. This material was converted to the solid picrate and the dihydrochloride.

2-Quinolyl β-Hydroxy-γ-morpholinopropyl Sulfide Picrate

One gram of the sulfide was dissolved in ethanol and a hot solution of picric acid was added. A yellow solid precipitated out which upon recrystallization from absolute ethanol melted at 171-172°.

Anal. Calcd. for $C_{22}H_{23}O_9N_5S$: N, 13.13. Found: N. 13.30.

2-Quinolyl β-Hydroxy-γ-morpholinopropyl Sulfide Dihydrochloride

Two grams of the sulfide was dissolved in anhydrous ether and ethereal hydrogen chloride was added. After the addition of a small quantity of ethyl acetate a white hydrochloride came down. Recrystallization from an absolute methanol-ethyl acetate mixture gave a product which melted at 198-200°.

Anal. Calcd. for $C_{16}H_{22}O_2N_2SCl$: N, 7.45; S, 8.51. Found: N, 7.34; S, 8.53.

The 1-morpholino-2,3-epoxypropane used in this preparation was prepared according to the directions of Drozdov and Cherntzov[121] using 46 g. (0.46 mole) of epichlorohydrin, 37.3 g. (0.4 mole) of morpholine and 2 ml. of water.

121. Drozdov and Cherntzov, J. Gen. Chem. (U.S.S.R.), 4 969 (1934) /C. A., 29, 2148 (1935)/.

2-Quinolyl β-Hydroxy-γ-piperidylpropyl Sulfide

A solution of 10.5 g. (0.06 mole) of 2-thiolquinoline[42] in absolute ethanol was added to a stirred and gently refluxing solution of sodium ethoxide prepared from 2.3 g. (0.1 g. atom) of sodium in 50 ml. of absolute ethanol. After refluxing for thirty minutes there was added to the sodium mercaptide a solution of approximately 0.15 mole of 1-piperidyl-2,3-epoxypropane in absolute ethanol and the resulting mixture was refluxed for four hours. The solution was filtered from the salt which had formed and the ethanol was removed under reduced pressure. All attempts at crystallization of the semi-solid material which remained were unsuccessful. The yield of this crude product was 81%.

A small amount of the semi-solid was treated with ethereal hydrogen chloride and a very hygroscopic hydrochloride formed melting from 169-172°.

An alcoholic solution of another portion of the material was treated with a hot alcoholic solution of picric acid and the resulting picrate came down as a yellow solid melting at 188-190° after one recrystallization from absolute ethanol.

Anal. Calcd. for $C_{23}H_{25}O_8N_5S$: N, 13.18; S, 6.02. Found: N, 13.18; S, 5.70.

The 1-piperidyl-2,3-epoxypropane was prepared according to the general directions of Drozdov and Cherntzov[121] using 25 g. (0.27 mole) of epichlorohydrin, 21.3 g. (0.25 mole) of piperidine and 1 ml. of water.

2-Quinolyl 2,4-Dinitrophenyl Sulfide

A solution of 10.6 (0.06 mole) of 2-thiolquinoline[42] in absolute ethanol was added to a stirred and gently refluxing solution of sodium ethoxide prepared from 1.38 g. (0.06 g. atom) of sodium in 50 ml. of absolute ethanol. After refluxing for thirty minutes there was added to the sodium mercaptide a solution of 12.1 g. (0.06 mole) of 2,4-dinitrochlorobenzene in absolute ethanol. The product precipitated out as a yellow solid immediately after the addition was made. Recrystallization from an acetone-ethanol mixture gave 11 g. (60%) of product melting at 160-161°.

Anal. Calcd. for $C_{15}H_9O_4N_3S$: N, 12.84. Found: N, 13.00.

p-Aminothiophenol

This compound was prepared according to the directions of Gainer.[122] A mixture of 128 g. (0.8 mole) of p-nitrochlorobenzene, 2 liters of water and 480 g. (2 moles) of

122. Gainer, G. C., Doctorial Dissertation, Iowa State College. (1946).

sodium sulfide was refluxed for eight hours. The mixture was saturated with sodium chloride and 4 moles of glacial acetic acid was added to liberate the sodium mercaptide. The mixture was extracted with ether and the ether extracts were dried over anhydrous sodium sulfate. The ether was removed and the residue was distilled to give 51 g. (51%) of product boiling at 140-141°/15 mm. Upon standing the product crystallized to a white solid melting at 42°.

2-Quinolyl p-Aminophenyl Sulfide Hydrochloride

To a solution of 1.6 g. (0.069 g. atom) of sodium in 50 ml. of absolute ethanol was added a solution of 8.7 g. (0.069 mole) of p-aminothiophenol and the mixture was refluxed for thirty minutes. A solution of 13 g. (0.09 mole) of 2-chloroquinoline in absolute ethanol was added and the reaction mixture was refluxed for two hours. The solution was filtered, the ethanol was removed under reduced pressure and the residue was dissolved in ether and dried over anhydrous sodium sulfate. After removal of the ether a yield of 13. g. (80%) of crude product remained. Ethereal hydrogen chloride was added to an ether solution of the free base and the hydrochloride precipitated out as a light yellow solid. Recrystallization from absolute ethanol gave a pure product melting at 226-228°.

Anal. Calcd. for $C_{15}H_{13}N_2SCl$: S, 11.11. Found: S. 11.20 and 11.00.

6-Methoxy-2-Quinolyl p-Aminophenyl Sulfide

To a stirred and gently refluxing solution of sodium ethoxide, prepared from 1.15 g. (0.05 g. atom) of sodium in 50 ml. of absolute ethanol, was added a solution of 6.25 g. (0.05 mole) of p-aminothiophenol and the mixture was refluxed for thirty minutes. A solution of 4.6 g. (0.03 mole) of 2-chloro-6-methoxyquinoline[113] in absolute ethanol was added and the reaction mixture was refluxed for ten hours in an atmosphere of nitrogen. The solution was filtered, the solvent was removed under reduced pressure and the residue was treated with a 20% solution of sodium hydroxide. The basic solution was extracted with ether, the ether layer was separated and the ether was removed. Recrystallization from absolute ethanol gave 2.5 g. (30%) of product melting at 117-119°.

Anal. Calcd. for $C_{16}H_{14}ON_2S$: N, 9.93. Found: N, 9.99.

6-Methoxy-2-quinolyl p-Aminophenyl Sulfide Hydrochloride

To an ether solution of the sulfide was added ethereal hydrogen chloride. A yellow solid formed which upon

recrystallization from absolute ethanol melted at 233-235°.

Anal. Calcd. for $C_{16}H_{15}ON_2SCl$: N, 8.80; S, 10.06. Found: N, 8.96; S, 10.30.

6-Methoxy-4-quinolyl p-Aminophenyl Sulfide

A solution of 6.25 g. (0.05 mole) of p-aminothiophenol was added to 0.05 mole of sodium ethoxide (prepared from 0.05 g. atom of sodium in 50 ml. of absolute ethanol) and the solution was refluxed for forty minutes. A solution of 5 g. (0.035 mole) of 4-chloro-6-methoxyquinoline[113] in absolute ethanol was added and the reaction mixture was refluxed for three hours in an atmosphere of nitrogen. The solution was filtered, the solvent was removed and the residue was treated with a 20% solution of sodium hydroxide. The basic solution was extracted with ether and the ether was removed. The residue was crystallized from absolute ethanol to give 4.5 g. (45%) of product melting at 145-146°.

Anal. Calcd. for $C_{16}H_{14}ON_2S$: N, 9.93; S, 11.34. Found: N, 9.60; S, 11.30 and 11.40.

6-Methoxy-4-methyl-2-quinolyl Methyl Sulfide

To 2 g. (0.009 mole) of 2-chloro-4-methyl-6-methoxy-

quinoline[117] dissolved in 20 ml. of methyl cellosolve was added 5 ml. of 3 molar sodium methyl mercaptide and the mixture was refluxed for one hour. The solvent was removed and the residue was treated with water. The salt which had formed dissolved and a white solid remained. Recrystallization from absolute ethanol gave 1.7 g. (90%) of product melting at 104-105°.

Anal. Calcd. for $C_{12}H_{13}ONS$: N, 6.39. Found: N, 6.20.

This reaction was repeated using ethanol as the solvent. Quantitative recovery of 2-chloro-4-methyl-6-methoxyquinoline was obtained, indicating that the temperature of boiling ethanol was not great enough to effect reaction.

4-Carboxy-2-quinolyl *p*-Aminophenyl Sulfide

Sodium ethoxide was prepared using 2.3 g. (0.1 g. atom) of sodium and 50 ml. of absolute ethanol. To this was added 12.5 g. (0.1 mole) of *p*-aminothiophenol and the mixture was refluxed for twenty minutes. A solution of 20.7 g. (0.1 mole) of 2-chlorocinchoninic acid in absolute ethanol was added and the mixture was refluxed in an atmosphere of nitrogen for sixteen hours. The solution was filtered and the solvent was removed under reduced

pressure. The residue was dissolved in sodium hydroxide solution and the product was precipitated as a yellow solid by the addition of hydrochloric acid. The yield of crude product (m.p., 334°) was 2.3 g. (80%). Recrystallization from methyl cellosolve gave a pure product melting at 336°.

Anal. Calcd. for $C_{16}H_{12}O_2N_2S$: N, 9.45; Neut. Equiv., 296. Found: N, 9.31; Neut. Equiv., 291.

7-Chloro-4-quinolyl 2-Benzimidazole Sulfide Hydrochloride#

To a solution of 5.91 g. (0.03 mole) of 4,7-dichloroquinoline in absolute ethanol was added a solution of 4.2 g. (0.03 mole) of 2-thiolbenzimidazole[123] in absolute ethanol and the reaction mixture was refluxed for two hours. The reaction mixture was cooled and a small quantity of ether was added to initiate crystallization. A yield of 8 g. (80%) of product melting at 194-197° was obtained. Upon

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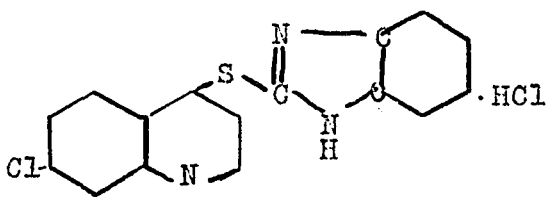

123. Kindly furnished by Parke, Davis and Company.

recrystallization from absolute ethanol the product melted at 195-196°.

Anal. Calcd. for $C_{16}H_{10}N_3ClS.HCl$: N, 11.76. Found: N, 11.95.

7-Chloro-4-quinolyl 2-(4,5'-Diphenylimidazolyl) Sulfide Dihydrochloride**

To a solution of 3.56 g. (0.018 mole) of 4,7-dichloroquinoline in absolute ethanol was added a solution of 4.5 g. (0.018 mole) of 4,5-diphenyl-2-thiolimidazole[133] in absolute ethanol and the reaction mixture was heated at reflux temperature for forty-five minutes. The reaction mixture was cooled and a yellow solid came out of solution. Recrystallization from 95% ethanol gave 6.5 g. (75%) of product melting at 166-167°.

