THE SYNTHESES OF SOME TERTIARY AMINE DERIVATIVES OF MIXED PHENYL ALKYL SULFIDES

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THE SYNTHESES OF SOME TERTIARY AMINE DERIVATIVES OF MIXED PHENYL ALKYL SULFIDES

By

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INTRODUCTION

An extensive amount of work has been done on the elucidation of the structural relationship of organic compounds to their physiological and pharmacological properties during the first half of this century. A compound which has the following features in its structure,

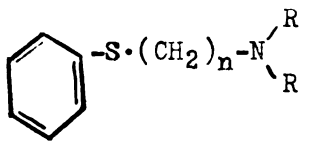
$$A\text{-}M\text{-}(C)_n\text{-}N\langle$$

where A represents an aryl group, and where M is a heteroatom, has been a keen object of these investigations since the historical syntheses of "Novocaine" by Einhorn.[1] Novocaine, an important local anaesthetic of more advantageous physiological action than that of the natural anesthetic "Cocaine", was the famous ancestor of compounds of similar structure. Since the beginning of these investigations an intensive effort has been directed toward the discovery of the types of chemical structures which are responsible for given physiological activities.

As a result of this common goal of many investigators, an important prediction was made by Pyman,[2] who generalized the relationship for compounds of the above general structure with respect to their physiological actions. Later Löfgren[3] proposed the detailed structural requirements of a compound which would possess local anesthetic properties.

Because of the similarity in the chemical structure of sulfides and of ethers, and because of the usefulness of the latter when they also contain a tertiary amine group, the investigation reported in

this thesis was undertaken for the purpose of synthesizing a similar group of mixed tertiary amino phenyl alkyl sulfides. These are represented by the general formula:



A second aim of the present investigation can be ascribed to a study of the effect of the length and branching of the alkyl chain on the physiological activities of these compounds. Thus a systematic attempt was made to vary from two to six carbon atoms the length of the alkyl chain which is attached between the arylthio radical and a few different types of secondary amino groups. In other words, the arylthio radical was kept a constant part of the molecule and the chain length as well as the end secondary amine groups were variables.

From the results obtained in such an investigation, one should be able to draw some comparison between the ether and sulfide analogs with respect to their chemical and physiological properties. Further, one might expect that the slight differences between the sulfides and ethers in their chemical properties may possibly manifest themselves in important differences in their physiological behaviors. However, it is clear that only the clinical tests, which have not yet been conducted, can establish the true value of their physiological usefulness.

HISTORICAL

Very little work has been reported on the investigation of the physiological and pharmacological effects produced by tertiary amine derivatives of mixed phenyl alkyl sulfides, although a great deal more work has been done regarding the same effects of their ether analogs.

Considering the fact that many of these ethers have been found to be useful for their local anesthetic, antihistaminic, sympathomimetic, and antimalarial properties, an expectation of usefulness for the sulfide analogs seemed reasonable because of the close similarity in the structures of the ethers and sulfides. In accordance with the anesthesiophoric principle relating to the structural constituents among the vast majority of local anesthetics, as proposed by Löfgren,[3] the tertiary amines of mixed phenyl alkyl sulfides of the general structure, $C_6H_5S\cdot(CH_2)_n\text{-}N(R)_2$ could also be classified under the category of Löfgren's general formula for local anesthetics. He suggested that the intermediate chain should consist of a hydrocarbon residue joined to the aromatic structure through either an ester or an amide linkage, which served to increase the physiological activity. The ester or amide linkage might also be replaced by the amine nitrogen, the ketonic carbonyl, or the ether oxygen.

The replacement of the ether oxygen by a sulfur atom would be expected to give rise to properties very similar to those possessed by the ethers. One of the very few cases of an investigation of the physiological actions of tertiary amine derivatives of mixed phenyl alkyl sulfides was carried out by Buchel and Tchonbar.[4] Their work

reported a comparison of β-diethylaminoethyl phenyl sulfide (I) and β-diethylaminoethyl o-tolyl sulfide (II) with β-diethylaminoethyl phenyl ether (III) and β-diethylaminoethyl o-tolyl ether (IV).

(I) $C_6H_5S\cdot CH_2CH_2\cdot N(C_2H_5)_2$ (II) $O\text{-}CH_3C_6H_4S\cdot CH_2CH_2\cdot N(C_2H_5)_2$

(III) $C_6H_5O\cdot CH_2CH_2\cdot N(C_2H_5)_2$ (IV) $O\text{-}CH_3C_6H_4O\cdot CH_2CH_2\cdot N(C_2H_5)_2$

They reported all of the above compounds were hypotensive, adrenolytic, and slightly antihistaminic, but that none showed any local anesthetic action. They also found that the sulfur compounds were slightly less potent than the oxygen compounds in the administration of the lethal intravenous dose in mice.

In other investigations carried out by Kohler,[5] it was reported that β-ethylaminoethyl phenyl sulfide (V) and β-ethylaminoethyl o-tolyl sulfide (VI) had no protective action against the acute pulmonary edema produced by a one-milligram dosage of adrenalin hydrochloride in the intravenous injection of a three-kilogram rabbit. However, β-dimethylaminoethyl phenyl ether (VII) and bis (β-o-toloxyethyl)methylamine (VIII) were found to be quite effective.

(V) $C_6H_5S\cdot CH_2CH_2\cdot N(H)C_2H_5$ (VI) $CH_3C_6H_4S\cdot CH_2CH_2\cdot N(H)C_2H_5$

(VII) $C_6H_5O\cdot CH_2CH_2\cdot N(CH_3)_2$ (VIII) $(CH_3C_6H_4O\cdot CH_2CH_2)_2\cdot NHCH_3$

However, in none of the limited investigations reported in the literature were sufficient compounds containing sulfur prepared to allow a complete physiological study to be made.

This work deals with the preparation of some tertiary amine derivatives of mixed phenyl alkyl sulfides, and is confined to their

chemistry and does not include any of the physiological studies, which will be reported elsewhere.

The historical review of the possible methods available for the synthesis of tertiary amine derivatives of mixed phenyl alkyl sulfides as well as of the intermediates used in their preparation, ω-hydroxyalkyl phenyl sulfides and ω-chloroalkyl phenyl sulfides, will be discussed in order to indicate why the methods employed in the present investigation were selected.

The reactions between sodium phenoxide and ethylenedichloride or 1,3-dibromopropane were reported by Marvel[6] to yield 55-56%, and 84-85% of the corresponding ω-chloroalkyl phenyl ethers respectively, but there was no assurance that this reaction can be applied to thiophenolate and the same dihalides. The use of β-chloroethyl-p-toluenesulfonate as a chloroalkylating agent for sodium phenoxide was initially employed by Clemo and Perkin[7] and gave a better yield of β-chloroethyl phenyl ether than in the previous method.*

$$CH_3C_6H_4\cdot SO_2Cl + ClCH_2CH_2OH \longrightarrow CH_3C_6H_4\cdot SO_2OCH_2CH_2Cl + HCl$$

$$C_6H_5OH + CH_3C_6H_4\cdot SO_2OCH_2CH_2Cl \xrightarrow{NaOH} C_6H_5O\cdot CH_2CH_2Cl + CH_3C_6H_4\cdot SO_3Na$$

Another method was used by Steinkopf[8] to prepare β-chloroethyl phenyl ether in a 76% yield. This consisted of passing gaseous

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*An unpublished investigation by Dr. R. D. Schuetz on the reaction between sodium thiophenolate and β-chloroethyl-p-toluenesulfonate gave a fair yield of α,β-dithiophenylethane, besides a rather poor yield of β-chloroethyl phenyl sulfide.

hydrogen chloride into a mixture of phenol, sodium hydroxide and ethylene chlorohydrin in alcoholic solution heated on a steam bath.

$$C_6H_5OH + NaOH + Cl(CH_2)_2OH \xrightarrow[\text{Alcohol}]{HCl} C_6H_5O\cdot CH_2CH_2Cl + NaCl$$

Although no extensive investigation has been carried out, olefins have been utilized to prepare ω-chloroalkyl phenyl sulfides from sulfenylchloride. Lecher and Stöcklin[9] passed ethylene into a carbontetrachloride solution of phenylsulfenyl chloride under anhydrous conditions and obtained β-chloroethyl phenyl sulfide in a good yield.

$$C_6H_5SCl + CH_2 = CH_2 \longrightarrow C_6H_5S\cdot CH_2CH_2Cl$$

β-hydroxyethyl phenyl sulfide was also obtained[10] by condensing ethylene oxide with thiophenol in the presence of active charcoal.

$$C_6H_5SH + \underbrace{CH_2-CH_2}_{\diagdown O \diagup} \xrightarrow{C} C_6H_5S\cdot CH_2CH_2OH$$

Similar reactions were reported for epoxides and phenol[11] in the presence of alcoholic sodium hydroxide, using a sealed-tube technique,

$$C_6H_5OH + \underbrace{R-CH-CH_2}_{\diagdown O \diagup} \xrightarrow[\text{Alcohol}]{NaOH} C_6H_5O\cdot CH_2\underset{\displaystyle R}{\underset{|}{C}}HOH$$

but there was no assurance of its applicability using thiophenol.

