Synthesis of 2-(ω-Aminoalkyl)imidazolin-4-ones by Ring Chain Transformation of Lactam Derivatives with α-Aminoamides

Antje Rottmann and Jürgen Liebscher*

Institut für Chemie, Humboldt-Universität Berlin, Hessische Str. 1-2, D-10115 Berlin, Germany

Received April 2, 1996

Dedicated to the memory of Professor Nicholas Alexandrou

Reaction of *N*-methylamides of biogenic (*S*)-α-aminoacids **3** with lactam acetals **1** or lactim ethers **2** gives three types of products, *i.e.* *N*-methyl-α-lactamiminoamides **5** by condensation, 2-(ω-aminoalkyl)imidazolin-5-ones **7** or 2-(ω-lactamiminoalkyl)imidazolin-4-ones **8** by ring chain transformation. All products represent novel optically active derivatives of biogenic α-aminoacids.

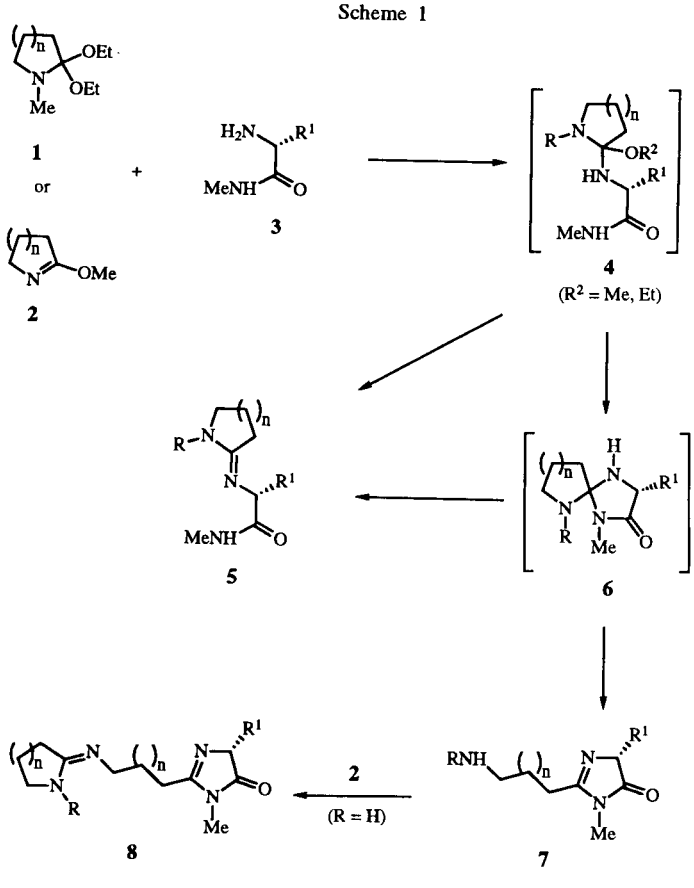
J. Heterocyclic Chem., **33**, 811 (1996).

Lactam acetals **1** and lactim ethers **2** were transformed to 2-(ω-aminoalkyl)azolines in reactions with binucleophilic α-aminoacids such as cysteine, penicillamine or serine bearing a second nucleophilic center (SH, OH) in the side chain [1]. In these reactions both nucleophilic centers of the aminoacid attacked the carbonyl carbon atom of the lactam derivatives forming a new azole ring. Resulting intermediate spiro compounds at last open the original lactam ring to afford the aminoalkyl chain of the final product (ring chain transformation). Depending on the ring size of the starting lactam derivative **1** or **2**, on the kind of nucleophilic center of the aminoacid and on the reaction conditions lactamimines, ω-lactamiminoalkylazolines or condensed imidazolidinones were formed as alternative products in some cases [1].

We report now on further investigations where (*S*)-α-aminoamides **3** were applied as binucleophiles in ring chain transformations of lactam derivatives **1** and **2** in order to synthesize novel derivatives of naturally occurring α-aminoacids. Although amide nitrogen atoms are weak nucleophilic sites, α-aminoamides turned out reactive enough to form imidazolinones in a smooth reaction with formamide acetals [2]. On the other hand simple amides of non-functionalized acids react with lactam acetals to give 2-acyliminopyrrolidines and higher homologs by electrophilic attack at the amide nitrogen atom [3].

