[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY AND PHARMACOLOGY, NEW YORK UNIVERSITY]

Thioesters of Choline and β-Methylcholine and their Physiological Activity. Onium Compounds. XIX

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The work described in the present paper is a continuation of an investigation of compounds in which sulfur was introduced into the structure of choline derivatives and into analogous compounds. Previous papers have described substances in which the onium element, nitrogen, has been replaced by sulfur to form sulfonium derivatives as well as to replace the oxygen of the hydroxyl group to form thiol derivatives, thioethers and sulfones. Certain acyl derivatives of "thiol-choline" are described here. In papers to be presented later, work on derivatives of sulfinic and sulfonic acids will be described.

Thiol-choline bromide, β-thiolethyltrimethylammonium bromide, was prepared in this Laboratory a number of years ago by the use of thiomethyluracil for replacing the halogen in bromocholine bromide by the thiol group.[2] Recently,[3] the introduction of the sulfur atom into the choline structure has been accomplished more readily by replacing the halogen in chloroethyldimethylammonium chloride by hydrolyzing the thiourea addition product of this compound. The same procedure was used in the present work and extended to the preparation of the β-thiolpropyldimethylamine.

The thiourea addition complexes of these halogen amines can be obtained in practically theoretical yield by heating the reactants in various alcoholic solutions. The thiolamines are obtained readily in good yield from the thiourea complex by hydrolyzing the latter with dilute bases. When the quantity of base used is sufficient to give marked alkalinity to the final reaction mixture, notable quantities of the disulfide are formed due to the ready oxidation of the thiol. For the preparation of certain derivatives, it is more convenient to oxidize the thiol at this stage and isolate the product as the disulfide.

The tertiary aminothiols acylate readily with acyl chlorides. The resulting thiol esters undergo hydrolysis and alcoholysis surprisingly easily considering the relative stability of compounds of similar structure (thiocaine) described by Hansen and Fosdick.[4] These tertiary amino thiol esters are readily converted into the quaternary compounds with alkyl halides. The resulting esters are more stable to alcoholysis and hydrolysis in acid solutions than the esters of the tertiary amines.

The addition of alkyl halides to the tertiary aminothiols to form the quaternary compounds does not take place in a clear-cut manner due to a simultaneous alkylation of the thiol group with the formation of tertiary amino thioethers. The latter may then be alkylated either on the nitrogen or sulfur atom or both.

By the action of the methyl iodide on β-thiolpropyldimethylamine a mixture of products was obtained from which two substances were isolated. The analysis of one product indicated a composition corresponding to the β-methyl thioether of propyltrimethylammonium iodide. This product melted nearly 40° higher than a product obtained by Mylius[5] by the action of methyl iodide on the methyl thioether of the corresponding primary amine. It has not been determined which of these products is the ammonium and which the sulfonium derivative. The second product isolated in small quantity showed, upon analysis, the composition of the expected β-methylthiolcholine. While it contained one active hydrogen, it did not show a thiol test and was probably the hydroiodide of the methyl thioether of the tertiary amine.

The quaternary thiols are best prepared by reduction of the *bis*-quaternary disulfide which may be obtained in nearly quantitative yields from the disulfides of the tertiary amines. They are also readily obtained by hydrolysis of the thioacyl derivative of the quaternary compounds.

Preliminary experiments carried out in this Laboratory in August, 1936, on the activities of acetylthiocholine and β-methyl-acetylthiocholine showed a remarkable variation in one of the ac-

(1) The chemical part of this paper has been constructed from a thesis presented by P. F. Dreisbach, December, 1936, for the degree of Doctor of Philosophy at New York University.

(2) Harada, *Bull. Chem. Soc., Japan*, **4**, 171 (1929); see also, *ibid.*, **6**, 25 (1931).

(3) Williams, Doctoral Dissertation, New York University, June, 1933.

(4) Hansen and Fosdick, THIS JOURNAL, **55**, 2873 (1933).

