# Synthesis of *N*-Substituted Muscimol Derivatives Including *N*-Glycylmuscimol

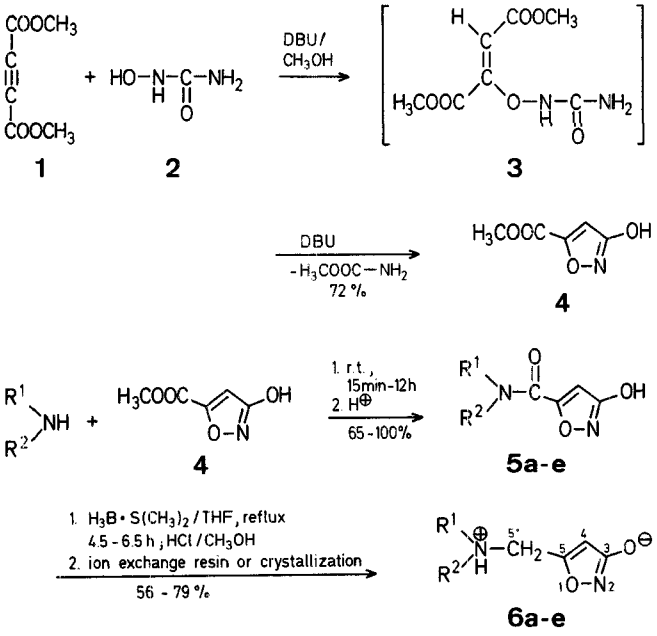
Michael FREY, Volker JÄGER*

Institut für Organische Chemie der Universität, Am Hubland, D-8700 Würzburg, Federal Republic of Germany

The preparation of muscimol (a potent but toxic GABA neurotransmitter agonist), from dimethyl acetylenedicarboxylate via methyl 3-hydroxyisoxazole-5-carboxylate and the corresponding amide, has been improved and extended to a general synthesis of *N*-alkyl and *N,N*-dialkyl derivatives. The efficient route to muscimol itself [muscimol itself costs 60 - 170 DM/10 mg] has enabled a study of its chemistry to be undertaken, a first result of which is its incorporation into a peptide, i.e. the preparation of *N*-glycylmuscimol.

Muscimol **(6a)** is a structural analogue of γ-aminobutyric acid (GABA), with restricted conformational mobility[1]. In contrast to GABA and despite its zwitterionic structure, muscimol can cross the blood-brain barrier, to exhibit diverse activities in the central nervous system[2]. However, its use in the therapy of neuro-psychiatric disorders is not possible as muscimol is toxic, presumably due to (unknown) metabolites (muscimol is metabolized rapidly, probably by the GABA-metabolizing enzyme GABA-T)[2]. Consequently, it is desirable to have access to derivatives of muscimol that are *not* metabolized, while retaining specific activities. A number of related compounds has been designed and prepared using muscimol as the primary lead structure, notably by Krogsgaard-Larsen's group[3], the most promising of these being 4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol[3]. In this respect, the preparation of *N*-substituted derivatives of muscimol attracted our attention: the altered (increased) lipophilicity should affect both the receptor binding properties as well as the metabolic pathways (hence the toxicity)[4].

*N*-Methyl derivatives of muscimol have been mentioned without details as to their preparation or to their pharmacological activity[1b,5a]; recently *N*-methyl- and *N,N*-dimethylmuscimol have been tested *in vivo* and *in vitro*[5b]. Methylation of the silver salt of muscimol with methyl iodide leads to a mixture of *O*- and *N*-alkylation products[1]. Further difficulties concerning this approach, as well as the exploration of the chemistry of muscimol in general, result from its *high cost*[6] and (mostly) inconvenient preparations[7,8,9]. To change this situation, we recently outlined a short, 3-step/30% yield sequence which enables the preparation of muscimol **(6a)** in gram quantities from dimethyl acetylenedicarboxylate **(1)**, via the isoxazole ester **4**[8,9a,10] and its amide **5a**[8]. We now report an improved synthesis of muscimol **(6a)** itself, a general route to *N*-mono- and *N,N*-disubstituted derivatives **6b–e** of muscimol via 3-hydroxyisoxazole-5-carboxamides **5** (Scheme **A**), and the synthesis of *N*-glycylmuscimol **(9)** from unprotected muscimol **(6a**; Scheme **B**).



