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

Preparation and Properties of Acetyl Dextro- and Acetyl Levo-β-methylcholine Chloride

BY RANDOLPH T. MAJOR AND HOWARD T. BONNETT

Acetyl β-methylcholine chloride[1] has recently been shown to be a useful therapeutic agent.[2] It has been carefully studied pharmacologically and has been found to possess a strong muscarine-like action with none of the nicotine-like action observed with choline and many of its derivatives.[3]

An examination of the chemical formula of acetyl β-methylcholine chloride, $(CH_3)_3NClCH_2CH(CH_3)OCOCH_3$, reveals the fact that it contains one asymmetric carbon atom. Theoretically it should be possible to prepare two optically active forms of this compound. It is generally recognized that one of the optical isomers of a drug is usually much more active physiologically than the other.[4] In order to determine this in the case of acetyl β-methylcholine chloride the optical isomers of the compound have been prepared.

Dextro-dimethylaminoisopropanol was obtained by resolving the *dl* amine with bromocamphorsulfonic acid. Methyl iodide reacted with this to give dextro-β-methylcholine iodide from which acetyl dextro-β-methylcholine chloride was obtained by standard procedures.

Levo-dimethylaminoisopropanol was obtained by resolution of the *dl* amine with *d*-tartaric acid. Acetyl levo-β-methylcholine chloride was obtained by procedures similar to those indicated above for the dextro isomer.

Dr. Hans Molitor, Director of the Merck Institute for Therapeutic Research, has tested these compounds pharmacologically and reports that the muscarine-like action on the blood pressure of acetyl *l*-β-methylcholine chloride is one one-hundredth of that of acetyl *dl*-β-methylcholine chloride. The action of the former on isolated intestine was considerably less than the action of the latter. The muscarine-like action on the blood pressure of acetyl *d*-β-methylcholine chloride is somewhat greater than the action of the *dl* form. The action on isolated intestine is comparable to that of the *dl* form.

Experimental Part

Preparation of *d*-Dimethylaminoisopropanol.—Dimethylaminoisopropanol (b. p. 124–126°) was treated with a 5% excess of bromocamphor sulfonic acid in ethyl acetate solution. The salt was recrystallized from a mixture of 5 cc. of ethyl acetate and 1 cc. of absolute alcohol per gram of salt. Its rotation attained a value of +83.5° after five recrystallizations and was unchanged by additional recrystallizations. The amine was obtained from the salt by treating the latter with excess sodium hydroxide, extracting with ether, drying the ether solution with anhydrous potassium carbonate and distilling at atmospheric pressure; b. p. (770 mm.) 124.5–126°; $[\alpha]^{25}D$ +17.1°.

Anal. Calcd. for $C_6H_{13}ON$: N, 13.59. Found: N, 13.61, 13.48.

Preparation of *l*-Dimethylaminoisopropanol.—Dimethylaminoisopropanol (b. p. 124–126°) was treated with 1.05 moles of *d*-tartaric acid in 95% alcohol solution. The salt was recrystallized from 6 cc. of 96% ethyl alcohol per gram of salt. A series of fifteen recrystallizations gave a salt having $[\alpha]^{25}D$ −10.7°, the last four crystallizations changing the rotation from −10.3 to −10.7°. The amine was obtained from the salt as described above; b. p. 125°, $[\alpha]^{25}D$ −14.8°.

Anal. Calcd. for $C_6H_{13}ON$: N, 13.59. Found: N, 13.00, 12.96.

Preparation of Acetyl *d*- and Acetyl *l*-β-Methylcholine Chlorides.—The methiodides of the optically active am-

PREPARATION AND PROPERTIES OF ACETYL DEXTRO AND ACETYL LEVO β-METHYLCHOLINE CHLORIDE

		β-Methylcholine iodide	β-Methylcholine	Acetyl-β-methylcholine chloride
Dextro form	M. p., °C.	176–177	165–167	200–201[a]
	[α]	+24.7	+38.8	+41.9
	N found, %	5.87 5.74	9.34 9.35	6.79 6.98
N calcd., %		5.71	9.12	7.16
Levo form	N found, %	5.39 5.53	9.45 9.25	7.04 6.89
	M. p., °C.	176.5–177.5	165–167	201–202[a]
	[α]	−24.7	−38.2	−41.3

[a] A mixed melting point of equal quantities of the *d*- and *l*-forms melted at 172–174°. Major and Cline [THIS JOURNAL, **54**, 247 (1932)] give 172–173° for *dl*-acetyl-β-methylcholine chloride.

