dehydration and/or to desorption of stabilizing ions.[3] It is interesting to note also the form of the flocculation curves for samples B-67-2, B-67-3 and B-89-2; in the temperature region of 210–250° the curves flatten out considerably, becoming almost parallel to the temperature axis. This temperature range is the region in which the viscosity curves for these samples are rising toward maxima, prior to precipitation by heat treatment alone. A somewhat similar effect has been reported for zirconium oxide sols,[11] and is also in agreement with the results obtained by Thomas and co-workers,[6,15] who found that "aging" at elevated temperature made aluminum oxyhalide and chromium oxychloride sols less responsive to the action of chloride and sulfate.

The author takes pleasure in acknowledging many valuable suggestions made by Dr. H. E. Wells during the course of this investigation.

(15) Thomas and Tai, THIS JOURNAL, **54**, 841 (1932).

Summary

1. Hydrous chromic oxide sols have been prepared, and samples of various concentrations heated to temperatures up to 260°.

2. Viscosity measurements have been made on the samples which were heat treated. In the lower temperature range, heating was found to decrease the viscosity, whereas at still higher temperatures the viscosity was increased. Concentrated sols were caused to set to rigid gels, whereas dilute samples were finally precipitated by heat treatment to temperatures around 250–260°.

3. Heating caused, in all cases, a decrease in the stability of the colloid, as measured by flocculation values with potassium sulfate.

4. Various means of accounting for the observed effects have been suggested.

NORTHAMPTON, MASS. RECEIVED SEPTEMBER 6, 1935

[CONTRIBUTION FROM THE LABORATORY FOR PURE RESEARCH, MERCK & CO., INC.]

The Preparation and Properties of Beta-*n*-Alkylcholine Chlorides and their Acetyl Esters[1]

BY RANDOLPH T. MAJOR AND HOWARD T. BONNETT

Recent investigations have shown that acetyl-β-methylcholine is a powerful drug with many of the physiological properties of muscarine without the nicotine-like action of the related acetylcholine.[2]

When the present work was begun none of the esters of the higher homologs of β-methylcholine had been prepared and only one of the higher homologs of β-methylcholine itself was known namely, β-amylcholine iodide,[3] and apparently this had not been studied pharmacologically. Due to the interest in β-methylcholine and its esters as medicinals it became necessary, specifically due to the request of Dr. A. Simonart, to prepare some of these homologs and their acetyl esters.

These compounds were prepared as follows. The appropriate chlorohydrin[4] was treated with dimethylamine. The resulting dimethylaminoalkanol yielded a methiodide from which the acetyl ester of the β-*n*-alkylcholine chloride was prepared by standard procedures. Some of the lower homologs, namely, β-ethyl, β-*n*-propyl, and β-*n*-butylcholine chlorides, were prepared by treating the appropriate chlorohydrin with trimethylamine. Because of the rapid increase in hygroscopicity with size of the alkyl group it was found more convenient to proceed by means of the reaction of methyl iodide on dimethylaminoalkanol so that the necessary purification could be effected.

During the course of the work a number of intermediate compounds were prepared which have not been reported previously. These are 1-chlorononanol-2, 1-dimethylaminobutanol-2, 1-dimethylamino-hexanol-2, 1-dimethylaminooctanol-2 and 1-dimethylaminononanol-2.

We are indebted to Doctor Hans Molitor, Director of the Merck Institute of Therapeutic Research, for the following report of the pharmacological action of this series of compounds.

(1) Presented before the Division of Medicinal Chemistry at the Cleveland Meeting of the American Chemical Society, September, 1934.

(2) Simonart, *J. Pharmacol.*, **46**, 157 (1932); Comroe and Starr, *ibid.*, **49**, 283 (1933); Starr, Elsom and Reisinger, *Am. J. Med. Sci.*, **186**, 313 (1933); Abbott, *ibid.*, **186**, 323 (1933); Starr, *ibid.*, **186**, 330 (1933).

(3) Von Braun and Schirmacher, *Ber.*, **56B**, 1845–1850 (1923).

(4) Levene and Haller, *J. Biol. Chem.*, **77**, 560 (1928).

"The series of β-n-alkylcholine chlorides and their acetyl esters have been tested pharmacologically on dogs, cats and rabbits and their action on the blood pressure, respiration and intestinal movements have been observed.

"All of the acetyl esters show a typical muscarinic action, although the degree of activity of the various esters varies. One hundred to one thousand times as large doses of these compounds as of acetyl-β-methylcholine were required in order to produce a corresponding drop of blood pressure and increase of intestinal activity.