(5) Mylius, *Ber.*, **49**, 1100 (1916).

tions of these compounds from what one would expect from the properties of other choline derivatives. It has been shown previously[6] that when the hydroxyl group of choline is replaced by the thiol group there is only a slight weakening of the typical depressor acetylcholine action. On the other hand, the stimulating nicotine action was diminished markedly and the paralyzing nicotine and curare actions augmented largely. In a more recent study of the acetyl derivatives of these thiols, the earlier results have been confirmed and extended.

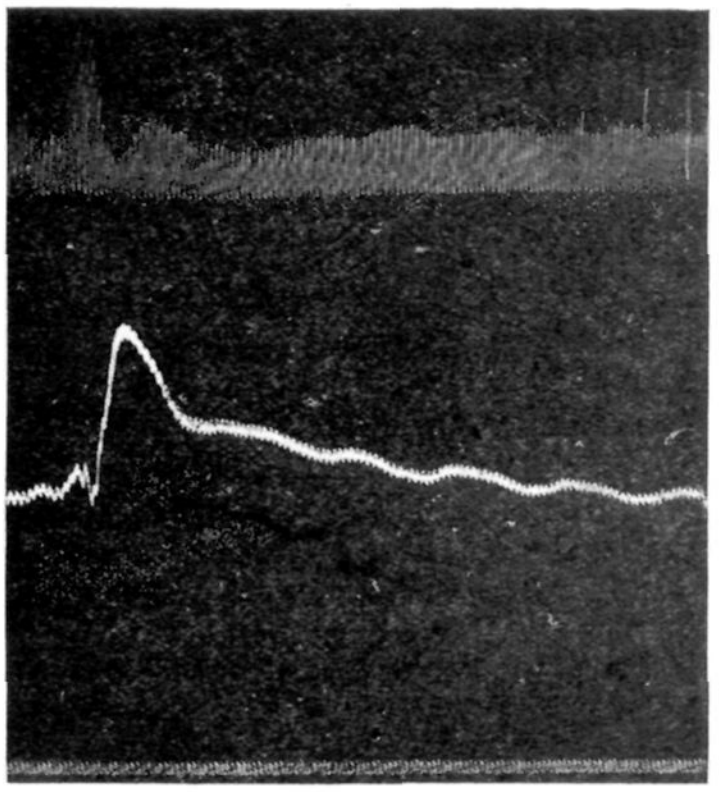

Fig. 1.—0.1 Mg. of thioacetyl-β-methylcholine iodide after atropine.

The acetylation of the thiocholine brings about a reversal of the effect of introducing the sulfur atom and produces a marked augmentation of the stimulating nicotine action. After atropine, 0.1 mg. of this product caused a rise of blood pressure from 128 to 166 mm. More remarkable is the fact that the acetyl derivative of the β-methyl-thiocholine produces a greater augmentation of the stimulating nicotine action. After atropine, 0.1 mg. of this substance caused the blood pressure to rise from 130 to 210 mm. The intensity of the activity of this compound was not greatly affected by the removal of the adrenals although the blood pressure returned to normal much more quickly after adrenalectomy. When one recalls that the introduction of the β-methyl group into acetylcholine nullifies the stimulating nicotine action of the latter, one is amazed at the extraordinary pressor activity of this sulfur β-methyl derivative. In large doses, both of these products have marked paralyzing nicotine and curare actions.

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

Chemical Experimental Part

WITH P. F. DREISBACH

β-(Chlorido-thiourea)-propyldimethylammonium Chloride.—A mixture of 50 g. of β-methyl-β-chloroethyldimethylammonium chloride and 25 g. of thiourea, dissolved in just enough *n*-propyl alcohol to effect solution when hot, was refluxed for nine hours and then allowed to stand at ice-box temperature for two days. The product formed was recrystallized from propyl alcohol, from which it separates in clusters of fine needles. These are slightly soluble in acetone and insoluble in ether; additional material obtained from the mother liquor gave a total yield of 92%, m. p. 201–202°.

