RESEARCHES ON SUBSTITUTED ARYLAMIDES OF DITHIOCARBOXYLIC ACIDS

IX. Cyclizing N-Arylcyanoacetamides to Pyrazole Derivatives*

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 4, 713–715, 1967

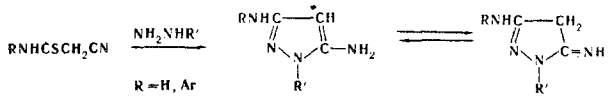
UDC 547.773:543.422

Reaction of N-aryl cyanoacetamides with hydrazine hydrate, or its monoaryl-substitution products, gives 3-arylamino-5-aminopyrazoles and 1-aryl-3-arylamino-5-aminopyrazoles. Treatment of aminopyrazoles with aryldiazonium chlorides leads to isolation of the arylazo derivatives. A hypothesis that the pyrazole derivatives synthesized have an amine structure is put forward on the basis of their chemical properties and IR spectra.

Pyrazole derivatives have found extensive application as medicinals. The series of this class of compounds contains physiologically active substances acting on the central nervous system [1], having a considerable antispasmodic activity [2], and also analgesic [3] and other properties.

To synthesize amino- and iminopyrazoles, use is made of the condensation of hydrazine hydrate and its derivatives with β-ketonitriles and similar compounds.

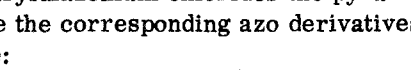
The present authors previously described the preparation of N-aryl cyanoactamides [4]. It was of interest to use these compounds to prepare hitherto unreported 3-arylamino-5-aminopyrazoles and 1-aryl-3-arylamino-5-aminopyrazoles, and to investigate some of their properties.



It can be assumed that the reaction of N-aryl cyanoacetamides with hydrazine hydrate proceeds via the formation of the hydrazone RNHC(=NNH$_2$)CH$_2$CN, since when the reactants were mixed, there is spontaneous heating, and copious evolution of hydrogen sulfide. However, even when the reaction was run with cooling, it proved impossible to isolate a hydrazone with the postulated structure.

It is to be noted that cyanoacetanulide does not react with hydrazine hydrate, even on prolonged heating on a steam bath.

With aryldiazonium chlorides the pyrazole derivatives give the corresponding azo derivatives, with structure:



Heating 3-anilino-5-aminopyrazole in excess acetic anhydride gives a substance, which analyzes as a diacetyl derivative. Acylation of 1-phenyl-3-anilino-5-aminopyrazole also gives a compound analyzing as a diacyl derivative. Acylation of 3-anilino-4-phenylazo-5-amino-pyrazole gives a compound analyzing as a monoacyl derivative.

The aminopyrazoles obtained give with hydrochloric acid salts, which on neutralization readily revert to the bases. The IR spectrum of 3-anilino-5-aminopyrazole shows intense absorption bands at 1590 and 1630 cm^{-1}, corresponding to NH$_2$ group frequencies.

The results stated above justify the assumption that the compounds obtained under the particular conditions are amino derivatives of pyrazole.

EXPERIMENTAL

3-Anilino-5-aminopyrazole. 0.7 ml Hydrazine hydrate was slowly dripped into a solution of 2 g (0.011 mole) cyanoacetanilide in 2 ml EtOH. When the first drops of hydrazine hydrate were added, formation of H_2S was observed (test portion on lead acetate paper), accompanied by slight heating of the reaction mixture. After 1–2 hr formation of H_2S had completely ceased, and a crystalline preciptate had formed; this was filtered off, and washed on the funnel with EtOH and water, then dried in air. After removing the EtOH from the filtrate, a further quantity of reaction product was obtained. Purification was effected by recrystallizing from EtOH, yield 1.1 g.

The compounds listed in Table 1, were prepared similarly.

3-Arylamino-5-aminopyrazole I–IV were slightly colored crystalline substances, soluble in hot water, EtOH and mineral acids, slightly soluble in alcoholic and aqueous alkalies to give bluish-violet solutions, which gradually turned brown; insoluble in ether, benzene, $CHCl_3$ and a series of organic solvents.

3-Anilino-5-aminopyrazole hydrochloride formed colorless crystals mp 89°–90° (ex EtOH). Found: Cl 16.00; 15.90; N 24.42; 24.50%, calculated for Ca $H_{10}N_4$·HCl·H_2O: Cl 15.53; N 24.50%.

