Tetrahedron Vol 33, pp 3285 to 3288 Pergamon Press 1977 Printed in Great Britain

UNAMBIGUOUS SYNTHESIS OF N-HYDROXYPEPTIDES†

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(*Received in UK* 31 *May* 1977; *Accepted for publication* 8 *June* 1977)

Abstract—The two last stages of the unambiguous synthesis of N-hydroxypeptides, i.e. acylation of N-benzyloxyaminoacid esters and deprotection of the resulting N-benzyloxypeptide, are presented.

The large number of peptide analogues so far obtained not only include depsipeptides[1] and hydrazino-peptides,[2] but also sulphamide[3] and phosphonic analogues.[4] Since all these compounds differ drastically from their prototype, their physiological properties are radically changed. It is, however, very likely that the action of N-hydroxypeptides, which are closest to natural amides, will be only slightly modified.

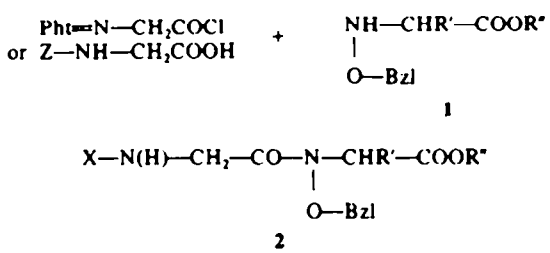
The possibility of peptide bond oxidation has not yet been reported, although several examples of amide oxidation *in vivo* to hydroxamic acids have been cited in the literature.[5] N-hydroxypeptides can therefore be connected with the metabolism of natural peptides, a fact that may account for the presence of N-hydroxypeptides observed in tumour protein.[6] Considering the possibility mentioned above, Scott[7] assumed oxidation of the peptide bond to be an element of the biosynthesis of β-lactam antibiotics. The suggestion has also been made that biological dehydrogenation of peptides to dehydropeptides may occur through the N-hydroxylation process.[8]

These interesting, though incomplete data, prompted us more than did the considerable number of the none too useful natural hydroxamic acids,[9] to continue our programme of N-hydroxypeptide synthesis. At the 12th Peptide Symposium we proposed[10] an unambiguous synthesis of these compounds with N-alkoxyamino acids as key substrates.[11] Oxygen atom alkylation excluded the redox processes which are troublesome in the work with N-hydroxyamino acids and prevent O-acylation which is characteristic of hydroxylamino derivatives.[12] Having found O-benzyl to be the most convenient protecting group, we described a method for obtaining N-benzyloxyamino acid esters.[13] The present study deals with the last two stages of the synthesis, i.e. ester acylation and deprotection of the N-benzyloxy peptides.

Acylation possibilities with phthalyl-glycine were studied on the model compounds: N-benzyloxy alanine t-butyl (**1a**) or methyl ester (**1b**). The best yields (about 60–80%) were obtained by the acid chloride and mixed anhydride methods.

The use of such reagents as DCCI and EEDQ‡ led only to 20–30% of phthalyl-glycyl-N-benzyloxy-DL-alanine ester (**2a**). Acylation of the N-benzyloxy-DL-alanine esters with N-hydroxyphthalimide or the *p*-nitrophenyl ester of phthalyl-glycine failed.

As can be seen, the acylation reaction is relatively difficult. Analogies found in the literature only refer to acylation of N-β-protected hydrazino acid esters on the α atom.[14] The difficulties encountered in either of these cases must be accounted for both by decrease in the basicity of the N atom and, above all, by steric hindrance, although acylation of simple O-alkyl or N,O-alkyl derivatives does not present any difficulty in the chemistry of hydroxylamines.[15]



1a: R′ = Me, R″ = t-Bu
1b: R′ = R″ = Me
1c: R′ = H, R″ = t-Bu
1d: R′ = i-Bu, R″ = t-Bu
1e: R′ = Me; R″ = Bzl

2a: X = Pht; R′ = Me, R″ = t-Bu
2b: X = Pht; R′ = R″ = Me
2c: X = Pht; R′ = H, R″ = t-Bu
2d: X = Pht; R′ = i-Bu, R″ = t-Bu
2e: X = Z; R′ = R″ = Me
2f: X = Z; R′ = Me, R″ = Bzl

(where: Pht—phthalyl; Z—carbobenzoxy)

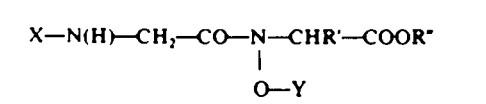
Scheme 1.