Anal. Calcd. for $C_6H_{17}Cl_2N_3S$: Cl, 30.29. Found: Cl, 30.38, 30.37.

β-Thiol-propyldimethylamine.—A solution of 47 g. of β-chlorido-thiourea-propyldimethylammonium chloride and 22.5 g. of potassium hydroxide in 234 cc. of water was allowed to stand overnight at room temperature. The solution was then continuously extracted with ether for several days, a small amount of dicyandiamide separating out in the ether extract. From the dried ether extract, there was obtained by distillation 14.4 g. (61%) of a product boiling from 153 to 154° at 762 mm. and 46 to 51° at 14 to 18 mm. The amino thiol is soluble in water and the common organic solvents. With sodium nitroprusside it gives a positive test for the thiol group. It is relatively stable in air and in acid solution, but oxidation to the disulfide takes place rapidly in alkaline solution.

Anal. Calcd. for $C_5H_{13}NS$: H, 10.99; C, 50.34. Found: H, 11.39; C, 50.20.

The picrate crystallizes from glacial acetic acid in the form of needles melting with decomposition from 159 to 166° (sinters before melting).

Anal. Calcd. for $C_5H_{13}NS \cdot C_6H_3N_3O_7$: N, 16.09. Found: N, 15.99.

The cyano-mercury salt was obtained by treating the product with a saturated aqueous solution of mercuric cyanide. This salt crystallizes from water in the form of needle crystals which, when heated, gradually decompose from 125° upward.

Anal. Calcd. for $C_6H_{12}N_2SHg$: Hg, 58.18. Found: Hg, 57.93.

β,β'-Dithio-*bis*-(propyldimethylamine).—The hydrolysis of 48 g. of crude thiourea complex was carried out as above excepting that a small excess of potassium hydroxide was used so that the reaction solution acquired a decidedly alkaline reaction. Distillation of the ether extract gave 4 g. of pure thiol and, as the main product, 11 g. of the disulfide which boils at 151–154° at 14 mm. It is insoluble in water and alkali and soluble in dilute mineral acid, alcohol and ether. The disulfide was readily reduced to the thiol.

Anal. Calcd. for $C_{10}H_{24}N_2S_2$: H, 10.24; C, 50.77; mol. wt., 236.3. Found: H, 9.90; C, 50.55; mol. wt., 240.

β,β'-Dithio-*bis*-(propyltrimethylammonium Iodide).—Treatment of β,β'-dithio-*bis*-(propyldimethylamine) with excess methyl iodide in ethyl alcohol gave this product in almost theoretical yield. It crystallizes from ethyl alcohol as spheres of feather-like crystals which are soluble in water, slightly soluble in propyl alcohol and insoluble in acetone and ether; m. p. 207–208° (dec.).

Anal. Calcd. for $C_{12}H_{30}I_2N_2S_2$: H, 5.81; C, 27.69; N, 5.39; I, 48.79; active hydrogen, 0. Found: H, 5.91; C, 27.33; N, 5.53; I, 48.92; active hydrogen, 0.

Treatment of β-Thiol-propyldimethylamine with Methyl Iodide.—The addition of excess methyl iodide to an ether, benzene or toluene solution of β-thiol-propyldimethylamine gave, after three days of standing at room temperature, a precipitate consisting of a mixture of compounds from which there was isolated, by a series of fractional recrystallizations, a pure compound which turned brown at 189–195° and decomposed at 197–200°. The analysis of this is in agreement with the theoretical for β-(methyl-thio)-propyltrimethylammonium iodide, but the melting point does not agree with that of the product described by Mylius[5] as β-(methyl-thio)-propyltrimethylammonium iodide which he obtained by the action of methyl iodide on the thioether of isopropylamine. His product melted at 162–163°. Evidently, either his product or ours is the sulfonium iodide rather than the ammonium iodide. We did not attempt to prove the structure of this substance, but, due to the fact that our product is the higher melting, we suspect that it is the quaternary ammonium compound.