Anal. Calcd. for $C_{24}H_{16}N_3ClS.2HCl$: N, 8.65. Found: N, 8.16 and 8.30.

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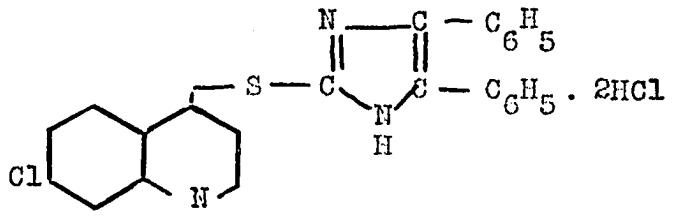


2-Quinolyl 2-Thiazolinyl Sulfide Hydrochloride*

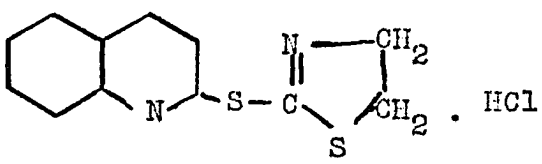
To a solution of 6.5 g. (0.04 mole) of 2-chloroquinoline in absolute ethanol was added 4.76 g. (0.04 mole) of 2-mercaptothiazoline[123] in absolute ethanol. The reaction mixture was refluxed for two hours. Upon cooling a yellow solid separated out. Recrystallization from absolute ethanol gave 38% of product melting at 189-191°.

Anal. Calcd. for $C_{12}H_{11}N_2ClS_2$: N, 9.93. Found: N, 10.09.

7-Chloro-4-quinolyl β-Diethylaminoethyl Sulfone Dihydrochloride

Two grams (0.006 mole) of 7-chloro-4-quinolyl β-diethylaminoethyl sulfide dihydrochloride was suspended in 50 ml. of glacial acetic acid and 6 ml. of 30% hydrogen peroxide was added. After the sulfide went into solution the solution was heated to 80° for fifteen minutes and allowed to stand at room temperature for twenty-four hours. A white solid came out of solution and after recrystallization from ethanol melted at 337-338°.

*



Anal. Calcd. for $C_{15}H_{21}O_2N_2ClS.2HCl$: N, 7.03. Found: N, 6.98.

2-Mercaptopyridine

2-Mercaptopyridine was prepared essentially according to the method of Phillips and Shapiro.[45] A mixture of 11.5 g. (0.072 mole) of 2-bromopyridine, 10.64 g. of thiourea and 30 ml. of absolute ethanol was refluxed for one hour. The solution was cooled, poured into 30 ml. of concentrated ammonia and allowed to stand at room temperature for thirty-six hours. The solution was made slightly acid with acetic acid and extracted with chloroform. Removal of the solvent gave 6 g. (75%) of solid product which after crystallization from ethanol melted at 125-126°. Phillips and Shapiro report a yield of 47% of material melting at 125°.

2-Bromopyridine was prepared in 77% yield according to the directions of Craig.[124]

2-Pyridyl 2,4-Dinitrophenyl Sulfide

To a stirred solution of 1.15 g. (0.05 g. atom) of sodium in 50 ml. of absolute ethanol was added a solution of 5 g. (0.05 mole) of 2-mercaptopyridine in absolute ethanol

124. Craig, J. Am. Chem. Soc., 56, 231 (1936).

and the mixture was refluxed for thirty minutes. A solution of 10 g. (0.05 mole) of 2,4-dinitrochlorobenzene in absolute ethanol was added and the reaction mixture was refluxed for six hours. The ethanol was removed and the residue was dissolved in a 20% sodium hydroxide solution and extracted with ether. The ether solution was dried over anhydrous sodium sulfate. Removal of the ether gave a solid product which after recrystallization from absolute ethanol melted at 115-116°. The yield of pure product was 9.6 g. (70%).

Anal. Calcd. for $C_{11}H_7O_4N_3S$: N, 15.16. Found: N, 15.19.

2-(β-Chloroethyl)pyridine Hydrochloride

To 300 ml. of chloroform was added 295 g. of thionyl chloride and the solution was cooled in an ice-bath to 0°. A solution of 129 g. (1 mole) of 2-pyridineëthanol[125] in chloroform was added slowly and with stirring by means of a dropping funnel. The reaction mixture was allowed to warm up to room temperature and was refluxed for ten hours. The reaction mixture was cooled, 200 ml. of water was added and the mixture was extracted with 6N hydrochloric acid.

125. This compound was obtained from Reilly Tar and Chemical Company.

The hydrochloric acid was removed on the water pump, ethanol was added and the material was evaporated to dryness. Recrystallization from absolute ethanol using Norite gave 100 g. (56%) of product melting at 119-121°.

Anal. Calcd. for C_7H_9NCl: N, 7.90. Found: N, 8.00.

β-(2-Pyridyl)ethyl γ-Diethylaminopropyl Sulfide

To a solution of 15.6 g. (0.06 mole) of γ-diethylaminopropylisothiouronium chloride hydrochloride[38] in 100 ml. of absolute ethanol was added a solution of 10.6 (0.06 mole) of 2-(β-chloroethyl)pyridine hydrochloride. The mixture was heated under reflux with stirring and treated with a solution of 5.5 g. (0.25 g. atom) of sodium in absolute ethanol, added in a thin stream over a period of one hour. When the addition was complete the reaction mixture was refluxed for four hours. The solution was filtered, the ethanol was removed under reduced pressure and the residue was taken up in ether and dried. The ether was removed and the residue was distilled to give 8 g. (53%) of product boiling at 136-139°/1 mm.

Anal. Calcd. for $C_{14}H_{24}N_2S$: N, 11.11. Found: N, 11.37.

β-(2-Pyridyl)ethyl β-Diethylaminoethyl Sulfide

To a solution of 17.29 g. (0.07 mole) of β-diethylaminoethylisothiouronium chloride hydrochloride[37] in absolute ethanol was added a solution of 12.3 g. (0.07 mole) of 2-(β-chloroethyl)pyridine hydrochloride dissolved in a minimum of absolute ethanol. The mixture was heated under reflux with stirring and treated with a solution of 6.4 g. (0.26 g. atom) of sodium in absolute ethanol added in a thin stream over a period of one hour. After the addition was complete the reaction mixture was refluxed for six hours. The solvent was removed and the residue was treated with ether and water. The ether layer was separated and dried over anhydrous sodium sulfate. The ether was removed and the residue was distilled to give 12 g. (75%) of product boiling at 132-135°/0.5 mm.

The dihydrochloride was prepared by adding ethereal hydrogen chloride to an ether solution of the free base. Recrystallization of the product from absolute ethanol gave very hygroscopic material melting at 156-158°.

Anal. Calcd. for $C_{13}H_{24}N_2Cl_2S$: N, 9.03; S. 10.32. Found: N, 9.28; S, 10.62 and 10.57.

Diphenylmethyl Mercaptan

Diphenylmethyl isothiourea hydrobromide[123] (0.15 mole) was dissolved in water and the solution was made alkaline with sodium hydroxide. The alkaline solution was extracted with ether and the ether extract was dried over anhydrous sodium sulfate. The mercaptan was distilled at 128-130°/1.2 mm. in 60% yield. Staudinger[126] reports a boiling point of 128-130°/1.2 mm. for this compound.

Diphenylmethyl β-(2-Pyridyl)ethyl Sulfide Picrate

Method A

A mixture of 7.08 g. (0.04 mole) of 2-(β-chloroethyl)pyridine hydrochloride and 12.92 g. (0.04 mole) of diphenylmethyl isothiourea hydrobromide[123] was dissolved in a minimum of absolute ethanol. The mixture was heated to reflux temperature and was treated with stirring with a solution of 3.78 g. (0.16 g. atom) of sodium in absolute ethanol. The reaction mixture was refluxed for six hours. The solution was filtered, the solvent was removed and the residue was taken up in ether, washed with water and dried over anhydrous sodium sulfate. An unsuccessful

126. Staudinger and Siegwart, Ber., 49, 1920 (1916).

attempt was made to distil the product so it was purified through the picrate. A saturated solution of picric acid was added to a warm ether solution of diphenylmethyl β-(2-pyridyl)ethyl sulfide. A yield of 50% of product melting at 146-147° after one recrystallization from absolute ethanol was obtained.

Anal. Calcd. for $C_{26}H_{22}O_7N_4S$: N, 10.48; S, 5.86. Found: N, 10.71; S, 6.00.

Method B

To a solution of 1.4 g. (0.06 g. atom) of sodium in 50 ml. of absolute ethanol was added a solution of 13 g. (0.06 mole) of diphenylmethyl mercaptan and the solution was refluxed for thirty minutes. A solution of 0.06 mole of 2-(β-chloroethyl)pyridine in absolute ethanol was added and the reaction mixture was refluxed for six hours. The solution was filtered, the solvent was removed and the residue was taken up in ether and dried. The ether solution was converted to the picrate by treatment with a saturated solution of picric acid and a yield of 15 g. (57%) of product melting at 146-147° was obtained. A mixed melting point with the picrate from method A showed no depression.

Diphenylmethyl β-(2-Pyridyl)ethyl Sulfide Hydrochloride

Diphenylmethyl β-(2-pyridyl)ethyl sulfide picrate (15 g.) was converted to the free base by dissolving it in a dilute solution of ammonium hydroxide. The solution was extracted with ether and dried over anhydrous sodium sulfate. Ethereal hydrogen chloride was added to the ether solution and the hydrochloride came out as a white solid. Recrystallization from absolute ethanol gave 4.5 g. (26%) of product melting at 152-153°.

Anal. Calcd. for $C_{20}H_{20}NClS$: N, 4.10. Found: 4.10.

2-(γ-Chloropropyl)pyridine Hydrochloride

To a solution of 51 g. of thionyl chloride in 100 ml. of chloroform, cooled in an ice-bath, was added a solution of 20 g. (0.17 mole) of 2-propanolpyridine[125] in chloroform. The addition was made dropwise through a dropping funnel. After all of the 2-pyridinepropanol had been added, the solution was allowed to warm up to room temperature and was refluxed for two hours. The reaction mixture was cooled, 100 ml. of water was added and the mixture was extracted with 6 N hydrochloric acid. The hydrochloric acid was removed on the water pump and two 50 ml. portions of ethanol were added and distilled. The residue

crystallized to a tan solid. Recrystallization from absolute ethanol using Norite gave 10 g. (50%) of product melting at 109-110°.

Anal. Calcd. for $C_8H_{10}NCl.HCl$: HCl, 18.85. Found: HCl, 18.71.

