REACTION OF L-TRYPTOPHAN WITH ALKYL ISOCYANATES

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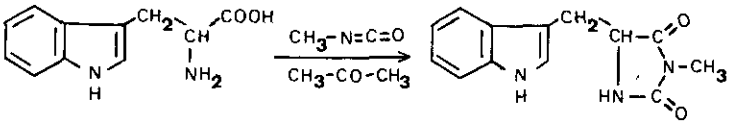
Abstract- L-Tryptophan reacts with alkyl isocyanates to give the corresponding hydantoins 2,4-7. Alternatively, the reactions with ethyl, propyl and isopropyl isocyanates in acetone provide the corresponding 2-[(3-alkyl-4,4-dimethyl-2-oxo)-1,3-diazetidinyl]-3-(3-indolyl)propionic acids 3, 8 and 9.

In continuation of our efforts to develop new tryptophan derivatives[1,2], we now report the reaction of L-tryptophan with alkyl isocyanates[3].

Treatment of L-tryptophan 1 with methyl isocyanate in acetone gave 3-methyl-5-(3-indolylmethyl)hydantoin 2. The ir, ^{1}H and ^{13}C nmr spectra (Tables I and II) define the structure of 2, and, as expected, mass spectral analysis shows the production of fragments corresponding to M^+ and $M^+-C_4H_5N_2O_2$.



1 2

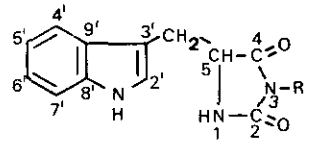
The treatment of 1 with ethyl isocyanate in acetone unexpectedly gave rise to the formation of 2-[(3-ethyl-4,4-dimethyl-2-oxo)-1,3-diazetidinyl]-3-(3-indolyl)propionic acid 3 (Scheme I). None of the corresponding hydantoin was formed. The structural assignment was based on the spectral data given in Tables III and IV. Ms (m/z) 315 (M^+), 244 ($M^+-C_3H_5NO$), 130 ($M^+-C_8H_{13}N_2O_3$). However, by carrying out the reaction of 1 with ethyl isocyanate in pyridine, the expected hydantoin 4, was obtained (Tables I and II). Similarly, the hydantoins 5,6 and 7 were isolated by the reactions of 1 with propyl, isopropyl and t-butyl isocyanates in pyridine.

Table I. 3-Alkyl-5-(3-indolylmethyl)hydantoins

compd.	R	ir (ν, cm^{-1}) (KBr)			^{1}H nmr (δ, ppm)[a]
		NH	C=O	N-CO-N	
2	CH_3	3400,3300	1750	1700	2.7(s,3H,CH_3), 3.0-3.3(m,2H,CH_2), 4.3(t,1H,CH), 6 9-7.6 (m,6H,5ArH,NH), 8.1(s-br,1H,NH)
4	CH_3CH_2	3360,3280	1750	1700	0.6(t,3H,CH_3), 2.9-3.4(m,4H,$2CH_2$), 4.2(t,1H,CH), 6.7-7.5(m,6H,5ArH,NH), 7.9(s,1H,NH).
5	$CH_3CH_2CH_2$	3400,3280	1760	1710	0.4(t,3H,CH_3), 0.7-1.3(m,2H,CH_2), 2.7-3.3(m,4H,$2CH_2$), 4.1(t,1H,CH), 6.6-7.4(m,6H,5ArH,NH), 7.8(s,1H,NH).
6	$(CH_3)_2CH$	3400,3290	1760	1710	1.0(d,6H,$2CH_3$), 2.8-3 1(m,2H,CH_2), 3.4-4.1(septet,1H,CH), 4.3(t,1h,CH), 5.8-6.0 (m,1H,NH), 6.6-7.5(m,6H,5ArH,NH).
7	$(CH_3)_3C$	3400,3360	1720	1650	1.3(s,9H,$3CH_3$), 2.9-3.2(m,2H,CH_2), 4.3-4.6(m,1H,CH), 6.9-7.7(m,6H,5ArH,NH), 8.0(s-br,1H,NH).