The protecting group has been removed from the N-benzyloxy peptides selectively without difficulty. It was also possible, without disturbing the N-hydroxypeptide bond, to split off t-butyl with trifluoroacetic acid from such esters of phthalyl-glycyl-N-benzyloxy-DL-alanine (**2a**) or phthaly-glycycl-N-benzyloxy-glycine (**2c**). The phthalyl group was removed from the former substrate (**2a**) by hydrazinolysis to obtain t-butyl ester of glycyl-N-benzyloxy-DL-alanine which was isolated as acetate (**4a**).[16]

Acidolysis of the methyl ester of benzyloxycarbonyl-glycyl-N-benzyloxy-DL-alanine (**2e**) with hydrogen bromide in acetic acid led only to the removal of the benzyloxycarbonyl group. The benzyl group could be selectively removed from the oxygen in the central amide bond, giving the protected N-hydroxypeptide (**6**). This has been evidenced by the example of hydrogen

†Presented at the 14th European Peptide Symposium (EPS), Wepion, Belgium (April 1976).

‡DCCI—dicyclohexylcarbodiimide; EEDQ-N-carboethoxy-2-1,2-dihydroquinoline.



3a: X = Pht, Y = Bzl; R' = Me, R" = H
3b: X = Pht, Y = Bzl; R' = R" = H
4a: X = H, Y = Bzl; R' = Me, R' = t-Bu
4b: X = H, Y = Bzl; R' = R" = Me
5a: X = H, Y = Bzl; R' = CH_3, R" = H
5b: X = H, Y = Bzl; R' = R" = H
5c: X = H, Y = Bzl; R' = i-Bu, R" = H
6: X = Pht, Y = H; R' = R" = Me
7a: X = H, Y = H; R' = Me, R" = H
7b: X = H, Y = H; R' = R" = H
7c: X = H, Y = H; R' = i-Bu, R" = H

Scheme 2.

reduction on a palladium catalyst of the methyl ester of phthalyl-glycyl-N-benzyloxy-alanine (**2a**) or by the experiment with acidolysis of this substrate by boron trifluoracetate. We first used that reagent in earlier work[11] to remove the benzyl group from N-benzyloxyamino acids.

Finally, all protecting groups could be removed simultaneously by using an adequate set of protections, as in the example of the benzyl ester of benzyloxycarbonyl-glycyl-N-benzyloxy-DL-alanine (**2d**).

The free N-hydroxypeptides glycyl-N-hydroxyalanine (**7a**), glycyl-N-hydroxyglycine (**7b**) and glycyl-N-hydroxyleucine (**7c**) are crystalline, chromatographically and analytically pure substances whose structure has been confirmed by spectral and elemental analysis. They are water soluble and can be isolated using ion exchange resin. They give a test characteristic of hydroxamic acids. Their R_f value in chromatographic processes in the common peptide solvent system is somewhat higher than is this value for parent peptides.

NMR spectra of a considerable number of N-benzyloxy- and N-hydroxypeptides have been obtained. Table 1 summarizes the spectra of peptides with alanine residue and gives a comparison of the chemical shifts of protons at the α carbon on the N-hydroxyamino acid residue. Owing to the presence of the O atom on the amide bond, these protons are more deshielded than are normal peptides by about 0.2 ppm for N-benzyloxypeptides and 0.82 ppm for N-hydroxypeptides.

As can be seen, the method of N-hydroxypeptide synthesis has been tested only on N-terminal glycyl N-hydroxypeptides. In the case of other amino acids the acylation processes are likely to be difficult.

We are undertaking further work to study the synthesis of N-hydroxypeptides not containing glycine residue, and to find other procedures for the formation of the N-hydroxypeptide bond. Investigations of the stereochemistry of N-benzyloxy- and N-hydroxypeptides are in progress.

EXPERIMENTAL

M.ps are uncorrected. Chromatograms were run on thin layers of silica gel (Kieselgel G., Merck). For developing were used ninhydrin, iodine or ferric chloride. NMR spectra were recorded on a Tesla, Brno BS 487, apparatus at 80 MHz. All solvents were evaporated under reduced pressure in a rotary evaporator. Solns in organic solvents were dried over $MgSO_4$. Products obtained by various methods were identified by comparing their IR and NMR spectra and thin layer chromatograms.

