Reaction of 5-Hydroxy-L-tryptophan with Alkyl Isocyanates

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Received June 11, 1987

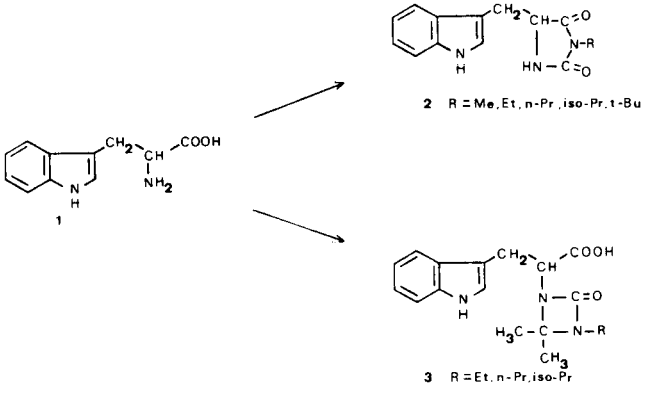
5-Hydroxy-L-tryptophan **4** with potassium cyanate gives 5-(5-hydroxy-3-indolylmethyl)hydantoin **5** or N_b-carbamoyl-5-hydroxy-L-tryptophan **6** depending on the reaction conditions. Reaction of **4** with methyl isocyanate in acetone provides 5-hydroxy-N_b-methylcarbamoyl-L-tryptophan **7**. Treatment of **4** with ethyl, propyl and isopropyl isocyanates in acetone gives rise to the formation of the corresponding 2-[(3-alkyl-4,4-dimethyl-2-oxo)-1,3-diazetidinyl]-3-(5-hydroxy-3-indolyl)propionic acids **8-10**.

J. Heterocyclic Chem., **24**, 1725 (1987).

5-Hydroxytryptophan is a new naturally occuring amino acid, the precursor of serotonine, whose importance as a neurotransmitter, a precursor of melatonin, a regulator of sleep and effective disorders is still increasing [1].

In a previous publication [2] was presented that L-tryptophan **1** reacts with alkyl isocyanates in pyridine to give the corresponding hydantoins **2**. Alternatively, the reactions with ethyl, propyl and isopropyl isocyanates in acetone provide the corresponding 2-[(3-alkyl-4,4-dimethyl-2-oxo)-1,3-diazetidinyl]-3-(3-indolyl)propionic acids **3**.

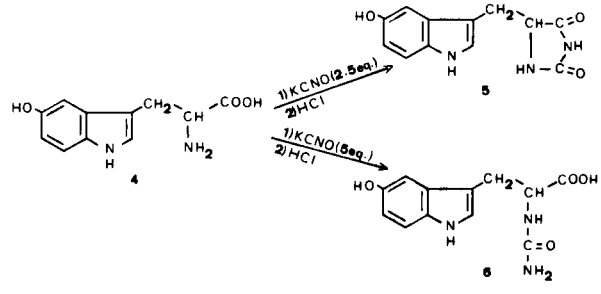
Scheme 1



As continuation of our work in the synthesis and pharmacological properties of new derivatives of tryptophan [2-5] and as a complementary part of the above reactions, we report the reactivity of 5-hydroxy-L-tryptophan **4** with potassium cyanate and alkyl isocyanates. The importance of these reactions is due to the interesting biological properties of **4** as well as the reactivity of its functional groups.

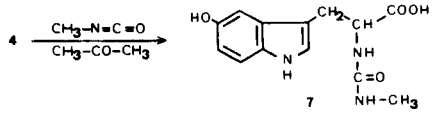
Treatment of 5-hydroxy-L-tryptophan **4** with potassium cyanate (1:2.5) in water for 1 hour followed by acidification with hydrochloric acid using the method of Suarov *et al.* [6] provides 5-(5-hydroxy-3-indolylmethyl)hydantoin **5**. No N_b-carbamoyl-5-hydroxy-L-tryptophan **6** was obtained as this author reported. Nevertheless, the formation of **6** can be performed reducing the water amount and increasing the reaction time (2 hours) and concentration of potassium cyanate (the ratio of **4**:potassium cyanate was 1:5).