a.- Me_2So-d_6

Table II. ^{13}C nmr (δ,ppm)[a] of 3-Alkyl-5-(3-indolylmethyl)hydantoins



compd.	R	C_4	C_2	$C_{8'}$	$C_{9'}$	$C_{2'}$	$C_{6'}$	$C_{4'}$ or $C_{5'}$	$C_{7'}$	$C_{3'}$	C_5	CH_2 indole	R: C	R: CH	R: CH_2	R: CH_3
2	CH_3	174.2	157.0	136.0	127.4	124.0	120.9	118.4or118.3	111.3	108.0	57.2	26.8	--	--	--	23.8
4	CH_3CH_2	173.5	157.3	136.6	127.3	123.1	122.7	120.1or118.7	111.4	109.9	57.9	28.2	--	--	33.6	13.1
5	$CH_3CH_2CH_2$	174.0	157.1	136.0	127 5	124.2	120.0	118.5or118.2	111.1	107.5	56.5	26 6	--	--	39.3,20.5	10.5
6	$(CH_3)_2CH$	171.2	156.8	136.0	127.6	123.3	120.6	118.6or118.0	111.0	110.1	53.6	29 1	--	40.8	--	23.1,22.2
7	$(CH_3)_3C$	174.4	156.8	136.0	127.3	123.5	120.8	118.4or118.3	111.2	109.7	53.1	28.3	49.0	--	--	29.1

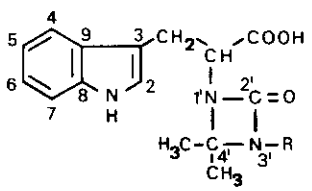
a.- Me_2SO-d_6

Table III. 2-[(3-Alkyl-4,4-dimethyl-2-oxo)-1,3-diazetidinyl]-3-(3-indolyl)propionic Acids

compd.	R	ir (ν, cm^{-1}) (KBr)				^{1}H nmr (δ, ppm)[a]
		OH	NH	C=O	N-CO-N	
3	CH_3CH_2	3400	3280	1780	1650	0.6(s,3H,CH_3-C-N), 1.1(t,3H,CH_3-ethyl), 1.4(s,3H, CH_3-C-N), 3.3-3.4(m,4H,2CH_2), 4.6-4.8(m,1H,CH), 6.8-7.5 (m,6H,5ArH,NH), 10.9(s,1H,COOH).
8	$CH_3CH_2CH_2$	3400	3270	1770	1640	0.6(s,3H,CH_3-C-N), 0.8(t,3H,CH_3-propyl), 1.2-1.7(m, 5H,CH_2-propyl,CH_3-C-N), 2.9-3.7(m,4H,CH_2N,CH_2-indole) 4.6-4.8(m,1H,CH), 6.3-7.5(m,6H,5ArH,NH), 10.7(s,1H,COOH).
9	$(CH_3)_2CH$	3400	3290	1770	1635	0.7(s,3H,CH_3-C-N), 1.1(d,3H,CH_3-isopropyl), 1.3(d,3H CH_3-isopropyl), 1.5(s,3H,CH_3-C-N), 3.1-4.2(m,3H,CH-isopropyl,CH_2), 4.8-5.0(m,1H,CH), 6.2(d,1H,NH), 6.9-7.6 (m,5H,ArH), 10.8(s,1H,COOH).

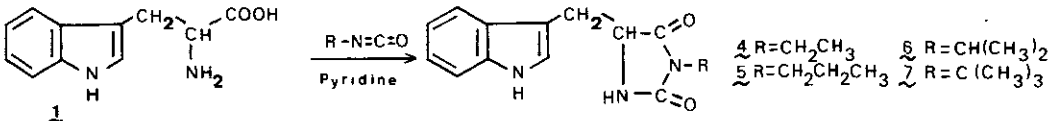
a.- Me_2SO-d_6

Table IV. ^{13}C nmr (δ, ppm)[a] of 2-[(3-Alkyl-4,4-dimethyl-2-oxo)-1,3-diazetidinyl]-3-(3-indolyl)-propionic Acids



compd.	R	C=O acid	$C_{2'}$	C_8	C_9	C_2	C_6	C_5,C_4	C_7	C_3	$C_{4'}$	CH	CH_3 or CH_2 indole	R CH	R CH_2	R CH_3
3	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
9	$(CH_3)_2CH$	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	--	23.3622.9

