2-methyl-4-hydroxyquinoline (15.9 Gm., 0.4 mole) in 150 ml. of aqueous potassium hydroxide (5%), was added dimethyl sulfate (8 ml.). After shaking the mixture for 30 min., potassium hydroxide solution (50 ml.) was added with continuous shaking during an additional 30 min. The reaction mixture was kept for 48 hr. at room temperature. The product was extracted with chloroform, then recrystallized several times from benzene to give 2.59 Gm. (15% yield) of II in the form of light-red needles, m.p. 158–160°. [Lit. m. p. 156–160° (10).]

6,8 - Dinitro - 1,2 - dimethyl - 4 - quinolone (V).—To a solution of 1,2-dimethyl-4-quinolone (0.173 Gm.) in sulfuric acid (5 ml.) was added a mixture of nitric acid (1 ml.) and sulfuric acid (3 ml.) by the same method as described for 1,4-dimethyl-2-quinolone (I). The product obtained, m.p. 258°, when recrystallized from ethanol, gave 0.17 Gm. (65% yield) of V, m.p. 259–261°.

Anal.—Calcd. for $C_{11}H_{12}N_3O_5$: C, 49.62; H, 4.51; N, 15.78. Found: C, 50.02; H, 4.45; N, 15.98.

6 - Nitro - 1,2 - dimethyl - 4 - quinolone (VI).—To a solution of 6-nitro-2-methyl-4-hydroxyquinoline (7) (2.04 Gm.) in 50 ml. of aqueous potassium hydroxide (5%) was added dimethyl sulfate (3.3 Gm.). The mixture was stirred at 70° for 30 min. and kept at room temperature overnight. The formed yellow precipitate, m.p. 215°, was recrystallized from hot benzene to give 1.27 Gm. (40% yield) of VI, m.p. 218–220°.

Anal.—Calcd. for $C_{11}H_{10}N_2O_5$: C, 60.55; H, 4.58; N, 12.88. Found: C, 60.37; H, 4.46; N, 12.75.

6,8 - Dinitro - 1,2 - dimethyl - 4 - quinolone (V).—To a solution of 6-nitro-1,2-dimethyl-4-quinolone (VI) (1.5 Gm.) in concentrated sulfuric acid (10 ml.) at 10° was added a mixture of nitric acid (d. 1.42, 1 ml.) and concentrated sulfuric acid (3 ml.). After standing for 24 hr. at room temperature, the mixture was poured onto crushed ice, the isolated product, m.p. 257°, was recrystallized from ethanol to give 1.13 Gm. (90% yield) of V, m.p. 259–261°. It was identical in melting point with an authentic sample of V, and showed no depression of mixed melting point.

Anal.—Calcd. for $C_{11}H_{12}N_3O_5$: C, 49.62; H, 4.51; N, 15.78. Found: C, 49.78; H, 4.62; N, 15.92.

6,8 - Dinitro - 2 - methyl - 4 - hydroxyquinoline.—A solution of 8-nitro-2-methyl-4-hydroxyquinoline (8) (2.04 Gm., 0.01 mole) in concentrated sulfuric acid (10 ml.) was treated with a mixture of nitric acid and sulfuric acid, as described above. The isolated product, m.p. 258°, was recrystallized from ethanol to give 1.85 Gm. of 6,8-dinitro-2-methyl-4-hydroxyquinoline (75% yield), m.p. 247–249°.

Anal.—Calcd. for $C_{10}H_7N_3O_5$: C, 48.19; H, 2.81; N, 16.86. Found: C, 48.21; H, 3.04; N, 16.85.

When this compound was treated with dimethyl sulfate in an alkaline medium, as for the preparation of 6-nitro-1,2-dimethyl-4-quinolone, the isolated product was identical with V, with no depression of the mixed melting point.

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N-Aminoalkyl-α-aminoacids and Their Corresponding Ethyl Esters

By TIBERIO BRUZZESE and ELDA CRESCENZI

Fourteen *N*-aminoalkyl-α-aminoacids and their corresponding ethyl esters have been prepared for pharmacological screening. The physicochemical properties and optimal reaction conditions are reported.

DURING RECENT years, α-aminoacid derivatives have been the subject of several studies of biological interest. In particular, Goldin *et al.* (1) have reported that glycine, although free from hypnotic activity, potentiates barbiturate-induced sleep, while Edwards *et al.* (2, 3) have found that the esters of some α-phenylglycines possess good antispasmodic and local anesthetic activity. Furthermore, it has been reported that ethyl esters of *N,N*-disubstituted glycines exert antispasmodic, antihistaminic, and hypotensive activity (4), and that other similar derivatives have been studied in tuberculostatic (5) and herbicidal tests (6).

