IVb: yield 95.9%, mp 275-276°C (DMF—ethyl acetate). Found, %: C 60.62; H 8.30; Cl 13.42. $C_{13}H_{21}ClN_2O$. Calculated, %: C 60.75; H 8.18; Cl 13.85.

IVd: yield 80.3%, mp 141-143°C. Found, %: C 57.64; H 7.37; N 12.06; Cl 16.08. $C_{11}H_{17}ClN_2O$. Calculated, %: C 57.68; H 7.43; N 12.26; Cl 15.83.

IVe: yield 87.8%, mp 190-193°C (DMF—ether). Found, %: N 13.54. $C_8H_{17}ClN_2O_2$. Calculated, %: N 13.43.

VI: yield 81.7%, mp 125-128°C (DMF—ethyl acetate). Found, %: C 34.98; H 7.94; N 20.16; Cl 24.69. $C_4H_{11}ClN_2O$. Calculated, %: C 34.66; H 7.94; N 20.22; Cl 25.63.

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SYNTHESIS OF THE CHOLINE ESTER OF GLYCINE

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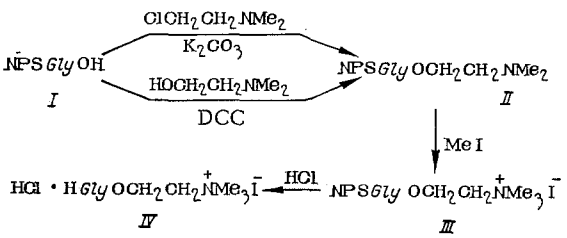
We have continued our work on the synthesis of acetylcholine analogs, and specifically of choline esters of amino acids and peptides [1], by preparing the choline ester of glycine using o-nitrophenylsulfenyl (NPS) to protect the amino group of glycine



The NPS-amino acids are readily accessible and are reasonably stable during preparation of the peptides. The protecting group can be removed under very mild conditions even in the presence of the benzyloxycarbonyl group (Cbo) [2].

In the synthesis of NPS-glycine (I) we replaced o-nitrophenylsulfenyl chloride [3] with the bromide, synthesized by reaction of di-o-nitrophenyl disulfide with bromine. The yield of I was reasonably high and the compound corresponded to literature data in terms of qualitative indices [4].

We synthesized NPS-glycine β-dimethylaminoethyl ester (II) by two methods — interaction of I with β-dimethylaminoethyl chloride in the presence of potassium carbonate or with β-dimethylaminoethanol using N,N'-dicyclohexylcarbodiimide (DCC).

In the first case the yield of amino acid ester II did not exceed 40-42% even after prolonged (10-12 h) heating of the reaction mixture. We got better results (75-80%) by using the carbodiimide method.

Reaction of II with methyl iodide in diethyl ether gave chromatographically pure quaternary ammonium salt III. Removal of the NPS group from III with hydrogen chloride in methanol led to hydrochloride IV.

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The interaction of equimolar quantities of II and hydrogen chloride in diethyl ether was accompanied by formation of NPS-glycine β-dimethylaminoethyl ester monohydrochloride (V) and deblocking of the protected amino group, giving glycine β-dimethylaminoethyl ester dihydrochloride (VI).

$$\text{II} \xrightarrow[\text{ether}]{\text{HCl}} \underset{\text{V}}{\text{NPSGlyOCH}_2\text{CH}_2\text{NMe}_2\cdot\text{HCl}} + \underset{\text{VI}}{2\text{HCl}\cdot\text{HGlyOCH}_2\text{CH}_2\text{NMe}_2}$$

Reaction of oxalic acid with II in ether—alcohol forms NPS-glycine β-dimethylaminoethyl ester oxalate.

We have previously synthesized choline esters of amino acids and peptides by the mixed anhydride method [1].

We carried out an independent synthesis of N-Cbo-glycine choline ester (VII) by reaction of N-Cbo-glycine p-nitrophenyl ester (VIII) with choline (IX). This reaction gave reasonably good results in DMF.

$$\underset{\text{VIII}}{\text{CboGlyONP}} + \underset{\text{IX}}{\text{HOCH}_2\text{CH}_2\text{N}^+\text{Me}_3\text{I}^-} \longrightarrow \underset{\text{VII}}{\text{CboGlyOCH}_2\text{CH}_2\text{N}^+\text{Me}_3\text{I}^-}$$

$$\text{ONP} = \text{NO}_2\text{C}_6\text{H}_4\text{O}$$

We monitored the course of the reaction by chromatography; formation of the end product VII ceased after 7-8 h.

Examination of the cholinergic activity of NPS-glycine β-dimethylaminoethyl ester methiodide revealed that it has a weak cholinomimetic effect. Compound III has neither sympathomimetic nor adrenolytic activity but has marked antibacterial activity *in vitro* toward *Staphylococcus aureus*. However in preliminary tests the compound gave no therapeutic effect in experimental staphylococcal infection of white mice.

EXPERIMENTAL

The purity of the synthetic compounds was checked by thin-layer chromatography on Silufol UV-254 plates in: system A: propanol—water (7:3); system B: acetic acid—ethanol—butanol—water (1:2:3:8). Visualization was carried out with iodine vapor and Dragendorff's reagent. The IR spectra were recorded on a UR-20 spectrometer.

