SECTION C
Organic Chemistry

α-Aminoacyl Derivatives of Aminobenzoic Acid and of Amino-oxy-acids by Reaction of their Hydrochlorides with Amino-acid *N*-Carboxy-anhydrides

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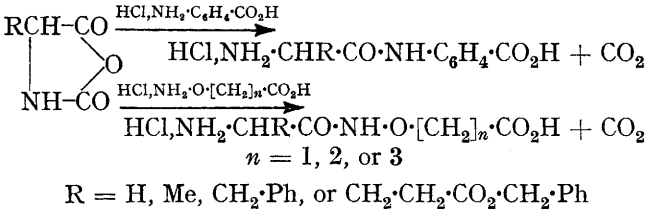
The reaction of amino-acid *N*-carboxyanhydrides with hydrochlorides of aminobenzoic acids and of amino-oxy-acids gave amino-acid amides in a one-step synthesis. The coupling of L-alanine *N*-carboxyanhydride with anthranilic and with *p*-aminobenzoic acid hydrochloride gave peptide-like compounds of high optical activity, indicating the presence of little or no racemate. Glycyl and DL-phenylalanyl amides with aminobenzoic acid were obtained in this way, and trimers were formed by reaction of the *N*-carboxyanhydrides with *p*-aminobenzoyl-L-glutamic acid hydrochloride.

Parallel procedures led to the α-, β-, and γ-amido-oxy-peptides of amino-oxy-acetic, -propionic, and -butyric acid, respectively.

THE reaction of amino-acid *N*-carboxyanhydrides with amine salts was outlined previously as a useful synthesis of aminoacyl derivatives of weakly basic amines.[1] The applicability of the reactions has been extended to give peptide-like derivatives of weakly basic amino-acids, such as aminobenzoic acids and amino-oxy-acids. These coupling reactions could be carried out with hydrochlorides of unprotected amino-acids, by virtue of the pronounced difference in ability to form salts between the starting material and the product.



$$\mathrm{RCH(NH)CO} \xrightarrow{\mathrm{HCl,NH_2{\cdot}C_6H_4{\cdot}CO_2H}} \mathrm{HCl,NH_2{\cdot}CHR{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}CO_2H} + \mathrm{CO_2}$$

$$\mathrm{RCH(NH)CO} \xrightarrow{\mathrm{HCl,NH_2{\cdot}O{\cdot}[CH_2]_n{\cdot}CO_2H}} \mathrm{HCl,NH_2{\cdot}CHR{\cdot}CO{\cdot}NH{\cdot}O{\cdot}[CH_2]_n{\cdot}CO_2H} + \mathrm{CO_2}$$

$n = 1$, 2, or 3

R = H, Me, $CH_2{\cdot}Ph$, or $CH_2{\cdot}CH_2{\cdot}CO_2{\cdot}CH_2{\cdot}Ph$

Amino-acid *N*-carboxyanhydrides were coupled with hydrochlorides of anthranilic acid, *p*-aminobenzoic acid, and their esters by dissolving both reagents in dimethylformamide. The reaction proceeded at room temperature with slow evolution of carbon dioxide. The products were obtained as precipitates from solution or after removal of the solvent (see Table 1).

As carbon dioxide is the predominant by-product, the peptide-like derivatives prepared by this method could be obtained in a high state of purity. The facts that the reaction takes place in one step and that only weakly acidic conditions are required during reaction and recrystallisation made possible the production of amides with high specific rotations. This method thus compares well with others reported.[2-4]

Optically active L-alanylanthranilic acid hydrochloride and L-alanyl-*p*-aminobenzoic acid hydrochloride were prepared; their optical purity was proved by hydrolysis, which regenerated L-alanine with the correct rotation.

