

[COMMUNICATION NO. 887 FROM THE KODAK RESEARCH LABORATORIES]

Investigation of Pyrazole Compounds. II.¹ The Synthesis of 1-Phenyl-3-hydroxy-5-pyrazolone Imide

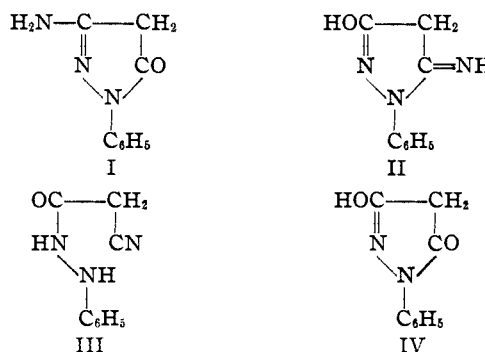
BY A. WEISSBERGER AND H. D. PORTER

In the first paper of this series it was shown that the compound synthesized by Conrad and Zart² and called 1-phenyl-3-hydroxy-5-pyrazolone imide is in fact the isomeric 1-phenyl-3-amino-5-pyrazolone I. The real 1-phenyl-3-hydroxy-5-pyrazolone imide II has now been prepared. Phenylhydrazine was condensed with cyanoacetyl chloride to give β -cyanoacetylphenylhydrazine III. Instead of the acid chloride, cyanoacetazide³ can be used, giving a somewhat higher yield. III is a colorless well-crystallizing substance. It is soluble in aqueous sodium carbonate, slightly soluble in cold water, and the addition of mineral acid does not increase its solubility in the latter. With acetic anhydride or benzoyl chloride, even when used in excess, III forms a monoacyl derivative only. Both acyl derivatives are soluble in 3% sodium carbonate and stable in cold caustic alkali. They are most likely α -acetyl- β -cyanoacetylphenylhydrazine and α -benzoyl- β -cyanoacetylphenylhydrazine, respectively.

Under the influence of sodium ethylate, III yields an isomer, which is very soluble, not only in bases but also in mineral acids. In sodium carbonate solution containing *p*-aminodimethylaniline it forms a magenta dye on addition of an oxidizing agent (potassium persulfate). This color is characteristic for pyrazolone and for many of its derivatives, *e. g.*, the 1-phenyl-3-amino-5-pyrazolone I,⁴ while III, in the same test, gives an orange-yellow dye. The new compound therefore appears to be II, formed from III by ring closure. This assignment is confirmed by the acid hydrolysis which yields 1-phenyl-3-hydroxy-5-pyrazolone IV, and ammonia. IV was identified by comparison with samples prepared according to the literature.^{2,5} The interrelation of I and II is demonstrated by the acid hydrolysis of I which likewise gives IV. The yield in this latter reaction, 71% of the theoretical, is good enough to make it practical for the preparation of IV. A peculiar resolidification above the melting point of all four

samples, and the color test with *p*-aminodimethylaniline, confirmed their identity.

II differs from I by its higher solubility in all solvents. While I is almost insoluble in water, II can be recrystallized from it to give two polymorphic forms. The crystals which separate rapidly from a concentrated (7 ml./g.) solution melt at 142°, and those which separate slowly from a more dilute (20 ml./g.) solution at 160°. The melt of either form on cooling to room temperature yields the lower-melting polymorphic variety. However, if the melt is kept at a temperature only a few degrees below the lower melting point, the high-melting form is obtained.



For the microanalyses we wish to thank Dr. L. T. Hallett and his associates.

Experimental

Cyanoacetyl Chloride.—Two hundred and fifty grams of cyanoacetic acid (90%) was extracted with 1 liter of ether in three portions, the solution dried with magnesium sulfate, and the solvent removed *in vacuo*, leaving 200 g. of the acid. Fifty-seven and five-tenths grams of the latter was treated with phosphorus trichloride and chlorine according to the literature.⁶ However, instead of weighing the reaction mixture, it was found convenient to measure the liquid chlorine, obtained from an inverted cylinder, into a flask fitted with a tube leading to the reaction vessel. The product distilled at 56–58° (0.5 mm.); yield 38 g. (54%). It is advisable to use the chloride the same day, because even in a refrigerator it does not keep longer than two to three days without considerable decomposition.

