Cyclodehydration of *N*-[(2-Heteroarylcarbamoyl)methyl]benzamides. Preparation of 5-(Heteroarylamino)oxazoles (1)

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The cyclodehydration of *N*-[heteroarylcarbamoyl)methyl]benzamides was found to yield 5-(heteroarylamino)oxazoles.

N-Substituted amides of α-acylamino acids may undergo a cyclodehydration at several alternate sites. In the more simple case of an unreactive substituent at the amide nitrogen, the cyclodehydration is believed to result in the formation of imidazole derivatives (3,4). However, the literature contains conflicting reports concerning the identity of the products of this reaction. Some have not been assigned structures, while others have been shown, by alternate synthetic routes, to be oxazoles and not imidazoles (5,6). In the case of a reactive substituent at the amide nitrogen, the situation is further complicated by the potential for formation of fused ring systems.

The purpose of this investigation was to study the cyclodehydration of *N*-substituted amides of α-acylaminoacids such as *N*-[(2-heteroarylcarbamoyl)methyl]benzamides in order to clarify the nature of the products and to explore the feasibility of this route for the formation of novel fused diazepine and triazepine ring systems.

The synthetic scheme consisted of the reaction of an aminoheterocycle with 2-phenyl-5-oxazolone (**2**) followed by cyclodehydration of the resulting *N*-[(2-heteroarylcarbamoyl)methyl]benzamides.

For example, when 2-aminoindole (**1a**) was allowed to react with 2-phenyl-5-oxazolone (**2**), *N*-[(2-indolylcarbamoyl)methyl]benzamide (**3a**) was obtained. Cyclodehydration of **3a** with polyphosphate ester (PPE) gave a single product having four possible structures. An imidazolylindole **5a** or an oxazolylaminoindole **6a** could arise from the reaction within the carbamoyl side chain, and an indolo[2,1-*b*]-1,3,5-triazepine **4** or an indolo[2,1-*e*]-1,4-diazepine **7a** could result from the cyclization at the indole 1 and 3 positions, respectively. (Scheme I)

The infrared spectrum of the cyclodehydration product revealed major peaks at 1530 and 1640 cm^{-1} indicating the presence of an amide or imine function and the 3150 cm^{-1} band which is characteristic of a hydroxyl or an amine group. The lack of solubility in available deuterated solvents precluded reliable nmr spectral analysis. The product gave a positive color reaction with *p*-dimethylaminobenzaldehyde (Ehrlich reagent) (7) characteristic of an unsubstituted indole-3 position. This finding strongly decreased the likelihood of the diazepine structure **7a**. The ultraviolet spectrum was nearly identical to that derived from the corresponding N-CH_3 product which was prepared by the cyclodehydration of **3b**. This observation rendered improbable the triazepine structure **4**. In order to distinguish between the remaining structures **5** and **6**, it was necessary to resort to high resolution mass spectrometry. The mass spectra were devoid of imidazole fragments but displayed a benzoyl fragment at m/e 105 and a phenyloxazole fragment at m/e 144. On the basis of this finding oxazole structures **6a** and **6b** were assigned to the cyclodehydration products of **3a** and **3b**.

The reaction of 2-aminopyridine with 2-phenyl-5-oxa-

Scheme I

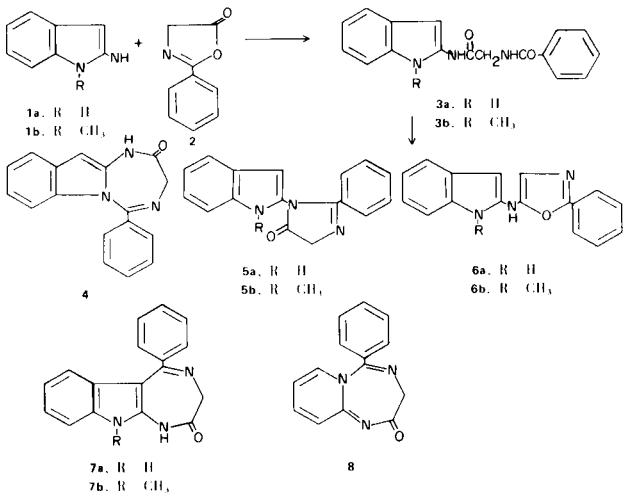
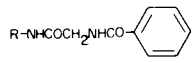
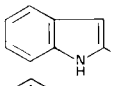
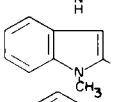
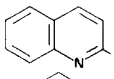
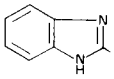
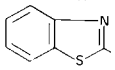