Anal. Calcd. for $C_7H_{18}INS$: C, 30.55; H, 6.59; I, 46.11. Found: C, 30.40; H, 6.87; I, 46.31, 46.17.

β-(Acet-thio)-propyldimethylammonium Chloride.—This product was obtained in almost theoretical yield by the slow addition of 4.4 g. of β-thiol-propyldimethylamine in 20 cc. of dry ether to 8 g. of acetyl chloride in 10 cc. of dry ether with vigorous agitation, while cooling the mixture in ice. When purified from an ether–amyl alcohol mixture, it forms hard, clear needles which are very hygroscopic and soluble in the common alcohols and esters; m. p. 91–92°. This ester is hydrolyzed rapidly in alkaline solution. Attempts to liberate the free base with sodium carbonate or sodium bicarbonate caused considerable hydrolysis. The free base also readily undergoes alcoholysis in alcohol solution.

Anal. Calcd. for $C_7H_{16}ClNOS$: Cl, 17.94. Found: Cl, 18.07, 18.28.

β-(Acet-thio)-propyltrimethylammonium Iodide.—A water solution of 7.5 g. of β-(acet-thio)-propyldimethylammonium chloride was shaken with excess silver oxide and the mixture then immediately extracted with ether. Addition of excess methyl iodide to the dried ether extract gave a product as a precipitate after standing at room temperature for five days. Recrystallized from butyl alcohol, it forms fine prisms which are very soluble in water and ethyl alcohol; yield 64%; m. p. 144–145°.

Anal. Calcd. for $C_8H_{18}NOSI$: I, 41.86. Found: I, 41.90, 41.78.

β-(Benz-thio)-propyldimethylammonium Chloride.—To 10 g. of benzoyl chloride in 10 cc. of dry ether there was added, slowly and with cooling, an ether solution of 5 g. of β-thiol-propyldimethylamine. The product began to precipitate immediately and the solution was then warmed on the steam-bath for one hour to complete the reaction. The product was obtained as clusters of fine, white needles by dropwise addition of ether to an ethyl alcohol solution. They are soluble in ethyl alcohol, slightly soluble in benzene and insoluble in ether and acetone; yield 90%; m. p. 122.5°.

The free base, which may be liberated from the hydrochloride by sodium bicarbonate, slowly undergoes alcoholysis on standing in ethyl alcohol.

Anal. Calcd. for $C_{12}H_{18}ClNOS$: Cl, 13.65. Found: Cl, 13.79, 13.74.

β-(Benz-thio)-propyltrimethylammonium Iodide.—An ether solution of β-(benz-thio)-propyldimethylamine was prepared by treating 5 g. of its hydrochloride in water with excess dilute sodium bicarbonate solution and immediately extracting with ether. The free base precipitated in the water solution as an emulsion. Excess methyl iodide was added to the dried ether extract and, after standing for several days at room temperature, the product had precipitated completely. It crystallizes from ethyl alcohol and from concentrated aqueous solution in the form of rosets of needles which are soluble in water and ethyl alcohol and slightly soluble in the higher alcohols; yield 85%; m. p. 185–186°. The substance is fairly stable in acid solution.

Anal. Calcd. for $C_{13}H_{20}INOS$: H, 5.52; C, 42.72; I, 34.75. Found: H, 5.55; C, 42.39; I, 34.53, 34.71.

β-(*p*-Nitrobenz-thio)-propyldimethylammonium Chloride.—A solution of 5.2 g. of β-thiol-propyldimethylamine in 25 cc. of benzene was added dropwise to 8 g. of *p*-nitrobenzoyl chloride in 20 cc. of benzene with cooling and shaking. The mixture was then refluxed for half an hour, after which precipitation of the product was complete. The product was purified by several recrystallizations from an absolute alcohol solution, m. p. 199–200°.

