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STUDIES OF PYRAZOLES. XLIII*. SOME AMINOPYRAZOLES

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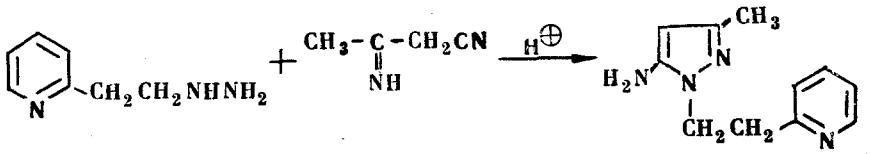
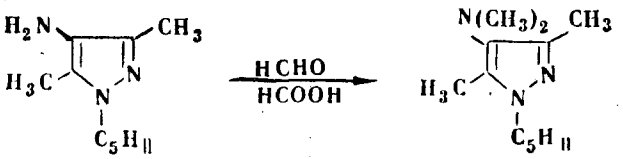
A series of alkyl and acyl derivatives of 3-, 4-, and 5-aminopyrazoles are synthesized with a view to determining their biological activities. The chromatographic properties of most of the compounds prepared are determined.

Since many aminopyrazoles have rather high pharmacological activity [1], it was of interest to synthesize a series of amino derivatives of pyrazole to ascertain their biological activities. To synthesize the 5-aminopyrazoles we used a method of cyclizing a diacetonitrile with substituted hydrazines [2].



The Leuckart reaction was used to introduce the dimethylamino group at the 4 position of the pyrazole ring.

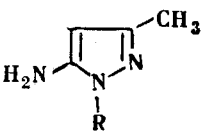


Acylation of the amino group in isomeric 1-phenyl-n-aminopyrazoles with trichloracetic chloroanhydride and benzene sulfonic acid or acetic anhydride was carried out by the usual methods. β-Pyridylethylhydrazines are synthesized from vinylpyridines by a method worked out by A. N. Kost and S. I. Siminovyi. Purification of the compounds was checked by thin-layer chromatography using unstabilized alumina or silica gel. These methods have already been described in detail [3, 4].

EXPERIMENTAL

N-Substituted 3-methyl-5-aminopyrazoles (Table 1). 0.2 mole of the appropriate substituted hydrazine is dissolved in 200 ml 2 N hydrochloric acid, 0.21 mole diacetonitrile is sprinkled in while stirring (temperature 80°), and the mixture is boiled for 10 min, after which 30 ml conc. hydrochloric acid are added, and boiling is continued for 20 min more. The reaction mixture is cooled and made alkaline with 100 g sodium hydroxide, after which the separated aminopyrazole is extracted with benzene. The benzene extract is dried with fused potassium hydroxide and vacuum-distilled.

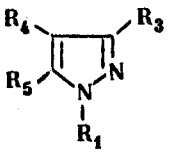
TABLE 1



R	Yield, %	M.p., °C	Empirical formula	Found N, %	Calculated N, %
β-(Pyridyl-2)ethyl . .	61	50	$C_{11}H_{14}N_4$	27.58; 27.43	27.76
β-(Pyridyl-4)ethyl . .	70	47	$C_{11}H_{14}N_4$	27.69; 27.54	27.76
n-Amide	76	49	$C_9H_{17}N_3$	25.31; 25.20	25.14
		B.p. 178—179 (22 *mm*)			
β-Diethylaminoethyl . .	69	B.p. 180—183 (16 *mm*)	$C_{10}H_{20}N_4$	28.34; 28.31	28.56

*For Part XLII see [4].

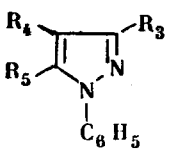
TABLE 2



X=CH_3CONH,
Y=Cl_3CCONH,
Z=$C_6H_5SO_2NH$
$R_1=C_6H_5$

R_3	R_4	R_5	Yield, %	M.p., °C	Empirical formula	Found, %		Calculated, %	
						C	H	C	H
X	H	H	67	130°	$C_{11}H_{11}N_3O$	65.65 65.63	5.49 5.38	65.65	5.51
Y	H	H	70	103	$C_{11}H_8Cl_3N_3O$	43.11 43.07	2.78 2.71	43.52	2.62
Z	H	H	39	88	$C_{15}H_{13}N_3O_2S$		N 14.23 14.21		N 14.03
H	X	H	58	120	$C_{11}H_{11}N_3O$		N 20.81 20.77		N 20.88
H	Y	H	51	168	$C_{11}H_8Cl_3N_3O$		N 13.67 13.58		N 13.88
H	Z	H	41	143	$C_{15}H_{13}N_3O_2S$		N 13.89 13.81		N 14.03
H	H	X	67	86	$C_{11}H_{11}N_3O$	65.47 65.24	5.54 5.51	65.65	5.51
H	H	Y	77	137	$C_{11}H_8Cl_3N_3O$		N 13.55 13.46		N 13.88
H	H	Z	40	164	$C_{15}H_{13}N_3O_2S$		N 14.09 13.84		N 14.03
CH_3	H	X	49	109	$C_{12}H_{13}N_3O$		N 19.76 19.61		N 19.54
CH_3	H	Y	55	134	$C_{12}H_{10}Cl_3N_3O$	45.41 45.30	3.36 3.30	45.29	3.16
CH_3	H	Z	48	154	$C_{16}H_{15}N_3O_3S$		N 13.31 13.27		N 13.39