Reactions of cyclic amide acetals **1** and lactim ethers **2** with α-aminoamides **3** turned out to be more complicated. Three types of products were obtained namely lactamimines **5**, 2-(ω-aminoalkyl)imidazolin-4-ones **7**, and 2-(ω-lactamiminoalkyl)imidazolin-4-ones **8**. The reaction pathway is very likely to start with an electrophilic attack of the lactam derivative **1** or **2** at the amino group of the α-aminoamide **3** followed by elimination of alcohol from the intermediate **4**. The non-ring transformed α-lactamiminoamides **5** could either be formed directly or eventually *via* a spirointermediate **6** which however could not be isolated or detected. The latter must act as transient compounds in the ring transformation to 2-(ω-aminoalkyl)imidazolinones **7**. If lactim ethers **2** had been used (*i.e.* R = H in **7**) the terminal amino group of **7** was further attacked by lactim ether **2** to give the 2-(ω-lactamiminoalkyl)imidazolinones **8**. Non-ring transformed amides **5** were obtained if the five-ring lactim ether **2** (n = 1) was used. Higher lactim ethers as well as five-ring and seven-ring lactam acetals **1** (n = 1, 3) afforded ring transformation to

Scheme 1



R	R¹	n	5	7	8
H	Me	1	a		
H	*i*-Pr	1	b		
H	Me	2			c
H	Me	3			d
H	*i*-Pr	3			e
Me	Me	1		f	
Me	Me	3		g	

2-(ω-lactamiminoalkyl)imidazolin-4-ones **8** or 2-(ω-aminoalkyl)imidazolin-4-ones **7** respectively. It is worth mentioning that lactamiminoalkylimidazolinones **8** were found as sole products too, if equimolar quantities of reactants **2** and **3** had been used. The yields however were less than 50% while unreacted starting material remained.

Although the results reported in Scheme 1 resemble reactions of lactam derivatives with binucleophilic aminoacids [1] the former reactions run in a smoother way, *i.e.* no mixtures of products were obtained and yields are generally high. In some cases however loss of product was found during the isolation and purification procedure. All products **5**, **7**, and **8** were obtained as highly viscous oils and were purified by Kugelrohr distillation. Although these compounds gave clean nmr-spectra no satisfactory microanalysis could be obtained. Attempts for further purification of the products by column chromatography failed because of their highly polar nature. Hence the molecular composition was determined by high resolution mass spectroscopy. Further structure elucidation of the products **5**, **7** and **8** was possible by spectroscopic methods. In the lactam derivative series (R = Me) typical shifts (δ = 2.6-2.75 ppm) of the *N*-methyl protons (R = Me) were found in the ^{1}H nmr spectra, which are characteristic for *N*-methylaminoalkyl chains attached to heterocycles [1] but do not fit into shift ranges expected for isomeric lactamimines **5**. Furthermore ring transformed ω-aminoalkylimidazolinones **7** (R = Me) exhibited m/z 44 as base peak in the mass spectra which is typical for ω-methylaminoalkylheterocycles. In the lactim ether derivative series (R = H) a corresponding basis peak m/z 30 which would appear in *N*-unsubstituted 2-(ω-aminoalkyl)imidazolin-5-ones **7** (R = H) was not found thus substantiating structure **5** rather than **7**.

By the aforementioned results it was possible to contribute an additional example to the versatile synthetic approach to partly ω-functionalized alkylazolines by the general ring chain transformation principle based on the reaction of lactones, lactams or their derivatives with binucleophiles [1,4,5,6,7]. It could be demonstrated that also weak binucleophiles, *i.e.* α-aminoamides **3** can be used as reactants. Novel derivatives of biogenic (*S*)-α-aminoacids were synthesized maintaining the optical activity of the starting material.

EXPERIMENTAL

General.

The ^{1}H nmr and ^{13}C nmr spectra were recorded at 300 and 75.5 MHz respectively on a Bruker AC-300 with TMS as internal standard. Mass spectra (HP 5995 A) and high-resolution mass spectra (MAT 711, Varian) were measured at 70eV. Optical rotation was determined with a Perkin Elmer polarimeter 241. Lactam derivatives **1** [11] and **2** [12] and α-aminoamides **3** [13] were prepared according to known procedures.

General Procedure for the Synthesis of Lactamiminoamides **5**, 2-(ω-Aminoalkyl)imidazolin-4-ones **7**, and 2-(ω-Lactamiminoalkyl)imidazolin-4-ones **8**.

A solution of lactam acetal **1** (5 mmoles) or lactim ether **2** (5 mmoles for **5** and **7**, 10 mmoles of **8**) in 10 ml of dry methanol was added to a stirred solution of (*S*)-α-amino-*N*-methylamide **3** (5 mmoles) in 30 ml of dry methanol. After reflux the solvent was evaporated under vacuum and the remaining product was purified by Kugelrohr distillation.

