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RESEARCHES ON PYRAZOLES

LIV. Synthesis of (Pyrazolyl-4) Glycines*

I. I. Grandberg, L. F. Morozova, and A. N. Kost

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The Strecker method is used to synthesize a number of (pyrazolyl-4) glycines, which are new α-amino-acids, containing the pyrazole ring.

Continuing work on synthesizing amino acids containing a pyrazole ring, the present authors have now prepared four (pyrazolyl-4) glycines.

Attempts to use N. D. Zelinskii and G. L. Stadnikov's method [2, 3] were unsuccessful. The reaction mixture partly resinified, and the starting aldehyde was recovered unchanged. A variant of the Strecker synthesis [4] proved more successful. The yields were those generally obtained in this reaction, and varied from 15% to 41% . The amino acids were characterized by measuring their R_f values when they were chromatographed in various solvent systems, as well as their electrophoretic characteristics in various systems, and their UV absorption spectra (see table).

The previously prepared [6] pyrazolyl-4-alanine was tested as an antibacterial and antifungal agent, and found not to exhibit any activity at a dilution of 1 : 1000.**

Experimental

1-Phenyl-4-formyl-, 1-phenyl-3-methyl-5-chloro-4-formyl- and 1-phenyl-3, 5-dimethyl-4-formylpyrazole were prepared by formylation of the corresponding pyrazoles with dimethylformamide and phosphorus oxychloride [5].

1-Benzyl-3, 5-dimethyl-4-formylpyrazole was prepared by the method previously described by the present authors [6].

Synthesis of (pyrazolyl-4) glycines. A pressure bottle was charged with 20 ml of an aqueous solution containing 0.11 mole ammonium chloride, 20 ml concentrated aqueous ammonia, and a solution of 0.11 mole potassium cyanide, plus 20-50 ml methanol (the amount of this depended on the solubility of the starting aldehyde in the aqueous alcohol). The whole was cooled to 0°, and 0.10 mole of the appropriate aldehyde added gradually, with shaking. The pressure bottle was then closed, and shaken on a rocker for 50 hr at room temperature. The color of the reaction mixture gradually changed from colorless to reddish brown. Sometimes a viscous oil was seen to separate out. The pressure bottle was strongly cooled (HCN!), and the contents transferred to a distilling flask. Most of the water and alcohol were distilled off under reduced pressure at 30-40°. Then 60 ml conc. HCl was run into the flask (evolution of HCN!), and the reaction mixture refluxed for 3 hr on a water bath to decompose the aminonitrile. Resinification of the reaction mixture was observed, which greatly complicated further isolation of the amino-acid. Then the solution was evaporated to dryness under reduced pressure on a water bath. The hot residue was thrice extracted with boiling methanol (20 ml each time). The methanol filtrates were bulked and cooled, when a further small amount of ammonium chloride separated, and was filtered off. To isolate the amino acid from the methanol solution of its hydrochloride, diethylamine was added dropwise till the reaction was slightly alkaline (pH8).

Separation and purification of the amino acids.

(1-Phenylpyrazolyl-4) glycine. The methanol solution of (1-phenylpyrazolyl-4) glycine hydrochloride was boiled with a small amount of active carbon, filtered, and diethylamine added dropwise to the filtrate to bring it to pH 8. Crystals of amino acid separated, which were filtered off, and washed with ethanol on the filter. Recrystallization was from 70% aqueous dioxane.

(1-Phenyl-3-methyl-5-chloropyrazolyl-4) glycine. After neutralizing with diethylamine, the solution was again boiled with active carbon, and evaporated to half volume. On cooling very small crystals separated, which proved very difficult to filter off from accompanying gummy material when filtering was done with suction on a glass filter. The amino acid was washed in the filter with a small amount of methanol and ether, and purified by reprecipitation from aqueous solution, by adding five volumes of acetone.

*For Part LIII see [1].

**The tests were run at the Milovanova All-Union Pharmaceutical Chemistry Scientific Research Institute.

Yields and Properties of (Pyrazolyl-4) glycines.

R_1	R_3	R_5	Mp, °C (decomp)	UV spectrum (SF-4) in 80% MeOH		R_f		Electrophoretic mobility	Formula	Found, %		Calculated, %		Yield, %
				λ_{max}, mμ	lg ε	System I	System II			C	H	C	H	
C_6H_5	H	H	196—8	245	4.39	0.46	0.29	4.6	$C_{13}H_{11}N_3O_2$	60.25 60.44	5.34 5.27	60.82	5.10	32.6
C_6H_5	CH_3	Cl	201—203	246	3.96	0.63	0.36	2.7	$C_{12}H_{12}N_3O_2Cl$	53.94 53.84	4.95 4.98	54.23	4.55	18.3
C_6H_5	CH_3	CH_3	201—204	245	3.90	0.56	0.33	3.7	$C_{13}H_{15}N_3O_2 \cdot H_2O$	59.69 59.39	6.77 6.72	59.30	6.50	41.4
$CH_2C_6H_5$	CH_3	CH_3	245—247	224, 258	3.70, 2.40	0.61	0.38	4.7	$C_{14}H_{17}N_3O_2$	62.62 62.39	6.26 6.17	62.62	6.61	15

(1-Phenyl-3, 5-dimethylpyrazolyl-4) glycine. Crystals did not separate after adding the diethylamine. The methanol solution was boiled with active charcoal, and evaporated to half volume. Then on cooling a thick gelatinous mass formed. Crystals of amino acid separated when three volumes of acetone were added. They were purified by reprecipitating from concentrated aqueous solution with acetone. The acid contained one molecule of water of crystallization.

(1-Benzyl-3, 5-dimethylpyrazolyl-4) glycine. Crystals did not form after neutralizing with diethylamine. Evaporating off a small amount of the liquid, followed by cooling gave a gelatinous mass which was readily soluble in ethanol, chloroform, and acetone. Addition of water or ether to the methanol solution precipitated an oil. Further extensive evaporation of the methanol solution under reduced pressure on a water bath gave a semicrystalline mass. Prolonged suction filtration led to separation of the viscous brown liquid from crystals of diethylamine hydrochloride. The viscous filtrate was dried over H_2SO_4 in a vacuum desiccator, to give a solid glassy mass (about two weeks). Solution of this in dry acetone gave crystals of (1-benzyl-3, 5-dimethylpyrazolyl-4) glycine, recrystallized from 70% aqueous dioxane.

Chromatography of the prepared amino acids. The R_f values of the amino acids were determined by ascending chromatography on Grade B chromatography paper, from the Volodarskii Leningrad works, using two solvent systems: butanol: water: acetic acid = 4:5:1 (I), and butanol saturated with 5% NH_4OH solution (II). The visualizer was ninhydrin (yellowish brown color, after 24 hr changing to a typical bluish-violet).

Electrophoresis of the amino acids prepared. The electrophoretic speeds of the amino acids were determined in an electrophoresis instrument (Frunzenskii physical apparatus factory PEF-1 rectifier and chamber). Carbon electrodes were used, voltage 400, potential gradient on the paper 15.7 v/cm, the paper used was Chromatography paper, Grade B, from the Volodarskii Leningrad works (28 × 10 cm). Electrolytes were 30% acetic acid (system I, pH 1.4) and system II (pyridine: acetic acid: water = 1:4: 994 ml, pH 4.3). With system I the current was passed for 4 hr, with system II for 6 hr. The visualizer was the same as that used in paper chromatography. In system II the amino acids moved at approximately the same speeds.

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Lomonosov Moscow State University