Unambiguous Structure of the Compounds in the Reaction of L-Tryptophan and 5-Hydroxy-L-tryptophan with Alkyl Isocyanates in Acetone

Mercedes Garrido, Maria L. López Rodríguez* and M. José Morcillo

Departamento de Química Orgánica I, Facultad de Ciencias Químicas, Universidad Complutense, 28040-Madrid, Spain

Virginia Pérez Garcia and A. Monge

C. Difracción de Rayos X, Facultad de Ciencias Químicas, Universidad Complutense, 28040-Madrid, Instituto de Ciencia de Materiales, Serrano 113, 28006-Madrid, Spain

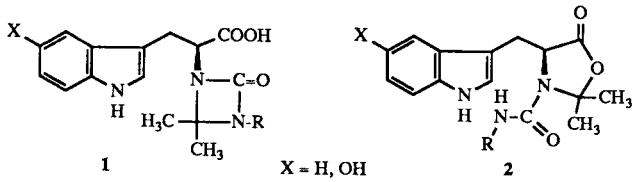
Received December 21, 1989

On the basis of X-ray crystallographic analysis, it is shown that the reaction of L-tryptophan and 5-hydroxy-L-tryptophan with alkyl isocyanates in acetone affords, in agreement with Claesson's work, 3-alkylcarbamoyl-4-(3-indolylmethyl)-1,3-oxazolidin-5-ones **2** and not 2-[(3-alkyl-4,4-dimethyl-2-oxo)-1,3-diazetidinyl]-3-(3-indolyl)propionic acids **1** as previously proposed.

J. Heterocyclic Chem., **27**, 1513 (1990).

In previous work on new derivatives of tryptophan, the formation of 2-[(3-alkyl-4,4-dimethyl-2-oxo)-1,3-diazetidinyl]-3-(3-indolyl)propionic acid **1** by reaction of L-tryptophan [1] and 5-hydroxy-L-tryptophan [2] with alkyl isocyanates in acetone was proposed. In a recent paper by Claesson [3] he reports that the reaction of L-tryptophan with ethyl isocyanate in refluxing acetone gives rise to the formation of the corresponding 1,3-oxazolidin-5-one **2** (X = H, R = CH_2CH_3) and not 1,3-diazetidinone **1**.

Scheme 1



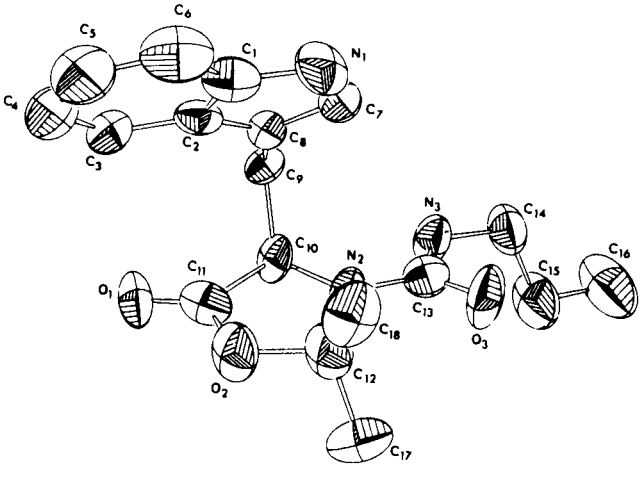


Figure 1. ORTEP (Johnson, 1965) Drawing of the Molecule Showing the Atom Numbering.

In order to unambiguously identify a representative example, the X-ray crystal structure of the compound isolated in the reaction of L-tryptophan with propyl isocyanate in acetone was obtained. The X-ray study showed the structure **2** (X = H, R = $CH_2CH_2CH_3$). The final atomic parameters are given in Table I.