The present note deals with the preparation of a series of *N*-aminoalkyl-α-aminoacids and their corresponding ethyl esters for submitting to pharmacological screening. In addition, these compounds were useful intermediates for the synthesis of 3-substituted sydnones, as we have recently reported (7).

The esters in question were prepared by alkylation with α-bromo esters of suitable *N*-aminoalkyl-amines. Because of the side reactions resulting from the competitive aminolysis of the ester group (8), the authors studied the synthesis procedure in detail, and found it an advantage to use

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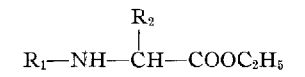
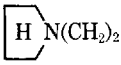
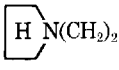
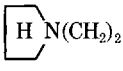
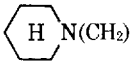
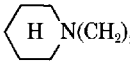
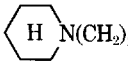
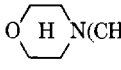
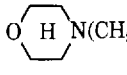
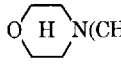
TABLE I.—*N*-AMINOALKYL-α-AMINOESTERS



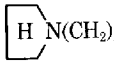
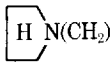
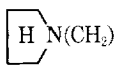
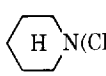
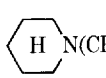
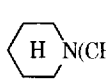
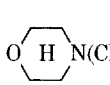
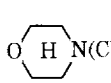
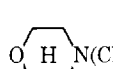
Compd.	R_1	R_2	Reflux Time, hr.	Yield,[a] %	B.p., °C., mm.	Formula	Anal., % Calcd.	Found
I[b]	$(C_2H_5)_2N(CH_2)_2$	H	1	75	77–80 (0.5)	$C_{10}H_{22}N_2O_2$	C, 59.37 H, 10.96 N, 13.85	58.94 10.81 13.54
II	$(C_2H_5)_2N(CH_2)_2$	CH_3	2	55	73–76 (0.8)	$C_{11}H_{24}N_2O_2$	C, 61.07 H, 11.18 N, 12.95	60.89 11.20 12.75
III[c]	$(C_2H_5)_2N(CH_2)_2$	C_6H_5	1	54	125–126 (0.3)	$C_{16}H_{26}N_2O_2$	C, 69.03 H, 9.41 N, 10.06	68.95 9.26 9.87
IV		H	1	51	100–103 (1.0)	$C_{10}H_{20}N_2O_2$	C, 59.97 H, 10.07 N, 13.99	59.56 9.92 14.14
V		CH_3	2	67	92–94 (1.0)	$C_{11}H_{22}N_2O_2$	C, 61.65 H, 10.35 N, 13.07	61.11 10.17 12.80
VI[d]		C_6H_5	1	74	125–127 (0.2)	$C_{16}H_{24}N_2O_2$	C, 69.53 H, 8.75 N, 10.14	69.00 8.85 10.13
VII		H	1	87	99–102 (0.5)	$C_{11}H_{22}N_2O_2$	C, 61.65 H, 10.35 N, 13.07	62.03 10.26 13.31
VIII		CH_3	2	64	98–101 (1.0)	$C_{12}H_{24}N_2O_2$	C, 63.12 H, 10.60 N, 12.27	62.94 10.39 12.45
IX[e]		C_6H_5	1	78	147–149 (0.5)	$C_{17}H_{26}N_2O_2$	C, 70.31 H, 9.02 N, 9.65	70.76 9.20 9.50
X		H	0.5	42	94–98 (0.2)	$C_{10}H_{20}N_2O_3$	C, 55.53 H, 9.32 N, 12.95	55.76 9.29 13.16
XI		CH_3	2	50	106–108 (1.0)	$C_{11}H_{22}N_2O_3$	C, 57.36 H, 9.63 N, 12.17	57.04 9.70 12.42
XII		C_6H_5	1	31	155–158 (0.3)	$C_{16}H_{24}N_2O_3$	C, 65.72 H, 8.27 N, 9.58	66.08 8.32 9.56
XIII	$(CH_3)_2N(CH_2)_3$	H	1	38	76–78 (1.0)	$C_9H_{20}N_2O_2$	C, 57.41 H, 10.71 N, 14.88	57.24 10.58 14.55
XIV	$(CH_3)_2N(CH_2)_3$	CH_3	2	69	72–74 (1.0)	$C_{10}H_{22}N_2O_2$	C, 59.37 H, 10.96 N, 13.85	58.87 10.85 13.66

