1 to 6 above. This was accomplished in the following manner. The crotyl alcohol or methylvinylcarbinol called for in methods 1 to 6 was replaced by the same number of moles of water and of the pure bromides or known mixtures of them. Each method of synthesis was then carried out exactly as described and the bromide was washed, dried and distilled. The corrected refractive index of the product was then compared with the refractive index of the bromide at the start of the procedure to see if any allylic rearrangement had occurred. The results of these experiments are listed in Table I.

Determination of the Equilibrium Mixture from the Butenyl Bromides.—In order to analyze butenyl bromide samples it is necessary to apply a small correction to the observed refractive index as described above. This correction is calculated with the aid of the refractive index of the equilibrium mixture obtained by thermally rearranging the sample under consideration at 100°. For the determination of the equilibrium values, small samples of the purified bromides from the low temperature distillations as described in synthesis (1) above, were sealed in 8-cm. test-tubes and placed in boiling water for one hour. The tubes were then removed, chilled in a mixture of ice and hydrochloric acid and opened. The refractive indices of the rearranged mixtures were then taken. Four or five tubes were ordinarily used and the average refractive index obtained is the value reported in the columns marked "refractive indices of equilibrium mixture" listed in Tables I and II.

The authors are indebted to Dr. G. Ross Robertson and Mr. Saul Winstein for helpful suggestions during the course of the investigations.

Summary

Crotyl alcohol and methylvinylcarbinol have been converted into butenyl bromide mixtures by the action of hydrogen bromide and phosphorus tribromide under controlled low-temperature conditions.

The experiments were designed to distinguish between allylic rearrangements which arise during the act of forming the bromides and those which are due to the method of isolation and purification of the product.

Known samples of butenyl bromides were subjected to the same conditions used in the synthesis, washing, drying and purifying of a product without undergoing appreciable change in composition.

Mixtures of crotyl and methylvinylcarbinyl bromides are formed from either crotyl alcohol or methylvinylcarbinol by all methods investigated. The composition of these mixtures depends on the butenol employed and on the character of the reagent used in converting the alcohol into the bromide mixture.

LOS ANGELES, CALIF. RECEIVED JULY 6, 1937

[CONTRIBUTION FROM THE NICHOLS CHEMICAL LABORATORY OF NEW YORK UNIVERSITY]

Thioethers of Formocholine and their Sulfones. Onium Compounds. XVII

BY R. R. RENSHAW AND D. E. SEARLE[1]

Due to the interesting pharmacological properties of the thiol derivatives of choline, $(CH_3)_3N(Br)CH_2CH_2SH$,[2] it seemed desirable to prepare and investigate the properties of other derivatives of choline in which the oxygen atom had been replaced by sulfur. We have, therefore, prepared a series of thioethers of the formocholine type, $R_3N(I)CH_2SR$, and have oxidized some of these to the corresponding sulfones.

Schneider[3] prepared the methyl and ethyl thioethers of choline from beta-aminoethyl thioethers, formed from the interaction product of bromoethylphthalimide and the appropriate thiol. The pharmacological properties of these thiocholine ethers were not investigated. Schneider[4] was unsuccessful in the preparation of thioether of the formocholine type.

In this work, advantage was taken of the interesting reactions of McLeod and Robinson[5] for the preparation of tertiary aminomethyl ethers by condensing secondary amines with formaldehyde and an alcohol, in the presence of potassium carbonate. These workers also obtained propyl and ethyl thioethers by replacing the alcohol with propyl and ethylthiol. As was to be expected, this method was found to be of very general application, giving yields of the tertiary aminothioethers of 60–72%.

The onium compounds were prepared by condensing the tertiary amines with methyl or

(1) This is the second paper from a thesis presented by D. S. Searle, June, 1930, for the degree of Doctor of Philosophy at New York University; Paper I, THIS JOURNAL, **55**, 4951 (1933).

(2) Hunt and Renshaw, *J. Pharmacol.*, **44**, 154 (1932).

(3) Schneider, *Ann.*, **386**, 339 (1911).

(4) Schneider, *ibid.*, **386**, 349 (1911).

(5) McLeod and Robinson, *J. Chem. Soc.*, **119**, 1470 (1921).

TABLE I

Formocholine thioethers	M. p., °C. (corr.)	Iodine, % Calcd.	Found	
$(CH_3)_3N(I)CH_2SCH_3$[a]	136–137	51.42	51.48	51.48
$(CH_3)_3N(I)CH_2SCH_2CH_3$[b]	119–120	48.66	48.85	48.52
$(CH_3)_3N(I)CH_2SCH_2CH_2CH_3$[c]	111–113	46.18	46.18	46.42
$(CH_3)_3N(I)CH_2SCH(CH_3)_2$[d]	143–145	46.18	46.26	46.30
$(CH_3)_3N(I)CH_2SCH_2CH_2CH_2CH_3$[e]	123–126	43.94	44.01	44.03
$(CH_3)_3N(I)CH_2SCH_2CH(CH_3)_2$[f]	153–154	43.94	43.99	44.10
$(C_2H_5)_3N(I)CH_2SCH_3$[g]	134–136	43.95	44.60	44.39
$(C_2H_5)_3N(I)CH_2SCH_2CH_3$[h]	102–103.5	41.83	41.70	41.83
$(C_2H_5)_3N(I)CH_2SCH_2CH_2CH_3$[i]	81–85	40.01	40.21	
$(C_2H_5)_3N(I)CH_2SCH(CH_3)_2$[j]	132–133	40.01	40.14	39.98
$(C_2H_5)_3N(I)CH_2SCH_2CH(CH_3)_2$[k]	100–101	38.32	38.07	38.28