β-(2-Pyridyl)ethyl p-Aminophenyl Sulfide

Fifteen grams of 2-(β-chloroethyl)pyridine hydrochloride was converted to the free base by treatment with sodium bicarbonate. The alkaline solution was extracted with ether and the ether solution was dried and evaporatively distilled. This material was used directly for the following preparation since it is unstable on distillation.

To a solution of 1.38 g. (0.06 g. atom) of sodium in 50 ml. of absolute ethanol was added a solution of 7.5 g. (0.06 mole) of p-aminothiophenol in absolute ethanol and the mixture was refluxed for thirty minutes. Approximately 0.06 mole of 2-(β-chloroethyl)pyridine was added and the reaction mixture was refluxed for five hours. The solution was filtered and the ethanol was removed under reduced pressure. The residue was taken up in ether, washed with a 10% solution of sodium hydroxide and dried over anhydrous sodium sulfate. The ether was removed and an attempt was made to prepare a hydrochloride and a picrate.

In both cases only oils were obtained. This material was distilled to give a fraction boiling at 125-160°/1 mm. and a small amount of very viscous material which came over at 160-165°/1 mm. No solid derivatives could be obtained from either of these fractions.

The lower boiling material was fractionated and the following fractions were obtained:

Fraction I 55-60°/0.5 mm.

Fraction II 110-115°/0.5 mm.

Fraction III 140°/0.5 mm.

A picrate was made of fraction I and after recrystallization from absolute ethanol material melting at 156-158° was obtained. A mixed melting point with a picrate (m.p. 156-158°) obtained by Seibert[127] from a preparation using 2-(β-chloroethyl)pyridine showed no depression. Analysis of this picrate indicates that it is a polymer of vinylpyridine. Its structure was not definitely established.

A saturated solution of picric acid was added to a hot alcoholic solution of fraction II. Recrystallization from ethanol gave a product melting at 142-143°. The same picrate was obtained from fraction III.

Anal. Calcd. for $C_{19}H_{17}O_7N_5S$: N, 15.25. Found: N, 15.51.

127. Seibert, R. A., Unpublished Studies, Iowa State College.

β-Diethylaminoethyl γ-Diethylaminopropyl Sulfide Dihydrochloride

A solution of 8.8 g. (0.06 mole) of γ-diethylaminopropyl chloride in absolute ethanol was added to 0.07 mole of sodium β-diethylaminoethyl mercaptide and the mixture was refluxed for two hours in an atmosphere of nitrogen. After removal of the ethanol, the residue was treated with ether and water. The ether layer was separated, dried over anhydrous sodium sulfate and treated with ethereal hydrogen chloride. Recrystallization of the dihydrochloride from absolute ethanol gave 44% of product melting at 234-235°.

Anal. Calcd. for $C_{13}H_{32}N_2Cl_2S$: N, 8.80; S, 10.06. Found: N, 8.61; S, 9.80.

β-Diethylaminoethyl β'-(N-Piperidyl)ethyl Sulfide

A solution of 11 g. (0.07 mole) of β-chloroethylpiperdine[114] in absolute ethanol was added to 0.11 mole of sodium β-diethylaminoethyl mercaptide and the mixture was refluxed for three hours in an atmosphere of nitrogen. After removal of the ethanol the residue was treated with ether and water. The ether layer was separated, dried over anhydrous sodium sulfate and distilled to give 17 g. (77%) of product boiling at 133-135°/1.5 mm.; $n^{20}D$

1.495; d^{20} 0.9367; MR: calcd., 75.61; found, 75.96.

The dihydrochloride, obtained by the addition of ethereal hydrogen chloride to an ether solution of the base, melted at 235-237° after crystallization from absolute ethanol.

Anal. Calcd. for $C_{13}H_{30}N_2Cl_2S$: N, 8.86, Found: 8.86.

β-Diethylaminoethyl β'-(N-Morpholino)ethyl Sulfide

A solution of 13 g. (0.09 mole) of N-β-chloroethylmorpholine[35] in absolute ethanol was added to 0.11 mole of sodium β-diethylaminoethyl mercaptide and the mixture was refluxed for four hours in an atmosphere of nitrogen. After removal of the ethanol, the residue was treated with ether and water. The ether layer was separated, dried over anhydrous sodium sulfate and distilled to give 16 g. (72%) of product boiling at 147-149°/2.5 mm.; $n^{20}D$ 1.494; d^{20} 0.9855; MR; calcd., 71.62; found, 72.66.

The dihydrochloride, obtained by the addition of ethereal hydrogen chloride to an ether solution of the base, melted at 199-201°.

Anal. Calcd. for $C_{12}H_{28}ON_2Cl_2S$: N, 8.80. Found: N, 8.60 and 8.70.

γ-Diethylaminopropyl β'-(N-Morpholino)ethyl Sulfide

A solution of 10 g. (0.07 mole) of N-β-chloroethylmorpholine[35] in absolute ethanol was added to 0.11 mole of sodium γ-diethylaminopropyl mercaptide and the mixture was refluxed in an atmosphere of nitrogen for four hours. After removal of the ethanol, the residue was treated with ether and water. The ether layer was separated, dried over anhydrous sodium sulfate and distilled to give 11 g. (60%) of product boiling at 142-145°/1 mm. $n^{20}D$ 1.591; d^{20} 0.9766; MR; calcd. 76.24; found, 77.10.

The dihydrochloride, obtained by addition of ethereal hydrogen chloride to an ether solution of the base, melted at 216-217°.

Anal. Calcd. for $C_{13}H_{30}ON_2Cl_2S$: N, 8.43. Found: N. 8.70.

2-Benzothiazyl β-Diethylaminoethyl Sulfide Hydrochloride

To a solution of sodium ethoxide prepared from 0.1 g. atom of sodium in 50 ml. of absolute ethanol was added 16.7 g. (0.1 mole) of 2-mercaptobenzothiazole. After refluxing for thirty minutes there was added to the sodium mercaptide 13.5 g. (0.1 mole) of β-diethylaminoethyl

chloride and the reaction mixture was refluxed for three hours in an atmosphere of nitrogen. The solution was filtered, the ethanol was removed under reduced pressure and the residue was treated with a 20% solution of sodium hydroxide. The alkaline solution was extracted with ether and dried over anhydrous sodium sulfate. Ethereal hydrogen chloride was added to the ether solution and a light yellow solid precipitated out. After several recrystallizations from absolute ethanol a yield of 116 g. (50%) of pure product melting at 183-184° was obtained.

Anal. Calcd. for $C_{13}H_{19}N_2ClS$: N, 9.27; S, 21.19. Found: N, 9.42; S, 20.94 and 21.30.

Diphenylmethyl p-Aminophenyl Sulfide Hydrochloride

To a solution of 1.38 g. (0.06 g. atom) of sodium in absolute ethanol was added 7.50 g. (0.06 mole) of p-aminothiophenol and the mixture was refluxed with stirring for twenty minutes. A solution of 14.8 g. (0.06 mole) of benzohydryl bromide[123] in 20 ml. of absolute ethanol was added slowly through a dropping funnel to the stirred solution and the reaction mixture was refluxed for five hours. The solution was filtered and the solvent was removed. The residue was dissolved in ether and the ether solution was washed with water and dried. Ethereal hydrogen chloride was added to the ether solution and the

hydrochloride separated out as a white solid. Recrystallization from absolute ethanol gave 50% of product melting at 229-230°.

Anal. Calcd. for $C_{19}H_{18}NClS$: N, 4.28; Cl, 10.70. Found: N, 4.38; Cl. 10.59.

γ-(2-Piperidyl)propyl p-Aminophenyl Sulfide Dihydrochloride

Six grams of γ-chloropropylpiperidine hydrochloride[128] was converted to the free base by treatment with sodium bicarbonate. The alkaline solution was extracted with ether and the ether solution was dried and evaporatively distilled. This material was used directly for the following preparation since it is unstable on distillation.

To a solution of sodium ethoxide, prepared from 0.7 g. (0.03 g. atom) of sodium in 50 ml. of absolute ethanol, was added 5 g. (0.03 mole) of p-aminothiophenol in absolute ethanol. The mixture was refluxed for thirty minutes. Approximately 0.03 mole of γ-chloropropylpiperidine in 25 ml. of absolute ethanol was added slowly and with stirring to the sodium mercaptide. The reaction mixture was refluxed for ten hours. The solution was filtered and the ethanol was removed under reduced pressure. The residue

128. Kindly furnished by F. J. Marshall.

was taken up in ether and washed with a 10% sodium hydroxide solution. The ether solution was dried over anhydrous sodium sulfate. The dihydrochloride was precipitated by the addition of ethereal hydrogen chloride. Recrystallization from absolute ethanol gave material melting at 228-230°.

Anal. Calcd. for $C_{14}H_{23}N_2Cl_2S$: N, 8.72. Found: N, 8.70.

2-Quinolyl 2'-Pyridyl Sulfide (attempted)

Sodium ethoxide was prepared using 2.3 g. (0.1 g. atom) of sodium in 50 ml. of absolute ethanol. To this was added 16.1 g. (0.1 mole) of 2-thiolquinoline and the mixture was refluxed for thirty minutes. Then 15.8 g. (0.1 mole) of 2-bromopyridine was added and the reaction mixture was refluxed for sixteen hours. The solution was filtered and the ethanol was removed under reduced pressure. The residue was taken up in ether and washed with sodium hydroxide solution. The ether solution was concentrated and set aside. After several days a solid settled out which upon recrystallization from chloroform melted at 145-146°. Sulfur analyses on this compound indicated that it was 2,2'-diquinolyl disulfide so an authentic sample was prepared by the method of Roos[43] using 8.05 g. (0.05 mole) of sodium 2-thiolquinoline mercaptide and 0.025 mole of iodine.

Material (63%) melting at 143-145° after one recrystallization from chloroform was obtained. A mixed melting point with the material from above showed no depression.

Anal. Calcd. for $C_{18}H_{12}N_2S_2$: S, 20.00. Found: S, 19.70 and 19.70.

Bis-(β-diethylaminoethyl) Disulfide Dihydrochloride

This disulfide was obtained in a 25% yield by adding 3.78 g. (0.03 mole) of iodine in ethanol to the sodium mercaptide solution prepared in absolute ethanol from 8 g. (0.06 mole) of β-diethylaminoethyl mercaptan and 0.06 g. atom of sodium. The sulfide, which distilled over at 155-160°/20 mm. was converted to the dihydrochloride by adding ethereal hydrogen chloride to an ether solution of the base. Recrystallization from absolute ethanol gave a product melting at 216-217°.

The dihydrobromide of bis-(β-diethylaminoethyl) disulfide, prepared from the free base and hydrogen bromide in an ether solution melted at 222-223°.

Anal. Calcd. for $C_{12}H_{30}N_2Cl_2S_2$: N, 8.33; Cl, 20.83. Found S, 8.06; Cl, 20.80 and 20.80.

