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UNUSUAL AMINO ACIDS
VII. ASYMMETRIC SYNTHESIS OF 3- AND 4-PYRIDYLALANINES

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Abstract: (*Z*)-2-*N*-Acylamino-3-pyridyl-acrylic acids and their esters were prepared by partially known procedures and hydrogenated in the presence of HBF_4 to the corresponding optically active 2-*N*-acetyl-(or benzoyl-)-3-(3- or 4-pyridyl)-alanines or analogous methyl esters with enantiomeric excesses up to 90%. The rhodium complexes of PROPRAPHOS, **6a,b,** or of *O,N*-bis(diphenylphosphino)-2-*exo*-hydroxy, 3-*endo*-methylamino-norbor-nane, **6c**, as chiral catalysts have been used in the presence of HBF_4 to generate the corresponding pyridinium salts. Deacylation of the recrystallized amino acid derivatives or further recrystallization of the free amino acids yielded enantiomerically pure D- and L-pyridylalanines.

Introduction

It is well known that pyridylalanines and substituted analogues exhibit diverse pharmacological effects when introduced in biologically active systems.[1] Replacement of L-histidine in angiotensin II,[2] antagonists of phenylalanine,[3] and numerous pharmaceuticals[4-5] are only some examples concerning the importance of this type of unusual amino acids. Several routes are to be found in the literature to obtain either the racemic 2-, 3- or 4-pyridylalanines via the malonate,[6] the azlactone/acrylic acid[7] or the oxazolone method.[8] To achieve the homochiral amino acids in most approaches the resolution techniques with tartaric acid[9-10] or the enzymatic resolution of methyl 2-acetamido-pyridylpropanoates[2,11-14] or of methyl 2-benzamido-pyridylpropanoates[4,15-16] have been applied. Only two papers have been appeared describing the route of asymmetric hydrogenation to accomplish 3- or 4-pyridylalanines.[17-18] In ref.[17] the catalyst (*R,R*)- or (*S,S*)-[Rh-DIPAMP(COD)]BF_4 (65-70 psi, 24 h, 40-50 °C) gave the *N*-acetamido-pyridylalanine ester in 86-99 % ee whereas in ref.[18] Rh-DIOP as catalyst provides at 50 °C, 48 h, substrate/rhodium=30 in the case of methyl 2-acetamido-3-(3-pyridyl)-acrylate only 34 % ee, and the corresponding 4-pyridyl derivative could not be hydrogenated. An analogous benzamido derivative resulted in 20 % ee under 4 atm. hydrogen pressure.

Results and Discussion

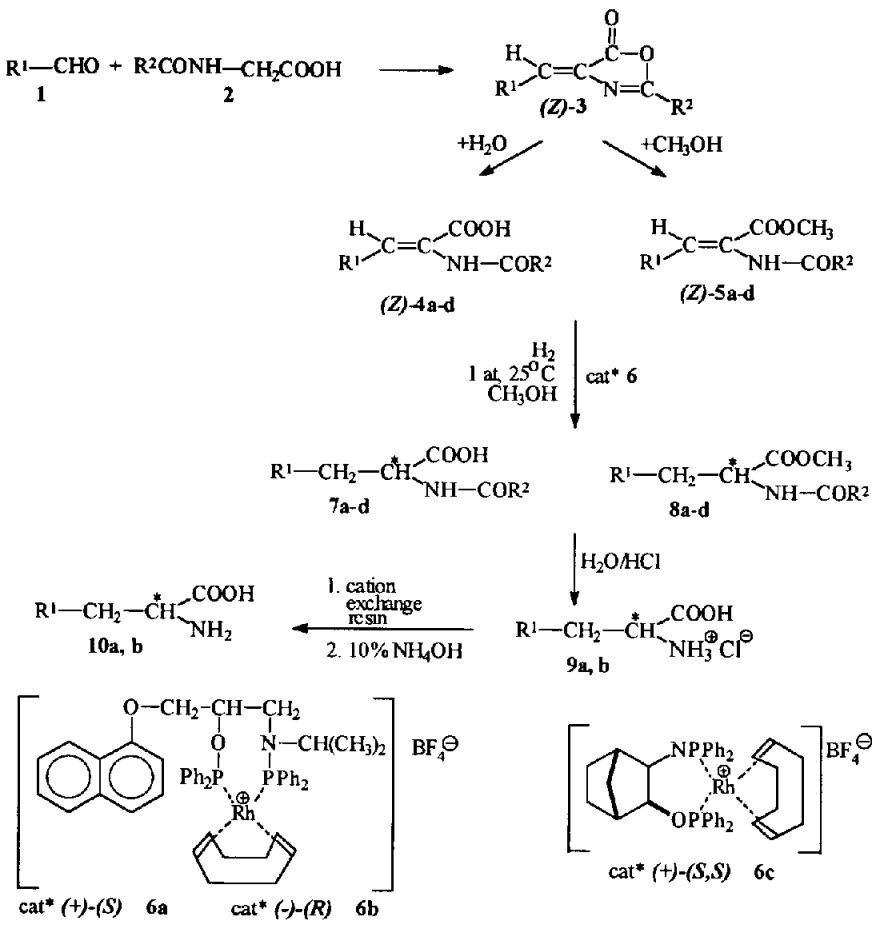
The enamides (*Z*)-**4a-d** and (*Z*)-**5a-d** as depicted in Scheme 1 were prepared by standard procedures[19] using the classical Erlenmeyer methodology. **4a-d** and **5a-d** were obtained without difficulties by reaction of the oxazolone with water or methanol, but synthesis of (*Z*)-2-benzamido-3-(2-pyridyl)-acrylic acid (and ester) was unsuccessful.[20] The hydrogenation reaction was catalyzed by the cationic rhodium complexes **6a-c** which have been previously applied in a series of asymmetric hydrogenations to provide unusual amino acid deri-vatives.[21] But, contrary to the earlier experiences, the asymmetric hydrogenation under normal pressure and at room temperature failed. This led us to the assumption that a close neighbourhood of the basic nitrogen and the metal may restrict the coordination of the bidentate substrate thereby blocking the formation of the active metal-substrate complex. This should be avoided by protonation of the basic pyridyl nitrogen taking non-complexing acids like HBF_4. Indeed, addition of a small excess of acid results in the normal catalysis. The results are shown in Table 1 and 2.