[a] From the fraction of dimethylaminomethyl-methyl sulfide boiling at 118–124°. [b] From the fraction of dimethylaminomethyl-ethyl sulfide boiling at 140–144°. [c] From the fraction of dimethylaminomethyl-*n*-propyl sulfide boiling at 164–165° (765 mm.). [d] From the fraction of dimethylaminomethyl-isopropyl sulfide boiling at 150–153° (765 mm.). [e] From the fraction of dimethylaminomethyl-*n*-butyl sulfide boiling at 178–183°. [f] From the fraction of dimethylaminomethyl-isobutyl sulfide boiling at 171–177°. [g] From the fraction of diethylaminoethyl-methyl sulfide boiling at 159–162° (745 mm.). [h] From the fraction of diethylaminomethyl-ethyl sulfide boiling at 173–175°. This aminothioether was prepared previously by McLeod and Robinson. [i] From the fraction of diethylaminomethyl-*n*-propyl sulfide boiling at 194–197° (755 mm.). [j] From the fraction of diethylaminomethyl-isopropyl sulfide boiling at 183–184° (745 mm.); previously prepared by McLeod and Robinson. [k] From the fraction of diethylaminomethyl-isobutyl sulfide boiling at 205–208° (755 mm.).

ethyl iodide. It was found that the alkyl iodide added onto the nitrogen only and not to the sulfur. Schneider[3,4] found that in his propyl and butyl series, where the nitrogen and sulfur atoms were separated by three and four carbon atoms, respectively, the methyl iodide first added on to the nitrogen and then to the sulfur, forming an ammonium–sulfonium type of compound, the sulfonium structure decomposing to the sulfide in hot alcohol. In the ethyl series, where the hetero elements were separated by two carbon atoms, the methyl iodide added on to the nitrogen only. Schneider[3,4] interpreted this in terms of steric hindrance where the ammonium group was near the sulfur atom. The results now obtained with formocholine derivatives seem to be consistent with this theory.

The action of methyl iodide on the dimethylaminothioether series was vigorous and complete in a few minutes, while that of ethyl iodide on the diethylamino series was very slow, being, in some cases, incomplete after several weeks.

Furthermore, the onium compounds of the methyl series were very stable, showing little or no tendency to form oils, and very little tendency to dissociate as evidenced by absence of color and odor. The triethyl onium compounds, however, were very difficult to purify because of their considerable tendency to form oils, especially in the cases of the higher thioethers as *n*-butyl.

Sulfones were prepared from certain of the formocholine thioethers for the purpose of testing their physiological activity, and, also, to show definitely that no alkyl halide had added onto the sulfur atom. Schneider[3,4] prepared sulfones of some related compounds by oxidizing the sulfur in the primary aminothioethers, instead of oxidizing the onium compounds, as was done in the cases to be described here.

Experimental Part

The formocholine thioethers were prepared by adding gradually, with cooling, a slight excess of 40% formalin solution to one mole of a 10% aqueous solution of dimethyl amine. One mole of the desired thiol[6] was next added quickly; the mixture was shaken, cooled, then saturated with potassium carbonate and shaken for about an hour. The top non-aqueous layer, consisting of the desired aminothioether and unreacted thiol, was separated, dried over

(6) All the thiols which were used in this work, except methyl, were prepared by hydrolyzing the corresponding alkyl halide–thiourea complexes with slightly more than one equivalent of 10% alkali solution. At the time this work was done (1929), this reaction had not been used generally for the preparation of thiols. In recent times, many applications have been made. [Note especially Backer, *Rec. trav. chim.*, **54**, 215 (1935), and earlier articles.] With the prospects of very cheap thiourea, this method of preparation of thiols has much to commend itself. We found that a large number of alkyl halide–thiourea addition products, formed by refluxing equivalent quantities of the alkyl bromides and thiourea in 95% ethyl alcohol for from one to five hours, yield nearly quantitative amounts of the crude thiols upon alkaline hydrolysis. It is of some interest to note that this reaction is not restricted to thiourea, its simple substitution products and thiopyrimidines. We found that a large number of compounds, having the thiourea grouping of elements, yield benzylthiol with benzyl chloride even in cases where all the hydrogen atoms attached to nitrogen atoms have been replaced. It would appear that this reaction might be used as a test for the so-called carbon–sulfur double bond.

anhydrous potassium carbonate, and fractionally distilled. The nearly constant boiling fraction was then condensed with methyl iodide in a toluene solution. This condensation took place rapidly, the onium compounds being recrystallized from alcohol or acetone. Further data for these compounds are listed in Table I.

