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Some substituted alkylamino sulfides and sulfones

Lawrence Fullhart Jr.
Iowa State College

NOTE TO USERS

SOME SUBSTITUTED ALKYLAMINO SULFIDES AND SULFONES

by

Lawrence Fullhart, Jr.

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In Charge of Major Work

Signature was redacted for privacy.

Head of Major Department

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Dean of Graduate College

Iowa State College

1946

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The author wishes to express his sincere appreciation to Dr. Henry Gilman for his encouragement, suggestions and helpful criticisms throughout the course of this investigation.

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I. INTRODUCTION

During the past five years considerable research work has been done on the preparation of synthetic antimalarials. This work was made necessary primarily by the conquest of the Dutch East Indies by the Japanese, since Java produces over 98 percent of the world's supply of cinchona bark. The danger of the loss of Java was foreseen in this country, as indicated by the sharp increase in imports of cinchona bark at least two years before our entry into the war. A desperate attempt was also made to plant cinchona seeds in Latin American countries in order to become independent of the Java imports.

It was known also that quinine was not a cure for malaria but merely served to suppress the clinical symptoms. This fact emphasized the need for an antimalarial which would have prophylactic action. At the outbreak of the war there were two synthetic drugs, plasmoquin and atebrin, which were capable of suppressing the malaria parasites. During the war a biguanidine derivative, paludrine, was developed which gives promise of having some prophylactic action. The clinical tests on this compound, however, have not been completed. Although these compounds represent an advancement in the treatment of malaria, the "ideal antimalarial" has not been discovered.

The preparation of a large number of new compounds as antimalarial agents has led to the investigation of some of their other pharmacological properties. One of the more

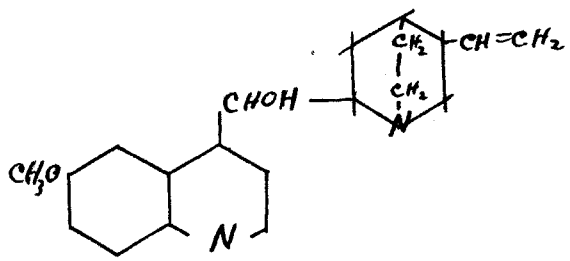
important of these has been for antituberculous activity. The attack on this problem has been largely to prepare sulfur antagonists of p-aminobenzoic acid. The present promising compounds, promin, diasone, and promizole, are a result of this program.

In the work reported in this thesis a number of new compounds containing sulfur have been synthesized in which the action of the sulfur was of particular interest. The therapeutic activity of most of these compounds will be found in a monograph, "A Survey of Antimalarial Drugs, 1941-1945", to be published by the Committee on Medical Research of the Office of Scientific Research and Development; the activity of the others will be reported later. It will be the purpose of this thesis to give a discussion of the use of sulfur in some therapeutic agents and of the possible mechanisms involved in the preparation of some of these compounds.

II. HISTORICAL

Antimalarial Agents

The curative treatment of malaria has been one of the greatest problems facing medical workers throughout the world. The first successful suppressor of the syndrome of malaria was the cinchona bark. The active ingredient of this bark, quinine, was extracted in 1820 by Pelletier and Coventou. The structure of quinine was proposed by Rabe in 1908 and the complete synthesis has recently been accomplished.[1] The complicated structure of quinine, however, is not essential for antimalarial activity.



I

Demonstration of the antimalarial activity of methylene blue in 1891 by Guttmann and Ehrlich[2] initiated a program of synthesis and testing of compounds as antimalarial agents. The derivatives of phenothiazine,[3] the methylene blue nucleus, however, have not shown exceptional activity.

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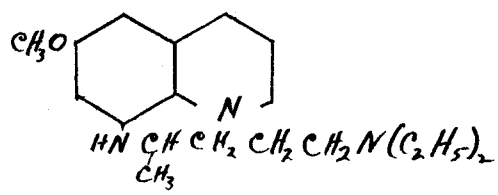
1. Woodward and Doering, J. Am. Chem. Soc., 67, 860 (1945).
2. Guttmann and Ehrlich, Berlin klin. Wochschr., 28, 593 (1891) [Chem. Zentr., 63 [I], 221 (1892)].
3. Shirley, D.A., Doctoral Dissertation, Iowa State College (1943).

The investigations of the I. G. Farbenindustrie produced in 1924 the first of the present good antimalarials, plasmoquin.[4]



II

Plasmoquin has remained one of the most effective antimalarials in use today. It is about sixty times as potent as quinine; however, because of its toxic properties treatment with plasmoquin must be watched closely. The present method of administration is in combination with quinine.

The introduction of atebrin[5] in 1930 was another advancement as it has proved to be an excellent antimalarial agent.

III

Atebrin is almost as effective as plasmoquin, but it is much less toxic so that its use has been much more extensive. It was perhaps the most widely used antimalarial during World War II.

During the war the Germans prepared 7-chloro-4-(4'-diethyl-

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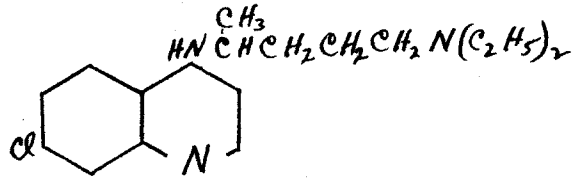
4. Schuleman, Schonhofer, and Wingler, Ger. Patent 486,079 (1924) [C.A., 24, 1937 (1930)].
5. Mietsch and Mauer, Klin. Wochschr., 12, 1276 (1933); U.S. Patent 2,077,249 (1937) [C.A., 31, 4060 (1937)].

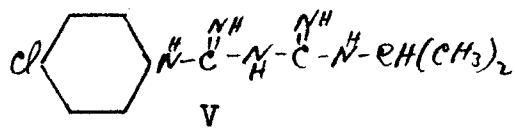
amino-1-methylbutylamino)quinoline[6] (IV). The preliminary report



IV

on its antimalarial activity indicates that it is as effective as atebrin and plasmoquin and possibly better.

More recent has been the development of paludrine,[7] N-p-chlorophenyl-N[5]-isopropylbiguanide (V). The first reports on the activity of paludrine indicated that it would have prophy-



V

lactic action, which is highly desirable. This was the first compound tested to exhibit this action. The results of the clinical testing of paludrine will be of extreme interest.

The introduction of the sulfanilamide type of compounds into the field of chemotherapy has been of paramount importance. They are used widely in β-hemolytic streptococcal infections, meningococcal infections, gonococcal infections, skin infections, such as impetigo and erysipelas, and for many other purposes. Their use in the treatment of malaria has also been investigated. Marshall[8] has reviewed the application of these compounds

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6. Anderson, Breitner, and Jung, Ger. Patent 683,692 (1939) [C.A., 36, 4973 (1942)].
7. Curd and Rose, Chemistry & Industry, 24, 75 (1946).
8. Marshall, J. Pharmacol., 75, 89 (1942).

to malaria and some antimalarial activity was indicated.

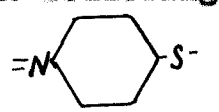
The fact that the sulfanilamide derivatives may have antimalarial activity and that the introduction of sulfur into organic molecules tends to reduce their toxicity has led many investigators to undertake the synthesis of sulfur-containing compounds. It will also be noticed in the next section that the chemistry of sulfur has played a major role in the treatment of tuberculosis. These facts have instigated the preparation of the sulfur-containing compounds which are reported here. The compounds were of such a character that they were tested as antimalarial agents and also for antituberculous activity.

Antituberculous Agents

Tuberculosis is perhaps one of the oldest diseases which man has sought to cure by chemotherapy. The use of gold in the treatment of tuberculosis dates back to the time of Paracelsus (1500 A.D.) and his so-called "elixir of life" which was composed of mercury and gold. The use of gold has received spasmodic attention since that time, but its toxic effect has never been completely overcome. The recent application of gold therapy has been to combine it with sulfur-containing molecules. Some of the compounds resulting from this work are: triphal (sodium aurothiobenzimidazolecarboxylate), sanocrysin (sodium aurothiosulfate), and lopion (sodium auroallylthioureabenzoate).

The non-toxic properties of dyes prompted their investigation as chemotherapeutic agents. In 1912 DeWitt[9] showed that methylene blue penetrated the tubercle bacillus *in vitro* and the tubercle in the living body. The exact value of methylene blue in the treatment of tuberculosis is not definite as many conflicting reports have been published. It is interesting to note, however, that in both tuberculosis and malaria, methylene blue has shown some activity.

The introduction of the theory of metabolite antagonists advanced by Woods and Fildes[10] led to the preparation of compounds structurally related to p-aminobenzoic acid. The theory embraces the principle that there is an essential growth factor for many bacteria and p-aminobenzoic acid may be this essential factor. The introduction of similarly constructed molecules may result in their assimilation by the bacteria. The non-essential characteristics of the substituted compounds would destroy the bacteria or at least materially weaken them so that they could be eliminated by the normal body defense mechanisms. The fact that the sulfanilamide drugs exhibited bacteriostasis prompted the investigation of thousands of derivatives. In all of these compounds the following group has been maintained:



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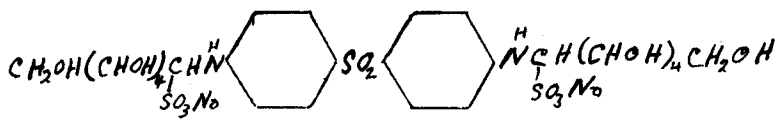
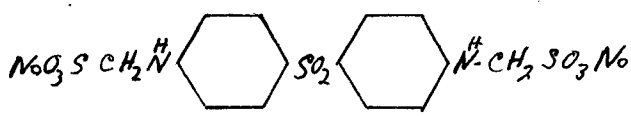
9. DeWitt, J. Infectious Diseases, 13, 378 (1913).
10. Woods and Fildes, Chemistry & Industry, 18, 133 (1940).

It is thought that this group represents the active part of the molecule. Corper, Cohn, and Bawer[11] have reviewed the use of sulfanilamides in tuberculosis up to 1939. One of the significant derivatives of this type is 4,4′-diaminodiphenyl sulfone. It is quite active, but it has the disadvantages of high toxicity and low solubility. Two derivatives of this compound have been made which reduce its toxicity and increase the water solubility without inhibiting the activity. These two compounds, promin[12] (VI) and diasone[13] (VII), have received



VI



VII

considerable attention, but a complete report of their therapeutic properties has not warranted their general application.

The synthesis of promizole, 4-aminophenyl 2′-amino-5′-thiazolyl sulfone (VIII), by Bambas[14] is the most recent antitubero-

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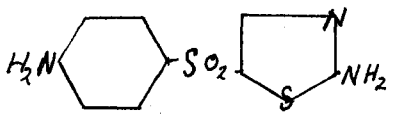
11. Corper, Cohn, and Bawer, Am. Rev. Tubero., 40, 452 (1939).
12. Feldman, Hinshaw, and Moses, Proc. Staff Meetings Mayo Clinic, 15, 695 (1940).
13. Raiziss, Science, 98, 350 (1943).
14. Bambas, J. Am. Chem. Soc., 67, 671 (1945).

ulous agent to receive widespread recognition. It is being used



VIII

clinically in the treatment of tuberculosis and has also shown possibilities as a cure in the treatment of leprosy.

Addition of Mercaptans to α,β-Unsaturated Ketones

The addition of mercaptans and aromatic thiols to α,β-unsaturated ketones has received considerable attention by research workers. The work was begun by Posner[15] in 1901. He condensed ethyl mercaptan with mesityl oxide $[(CH_3)_2C{=}CHCOCH_3]$, phorone $[(CH_3)_2C{=}CHCOCH{=}C(CH_3)_2]$, benzalacetone $[C_6H_5CH{=}CHCOCH_3]$, dibenzalacetone $[C_6H_5CH{=}CHCOCH{=}CHC_6H_5]$, benzalacetophenone $[C_6H_5CH{=}CHCOC_6H_5]$, and dypnone $[(C_6H_5)(CH_3)C{=}CHCOC_6H_5]$. The compounds obtained were oxidized with cold potassium permanganate to the sulfones for identification. In the case of mesityl oxide, benzalacetone, benzalacetophenone, and dypnone, three molecules of the mercaptan reacted, while with dibenzalacetone and phorone only two molecules of the mercaptan were taken up. The reactions were proposed as taking place in the following manner:

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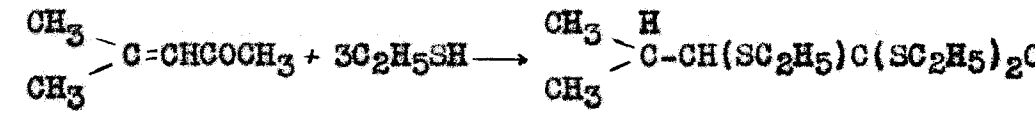
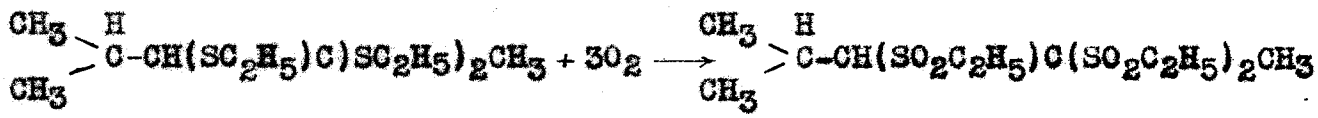
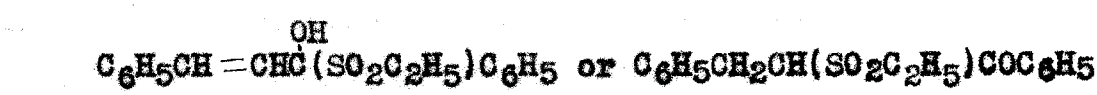
15. Posner, Ber., 34, 1395 (1901).



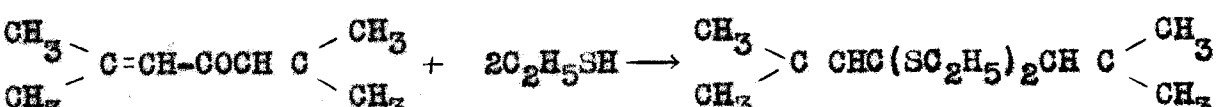


The suggested mechanism is that two molecules of the mercaptan react first with the oxygen of the carbonyl group to form the mercaptole, and the third molecule of the mercaptan reacts with the carbon-carbon double bond.

Posner[15] placed the mercapto group which added to the unsaturated linkage on the α-carbon atom with respect to the carbonyl group but stated that it might be on the β-carbon atom. The mercaptoles are somewhat unstable as shown by the oxidation of 1,1,2-triethylmercapto-1,3-diphenylpropane. In this case a single sulfone was obtained. The formula was postulated as being:



With respect to the diolefinic ketones, phorone and dibenzalacetone, only the formation of the mercaptole was thought to take place. The reaction is illustrated as follows:

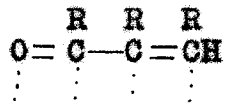


In the following year (1902) Posner[16] revised his work and postulated that the addition of the mercaptan to the double bond takes place first, with the mercapto group ending up on the β-carbon atom. He also stated that the compounds resulting from the addition of the mercaptan to the di-unsaturated compounds are not mercaptoles but compounds formed by adding the mercaptan to the unsaturated linkages. Thus the compound thought to be 4,4-dithioethyl-2,6-dimethylhepta-2,5-diene, $(CH_3)_2C{=}CHC(SC_2H_5)_2CH{=}C(CH_3)_2$, becomes 2,6-dimethyl-2,6-dithioethylheptan-4-one, $(CH_3)_2C(SC_2H_5)CH_2\overset{O}{C}CH_2C(SC_2H_5)(CH_3)_2$. The reactions were carried out in the presence of hydrogen chloride and sometimes with zinc chloride using ethanol or acetic acid as the solvent.

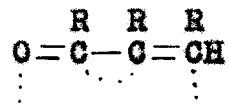
In 1904[17] the work was further revised, and the mechanism of the reaction was explained on the basis of Thiele's theory of partial valence.[18] According to this theory the unsaturated linkage is thought of as being made up of four valences which have united to form a double bond. However, two of the valences are mutually and completely saturated while the second pair is held together by only a fraction of the unit of affinity leaving a residue of affinity. This residue of free affinity was given the name "Partial Valency" by Thiele. When the unsaturated group becomes a part of a conjugated system, there arises

16. Posner, ibid., 35, 799 (1902).
17. Posner, ibid., 37, 502 (1904).
18. Henrich, "Theories of Organic Chemistry," John Wiley and Sons, Inc., New York, (1922), Chapter IV.

what is called an "inactive double bond". This is illustrated in the following manner. If figure IX represents a conjugated

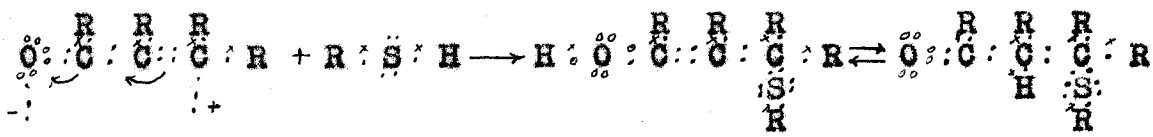


IX



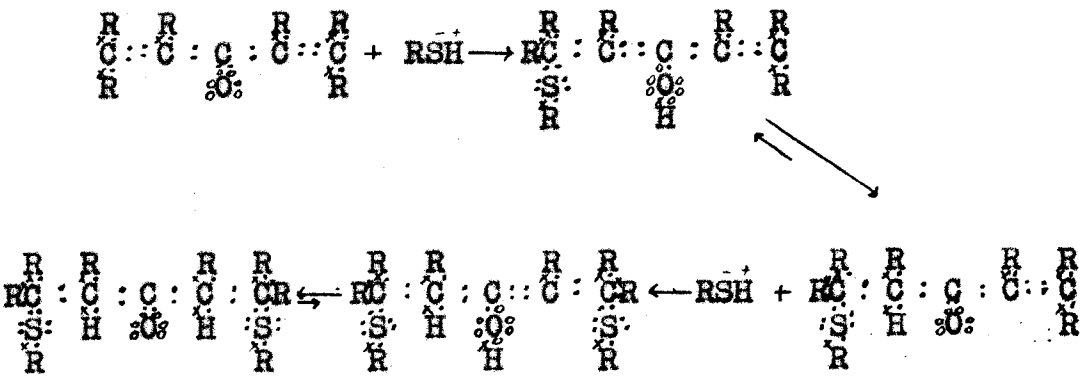
X

system then the dotted lines represent the partial valences. The behavior of this system can be explained by the fact that the partial valences on atoms 2 and 3 mutually saturate each other and give rise to the so-called "inactive double bond" represented by figure X. It is easy to see by this method why 1,4-addition takes place. With electronic formulae the addition of mercaptans to α,β-unsaturated ketones can be shown to take place in the following manner. In the intermediate state illustrated by formula XI, the electrons are shifted in the



XI

direction of the oxygen atom resulting in a loss of negativity about the β-carbon atom. The equilibrium is re-established by the attachment of the negative thiol residue to this position. By similar reasoning the method of addition to di-α,β-unsaturated ketones can be demonstrated.



Posner,[17] however, stated that he was also able to add two molecules of thiophenol to 1,5-diphenyl-2,4-pentadien-1-one to obtain the following product, $C_6H_5CH(SC_6H_5)CH_2CH(SC_6H_5)CH_2COC_6H_5$. In a continuation of the study on the combination of mercaptans and aromatic thiols with olefinic ketones, Ruhemann[19] has shown that only one molecule of the mercaptan adds to 1,5-diphenyl-2, 4-pentadien-1-one. It will be recalled that Posner[16] made his condensations in acid media. This was probably done in order to facilitate the reaction of the mercaptans with the carbonyl group to form sulfonals. In the work of Ruhemann,[19] basic conditions were employed to prevent this reaction. He found that either sodium ethoxide or piperidine could be used. In all cases the products obtained were the result of 1,4-addition. In the case of 1,5-diphenyl-2,4-pentadien-1-one he reports that the compound obtained by Posner[17] has the formula

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19. Ruhemann, J. Chem. Soc., 87, 17 (1905).

$C_6H_5CH{=}CHCH(SC_6H_5)CH_2COC_6H_5$. The position of the thiol group, however, was not determined, and it is possible from the mechanism already given that the formula could be $C_6H_5CH(SC_6H_5)CH{=}CH{-}CH_2COC_6H_5$. This would be the result of 1,6-addition. A further study by Ruhemann[20] on 6-phenyl-3,5-hexadien-2-one, 1,7-diphenyl-1,4,6-heptatrien-3-one, benzalacetophenone, and some cyclic unsaturated ketones, such as 1-phenyl-3-methyl-4-benzal-5-pyrazolone, has extended the evidence for 1,4-addition. He has also attempted the addition of thiophenol to methoxybenzoylphenylacetylene, $C_6H_5C{\equiv}C{-}COC_6H_4(OCH_3)$. The addition of one molecule of the thiophenol was successful, but the structure of the product was not proved.

Of particular interest is the work of Nicolet[21] on the reversibility of the addition of p-thiocresol to benzalacetophenone and benzalacetone. His investigations indicate that in the reaction shown below the equilibrium is shifted far to the

$$CH_3C_6H_4SH + C_6H_5CH{=}CHCOC_6H_5 \rightleftarrows C_6H_5\underset{SC_6H_4CH_3}{CHCH_2}COC_6H_5$$

left in the presence of base. In the case of β-(p-tolylmercapto) benzylacetophenone, $C_6H_5CH(SC_6H_4CH_3)CH_2COC_6H_5$, it was shown that in a solution of 0.1 molar in sodium hydroxide the lead salt of the p-thiocresol precipitated immediately at room temperature.

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20. Ruhemann, ibid., 87, 461 (1905).
21. Nicolet, J. Am. Chem. Soc., 53, 3066 (1931).

Furthermore, if the reaction was stopped after one minute by the addition of acetic acid, the decomposition was shown to be nearly quantitative. It was also observed that when β-(p-tolylmercapto) benzalacetophenone was warmed on a steam bath with phenylhydrazine in acetic acid a rapid formation of the sulfur-free 1,3,5-triphenylpyrazoline took place. These results would indicate that the reaction of mercaptans with similar α, β-unsaturated ketones might proceed equally as well in a neutral or acid medium. This was verified in a later study by Nicolet[22] in which he condensed thiophenol and p-thiocresol with benzalacetophenone directly to obtain the identical products reported earlier.[21] The yields were somewhat better, but the reaction time had to be lengthened slightly.