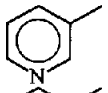
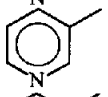
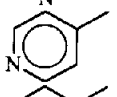
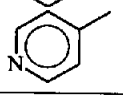
Table 1 Catalytic asymmetric hydrogenation of **4a-d**

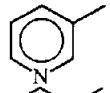
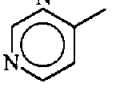
Entry	Substrate[a]	Catalyst	Substr./Cat.	Product (config.)	t/2 (min)[b]	ee (%)
1	**4a**	**6a**	100	**7a** (*R*)	2	89
2	**4a**	**6a**	500	**7a** (*R*)	16	85
3	**4a**	**6a**	1000	**7a** (*R*)	27	78
4	**4a**	**6c**	100	**7a** (*R*)	5	86
5	**4b**	**6a**	100	**7b** (*R*)	4	86[c]
6	**4c**	**6b**	100	**7c** (*S*)	2	89
7	**4c**	**6a**	500	**7c** (*R*)	15	84
8	**4c**	**6c**	100	**7c** (*R*)	6	82
9	**4d**	**6a**	100	**7d** (*R*)	3	87
10	**4d**	**6c**	100	**7d** (*R*)	5	74

Conditions: Catalyst 0.01 mmol, substrate 1-10 mmol, 15-25 ml MeOH, 25 °C, 0.1 MPa H_2. [a]Addition of 1.5 mmol HBF_4/mmol substrate. [b] t/2 time for the uptake of 50 % of the theoretical volume of hydrogen. The values give a rough indication of the rate. Exact measurements taking the diffusion control into account have not been performed. [c] Partial reaction with the MeOH to the ester **8b**.

The rhodium complexes **6a-6c** are again highly active giving rise to 84-90 % ee both for 3- and 4-pyridylalanine derivatives showing no significant differences in activity and selectivity between the *N*-acetyl- or *N*-benzoyl derivatives. At the end of the hydrogenation of **4a-d** (Table 1) carried out in methanol normally small amounts of the methylester could be detected in the reaction mixture increasing in case of **4b** to 30 % **8b**. The esterification obviously was catalyzed by the excessive HBF_4. (S)-**6a** yields R-configured pyridylalanine derivatives and vice versa in accordance with the results obtained on other enamide substrates.



3, 4, 5, 7, 8,	R¹	R²
a		CH_3
b		C_6H_5
c		CH_3
d		C_6H_5

9, 10	R¹	R²
a		-
b		-

SCHEME 1

6c furnishes R-configured product, the catalyst therefore is assumed to have the (*S*,*S*)-configuration. Hydrogenation of **5a-d** (Table 2) shows some advantages concerning the activity and selectivity allowing the upscaling of the substrate to rhodium ratio to 500-1000 mol/mol both for *N*-acetyl and *N*-benzoyl enamides.

