The Synthesis and Chelation Properties of *N*-Substituted Amidrazones and Related Azines Containing the 2-Pyridyl Group

*Francis H. Case**

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122

and

A. A. Schilt and T. A. Fang

Department of Chemistry, Northern Illinois University, DeKalb, Illinois 60115

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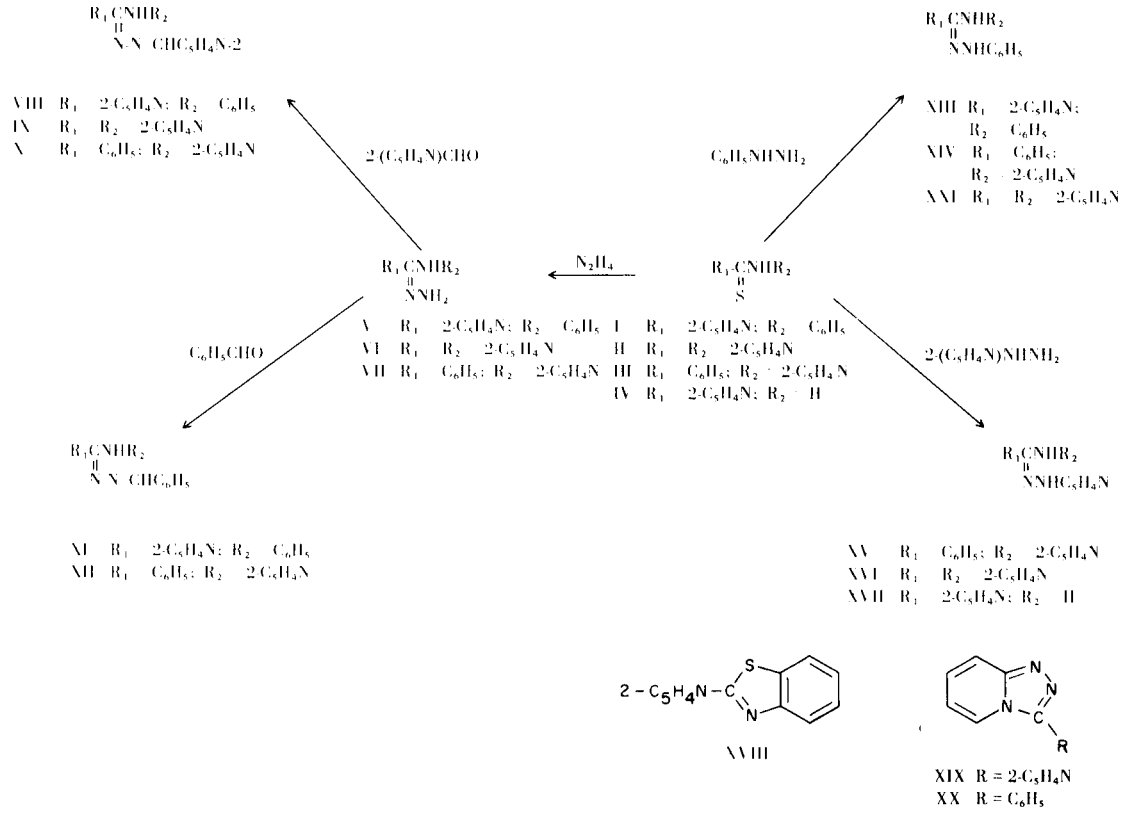
The preparation and properties of certain *N*-substituted amidrazones from thioamides containing the 2-pyridyl group and the azines derived from them by reaction with benzaldehyde and 2-pyridinecarboxaldehyde is described.

In previous communications (1,2), the preparation and reactions of *C*-substituted amidrazones have been described. The preparation of *N*-substituted amidrazones has received less attention. In 1962, Spassov and Golovinsky (3) described the preparation of picolineanilide hydrazone (V) and its *p*-carbethoxy derivative as well as the azines derived from these by the action of 5-nitrofurfural, *p*-dimethylaminobenzaldehyde, and salicylaldehyde. In 1963, Spassov *et al.* (4) prepared picolineanilide hydrazone and phenylhydrazone as well as the azine of the former with *p*-nitrobenzaldehyde.

