SYNTHESIS OF (5-HYDROXY-2-PYRIDYL)GLYCINE. OXAZOLE FORMATION IN THE BUCHERER-BERGS REACTION. STUDIES ON AMINO ACIDS VI[1]

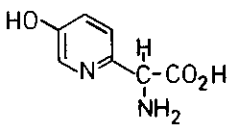
Claus Herdeis* and Rolf Gebhard

Institut für Pharmazie und Lebensmittelchemie der Universität München

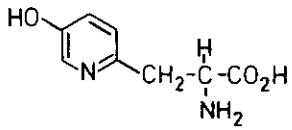
Sophienstraße 10, D-8000 München 2, Federal Republic of Germany

Abstract - (5-Hydroxy-2-pyridyl)glycine (1) has been prepared. Bucherer-Bergs reaction of (5-benzyloxy-2-pyridyl)carbaldehyde (6) furnished the oxazole 7b and not the hydantoin 9. Hydrolysis of the oxazole 7b gave the sodium salt of the hydantoic acid 11. After acidic workup the urea derivative 12 was obtained. This demonstrates that the oxazole 7b and not the former postulated isomer 5a is the product of 2-pyridylcarbaldehyde derivatives in the Bucherer-Bergs reaction.

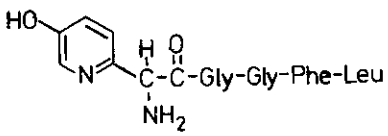
As a part of our investigation in the field of heterocycle-substituted amino acids[2] we are interested first in the pharmacologic properties of (5-hydroxy-2-pyridyl)-glycine (1), secondly in replacing the tyrosine moiety in leu-enkephaline with 1 to test the opiate receptor affinity of this new pentapeptide 3. The homologue of 1 namely 2 was found in *Streptomyces chibaensis*[3] and shows antiviral activity.



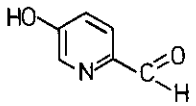
1



2



3

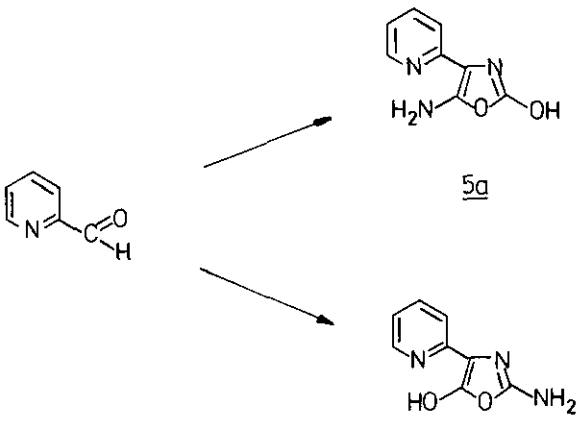


4

Results and discussion

The aldehyde 4 could be prepared via oxidation of 6-(hydroxymethyl)pyridin-3-ol[4] with activated manganese dioxide[5]. Due to the extreme hydrophilic properties of 4 isolation of the aldehyde and the Bucherer-Bergs product was tedious and unpractical for large-scale-production. In order to overcome the difficulties, the hydroxy function was protected with benzyl group. (5-Benzyloxy-2-pyridyl)carbaldehyde[5] (6) was treated with potassium cyanide, ammonium chloride[6] and ammonium carbonate in boiling ethanol/water. The spectroscopic properties of the isolated product were not in the agreement with a hydantoin derivative. In 1959 Viscontini and Raschig[7] published the synthesis of 2-pyridylglycine. They postulated that an oxazole derivative 5a or 5b was the product of the Bucherer-Bergs reaction with 2-pyridylcarbaldehyde. Chemical and spectroscopic properties of this product led them to the preference for structure 5a.