Fuson and Koehneke[12] prepared β-hydroxypropyl phenyl sulfide by the reaction between sodium thiophenolate and chloroacetone, giving rise to thiophenylacetone which was then reduced by the Meerwein-Ponndorf[13] method.

$$C_6H_5SNa + ClCH_2\overset{\overset{O}{\|}}{C}\cdot CH_3 \longrightarrow C_6H_5S\cdot CH_2\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow{Al(O(CH_3)_2CH)_3} C_6H_5S\cdot CH_2\overset{\overset{CH_3}{|}}{C}HOH$$

They also prepared β-hydroxyisopropyl phenyl sulfide by the sulfur-catalyzed reaction between thiophenol and allyl alcohol. This latter

$$C_6H_5SH + CH_2{=}CHCH_2OH \xrightarrow{S} C_6H_5S\cdot\underset{\underset{CH_3}{|}}{C}HCH_2OH$$

compound rearranged, when treated with thionyl chloride or hydrogenchloride to replace the hydroxyl group by chlorine, to give β-chloropropyl phenyl sulfide instead of the expected β-chloroisopropyl phenyl sulfide.

$$C_6H_5S\text{-}\underset{\underset{CH_3}{|}}{C}HCH_2OH \xrightarrow[\text{or HCl}]{SOCl_2} C_6H_5S\cdot\underset{\underset{CH_3}{|}}{C}HCH_2Cl$$

Ranshaw[14] and co-workers reported that α-dialkylaminomethyl alkyl sulfides may be obtained in good yields by the reaction of mercaptans and secondary amines with formaldehyde, but an extension of this reaction to thiophenol has not been reported.

$$RSH + HCHO + HNR_2 \longrightarrow RSCH_2NR_2 + H_2O$$

An interesting synthesis of β-diethylaminoethyl 2,4-dinitrophenyl sulfide and of γ-diethylaminopropyl 2,4-dinitrophenyl sulfide was carried out by Gilman[15] and co-workers in the reactions between β-diethylaminoethyl and γ-diethylaminopropyl mercaptans with 2,4-dinitrochlorobenzene. The β-and γ-diethylaminomercaptans were prepared

in two different ways. The β-diethylaminoethylmercaptan has been prepared from ethylene sulfide and lithiumdiethylamide,[16] and from the interaction of β-diethylaminoethyl chloride with sodium hydrosulfide. The later reaction also yields bis(β-diethylaminoethyl) sulfide.

$$(C_2H_5)_2N\cdot CH_2CH_2SH + ClC_6H_3(NO_2)_2 \longrightarrow (C_2H_5)_2N\text{-}CH_2CH_2\cdot SC_6H_3(NO_2)_2$$

$$(C_2H_5)_2N\cdot CH_2CH_2CH_2SH + ClC_6H_3(NO_2)_2 \longrightarrow (C_2H_5)_2N\cdot CH_2CH_2CH_2\cdot SC_6H_3(NO_2)_2$$

$$(C_2H_5)_2NLi + \begin{matrix} CH_2\text{-}CH_2 \\ \diagdown\ \diagup \\ S \end{matrix} \longrightarrow (C_2H_5)_2N\cdot CH_2CH_2SLi \xrightarrow[48\%]{HCl} (C_2H_5)_2N\cdot CH_2CH_2SH$$

$$(C_2H_5)_2NCH_2CH_2Cl + NaSH \longrightarrow (C_2H_5)N\cdot CH_2CH_2SH + (Et_2N\text{-}CH_2CH_2)_2S$$

The γ-diethylaminopropyl mercaptan was prepared in a 55% yield by the reaction of γ-diethylaminopropyl chloride with sodium hydrosulfide, using essentially the same procedure as was used for the preparation of the lower homolog. It also gave γ-diethylaminopropyl 2,4-dinitrophenyl sulfide by reaction with 2,4-dinitrochlorobenzene as shown in the above equations.

The first attempt to prepare β-hydroxyethyl phenyl sulfide was made by Bennet and Berry[17] by adding ethylene chlorohydrin to a sodium thiophenolate solution. However, they did not succeed in isolating the pure product and reported its transformation into an unsaturated compound on distillation. However, this unstability to heat was not confirmed by Kirner.[18] Steinkopf[8] and his co-workers, as previously named, prepared β-hydroxyethyl phenyl sulfide in a similar manner,

but made no attempt to isolate it. The method employed in the present work was analogous to that suggested by Powell[19] for the preparation of the oxygen analogs and followed the procedure of Kirner[18] which was based essentially upon Powell's method. Kirner[18] prepared two ω-hydroxyalkyl phenyl sulfides, namely β-hydroxyethyl and γ-hydroxypropyl phenyl sulfides. This method gave a smooth reaction with sodiumthiophenolate and the corresponding chlorohydrins giving good yields of 80-90% of the theoretical in a one hour period at reflux temperatures.

$$C_6H_5SH + Cl(CH_2)_nOH \xrightarrow{NaOH} C_6H_5S\text{-}(CH_2)_nOH$$

Preparation of the first member of the homologous series of ω-chloroalkyl phenyl sulfides was first carried out by Steinkopf and his co-workers[8] in their synthesis of β-chloroethyl phenyl sulfide by passing hydrogen chloride into the crude β-hydroxyethyl phenyl sulfide to obtain a fair yield of the corresponding chloride. Bennet and Berry[17] obtained both the β-chloroethyl and γ-chloropropyl compounds by the application of the Darzens'[20] reaction to the corresponding hydroxy compounds.

The amination of the omega-halogen atom has been reported in the case of β-bromoethyl β-naphthyl ether to occur in alcoholic ammonia in a closed system at 100° C. by Koelle.[21] Clemo and Perkin[7] obtained a better yield of dimethylaminoethyl naphthyl ether using a sealed tube technique and a sixteen-hour period of reaction at 120-140° C. Extension of this reaction to the ω-chloroalkyl phenyl sulfides seemed possible.

DISCUSSION

After a careful consideration of the various methods which have been used for the preparation of a few of the simpler ω-hydroxy and ω-chloroalkyl phenyl sulfides, as well as those used in the synthesis of the tertiaryamine derivatives of mixed naphthyl alkyl ethers, the following procedure was decided upon for use in the present investigations:

$$C_6H_5SH + Cl(CH_2)_nOH \xrightarrow{NaOH} C_6H_5S\cdot(CH_2)_nOH + NaCl + H_2O$$

$$C_6H_5S\cdot(CH_2)_nOH + SOCl_2 \xrightarrow{\text{pyridine}} C_6H_5S\cdot(CH_2)_nCl + SO_2 + \text{pyridine}\cdot HCl$$

$$C_6H_5S\cdot(CH_2)_nCl + R_2NH \xrightarrow{\text{3-methylpyridine}} C_6H_5S\cdot(CH_2)_n\text{-}NR_2$$

The ω-hydroxyalkyl phenyl sulfides with two to six carbon atoms in the alkyl chain, including one with a branched alkyl chain of three carbon atoms, were prepared by the interaction of thiophenol with the corresponding polymethylene chlorohydrins in aqueous sodium hydroxide, following the procedure developed by Kirner.[18] The reactions were carried out smoothly using all reagents in stochiometric quantities and were completed in a period of two-thirds of an hour to an hour and a half at a temperature of 80 to 100° C. In general yields of 80-90% were obtained. The ω-hydroxyalkyl phenyl sulfide with a branched chain was prepared from propylene chlorohydrin. The distillation of the ω-hydroxy compounds generally required high temperature and high vacuum. For the ω-hydroxyhexyl phenyl sulfide, a waxy solid at room

temperature, a short fractionating column with a resistance heater on the side arm was necessary. The properties of the ω-hydroxyalkyl phenyl sulfides which are new are summarized in Table I.

The ω-hydroxyalkyl phenyl sulfides were further characterized by preparation of their 3,5-dinitrobenzoates and *p*-nitrobenzoates. The properties of those derivatives which have not been previously reported have been listed in Tables II and III.

The ω-chloroalkyl phenyl sulfides were obtained from the corresponding ω-hydroxyalkyl phenyl sulfides by means of the Darzens[20] reaction using pyridine as the solvent. Yields of approximately 50 to 90 percent were obtained by treating the ω-hydroxyalkyl phenyl sulfides with a 25% excess of thionyl chloride under carefully controlled conditions in order to prevent a sudden rise of the reaction temperature during the addition of the thionyl chloride. This was done by using a cold water bath around the reaction flask. The temperature used to complete the reactions after the addition of the thionyl chloride ranged from 50 to 90° C. At higher temperatures considerable tarring was apt to occur. The end of the reaction was determined by observing the formation of the pyridine hydrochloride in an amount approximately equivalent to the alcohol used. Generally the end of the reaction was reached in about one to one and a half hours in which time the color of the reaction mixture became light brown. The properties of the ω-chloroalkyl phenyl sulfides which have been prepared for the first time are listed in Table IV.

TABLE I

PHYSICAL CONSTANTS OBTAINED FOR THE ω-HYDROXYALKYL PHENYL SULFIDES

Compound[a]	Formula	B.P. °C./mm.	N_D^{20}	Sulfur %	
				Calc'd	Found
δ-hydroxybutyl phenyl sulfide	$C_{10}H_{14}OS$	119-22/3-4	1.5723	17.61	17.73
ε-hydroxyamyl phenyl sulfide	$C_{11}H_{16}OS$	155-6/1-2	1.5610*	16.35	16.09
ω-hydroxyhexyl phenyl sulfide	$C_{12}H_{18}OS$	152/ 0.5	1.5483*	15.26	14.76

* Measured immediately after distillation.

a The ω-hydroxyalkyl phenyl sulfides; β-hydroxyethyl phenyl sulfide,[18] γ-hydroxypropyl phenyl sulfide,[18] and β-hydroxypropyl phenyl sulfide[12] were also prepared, but they have been previously reported.