a.- Me_2SO-d_6



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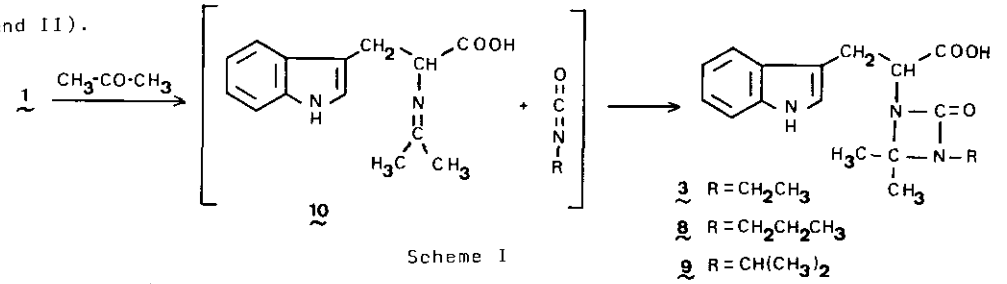
Because of the interesting formation of 3, other analogous reactions of 1 with n-propyl, isopropyl and t-butyl isocyanates have been carried out. The treatment of 1 with n-propyl and isopropyl isocyanates in acetone afforded the expected sustituted propionic acids 8 and 9 (Tables III and IV. Scheme I). Finally the reaction of 1 with t-butyl isocyanate in acetone yielded 3-t-butyl-5-(3-indolylmethyl)hydantoin 7 (Tables I and II).



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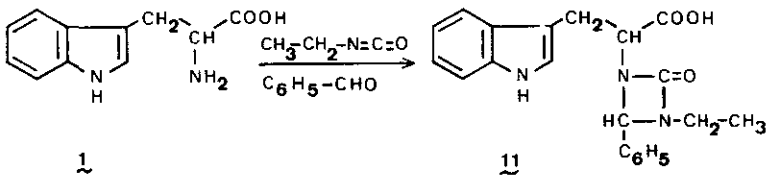
Scheme I

The formation of 3, 8 and 9 may be explained by condensation of 1 with the solvent (acetone) followed by [2+2] cycloaddition to 10 with the corresponding alkyl isocyanate (Scheme I). This reaction is not exclusive of acetone. So, the treatment of 1 with ethyl isocyanate in benzaldehyde yielded 2-[(3-ethyl-4-phenyl-2-oxo)-1,3-diazetidinyl]-3-(3-indolyl)propionic acid 11.



1 11

Presumably, the fact that methyl and t-butyl isocyanates did not form diazetidinones is easily understood by the assumptions that in the methyl isocyanate case the reaction between tryptophan and the isocyanate is more rapid that the formation of the Schiff base while in the t-butyl isocyanate case, steric effects are influencing the reaction.

On the other hand, the differnces observed in the [α] values for hydantoins and diazetidinones could be explained by racemization of both compounds. So, hydantoins may racemize through the enol or enolate form during long refluxing in pyridine. And Schiff base like 10 may racemize by isomerization.

EXPERIMENTAL

Melting points were measured with a Büchi apparatus and are uncorrected. Ir spectra were determined on a Perkin-Elmer 781 spectrophotometer. ^{1}H and ^{13}C nmr spectra were recorded on a Varian T-60A (60 MHz) and Varian FT-80A spectrometers, respecti-

vely. Mass spectrometry was performed with a Varian MAT-711 apparatus. Specific rotations, [α] , were determined on a Perkin-Elmer Model 141 polarimeter. The elemental analyses were performed by "Centro Nacional de Química Orgánica", Madrid.

General Procedures

Method 1.

Alkyl isocyanate (0.024 mol) in 20 ml of dry acetone was added to a suspension of L-tryptophan (5.0g, 0.024 mol) in 20 ml of acetone. The reaction mixture was refluxed for 40 h. L-tryptophan was removed by filtration and the solvent was evaporated to dryness. The residue solidified on trituration with ethyl acetate or ethyl ether.

Method 2.

A suspension of L-tryptophan (5.0g, 0.024 mol) and alkyl isocyanate (0.024 mol) in 50 ml of pyridine was refluxed for 40 h. L-triptophan was removed by filtration and the solvent was evaporated. The residue was dissolved in chloroform, washed with H_2O twice, dried over $MgSO_4$ and evaporated to yield an oil, which was chromatographed on a silica gel column with benzene as eluent, affording the corresponding dialkyl urea. Futher elution of the column with benzene-ethanol 9-1 afforded the compounds.

3-Methyl-5-(3-indolylmethyl)hydantoin 2

Method 1; trituration with ethyl acetate; yield 35%; mp 207-209 ºC (ethyl acetate); $[\alpha]_D^{20}$= -53.2º (c 0.7, MeOH); Anal. Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.38; N, 17.27. Found: C, 64.46; H, 5.49; N, 17.37.