Anal. Calcd. for $C_{12}H_{17}ClN_2O_3S$: H, 5.62; C, 47.26; Cl, 11.64. Found: H, 5.77; C, 46.93; Cl, 11.77, 11.85.

The free base of this compound, prepared from its hydrochloride by dilute sodium bicarbonate solution, crystallizes from ligroin as orange-yellow plates, m. p. 85°. It is soluble in ether and insoluble in water. This product undergoes some hydrolysis even on standing in moist air. In alcohol solution, it alcoholizes almost immediately as is shown by the precipitation of ethyl *p*-nitrobenzoate from a freshly prepared alcoholic solution upon the addition of water.

Anal. Calcd. for $C_{12}H_{16}N_2O_3S$: N, 10.44. Found: N, 10.20, 10.35.

β-(*p*-Nitrobenz-thio)-propyltrimethylammonium Iodide.—An ether solution of the free base from 1 g. of β-(*p*-nitrobenz-thio)-propyldimethylamine hydrochloride was treated with excess methyl iodide and allowed to stand for two days at room temperature when precipitation of the product was complete. Recrystallized from a relatively small amount of water, it forms clear, orange-yellow needles; yield, 59%. It is moderately soluble in

water and alcohol and insoluble in ether. In boiling alcohol, decomposition takes place; m. p. 190–191°.

Anal. Calcd. for $C_{13}H_{19}IN_2O_3S$: I, 30.94. Found: I, 30.91, 30.74.

β-(Chlorido-thiourea)-ethyldimethylammonium Chloride (WITH J. H. WILLIAMS[3]).—This product was obtained in practically theoretical yield when 55 g. of β-chloroethyldimethylammonium chloride and 30 g. of thiourea were refluxed for four and one-half hours in 60 cc. of absolute ethanol. Recrystallization from an acetone–ethanol mixture gave fine, colorless needles; m. p. 181–182°.

Anal. Calcd. for $C_5H_{15}N_3SCl_2$: Cl, 32.22. Found: Cl, 32.24, 32.19.

β,β'-Dithio-*bis*-(ethyltrimethylammonium Iodide).—Air was aspirated slowly for twenty minutes through a solution of 1 g. of β-thiol-ethyldimethylamine in 10 cc. of dilute potassium hydroxide solution kept at 80°. A layer of water insoluble liquid formed on the top surface and the whole was extracted with ether. Excess methyl iodide was added to the dried ether solution and, after six hours of standing, 1.1 g. of material had precipitated. This crystallizes from methyl alcohol solution as needles which turn brown at 220° and decompose at 230° when heated at the rate of 6° per minute, or at 235° heated at the rate of 12° per minute.

From the melting points and mixed melting point, this product was shown to be identical with a product isolated by Williams[3] in this Laboratory from the action of methyl iodide on β-thiol-ethyldimethylamine.

Anal. Calcd. for $C_{10}H_{26}N_2S_2I_2$: I, 51.56. Found: I, 51.35, 51.28.

β-(Acet-thio)-ethyldimethylammonium Chloride.—This product was prepared from β-thio-ethyldimethylamine and acetyl chloride according to the method outlined above for the corresponding β-methyl substituted compound in a yield of 78%. It recrystallized in needles from an ether–amyl alcohol mixture. The product is very hygroscopic; m. p. 95°.

Anal. Calcd. for $C_6H_{14}ClNOS$: Cl, 19.31. Found: Cl, 19.21, 19.24.

β-(Acet-thio)-ethyltrimethylammonium Iodide.—This was obtained from β-(acet-thio)-ethyldimethylammonium chloride, using silver oxide to liberate the free base, and methyl iodide by a method similar to that outlined for the preparation of the corresponding β-methyl substituted compounds; yield 77%. Recrystallized from propyl alcohol, it forms glistening plates which are soluble in water and the alcohols and insoluble in acetone and ether; m. p. 203–204°.

Anal. Calcd. for $C_7H_{16}INOS$: I, 43.90. Found: I, 43.70, 43.69.