TABLE II

3,5-DINITROBENZOATES OF ω-HYDROXYALKYL PHENYL SULFIDES

3,5-Dinitrobenzoate of [a]	Formula	M.P.°C.	Sulfur % Calc'd.	Sulfur % Found
β-hydroxyethyl phenyl sulfide	$C_{15}H_{12}O_6SN_2$	112-.5	9.21	9.48 9.38
γ-hydroxypropyl phenyl sulfide	$C_{16}H_{14}O_6SN_2$	84-5	8.85	8.86
β-hydroxypropyl phenyl sulfide	$C_{16}H_{14}O_6SN_2$	108-10	8.85	8.72
δ-hydroxypropyl phenyl sulfide	$C_{17}H_{16}O_6SN_2$	84	8.53	8.75 8.78
ε-hydroxyamyl phenyl sulfide	$C_{18}H_{18}O_6SN_2$	73	8.22	8.52 8.50
ω-hydroxyhexyl phenyl sulfide "a"	$C_{19}H_{20}O_6SN_2$	136-41	7.93	6.06

a All crystallized from ethanol except "a" which was crystallized from a mixture of ethanol and n-propyl alcohol.

TABLE III

P-NITROBENZOATES OF THE ω-HYDROXYALKYL PHENYL SULFIDES

p-Nitrobenzoate[a] of	Formula	M.P.°C.	Sulfur % Calc'd.	Sulfur % Found
β-hydroxyethyl phenyl sulfide	$C_{15}H_{13}O_4SN$	58-59	10.58	10.68
γ-hydroxypropyl phenyl sulfide	$C_{16}H_{15}O_4SN$	59-60	10.17	10.43
β-hydroxypropyl phenyl sulfide	$C_{16}H_{15}O_4SN$	63-64	10.17	10.35
δ-hydroxybutyl phenyl sulfide	$C_{17}H_{17}O_4SN$	59-60	9.69	9.92
ε-hydroxyamyl phenyl sulfide	$C_{18}H_{19}O_4SN$	54-55	9.29	9.39
ω-hydroxyhexyl phenyl sulfide	$C_{19}H_{21}O_4SN$	104-109	8.93	3.37

a All crystallized from ethanol.

TABLE IV

PHYSICAL CONSTANTS OBTAINED FOR THE ω-CHLOROALKYL PHENYL SULFIDES

Compound [a]	Formula	B.P. °C./mm.	N_D^{20}	Sulfur %	
				Calc'd	Found
δ-chlorobutyl phenyl sulfide	$C_{10}H_{13}SCl$	123/2 107/1	1.5670	15.99	16.35
ϵ-chloroamyl phenyl sulfide	$C_{11}H_{15}SCl$	146/1-2* 127-37/1	1.5600* 1.5680	14.95	16.25
ω-chlorohexyl phenyl sulfide	$C_{12}H_{17}SCl$	144-7/1	1.5490	14.03	14.10

a The ω-chloroalkyl phenyl sulfides; β-chloroethyl phenyl sulfide,[18] γ-chloropropyl phenyl sulfide,[18] and β-chloropropyl phenyl sulfide[12] were also prepared, but they have been previously reported.

* Data from duplicate preparations.

The tertiary amine derivatives of the mixed phenyl alkyl sulfides were obtained from the ω-chloroalkyl phenyl sulfides by treatment with a two-molar excess of the corresponding secondary amines which were piperidine, morpholine, dimethylamine, or diethylamine, in toluene as the solvent. The reaction conditions varied widely with respect to time and temperature, depending on the nature of the secondary amine and the reactivity of the particular ω-chloroalkyl phenyl sulfide used. The reaction periods ranged from one to nine hours and the reaction temperatures varied from 70 to 130° C. The reactions were considered complete when no more secondary amine salt formed. Rather large differences in the reactivities of the different members of the homologues series of ω-chloroalkyl phenyl sulfides was qualitatively observed. Although no attempts were made to obtain any quantitative determination of the reactivity of the chlorine atom in the ω-chloroalkyl phenyl sulfides prepared in this work, it was found that the reactivity of the chlorine in the first three members of the homologous series of ω-chloroalkyl phenyl sulfides was in general agreement with Kirner's[18] results on such activity.

Upon the completion of the reactions the free amines were isolated by the following method. To the reaction mixture was added water to dissolve the salt formed, followed by sodium hydroxide until the solutions became alkaline, then the mixture was distilled with steam until the distillate gave a negative Simon's color test for a secondary amine.[28] The steam distillation removed the excess secondary amine and the toluene from the reaction mixture. The remaining

aqueous mixture of oil was treated with hydrochloric acid to convert the oily tertiary amine into a soluble salt. Extraction with ether at this point removed any unused ω-chloroalkyl phenyl sulfide. In all cases, there was no appreciable amount of unused ω-chloroalkyl phenyl sulfide. The mixtures were then made alkaline again, whereupon an oil layer formed which was separated and later the oil was combined with the benzene extracts of the aqueous layers. After drying over anhydrous sodium sulfate, the benzene was removed on a steam bath and the remaining free amine was taken up in dry ether into which hydrogen chloride gas was passed to precipitate the amine hydrochloride. The crude amine hydrochlorides were recrystallized from a variety of solvents due to their different solubility. In general isopropyl alcohol, benzene, and 1,4-dioxane were found suitable for the recrystallization of the ω-piperidyl and ω-morpholylalkyl phenyl sulfide hydrochlorides, while only 1,4-dioxane was suited for the ω-dimethyl and ω-diethylaminoalkyl phenyl sulfides.

In addition to the reaction conditions previously discussed, the sealed tube technique was applied for the interaction of dimethyl and diethylamine with the corresponding ω-chloroalkyl phenyl sulfides. In the reactions involving dimethylamine 1,4-dioxane was used as a solvent since it was expedient to employ the amine in a 25% aqueous solution.

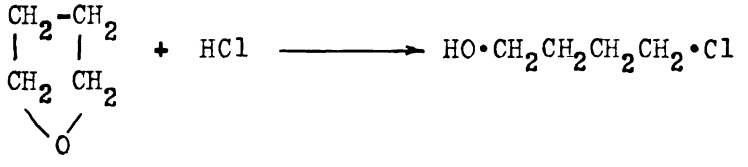
In general, it may be said that there are a variety of influencing factors in the amination reaction. Among these factors are the reactivity of the chlorine atom in the ω-chloroalkyl phenyl sulfides and the basicity of the secondary amines.

The overall yields of the morpholine derivatives were in general lower then those of the piperidine derivaties, presumably because of the different basicities of the two secondary amines.

Altogether, fourteen new tertiary amine derivatives of mixed phenyl alkyl sulfides which have not previously been reported were prepared and some of their properties are summarized in Table V.

Of the polymethylene chlorohydrins used for the preparations of the ω-hydroxyalkyl phenyl sulfides in this investigation, ethylene chlorohydrin, trimethylene chlorohydrin and propylene chlorohydrin were readily available.

Tetramethylene chlorohydrin was prepared by treating tetrahydrofuran with gaseous hydrogenchloride according to the method employed by Starr and Hixson,[22] who obtained a yield of 54-57% of the theoretical:



Contrary to the report of Starr and Hixson,[22] who reported it required only five hours of passing hydrogen chloride gas into the reaction flask to reach a constant reaction temperature of 105° C., it was found to take a period of thirteen hours before the reaction mixture reached a constant temperature at which point no more high boiling products were formed.

The tetrahydrofuran was first heated to its boiling point (64-65° C.) on a water bath, then a slow stream of hydrogen chloride was passed

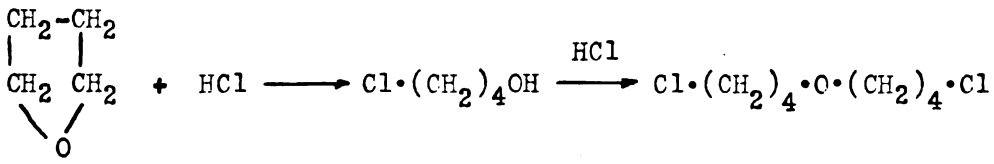
TABLE V

TERTIARY AMINE DERIVATIVES OF MIXED PHENYLALKYL SULFIDES

Compound: Hydrochloride	Formula	M.P.°C.	Nitrogen %		Sulfur %	
			Calc'd.	Found	Calc'd.	Found
β-piperidylethyl phenyl sulfide	$C_{13}H_{20}SNCl$	185-6	5.44	5.56 5.44	12.45	12.36 12.25
β-morpholylethyl phenyl sulfide	$C_{12}H_{18}OSNCl$	123-5	5.39	5.38 5.14	12.35	12.36 12.04
γ-piperidylpropyl phenyl sulfide	$C_{14}H_{22}SNCl$	149-50	5.16	5.15 5.05	11.81	11.85 12.03
γ-morpholylpropyl phenyl sulfide	$C_{13}H_{20}OSNCl$	142-3	5.12	5.10 5.40	11.72	11.47 11.58
β-piperidylpropyl phenyl sulfide	$C_{14}H_{22}SNCl$	128-0	5.16	5.17 5.18	11.81	11.25 11.50
β-morpholylpropyl phenyl sulfide	$C_{13}H_{20}OSNCl$	146-8	5.12	5.07 5.18	11.72	11.34 11.33
δ-piperidylbutyl phenyl sulfide	$C_{15}H_{24}SNCl$	137-8	4.90	4.97 4.83	11.23	11.03 11.05
δ-morpholylbutyl phenyl sulfide	$C_{14}H_{22}OSNCl$	113-4	4.87	4.83 5.00	11.15	11.10 11.05
ε-piperidylamyl phenyl sulfide	$C_{16}H_{26}SNCl$	118-22	4.67	5.24* 5.33	10.70	10.10* ---
ε-morpholylamyl phenyl sulfide	$C_{15}H_{24}OSNCl$	117-0	4.64	4.67 4.77	10.63	10.70 10.67
ω-piperidylhexyl phenyl sulfide	$C_{17}H_{28}SNCl$	119-21	4.47	4.66 4.66	10.22	9.83 9.96
ω-morpholylhexyl phenyl sulfide	$C_{16}H_{26}OSNCl$	112-4	4.44	4.31 4.52	10.16	9.71 9.83
β-dimethylaminoethyl phenyl sulfide	$C_{10}H_{16}SNCl$	140-50	6.44	6.25 6.55	14.74	14.74 14.88
γ-diethylaminopropyl phenyl sulfide	$C_{13}H_{22}SNCl$	131-2	5.46	6.13* 6.26	12.36	12.80 13.07*

* These two compounds were impure because of difficulties in their preparation.

into it. The temperature of the bath and the flow of hydrogen chloride were adjusted in a manner to maintain a constant rate of reflux. As the reaction proceeded the temperature of the reaction mixture rose, indicating an increase in the high-boiling products. The temperature of the flask was raised very slowly so as to keep the unused low-boiling tetrahydrofuran in contact with the hydrogen chloride. At the end of thirteen hours, the temperature remained practically constant at 90-91° C. The yield obtained from the distillation of the reaction mixture was rather low, 26% of the theoretical. The possible side reactions which could be ascribed to the low yields have been reported.[23] It was found that tetramethylene chlorohydrin reacted with hydrogen chloride in the liquid phase under pressure and at a temperature of 110° C. to give bis(4-chlorobutyl)ether.