Cleavage of Unsymmetrical Epoxides

The data in the literature are somewhat ambiguous as to the exact products obtained in the cleavage of unsymmetrical epoxy compounds. In reactions involving the cleavage of unsymmetrical epoxides with ammonia, Krassuskii[23] has completed the following reactions:

$$CH_3CH\text{-}C(CH_3)_2 \;(\text{O bridge}) + NH_3 + H_2O \longrightarrow CH_3CH(NH_2)C(OH)(CH_3)_2$$

$$(CH_3)_2CHCH_2 \;(\text{O bridge}) + NH_3 + H_2O \longrightarrow (CH_3)_2C(OH)CH_2NH_2$$

22. Nicolet, ibid., 57, 1098 (1935).
23. Krassuskii, Compt. rend., 146, 236 (1908).

The structures of the compounds obtained were proved by preparing them in another manner. He made the generalization that the reaction of unsymmetrical epoxides with ammonia to form amino-alcohols results in the formation of compounds in which the hydroxyl group is attached to the carbon atom which in the original compound was associated with the lesser number of hydrogen atoms. This principle has been proved in a number of other cases. Levene and Walti[24] have shown that the reaction of ammonia and propylene oxide gives 1-amino-2-hydroxypropane. In a recent article by Castro and Noller[25] 1-phenyl-2,3-epoxypropane and ammonia were combined to give 1-amino-2-hydroxy-3-phenylpropane. The structure of the product was determined by the following synthesis:

$$C_6H_5CH_2CHO + CH_3NO_2 \longrightarrow C_6H_5CH_2CHOHCH_2NO_2 \longrightarrow C_6H_5CH_2CHOHCH_2NH_2$$

There are many reactions of this type with ammonia and alkyl amines,[26,27,28,29] in the literature but the structures of the products have not been proved.

Somewhat opposed to the consistent reaction of epoxides with ammonia and its derivatives is the situation regarding the addition of alcohols in acid or alkaline catalyzed reactions.

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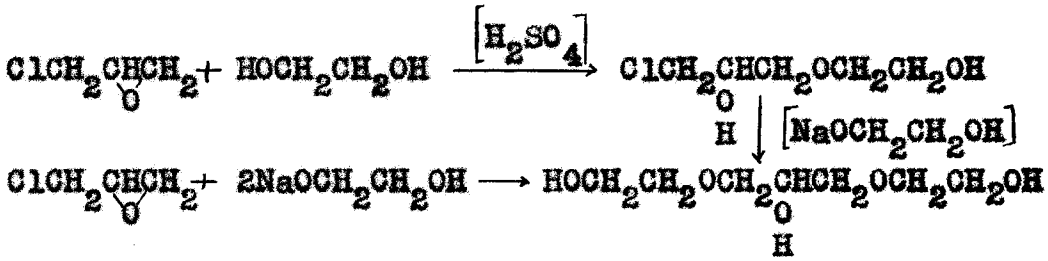
24. Levene and Walti, J. Biol. Chem., 7, 461 (1927).
25. Castro and Noller, J. Am. Chem. Soc., 68, 203 (1946).
26. Krasuskii and Pilyugin, Ukrain. Khem. Zhur. 5, Sci. Pt. 135-8 (1930) [C.A., 25, 2690 (1931)]; Krivonos, Ukrain. Khem. Zhur. 5, Sci. Pt., 141-6 (1930) [C.A., 25, 2690 (1931)].
27. Levy and Sfiras, Compt. rend., 191, 261 (1930).
28. Fourneau, J. pharm. chim., [7] 2, 109-17 (1910) [C.A., 5, 3798 (1911)].
29. Kitchen and Pollard, J. Org. Chem., 8, 342 (1943).

Kharasch and Nudenberg[30] have reported that the reaction of epichlorohydrin with ethylene glycol in either acid or alkaline medium results in the formation of a secondary alcohol. This was shown in the following series of reactions:



A similar study on the cleavage of styrene oxide has been undertaken by Emerson.[31] He reported that the cleavage of styrene oxide by ethyl and butyl alcohols in the presence of sulfuric or phosphoric acid gave 2-alkoxy-1-phenylethyl alcohols. Supposedly the same compounds were obtained when styrene chlorohydrin was reacted with the corresponding alcohols in the presence of potassium hydroxide. There seems to be little doubt but that, in the latter case, styrene oxide is a transitory intermediate.

In the reaction of anhydro-sugars of the ethylene oxide type, Peat[32] stated that cleavage by alkaline reagents results in the formation of both possible products. A number of illustrations of this type of reaction is given.

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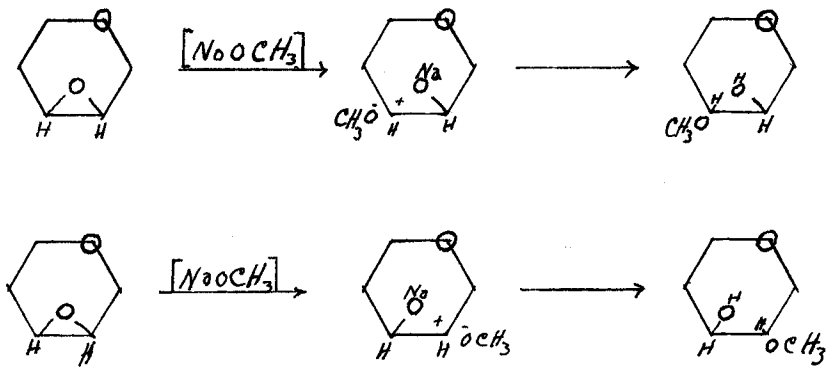
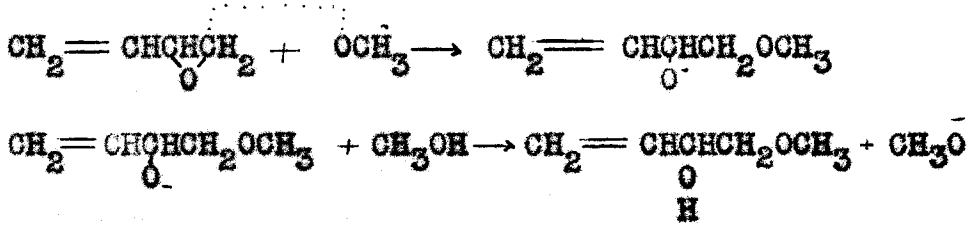
30. Kharasch and Nudenberg, ibid., 9, 189 (1943).
31. Emerson, J. Am. Chem. Soc., 67, 516 (1945).
32. Peat, Ann. Rept. Progress Chem., Chem. Soc., London, 36, 262-3 (1939).



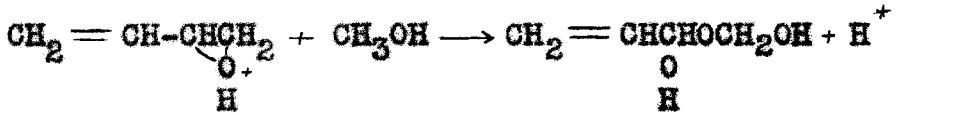
Recently Kadesch[33] made a thorough study of the reactions of 3,4-epoxy-1-butene with methanol in both acid and alkaline media. He showed that the reaction of 3,4-epoxy-1-butene with methanol in the presence of 0.5% sulfuric acid results in 2-methoxy-3-buten-1-ol. When the reaction was performed in methanol containing 1.0-1.5% of sodium, the expected 1-methoxy-2-buten-2-ol was obtained. This is in agreement with the investigations of Petrou.[34] The structures of the products obtained were completely identified.[33] The mechanism of the reaction in an alkaline medium as indicated by Kadesch is a bimolecular nucleophilic displacement on carbon.[32,35] This is shown by the kinetics[36] of epoxy ring cleavage and the occurrence of Walden inversion in a number of instances.[37] In the

33. Kadesch, J. Am. Chem. Soc., 68, 41 (1946).
34. Petrou, J. Gen. Chem. (U.S.S.R.), 8, 131 (1938) [C.A., 32, 4524, 5369 (1938)].
35. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N.Y., 1940, p. 301-303.
36. Bronsted, Kilpatrick, and Kilpatrick, J. Am. Chem. Soc., 51, 428 (1929).
37. Wilson and Lucas, ibid., 58, 2396 (1936); Winstein and Lucas, ibid., 61, 1576 (1939); Lucas and Gould, ibid., 63, 2541 (1941).

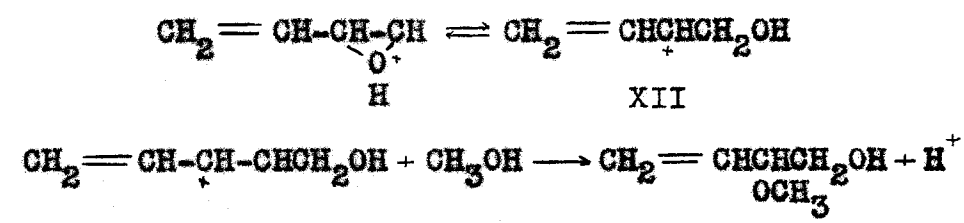
reaction of sodium methoxide with 3,4-epoxy-1-butene the nucleophilic reagent attacks the least substituted carbon atom which has the lowest electron density. The methoxide ion is then regenerated. This same type of reasoning could also



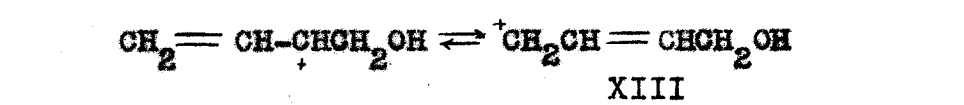
lead to the formation of the same compound in an acid-catalyzed



reaction, In view of the fact that the normal addition product was not obtained in the acid-catalyzed reaction, Kadesch has suggested that a unimolecular ring opening[38] takes place. The intermediate carbonium ion (XII) is stabilized by its



resonant structure (XIII). The existence of the carbonium ion



(XIII) would present the possibility of the formation of 1-methoxy-4-hydroxy-2-butene. This type of reaction has been

38. Winstein and Buckles, ibid., 64, 2780 (1942).

observed by Kadesch in the cleavage of 3,4-epoxy-1-butene with hydrochloric acid, in which some 1-chloro-4-hydroxy-2-butene was obtained.

The reactions of propylene oxide with alcohols have been investigated by Chitwood and Freure.[39] They found that the reaction of alcohols with propylene oxide in the presence of sulfuric acid (1.3%) led to the formation of both isomers in approximately equal amounts. A decrease in the acid concentration gave a higher percentage of the primary ether. In the absence of any catalysts similar mixtures were obtained. However, in the case of basic catalysis practically quantitative formation of the primary ethers was obtained.

The above evidence indicates that in reactions catalyzed by base the nucleophilic alkoxide ion attacks preferentially the carbon atom having the lower electron density. In additions involving no catalysts or in acid-catalyzed reactions the mechanism is not so clearly defined, showing that the medium and conditions required for reaction may have a more pronounced influence in these cases.

The reactions of unsymmetrical epoxides with mercaptans have not been studied extensively. Nenitzescu and Scarlatescu[40] have reported the addition of various alkyl mercaptans to epichlorohydrin. The following reactions were reported. The

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39. Chitwood and Freure, ibid., 68, 680 (1946).
40. Nenitzescu and Scarlatescu, Ber., 68, 587-91 (1944).

$$C_2H_5SH + CH_2\!\!\diagdown\!\!\diagup\!\!O\!\!\diagdown\!\!\diagup\!\!CHCH_2Cl \longrightarrow C_2H_5SCH_2\underset{\underset{H}{|}}{\underset{O}{\diagdown\diagup}}CHCH_2Cl$$

XIV

$$C_2H_5SK + CH_2\!\!\diagdown\!\!\diagup\!\!O\!\!\diagdown\!\!\diagup\!\!CHCH_2Cl \longrightarrow C_2H_5SCH_2\underset{O}{\diagdown\diagup}CHCH_2$$

XV

proof of the structure of compound (XV) was based on the fact that treatment of XIV with aqueous potassium hydroxide resulted in the formation of XV. Compound XV was then converted into

$$C_2H_5SCH_2\underset{\underset{H}{|}}{\underset{O}{\diagdown\diagup}}CHCH_2Cl \xrightarrow{[Aq.\ KOH]} C_2H_5SCH_2\underset{O}{\diagdown\diagup}CHCH_2$$

XV

2-hydroxy-3-diethylaminopropyl ethyl sulfide XVI by reacting it

$$C_2H_5SCH_2\underset{O}{\diagdown\diagup}CHCH_2 + (C_2H_5)_2NH \longrightarrow C_2H_5SCH_2\underset{\underset{H}{|}}{\underset{O}{\diagdown\diagup}}CHCH_2N(C_2H_5)_2$$

XVI

with diethylamine. The structures of the compounds were not proved so it is possible that isomeric compounds could have been formed. This possibility is illustrated below.

$$C_2H_5SH + CH_2\!\!\diagdown\!\!\diagup\!\!O\!\!\diagdown\!\!\diagup\!\!CHCH_2Cl \longrightarrow C_2H_5S\underset{CH_2OH}{\underset{|}{CH}}CH_2Cl \xrightarrow{[Aq.\ KOH]}$$

$$C_2H_5SK + CH_2CHCH_2Cl \longrightarrow C_2H_5S\underset{CH_2OK}{\underset{|}{CH}}CH_2Cl \longrightarrow C_2H_5S\underset{CH_2O}{\underset{|}{CH}}CH_2$$

A reaction similar to the reaction of potassium ethyl mercaptide and epichlorohydrin has been reported by Gilman and Woods[41] in which they treated epichlorohydrin with sodium β-diethylaminoethyl mercaptide and obtained β-diethylaminoethyl

41. Gilman and Woods, J. Am. Chem. Soc., 67, 1842 (1945).

2,3-epoxypropyl sulfide (XVII). The structure of this compound,

$$(C_2H_5)_2NCH_2CH_2SNa + \underset{O}{CH_2}\!\!\diagup\!\!\diagdown CHCH_2Cl \longrightarrow (C_2H_5)_2NCH_2CH_2SCH_2\underset{O}{CH}\!\!\diagup\!\!\diagdown CH_2$$

XVII

however, was not definitely established. Another example is provided by Fromm, Kapeller, and Taubmann[42] who combined epichlorohydrin and sodium benzyl mercaptide and assumed that the symmetrical 1,3-dibenzylmercapto-2-hydroxypropane was formed.

A definite proof of structure regarding the cleavage of unsymmetrical epoxides with mercaptides has not been demonstrated. The investigations reported in this dissertation will serve to clarify to a certain extent the mode of addition.

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42. Fromm, Kapeller, and Taubmann, Ber., 61, 1353 (1928).

III. EXPERIMENTAL

γ-Diethylaminopropyl Isothiouronium Chloride Hydrochloride.

γ-Diethylaminopropyl chloride was prepared according to the method of Gilman and Shirley.[43] To a solution of 200 g. (1.37 moles) of γ-diethylaminopropyl alcohol in 700 ml. of chloroform cooled in an ice bath was added 324 g. (2.74 moles) of thionyl chloride. After the addition was completed the solution was refluxed for one hour. The chloroform and excess thionyl chloride were distilled off under reduced pressure. To the residue was added absolute ethanol which was then distilled off leaving a crystalline residue of γ-diethylaminopropyl chloride hydrochloride. The residue was dissolved in 500 ml. of 95% ethanol and added to a suspension of 114.5 g. (1.45 moles) of thiourea in 300 ml. of 95% ethanol. The solution was heated for six hours and cooled. To the solution was added 365 ml. of ligroin (boiling point 60-68°) and 1450 ml. of ethyl acetate. The product, however, did not crystallize out on cooling. The solvents were removed and the residue crystallized from absolute ethanol and ether to give 322 g. (90%) of product which melted at 128-30°.

Anal. Calcd. for $C_8H_{21}N_3Cl_2S$: S, 12.21. Found: S, 12.03 and 12.07.

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

γ-Diethylaminopropyl Mercaptan.

The γ-diethylaminopropyl mercaptan used in these experiments was prepared by the method described by Gilman and coworkers[44] or from the isothiouronium salt as given here. The yields from the isothiouronium method were more consistent and the product was of a better quality than that prepared by the sodium hydrosulfide method.

To 312 g. (1.18 moles) of crude γ-diethylaminopropyl isothiouronium chloride hydrochloride dissolved in 330 ml. of warm water was added 67 g. of sodium hydroxide dissolved in 250 ml. of water. The solution was stirred for twenty minutes and saturated with sodium chloride. The suspended oil was extracted with ether and dried over sodium sulfate. The ether was evaporated and the residue distilled to give 76 g. (44%) of product distilling at 87°/27 mm.; n_D^{20} 1.4670. The yield in this conversion is considerably increased when the pure isothiouronium complex is used.

β-(2-Diethylaminoethylmercapto)-β-phenylpropiophenone Hydrochloride.

A suspension of 3.0 g. (0.0144 mole) of chalcone and 2.44 g. (0.0144 mole) of β-diethylaminoethyl mercaptan hydrochloride[44] in 10 ml. of benzene was refluxed for eight hours. The benzene was distilled off and the residue was taken up in a small amount

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44. Gilman, Plunkett, Tolman, Fullhart, and Broadbent, J. Am. Chem. Soc., 67, 1845 (1945).

of absolute ethanol and petroleum ether (boiling point 60-68°) added until precipitation began. The yield of crystalline product was 5 g. (92%) melting at 113-15°.

Anal. Calcd. for $C_{21}H_{28}ONClS$: N, 3.71; S, 8.48. Found: N, 3.67 and 3.76; S, 8.44 and 8.44.

Several attempts were made to initiate the reaction between the mercaptan and the chalcone in alkaline media. To β-diethylaminoethyl mercaptan and chalcone was added either a solution of sodium methoxide (10 ml.) or 4-5 drops of piperidine. From all of these reactions only starting materials were obtained. An attempt will be made to explain this apparent inactivity in the discussion.

β-(3-Diethylaminopropylmercapto)-β-phenylpropiophenone Methiodide.

γ-Diethylaminopropyl mercaptan hydrochloride, 2.64 g. (0.0144 mole), was condensed with chalcone, 3 g. (0.0144 mole), in benzene to give a very hygroscopic product which was not easily crystallized. The material was washed with sodium bicarbonate and extracted with ether. The ether was removed and the residual oil was refluxed in methyl iodide for one hour and allowed to cool in the refrigerator overnight. The crystalline product which precipitated, 1 g. (17%), was separated, melting point 111-12°. Recrystallization from a solution of absolute ethanol and ethyl acetate gave a melting point of 112-13°.

Anal. Calcd. for $C_{23}H_{32}ONIS$: N, 3.01. Found: N, 2.90.

4-Dimethylamino-4′-methoxychalcone.

To a solution of 14.9 g. (0.1 mole) of p-dimethylamino-benzaldehyde and 15 g. (0.1 mole) of p-methoxyacetophenone in 40 ml. of absolute ethanol was added a solution of sodium ethoxide prepared from 1 g. of sodium in 10 ml. of absolute ethanol. The solution was warmed and allowed to crystallize. The crude yield was 24 g. (80%). Recrystallization from ethyl acetate gave the pure compound, 22.2 g. (74%), melting at 127°. Pfeiffer[45] reports a melting point of 127° and a yield of 40%.

4-Dimethylamino-4′-chlorochalcone.

To a solution of 14.9 g. (0.1 mole) of p-dimethylamino-benzaldehyde and 15.4 g. (0.1 mole) of p-chloroacetophenone in 40 ml. of absolute ethanol was added a solution of sodium ethoxide prepared from 1 g. of sodium in 10 ml. of absolute ethanol. The crude yield was 28.5 g. (94%). Recrystallization from ethyl acetate gave the pure compound, 20 g. (66%), melting at 140-1°. Pfeiffer and Kleu[46] report a melting point of 140-140.5° but give no yield.

p-Methoxy-β-(2-diethylaminoethylmercapto)-β-(p-dimethyl-aminophenyl)propiophenone Hydrochloride.

A mixture of 3 g. (0.017 mole) of 4-dimethylamino-4-methoxy-chalcone and 2.44 g. (0.0144 mole) of β-diethylaminoethyl

45. Pfeiffer, Ann., 441, 253 (1925).
46. Pfeiffer and Kleu, Ber., 66, 1704 (1933).

mercaptan hydrochloride in 15 ml. of absolute ethanol was refluxed for thirty hours. The solution was concentrated and the crystalline residue filtered and washed with ethyl acetate. The yield was 4.2 g. (87.5%), melting point 145-6°.

Anal. Calcd. for $C_{24}H_{35}O_2N_2ClS$: N, 6.22. Found: N, 6.28.

p-Chloro-β-(2-diethylaminoethylmercapto)-β-(p-dimethylaminophenyl)propiophenone Hydrochloride.

The preparation was the same as that given above. The yield from 6.0 g. (0.02 mole) of 4-dimethylamino-4'-chlorochalcone and 4.0 g. (0.0236 mole) of β-diethylaminoethyl mercaptan hydrochloride was 7 g. (71%), melting at 130-2°. Several recrystallizations from an ethyl acetate-ethanol mixture raised the melting point to 142-3°.

Anal. Calcd. for $C_{23}H_{32}ON_2Cl_2S$: N, 6.16. Found: N, 6.14.

4-Dimethylamino-4'-acetaminochalcone.

To 17.3 g. (0.098 mole) of p-acetaminoacetophenone and 14.5 g. (0.098 mole) of p-dimethylaminobenzaldehyde in 100 ml. of absolute ethanol was added a solution of sodium methoxide prepared from 1 g. of sodium in 10 ml. of methanol. The solution was allowed to stand for several hours. The crystalline precipitate was filtered and recrystallized from ethanol to give 25 g. (79%) of product melting at 202-3°.

Anal. Calcd. for $C_{19}H_{20}O_2N_2$: N, 9.09. Found: N, 9.12.

p-Acetamino-β-(2-diethylaminoethylmercapto)-β-(p-dimethylaminophenyl)propiophenone Hydrochloride.

The preparation was made by refluxing 6.0 g. (0.0195 mole) of 4-dimethylamino-4'-acetaminochalcone and 4.0 g. (0.0236 mole) of β-diethylaminoethyl mercaptan hydrochloride in absolute ethanol for twenty-one hours. The solvent was removed to give a crude yield of 8.5 g. (87%). The pure compound melted at 153-4° after several recrystallizations from a mixture of absolute ethanol, ethyl acetate, and ether.

