this work differs somewhat from their value because of the small change of pK_A with ionic strength.

Comparison of the thermodynamic ionization constants at zero ionic strength for the three amines with the corresponding values in water[11] gives the following values for the difference in the logarithmic constants, $\Delta pK'_B$, in the two media: butylamine, 1.68; piperidine, 2.20; triethylamine, 2.87. The ratio of the ionization constants in water and in methanol for these three cases thus increases as the amine changes from primary to secondary to tertiary.

Summary

The concentration and thermodynamic ionization constants of butylamine, piperidine, triethylamine and of their conjugate acids in methanol at room temperature have been determined by an indicator method.

COLUMBUS, OHIO RECEIVED JUNE 8, 1944

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[11] Butylamine, $pK'_B = 3.39$ (Goodhue and Hixon, ref. 10); Piperidine, $pK'_B = 2.94$ (Wynne-Jones and Salomon, *Trans. Faraday Soc.*, **34**, 1321 (1938)); Triethylamine, $pK'_B = 3.13$ (Ablard, McKinney and Warner, THIS JOURNAL, **62**, 2181 (1940)).

[COMMUNICATION NO. 980 FROM THE KODAK RESEARCH LABORATORIES]

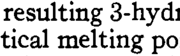
Investigation of Pyrazole Compounds. VI.[1] The Condensation of Some Heterocyclic Hydrazines with Ethyl Cyanoacetate

BY A. WEISSBERGER AND H. D. PORTER

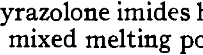
In the first paper of this series[2] it was shown that phenylhydrazine condenses with ethyl cyanoacetate in the presence of sodium ethylate to form 1-phenyl-3-amino-5-pyrazolone, I. This compound readily yields a magenta dye when heated with alcoholic *p*-nitrosodimethylaniline.[3] The isomeric 1-phenyl-3-hydroxy-5-pyrazolone imide, II,[4] produces no dye under the same conditions.[3] If a solution of I is oxidized in the presence of *p*-aminodimethylaniline,[4] or I is subjected to the film-strip test,[5] it forms a bright magenta while with II in either of these oxidation tests only a dull, bluish magenta is obtained.

When 2-pyridylhydrazine was condensed, as above, with ethyl cyanoacetate, a compound resulted which, in its behavior with *p*-nitrosodimethylaniline and in both oxidation tests, resembled II rather than I. The synthesis by means of β-cyanoacetyl-2-pyridylhydrazine, III, in analogy with the synthesis[4] of II, confirmed that the new compound is 1-(2-pyridyl)-3-hydroxy-5-pyrazolone imide, IV. Hence, the condensation of hydrazines with ethyl cyanoacetate does not always yield 3-amino-5-pyrazolones, but can result in 3-hydroxy-5-pyrazolone imides, according to the nature of the hydrazine. This was confirmed by tests with a number of substituted phenylhydrazines and with several heterocyclic hydrazines: *m*-Tolylhydrazine, *m*-chlorophenylhydrazine, *p*-methoxyphenylhydrazine, *p*-sulfamylphenylhydrazine, 3-pyridylhydrazine, and 4-pyridylhydrazine gave the respective 3-amino-5-pyrazolones, while 2-quinolylhydrazine and 2-benzothiazolylhydrazine, like 2-pyridylhydrazine, yielded the respective 3-hydroxy-5-pyrazolone imides. The structures of the pyrazolones were assigned according to the presence or absence of dye formation with *p*-nitrosodimethylaniline and according to the oxidation tests mentioned. Moreover, the two additional 3-hydroxy-5-pyrazolone imides were also synthesized by the cyclization of the respective β-cyanoacetylhydrazines. The resulting 3-hydroxy-5-pyrazolone imides have identical melting points and mixed melting points with the compounds obtained by condensation of the hydrazines with ethyl cyanoacetate.