Scheme 1 (Viscontini and Raschig)



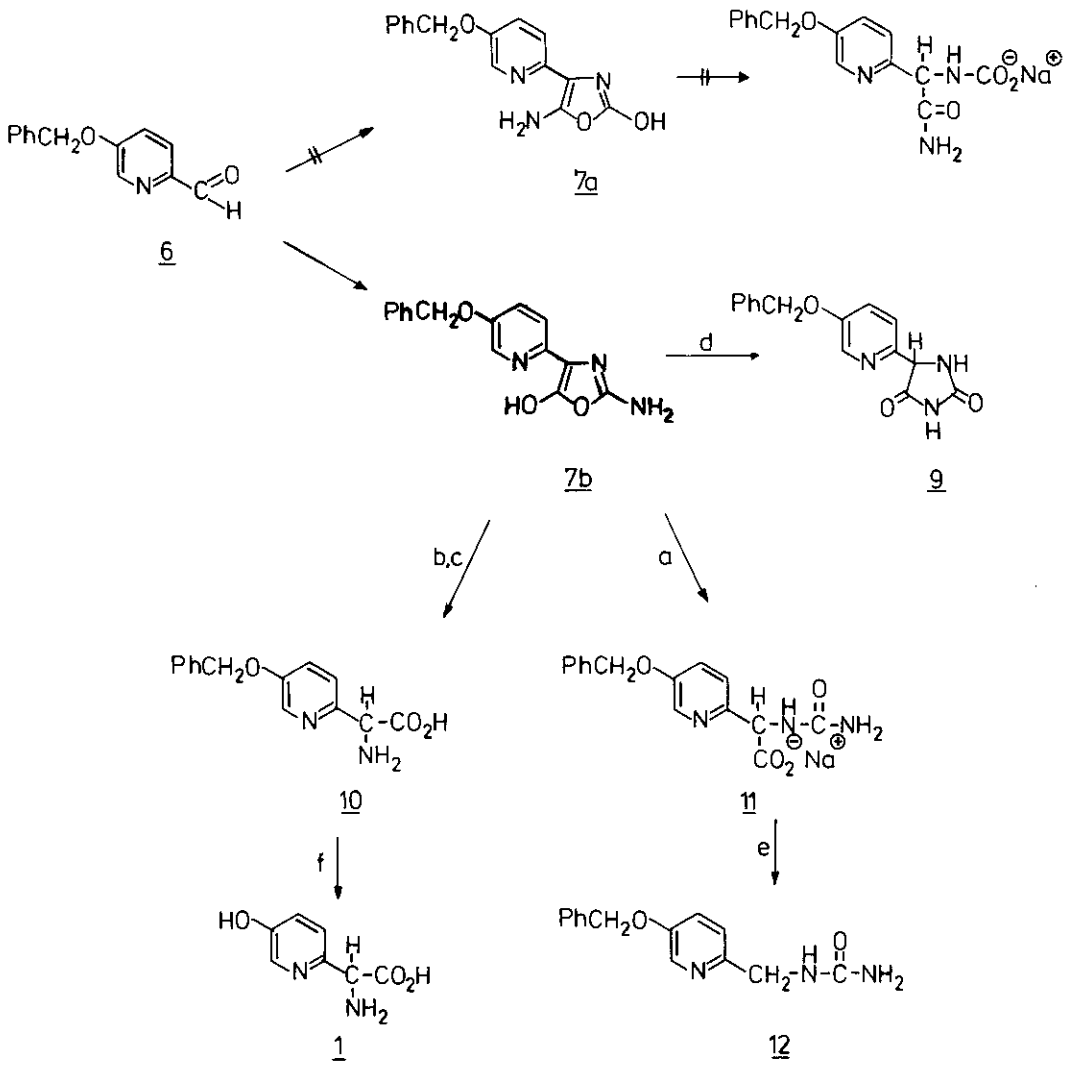
5a

5b

In agreement with Viscontini and Raschig we found yellow, flourescent needles crystallized from DMF as the product of the Bucherer-Bergs reaction of 6. Upon heating in glacial acetic acid, the product was transformed to hydantoin 9 which is unambiguously characterized by its ^{1}H-NMR spectrum.