Scheme 2



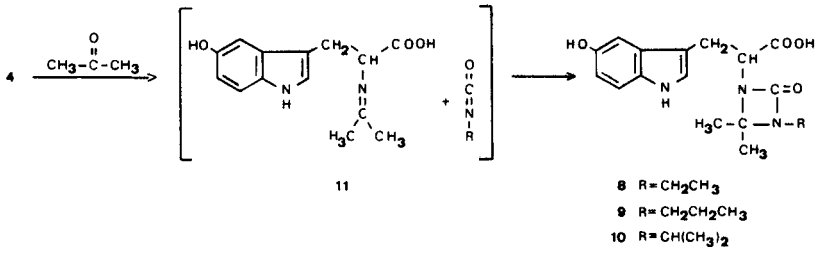
Reaction of **4** with methyl isocyanate in acetone leads to the formation of 5-hydroxy-N_b-methylcarbamoyl-L-tryptophan **7**.

Scheme 3



The treatment of **4** with ethyl, propyl and isopropyl isocyanates in acetone give rise to the formation of the corresponding 2-[(3-alkyl-4,4-dimethyl-2-oxo)-1,3-diazetidinyl]-3-(5-hydroxy-3-indolyl)propionic acids **8-10**. The structural assignment was established on the basis of elemental analysis and spectral data. Finally in the reaction of **4** with *t*-butyl isocyanate in acetone, the 5-hydroxy-L-tryptophan **4** is recovered and only di-*t*-butylurea was formed.

Scheme 4



11

8 R = CH_2CH_3
9 R = $CH_2CH_2CH_3$
10 R = $CH(CH_3)_2$

The formation of **8-10** may be explained as in the tryptophan case [2] by condensation of **4** with the solvent followed by [2+2] cycloaddition to **11** with the corresponding alkyl isocyanate. The fact that methyl and *t*-butyl isocyanates did not form diazetidinones is understood by the assumptions that in the methyl isocyanate case the reaction between **4** and the isocyanate is more rapid that the formation of Schiff base, while in the *t*-butyl isocyanate case, steric effects are influencing the reaction.

EXPERIMENTAL

Melting points were measured with a Büchi apparatus and are uncorrected. The ir spectra were determined on a Perkin-Elmer 781 spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded on a Varian T-60A (60 MHz) and Varian FT-80A spectrometers, respectively. Mass spectrometry was performed with a Varian MAT-711 apparatus. Specific rotations, [α], were determined on a Perkin-Elmer 241MC polarimeter. The elemental analyses were performed by "Cento Nacional de Química Orgánica", Madrid.

5-(5-Hydroxy-3-indolylmethyl)hydantoin (**5**).

A suspension of 5-hydroxy-L-tryptophan **4** (6.0 g, 0.027 mole) and potassium cyanate (6.0 g, 0.07 mole) in 300 ml of water was refluxed for 1 hour. After cooling, the mixture was acidified with hydrochloric acid to *p*H 4. The inorganic solid was removed by filtration and the solvent was evaporated. The yield was 1.5 g (23%), mp 256-258° (water), (lit [6] mp 239-240°); $[\alpha]_D^{20}$ −59.8° (c 0.41, methanol); ir (potassium bromide): ν 3400 (OH), 3390, 3330, 3320 (NH), 1760 (C=O), 1730 (N−CO−N), 1620, 1590 (ArC=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.9-3.4 (m, 2H, CH_2), 4.1-4.4 (m, 1H, CH), 6.5-7.3 (m, 4H, ArH), 7.8 (s, 1H, NH-indole), 8.4 (s, 1H, OH), 10.1 (s, 1H, NH), 10.4 (s, 1H, NH); ^{13}C nmr (DMSO-d_6): δ 27.3 (CH_2), 59.1 (CH), 103.2, 107.6, 112.0, 112.1, 125.3, 128.8, 131.1, 150.7 (indole), 158.2 (N−CO−N), 176.4 (C=O); ms: m/e (relative intensity) 245 (M^+, 9), 146 ($M^+ - C_3H_3N_2O_2$, 100).

Anal. Calcd. for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.60; H, 4.62; N, 16.83.

N_b-Carbamoyl-5-hydroxy-L-tryptophan (**6**).