Bis-(4-methyl-2-quinolyl) disulfide

To a solution of 0.1 mole of sodium ethoxide prepared

from 0.1 g. atom of sodium in 60 ml. of absolute ethanol was added a solution of 16. g. (0.1 mole) of 4-methyl-2-thiolquinoline in a mixture of equal parts of methyl cellosolve and ethylene glycol and the mixture was refluxed for thirty minutes. A solution of 6.9 g. (0.1 mole) of iodine in absolute ethanol was added dropwise to the stirred and refluxed solution and, after the addition was complete, the reaction mixture was refluxed for two hours. The solution was filtered and most of the solvent was removed. The residue was extracted with ether and upon standing a solid product separated out. Recrystallization from absolute ethanol gave 8 g. (56%) of product melting at 175-176°.

Anal. Calcd. for $C_{20}H_{16}N_2S_2$: S, 18.39. Found: S. 18.18.

This disulfide has been prepared by Rosenhauer[42] from 2-thiolquinoline and hydrogen peroxide. He reports a melting point of 167°.

Triphenyl(p-dimethylaminophenyl)silane

Approximately 0.15 mole of triphenylchlorosilane was prepared by adding 0.45 mole of phenyllithium to 0.15 mole of freshly distilled silicon tetrachloride. The reaction was carried out in an atmosphere of nitrogen, the addition of the phenyllithium being made at a rate so as to maintain

gentle reflux. To the triphenylchlorosilane was added slowly and with stirring p-dimethylaminophenyllithium. After the addition of 0.1 mole of p-dimethylaminophenyllithium the reaction mixture gave a positive color test #1.[129] The reaction mixture was hydrolyzed and the ether layer was separated and dried over anhydrous sodium sulfate. Most of the ether was removed and solid product (46%) separated out from the ether solution. Recrystallization from Skelly B several times gave material melting at 144-146°. Four grams (10%) of tetraphenylsilane (m.p. 233-235°) was also obtained in this reaction.

Anal. Calcd. for $C_{26}H_{25}NSi$: N, 3.69; Si, 7.38. Found: N, 3.79; Si, 7.46.

Triphenyl(p-dimethylaminophenyl)silane Hydrochloride

Ethereal hydrogen chloride was added to an ether solution of triphenyl(p-dimethylaminophenyl)silane. The white hydrochloride, after recrystallization from absolute ethanol, melted at 227-229°.

Anal. Calcd. for $C_{26}H_{26}NClSi$: N, 3.37. Found: N. 3.00.

129. Gilman and Schulze, J. Am. Chem. Soc., 47, 2002 (1925).

Diphenyl[di(p-dimethylamino)phenyl]silane

Approximately 0.03 mole of diphenyldiethoxysilane was prepared by adding 0.06 mole of phenyllithium to 0.03 mole of ethyl silicate in anhydrous ether. The reaction was carried out in an atmosphere of nitrogen, the addition of the phenyllithium being made at such a rate as to maintain gentle reflux. To the diphenyldiethoxysilane was added slowly and with stirring 0.06 mole of p-dimethylaminophenyllithium. When the addition was complete the reaction mixture gave a positive color test #1.[129] The reaction mixture was hydrolyzed and the ether layer was separated and dried. Most of the ether was removed and upon standing a white solid came down. Recrystallization from an ethanol-Skelly B mixture gave 4.7 g. (40%) of product melting at 180-181°.

Anal. Calcd. for $C_{28}H_{32}N_2Si$: N, 6.63; Si 6.64 Found: N, 6.90; Si, 6.10.

Tetra(p-dimethylaminophenyl)silane

To 3.3 ml. (0.03 mole) of freshly distilled silicon tetrachloride in 200 ml. of anhydrous ether was added with stirring approximately 0.16 mole of p-dimethylaminophenyllithium, the addition being made under nitrogen and at such a rate as to maintain gentle reflux. After the addition was complete the reaction mixture gave a positive color test

#1.[129] The reaction mixture was hydrolyzed and the ether layer was separated and dried over anhydrous sodium sulfate. Most of the ether was removed and the residue was set in the ice-box. Solid product separated out overnight. Recrystallization from benzene and Skelly B gave a yield of 4 g. (41%) of product melting at 234-235°.

Anal. Calcd. for $C_{32}H_{40}N_4Si$: N, 11.02; Si, 5.51. Found: N, 11.20; Si, 5.44.

Tri(p-dimethylaminophenyl)phenylsilane

Approximately 0.03 mole of tri(p-dimethylaminophenyl)-ethoxysilane was prepared by adding 0.096 mole of p-dimethylaminophenyllithium to 0.032 mole of ethyl silicate in 50 ml. of ether. The addition was made under nitrogen and at a rate so as to maintain gentle reflux. The mixture was refluxed for thirty minutes and at the end of this time the reaction mixture gave a negative color test #1.[129] To the tri(p-dimethylaminophenyl)ethoxysilane was added 0.032 mole of phenyllithium slowly and with stirring. After an additional milliliter of phenyllithium was added the reaction mixture gave a positive color test #1.[129] The reaction mixture was refluxed for one hour and hydrolyzed. The ether layer was separated and dried over anhydrous sodium sulfate. Most of the ether was removed and after the addition of a small amount of Skelly B an oil separated out which upon

working crystallized. Recrystallization from absolute ethanol gave 2.4 g. (17%) of product melting at 171-172°.

Anal. Calcd. for $C_{30}H_{35}N_3Si$: N, 9.03; Si 6.02. Found: N, 9.30; Si, 6.29.

Triphenyl(2-thienyl)silane

This compound was prepared according to the directions of Benkeser.[130] To 41.6 g. (0.2 mole) of ethyl silicate was added a solution of 0.6 mole of phenyllithium. The reaction was carried out in an atmosphere of nitrogen. When the reaction was complete 2-thienyllithium was added until the reaction mixture gave a positive color test #1.[129] The reaction mixture was hydrolyzed and the solid product was filtered to give a crude yield of 66 g. (99%). After three recrystallizations from dioxane 45.5 g. (68%) of product softening at 190° and melting at 195-197° was obtained.

The 2-thienyllithium was prepared from 35 g. (a slight excess of 0.4 mole) of dry thiophene and 0.4 mole of n-butyllithium.[131]

130. Benkeser, R. A., Unpublished Studies, Iowa State College.

131. The titer of the n-butyllithium solution was determined by the procedure of Gilman and Haubein, J. Am. Chem. Soc., 66, 1515 (1944).

Triphenyl[2-(5-lithio)thienyl]silane

To a solution of 5.5 g. (0.016 mole) of triphenyl(2-thienyl)silane in a mixture of equal parts of benzene and anhydrous ether and in an atmosphere of nitrogen was added 0.016 mole of n-butyllithium[131] and the reaction mixture was refluxed for five hours. The reaction mixture gave a negative color test #2[132] and was used on the basis of an 80% yield.

Triphenyl[5-(2'-quinolyl)-2-thienyl]silane

To approximately 0.012 mole of triphenyl 2-(5-lithio)-thienyl silane was added 1.5 g. (0.012 mole) of freshly distilled quinoline which had previously been dried over potassium hydroxide and distilled, the addition being made under nitrogen. A very slow reflux set in as the addition was made and the reaction mixture changed from red to dark yellow. The reaction mixture was refluxed for one hour and was hydrolyzed. The ether layer was separated and the ether was removed, to give 5 g. (89%) of crude product. Upon recrystallization from dilute dioxane the material melted at 168-170°.

Anal. Calcd. for $C_{31}H_{23}NSSi$: N, 2.98; S, 6.82. Found: N, 2.86; S, 6.61.

132. Gilman and Swiss, J. Am. Chem. Soc., 62, 1847 (1940).

This reaction was repeated using 0.028 mole of quinoline. After the removal of the ether the solid material which remained was dissolved in dioxane and was treated with a hot alcoholic solution of picric acid. The solution became red and on cooling a red picrate came down. This picrate was boiled with a 5% solution of sodium hydroxide and 10 g. (79%) of crude product was filtered off. Recrystallization from dilute dioxane gave 5.5 g. (40%) of pure material melting at 168-170°.

All attempts to purify the picrate resulted in decomposition of the picrate to triphenyl[5-(2'-quinolyl)-2-thienyl]silane.

Triphenyl[5-(6'-methoxy-2'-quinolyl)-2-thienyl]silane*

To approximately 0.024 mole of triphenyl[2-(5-lithio)-thienyl]silane was added 3.9 g. (0.024 mole) of freshly distilled 6-methoxyquinoline. The reaction mixture was refluxed

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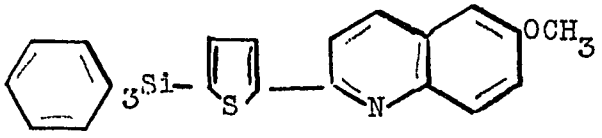


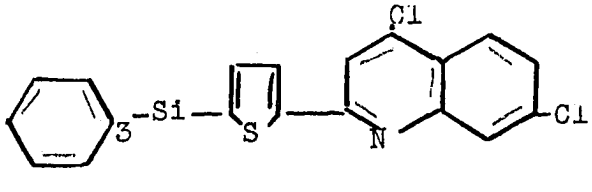
for one hour in an atmosphere of nitrogen and at the end of this time it gave a negative color test #1.[129] The reaction mixture was hydrolyzed and the ether layer was separated. The ether was removed and upon standing the residue crystallized. Recrystallization several times from a benzene-Skelly B mixture gave 4.5 g. (41%) of product melting at 227-228°.

Anal. Calcd. for $C_{32}H_{25}ONSSi$: N, 2.80. Found: N, 3.14.

Triphenyl[5-(4',7'-dichloro-8'-quinolyl)-2-thienyl]silane*

To approximately 0.024 mole of triphenyl[2-(5-lithio)-thienyl]silane, cooled to 0° and in an atmosphere of nitrogen, was added a solution of 4.7 g. (0.024 mole) of 4,7-dichloroquinoline in ether. The addition was made over a period of four minutes. The reaction mixture was refluxed for an additional four minutes and was hydrolyzed. The

*



ether layer was separated and the ether was removed. The residue was dissolved in dioxane and treated with a hot alcoholic solution of picric acid. The solution became red and a yellow picrate settled out. This crude picrate (m.p. 173-178°) was treated with a 5% sodium hydroxide solution and 9 g. (70%) of product which melted at 196-200° was filtered off. Recrystallization from dilute dioxane gave 4 g. of product melting at 200-203°.

Anal. Calcd. for $C_{31}H_{21}NCl_2SSi$: S, 5.85; Cl, 13.03. Found: S, 6.26; Cl, 13.30.