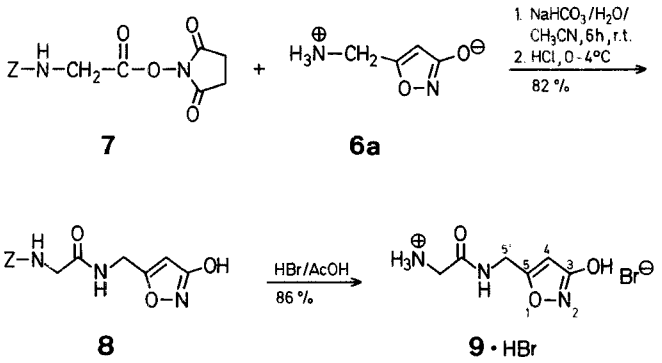

| 5,6 | $R^1$ | $R^2$ |
|---|---|---|
| **a** | H | H |
| **b** | $CH_3$ | H |
| **c** | *i*-$C_3H_7$ | H |
| **d** | $-(CH_2)_4-$ | |
| **e** | $-(CH_2)_2-O-(CH_2)_2-$ | |

Scheme A

The isoxazole ester **4** was obtained more conveniently and in better yield from dimethyl acetylenedicarboxylate (**1**) and *N*-hydroxyurea (**2**) by employing nearly stoichiometric amounts of the stronger base 1,5-diazabicyclo[5.4.0]undec-5-ene instead of the previously used 5 equivalents of triethylamine[8,9b,10]. Treatment of **4** with ammonia, methylamine, isopropylamine, pyrrolidine, or morpholine gave the corresponding 5-carboxamides **5** (Table 1). The product **5a** was isolated and reacted further as its ammonium salt[8].

The borane/dimethyl sulfide reduction procedure and work-up, introduced for muscimol (**6a**)[8], also proved to be successful in the cases of the secondary amides **5b**, **5c**, and the tertiary amides **5d**, **5e**. *N*-Methyl-and *N*-isopropylmuscimol **6b** and **6c**, after elution from the acidic ion exchange resin (Lewatit S 100 G1) with 2 normal aqueous ammonia, were obtained pure in 57 and 79% yield, respectively. The pyrrolidine and the morpholine derivatives **6d** and **6e** were isolated from the reaction mixture by crystallization in the form of their hydrochlorides in 75 and 79% yield, respectively. Overall yields based on **1** range from 27 to 50% (**6a**: 40%; **6b**: 27%; **6c**: 50%; **6d**: 49%; **6e**: 41%).

With muscimol available in gram quantities, its incorporation into peptides was tested and *N*-glycylmuscimol (**9**) was chosen as simplest target. For this purpose we considered methods[11] which would allow use of unprotected muscimol (**6a**) as the amino component and an *N*-benzyloxycarbonyl-protected amino acid such as Z-glycine as the carboxyl component. The mixed anhydride methodology[12] (21% yield of **8**) and the 1-hydroxybenzotriazole/dicyclohexylcarbodiimide procedure[13] (43% yield of impure **8**, together with 30% of *N,N'*-dicyclohexyl urea) proved less satisfactory. The *N*-hydroxysuccinimide/dicyclohexylcarbodiimide method[14] for carboxyl activation appeared to be more promising as the activated Z-glycine ester **7** is stable and can be isolated in crystalline form. In addition, esters of this type are sufficiently reactive towards free amino groups and give the water-soluble *N*-hydroxysuccinimide as by-product, thus facilitating the work-up. Formation of the protected dipeptide **8** was effected by reacting **6a** and **7** in the presence of two equivalents of sodium hydrogen carbonate in aqueous medium. After acidification, the product **8** was obtained in pure form (82% yield). In view of the facile reductive cleavage of the isoxazole nucleus by catalytic hydrogenation[15], it was desirable to deprotect **8** by acidolysis[16]. This was easily achieved by treating **8** with hydrobromic acid/acetic acid. Precipitation with ether and recrystallization furnished the pure hydrobromide of *N*-glycylmuscimol (**9** · HBr) in 86% yield.