Table 2 Catalytic asymmetric hydrogenation of **5a-d**

Entry	Substrate[a]	Catalyst	Subst/Cat.	Product (config.)	t/2 (min)	ee (%)	After Recr.
1	**5a**	**6b**	100	**8a** (*S*)	2	89	> 99[b]
2	**5a**	**6a**	1000	**8a** (*R*)	30	83	
3	**5a**	**6c**	100	**8a** (*R*)	4	84	
4	**5b**	**6a**	100	**8b** (*R*)	6	88	> 99[c]
5	**5b**	**6a**	500	**8b** (*R*)	25	84	
6	**5b**	**6a**	1000	**8b** (*R*)	40	81	
7	**5b**	**6c**	100	**8b** (*R*)	11	70	
8	**5c**	**6a**	100	**8c** (*R*)	2	89	> 99[c]
9	**5c**	**6a**	1000	**8c** (*R*)	25	86	
10	**5c**	**6c**	100	**8c** (*R*)	4	74	
11	**5d**	**6b**	100	**8d** (*S*)	3	90	
12	**5d**	**6a**	1000	**8d** (*R*)	25	86	

Conditions see Table 1. [a] Addition of 1.5 mmol HBF_4/mmol substrate. [b] From $CHCl_3$/hexane. [c] From ethylacetate/hexane.

Except for methyl 2-benzamido-3-(4-pyridyl)-propanoate, after work up and recrystallization enantiomerically pure esters (ee >99 %) could be isolated. In order to remove HBF_4 the *N*-acyl-esters were treated with alkaline and extracted with $CHCl_3$. Free *N*-acyl acids resulted via cation exchange resin by elution with NH_4OH.

Acidolysis of **7a-d, 8a-d** with HCl provides the hydrochlorides **9a** and **9b**, which by cation exchange and elution by diluted NH_4OH result in D-(or L-)3-(or 4-)pyridylalanines **10a** and **10b**. The compounds **7, 8** and **10** were characterized by the ^1H and ^{13}C NMR spectra. The NMR data are given in the experimental part. The assignment of the signals was additionally established by recording the DEPT and $^{13}C/^1H$ correlation spectra[22] for **8b** and **8d.**

Conclusion

The unusual amino acids 3- and 4- pyridylalanine or their esters are readily available by asymmetric hydrogenation when catalyzed by chiral rhodium complexes derived from aminophosphine phosphinites as e.g. PROPRAPHOS. The rate of hydrogenation depends decisively on the presence of additional non-complexing acids in order to protonate the basic nitrogen of the substrate which otherwise can interact with the rhodium in

the coordination sphere and lower or stop the reaction. The excessive acid do not influence the rate or selectivity which lies in the range observed in the hydrogenation of other enamides.

Experimental

^1H and ^{13}C NMR measurements were performed with DMSO-d_6 solutions of **7** and **8** and D_2O solutions of **10**, respectively, on a Bruker ARX-300 spectrometer (^1H: 300.13 MHz and ^{13}C: 75.47 MHz). The calibration of the DMSO-d_6 spectra was made using the solvent peaks (DMSO-d_6: δ ^1H=2.50, δ ^{13}C=39.7) and for calibration of the D_2O spectra 1.4-dioxane was used as internal standard (1.4-dioxane: δ ^1H=3.71, δ ^{13}C=67.6). For recording the DEPT and two-dimensional $^{13}C/^1H$ correlation spectra[22] for **8b** and **8d** the standard programs of Bruker have been used. The $^1H/^1H$ couplings were determined using Gaussian multiplication and a first-order analysis.

