and glucose. These combined sources should yield more formic acid than an equivalent solution of glucose. This was found to be true.

9. Acetic acid is obtained in much smaller amounts from glucose than it is from erythrose. On the basis of the above-outlined decomposition of maltose, less acetic acid should be obtained from it than from glucose. Our data are in harmony with this point of view.

10. An experiment was made with maltose in the presence of phenylhydrazine at the lower alkalinities, seeking mannose hydrazone as an index of hydrolysis, a control being run with glucose. Mannose hydrazone was first obtained from maltose in eleven days, at 25°; after nineteen days the production reached a constant value. The hydrazone was obtained between 0.05–0.42 *N* potassium hydroxide. The presence of mannose is thought to be due to its formation from the glucose obtained by the hydrolysis of maltose or of 4-glucosido-mannose at the lower alkalinities.

11. The assumption of the presence of glucosido-hexose enediols and their degradation products in alkaline solutions of maltose seems to be in harmony not only with our experimental data, but also with those of Lewis and Buckborough,[1] and Glattfeld and Hanke.

12. Our data seem to be in harmony with the view that the two kinds of decomposition open to the maltose molecule—enediolic splitting and hydrolysis—go on simultaneously in alkaline solution, but whereas the former is a rapid function of the time, the latter is a very slow one.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

ACETYL CHOLINE CHLORIDE

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Choline and its esters have achieved considerable importance in recent years due to their property of producing a marked vasodilation[1] and also because it has been shown that they are normally present in the serous coat of the intestine and probably are the normal peristaltic hormones.[2] The acetyl derivative is especially interesting since it has been found that it possesses a depressor effect 100,000 times as great as that produced by choline itself and yet it is only three times as toxic as this substance.[3]

Salts of acetyl choline have been found in certain natural products.[4] Baeyer and later Nothnagel synthesized the chloride by acetylating

[1] Fraenkel, "Arzneimittel-Synthese," Julius Springer, Berlin, **1927,** p. 336.

[2] Le Heux, *Arch. ges. Physiol.* (*Pflüger's*), **173,** 8 (1918).

[3] Hunt and Taveau, *U. S. Hyg. Lab. Bull.*, No. 73 (1911); Hunt, *Pharmacol.*, **7,** 301 (1915).

[4] Ewins, *Biochem. J.*, **8,** 44 (1914); Boruttau and Cappenburg, *Arch. Pharm.*, **259,** 33 (1921); *C. A.*, **15,** 2692 (1921).

choline chloride with acetyl chloride.[5] Fourneau and Page have made acetyl choline chloride by treating trimethylamine with chloro-ethyl acetate,[6] and recently Abderhalden and Paffrath have obtained small yields of acetyl choline by the action of sodium acetate on choline in the presence of an enzyme.[7]

However, none of these investigators seem to have isolated pure acetyl choline chloride, analyzed it and determined its physical properties. Fourneau and Page unsuccessfully attempted to obtain the pure salt by recrystallizing the product formed by the interaction of trimethylamine and chloro-ethyl acetate. They used a methanol-acetone solution as a crystallizing medium, but found that acetyl choline chloride was hydrolyzed in this process.[6] Later Hunt reported that a solution of acetyl choline chloride in ethyl alcohol decomposed extremely slowly.[8]

Due to the rather widespread use of acetyl choline chloride in pharmacological investigations, it was thought that it might be of interest to isolate the pure salt, to determine its melting point and its other properties. This has been done and it has been possible to corroborate the statement made by Hunt that the compound is not appreciably hydrolyzed when it is dissolved for a short time in ethyl alcohol. Also because of the interest in this substance it was thought that another method of synthesizing it would be of value.