(1) Major and Cline, THIS JOURNAL, **54**, 242 (1932).

(2) Kovacs, *Am. J. Med. Sci.*, **188**, 32 (1934); Abbott, *ibid.*, **186**, 323 (1933); Starr, *ibid.*, **186**, 330 (1933).

(3) Simonart, *J. Pharmacol. Exptl. Therap.*, **46**, 157 (1932).

(4) Sollman, "A Manual of Pharmacology," W. B. Saunders & Co., Philadelphia, 1932, p. 364.

ines were prepared in the usual manner. They were recrystallized from hot absolute alcohol to which about 30% of acetone was added after solution, and were obtained as white non-hygroscopic crystals. The optically active β-methylcholine iodides were converted to the corresponding chlorides using silver chloride in alcohol according to standard procedures. The chlorides were recrystallized from butyl alcohol,[5] and were obtained as white hygroscopic crystals. The optically active β-methylcholine chlorides were acetylated according to the method of Major and Cline.[5] The acetyl esters thus obtained were white hygroscopic crystalline solids. The properties and analyses of the above-mentioned compounds are recorded in the table.

(5) Major and Cline, THIS JOURNAL, **54**, 247 (1932).

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

Summary

1. *dl*-Dimethylaminoisopropanol has been resolved into its optically isomeric forms.

2. The dextro and levo isomers of β-methylcholine iodide, β-methylcholine chloride, and acetyl-β-methylcholine chloride have been prepared and characterized.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

Potassium Thiocyanate as a Primary Standard Substance

BY I. M. KOLTHOFF AND J. J. LINGANE

Although potassium thiocyanate has long been used as a reagent in the classical Volhard method for the titration of silver, the use of the pure salt as a primary standard substance in argentimetry has been discouraged in the literature.[1]

The initial purpose of the present investigation was to investigate the possibility of preparing the pure salt for use as a standard substance. A secondary purpose was to determine the *accuracy* of the potentiometric and the Volhard methods for the titration of thiocyanate with silver, which has never been established, although the *precision* of the titration has been the subject of several studies.[2]

The second part of this work has led to the discovery of a hitherto unsuspected side reaction (or reactions) that takes place when thiocyanate is precipitated with silver.

Preparation of Pure Potassium Thiocyanate

Potassium thiocyanate from Kahlbaum and the reagent quality product of the Mallinckrodt Company have both been used in this study, and except for a considerable amount of hygroscopic water, the salts were found to be quite pure and suitable starting materials.

Samples of the salt were repeatedly recrystallized from water, ethanol and methanol. Recrystallization from the alcohols is somewhat simpler than from water, with respect to the manipulative details, but we have found that removal of chloride is incomplete on crystallization from alcohol and therefore it is preferable to recrystallize from water when the original salt contains appreciable amounts of chloride. The yield in either case is approximately 50%.

Other samples of the pure salt were prepared by fractional precipitation from a saturated ethanol solution by the addition of ether; four successive fractions were collected.

In all cases, the crystals were collected on a Büchner funnel without paper, the adhering mother liquor was removed by suction, and the products were dried in a desiccator at room temperature. The samples were then heated for an hour at 150° and were finally heated to 200° (m. p. 172°) and kept melted for ten to twenty minutes, to remove the last traces of solvent.

Experiments were made to determine whether chloride and ammonium thiocyanate can be removed completely from potassium thiocyanate by recrystallization from water or alcohol. A sample to which 1% of potassium chloride had been added still contained 0.6% after three recrystallizations from alcohol, but after three recrystallizations from water the final product contained less than 0.005% of chloride.

A sample to which 1% of ammonium thiocyanate had been added contained less than 0.005% of ammonia after three recrystallizations from alcohol or from water.

It was found occasionally that the salt became colored yellow on heating and melting. Systematic study showed that this yellow discoloration was only obtained when the salt was heated in an atmosphere that was slightly contaminated by acid vapors. The discoloration also takes place at room temperature when the dried salt is exposed for some time in an acid contaminated atmosphere. The yellow coloration was more frequently observed with products that had been recrystallized from alcohol, even though the atmosphere in which the salt was heated was entirely free from acid fumes.

The yellow coloration is probably due to the formation of isoperthiocyanic acid ($H_2C_2N_2S_3$) and isodithiocyanic acid

(1) I. M. Kolthoff, "Die Massanalyse," 2 Aufl., Julius Springer, Berlin, 1931.

(2) *Cf.* I. M. Kolthoff and L. H. van Berk, *Z. anal. Chem.*, **70**, 369 (1927).