Optical rotation was measured on a GYROMAT-HP Polarimeter (Fa. Dr. Kernchen, Seelze). The enantiomeric excesses were determined by GLC on a Hewlett-Packard chromatograph 5880 A fitted with a silica fused 4 m capillary column XE-60 (*N*-L-valine-tert.butylamide, acetyl derivatives 162 °C, benzoyl derivatives 172 °C) for the acylated amino acid derivatives, for **7a-d** after esterification. HPLC measurements (**9,10**) were carried out on a Hewlett-Packard 1090 chromatograph Series II equipped with a CHROWNPAK CR column (eluent aqu. $HClO_4$, temp. 1 °C, detection by DAD and chiralizer). Melting points are uncor-rected and were determined on a Boetius microscope. The hydrogenation was carried out in standard apparatus. For GLC measurements of ee 1 ml of the hydrogenated solution was treated with solid Na_2SO_4/Na_2CO_3, **7a-d** were esterified by a freshly prepared solution of diazomethane. The other part was freed from the solvent. In order to get the free esters **8a-d**, the residue was treated with alkaline and extracted with $CHCl_3$. In case of the acids the HBF_4 was removed by binding the products to cation resin DOWEX 50. Subsequent elution with diluted NH_4OH results in the acid **7d**, the isolation of **7b** failed. The *N*-acetyl compounds **7a**, **7c** were obtained as ammonium salts, recrystallization of the latter yielded enantiomerically pure products (ee >99 %). Deacylation: The hydrogenation products **7a-d**, **8a-d**, the recrystallized free derivatives on the one hand, or the BF_4-derivatives from the reaction solution on the other hand, were refluxed in 6N HCl for 3 hours (acetyl derivatives) or in 10N HCl (benzoyl derivatives) for 6 hours. The solution was filtered and extracted with ether. The aqueous solution was treated with charcoal filtered and concentrated under reduced pressure at 35-40 °C. The crystals were washed several times with absolute acetone and dried over phosphorus pentoxide under vacuo giving the dihydrochlorides **9a,b**. Free amino acids **10a,b**, 70-86 % ee (from the reaction solution) or 94-97 % ee (recrystallized products) resulted from the hydrochlorides **9a,b** by cation exchange resin and elution by diluted NH_4OH. Recrystallization from H_2O/acetone gives enantio-merically pure compounds. All solvents were purified and dried by usual methods and stored, if necessary, under argon. Catalysts were prepared according to published methods.[21]

Ammonium-*N*-acetyl-3-(3-pyridyl)-D-alaninate 7a-NH_4

m. p. 181-183 °C (H_2O/acetone), $[\alpha]_D^{25}$ -87.1 (c 1, EtOH), 92 % ee (GLC). $C_{10}H_{15}N_3O_4$ (225.3), calcd. C 53.32 H 6.71 N 18.65, found C 53.39 H 6.97 N 18.85.

^{1}H NMR (DMSO-d_6): δ 8.36 (m, 2H, pyridyl H-2, pyridyl H-6), 7.73 (d, 1H, $J_{NH,CH}$~8.0, NH), 7.58 (ddd, 1H, $J_{4,5}$~7.8, $J_{4,2}$~2.0, $J_{4,6}$~2.0, pyridyl H-4), 7.25 (ddt, 1H, $J_{4,5}$~7.8, $J_{5,6}$~4.9, J~0.8, pyridyl H-5), 5.60 (br, 4 H, NH_4), 4.25 (ddd, 1H, $J_{CH,CH_2(A)}$~8.0, $J_{CH,NH}$~8.0, $J_{CH,CH_2(B)}$~4.9, CH), 3.07 (dd, 1H, J_{gem}~13.7, $J_{CH_2(B),CH}$~4.9, CH_2), 2.84 (dd, 1H, J_{gem}~13.7, $J_{CH_2(A),CH}$~8.0, CH_2), 1.76 (s, 3H, CH_3CO). ^{13}C NMR (DMSO-d_6): δ 173.5 (COO), 168.9 (NHCO), 150.4 (pyridyl C-2), 147.4 (pyridyl C-6), 136.8 (pyridyl C-4), 134.4 (pyridyl C-3), 123.3 (pyridyl C-5), 54.6 (CH), 34.9 (CH_2), 22.8 (CH_3CO).

Ammonium-*N*-acetyl-3-(4-pyridyl)-D-alaninate 7c-NH_4

m. p. 199-201 °C (H_2O/acetone), $[\alpha]_D^{25}$ -92.4 (c 1, EtOH, >99 % ee (GLC). $C_{10}H_{15}N_3O_4$ (225.3), found C 53.46 H 6.74 N 18.46.

^{1}H NMR (DMSO-d_6): δ 8.40 (m, 2H, pyridyl H-2,6), 7.78 (d, 1H, $J_{NH,CH}$~8.0, NH), 7.19 (m, 2H, pyridyl H-3, 5), 5.20 (br, 4H, NH_4), 4.30 (ddd, 1H, $J_{CH,CH_2(A)}$~8.3, $J_{CH,NH}$~8.0, $J_{CH,CH_2(B)}$~5.0, CH), 3.07 (dd, 1H, J_{gem}~13.8, $J_{CH_2(B),CH}$~5.0, CH_2), 2.84 (dd, 1H, J_{gem}~13.8, $J_{CH_2(A),CH}$~8.3, CH_2), 1.76 (s, 3H, CH_3CO). ^{13}C NMR (DMSO-d_6): δ 173.4 (COO), 168.8 (NHCO), 149.2 (pyridyl C-2,6), 148.0 (pyridyl C-4), 124.9 (pyridyl C-3,5), 54.0 (CH), 37.0 (CH_2), 22.7 (CH_3CO).