[a] Distilled once. [b] Lit. (8) b.p. 78° (1.1 mm.), yield 45%. [c] Lit. (2) b.p. 156–158° (1.5 mm.), yield 52%. [d] Lit. (2) b.p. 163–166° (1.5 mm.), yield 80%. [e] Lit. (2) b.p. 172–176° (2 mm.), yield 76%.

ether as the solvent and 1 mole of triethylamine as scavenger of the hydrobromic acid formed during the reaction. By contrast, the use of boiling benzene and excess *N*-aminoalkyl-amine as acid scavenger (9, 10), as also the use of α-chloro esters instead of the more reactive α-bromo derivatives, were found to give rise to *N*,*N*′-diaminoalkylglycinamides as by-products. Table I gives the reaction conditions, yields, and physical and analytical properties of the esters prepared. All the compounds are colorless oils which may easily be purified by vacuum distillation.

The *N*-aminoalkyl-α-aminoacids were obtained by hydrolyzing the above esters with 20% sodium hydroxide at 60–70°. Brown products difficult to crystallize were obtained at the refluxing tempera-

TABLE II.—*N*-AMINOALKYL-α-AMINOACID DIHYDROCHLORIDES

Compd.	R_1	R_2	Yield,[a] %	M.p.,[b] °C.	Recrystn. Solvent	Formula	Anal., % Calcd.	Found
XV	$(C_2H_5)_2N(CH_2)_2$	H	78	143–144	Ethanol	$C_8H_{20}Cl_2N_2O_2$	C, 38.87 H, 8.15 Cl, 28.69 N, 11.33	38.33 8.26 28.60 11.42
XVI	$(C_2H_5)_2N(CH_2)_2$	CH_3	86	193–195	Ethanol–acetone	$C_9H_{22}Cl_2N_2O_2$	C, 41.38 H, 8.49 Cl, 27.12 N, 10.72	41.57 8.40 26.98 10.73
XVII[c]	$(C_2H_5)_2N(CH_2)_2$	C_6H_5	74	229–230	Ethanol–methanol	$C_{14}H_{24}Cl_2N_2O_2$	C, 52.01 H, 7.48 Cl, 21.93 N, 8.67	51.58 7.37 22.18 8.71
XVIII		H	81	190–191	Ethanol, 98%	$C_8H_{18}Cl_2N_2O_2$	C, 39.19 H, 7.40 Cl, 28.93 N, 11.43	39.01 7.46 28.83 11.23
XIX		CH_3	95	189–190	Ethanol–acetone	$C_9H_{20}Cl_2N_2O_2$	C, 41.70 H, 7.78 Cl, 27.36 N, 10.81	40.91 7.86 26.95 10.81
XX		C_6H_5	84	219–220	Ethanol	$C_{14}H_{22}Cl_2N_2O_2$	C, 52.34 H, 6.90 Cl, 22.07 N, 8.72	52.30 7.01 22.03 8.56
XXI		H	86	172–173	Ethanol	$C_9H_{20}Cl_2N_2O_2$	C, 41.70 H, 7.78 Cl, 27.36 N, 10.81	41.39 7.90 27.12 10.56
XXII		CH_3	95	210–211	Ethanol	$C_{10}H_{22}Cl_2N_2O_2$	C, 43.92 H, 8.12 Cl, 25.96 N, 10.25	44.11 8.09 26.05 10.03
XXIII[d]		C_6H_5	80	224–225	Ethanol	$C_{15}H_{24}Cl_2N_2O_2$	C, 53.73 H, 7.22 Cl, 21.15 N, 8.36	53.70 7.47 21.09 8.29
XXIV		H	92	190–192	Methanol	$C_8H_{18}Cl_2N_2O_3$	C, 36.79 H, 6.95 Cl, 27.15 N, 10.72	36.39 7.04 27.00 10.54
XXV		CH_3	95	223–224	Methanol	$C_9H_{20}Cl_2N_2O_3$	C, 39.29 H, 7.33 Cl, 25.75 N, 10.18	39.66 7.32 25.78 9.95
XXVI[d]		C_6H_5	93	231–232	Acetic acid	$C_{14}H_{22}Cl_2N_2O_3$	C, 49.85 H, 6.57 Cl, 21.02 N, 8.31	49.35 6.67 20.71 8.33
XXVII	$(CH_3)_2N(CH_2)_3$	H	92	190–191	Ethanol–methanol	$C_7H_{18}Cl_2N_2O_2$	C, 36.05 H, 7.78 Cl, 30.40 N, 12.01	35.77 7.71 30.22 11.96
XXVIII	$(CH_3)_2N(CH_2)_3$	CH_3	83	227–228	Ethanol, 95%	$C_8H_{20}Cl_2N_2O_2$	C, 38.87 H, 8.15 Cl, 28.69 N, 11.33	39.06 8.30 28.48 11.25