The corresponding compounds derived from diethylamine were prepared in the same way, except that an equivalent quantity of pure diethylamine was used instead of the aqueous dimethylamine. The yields of the redistilled products were about 10% higher than those in the dimethyl series, the highest being 72% for diethylaminomethyl-*n*-propyl sulfide, and 64% or dimethylaminomethylisobutyl sulfide.

The onium compounds of the diethyl series were prepared by condensation of ethyl iodide with the tertiary amine sulfide, without any solvent. This reaction proceeded very slowly. Table I gives the data for the compounds prepared.

The sulfones were prepared from formocholine thioethers after converting the iodides into sulfates by oxidizing with 5% permanganate in a neutral solution. The slightly acidified filtrates from these oxidations were evaporated on a steam-bath to dryness. The residues were extracted with hot 95% alcohol and the extracted sulfones were purified by recrystallization from that solvent. These products are soluble in water and hot alcohols, and insoluble in acetone and ether.

TABLE II

Sulfones	Dec. point, °C.	Sulfate sulfur, % Calcd.	Found	
$[(CH_3)_3NCH_2SO_2CH_2CH_3]_2SO_4$	178	7.49	7.50	7.47
$[(CH_3)_3NCH_2SO_2CH_2CH_2CH_3]_2SO_4$	190	7.02	7.04	7.05
$[(CH_3)_3NCH_2SO_2CH(CH)_2]_2SO_4$	190	7.02	7.64	
$[(CH_3)_3NCH_2SO_2CH_2CH_2CH_2CH_3]_2SO_4$	190	6.61	6.51	6.55
$[(CH_3)_3NCH_2SO_2CH_2CH(CH_3)_2]_2SO_4$	197	6.61	6.62	6.66

The pharmacological properties have been investigated by Hunt.[7] These thioethers of formocholine have pronounced acetylcholine and stimulating nicotine actions, being possibly slightly more active than the corresponding oxygen compounds. However, the methyl and *n*-propyl derivatives are definitely less toxic to mice. The maximum acetylcholine action was reached in the ethyl and *n*-propyl compounds, while the stimulating nicotine action increased from the methyl to the *n*-butyl derivatives.

The thioethyl analogs of formocholine ethers, like the oxygen ethers, have neither acetylcholine action nor the stimulating nicotine action. They have, however, a paralyzing nicotine action, being somewhat more active in this respect than the oxygen compounds. The most active was the isobutyl thioether. It had a powerful but brief curare action. The oxidation of the thioether sulfur to the sulfonyl group brought about great reduction in the toxicity of the compounds and a marked diminution in the acetylcholine action.

Summary

1. A number of thioethers of formocholine and their triethyl anologs have been prepared and their pharmacological properties investigated.

2. The thioethers were oxidized to the corresponding sulfones. This change of structure reduced markedly the physiological activity of the compounds.

(7) Hunt and Renshaw, *J. Pharmacol.*, **44**, 151 (1932).

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

Phenylbenzyl Ketimine and Derivatives[1]

BY KENNETH N. CAMPBELL[2]

In the course of other work, it became necessary to prepare and study the properties of phenylbenzyl ketimine and some of its derivatives.

Phenylbenzyl ketimine hydrochloride was first reported by Moureu and Mignonac,[3] who did not obtain it in pure form. Ectors[4] later prepared a compound by an indirect method which he called phenylbenzyl ketimine hydrochloride, but which did not have the physical constants of the substance obtained by us.

(1) This paper presents a portion of the dissertation submitted by the author in partial fulfilment of the requirements for the degree of Doctor of Philosophy at the University of Chicago in 1932. The investigation was carried out under the direction of the late Professor Julius Stieglitz.

(2) Present address: Department of Chemistry, University of Notre Dame.

(3) Moureu and Mignonac, *Ann. chim.*, [9] **14**, 322–59 (1920).

(4) Ectors [*Bull. acad. roy. Belg., Classes des Sciences*, [5] **10**, 347–52 (1924)] prepared a crude hydrochloride (m. p. 213°) which he believed was a mixture of phenylbenzyl ketimine hydrochloride (m. p. 137°) and 3,4,5-triphenylpyrazoline hydrochloride (m. p. 221°). His evidence for this belief was the fact that the free base, liberated from this hydrochloride, gave, on distillation under reduced pressure, desoxybenzoin and triphenylpyrazoline. He prepared a compound (m. p. 137°), from N-acetylphenylbenzyl ketimine, which he called phenylbenzyl ketimine hydrochloride, and which he believed was formed according to the equation $C_6H_5—C(=N—CO—CH_3)CH_2C_6H_5 + HCl + C_2H_5OH \longrightarrow CH_3—C(=O)—OC_2H_5 + [C_6H_5—C(NH_2)—CH_2C_6H_5^+] + Cl^-$. He liberated a free base from this hydrochloride, and it melted at 92–93°. It is possible that the phenylbenzyl ketimine and its hydrochloride obtained by Ectors are geometrical isomers of the ones prepared in our study.