Anal. Calcd. for $C_{25}H_{36}O_2N_3ClS$: N, 8.98. Found: N, 8.75.

2-Chloro-4'-acetaminochalcone.

To a solution of 17.7 g. (0.1 mole) of p-acetaminoacetophenone and 14.0 g. (0.1 mole) of o-chlorobenzaldehyde in ethanol was added a solution of sodium methoxide prepared from 1 g. of sodium and 10 ml. of methanol. On standing the product crystallized to give 21.3 g. (69%), melting at 167°. Recrystallization from ethanol did not change the melting point.

Anal. Calcd. for $C_{17}H_{14}O_2NCl$: N, 4.68. Found: N, 4.97.

p-Acetamino-β-(p-tolylmercapto)-β-(o-chlorophenyl)propiophenone.

To a solution of 6.26 g. (0.02 mole) of 2-chloro-4'-acetaminochalcone and 2.48 g. (0.02 mole) of p-thiocresol in ethanol was added 2 drops of piperidine. The solution was warmed

and set aside to crystallize. The yield of pure compound after crystallization from ethanol was 7.5 g. (85%) melting at 148-9°.

Anal. Calcd. for $C_{24}H_{22}O_2NClS$: N, 3.32. Found: N, 3.57.

4-Methoxy-4'-acetaminochalcone.

To a solution of 17.7 g. (0.1 mole) of p-acetaminoacetophenone and 13.7 g. (0.1 mole) of p-methoxybenzaldehyde in ethanol was added a solution of sodium ethoxide prepared from 1 g. of sodium in 10 ml. of absolute ethanol. The yield of product melting at 199-200° was 20 g. (64.5%). Recrystallization from 95% ethanol gave a melting point of 200-1°. Dilthey and co-workers[47] report a melting point of 198° by a preparation in another manner.

p-Acetamino-β-(p-tolylmercapto)-β-(p-methoxyphenyl)propiophenone.

A solution of 4.19 g. (0.01 mole) of 4-methoxy-4'-acetaminochalcone and 1.24 g. (0.01 mole) of p-thiocresol was heated in ethanol for ten minutes and allowed to cool. The yield of pure product was 5 g. (91%) melting at 130-1° after recrystallization from ethanol.

Anal. Calcd. for $C_{25}H_{25}O_3NS$: N, 3.34. Found: N, 3.35.

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47. Dilthey, Neuhaus, Reis, and Schommer, J. prakt. Chem., 124, 81 (1930).

Methyl β-Phenyl-β-hydroxyethyl Sulfide.

In a reaction flask, equipped with a stirrer and a reflux condenser, and cooled in an ice-salt bath, was placed 33 g. (0.5 mole) of 85% potassium hydroxide, 25 g. (0.52 mole) of methyl mercaptan, and 57.6 g. (0.48 mole) of styrene oxide. The suspension was stirred and the condenser was closed off to give a closed system. The ice bath was removed and the temperature of the solution allowed to rise gradually. An exothermic reaction took place very rapidly, the flask becoming quite hot and the solution turning a dark red. The reaction mixture was cooled immediately and diluted with water. The solution was acidified with glacial acetic acid and extracted with ether to give 17.3 g. (22%) of product distilling at 127°/0.8 mm.; n_D^{20} 1.5690; d_{20}^{20} 1.1082; MR 49.38 (calcd.), 49.67 (obs.). A like amount of forerun was obtained. The main fraction was redistilled but the constants were not changed. Prelog[48] and co-workers gave the boiling point of methyl β-phenyl-β-hydroxyethyl sulfide as 141-2°/12 mm.

Methyl β-Phenyl-β-hydroxyethyl Sulfide Methiodide.

A solution of 1 g. of methyl β-phenyl-β-hydroxyethyl sulfide and 5 ml. of methyl iodide in 5 ml. of methanol was refluxed

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48. Prelog, Hahn, Brauchli, and Beyerman, Helv. Chim. Acta, 27, 1209-24 (1944) [C.A., 40, 848 (1946)].

for six hours. The solution was concentrated and ether added to incipient precipitation. The white crystalline precipitate was filtered and dried and had a melting point of 131-3°. Reprecipitation from absolute ethanol and ether gave the pure product melting at 138-9° (decomp.). Prelog[48] and co-workers reported the methiodide as melting with decomposition at 132.5-3.5°.

Anal. Calcd. for $C_{10}H_{15}OIS$: I, 40.92; S, 10.30. Found: I, 41.15; S, 10.47.

Methyl Phenacyl Sulfide.

Into a solution of absolute ethanol containing 0.5 mole of sodium ethoxide was bubbled 25 g. (0.52 mole) of methyl mercaptan. The reaction mixture was cooled in an ice bath during the addition of the mercaptan. The ice bath was removed and 99 g. (0.5 mole) phenacyl bromide in 200 ml. of absolute ethanol was added. The solution was refluxed for two hours, cooled, and the precipitated salt filtered. The filtrate was concentrated and extracted with ether. The ether was dried and distilled to give 52 g. (62%) of product distilling at 130-2°/0.8 mm.; n_D^{20} 1.5794; d_{20}^{20} 1.1356; MR 47.86 (calcd.), 48.61 (obs.). Prelog and co-workers (loc. cit.) reported a boiling point of 94-6°/3 mm.

Methyl Phenacyl Sulfide 2,4-Dinitrophenylhydrazone.

The 2,4-dinitrophenylhydrazone was prepared according to

the method given by Shriner and Fuson[49] and melted at 164-5.5° after several recrystallizations from 95% ethanol and acetone.

Anal. Calcd. for $C_{15}H_{14}O_5N_4S$: N, 16.17. Found: N, 16.40.

Methyl β-Phenyl-β-hydroxyethyl Sulfide.

A suspension of 20 g. (0.12 mole) of phenacyl methyl sulfide and 24.6 g. (0.12 mole) of aluminum isopropoxide and 175 ml. of dry isopropyl alcohol was distilled at a rate of 20 ml. per hour. The distillation was continued until no acetone could be detected in the distillate, approximately five hours. The suspension was cooled and poured into dilute hydrochloric acid and extracted with ether. The ether was distilled to give 5.5 g. (25%) of product distilling at 115°/0.6 mm.; n_D^{20} 1.5676. The methiodide of this material melted at 138-9° after recrystallization from an absolute ethanol-ether solution. A mixed melting point with the methiodide obtained by the condensation of styrene oxide and methyl mercaptan in the presence of potassium hydroxide was not depressed.

γ-Diethylaminopropyl Phenacyl Sulfide.

To a 0.1 mole solution of sodium ethoxide was added 14.7 g. (0.1 mole) of γ-diethylaminopropyl mercaptan in absolute ethanol. To this solution was added 19.9 g. (0.1 mole) of phenacyl bromide in absolute ethanol. The reaction mixture was

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49. Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N.Y., (1940) p. 143.

refluxed under nitrogen for two hours and cooled. The suspended salt was filtered, and the filtrate was concentrated under reduced pressure and extracted with ether. The ether extract was dried and distilled to give 16 g. (62%) of product distilling at 158-60°/0.8 mm.; n_D^{20} 1.5240; d_{20}^{20} 1.0027; MR 79.79 (calcd.), 81.02 (obs.). In another preparation the following constants were obtained: boiling point 157-61°/1 mm.; n_D^{20} 1.5226.

Anal. Calcd. for $C_{15}H_{23}ONS$: N, 5.28. Found: N, 5.62.

γ-Diethylaminopropyl Phenacyl Sulfide 2,4-Dinitrophenylhydrazone.

The 2,4-dinitrophenylhydrazone was prepared by the usual method[49] to give a melting point of 183-4° after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{21}H_{30}O_8N_5S$: N, 14.90. Found: N, 14.80.

γ-Diethylaminopropyl β-Phenyl-β-hydroxyethyl Sulfide.

To a solution of 10 g. (0.0378 mole) of β-diethylaminopropyl phenacyl sulfide in 100 ml. of dry isopropyl alcohol was added 15.4 g. (0.0756 mole) of aluminum isopropoxide. The mixture was slowly distilled and tests were made periodically of the distillate for the presence of acetone by testing with 2,4-dinitrophenylhydrazine. A negative test was obtained after two hours. The reaction mixture was poured into dilute hydrochloric acid. The solution was extracted with ether and dried. The ether solution distilled to give three fractions:

(1) boiling point 168°/1.5 mm.; n_D^{20} 1.5413; 2 g. (2) boiling point 168-70°/1.5 mm.; n_D^{20} 1.5218; 3 g. (3) boiling point 174-5°/1.5 mm.; n_D^{20} 1.5380; 3 g. The reduction product was fraction #3.

γ-Diethylaminopropyl β-Phenyl-β-hydroxyethyl Sulfide.

To a boiling solution of 15.8 g. (0.107 mole) of γ-diethylaminopropyl mercaptan and 5.6 g. (0.1 mole) of potassium hydroxide was added 8.4 g. (0.07 mole) of styrene oxide. The solution was heated for thirty minutes and diluted with water. The solution was acidified with 6 g. of glacial acetic acid and extracted with benzene. The benzene was dried over sodium sulfate and distilled. The residue distilled at 149-52°/0.5 mm. to give 9.5 g. (50.5%); n_D^{20} 1.5363; d_{20}^{20} 1.0122; MR 81.49 (calcd.), 82.24 (obs.).

Anal. Calcd. for $C_{15}H_{25}ONS$: N, 5.24. Found: N, 5.44.

Styrene Chlorohydrin.

A suspension of 30.9 g. (0.2 mole) of phenacyl chloride and 40.8 g. (0.2 mole) of aluminum isopropoxide in 150 ml. of isopropyl alcohol was slowly distilled. The distillate was tested periodically with 2,4-dinitrophenylhydrazine for the presence of acetone. After three and one-half hours the tests were negative. The solution was poured into dilute hydrochloric acid and extracted with benzene. The benzene was dried and distilled to give 26.5 g. (86%) of product boiling at 144°/36 mm.;

n_D^{20} 1.5510. Emerson[31] reports the boiling point as 118-21°/14 mm.; n_D^{25} 1.5520-1.5538; and a yield of 76%.

β-Diethylaminoethyl β-Phenyl-β'-hydroxyethyl Sulfide.

To a solution of 0.1 molar sodium ethoxide was added 13.3 g. (0.1 mole) of β-diethylaminoethyl mercaptan in 25 ml. of absolute ethanol. To this solution was added 15.6 g. (0.1 mole) of styrene chlorohydrin in 25 ml. of absolute ethanol. The solution was refluxed for one hour in an atmosphere of nitrogen. The solution was cooled and the precipitated salt filtered. The filtrate was distilled to give 19.5 g. (78%) of product distilling at 152-5°/1.5 mm.; n_D^{20} 1.5425.

β-Diethylaminoethyl β'-Phenyl-β'-hydroxyethyl Sulfide.

To a solution of 30 g. (0.225 mole) of β-diethylaminoethyl mercaptan and 11.2 g. (0.2 mole) of potassium hydroxide was added 21.6 g. (0.18 mole) of styrene oxide. The solution was heated for fifteen minutes and diluted with water. The solution was acidified with 12 g. (0.2 mole) of glacial acetic acid and the solution extracted with benzene. The benzene was dried over sodium sulfate and distilled. The product distilled between 125-55°/0.5 mm. Redistillation gave 9 g. (20%) of pure product distilling at 132°/0.5 mm.; n_D^{20} 1.5423; d_{20}^{20} 1.0175; MR 76.87 (calcd.), 78.18 (obs.).

Anal. Calcd. for $C_{14}H_{23}ONS$: N, 5.54. Found: N, 5.56 and 5.65.

γ(β-Diethylaminoethylmercapto)propyl β'-Phenyl-β'-hydroxyethyl Ether.

To a solution of 43 g. (0.225 mole) of β-diethylaminoethyl γ-hydroxypropyl sulfide and 11.2 g. (0.2 mole) of potassium hydroxide was added 21.6 g. (0.18 mole) of styrene oxide. The solution was refluxed for one hour and poured into water. The solution was acidified with 12 g. (0.2 mole) glacial acetic acid and extracted with benzene. The benzene was dried and distilled to give 10 g. (15%) of product distilling at 160-74°/0.6 mm. Redistillation gave the pure compound distilling at 180-2°/1.5 mm.; n_D^{20} 1.5448. The compound has a tendency to distil in a direct ratio with the bath temperature; that is, by increasing the bath temperature the boiling point would rise.

Anal. Calcd. for $C_{17}H_{29}O_2NS$: N, 4.50. Found: N, 4.35.

3-Diethylamino-1,2-epoxypropane.[50]

In a 3 liter, three-necked flask, equipped with a stirrer, dropping funnel, and thermometer was placed 556 g. (6.0 moles) of epichlorohydrin, 432 g. (5.9 moles) of diethylamine, and 18 g. (1.0 mole) of water. The solution was stirred for six hours at a temperature of 28-30°. The temperature was then

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50. This compound was prepared by a modification of a procedure submitted in a N.D.R.C. report from the Laboratory of Columbia University, New York, New York. The compound has also been prepared by Drazdov and Cherntov, J. Gen. Chem. (U.S.S.R.), 4, 969 (1934) [C.A., 29, 2148 (1935)] and Eisleb, U.S. Patent 1,845,403 (1932) [C.A., 26, 2199 (1932)].

lowered to 22° and 280 g. (7.0 moles) of sodium hydroxide in 456 ml. of water was added keeping the temperature below 25°. The solution was stirred for forty minutes; a yellow layer separated out during this time. The yellow layer was separated and the water layer extracted with ether. The ether extracts and the original layer were combined and dried over potassium hydroxide. The ether was decanted and distilled to give 430 g. (56.5%) of product distilling at 69°/32 mm.; n_D^{20} 1.4362.

γ-Diethylaminopropyl γ'-Diethylamino-β'-hydroxypropyl Sulfide.

To a solution of 12.9 g. (0.1 mole) of 3-diethylamino-1, 2-epoxypropane in approximately 40 ml. of benzene was added 14.7 g. (0.1 mole) of γ-diethylaminopropyl mercaptan in approximately 200 ml. of toluene which contained 2.3 g. (0.1 g. atom) of sodium. The solution was refluxed for sixteen hours in a nitrogen atmosphere. The solution was extracted with dilute base; the benzene layer was separated, dried, and distilled. The product, 15 g. (54%), distilled at 131-4°/0.5 mm.; n_D^{20} 1.4830; d_{20}^{20} 0.9431; MR 84.57 (calcd.), 83.85 (obs.).

Anal. Calcd. for $C_{14}H_{32}ON_2S$: N, 10.14; S, 11.57. Found: N, 10.05; S, 11.40.

β-Diethylaminoethyl γ'-Diethylamino-β'-hydroxypropyl Sulfide.

To a solution of 10 g. (0.075 mole) of β-diethylaminoethyl mercaptan and 1.73 g. (0.075 g. atom) of sodium in toluene

was added 9.7 g. (0.075 mole) of 3-diethylamino-1,2-epoxypropane. The reaction mixture was refluxed for eight hours, cooled, and extracted with dilute base. The toluene layer was separated, dried, and distilled to give 11 g. (57%) of product boiling at 121-2°/0.8 mm.; n_D^{20} 1.4850.

Anal. Calcd. for $C_{13}H_{30}ON_2S$: N, 10.69. Found: N, 10.50.

Thiophenol.

In a 500 ml. three-necked flask, equipped with a stirrer, reflux condenser, and dropping funnel swept out with nitrogen, was placed 60 ml. of dry ether and 2.8 g. (0.4 g. atom) of lithium. To this was added a solution of 31.4 g. (0.2 mole) of bromobenzene in 65 ml. of ether. The solution was refluxed for one hour after the addition had been completed. The solution was filtered under nitrogen into a three-necked flask equipped as before. A titration of the organometallic compound showed a yield of 97% of phenyllithium. The titration was made by hydrolyzing a known volume of the organometallic compound with water and titrating it with standard acid. To this solution was added 6.25 g. (0.195 g. atom) of sulfur. The addition was made cautiously as the reaction was exothermic and instantaneous. When all of the sulfur had been added a color test (No. 1)[51] for the presence of an organometallic compound was negative. To the solution was then added dilute hydrochloric acid and the ether layer was separated and dried. On distillation there was

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

obtained 13 g. (62%) of thiophenol distilling at 68°/20 mm.; n_D^{20} 1.5885. Approximately 3 g. of material distilled at 115-21°/0.5 mm., which later solidified. This is probably the disulfide.

γ-Diethylamino-β-hydroxypropyl Phenyl Sulfide.

In a 500 ml. three-necked flask equipped with a stirrer, reflux condenser, and dropping funnel was prepared 0.2 mole of phenyllithium as above. To the ether solution under nitrogen was added 6.25 g. (0.195 g. atom) of sulfur. The reaction was spontaneous and complete as shown by a negative color test (No. 1)[51] for an organometallic compound. To this reaction mixture was added a solution of 23.2 g. (0.18 mole) of 3-diethylamino-1,2-epoxypropane in dry ether. The solution was added slowly as the reaction was exothermic. The reaction mixture was refluxed overnight and hydrolyzed with water. The ether was separated and dried. On distillation there was obtained 25 g. (58%) of product boiling at 124-30°/0.5 mm.; n_D^{20} 1.5452.

This compound was also prepared by reacting the sodium salt of thiophenol with the 3-diethylamino-1,2-epoxypropane in a dry benzene solution. The yield of product distilling at 125-8°/0.5 mm. was 56%.

Anal. Calcd. for $C_{13}H_{21}ONS$: N, 5.85. Found: N, 5.88.

p-Dimethylaminothiophenol.

In a 1-liter three-necked flask, equipped with stirrer, reflux condenser, and dropping funnel which had been swept out

with nitrogen, was placed 80 ml. of anhydrous ether and 2.8 g. (0.5 g. atom) of lithium. To this suspension was added 40 g. (0.2 mole) of p-bromodimethylaniline in 120 ml. of dry ether. The solution was heated for one hour following the addition of the p-bromodimethylaniline. To this solution was then added portion-wise 6.4 g. (0.2 g. atom) of sulfur. The reaction was instantaneous and exothermic and a precipitate formed. When the addition of the sulfur was complete the suspension was hydrolyzed with the theoretical amount of dilute hydrochloric acid. The ether layer was separated and dried. On distillation there was obtained 15 g. (50%) of product distilling at 122°/2 mm. The boiling point reported by Leuckart[52] is 259-60°.

γ-Diethylamino-β-hydroxypropyl p-Dimethylaminophenyl Sulfide.

To a solution of 11.4 g. (0.075 mole) of p-dimethylamino-thiophenol and 1.72 g. (0.075 g. atom) of sodium in toluene was added 9.7 g. (0.075 mole) of 3-diethylamino-1,2-epoxypropane. The reaction mixture was refluxed for five hours under a nitrogen atmosphere. The toluene solution was extracted with dilute base. The toluene layer was dried and distillation was attempted. The compound began to decompose at 180° under a reduced pressure of 0.5 mm. The product was then distilled under hy-vacuum to give 11 g. (52%) distilling at 145-7°/0.001 mm.; n_D^{20} 1.5680.

Anal. Calcd. for $C_{15}H_{20}ON_2S$: N, 9.93. Found: N, 9.96.

52. Leuckart, J. prakt. Chem., [2] 41, 208 (1890).

γ-Diethylamino-β-hydroxypropyl p-Tolyl Sulfide.

To a solution of 12.4 g. (0.1 mole) of p-thiocresol and 2.3 g. (0.1 g. atom) of sodium in toluene was added 12.9 g. (0.1 mole) 3-diethylamino-1,2-epoxypropane. This solution was refluxed for eight hours under a nitrogen atmosphere. The toluene was extracted with dilute base after which the toluene layer was dried and distilled. Distillation yielded 15.5 g. (65%) of product distilling at 137°/0.8 mm.; n_D^{20} 1.5412.

Anal. Calcd. for $C_{14}H_{23}ONS$: N, 5.53. Found: N, 5.65

γ-Diethylamino-β-hydroxypropyl p-Aminophenyl Sulfide.

To a solution of 12.4 g. (0.1 mole) of p-aminothiophenol in toluene was added 2.3 g. (0.1 g. atom) of sodium. The solution was refluxed under nitrogen and 12.9 g. (0.1 mole) of 3-diethylamino-1,2-epoxypropane was added. The solution was refluxed for twelve hours and diluted with water. The toluene layer was separated, dried, and distilled. The product distilled at 153°/1 mm. to give 13.5 g. (53.5%); n_D^{20} 1.5763.

Anal. Calcd. for $C_{13}H_{22}ON_2S$: N, 11.02. Found: N, 11.04.

γ-Diethylamino-β-hydroxypropyl p-Chlorophenyl Sulfide.

To a solution of 1.27 g. (0.055 g. atom) of sodium and 8 g. (0.055 mole) of p-chlorothiophenol in toluene was added 7.25 g. (0.055 mole) of 3-diethylamino-1,2-epoxypropane. The solution was refluxed for six hours and diluted with water. The toluene layer was separated and dried over sodium sulfate. Distillation of the toluene extract yielded 3.5 g. (23%) of product

distilling at 149-52°/1.5 mm.; n_D^{20} 1.5517.

Anal. Calcd. for $C_{13}H_{20}ONClS$: N, 5.13. Found: N, 5.29.

γ-Diethylamino-β-hydroxypropyl p-Tolyl Sulfone.

A suspension of 17.9 g. (0.1 mole) of sodium p-toluenesulfinate and 12.9 g. (0.1 mole) of 3-diethylamino-1,2-epoxypropane in toluene was refluxed under a nitrogen atmosphere for twelve hours. The solution was diluted with water and the toluene layer separated. The toluene was dried and distilled to give 5 g. (17.5%) of product distilling at 217°/1 mm., and melting at 65-7°.

Anal. Calcd. for $C_{14}H_{23}O_3NS$: N, 4.92. Found: N, 5.12.

p-Aminophenyl β-Phenyl-β-hydroxyethyl Sulfide.

To a suspension of 2.48 g. (0.108 g. atom) of sodium and 13.5 g. (0.108 mole) of p-aminothiophenol in toluene was added 12 g. (0.1 mole) of styrene oxide in toluene. The solution was refluxed under an atmosphere of nitrogen for three hours and diluted with water. The toluene layer was separated, dried, and distilled. Attempts at distillation of the product under a reduced pressure of 1 mm. resulted in decomposition. The product was finally distilled at 185°/0.001 mm. to give 17 g. (68%).