***N*-Benzoyl-3-(4-pyridyl)-D-alanine 7d**

m. p. 246-248 °C (EtOH), ref.[23] 246 °C (rac.), ref.[6] 250 °C (rac.); $[\alpha]_D^{25}$ 98.6 (c 1, 1N HCl), 84 % ee (GLC). $C_{15}H_{14}N_2O_3$ (270.3), calcd. C 66.65 H 5.22 N 10.37, found C 66.78 H 5.16 N 10.53.

^{1}H NMR (DMSO-d_6): δ 8.75 (d, 1H, $J_{NH,CH}$~8.2, NH), 8.46 (m, 2H, pyridyl H-2, 6), 7.79 (m, 2H, ortho-ph), 7.52 (m, 1H, para-ph), 7.46 (m, 2H, meta-ph), 7.33 (m, 2H, pyridyl H-3, 5), 4.72 (ddd, 1H, $J_{CH,CH_2(A)}$~10.7, $J_{CH,NH}$~8.2, $J_{CH,CH_2(B)}$~4.6, CH), 3.24 (dd, 1H, J_{gem}~14.0, $J_{CH_2(B),CH}$~4.6, CH_2), 3.11 (dd, 1H, J_{gem}~14.0, $J_{CH_2(A),CH}$~10.7, CH_2). ^{13}C NMR (DMSO-d_6): δ 172.8 (COO), 166.5 (NHCO), 149.5 (pyridyl C-2, 6), 147.3 (pyridyl C-4), 133.9 (ipso-ph), 131.5 (para-ph), 128.4 (meta-ph), 127.4 (ortho-ph), 124.6 (pyridyl C-3, 5), 53.1 (CH), 35.6 (CH_2).

Methyl *N*-acetyl-3-(3-pyridyl)-D-alaninate 8a

m. p. 101-103 °C ($CHCl_3$/hexane), ref.[17] 105-106 °C; $[\alpha]_D^{25}$ -103.4 (c 1, $CHCl_3$), >99 % ee (GLC), ref.[17] $[\alpha]_D^{25}$ -105.6 (c 1.8, $CHCl_3$), 86 % ee, L-compound $[\alpha]_D^{25}$ 105.1 (c 1.08, $CHCl_3$), >99 % ee. $C_{11}H_{14}N_2O_3$ (222.3), calcd. C 59.45 H 6.35 N 12.61, found C 59.52 H 6.42 N 12.48.

^{1}H NMR (DMSO-d_6): δ 8.42 (m, 2H, pyridyl H-2, 6), 8.35 (d, 1H, $J_{NH,CH}$~8.0, NH), 7.64 (ddd, 1H, $J_{4,5}$~7.8, $J_{4,2}$~2.0, $J_{4,6}$~2.0, pyridyl H-4), 7.30 (ddt, 1H, $J_{5,4}$~7.8, $J_{5,6}$~4.7, J~0.8, pyridyl H-5), 4.49 (ddd, 1H, $J_{CH,CH_2(A)}$~9.4, $J_{CH,NH}$~8.0, $J_{CH,CH_2(B)}$~5.3, CH), 3.61 (s, 3H, OCH_3), 3.05 (dd, 1H, J_{gem}~13.9, $J_{CH_2(B),CH}$~5.3,

CH_2), 2.89 (dd, 1H, J_{gem}~13.9, $J_{CH_2(A),CH}$~9.4, CH_2), 1.78 (s, 3H, CH_3CO). ^{13}C NMR (DMSO-d_6): δ 172.0 (COO), 169.5 (NHCO), 150.3 (pyridyl C-2), 147.9 (pyridyl C-6), 136.7 (pyridyl C-4), 133.0 (pyridyl C-3), 123.4 (pyridyl C-5), 53.2 (CH), 52.0 (OCH_3), 34.0 (CH_2), 22.3 (CH_3CO).