The degree of racemisation during acylation of benzocaine hydrochloride with L-alanine *N*-carboxyanhydride has been compared with that occurring during coupling by the dicyclohexylcarbodi-imide method.[5] The L-alanyl-*p*-aminobenzoic acid ethyl ester hydrochloride obtained was treated with benzyloxycarbonyl chloride. The derivative produced (*N*-benzyloxycarbonyl-L-alanyl-*p*-aminobenzoic acid ethyl ester) was also prepared by condensing *N*-benzyloxycarbonyl-L-alanine with benzocaine by use of dicyclohexylcarbodi-imide. No significant difference between the specific rotations of the compounds was observed.

Compounds related structurally to folic acid were synthesised by treating *p*-aminobenzoyl-L-glutamic acid hydrochloride with DL-phenylalanine, glycine, or γ-benzyl-L-glutamic acid *N*-carboxyanhydride.

Amino-acid *N*-carboxyanhydrides were coupled with amino-oxy-acid hydrochlorides in ethanol–water at room temperature. The pronounced nucleophilic activity of the amino-oxy-group and the high degree of dissociation of the amino-oxy-acid hydrochlorides in water allow interaction in aqueous ethanol. Data for

[1] Y. Knobler, S. Bittner, and M. Frankel, *J. Chem. Soc.*, 1964, 3941.
[2] F. E. King, J. W. Clark-Lewis, D. A. A. Kidd, and G. R. Smith, *J. Chem. Soc.*, 1954, 1039.
[3] W. Langebeck and D. Weisbrod, *J. prakt. Chem.*, 1965, **28**, 78.
[4] R. F. Lloyd, C. G. Skinner, W. Shive, and R. J. Stedman, *J. Medicin. Chem.*, 1965, **8**, 398.
[5] J. C. Sheehan and G. P. Hess, *J. Amer. Chem. Soc.*, 1955, **77**, 1067.

glycyl, DL-phenylalanyl, and γ-benzyl-L-glutamyl amido-oxypeptides of amino-oxyacetic, β-amino-oxypropionic, and γ-amino-oxybutyric acid are given in Table 2.

EXPERIMENTAL

L-Alanine *N*-carboxyanhydride was prepared by the method of Bailey.[6] *N*-Benzyloxycarbonyl-L-alanine was obtained as described by Bergman and Zervas.[7] Anthranilic acid ethyl ester hydrochloride and *p*-aminobenzoic acid ethyl ester (benzocaine) hydrochloride were prepared by esterification of the acids in ethanol saturated with hydrogen chloride.[8] *p*-Aminobenzoyl-L-glutamic acid was obtained as described by King, Acheson, and Spensley.[9] The *N*-carboxyanhydrides of glycine and DL-phenylalanine were prepared by the procedure of Farthing;[10] γ-benzyl-*N*-carboxy-L-glutamate anhydride was made by the method of Blout and Karlson.[11] β-Amino-oxypropionic acid hydrochloride was prepared by condensation of β-bromopropionic acid with aqueous sodium benzohydroxamate and hydrolysis of β-benzamido-oxypropionic acid (formed along with phenylcarbamoyl benzohydroxamate) with 6% hydrochloric acid.[12]

L-Alanylanthranilic Acid Hydrochloride.—L-Alanine *N*-carboxyanhydride (1·15 g., 0·01 mole) and anthranilic acid hydrochloride (1·73 g., 0·01 mole) were dissolved in dimethylformamide (5 ml.) by shaking for some minutes. The solution, protected from moisture ($CaCl_2$), was left at room temperature for 40 hr., during which time carbon dioxide was evolved. After filtration and evaporation (35°/2 mm.) the residue was dissolved in ethanol (charcoal). The *hydrochloride* (2·05 g., 85%) crystallised on addition of ether and light petroleum. Washed with ether and dried (P_2O_5) it melted at 220—228°, $[\alpha]_D^{23}$ −40°. Recrystallisation from propan-2-ol–ether or ethanol–ether with addition of light petroleum gave crystals (80% recovery), m.p. 228—230° [Found: C, 49·0; H, 5·4; Cl, 14·7; N, 11·3; N(Van Slyke), 6·0. $C_{10}H_{13}ClN_2O_3$ requires C, 49·1; H, 5·4; Cl, 14·5; N, 11·5; N(Van Slyke), 5·8%], $[\alpha]_D^{23}$ −40·0° (*c* 1 in N-HCl), $\lambda_{max.}$ (Nujol) 3·8, 4·1, and 4·9 (NH_3^+), 5·9 (C=O, un-ionised carboxy-group), 6·0 (amide I), 6·2 (NH_3^+, C=C), 6·3 (*ortho*-substituted phenyl), 6·55 (amide II), and 13·3 (*ortho*-substituted phenyl) μ.