Accordingly, the hydrochloride of dimethylamino-ethyl acetate has been prepared from dimethylamino-ethyl alcohol and acetyl chloride, according to the equation

$$(CH_3)_2NC_2H_4OH + CH_3COCl \longrightarrow (CH_3)_2NHClC_2H_4OCOCH_3$$

Alkali converted this into its free base. This compound had previously been prepared by methylating amino-ethyl acetate, but only its physiological properties were described.[9] Treatment of dimethylamino ethyl acetate with methyl iodide gave acetyl choline iodide

$$(CH_3)_2NC_2H_4OCOCH_3 + CH_3I \longrightarrow (CH_3)_3NIC_2H_4OCOCH_3$$

from which the chloride was obtained by shaking a solution of the iodide in alcohol with silver chloride. Acetyl choline chloride was found to be a white hygroscopic solid melting at 151°. From this the chloroplatinate was prepared; the temperature at which decomposition occurred, 227°, corresponded rather closely to the temperature of decomposition, 223–224°, assigned by Nothnagel[5] to the chloroplatinate of acetyl choline,

[5] Baeyer, *Ann.*, **142**, 325 (1867); Nothnagel, *Arch. Pharm.*, **232**, 265 (1894).

[6] Fourneau and Page, *Bull. soc. chim.*, [4], **15**, 552 (1914).

[7] Abderhalden and Paffrath, *Fermentforschung*, **8**, 299 (1925); *C. A.*, **19**, 2532 (1925).

[8] Hunt, *Pharmacol.*, **7**, 306 (1915).

[9] Rawita-Witanowski, *Travaux et Publ. de l'Inst. M. Nencki*, 36 (1924); *Ber. ges. Physiol. exptl. Pharmakol.*, **32**, 675 (1925).

but differed markedly from the value 256–257° given to this compound by Ewins.[10] A chloro-aurate of acetyl choline was also prepared by the method described by Baeyer[5] and later by Nothnagel.[5] The analysis of this compound agreed with that of acetyl choline chloro-aurate and all of its properties corresponded with those ascribed to this substance by Baeyer and Nothnagel except that our acetyl choline chloro-aurate melted at 168–169° while Nothnagel[5] found the melting point to be 154–155°. The reason for this difference in the melting points of these apparently otherwise identical chloro-aurates is not clear but it is well known that, due to different physical modifications, the melting point often is a criterion of little significance when one is investigating salts such as chloro-aurates and chloroplatinates.[11]

Experimental Part

Preparation of Dimethylamino-ethyl Acetate, $(CH_3)_2NC_2H_4OCOCH_3$.—To a solution of 0.2 of a mole of acetyl chloride in dry ether was slowly added, under a reflux condenser, 0.2 of a mole of dimethylamino-ethyl alcohol (Eastman Kodak Company). There was a vigorous reaction and a white solid formed at once. The solid was collected on a filter and dissolved in water. This solution was extracted with ether to remove any excess of acetyl chloride, after it had been made slightly more acidic with a little hydrochloric acid, in order more readily to hold all of the amine in the aqueous layer. More ether was then added and, while it was kept cold and stirred, the solution was made basic to phenolphthalein with solid potassium carbonate and a little caustic soda. The ether layer was separated and the aqueous solution was repeatedly extracted with ether. The ether extracts were combined and dried with anhydrous potassium carbonate. Fractional distillation yielded dimethylamino-ethyl acetate as a colorless oil; b. p. (80 mm.) 86–88°; yield, 47%.

Hydrochloride.—Dry hydrogen chloride was passed into a solution of dimethylamino-ethyl acetate in anhydrous ether. A white solid precipitated. It was recrystallized by dissolving it in absolute alcohol and reprecipitating it with ether; m. p. 129–130°. It was very hygroscopic.

Anal. Subs., 0.2038: AgCl, 0.1752. Calcd. for $C_6H_{14}O_2NCl$; Cl, 21.18. Found: Cl, 21.31.

Preparation of Acetyl Choline Iodide, $(CH_3)_3NC_2H_4OCOCH_3$.—To a solution of 0.02 of a mole of dimethylamino-ethyl acetate in dry ether was added 0.02 of a mole of methyl iodide. A white solid at once formed. This solid was recrystallized from hot absolute alcohol; m. p. 160–162°; yield, 90%.