Diacetyl derivative of 3-anilino-5-aminopyrazole, mp 218–219° (ex EtOH). Found: N 21.35; 21.34%, calculated for $C_{13}H_{14}N_4O_2$: N 21.79%.

1-Aryl-3-arylamino-5-aminopyrazoles (Table 1, V–VII) were slightly colored crystalline substances, soluble in mineral acids, slightly soluble in dilute alkalies to give colored solutions, insoluble in water, and a series of organic solvents. They were purified by recrystallizing from EtOH.

1-Phenyl-3-anilino-5-aminopyrazole hydrochloride, mp 92–93° (ex EtOH).

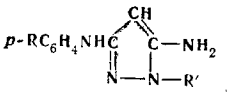
Diacetyl derivative of 1-phenyl-3-anilino-5-aminopyrazole mp 204° (ex EtOH). Found: N 16.91; 17.15%, calculated for $C_{19}H_{18}N_4O_2$: N 16.76%.

3-Anilino-4-phenylazo-5-aminopyrazole. 3 g AcONa and 3 ml water were added to a solution of 0.2 g (1.2 mM) 3-anilino-5-aminopyrazole in 3 ml EtOH. The whole was cooled with ice water, stirred vigorously, and a diazo solution prepared, from 0.1 g (1.1 mM) aniline and 0.13 g (1.9 mM) $NaNO_2$, added. Stirring continued for about an hour, and the products were poured on to ice. The precipitate was filtered off, washed on the funnel with water, and air dried, yield 0.3 g (95%), mp 177° (ex MeOH on dilution with water).

The compounds listed in Table 2 were prepared similarly. They were crystalline and yellow to dark red. They were soluble in ether,

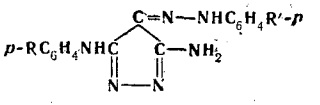
*For Part VIII see [5].

Table 1



Compound	R	R′	Mp, °C	Formula	N, % Found	N, % Calculated	Yield, %
I	H	H	166	$C_9H_{10}N_4$	31.94; 32.05	32.18	60
II	CH_3	H	167—168	$C_{10}H_{12}N_4$	30.30; 30.24	29.78	51
III	Br	H	204	$C_9H_9BrN_4$	22.08; 22.19	22.13	62
IV	NO_2	H	192—193	$C_9H_9N_5O_2$	32.46; 32.50	31.96	81
V	H	C_6H_5	177	$C_{15}H_{14}N_4$	22.16; 22.18	22.40	67
VI	H	p-$CH_3C_6H_4$	141	$C_{16}H_{16}N_4$	21.29; 21.40	21.21	40
VII	Br	C_6H_5	230	$C_{15}H_{13}BrN_4$	16.47; 16.59	17.02	21

Table 2



R	R′	Mp, °C	Formula	N, % Found	N, % Calculated	Yield, %
H	H	177	$C_{15}H_{14}N_6$	30.00; 30.09	30.21	95
H	H_2NSO_2	250—252	$C_{15}H_{15}N_7O_2S$	26.82; 26.80	26.70	64
H	CH_3	192—193	$C_{16}H_{16}N_6$	28.40; 28.35	28.76	60
H	NO_2	>250	$C_{15}H_{13}N_7O_2$	29.79; 29.88	30.34	66
H	Cl	215	$C_{15}H_{13}ClN_6$	25.96; 25.86	26.88	69
CH_3	HOOC	>250	$C_{16}H_{16}N_6O_2$	24.57; 24.61	25.00	67

$CHCl_3$, dioxane, and many other organic solvents, as well as in mineral acids, slightly soluble in alkalies, insoluble in water.

The acyl derivative of 3-anilino-4-phenylazo-5-aminopyrazole was a crystalline dark red compound, mp 193-194°. Found: N 25.97; 26.06%, calculated for $C_{17}H_{16}N_6O$: N 26.25%.

REFERENCES

1. G. N. Pershin, N. A. Novitskaya, A. N. Kost, and I. I. Grandberg, DAN **123**, 200, 1958.

2. J. E. Owen, E. E. Swanson, and D. B. Mayers, J. Am. Pharm. Assoc., 47, 70, 1958; C. A. **52**, 5662, 1958.

3. H. Kraft, German Patent 928 296, 1965; RZhKh 79413, 1956.

4. A. D. Grabenko, P. S. Pel'kis, and L. N. Kulaeva, ZhOKh, **32**, 2248, 1962.

5. A. D. Grabenko, L. N. Kulaeva, and P. S. Pel'kis, KhGS [Chemistry of Heterocyclic Compounds], 364, 1966.

10 September 1965

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