Anal. Calcd. for $C_{14}H_{15}ONS$: N, 5.72. Found: N, 5.60.

γ-Diethylaminopropyl β-Hydroxy-Δ^3-butenyl Sulfide.

To a solution of 3.13 g. (0.136 g. atom) of sodium and

20 g. (0.136 mole) of γ-diethylaminopropyl mercaptan in toluene was added 9.5 g. (0.136 mole) of 3,4-epoxy-1-butene. The solution was refluxed for eight hours and diluted with water. The toluene layer was separated and dried over sodium sulfate and distilled. The yield of pure product was 18 g. (62%) distilling at 123°/0.8 mm.; n_D^{20} 1.5028; d_{20}^{20} 0.9865; MR 66.22 (calcd.), 65.97 (obs.).

Anal. Calcd. for $C_{11}H_{23}ONS$: N, 6.45. Found: N, 6.64.

β-Diethylaminoethyl β'-Hydroxy-Δ^3-butenyl Sulfide.

To a solution of 3.5 g. (0.15 g. atom) of sodium and 20 g. (0.15 mole) of β-diethylaminoethyl mercaptan in dry benzene was added a solution of 10.5 g. (0.15 mole) of 3,4-epoxy-1-butene in dry benzene. The solution was refluxed under a nitrogen atmosphere for twelve hours and diluted with water. The benzene layer was separated, dried, and distilled to give 26.5 g. (87%) of product distilling at 111°/1.5 mm.; n_D^{20} 1.5044; d_{20}^{20} 0.9829; MR 61.20 (calcd.), 61.35 (obs.).

Anal. Calcd. for $C_{10}H_{21}ONS$: N, 6.90. Found: N, 7.17.

p-Aminophenyl β-Hydroxy-Δ^3-butenyl Sulfide.

To a suspension of 3.89 g. (0.168 mole) of p-aminothiophenol in toluene was added 7.75 g. (0.168 mole) of 3,4 epoxy-1-butene in toluene. The solution was refluxed under a nitrogen atmosphere for three hours and then diluted with water. The toluene layer was separated, dried, and distilled to give

16.5 g. (51.5%) of product distilling at 165-8°/0.8 mm.

Anal. Calcd. for $C_{10}H_{13}ONS$: N, 7.18; S, 16.42. Found: N, 7.20; S, 16.42 and 16.60.

β-Diethylaminoethyl β'-Phenyl-β'-hydroxyethyl Ether.

To a boiling solution of 100 ml. of β-diethylaminoethyl alcohol and 20 g. (0.36 mole) of potassium hydroxide was added, during five minutes, 40 g. (0.25 mole) of styrene oxide. The solution was extracted with benzene, dried, and distilled. The product distilled at 142-4°/0.5 mm. to give 30 g. (49%) of product; n_D^{20} 1.5103; d^{20} 1.0102; MR 70.36 (calcd.), MR 70.20 (obs.).

Anal. Calcd. for $C_{14}H_{23}O_2N$: N, 5.91. Found: N, 5.68 and 5.67.

β-Diethylaminoethyl β'-Phenyl-β'-acetoxyethyl Ether.

A solution of 10 g. (0.042 mole) of β-diethylaminoethyl β'-phenyl-β'-hydroxyethyl ether, 40 ml. of acetic anhydride, and 3 g. of sodium acetate was heated on a steam cone for three hours. The solution was poured into ice water and 125 ml. of ammonium hydroxide added. The solution was extracted with benzene and dried over anhydrous sodium sulfate. The benzene was evaporatively distilled and the residue distilled at 138-41°/0.5 mm. to give 9.2 g. (78%) of product; n_D^{20} 1.4910; d_{20}^{20} 1.0096; MR 79.61 (calcd.); 80.21 (obs.).

Anal. Calcd. for $C_{16}H_{25}O_3N$: N, 5.02. Found: N, 4.74 and 4.88.

Hydrolysis of β-Diethylaminoethyl β'-Phenyl-β'-hydroxyethyl Ether.

To 10 g. of β-diethylaminoethyl β'-phenyl-β'-hydroxyethyl ether was added 40 ml. of 10% hydrochloric acid. The reaction mixture became warm (60-70°) and the suspended oil went into solution. The solution was allowed to stand for twenty minutes and was then extracted with ether. The ether layer was dried and distilled to leave a residue of approximately 0.6 g. The 2,4-dinitrophenylhydrazone of this oil melted at 242-3° after several recrystallizations from an ethanol-methyl cellosolve mixture. A mixed melting point with the 2,4-dinitrophenylhydrazone prepared from a known sample of acetophenone, melting point 243-4°, was not depressed. The acid-water layer was neutralized with 5N sodium hydroxide and extracted with ether. The ether was dried and distilled to give 7 g. of starting material. The distilling flask contained a slight residue.

A solution of 7.0 g. of β-diethylaminoethyl β'-phenyl-β'-hydroxyethyl ether in 40 ml. of 10% hydrochloric acid was refluxed for six and one-half hours. An oil, insoluble in the acid solution, separated during the reflux period. The suspension was cooled and extracted with ether. The ether extract was dried and distilled to give 0.4 g. of material distilling at 47°/0.8 mm. and a second fraction distilling at 145°/0.5 mm.; 0.2 g.; n_D^{20} 1.5995. The 2,4-dinitrophenylhydrazone of the first fraction melted at 116-7° after recrystallization from ethanol. (Shriner and Fuson give 121° for the 2,4-dinitrophenylhydrazone

of phenylacetaldehyde.)[53] A mixed melting point with an authentic sample of phenylacetaldehyde 2,4-dinitrophenylhydrazone also melting at 116-7° was not depressed. The 2,4-dinitrophenylhydrazone of the second fraction melted at 203-4° after several recrystallizations from an ethanol-methyl cellosolve mixture. The recrystallizations can also be made equally well using a mixture of ethanol and acetone.

Anal. Calcd. for $C_{22}H_{18}O_4N_4$: N, 13.92. Found: N, 13.96 and 14.17.

The acid solution following the ether extraction was neutralized with 5N sodium hydroxide and extracted with ether. The ether solution was dried and distilled to give 2 g. of material boiling at 145°; n_D^{20} 1.4388, plus a slight fore-run. The picrate of the distillate melted at 77-9° after recrystallization from ethanol. The picrate from a sample of β-diethylaminoethyl alcohol (Eastman Kodak) was also found to melt at 77-9°. (This picrate had not previously been described.) A mixed melting point of the two was not depressed.

Anal. Calcd. for $C_{12}H_{18}O_8N_4$: N, 16.20. Found: N, 16.30.

Phenethylideneacetophenone.

To 0.1 mole of phenylacetaldehyde (Eastman Kodak practical 50% in ethanol) and 0.1 mole of acetophenone in ethanol was added 10 ml. of methanol containing 1 g. of sodium. The solution was

53. Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N.Y., (1940) p. 186.

heated for ten minutes on the steam cone, cooled, and distilled. Most of the starting materials were recovered plus a small fraction distilling at 150-60°/0.5 mm. The 2,4-dinitrophenylhydrazone of this material melted at 203-4° after recrystallization from an ethanol-acetone mixture. A mixed melting point with the 2,4-dinitrophenylhydrazone of the material distilling in the same range resulting from the hydrolysis of β-diethylaminoethyl β'-phenyl-β'-hydroxyethyl ether was not depressed.

In another experiment phenethylideneacetophenone was prepared according to the method given by Kohler and Chadwell[54] for the preparation of benzalacetophenone. To a solution of 14 g. (0.25 mole) of potassium hydroxide pellets in 120 ml. of water was added 24 g. (0.2 mole) of acetophenone and 24 g. (0.2 mole) of phenylacetaldehyde (distilled from Eastman practical 50% in ethanol). The temperature of the solution was maintained at about 22-3° for six hours. The solution was extracted with ether and distilled. A large fore-run of starting material was obtained and 6 g. of material distilling at 166-70°/0.5 mm.; n_D^{20} 1.5945. The material was redistilled at 162-3°/.5 mm., n_D^{20} 1.6040. The melting point of the 2,4-dinitrophenylhydrazone, 203-4°, was not depressed when mixed with that obtained when using sodium methoxide.

The phenethylideneacetophenone was also prepared by condensing phenylacetaldehyde and acetophenone under the conditions

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54. Kohler and Chadwell, Org. Syntheses, Coll. Vol. I, 78 (1941)

of the hydrolysis. A mixture of 3.5 g. of phenylacetaldehyde and 3.5 g. of acetophenone in 30 ml. of 10% hydrochloric acid was refluxed for six hours. The solution was extracted with ether, dried, and distilled. A small amount of material was obtained distilling at 150°/0.8 mm. The 2,4-dinitrophenylhydrazone of this material melted at 203-4°, after recrystallization from an ethanol-acetone mixture, and the melting point was not depressed when mixed with that obtained in the above condensations. An attempt to form a bromo derivative did not result in any isolable material.

The boiling points in these experiments are not entirely satisfactory as the amount of material distilled was not sufficient to give a true boiling point.

4-Methyl-2-mercaptothiazole.

This preparation was made according to the procedure of Buckman, Reims, and Sargent.[55] From a 0.78 mole run there was obtained 87 g. (85%) of product melting at 86-8°. The yield was the same as that obtained by them.

7-Chloro-4-quinolyl 4'-Methyl-2'-thiazolyl Sulfide Hydrochloride.

A suspension of 9.9 g. (0.05 mole) of 4,7-dichloroquinoline and 6.5 g. (0.05 mole) of 4-methyl-2-mercaptothiazole in 35 ml. of absolute ethanol was refluxed for twenty minutes and cooled.

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55. Buckman, Reims, and Sargent, J. Org. Chem., 6, 764 (1941).

A light yellow solid crystallized out. The precipitate was filtered to give 16.5 g., a quantitative yield of product melting at 167-8°. Recrystallization from absolute ethanol gave a melting point of 169-70°.

Anal. Calcd. for $C_{13}H_{10}N_2Cl_2S_2$: N, 8.78. Found: N, 8.90.

7-Chloro-4-quinolyl β-Hydroxyethyl Sulfide.

A solution of 7.8 g. (0.1 mole) of β-hydroxyethyl mercaptan in absolute ethanol was added to a solution of absolute ethanol containing 0.1 mole of sodium ethoxide. To this solution was added 19.8 g. (0.1 mole) of 4,7-dichloroquinoline in 200 ml. of absolute ethanol. The reaction was refluxed for two hours and cooled in an ice bath. A white solid precipitated and was filtered and washed with water. The product melted at 113-15° after recrystallization from ethanol. The yield was 17 g. (71%).

Anal. Calcd. for $C_{11}H_{10}ONClS$: N, 5.86. Found: N, 6.07 and 5.97.

7-Chloro-4-quinolyl β-Chloroethyl Sulfide Hydrochloride.

To a suspension of 10 g. (0.0418 mole) of 7-chloro-4-quinolyl β-hydroxyethyl sulfide in 40 ml. of chloroform was added 16 g. (0.133 mole) of thionyl chloride in 10 ml. of chloroform. The solution was refluxed for one hour and the chloroform and excess thionyl chloride distilled. The solid residue was taken up in hot absolute ethanol from which it crystallized on cooling. The yield of pure product was 12 g.

(97%) melting at 196-7°.

Anal. Calcd. for $C_{11}H_{10}NCl_3S$: Cl present as HCl, 12.04. Found: Cl, 11.92.

7-Chloro-4-quinolyl β-Chloroethyl Sulfide.

The hydrochloride was decomposed with sodium bicarbonate to give the free base. The free base melted at 107-8° after recrystallization from ethanol.

Anal. Calcd. for $C_{11}H_9NCl_2S$: N, 5.43. Found: N, 5.52.

7-Chloro-4-quinolyl β-(γ'-diethylaminopropylmercapto)ethyl Sulfide Dihydrochloride.

To an absolute ethanol solution of sodium ethoxide prepared from 0.4 g. (0.0174 mole) of sodium was added 2.58 g. (0.0174 mole) of γ-diethylaminopropyl mercaptan in absolute ethanol. To the solution was then added 4.5 g. (0.0174 mole) of 7-chloro-4-quinolyl β-chloroethyl sulfide dissolved in absolute ethanol. The solution was refluxed for twenty-five minutes and cooled. The suspended salt was filtered, and the filtrate concentrated. The concentrate was treated with ethereal hydrogen chloride and the crystalline precipitate after filtration melted at 159-63°. On recrystallization from an ethanol-ether solution the compound melted at 176-7°.

Anal. Calcd. for $C_{18}H_{27}N_2Cl_3S_2$: N, 6.34. Found: N, 6.39.

7-Chloro-4-quinolyl β-(4-Methyl-2'-thiazolylmercapto)ethyl Sulfide Hydrochloride.

A solution of 2.58 g. (0.01 mole) of 7-chloro-4-quinolyl

β-chloroethyl sulfide and 1.21 g. (0.01 mole) of 4-methyl-2-mercaptothiazole in 25 ml. of absolute ethanol was refluxed for two and three-fourths hours. On cooling a sample of the material which precipitated was identified as starting material. The reaction mixture was refluxed for an additional eight hours. The solution was treated with ether and the solvent decanted. The residue was treated with ethereal hydrogen chloride. The solid material was taken up in ethanol and clarified with charcoal. The hydrochloride melted at 205-8°.

Anal. Calcd. for $C_{15}H_{14}N_2Cl_2S_3$; N, 7.20; Cl present as HCl, 9.25. Found: N, 6.96; Cl, 9.24.

1,5-Diphenyldithiobiuret.

A mixture of 1.5 g. (0.01 mole) of phenylthiourea and 1.5 g. (0.011 mole) of phenyl isothiocyanate was heated for three hours at 120-50°. The mixture melted, then solidified. The crystalline residue was taken up in 95% ethanol and recrystallized to give 2 g. (70%) of material melting at 143-6°. Several recrystallizations were required to obtain the compound melting at 151-2°. The melting point given in the literature[56] is 149°. The yield of pure product by this method was inferior to that obtained by the method of Johnson[57] and Underwood and Dains[58] so their method was used in the following experiment.

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56. Olin and Dains, J. Am. Chem. Soc., 52, 3322 (1930).
57. Johnson, Am. Chem. J., 30, 167 (1903).
58. Underwood and Dains, Univ. Kansas Sci. Bull., 24, 5 (1936).

The chief advantage of the above method is that it involves two less steps.

p-Chlorophenyl Isothiocyanate.

The p-chlorophenyl isothiocyanate used in these experiments was prepared by the method given in Organic Syntheses[59] as a modified procedure for aryl isothiocyanates. This method was used instead of the directions of Dyson[60] in view of the objectionable properties of thiophosgene.

A suspension of 100 g. (0.784 mole) of p-chloroaniline and 62 g. (0.80 mole) of carbon disulfide in 45 ml. of 95% ethanol was cooled in an ice bath and 84 ml. of concentrated ammonium hydroxide added. The cooled solution was shaken in a stoppered flask at intervals until it solidified. Care should be exercised in shaking the flask and the pressure should be equalized occasionally. The solid was filtered and washed with ether. The residue was dissolved in three liters of warm water and 260 g. (0.784 mole) of lead nitrate added. The suspension was heated for fifteen minutes and then steam distilled. The yield of product melting at 45-6° was 66 g. (50%).

p-Chlorophenylthiourea.[61]

p-Chlorophenyl isothiocyanate, 16.9 g. (0.1 mole) was dissolved in 40 ml. of liquid ammonia. The ammonia was allowed

59. Dains, Brewster, and Olander, Org. Syntheses, Coll. Vol. I, 447 (1941).
60. Dyson, ibid., Coll. Vol. I, 165 (1941).
61. Chattaway, Hardy, and Watts, J. Chem. Soc., 125, 1552 (1924); Dyson and George, ibid., 125, 1702 (1924).

to evaporate and the solid residue was recrystallized from 95% ethanol. The yield of pure product was 18.5 g. (98%) melting at 124-5°.

1-p-Chlorophenyl-2-thiolmethylpseudothiourea Hydroiodide.

The method used in the preparation of the thiolmethyl derivatives is that of Johnson[57] and Tursini.[62]

A solution of 4 g. (0.021 mole) of p-chlorophenylthiourea, 3.12 g. (0.022 mole) of methyl iodide, and a few drops of ethanol was refluxed for two hours. The solution was cooled and a small amount of dry ether was added. The product crystallized out to give 7 g. (98%) of product melting at 164-6°. Recrystallization from a mixture of absolute ethanol and ether gave a melting point of 165-7°.

Anal. Calcd. for $C_8H_{10}N_2ClIS$: I, 38.64. Found: I, 38.73.

Isopropyl Isothiocyanate.

To 62 g. (0.8 mole) of carbon disulfide was added 46.4 g. (0.78 mole) of isopropyl amine, followed by 84 ml. of ammonium hydroxide. The reaction flask was cooled in an ice-salt bath during the addition of the ammonium hydroxide. The ammonium dithiocarbamate which precipitated was filtered and dissolved in 800 ml. of warm water. A solution of 256 g. (0.78 mole) of lead nitrate in 500 ml. of water was added to the reaction mixture and the product steam distilled. Care should be taken in the steam distillation as some carbon disulfide may be present.

62. Tursini, Ber., 17, 585 (1884).

The distillate was extracted with ether and dried. Distillation of the ether solution gave 36.5 g. (46%) of isopropyl isothiocyanate boiling at 135-6°.[63]

1-p-Chlorophenyl-5-isopropyldithiobiuret.

To a solution of 10 g. (0.03 mole) of 1-p-chlorophenyl-2-thiolmethylpseudothiourea hydroiodide in 50% ethanol was added 1.63 g. (0.015 mole) of sodium carbonate. The solution was heated to 70° and 3.33 g. (0.03 mole) of isopropyl isothiocyanate was added. The suspended oil was shaken occasionally over a period of a week but did not solidify. The oil was separated and treated in the usual manner with sodium hydrosulfide. On neutralizing the solution there was obtained 7 g., a yield of 80% based on the starting hydroiodide, of a white solid melting at 125-33°. Recrystallization from ethanol raised the melting point to 135-7°.

Anal. Calcd. for $C_{11}H_{14}N_3ClS_2$: N, 14.63. Found: N, 14.49.

In another experiment an attempt was made to isolate the intermediate 1-p-chlorophenyl-2-thiolmethyl-5-isopropylpseudodithiobiuret. The material was quite soluble in the ordinary solvents and all attempts at formation of a solid derivative failed.

1,5-Di-(p-chlorophenyl)-2-thiolmethylpseudodithiobiuret.[62]

To a solution of 10 g. (0.03 mole) of 1-p-chlorophenyl-2-thiolmethylpseudothiourea hydroiodide in 1:1 ethanol-water was

63. John, Monatsh., 3, 168 (1882).

added 1.63 g. (0.015 mole) of sodium carbonate. The suspension was warmed to 70° and 5.15 g. (0.03 mole) of p-chlorophenyl isothiocyanate was added. The suspended oil was shaken at intervals for three hours during which time it solidified. The solid was filtered and recrystallized from a mixture of ethanol and methyl cellosolve to give 10.5 g. (95%) of product melting at 154-5°.

Anal. Calcd. for $C_{15}H_{13}N_3Cl_2S_2$: N, 11.33. Found: N, 11.52.

1,5-Di-(p-chlorophenyl)dithiobiuret.

To a suspension of 10 g. (0.027 mole) of 1,5-di-(p-chlorophenyl)-2-thiolmethylpseudodithiobiuret in 150 ml. of boiling ethanol was added a saturated solution of sodium hydrosulfide, prepared by bubbling hydrogen sulfide through 15 g. of melted sodium sulfide nonahydrate. Hydrogen sulfide was bubbled through the reaction mixture for two hours and the suspended material gradually went into solution. The solution was decanted and diluted with an equal volume of water and neutralized with acetic acid. The solid precipitate was filtered and recrystallized from absolute ethanol to give 8 g. (83%) of product melting at 168°.

Anal. Calcd. for $C_{14}H_{11}N_3Cl_2S_2$: N, 11.80. Found: N, 11.93.

1-p-Chlorophenyl-2-thiolmethyl-5-phenylpseudomonothiobiuret.

To a solution of 10 g. (0.03 mole) of 1-p-chlorophenyl-2-thiolmethylpseudothiourea hydroiodide in 50% ethanol was added

1.63 g. (0.015 mole) of sodium carbonate. The solution was warmed to 70° and 3.62 g. (0.03 mole) of phenylisocyanate was added. A solid crystallized out immediately. Recrystallization of the solid material from 95% ethanol gave 6 g. (73%) of product melting at 153-4°.

Anal. Calcd. for $C_{15}H_{14}ON_3ClS$: N, 13.17. Found: N, 13.50.

1-p-Chlorophenyl-5-phenyl-2-monothiobiuret.

A suspension of 3 g. (0.094 mole) of 1-p-chlorophenyl-2-thiolmethyl-5-phenylpseudothiobiuret in 50% ethanol was heated to boiling and a solution of sodium hydrosulfide, prepared from 10 g. of fused sodium sulfide nonahydrate, was added. The solution was refluxed for two hours with hydrogen sulfide bubbling through the reaction mixture. The solution was decanted into an equal volume of water and neutralized with acetic acid. The precipitate was a very fibrous material. It was reprecipitated from 85% ethanol in the same form. The product weighed 2 g. (70%) and melted at 163-5°.

Anal. Calcd. for $C_{14}H_{12}ON_3ClS$: N, 13.82. Found: N, 13.88.

Methylisocyanate.[64]

In a 250 ml. distilling flask was placed 50 g. of potassium cyanate, 10 g. of anhydrous sodium carbonate, and 65 g. of freshly distilled dimethyl sulfate. The condenser was attached to another distilling flask in an ice bath. The distilling flask

64. Slotta and Lorenz, Ber., 58B, 1320 (1925).

in the ice bath was in turn connected to a condenser ending in a receiver immersed in an ice bath. The reaction mixture was heated until the reaction began to distill spontaneously then the heat was removed and the distillation controlled by a water bath. When the distillation temperature reached 70°, the reaction mixture was cooled and the distillation stopped. The product was then distilled from the second distilling flask to give 9 g. (32%) of product distilling at 42-5°.

1-p-Chlorophenyl-2-thiolmethyl-5-methylpseudomonothiobiurat.