Table I
Atomic Coordinates and Thermal Parameters*

Atom	X/A	Y/B	Z/C	UEQ
N1	0.8878 (10)	0.3047 (12)	0.8766 (5)	69 (4)
N2	0.4824 (10)	0.1406 (8)	0.8717 (4)	53 (3)
N3	0.5153 (10)	-0.0674 (9)	0.9240 (4)	62 (4)
O1	0.4707 (8)	0.2216 (8)	0.6909 (4)	64 (3)
O2	0.4274 (9)	0.3120 (8)	0.7971 (4)	74 (3)
O3	0.4801 (10)	0.1177 (8)	0.9916 (4)	80 (4)
C1	0.8803 (12)	0.3691 (12)	0.8112 (7)	61 (5)
C2	0.7990 (10)	0.2861 (12)	0.7671 (6)	48 (4)
C3	0.7796 (11)	0.3278 (12)	0.6959 (6)	56 (4)
C4	0.8361 (14)	0.4472 (15)	0.6729 (7)	79 (6)
C5	0.9133 (13)	0.5243 (14)	0.7181 (9)	88 (6)
C6	0.9406 (13)	0.4880 (13)	0.7885 (8)	79 (6)
C7	0.8116 (12)	0.1883 (12)	0.8751 (6)	55 (4)
C8	0.7556 (10)	0.1723 (11)	0.8078 (5)	47 (4)
C9	0.6666 (10)	0.0615 (10)	0.7867 (5)	41 (3)
C10	0.5145 (11)	0.0932 (9)	0.7991 (5)	50 (4)
C11	0.4696 (12)	0.2109 (12)	0.7542 (8)	60 (5)
C12	0.4291 (16)	0.2813 (14)	0.8745 (7)	78 (6)
C13	0.4916 (11)	0.0656 (12)	0.9336 (6)	53 (4)
C14	0.5131 (13)	-0.1592 (13)	0.9850 (6)	70 (5)
C15	0.3739 (15)	-0.1956 (16)	1.0087 (7)	98 (6)
C16	0.3757 (17)	-0.2981 (18)	1.0700 (8)	129 (8)
C17	0.2886 (13)	0.2909 (15)	0.9011 (8)	84 (6)
C18	0.5275 (16)	0.3806 (12)	0.9083 (7)	80 (6)

*Equivalent isotropic U defined as one third of the trace of the orthogonalised Uij tensor (A^2 x10^3).

Figure 1 shows the geometry of the structure and the atom labelling [4]. Bond lengths and angles together with their e.s.d.'s are given in Table II.

Table II
Bond Distances (Å) and Angles (o) with e.s.d.'s in Parentheses

N1-C1	1.38 (2)	N1-C7	1.38 (2)
N2-C10	1.47 (1)	N2-C12	1.50 (2)
N2-C13	1.38 (1)	N3-C13	1.35 (1)
N3-C14	1.46 (1)	O1-C11	1.19 (2)
O2-C11	1.35 (1)	O2-C12	1.48 (2)
O3-C13	1.21 (1)	C1-C2	1.42 (2)
C1-C6	1.39 (2)	C2-C3	1.40 (1)
C2-C8	1.43 (2)	C3-C4	1.38 (2)
C4-C5	1.37 (2)	C5-C6	1.39 (2)
C7-C8	1.38 (2)	C8-C9	1.47 (1)
C9-C10	1.56 (1)	C10-C11	1.51 (2)
C12-C17	1.49 (2)	C12-C18	1.53 (2)
C14-C15	1.50 (2)	C15-C16	1.53 (2)
C1-N1-C7	109.9 (9)	C12-N2-C13	120 (1)
C10-N2-C13	125.8 (9)	C10-N2-C12	114.1 (8)
C13-N3-C14	120.3 (9)	C11-O2-C12	115 (1)
N1-C1-C2	106 (1)	N1-C1-C6	130 (1)
C2-C1-C6	124 (1)	C1-C2-C8	109 (1)
C1-C2-C3	117 (1)	C3-C2-C8	134 (1)
C2-C3-C4	119 (1)	C3-C4-C5	121 (1)
C4-C5-C6	123 (1)	C1-C6-C5	115 (1)
N1-C7-C8	109 (1)	C2-C8-C7	106 (1)
C7-C8-C9	125 (1)	C2-C8-C9	129.3 (9)
C8-C9-C10	113.2 (8)	N2-C10-C9	114.3 (8)
C9-C10-C11	111.2 (9)	N2-C10-C11	101.5 (8)
O2-C11-C10	110 (1)	O1-C11-C10	128 (1)
O1-C11-O2	122 (1)	N2-C12-O2	99.4 (9)
O2-C12-C17	108 (1)	O2-C12-C18	106 (1)
N2-C12-C17	114 (1)	N2-C12-C18	113 (1)
C17-C12-C18	115 (1)	N3-C13-O3	124 (1)
N2-C13-O3	121 (1)	N2-C13-N3	115 (1)
N3-C14-C15	113 (1)	C14-C15-C16	112 (1)

The error regarding the diazetidinone structures was possibly due to the low resolution (60 MHz) of the spectrometer in which ^{1}H nmr spectra were obtained. We have recorded again the ^{1}H nmr spectra on a Bruker AC-200 and Varian VXR-300S spectrometers. The physical properties, ir, ^{1}H and ^{13}C nmr spectra that define the structure **2** are summarized in Tables III-VI.