Trimethyl(p-lithiophenyl)silane

This compound was prepared according to the directions of Clark.[133] To 0.029 g. (0.04 g. atom) of lithium in 30 ml. of anhydrous ether and in an atmosphere of nitrogen was added 4.58 g. (0.02 mole) of trimethyl(p-bromophenyl)silane in 50 ml. of ether. A spontaneous reaction occurred and the reaction mixture became red. After refluxing for one hour the reaction mixture gave a positive color test #1[129] and was used after filtering under nitrogen in the attempted preparation of trimethyl p-(2-quinolyl)phenylsilane on the basis of 60% as indicated by titration.

133. Clark, R., Doctoral Dissertation, Iowa State College, (1946).

Trimethyl[p-(2-quinolyl)phenyl]silane (Attempted)

To 0.012 mole of trimethyl(p-lithiophenyl)silane in ether and in an atmosphere of nitrogen was added 1.8 g. (0.014 mole) of freshly dried and distilled quinoline in ether and the reaction mixture was refluxed for three hours. After hydrolysis the ether solution was separated and dried. The ether was removed and the residue was treated with a hot alcoholic solution of picric acid. The picrate which formed after several recrystallizations from ethanol melted at 200-202°. A mixed melting point with an authentic specimen of quinoline picrate showed no depression. The quinoline picrate was obtained in 75% yield.

Triphenyl(phenylethynyl)silane

To 0.07 mole of triphenyl(ethoxy)silane prepared from 0.21 mole of freshly distilled ethyl silicate was added slowly and with stirring approximately 0.07 mole of phenylethynyllithium. The reaction was carried out in an atmosphere of nitrogen and gentle reflux set in as the reaction proceeded. After stirring for two hours, the reaction mixture was hydrolyzed, the ether layer was separated and dried over anhydrous sodium sulfate. Most of the ether was removed and the residue was set in the ice-box. A solid settled out overnight. Recrystallization from a Skelly B-ethanol

mixture gave 10.0 g. (60%) of crystalline product melting at 95-96°.

Anal. Calcd. for $C_{26}H_{20}Si$: Si, 7.77. Found: Si, 7.55.

The phenylethynyllithium was prepared according to the directions of Gilman and Young[134] using 10 g. (0.1 mole) of phenylacetylene and 0.1 mole of phenyllithium.

134. Gilman and Young, J. Org. Chem. 1, 315 (1936).

Reaction of p-Dimethylaminophenyllithium with Silicon Tetrachloride

To 0.04 mole of freshly distilled silicon tetrachloride in 75 ml. of anhydrous ether was added 0.12 mole of p-dimethylaminophenyllithium, the addition being made under nitrogen and at such a rate as to maintain gentle reflux. After the addition was complete the reaction mixture was stirred for one and one-half hours and was hydrolyzed. The ether layer was washed with dilute ammonia and dried over anhydrous sodium sulfate. The ether was removed and the residue was crystallized from benzene and Skelly D to give 4 g. of crude material softening at 120° and melting at 169°. Further recrystallization gave a very small amount of material melting at 173-174° which analyzed for di(p-dimethylaminophenyl)-silanediol.

Anal. Calcd. for $C_{16}H_{22}N_2O_2Si$: N, 9.27; Si, 9.27. Found: N, 9.43; Si, 9.10.

In another reaction the same quantities of p-dimethylaminophenyllithium and silicon tetrachloride were used but the reaction mixture was kept at a temperature of 0°. Only a very small amount of material melting at 173-174° was isolated. A mixed melting point with the material from the first reaction melted at 173-174°. A mixed

melting point with tri(p-dimethylaminophenyl)silanol (m.p. 184-185°) melted at 160-165°.

Reaction of p-Dimethylaminophenyllithium with Ethyl Silicate

To 0.04 mole of ethyl silicate in 75 ml. of anhydrous ether was added 0.12 mole of p-dimethylaminophenyllithium, the addition being made slowly under nitrogen. When color test #1 was negative the mixture was hydrolyzed and the ether was separated and dried. Most of the ether was removed and upon standing for several days solid product separated out. Recrystallization from ethanol-benzene gave 2 g. of material melting at 125-126°. This material was later identified as tri(p-dimethylaminophenyl)ethoxysilane.

Tri(p-dimethylaminophenyl)ethoxysilane was prepared by adding to 14.3 g. (0.069 mole) of ethyl silicate in 50 ml. of anhydorus ether 0.208 mole of p-dimethylaminophenyllithium. The addition was made in an atmosphere of nitrogen and the reaction mixture was stirred for thirty-six hours. The ether was filtered from the salt which had formed and upon standing solid material separated out. Recrystallization from ethanol-benzene gave 3.5 g. (12%) of pure product melting at 125-126°. A mixed melting point with the 125-126° material from the attempted preparation above showed no depression.

Anal. Calcd. for $C_{26}H_{31}N_3OSi$: N, 9.79; Si, 6.52. Found: N, 9.44; Si, 6.33, 6.33.

Di(p-Dimethylaminophenyl)diethoxysilane[135]

To 13.3 g. (0.064 mole) of ethyl silicate in 50 ml. of anhydrous ether and in an inert atmosphere was added slowly and with stirring 0.128 mole of p-dimethylaminophenyllithium. When the addition was complete a satisfactory negative color test #1[129] could not be obtained due to the color of the reaction mixture; consequently, the mixture was stirred overnight. The ether was filtered from the salt which had formed, the ether was removed and the residue was distilled to give a main fraction of 7.5 g. (33%) of material boiling at 223-230°/1 mm., $n^{25}D$ 1.571. Smart reports a refractive index of $n^{25}D$ 1.571.

Reaction of p-Dimethylaminophenyllithium with Silicochloroform

To 10 g. (0.078 mole) of silicochloroform[136] in 50 ml. of anhydrous ether and in an atmosphere of nitrogen was added 0.234 mole of p-dimethylaminophenyllithium. The

135. Prepared according to the method of Smart, G. N. Russell, Unpublished Studies, Iowa State College.

136. The silicochloroform was kindly furnished by Professor W. C. Schumb, Massachusetts Institute of Technology.

reaction flask was kept in an ice-salt bath and the reaction mixture was not allowed to reflux. When the addition of the organolithium compound was complete, color test #1[129] gave a blue color so the reaction mixture was stirred overnight. After hydrolysis with two equivalents of ammonia, insoluble material melting at 153-157° separated out. Additional material melting at 153-157° was obtained by concentration of the ether layer. Recrystallization from ethanol-benzene gave 5 g. of material melting at 155-157°. A test with methylmagnesium iodide gave no indication of the presence of active hydrogen; a test for the Si-H linkage with piperidine and potassium hydroxide was negative.[137] This material is believed to be hexa(p-dimethylaminophenyl)-disiloxane. It was obtained in another reaction with silicochloroform when an attempt was made to prepare tri-(p-dimethylaminophenyl)silane (preparation given below).

To 0.062 mole of silicochloroform in anhydrous ether and cooled to 0° was added 0.186 mole of p-dimethylamino-phenyllithium, the addition being made dropwise and in an atmosphere of nitrogen. The reaction mixture was stirred overnight, the ether was filtered from the salt which had formed and most of the ether was removed. Solid material

137. Kipping and Sands, J. Chem. Soc., 119, 848 (1921).

separated out of the ether and, after recrystallization from ethanol-benzene, melted at 155-157°. This material analyzed for hexa(p-dimethylaminophenyl)disiloxane. It gave a negative test for active hydrogen and a negative test for the presence of the Si-H bond with piperidine and potassium hydroxide.[137] A mixed melting point with the 155-157° material from the preparation above showed no depression.

Anal. Calcd. for $C_{48}H_{60}N_6OSi$: N, 10.60; Si, 7.07. Found: N, 10.56; Si, 6.92.

In another preparation using the same quantities of silicochloroform and p-dimethylaminophenyllithium the reaction mixture was treated with 0.1 N hydrochloric acid before filtration. Two grams of product melting at 154-157° was obtained. A mixed melting point with the other 155-157° material was not depressed.

Hydrolysis of Tri(p-dimethylaminophenyl)ethoxysilane

Seven grams (0.016 mole) of tri(p-dimethylaminophenyl)-ethoxysilane was dissolved in two equivalents of hydrochloric acid. When solution was complete 0.2 N sodium hydroxide was added until precipitation was complete. The precipitate was washed with dilute acetic acid and recrystallized from absolute ethanol to give 5.7 g. (80%) of product melting at 184-185°. A Zerewitinoff determination showed the

presence of one active hydrogen. A sample of 0.1593 g. gave 10.7 ml. of methane at 737.5 mm. and 34° and a sample of 0.2199 g. gave 11.9 ml. of methane at 737.5 mm. and 34°.

Anal. Calcd. for $C_{24}H_{31}N_3OSi$: N, 10.37; Si, 6.91; active H, 1. Found: N, 10.48; Si, 6.73; active H, 1.2, 0.9.

Hydrolysis of Di(p-dimethylaminophenyl)-diethoxysilane

Two grams (0.005 mole) of di(p-dimethylaminophenyl)-diethoxysilane was dissolved in a generous excess of 0.1 N hydrochloric acid at room temperature and sodium hydroxide was immediately added to precipitate the diol. The white precipitate was washed with dilute acetic acid and was recrystallized from benzene to give 1 g. (63%) of product melting at 172-173°. A mixed melting point with the 173-174° material from the reaction of p-dimethylaminophenyllithium with silicon tetrachloride was not depressed. A test with methylmagnesium iodide showed the presence of active hydrogen.

The results of the reactions involving p-dimethylaminophenyllithium and silicon tetrachloride, ethyl silicate and silicochloroform and the products which are believed to be obtained in each case, are summarized in

in Table I.

Hexa(p-dimethylaminophenyl)disiloxane (Attempted)

To 2 g. (0.0049 mole) of tri(p-dimethylaminophenyl)-silanol was added 5 parts by weight of formic acid and the reaction mixture was refluxed for four hours. The glass-like substance which formed was filtered and upon thorough drying there was obtained a blue insoluble material which decomposed when heated above 200° leaving a residue. This insoluble material was extracted with benzene, petroleum ether and ethanol, and in each case the solvents were distilled leaving no residue.

The reaction was repeated using glacial acetic acid. As soon as the reaction mixture was heated a glass-like substance formed which behaved in a manner similar to the material from the first preparation. No product could be extracted from the intractable material.

A third reaction was run using absolute methanol and hydrochloric acid as the reaction medium. After refluxing the mixture for four hours, the solvent was removed and an oil remained which could not be made to crystallize. No attempt was made to distil the oil since it was obtained in such a small quantity that distillation did not seem feasible.