2-[(3-Ethyl-4,4-dimethyl-2-oxo)-1,3-diazetidinyl]-3-(3-indolyl)propionic Acid 3

Method 1; trituration with ethyl ether; yield 45%; mp 163-164 ºC (ethyl ether); $[\alpha]_D^{20}$= +13.1 (c 2.2, MeOH); Anal. Calcd. for $C_{17}H_{21}N_3O_3$: C, 64.70; H, 6,66; N, 13.23. Found: C, 64.45; H, 6.92; N, 13.40.

3-Ethyl-5-(3-indolylmethyl)hydantoin 4

Method 2; yield 32%; mp 124-125 ºC (ethyl ether); $[\alpha]_D^{20}$= -6.2º (c 0.4, MeOH); Anal. Calcd. for $C_{14}H_{15}N_3O_2$: C, 65.37; H, 5.83; N, 16.34. Found: C, 65.49; H, 5.78; N, 16.38.

3-Propyl-5-(3-indolylmethyl)hydantoin 5

Method 2; yield 37%; mp 204-206 ºC (ethyl acetate); $[\alpha]_D^{20}$= -37.9º (c 2.3, MeOH); Anal. Calcd. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.31; N, 15.48. Found: C, 66.31; H, 6.18; N, 15.60.

3-Isopropyl-5-(3-indolylmethyl)hydantoin 6

Method 2; yield 35%; mp 160-162 ºC (ethyl acetate); $[\alpha]_D^{20}$= -30.4º (c 1.8, MeOH);

Anal. Calcd. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.31; N, 15.48. Found: C, 66.50; H, 6.17; N, 15.63.

3-t-Butyl-5-(3-indolylmethyl)hydantoin 7

Method 1; the residue was purified with silica gel column chromatography (ethyl acetate); yield 22%. Method 2; yield 15%; mp 140-143 ºC (water); Anal. Calcd. for $C_{16}H_{19}N_3O_2$: C, 67.35; H, 6.71; N, 14.72. Found: C, 66.95; H, 6.50; N, 14.48.

2-[(3-n-Propyl-4,4-dimethyl-2-oxo)-1,3-diazetidinyl]-3-(3-indolyl)propionic Acid 8

Method 1; trituration with ethyl ether; yield 20%; mp 165-167 ºC (ethyl acetate); $[\alpha]_D^{20}$= +80º (c 1.1, MeOH); Anal. Calcd. for $C_{18}H_{23}N_3O_3$: C, 65.65; H, 6.99; N, 12.76. Found: C, 65.93; H, 7.07; N, 12.74.

2-[(3-Isopropyl-4,4-dimethyl-2-oxo)-1,3-diazetidinyl]-3-(3-indolyl)propionic Acid 9

Method 1; trituration with ethyl acetate; yield 20%; mp 138-140 ºC (ethyl acetate); $[\alpha]_D^{20}$= +30.3º (c 2.0, MeOH); Anal. Calcd. for $C_{18}H_{23}N_3O_3$: C, 65.65; H, 6.99; N, 12.76. Found: C, 65.45; H, 6.92; N, 12.52.

2-[(3-Ethyl-4-phenyl-2-oxo)-1,3-diazetidinyl]-3-(3-indolyl)propionic Acid 11

Method 1; solvent (benzaldehyde); trituration with ethyl acetate; yield 23%; mp 156-158 ºC (ethyl acetate); $[\alpha]_D^{20}$= +32.3º (c 1.5, MeOH); ir (ν,cm^{-1}) (KBr): 3420 (OH), 3280 (NH), 1800 (C=O), 1660 (N-CO-N); ^{1}H nmr (δ,ppm): 0.9 (t, 3H, CH_3), 2.8-3.6 (m, 4H, $2CH_2$), 4.6-4.8 (m, 1H, CH), 5.6-5.9 (m, 1H, N-CH-N), 6.4-7.6 (m, 11H, 10ArH, NH), 10.8 (s, 1H, COOH); ^{13}C nmr (δ,ppm): 172.7 (C=O, acid), 152.1 (N-CO-N), 137.9, 136.3, 136.2, 128.7, 127.8, 126.6, 124.4, 121.2, 118.7, 118.6, 111.5, 108.5 (aromatic), 89.1 (N-CH-N), 57.6 (CH), 34.8 (CH_2), 27.2 (CH_2-indole), 15.0 (CH_3); Anal. Calcd. for $C_{21}H_{21}N_3O_3$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.48; H, 5.91; N, 11.61.

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