Optical purity. L-Alanylanthranilic acid hydrochloride (0·275 g.) was heated under reflux in 5N-hydrochloric acid (20 ml.); the rotation of the solution gradually changed to the value for L-alanine (freed by hydrolysis). After 2½ hr. under reflux the solution was treated with charcoal and filtered; $[\alpha]_D^{23}$ +7·2° (calc. as L-alanine, *c* 0·5 in 5N-HCl). For comparison a solution (in 5N-HCl) of L-alanine (0·1 g., 1 mol.) and anthranilic acid (0·154 g., 1 mol.) was heated under reflux under the same conditions; it then

TABLE 1

α-Aminoacylamidobenzoic acids $NH_2{\cdot}CHR^1{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}CO{\cdot}R^2$ (I)

						C (%)		H (%)		N (%)	
(I)	R^1	R^2	M.p.	Yield (%)	Formula	Calc.	Found	Calc.	Found	Calc.	Found
a	$PhCH_2$	OEt(*p*)	111°	70	$C_{18}H_{20}N_2O_3$	69·2	69·0	6·4	6·4	9·0	8·9
b	$PhCH_2$	OH(*p*)	190	72	$C_{16}H_{16}N_2O_3$	67·6	67·3	5·7	5·8	9·8	9·7
c	H	OEt(*p*)	255—260 †	90 *	$C_{11}H_{15}N_2O_3Cl$	51·1	50·9	5·8	5·7	10·8	10·8
d	H	OH(*p*)	238	75 *	$C_9H_{11}N_2O_3Cl$	46·7	46·5	4·8	5·0	12·1	12·3
e	L-$PhCH_2{\cdot}CO_2{\cdot}[CH_2]_2$	OH(*p*)	172	45	$C_{19}H_{20}N_2O_5$	64·0	63·7	5·7	5·6	7·9	8·0
f	$PhCH_2$	OEt(*o*)	145	38	$C_{18}H_{20}N_2O_3$	69·2	68·9	6·4	6·3	9·0	8·8
g	$PhCH_2$	OH(*o*)	142	44	$C_{16}H_{16}N_2O_3$	67·6	66·9	5·7	5·7	9·8	9·7
h	H	OEt(*o*)	250—252	75 *	$C_{11}H_{15}N_2O_3Cl$	51·1	51·0	5·8	5·9	10·8	10·6
i	H	OH(*o*)	241—243	85 *	$C_9H_{11}N_2O_3Cl$	46·7	46·7	4·8	4·9	12·1	12·1

* Isolated as hydrochloride. † Lit.,[2] 244—246° (decomp.).

TABLE 2

Amido-oxy-peptides $NH_2{\cdot}CHR{\cdot}CO{\cdot}NH{\cdot}O{\cdot}[CH_2]_n{\cdot}CO_2H$ (II)