Table I

Reaction of p-Dimethylaminophenyllithium with Silicon-tetrachloride, Ethyl Silicate and Silicochloroform

Reactant	Experimental Conditions	Hydrolysis Medium	Product
$SiCl_4$	Room temp., 1 1/2 hrs.	water	$[(Me)_2NC_6H_4]_2Si(OH)_2$ (?) I
$SiCl_4$	0°; 1 1/2 hrs.	water	$[(Me)_2NC_6H_4]_2Si(OH)_2$ (?) I
$Si(OC_2H_5)_2$	Room temp., 2 hrs.	water	$[(Me)_2NC_6H_4]_3SiOC_2H_5$ II
$Si(OC_2H_5)_2$	Room temp., 36 hrs.	-	$[(Me)_2NC_6H_4]_3SiOC_2H_5$ II
$HSiCl_3$	0°, overnight	NH_4OH	$[(Me)_2NC_6H_4]_3SiOSi[C_6H_4N(Me)_2]_3$ (?) III
$HSiCl_3$	0°, overnight	-	$[(Me)_2NC_6H_4]_3SiOSi[C_6H_4N(Me)_2]_3$ (?) III
$Si(OC_2H_5)_2$	Room temp., overnight	-	$[(Me)_2NC_6H_4]_2Si(OC_2H_5)_2$ IV
II[b]	Room temp.	NaOH	$[(Me)_2NC_6H_4]_3OH$ (?) V
IV[b]	Room temp.	NaOH	$[(Me)_2NC_6H_4]_2(OH)_2$ (?) I

[a] b.p. at 1 mm.

[b] Hydrolysis only

[c] Active hydrogen calcd.: 1. Found: 0.9, 1.2.

:ide,

	M.P. °C	Formula	Analyses Calcd. % N	Si	Found % N	Si
	173-4	$C_{16}H_{22}N_2O_2Si$	9.27	9.27	9.43	9.10
	173-4	-	-	-	-	-
	125-6	$C_{26}H_{31}N_3OSi$	9.79	6.52	9.44	6.33 6.33
	125-6	-	-	-	-	-
e)$_2$]$_3$(?)III	155-7	$C_4H_{60}N_6OSi_2$	10.60	7.07	10.56	6.92
e)$_2$]$_3$(?)III	155-7	-	-	-	-	-
	223-30[a]	-	-	-	-	-
	184-5	$C_{24}H_{31}N_3OSi$[c]	10.37	6.11	10.48	6.73
	173-4	-	-	-	-	-

IV. DISCUSSION

A. Quinoline Sulfides

The quinoline ethers, especially the 6-methoxy derivatives, have proved to be very good antimalarial agents. Three of the most effective antimalarials, plasmoquin, quinine and atebrin, are 6-methoxyquinoline derivatives. The ether-linkage has been shown to have some additional value as a therapeutic agent. The bactericidal action of aromatic phenols against B, typhosus and staph. aureus has been found to increase when the oxygen atom is replaced by sulfur.[138] The ether-linkage was found to have some value in anti-tuberculous studies.[139,124] The presence of the tertiary amino group in many effective therapeutic agents together with the considerations just mentioned, made it seem desirable to prepare and examine a series of quinoline sulfides having tertiary alkylaminoalkyl

138. (a) Hilbert and Johnson, J. Am. Chem. Soc., 51, 1526 (1929); (b) Dunning, Dunning and Drake, ibid., 53, 3455 (1922); (c) Klormann, Gates and Shternov, ibid., 54, 1204 (1932); (d) Suter and Hansen, ibid., 54, 4100 (1932).

139. Freedlander, Am. Rev. Tuberc., 49, 513 (1944).

groupings in their molecules.

A series of tertiary alkylaminoalkyl quinoline sulfides was prepared. The two important factors considered in this series of compounds were the side chain and the quinoline nucleus. The logical approach seemed to be that of varying: (1) the length of the tertiary alkylaminoalkyl side chain; (2) the amino group in the side chain; and (3) the substituents on the quinoline nucleus.

Four alkylamino side chains were used in this first group of compounds: β-diethylaminoethyl-, γ-diethylaminopropyl-, β-(N-piperidyl)ethyl- and β-(N-morpholino)ethyl-. The first two side chains were usually introduced by means of the sodium mercaptide and an active chloroquinoline compound. The last two were usually introduced by means of an alkylaminoalkylchloro-compound and the quinoline sodium mercaptide.

Various methods for the preparation of the mercaptans used in these condensations were tried. β-Diethylaminoethyl mercaptan was prepared in three different ways: (1)[35] by the reaction of lithium diethylamide and ethylene sulfide in 48% yield; (2)[36] by the reaction of sodium hydrosulfide and β-diethylaminoethyl chloride in yields varying from 25-75%; and (3)[37] by the formation of β-diethylaminoethylisothiouronium chloride hydrochloride from

thiourea and β-diethylaminoethyl chloride hydrochloride with subsequent decomposition of the complex with sodium hydroxide in 60% yield. Of the three methods the last mentioned seems to be preferable for several reasons: (1) the yields are higher and can be obtained consistently; (2) there is some difficulty in determining the point of saturation of the sodium sulfide used in method (2); and (3) the isothiouronium complex is useful as such in the preparation of sulfides and avoids the necessity of isolating the mercaptan.

γ-Diethylaminopropyl mercaptan was prepared from γ-diethylaminopropyl chloride and sodium hydrosulfide[36] and from γ-diethylaminopropyl chloride and thiourea with subsequent decomposition of the isothiouronium complex with sodium hydroxide. For the preparation of this compound the isothiouronium salt synthesis appears to be the best method. The product obtained by this method is purer, since in the sodium hydrosulfide method some difficulty is encountered in separating the mercaptan from any unreacted starting chloride (boiling point of mercaptan 76-77.5°/26 mm.; boiling point of chloride 73-75°/20 mm.). The γ-isothiouronium complex is also useful in synthesis. If a basic extraction is used to separate the mercaptan from the chloride a much lower yield is obtained. The low yield in

this last instance might be accounted for to some extent by the fact that mercaptans are somewhat unstable in basic media forming disulfides.

The second group of tertiary alkylaminoalkyl quinoline sulfides included 4-methylquinoline derivatives. The apparent activity of the lepidines, such as 6-methoxy-8-(4-isopropylamino-1-methylbutylamino)-lepidine, initiated the preparation of these compounds. Two compounds in this group were prepared by condensing the sodium salt of 2-mercapto-4-methylquinoline with the alkylaminoalkyl chloride. The quinoline mercaptan proved to be only slightly soluble in ethanol and it was found most satisfactory to carry out the condensation in a mixture of equal parts of methyl cellosolve and ethylene glycol. 4-Methyl-2-quinolyl β-(N-morpholino)ethyl sulfide and 4-methyl-2-quinolyl β-(N-piperidyl)ethyl sulfide were isolated as the free bases which proved to be solids melting at 75-76° and 85-85.5°, respectively.

A group of 6-methoxyquinoline sulfides was prepared, the side chain being introduced into both the 2-position and the 4-position in the quinoline nucleus. 6-Methoxy-2-quinolyl β-diethylaminoethyl sulfide was prepared in two different ways. In the first preparation 2-chloro-6-methoxyquinoline was condensed with sodium β-diethylamino-

ethyl mercaptide; in the second preparation the sodium salt of 2-mercapto-6-methoxyquinoline was condensed with β-diethylaminoethyl chloride. There was no appreciable difference in the yield (33% and 30%) or the purity of the product obtained in the two cases.

In the preparation of the 6-methoxyquinoline sulfide some difficulties were encountered which proved to be rather interesting and significant. In the early preparations it was found that the same compound was obtained in the reaction between sodium β-diethylaminoethyl mercaptide and 2-chloro-6-methoxyquinoline and sodium β-diethylaminoethyl mercaptide and 4-chloro-6-methoxyquinoline. Both nitrogen and chlorine analyses were made on these products but it was impossible to identify the compound on the basis of these analyses alone. Consequently, absorption spectra data[140] were obtained on the compound and the curves prepared from these data indicated that the quinoline nucleus was not present in the molecule. Then, carbon, hydrogen[140] and sulfur analyses were run and with these additional data the compound appeared to be bis-(β-diethylaminoethyl) disulfide dihydrochloride. An authentic specimen of bis-(β-diethylaminoethyl) disulfide dihydro-

140. Absorption spectra data and carbon-hydrogen analyses were kindly furnished by Parke, Davis and Company.

chloride was prepared and a mixed melting point established the identity of the two compounds.

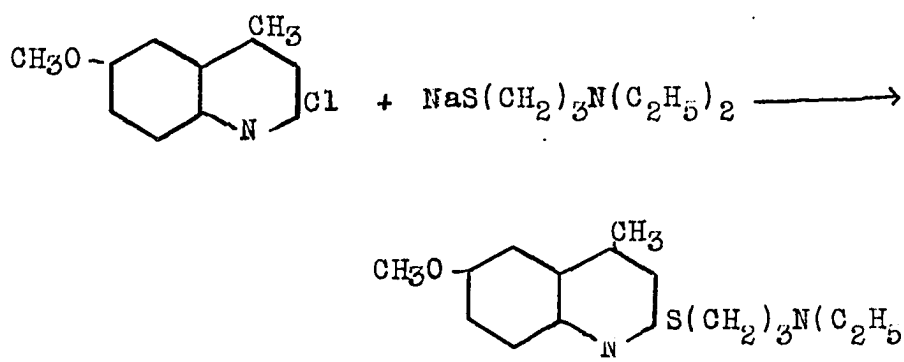
Bis-(β-diethylaminoethyl) disulfide dihydrochloride was obtained earlier by Cook and Kreke[141] incidental to an attempt to prepare the mercaptan from the reaction of β-diethylaminoethylbromide hydrobromide with sodium sulfide and hydrogen sulfide. The disulfide was also obtained in one preparation of β-diethylaminoethyl mercaptan upon prolonged exposure of the mercaptan to the air in the presence of sodium hydroxide.[36] The disulfide was obtained in another reaction when the sodium salt of -diethylaminoethyl mercaptan was treated with iodine.[36] It has also been made from ethylene sulfide and diethylamine.[35] The dihydrobromide of the disulfide had been previously obtained by Lischer and Jordan[142] in an attempt to prepare the mercaptan from β-diethylaminoethylbromide hydrobromide and sodium hydrosulfide in ethanolic solution. In the work of this thesis conversion of the hydrochloride to the free amine and subsequent treatment of the free amine with hydrogen bromide gave a white hydrobromide melting at 222-223°. The reported melting point is 223°.[142]

The most probable explanation for the formation of

141. Cook and Kreke, J. Am. Chem. Soc., 61, 2971 (1939).
142. Lischer and Jordan, ibid., 59, 1523 (1937).

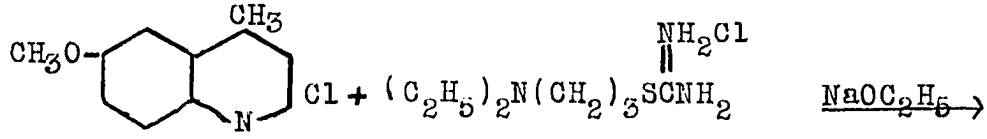
bis-β-(diethylaminoethyl) disulfide in these reactions seems to be oxidation of the mercaptan in boiling ethanolic solution containing sodium ethoxide by atmospheric oxygen to the disulfide. As a result of this conclusion all other condensations with mercaptans were carried out in an inert atmosphere.