Phthalyl - glycyl - N - benzyloxy - DL - alanine t-butyl ester (**2a**)

(a) *Acid chloride method.* To a soln of **1a** (4.8 g; 19 mmol) in EtOAc with sat $NaHCO_3$ aq was added dropwise a soln of phthalyl-glycine chloride (4.2 g; 19 mmol) in the same solvent. The mixture was stirred for 12 hr, the organic layer was then separated, washed and dried, and the solvent was evaporated to yield 6 g (72%) of **2a**; m.p. after crystallization from EtOAc 113–5°. NMR data are shown in Table 1. (Found: N, 6.40. Calc. for $C_{24}H_{26}N_2O_6$: N, 6.39%).

(b) *DCCI procedure.* To a soln of **1a** (1.26 g; 5 mmol) was added an equimolar quantity of phthalyl-glycine and DCCI in THF. The mixture was left standing for 36 hr at 20°. 0.6 g of a product identical with the peptide prepared by method (a) was obtained by the standard procedure in 27% yield, m.p. 112–6°.

Table 1. NMR data (δ in $CDCl_3$) of N-benzyloxy- and N-hydroxypeptides (only alanine deriv.)
X—N(H)—CH_2—CO—N(OY)—CHMe—COOR" (X = Pht or Z; Y = Bzl or H)

Compound	X	NH	CH_2	Y	CH	CH_3(d)	R"
2a	7.65(m, 4H)		4.5(s, 2H)	5.0(s, 2H) 7.32(s, 5H)	4.72(q, 1H)	1.5(d, 3H)	1.45(s, 9H)
2b	7.62(m, 4H)		4.48(s, 2H)	4.95(s, 2H) 7.27(s, 5H)	4.77(q, 1H)	1.5(d, 3H)	3.67(s, 3H)
2e	7.25(s, 5H) 5.05(s, 2H)	5.7(m, 1H)	4.12(d, 2H)	4.85(s, 2H) 7.22(s, 5H)	4.82(m, 1H)	1.45(d, 3H)	3.57(s, 3H)
2f	7.25(s, 5H) 5.05(s, 2H)	5.5(m, 1H)	4.08(d, 2H)	4.8(s, 2H) 7.2(s, 5H)	4.82(m, 1H)	1.5(d, 3H)	5.02(s, 2H) 7.22(s, 5H)
3a†	7.97(m, 4H)		4.75(s, 2H)	5.20(s, 2H) 7.55(m, 5H)	4.95(q, 1H)	1.65(d, 3H)	
4a		8.62(s, 3H) 1.87(s, 3H)	3.82(s, 2H)	4.85(s, 2H) 7.25(s, 5H)	4.70(q, 1H)	1.4(d, 3H)	1.32(s, 9H)
4b†			4.1(d, 2H)	5.12(s, 2H) 7.6(s, 5H)	4.38(q, 1H)	1.6(d, 3H)	3.6(s, 3H)
5a‡		7.0(m, 3H)	3.8(m, 2H)	4.85(s, 2H) 7.22(s, 5H)	4.75(m, 1H)	1.58(d, 3H)	
6	7.65(m, 4H)		4.62(s, 2H)		5.06(q, 1H)	1.38(d, 3H)	3.62(s, 3H)
7a‡		7.37(m, 3H)	4.5(m, 2H)		5.37(q, 1H)	1.7(d, 3H)	
Gly-Ala‡		7.18(m, 3H)	4.02(m, 2H)	7.55(d, 1H)	4.55(m, 1H)	1.38(d, 3H)	

†In DMSO d_6.
‡In TFA.

(c) *Mixed anhydride procedure.* To a chloroform soln of phthalylglycine (0.82 g; 4 mmol) and triethylamine (0.56 ml; 4 mmol) at −10°, was added dropwise with stirring isobutyl chloroformate (0.55 ml; 4 mmol), keeping the temp. at 0°. After 10 min, **1a** (1 g; 4 mmol) was added. The mixture was kept for 24 hr at 0°, then for 3 days at 20°. The chloroform soln was washed with Na_2CO_3 aq, then with water, and dried, giving after evaporation of the solvent 1.35 g (77%) of crude product, m.p. and structure (NMR) were identical with those of the derivatives obtained at (a) and (b).