β -Cyanoacetylphenylhydrazine, III.—1. To a solution of 47 g. of phenylhydrazine in 250 ml. of dry ether, which was stirred and cooled in an ice-bath, was added, during fifteen minutes, 24 g. of cyanoacetyl chloride in 80 ml. of

(1) Investigation of Pyrazole Compounds. I, THIS JOURNAL, **64**, 2133 (1942).

(2) Conrad and Zart, *Ber.*, **39**, 2283 (1906).

(3) Caution is necessary in working with this explosive compound.

(4) British Patent 478,990.

(5) Michaelis and Schenk, *Ber.*, **40**, 3569 (1907).

(6) Schroeter and Zink, *ibid.*, **71**, 675 (1938).

dry ether. Stirring and cooling was continued for one hour, the granular crystalline mass collected at the pump, rinsed with ether, and slurried and filtered twice with 400 ml. of water. The solid was extracted with 150 ml. of boiling 60% ethanol, leaving 7 g. of high melting insoluble residue. The solution on cooling gave 15.5 g. of cream-colored needles, m. p. 98–101°, and recrystallized (Norite) twice from 50% ethanol, 10 g. (33%) of fine white needles; m. p. 105–106°.

Anal. Calcd. for $C_9H_8N_3O$: C, 61.7; H, 5.14; N, 24.0. Found: C, 61.59; H, 4.88; N, 24.00.

2. A suspension of 84 g. of cyanoacetylhydrazide⁷ in 300 ml. of water and 300 ml. of ethyl ether was cooled to 5° and 71 ml. of concd. hydrochloric acid was added with stirring. After cooling to 0°, 58 g. of sodium nitrite in 150 ml. of water was added within ten to fifteen minutes, while stirring vigorously, at a reaction temperature maintained below 10° by the addition of dry-ice.

After stirring and cooling for another fifteen minutes, 90 g. of phenylhydrazine was added dropwise during fifteen minutes at 5–10°. After another hour, the mixture was filtered. The residue was slurried with 300 ml. of ether, filtered, rinsed with ether, then washed with 150 ml. of water, and recrystallized from 350 ml. of 35% ethanol, 75 g. (52%) of fine white needles; m. p. 105–106°.

The isolation of the cyanoacetazide,⁷ after the first step in the above reaction, is dangerous. This isolation was done with several samples until a small batch, after one day's standing, detonated with extreme violence when the ethereal solution was concentrated. Moreover, it was found that a better over-all yield was obtained with the procedure given above than when the azide was isolated.

If, in the preparation of the azide, the nitrite solution is added more slowly, a solid (up to 16%) separates from the reaction mixture. The compound crystallized from water in thick needles, m. p. 194–196°, and is presumably α,β -di(cyanoacetyl)-hydrazine.

Anal. Calcd. for $C_8H_6N_4O_2$: C, 43.4; H, 3.61; N, 33.7. Found: C, 43.69; H, 3.89; N, 33.56.

Coupling Test with *p*-Aminodimethylaniline.—A small amount (about 0.01 g.) of β -cyanoacetylphenylhydrazine was dissolved in 5 ml. of 3% aqueous sodium carbonate containing about 0.01 g. of *p*-aminodimethylaniline, and to the solution was added about 2 ml. of 2% potassium persulfate solution. Immediately, a bright yellow-orange color appeared which faded on addition of mineral acid.

α -Acetyl- β -cyanoacetylphenylhydrazine.—One gram of β -cyanoacetylphenylhydrazine in 5 ml. of acetic anhydride was heated on the steam-bath for one hour. The solution was vacuum-concentrated, and the residue taken up in 5 ml. of hot benzene from which crystals separated. These were recrystallized twice from methanol, yielding fine white needles; m. p. 149–150°.

Anal. Calcd. for $C_{11}H_{11}N_3O_2$: N, 19.35. Found: N, 19.27.