7 6a 8 9 · HBr

Scheme **B**

Binding studies to several receptor systems[17] were effected with compounds **4**, **5a** · $NH_3$, **5c**, **5d**, **5e**, **6b**, **6c**, **6d**, **6e**, **8**, and **9** · HBr. None of these were found to bind to the $GABA_A$ receptor ($^3$H-muscimol as the radioligand), except for *N*-methylmuscimol (**6b**; at 23 μmol/l). Compounds **4**, **5a** · $NH_3$, **5e**, and **6e** did not bind to the benzodiazepine receptor, nor did **5c** and **6c** bind to the serotonine receptor. The binding of $^3$H-*N*-methylscopolamine, a standard radioligand, to muscarinic receptors of acetylcholine was unaffected by compounds **5a** · $NH_3$, **5c**, **6b**, **6c**, and **9** · HBr, but was decreased to 70% by Z-glycylmuscimol (**8**) at a concentration of 10 μmol/l.

Melting points are uncorrected, Büchi apparatus (system Dr. Tottoli); I.R. spectra: Perkin-Elmer 157 G or Beckman Acculab 4 spectrometers; $^1$H-N.M.R. spectra: Varian EM 360 (60 MHz), T 60 (60 MHz); $^{13}$C-N.M.R.: Bruker WH 400 (100.6 MHz).

**Methyl 3-Hydroxyisoxazole-5-carboxylate (4):**
Dimethyl acetylenedicarboxylate (**1**; 7.10 g, 50 mmol) is added with stirring at 0–10 °C to a solution of *N*-hydroxyurea (**2**; 3.80 g, 50 mmol) and 1,5-diazabicyclo[5.4.0]undec-5-ene (8.37 g, 55 mmol) in methanol (50 ml). Evaporation of the solvent leaves a red oil, which is dissolved in water (20 ml) and acidified to pH 1 by addition of concentrated hydrochloric acid (added with ice cooling). The solution is extracted with ether (3 × 25 ml, and then 2 × 25 ml after saturation with sodium chloride). The combined extracts are dried with sodium sulfate, concentrated in vacuo, and dried with phosphorus pentoxide/potassium hydroxide to give a yellow solid [yield: 5.70 g; m.p. 161–164 °C] which is purified by recrystallization from chloroform; yield: 5.17 g (72%); m.p. 164–165 °C. (Ref.[10], m.p. 165 °C).

**3-Hydroxyisoxazole-5-(*N*-methyl)-carboxamide (5b); Typical Procedure A:**
The methyl ester **4** (840 mg, 5.87 mmol) is added portionwise with stirring to a mixture of 40% aqueous methylamine and methanol (2 ml each). After 1 h at room temperature the solvents are evaporated, the residue is taken up in methanol (8 ml) and shaken for 10 min with acidic ion exchange resin (Lewatit S 100 G1, with indicator; 6 g, 10.2 mmol). The precipitate formed during this operation is redissolved in dichloromethane (4 ml). The resin is filtered off and washed thoroughly with dichloromethane. From the solutes, after concentration and drying in vacuo, the crude amide **5b** is obtained as a colourless solid (613 mg, 74%; spectroscopically pure, m.p. 216–217 °C) which is recrystallized from ethanol; yield: 507 mg (65%); colourless needles; m.p. 218 °C (Table).

