The Synthesis of 7,8-Dihydroimidazo[1,2-*e*]pyrazolo[1,5-*a*]-1,3,5-triazines, 8,9-Dihydro-7*H*-pyrimido[1,2-*e*]pyrazolo[1,5-*a*]-1,3,5-triazines and 7,8,9,10-Tetrahydro[1,3]diazepino[1,2-*e*]pyrazolo[1,5-*a*]triazines (1)

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Cyclic hydrazino amidines were converted to the corresponding aminopyrazolyl derivatives. Ring closure between the amino groups of pyrazoline moieties and NH groups of cyclic amidines afforded the following ring systems: 7,8-Dihydroimidazo[1,2-*e*]pyrazolo[1,5-*a*]-1,3,5-triazines, 8,9-dihydro-7*H*-pyrimido[1,2-*e*]pyrazolo[1,5-*a*]-1,3,5-triazines and 7,8,9,10-tetrahydro[1,3]diazepino[1,2-*e*]pyrazolo[1,5-*a*]-1,3,5-triazines.

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An investigation on the synthesis of polyheterocyclic compounds with hydrazine moieties for possible biological activity produced some novel ring systems.

7,8-Dihydroimidazo[1,2-*e*]pyrazolo[1,5-*a*]-1,3,5-trizines were prepared as follows: 2-Hydrazinoimidazoline (**2a**) (2) which was obtained by hydrazinolysis of the readily available 2-emthylthioimidazoline (**1a**) (3) was reacted with α-iminobutyronitrile (**3a**), α-cyanoacetophenone (**3b**) or α-cyano *p*-methylacetophenone (**3c**) to give 3′-methyl-2-[5′-aminopyrazolyl]imidazoline (**4a**) and its 3′-phenyl (**4b**) and 3′-p-tolyl derivatives (**4c**), respectively. The latter compounds were reacted with *ortho* esters to give substituted 7,8-dihydroimidazo[1,2-*e*]pyrazolo[1,5-*a*]-1,3,5-triazines (**7a**) (1). Starting with 2-methylthio-1,4,5,6-tetrahydropyrimidine (**1b**) (4) and 2-methylthio-4,5,6,7-tetrahydro-1*H*-[1,3]diazepine (**1c**) (4), after hydrazinolysis (2) and interaction of the appropriate 2-hydrozino derivitives, **2b** and **2c**, with **3a**, **3b** and **3c** the desired 2-[3′-substituted-5-aminopyrazolyl]-1,4,5,6-tetrahydropyrimidines (**5a-c**) and 2-[3′-substituted-5′-aminopyrazolyl]-4,5,6,7-tetrahydro-1*H*-[1,3]diazepines (**6a-c**) were obtained, respectively. Substituted aminopyrazolyls **5a-c** and **6a-c** were reacted with *ortho* esters to give the corresponding 8,9-dihydro-7*H*-pyrimido[1,2-*e*]pyrazolo[1,5-*a*]-1,3,5-triazines (**8a-k**) and

Scheme I

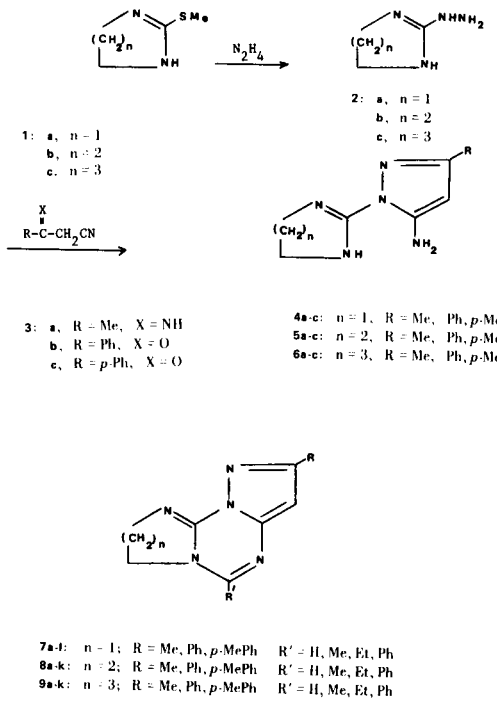
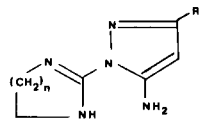