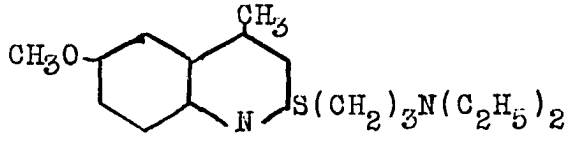
6-Methoxy-4-methyl-2-quinolyl γ-diethylaminopropyl sulfide was prepared by two methods. In both cases methyl cellosolve was used as the solvent. This was found desirable after a reaction had been run using 2-chloro-4-methyl-6-methoxyquinoline and sodium methyl mercaptide. When ethanol was used as the solvent quantitative recovery of starting material was made, but when methyl cellosolve was used 90% of product (6-methoxy-4-methyl-2-quinolyl methyl sulfide) was obtained. In method A 2-chloro-4-methyl-6-methoxyquinoline was condensed with sodium γ-diethylaminopropyl mercaptide in methyl cellosolve according to the reaction:



In method B, sodium ethoxide was added to a refluxing mixture of γ-diethylaminopropylisothiouronium chloride hydrochloride and 2-chloro-4-methyl-6-methoxyquiniline in

methyl cellosolve. The reaction proceeded according to the equation:





The time of reaction for the two methods was the same and there was very little difference in the yields (50% and 46%). Method B has an advantage over method A in that it is not necessary to first isolate the mercaptan in order to carry out the reaction.

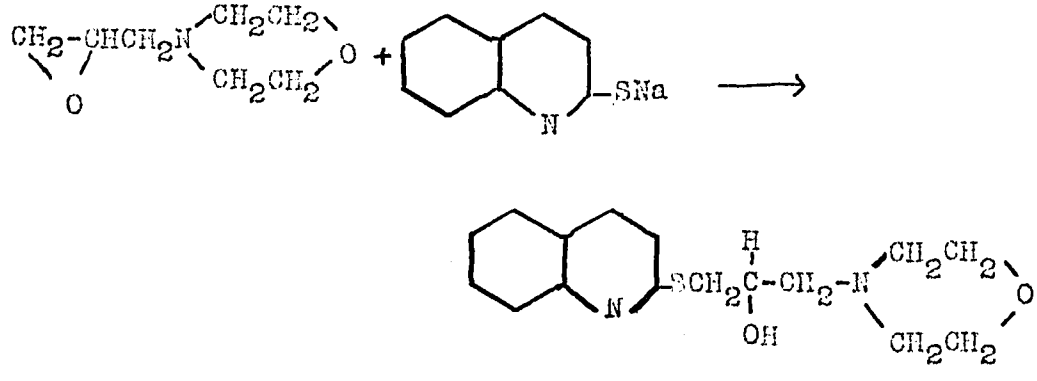
The recent observation[92] that 7-chloroquinoline derivatives have favorable physiological action initiated the preparation of another member of this series, 7-chloro-4-quinolyl β-diethylaminoethyl sulfide. This compound was prepared from 4,7-dichloroquinoline and sodium β-diethylaminoethyl mercaptide in good yield (75% as the dihydrochloride).

Isolation of most of the products in this series as the hydrochloride proved to give better yields and purer products than low pressure distillations of the free bases. The hydrochlorides came down as white solids with definite melting points.

B. Hydroxy Sulfides

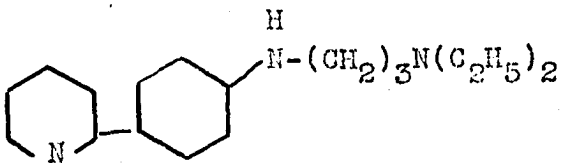
The preparation of quinolyl hydroxy sulfides as potential medicinal agents seemed desirable because of the therapeutic value of the secondary carbinol group, the sulfide group and the quinoline nucleus. Accordingly, 2-quinolyl β-hydroxy-γ-morpholinopropyl sulfide and 2-quinolyl β-hydroxy-γ-piperidylpropyl sulfide were prepared.

Epichlorohydrin was reacted with morpholine according to the method of Drozdov and Cherntzov.[121] This product was not isolated but was reacted directly with sodium 2-quinolyl mercaptide. Only two reactions of this type were carried out and the mechanism was not proved but was assumed to take place as indicated by the work of Fullhart[38] and Massie[79] on the cleavage of epoxy compounds with mercaptans according to the following equation:



C. Pyridine Sulfides

Since the central nucleus in atebrin is the simple pyridine ring and since the compound 2-(p-γ-diethylaminopropylaminophenyl)-pyridine (XI) has been shown to be physiologically active, it seemed desirable to prepare a series of pyridine sulfides.



(XI)

2-(β-chloroethyl)pyridine hydrochloride and 2-(γ-chloropropyl)pyridine hydrochloride were prepared and used as bases for these compounds. These particular compounds were used since they could be fairly easily prepared from readily available starting materials. 2-Pyridineethanol and 2-pyridinepropanol were obtained from Reilly Tar and Chemical Company and were used without any purification. Treatment of the alcohols with thionyl chloride gave the products in 50% yields. It was found to be preferable to isolate the chloro-compounds as the hydrochlorides since the free bases proved to be unstable on

distillation. In some cases the hydrochloride was neutralized and the free base was used immediately, without distillation.

β-(2-Pyridyl)ethyl β-diethylaminoethyl sulfide was prepared by treating a mixture of 2-(β-chloroethyl)-pyridine hydrochloride and β-diethylaminoethylisothiouronium chloride hydrochloride with sodium ethoxide. β-(2-Pyridyl)-ethyl γ-diethylaminopropyl sulfide was prepared in a similar manner. Both of these compounds were isolated as the hydrochlorides.

Some difficulty was encountered with 2-(β-chloroethyl)pyridine when it was reacted with sodium p-aminophenyl mercaptide. This will be discussed in the section devoted to p-aminophenyl sulfides.

D. p-Aminophenyl Sulfides

The value of the p-aminophenyl group in chemotherapeutic agents is well known, the most common of the compounds containing this grouping being sulfanilamide. 4,4'-Diamino-diphenyl sulfone, promin (VIII), diasone (IX) and promizole (X) have proved to have very interesting and significant physiological effects in clinical testing. Many of the derivatives of 4,4'-diaminodiphenyl sulfone

that have been prepared as chemotherapeutic agents have been tested for antimalarial activity[143] as well as for antituberculous activity and for other physiological properties. These facts led to the preparation of a series of p-aminophenyl sulfides.

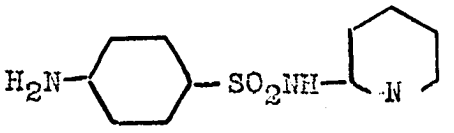
The compounds in this series were prepared by condensing sodium p-aminophenyl mercaptide with an active chloro-compound. In nearly all cases the product was isolated as the free base which was a solid and could be readily recrystallized from the common solvents. Variety was obtained in this series by changing the substituents on the nucleus, by changing the position of the p-aminophenyl group on the nucleus and by changing the nucleus itself.

The preparation of β-(2-pyridyl)ethyl p-aminophenyl sulfide seemed particularly worthwhile because of its relationship to 2- p-aminobenzenesulphonamide pyridine (XII) which has been shown to have a destructive action on the protective capsule of the pneumococcus.[144,145]

143. (a) Heymann and Fieser, J. Am. Chem. Soc., 67, 1979 (1945); (b) Heymann and Heidelberger, Ibid., 67, 1986 (1945).

144. Whitby, Lancet, 242, 1210 (1938).

145. Evans and Gaisford, Lancet, 242, 14 (1938).



(XII)

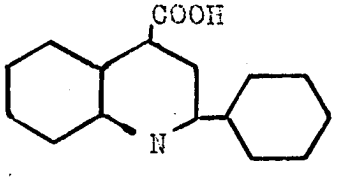
β-(2-Pyridyl)ethyl p-aminophenyl sulfide has a $-CH_2CH_2S-$ group in place of the $-SO_2NH-$ group of XII.

The preparation of β-(2-pyridyl)ethyl p-aminophenyl sulfide proved to be interesting. 2(β-Chloroethyl)pyridine hydrochloride was converted to the free base and the free base was treated with a solution of sodium p-aminophenyl mercaptide. After the crude product had been isolated, attempts were made to prepare a solid picrate and a hydrochloride but in each case only oils were obtained. This crude material was distilled to give a product which boiled over a large range (125-160°/1 mm.). This material was fractionated and three fractions were obtained. The lower boiling fraction (55-60°/0.5 mm.) was converted to a picrate which melted at 156-158°. This picrate was found to be identical with a picrate[127] obtained in some other reactions with 2-(β-chloroethyl)pyridine carried out in these laboratories. Analysis indicated that the picrate is a polymer of vinylpyridine but its structure was not definitely established. Picrates were made of the two higher boiling fractions (110-115°/0.5 mm. and 140°/0.5 mm.). These picrates melted at 142-143° and proved to be identical.

Analysis showed that the picrate was that of β-(2-pyridyl)-ethyl p-aminophenyl sulfide.

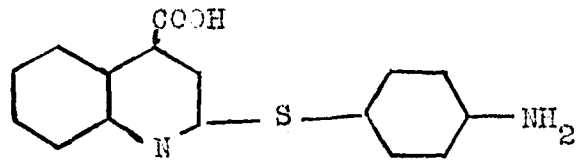
Since the p-aminophenyl group is known to be of therapeutic value and the quinoline nucleus has proved useful, it seemed of interest to prepare some p-aminophenyl quinolyl sulfides. Accordingly, 2-quinolyl p-aminophenyl sulfide, 6-methoxy-2-quinolyl p-aminophenyl sulfide and 6-methoxy-4-quinolyl p-aminophenyl sulfide were prepared. These compounds were made by condensing sodium p-aminophenyl mercaptide with the desired chloroquinoline compound.

Quinine on oxidation gives 6-methoxycinchoninic acid. The discovery of this fact has stimulated a large amount of research on various acids of this type. Cinchoninic acids, themselves, have been useful as therapeutic agents, especially in the treatment of gout and rheumatic fever. Cinophen, 2-phenylcinchoninic acid (XIII) has antipyretic and analgesic activities, similar to that of the salicylates.



(XIII)

The activity of cinchophen and the therapeutic value of the p-aminophenyl group initiated the preparation of 4-carboxy-2-quinolyl p-aminophenyl sulfide (XIV). This compound was prepared in 80% (crude) yield by treating 2-chlorocinchoninic acid with sodium p-aminophenyl mercaptide. The product was isolated as the hydrochloride.