| | | | | |
|---|---|---|---|---|
| $C_5H_6N_2O_3$ | calc. | C 42.25 | H 4.26 | N 19.71 |
| (142.1) | found | 42.13 | 4.14 | 19.70 |

**3-Hydroxyisoxazole-5-(*N*-isopropyl)-carboxamide (5c):**
Prepared as described in Typical Procedure A from the ester **4** (150 mg, 1.05 mmol) and dry isopropylamine (4 ml) with stirring overnight at room temperature. Work up as described with rinsing of the resin with methanol, gives the crude amide **5c** [pure by $^1$H-N.M.R.; yield: 165 mg (93%); m.p. 198–200 °C], which is purified by crystallization from chloroform; yield: 143 mg (88%); colourless needles, m.p. 200–201 °C (Table).

| | | | | |
|---|---|---|---|---|
| $C_7H_{10}N_2O_3$ | calc. | C 49.40 | H 5.92 | N 16.46 |
| (170.2) | found | 49.37 | 5.85 | 16.24 |

**3-Hydroxyisoxazole-5-(*N*-pyrrolidino)-carboxamide (5d):**
Procedure A is followed using ester **4** (2.40 g, 16.8 mmol) and dry pyrrolidine (10 ml); reaction time 15 min; work-up as above using ion exchange resin (20 g, 34 mmol); yield: 2.72 g (90%); colourless needles (from methanol); m.p. 212–213 °C (Table).

| | | | | |
|---|---|---|---|---|
| $C_8H_{10}N_2O_3$ | calc. | C 52.74 | H 5.543 | N 15.38 |
| (182.2) | found | 52.68 | 5.49 | 15.22 |

**3-Hydroxyisoxazole-5-(*N*-morpholino)-carboxamide (5e):**
Procedure A is followed using the ester **4** (734 mg, 5.13 mmol) and dry morpholine (4 ml); reaction time 1 h at room temperature; work-up as above using the acidic resin (10 g, 17 mval) gives the spec-