It has also been reported that the cleavage of tetrahydrofuran to form the corresponding dihalides could be effected with hydrogen iodide, hydrogen bromide, and hydrogen chloride.[24,25] For example 1,4-dichlorobutane was readily prepared by passing a mixture of tetrahydrofuran and hydrogen chloride under pressure through a reactor maintained at 180° C., and with a proper choice of reaction concentration and recycling of by-products, substantially quantitative yields of 1,4-dichlorobutane were obtained.[26]

The preparation of pentamethylene chlorohydrin was accomplished by the method which Marvel and Calvery[26] used for the synthesis of trimethylene chlorohydrin. This involved the interaction of the corresponding glycol and gaseous hydrogen chloride.

$$HO\cdot CH_2CH_2CH_2CH_2CH_2\cdot OH + HCl \longrightarrow HO\cdot CH_2CH_2CH_2CH_2CH_2\cdot Cl + H_2O$$

The method was based upon the quick distillation of a small quantity of the glycol by means of a rapid stream of gaseous hydrogen chloride. Because of the higher boiling point of the product prepared here the distillation could not be carried out as rapidly as in the case of trimethylene chlorohydrin, causing difficulties in obtaining a good yield. The final yield after fractionation of the distillate was 47% of the theoretical. The product obtained was still impure and caused the low yield in the preparation of the ω-hydroxyamyl phenyl sulfide.

Hexamethylene chlorohydrin was prepared satisfactorily according to the method of Müller and Vanc.[27] The procedure was different from that used in the preparation of pentamethylene chlorohydrin. It eliminated the procedure of immediate distillation of the product as it formed. This was done by replacing the downward condenser with a reflux condenser and the reaction was completed in a single operation in place of the multiple operations on small batches of the glycol as in the case of the pentamethylene glycol.

$$HO\cdot(CH_2)_6\cdot OH + HCl \longrightarrow HO\cdot(CH_2)_6\cdot Cl + H_2O$$

The procedure was based upon the saturation by hydrogen chloride of the corresponding glycol at relatively low temperature over a designated period of time according to Müller's data. He established the empirical relationships between the amount of glycol used, temperature of the reaction, period and rate of treatment with hydrogen chloride, yield of 1,6-dichlorohexane, 1,6-hexamethylene chlorohydrin, recovery of unreacted glycol, and the ratio of the chlorohydrin to the dichloride. The optimum reaction conditions for obtaining a high ratio of chlorohydrin to dichloride and a low recovery of the unreacted glycol were selected on the basis of Müller's[27] work. The reaction temperature actually used was 88-94° C. and the period of treatment with gaseous hydrogen chloride was three hours. Upon fractionation the crude reaction mixture a 51% yield of the pure 1,6-hexamethylene chlorohydrin was obtained, while Müller reported a 43.6% yield of the chlorohydrin.

EXPERIMENTAL

β-Hydroxyethyl Phenyl Sulfide

In a 300 ml. three-necked round-bottom flask fitted with a stirrer, a dropping funnel, and a reflux condenser was placed 22 g. (0.2 moles) of thiophenol dissolved in 72 ml. of 10% aqueous sodium hydroxide. To this solution with stirring was added dropwise 20 g. (0.25 moles), of ethylene chlorohydrin over a period of a quarter hour. Immediately after the addition of the chlorohydrin was completed an exthothermic reaction set in. Moderate heating was applied to the reaction flask by means of an electric mantle, whereupon a sudden cloudiness was observed in the reaction mixture. The reaction was kept at reflux for an hour to ensure completeness, in which time a clear oily layer separated. At this point heating was discontinued and the flask and its contents were allowed to cool to room temperature. The oily layer was separated by means of a separatory funnel, and the aqueous fraction was extracted twice with ether. The oil combined with the ether extract was washed twice with water and then dried over anhydrous sodiumsulfate, followed by removal of the ether on a steam bath. The oil was vacuum-distilled using a column 30 cm. in height and 12 mm. in diameter packed with 1/8" glass helices. The 37 g. of crude oil gave a few ml. of forerun and then a clear oil which had no unpleasant odor. The yield of the product was 24.7 g., 80.2% of the theoretical. Its physical properties were, $n_D^{20} = 1.5900$, B. P. 88-97° C./1 mm. Reported values are $n_D^{20} = 1.5917$, B. P. 115-116° C./2 mm.[18] During the distillation about 4 g. of thiophenol were recovered from the dry-ice trap together with small amount of unreacted chlorohydrin.

γ-Hydroxypropyl Phenyl Sulfide

Using the same apparatus as was described above, 69 g. (0.73 moles) of trimethylene chlorohydrin were added dropwise to 66 g. (0.6 moles) of thiophenol dissolved in 140 ml. of 15% aqueous sodium hydroxide over a period of a quarter hour. The reaction mixture was then refluxed one hour with moderate heating and stirring. A clear, oily layer separated at this point and the reaction was stopped. After the separation, extraction, washing, and drying as was done in the preceeding preparation, the reaction mixture gave 120 g. of a crude oily product. This oil on fractionation gave 92 g. or 91.8% of the theoretical of the desired γ-hydroxypropyl phenyl sulfide which boiled at 133-135° C./1.5-3 mm. The refractive index of this material was, $n_D^{20} = 1.5793$. The reported properties of this compound are $n_D^{20} = 1.5813$, B. P. 134-135° C./2 mm.[18]

β-Hydroxypropyl Phenyl Sulfide

The same procedure and apparatus was used as in the previous preparations. To 22 g. (0.2 moles) of thiophenol dissolved in 72 ml. of 10% aqueous sodium hydroxide were added dropwise 22 g. (0.23 moles) of propylene chlorohydrin over a period of a 15 minutes with stirring. After refluxing one hour, 40 g. of the crude product were obtained at the end of the same procedure used in the previous preparations. The crude was fractionated to give a pure product weighing 30.7 g., 91% of the theoretical, which boiled at 95-100° C./0.5-1 mm. The refractive index of the product was, $n_D^{20} = 1.5718$. The reported values for these

properties are, n_D^{20} = 1.5705, B. P. 78° C./2 mm.[12] A second preparation of this compound gave similar results; a 91% yield, B. P. 84-101° C./3.5mm and n_D^{20} = 1.5750.

δ -Hydroxybutyl Phenyl Sulfide

Using the same technique as that used in the foregoing experiments, the interaction of 33 g. (0.3 moles) of thiophenol dissolved in 68 ml. of 15% aqueous sodium hydroxide and 33.5 g. (0.31 moles) of tetramethylene chlorohydrin gave 63 g. of a crude oil in a one-hour reaction period under reflux. The fractionation of the crude product yielded 48 g., 88% of the theoretical, of the pure product which distilled at 119-122°C./3-4mm. Its refractive index was, n_D^{20} = 1.5723. Analysis for sulphur of the product gave the following results,

Subs. 0.06479; $BaSO_4$ 0.04680; S% Calc'd. 9.69; S% Found 9.92.