The directions are essentially the same as those given above. To a solution of 10 g. (0.03 mole) of 1-p-chlorophenyl-2-thiolmethylpseudothiourea hydroiodide in 50% ethanol was added 1.63 g. (0.015 mole) of sodium carbonate and the solution heated to 70°. The solution was placed under the hood and 1.71 g. (0.03 mole) of methylisocyanate added. On cooling the product crystallized out to give 7.5 g. (97%) of crude material. Recrystallization from dilute ethanol gave 5 g. (65%) of pure material melting at 160-1°.

Anal. Calcd. for $C_{10}H_{12}ON_3ClS$: N, 16.32. Found: N, 16.15.

1-p-Chlorophenyl-5-methyl-2-monothiobiuret.

A solution of 4 g. (0.0155 mole) of 1-p-chlorophenyl-2-thiolmethyl-5-methyl pseudomonothiobiuret in 50% ethanol was heated to reflux and 10 g. of sodium hydrosulfide added. Hydrogen sulfide was bubbled through the boiling solution for two

hours and then the hot solution was decanted into an equal volume of water. On neutralization with acetic acid there was obtained 3.5 g. (92%) of product melting at 182-3°. Recrystallization from ethanol did not change the melting point.

Anal. Calcd. for $C_9H_{10}ON_3ClS$: N, 17.29. Found: N, 17.23.

γ-(p-Nitrophenoxy)propyl β-Morpholinoethyl Sulfone.

A mixture of 20 g. (0.065 mole) of γ-(p-nitrophenoxy) propyl β-chloroethyl sulfone,[65] 4.5 g. (0.0375 mole) of potassium carbonate, and 5.65 g. (0.08 mole) of morpholine in 75 ml. of absolute ethanol was refluxed for eight hours. On cooling an oil precipitated which later solidified. The compound was purified as the hydrochloride, giving 10 g. (39%) melting at 207-8°. The free base melted at 98-99°. On larger runs (0.3-0.5 mole) the yields of the free base averaged 60%.

Anal. Calcd. for $C_{15}H_{23}O_6N_2ClS$: N, 7.12. Found: N, 7.22 and 7.04.

γ-(p-Aminophenoxy)propyl β-Morpholinoethyl Sulfone.

A solution of 15 g. (0.038 mole) of γ-(p-nitrophenoxy)-propyl β-morpholinoethyl sulfone in 200 ml. of absolute ethanol was placed in the hydrogenator with 7 ml. of Raney nickel. The reduction was carried out under 45 lbs. of hydrogen

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65. Gilman and Fullhart, J. Am. Chem. Soc., 67, 1585 (1945).

at 100°. The pressure was released after twenty minutes and the suspension filtered hot. On cooling there was obtained 12.8 g. (92%) of white needles melting at 108-10°. Several recrystallizations from ethanol raised the melting point to 117°. The melting point was preceded by some sintering.

γ-(p-Isopropylaminophenoxy)propyl β-Morpholinoethyl Sulfone (?).

An attempt to reduce γ-(p-nitrophenoxy)propyl β-morpholinoethyl sulfone in a solution of acetone and ethanol resulted in the probable formation of γ-(p-isopropylaminophenoxy)propyl β-morpholinoethyl sulfone melting at 106-8°, the compound being the result of a reaction between the amine and acetone. A similar reaction has been reported by Major.[66]

Anal. Calcd. for $C_{18}H_{30}O_4N_2S$: N, 7.56. Found: N, 7.58 and 7.42.

γ-Bromopropyl β-Morpholinoethyl Sulfone (attempted).

A solution of 10 g. (0.03 mole) of γ-(p-aminophenoxy) propyl β-morpholinoethyl sulfone in 26.6 g. of 48% hydrobromic acid was refluxed for nine hours. The solution was cooled and poured into a separatory funnel. The mixture was covered with a layer of ether and sodium hydroxide was added slowly with cooling. During the neutralization a white precipitate formed. The precipitate was filtered and the ether layer separated. The precipitate was shown to be starting material and a small

66. Major, ibid., 53, 1901, 2803, 4373 (1931).

additional amount was obtained from the ether. The recovery of starting material was slightly more than 70%.

β-Hydroxyethyl 2-Pyridyl Sulfide Picrate.

To a solution 0.2 molar in sodium ethoxide was added 15.6 g. (0.2 mole) of β-hydroxyethyl mercaptan. The solution was stirred for five minutes, and 31.6 g. (0.2 mole) of 2-bromopyridine was added. The reaction mixture was refluxed for two and one-half hours and cooled. The suspended salt was filtered and the filtrate concentrated. Distillation of the residue gave 20 g. (65%) of product distilling at 122°/1 mm.; n_D^{20} 1.5939. The picrate, prepared in the usual manner, melted at 113-4°.

Anal. Calcd. for $C_{13}H_{15}O_8N_4S$: N, 14.47. Found: N, 14.49.

3-Nitro-4-acetaminoanisole.

The nitration of p-acetaminoanisole was made essentially according to the directions of Reverdin.[67] It was found,[68] however that excellent results could be obtained by heating the suspension to 70° rather than to boiling as reported.[67] A suspension of 99 g. (0.6 mole) of p-acetaminoanisole in 1200 ml. of 11% nitric acid in a 3-liter beaker, equipped with a mechanical stirrer, was heated to 70° over a period of fifteen minutes.

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67. Reverdin, Ber., 29, 2595 (1895).
68. Woods, L.A., Unpublished studies in these laboratories.

The suspension of orange solid was poured into a 3-liter beaker containing 1 liter of crushed ice. The precipitate was filtered and washed with 400 ml. of water. The precipitate was dried to give a crude yield of 107.5 g. (85.5%) of 3-nitro-4-acetaminoanisole melting at 114-16°. The pure compound melted at 117°.

3-Nitro-4-aminoanisole.

To 107.5 g. (0.512 mole) of 3-nitro-4-acetaminoanisole in a 1-liter Erlenmeyer flask with 100 ml. of ethanol was added a hot solution of 30 g. of potassium hydroxide dissolved in 200 ml. of ethanol. The solution turned dark red. The solution was refluxed for fifteen minutes and set in the refrigerator to cool. The product crystallized in large red crystals. The yield of 3-nitro-4-aminoanisole was 78 g. (91%) melting at 122.5-24°.

3-Nitro-4-bromoanisole.

This preparation was made using the directions of Samant.[69] In a 3-liter, one-necked, round-bottomed flask was placed 26 g. (0.104 mole) of crystallized copper sulfate, 8.22 g. (0.129 mole) of copper turnings, 47.2 g. (0.458 mole) of sodium bromide, 11.4 g. (0.116 mole) of concentrated sulfuric acid, and 500 ml. of water. The mixture was refluxed for four hours (Samant does not give boiling period). A suspension of 70 g. (0.416 mole) of concentrated sulfuric acid and 500 ml. of water was warmed

69. Samant, Ber., 75B, 1008 (1942).

until the amine was in solution. The solution was cooled to 0° and diazotized with 29.2 g. (0.416 mole) of sodium nitrite in 60 ml. of water. The diazonium compound was added slowly to the boiling cuprous bromide solution prepared above. The solution was refluxed for one hour and cooled. The reaction mixture was extracted with ether and dried over potassium carbonate. The ether was distilled to give 76 g. (75%) of pure 3-nitro-4-bromoanisole distilling at 134-6°/1.5 mm. The yield and boiling point were the same as those reported by Samant.

3-Amino-4-bromoanisole.

In a 500 ml. three-necked flask, equipped with a reflux condenser and stirrer, was placed 40 g. (0.1724 mole) of 3-nitro-4-bromoanisole, approximately 300 ml. of 95% ethanol, and 2 ml. of concentrated hydrochloric acid. Forty grams of reduced iron was added slowly and a spontaneous exothermic reaction took place. The mixture was refluxed for five to six hours and the solvent was distilled off. The residue was extracted three times with ether. The ether extracts were combined and dried over potassium carbonate and then evaporatively distilled. The residue distilled as a straw-colored oil at 105°/6.7 mm. to give 27.5 g. (79%) of 3-amino-4-bromoanisole. The hydrochloride melted with decomposition at 183-6°. This is in agreement with that reported by Hodgson and Dyson.[70]

70. Hodgson and Dyson, J. Chem. Soc., 946 (1935).

An attempt to reduce the 3-nitro-4-bromoanisole using stannous chloride in 1:1 hydrochloric acid resulted in the removal of the bromine. The isolation of m-anisidine was almost quantitative.

N-γ-Diethylaminopropyl-3-methoxy-6-bromoaniline Picrate.

A mixture of 25 g. (0.124 mole) of 3-amino-4-bromo anisole and 26.7 g. (0.166 mole) of γ-diethylaminopropyl chloride was heated in an oil bath at 155° for six hours. The thick syrupy residue was taken up in distilled water and neutralized. The solution was then extracted with ether, dried, and evaporatively distilled. The residue distilled at 165°/1.6 mm. to give 20.2 g. (51.8%); n_D^{20} 1.5478, of N-γ-diethylaminopropyl-3-methoxy-6-bromoaniline. The picrate melted at 116-17°.

Anal. Calcd. for $C_{20}H_{23}O_8N_5Br\ H_2O$: N, 12.50. Found: N, 12.20 and 12.10.

2-[2'-(γ-Diethylaminopropylamino)-4'-methoxyphenyl]quinoline (attempted).

A solution of 0.096 mole of n-butyllithium in dry ether was added to a solution of 15.8 g. (0.05 mole) of 3-(γ-diethylaminopropylamino)-4-bromoanisole. The solution was refluxed in a nitrogen atmosphere for one hour following the addition of the n-butyllithium. A test for an organometallic compound by color test (No. 1)[51] was positive; a test for an alkyl

organometallic color test (No. 2)[71] was negative. A solution of 12.9 g. (0.1 mole) of quinoline in ether was added during fifteen minutes. The solution turned a deep red and was refluxed for four hours. The solution was hydrolyzed and the ether layer separated. The ether extract was dried and the ether distilled. The residue was refluxed with nitrobenzene for thirty minutes and the nitrobenzene distilled off. The residue would not distill under a reduced pressure of 0.5 mm. All attempts at crystallizing the residue or forming a solid derivative were unsuccessful.

Preparation of N-γ-Diethylaminopropyl-o-bromoaniline Dihydrochloride.

A mixture of 20 g. (0.116 mole) of o-bromoaniline and 32.4 g. (0.174 mole) of γ-diethylaminopropyl chloride hydrochloride was heated on a boiling water bath for thirty minutes. The solution was then heated in an oil bath for three hours at 130-60°. The solution was dissolved in 80 ml. of warm 2% hydrochloric acid and was made basic with 20% potassium hydroxide. A reddish-purple oil separated which was extracted with ether and dried over anhydrous potassium carbonate. The ether was distilled to leave 37 g. of crude product. The crude product was distilled from a Claisen flask under reduced pressure. The product distilled slowly at 175-80°/1.8-1.5 mm. to give 22.5 g. of material. Redistillation gave 20.5 g. (62%) of product

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

distilling between 152-72°/3.8 mm. The refractive index for different fractions between 152° and 172° were n_D^{15} 1.5500 and n_D^{15} 1.5520 becoming constant after a few minutes at n_D^{15} 1.5590. The hydrochloride crystallized from an ether-ethanol mixture as clear colorless crystals. The material changed from clear to opaque white crystals at 106-8° and melted at 171-3°. The picrate melted at 129-30°.

Anal. Calcd. for $C_{13}H_{23}N_2BrCl_2$: N, 7.83. Found: N, 7.88.

2-[2'-(γ-Diethylaminopropylamino)phenyl]pyridine (attempted).

In a 500 ml. three-necked flask, equipped with a reflux condenser, stirrer, and dropping funnel was placed 163 ml. (0.108 mole) of n-butyllithium in dry ether. The flask was filled with nitrogen. The solution was cooled to -60° and 15 g. (0.525 mole) of o-bromo-N-(γ-diethylaminopropyl)aniline in 52 ml. of ether was added. The addition was made over a period of eighteen minutes. A 25 ml. portion of the reaction mixture was removed and carbonated. To the original solution was then added 4.15 g. (0.525 mole) of dry pyridine (distilled from barium oxide) in 23 ml. of anhydrous ether. The temperature of the solution was allowed to rise slowly to -50°, and then the bath was removed. A small amount of oily precipitate appeared during this time. The solution was stirred for one hour and hydrolyzed. The ether layer was removed and dried over potassium carbonate. The ether was evaporated and the residue distilled at 130-78°/5 mm. A picrate of the material identified it as the

starting o-bromo-N-(γ-diethylaminopropyl)aniline. The carbonation sample was worked up in the usual manner but no aromatic acid could be isolated.

Preparation of 6-Methoxy-2-(2',5-dimethylpyrryl-1')quinoline (attempted).

In a 100 ml. acetylating flask equipped with a water cooled reflux condenser and containing a nitrogen atmosphere was placed 5.8 g. (0.03 mole) of 6-methoxy-2-chloroquinoline and 10 g. (0.105 mole) of 2,5-dimethylpyrrole.[72] The mixture was heated in an oil bath at 155-65° for nine hours during which time the solution became dark red. The solution was cooled and the thick oily residue was treated with a small amount of base and extracted with ether. On distilling the dried ether extract a small amount of 2,5-dimethylpyrrole was obtained. The residue from the distillation was extracted with ethanol and a small amount of 6-methoxy-2-chloroquinoline was recovered. No other products could be isolated.

Preparation of 2-(2',5-Dimethylpyrryl-1')quinoline (attempted).

In order to conserve the more expensive 6-methoxy-2-chloroquinoline several attempts were made to condense 2,5-dimethylpyrrole with 2-chloroquinoline.

A mixture of 5 g. (0.03 mole) of 2-chloroquinoline, 2.9 g.

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72. Young and Allen, Org. Syntheses, 16, 25 (1936).

(0.03 mole) of 2,5-dimethylpyrrole, 5 g. (0.036 mole) of potassium carbonate, and 0.5 g. of copper bronze was heated in an atmosphere of nitrogen in an oil bath for ten hours at 160-70°. The mixture was cooled and extracted with ether and ammonium hydroxide. The ether was dried and distilled to give the unreacted 2,5-dimethylpyrrole and 2-chloroquinoline. The same results were obtained in another experiment using the same quantity of materials in which the temperature was raised to 195-200° and the time extended to twenty-four hours.

In another experiment an attempt was made to condense N-lithio-2,5-dimethylpyrrole with 2-chloroquinoline. To a solution of 17.1 g. (0.18 mole) of 2,5-dimethylpyrrole in 50 ml. of dry ether in a nitrogen atmosphere was added a solution containing 0.203 mole of methyllithium. The solution became milky in color and gave a negative color test (No. 1) for an organometallic compound. A negative test was also obtained in using color test (No. 4)[73] for an R_2N-Li compound. To the reaction mixture was added 29.4 g. (0.18 mole) of 2-chloroquinoline and the solution refluxed for fifteen hours. There was no visible sign of reaction during this time so the ether was distilled and 200 ml. of dry xylene added. The solution was refluxed for forty-four hours and hydrolyzed. The xylene was separated and distilled to give the starting 2-chloroquinoline.

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73. Gilman and Woods, J. Am. Chem. Soc., 65, 33 (1943).

2-Morpholinoquinoline.

A solution of 8.6 g. (0.052 mole) of 2-chloroquinoline and 9 g. (0.103 mole) of morpholine was heated at 140° for eight hours. The solution became almost solid. The mixture was poured into approximately 100 ml. of 5-10% sodium hydroxide and the precipitate filtered and washed with water. Recrystallization from 50-75% ethanol gave 10.4 g. (93%) of product melting at 95°. The picrate melted at 164°.

Anal. Calcd. for $C_{13}H_{14}ON_2$: N, 13.08. Found: N, 13.58.

6-Methoxy-2-morpholinoquinoline.

The conditions were essentially those used above. A mixture of 3.5 g. (0.0181 mole) of 6-methoxy-2-chloroquinoline and 3.15 g. (0.0362 moles) of morpholine was heated at 140° for eight hours. The mixture was poured into sodium hydroxide and diluted with water. The precipitate was filtered and washed with water. After recrystallization from 50% ethanol the yield of pure product was 4.2 g. (95%) melting at 130°. The picrate melted at 182-4°.

Anal. Calcd. for $C_{14}H_{16}O_2N_2$: N, 11.48. Found: N, 11.70.

6-Methoxy-4-morpholinoquinoline.

A mixture of 3.5 g. (0.018 mole) of 6-methoxy-4-chloroquinoline and 3.15 g. (0.036 mole) of morpholine was heated at 140° for eight hours. The mixture was poured into 20% sodium hydroxide. The product formed an oil which required several

washings with water and long standing to solidify. Several recrystallizations from dilute ethanol and finally from petroleum ether (boiling point 60-68°) gave 3.5 g. (79%) of product melting at 102-3°. The picrate melted at 227°.

Anal. Calcd. for $C_{14}H_{16}O_2N_2$: N, 11.48. Found: N, 11.62.

9-[p-(2',5'-dimethylpyrryl-1')phenyl]acridine.

To 1.93 g. (0.28 g. atom) of lithium in 70 ml. of anhydrous ether under nitrogen in a 500 ml. three-necked flask, equipped with stirrer, reflux condenser, and dropping funnel, was added 35.7 g. (0.14 mole) of N-p-bromophenyl-2,5-dimethylpyrrole in 150 ml. of ether over a period of approximately one and one-half hours. The reaction mixture was stirred for three-fourths of an hour and filtered under nitrogen into another dropping funnel. The organometallic compound was then added to 17.9 g. (0.1 mole) of acridine suspended in 175 ml. of anhydrous ether. The addition was made over a period of one and one-half hours. The solution was stirred for one hour and hydrolyzed with water. The ether layer was separated, dried over sodium sulfate, and evaporated. The crystalline residue was refluxed for ten minutes in nitrobenzene and allowed to cool. The yellow crystalline precipitate was filtered and washed with xylene. The yield of pure material was 23 g. (66%) melting at 145-7°.

Anal. Calcd. for $C_{25}H_{20}N_2$: N, 8.05. Found: N, 8.61 and 8.72.

p-Methoxy-p-nitrobenzophenone.[74]

To 20 g. (0.107 mole) of freshly prepared p-nitrobenzoyl-chloride[75] and 11.6 g. (0.10 mole) of anisole in 125 ml. of carbon disulfide, distilled from phosphorous pentoxide, was added 130 g. (1 mole) of anhydrous aluminum chloride. The addition of the aluminum chloride was made slowly, the system being maintained under anhydrous conditions. The reaction took place at room temperature. The carbon disulfide was distilled and ice-cold, dilute hydrochloric acid was added cautiously. The precipitate was filtered and washed with water. Recrystallization from 95% ethanol gave 22 g. (80%) of pure product melting at 121°.

p-Methoxy-p-acetaminobenzophenone.

To a boiling suspension of 10 g. (0.039 mole) of p-methoxy-p-nitrobenzophenone in 100 ml. of 95% ethanol and 1 ml. of concentrated hydrochloric acid was added portion-wise 10 g. of powdered iron. The reaction mixture was refluxed for two hours and filtered hot. The filtrate was concentrated but the product refused to crystallize. The residue was treated twice with benzene and distilled. The residue was again taken up in benzene, and 5 ml. of acetic anhydride was added. The solution was brought to a boil and cooled. The material crystallized out to give 10 g. of product melting at 165-6°. Recrystallization

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74. Auwers, Ber., 36, 3898 (1903).
75. Adams and Jenkins, Org. Syntheses, Coll. Vol. I, 394 (1941).

from 85% ethanol gave 8.5 g. (83%) of pure p-methoxy-p-acetaminobenzophenone melting at 170-1°.

Anal. Calcd. for $C_{16}H_{15}O_3N$: N, 5.20. Found: N, 5.42 and 5.43.

p-Methoxy-p-aminobenzophenone.

A sample of p-methoxy-p-acetaminobenzophenone was heated in 5-6 N hydrochloric acid until it went into solution. The mixture was cooled and neutralized with sodium hydroxide. The precipitate was filtered and recrystallized from 95% ethanol to give the corresponding amine melting at 121-2°.

Anal. Calcd. for $C_{14}H_{13}O_2N$: N, 6.16. Found: N, 6.21.

This compound was also prepared by reducing p-methoxy-p-nitrobenzophenone in ethanol with hydrogen and Raney nickel. The product was identical with that above as shown by a mixed melting point. It was also acetylated to give the same acetylated derivative obtained by the iron reduction.

DISCUSSION

1. Method of Testing Antimalarials

A general discussion of the testing of antimalarial compounds has been given by Tolman[76] but the actual procedure used was not given. The material given below is a detailed description of the method used for testing antimalarial compounds as given by Doctors Coggeshall[77] and Porter of the University of Michigan, who tested the majority of the compounds prepared in this investigation.

The principal test used is aimed at the detection of causal prophylactic activity of drugs as indicated by their ability to prevent or delay infection in chicks inoculated with sporozoites of Plasmodium gallinaceum. White Rock chicks from a single hatchery are used at an age of zero to fifteen, usually five to ten days.

Infections are transmitted with insectary-reared mosquitoes, Aedes aegypti or Aedes albopictus. Females are separated under ether and infected two to six days after emerging by feeding on chickens showing twenty-five or more gametocytes per 10,000 erythrocytes. The fed females are selected under ether and held at about 28° and 70 percent relative humidity for ten to twenty days to allow sporozoites to concentrate in the

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76. Tolman, L.L., Doctoral Dissertation, Iowa State College (1945).
77. See Coggeshall, Ind. Eng. Chem. News Ed., 21, 1152 (1943) for a general discussion of this method.

salivary glands. For inoculation these mosquitoes are killed with ether. The salivary glands are removed in normal (0.85%) saline solution and placed immediately in 0.5 ml. heparinized normal chick blood (normal blood to each 0.9 ml. of which has been added 0.1 ml. of normal saline solution containing 2 mg. of heparin). One-third to one mosquito is dissected for each chick to be infected. This mixture of glands and blood is ground for about fifteen minutes in a small roller mill, and dry smears are then made of the suspension and stained with Giemsa. Ten sporozoites are counted in the smear and the number of sporozoites per 10,000 erythrocytes determined. From this figure and the fact that such suspensions contain about 1,000,000,000 erythrocytes in 0.5 ml. the total number of sporozoites in the suspension is calculated. The suspension is now diluted with saline and heparinized blood (about five parts saline to one part blood) to give a suspension containing 40,000-100,000 sporozoites per ml. Each chick is inoculated intravenously (wing vein usually, occasionally leg vein or external jugular) with 0.2 ml. of this suspension (8,000 to 20,000 sporozoites, the upper limit being preferable). In untreated chicks parasites appear in the peripheral blood on the fifth to seventh day, and the chicks normally die on the ninth to twelfth day after inoculation, showing more than 50 percent of the erythrocytes infected and abundant exoerythrocytic stages in the tissue capillaries. Within experiments individual

infections are fairly uniform, variations of more than a day in incubation period or more than two days in time of death being uncommon.