TABLE 3



Chromatographic properties of aminopyrazoles and their derivatives

X=CH_3CONH, Y=Cl_3CCONH,
Z=$C_6H_5SO_2NH$, T=NH_2

R_3	R_4	R_5	Unstabilized alumina*					silica gel
			I	II	III	IV	V	
X*	H	H	0.90	0.82	0.35	0.45	0.19	—
Y	H	H	0.90	0.88	0.30	0.73	0.18	—
Z	H	H	0	0	0	0	0.14	0.68
T	H	H	0.81	0.75	0.30	0.33	0.18	—
H	X	H	0.78	0.72	0.27	0.35	0.13	—
H	Y	H	0.85	0.88	0.66	0.52	0.12	—
H	Z	H	0	0	0	0	0.26	0.65
H	T	H	0.73	0.61	0.20	0.44	0.13	—
H	H	X	0.81	0.70	0.23	0.41	0.18	—
H	H	Y	0.21	0.62	0.18	0.14	0.17	—
H	H	Z	0	0	0	0	0.12	0.66
H	H	T	0.86	0.78	0.36	0.46	0.23	—
CH_3	H	X	0.81	0.73	0.23	0.39	0.10	—
CH_3	H	Y	0.32	0.11	0.19	0.30	0.09	—
CH_3	H	Z	0	0	0	0	0	0.64
CH_3	H	T	0.85	0.77	0.41	0.12	0.23	—

*I, ethyl acetate; II, ethyl acetate-petroleum ether (3:1); III, ethyl acetate-petroleum ether (1:3), IV, methylethyl ketone-petroleum ether (1:3); V, benzene-petroleum ether (3:1); VI, on silica gel, solvent ethyl acetate.

Phenylsulfamide derivatives (Tables 2 and 3). 0.1 mole aminopyrazole is suspended in 20 ml dry pyridine, and 0.1 mole benzosulfochloride is added dropwise over a period of 15 min while stirring and cooling. The reaction mixture is left 24 hr at room temperature, and then heated 30 min on a steam bath, after which it is poured into 80 ml 2 N hydrochloric acid and the whole agitated for one half hour. The crystals or oil precipitated are separated off and crystallized from 60% methanol, then recrystallized from benzene-petroleum ether (2:1).

Trichloroacetamidopyrazole (Tables 2 and 3). 0.025 mole trichloracetic chloroanhydride is slowly dropped into 0.02 mole aminopyrazole in 10 ml absolute pyridine with stirring and cooling. The reaction mixture is left 4 hr, then 20 ml methanol are added, and the mixture is boiled for 10 min and filtered; 15 ml solvent are distilled off, 10 ml water added, and the mixture is cooled in a refrigerator. The crystals are filtered off with suction and crystallized from benzene-petroleum ether (1:2).

β-Diethylaminoethylhydrazine. A solution of 86 g β-chlorotriethylamine hydrochloride in 100 ml water is slowly dropped into 300 ml boiling hydrazine hydrate (96%), which is vigorously stirred. The addition takes about 3 hr, and when it is complete the mixture is refluxed for a further 3 hr, then cooled; 100 g sodium hydroxide are added, and the whole is extracted with ether in a continuous extractor for 60 hrs. The ether extract is dried with fused potassium hydroxide, and vacuum-distilled to give 33 g (50%) crude β-diethylaminoethylhydrazine b.p. 102-114° (60 mm). After redistilling it boils at 109° (56 mm), n_D^{20} 1.4479. Found: N 32.16; 32.07%. Calculated for $C_6H_{17}N_3$: N 31.99%.

1-Amyl-3, 5-dimethyl-4-aminopyrazole is prepared in 61% yield by reducing the appropriate 4-nitroso derivatives [5] with hydrazine hydrate. B.p. 154-156° (6 mm), n_D^{20} 1.5025, d_4^{20} 0.9728. Found: N 23.41, 23.34%. Calculated for $C_{10}H_{19}N_3$: N 23.17%.

1-Amyl-3, 5-dimethyl-4-dimethylaminopyrazole. 0.2 g Raney nickel catalyst and 8.2 g finely-powdered paraform are added to a mixture of 14 g 1-amyl-3, 5-dimethyl-4-aminopyrazole and 39 ml 85% formic acid, and the whole refluxed for 10 hrs. Excess formic acid is distilled off from the reaction mixture, and the residue is made alkaline with sodium hydroxide and extracted with benzene. Distillation of the benzene extract gives 9.5 g (59%) dimethylaminopyrazole b.p. 152-154° (12 mm), n_D^{20} 1.4780, d_4^{20} 0.9231. Found: N 19.97; 19.88%. Calculated for $C_{12}H_{23}N_3$: N 20.08%.

β-Pyridylethylhydrazines. A mixture of 160 ml 92% hydrazine hydrate, 135 ml methanol, and 186 g 4-vinylpyridine is refluxed for 7 hrs. Then the reaction mixture is vacuum-distilled in a stream of inert gas. Yield 200 g (82.4%) β-(pyridyl-4)ethylhydrazine, b.p. 160-162° (9 mm). β-(Pridyl-2)ethylhydrazine is similarly obtained from 2-vinylpyridine. Yield 84.9% (362 g from 350 g 2-vinylpyridine), b.p. 139-142° (9 mm).

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