β-(Benz-thio)-ethyldimethylammonium Chloride.—This compound was obtained from the tertiary amino thiol and benzoyl chloride; yield, almost the theoretical. Recrystallized from amyl alcohol, it forms colorless plates soluble in water and alcohols; m. p. 164.5–165°.

Anal. Calcd. for $C_{11}H_{16}ClNOS$: Cl, 14.44. Found: Cl, 14.61, 14.74.

β-(Benz-thio)-ethyltrimethylammonium Iodide.—This product was obtained from the corresponding amino-thiol hydrochloride, using dilute sodium bicarbonate solution to liberate the free base, and methyl iodide. Recrystallized from water, it forms glistening plates decomposing at 257° dependent on rate of heating; yield 84%. The product is soluble in water, slightly soluble in ethyl alcohol and insoluble in ether.

Anal. Calcd. for $C_{12}H_{18}INOS$: I, 36.15. Found: I, 36.12, 35.98.

β-(*p*-Nitrobenz-thio)-ethyldimethylammonium Chloride.—This *p*-nitrobenzoyl derivative was obtained in practically theoretical yield by a procedure analogous to the preceding. Recrystallized from isoamyl alcohol, it forms fine plates. It is soluble in water, ethyl alcohol and hot propyl and amyl alcohols; insoluble in ether and benzene; m. p. 187° (dec.).

Anal. Calcd. for $C_{11}H_{15}ClN_2O_3S$: Cl, 12.20. Found: Cl, 12.29, 12.31.

β-(*p*-Nitrobenz-thio)-ethyltrimethylammonium Iodide.—This quaternary ammonium compound was obtained from β-(*p*-nitrobenz-thio)-ethyldimethylammonium chloride, using dilute sodium bicarbonate solution to liberate the free base, and methyl iodide according to the method described above for the preparation of the corresponding β-methyl compound; yield 81%. The compound is moderately soluble in water, slightly soluble in the alcohols and insoluble in ether. Recrystallized from water, it forms yellow-orange plates which darken at 195° and melt at 212–216° to a red melt.

Anal. Calcd. for $C_{12}H_{17}IN_2O_3S$: I, 32.05. Found: I, 32.08, 32.05.

Pharmacological Experimental Part

WITH D. GREEN AND M. ZIFF

The experiments were performed upon cats anesthetized by means of nembutal. The following effects were noted:

1. Acetylcholine or "muscarine" action: a fall in blood pressure of vascular origin and prevented by atropine.

2. "Stimulating nicotine" action: a rise in pressure due to stimulation of sympathetic ganglia cells.

3. "Paralyzing nicotine" action: abolition of effects on the eye upon electrical stimulation of the cervical sympathetic; abolition of the rise in pressure caused by small doses of nicotine.

4. "Curare" action: abolition of response to electrical stimulation of motor nerves (femoral).

β-Acet-thio-ethyltrimethylammonium iodide had a moderate acetylcholine effect, being in the order of one hundredth as active as acetylcholine. In one experiment, 0.1 mg. of the drug caused a fall of 48 mm. as compared with a fall of 64 mm. produced by 0.001 mg. of acetylcholine. This effect was most marked in doses of the order of 0.1 mg. In larger doses, the "stimulating nico-

tine" effect was so great—even without previous administration of atropine—as to partially neutralize the fall in pressure by the production of a secondary rise. After atropine, the pressure rose abruptly and then fell rather slowly to normal. A curious feature of this return, after atropine, was the occcurrence of marked Traube–Hering waves.

After adrenalectomy, the "stimulating nicotine" effect was somewhat diminished, but still pronounced. The return of pressure to normal was much more rapid, however. The relationship of the acetylcholine to the "stimulating nicotine" effect, under various conditions, is shown in Table I.