Drugs are tested against these infections by administration in the diets of the test chicks in the manner of Marshall, Litchfield and White.[78] Where possible a concentration of 0.5 percent drug is used, the dosage being reduced if this is toxic or increased when doubtful activity is seen. Chicks of the ages usually used average fifty to sixty grams in weight and consume six to twelve grams of mash a day; thus, they receive thirty to sixty milligrams of drug a day (0.6 to 1 gm./kilogram body weight) at a concentration of 0.5 percent in the mash.

The drug is first powdered in a mortar if necessary, then mixed in a mortar with a small amount of the mash ("Larro Chick Builder"). This mixture is added to the remainder of the mash, a small amount of 95 percent ethyl alcohol being used, if necessary to remove all the drug from the mortar. The diet is then stirred for thirty minutes in a rotating mechanical mixer. Chicks are isolated in divided brooders in groups of three to fifteen (usually six), and fed the drug mash mixtures from twenty-four hours or more before to four days after infection, the light in the chick room being controlled by a time switch to give alternating three-hour periods of light and dark throughout the course of the experiment.

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78. Marshall, Litchfield and White, J. Pharmacol., 75, 89 (1942).

Activity of the test drugs is determined from peripheral blood smears made on the seventh day after inoculation; further smears are made in doubtful cases or where the appearance of parasites is delayed. The numbers of parasitized cells per 10,000 erythrocytes are determined and possible drug activity detected by comparison of figures from test and control chicks. Chicks which fail to show infection are further checked for complete absence of parasites by one or both of the following methods. In the first method one ml. or more of blood from each test bird is inoculated into each of two normal chicks, and these are examined repeatedly for infection. More commonly the test chicks and uninfected controls are inoculated with parasitized blood; if the course of infection in the test birds is normal they are considered to have been uninfected.

Activities detected range from a consistent delay of as little as one day in the appearance of parasites to complete prevention of infection. The prophylactic specificity of the test is indicated by the complete inactivity of highly curative drugs such as atebrin and quinine.

Variations from the above routine are infrequent. It appears desirable to administer some drugs parenterally. These are given in individual doses, usually twice a day, during the same period as above, one day before to four days after infection. In some cases where it seems desirable to ascertain the time of maximum activity of a drug or the shortest effective

treatment, drugs are administered in single doses or in the mash for a shorter time than that indicated above.

2. Sulfur Derivatives of Chalcones

The preparation of compounds containing sulfur was an attempt to prepare physiologically active agents which would be more soluble and less toxic than those currently available. A study of the large number of compounds tested for antimalarial activity in recent years shows that a "basic side-chain" is present in the majority of active compounds, as illustrated by plasmoquin, atebrin, and to some extent in quinine. Another feature of the above compounds is that they contain a quinoline nucleus. It has already been noted, however, that paludrine, which is an active antimalarial, does not contain a quinoline nucleus but a benzene ring. The present figures indicate that about 16% of the compounds prepared which are not quinoline derivatives have some antimalarial activity. This, therefore, presents the possibility of approaching the problem from two different directions; one, to prepare quinoline derivatives containing sulfur and, two, to prepare compounds of a type which has not heretofore been tested. Both methods of approach have been used in the work reported in this thesis.

Sulfur was introduced into these compounds by means of the "basic side-chain". Instead of the dialkylaminoalkylamino group commonly used in connection with the quinoline type

derivatives, a dialkylaminoalkylmercapto group has been used.

The β-diethylaminoethylmercaptan used in these experiments was prepared in the beginning by the sodium hydrosulfide method[44] (equation 1) and later by the isothiouronium method (equations 2 and 3) of Albertson and Clinton.[79]

$$(C_2H_5)_2NCH_2CH_2Cl + NaSH \longrightarrow (C_2H_5)_2NCH_2CH_2SH + NaCl \qquad (1)$$

$$(C_2H_5)_2NCH_2CH_2Cl \cdot HCl + H_2NCSNH_2 \longrightarrow (C_2H_5)_2NCH_2CH_2SC(=NHHCl)NH_2 \cdot HCl \qquad (2)$$

$$(C_2H_5)_2NCH_2CH_2SC(=NHHCl)NH_2 \cdot HCl \xrightarrow{[NaOH]} (C_2H_5)_2NCH_2CH_2SH \qquad (3)$$

The preparation of γ-diethylaminopropyl mercaptan from the isothiouronium complex was also found to be a better method than the sodium hydrosulfide method. The yields from the former method were consistently higher and the quality of product was much better. In the method using sodium hydrosulfide it is difficult to separate the γ-diethylaminopropyl mercaptan from the unreacted starting chloride by fractional distillation (boiling point of mercaptan 76-77.5°/26 mm.; boiling point of chloride 73-75°/20 mm.). The use of a basic extraction as a means of separating the mercaptan from the chloride results in a much lower yield. The fact that mercaptans are somewhat unstable in basic media forming disulfides, may account to some extent for the lower yield. The method using the isothiouronium

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79. Albertson and Clinton, J. Am. Chem. Soc., 67, 1222 (1945).

chloride is like that used by Albertson and Clinton[79] in the preparation of β-diethylaminoethyl mercaptans.

The chalcone nucleus has not been tested extensively in the antimalarial or antituberculous field but it has served as an intermediate in the preparation of many physiologically[80] active compounds. The known ability of chalcones to undergo 1,4-addition presented an excellent method for introducing the dialkylaminoalkylmercapto group. The addition of mercaptans and aromatic thiols to chalcones has been made in both acid[15] and basic[19] media. An attempt to react β-diethylaminoethyl mercaptan with chalcone in a basic medium failed although it worked in the case of aromatic thiols containing no nitrogen atoms. The reaction, however, was found to go when the hydrochloride of the amine was used. The decrease in reactivity of the β-diethylaminoethylmercaptan as opposed to the activity of the alkylmercaptans has been attributed to the nitrogen atom. Since the nitrogen atom contains an extra pair of electrons it is possible that the increased negativity would be transmitted to the sulfur atom thus decreasing the activity of the hydrogen atom. This is illustrated in the formula given below:

$$(C_2H_5)_2\ddot{N}\underbrace{CH_2}\overset{+}{\underbrace{CH_2}}\ \bar{S}H$$

It can be seen that an increase in the negativity of the sulfur atom would tend to reduce the strength of the carbon-sulfur bond,

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80. Blicke and Maxwell, ibid., 64, 428 (1942).

but would increase the strength of the hydrogen-sulfur bond.

In making the hydrochloride salt of the amine, the extra pair of electrons about the nitrogen atom is occupied. The electrons would no longer be forced toward the sulfur atom and its negativity, therefore, would decrease. This would have the effect of reducing the strength of the hydrogen-sulfur bond. The amino mercaptan would then function more like a pure alkyl mercaptan.

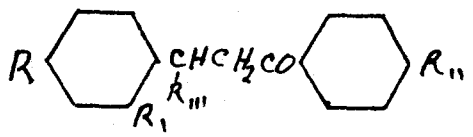
$$(C_2H_5)_2\overset{H}{\overset{|}{N}}CH_2CH_2S\overset{+}{H}$$

The reactions involving the alkylamino mercaptans were best carried out in benzene and the product isolated directly as the hydrochloride. The conversion to the free base is complicated by the reversibility of the reaction. The reactions involving the aromatic thiols were carried out by the general method of Nicolet.[21] In all cases excellent yields were obtained. The new compounds prepared in this series are given in Table I.

These compounds were tested for antimalarial action and for antituberculous activity. The compounds did not exhibit any antimalarial activity when tested against the Plasmodium gallinaceum. (See page 72 for a description of the tests). Of particular interest, however, was the fact that these compounds did not produce any toxic effects.

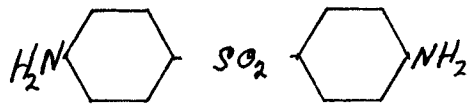
However, p-methoxy-β-(2-diethylaminoethylmercapto)-β-(p-dimethylaminophenyl)propiophenone hydrochloride exhibited

Table I



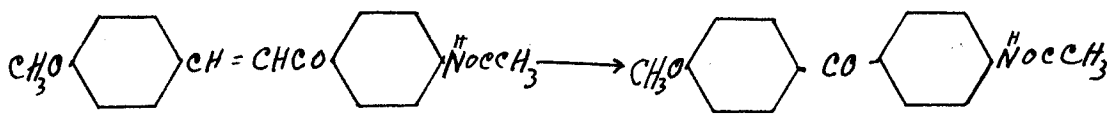
R	R'	R"	R'''	m.p.	Yield %	Analysis, N Calcd.	Found
H	H	H	$SCH_2CH_2N(C_2H_5)_2$	113-15°	92	3.71	3.67, 3.76
H	H	H	$SCH_2CH_2CH_2N(C_2H_5)_2$	112-13°	17	3.01	2.90
$(CH_3)_2N$	H	OCH_3	$SCH_2CH_2N(C_2H_5)_2$	145-6°	87.5	6.22	6.28
$(CH_3)_2N$	H	Cl	$SCH_2CH_2N(C_2H_5)_2$	142-3°	71	6.16	6.14
$(CH_3)_2N$	H	H $NOCCH_3$	$SCH_2CH_2N(C_2H_5)_2$	153-4°	87	8.98	8.75
CH_3O	H	H $NOCCH_3$	$SC_6H_4CH_3$	130-1°	91	3.34	3.35
	Cl	H $NOCCH_3$	$SC_6H_4CH_3$	148-9°	85	3.32	3.57

some antituberculous activity. The results showed it to be one-half as active as the standard, 4,4′-diaminodiphenyl sulfone XVIII.



XVIII

In this series particular attention is drawn to the fact that the intermediate chalcones were quite active as antituberculous agents. The report shows the 4-methoxy-4′-acetaminochalcone to be as effective as the 4,4′-diaminodiphenyl sulfone (XVIII) while the 2-chloro-4′-acetaminochalcone was twice as effective as the standard. In connection with this fact it was of interest to see if the activity exhibited by these compounds would be affected by the removal of the vinyl group.

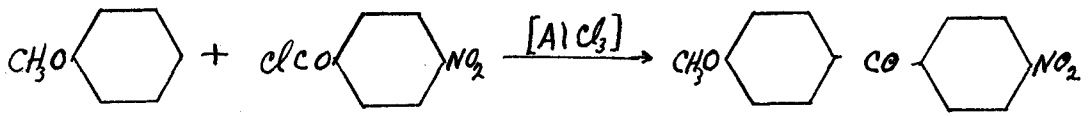


A similar study has been made by Gilman, Heckert, and McCracken[81] on the anesthetic action of some β-diethylaminoethyl esters. They prepared β-diethylaminoethyl acrylate hydrochloride, $CH_2=CHCO_2CH_2CH_2N(C_2H_5)_2 \cdot HCl$, which showed local anesthetic action. β-Diethylaminoethyl acetate hydrochloride,

81. Gilman, Heckert, and McCracken, ibid., 50, 437 (1928).

$CH_3CO_2CH_2CH_2N(C_2H_5)_2 \cdot HCl$, however, was not active. A study of γ-diethylaminopropyl cinnamate (Apothesin) showed the same effect when the vinyl group was hydrogenated.[82] By the principle of vinyology, therefore, the 4-methoxy-4'-acetaminobenzophenone should exhibit antituberculous activity. The results on these tests, however, have not been received.

The substituted ketone was prepared by the Friedel-Crafts reaction using p-nitrobenzoyl chloride and anisole in the presence of anhydrous aluminum chloride. The nitro compound



was reduced to the amine by iron and hydrochloric acid and also catalytically with hydrogen and Raney nickel.

3. β-Hydroxyethyl Sulfides

Increasing evidence obtained from the testing of many compounds indicated that many sulfides and sulfones were active antituberculous agents. Most of the compounds being synthesized for antituberculous activity were derivatives of diphenyl sulfide. While it was possible to obtain activity in derivatives of this type no significant difference in activity has been observed. In view of this fact a new series of sulfides was synthesized.

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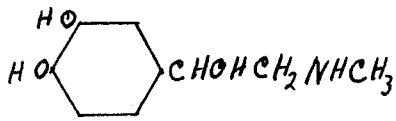
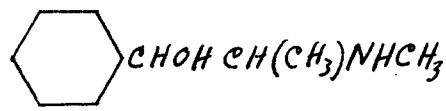
82. Gilman and Pickens, ibid., 47, 245 (1925). For leading references see also Pyman, J. Chem. Soc., 111, 167, 1119 (1917); Kamm and Volwiler, U.S. Patent 1,388,573; v. Braun and Braunsdrof, Ber., 54, 2081 (1921).

They were patterned after the physiologically active drugs epinephrine (XIX) and ephedrine (XX). Epinephrine is a hormone



XIX

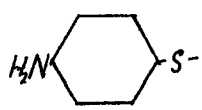


XX

obtained from the adrenal glands. It was the first hormone to be isolated, the structure of which was proved by synthesis. Epinephrine stimulates the vasoconstrictor mechanism of the systemic vessels and the accelerator mechanism of the heart in producing a rise in blood pressure. It is also used to arrest hemorrhage and to enhance the activity of local anesthetics.

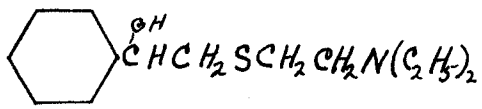
Ephedrine is an alkaloid obtained from various species of Ephedra. It simulates epinephrine in action but its effects are somewhat more prolonged.

In the series just completed the nitrogen atom, in the α-position to the hydroxyl group, has been replaced by a sulfur atom. The sulfur atom instead of being attached to an alkyl radical is connected with a dialkylaminoalkyl group in most cases. In some instances the p-aminophenyl group is attached to the sulfur atom giving the so-called active grouping,

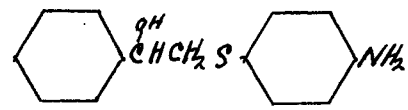


present in most of the active antitubercuious agents. In still other instances the benzene ring attached to the carbon containing the hydroxyl group has been replaced by a vinyl group.

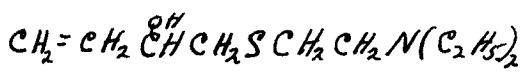
The types of compounds prepared are illustrated in the formulae shown below.



XXI



XXII



XXIII

The pharmacological tests on the above types of compounds are not complete. The results of the tests on these compounds for antimalarial activity are available. They failed to show any activity against avian malaria but were non-toxic. This last fact is interesting in view of the large changes in activity brought about by slight changes in chemical structure while the toxicity of compounds is more inherent in the type of compound. Thus slight changes in the structure of these compounds might result in an increased activity without increasing their toxicity. Some purely aliphatic hydroxy substituted bis-(dialkylaminoalkyl) sulfides, such as, β-diethylaminoethyl γ-diethylamino-β-hydroxypropyl sulfide (XXIV) were also made.

$$(C_2H_5)_2NCH_2CH_2SCH_2\overset{OH}{\overset{|}{C}}HCH_2N(C_2H_5)_2$$

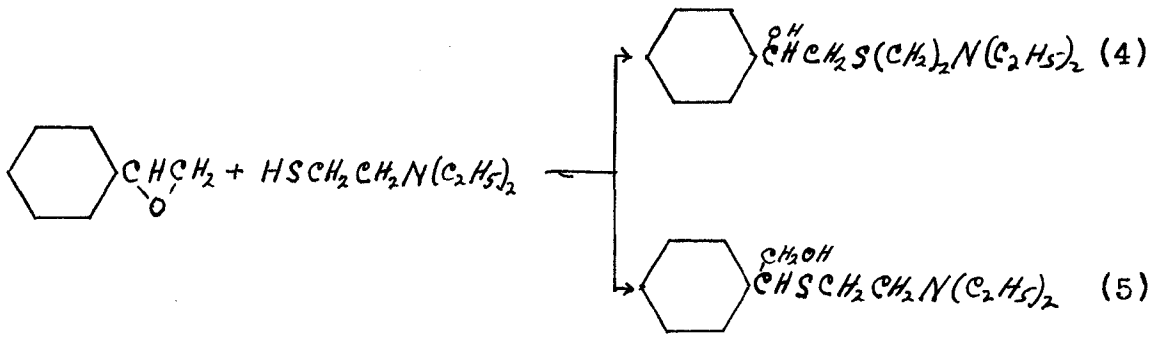
XXIV

These compounds were shown to exhibit some antimalarial activity.

The results of the testing of the above compounds as antituberculous agents are not available. They are also being tested for such physiological properties as coronary dilation, analgesic activity, antihistamine, antiasthmatic, and antispasmotic activity. The oxygen analog of the compounds of type (XXI) was also prepared as well as its acetyl derivative.

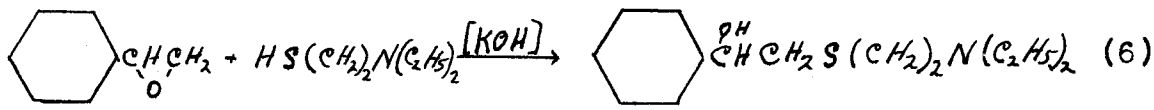
The method of preparing these compounds was to react the dialkylaminoalkyl mercaptan or aromatic thiol, as the sodium salt, with an unsymmetrical epoxide. The following epoxides were used: styrene oxide,[83] 3,4-epoxy-1-butene,[84] and 3-diethylamino-1,2-epoxypropane.[50]

It has already been pointed out on page fifteen of this dissertation that the cleavage of epoxy compounds may take place in either of two ways. The compound formed may be either a primary alcohol or a secondary alcohol depending somewhat on the medium used. This reaction is illustrated in the following equations:



83. The styrene oxide was furnished by the courtesy of the Dow Chemical Company.
84. The 3,4-epoxy-1-butene was kindly furnished by the Pittsburgh Plate Glass Company.

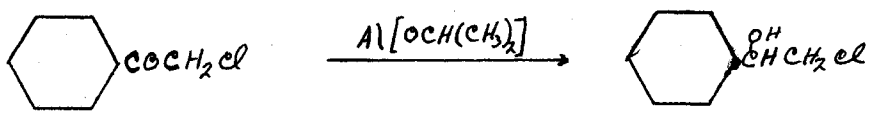
Since the exact position taken by the mercapto group in the cleavage of unsymmetrical epoxides had not been proved, it was necessary to devise a method for proving the structure of the compounds obtained. In this connection β-diethylaminoethyl β′-phenyl-β′-hydroxyethyl sulfide (XXV) was made by two different procedures. In the first method β-diethylaminoethylmercaptan was reacted with styrene oxide in the presence of potassium hydroxide.



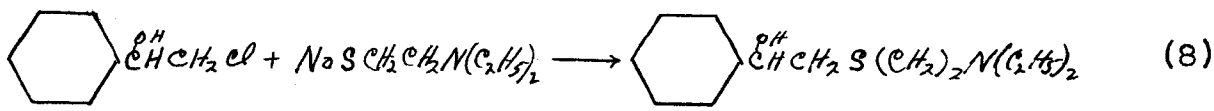
(6)

XXV

A compound having similar constants was prepared by reducing phenacyl chloride to styrene chlorohydrin by the Meerwein-Ponndroff[85] method, using aluminum isopropoxide, and then reacting the styrene chlorohydrin with sodium β-diethylaminoethyl mercaptide. It is evident, however, that this method does not



(7)



(8)

XXV

85. Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N.Y., Vol. II, (1944) p. 178.

constitute a valid structure proof as it is possible for styrene oxide to be formed as an intermediate. The formation of epoxides from chlorohydrins and metal alkoxides has been reported.[86,87] The alkyl amine is apparently also capable of closing the ring as evidenced by a recent note by Whitmore and co-workers.[88] He reacted 2,3-dibromopropanol with piperidine and obtained the expected 2,3-dipiperidylpropanol and also the symmetrical compound, 1,3-dipipridylpropan-2-ol. The latter compound was postulated as being formed from an intermediate epoxide. A similar type of reaction had been indicated earlier.[89]

In order to establish a valid proof of structure the following series of reactions was carried out. Methyl mercaptan was condensed with styrene oxide in the presence of potassium hydroxide. The hydroxy sulfide obtained was converted into the methiodide by the method of Bost and Everett.[90] The methiodide was then prepared in the following manner. Sodium methyl mercaptide was reacted with phenacyl bromide to give phenacyl methyl sulfide. Reduction of the phenacyl methyl sulfide by the Meerwein-Pondroff method[85] gave the corresponding β-phenyl-β-hydroxyethyl methyl sulfide. Conversion of this sulfide to the methiodide by the method already cited gave a compound of

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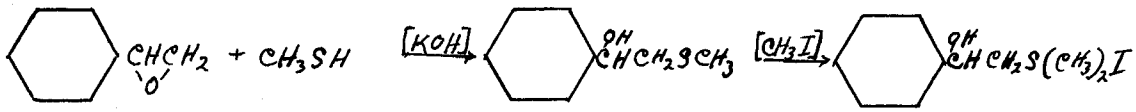
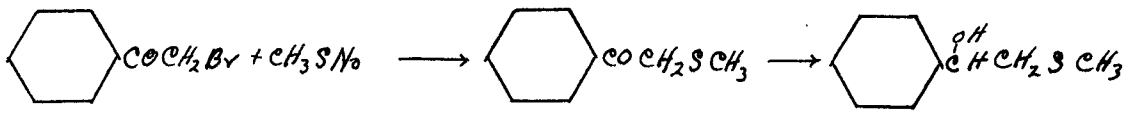
86. Rider and Hill, J. Am. Chem. Soc., 52, 1521 (1930).
87. Spath, Monatsh., 36, 1 (1915).
88. Whitmore, Mosher, Spalding, Taylor, Moersch, and Yanko, J. Am. Chem. Soc., 68, 53 (1946).
89. Hartmann, H., Inaug. Dissert. Marburg, 1-56 (1896) [Chem. Zentr., 67 [1], 999 (1896)].
90. Bost and Everett, J. Am. Chem. Soc., 62, 1752 (1940).

identical melting point. A mixed melting point with (XXVI) and (XXVII) was not depressed. The reactions involved are:

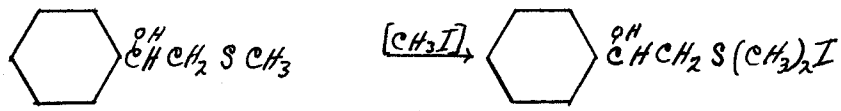


(9)

XXVI



(10)



(11)

XXVII

This structure proof shows that the product isolated in equation (9) contained a secondary alcohol group. Thus it can be assumed that the general reaction is the one given by equation (4). A similar conclusion was later reached by Massie[91] for the cleavage of styrene oxide with sodium dodecyl mercaptide. In the proof of structure performed by him, the hydroxy sulfide formed by the cleavage of styrene oxide with sodium dodecyl mercaptide was oxidized to the corresponding ketone. The 2,4-dinitrophenylhydrazone prepared from this ketone was identical with that prepared from the reaction of phenacyl bromide and sodium dodecyl mercaptide. These reactions are shown below:

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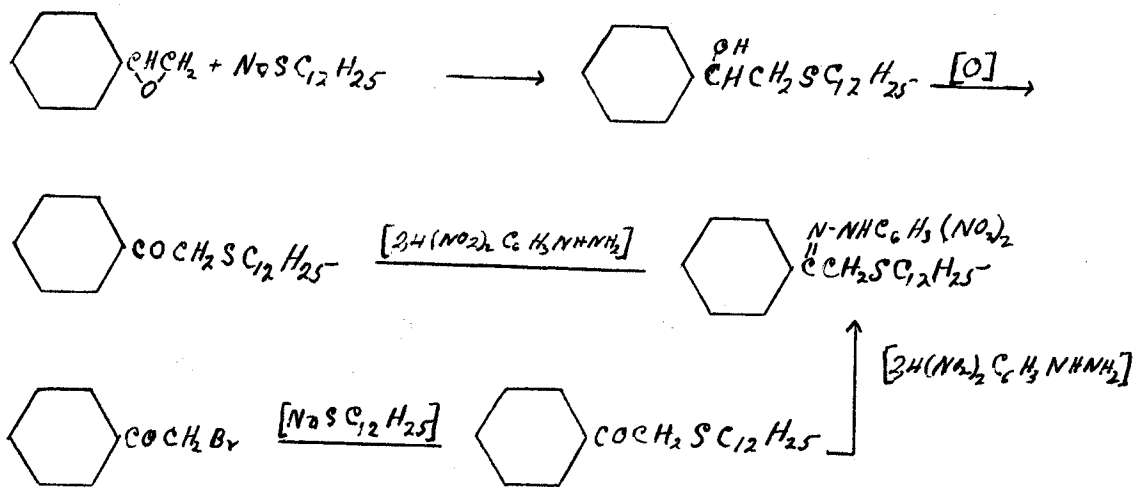
91. Massie, S.P., Doctoral Dissertation, Iowa State College (1946).