"The non-acetylated alkylcholines, however, differed in their action not only quantitatively but also qualitatively. While β-hexylcholine and β-heptylcholine when injected intravenously in doses of from 1 to 10 mg. caused a drop in blood pressure and increase of intestinal action which was almost identical in form and degree to that produced by their acetyl esters, β-ethylcholine and β-amylcholine produced a somewhat smaller fall of pressure than their esters which was followed by a slight but definite rise. This rise was much more pronounced with β-propylcholine; β-butylcholine produced a still greater rise of blood pressure, usually without the short initial drop which was found with β-propylcholine. This is a typical so-called nicotinic action, since it disappeared after repeated administrations of very large doses of β-butylcholine or of smaller doses of nicotine. When injection of the choline derivative was followed by a rise in blood pressure the intestines showed decreased activity and tonus.

"It should be emphasized that this action was found in animals which had not received atropine previously. It is well known that after sufficient atropinization many choline and acetylated choline compounds produce a rise instead of a fall in blood pressure. However, in the case of β-propylcholine and especially β-butylcholine no previous injection of atropine was necessary to suppress the muscarinic action and bring about the nicotinic action. This fact is most remarkable and may be of practical significance for therapeutic purposes, since these drugs liberate endogenic adrenaline."

The pharmacological action of the β-n-alkylcholine derivatives is being further investigated and a detailed report will be given elsewhere.

Professor A. Simonart has also studied the pharmacological action of some of these compounds; a report of his findings is published elsewhere.[5]

Experimental Part

Preparation of 1-Chlorononanol-2.—This was prepared by the method of Levene and Haller;[6] b. p. (13 mm.) 114.5–116.5°.

Anal. Calcd. for $C_9H_{19}OCl$: C, 60.50; H, 12.02; Cl, 19.86. Found: C, 63.13, 63.05; H, 11.06, 11.27; Cl, 18.19, 18.42.

This material was contaminated by an impurity which, however, seemed not to interfere with the subsequent steps in the synthesis.

Preparation of 1-Dimethylaminoalkanol-2.—The appropriate chlorohydrin was heated with a solution of two moles of dimethylamine in benzene at 115–120° for fifteen hours and isolated from the resulting mixture by the usual methods. The compounds were mobile, colorless liquids possessing a strong amine-like odor. 1-Dimethylaminobutanol-2 and 1-dimethylaminopentanol-2 were very soluble in water; the higher homologs were insoluble in water. All were soluble in the usual organic solvents. The boiling points and analyses of the amino alcohols obtained are given in Table I.

TABLE I

$(CH_3)_2NCH_2$-CHOH—R	B. p., °C.	Analyses, % N Calcd.	Found	
R = C_2H_5	142–144 (760 mm.)	12.00	12.43	12.31
n-C_3H_7[a]	73–74 (30 mm.)	10.69	10.92	10.73
n-C_4H_9	89–90 (25 mm.)	9.66	9.84	9.71
n-C_6H_{13}	99–101 (10 mm.)	8.10	8.17	8.20
n-C_7H_{15}	104–106 (5 mm.)	7.50	7.37	7.34

[a] A. Walti, THIS JOURNAL, **56**, 2725 (1934).

Preparation of β-n-Alkylcholine Iodide.—The methiodides of 1-dimethylaminoalkanol-2 were prepared in the usual manner and recrystallized to constant melting point from warm acetone to which ether was added short of producing cloudiness. They were non-hygroscopic, white, microcrystalline solids (see Table II).

Preparation of β-n-Alkylcholine Chloride.—The β-n-alkylcholine iodide was converted to the corresponding chloride by means of silver chloride in alcohol by the methods used by Jones and Major.[7] The products were white extremely hygroscopic solids. β-Ethylcholine chloride may be recrystallized from butyl alcohol, β-propylcholine chloride from a mixture of butyl alcohol and isopropyl ether, and β-butylcholine chloride may be recrystallized with difficulty from a mixture of butyl alcohol and benzene. The others were obtained as gums which crystallized on standing in a desiccator. β-Butyl and β-amylcholine chlorides were the most hygroscopic in the series studied (see Table II).

Preparation of Acetyl β-n-Alkylcholine Chloride.—β-n-Alkylcholine chloride was acetylated and isolated by the method of Major and Cline.[8] The products were white crystalline hygroscopic solids.

(5) A. Simonart, *Arch. intern. Pharmacodynamie*, **48**, 328–332 (1934); *J. Pharmacol.*, **50**, 6 (1934).

(6) Levene and Haller, *J. Biol. Chem.*, **77**, 560 (1928).

(7) Jones and Major, THIS JOURNAL, **52**, 309 (1930).

(8) Major and Cline, *ibid.*, **54**, 242 (1932).

