The Synthesis and Chelation Properties of the Oximes of Certain Pyridinyl- and Diazinylmethyl Ketones

*Francis H. Case**

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122

and

A. A. Schilt

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

Received September 16, 1976

Two series of oximes derived from pyridinyl and diazinylmethyl ketones have been prepared and tested with regard to their metal-chelation properties.

J. Heterocyclic Chem., **14**, 1 (1977).

The preparation of pyrazinylmethyl phenyl (I) and pyrazinylmethyl 2-pyridinyl ketone (II) (1) and of 4-pyrimidinylmethyl phenyl ketone (III) (2) in liquid ammonia reactions have previously been described. In this laboratory, using similar methods, we have prepared the following ketones: 4-pyrimidinylmethyl 2-pyridinyl (IV) (from 4-methylpyrimidine and ethyl picolinate) and 4-pyrimidinylmethyl 4-pyrimidinyl (V) (from 4-methylpyrimidine and ethyl pyrimidine-4-carboxylate).

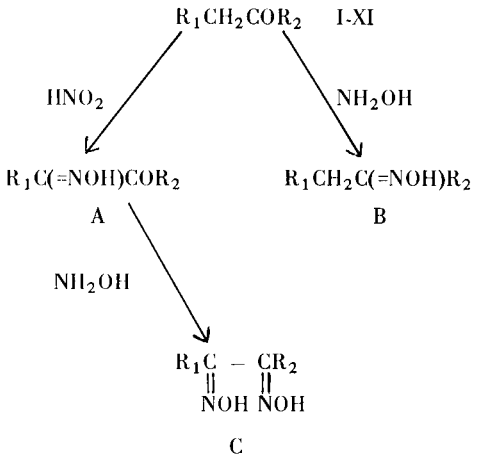
The preparation of desoxy-α-pyridoin (VII) from 2-picoline and ethyl picolinate in the presence of potassium ethoxide has been described (3). This method, with substitution of benzene for ether as the solvent medium, was found to be advantageous for the preparation of the following ketones: 4-pyrimidinylmethyl pyrazinyl (VI), 2-pyridinylmethyl pyrazinyl (VIII), 2-pyridinylmethyl 4-pyrimidinyl (IX), pyrazinylmethyl pyrazinyl (X) and pyrazinylmethyl 4-pyrimidinyl (XI) by treating 2-picoline or a methyldiazine with the appropriate methyl pyrazinecarboxylate or ethyl pyrimidine-4-carboxylate.

The synthesis and characterization of a number of ketoximes containing the ferroin group has been previously described (6,7). With the object of furnishing additional compounds of this type capable of metal-chelation, two series of oximes containing the ferroin group (except XIII and XVII) were synthesized from the aforementioned ketones. By the action of nitrous acid on ketones I-XI, substituted glyoxal monoximes were prepared of all but VIII and X, while that from VII is known (3). The action of hydroxylamine produced substituted methyl ketoximes of all but V and VI, that of I being known (1).

Since all the monoximes containing the -N=C-C=N- group give a positive ferroin reaction it is probable on the basis of past experience (7) that they contain the hydroxyl group in the anti position to the pyridyl or diazinyl group (7).

From oximes XIV, XVI, XVIII and XX, dioximes were prepared by the action of hydroxylamine. All are assumed to have the amphi configuration (C), based upon the following facts: (1) they yield no red precipitate with nickel (II), (2) they were prepared from monoximes of definite configuration, and (3) they give a strong positive ferroin test. An X-ray crystallographic structural determination of a single crystal (0.07 x 0.12 x 0.22 mm) of XXXI, performed by Dr. David Zacharias, confirmed the amphi configuration for that dioxime (8).

Reactions of the compounds with the ions of iron, copper, cobalt, and nickel were investigated as a function of *p*H for the purpose of evaluating their usefulness as chromogenic reagents. Only iron (II) yielded sufficiently intense colors to merit further detailed examination. The other metal ions formed pale yellow complexes, not much different from the reagent blanks in color. Compounds XIII and XVII, as expected, failed to give colored products with any of the metal ions, due to their lack of a ferroin group. Most of the complexes formed over the *p*H range 3 to 14, with maximum color formation generally between *p*H 6 and 13. All of the iron (II) complexes exhibited colors in alkaline solution markedly different from those in neutral or slightly acidic solutions. The color change with increasing *p*H occurs over the *p*H range of about 9 to 10 in each case. It is undoubtedly associated with ionization of hydrogen atoms from the oxime groups of the coordinated ligands. The bathochromic shift in absorption with increasing *p*H and the unusual ability of the complexes to form in strongly alkaline solutions are both consistent with the increased electron delocalization that



		A	B	C
R_1 = pyrazinyl; R_2 = C_6H_5	I	XII	XIII	
R_1 = pyrazinyl; R_2 = 2-C_5H_4N	II	XIV	XV	XXX
R_1 = 4-pyrimidinyl; R_2 = C_6H_5	III	XVI	XVII	XXXI
R_1 = 4-pyrimidinyl; R_2 = 2-C_5H_4N	IV	XVIII	XIX	XXXII
R_1 = R_2 = 4-pyrimidinyl	V	XX		XXXIII
R_1 = 4-pyrimidinyl; R_2 = pyrazinyl	VI	XXI		
R_1 = R_2 = 2-C_5H_4N	VII	XXII	XXIII	
R_1 = 2-C_5H_4N; R_2 = pyrazinyl	VIII		XXIV	
R_1 = 2-C_5H_4N; R_2 = 4-pyrimidinyl	IX	XXV	XXVI	
R_1 = R_2 = pyrazinyl	X		XXVII	
R_1 = pyrazinyl; R_2 = 4-pyrimidinyl	XI	XXVIII	XXIX	

should result on loss of oxime protons.