TABLE I

Dose (mg./kg.)	Initial pressure	Fall to	2° Rise to
	Acet-thiocholine iodide		
0.0277	158	110	164
.057	150	134	178
.33	136	98	194
.57	136	112	190
.75	122	76	120
2.2	144	40	74
	After atropine		
0.0277	128	...	162
	After atropine and adrenalectomy		
0.0277	144	...	164
.055	148	...	184
	β-Methyl-acet-thiocholine iodide		
0.0277	158	136	190
.057	120	...	214
.50	114	96	148
.75	106	76	104
	After atropine		
0.0277	130	...	208
	After atropine and adrenalectomy		
0.0277	142	...	208
.055	154	...	236
	Methyl-thiocholine iodide		
0.0455	138	104	150
.091	110	66	126
.435	128	84	132

The "paralytic nicotine" and "curare" effects of this compound became evident rather abruptly as one increased the dosage. Thus, evidences of these effects were lacking in doses of 0.285 and 0.33 mg. per kilogram; whereas, in doses of 0.75, 0.90 and 2.2 mg. per kilogram, both effects were not only strong but the curariform paralysis of respiration was ultimately sufficient to produce death.

β-(Acet-thio)-propyltrimethylammonium iodide had an acetylcholine action somewhat weaker than the acet-thiocholine. In one experiment 0.1 mg. caused a fall of 32 mm. as compared with a fall of 48 mm. produced by the same amount of the latter. The acetylcholine action of the compound was obscured to a far greater extent, however, by the "stimulating nicotine" effect, which was very pronounced, in some cases so great that the only observable blood pressure effect was a rise. The effect of the β-methyl group of this substance, which caused more than a two-fold increase in the pressor activity over that of the parent substance, seems remarkable. After atropine, the pressor effect was enhanced, and Traube–Hering waves observed. Adrenalectomy again diminished, somewhat, the "stimulating nicotine" action and markedly shortened its duration. "Curare" and "paralytic nicotine" effects were observed in doses of 0.5 to 0.75 mg. per kilogram, but unlike the effects with corresponding doses of acet-thiocholine they were transient and did not cause death of the animal.

β-Methylthio-ethyltrimethylammonium iodide was investigated briefly. It exhibited a moderately strong and consistent acetylcholine action, being in that respect about equal to that of the acetyl-thio derivative. There was in this compound (as in the others of the series) a definite rise in pressure observable even without the administration of atropine, as seen in Table I. "Curare" and "paralytic nicotine" effects were observed in doses of 0.435 mg. per kilogram. Respiratory paralysis was transient, however, and did not cause death.

PROTOCOL

Cat No. 11; 3.6 kg.; Nembutal 2.8 grains; blood pressure from the carotid artery; injections into femoral vein. AcC = acetylcholine bromide; PD-1 = acet-thiocholine iodide; PD-2 = β-methyl-acet-thiocholine iodide.

9:32 AcC, 0.001 mg. Blood pressure fell 64 mm. (160 to 96).
9:51 PD-1, 0.1 mg. Blood pressure fell from 158 to 110 mm. and then rose to 164. Respiratory stimulation.
9:54 PD-2, 0.01 mg. Practically no effect.
9:57 PD-2, 0.1 mg. Blood pressure fell from 158 to 136 mm. and then rose to 190 mm. Respiratory stimulation.
10:10 Atropine sulfate, 4 mg.
10:18 AcC, 0.001 mg. Blood pressure rose from 108 to 118 mm.
10:26 PD-1, 0.1 mg. Blood pressure rose from 128 to 162 mm. Traube–Hering waves noted.
10:30 PD-2, 0.1 mg. Blood pressure rose from 130 to 208 mm. and slowly returned to 136 mm.
10:40 Adrenalectomy bilaterally.

11:29 AcC, 0.001 mg. Little effect.
11:32 PD-2, 0.1 mg. Blood pressure rose from 142 to 208 mm. Rapid return to normal.
11:35 PD-1, 0.1 mg. Blood pressure rose from 144 to 164 mm. Traube–Hering waves. Transitory respiratory stimulation.
11:38 PD-2, 0.2 mg. Blood pressure rose from 154 to 236 mm. Traube–Hering waves. Transitory respiratory stimulation.
11:43 PD-1, 0.2 mg. Blood pressure rose from 148 to 184 mm. Traube–Hering waves. Transitory respiratory stimulation.