Phthalyl - glycyl - N - benzyloxy - DL - alanine methyl ester (**2b**)[1]

(a) *Acid chloride method.* This ester was prepared in the same manner as **2a**. From **1b** (1.25 g; 6 mmol) and phthalylglycine chloride (1.33 g; 6 mmol), **2b** (1.3 g; 55%) with m.p. 128–30°, was obtained. After crystallization from EtOAc petroleum ether mixture: m.p. 132–4°, NMR data in Table 1. (Found: N, 7.12. Calc. for $C_{21}H_{20}N_2O_6$: N, 7.07%).

(b) *EEDQ method.* Standard procedure.[17] A soln of N-benzyloxy-DL-alanine methyl ester(1.25 g; 6 mmol), EEDQ (1.50 g; 6.1 mmol) and phthalyl glycine (1.23 g; 6 mmol) in THF gave **2a** (0.6 g; 25%) identical with the former.

Phthalyl - glycyl - N - benzyloxy - glycine t-butyl ester (**2c**)

This compound was obtained like **2b**—method (a) from **1c** (3.5 g; 1.5 mmol) and phthalylglycine chloride, yield 4.2 g, 66%, m.p. 140–2°. NMR δ (in $CDCl_3$): 1.5 (s, 9H, CMe_3), 4.25 (s, 2H), 4.6 (s, 2H), 5.0 (s, 2H, CH_2O), 7.42 (s, 5H, C_6H_5), 7.8 (m, 4H, C_6H_4). (Found: N, 6.89. Calc. for $C_{23}H_{24}N_2O_6$: N, 6.60%).

Phthalyl - glycyl - N - benzyloxy - DL - leucine t-butyl ester (**2d**)

This N-benzyloxypeptide was obtained by the acid chloride method previously described, from **1d** (2.5 g; 8.5 mmol), yield 2.3 g (56%), m.p. 67–71°. Recrystallization from EtOAc–petroleum ether mixture raised the m.p. to 73–6°.

NMR spectrum (in $CDCl_3$): 0.9 (m, 6H, 2 × Me), 1.18 (t, 2H, CH_2–C), 1.4 (s, 9H, CMe_3), 1.78 (m, 1H, CH–C), 4.12 (t, 1H, CH–N), 4.52 (s, 2H, CH_2–N), 5.02 (s, 2H, CH_2–O), 7.32 (s, 5H, C_6H_5), 7.65 (m, 4H, C_6H_4). (Found: N, 6.06. Calc. for $C_{27}H_{32}N_2O_6$: N, 5.83%).

Carbobenzoxyglycyl - N - benzyloxy - DL - alanine methyl ester (**2e**)

This N-benzyloxypeptide was prepared like **2a** by the mixed anhydrides method in chloroform from carbobenzoxyglycine (3.8 g; 18 mmol) and N-benzyloxy-DL-alanine methyl ester (3.8 g; 18 mmol). 4.0 g (55%) of an oily product was obtained. NMR data are in Table 1. (Found: N, 7.14. Calc. for $C_{21}H_{24}N_2O_6$: N, 6.99%).

Carbobenzoxyglycyl - N - benzyloxy - DL - alanine benzyl ester (**2f**)

A crude oily product (2.5 g) was obtained by the mixed anhydride method from benzyloxy carbonyl-glycine (1.5 g; 7.1 mmol) and **1d** (2.3 g; 7.1 mmol). The product was purified on a silica gel column using benzene–EtOAc (9:1) as eluent and gave 2.0 g analytically pure oil, yield 59%. For NMR data see Table 1. (Found: N, 5.87. Calc. for $C_{27}H_{28}N_2O_6$: N, 5.88%).

Phthalylglycyl - N - benzyloxy - DL - alanine (**3a**)

Compound **2a** (438 mg; 1 mmol) was treated with 1 ml of trifluoracetic acid and kept at room temp. for 30 min.

The acid was evaporated under reduced pressure. After addition of ethyl ether, 380 mg (99%) of the product was collected, which had, m.p. 184–185° and 185–186° after recrystallization from EtOAc–petrol ether. See NMR data in Table 1. (Found: N, 7.26. Calc. for $C_{20}H_{18}N_2O_6$: N, 7.33%).