**Table.** Spectral Data for Compounds **5**, **6**, **8** and **9** prepared

| Product | I.R. (KBr) $\nu$ [cm$^{-1}$] | $^1$H-N.M.R. (60 MHz) $\delta$ [ppm][a] | | | | | $^{13}$C-N.M.R. (100.6 MHz) $\delta$ [ppm][b,f] | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | solvent | 4-H | 5′-H | $R^1$ | $R^2$ | solvent | C-3 | C-4 | C-5 | C-5′ | $R^1$ | $R^2$ |
| **5b** | 3400–2400 (b, m), 3145 (m), 1730 (s), 1620 (m), 1510 (m) | DMSO-$d_6$ | 6.40 (s) | – | 2.60, 2.65 | 8.35 (br.s) | DMSO-$d_6$ | 170.3 | 97.2 | 156.3 | 163.6 | 25.6 | – |
| **5c** | 3500–2400 (b, m), 3250 (s), 1705 (s), 1600 (s), 1525 (s) | $CD_3OD$ | 5.95 (s) | – | 1.80 [d, $J$ = 6 Hz, $CH(CH_3)_2$]; 3.60 [sept, $J$ = 6 Hz, $CH(CH_3)_2$] (no $R^2$) | | $CD_3OD$ | 172.0 | 98.6 | 157.4 | 164.9 | 22.9 [$CH(CH_3)_2$]; 42.9 [$CH(CH_3)_2$] | – |
| **5d** | 3400–2400 (b, m), 2890 (m), 1600 (s), 1450 (s), 1345 (s) | $CD_3OD$ | 6.45 (s) | – | 1.60–2.20 (m, $CH_2CH_2CH_2CH_2$); 3.35–3.90 (m, $CH_2NCH_2$) | | $CD_3OD$ | 170.0 | 98.6 | 155.3 | 164.0 | 23.3, 25.8 ($CH_2CH_2CH_2CH_2$); 46.6, 47.3 ($CH_2NCH_2$); | |
| **5e** | 3200–2400 (b, m), 1600 (s), 1400 (m), 1395 (s) | DMSO-$d_6$ | 6.40 (s) | – | 3.60 (′s′) | | DMSO-$d_6$ | 169.9 | 98.4 | 156.8 | 163.0 | 42.2, 46.6 ($CH_2NCH_2$); 65.8, 66.1 ($CH_2OCH_2$) | |
| **6b** | 3130 (m), 3100–1900 (b, s), 1535 (s), 1515 (s), 1460 (s) | $D_2O$ | 5.80 (s) | 4.15 (s) | 2.65 | – | $D_2O$ | 178.1 | 101.8 | 162.7 | 33.2 | 44.3 | – |
| **6c** | 3115 (m), 3160–1900 (b, m), 1620 (s), 1495 (s) | $D_2O$ | 5.80 (s) | 4.05 (s) | 1.30 [d, $J$ = 7 Hz, $CH(CH_3)_2$]; 3.30 [sept, $J$ = 7 Hz, $CH(CH_3)_2$] (no $R^2$) | | $D_2O$ | 178.4 | 100.4 | 165.2 | 50.0 | 19.7 [$CH(CH_3)_2$]; 50.6 [$CH(CH_3)_2$] | – |
| **6d** · HCl | 3600–2200 (b, m), 3120 (m), 1625 (s), 1510 (s) | $CD_3OD$ | 6.05 (s) | 4.30 (s) | 1.75–2.20 (m, $CH_2CH_2CH_2CH_2$); ~3.10–3.50 (m[c], $CH_2NCH_2$) | | $CD_3OD$ | 172.0 | 100.0 | 163.9 | ~49[c] | 24.1 ($CH_2CH_2CH_2CH_2$); 55.4 ($CH_2NCH_2$) | |
| **6e** · HCl | 3500–2400 (b, m), 3110 (s), 1640 (s), 1535 (m) | $D_2O$ | 6.25 (s) | 4.40 (s) | 3.15–3.50 (m, $CH_2NCH_2$); 3.65–4.00 (m, $CH_2OCH_2$) | | $D_2O$[d] | 171.3 | 101.5 | 162.1 | 51.5[e] | 52.7 ($CH_2NCH_2$)[e]; 64.5 ($CH_2OCH_2$) | |
| **8** | 3410 (s), 3290 (s), 1740 (s), 1670 (s), 1635 (m) | $CDCl_3$/ $CD_3OD$ | 5.75 (s) | 4.15 (d, $J$ = 6 Hz) | 8.35–8.65 | 3.60 (d, $J$ = 6 Hz, $NHCH_2CO$); 4.95 (s, $C_6H_5CH_2O$); 7.30 (′s′, $C_6H_5$); 8.35–8.65 (NH) | DMSO-$d_6$ | 170.8[e] | 93.8 | 169.8 | 35.3 | 43.7 ($NHCH_2CO$); 66.0 ($C_6H_5CH_2O$); 128.1, 128.2, 128.7, 135.2 ($C_6H_5$); 156.9 (NHCOO); 170.5 ($CH_2CONH$)[e] | – |
| **9** · HBr | 3600–2400 (m), 3300 (s), 1675 (s), 1635 (s), 1575 (s) | $D_2O$ | 6.05 (s) | 4.00 (s) | 4.55 (s, $COCH_2N$) | – | $D_2O$ | 171.2[e] | 95.3 | 168.2 | 36.3 | 42.5 ($COCH_2N$); 171.7 ($CH_2CONH$)[e] | – |

[a] TMS as external standard when $D_2O$ is used as solvent.
[b] 1,4-Dioxane ($\delta$ = 67.3 ppm) as internal standard when $D_2O$ is used as solvent.
[c] Partially superimposed by $CD_3OD$ signals.
[d] $CD_3CN$ ($\delta$ = 1.8 ppm) as internal standard.
[e] Assignments may be reversed.
[f] Compare with the $^{13}$C-N.M.R. data of isoxazole[18] [$\delta$ = 149.1 (C-3); 103.7 (C-4); 157.9 ppm (C-5)] and 3-hydroxy-5-methylisoxazole[9c] [$\delta$ = 171.3, 170.3 (C-5, C-3); 93.8 (C-4); 12.7 ppm ($CH_3$)].