ϵ -Hydroxyamyl Phenyl Sulfide

Following the same general procedure discussed above, the interaction of 33 g. (0.3 moles) of thiophenol dissolved in 45 ml. of 25% aqueous sodium hydroxide with 37.6 g. (0.31 moles) of 1,5-pentamethylene chlorohydrin gave 60 g. of a crude oil after two hours at reflux temperature. The fractionation of the crude product gave 49 g., 83.4% of the theoretical, of the pure product which boiled at 155-156°C./1-2mm. The refractive index measured immediately after the distillation and before solidification was, n_D^{20} = 1.5610. The sulfur analysis for the product was as follows:

Sub. 0.12783; $BaSO_4$ 0.14975; S% Calc'd. 16.35; S% Found 16.09

ω -Hydroxyhexyl Phenyl Sulfide

By a similar procedure involving the interaction of 20 g. (0.177 moles) of thiophenol dissolved in 30 ml. of 19% aqueous sodium hydroxide solution with 24.4 g. (0.18 moles) of 1,6-hexamethylene chlorohydrin there was obtained 31 g. of a crude oil in an 90-minute period at reflux temperature. Fractionation of the crude product yielded 24.7 g., 65.8% of the theoretical, of the pure product which distilled at 152-156°C./0.5mm. It was necessary in the distillation of this compound to use a shorter fractionating column, 20 cm. in height and 12 mm. diameter, and the side arm of the distilling flask was heated by a Ni-Cr electric heating element to prevent the solidification of the product in the side arm during the distillation. The refractive index measured right after the distillation and before the product solidified was, $n_D^{20} = 1.5483$. The sulfur analysis for this waxy compound showed the following results:

Subs. 0.11860; $BaSO_4$ 0.12739; S% Calc'd. 15.26; S% Found 14.76

TABLE VI

REACTION CONDITIONS AND YIELDS OBTAINED FOR THE ω-HYDROXYALKYL PHENYL SULFIDES

	Reactants							Reflux Period	Yield	
	Chlorohydrins		Thiophenol		NaOH		Water			
	g.	moles	g.	moles	g.	moles	ml.	Min.	g.	% theor.
ethylene	20	0.25	22	0.2	8	0.2	72	45	24.7	80.2
trimethylene	69	0.73	66	0.6	24	0.6	140	50	92	91.8
propylene	22	0.23	22	0.2	8	0.2	72	60	30.7	91
propylene	110	1.06	110	1.0	40	1.0	360	60	153	91
tetramethylene	33.5	0.31	33	0.3	12	0.3	68	60	48	88
pentamethylene	37.6	0.31	22	0.3	15	0.34	45	120	49	83.4
hexamethylene	24.4	0.18	20	0.18	7.2	0.18	30	90	24.7	65.8

γ-Chloropropyl Phenyl Sulfide

To 56 g. (0.51 moles) of γ-hydroxypropyl phenyl sulfide dissolved in 40.3 g. (0.51 moles) of anhydrous pyridine contained in a dry three-necked ground-glass flask fitted with reflux condenser, stirrer, and dropping funnel was added with stirring 76 g. (0.64 moles), a 25% excess of the theoretical, of thionyl chloride. The latter reagent was added dropwise at such a rate that no sudden temperature rise took place in the reaction mixture. The temperature of the reaction mixture was conveniently read by dipping a long-stemmed thermometer through the condenser. The reaction was completed in a period of an hour and a half. The reaction temperature should be kept below 90° C. After cooling to room temperature, the reaction mixture was washed with water to remove the excess thionyl chloride and the pyridine hydrochloride formed. The brownish, oily organic layer was separated by means of a separatory funnel and the aqueous layer was extracted repeatedly with small portions of ether. The combined oil and ether extract was again washed with water and dried over anhydrous sodium sulfate. After removal of the ether the crude product weighed 93 g. Fractionation of the crude product using the column previously described gave an oily product boiling at 102-103°C./2-3mm. The product weighed 90.8 g., 96% of the theoretical, and was slightly yellowish in color. Its refractive index was, $n_D^{20} = 1.5742$. The reported value is $n_D^{20} = 1.5722$.[18]

β-Chloroethyl Phenyl Sulfide

Using the above technique the interaction of 20 g. (0.13 moles) of β-hydroxyethyl phenyl sulfide, dissolved in 10.3 g. (0.13 moles) of pyridine, with 18 g. (0.16 moles) of thionyl chloride gave 20 g. of a crude oil in a one-hour period of reaction at a temperature of 80-120° C.

The subsequent distillation of the crude product gave 12.5 g., 55% of the theoretical, of the pure product which distilled at 99-113° c./4-6mm. The refractive index of the material was $n_D^{20} = 1.5828$; reported value $n_D^{20} = 1.5838$.[18]

β-Chloropropyl Phenyl Sulfide

The reaction of 148 g. (0.88 moles) of β-hydroxypropyl phenyl sulfide, dissolved in 70 g. (0.88 moles) of anhydrous pyridine, and 130 g. (1.1 moles) of thionyl chloride gave 160 g. of a crude oil in a one-hour period at a temperature ranging from 50 to 90° C., following the same procedure as was used in the previous preparations. A rapid tendency toward tarring was characteristic of this reaction. Fractional distillation gave 146 g., 90% of the theoretical, of the pure product which boiled at 80-80.5°C./1mm. The refractive index of the product was, $n_D^{20} = 1.5635$. The reported values are, B. P. 83-86° C./0.1-0.2mm., $n_D^{20} = 1.5680$.[12]

δ-Chlorobutyl Phenyl Sulfide

Following the same procedure as in the previous preparations, 23.7 g. (0.13 moles) of δ-hydroxybutyl phenyl sulfide dissolved in a

slight excess of anhydrous pyridine were treated with 18 g. (0.16 moles) of thionyl chloride. The reaction mixture was kept, with stirring, at a temperature between 50 to 80° C. for one and a half hours. The amount of crude product obtained amounted to 25.5 g. On distillation, 16.5 g., 66% of the theoretical, of a pure product were obtained which boiled at 123°C./2mm. The refractive index of this material was, n_D^{20} = 1.5670 and the results of analysis for sulfur were as follows: Subs. 0.09534; $BaSO_4$ 0.11352; S% Calc'd. 15.99; S% Found 16.35

ϵ-Chloroamyl Phenyl Sulfide

Using 45 g. (0.23 moles) of ϵ-hydroxyamyl phenyl sulfide dissolved in 18 g. (0.23 moles) of pyridine and adding 29 g. (0.25 moles) of thionyl chloride, there was obtained 35 g. of a crude oil after a two and a half hour period of reaction at a temperature of 50 to 65° C. There was obtained by distillation 25.5 g., 71% of the theoretical, of the pure product which boiled at 127-137°C./1mm. The refractive index of this viscous product was, n_D^{20} = 1.5600 and the analysis for sulfur was as follows:

Sub. 0.13151; $BaSO_4$ 0.15565; S% Calc'd. 14.95; S% Found 16.25

ω-Chlorohexyl Phenyl Sulfide

The same general procedure as previously described was employed, using 62 g. (0.32 moles) of the corresponding ω-hydroxyalkyl phenyl sulfide dissolved in 25.3 g. (0.32 moles) of anhydrous pyridine and 47.2 g. (0.4 moles) of thionyl chloride. This gave rise to 52 g. of a crude oil at a reaction temperature of 60-80°C. during a one-hour

reaction period. The fractionation of the crude product gave 44 g., 46% of the theoretical, of a pure viscous liquid which distilled at 144-147° C./1mm. About 25 g. of a tarry residue remained after the distillation due to some decomposition. The refractive index of the product was $n_D^{20} = 1.5490$ and the analysis for sulfur were as are indicated below:

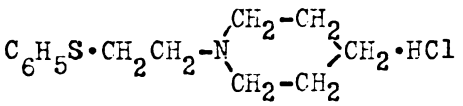
Subs. 0.13166; $BaSO_4$ 0.13522; S% Calc'd. 14.03; S% Found 14.10

TABLE VII

REACTION CONDITIONS AND YIELDS OBTAINED FOR THE ω-CHLOROALKYL PHENYL SULFIDES

	Reactants						Reaction Period	Reaction Temperature	Yield	
	Phenyl Sulfides		$SOCl_2$		Pyridine					
	g.	mol.	g.	mol.	g.	mol.	Min.	°C.	g.	% theor.
β-hydroxyethyl	20	0.13	18	0.16	10.3	0.13	60	80-120	12.5	55
γ-hydroxypropyl	56	0.51	76	0.64	40.3	0.51	90	60-90	90.8	96
β-hydroxypropyl	148	0.88	130	1.1	70	0.88	60	50-90	146	90
δ-hydroxybutyl	23.7	0.13	18	0.16	10.3	0.13	90	50-80	16.5	66
ε-hydroxyamyl	45	0.23	29	0.25	18	0.23	150	50-65	25.5	71
ω-hydroxyhexyl	62	0.32	47.2	0.4	25.3	0.32	60	60-80	44	46

β-Piperidylethyl Phenyl Sulfide Hydrochloride



Into a dry three-necked 300 ml. ground-glass flask fitted with stirrer, reflux condenser and dropping funnel was poured a solution of 27.5 g. (0.32 moles) of piperidine dissolved in 25 ml. dried toluene. To this was added 18.5 g. (0.107 moles) of β-chloroethyl phenyl sulfide dissolved in 25 ml. of dry toluene from a dropping funnel. The reaction mixture was stirred and allowed to proceed to completion. This was determined by the separation of sufficient piperidine hydrochloride salt, which required one and a half hours at a reflux temperature of 100° C. The initial separation of the salt started at the end of 30 minutes of reflux. After refluxing an hour and a half, there was no appreciable increase in the amount of the salt at which point the reaction was discontinued. After cooling to room temperature, 60 ml. of water were added to dissolve the salt formed. The reaction mixture was then made alkaline by adding a solution of 4.28 g. (0.107 moles) of sodium hydroxide dissolved in a small amount of water which caused the separation of a yellow oily layer. The mixture was steam distilled to remove the excess piperidine and toluene. From time to time the Simon's color test for secondary amines[28] was applied to the distillate. Upon the complete removal of all the secondary amine and toluene, which required 70 minutes, the reaction mixture, while still warm, was treated with 10.4 ml. of concentrated