The results given here indicate that the cleavage of unsymmetrical epoxides by mercaptan in basic media follows very closely that observed with alcohols,[33,34,39] the reaction being a bimolecular nucleophilic displacement on carbon.

The cleavage of unsymmetrical epoxides by mercaptans in an acid media has not been investigated. It would be of special interest to determine the mode of ring opening under these conditions.

The compounds prepared in this series and their physical constants are given in Table II.

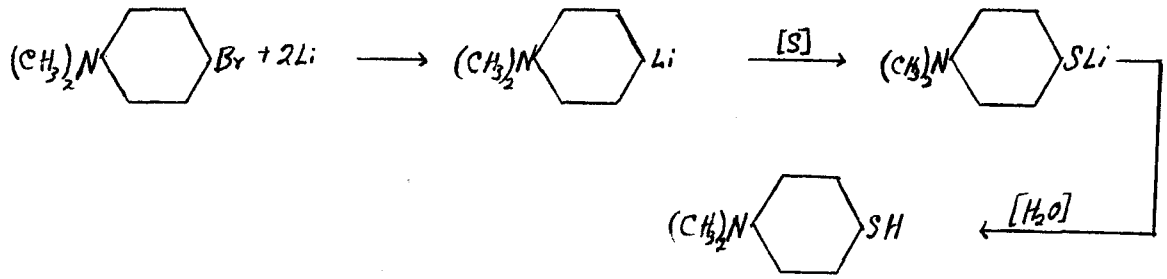
In connection with the preparation of the above series of compounds, thiophenol and p-dimethylaminothiophenol were prepared by a new method. The bromobenzene or its derivative p-dimethylaminobromobenzene was added to an ether suspension of metallic lithium. The organolithium compound formed was then treated with sulfur to form the lithium mercaptide. The reactions

Table II

OH
R-CH-CH_2SR'

R	R'	b.p./mm.	Yield-%	Analysis, N Calcd.	Found
C_6H_5	$(CH_2)_3N(C_2H_5)_2$	149-52°/0.5	50.5	5.24	5.44
C_6H_5	$(CH_2)_2N(C_2H_5)_2$	132°/0.5	78	5.54	5.65
$(C_2H_5)_2NCH_2$	$(CH_2)_3N(C_2H_5)_2$	131-4°/0.5	54	10.14	10.05
$(C_2H_5)_2NCH_2$	$(CH_2)_2N(C_2H_5)_2$	121-2°/0.8	57	10.69	10.50
$(C_2H_5)_2NCH_2$	C_6H_5	125-8°/0.5	56	5.85	5.88
$(C_2H_5)_2NCH_2$	p-$(CH_3)_2NC_6H_4$	147-7°/0.001	52	9.93	9.96
$(C_2H_5)_2NCH_2$	p-$CH_3C_6H_4$	137°/0.8	65	5.53	5.65
$(C_2H_5)_2NCH_2$	p-$NH_2C_6H_4$	153°/1.0	53.5	11.02	11.04
$(C_2H_5)_2NCH_2$	p-ClC_6H_4	149-52°/1.5	23	5.13	5.29
C_6H_5	p-$NH_2C_6H_4$	185°/0.001	68	5.72	5.60
$CH_2=CH$	p-$NH_2C_6H_4$	165-8°/0.8	51.5	7.18	7.20
$CH_2=CH$	$(CH_2)_2N(C_2H_5)_2$	111°/1.5	87	6.90	7.17
$CH_2=CH$	$(CH_2)_3N(C_2H_5)_2$	123°/0.8	62	6.45	6.64

proceeded smoothly giving yields averaging 60%. The indications are that the by-products are mainly the disulfides.



This method of preparation should be of value in preparing heretofore unobtainable mercaptans. The reaction will be of value in cases where metalation takes place in a different position than that involved in nitration. For example, the nitration of benzothiazole results in the nitro group becoming attached to the benzene ring while metalation occurs in the 2-position of the thiazole ring.

The Grignard reagent has been reacted with sulfur many times.[92] The complementary nature of the Grignard reagents and the organometallic compounds of lithium[93] should increase the value of this method.

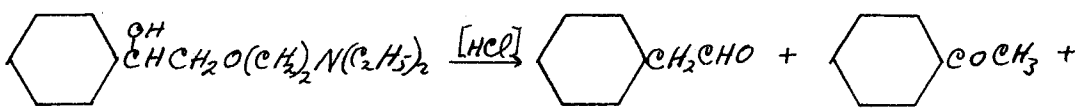
4. Hydrolysis of β-Diethylaminoethyl β'-Hydroxy-β'-phenylethyl Ether.

In connection with the study of the physiological action of β-diethylaminoethyl β'-hydroxy-β'-phenylethyl ether it was

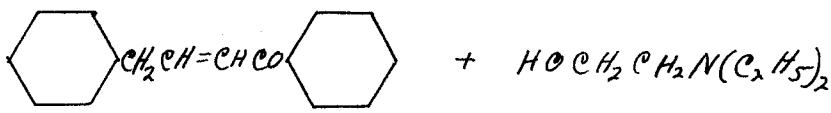
92. Runge, "Organometall verbindungen. I Teil: Organomagnesium verbindungen," Wissenschaftliche Verkgsgeselkschaft, m.b.l., Stuttgart (1932), p. 261.
93. Gilman, "Organic Chemistry, An Advanced Treatise," John Wiley and Sons, Inc., New York, Vol. I (1943), p. 524.

observed[94] that the treatment of the ether with 10% hydrochloric acid resulted in the formation of an aldehydic odor. The presence of a carbonyl group was shown by the formation of a 2,4-dinitrophenylhydrazone. An attempt has been made to determine the nature of the cleavage and the identity of the compounds formed.

When β-diethylaminoethyl β'-hydroxy-β'-phenylethyl ether was treated with 10% hydrochloric acid a slight exothermic reaction took place. The solution was worked up immediately and gave largely starting material plus a small amount of acetophenone. When the acid solution was refluxed for a period of six hours the following products were obtained, phenylacetaldehyde, β-diethylaminoethyl alcohol and a compound which is probably $C_6H_5CH_2CH{=}CHCOC_6H_5$. A general equation for the reaction is shown below:



XXVIII XXIX



XXX

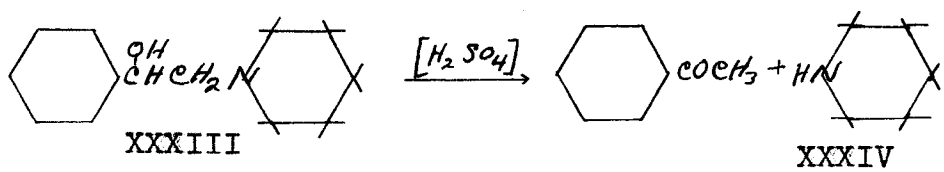
94. Dr. Jones, Parke, Davis and Co., Private Communication.

It has been shown by other authors[95] that phenyl-1,2-ethanediol decomposes in the presence of mineral acids to give phenylacetaldehyde. Tiffeneau[96] reports that when 1-phenyl-2-alkoxyethanols are heated with 1/2 N sulfuric acid, phenylacetaldehyde is formed with no acetophenone. He gives the following reaction:

$$C_6H_5CHOHCH_2OR \xrightarrow{[-H_2O]} C_6H_5CH{=}CHOR \longrightarrow C_6H_5CH_2CHO + HOR \qquad (12)$$

XXXI XXXII

However, in one experiment he reports that when styrene iodohydrin was treated with sodium methoxide, the expected 1-phenyl-2-methoxyethanol, $C_6H_5CHOHCH_2OCH_3$, was obtained plus a compound, $C_{16}H_{16}O_2$, which absorbed bromine and decomposed into acetophenone. This would indicate that under some conditions it would be possible to obtain acetophenone as well as phenylacetaldehyde from the hydrolysis of 1-phenyl-2-alkoxy-ethanols. Further evidence for the formation of phenylacetaldehyde and acetophenone from reactions involving phenyl-1,2-ethanediol is given by Rabe.[97] He heated 1-phenyl-2-piperidylethanol with N sulfuric acid and obtained acetophenone and piperidine.



XXXIII XXXIV (13)

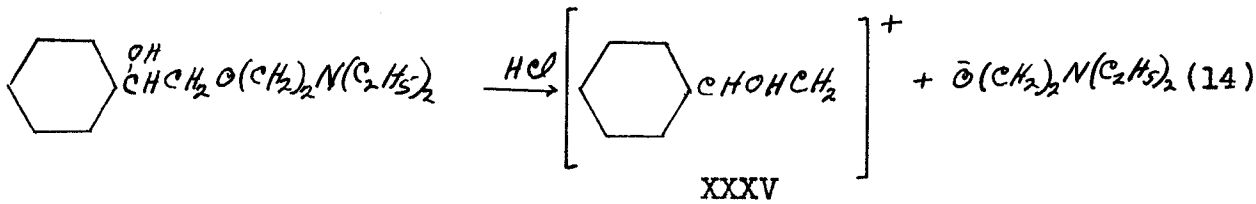
95. Tiffeneau, Ann. chim. phys. [8] 10, 322-78 (1907); Zincke, Ann., 216, 303 (1882); Krohnke and Schulze, Ber., 75B, 1154 (1942).
96. Tiffeneau, Compt. rend., 145, 811 (1907).
97. Rabe, Ann., 365, 380 (1909).

Krohnke and Schulze[95] have reported cleaving compound (XXXIII) using aqueous hydrobromic acid in acetic acid to obtain piperidine (XXXIV) and phenylacetaldehyde (XXVIII) but no acetophenone (XXIX).

The compound (XXX) was also prepared by two other methods; by refluxing a suspension of equal amounts of phenylacetaldehyde and acetophenone in a 10% hydrochloric acid solution and also in the presence of sodium methoxide and sodium hydroxide. The 2,4-dinitrophenylhydrazone of the compound prepared by these methods melted at the same temperature as that obtained from the cleavage. The melting point was not depressed when mixed with that obtained from the cleavage. Attempts at formation of derivatives by reactions involving 1,4-addition to compound (XXX) did not result in any isolatable addition products. An attempt was also made to form a bromo derivative. The failure to do this was probably due to the active hydrogens in the γ-position.

The exact mechanism of the hydrolysis has not been definitely established. Tiffeneau[95] in equation (12) has postulated that the first step in the hydrolysis is a dehydration. The styryl ether is then cleaved to give 2-phenylethenol followed by rearrangement of the keto-enol type to give phenylacetaldehyde. This mechanism, however, would not account for the formation of acetophenone.

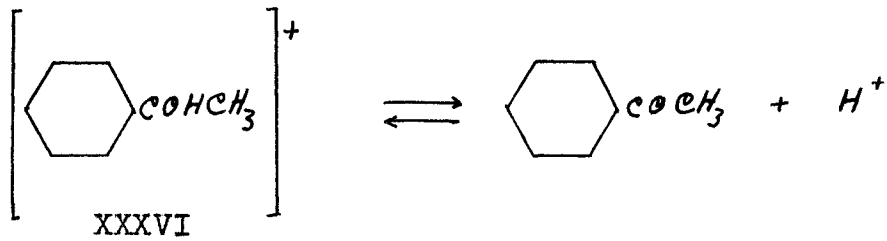
In order to obtain acetophenone it appears that an ionic rearrangement occurs following the rupture of the ether linkage. By this method the cleavage of the ether would result in the formation of the carbonium ion XXXV. The intermediate structure



(14)

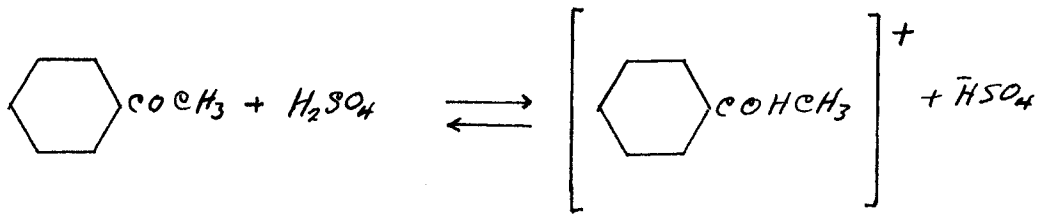
XXXV

XXV, is stabilized by its resonant ion XXXVI which can lose a



XXXVI

proton to form acetophenone. This reaction is illustrated with



acetophenone in concentrated sulfuric acid.[98] In sulfuric acid the reaction proceeds to the right while in dilute acid the reaction is reversed. Therefore, the hydrolysis in dilute acid would favor the formation of acetophenone. The need for further data on reaction rates prevents a more detailed discussion of the mechanism.

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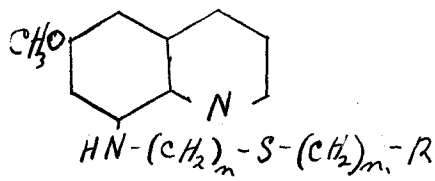
98. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, (1940), p. 46.

5. Quinoline Sulfides

The preparation of quinoline compounds with sulfur containing side chains was first reported in 1929.[99] The compound prepared was 8-[β-(β'-diethylaminoethylmercapto)ethylamino]-6-methoxyquinoline. Later the dimethoxy derivative, 8-[β-(β'-diethylaminoethylmercapto)ethylamino]-5,6-dimethoxyquinoline was prepared.[100] The physiological properties of these compounds were not available but they appeared to be of such a structure as to warrant investigation. In these laboratories a series of compounds was prepared in which the length of the alkyl groups in the side-chain was varied and also the nature of the terminal amino group.[101,76] These compounds are illustrated in the following general formula (XXXVII).



XXXVII

n=2 or 3
n₁=2 or 3
R=diethylamino, piperidino, morpholino, or thiomorpholino.

Very similar work was carried on at the same time by the Winthrop Chemical Company.[102] The fact that the compound 4-(δ-diethylamino-α-methylbutylamino)-7-chloroquinoline

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99. Brit. Patent 286,087 (1926) [C.A., 23, 241 (1929)].
100. Brit. Patent 354,352 (1930) [C.A., 26, 5312 (1932)]; U.S. Patent 1,938,047.
101. Gilman and Woods, J. Am. Chem. Soc., 67, 1843 (1945); Gilman and Tolman, ibid., 67, 1847 (1945).
102. Huber, Bair, Boehme, Laskowski, Jackman, and Clinton, J. Am. Chem. Soc., 67, 1849 (1945).

possessed antimalarial activity apparently suggested the placing of the sulfur side-chain in the 4-position of 7-chloroquinoline, as compounds of this type have recently been reported.[103]

This type of side-chain has also been placed on other nuclei as in the 9-position of 6-chloro-2-methoxyacridine[76,102,104,105] and in the meta-position of trifluoromethylbenzene.[76]

The formation of the corresponding sulfones of compounds of this type have also been made. The preparation of 9-[β-(β'-diethylaminoethylsulfonyl)ethylamino]-2-methoxy-6-chloroacridine dihydrochloride was made by Huber and co-workers.[102] They also attempted the preparation of 8-[x-(β-diethylaminoethylsulfonyl)alkylamino]-6-methoxyquinoline. The alkyl group used was not mentioned in their article. The formation of the sulfone was attempted by oxidizing the corresponding sulfide with hot permanganic acid. A homolog of this compound, if not the same one, has been prepared by Gilman and Fullhart[65] by the following series of reactions.

$$p\text{-}O_2NC_6H_4ONa + ClCH_2CH_2CH_2OH \longrightarrow p\text{-}O_2NC_6H_4O(CH_2)_3OH \xrightarrow{[SOCl_2]}$$

$$p\text{-}O_2NC_6H_4O(CH_2)_3Cl \xrightarrow{[NaSCH_2CH_2OH]} p\text{-}O_2NC_6H_4O(CH_2)_3SCH_2CH_2OH \xrightarrow{[SOCl_2]}$$

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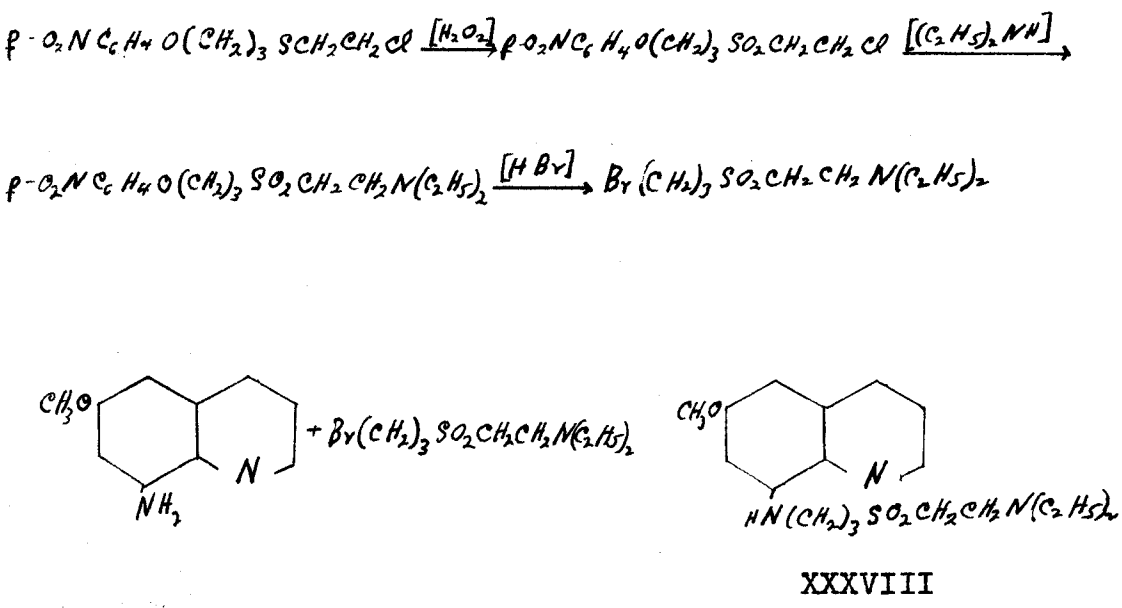
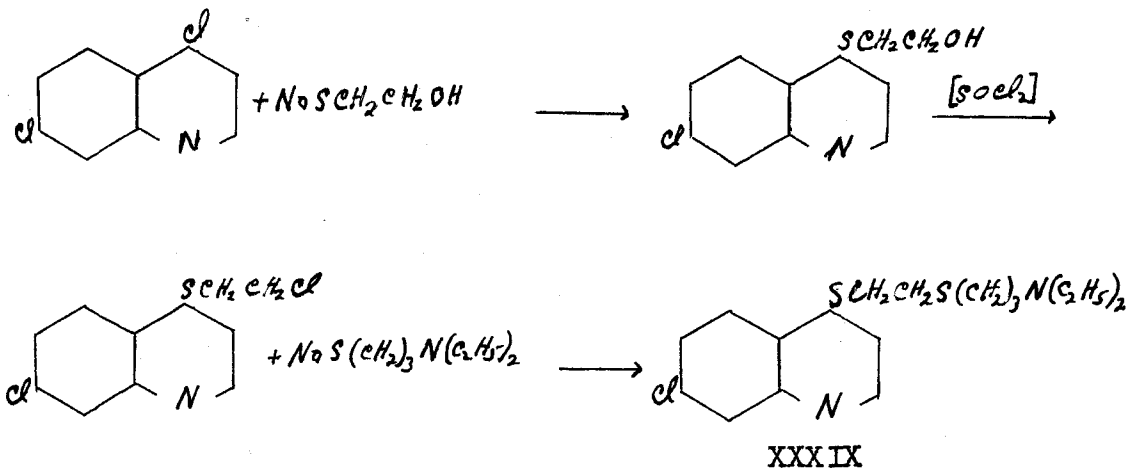
103. U.S. Patent 2,233,970 (1941) [C.A., 35, 3771 (1941)]; Ger. Patent 683,692 (1939) [C.A., 36, 4973 (1942)].
104. U.S. Patent 2,082,171 (1937) [C.A., 31, 5112 (1937)].
105. U.S. Patent 2,077,249 (1937) [C.A., 31, 4060 (1937)].