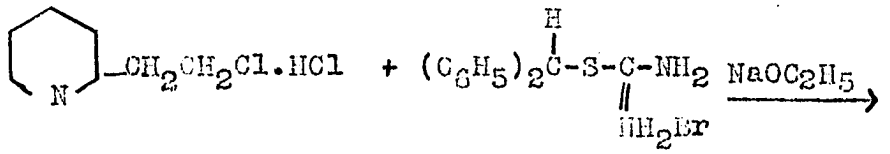
(XIV)

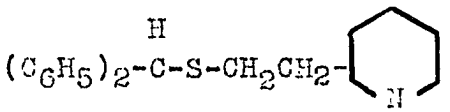
E. Miscellaneous Sulfides

Benadryl types

Interest in compounds of the benadryl type was awakened when the physiological activity of diphenylmethyl β-dimethylaminoethyl ether was discovered. It was felt of value to prepare some compounds of this type having a sulfide linkage instead of the ether linkage. Diphenylmethyl β-(2-pyridylethyl) sulfide (XV) was prepared by two methods. In method A a mixture of 2-(β-chloethyl)-pyridine hydrochloride and diphenylmethylisothiourea

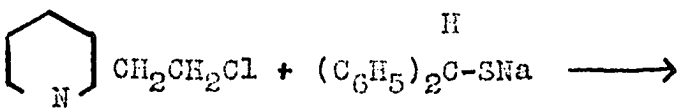
hydrobromide was treated with sodium ethoxide. The product could not be distilled at 1 mm. and so was purified through the picrate. A yield of 50% of picrate melting at 146-147° was obtained.

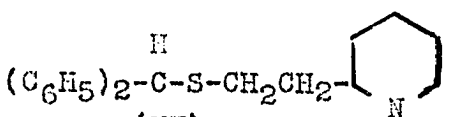




(XV)

In method B sodium diphenylmethyl mercaptide was treated with 2-(-chloethyl)pyridine and a yield of 57% of the picrate (m.p. 146-147°) was obtained from this reaction mixture.





(XV)

Some of the picrate was converted to the free base and the hydrochloride was made.

Diphenylmethyl p-aminophenyl sulfide was prepared from sodium p-aminophenyl mercaptide and benzohydryl bromide. The product was isolated as the hydrochloride and was obtained in 40% yield.

Alkylaminoalkyl sulfides

The biological importance of the amino-nitrogen group is usually found in compounds of rather complex structure, or in compounds which contain other functional groups. However, a few very simple amines have found use as therapeutic agents. One of the most simple of these is ethylenediamine hydrochloride, administered in the form of keratin-coated pills to acidify the urine. Simple amines are becoming available in increasing quantities. They are prepared for use as intermediates in various more complicated syntheses. Some of the higher aliphatic amines, such as $C_{17}H_{35}NH_2$, are reported to possess germicidal activity.

It seemed pertinent to prepare some simple alkylaminoalkyl sulfides using the compounds which were prepared as starting materials for some of the other work in this thesis. These sulfides were prepared by condensing a sodium alkylaminoalkyl mercaptide with an alkyamino-

alkyl halide. The reactions were carried out in ethanol at reflux temperature and in an inert atmosphere. Some of the products were distilled at low pressure but it was found more satisfactory to isolate them as hydrochlorides. Yields for these preparations varied from 44-77%.

F. Organosilicon Compounds

Fleming[107] has demonstrated the use of organolithium reagents in place of Grignard reagents to introduce alkyl or aryl radicals into the silane molecule. Recent work[133] in these laboratories has shown that such reagents are extremely useful in the preparation of variously substituted silanes.

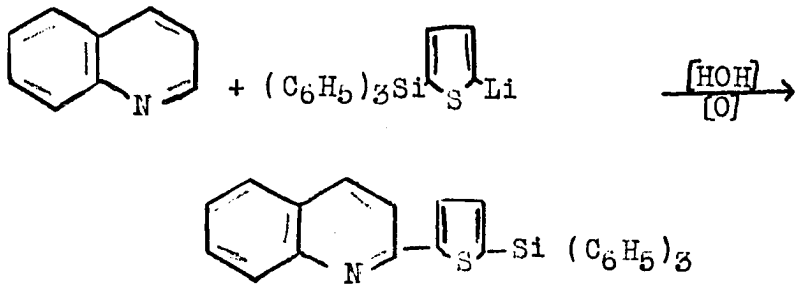
In the work of this thesis silicon tetrachloride and ethyl silicate were used in most instances as starting materials. Clark[133] states that ethyl silicate has definite advantages over silicon tetrachloride and this work corroborates his conclusions. The use of ethyl silicate involves none of the special precautions that are necessary with silicon tetrachloride due to the extreme readiness with which it hydrolyzes and its high vapor pressure at room temperature. In addition to these two reagents silicochloroform has been found useful in the synthesis of organosilanes. It must, however, be handled with the same care that is necessary with silicon tetrachloride, since it is easily hydrolyzed and is very volatile as well as being inflammable and corrosive.

An attempt was made in this work to prepare a group of organosilicon compounds containing nitrogen. Consequently, triphenyl(p-dimethylaminophenyl)silane,

diphenyl[di(p-dimethylamino)phenyl]silane, tri(p-dimethylaminophenyl)phenylsilane and tetra(p-dimethylaminophenyl)-silane were prepared. In these preparations practically comparable yields were obtained using either silicon tetrachloride or ethyl silicate.

In connection with the preparation of these silanes it seemed of interest to study the effect of the presence of one, two, three and finally four water solubilizing groups on these extremely water insoluble compounds. Consequently, an attempt was made to prepare the hydrochlorides of each of the silanes by treating an ether solution of the free bases with hydrogen chloride. It was possible to obtain only one, triphenyl(p-dimethylaminophenyl)silane hydrochloride, in pure solid form. Two of the other three hydrochlorides oiled out and could not be made to crystallize. In the case of diphenyl[di(p-dimethylaminophenyl]-silane a very hygroscopic solid formed but it could not be purified.

In view of the biological importance of the quinoline nucleus, it was desirable to make a molecule containing both the quinoline nucleus and silicon. Therefore, some compounds were prepared in which a lithiosilane was added to the anil linkage of a quinoline compound according to the reaction:



Specifically, triphenyl 2-(5-lithio)thienyl silane was added to quinoline, to 6-methoxyquinoline and to 4,7-dichloroquinoline, yielding in each case a high melting solid. Trimethyl(p-lithiophenyl)silane was prepared[133] and an attempt was made to add it to quinoline but no product could be obtained, the quinoline being recovered in 75% yield.

In connection with some studies on halochromism being made in these laboratories[146] it was desirable to prepare tri(p-dimethylaminophenyl)silanol. Several attempts were made before the desired product was finally obtained. The reaction between silicon tetrachloride and p-dimethylaminophenyllithium gave only a small amount of material which analyzed for di(p-dimethylaminophenyl)silanediol; the reaction between ethyl silicate and p-dimethylaminophenyllithium with a subsequent water hydrolysis gave only tri(p-dimethylaminophenyl)ethoxysilane-identified by a mixed melting point with an authentic specimen; the reaction between silicochloroform and p-dimethylaminophenyllithium followed by hydrolysis with ammonia gave what is believed to be hexa(p-dimethyl-

146. Meikle, W. J., Unpublished Studies, Iowa State College.

aminophenyl)disiloxane; and finally hydrolysis of tri-(p-dimethylaminophenyl)ethoxysilane with sodium hydroxide gave 80% of what appears to be the desired silanol.

The preparation of tri(p-dimethylaminophenyl)silanol is reported in the patent literature along with a group of compounds prepared from RLi compounds and silicon tetrachloride or ethyl silicate.[107] It is described as a liquid, b. p. 275-80°/12 mm.

Three attempts were made to prepare an authentic specimen of hexa(p-dimethylaminophenyl)disiloxane. In the first preparation tri(p-dimethylaminophenyl)silanol was treated with five parts of formic acid and the mixture was refluxed for four hours according to a method used successfully in these laboratories for the preparation of hexaphenyldisiloxane.[147] The reaction yielded a blue glassy substance which later solidified to an extremely refractory solid which decomposed when heated above 200° leaving a residue. In the second preparation the silanol was treated with an excess of glacial acetic acid. Upon heating to reflux temperature a blue glassy substance formed which later solidified to a material equally as intractable as the first. Hexaphenyldisiloxane has been obtained in 50% yield by this method.[147] In the

147. Melvin, H., Unpublished Studies, Iowa State College.

third preparation the silanol was heated with absolute methanol and hydrochloric acid according to a method suggested by Kipping.[148] A dark oil which could not be made to crystallize was obtained.

It is evident that the conditions for these preparations were drastic enough to cause some decomposition of the molecule in addition to some polymerization. Apparently, the presence of the p-dimethylaminophenyl group makes the molecule much more susceptible to attack than does the phenyl group alone. The work on the preparation of hexaphenyldisiloxane by the formic acid and acetic acid methods[147] mentioned above substantiates this view. In addition, studies being made in these laboratories on the cleavage of silanes by hydrogen chloride[149] indicate that the p-dimethylaminophenyl group is more labile than the phenyl group. Triphenyl(p-dimethylaminophenyl)silane is cleaved by hydrogen chloride to give 80% and 76.2% dimethylaniline, while tetraphenylsilane under the same conditions gives an 85% recovery of the silane. Kipping and Lloyd[150] report that tetraphenylsilane is cleaved slowly by hydrogen chloride.

148. Kipping, J. Chem. Soc., 79, 455 (1901).
149. Marshall, F. J., Unpublished Studies, Iowa State College.
150. Kipping and Lloyd, J. Chem. Soc., 79, 449 (1901).

V. SUMMARY

1. A brief survey of the outstanding methods of preparing mercaptans was made. This survey includes general preparations and more specifically those of tertiary alkylaminoalkyl mercaptans, quinoline mercaptans and pyridine mercaptans.

2. General methods of preparing sulfides were discussed, particular attention being given to the preparation of alkylaminoalkyl sulfides, quinoline sulfides and pyridine sulfides.

3. Some of the most recent outstanding chemotherapeutic agents which have proved of value in the treatment of malaria and tuberculosis were discussed in relation to the work of this thesis. These agents contain nitrogen - usually in the form of a basic side chain, or sulfur - in the form of a sulfide or sulfur; and in many cases both elements are present in the active molecule.

4. Organosilicon chemistry was reviewed briefly.

5. A group of substituted quinoline sulfides was prepared as potential chemotherapeutic substances. These sulfides were made by condensing an active chloroquinoline with a sodium alkylamino mercaptide; by condensing a

sodium quinoline mercaptide with an alkylamino chloride; or by treating an active chloroquinoline with an isothiouronium salt and subsequently decomposing the complex with base.

6. A series of pyridine sulfides modeled after biologically active compounds was synthesized.

7. A group of miscellaneous sulfides, including alkylaminoalkyl and benadryl types, was prepared.

8. A study of some nitrogen containing organosilicon compounds was made. These compounds were prepared from silicon tetrachloride, ethyl silicate or silicochloroform and organolithium reagents.