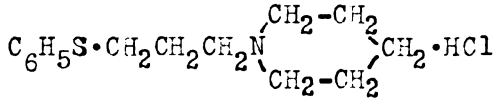
hydrochloric acid and agitated. The oily product became soluble in the acid media. The solution was then extracted with ether to remove any unreacted β-chloroethyl phenyl sulfide. Following this 5.2 g. (0.13 moles) of sodium hydroxide were added to obtain the free amine as an oily layer. The total volume of the mixture was then about 400 ml. The oil layer was separated and the aqueous layer was extracted with benzene until no cloudiness was visible. The combined benzene extract and oil were washed with water and dried over anhydrous sodium sulfate. Removal of the benzene was hastened by bubbling air through the solution on a steambath. The fish-odored oily free amine weighing 13 g., 50% of the theoretical, was taken up in 400 ml. of dry ether. A gentle stream of hydrogenchloride gas was passed through a small nozzle into the ether solution, kept cold, until no more precipitate formed. Difficulties were frequently encountered in filtering off the sticky hydrochloride. These were best overcome by passing just enough hydrogenchloride gas for complete precipitation. The bulky hydrochloride in ether was kept cold over night to help its crystallization. The salt was filtered on a Buchner funnel and the filtrate was tested with hydrogenchloride gas for complete removal of amine. The crude hydrochloride weighing 13.8 g., 50% of the theoretical, was dissolved in 100 ml. of hot, dry isopropyl alcohol and decolorized twice with Norite. Overheating of the solution was avoided since the hydrochloride was apt to decompose giving rise to a brown color in the solution. Two recrystallizations from isopropyl alcohol and a final washing with a small amount of ether followed by drying gave 6.8 g. of a pure

product which crystallized in needles and melted at 185-186° C. Analysis of the compound for nitrogen and sulfur gave the following results:

N% Calc'd. 5.44; N% Found 5.56, 5.44

Subs. 0.08992; $BaSO_4$ 0.08093; S% Calc'd. 12.45; S% Found 12.36,12.25
0.08852 0.07895

γ -Piperidylpropyl Phenyl Sulfide Hydrochloride



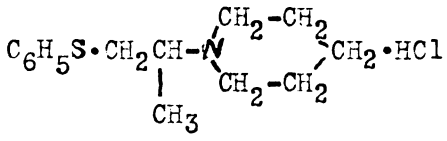
Using the same apparatus and technique as described above 18 g. (0.1 moles) of γ-chloropropyl phenyl sulfide dissolved in 25 ml. of toluene were added to a solution of 25.5 g. (0.3 moles) of piperidine dissolved in 15 ml. of toluene. The reaction was slower in this case and required one hour of refluxing before the piperidine hydrochloride started to separate. After similar treatment with water and alkali as in the preceding preparation, the reaction mixture was steam distilled until it gave a negative Simon's test. This was followed by acidification, benzene extraction, and finally isolation of the free amine in an alkaline solution. After separation of the oil and extraction of the aqueous layer with benzene followed by the removal of the benzene, the free amine was dissolved in 500 ml. of dry ether. Treatment of the ether solution with hydrogen chloride gas gave 30 g. of a crude salt which was decolorized and recrystallized from isopropyl alcohol three times yielding 10.6 g., 39% of the theoretical, of the pure

crystalline compound. The product melted at 149-150° C. and the analyses of the compound for nitrogen and sulfur gave the following results:

N% Calc'd 5.16; N% Found 5.15, 5.05

Subs. 0.07259; $BaSO_4$ 0.06355; S% Calc'd. 11.81; S% Found 12.03

β -Piperidylpropyl Phenyl Sulfide Hydrochloride

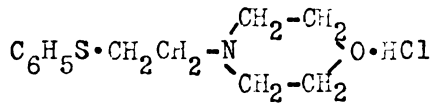


Following the same procedure as before, a solution of 28 g. (0.15 moles) of β-chloropropyl phenyl sulfide in 30 ml. of toluene was added to 38.2 g. (0.45 moles) of piperidine dissolved in 30 ml. of dry toluene. The separation of piperidine hydrochloride required an hour and a half at a reflux temperature of 100° C. The reaction was continued for seven hours, after which no more salt appeared to form. After the usual treatment of the reaction mixture, there was obtained 36 g., 90% of the theoretical, of the free amine which was converted into 45 g. of the crude hydrochloride by the usual method. The product was recrystallized from benzene four times giving 8.5 g. of the pure crystalline salt which melted 128-129° C. The analyses of the compound for nitrogen and sulfur gave the following results:

N% Calc'd. 5.16; N% Found 5.17, 5.12

Subs. 0.05613; $BaSO_4$ 0.04598; S% Calc'd. 11.81; S% Found 11.25, 11.50
0.07313 0.06122

β -Morpholylethyl Phenyl Sulfide Hydrochloride

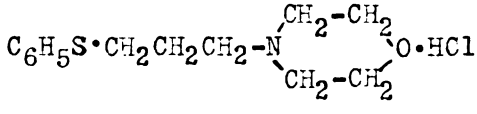


The procedure was the same as in the previous preparations. Using 18.5 g. (0.107 moles) of β-chloroethyl phenyl sulfide and 26.1 g. (0.3 moles) of morpholine in 30 g. of toluene as a solvent, the salt separation failed to start after seven hours of heating at 80° C. However, morpholine hydrochloride started to separate on raising the reaction temperature to 120° C. after one and a half hours of additional heating. There was obtained by the usual treatment of the reaction mixture 19 g. of the crude hydrochloride, 68.6% of the theoretical. The product was recrystallized from 1,4-dioxane twice giving rise to 9 g. of a pure crystalline hydrochloride salt which melted at 123-125° C. The analyses of the product gave the following results:

N% Calc'd. 5.39; N% Found 5.38, 5.14

Subs. 0.05813; $BaSO_4$ 0.05235 ; S% Calc'd. 12.35; S% Found 12.36, 12.04
0.05853 0.05127

γ -Morpholylpropyl Phenyl Sulfide Hydrochloride



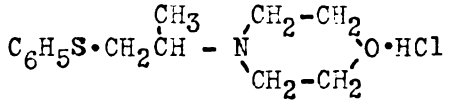
By using 20.5 g. (0.11 moles) of γ-chloropropyl phenyl sulfide and 26.1 g. (0.3 moles) of morpholine in 20 ml. of toluene as a solvent, the morpholine hydrochloride salt separation took place after 20 minutes refluxing at 120° C. and the reaction was completed in two and a

half hours. After the usual manipulations, 50 g. of the crude tertiary amine hydrochloride which corresponded to 100% of the theoretical were obtained. Since most alcohols commonly available were poor solvents for the product, recrystallization was carried out by saturating hot benzene with the salt and decanting the benzene solution and allowing it to cool. The material obtained from the benzene extractions was recrystallized from 1,4-dioxane. The pure crystalline material obtained from three recrystallizations using 1,4-dioxane weighed 14.4 g., 44.8% of the theoretical, and melted at 142-143° C. The analysis for nitrogen and sulfur are indicated below.

N% Calc'd. 5.12; N% Found 5.10, 5.40

Subs. 0.08127; $BaSO_4$ 0.06783; S% Calc'd. 11.72; S% Found 11.47, 11.58
0.07859 0.06626

β-Morpholylpropyl Phenyl Sulfide Hydrochloride



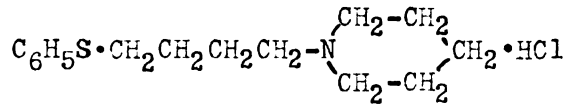
Interaction of 32.45 g. (0.174 moles) of β-chloropropyl phenyl sulfide and 40 g. (0.45 moles) of morpholine dissolved in 30 g. of toluene gave morpholine hydrochloride salt separation after a period of five hours refluxing at 125° C. and the reaction was completed with an additional seven hours at the same temperature. After the usual treatment of the reaction mixture, 24 g., 55% of the theoretical, of the crude hydrochloride were obtained. On two recrystallizations from 1,4-dioxane, 9.9 g., 20.8% of the theoretical, of a pure crystalline

salt with a melting point of 146-148° C. was obtained. The analyses for nitrogen and sulfur of the compound gave the following results:

N% Calc'd. 5.12; N% Found 5.07, 5.18

Subs. 0.08787; $BaSO_4$ 0.07253; S% Calc'd. 11.72; S% Found 11.33, 11.34
0.08590 0.07086

δ -Piperidylbutyl Phenyl Sulfide Hydrochloride

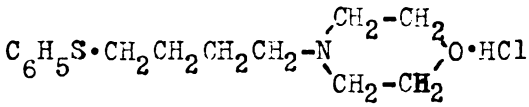


Employing 14 g. (0.07 moles) of δ -chlorobutyl phenyl sulfide, 18 g. (0.21 moles) of piperidine, and 20 ml. of toluene as a solvent, produced the first piperidine hydrochloride salt separation after ten minutes of reaction at 80° C. The total period required for the completion of the reaction was only one hour at the same temperature. The hydrochloride obtained through the usual procedure was dissolved directly in 1,4-dioxane and on further recrystallizations gave 6.7 g., 34% of the theoretical, of the pure crystalline product which melted at 137-138° C. The analyses for nitrogen and sulfur in the compound gave the following data:

N% Calc'd. 4.90; N% Found 4.97, 4.83

Subs. 0.08891; $BaSO_4$ 0.07139; S% Calc'd. 11.23; S% Found 11.03, 11.05
0.07269 0.05848

δ -Morpholylbutyl Phenyl Sulfide Hydrochloride

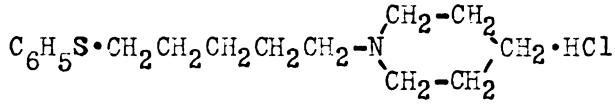


Reacting together 18 g. (0.09 moles) of δ -chlorobutyl phenyl sulfide and 23.5 g. (0.27 moles) of morpholine in 20 ml. of toluene as a solvent caused an initial salt separation after an hour and a quarter at a reaction temperature of 78° C. The reaction was completed after an additional twenty-four period at the same temperature. By the usual procedures, 10 g., 38.7% of the theoretical, of a crude hydrochloride were obtained. Three recrystallizations of the product from 1,4-dioxane yielded 3.7 g. of the pure, crystalline product which melted at 113-114° C. The analyses for nitrogen and sulfur for the compound gave the following data.