Methyl *N*-benzoyl-3-(3-pyridyl)-D-alaninate 8b

m. p. 108-109 °C (ethylacetate/hexane), ref.[11] 109-110 °C; $[\alpha]_D^{25}$ 75.9 (c 1, MeOH), $[\alpha]_D^{25}$ 91.9 (c 1, DMF), >99 % ee (GLC), ref.[11] $[\alpha]_D$ 76.5 (c 1, MeOH), ref.[15] $[\alpha]_D^{25}$ 84.5 (c 1, DMF) ref.[16] $[\alpha]_D^{25}$ 89.5 (c 1, DMF). $C_{16}H_{16}N_2O_3$ (284.3), calcd. C 67.59 H 5.67 N 9.85, found C 67.67 H 5.77 N 9.81.

^1H NMR (DMSO-d_6): δ 8.88 (d, 1H, $J_{NH,CH}$~8.0, NH), 8.51 (br, 1H, pyridyl H-2), 8.40 (br, 1H, pyridyl H-6), 7.79 (m, 2H, ortho-ph), 7.72 (ddd, 1H, $J_{4,5}$~7.8, $J_{4,2}$~2.0, $J_{4,6}$~2.0, pyridyl H-4), 7.52 (m, 1H, para-ph), 7.46 (m, 2H, meta-ph), 7.29 (dd, 1H, $J_{5,4}$~7.8, $J_{5,6}$~4.7, pyridyl H-5), 4.73 (ddd, 1H, $J_{CH,CH_2(A)}$~10.4, $J_{CH,NH}$~8.0, $J_{CH,CH_2(B)}$~5.2, CH), 3.66 (s, 3H, OCH_3), 3.23 (dd, 1H, J_{gem}~13.9, $J_{CH_2(B),CH}$~5.2, CH_2), 3.12 (dd, 1H, J_{gem}~13.9, $J_{CH_2(A),CH}$~10.4, CH_2). ^{13}C NMR (DMSO-d_6): δ 172.0 (COO), 166.6 (NHCO), 150.4 (pyridyl C-2), 147.9 (pyridyl C-6), 136.7 (pyridyl C-4), 133.7 (ipso-ph), 133.4 (pyridyl C-3), 131.6 (para-ph), 128.4 (meta-ph), 127.4 (ortho-ph), 53.8 (CH), 52.1 (OCH_3), 33.5 (CH_2).

Methyl *N*-acetyl-3-(4-pyridyl)-D-alaninate 8c

m. p. 77-79 °C (ethylacetate/hexane), $[\alpha]_D^{25}$ -99.8 (c 1, $CHCl_3$), >99 % ee (GLC), ref.[17] $[\alpha]_D^{25}$ -78.5 (c 1.36, $CHCl_3$), 92 % ee, L-compound: $[\alpha]_D^{25}$ 84.7 (c 1.04, $CHCl_3$), 94 % ee. $C_{11}H_{14}N_2O_3$ (222.3), calcd. C 59.45 H 6.35 N 12.61, found C 59.64 H 6.53 N 12.58.

^1H NMR (DMSO-d_6): δ 8.46 (m, 2H, pyridyl H-2, 6), 8.36 (d, 1H, $J_{NH,CH}$~8.0, NH), 7.24 (m, 2H, pyridyl H-3,5), 4.54 (ddd, 1H, $J_{CH,CH_2(A)}$~9.6, $J_{CH,NH}$~8.0, $J_{CH,CH_2(B)}$~5.3, CH), 3.62 (s, 3H, OCH_3), 3.05 (dd, 1H, J_{gem}~13.9, $J_{CH_2(B),CH}$~5.3, CH_2), 2.90 (dd, 1H, J_{gem}~13.9, $J_{CH_2(A),CH}$~9.6, CH_2), 1.78 (s, 3H, CH_3CO). ^{13}C NMR (DMSO-d_6): δ 171.9 (COO), 169.5 (NHCO), 149.6 (pyridyl C-2,6), 146.5 (pyridyl C-4), 124.6 (pyridyl C-3, 5), 52.6 (CH), 52.1 (OCH_3), 36.0 (CH_2), 22.3 (CH_3CO).

Methyl *N*-benzoyl-3-(4-pyridyl)-D-alaninate 8d

Oil, that crystallized slowly upon standing for several month. $[\alpha]_D^{25}$ -84.3 (c 1, $CHCl_3$), 86 % ee (GLC). $C_{16}H_{16}N_2O_3$ (284.3), calcd. C 67.59 H 5.67 N 9.85, found C 67.30 H 5.60 N 9.60.