2(*S*)-*N*-Methyl-2-(pyrrolidin-2-ylidenamino)propionamide (**5a**).

After 2 hours of reflux and working up the product was obtained in 71% yield, bp 120-150°/0.5 mbar; α_D^{20} = + 21.0 (c 1.0 in chloroform); ^{1}H nmr (deuteriochloroform): δ 1.37-1.39 (d, J = 6.8 Hz, 3H, CH_3), 2.07-2.17 (m, 2H, CH_2), 2.69 (d, J = 4.5 Hz, 3H, N-CH_3), 2.83-2.88 (t, J = 8.0 Hz, 2H, CH_2), 3.56-3.59 (m, 1H, N-CH), 3.65-3.70 (t, J = 7.2 Hz, 2H, N-CH_2), 4.64-4.68 (m, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 18.2 CH_3, 20.6 CH_2, 26.2 N-CH_3, 31.1 CH_2, 48.1 N-CH_2, 53.1 N-CH, 167.7 C=N, 171.4 C=O; ms: m/z (relative intensity/%) 170 (M^++1, 2), 169 (M^+, 0.5), 111 (94), 69 (53), 44 (65), 41 (76), 30 (100), 28 (58), 15 (67); ir (chloroform): ν 3400, 2940, 1740, 1650 cm^{-1}; Exact mass calcd. for $C_8H_{15}N_3O$ (M+1): 170.1293. Found: 170.1296.

2(*S*)-*N*-Methyl-2-isopropyl-2-(pyrrolidin-2-ylidenamino)-acetamide (**5b**).

After 2 hours of reflux and working up the product was obtained in 61% yield, bp 120-160°/0.5 mbar; α_D^{20} = -9.3 (c 1.1 in chloroform), ^{1}H nmr (deuteriochloroform): δ 0.86-0.88 (d, J = 5.6 Hz, 3H, CH_3), 0.89-0.92 (d, J = 5.8 Hz, 3H, CH_3), 1.93-2.24 (m, 3H, CH, CH_2), 2.70 (d, J = 3.3 Hz, 3H, N-CH_3), 2.84-2.89 (q, J = 8.2 Hz, 2H, CH_2), 3.30-3.38 (m, 1H, N-CH), 3.60-3.66 (m, 2H, N-CH_2), 4.26-4.29 (m, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 18.3 CH_3, 18.6 CH_3, 20.5 CH_2, 25.9 N-CH_3, 31.0 CH, 31.1 CH_2, 47.9 N-CH_2, 63.8 N-CH, 168.3 C=N, 170.3 C=O; ms: m/z (relative intensity/%) 198 (M^++1, 3), 197 (M^+, 1), 154 (30), 139 (30), 67 (56), 58 (60), 51 (38), 45 (86), 42 (49), 30 (100), 28 (68), 15 (48); ir (chloroform): ν 3290, 2980, 2500, 1690, 1670, 1580, 1470, 1420 cm^{-1}; Exact mass calcd. for $C_{10}H_{19}N_3O$ (M+1): 198.1606. Found: 198.1607.

5(*S*)-2-(3-Methylaminopropyl)-3,5-dimethyl-3, 5-dihydroimidazol-4-one (**7f**).

After 3.5 hours of reflux and working up the product was obtained in 44% yield, bp 145-150°/0.5 mbar; α_D^{20} = +2.3 (c 1.1 in chloroform); ^{1}H nmr (deuteriochloroform): δ 1.23-1.26 (d, J = 6.9 Hz, 3H, CH_3), 1.87-1.97 (m, 2H, CH_2), 2.36-2.41 (m, 2H, CH_2), 2.75 (d, J = 4.9 Hz, 3H, N-CH_3), 2.82 (s, 3H, N-CH_3), 3.22-3.28 (sext, J = 2.8, 6.9 Hz, 2H, N-CH_2), 3.66-3.73 (dd, J = 6.9, 13.8 Hz, 1H, N-CH), 7.48 (br s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 19.4 CH_2, 20.9 CH_3, 25.7 N-CH_3, 26.4 CH_2, 31.4 N-CH_3, 51.4 N-CH_2, 59.3 N-CH, 163.7 C=N, 176.1 C=O; ms: m/z (relative intensity/%) 183 (M^+, 3), 182 (M^+-1, 5), 125 (100), 55 (25), 44 (95), 28 (52), 15 (74); ir (chloroform): ν 3450, 2950, 1740, 1700, 1660, 1505, 1405 cm^{-1}; Exact mass calcd. for $C_9H_{17}N_3O$ (M+1): 184.1449. Found: 184.1446.