The most promising compounds for which colorimetric applications can be profitably explored are XX, XXV and XXXIII. Advantages afforded by these are high sensitivity and improved selectivity for iron, as well as easy adaptability to direct determination of iron in strongly alkaline systems. Interference from copper and cobalt, which ordinarily form highly colored complexes with ferroin-type ligands, should be negligible or much less severe with these new chromogens.

Table I

Diazinyl- or 2-Pyridinylmethyl Ketones

$R_1CH_2COR_2$

	R_1	R_2	Yield (%)	M.p. (°C)	Crystallization Solvent	Formula	Analysis Caled. C	Caled. H	Caled. N	Found C	Found H	Found N
IV	4-Pyrimidinyl	2-C_5H_4N	50.4 (a)	99	Methanol	$C_{11}H_9N_3O$	66.32	4.55	21.09	66.21	4.65	21.10
V	4-Pyrimidinyl	4-Pyrimidinyl	50.0	221	Methyl cellosolve	$C_{10}H_8N_4O$	60.0	4.03	27.99	59.88	4.12	27.91
VI	4-Pyrimidinyl	Pyrazinyl	22.7	178	Methanol	$C_{10}H_8N_4O$	60.0	4.03	27.99	59.96	3.81	27.87
VIII	2-C_5H_4N	Pyrazinyl	8.3	122	Methanol	$C_{11}H_9N_3O$	66.32	4.55	21.09	66.19	4.50	21.01
IX	2-C_5H_4N	4-Pyrimidinyl	22.0	130	Methanol	$C_{11}H_9N_3O$	66.32	4.55	21.09	66.07	4.60	20.95
X	Pyrazinyl	Pyrazinyl	14.3	186	Ethanol	$C_{10}H_8N_4O$	60.00	4.03	27.99	60.07	4.08	28.41
XI	Pyrazinyl	4-Pyrimidinyl	63.3	179	Ethanol	$C_{10}H_8N_4O$	60.00	4.03	27.99	59.91	4.09	28.15

(a) Based on material, m.p. 95°.

Table II

Substituted Glyoxal Monoximes

$R_1C(=NOH)\text{-}\overset{\overset{O}{\|}}{C}\text{-}R_2$

	R_1	R_2	M.p. (°C)	Crystallization Solvent	Formula	Analysis Calcd. C	H	N	Found C	H	N
XII	Pyrazinyl	C_6H_5	157	Methanol	$C_{12}H_9N_3O_2$	63.43	3.99	18.49	63.25	4.18	18.50
XIV	Pyrazinyl	C_5H_4N	201	Methanol	$C_{11}H_8N_4O_2$	57.89	3.53	24.55	57.44	3.70	24.73
XVI	4-Pyrimidinyl	C_6H_5	183	Methanol	$C_{12}H_9N_3O_2$	63.43	3.99	18.49	63.21	3.82	18.56
XVIII	4-Pyrimidinyl	C_5H_4N	230	Ethanol	$C_{11}H_8N_4O_2$	57.89	3.53	24.55	57.74	3.64	24.68
XX	4-Pyrimidinyl	4-Pyrimidinyl	202	Methanol	$C_{10}H_7N_5O_2$	52.40	3.08	30.56	52.36	2.96	30.39
XXI	4-Pyrimidinyl	Pyrazinyl	251	Methyl cellosolve	$C_{10}H_7N_5O_2$	52.40	3.08	30.56	51.96	3.32	30.22
XXII	2-C_4H_5N	2-C_4H_5N (a)	193	Methanol							
XXV	2-C_4H_5N	4-Pyrimidinyl	155	Methanol	$C_{11}H_8N_4O_2$	57.89	3.53	24.55	57.47	3.51	24.23
XXVIII	Pyrazinyl	4-Pyrimidinyl	184	Methanol	$C_{10}H_7N_5O_2$	52.40	3.08	30.56	52.12	3.17	30.70

(a) Not previously tested for chelation properties. See Reference (3).