Phthalylglycyl - N - benzyloxy - glycine (**3b**)

This compound was obtained as previous using trifluoracetic acid, yield from 212 mg (0.5 mmole) of ester (**2c**): 178 mg—97% m.p. 147–8°. NMR δ (in DMSO d_6): 4.7 (s, 2H), 4.85 (s, 2H), 5.3 (s, 2H, CH_2–O), 7.7 (s, 5H, C_6H_5), 8.15 (m, 4H, C_6H_4). (Found: N, 7.12. Calc. for $C_{19}H_{16}N_2O_6$: N, 7.60%).

Glycyl - N - benzyloxy - DL - alanine t-butyl ester acetate (**4a**)

Compound **2a** (438 mg; 1 mmol) was dissolved in 12 ml of benzene–MeOH mixture (5:1) and refluxed for 30 min with 0.13 g (2 mmol) of hydrazine hydrate (80% aq. solution). The resulting phthalazinodion-1.4 was dissolved in 10% Na_2CO_3 aq and the ester was extracted with ether. The ether was evaporated and 0.3 g (97%) of an oily product was obtained which after addition of AcOH was converted into acetate, m.p. 63–66° after crystallization from ether–petrol ether. For NMR data see Table 1. (Found: N, 7.87. Calc. for $C_{18}H_{28}N_2O_6$: N, 7.60%).

Glycyl - N - benzyloxy - DL - alanine methyl ester hydrochloride (**4b**)

Compound **2e** (250 mg; 0.63 mmol) was dissolved in 2 ml HBr in AcOH and left for 90 min. The solvent was evaporated and the oily residue was dissolved in Na_2CO_3aq. The free ester was extracted using EtOAc. After evaporation of the solvent an oil was obtained which was treated with ethereal HCl and gave 100 mg of crystalline hydrochloride, yield 53%, m.p. 142–144°. NMR data are in Table 1. (Found: N, 10.0. Calc. for $C_{13}H_{19}N_2O_4Cl$: N, 9.25%).

Glycyl - N - benzyloxy - DL - alanine (**5a**)

(a) *Hydrazinolysis and acidolysis.* **2a** (876 mg; 2 mmol) was refluxed with hydrazine as above. The oily product was dissolved in 2 ml trifluoracetic acid. The acid residue was evaporated and 700 mg of oil was obtained. The oil was dissolved in EtOH–water mixture (4:1) and filtered through a Zerolite 225 (H^+) column, then washed until the eluates were acid free. The N-benzyloxypeptide was eluted with 3% aqueous ammonia. The eluent was evaporated and 296 mg (59%) of a crystalline product, m.p. 158–159° (dec.) was obtained. NMR data are in Table 1. (Found: N, 11.14. Calc. for $C_{12}H_{16}N_2O_4$: N, 11.11%).

(b) *Acidolysis.* **2f** (476 mg; 1 mmol) was dissolved in 3.2 ml of 36% HBr in AcOH and kept for 10 days. The acids were evaporated uhder reduced pressure and the oily residue was purified by repeated addition and evaporation of benzene. The N-benzyloxypeptide was isolated using Zerolite as described. 220 mg of a crude crystalline product was obtained, and after recrystallization from water–EtOH. 180 mg (71%) of **5a** identical with that described above, m.p. 153–156° (dec.).

Glycyl - N - benzyloxy - glycine (**5b**)

Compound **2c** (640 mg; 1.5 mmol) was treated with hydrazine hydrate and then with trifluoracetic acid, yielding **5b** (220 mg; 61%), m.p. 158–161°. NMR δ (in trifluoroacetic acid): 3.9 (m, 2H), 4.5 (s, 2H), 4.85 (s, 2H, CH_2–O), 7.3 (s, 5H, C_6H_5), 7.1 (NH_3^+). (Found: N, 11.80. Calc. for $C_{11}H_{14}N_2O_4$: N, 11.76%).

Glycyl - N - benzyloxy - DL - leucine (**5c**)

After gradual removal of the protecting groups from 1 mmol of **2d** and purification with a Zerolite was obtained 180 mg (61%) of a product with m.p. 125–128° (cryst.: water–EtOH). NMR δ (in TFA), 0.82 (d, 6H, 2 × Me), 1.25–2.12 (m, 3H, CH_2–CH), 3.88 (m, 2H, CH_2–N), 4.75 (m, 1H, CH–N), 4.87 (s, 2H, CH_2–O), 7.2 (s, 5H, C_6H_5), 7.1 (s, NH_3^+). (Found: N, 9.55. Calc. for $C_{15}H_{22}N_2O_4$: N, 9.52%).