Anal. Subs., 0.2297: AgI, 0.1962. Calcd. for $C_7H_{16}O_2NI$: I, 46.40. Found: I, 46.25.

Preparation of Acetyl Choline Chloride, $(CH_3)_3NClC_2H_4OCOCH_3$.—A concentrated solution of acetyl choline iodide in warm absolute alcohol was shaken with a slight excess of silver chloride until the solution gave no further test for the iodide ion. The silver salts were removed by filtration and acetyl choline chloride was precipitated as a white solid by adding dry ether to the filtrate. In order to rid this solid of a trace of silver chloride it was added to some absolute alcohol which had previously been saturated

[10] Ewins, *Biochem. J.*, **8**, 48 (1914).

[11] F. Beilstein, "Handbuch der organischen Chemie," Julius Springer, 1922, 4th ed., Vol. 4, pp. 204, 280; Willstätter, *Ber.*, **35**, 2700 (1902).

with hydrogen sulfide. The silver precipitated as silver sulfide but the acetyl choline chloride readily dissolved. In order to separate the silver sulfide more easily, activated charcoal which previously had been washed with absolute alcohol was added. The mixture was shaken for a few minutes and then filtered. Acetyl choline chloride was reprecipitated from the filtrate by the addition of dry ether; m. p. 151°; yield, 65%. It was very soluble in water and alcohol, but insoluble in ether. It was extremely hygroscopic.

Anal. Subs., 0.2344: AgCl, 0.1867. Calcd. for $C_7H_{16}O_2NCl$; Cl, 19.53. Found: Cl, 19.70.

Chloroplatinate.—The calculated amount of a concentrated solution of chloroplatinic acid in absolute alcohol was added to 0.1 g. of acetyl choline chloride in absolute alcohol. An orange-colored precipitate soon formed. It was recrystallized from hot water and then washed with water and alcohol; m. p. 227° with decomposition.

Anal. Subs., 0.1296: Pt, 0.0362. Calcd. for $C_{14}H_{34}O_4N_2PtCl_6$: Pt, 27.81. Found: Pt, 27.93.

Chloro-aurate.—To 0.46 g. of acetyl choline chloride dissolved in water was added the calculated amount of a concentrated solution of auric chloride in water. An orange-colored solid at once precipitated. It was recrystallized from hot water; m. p. 168–169°.

Anal. Subs., 0.2212: Au, 0.0894. Calcd. for $C_7H_{16}O_2NAuCl_4$: Au, 40.55. Found: Au, 40.42.

Summary

1. Dimethylamino-ethyl acetate has been prepared by adding alkali to the product formed by the interaction of acetyl chloride and dimethylamino-ethyl alcohol.

2. Acetyl choline iodide was formed when dimethylamino-ethyl acetate was treated with methyl iodide. From the iodide the corresponding chloride, chloroplatinate and chloro-aurate were made.

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PAPAVERINE: AN ATTEMPTED RÜGHEIMER SYNTHESIS

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A simple general synthesis of the papaverine type of alkaloid is for many reasons of great importance, particularly so as it would offer a possible means of synthesizing the tetrahydroberberine type of alkaloid.[1] The two methods[2] for synthesizing papaverine which have been worked out are probably only of scientific interest on account of the inaccessibility of the starting materials. An ideal starting point for the synthesis of isoquinoline alkaloids would be a benzoin or a benzil. Such a synthesis was attempted by Fritsch,[3] who condensed desoxyveratroin with amino-acetal and at-

[1] Späth and Kruta, *Monatsh.*, **50**, 341 (1928).

[2] Pictet and Gams, *Ber.*, **42**, 2943 (1909); Buck, Haworth and Perkin, *J. Chem. Soc.*, **125**, 2176 (1924).

[3] Fritsch, *Ann.*, **329**, 37 (1903).