NPS-Glycine (I). Glycine (3 g, 0.05 mole) was dissolved in 2 N NaOH (30 ml) and dioxane (30 ml). Over a period of 30 min o-nitrophenylsulfenyl bromide (12.87 g, 0.05 mole) and 2 N NaOH (30 ml) were added portionwise. The mixture was stirred at 20°C for 1 h. Water (200 ml) was added, the precipitate was filtered off, and the filtrate was acidified with dilute H_2SO_4. The oily compound crystallized over a period of 2-3 h at 5°C and had mp 147°C after recrystallization from ethyl acetate—petroleum ether. Literature: mp 147°C [3], 125-126°C [4]. The yield was 7.5 g (80%). Found, %: C 42.06; H 3.33; N 12.20. $C_8H_8N_2O_4S$. Calculated, %: C 42.11; H 3.53; N 12.27. IR spectrum, cm^{-1}: $\nu C{=}NO_2$ 1350, 1530; νCO 1710; νNH 3340.

NPS-Glycine β-Dimethylaminoethyl Ester (II). Method A. To a solution of I (4.5 g, 0.02 mole) in ethyl acetate (100 ml) and DMF (10 ml) were added β-dimethylaminoethyl chloride hydrochloride (4.32 g, 0.02 mole) and potassium carbonate (5.52 g, 0.04 mole). The mixture was refluxed for 6 h. The precipitate was filtered off. The filtrate was washed with water until neutral and dried over sodium sulfate. The solvent was evaporated. The residue was dissolved in methanol and after filtering the solvent was stripped off to give an oily compound (2.5 g, 41.8%). Found, %: N 13.87; S 10.80. $C_{12}H_{17}N_3O_4S$. Calculated, %: N 14.04; S 10.69. R_f: A 0.89. IR spectrum, cm^{-1}: $\nu C{=}NO_2$ 1350, 1535; νCO 1757; νNH 3380.

Method B. To a solution of I (1 g, 0.004 mole) in tetrahydrofuran (30 ml) cooled to −5°C was added DCC (0.9 g, 0.0044 mole). The mixture was kept under cooling for 20 min. β-Dimethylaminoethanol (0.39 g, 0.0044 mole) was then added and the mixture was kept at 5°C for 3 days. The precipitated N,N'-dicyclohexylurea was filtered off. The residue was washed with tetrahydrofuran (2 × 10 ml) and the combined filtrates were evaporated. The residue was dissolved in ethyl acetate (100 ml). The solution was kept at 5°C for 5 h and then filtered. The filtrate was washed with 5% potassium carbonate solution (3 × 20 ml) and then with water until neutral, and dried over sodium sulfate. Removal of the solvent gave an oily compound (1.04 g, 80%). Found, %: N 13.77; S 10.90. $C_{12}H_{17}N_3O_4S$. Calculated, %: N 14.04; S 10.69. R_f: A 0.90; B 0.79. IR spectrum, cm^{-1}: $\nu C{=}NO_2$ 1350; νCO 1755; νNH 3380.

NPS-Glycine β-Dimethylaminoethyl Ester Methiodide (III). To a solution of II (0.5 g, 0.0017 mole) in absolute acetone (20 ml) was added methyl iodide (0.002 mole). The mixture was left at 20°C for 24 h. Ether (100 ml) was then added and the precipitate was filtered off and reprecipitated from absolute alcohol—ether to give yellow crystalline III (0.58 g, 79.2%), mp 191-192°C. Found, %: I 29.00. $C_{13}H_{20}N_3O_4SI$. Calculated, %: I 28.75. R_f: A 0.77; B 0.73. IR spectrum, cm^{-1}: $\nu_{C=NO_2}$ 1350, 1535; ν_{CO} 1760; ν_{NH} 3370.

Glycine β-Dimethylaminoethyl Ester Methiodide Hydrochloride (IV). Compound II (0.5 g, 0.0011 mole) was dissolved in absolute methanol (10 ml) and a 10% solution of HCl in methanol (0.73 ml, 0.0022 mole) was added. The mixture was kept at 5°C for 2-3 h. The solvent was then stripped off and the residue was washed with absolute ether and dried in a dessicator. The yield of IV was 0.30 g (81.5%), mp 248-249°C (decomposition). Found, %: C 26.87; H 5.61. $C_7H_{18}ClIN_2O_2$. Calculated, %: C 27.07; H 5.61. R_f: A 0.09. IR spectrum, cm^{-1}: ν_{CO} 1763; ν_{NH} 3400.

Glycine β-Dimethylaminoethyl Ester Dihydrochloride (VI). Compound II (0.5 g, 0.0017 mole) was dissolved in absolute methanol (10 ml) and methanol saturated with gaseous HCl was added to pH 3.0. The mixture was kept at 5°C for 1 h and the crystals were filtered off to give VI (0.33 g, 89.5%), mp 142-143°C. Found, %: Cl 32.03. $C_6H_{16}Cl_2N_2O_2$. Calculated, %: Cl 32.38. R_f: A 0.55; B 0.31. IR spectrum, cm^{-1}: ν_{CO} 1760; ν_{NH} 3330-3410.

NPS-Glycine β-Dimethylaminoethyl Ester Oxalate. Compound II (0.5 g, 0.0017 mole) was dissolved in absolute ether (20 ml) and a solution of oxalic acid (0.31 g, 0.034 mole) in absolute alcohol was added. The precipitate was recrystallized from methanol—ether, mp 190-192°C.

N-Cbo-Glycine β-Dimethylaminoethyl Ester Methiodide (VII). To a solution of VIII (0.4 g, 0.019 mole) in anhydrous DMF (10 ml) was added IX (0.67 g, 0.0029 mole). The mixture was left at 20°C for 12 h. The solvent was then stripped off under vacuum at 40°C. The residue was dissolved in absolute alcohol and after filtration the compound was isolated by adding absolute ether. The yield was 0.39 g (78%), mp 115-116°C. Literature [5]: mp 110-112°C. Found, %: I 30.05. $C_{15}H_{23}IN_2O_4$. Calculated, %: I 29.85. R_f: A 0.75.

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