Synthesis and Spectroscopic Properties of *N*-Azolylpropanamides

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Fourteen *N*-azolylpropanamides have been prepared by Michael addition of azoles on acrylamide. The compounds have been fully characterized by IR and by ^1H and ^{13}C-nmr. The isolated compounds are the most stable derivatives; kinetic compounds were observed but could not be isolated.

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N-Azolylpropanamides, Az-CH_2-CH_2-$CONH_2$, where Az is an *N*-substituted azole ring, are interesting synthons in medicinal chemistry. A careful survey of the literature shows that several *N*-azolylpropanamides are known, but that no systematic work has been carried out on these compounds, and neither have their spectroscopic characteristics been described. We report here the synthesis, infrared, proton and carbon-13 nmr spectra of the following compounds (Scheme I).

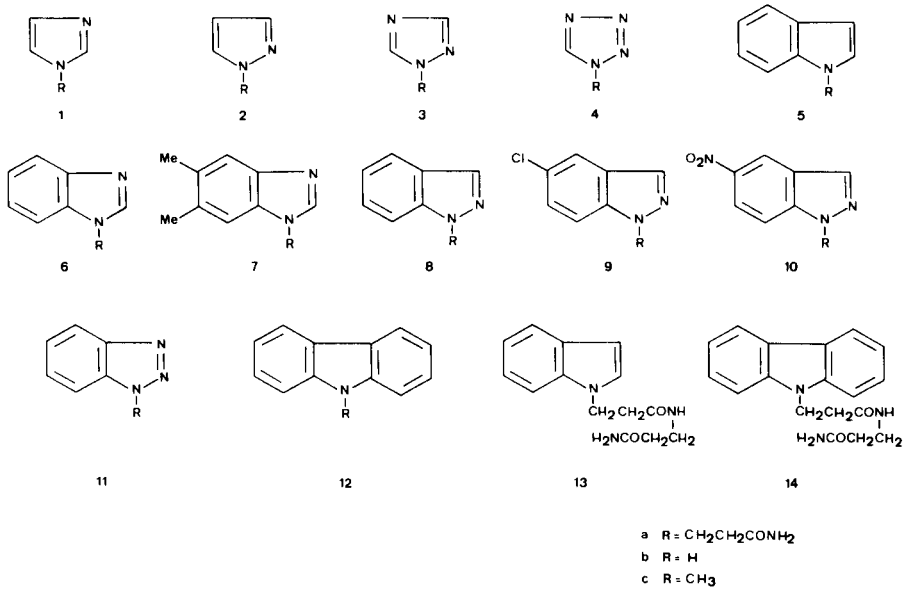
Syntheses.

The compounds have been prepared by Michael addition of the corresponding azole **1b-12b** (R = H) to acrylamide in basic medium (pyridine-sodium methoxide as catalyst). After 3-8 hours reflux the propanamides were obtained with yields which range from 22%, **4a**, to 96%, **11a** (Table I). Only the benzimidazole derivative **6a** had been prepared by this procedure [1].

Compound **11a** had been described but its preparation [2] was more complicated and proceeded in lower yield: *N*-substitution with chloropropanoic acid, esterification and ammonolysis. Compounds **5a** [3] and **8a** [4] were prepared by addition to acrylamide, but in dioxane/potassium hydroxyde for the first one and in *t*-butyl alcohol (2 days reaction time) for the second. Three patents reported the preparation of **1a** [5], **3a** [6] and **12a** [7], but experimental procedures are obscure.

In the case of indole and carbazole, the less nucleophilic azoles [8], in addition to the propanamides **5a** and **12a**, compounds **13** and **14** were respectively isolated. These last compounds, resulting from a double addition to acrylamide, were also formed when compounds **5a** and **12a** were treated with acrylamide in the same experimental conditions.