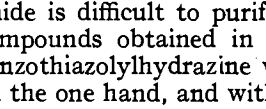
1-(2-Benzothiazolyl)-3-hydroxy-5-pyrazolone imide is difficult to purify. The identity of the compounds obtained in the condensation of 2-benzothiazolylhydrazine with ethyl cyanoacetate on the one hand, and with cyanoacetazide, on the other hand, was therefore established by comparison of the acetyl derivatives. A diacetyl derivative was prepared from the parent substance with acetic anhydride. Partial deacetylation yielded a mono acetyl compound which forms a dye when subjected to the film-strip test.[5] The mono acetyl derivative is therefore most probably 1-(2-benzothiazolyl)-3-hydroxy-5-pyrazolone acetylimide,



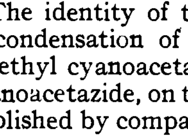
I



II



III



IV

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[1] Investigation of Pyrazole Compounds. V, THIS JOURNAL, **65**, 2180 (1943).

[2] Weissberger and Porter, *ibid.*, **64**, 2133 (1942).

[3] Weissberger and Porter, *ibid.*, **65**, 732 (1943).

[4] Weissberger and Porter, *ibid.*, **65**, 52 (1943).

[5] Weissberger and Porter, *ibid.*, **65**, 1495 (1943).

while the diacetyl compound, which is insoluble in carbonate, is 1-(2-benzothiazolyl)-3-acetoxy-5-pyrazolone acetylimide.[6]

Experimental

Reaction of Hydrazines with Ethyl Cyanoacetate.—To a solution of sodium ethylate (2 equivalents of sodium in 17.5 ml. per g. of absolute ethanol) was added 1.1 equivalent of ethyl cyanoacetate and 1 equivalent of the respective hydrazines. The mixture was refluxed in an oil-bath at 120° for sixteen hours.

1-*m*-Tolyl-3-amino-5-pyrazolone.—The reaction mixture from 10 g. of *m*-tolylhydrazine[7] was concentrated *in vacuo*. The residue was dissolved in 150 ml. of water, extracted twice with 50-ml. portions of ethyl ether, and the alkaline solution acidified with acetic acid. The crude product obtained on filtration (8 g., m. p. 150–165°) was recrystallized from 25 ml. of methanol and filtered hot from a small amount of insoluble material, to give a yield of 1.5 g. (10%) of brown microcrystals melting at 175–178°. Recrystallization from methanol gave light tan microcrystals, m. p. 182–183°.

Anal. Calcd. for $C_{10}H_{11}N_3O$: N, 22.2. Found: N, 21.88.

1-*m*-Chlorophenyl-3-amino-5-pyrazolone.—The reaction mixture from 10 g. of *m*-chlorophenylhydrazine[8] was worked up like the 1-*m*-tolyl derivative; crude yield, 9 g. (64%) of tan microcrystals melting at 195–198°. A sample recrystallized from methanol gave ivory microcrystals, m. p. 205–208° dec.

Anal. Calcd. for $C_9H_8ClN_3O$: N, 20.0. Found: N, 19.72.

1-*p*-Methoxyphenyl-3-amino-5-pyrazolone.—The reaction mixture from 9 g. of *p*-methoxyphenylhydrazine[9] was worked up like the 1-*m*-tolyl derivative; crude yield, 8 g. (60%) of brown microcrystals, melting at 175–180°. Recrystallization from 50 ml. of methanol and then from 50 ml. of methanol plus 15 ml. of dioxane gave 2.2 g. (16.5%) of light tan crystals, m. p. 188–190° dec.

Anal. Calcd. for $C_{10}H_{11}N_3O_2$: N, 20.5. Found: N, 20.23.

1-*p*-Sulfamylphenyl-3-amino-5-pyrazolone.—The reaction mixture from 11 g. of *p*-sulfamylphenylhydrazine[10] was concentrated *in vacuo* and the residue dissolved in 75 ml. of water. After acidification with acetic acid, the precipitated product was recrystallized from 65 ml. of 50% methanol; yield, 0.3 g. (2%) tan flakes, m. p. 258–260°.

Anal. Calcd. for $C_9H_{10}N_4O_3S$: C, 42.5; H, 3.93. Found: C, 42.88; H, 4.10.