EXPERIMENTAL

The ^{1}H nmr spectra were recorded on a Bruker AC-200 and Varian VXR-300S spectrometers. The ^{13}C nmr spectra were obtained using a Varian FT-80A spectrometer. The ir spectra were determined on a Perkin-Elmer 781 spectrophotometer.

3-Alkylcarbamoyl-4-(3-indolylmethyl)-1,3-oxazolidin-5-ones **2a-e** were prepared following references [1] [2].

X-Ray Crystallography.

Single crystals of **2b** were obtained by recrystallization from ethyl acetate. Crystal data and data collection parameters are given in Table VII.

The standard reflexions monitored periodically during data collection showed no crystal decomposition. Intensities were corrected for Lorentz polarization effects. Scattering factors for neutral atoms from International Tables [4] for X-ray Crystallography. The structure was solved by direct methods [5]. Final refinement with fixed isotropic temperature factors and calculated coordinates for H atoms, and unit weights led to R = 0.061. Final difference synthesis had no significant electron density. Most of the calculations were carried out with XRAY80 System [6].

Table III
Characterization Data of Compounds **2a-e**

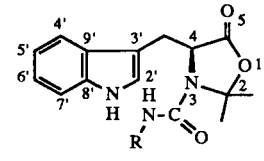
Compound	X	R	Mp °C	Yield %	Molecular Formula	Analysis (%) Calcd./Found C	H	N
2a	H	CH_3CH_2	163-164	45	$C_{17}H_{21}N_3O_3$	64.70	6.66	13.23
						64.45	6.92	13.40
2b	H	$CH_3CH_2CH_2$	166-167	23	$C_{18}H_{23}N_3O_3$	65.65	6.99	12.76
						65.73	7.05	12.80
2c	H	$(CH_3)_2CH$	139-141	22	$C_{18}H_{23}N_3O_3$	65.65	6.99	12.76
						65.50	6.95	12.55
2d	OH	CH_3CH_2	172-173	28	$C_{17}H_{21}N_3O_4$	61.62	6.39	12.68
						61.65	6.47	12.61
2e	OH	$CH_3CH_2CH_2$	123-125	20	$C_{18}H_{23}N_3O_4$	62.59	6.79	12.16
						62.30	6.97	11.89
2f	OH	$(CH_3)_2CH$	137-138	29	$C_{18}H_{23}N_3O_4$	62.59	6.79	12.16
						62.47	6.73	12.20