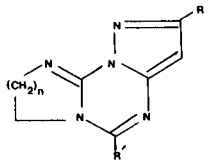
Table I



Compound	n	R	M.p. °C (a)	Yield %	Formula	Analyses C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
4a	1	Me	110	85	$C_7H_{11}N_5$	50.90	50.82	6.66	6.39	42.42	42.49
4b	1	Ph	125	95	$C_{12}H_{13}N_5$	63.43	63.40	5.85	5.66	30.83	31.03
4c	1	*p*-MePh	105	80	$C_{13}H_{15}N_5$	64.73	64.81	6.22	6.32	29.04	29.11
5a	2	Me	55	84	$C_8H_{13}N_5$	53.63	53.70	7.26	7.26	39.10	39.02
5b	2	Ph	110	91	$C_{13}H_{15}N_5$	64.73	64.69	6.22	6.19	29.04	29.11
5c	2	*p*-MePh	160	92	$C_{14}H_{17}N_5$	65.88	65.93	6.66	6.41	27.45	27.66
6a	3	Me	80	80	$C_9H_{15}N_5$	55.95	56.11	7.77	7.70	36.26	36.19
6b	3	Ph	110	85	$C_{14}H_{17}N_5$	65.88	65.79	6.66	6.60	27.45	27.33
6c	3	*p*-MePh	155	75	$C_{15}H_{19}N_5$	66.91	67.06	7.06	7.16	26.02	25.18

(a) Free base.

Table II



Compound	n	R	R′	M.p. °C	Yield %	Formula	Analyses C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd	N% Found
7a	1	Me	H	150	80	$C_8H_9N_5$	54.85	54.91	5.14	5.17	40.00	39.86
7b	1	Me	Me	170-175	85	$C_9H_{11}N_5$	57.14	57.09	5.82	5.96	37.03	37.11
7c	1	Me	Et	175	86	$C_{10}H_{13}N_5$	59.11	58.98	6.40	6.33	34.48	34.44
7d	1	Me	Ph	245	50	$C_{14}H_{13}N_5$	66.93	66.69	5.18	5.19	27.89	27.71
7e	1	Ph	H	236-239	95	$C_{13}H_{11}N_5$	65.82	65.85	4.64	4.71	29.53	29.69
7f	1	Ph	Me	285	79	$C_{14}H_{13}N_5$	66.93	66.83	5.17	5.21	27.88	28.03
7g	1	Ph	Et	218	90	$C_{15}H_{15}N_5$	67.92	67.97	5.66	5.63	26.42	26.55
7h	1	Ph	Ph	212-215	61	$C_{19}H_5N_5$	72.84	72.79	4.79	4.86	22.39	22.22
7i	1	*p*-MePh	H	265-270	69	$C_{14}H_{13}N_5$	66.93	66.88	5.17	5.09	27.88	27.59
7j	1	*p*-MePh	Me	290	74	$C_{15}H_{15}N_5$	67.92	67.90	5.66	5.80	26.42	26.46
7k	1	*p*-MePh	Et	240	77	$C_{16}H_{17}N_5$	68.82	68.69	6.09	5.99	25.09	25.11
7l	1	*p*-MePh	Ph	205	48	$C_{20}H_{17}N_5$	73.39	73.33	5.20	5.17	21.41	21.41
8a	2	Me	H	120	73	$C_9H_{11}N_5$	57.14	57.18	5.82	5.86	37.03	37.00
8b	2	Me	Me	175	85	$C_{10}H_{13}N_5$	59.11	59.20	6.40	6.33	34.48	34.39
8c	2	Me	Et	195	90	$C_{11}H_{15}N_5$	60.82	60.88	6.91	6.89	32.25	32.32
8d	2	Ph	H	260-262	83	$C_{14}H_{13}N_5$	66.93	67.01	5.17	5.19	27.88	27.91
8e	2	Ph	Me	268	81	$C_{15}H_{15}N_5$	67.92	67.99	5.66	5.60	26.41	26.39
8f	2	Ph	Et	216	87	$C_{16}H_{17}N_5$	68.81	68.80	6.09	6.11	25.08	25.17
8g	2	Ph	Ph	215	49	$C_{20}H_{17}N_5$	73.39	73.44	5.20	5.17	21.41	21.50
8h	2	*p*-MePh	H	262	69	$C_{15}H_{15}N_5$	67.92	68.01	5.66	5.69	26.41	26.44
8i	2	*p*-MePh	Me	240	74	$C_{16}H_{17}N_5$	68.82	68.76	6.09	6.13	28.09	25.13
8j	2	*p*-MePh	Et	235	93	$C_{17}H_{19}N_5$	69.62	69.57	6.48	.650	23.89	23.79
8k	2	*p*-MePh	Ph	234	59	$C_{21}H_{19}N_5$	73.90	73.81	5.57	5.55	20.52	20.66
9a	3	Me	H	230	57	$C_{10}H_{13}N_5$	59.11	59.20	6.40	6.37	34.45	34.40
9b	3	Me	Me	250	69	$C_{11}H_{15}N_5$	60.82	60.91	6.91	6.87	32.25	32.32
9c	3	Me	Et	125	76	$C_{12}H_{17}N_5$	62.33	62.40	7.35	7.34	30.30	30.22
9d	3	Me	Ph	218	64	$C_{16}H_{17}N_5$	68.81	68.80	6.09	6.10	25.08	25.11
9e	3	Ph	H	160	52	$C_{15}H_{17}N_5$	67.92	67.82	5.66	5.70	26.41	26.44
9f	3	Ph	Me	215	87	$C_{16}H_{17}N_5$	68.81	68.89	6.09	5.99	25.08	25.02
9g	3	Ph	Et	190	82	$C_{17}H_{19}N_5$	69.62	69.49	6.48	6.50	23.89	23.83
9h	3	MePh	H	180	51	$C_{16}H_{17}N_5$	68.81	68.68	6.09	6.13	25.08	25.06
9i	3	*p*-MePh	Me	225	76	$C_{17}H_{19}N_5$	69.62	69.69	6.48	6.50	23.89	23.77
9j	3	*p*-MePh	Et	175	78	$C_{18}H_{21}N_5$	70.35	70.40	6.84	6.90	22.80	22.71
9k	3	*p*-MePh	Ph	250	55	$C_{22}H_{21}N_5$	74.36	74.39	5.91	5.99	19.71	19.66