						C (%)		H (%)		N (%)	
(II)	*n*	R	M.p.	Yield (%)	Formula	Calc.	Found	Calc.	Found	Calc.	Found
a	1	H	170°	74	$C_4H_8N_2O_4$	32·4	32·4	5·4	5·6	18·9	18·5
b	1	$PhCH_2$	177	60	$C_{11}H_{14}N_2O_4$	55·5	55·2	5·9	5·8	11·8	11·6
c *	1	L-$PhCH_2{\cdot}CO_2{\cdot}[CH_2]_2$	147	58	$C_{14}H_{18}N_2O_6$	54·2	54·2	5·8	5·8	9·0	9·1
d	2	H	161	58	$C_5H_{10}N_2O_4$	37·0	37·1	6·2	6·1	17·3	17·1
e	2	$PhCH_2$	133	60	$C_{12}H_{16}N_2O_4$	57·1	56·8	6·4	6·3	11·1	10·9
f	3	H	159	72	$C_6H_{12}N_2O_4$	40·9	40·7	6·9	6·7	15·9	16·0
g	3	$PhCH_2$	181	59	$C_{13}H_{18}N_2O_4$	58·6	58·3	6·8	6·9	10·5	10·3

* $[\alpha]_D^{23}$ +21·6° (*c* 12·5 in N-HCl).

[6] J. L. Bailey, *J. Chem. Soc.*, 1950, 3461.
[7] M. Bergman and L. Zervas, *Ber.*, 1932, **65**, 1192.
[8] D. Vorländer and F. Meyer, *Annalen*, 1902, **320**, 135; H. Salkowski, *Ber.*, 1895, **28**, 1921.
[9] F. E. King, R. M. Acheson, and P. C. Spensley, *J. Chem. Soc.*, 1949, 1401.
[10] A. C. Farthing, *J. Chem. Soc.*, 1950, 3213.
[11] E. R. Blout and R. H. Karlson, *J. Amer. Chem. Soc.*, 1956, **78**, 941.
[12] N. Frydman, M.Sc. Thesis, Hebrew University of Jerusalem, 1965.

showed $[\alpha]_D^{23}$ +7·2° (*c* 0·5 in 5N-HCl); the same optical activity (±0·1°) was recorded if the solution was not heated.

The same specific rotations were obtained for the hydrolysates of the amino-acid amide hydrochloride from the first precipitation. This shows that the products obtained in the reaction are optically pure and do not arise from preferential removal of stereoisomers.

L-*Alanyl*-p-*aminobenzoic Acid Hydrochloride*.—A solution of *p*-aminobenzoic acid (1·73 g., 0·01 mole) and L-alanine *N*-carboxyanhydride (1·15 g., 0·01 mole) in dimethylformamide was kept at room temperature for 40 hr. and then worked up as before. Recrystallised from ethanol–ether on addition of light petroleum, the hydrochloride (2 g., 81%) melted at 262—265° (decomp.) [Found: C, 49·2; H, 5·3; Cl, 14·5; N, 11·2; N(Van Slyke), 5·7%], $[\alpha]_D^{23}$ +28·3° (*c* 1 in N-HCl), $\lambda_{max.}$ (Nujol) 3·7, 3·9, and 5·0 (NH_3^+), 5·9 (CO_2H), 6·0 (amide I), 6·25 (NH_3^+, C=C), 6·5 (amide II), and 12·95 (*para*-substituted phenyl) μ.

Optical purity. L-Alanyl-*p*-aminobenzoic acid hydrochloride (0·275 g.) was heated under reflux in 5N-hydrochloric acid for 2½ hr. The optical activity of the hydrolysate, purified with charcoal, was the same as that of a solution of L-alanine (0·1 g.) and of *p*-aminobenzoic acid (0·154 g.) in 5N-hydrochloric acid (20 ml.): [α] +7·2° (±0·1). A hydrolysate of twice-recrystallised dipeptide hydrochloride had the same specific rotation.