The authors wish to express their appreciation and thanks to Professor George B. Wallace, in whose laboratory most of the experiments were performed.

Summary

1. Methods of preparation of tertiary amino alkyl thiols are described.

2. Thioethyldimethylamine and its β-methyl derivative have been acylated and the resulting thioesters converted into quaternary ammonium derivatives yielding thioesters of choline and β-methylcholine.

3. The acetyl derivatives of thiocholine and the acetyl derivative and methyl thioether of β-methylthiocholine have been tested pharmacologically for their acetylcholine, "stimulating" and "paralytic nicotine" and "curare" actions.

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[A COMMUNICATION FROM THE LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Effects of Solvents on Polarographic Wave Heights

BY EDMOND S. PERACCHIO[1] AND VILLIERS W. MELOCHE

Since the discovery of the polarograph by Heyrovsky, many contributions have been made to the literature involving the use of the instrument. Aside from describing the process at the dropping mercury capillary electrode and developing equations for the polarographic curve, most papers were concerned with proof of reduction or qualitative detection of a great variety of substances. Actual applications of the method to quantitative analysis were few in number and often the procedures were poorly defined. Heyrovsky, Ilkovic and others have mentioned variables which affect wave height and its relationship to concentration of a given ion. In this connection they have included the mobility of the reducible ion as an important consideration. When one examines several papers which have appeared in the literature,[2] it may seem that a given amount of one reducible substance will give a wave height equal to that of an equivalent amount of another reducible substance or that differences between the wave for equivalent amounts of two different ions are not significant in quantitative analysis. From our studies it became evident that this was not necessarily true. At the same time it is true that the order of magnitude of these differences could be changed by the addition of various reagents to the solution of the sample.

Since in a preliminary investigation we found that the wave for lithium chloride was defined better in a solution containing ethyl alcohol than it was in water, it was decided to extend the study of the polarographic wave heights to systems containing high concentrations of non-aqueous solvents.

The purpose of this investigation is to illustrate the differences in wave heights which exist for equivalent weights of the alkali metals in certain aqueous solutions and to show how these differences are affected by the introduction of certain organic solvents.

Apparatus.—The usual Heyrovsky[3] polarographic system was used. A few changes were made in the manipulation and construction of the dropping mercury cathode. In the usual construction of the cathode, a mercury reservoir is suspended about 15 inches (38 cm.) above the capillary tip and is connected to the tip by means of gum rubber tube. This arrangement was not satisfactory even when the tube received special treatment. For our experiments, a 100-ml. dropping funnel was used as the reservoir, Fig. 1. The glass tube below the stopcock was long enough so that the distance from the surface of the mercury in the reservoir to the capillary tip afforded a mercury pressure of about 15 to 20 inches (38–51 cm.). The capillary was attached to the glass tube from the reservoir by a short piece of rubber tube which had been conditioned by

(1) This paper is offered in partial fulfilment of the requirements for the degree of Doctor of Philosophy. The work was supported by a grant from the Wisconsin Alumni Research Foundation.

(2) References on wave height discrepancies: Heyrovsky and Nejedly, *Coll. Czech. Chem. Comm.*, **3**, 126 (1931); Suchy, *ibid.*, **3**, 358 (1931); Prajzler, *ibid.*, **3**, 408 (1930); Ilkovic and Semerano, *ibid.*, **4**, 176 (1932); Tokuoka, *ibid.*, **4**, 452 (1935); Rylich, *ibid.*, **7**, 290 (1935).

(3) Hohn, *Z. Elektrochem.*, **43**, 127 (1937); Winkle and Proske, *Angew. Chem.*, **50**, 18 (1937).