[a] Crude product. [b] The compounds melt with decomposition. [c] Reported as the hydrobromide by Szarvasi, E., and Neuvy, L., *Bull. Soc. Chim. France*, **1957**, 1019. [d] Reported as the free base by Kawahara, S., and Katsuno, K., *Yakugaku Zasshi*, **82**, 912(1962).

ture. All the compounds were isolated from the reaction mixture as the dihydrochlorides; they are colorless crystalline solids, and their properties are reported in Table II.

Preliminary data on the pharmacological screening which was performed in accordance with the techniques previously described (11), have shown that some members of both series possess a certain degree of antispasmodic, local anesthetic, and antitussive activity.

EXPERIMENTAL

Boiling points are uncorrected. Melting points are corrected and were taken on a Büchi capillary melting point apparatus. The intermediates were commercial products or else obtained according to the procedures reported in the literature.

Typical preparations of both the esters and the acids are illustrated in the following examples.

N - (3 - Dimethylaminopropyl)-alanine Ethyl Ester (XIV).—Ethyl α-bromo-propionate (54.3 Gm., 0.3 mole) dissolved in ether (60 ml.) was added dropwise to a solution of 3-dimethylamino-1-propylamine (30.6 Gm., 0.3 mole) and triethylamine (30.3 Gm., 0.3 mole) and ether (150 ml.), stirring and cooling moderately to room temperature. The mixture was stirred for 1 hr., then refluxed for 2 hr., and allowed to stand overnight. The precipitated triethylamine hydrobromide was filtered off and the solvent removed under reduced pressure. The residue was then distilled, b.p. 72–74° (1 mm.), giving a colorless oil (41.9 Gm.).

N - (2 - Pyrrolidinylethyl) - glycine Dihydrochloride (XVIII).—A mixture of IV (20 Gm., 0.1 mole), sodium hydroxide (6 Gm., 0.15 mole), and water (24 ml.) was cautiously heated to 65°, with efficient stirring. At this temperature hydrolysis continued spontaneously, without necessitating further heating. The solution so obtained was washed with ether and acidified to pH 1 by cautious addition of concentrated hydrochloric acid. The reaction mixture was evaporated to dryness *in vacuo* and the residue was extracted with 300 ml. of boiling ethanol in portions. The combined alcoholic extracts were then distilled and the residue (19.8 Gm.) was crystallized from 98% ethanol. After drying at 90° *in vacuo*, colorless crystals were obtained, m.p. 190–191° dec.

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Effect of Germicidal Aerosol Treatment on the Microbial Flora of Laboratory Air

By LEO GREENBERG

Metered doses of a quaternary ammonium, glycol, alcohol formulation were dispensed automatically by motorized apparatus at 15-min. intervals around the clock for 1 month, and the effects of such treatment on the microbial flora of the air in a heavily trafficked area were studied. Data indicate that, despite large variations in number and types of microorganisms found in the air, especially during periods of heavy traffic, continued aerosol treatment was capable of sharply reducing mean population values and in altering the flora from a predominantly bacterial population to one dominated by members of the *Penicillium–Aspergillus* group of fungi.

In recent years, the subjects of microbiological air pollution and air sanitation have gained considerable importance, and much information is now available concerning the immediate and latent effects caused by inhalation and retention of foreign airborne particles and bacteria. Present knowledge *indicates* that particles approximately 1–5 μ in diameter are most effective for penetration and retention in the deep pulmonary spaces (1), and in addition, larger particles bearing many organisms may infect open wounds. In light of recent experiences with hospital-associated staphylococcic infections, much attention has been devoted to the removal or inactivation of biological particles of all sizes from the air used in critical spaces.

To accomplish these ends, a widely diversified group of chemical agents and methods has been proposed, including the use of the gaseous fumigants formaldehyde, β-propiolactone, and ethylene oxide. For more limited and routine use, numerous commercial products designed to reduce air contamination have been developed, and are designed for aerosolization either by mechanical spray or by means of propellants such as the freons. Among the agents utilized for such purposes have been various alcohols, glycols, volatile oils, phenols, and quaternaries.

In general, such commercial aerosols have been

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