L-*Alanyl*-p-*aminobenzoic Acid Ethyl Ester Hydrochloride*.—A solution of *p*-aminobenzoic acid ethyl ester hydrochloride (2·02 g., 0·01 mole) and L-alanine *N*-carboxyanhydride (1·15 g., 0·01 mole) in dimethylformamide was kept at room temperature for 20 hr. The solvent was removed (35°/2 mm.) and the residue was dissolved in ethanol (charcoal). Addition of ether and an excess of light petroleum precipitated the crude *ester hydrochloride* (2·3 g.), m.p. 245—248°, $[\alpha]_D^{23}$ +15·8° (*c* 1 in 80% EtOH) and +25·9° (*c* 1 in N-HCl). Recrystallised from ethanol–ether and light petroleum the product (2·05 g., 75%) melted at 250—252° [Found: C, 52·7; H, 6·1; Cl, 13·2; N, 10·3; N(Van Slyke), 5·2; OEt, 16·8. $C_{12}H_{17}ClN_2O_3$ requires C, 52·8; H, 6·3; Cl, 13·0; N, 10·3; N(Van Slyke), 5·2; OEt, 16·5%], $[\alpha]_D^{23}$ +17·5° (*c* 1 in 80% EtOH), $[\alpha]_D^{23}$ +27·5° (*c* 1 in N-HCl), $\lambda_{max.}$ (Nujol) 3·85, 3·5—4·1, and 5·2 (NH_3^+), 5·88sh—5·92 (ester and amide I), 6·25 (NH_3^+, C=C), 6·45 (amide II), and 12·95 (*para*-substituted phenyl) μ.

N-*Benzyloxycarbonyl*-L-*alanyl*-p-*aminobenzoic Acid Ethyl Ester*.—(*a*) To a stirred solution of ethyl L-alanyl-*p*-aminobenzoic acid ethyl ester hydrochloride (0·546 g., 0·002 mole) and benzyloxycarbonyl chloride (0·375 g., 0·0022 mole) in chloroform (10 ml.), triethylamine in chloroform (5 ml.) was added (during ½ hr.), with the temperature kept between −5 and 0°. The mixture was stirred for a further 30 min. at room temperature. Chloroform was added (10 ml.) and the mixture was washed with 1% hydrochloric acid (15 ml.) with stirring and cooling (0°). Washing with 1% hydrochloric acid was repeated and the chloroform solution was shaken with water (2 × 15 ml.). The chloroform solution was dried ($MgSO_4$) and evaporated under reduced pressure, and the solid residue was recrystallised from ethyl acetate and light petroleum. The *benzyloxycarbonyl derivative* (0·6 g., 81%) melted at 155° (Found: C, 64·9; H, 6·2; N, 7·5; OEt, 11·9. $C_{20}H_{22}N_2O_5$ requires C, 64·9; H, 6·0; N, 7·6; OEt, 12·1%), $[\alpha]_D^{23}$ −43·0° (*c* 1 in EtOH), $[\alpha]_D^{23}$ −27·7° (*c* 1 in AcOH), $\lambda_{max.}$ (Nujol) 3·05 (NH), 5·8 (urethane CO), 5·93 (conjugated ester CO), 6·03 (amide I), and 6·55 (amide II); overall yield based on L-alanine 52—54%.

(*b*) *N*-Benzyloxycarbonyl-L-alanine, m.p. 88°, $[\alpha]_D^{23}$ −14·5° (*c* 1 in AcOH) (2·23 g., 0·01 mole) was dissolved in chloroform (50 ml.) and dicyclohexylcarbodi-imide (2·06 g., 0·01 mole) was added to the cooled (0°) and stirred solution. *p*-Aminobenzoic acid ethyl ester hydrochloride (2·02 g., 0·01 mole) and triethylamine (1·0 g., 0·001 mole) were added and the mixture was stirred for 30 min. with cooling, then for 3 hr. without cooling. It was left overnight at room temperature and dicyclohexylurea was filtered off. An excess of light petroleum precipitated the product mixed with triethylamine hydrochloride. The filtrate was concentrated and more crude product was obtained on addition of light petroleum. Washing with 2—3% hydrochloric acid and recrystallisation from ethanol–water gave the *benzyloxycarbonyl ester* (1·6 g., 59%), m.p. 146—148°. Recrystallised from ethyl acetate and light petroleum it melted at 152—153° and had an i.r. spectrum identical with that of the product obtained by method (*a*) (Found: C, 65·1; H, 5·9; N, 7·8; OEt, 12·2%), $[\alpha]_D^{23}$ −41·2° (*c* 1 in EtOH), $[\alpha]_D^{23}$ −27·2° (*c* 1 AcOH); overall yield based on L-alanine 40—42%.