1-(3-Pyridyl)-3-amino-5-pyrazolone.[11]—The reaction mixture from 3.27 g. of 3-pyridylhydrazine[12] was concentrated *in vacuo*, the residue dissolved in 25 ml. of water, filtered, and the filtrate made acid to litmus with (1:1) hydrochloric acid (about 18%). The solution was concentrated to 5 ml., cooled, filtered, and the crude product (1.58 g., m. p. 204–205° dec.) recrystallized from 20 ml. of water (Norite) forming 0.9 g. (17%) of light brown needles, m. p. 216–218° dec.

Anal. Calcd. for $C_8H_8N_4O$: C, 54.5; H, 4.54. Found: C, 54.60; H, 4.40.

1-(4-Pyridyl)-3-amino-5-pyrazolone.—The reaction mixture from 5.3 g. of 4-pyridylhydrazine hydrochloride,[13] using an additional equivalent of sodium ethylate to neutralize the hydrogen chloride, was concentrated *in vacuo*, the sticky residue dissolved in 20 ml. of water, acidified with glacial acetic acid, and cooled in an ice-bath. The product, 0.5 g., m. p. 230–235°, crystallized out and was recrystallized (Norite) from a mixture of 25 ml. of 95% ethanol and 11 ml. of dioxane; yield, 0.3 g. (5%), m. p. 239–241° dec.

Anal. Calcd. for $C_8H_8N_4O$: C, 54.6; H, 4.55; N, 31.8. Found: C, 54.27; H, 4.63; N, 31.50.

1-(2-Pyridyl)-3-hydroxy-5-pyrazolone Imide.—(1) The reaction mixture from 22 g. of 2-pyridylhydrazine[14] was concentrated *in vacuo* to dryness, dissolved in 100 ml. of hot water, acidified with glacial acetic acid, and cooled in an ice-bath. The crystalline precipitate, 6.2 g., m. p. 158–165°, was recrystallized from 40 ml. of methanol (Norite); 3.3 g. (30%), m. p. 185–187°; recrystallized again from 12% methanol, yielding white needles, m. p. 189–190°.

Anal. Calcd. for $C_8H_8N_4O$: C, 54.5; H, 4.54; N, 31.8. Found: C, 54.98; H, 4.56; N, 31.66.

(2) **By Means of β-Cyanoacetyl-2-pyridylhydrazine.**—To 5.5 g. of cyanoacetazide[15] in 25 ml. of ethyl ether was added, with stirring, a solution of 5.5 g. of 2-pyridylhydrazine in 25 ml. of ethyl ether. After standing at room temperature overnight, the mixture was filtered from the gummy product, which was triturated with 10 ml. of water and again filtered, and recrystallized from 5.5 ml. of water, 1.5 g. (17%), m. p. 137–138°. After a second recrystallization, tan needles formed, m. p. 138–139°.

Anal. Calcd. for $C_8H_8N_4O$: N, 31.8. Found: N, 31.16.

The compound refluxed in two equivalents of sodium methylate solution for one hour gave 1-(2-pyridyl)-3-hydroxy-5-pyrazolone imide, isolated as described for this compound, and identified by m. p. and mixed m. p.

1-(2-Quinolyl)-3-hydroxy-5-pyrazolone Imide.—(1) The reaction mixture from 80 g. of 2-quinolylhydrazine[16] was dissolved in 2.5 liters of hot water, acidified with 60 ml. of glacial acetic acid, cooled, and filtered, yielding 90 g. of brick red granular crystals, m. p. 203–208° dec. It was recrystallized twice from eight parts of dioxane forming 59 g. (52%) of light tan microcrystals; m. p. 218–219° dec.

Anal. Calcd. for $C_{12}H_{10}N_4O$: N, 24.8. Found: N, 24.65.

(2) **By Means of β-Cyanoacetyl-2-quinolylhydrazine.**—To 5.5 g. of cyanoacetazide[15] in 75 ml. of dioxane was added portionwise, with stirring, 8 g. of 2-quinolylhydrazine.[13] The mixture was warmed on the steam-bath for fifteen minutes, filtered from insoluble material and cooled, forming tan crystals, m. p. 152–155°. Attempts at purification, by recrystallization from 66% ethanol, or taking through alkali, failed, the product being converted to 1-(2-quinolyl)-3-hydroxy-5-pyrazolone imide, identified by m. p. and mixed m. p.