^1H NMR (DMSO-d_6): δ 8.88 (d, 1H, $J_{NH,CH}$~8.0, NH), 8.46 (m, 2H, pyridyl, H-2,6), 7.78 (m, 2H, ortho-ph), 7.52 (m, 1H, para-ph), 7.46 (m, 2H, meta-ph), 7.32 (m, 2H, pyridyl H-3, 5), 4.77 (ddd, 1H, $J_{CH,CH_2(A)}$~10.4, $J_{CH,NH}$~8.0, $J_{CH,CH_2(B)}$~5.3, CH), 3.66 (s, 3H, OCH_3), 3.22 (dd, 1H, J_{gem}~13.7, $J_{CH_2(B),CH}$~5.3, CH_2), 3.12 (dd, 1H, J_{gem}~13.7, $J_{CH_2(A)CH}$~10.4, CH_2). ^{13}C NMR (DMSO-d_6): δ 171.9 (COO), 166.6 (NHCO), 149.5 (pyridyl C-2,6), 146.8 (pyridyl C-4), 133.7 (ipso-ph), 131.7 (para-ph), 128.4 (meta-ph), 127.4 (ortho-ph), 124.6 (pyridyl C-3,5), 53.2 (CH), 52.2 (OCH_3), 35.6 (CH_2).

3-(3-Pyridyl)-D-alanine-dihydrochloride 9a

m. p. 238-242 °C, ref.[16] 239-241 °C, $[\alpha]_D^{25}$ -19.5 (c 1, H_2O), 97 % ee (HPLC), ref.[16] $[\alpha]_D^{25}$ -18.15 (c 1, 1N HCl). $C_8H_{12}Cl_2N_2O_2$ (239.1), calcd. C 40.18 H 5.06 N 11.72 Cl 29.65, found C 40.11 H 5.10 N 11.53 Cl 29.47.

3-(4-Pyridyl)-D-alanine-dihydrochloride 9b

m. p. 234-238 °C, $[\alpha]_D^{25}$ -22.3 (c 1, H_2O), 96 % ee (HPLC). $C_8H_{12}Cl_2N_2O_2$ (239.1), found C 40.03 H 4.98 N 11.59 Cl 29.40.

3-(3-Pyridyl)-D-alanine 10a

m. p. 250-253 °C, ref.[12] 253-256 °C, ref.[16] 259-260 °C; $[\alpha]_D^{25}$ -24.6 (c 1, 1N HCl), >99 % ee (HPLC), ref.[12] $[\alpha]_D^{25}$ -26.1 (c 1, 1N HCl), ref.[16] $[\alpha]_D^{25}$ -26.3 (c 1, 1N HCl). $C_8H_{10}N_2O_2$ (166.2), calcd. C 57.82 H 6.06 N 16.86, found C 57.57 H 6.01 N 16.61.

^{1}H NMR (D_2O): δ 8.38 (dd, 1H, $J_{6,5}$~5.0, $J_{6,4}$~1.7, pyridyl H-6), 8.34 (dd, 1H, $J_{2,4}$~2.3, $J_{2,5}$~0.9, pyridyl H-2), 7.71 (ddd, 1H, $J_{4,5}$~7.9, $J_{4,2}$~2.3, $J_{4,6}$~1.7, pyridyl H-4), 7.37 (ddd, 1H, $J_{5,4}$~7.9, $J_{5,6}$~5.0, $J_{5,2}$~0.9, pyridyl H-5), 3.95 (dd, 1H, $J_{CH,CH_2(A)}$~7.2, $J_{CH,CH_2(B)}$~5.8, CH), 3.20 (dd, 1H, J_{gem}~14.7, $J_{CH_2(B),CH}$~5.8, CH_2), 3.12 (dd, 1H, J_{gem}~14.7, $J_{CH_2(A),CH}$~7.2, CH_2). ^{13}C NMR (D_2O): δ 174.4 (COO), 150.1 (pyridyl C-2), 148.8 (pyridyl C-6), 139.4 (pyridyl C-4), 132.7 (pyridyl C-3), 125.5 (pyridyl C-5), 56.6 (CH), 34.6 (CH_2).

3-(4-Pyridyl)-D-alanine 10b

m. p. 246-248 °C, ref.[9] 248-250 °C; $[\alpha]_D^{25}$ -34.5 (c 1, 1N HCl), >99 % ee (HPLC), ref.[11] $[\alpha]_D^{18}$ -35.0 (c 1, 1N HCl). $C_8H_{10}N_2O_2$ (166.2), found C 57.61 H 6.23 N 16.69.