Table IV
3-Alkylcarbamoyl-4-(3-indoylmethyl)-1,3-oxazolidin-5-ones

Compound	X	R	ir (υ,cm^{-1}) (KBr)	^{1}H NMR (δ, ppm) [a]
2a	H	CH_3CH_2	3400, 3280 (NH), 1700 (C=O), 1650 (C=O amide)	0.65 (s, 3H, CH_3), 1.15 (t, 3H, CH_3-ethyl, J = 7 Hz), 1.50 (s, 3H, CH_3), 3.0-3.70 (m, 4H, $2CH_2$), 4.75 (dd, 1H, CH-N, J = 1.8, 5.1 Hz), 6.45 (t, 1H, NH-amide, J = 5.2 Hz), 6.8-7.1 (m, 3H, H_2, H_5 and H_6-ind.), 7.35 (d, 1H, H_7-ind, J_{ortho} = 7.8 Hz), 7.45 (d, 1H, H_4-ind, J_{ortho} = 7.8 Hz), 10.95 (s, 1H, NH-ind)
2b	H	$CH_3CH_2CH_2$	3400, 3270 (NH), 1770 (C=O) 1640 (C=O amide)	0.65 (s, 3H, CH_3), 0.95 (t, 3H, CH_3-pr, J = 7.3 Hz), 1.53 (s, 3H, CH_3), 1.50-1.65 (m, 2H, CH_2-pr), 2.90-3.40 (m, 3H, CH_2-pr, CH_a-ind), 3.57 (dd, 1H, CH_b-ind J = 5.1, 14.9 Hz), 4.78 (dd, 1H, CH-N, J = 1.9, 5.1 Hz), 6.58 (t, 1H, NH-amide, J = 5.1 Hz), 6.92-7.07 (m, 3H, H_2, H_5 and H_6- ind), 7.34 (d, 1H, H_7-ind, J_{ortho} = 7.8 Hz), 7.44 (d, 1H, H_4-ind, J_{ortho} = 7.8 Hz), 10.95 (s, 1H, NH-ind)
2c	H	$(CH_3)_2CH$	3400, 3290 (NH), 1770 (C=O) 1635 (C=O amide)	0.63 (s, 3H, CH_3), 1.15 (d, 3H, CH_3-isopr, J = 6.6 Hz), 1.24 (d, 3H, CH_3-isopr, J = 6.6 Hz), 1.50 (s, 3H, CH_3), 3.12 (dd, 1H, CH_a-ind, J = 1.7, 14.8 Hz), 3.52 (dd, 1H, CH_b-ind, J = 5.1, 14.9 Hz) 3.92 (m, 1H, CH-isopr, J = 6.6 Hz), 4.81 (dd, 1H, CH-N, J = 1.9, 5.1 Hz), 6.22 (d, 1H, NH-amide, J = 7.6 Hz), 6.92-7.06 (m, 3H, H_2, H_5 and H_6-ind), 7.33 (d, 1H, H_7-ind, J_{ortho} = 7.8 Hz), 7.43 (d, 1H, H_4-ind, J_{ortho} = 7.8 Hz), 10.95 (s, 1H, NH-ind)
2d	OH	CH_3CH_2	3460 (OH), 3400, 3220 (NH), 1775 (C=O), 1630 (C=O amide)	0.69 (s, 3H, CH_3), 1.13 (t, 3H, CH_3-ethyl, J = 7 Hz), 1.50 (s, 3H, CH_3), 2.96-3.50 (m, 4H, $2CH_2$), 4.66 (dd, 1H, CH-N, J = 1.7, 5.2 Hz), 6.43 (t, 1H, NH-amide, J = 5.3 Hz), 6.55 (dd, 1H, H_6-ind, J_{ortho} = 8.6 Hz, J_{meta} = 2.2 Hz), 6.72 (d, 1H, H_2-ind, J = 1.9 Hz), 6.79 (d, 1H, H_4-ind, J_{meta} = 2.2 Hz), 7.08 (d, 1H, H_7-ind, J_{ortho} = 8.6 Hz), 8.49 (s, 1H, OH), 10.60 (s, 1H, NH-ind)
2e	OH	$CH_3CH_2CH_2$	3460 (OH), 3420, 3240 (NH) 1740 (C=O), 1625 (C=O amide)	0.70 (s, 3H, CH_3), 0.95 (t, 3H, CH_3-pr, J = 7.3 Hz), 1.50 (s, 3H, CH_3), 1.45-1.60 (m, 2H, CH_2-pr), 2.80-3.40 (m, 3H, CH_2-pr, CH_a-ind), 3.60 (dd, 1H, CH_b-ind, J = 5.1, 14.9 Hz), 4.75 (dd, 1H, CH-N, J = 1.9, 5 Hz), 6.40 (t, 1H, NH-amide, J = 5.2 Hz), 6.55 (dd, 1H, H_6-ind, J_{ortho} = 8.6 Hz, J_{meta} = 2.3 Hz), 6.71 (d, 1H, H_2-ind, J = 2.1 Hz), 6.80 (d, 1H, H_4-ind, J_{meta} = 2.3 Hz), 7.08 (d, 1H, H_7-ind, J_{ortho} = 8.6 Hz), 8.50 (s, 1H, OH), 10.60 (s, 1H, NH-ind)
2f	OH	$(CH_3)_2CH_2$	3500-3100 (broad, OH), 3380, 3320 (NH) 1700 (C=O), 1630 (C=O amide)	0.69 (s, 3H, CH_3), 1.09 (d, 3H, CH_3-isopr, J = 6.5 Hz), 1.19 (d, 3H, CH_3-isopr, J = 6.5 Hz), 1.49 (s, 3H, CH_3), 3.01 (dd, 1H, CH_a-ind, J = 1.7, 15 Hz), 3.38 (dd, 1H, CH_b-ind, J = 5.1, 15 Hz), 3.85 (m, 1H, CH-isopr, J = 6.5 Hz), 4.72 (dd, 1H, CH-N, J = 1.8, 5.1 Hz), 6.13 (d, 1H, NH-amide, J = 7.6 Hz), 6.55 (dd, 1H, H_6-ind, J_{ortho} = 8.6 Hz, J_{meta} = 2.3 Hz), 6.72 (d, 1H, H_2-ind, J = 2.1 Hz), 6.80 (d, 1H, H_4-ind, J_{meta} = 2.3 Hz), 7.08 (d, 1H, H_7-ind, J_{ortho} = 8.6 Hz), 8.61 (s, 1H, OH), 10.60 (s, 1H, NH-ind)

[a] • - Me_2SO-d_6.