DL-*Phenylalanyl*-p-*aminobenzoyl*-L-*glutamic Acid*.—*p*-Aminobenzoyl-L-glutamic acid [9] (1·33 g., 0·005 mole) was dissolved in dry dimethylformamide (10 ml.). A 16% solution of hydrogen chloride in dimethylformamide (1·1 g., 0·005 mole) and DL-phenylalanine *N*-carboxyanhydride [10] (0·96 g., 0·005 mole) were added and the solution was left at room temperature for 3 days. After removal of the solvent under vacuum, water (10 ml.) was added to the oily residue, and a small amount of undissolved material was filtered off. The clear solution was brought to pH 5·0 with triethylamine and left in the cold overnight. The *product* was obtained as an oil which was recrystallised from ethanol–water; m.p. 207—208° (Found: C, 60·8; H, 5·9; N, 10·3. $C_{21}H_{23}N_3O_6$ requires C, 61·0; H, 5·6; N, 10·2%), $[\alpha]_D^{25}$ +12·3° (*c* 6·2 in N-HCl).

Glycyl-p-*aminobenzoyl*-L-*glutamic Acid*.—Prepared as already described, from glycine *N*-carboxyanhydride [10] (0·5 g., 0·005 mole), the *product* (1 g., 64%) melted at 255° (lit.,[2] 253°) (Found: C, 51·8; H, 5·3; N, 12·8. Calc. for $C_{14}H_{17}N_3O$: C, 52·0; H, 5·3; N, 13·0%), $[\alpha]_D^{25}$ −4·2° (*c* 12·5 in N-HCl).

γ-*Benzyl*-L-*glutamyl*-p-*aminobenzoyl*-L-*glutamic Acid*.—Prepared as before, from γ-benzyl-*N*-carboxy-L-glutamate anhydride [11] (1·33 g., 0·005 mole), the *product* (1·40 g., 62%) melted at 168—169° [Found: C, 59·5; H, 5·6; N, 8·9; N(Van Slyke), 2·7. $C_{24}H_{27}N_3O_8$ requires C, 59·4; H, 5·6; N, 8·7; N(Van Slyke), 2·9%], $[\alpha]_D^{25}$ +52° (*c* 12·5 in N-HCl).

Glycylaminobenzoic Acids and Ethyl Ester Hydrochlorides.—Glycylaminobenzoic acids and esters were prepared by dissolving the hydrochloride of the aminobenzoic acid or of its ethyl ester with glycine *N*-carboxyanhydride (1 mol.) in dimethylformamide. The solution was kept at room temperature for 20 hr., the solvent was removed under vacuum, and the hydrochloride of the product was isolated and recrystallised as described for the L-alanyl peptides. Data for the following glycyl amides (Ic, d, h, and i) are recorded in Table 1.

DL-*Phenylalanylaminobenzoic Acids and Esters. General Procedure*.—A solution of DL-phenylalanine *N*-carboxyanhydride [10] (0·01 mole) and the aminobenzoic acid hydrochloride or its ester hydrochloride (0·01 mole) in dry dimethylformamide was kept at room temperature for 3 days,

protected from moisture ($CaCl_2$). After filtration and removal of the solvent under vacuum, the oily residue was dissolved in water (25 ml.). Undissolved polymer and unchanged *N*-carboxyanhydride were filtered off, and to the clear solution triethylamine was added dropwise (to pH 6·5—7·0). Cooling and scratching initiated precipitation within a few minutes, completed by storage overnight at 0°. The amides and the esters were recrystallised from ethanol, propan-2-ol, or ethanol–ether.

The DL-phenylalanylaminobenzoic acid ethyl esters obtained were hydrolysed with 2N-sodium hydroxide. After filtration and acidification with conc. hydrochloric acid to pH 6·0, the precipitated DL-phenylalanyl amides were identified by analysis, mixed m.p., and i.r. spectra with those obtained from the acid hydrochlorides with DL-phenylalanine *N*-carboxyanhydride.