7,8,9,10-tetrahydro[1,3]-diazepino[1,2-*e*]pyrazolo[1,5-*a*]-1,3,5-triazines (**9a-k**). (See Scheme I).

The structure of compounds **4-9** were confirmed by elemental analysis, ir, nmr and mass spectroscopy. Compounds prepared are reported in Tables I and II.

EXPERIMENTAL

Melting points were taken on a Kofler hot stage microscope and are uncorrected. The ir spectra were obtained on a Perkin-Elmer 167 spectrograph. Nmr spectra were recorded using a Varian T-60A spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian 311 spectrometer at 70 ev.

3′-methyl-2-[5′-aminopyrazolyl]imidazoline (**4a**).

To a solution of 4.5 g. (0.02 mole) of 2-hydrazinoimidazoline hydroiodide (**2a**) in 10 ml. of acetic acid 1.64 g. (0.02 mole) of freshly prepared α-iminobutyronitrile was added and the mixture heated with stirring on a water bath for one half hour. After cooling the yellow crystalin mass was filtered and recrystallized from ethanol to give 5.60 g. (85%) **4a** as hydroidide, m.p. 220°. The free base was obtained by alkalinization of a solution of hydroiodide with dilute sodium hydroxide solution and extraction with chloroform. After evaporation of the solvent, the solide was recrystallized from aqueous ethanol, m.p. 110°; nmr (deuteriochloroform): δ 2.03 (s, 3H, CH_3), 3.62 (s, 4H, CH_2,), 5.0 (s, 1H, CH), 5.74 (b, 3H, NH and NH_2); molecular weight by mass spectroscopy, m/e 165.

Compound **4b-c**, **5a-c** and **6a-c** were prepared in a similar man-

ner and are summarized in Table I.

2-Methyl-7,8-dihydroimidazo[1,2-*e*]pyrazolo[1,5-*a*]-1,3,5-triazine (**7a**).

A mixture of 1.65 g. (0.01 mole) of 3-methyl-2-[5′-aminopyrazolyl]imidazoline (**4a**) and 6.72 g. (0.03 mole) of triethylorthobenzoate in 15 ml. of absolute ethanol was refluxed for four hours. After evaporation of the solvent, the solid was recrystallized from ethyl acetate to give 1.25 g. (50%) of **7a**, m.p. 245°; molecular weight by mass spectroscopy, m/e 251; uv (methanol): 238 nm (ϵ 4.75), 304 (ϵ 4.32); ir (potassium bromide) 1680, 1578, 1538, 1426, 1368, 1329, 1300, 1198, 1001, 982, 776, 705 and 671 cm^{-1}; nmr (deutriochloroform): δ 2.33 (s, 3H, CH_3), 4.10 (s, 4H, CH_2,), 6.13 (s, 1H, CH), 7.33-7.82 (m. 5H, C_6H_5).

All other compounds of this series and compounds **8a-k** and **9a-k** were prepared similarly except that the refluxing time in the case of triethylorthoformate, triethylorthoacetate and triethylorthopropionate was only one hour (see Table II).

Acknowledgments.

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REFERENCES AND NOTES

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