TABLE I

N-[(2-Heteroarylcarbamoyl)methyl]benzamides



	R	M.p. °C	% Yield	Empirical Formula	Analyses, % Calcd. C	H	N	S	Found C	H	N	S
3a		211-212	81	$C_{17}H_{15}N_3O_2$	69.61	5.15	14.33		69.53	5.39	14.53	
3b		202-204	58	$C_{18}H_{17}N_3O_2$	70.34	5.58	13.67		70.14	5.78	13.51	
9		172-174	62	$C_{14}H_{13}N_3O_2$	65.87	5.13	16.46		65.85	5.07	16.65	
12		229-230	71	$C_{14}H_{12}N_3O_2Cl$	58.04	4.18	14.50		57.77	4.16	14.25	
13		218-219	81	$C_{18}H_{15}N_3O_2$	70.80	4.95	13.76		70.98	5.00	13.95	
14		219-220	5	$C_{13}H_{12}N_4O_2$	60.93	4.72	21.87		60.78	4.74	21.87	
15		238-239	50	$C_{12}H_{11}N_3O_2S$	55.16	4.24	16.08	12.21	55.32	4.40	16.29	12.27
16		303-305	82	$C_{16}H_{14}N_4O_2$	65.29	4.80	19.04		65.21	4.92	18.89	
17		262-264	70	$C_{16}H_{13}N_3O_2S$	61.72	4.21	13.50	10.43	61.75	4.31	13.48	10.30
18(a)		254-256	91	$C_{10}H_{10}N_6O_2$	48.78	4.09	34.14		48.56	4.15	34.17	

(a) This compound failed to undergo cyclodehydration. Recrystallization solvents: 95% ethanol – **3a**, **16**, **17**; absolute ethanol – **3b**, **12**, **13**, **15**; ethyl acetate – **9**, **14**; tetrahydrofuran – **18**.

zolone (**2**) gave *N*-[(2-pyridylcarbamoyl)methyl]benzamide (**9**, Table I). The cyclodehydration of **9** could theoretically lead to any of the pyridine analogs of **4-7**. In this case, the diazepine structure seemed less likely because of the low nucleophilicity of the pyridine ring. Triazepine formation (**8**), however, appeared feasible since pyridopyrimidinones have been prepared by the cyclodehydration of ethyl 2-pyridylaminomethylenemalonates (8).

The cyclodehydration product of **9** had the following properties: λ max mμ (ε): 235 (9,800), 261 (8,200), 334 (22,000); ν max 1550 (m), 1585 (s), 1600 (m) cm^{-1}; δ (DMSO) ten protons in the 6.75 to 8.75 ppm region and a one-proton signal at 10.02 ppm. Consideration of this data reveals a significant shift of the ultraviolet absorption to a longer wavelength as compared to that of the starting amide **9** (Table I), signifying a higher degree of conjugation. The infrared spectrum is devoid of any characteristic amide absorption and there is an absence of any methylene group in the nmr spectrum. This evidence strongly suggested oxazole structure **10** (Table II). This was confirmed by the mass spectrum, which displayed the m/e 105 (benzoyl) and m/e 144 (phenyloxazole) fragments.

In order to establish the generality of the preference for oxazole formation over imidazole in this series, additional *N*-[(2-heteroarylcarbamoyl)methyl]benzamides were prepared (Table I) and subjected to cyclodehydration (Table II).

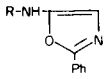
The mass spectra of these compounds all displayed the m/e 144 fragment indicating the oxazole structure.