TABLE II

Radical R =	$(CH_3)_2NICH_2CHOH-R$ M. p., °C.	Analyses, % N Calcd.	Found		$(CH_3)_2NClCH_2CHOHR$ M. p., °C.	Analyses, % N Calcd.	Found		$(CH_3)_2NClCH_2CH(OOCCH_3)R$ M. p., °C.	Analyses, % N Calcd.	Found	
C_2H_5	162–163	5.40	5.31	5.38	174–176[a]	8.36	8.36	8.35	144–146	6.68	6.79	7.04
n-C_3H_7	198–200[b]	5.13	5.07	4.98	115–117	7.71	7.58	7.73	168–169	6.26	6.16	6.25
n-C_4H_9	90–92	4.88	4.71	4.66	100.5–102	7.16	6.89	7.04	186–187	5.89	5.83	5.74
n-C_5H_{11}	98–100[c]	4.65	4.77	4.83	72–74	6.67	6.54	6.62	182–184	5.57	5.55	5.49
n-C_6H_{13}	109–110	4.44	4.16	4.22	69–71	6.28	6.45	6.22	169–171	5.26	5.06	4.98
n-C_7H_{15}	122.5–123.5	4.25	3.88	4.04	97–99	5.90	5.85	5.93	176–177	5.00	5.03	4.83

[a] β-Ethylcholine chloride and acetyl-β-ethylcholine sulfate were prepared first in this Laboratory by Dr. Albert B. Boese, Jr., at the request of one of us. [b] Walti [THIS JOURNAL, **56**, 2725 (1934)] reports that β-propylcholine iodide prepared from 1-dimethylaminopentanol-2 which had been obtained from pentene oxide-1,2 melted at 198°. [c] Braun and Schirmacher [*Ber.*, **56B**, 1845–1850 (1923)] report that β-amylcholine iodide melts at 106–108°. β-Amylcholine iodide was prepared in this Laboratory from 1-dimethylaminoheptanol-2 which had been prepared from *n*-amylethylene oxide, and that which had been prepared by the direct condensation of dimethylamine with 1-chloroheptanol-2. In both cases the β-amylcholine iodide after recrystallization from acetone–ether melted at 98–100°. No explanation for the discrepancy has been found.

The authors wish to express their appreciation to Messrs. Douglass F. Hayman and Sol Adler for the analyses recorded in this paper.

Summary

1. 1-Chlorononanol-2 has been prepared.

2. Several new dimethylaminoalkanols have been prepared, including 1-dimethylaminobutanol-2, 1-dimethylaminohexanol-2, 1-dimethylaminooctanol-2 and 1-dimethylaminononanol-2.

3. The homologous series of β-*n*-alkylcholine iodides from β-ethylcholine iodide to β-*n*-heptylcholine iodide inclusive has been prepared and characterized.

4. The homologous series of β-*n*-alkylcholine chlorides from β-ethylcholine chloride to β-*n*-heptylcholine chloride and their acetyl esters have been prepared and characterized.

5. A preliminary report upon the pharmacological action of the β-alkylcholines and their acetyl esters is presented.

RAHWAY, N. J. RECEIVED OCTOBER 25, 1935

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

The Relative Rates of Ozonation of Unsaturated Compounds

BY C. R. NOLLER, J. F. CARSON, H. MARTIN AND K. S. HAWKINS

During the ozonation of dicyclohexenyl-1,1′ it was observed[1] that approximately one mole of ozone added rapidly but that the second mole of ozone added only slowly. A search of Harries' work revealed a statement[2] that compounds containing two conjugated double bonds add the first mole of ozone more rapidly than the second. While the work on dicyclohexenyl-1,1′ was in progress several articles by Brus and Peyresblanques[3] appeared in which they followed the course of ozonation by measuring the amount of unabsorbed ozone during the reaction. They gave curves for oleic acid, styrene, phenylcyclohexene, limonene, pinene, benzene and heptyne. With the concentrations of ozone used benzene added ozone extremely slowly, heptyne moderately so, while the other compounds added one mole of ozone very rapidly. During the past three years, the procedure of Brus and Peyresblanques has been used on a considerable number of compounds and the results of this exploratory work are of considerable interest.

A brief review of the procedure will be given in lieu of the experimental part. An ozone machine of the Henne type[4] is equipped with a flow meter and fitted by means of interchangeable ground joints to two 200-cc. gas washing bottles in series. The ozone machine is operated at constant voltage and temperature and a constant stream of air or oxygen passed through. Immediately before and after each run the ozonized air is passed for five minutes through 125 cc. of a 5% potassium iodide solution and the average

(1) Noller and Kaneko, THIS JOURNAL, **57**, 2442 (1935).

(2) Harries, *Ann.*, **374**, 304 (1910).

(3) Brus and Peyresblanques, *Compt. rend.*, **190**, 501, 685 (1930).

(4) Henne, THIS JOURNAL, **51**, 2676 (1929).