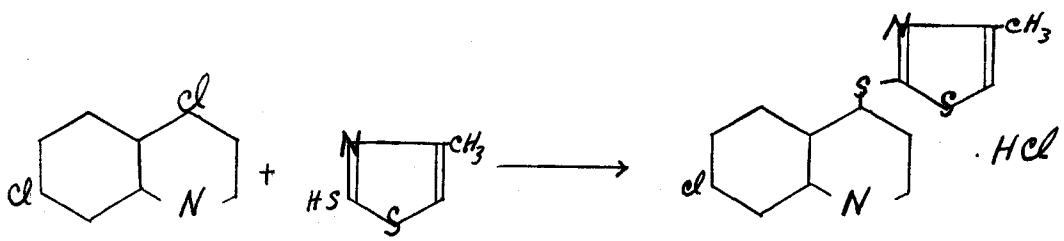
XXXVIII

The 8-quinolylaminoalkyl sulfides and the sulfone exhibited considerable antimalarial activity, therefore the series was extended to include some compounds in which the sulfur containing side-chain was connected to the quinoline ring by a sulfur atom instead of the usual amino group. 7-Chloro-4-quinolyl p-(γ'-diethylaminopropylmercapto)ethyl sulfide (XXXIX) was prepared in the following manner.



XXXIX

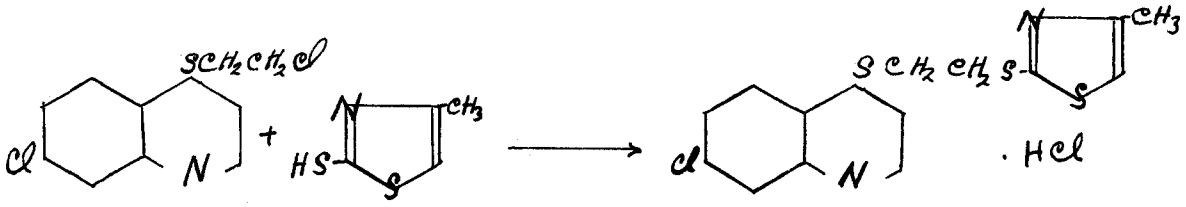
In view of the high physiological activity of compounds containing the thiazole ring such as sulfathiazole and promizole, two sulfides were made containing both the quinoline ring and the thiazole ring. Thus, 7-chloro-4-quinolyl 4'-methyl-2'-thiazolyl sulfide hydrochloride (XL) was prepared by reacting 4,7-dichloroquinoline and 4-methyl-2-mercaptothiazole in boiling ethanol.



XL

The condensation was made directly and gave a quantitative yield of the product as the hydrochloride.

The preparation of 7-chloro-4-quinolyl β-(4'-methyl-2'-thiazolylmercapto)ethyl sulfide hydrochloride (XLI) was made by condensing the quinolyl β-chloroethyl sulfide with 4-methyl-2-mercaptothiazole. Of particular interest is the fact that in

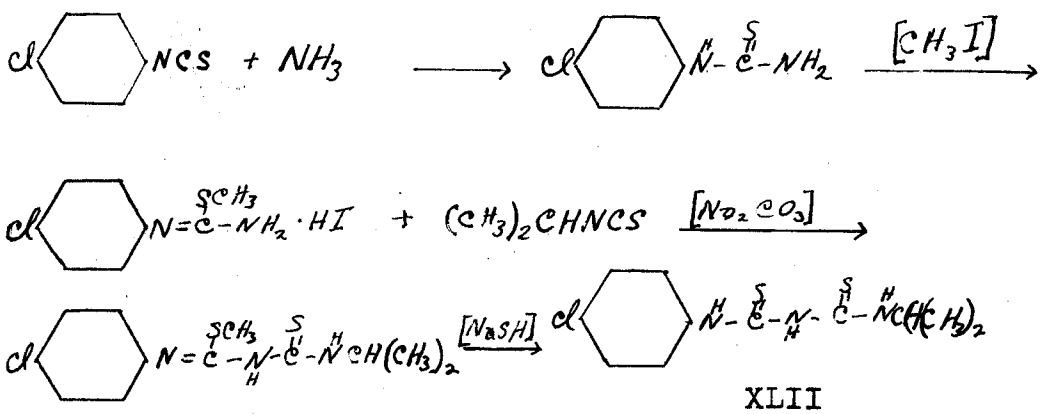


XLI

the last two reactions it was not necessary to add any basic material as a condensing agent. Work of this type may have a general application where one of the reactants has a basic group. Some similar condensations are being made by White.[106] The results of the testing of these compounds are not available at this time.

6. Some Sulfur Modification of Paludrine

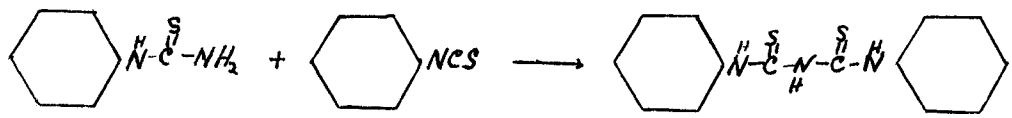
The recent publication[7] of the antimalarial activity of N-p-chlorophenyl-N[5]-isopropylbiguanide (Paludrine) (IV) and the fact that it exhibited prophylactic activity against avian malaria prompted an investigation of this type of compound in which one or more of the nitrogen atoms were replaced by sulfur or oxygen. Thus 1-p-chlorophenyl-5-isopropyldithiobiuret (XLII) a dithio analog of paludrine was prepared. The preparation was made by condensing isopropyl isothiocyanate with 1-p-chlorophenyl-2-thiolmethylpseudothiourea followed by demethylation. The reactions involved are given below:



XLII

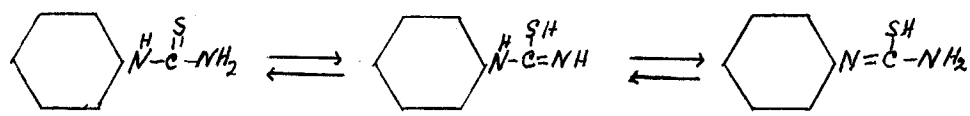
106. White, D., Unpublished studies in these laboratories.

An attempt was made to prepare this type of compound by condensing the isothiocyanate directly with the substituted thiourea. It was possible to prepare 1,5-diphenyldithiobiuret (XLIII) by this method but the yield was not so good as that

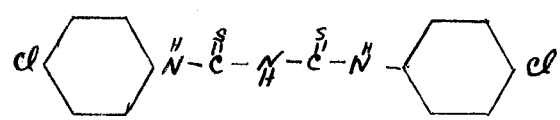


XLIII

by the method already given. The lower yield in this reaction is probably the result of the stability of the phenythiourea due to its resonating structure.

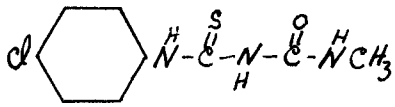


The formation of the thiolmethyl derivative in the method finally used probably dampens this resonating effect. By the same method used for the preparation of (XLII) it was possible to prepare 1,5-bis(p-chlorophenyl)dithiobiuret (XLIV).

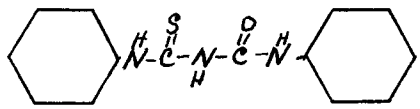


XLIV

In order to test the relationship of some sulfur and oxygen analogs as antimalarial agents, 1-p-chlorophenyl-5-methyl-2-monothiobiuret (XLV) and 1-p-chlorophenyl-5-phenyl-2-monothiobiuret (XLVI) were prepared. The method was the same



XLV



XLVI

as that given above except that the respective isocyanates were used instead of the isothiocyanates.

7. Miscellaneous Sulfones

In addition to the compounds already reported in the preparation of 8-[γ-(β'-diethylaminoethylsulfonyl)propylamino]-6-methoxyquinoline[64] the following were also prepared: γ-(p-nitrophenoxy)propyl β-morpholinoethyl sulfone, γ-(p-aminophenoxy)propyl β-morpholinoethyl sulfone and γ-(p-isopropylaminophenoxy)propyl β-morpholinoethyl sulfone (?) (XLVII). An attempt was also made to prepare γ-bromopropyl β-morpholinoethyl sulfone. The morpholine derivatives were made because of their ease of crystallization. In the preparation of γ-bromopropyl β-diethylaminoethyl sulfone already mentioned considerable difficulty was experienced in cleaving the p-nitrophenyl γ-(β'-diethylaminoethylsulfonyl)propyl ether. A survey of the

literature indicated that p-nitrophenyl alkyl ethers were more difficult to cleave than phenyl, p-halophenyl or p-aminophenyl ethers. Thus the ease of cleavage increases as the para substituent becomes more positive. This is borne out in the work of Stoermer[107] who reports the percent of cleavage of the following ethers with hydrobromic acid in acetic acid. The time of reaction was two hours unless otherwise indicated. These results show that the compounds with the more negative

Ether	Percent cleaved
Anisole	85
p-Bromoanisole	75
p-Bromophenetole	75
o-Bromoanisole	17.8 (4 hours)
p-Acetylanisole	28.6
p-Carboxyanisole	48

substituent were the most resistant to cleavage. Similar evidence was obtained by Raiford and Colbert[108] and Birosel.[109]

An excellent study of the cleavage of substituted aryl alkyl ethers has been made by Kolhatkar and Ghaswalla.[110] They covered a rather complete range of substituted phenyl alkyl ethers using 10 normal hydrochloric acid at 130° for two hours in a sealed tube as the method for cleavage. A table of their

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107. Stoermer, Ber., 41, 321 (1908).
108. Raiford and Colbert, J. Am. Chem. Soc., 48, 2652 (1926).
109. Birosel, ibid., 52, 1944 (1930).
110. Koshatkar and Ghaswalla, J. Indian Chem. Soc., 8, 511 (1931).

results is given below.

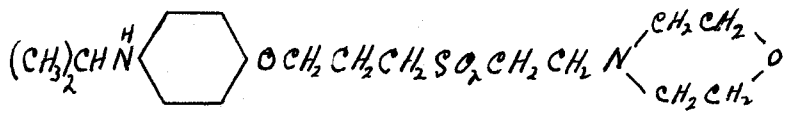
Ether	Percent cleaved
Anisole*	33
Phenetole	14.8
m-Nitroanisole	6.4
o-Nitroanisole	10.8
p-Nitroanisole*	12.7
m-Chloroanisole	3.5
o-Chloroanisole	9.9
p-Chloroanisole*	12.8
m-Bromoanisole	2.2
o-Bromoanisole	4.6
p-Bromoanisole*	6.3
m-Methylanisole	11.4
o-Methylanisole	12.1
p-Methylanisole*	16.1
m-Aminoanisole	12.0
o-Aminoanisole	35.5
p-Aminoanisole*	75.0

An examination of the para substituted ethers marked with an asterisk gives the following order for the ease of cleavage.

$$NH_2 \rangle H \rangle CH_3 \rangle Cl \rangle NO_2 \rangle Br$$

The groups given are the <u>para</u> substituents of the phenyl methyl ethers.

This evidence prompted the reduction of γ-(<u>p</u>-nitrophenoxy)-propyl β-morpholinoethyl sulfone to γ-(<u>p</u>-aminophenoxy)propyl β-morpholinoethyl sulfone. The reduction was carried out in absolute ethanol using Raney nickel as a catalyst. In an attempt to reduce the compound using a mixture of acetone and ethanol as the solvent there was apparently obtained a condensation product between the amine and acetone. The analysis indicated the compound as being γ-(<u>p</u>-isopropylaminophenyl) propyl β-morpholinoethyl sulfone (XLVII).



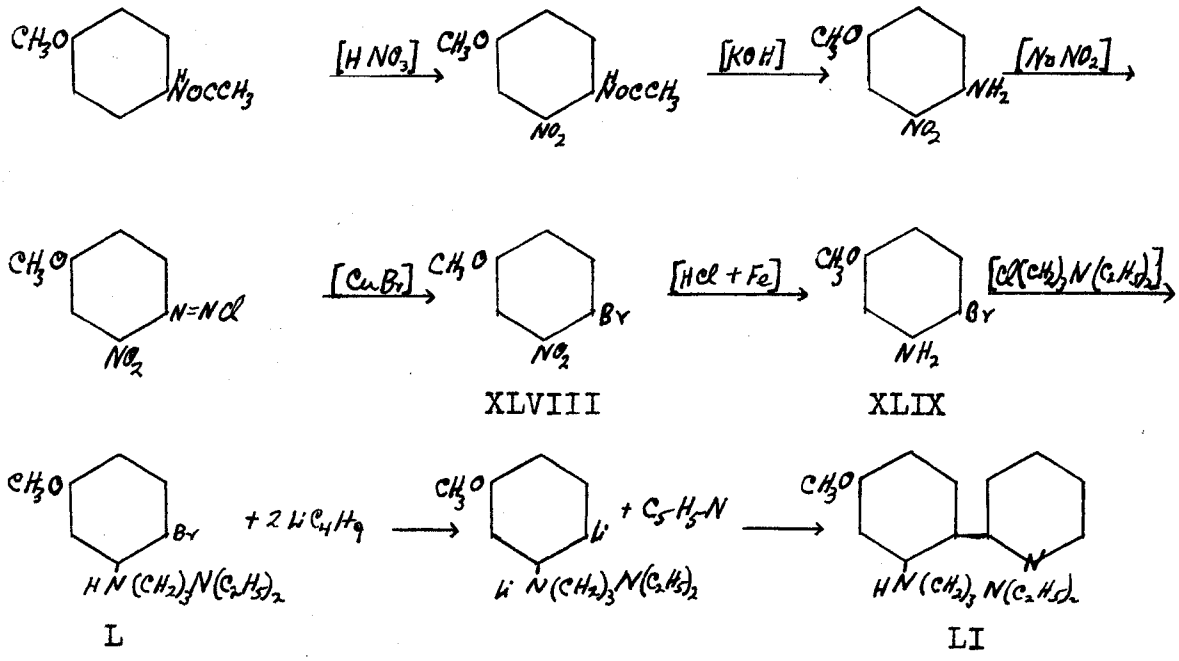
XLVII

Major[66] has reported a similar condensation in a reduction with platinum. The reduction of <u>p</u>-nitrophenol in an acetone solution with hydrogen and platinum produced <u>p</u>-hydroxy-N-isopropylaniline.

In the only attempt made to cleave the γ-(<u>p</u>-aminophenoxy)propyl β-morpholinoethyl sulfone, it was refluxed with 48% hydrobromic acid for nine hours. The starting material was recovered unchanged. It should be emphasized that this is not conclusive evidence against the ease of cleavage of this compound, but that further study is necessary.

8. Attempted Preparation of an "Open Model" of Plasmoquin

In view of the success of Spatz[111,112] in preparing an "open model" of atebrine which combined the gametocidal activity of quinine and plasmoquin and the schizonticidal action of atebrin, an attempt was made to prepare the "open-model" (LI) of plasmoquin. The preparation of this compound was proposed by the following series of reactions.



The first four steps are standard reactions and the compounds were prepared in good yields. The reduction of 3-nitro-4-bromoanisole (XLVIII), however, was somewhat unusual in that

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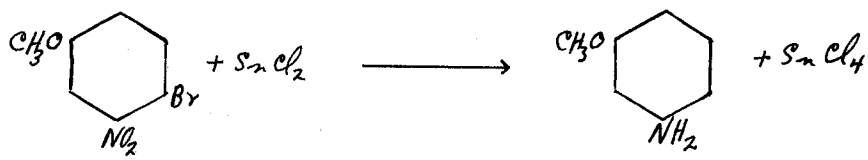
111. Spatz, S.M., Doctoral Dissertation, Iowa State College (1941); Gilman and Spatz, J. Am. Chem. Soc., 66, 621 (1944).
112. See also, Gilman, Christian, and Spatz, ibid., 68, 979 (1946), for some quinolines patterned as "open models" of a modified atebrin.

very mild conditions were necessary. An attempt to reduce this compound with stannous chloride resulted in the removal of the halogen atom also.



XLVIII LII

In this reaction almost a quantitative yield of m-anisidine (LII) was obtained. The reduction to (XLIX) was accomplished in a 79% yield using iron and hydrochloric acid. The condensation of 3-amino-4-bromoanisole (XLIX) and γ-diethylaminopropyl chloride was made by heating the two together at 155° for six hours. In order to conserve the N-γ-diethylaminopropyl-3-methoxy-6-bromoaniline (L), N-γ-diethylaminopropyl-2-bromoaniline was prepared. The halogen-metal interconversion of p-bromoaniline has been made by Gilman and Stuckwisch[113] in at least a 68% yield. The addition of the organometallic compound, p-lithio-N,N-dilithioaniline to the anil of isoquinoline was later made by Gainer.[114]

The halogen-metal interconversion was made by adding 2 moles of n-butyllithium to 1 mole of N-γ-diethylaminopropyl-2-bromoaniline in dry ether at -60°. To the solution was then

113. Gilman and Stuckwisch, ibid., 63, 2844 (1941).
114. Gainer, G.C., Unpublished studies in these laboratories.

added 1 mole of dry pyridine. The reaction mixture was allowed to rise to room temperature and was stirred for one hour and worked up in the usual manner. Only the starting, N-γ-diethylaminopropyl-2-bromoaniline, could be isolated from the reaction. The addition of N-γ-diethylaminopropyl-N-lithio-3-methoxy-4-lithioaniline to quinoline was also attempted without success. An extensive study of the conditions necessary for the reaction of organolithium compounds, containing primary or secondary amino groups, with anil linkages would undoubtedly lead to the successful completion of this synthesis.

9. Miscellaneous Compounds

A study of the more promising antimalarials derived from quinoline revealed that they usually contained a methoxyl group in the 6-position and a basic "side-chain" in either the 4- or 8-position. In order to determine whether the activity of these compounds was restricted to the positions occupied by these groups or if some other combination would also result in antimalarial activity, a series[115] of isomeric (methoxy)-(2,5-dimethylpyrryl-1)quinolines was prepared. This series utilized the 2,5-dimethylpyrryl group as the basic "side-chain" because of the ease of preparation and because compounds of this type[116] had shown significant activity.

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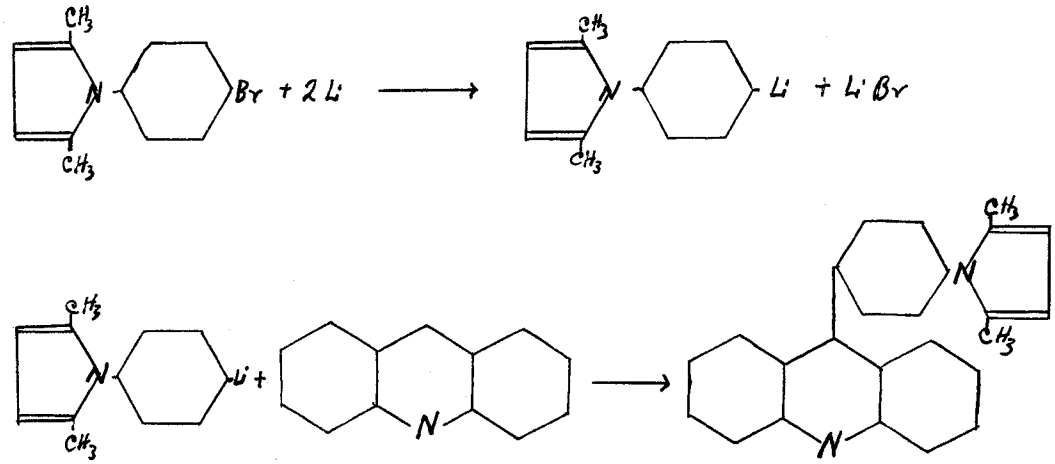
115. Gilman and Fullhart, J. Am. Chem. Soc., 68, 978 (1946).
116. Gilman, Stuckwisch, and Nobis, ibid., 68, 326 (1946).

It will be observed, however, that the 2,5-dimethylpyrryl group was only placed on the benzene ring. An attempt was therefore made to place the 2,5-dimethylpyrryl group in the 2-position of quinoline by condensing 6-methoxy-2-chloroquinoline with 2,5-dimethylpyrrole. The following methods of condensation were attempted: by condensing the two directly by heating at 155-60°; by heating the mixture with potassium carbonate and a small amount of copper bronze; and by refluxing a solution of 2-chloroquinoline and N-lithio-2,5-dimethylpyrrole in xylene. In no case was any of the desired product isolated.

It was found, however, that morpholine would condense with 2-chloroquinoline by heating the two together at 140° for eight hours. The morpholine group is known to possess about the same basic properties as the diethylamino group and, perhaps, some of the basic properties of 2,5-dimethylpyrrole. Therefore, by substituting morpholine for 2,5-dimethylpyrrole in some quinoline derivatives it might indicate some activity. The following compounds were prepared in this series; 2-morpholinoquinoline, 6-methoxy-2-morpholinoquinoline, and 6-methoxy-4-morpholinoquinoline.

In connection with the study of some 2,5-dimethylpyrrole derivatives, 9-[p-(2',5'-dimethylpyrryl-1')phenyl] acridine (LIII) was prepared. The preparation was made by the 1,4-addition of p-(2,5-dimethylpyrryl-1)phenyllithium to acridine.

The reactions involved are given below.



LIII

V. SUMMARY

1. A brief discussion of the present antimalarial and antituberculous agents has been given.

2. The mechanism of the addition of mercaptans to chalcones has been discussed and evidence given to indicate the reaction involves 1,4-addition. The conditions necessary for the addition of aminoalkylmercaptans to chalcones have been determined and a possible reason for these conditions has been advanced. The physiological properties of some substituted chalcones and their addition products with mercaptans have been discussed.

3. A new series of β-hydroxyethyl sulfides has been prepared for testing as antimalarial and antituberculous agents. The cleavage of unsymmetrical epoxides with mercaptans has been studied and a mechanism for the mode of ring opening has been postulated.

4. The sulfur atom has been introduced into a series of paludrine type compounds.

5. An attempt was made to prepare an "open-model" of plasmoquin.

6. Some miscellaneous quinoline compounds containing one or two sulfur atoms in a basic "side-chain" have been prepared as antimalarial agents.