α -Benzoyl- β -cyanoacetylphenylhydrazine.—To a solution of 1.75 g. of β -cyanoacetylphenylhydrazine and 1.6 g. of pyridine in 3.5 ml. of dioxane, was added 2.8 g. of benzoyl chloride. After heating on the steam-bath for half an hour, excess benzoyl chloride was decomposed by adding

5 ml. of methanol, and the mixture poured into water. The precipitated oil was washed with water and crystallized from benzene, yielding 1.2 g. (43%) of white needles; m. p. 153–155°; recrystallization from methanol raised the m. p. to 155–156°.

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: N, 15.05. Found: N, 15.12.

Both acyl derivatives were recovered unchanged on acidification after standing for one hour in 2% sodium hydroxide solution.

1-Phenyl-3-hydroxy-5-pyrazolone Imide, II.—A solution of 80 g. of β -cyanoacetylphenylhydrazine in sodium methylate (21 g. of sodium in 320 ml. of methanol) was refluxed for one hour. It was then concentrated *in vacuo* to dryness and the residue dissolved in 400 ml. of water. On acidifying with 60 ml. of glacial acetic acid, heating, Noriting, cooling, and filtering, 70.5 g. of crude product was obtained which half melted at about 140°, and totally at 158°. Recrystallized from 500 ml. of water, it formed fine white needles, m. p. 142–143°; yield, including 7.5 g. from the filtrate, 59.5 g. (74%). A polymorphous form of m. p. 160.5–161.5° was obtained as described on page 52.

Anal. Calcd. for $C_9H_8N_3O$: C, 61.7; H, 5.14; N, 24.0. Found: (142°) C, 61.81; H, 4.96; N, 24.01. Found: (160°) C, 61.55; H, 5.36; N, 23.8.

1-Phenyl-3-hydroxy-5-pyrazolone imide was also formed when a solution of β -cyanoacetylphenylhydrazine in 2% sodium hydroxide stood at room temperature for one hour. However, under these conditions, the solution darkened considerably and the yield was not as good as in the above procedure.

In the coupling test (carried out by the method described above), II formed a magenta dye which faded on addition of mineral acid or of caustic alkali.

1-Phenyl-3-hydroxy-5-pyrazolone, IV.—1. A suspension of 150 g. of 1-phenyl-3-amino-5-pyrazolone¹ in a mixture of 3 liters of water, 450 ml. of 95% ethanol, and 110 ml. of concd. hydrochloric acid was stirred on the steam-bath. As soon as solution was complete (fifteen minutes), it was Norited and filtered, heating the filtrate for forty-five minutes longer. After cooling, the crystals were collected at the pump and washed with water to give 107.5 g. (71%) of cream-colored plates; m. p. on rapid heating (5° per min.) 193–195° dec. The melt reset to a semi-solid at 205°.

2. A solution of 0.25 g. of 1-phenyl-3-hydroxy-5-pyrazolone imide in 5 ml. of water and 0.25 ml. of concd. hydrochloric acid was heated on the steam-bath for one hour. On cooling, 0.05 g. of white needles crystallized out. The yield was not increased by extending the time of heating to three hours, probably because IV itself is destroyed by hydrolysis. The product was recrystallized from water to give fine white plates; m. p. on rapid heating 193–195° dec. The melt reset to a semi-solid at 205°. Mixed melting points of both preparations with each other and with samples of 1-phenyl-3-hydroxy-5-pyrazolone, prepared according to the literature,^{2,5} showed no depression.

I and II were recovered unchanged on acidification, after heating their solutions in 2% sodium hydroxide for one hour on the steam-bath.

(7) Darapsky and Hillers, *J. prakt. Chem.*, **92**, 297 (1915).

Summary

1. 1-Phenyl-3-hydroxy-5-pyrazolone imide was prepared by ring closure of β -cyanoacetylphenylhydrazine obtained from phenylhydrazine and cyanoacetyl chloride or cyanoacetamide.

2. The relation of 1-phenyl-3-hydroxy-5-py-

razolone imide and 1-phenyl-3-amino-5-pyrazolone is shown by acid hydrolysis of both compounds to 1-phenyl-3-hydroxy-5-pyrazolone.