Data for the amides (Ia, b, f, and g) are given in Table 1. A similar preparation, from γ-benzyl-*N*-carboxy-L-glutamate anhydride [11] and *p*-aminobenzoic acid hydrochloride gave *γ-benzyl-L-glutamyl-p-aminobenzoic acid* (Ie) (see Table 1).

Amido-oxy-peptides of ω-Amino-oxy-acids (II).—The amido-oxy-peptides (IIa—g) were prepared by treatment of amino-oxy-acid hydrochlorides with *N*-carboxyanhydrides in 3 : 1 ethanol–water. Data are summarised in Table 2. The preparation of glycylamino-oxyacetic acid (Ia) is characteristic. The preparation of γ-amino-oxybutyric acid hydrochloride, applied in the synthesis of (IIf and g), is also described.

Glycylamino-oxyacetic Acid (IIa).—Amino-oxyacetic acid hemihydrochloride (0·55 g., 0·005 mole) and 36% hydrochloric acid (0·21 ml., 0·0025 mole) were added to 3 : 1 ethanol–water (8 ml.), followed by glycine *N*-carboxyanhydride (0·50 g., 0·005 mole). Evolution of carbon dioxide took place almost immediately and continued for about 20 min. The solution was then kept at room temperature for 1 hr. and the solvent was removed under vacuum (40°). The oily residue was dissolved in water (5 ml.) and cooled to 0°, and impurities were filtered off. The clear solution was neutralised (to pH 7·0—7·5) with triethylamine, ethanol (8 ml.) was added, and the mixture was kept overnight at 0°. The *amido-oxy-peptide* (0·55 g., 74%) precipitated as white crystals, m.p. 170° (decomp.).

Addition of hydrochloric acid (0·5 equiv.) to the reaction mixture was necessary in the case of the hemihydrochloride of amino-oxyacetic acid. With the other amino-oxy-acid hydrochlorides no hydrogen chloride was necessary.

γ-Benzamido-oxybutyric Acid.—Benzohydroxamic acid (10·96 g.) in absolute ethanol (70 ml.) was added to a solution of sodium ethoxide [from sodium (1·85 g.) in ethanol (70 ml.)]. To the mixture, which contained some precipitated sodium benzohydroxamate, ethyl γ-bromoethylbutyrate (7·80 g.) in absolute ethanol (70 ml.) was added. Stirring and heating to boiling caused dissolution. The solution was stirred at 55—60° for 48 hr., filtered, and evaporated under vacuum to small bulk. The oily residue was suspended in 2N-sodium hydroxide (70 ml.) and the mixture was stirred for 12 hr. Impurities were filtered off and the solution was acidified with concentrated hydrochloric acid to pH 6·0; storage at 0° overnight caused precipitation of the *acid* (6·6 g., 74%), m.p. 108—109°. Recrystallisation from water gave material, m.p. 112—113° (Found: C, 58·9; H, 6·0; N, 6·4. $C_{11}H_{13}NO_4$ requires C, 59·2; H, 5·9; N, 6·3%). A second crop was obtained by acidifying the filtrate to pH 5·0 and storage in the cold for 24 hr. (total yield 82%).

γ-Amino-oxybutyric Acid Hydrochloride.—γ-Benzamido-oxybutyric acid (2·2 g., 0·01 mole) was heated under reflux in 4% hydrochloric acid (15 ml.) for 15 min. then cooled. Precipitated benzoic acid was filtered off and the solvent was removed under vacuum. The residue was dissolved in ethanol and ether was added. The hygroscopic *acid hydrochloride* (0·65 g., 42%) was washed with 4 : 1 ether–ethanol; m.p. 129—130° (Found: C, 30·65; H, 6·6; N, 8·9. $C_4H_{10}ClNO_3$ requires C, 30·85; H, 6·5; N, 9·0%).

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