A suspension of 5-hydroxy-L-tryptophan **4** (10 g, 0.045 mole) and potassium cyanate (18 g, 0.22 mole) in 50 ml of water was refluxed for 2 hours. After cooling, the mixture was acidified with hydrochloric acid to *p*H 5 and treated with acetone just as the precipitation of potassium chloride. The inorganic solid was removed by filtration and the solvent was evaporated. The yield was 3.6 g (30%), mp 196-198° (water), (lit [6] mp 178-179°); $[\alpha]_D^{20}$ +6.5° (c 0.44, methanol); ir (potassium bromide): ν 3500-2500 (OH), 3480, 3440 (NH_2), 3400 (OH), 3340 (NH), 1690 (C=O, acid), 1650 (N−CO−N), 1590, 1550 (ArC=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.9-3.2 (m, 2H, CH_2), 4.2-4.6 (m, 1H, CH), 5.6 (s, 2H, NH_2), 6.1 (d, 1H, NH), 6.5-7.3 (m, 5H, 4ArH, NH-indole), 8.6 (s-broad, 1H, OH), 10.5 (s, 1H, OH-acid); ^{13}C nmr (DMSO-d_6): δ 27.9 (CH_2), 53.0 (CH), 102.3, 108.6, 111.3, 111.5, 123.9, 128.0, 130.6, 150.2 (indole), 158.3 (N−CO−N), 174.4 (C=O, acid).

Anal. Calcd. for $C_{12}H_{13}N_3O_4$: C, 54.78; H, 4.98; N, 15.96. Found: C, 54.45; H, 5.28; N, 15.66.

Reaction of 5-Hydroxy-L-tryptophan **4** with Alkyl Isocyanates.

General Procedure.

Alkyl isocyanate (0.022 mole) in 20 ml of dry acetone was added to a suspension of 5-hydroxy-L-tryptophan **4** (5 g, 0.022 mole) in 20 ml of acetone. The reaction mixture was refluxed for 12 hours. 5-Hydroxy-L-tryptophan was removed by filtration and the solvent was evaporated to yield an oil, which was chromatographed on a silica gel column with ethyl acetate as eluent, affording the corresponding compounds.

5-Hydroxy-N_b-methylcarbamoyl-L-tryptophan (**7**).

This compound was obtained in a yield of 19%, mp 230-232° (ethyl acetate); $[\alpha]_D^{20}$ −98.8° (c 0.24, methanol); ir (potassium bromide): ν 3500-2500 (broad OH), 3420, 3400, 3350, 3310 (NH and OH), 1750 (C=O, acid), 1690 (N−CO−N), 1580 (ArC=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.7 (s, 3H, CH_3), 2.9-3.1 (m, 2H, 2NH), 3.4 (s, 2H, CH_2), 4.1-4.4 (m, 1H, CH), 6.5-7.1 (m, 4H, ArH), 8.0 (s, 1H, NH-indole), 8.4 (s, 1H, OH), 10.3 (s, 1H, OH-acid); ^{13}C nmr (DMSO-d_6): δ 29.3 (CH_3), 27.1 (CH_2), 57.3 (CH), 102.5, 107.3, 111.4, 116.6, 124.5, 128.2, 130.6, 150.4 (indole), 157.1 (N−CO−N), 174.3 (C=O, acid); ms: m/e (relative intensity) 259 ($M^+ - H_2O$, 31), 146 ($M^+ - C_4H_7N_2O_3$, 100).

Anal. Calcd. for $C_{13}H_{15}N_3O_4$: C, 56.31; H, 5.45; N, 15.50. Found: C, 56.08; H, 5.24; N, 15.50.

2-[(3-Ethyl-4,4-dimethyl-2-oxo)-1,3-diazetidinyl]-3-(5-hydroxy-3-indolyl)propionic Acid (**8**).

This compound was obtained in a yield of 26%, mp 171-173° (ethyl acetate); $[\alpha]_D^{20}$ +93.9° (c 0.24, methanol); ir (potassium bromide): ν 3500-2500 (broad OH), 3460 (OH), 3400 (NH), 1775 (C=O, acid), 1630 (N−CO−N), 1600, 1580 (ArC=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.8 (s, 3H, CH_3-C-N), 1.2 (t, 3H, CH_3-ethyl), 1.6 (s, 3H, CH_3-C-N), 3.0-3.5 (m, 4H, CH_2, CH_2-ethyl), 4.7 (m, 1H, CH), 6.2-7.1 (m, 5H, 4ArH, NH-indole), 8.3 (s, 1H, OH), 10.4 (s, 1H, OH-acid); ^{13}C nmr (DMSO-d_6): δ 15.7 (CH_3-ethyl), 25.8, 26.1, 26.4 (CH_2, $2CH_3-C-N$), 37.5 (CH_2-ethyl), 56.9 (CH), 96.8 (N−C−N), 102.8, 107.1, 111.5, 111.6, 125.1, 128.7, 130.4, 150.4 (indole), 153.2 (N−CO−N), 171.9 (C=O, acid); ms: m/e (relative intensity) 331 (M^+, 3), 146 ($M^+ - C_6H_{13}N_2O_3$, 100).