troscopically pure product [yield: 841 mg (83%); m.p. 194–195°C] which is recrystallized from methanol; yield: 735 mg (72%); colourless needles; m.p. unchanged (Table).

| | | | | |
|---|---|---|---|---|
| $C_8H_{10}N_2O_4$ | calc. | C 48.48 | H 5.09 | N 14.14 |
| (198.2) | found | 48.53 | 5.07 | 14.14 |

**Muscimol [5-(Ammoniomethyl)-isoxazole-3-olate; 6a]:**
The ammonium salt of **5a** (6.0 g, 41 mmol; obtained from **4** in quantitative yield[8]) is reduced to muscimol (**6a**) as described[8]; yield: 2.72 g (56%); m.p. 174–175°C [Ref.[8] (7 mmol run), yield: 51%; m.p. 176–178°C].

***N*-Methylmuscimol [5-(*N*-Methylammoniomethyl)-isoxazole-3-olate; 6b]; Typical Procedure B:**
To a suspension of the amide **5b** (184 mg, 2 mmol) in tetrahydrofuran (5 ml) is added within 15 min neat borane·dimethyl sulfide (0.6 ml, 6 mmol) by means of a syringe with vigorous stirring. The mixture is refluxed for 6 h, and a voluminous precipitate forms. After cooling to room temperature, dry methanol (1 ml) is added dropwise (caution: gas evolution) and the mixture kept overnight. Dry hydrogen chloride is introduced for 1 h at 10–20°C and then the mixture is refluxed for 1 h. Volatiles are removed by distillation at atmospheric pressure (bath temperature up to 110°C), then at 20 torr. The residue, after drying, consists of a viscous yellow material (1.84 g) containing a considerable amount of tetrahydrofuran (by $^1$H-N.M.R.). This syrup (1.80 g) is dissolved in water (8 ml) and poured on to a column containing strongly acidic ion exchange resin (Lewatit S 100 G1, with indicator; 15 g, 25.5 mval). The column material is rinsed with water until chloride elution has ceased (silver nitrate test), then with ethanol (50 ml) and water (50 ml). Column elution is effected with 2 normal aqueous ammonia, monitored by the ninhydrin test. From the eluate on concentration a brown oil (225 mg) is obtained, which crystallizes slowly. This is recrystallized from ethanol to give colourless platelets of **6b**; yield: 140 mg (57%); m.p. 141–142°C (Table).

| | | | | |
|---|---|---|---|---|
| $C_5H_8N_2O_2$ | calc. | C 46.87 | H 6.29 | N 21.86 |
| (128.1) | found | 46.80 | 6.47 | 21.59 |

***N*-Isopropylmuscimol [5-(*N*-Isopropylammoniomethyl)-isoxazole-3-olate; 6c]:**
Procedure B is followed on a 2 mmol scale and 5 h reflux with borane-dimethyl sulfide to give a colourless solid (784 mg), a portion (764 mg) of which is subjected to ion exchange purification, resulting again in a colourless solid; yield: 317 mg. A sample of this material (297 mg) is recrystallized from ethanol; yield: 224 mg (79%); colourless platelets; m.p. 175–176°C (Table).

| | | | | |
|---|---|---|---|---|
| $C_7H_{12}N_2O_2$ | calc. | C 53.83 | H 7.74 | N 17.94 |
| (156.2) | found | 53.65 | 8.02 | 17.53 |