3. Color reactions of β -cyanoacetylphenylhydrazine and of the pyrazolone derivatives are described.

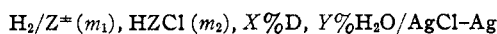
ROCHESTER, NEW YORK RECEIVED OCTOBER 14, 1942

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF YALE UNIVERSITY]

The Acidic Ionization Constant of Glycine in Dioxane-Water Solutions

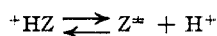
BY HERBERT S. HARNED AND CLAIR M. BIRDSALL¹

The ionization constants of acetic, formic, propionic acids and water² have been determined from 0 to 50° in water and in dioxane-water solutions from cells without liquid junction. In order to extend these results to include an ionization of another type of weak electrolyte, cells of the type



have been employed to evaluate the acidic ionization constant of glycine as a function of the composition of a medium of varying dielectric constant and of the temperature. In this cell, Z^{\pm} represents the amphion, $^+\text{NH}_3\text{CH}_2\text{COO}^-$, HZCl , glycine hydrochloride and X the percentage by weight of dioxane in the solvent. From these ionization data, the entropy, heat content and heat capacity of the ionization reaction may be evaluated with a fair degree of accuracy.

Cells of this type have been employed frequently³ in recent years to determine the acidic ionization constant of amino acids in water, and without modification may be adapted to the investigation of ionization equilibrium in water-organic solvent mixtures. The ionization under consideration is given by the expression



and the corresponding equation for the thermodynamic ionization constant is

(1) This contribution contains material from a dissertation presented by Clair M. Birdsall to the Graduate School of Yale University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1942.

(2) Harned and Kazanjian, *THIS JOURNAL*, **58**, 1912 (1936); Harned and Fallon, *ibid.*, **61**, 2374 (1939); Harned and Done, *ibid.*, **63**, 2579 (1941); Harned and Dedell, *ibid.*, **63**, 3308 (1941).

(3) Harned and Owen, *ibid.*, **52**, 5091 (1930); Harned and Owen, *Chem. Rev.*, **25**, 31 (1939); Owen, *THIS JOURNAL*, **56**, 24 (1934); Nims and Smith, *J. Biol. Chem.*, **101**, 401 (1933); P. K. Smith, A. C. Taylor and E. R. B. Smith, *ibid.*, **122**, 109 (1937).

$$K_A = \frac{m_Z m_H \gamma_Z \gamma_H}{m_{ZH} \gamma_{ZH}} \quad (1)$$

where m represents molality, γ activity coefficient and the ionic species are designated by the subscripts, Z , ZH and H .

The thermodynamic equation for the cell is

$$E = E^{0*} - RT/NF \ln \gamma_H \gamma_{Cl} m_H m_{Cl} \quad (2)$$

where E^{0*} is the standard potential in a given solvent. Since $\gamma_H \gamma_{Cl}$ in a solution containing glycine is not exactly known but can only be approximated by employing values for hydrochloric acid at the appropriate ionic strength in a solvent which does not contain glycine, it is necessary to define the quantities M_H' and K_A' by the equations

$$K_A' \equiv \frac{m_Z' m_H'}{m_{ZH}'} = \frac{(m_1 + m_H') m_H'}{(m_2 - m_H')} \quad (3)$$

$$\log m_H' \equiv \frac{(E - E^{0*})}{k} + 2 \log \gamma_{HCl} + \log m_2 \quad (4)$$

since $m_{Cl} = m_2 = m_{HZ}$. As the ionic strength decreases, the apparent hydrogen ion concentration m_H' approaches the actual hydrogen ion concentration m_H so that at infinite dilution K_A' equals K_A . E^{0*} and γ_{HCl} have been determined by Harned and Morrison,⁴ m_2 is known, so that measurement of E yields all the data necessary for the computation of m_H' . From these values of m_H' determined at a number of suitable concentrations, K_A' is determined by equation (3) and extrapolated to zero ionic strength where it equals the thermodynamic ionization constant K_A .

Experimental Procedure and Observed Electromotive Forces.—The experimental technique described in detail by Harned and Morrison⁵

(4) Harned and Morrison, *THIS JOURNAL*, **58**, 1908 (1936).

(5) Harned and Morrison, *Am. J. Sci.*, **33**, 161 (1937).