In this laboratory, we have revised the procedure for



the preparation of picolineanilide hydrazone to include the removal of considerable amounts of 2-(2-pyridyl)-benzothiazole (XVIII) which is also formed. The azines of this amidrazone with benzaldehyde (XI) and 2-pyridinecarboxaldehyde (VIII) were then prepared. The preparation of picolineanilide phenylhydrazone (XIII) from picolinethioanilide has already been described (4). We have attempted the preparation of the 2-pyridylhydrazone without success. Instead, the reaction was found to yield 3-(2-pyridyl)-*s*-triazolo[4,3-*a*]pyridine (XIX) by loss of hydrogen sulfide and aniline. This compound (XIX) was previously obtained by heating 2-pyridylhydrazine and ethyl picolinate at 190-200° (5). When the reaction temperature was 150° (6) it was found that the previously undescribed picolinic acid-2 pyridyl hydrazide, 2-C_5H_4-NCONHNHC$_5H_4$N-2, resulted.

By the action of hydrazine hydrate on *N*-2-pyridylpicolinethioamide (II), *N*-2-pyridylpicolinamide hydrazone (VI) was prepared and from it the azine with 2-pyridinecarboxaldehyde (IX). From the above thioamide, the phenylhydrazone (XXI) was made. The *N*-2-pyridylpicolinamide-2-pyridyl hydrazone (XVI) could be prepared (in dimethylformamide) but under other conditions (140° with no solvent) 3-(2-pyridyl)-*s*-triazolo[4,3-*a*]pyridine (XIX) was obtained (by loss of hydrogen sulfide and 2-aminopyridine).

From *N*-2-pyridylthiobenzamide (III) and hydrazine hydrate was prepared *N*-2-pyridylbenzamidehydrazone (VII) from which azines with benzaldehyde (XII) and 2-pyridinecarboxaldehyde (X) were prepared. The action of phenylhydrazine and 2-pyridylhydrazine on the above thioamide yielded 2-benzamidopyridinephenylhydrazone (XIV) and 2-pyridylhydrazone (XV), respectively.

From picolinthioamide (IV), the 2-pyridylhydrazone (XVII) was obtained as before, but from it the azines with benzaldehyde and pyridine-2-carboxaldehyde were not forthcoming, nor could the phenylhydrazone be obtained.

On treatment with 2-pyridylhydrazine, thiobenzamide yielded 3-phenyl-*s*-triazolo[4,3-*a*]pyridine (XX), identical with the compound obtained by heating benzoic acid with 2-pyridylhydrazine (5,6).

It was found that neither picolineanilidephenylhydrazone (XIII) nor *N*-2-pyridylpicolinamide-2-pyridylhydrazone (XVI) reacts with 2-pyridinecarboxaldehyde to form a triazoline.

Reactions of the new compounds with iron(II) and copper(I) were studied spectrophotometrically to evaluate them as potential chromogenic and chelation reagents. The results for those compounds that gave colored complexes are compiled in Table II. Of those which did not form colored complexes (VII, XII, XIV, and XX), none possess the ferroin chromophore group. In addition to

TABLE I

Substituted Amide Azines

$R_1C(=N\text{-}N{=}CHR_3)\text{-}NHR_2$

	R_1	R_2	R_3	Yield %	M.p., °C	Crystallization Solvent	Formula	Calcd. % C	Calcd. % H	Calcd. % N	Found % C	Found % H	Found % N
XII	C_6H_5	2-C_5H_4N	C_6H_5 (a)	47.6	111	C_2H_5OH	$C_{19}H_{16}N_4$	75.98	5.37	18.65	75.79	5.36	18.85
X	C_6H_5	2-C_5H_4N	2-C_5H_4N	54.5	159-160	C_2H_5OH	$C_{18}H_{15}N_5$	71.74	5.02	23.24	71.84	5.17	23.35
XI	2-C_5H_4N	C_6H_5	C_6H_5	21.4	245	CH_3OH	$C_{19}H_{16}N_4$	75.98	5.37	18.65	76.08	4.89	18.75
VIII	2-C_5H_4N	C_6H_5	2-C_5H_4N (b)	50.0	141-142	CH_3OH	$C_{18}H_{15}N_5$	71.74	5.02	23.24	71.73	4.97	23.32
IX	2-C_5H_4N	2-C_5H_4N	2-C_5H_4N (c)	46.4	156	C_2H_5OH	$C_{17}H_{14}N_6$	67.59	4.67	27.86	67.10	4.72	28.00