Under a carefully controlled hydrolysis condition with 2N NaOH, the product gave the amino acid 10 and the urea derivative 11 in the satisfactory yields. These facts show that the structure of the product is 7b. Hydrogenolytic debenzylation of 10 furnished 1 in a high yield. In an acidic medium, 1 decarboxylates very easy.

Schema 2



a) 2N NaOH, 15 h, 80 - 90 °C; b) 2N NaOH, 8 h, 110 - 120 °C; c) pH 7.2; d) AcOH; e) conc. HCl pH 4 - 5; f) Pd/C, H_2, MeOH/H_2O

When a solution of 11 was brought to pH 4 decarboxylation occurred to give 12. Resolution of 1 in its optically pure enantiomers on a HPLC column (silica gel, BSA, Serva) and peptide synthesis with 10 will be published in due course[8].

Table 1

Compound	Molecular formula	C	H	N	^{1}H-NMR - δ= (ppm)
		Calcd.			
		Found			
7b	$C_{15}H_{13}N_3O_3$	63.60	4.62	14.83	only soluble in hot DMF
		63.40	4.73	14.87	
9	$C_{15}H_{13}N_3O_3$	63.60	4.62	14.83	$CDCl_3$; δ= 5.12(s,1H), 5.19(s,2H), 7.36(m,7H)
		63.42	4.75	14.55	8.18(s,1H), 8.32(m,1H), 10.75(s,1H)
10	$C_{14}H_{14}N_2O_3$	65.11	5.46	10.84	d_6-DMSO + NaOD; δ= 4.27(s,1H), 5.21(s,2H)
		65.00	5.30	10.87	7.52(m,7H), 8.29(m,1H)
11	$C_{15}H_{14}N_3O_4Na$	55.73	4.36	13.00	d_6-DMSO; δ= 4.83(d,1H), 5.20(s,2H), 5.72(s,2H)
		55.56	4.53	12.70	6.77(d,J=7Hz,1H), 7.35(m,2H), 7.48(s,5H),
					8.25(m,1H)
12	$C_{14}H_{15}N_3O_2$	65.36	5.88	16.33	d_6-DMSO; δ= 4.29(d,J=6Hz,2H), 5.23(s,2H)
		65.65	5.87	16.15	5.68(s,2H), 6.56(t,J=6Hz,1H), 7.29(d,J=9Hz,1H),
					7.70-7.43(m,6H), 8.38(d,J=3Hz,1H)
1	$C_7H_8N_2O_3$	50.00	4.79	16.66	d_6-DMSO + NaOD; δ= 8.05(m,1H), 7.20(m,2H)
		50.13	4.92	16.48	

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-NMR spectra were recorded on a Varian EM-360 spectrometer using tetramethyl silane as internal reference.

2-Amino-4-(5-benzyloxy-2-pyridyl)-5-hydroxyoxazole (7b)

Potassium cyanide (0.38 g, 5.8 mmol) and ammonium carbonate (1.88 g, 16.5 mmol) were dissolved in 5 ml of water (40 - 50 °C). To this solution was added 6 (1 g, 4.7 mmol) in 5 ml of ethanol. The reaction temperature was kept for 4 h at about 60 °C, and then for 1 h at 80 °C. The brownish-yellow precipitate formed was filtered by suction and washed thoroughly with water and ethanol. The residue was crystallized from DMF to give 1 g (75 %) of yellow needles, mp 234 - 235 °C. IR (KBr): 3380 (NH,OH), 1690, 1640, 1570 cm^{-1}.

5-(5-Benzyloxy-2-pyridyl)imidazolidine-2,4-dione (9)

A solution of 7b (0.5 g, 1.76 mmol) was refluxed in glacial acetic acid (25 ml) for 24 h. After evaporation of the solvent the residue was crystallized from methanol giving 0.41 g of 9 (82 %) as colourless crystals, mp 188 - 189 °C. IR (KBr): 3170, 3050 (NH), 1765 (C=O), 1715 (C=O) cm^{-1}. ^{13}C-NMR (d_6-DMSO): δ (ppm) =173.9 (C=O), 157.9 (C=O), 147.5, 138.3, 136.4, 128.6, 128.1, 127.8, 123.4, 122.2 (all arom.), 69.2 (CH_2), 62.9 (CH).