Scheme I



a R = $CH_2CH_2CONH_2$
b R = H
c R = CH_3

Table I

Compound	Yield (%)	MP °C [a]	Molecular Formula	Analysis % Calcd./(Found) C	H	N	IR (cm^{-1}) NH_2	C=O	Reaction Time, Hours
1a	57	128-130 [b]	$C_6H_9N_3O$	51.79 (51.94)	6.52 (6.61)	30.19 (29.92)	3380 3120	1670 [h]	5
2a	82	80-82 [b]	$C_6H_9N_3O$	51.79 (52.07)	6.52 (6.53)	30.19 (30.50)	3360 3140	1690 [h] (1660)	7
3a	81	104-106 [b]	$C_5H_6N_4O$	42.85 (42.86)	5.75 (5.87)	39.98 (39.75)	3300 3100	1680-1640 (broad) [i]	7
4a	22	102-104 [b]	$C_4H_7N_5O$	34.04 (34.31)	4.99 (5.01)	49.62 (49.40)	3400 3300 3200	1680 [i] 1640	8
5a	39	90-92 [c]	$C_{11}H_{12}N_2O$	70.19 (70.02)	6.42 (6.41)	14.88 (15.15)	3400 3220 3180	1680 [h] 1660	3
6a	30	158-160 [d]	$C_{10}H_{11}N_3O$	63.48 (63.32)	5.86 (5.50)	22.21 (22.50)	3320 3160	1670 [h]	4
7a	70	138-140 [d]	$C_{12}H_{15}N_3O \cdot H_2O$	61.25 (61.20)	7.28 (7.19)	17.85 (18.08)	3500 3300 3180	1680 [h] 1640	4
8a	63	126-128 [d]	$C_{10}H_{11}N_3O$	63.48 (63.61)	5.86 (5.78)	22.21 (22.28)	3300 3160	1680 [h]	5
9a	70	138-140 [d]	$C_{10}H_{10}ClN_3O$	53.70 (53.45)	4.51 (4.25)	18.79 (19.01) [g]	3440 3380 3280	1650 [h]	5
10a	42	166-168 [d]	$C_{10}H_{10}N_4O_3$	51.28 (51.49)	4.30 (4.47)	23.92 (24.02)	3420 3290 3190	1660 [h]	8
11a	96	120-122 [b]	$C_9H_{10}N_4O$	56.83 (57.14)	5.30 (5.28)	29.45 (29.55)	3380 3180	1650-1620 (broad) [h]	8
12a	33	146-148 [e]	$C_{15}H_{14}N_2O$	75.61 (75.50)	5.92 (5.77)	11.75 (11.58)	3400 3140	1690 [h]	5
13	7	128-130 [b]	$C_{14}H_{17}N_3O_2$	64.85 (64.95)	6.61 (6.67)	16.20 (15.92)	3340 3180	1660 [h] (broad	
14	28	212-214 [f]	$C_{18}H_{19}N_3O_2$	69.88 (69.79)	6.19 (6.09)	13.58 (13.42)	3380 3300	1660 [i] 1630	

[a] Recrystallization solvents. [b] Ethanol. [c] Water/Ethanol. [d] Water. [e] Methanol/Water. [f] Methanol. [g] Cl: 15.85 (15.81). [h] In potassium bromide. [i] In nujol.

Spectroscopic Properties.

All the compounds (see Table I) show the characteristic bands of the -$CONH_2$ group [9] both the NH stretching bands, free and associated, and the CO bands (amide I band). The proton and carbon-13 nmr data are collected in Tables II and III respectively. The assignment is straightforward from the data of the corresponding *N*-methylazoles **1c-12c** [10-13]. In particular, the carbon-13 chemical shifts and the ^1H- ^{13}C coupling constants of series **a** and **c** are very similar. There is a slight effect on C_7 in carbon-13 nmr (Table III): it appears at about 1 ppm downfield in propanamides, probably a steric effect.

Concerning the signals of the carbon atoms, C_α and C_β, it is worth mentioning that C_α chemical shifts of compounds **1a**, **2a**, **3a**, **4a**, **5a**, **6a**, **8a**, **11a** and **12a** (all the non *C*-substituted derivatives) are well correlated with the corresponding *N*-methyl, *c* series, chemical shifts [12]:

$$\delta\ CH_2(\alpha) = 11.3 + 0.95\ \delta\ CH_3,\ n = 9,\ r^2 = 0.969$$

Carbon C_β signals are less sensitive to the azole nature. However, a relationship can be found with an empirical scale of β effects [13]:

$$\delta\ CH_2(\beta) = 35.1 + 1.17\ \delta(\beta),\ n = 9,\ r^2 = 0.964$$

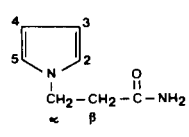
where $\delta(\beta)$ is 1.03 for imidazole, 0.53 for pyrazole, −0.30

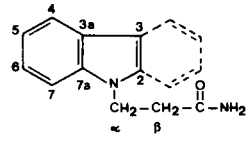
Table II

^{1}H-NMR Parameters: Chemical Shift (ppm) and Coupling Constants (Hz) (Solvent: DMSO-d_6)