(a) Ir (nujol) 1618 (CN), 1590, 1575, 1515 cm^{-1} (aromatic rings). (b) Ir (nujol) 1608 (CN), 1590, 1580, 1550, 1442, 1466 cm^{-1} (aromatic rings). (c) Ir (nujol) 1615 (CN), 1596, 1590, 1546, 1465 cm^{-1} (pyridine rings).

TABLE II

Properties of Chelates

	Iron(II) Chelate				Copper(I) Chelate		
Ligand	Color	λ max nm	ϵ l. mole^{-1} cm^{-1}	L:Fe Ratio	Color	λ max nm	ϵ l. mole^{-1} cm^{-1}
V	Orange	475	10000	(a)	Yellow	400 (b)	2500
VI	Orange	475	11000	(a)	Yellow	400 (b)	2900
VIII	Green	600	4500	3:1	Yellow	477	2140
IX	Green	618	4750	3:1	Yellow	407	3840
X	Green	602	4700	2:1	Yellow	420 (b)	2000
XI	None	---	----	--	Yellow	407 (c)	400 (c)
XIII	None	---	----	--	Gold	525 (b)	4900
XV	Orange	525	540	2:1	None	-----	----
XVI	Red	533	9900	2:1	Yellow	477	4800
XVII	Red	542	7900	2:1	Yellow	475	4900
XIX	Gold	463	9000 (a)	(a)	None	----	----
XXI	None	---	----	--	Orange	438	1340

(a) Complex too weakly formed for accurate measurement. (b) Wavelength not a maximum but at shoulder or side of ligand band just before absorption by free ligand is appreciable. (c) Complex extracted into chloroform-ethanol.

color, the wavelength (λ max) and corresponding molar absorptivity (ϵ) at maximum absorbance for each complex are reported in Table II. Ligand to metal ratios of the iron(II) chelates found by the mole ratio method are also listed. Except where noted, all solutions prepared for spectrophotometric examination were ethanol-water mixtures buffered at *p*H 7 with ammonium acetate.

In comparison to previously studied ferroin type chromogens, none of the new compounds are particularly promising as chromogenic reagents. With relatively low molar absorptivities for their iron(II) and copper(I) chelates, and thus lacking in high sensitivity, they afford no particular advantages. There are, however, a number of interesting aspects concerning their chelation properties which are noted below.

Even though it does not possess the ferroin chromophore group, XV forms a weakly colored iron(II) complex. Application of the mole ratio method demonstrated that it has a large and favorable formation constant and an iron to ligand ratio of 1 to 2. This is evidence that both ligands coordinate in a terdentate mode to satisfy the hexacoordinate requirements of iron(II). The three donor atoms used by each ligand are most probably the two pyridyl nitrogens and the one imine nitrogen, coordination of which would give rise to two chelate rings per ligand: one 5- and the other 6-membered.

The chelation properties of X, XVI, and XVII are unusual in that they act as terdentate ligands even though they each possess only one ferroin group.

Extreme curvature in the mole ratio plots for the iron(II) complexes of V, VI, and XIX indicates that the complexes are very weak. Reliable determination of their ligand to iron ratios was precluded by the curvature; however, a reasonable assumption consistent with their structures is that they coordinate as bidentate ligands.

Steric hindrance apparently is involved in preventing XI, XIII, and XXI from forming colored complexes with iron(II). Confirmation that these possess the so-called cuproine group (a sterically hindered ferroin group) is evidenced by the fact that they form appropriately colored copper(I) chelates.