Table V
^{13}C NMR (δ, ppm) [a] of 3-Alkylcarbamoyl-4-(3-indolylmethyl)-1,3-oxazolidin-5-ones

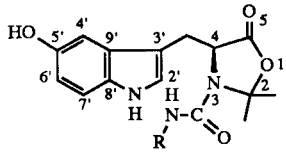


Compound	R	C_5	C=O carbamoyl	$C_{8'}$	$C_{9'}$	$C_{2'}$	$C_{6'}$	$C_{5'}$,$C_{4'}$	$C_{7'}$	$C_{3'}$	C_2	C_4	CH_3 or CH_2 indole	R CH	R CH_2	R CH_3
2a	CH_3CH_2	171.8	153.4	135.9	128.0	124.6	121.0	118.6	111.3	108.1	96.8	57.1	26.3, 26.0, 25.7	---	34.7	15.6
2b	$CH_3CH_2CH_2$	171.8	153.5	135.9	127.9	124.6	121.1	118.6	111.4	108.1	96.8	57.1	26.4, 26.0, 25.8	---	41.7,23.2	11.6
2c	$(CH_3)_2CH$	171.9	152.8	135.9	127.9	124.6	121.0	118.6	111.3	108.2	96.8	57.0	26.4, 26.1, 25.9	41.8	---	23.3,22.9

[a] DMSO-d_6.

Table VI

^{13}C NMR (δ, ppm) [a] of 3-Alkylcarbamoyl-4-(5-hydroxy-3-indolylmethyl)-1,3-oxazolidin-5-ones



Compound	R	C_5	C=O carbamoyl	$C_{5'}$	$C_{8'}$	$C_{9'}$	$C_{2'}$	$C_{6'}$,$C_{7'}$	$C_{3'}$	$C_{4'}$	C_2	C_4	CH_3 or CH_2 indole	R CH	R CH_2	R CH_3
2d	CH_3CH_2	171.9	153.2	150.4	130.4	128.7	125.1	111.6,111.5	107.1	102.8	96.8	56.9	26.4, 26.1, 25.8	---	37.5	15.7
2e	$CH_3CH_2CH_2$	172.1	153.5	150.6	130.6	128.7	125.3	111.6	107.2	103.0	97.0	56.0	26.6, 26.2, 26.0	---	41.8,23.23	11.8
2f	$(CH_3)_2CH$	172.2	153.0	150.6	130.7	128.7	125.4	111.8	107.3	103.1	97.2	57.0	26.7, 26.3, 26.2	41.9	---	23.5,23.1

[a] DMSO-d_6.

Table VII

Crystal and Refinement Data for **2b**

formula	$C_{18}N_3O_3H_{23}$	diffractometer	Enraf-Nonuis CAD4
crystal system	orthorhombic	radiation	graphite-monochromated Mo Kα (λ = 0.71069 Å)
space group	$P2_12_12_1$		
a, Å	9.944 (5)	scan technique	ω/2θ
b, Å	9.935 (2)	data collected	(0,0,0) to (14,14,26)
c, Å	18.66 (2)	rflns collected	3110
V, Å^3	1843 (2)	unique data	3013
z	4	unique data (Y) ≥ 2σ (I)	859
F(000)	704	R(int), %	0.013
ρ(calcd), g cm^{-3}	1.19	std rflns	3/96 reflections
temperature °C	22	decay	≤1% variation
μ, cm^{-1}	6.31	R_F, %	6.1
crystal dimensions, mm	0.20 x 0.20 x 0.30	Rw_F, %	6.1
average shift/error	0.479		

Acknowledgement.

The authors are grateful to Universidad Complutense, Madrid and to C.I.C.Y.T. for financial support (Projects No. UCP009/87 and FAR88-0514).

REFERENCES AND NOTES

[1] M. F. Braña, M. Garrido, M. L. López Rodríguez and M. J. Morcillo, *Heterocycles*, **26**, 95 (1987).

[2] M. F. Braña, M. Garrido, J. L. Hernando, M. L. López Rodríguez and M. J. Morcillo, *J. Heterocyclic Chem.*, **24**, 1725 (1987).

[3] A. Claesson, *Heterocycles*, **27**, 2087 (1988).

[4] International Tables for X-ray Crystallography, Kynoch Press, Birmingham, England, Vol IV, 1974, pp 72-98.

[5] P. Main, L. Lessinger, M. M. Woolfson, G. Germain and J. P. Declercq. Multan. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data, Universities of York, England and Louvain, Louvain, Belgium, 1977.

[6] J. M. Stewart, The XRAY80 System, Computer Science Center, University of Maryland, College Park, 1985.