1-(2-Benzothiazolyl)-3-hydroxy-5-pyrazolone Imide.—(1) The reaction mixture from 43.5 g. of 2-benzothiazolylhydrazine[17] was dissolved in 1.25 l. of hot water, acidified with 32 ml. of glacial acetic acid, and cooled. The crude material (50 g.) was extracted with 500 ml. of hot dioxane (on the steam-bath) and the product precipitated from the filtrate with 500 ml. of water. This material was dissolved in 1 liter of 2% sodium hydroxide (Darco) and precipitated with acetic acid, giving 23 g. (40%) of a tan granular powder, m. p. 233–235° dec. A sample, dissolved in a hot dioxane–ethanol (1:1) mixture, gave, on standing for

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[6] Weissberger and Porter, THIS JOURNAL, **65**, 2180 (1943).

[7] Eastman Organic Chemical.

[8] Willgerodt and Mühe, *J. prakt. Chem.*, [2] **44**, 451 (1891).

[9] Altschul, *Ber.*, **25**, 1849 (1892).

[10] Crippa and Maffei, *Gazz. chim. ital.*, **72**, 97 (1942); *C. A.*, **37**, 618 (1943).

[11] The authors wish to thank W. A. Gregory, of these Laboratories, for the preparation of this compound.

[12] Räth, *Ann.*, **486**, 95 (1931).

[13] Koenigs, Weiss and Zscharn, *Ber.*, **59**, 316 (1926). Methanol instead of ethanol was used for the recrystallization.

[14] Fargher and Furness, *J. Chem. Soc.*, **107**, 688 (1915).

[15] The hazards of isolating this compound have been noted in a previous communication.[4]

[16] Perkin and Robinson, *J. Chem. Soc.*, **103**, 1978 (1913).

[17] German Patent 614,327 (1935).

several days in the icebox, a small amount of light tan granular crystals; m. p. 234–235° dec.

Anal. Calcd. for $C_{10}H_8N_4OS$: C, 51.7; H, 3.45; N, 24.1. Found: C, 52.4; H, 3.61; N, 23.08.

In spite of the analysis, the compound gave derivatives which analyzed correctly.

(2) **By Means of β-Cyanoacetyl-2-benzothiazolylhydrazine.**—To a solution of 5.5 g. of cyanoacetazide[16] in 200 ml. of dioxane was added in small portions, with stirring, 8.25 g. of 2-benzothiazolylhydrazine.[17] After standing at room temperature overnight, the solution was filtered, yielding 7.7 g. (67%), m. p. 198–200°. It was recrystallized from dioxane, forming fine white granular crystals, m. p. 200–201°.

Anal. Calcd. for $C_{10}H_{18}N_4OS$: C, 51.7; H, 3.45; N, 24.1. Found: C, 51.70; H, 3.35; N, 24.25.

The compound, refluxed in two equivalents of sodium methylate solution for one hour, gave 1-(2-benzothiazolyl)-3-hydroxy-5-pyrazolone imide, isolated as previously described for this compound. The identity of the two was established by the m. p. and mixed m. p. of the parent substances and of the mono acetyl derivatives obtained therefrom.

1-(2-Benzothiazolyl)-3-acetoxy-5-pyrazolone Acetylimide.—A mixture of 3.4 g. of 1-(2-benzothiazolyl)-3-hydroxy-5-pyrazolone imide in 15 ml. of acetic anhydride was heated on the steam-bath for one hour after solution was complete. Then, 7 ml. of glacial acetic acid was added, followed by 6 ml. of water, to give, on cooling, 2.7 g. (58.5%), m. p. 181–182°. Recrystallized from methanol it gave white needles; m. p. 182–183°.

Anal. Calcd. for $C_{14}H_{12}N_4O_3S$: N, 17.7. Found: N, 17.57.

The compound is insoluble in 3% sodium carbonate and 2% sodium hydroxide.