EXPERIMENTAL

Picolinanilidehydrazone (V).

A mixture of 5 g. of thiopicolineanilide (5) and 15 ml. of 95% hydrazine was stirred at room temperature for one hour. The solution was then poured into water and the dried precipitate extracted with 100 ml. of hexane. The insoluble residue was crystallized from methanol yielding 1.5 g. (30.0%) of product melting at 112°. The residue from evaporation of the hexane, after repeated crystallization, yielded 2-(2-pyridyl)benzothiazole (XVIII), identical with the product obtained by heating picolinethioamide with nitrobenzene (7).

N-2-Pyridylpicolinamidehydrazone (VI).

A mixture of 5 g. of *N*-2-pyridylpicolinethioamide (8) and 15 ml. of 95% hydrazine was stirred at room temperature for one hour. The solution was poured into water, and the resulting precipitate dried, and crystallized from methanol. The yield of product melting at 110° was 4 g. (80.0%).

Anal. Calcd. for $C_{11}H_{11}N_5$: C, 61.96; H, 5.20; N, 32.84. Found: C, 61.54; H, 5.16; N, 33.21.

N-2-Pyriylthiobenzamide (III).

The following modification of the method previously described (9) was found to be desirable. A mixture of 4.7 g. of *N*-2-pyridylbenzamide, 5.7 g. of phosphorus pentasulfide and 50 ml. of pyridine was heated at reflux for 80 minutes, cooled and poured into ice water. The resulting precipitate was dried and dissolved in hot ethanol. Filtration of impurities and removal of ethanol from the filtrate yielded a solid which was crystallized from benzene. The yield of product melting at 146-147° was 2.5 g. (48.1%).

N-2-Pyridylbenzamidehydrazone (VII).

This was prepared like VI from 1 g. of *N*-2-pyridylthiobenzamide and 3 ml. of 95% hydrazine. The dried precipitate, crystallized from methanol, yielded 0.8 g. (80.0%) of pure product melting at 118°.

Anal. Calcd. for $C_{12}H_{12}N_4$: C, 67.91; H, 5.70; N, 26.40. Found: C, 67.86; H, 5.67; N, 26.21.

General Procedure for Preparation of Azines.

A mixture of 1 g. of benzaldehyde or 2-pyridinecarboxaldehyde and an equimolar quantity of the appropriate amidrazone, dissolved in 20 ml. of ethanol, was heated at reflux 2.5 hours. After removal of ethanol, the residue was crystallized from the solvent indicated in Table I.

Action of 2-Pyridylhydrazine on Picolinethioanilide.

A mixture of 2.1 g. of picolinethioanilide and 1.1 g. of 2-pyridylhydrazine was heated at 140° for 3.5 hours. The resulting solid residue, on crystallization from benzene, yielded 0.5 g. (26.3%) of pure product melting at 127-128° and unchanged when mixed with 3-(2-pyridyl)-*s*-triazolo[4,3-*a*]pyridine (XIX) prepared by heating ethylpicolinate with 2-pyridylhydrazine at 190-200° (5).

Anal. Calcd. for $C_{11}H_8N_4$: C, 67.34; H, 4.11; N, 28.55. Found: C, 67.50; H, 4.04; N, 28.39. M.W. (mass spectrum) 196; ir (nujol) 1629 (C=N), 1585 and 1495 cm^{-1} (pyridine rings).

Action of 2 Pyridylhydrazine on *N*-2-Pyridylpicolinethioamide.

When the above procedure was applied to *N*-2-pyridylpicolinethioamide (8), a yield of 1 g. (52.6%) of 3-(2-pyridyl)-*s*-triazolo-[4,3-*a*]pyridine was obtained. However, when the same quantities of starting products were dissolved in 15 ml. of dimethyl formamide, and heated on the steam bath, followed by addition of water, drying of the precipitate, and crystallization from methanol, 1.1 g. (37.9%) of *N*-2-pyridylpicolinamide-2-pyridylhydrazone (XVI) (m.p. 135°) was obtained.