Anal. Calcd. for $C_{17}H_{21}N_3O_4$: C, 61.62; H, 6.39; N, 12.68. Found: C, 61.64; H, 6.58; N, 12.59.

3-(5-Hydroxy-3-indolyl)-2-[(3-*n*-propyl-4,4-dimethyl-2-oxo)-1,3-diazetidinyl]propionic Acid (**9**).

This compound was obtained in a yield of 15%, mp 122-124° (ethyl acetate); $[\alpha]_D^{20}$ +55.9° (c 0.60, methanol); ir (potassium bromide): ν 3500-2500 (broad OH), 3460 (OH), 3420 (NH), 1740 (C=O, acid), 1620 (N−CO−N), 1610, 1580 (ArC=C) cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.7 (s, 3H,

CH_3-C-N), 0.9 (t, 3H, CH_3-propyl), 1.1-1.4 (m, 2H, CH_2-propyl), 1.5 (s, 3H, CH_3-C-N), 2.8-4.0 (m, 4H, CH_2-indole, CH_2-N), 4.7 (s, 1H, CH), 6.4-7.1 (m, 5H, 4ArH, NH), 8.5 (s, 1H, OH), 10.6 (s, 1H, OH-acid); ^{13}C nmr (DMSO-d_6): δ 11.8 (CH_3-propyl), 23.3 (CH_2-propyl), 26.0, 26.2, 26.6 (CH_2, $2CH_3-C-N$), 41.8 ($N-CH_2$), 56.0 (CH), 97.0 ($N-C-N$), 103.0, 107.2, 111.6, 125.3, 128.7, 130.6, 150.6 (indole), 153.5 ($N-CO-N$), 172.1 ($C=O$, acid).

Anal. Calcd. for $C_{18}H_{23}N_3O_4$: C, 62.59; H, 6.79; N, 12.16. Found: C, 62.30; H, 6.97; N, 11.89.

3-(5-Hydroxy-3-indolyl)-2-[(3-isopropyl-4,4-dimethyl-2-oxo)-1,3-diazetidinyl]propionic Acid (**10**).

This compound was obtained in a yield of 25%, mp 136-138° (ethyl acetate): $[\alpha]_D^{20}$ +72.8° (c 1.22, methanol); ir (potassium bromide): ν 3500-2500 (broad, OH), 3390 (OH), 3320 (NH), 1770 ($C=O$, acid), 1640 ($N-CO-N$), 1600, 1570 ($ArC=C$) cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.7 (s, 3H, CH_3-C-N), 1.0 (d, 3H, CH_3-isopropyl), 1.1 (d, 3H, CH_3-isopropyl), 1.5 (s, 3H, CH_3-C-N), 3.0-3.9 (m, 3H, CH_2, CH-isopropyl), 4.7 (m, 1H, CH), 5.9 (d, 1H, NH), 6.2-7.1 (m, 4H, ArH), 8.2 (s, 1H, OH), 10.3 (s, 1H, OH-acid); ^{13}C nmr (DMSO-d_6): δ 23.1, 23.5 ($2CH_3$-isopropyl), 26.2, 26.3, 26.7 (CH_2, $2CH_3-C-N$), 41.9 (CH-isopropyl), 57.0 (CH), 97.2 ($N-C-N$), 103.1, 107.3, 111.8, 125.4, 128.7, 130.7, 150.6 (indole), 153.0 ($N-CO-N$), 172.2 ($C=O$, acid); ms: m/e (relative intensity) 345 (M^+, 5), 146 ($M^+-C_9H_{15}N_2O_3$, 100).

Anal. Calcd. for $C_{18}H_{23}N_3O_4$: C, 62.59; H, 6.71; N, 12.16. Found: C, 62.45; H, 6.75; N, 12.25.

Acknowledgements.

We thank the "Comisión Asesora Investigación Científica y Técnica" for the financial support. We also thank Dr. Marten of Knoll AG (Lugwigshafen, FRG) for the specific rotations data.

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