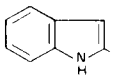
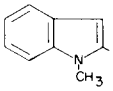
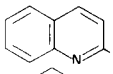
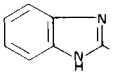
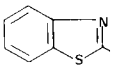
EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus which was calibrated against known stand-

TABLE II

5-(Heteroarylamino)oxazoles



	R	M.p. °C	% Yield	Empirical Formula	Analyses, % Calcd. C	H	N	S	Found C	H	N	S
6a		238-240	94	$C_{17}H_{13}N_3O$	74.16	4.73	15.25		74.11	4.95	15.05	
6b		205-206	60	$C_{18}H_{15}N_3O$	74.72	5.23	14.53		74.47	5.27	14.36	
10		169-170	33	$C_{14}H_{11}N_3O$	70.87	4.67	17.71		70.98	4.71	17.80	
19		231-232	62	$C_{14}H_{10}N_3OCl$	61.89	3.71	15.47		62.01	3.72	15.35	
20		190-192	72	$C_{18}H_{13}N_3O$	75.24	4.26	14.63		75.15	4.56	14.60	
21		242-244	64	$C_{13}H_{10}N_4O$	65.53	4.33	23.52		65.48	4.20	23.05	
22		190-191	63	$C_{12}H_9N_3O_5$	59.24	3.73	17.27	13.18	58.95	4.02	17.12	13.07
23		238-239	70	$C_{16}H_{12}N_4O$	69.55	4.38	20.28		69.61	4.39	20.57	
24		228-229	60	$C_{16}H_{11}N_3O_5$	65.51	3.78	14.32	10.93	65.55	3.89	14.31	11.16

Recrystallization solvents: acetonitrile – **6a**; absolute ethanol – **6b**, **10**, **22**, **24**; 95% ethanol – **19**, **23**; methanol – **21**; ethyl acetate – **20**.

ards. The amides (Table I) were prepared in a manner similar to that for **3a**. The cyclodehydration products (Table II) were prepared analogous to the preparation of **6a**, employing 20 g. of polyphosphate ester for each gram of amide and allowing the reaction to stir for 40-50 hours.

2-Aminoindole Hydrochloride (**1a**).

2-Amino-3-carbethoxyindole (9) (100 g., 0.5 mole) was dissolved in concentrated hydrochloric acid with heating on a steam bath until solution was complete. After another 20 minutes of heating, the solvent was removed *in vacuo* and the resulting crystals taken up in 95% ethanol (200 ml.). An equal amount of anhydrous ether was added to yield 80 g. (97%) of **1a** as white crystals, m.p. 222-224° (lit., 226°) (10).

N-[(2-Indolylcarbamoyl)methyl]benzamide (**3a**).

A suspension of **1a** (1.7 g., 0.01 mole), 2-phenyl-5-oxazolone (11) (1.6 g., 0.01 mole) and sodium acetate (0.9 g.) in tetrahydrofuran (100 ml.) was refluxed for 2 hours. The solvent was removed *in vacuo* and the resulting product was recrystallized from 95% ethanol to yield 2.5 g. (81%) of **3a** as white crystals, m.p. 211-212°.

2-[(2-Phenyl-5-oxazolyl)amino]indole (**6a**).

Compound **3a** (4.5 g., 0.016 mole) was stirred with polyphosphate ester (PPE) (12) (90 g.) at room temperature for 45 hours, poured onto ice (300 g.) and basified with concentrated ammonium hydroxide. The crude product was collected and recrystallized from acetonitrile to yield 3.8 g. (94%) of **6a**, m.p. 238-240°.

1-Methyl-2-amino-3-carbethoxyindole (**11**).

2-Amino-3-carbethoxyindole (25 g., 0.13 mole) in tetrahydrofuran (250 ml.) was added dropwise with stirring to a suspension of sodium hydride (7.25 g.) in tetrahydrofuran (200 ml.) under nitrogen. Methyl iodide (17.5 g., 0.12 mole) was added dropwise and the solution refluxed for 20 minutes. The solvent was removed *in vacuo* and the crude product recrystallized from methanol to yield 13 g. (48%) of **11** as white crystals, m.p. 137-139°.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 65.76; H, 6.40; N, 12.73.

1-Methyl-2-aminoindole Hydrochloride (**1b**).

Prepared in the same manner as **1a**, to yield 92% of **1b**, m.p. 260-270° dec., (lit.: decomposes over 260°) (10). To further

verify the position of the methyl group **1b** was hydrolyzed to 1-methyl-2-oxindole by heating an aqueous solution of **1b** in a sealed tube at 160-170° for 5 hours, m.p. 85-86°) (10).

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(1) Abstracted in part from Master Thesis of R. Glennon, Northeastern University, May 1969.

(2) Present address: Department of Pharmacology, School of Medicine, State University of New York, Buffalo, New York 14214.

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