Anal. Calcd. for $C_{16}H_{14}N_6$: C, 66.19; H, 4.86; N, 28.95. Found: C, 65.98; H, 4.79; N, 29.16. M.W. (mass spectrum) 290.

N-2-Pyridylpicolinamidephenylhydrazone (XXI).

A mixture of 2.1 g. of *N*-2-pyridylpicolinamide and 1.1 g. of phenylhydrazine was heated for 2 hours on the steam bath. The solid residue, after crystallization from ethanol yielded 2.4 g. (85.7%) of pure product, m.p. 160°.

Anal. Calcd. for $C_{17}H_{15}N_5$: C, 70.57; H, 5.23; N, 24.20. Found: C, 70.63; H, 5.09; N, 24.32.

N-2-Pyridylbenzamidephenylhydrazone (XIV).

A solution of 1.5 g. of *N*-2-pyridylthiobenzamide (9) and 0.75 g. of phenylhydrazine in 15 ml. of ethanol was heated on the steam bath for 3 hours. After cooling, the resulting precipitate was removed by filtration, and crystallized from methyl cellosolve, yielding 1.4 g. (70.0%) of pure product melting at 208°.

Anal. Calcd. for $C_{18}H_{16}N_4$: C, 74.98; H, 5.59; N, 19.43. Found: C, 74.80; H, 5.58; N, 19.74. M.W. (mass spectrum) 288.

N-2-Pyridylbenzamide-2-pyridylhydrazone (XV).

The procedure was the same as the previous one, substituting 2-pyridylhydrazine for phenylhydrazine. The yield of pure product (m.p. 200°) crystallized from ethyl acetate, was 1 g. (50.0%).

Anal. Calcd. for $C_{17}H_{15}N_5$: C, 70.57; H, 5.23; N, 24.20. Found: C, 70.35; H, 5.11; N, 24.30. M.W. (mass spectrum) 289.

Picolinamide-2-pyridylhydrazone (XVII).

A mixture of 1.4 g. of picolinthioamide, 1.2 g. of 2-pyridylhydrazine and 15 ml. of ethanol was heated at reflux for 2 hours. The residue, after removal of ethanol, was crystallized from methanol, yielding 1 g. (45.5%) of pure product melting at 160°.

The same product was obtained when a mixture of 1.5 g. of 2-cyanopyridine and 1.6 g. of 2-pyridylhydrazine was heated 3.5 hours on the steam bath, and the product allowed to crystallize. The yield was 1 g. or 48.4%.

Anal. Calcd. for $C_{11}H_{11}N_5$: C, 61.96; H, 5.20; N, 32.84. Found: C, 62.12; H, 5.26; N, 32.57.

Action of 2-Pyridylhydrazine on Thiobenzamide.

A mixture of 1.4 g. of thiobenzamide and 1 g. of 2-pyridylhydrazine was heated for 3 hours on the steam bath. The resulting precipitate, after crystallization from methanol, yielded 0.9 g. (45.0%) of pure product melting at 173°. The melting point was not depressed by admixture of 3-phenyl-*s*-triazolo[4,3-*a*]pyridine (XX), prepared by heating benzoic acid with 2-pyridylhydrazine at 190° (5); ir (nujol) 1630 (C=N), 1493 cm^{-1} (aromatic rings).

Anal. Calcd. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.85; H, 4.48; N, 21.57. M.W. (mass spectrum) 195.

Picolinic Acid 2-Pyridylhydrazide.

A mixture of 1 g. of 2-pyridylhydrazine and 1.3 g. of ethyl picolinate was heated for 24 hours at 150°. The residue, after crystallization from methanol, yielded 1.3 g. (72.2%) of pure product, m.p. 145-146°.

Anal. Calcd. for $C_{11}H_{10}N_4O$: C, 61.67; H, 4.71; N, 26.15. Found: C, 61.69; H, 4.66; N, 26.65.

Chelation Studies.

The procedures, reagents, and standard solutions used were the same as described previously (10). Spectra were recorded using a Cary Model 14 spectrophotometer. The mole ratio method (11) was employed to determine ligand to metal ratios of the iron(II) chelates.

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