^{1}H NMR (D_2O): δ 8.44 (m, 2H, pyridyl H-2,6), 7.34 (m, 2H, pyridyl H-3,5), 4.01 (dd, 1H, $J_{CH,CH_2(A)}$~7.6, $J_{CH,CH_2(B)}$~5.7, CH), 3.26 (dd, 1H, J_{gem}~14.5, $J_{CH_2(B),CH}$~5.7, CH_2), 3.14 (dd, 1H, J_{gem}~14.5, $J_{CH_2(A),CH}$~7.6, CH_2). ^{13}C NMR (D_2O): δ 174.3 (COO), 150.0 (pyridyl C-2,6), 147.2 (pyridyl C-4), 126.2 (pyridyl C-3,5), 56.2 (CH), 36.9 (CH_2).

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References

1. See reviews on amino acid analogues: (a) Roberts, D. C.; Vellaccio, F. *The Peptides*; Academic Press: New York, **1983**, Vol. 5, Chapter 6, 341. (b) Wilson, M. J.; Hatfield, D. L. *Biochim. Biophys. Acta* **1984**, 781, 205. (c) Lea, P. J.; Norris, R. D. *Phytochemistry* **1976**, 15, 585.
2. Hsieh, K.; Jorgensen, E. C. *J. Med. Chem.* **1979**, 22, 1199.
3. Sullivan, P. T.; Kester, M.; Norton, S. J. *J. Med. Chem.* **1968**, 11, 1172.
4. Shimeno, H.; Soeda, S.; Nagamatsu, A. *Chem. Pharm. Bull.* **1977**, 25, 2983.

5. JP 60/130591 A 2, **1985**; EP 98609 A 2, **1984.**
6. Agafonova, G. A.; Gerasimova, N. E.; Guseva, M. V.; Krainova, B. L.; Petrova, T. V.; Pozdnev, V. F.; Chaman, E. S. *Zh. Obshch. Khim.* **1970**, 40, 2502.
7. Griffith, R. K.; Harwood, H. J. *J. Org. Chem.* **1964**, 29, 2658.
8. Ali, M.; Khan, N. H.; Siddiqui, A. A. *Synth. Commun.* **1976**, 6, 227.
9. Weselova, L. N.; Chaman, E. S. *Zh. Obshch. Khim.* **1972**, 42, 1123.
10. Weselova, L. N.; Chaman, E. S. *Zh. Obshch. Khim.* **1973**, 43, 1637.
11. Chen, S. T.; Hsiao, S. C.; Chiou, A. J.; Wu, S. H.; Wang, K. T. *J. Chin. Chem. Soc.* **1992**, 39, 91.
12. Rivier, J. E.; Porter, J.; Rivier, C. L.; Perrin, M.; Corrigan, A.; Hook, W. A.; Siraganian, R. P.; Vale, W.W. *J. Med. Chem.* **1986**, 29, 1846.
13. Rao, P. N.; Burdett Jr., J. E.; Cessac, J. W.; DiNunno, C. M.; Peterson, D. M.; Kim, H. K. *Int. J. Peptide Protein Res.* **1987**, 29, 118.
14. Hoes, C.; Raap, J.; Bloemhoff, W.; Kerling, K. E. T. *Recl. Trav. Chim. Pays-Bas* **1980**, 99, 99.
15 Voskuyl-Holtkamp, I.; Schattenkerk, C. *Int. J. Peptide Protein Res.* **1979**, 13, 185.
16. Folkers, K.; Kubiak, T.; Stepinski, J. *Int. J. Peptide Protein Res.* **1984**, 24, 197.
17. Bozell, J. J.; Vogt, C. E.; Gozum, J. *J. Org. Chem.* **1991**, 56, 2584.
18. Cativiela, C.; Mayoral, J. A.; Melendez, E.; Oro, L. A.; Pinillos, M. T.; Uson, R. *J. Org. Chem.* **1984**, 49, 2502.
19. (a) Rao, Y. S.; Filler, R. *Synthesis* **1975**, 749. (b) Filler, R.; Rao, Y. S. *Advances in Heterocyclic Chemistry*, Academic Press: New York, **1977**, Vol. 21. (c) Cativiela, C.; Diaz de Villegas, M. D.; Garcia, J. I.; Mayoral, J. A.; Melendez, E. *Ann. Quim.* **1985**, 81, 56.
20. see also ref. 18.
21. Döbler, Chr.; Kreuzfeld, H.-J.; Krause, H.W.; Michalik, M. *Tetrahedron: Asymmetry* **1993**, 4, 1833 and therein further literature.
22. Günther, H. *NMR-Spektroskopie*; Georg-Thieme-Verlag: Stuttgart New York; **1992.**
23. Bixler, R. L.; Niemann, C. *J. Org. Chem.* **1958**, 23, 575.

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