1-(2-Benzothiazolyl)-3-hydroxy-5-pyrazolone Acetylimide.—To a solution of 2 g. of 1-(2-benzothiazolyl)-3-acetoxy-5-pyrazolone acetylimide in 20 ml. of absolute ethanol, plus 10 ml. of dioxane, was added 0.55 g. of piperidine. After refluxing for one hour, the mixture was cooled to give 1 g. (58%); m. p. 250–252°. Recrystallized from 10 ml. of absolute ethanol, plus 3 ml. of dioxane, it gave 0.75 g. of white microcrystals; m. p. 252–253°.

Anal. Calcd. for $C_{12}H_{10}N_4O_2S$: N, 20.4. Found: N, 20.15.

The compound is soluble in 3% sodium carbonate.

Summary

When *m*-tolylhydrazine, *m*-chlorophenylhydrazine, *p*-methoxyphenylhydrazine, *p*-sulfamylphenylhydrazine, 3-pyridylhydrazine, and 4-pyridylhydrazine are condensed with ethyl cyanoacetate in the presence of sodium ethylate, they, like phenylhydrazine, form the respective 3-amino-5-pyrazolones substituted in position 1.

2-Pyridylhydrazine, 2-quinolylhydrazine, and 2-benzothiazolylhydrazine under the same conditions yield the 3-hydroxy-5-pyrazolone imides substituted in position 1.

The structures of the pyrazolones were established by color tests and by synthesis of the 3-hydroxy-5-pyrazolone imides by means of the β-cyanoacetyl derivatives of the respective hydrazines.

ROCHESTER 4, NEW YORK RECEIVED JULY 20, 1944

[COMMUNICATION NO. 981 FROM THE KODAK RESEARCH LABORATORIES]

Investigation of Pyrazole Compounds. VII.[1] The Reaction of Some Hydrazines with Ethyl Malonate Monoimidoester

BY A. WEISSBERGER, H. D. PORTER AND W. A. GREGORY

The condensation of ethyl cyanoacetate with phenylhydrazine in sodium ethylate results in the formation of 1-phenyl-3-amino-5-pyrazolone I.[2] With other monosubstituted hydrazines, the corresponding 3-amino-5-pyrazolone, I, is not always obtained. No defined product was isolated from reaction mixtures with *p*-nitrophenylhydrazine or *p*-cyanophenylhydrazine. 2-Pyridylhydrazine, 2-quinolylhydrazine, and 2-benzothiazolylhydrazine yielded the respective 3-hydroxy-5-pyrazolone imides, II,[1] and not I, while 2-benzoxazolylhydrazine formed unidentified compounds which are neither I nor II.

All these hydrazines have now been converted to I by a new method of synthesis. In this the hydrazine is condensed with ethyl malonate monoimidoester, III, either directly to the respective 3-amino-5-pyrazolone, I, or with isolation of the intermediate ethyl β-(β-R-hydrazino)-β-iminopropionate, IV. The latter, on treatment with alkali, closes the ring, eliminating ethanol. The structure of the resulting pyrazolones was determined by their dye formation with *p*-nitrosodimethylaniline[3] and the film-strip test.[4] The reaction of 2-pyridylhydrazine with the imidoester was attempted several times but yielded only sporadically very small amounts of an impure product. This, by its dye formation with *p*-nitrosodimethylaniline, was also shown to be essentially I. With those hydrazines which gave I in the condensation with ethyl cyanoacetate, the new method also yielded I.

The pyrazolone derivatives of type I are colorless or pale tan in the solid state, as melts, and in any organic solvent. An exception is 1-(2-quinolyl)-3-amino-5-pyrazolone, which is obtained almost colorless by addition of water to its colorless solution in pyridine, but is bright yellow in glacial acetic acid. The latter solution becomes colorless upon addition of a little hydrogen chloride or of much pyridine. Water precipitates bright yellow microcrystals from the yellow solution. Both the white and the yellow modifications

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[1] Investigation of Pyrazole Compounds, VI, THIS JOURNAL, **66**, 1849 (1944.)

[2] Weissberger and Porter, *ibid.*, **64**, 2133 (1942).

[3] Weissberger and Porter, *ibid.*, **65**, 732 (1943).

[4] Weissberger and Porter, *ibid.*, **65**, 1495 (1943).