5(*S*)-2-(5-Methylaminopentyl)-3,5-dimethyl-3,5-dihydroimidazol-4-one (**7g**).

After 3.5 hours of reflux and working up the product was obtained in 26% yield, bp 145-150°/0.5 mbar; α_D^{20} = -2.6 (c 0.2 in chloroform); ^{1}H nmr (deuteriochloroform): δ 1.17-1.18 (d, J = 6.9 Hz, 3H, CH_3), 1.18-1.74 (m, 6H, 3 x CH_2), 2.19-2.22 (t, J = 6.9 Hz, 2H, CH_2), 2.63 (s, 3H, N-CH_3), 2.92 (s, 3H, N-CH_3), 3.22-3.27 (m, 2H, N-CH_2), 3.60-3.62 (m, 1H, N-CH); ^{13}C nmr (deuteriochloroform): δ 24.3 CH_3, 24.3 CH_2, 24.3 CH_2, 26.1 N-CH_3, 29.7 2 x CH_2, 33.9 N-CH_3, 60.3 N-CH, 59.3 N-CH, 164.2 C=N, 174.3 C=O; ms: m/z (relative intensity/%) 211 (M^+, 1), 210 (M^+-1, 2), 69 (23), 51 (21), 44 (100), 28 (29); Exact mass calcd. for $C_{11}H_{21}N_3O$ (M+1): 212.1763. Found 212.1758.

5(*S*)-3,5-Dimethyl-2-[4-(piperidin-2-ylidenamino)butyl]-3,5-dihydroimidazol-4-one (**8c**).

After 2 hours reflux and working up the product was obtained in 88% yield, bp 130-170°/0.5 mbar; α_D^{20} = -57.9 (c 1.0 in chloroform); ^{1}H nmr (deuteriochloroform): δ 1.57-1.62 (m, 4H, 2 x CH_2), 1.73-1.77 (d, J = 6.7 Hz, 3H, CH_3), 2.23-2.28 (m, 2H, CH_2), 2.43-2.55 (m, 4H, 2 x CH_2), 2.66-2.73 (m, 2H, CH_2), 2.83-2.87 (m, 2H, N-CH_2), 3.31-3.36 (m, 2H, N-CH_2), 3.35 (s, 3H, N-CH_3), 3.56-3.58 (m, 1H, N-CH), ^{13}C nmr (deuteriochloroform): δ 18.1 CH_3, 20.7 CH_2, 20.9 CH_2, 21.8 CH_2, 23.6 CH_2, 26.2 N-CH_3, 28.3 CH_2, 33.1 CH_2, 42.2 N-CH_2, 45.7 N-CH_2, 51.5 N-CH, 164.8 C=N, 172.6 C=N, 174.2 C=O; ms: m/z (relative intensity/%) 264 (M^+, 0.1), 263 (M^+-1, 10), 139 (82), 125 (75), 111 (41), 98 (30), 82 (64), 69 (68), 55 (100), 45 (89), 41 (82), 30 (75), 28 (90), 15 (53), ir (chloroform): ν 3340, 3200, 2960, 1730, 1630 (br), 1455, 1420 cm^{-1}; Exact mass calcd. for $C_{14}H_{24}N_4O$ (M^+): 264.1950. Found: 264.1948.

5(*S*)-2-[5-(Azepan-2-ylidenamino)pentyl]-3,5-dimethyl-3,5-dihydroimidazol-4-one (**8d**).

After 2 hours of reflux and working up the product was obtained in 92% yield, bp 170-190°/0.5 mbar; α_D^{20} = -3.0 (c 1.0 in chloroform), ^{1}H nmr (deuteriochloroform): δ 1.18-1.38 (m, 4H, 2 x CH_2), 1.42-1.68 (m, 9H, 2 x CH_2, CH_3), 2.19-2.25 (sext, J = 7.3, 1.7 Hz, 2H, CH_2), 2.61-2.81 (m, 4H, 2 x CH_2), 2.77-2.93 (m, 2H, N-CH_2), 3.18-3.20 (m, 2H, N-CH_2), 3.35 (s, 3H, N-CH_3), 3.57-3.58 (m, 1H, N-CH); ^{13}C nmr (deuteriochloroform): δ 18.6 CH_3, 23.7 CH_2, 24.2 CH_2, 25.9 CH_2, 26.9 CH_2, 28.1 CH_2, 28.7 N-CH_3; 29.6 CH_2, 32.0 CH_2, 33.6 CH_2, 42.1 N-CH_2, 44.1 N-CH_2, 51.4 N-CH, 168.7 C=N, 169.5 C=N, 174.1 C=O, ms: m/z (relative intensity/%) 292 (M^+, 11), 291 (M^+-1, 19), 167 (21), 153 (33), 139 (40), 96 (100), 69 (45), 55 (52), 51 (30), 44 (45), 41 (71), 30 (67), 28 (40), 15 (44); Exact mass calcd. for $C_{16}H_{28}N_4O$ (M+1): 293.2341. Found 293.2343.

