42. *The Synthesis of* N-*Trimethylglycylcholine.*

By Thomas S. Work.

Trimethylglycylcholine has been synthesised by the condensation of trimethylamine and a halogenoethyl ester of a halogenoacetic acid.

Dudley (J., 1921, **119**, 1256), in the hope of obtaining bases of pharmacological interest, began a study of amino-acid esters of choline. Glycylcholine was prepared, but the subject was not further pursued. It was suggested to me by Sir Henry Dale, P.R.S., that a completely methylated glycylcholine might possess the high physiological activity which Dudley sought.

Trimethylglycylcholine was readily obtained in a single step by heating a halogenoethyl ester of a halogenoacetic acid with anhydrous trimethylamine in a sealed tube:

$$\mathrm{Hal{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}CH_2Hal} + \mathrm{NMe_3} \longrightarrow \mathrm{Hal{\cdot}NMe_3{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CO{\cdot}CH_2{\cdot}NMe_3{\cdot}Hal}$$

The first synthetic attempt was made with β-*bromoethyl chloroacetate*. The bromoethyl ester was used in preference to the simpler chloroethyl ester in an attempt to make the halogens equally reactive. The yield by this method was poor, as the resultant mixture of chlorides and bromides was difficult to purify and only *trimethylglycylcholine dibromide* could be isolated. Subsequent preparations showed this precaution to be unnecessary, and yields up to 70% were obtained by using β-bromoethyl bromoacetate.

As analysis of *trimethylglycylcholine picrate* would not readily distinguish it from choline picrate, and as the melting points of the two picrates were very similar and showed very

little depression on mixing, it was found desirable to confirm the structure of the synthetic product by degradation. When trimethylglycylcholine dibromide was shaken with silver oxide in water, it decomposed immediately, and after removal of silver salts betaine was readily isolated from the filtrate. The synthetic ester was also readily distinguished from choline by the properties of its *platinichloride*, which was very much less soluble than choline platinichloride and did not show the dimorphism characteristic of the choline salt.

Pharmacological tests on trimethylglycylcholine dibromide by Dr. F. C. MacIntosh, to whom I wish to express my thanks, showed that it possessed an extremely weak muscarine-like activity and no perceptible curare-like, nicotine-like or eserine-like activity. It was, like glycylcholine, pharmacologically rather inert.

Experimental.

β-*Bromoethyl Chloroacetate.*—Chloroacetyl chloride (22·6 g.) was added slowly to ethylene bromohydrin (28·0 g.) so that the temperature did not rise above 50°. The product was poured into ether, washed thoroughly with water, dried, and distilled. The fraction, b. p. 112—114°/22 mm., was collected (Found: C, 24·1; H, 3·1. $C_4H_6O_2ClBr$ requires C, 23·8; H, 3·0%); yield, 90%.

β-Chloroethyl chloroacetate, b. p. 101°/32 mm., and β-bromoethyl bromoacetate, b. p. 118°/16 mm., were prepared in the same way (cf. Henry, *Bull. Soc. chim.*, 1884, **42**, 260; Vorländer, *Annalen*, 1894, **280**, 198) in approximately the same yield.

Trimethylglycylcholine Dibromide.—β-Bromoethyl chloroacetate (20·1 g.) was sealed in a thin-walled test-tube and placed inside a Carius tube cooled in ice-salt. Cold anhydrous trimethylamine (18 c.c.) and cooled dry benzene (20 c.c.) were added, and the tube sealed as rapidly as possible; the thin inner tube was broken, and the contents thoroughly mixed. The temperature rose rapidly and crystals separated. When the initial reaction had subsided, the tube was heated at 100° for 8 hours. The solid white cake produced was broken up, washed with dry benzene, and dissolved in alcohol. A small quantity of residual insoluble material was removed and found to be betaine bromide. After several days a crystalline crust separated from the alcohol and after five recrystallisations from alcohol it was obtained in white rosettes of needles, m. p. 238°. Analysis indicated that this least soluble fraction was *trimethylglycylcholine dibromide* (Found: Br, 43·5. $C_{10}H_{24}O_2N_2Br_2$ requires Br, 44·0%). The dibromide, treated with aqueous sodium picrate, gave a *dipicrate*, which crystallised readily from aqueous alcohol in long needles, m. p. 244° (Found: C, 39·4; H, 4·5; N, 17·2. $C_{10}H_{24}O_2N_2,2C_6H_3O_7N_3$ requires C, 39·8; H, 4·5; N, 16·9%).

The alcoholic mother-liquor from the dibromide crystallisation was concentrated in the hope of obtaining the dichloride, but no crystalline material could be isolated. The yield of dibromide was about 15%. With gold chloride or platinic chloride in dilute hydrobromic acid the dibromide gave crystalline salts sparingly soluble in cold water. The gold salt crystallised in short reddish needles, m. p. about 250° (decomp.); the platinum salt crystallised in twinned prisms and melted over a range of 20° depending on the rate of heating.

A second preparation of trimethylglycylcholine dibromide carried out as described above, but using β-bromoethyl bromoacetate as starting material, gave a yield of 68% of pure dibromide.

Trimethylglycylcholine Dichloride.—β-Chloroethyl chloroacetate (7·5 g.) reacted with trimethylamine (5·63 g.) in 16 hours by the above process, but difficulty was experienced in purifying the product as the dichloride. After removal of a small quantity of betaine chloride, trimethylglycylcholine picrate was isolated, m. p. 244°, identical with the picrate obtained above.

Trimethylglycylcholine Platinichloride.—Trimethylglycylcholine chloride gave with platinic chloride a yellow crystalline precipitate sparingly soluble in cold water. The platinichloride was crystallised from hot water and from 50% aqueous alcohol, but did not show the dimorphism characteristic of choline platinichloride and crystallised from both solvents in trigonal prisms containing no water of crystallisation; these melted over a range of about 20° with variation in the rate of heating (Found: Pt, 31·2. $C_{10}H_{24}O_2N_2,PtCl_6$ requires Pt, 31·8%).

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