N% Calc'd. 4.87; N% Found 4.83; 5.00

Subs. 0.05783; $BaSO_4$ 0.04676; S% Calc'd. 11.15; S% Found 11.10, 11.05
0.06815 0.05483

ε -Piperidylamyl Phenyl Sulfide Hydrochloride



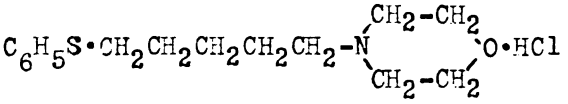
From the reaction of 8 g. (0.037 moles) of ε -chloroamyl phenyl sulfide and 8.6 g. (0.111 moles) of piperidine in 15 ml. of toluene as a solvent there resulted a poor yield of the corresponding tertiary amine at a reaction temperature of 70° C. The time required to the initial separation of piperidine hydrochloride was one hour and

required an additional hour and a half for completion of the reaction. The crude hydrochloride obtained by the subsequent treatment was recrystallized twice from 1,4-dioxane, giving rise to 1.0 g., 88% of the theoretical, of the final product which melted at 118-122° C. Analytical data are as follows:

N% Calc'd. 4.67; N% Found 5.24, 5.33

Subs. 0.02407; $BaSO_4$ 0.01768; S% Calc'd. 10.70; S% Found 10.10

ϵ-Morpholylamyl Phenyl Sulfide Hydrochloride

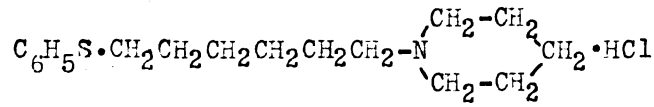


Treatment of 8 g. (0.037 moles) of ϵ-chloroamyl phenyl sulfide with 8.8 g. (0.111 moles) of morpholine in 15 ml. of toluene as a solvent produced initial separation of morpholine hydrochloride salt after one hour of reaction, and the reaction was completed in an additional half hour. A yield of 2.1 g., 15.2% of the theoretical, of the pure hydrochloride was obtained after several crystallizations from 1,4-dioxane. It melted at 117-119° C. and analyzed to give the following results:

N% Calc'd. 4.64; N% Found 4.67, 4.77

Subs. 0.06103; $BaSO_4$ 0.04758; S% Calc'd. 10.63; S% Found 10.70, 10.67
0.03277 0.02545

ω-Piperidylhexyl Phenyl Sulfide Hydrochloride

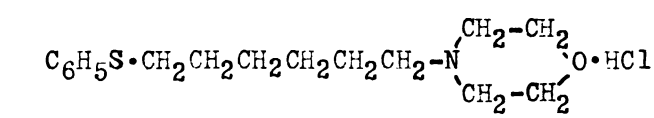


From 18 g. (0.079 moles) of ω-chlorohexyl phenyl sulfide, 20.2 g. (0.24 moles) of piperidine, and 10 ml. of toluene at a reaction temperature of 100° C. there was obtained the initial salt separation in two and a half hours and the reaction was completed in an hour of additional heating. The 15 g., 57% of the theoretical, of crude hydrochloride gave 8.25 g. of pure crystalline salt after several recrystallizations from 1,4-dioxane. The product had a melting point of 119-121° C. and was analyzed to give the following results:

N% Calc'd. 4.47; N% Found 4.66, 4.66

Subs. 0.06980; $BaSO_4$ 0.04993; S% Calc'd. 10.22; S% Found 9.83, 9.96
0.07534 0.05463

ω-Morpholylhexyl Phenyl Sulfide Hydrochloride



Interaction of 24 g. (0.11 moles) of ω-chlorohexyl phenyl sulfide and 28 g. (0.33 moles) of morpholine in 15 ml. of toluene as a solvent gave the first salt separation in three and a half hours of reaction at 110° C. The reaction was completed in an additional three hours. The 23 g. of crude hydrochloride, after a few recrystallizations from 1,4-dioxane, gave 15.6 g., 41% of the theoretical, of a white, waxy

material which melted at 112-124° C. The analyses of this compound showed the following results.

N% Calc'd. 4.44; N% Found 4.31, 4.52

Subs. 0.06033; $BaSO_4$ 0.04261; S% Calc'd. 10.16; S% Found 9.71, 9.83
0.08012 0.05734

γ -Diethylaminopropyl Phenyl Sulfide Hydrochloride

$$C_6H_5S\cdot CH_2CH_2CH_2\text{-}N(C_2H_5)_2\cdot HCl$$

The reaction was carried out in a heavy walled Pyrex sealed tube heated in an electric oven. A solution of 25 g. (0.134 moles) of γ -chloropropyl phenyl sulfide and 18 g. (0.253 moles) of dimethylamine in 20 ml. of toluene as a solvent was placed in the tube, after which it was sealed. Heating was slowly applied over a period of 22 hours reaching a final temperature of 130° C. The tube was allowed to cool over night without removing it from the oven. Procedure thereafter was identical to those used in the preceding preparations. The 25 g., 81% of the theoretical, of the free amine gave 25 g. of crude hydrochloride, which by subsequent crystallizations from 1,4-dioxane yielded 1.35 g. of a pure compound. The product melted at 131-132° C. The analyses of the product resulted in the following data:

N% Calc'd. 5.46; N% Found 6.13, 6.26

Subs. 0.05076; $BaSO_4$ 0.04731; S% Calc'd. 12.36; S% Found 12.80, 13.07
0.05514 0.05246

β -Dimethylaminoethyl Phenyl Sulfide Hydrochloride

$$C_6H_5S \cdot CH_2CH_2N \cdot (CH_3)_2 \cdot HCl$$

Using the same sealed-tube method, 16 g. (0.1 moles) of β-chloroethyl phenyl sulfide, 52 g. of a 25% aqueous solution of dimethylamine (equivalent to 13 g. or 0.29 moles), and 135 ml. of 1,4-dioxane as a solvent, there was obtained 7 g. of a pure hydrochloride after a 15 hour reaction period at 140-150° C. By similar manipulations as were applied in the previous preparations, a yield corresponding to 40% of the theoretical was obtained. The hydrochloride salt thus obtained melted at 114-115° C. The analyses for nitrogen and sulfur for the compound gave the following results:

N% Calc'd. 6.44; N% Found 6.26, 6.55

Subs. 0.11102; $BaSO_4$ 0.11918; S% Calc'd 14.74; S% Found 14.74, 14.88
0.08396 0.09099

TABLE VIII

REACTION CONDITIONS AND YIELDS OBTAINED FOR THE TERTIARY AMINE DERIVATIVES OF MIXED PHENYLALKYL SULFIDE HYDROCHLORIDES

Compounds: -Phenyl Sulfide Hydrochloride	Reactants: Chloroalkane g.	(moles)	Sec. Amine g.	(moles)	Toluene ml.	Reaction Conditions: Rx. Tempt °C.	Salt Form. hr.	Rx. Period hr.	Yield of Crude Hydrochloride g.	%	Cryst. Solvent
β-Piperidylethyl	18.5	(0.11)	27.5	(0.32)	30	100	0.5	1.5	13.8	50	a
β-Morpholylethyl	8.5	(0.11)	26.1	(0.30)	30	120	7.0	8.5	19.0	69	b
γ-Piperidylpropyl	18.0	(0.10)	25.5	(0.30)	30	---	1.0	---	30.0	100	a
γ-Morpholylpropyl	20.5	(0.11)	26.1	(0.30)	20	120	0.3	2.5	50.0	100	a + c
β-Piperidylpropyl	28.0	(0.15)	38.2	(0.45)	60	100-110	1.5	7.0	45.0	100	c
β-Morpholylpropyl	32.5	(0.17)	40.0	(0.45)	30	125	5.0	12.0	24.0	50	b
δ-Piperidylbutyl	14.0	(0.07)	18.0	(0.21)	20	84	0.2	1.0	13.0	65	b
δ-Morpholylbutyl	18.0	(0.09)	23.5	(0.27)	20	78	1.2	20.0	10.0	39	b
ε-Piperidylamyl	8.0	(0.04)	8.6	(0.11)	15	70	1.0	1.5	--	--	b
ε-Morpholylamyl	8.0	(0.04)	8.8	(0.11)	15	80	1.0	1.5	--	--	b
ω-Piperidylhexyl	18.0	(0.08)	20.2	(0.24)	10	100	2.5	3.5	--	--	b
ω-Morpholylhexyl	24.0	(0.11)	28.0	(0.33)	15	110	3.5	6.5	23.0	62	b
γ-Diethylamino-propyl	25.0	(0.13)	18.0	(0.25)	20 D.O.	130	---	22.0	--	--	b
β-Dimethylamino-ethyl	16.0	(0.10)	13.0	(0.29)	135	140-50	---	15.0	25.0	78	b

a Isopropyl alcohol, b 1,4-dioxane, c Benzene

Tetramethylene Chlorohydrin

A 500 ml. three-necked flask was fitted with a reflux condenser, a thermometer reaching to the bottom of the flask, and a bent-glass tube arranged to introduce gaseous hydrogen chloride near the bottom of the flask. A safety trap was placed in the line carrying the hydrogen chloride from the cylinder to the gas delivery tube of the flask. An exit tube from the upper end of the reflux condenser was connected to a perpendicular 150 ml. distilling flask which was placed in an ice-salt bath to trap any material entrained by the hydrogen chloride. In the reaction flask, 100 g. (1.38 moles) of tetrahydrofuran were introduced and treated for thirteen hours with gaseous hydrogen chloride at a temperature of 64-65° C. At the end of this time the temperature of the reaction mixture had reached a constant temperature of 90-91° C. From the above operation there resulted 87 g. of brownish oil in the reaction flask plus 10 g. of a clear liquid obtained from the trap. Excess hydrogen chloride in the oil was removed on the steam-bath with an air aspirator. After drying over anhydrous sodium carbonate, the product was first fractionated using a short Vigreux column to obtain 43.4 g. of a material boiling at 72-76°C./10mm. This material was re-fractionated, employing a column 20 cm. in height and packed with glass helices. This gave 38.5 g., 26% of the theoretical of product which boiled at 71-73° C./8mm. Its refractive index was $n_D^{20} = 1.4516$. The reported physical constants for this compound are $n_D^{20} = 1.4502$; B. P. 87°C./10mm.[29] Starr and Hixon,[22] whose procedure was used in the above preparation reported a yield of 54-57%.