***N*-Pyrrolidinomuscimol Hydrochloride [3-Hydroxy-5-(*N*-pyrrolidiniomethyl)-isoxazole Chloride; 6d·HCl]:**
Procedure B is followed, starting with amide **5d** (547 mg, 3.0 mmol) in tetrahydrofuran (12 ml) and borane·dimethyl sulfide (12 mmol). Reaction at reflux for 4.5 h produces a colourless, viscous residue (947 mg). A portion (934 mg) of this is recrystallized by dissolution in the minimum volume of hot acetonitrile (2–3 ml), filtering from a small amount of insolubles, and addition of dry ether until turbulence occurs; yield: 456 mg (75%); colourless powder; m.p. 112–113°C (Table).

| | | | | |
|---|---|---|---|---|
| $C_8H_{13}ClN_2O_2$ | calc. | C 46.96 | H 6.40 | N 13.69 |
| (204.7) | found | 46.79 | 6.21 | 13.29 |

***N*-Morpholinomuscimol Hydrochloride [3-Hydroxy-5-(*N*-morpholiniomethyl)-isoxazole Chloride; 6e·HCl]:**
Procedure B with amide **5e** (396 mg, 2.0 mmol) and borane·dimethyl sulfide (0.58 ml, 5.8 mmol) in tetrahydrofuran (8 ml) with reflux for 6.5 h gives a crude, sticky solid (498 mg). A portion of this product (458 mg) is crystallized from ethanol/water to yield two fractions of colourless platelets; 247 mg with m.p. 220–221°C and 73 mg with m.p. 219–220°C; total yield: 320 mg 79% (Table).

| | | | | |
|---|---|---|---|---|
| $C_8H_{13}ClN_2O_3$ | calc. | C 43.55 | H 5.94 | N 12.70 |
| (220.7) | found | 43.54 | 5.93 | 12.62 |

***N*-(*N*-Benzyloxycarbonylglycyl)-muscimol (Z-Glycylmuscimol; 8):**
To muscimol (**6a**; 178 mg, 1.5 mmol) dissolved in water (3 ml) sodium hydrogen carbonate (252 mg, 3 mmol) is added portionwise with stirring. After 5 min a solution of *N'*-succinimidyl *N*-benzyloxycarbonylglycinate[12] (**7**; 459 mg, 1.5 mmol) in acetonitrile (3 ml) is added and the mixture stirred for 6 h at room temperature. The mixture is cooled to 0°C (ice), acidified with concentrated hydrochloric acid (~ 0.5 ml), concentrated to about half of its volume in vacuo, and kept at 4°C overnight. The precipitate is collected by filtration, washed with ice/water, and dried, to afford colourless crystals of **8** [yield: 374 mg (82%) m.p. 159–161°C] suitable for conversion to **9** (see below). Recrystallization of a sample (11 mg) from 50% aqueous ethanol gives the analytically pure product **8** in the form of colourless platelets; yield: 8.5 mg (63%); m.p. 160–161°C (Table).

| | | | | |
|---|---|---|---|---|
| $C_{14}H_{15}N_3O_5$ | calc. | C 55.08 | H 4.95 | N 13.95 |
| (305.3) | found | 55.09 | 4.86 | 13.67 |

***N*-Glycylmuscimol Hydrobromide (9·HBr):**
The Z-protected dipeptide **8** (104 mg, 0.24 mmol) is dissolved in acetic acid saturated with hydrogen bromide (0.4 ml) by occasional swirling during 1 h (gas evolution). On addition of absolute ether (2 ml) a voluminous, colourless precipitate forms, which is kept at 4°C overnight. The liquid is removed by means of a pipette, the solid is washed repeatedly with absolute ether, and dried in vacuo to leave a cream-coloured powder; yield: 78 mg (91%); m.p. 179–183°C. Crystallization from 96% ethanol gives pale-yellow crystals in two fractions (68 mg; m.p. 182–184°C; 6 mg, m.p. 181–184°C); total yield: 74 mg (86%) (Table).

| | | | | |
|---|---|---|---|---|
| $C_6H_{10}BrN_3O_3$ | calc. | C 28.59 | H 4.00 | N 16.67 |
| (205.1) | found | 28.63 | 3.89 | 16.68 |

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