Compound	H-α [a]	H-β [a]	H-2	H-3	H-4	H-5	H-4,5,6,7	NH_2 [b]
1a	4.13	2.50	7.53	—	6.83	7.10	—	7.40
2a	4.30	2.60	—	7.37	6.13	7.60	—	6.87
3a	4.37	2.65	—	7.92	—	8.40	—	7.37 6.87
3a'	3.50	2.26	—	7.66	—	7.66	—	
4a	4.63	2.73	—	—	—	9.30	—	7.43 6.93
4a'	4.80	2.90	—	—	—	8.50	—	
5a	4.40	2.60	7.35	6.42	—	—	6.92-7.62	6.90
6a	4.56	2.66	8.03	—	—	—	7.30-7.80	6.83
7a [c]	4.46	2.60	7.96	—	—	—	7.33 H-4 7.36 H-9	6.93
8a	4.60	2.70	—	8.06	—	—	7.03-7.70	6.86
8a'	4.65	2.30	—	7.96	—	—		6.80
9a	4.56	2.66	—	8.03	—	—	7.30-7.76	6.83
9a'	3.20	2.20	—	—	—	—	—	
10a	4.66	2.70	—	8.36	—	—	7.80-8.80	7.40 6.83
10a'	3.50	2.27	—	—	—	—	—	
11a	4.86	2.80	—	—	—	—	7.30-8.06	6.90
11a'	3.52	2.30	—	—	—	—	—	
12a	4.56	2.60	—	—	—	—	7.10-8.13	6.82
13 [d]	4.40	2.60	7.30	6.43	—	—	6.96-7.63	6.83
14 [e]	4.60	2.56	—	—	—	—	7.06-8.06	6.76

[a] All these signals are triplets with an apparent coupling constant ^3J = 6 Hz. [b] Broad singlets. [c] δ 2.26 and 2.30 (s, 3H, CH_3). [d] δ 8.00 (t, 1H, NH), 3.20 (q, 2H, CH_2), 2.26 (t, 2H, CH_2) corresponding to the -CO-NH-CH_2-CH_2- fragment. [e] δ 7.93 (t, 1H, NH), 3.20 (q, 2H, CH_2), 2.13 (t, 2H, CH_2) corresponding to the -CO-NH-CH_2-CH_2- fragment.





for 1,2,4-triazole, −0.63 for 1,2,3,4-tetrazole, 0.49 for indole, −0.02 for benzimidazole, −0.24 for 1(*H*)-indazole, 0.12 for 1(*H*)benzotriazole and −0.54 for carbazole.

Orientation in the Michael Reaction.

Several compounds could only yield one addition compound either because they have only one nitrogen atom, **5** and **12**, or due to their symmetry, **1**, **2**, **6** and **7**. However, the remaining compounds, **3**, **4**, **8**, **9**, **10** and **11** could yield two isomeric derivatives.

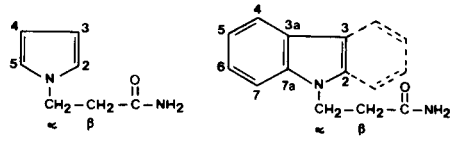
Generally speaking, substitution on the azole nitrogen can be kinetically or thermodynamically controlled. Alkylation (with methyl iodide, for instance) and arylation (with 1-fluoro-2,4-dinitrobenzene, for instance) yield a mixture of kinetic isomers. Acylation and metallation (for instance, trimethylsilylation) yield generally the most stable isomer [8]. Azolylpropanamides have an N-C (sp^3) as methyl derivatives, but the retro-Michael reaction would permit the thermodynamic equilibrium to be reached.

The isolated isomers **3a**, **4a**, **8a**, **9a**, **10a**, and **11a** have the substituent position unambiguously established by nmr (see the preceeding paragraph). They correspond in all cases to the most stable isomers [11]. However, although only one compound has been isolated in all cases the ^{1}H-nmr spectra recorded in the course of the reaction show, for *all of these azoles,* the signals [10] of the other isomer (**3a'**, **4a'**, **8a'**, **9a'**, **10a'**, and **11a'**). For instance, in the case of benzotriazole, the crude of the reaction is a 35:65 mixture of N(1) and N(2) isomers, **11a** and **11a'**, but after 24 hours, only the signals of the N(1) isomer **11a** are

Table III

^{13}C-NMR Parameters: Chemical Shift (ppm) and Coupling Constants (Hz) (Solvent: DMSO-d_6)