Phthalyl - glycyl - N - hydroxy - DL - alanine methyl ester (**6**)

(a) *Catalytical reduction.* **2b** (90 mg; 0.23 mmol) was reduced for 15 hr with H_2 in the presence of 10% Pd–C. The catalyst was then filtered off, the filtrate was evaporated, giving 60 mg (86%) of the product, m.p. after recrystallization from EtOAc–petrol ether 167–169°. NMR data are in Table 1. (Found: N, 9.46. Calc. for $C_{14}H_{14}N_2O_6$: N, 9.15%).

(b) *Acidolysis.* A soln of **2b** (150 mg; 0.4 mmol) in 2 ml trifluoroacetic acid and 2 mmol of boron tris-(trifluoracetate) was kept for 2 hr at room temp. After evaporation of the acid and addition of Na_2CO_3 aq, the product was extracted with EtOAc and the solvent was evaporated, giving (100 mg; 83%) identical with that previously obtained, m.p. 162–165°. The N-hydroxypeptide gives a red complex with ferrous chloride soln.

N-hydroxy-glycine

N-benzyloxy-glycine (181 mg; 1 mmol) in 5 ml of trifluoracetic acid was treated with 4 mmol of boron tris-(trifluoracetate) for 2 hr. After evaporation of the trifluoroacetic acid, the orthoboric acid was filtered off and the filtrate was evaporated, giving 72 mg of a product with m.p. 132–133° (dec) after recrystallization from water-EtOH (lit.[18] reports 132°). The product has the same R_f coefficient as N-hydroxyglycine and can be developed with ninhydrin or silver nitrate.

Glycyl - N - hydroxy - DL - alanine (**7a**)

(a) **5a** (200 mg; 0.8 mmol) was reduced with H_2 in the presence of 10% Pd–C. The catalyst was filtered off and the filtrate evaporated to dryness, giving 120 mg (yield 93%) of **7a**, m.p. 170–171° (dec) and 184–185° after crystallization from water-EtOH. The N-hydroxypeptide gave a positive test with ferric chloride. NMR data are in Table 1. (Found: C, 36.96; H, 6.06; N, 17.12. Calc. for $C_5H_{10}N_2O_4$: C, 37.04; H, 6.22; N, 17.28%).

(b) Catalytic reduction of 500 mg (1.05 mmol) of benzyloxycarbonyl-DL-alanine benzyl ester (**2f**) gave **7a** (130 mg; 76%) which was identical with that described above, m.p. 178–180°.

(c) To a soln of **5a** (126 mg; 0.5 mmol) in 2 ml trifluoracetic acid was added a soln of 2 mmol of boron tris-trifluoroacetate in 2 ml of the same solvent. The mixture was kept for 2 hr. The acid was evaporated, water and EtOH was added, the orthoboric acid was filtered off and the filtrate was introduced into a Zerolite 225 (H^+) column. Elution with aqueous ammonia gave 65 mg of a product identical with that obtained above, m.p. 152–155° and 182–184° after crystallization.

(d) The same N-hydroxypeptide (**7a**; 50 mg yielded 61%, m.p. 178–179) was obtained in the same manner from 238 mg (0.5 mmol) of **2f**.

Glycyl - N - hydroxy - glycine (**7b**)

Compound **5b** (600 mg; 2.5 mmol) was reduced with H_2 in the presence of Pd catalyst yielding 250 mg of **7b**, m.p. 194–6° (lit.[19] 192°), yield 70%. It gave the positive test with ferric chloride.

Glycyl - N - hydroxy - DL - leucine (**7c**)

Catalytic reduction (hydrogen, Pd/C) of 50 mg (0.17 mmol) of **5c** gave 33 mg (yield 94%) of N-hydroxypeptide, m.p. 178–182° and 187.5–188.5° after recrystallization. The compound gives a positive test with ferric chloride. NMR (in TFA): 1.05 (d, 6H, 2 × Me), 1.5–2.5 (m, 3H, CH_2–CH), 4.55 (m, 2H, CH_2–N), 5.4 (d–t, 1H, CH–N), 7.4 (NH_3^+). (Found: N, 13.43. Calc. for $C_8H_{16}N_2O_4$: N, 13.72%).

Acknowledgements—This work was financed in part by grant MR-12. We thank Mrs. T. Markowska for her technical assistance and to Mrs. I. Zacharczuk for the elemental analyses.

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