(5-Benzyloxy-2-pyridyl)-N-carbamoylglycine Sodium-salt (11)

Compound 7b (5 g, 17.6 mmol) was heated in 2N NaOH (25 ml) for 15 h. The bath temperature was kept at about 80 - 90 °C. The reaction mixture was then cooled down until a colourless solid separated. The solid was crystallized from ethanol/water (1:1) to give 4.3 g (76 %) of 11 as colourless platelets, mp 236 - 238 °C. IR (KBr): 3460, 3340 (NH), 1670 (C=O), 1610 (C=O) cm^{-1}.

(5-Benzyloxy-2-pyridyl)methyl Urea (12)

Compound 11 (5 g, 15.5 mmol) was dissolved in water (50 ml). Concentrated hydrochloric acid was added dropwise with stirring until pH 4.5 was reached. The precipitate obtained was filtered with suction and washed with ethanol. Recrystallization of the product from 500 ml of water gave colourless crystals. Yield 3 g (76 %), mp 157 - 158 °C. IR (KBr): 3360, 3190 (NH), 1650 (C=O), 1630 cm^{-1}. ^{13}C-NMR (d_6-DMSO): δ (ppm) = 158.8 (C=O), 153.3, 159.9, 136.9, 128.4, 127.9, 127.7, 122.4, 121.5 (all arom.), 69.9 (CH_2), 44.4 (CH_2).

(5-Benzyloxy-2-pyridyl)glycine (10)

Compound 7b (4 g, 14.12 mmol) was heated with 2N NaOH (40 ml) for 8 h (bath temp. 120 °C). The warm solution was filtered, cooled to 0 °C and neutralized with conc. hydrochloric acid with stirring and cooling in an ice bath (pH 7.2). The precipitate was washed with ethanol and crystallized from water (300 ml). Yield 1.95 g (53 %), mp 118 - 120 °C. IR (KBr): 3200 - 2600($^{+}NH_3$), 1655 (C=O), 1635, 1600, 1570 cm^{-1}.

(5-Hydroxy-2-pyridyl)glycine (1)

Compound 10 (0.5 g, 1.93 mmol) was hydogenated over Pd/C in methanol/water (1:1) for 3 h at 50 °C under 3 bar pressure. The catalyst was filtered and the solution evaporated to dryness. The residue was crystallized from methanol/water (1:1). Yield 270 mg (83 %), mp 174 - 175 °C. IR (KBr): 3300 - 2300 ($^{+}NH_3$,OH), 1630 (C=O), 1580, 1490 cm^{-1}.

ACKNOWLEDGEMENT

This paper is dedicated to Prof. F. Eiden on the occasion of his 60th birthday.

REFERENCES

1. Part V: C. Herdeis, Chirospecific synthesis of S(+)- and R(-) 5-Amino-4-hydroxypentanoic acid, Synthesis, in press.
2. C.Herdeis and U.Nagel, Heterocycles, 1983, 20, 2163.
3. S.Inouye, T.Shomura, T.Tsuruoka, Y.Ogawa, H.Watanabe, J.Yoshida and T.Niida, Chem.Pharm.Bull., 1975, 23, 2669.
4. L.W.Deady and M.Payne, Aust.J.Chem., 1983, 36, 2565.
5. T.Jen, J.S.Frazee, M.S.Schwartz, C.Kaiser, D.F.Collela and J.R.Wardell,Jr., J.Med.Chem., 1977, 20, 1258.
6. C.J.Abshire and L.Berlinguet, Can.J.Chem., 1965, 43, 1232.
   The addition of ammonium chloride to the reaction mixture did not alter the yield and the structure of the product. We preferred the method according to lit. 7.
7. M.Viscontini and H.Raschig, Helv.Chim.Acta, 1959, 42, 570.
8. C.Herdeis and R.Gebhard, Arch.Pharm. (Weinheim), to be published.

Received, 11th November, 1985