Compound	Cα	Cβ	CO	C_2	C_3	C_{3a}	C_4	C_5	C_6	C_7	C_{7a}
1a	42.3 ^1J = 141.8 ^2J = 6.7	36.5 ^1J = 125.3 ^2J = 5.8	171.7 ^2J = 4.5	137.2 ^1J = 206.4 ^3J = 9.8 ^3J = 6.9			128.2 ^1J = 176.3 ^2J = 10.5 ^3J = 10.8	119.3 ^1J = 188.8 ^2J = 16.5 ^3J = 2.9			
2a	47.3 ^1J = 141.3 ^2J = 5.0	35.6 ^1J = 128.0 ^2J = 7.2	171.8 ^2J = 4.0		138.5 ^1J = 183.5 ^2J = 7.8 ^3J = 7.8		104.8 ^1J = 174.5 ^2J = 9.4 ^2J = 10.3	129.7 ^1J = 184.4 ^2J = 7.7			
3a	45.0 ^1J = 143.2 ^2J = 4.5	34.7 ^1J = 126.3 ^2J = 4.8	171.5		151.2 ^1J = 205.9 ^3J = 11.9			144.1 ^1J = 212.0 ^3J = 7.5			
4a	44.0 ^1J = 145.8 ^2J = 3.8	34.4 ^1J = 126.3 ^2J = 4.1	171.8 ^2J = 4.2					144.2 ^1J = 218.4			
5a	41.7 ^1J = 139.6 ^2J = 5.4	35.7 ^1J = 128.7 ^2J = 6.6	172.0 ^2J = 4.6	128.1 ^1J = 183.2 ^2J = 7.0	100.5 ^1J = 173.5 ^2J = 6.9 ^3J = 2.8	128.4	118.3	120.3	120.9	109.6	135.5
6a	40.4 ^1J = 140.5 ^2J = 3.9	35.1 ^1J = 128.8 ^2J = 5.9	171.6	143.9 ^1J = 206.9		143.4	119.3	121.4	122.2	110.3	133.6
7a [a]	40.5 ^1J = 140.7 ^2J = 4.0	35.3 ^1J = 125.1 ^2J = 5.5	171.9	143.1 ^1J = 206.5		142.0	119.4	129.8	131.0	110.4	132.2
8a	44.4 ^1J = 145.3 ^2J = 4.6	35.2 ^1J = 128.0 ^2J = 7.2	171.8		132.7 ^1J = 189.3 ^3J = 2.2	123.5	120.6	120.3	125.8	109.7	139.2
9a	44.7 ^1J = 139.2 ^2J = 4.1	35.2 ^1J = 125.6 ^2J = 4.1	171.8 ^2J = 3.9		132.3 ^1J = 191.2 ^3J = 2.2	124.3	119.7	125.0	126.3	111.6	137.9
10a	44.9 ^1J = 144.4 ^2J = 4.3	35.0 ^1J = 128.3 ^2J = 6.2	171.7 ^2J = 4.1		136.2 ^1J = 193.8 ^3J = 2.4	122.5	118.7	141.0	120.7	110.8	141.6
11a	43.9 ^1J = 143.4 ^2J = 4.6	35.0 ^1J = 128.9 ^2J = 3.5	171.3 ^2J = 4.0			145.1	118.9	123.8	126.9	110.8	132.9
12a	39.0 ^1J = 138.7 ^2J = 2.9	34.5 ^1J = 128.1 ^2J = 3.5	172.2 ^2J = 3.1	139.8	122.2	122.2	120.1	118.7	125.6	109.3	139.8
13 [b]	41.9 ^1J = 139.6	34.9	172.6	128.1	100.6	128.4	120.3	120.9	118.8	109.6	135.5
14 [c]	39.2	34.9 ^1J = 129.1	172.5 ^2J = 4.6	139.7	122.2	122.2	118.7	120.1	125.6	109.2	139.7



[a] CH_3: δ 19.7 ^1J = 125.8; CH_3: δ 20.0 ^1J = 125.8. [b] δ 169.8; 36.1 (^1J = 128.6); 35.2 (^1J = 134.4) corresponding to the -CO-NH-CH_2-CH_2- fragment. [c] δ 170.0; 39.4; 35.3 corresponding to the -CO-NH-CH_2-CH_2- fragment.

observed. All attempts to isolate the N(2) isomer failed. Thus, the Michael addition yields the kinetic mixture which isomerizes with activation energies high enough to observe both isomers but not enough to prevent their equilibration.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257. The ^{1}H-nmr spectra were measured on a Varian EM-90 operating at 90 MHz. The ^{13}C-nmr spectra were recorded on a Bruker WP-SY-80 operating at 20 MHz and using TMS as internal standard.

General Procedure.

A suspension of acrylamide (0.075 mole) and the corresponding azole (0.05 mole) in pyridine and sodium methoxide (3 ml) as catalyst were refluxed for the reaction times specified in each case (Table I). After cooling, the crude solid was purified and recrystallized from the appropriate solvent (Table I).

Compounds **13** and **14** were obtained from the crude reaction mixtures of **5** and **12** respectively by column chromatography (eluent chloroform: methanol 15:1).

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