Pentamethylene Chlorohydrin

The apparatus used in this preparation consisted of a 200 ml. two-necked flask fitted with a dropping funnel, thermometer, a gas delivery tube reaching to the bottom of the flask, and an exit tube leading to a condenser set for downward distillation. The condenser was connected to a suction flask which acted as a receiver. To help prevent losses due to entrainment the suction flask was connected to a reflux condenser through the side arm of the flask. Unreacted gas issuing from the top of the reflux condenser was led to a gas-absorption trap. About 20 to 30 ml. of 1,5-pentamethylene glycol were run into the reaction flask from the dropping funnel and heated to 170-175° C. by means of an oil bath. A vigorous stream of hydrogen chloride gas was passed through the glycol, whereupon a reddish distillate consisting of water, the chlorohydrin, and unchanged glycol began to collect in the receiver. As soon as the glycol was nearly consumed, another 30 ml. of the glycol were added to the reaction flask. Operating in this manner, 250 ml. of glycol gave 180 ml. of distillate and a residue of 70 ml. of an undistillable material. The distillate was heated on steam bath with a slight suction to remove excess hydrogen chloride, followed by drying over anhydrous sodium carbonate. Fractionation of the product thus obtained gave 72.8 g., 46.8% of the theoretical, of a pure product which boiled at 52°C./13mm. and 65°C./16mm. The refractive index of the material was, $n_D^{20} = 1.4532$. The reported properties of this compound are; B. P. 103°C./8mm., $n_D^{20} = 1.4518$.[29]

Hexamethylene Chlorohydrin

The apparatus consisted of a 300 ml. three-necked flask fitted with a stirrer, thermometer, reflux condenser, and a gas delivery tube reaching to the bottom of the flask. An exit tube from the top of the reflux condenser led to a gas absorbtion trap to remove the unreacted hydrogen chloride. The glycol, 45 g. (0.38 moles), was heated at 89° C. and a stream of hydrogen chloride was passed into the glycol. The reaction was continued until the glycol became saturated with hydrogen chloride gas, which required 77 minutes. The temperature of the glycol was kept between 88 and 94° C. The reaction conditions used here were those determined by Müller.[27] The viscous, yellowish reaction mixture was heated on a steam-bath to remove hydrogen chloride and then dried over anhydrous potassium carbonate. The chlorohydrin was obtained by collecting the fraction boiling at 96-105°C./9-10mm. It had a refractive index of $n_D^{20} = 1.4552$. The reported value is $n_D^{20} = 1.4557$.[27] The yield obtained in this reaction was 26.5 g., 51.2% of the theoretical.

The 3,5-Dinitrobenzoates and p-Nitrobenzoates of the ω-Hydroxyalkyl Phenyl Sulfides

Following the method used by Schriner and Fuson,[30] one ml. of the ω-hydroxyalkyl phenyl sulfide was dissolved in 3 ml. of dry pyridine and treated with one gram of the corresponding benzoyl chloride. After the initial reaction had subsided, the mixture was heated gently with shaking until a clear solution resulted. It was then poured into 10 ml. of water with stirring. This caused an oil to separate and on cooling the oil solidified. The solid was recrystallized from a suitable solvent.

ANALYSES

Determination of Nitrogen

The procedure applied in this work was that of Clark[31] which employed the Kjeldahl method on a semimicro scale. Using a ground-glass micro-Kjeldahl distilling apparatus, a mixture of 40-100 mg. of sample, 0.1 g. of a mixture of mercuric oxide and potassium sulfate in a ratio of 8 to 100, and 3 ml. of concentrated sulfuric acid was digested over a six-hour period. After cooling the digestion mixture, it was diluted with 10 ml. of water and steam distilled after adding 10-12 ml. (40%) aqueous sodium hydroxide solution. The receiver contained 6 ml. of 4% boric acid and two drops of a 0.1% ethanolic solution of methyl red with about a one-half drop of methylene blue as an indicator. The distillation was continued until 50 ml. of distillate had been collected. The receiving flask was then lowered until the lower tip of the condenser was just above the content of the receiver and the distillation was continued until 2-3 ml. more of distillate had collected so as to wash off the inner surface of the condensing tube. The rate of distillation must be adjusted so that no mechanical carrying over of the distilling mixture into the receiver occurs. The temperature of the receiver must be kept below 40° C. The ammonia received in the boric acid solution was titrated with a standard hydrochloric acid solution using a microburet. The end point was easily determined by comparison with a reference solution. A blank due to reagents must also be determined and subtracted from the buret reading.

Determination of Sulfur

A semimicro determination of sulphur was carried out gravimetrically using the Parr bomb fusion method of Lincoln, Carney, and Wagner.[32] The organic sulfur compound in an amount corresponding to 20-100 mg. of barium sulfate was fused with a mixture of 0.2 g. of powdered potassium perchlorate, 0.15 g. of sucrose, and 4 g. of granular sodium peroxide. The sulfur was determined as barium sulfate.

SUMMARY

1. The three ω -hydroxyalkyl phenyl sulfides with four, five, and six carbon atoms in the alkyl chain were prepared for the first time and some of their properties were determined.

2. The 3,5-dinitrobenzoate derivatives of the ω -hydroxyalkyl phenyl sulfides with two, three, four, five and six carbon in the alkyl chain were prepared for the first time and some of their properties were determined. In addition the p-nitrobenzoates of the above ω -hydroxyalkyl phenyl sulfides with the exception β-hydroxypropyl phenyl sulfide were also prepared as new compound and some of their properties were determined.

3. The following ω-haloalkyl phenyl sulfides were prepared as new compounds and some of their properties were determined: δ-chlorobutyl; ϵ-chloroamyl, and ω-chlorohexyl.

4. Fourteen tertiary amine derivatives of mixed phenylalkyl sulfide hydrochlorides were synthesized for the first time and some of their properties were investigated.

BIBLIOGRAPHY

1. A. Einhorn and J. Uhlfelder, Ann. 371, 131 (1909).

2. F. L. Pyman, J. Chem. Soc., 93, 1793, (1908).

3. H. Erdtman and F. Löfgren, Svensk Kem. Tid. 49, 183 (1937), C. A., 31, 7854⁸.

4. M. L. Buchel and B. Tohauber, Compt. rend. soc. biol., 141, 34-5, (1947).

5. D. Kohler, Compt. rend. soc. biol., 141, 233-4, (1947).

6. C. S. Marvel and A. L. Tanenbaum, "Organic Syntheses," Col. V-I, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 435.

7. G. R. Clems and Perkin, J. Chem. Soc., 121, 642, (1922).

8. W. Steinkopf, J. Herold and J. Stöhr, Ber., 53, 1012, (1920).

9. H. Lecher and P. Stöcklin, Ber., 58, 414, (1925).

10. C. D. Nenitzesen and M. Scarlatescu, Ber., 68B, 589, (1935).

11. D. R. Boyd and E. R. Marli, Ber., 105, 2117-35, (1914).

12. R. C. Fuson and J. M. Koehneke, J. Org. Chem., 14, 706, (1949).

13. R. Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1944, V-II, p. 178.

14. R. R. Renshow and D. E. Searle, J. Am. Chem. Soc., 59, 2057, (1937).

15. H. Gilman, M. A. Plunkett, I. Tolman, L. Fullhart, and H. S. Broadbent, J. Am. Chem. Soc., 67, 1842-5, (1945).

16. H. Gilman and L. A. Woods, J. Am. Chem. Soc., 67, 1844, (1945).

17. G. M. Bennet and W. A. Berry, J. Chem. Soc., 130, 1676, (1927).

18. W. R. Kirner and G. H. Richter, J. Am. Chem. Soc., 51, 3409, (1929).

19. S. G. Powell, J. Am. Chem. Soc., 45, 2709, (1923).

20. G. Darzens, Compt. rend., 152, 1314, (1911); C. A., 5, 3410, (1911).

21. G. Koelle, Ber., 13, 1953, (1880).

22. D. Starr and R. N. Mixon, "Organic Syntheses," Col. V-II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 571.

23. U. S. Patent, 2,245,509.

24. S. Fried and R. D. Kleene, J. Am. Chem. Soc., 62, 3258 (1940); C. A., 35, 73.

25. S. Fried and R. D. Kleene, J. Am. Chem. Soc., 63, 2691, (1941); C. A., 36, 464.

26. C. S. Marvel and H. O. Calvery, "Organic Syntheses," Col. V-I, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 533.

27. A. Müller and M. Vanc, Monatshefte für Chemie, 77, 259-63, (1947).

28. S. P. Sulliken, "A Method for the Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1916, V-II, p. 43.

29. S. M. McElvain and T. P. Carney, J. Am. Chem. Soc., 68, 2596, (1946).

30. R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 165.

31. E. P. Clark, "Semimicro Quantitative Organic Analysis," N. Y. Academic Press, Inc., 1943, p. 37.

32. R. M. Lincoln, A. S. Carney and C. Wagner, Ind. Eng. Chem., Anal. Ed., 13, 358-61, (1941).

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