5(*S*)-2-[5-(Azepan-2-ylidenamino)pentyl]-3-methyl-5-isopropyl-3,5-dihydroimidazol-4-one (**8e**).

After 2 hours reflux and evaporating the solvent the pure product was obtained without distillation in 99% yield as an oil; α_D^{20} = -18.1 (c 1.1 in chloroform); ^{1}H nmr (deuteriochloroform): δ 0.85-0.88 (d, J = 6.7 Hz, 3H, CH_3), 0.91-0.93 (d, J = 6.9 Hz, 3H, CH_3), 1.31-1.69 (m, 10H, 5 x CH_2), 2.02-2.10 (m, 1H, CH), 2.19-2.27 (t, J = 7.6 Hz, 2H, CH_2), 2.30-2.37 (m, 2H, CH_2), 3.18-3.23 (t, J = 7.2 Hz, 2H, N-CH_2), 3.35 (s, 3H, N-CH_3), 3.36-3.39 (m, 2H, N-CH_2), 3.57-3.59 (m, 1H, N-CH); ^{13}C nmr (deuteriochloroform): δ 18.5 CH_3, 23.7 CH_2, 24.1 CH_2, 25.9 CH_2, 26.9 N-CH_3, 27.7 CH_2, 27.9 CH_2, 29.4 CH_3, 29.6 CH_2, 31.8 CH_2, 33.5 CH_2, 42.1 N-CH_2, 43.9 N-CH_2, 61.9 N-CH, 168.5 C=N, 169.0 C=N, 170.0 C=O; ms: m/z (relative intensity/%) 321 (M^++1, 0.4), 320 (M^+, 1.4), 167 (23), 153 (29), 139 (40), 96 (100), 69 (52), 55 (56), 45 (44), 41 (67), 30 (57), 15 (33); ir (chloroform): ν 3240, 3140, 2950, 1740, 1690, 1655, 1450 cm^{-1}; Exact mass calcd. for $C_{18}H_{32}N_4O$ (M+1): 321.2654. Found: 321.2650.

Acknowledgment.

We greatly acknowledge funding of the project by Deutsche Forschungsgemeinschaft and financial support by Fonds der Chemischen Industrie.

REFERENCES AND NOTES

[1] A. Rottmann and J. Liebscher, *J. Prakt. Chem.*, **337**, 548 (1995).

[2] B. Stanovnik and M. Tisler, *Synthesis*, 120 (1973).

[3] J. Liebscher, M. Pätzel and Y. F. Kelboro, *Synthesis*, 672 (1989).

[4] A. Botta, *Liebigs Ann. Chem.*, 336 (1976).

[5] H. Wammhoff and F. Korte, *Synthesis*, 151 (1972).

[6] R. L. Reitz, T. W. Hutton and S. N. Lewis, US-Patent, 4,247,671; *Chem. Abstr.*, **95**, 99433 (1982).

[7] J. P. Lokensgard, P. B. Comita and K. M. Rowland, *J. Org. Chem.*, **42**, 1467 (1977).

[8] S. P. McManus, P. J. Kelly, N. J. Patterson and C. U. Pittmann, *J. Org. Chem.*, **41**, 1642 (1976).

[9] E. M. Roberts, US-Patent, 3,399,197; *Chem. Abstr.*, **69**, 87028 (1968).

[10] A. Shpital'nyi, E. A. Meos and K. E. Perpelkin, *Zh. Obshch. Khim.*, **23**, 1382 (1953).

[11] V. G. Granik, A. M. Zhidkova, N. S. Kuryatov, V. P. Pakhomov and R. G. Glushkov, *Khim. Geterotsikl. Soedin.*, 1532 (1973).

[12] H. Lüssi, *Chimia*, **27**, 65 (1973).

[13] M. Iqbal, R. Nagarai and P. Balaram, *Int. J. Peptide Protein Res.*, **18**, 208 (1981).