Table III

Diazinyl- or 2-Pyridinylmethyl Ketone Monoximes

$R_1CH_2C(=NOH)R_2$

	R_1	R_2	M.p. (°C)	Crystallization Solvent	Formula	Analysis Calcd. C	H	N	Found C	H	N
XIII	Pyrazinyl	C_6H_5 (a)	136	Methanol							
XV	Pyrazinyl	2-C_5H_4N	122	Methanol	$C_{11}H_{10}N_4O$	61.67	4.71	26.15	61.41	4.84	26.15
XVII	4-Pyrimidinyl	C_6H_5 (b)	88	Ether-petroleum ether	$C_{12}H_{11}N_3O$	67.59	5.20	19.71	67.37	5.08	19.85
XIX	4-Pyrimidinyl	2-C_5H_4N	155	Methanol	$C_{11}H_{10}N_4O$	61.67	4.71	26.15	61.36	4.79	25.92
XXIII	2-C_5H_4N	2-C_5H_4N	122	Benzene	$C_{12}H_{11}N_3O$	67.59	5.20	19.71	67.56	5.29	19.59
XXIV	2-C_5H_4N	Pyrazinyl	154	Benzene	$C_{11}H_{10}N_4O$	61.67	4.71	26.15	62.14	4.78	25.81
XXVI	2-C_5H_4N	4-Pyrimidinyl	133	Benzene	$C_{11}H_{10}N_4O$	61.67	4.71	26.15	61.41	4.66	26.12
XXVII	Pyrazinyl	Pyrazinyl	136	Methanol	$C_{10}H_9N_5O$	55.81	4.22	32.54	55.62	4.08	32.09
XXIX	Pyrazinyl	4-Pyrimidinyl	175	Methanol	$C_{10}H_9N_5O$	55.81	4.22	32.54	55.74	4.23	32.88

(a) Not previously tested for chelation properties. See Reference (1). (b) Beckmann rearrangement yields benzoic acid.

Although reasonably sensitive as iron chromogens, most of the other new compounds lack promise as practical colorimetric reagents for iron. Failure to conform to Beer's law, unless a large excess of ligand is employed to favor complete color formation, severly limits their applicability. This is especially true for the iron (II) complexes of the ketone monoximes (type B ligands).

Table IV

Substituted Glyoxal Dioximes

$R_1C(=NOH)C(=NOH)R_2$

	R_1	R_2	M.p. (°C)	Crystallization Solvent	Formula	Analysis Calcd. C	H	N	Found C	H	N
XXX	Pyrazinyl	2-C_4H_5N	227	Methanol	$C_{11}H_9N_5O_2$	54.32	3.73	28.79	54.11	3.87	28.55
XXXI	4-Pyrimidinyl	C_6H_5	210	Methanol	$C_{12}H_{10}N_4O_2$	59.50	4.16	23.13	59.25	4.21	23.17
XXXII	4-Pyrimidinyl	2-C_4H_5N	214	Ethanol	$C_{11}H_9N_5O_2$	54.32	3.73	28.79	54.02	4.03	28.55
XXX	4-Pyrimidinyl	4-Pyrimidinyl	271 dec.	C_4H_6N + H_2O	$C_{10}H_8N_6O_2$	49.19	3.30	34.41	49.18	3.29	34.44

Table V

Properties of Iron (II) Chelates as a Function of *p*H

Ligand Type (a)	Numeral	at *p*H 7.0 Color	λ max nm	ε 1. mole^{-1} cm^{-1}	at *p*H 11.5 Color	λ max nm	ε 1. mole^{-1} cm^{-1}
A	XII	Magenta	550	3,900 (b)	Green	608	8,500
	XIV	Purple	555	7,900 (c)	Green	614	8,800
	XVI	Blue	576	9,700 (c)	Green	633	6,300 (c,d)
	XVIII	Blue	581	11,400	Green	639	10,600 (c,d)
	XX	Blue	579	13,700	Green	640	11,100 (d)
	XXI	Blue	582	10,700	Green	643	11,300 (d)
	XXII	Purple	576	10,900	Blue	590	10,700
	XXV	Blue	590	12,400	Green	635	11,000
	XXVIII	Purple	558	11,600 (b,c)	Green	615	7,600
B	XIII	None			None		
	XV	Red	522	8,600 (c)	Purple	537	11,300
	XVII	None			None		
	XIX	Red	522	8,400 (c)	Purple	537	9,900
	XXIII	Red	522	8,700 (c)	Purple	533	12,200 (c)
	XXIV	Magenta	543	11,200 (c)	Blue	585	8,450
	XXVI	Purple	570	10,300 (c)	Blue	611	8,120
	XXVII	Magenta	545	11,000 (b,c)	Blue	586	8,270
	XXIX	Violet	573	12,000 (b,c)	Blue	610	8,000
C	XXX	Purple	564	10,400 (c)	Blue	596	9,400 (c)
	XXXI	Purple	583	12,900 (c)	Blue	616	9,600 (c,d)
	XXXII	Purple	585	8,600	Blue	620	9,700 (c)
	XXXIII	Purple	570	12,100	Blue	630	8,800

(a) A, substituted glyoxal monoxime; B, diazinyl- or 2-pyridinylmethyl ketone monoxime; C, substituted glyoxal dioxime. (b) Slow color development. (c) Weak complex, requires large excess of ligand to conform to Beer's law. (d) Color fades noticeably within one day.

EXPERIMENTAL

Preparation of Substituted Pyrimidinylmethyl Ketones (IV, V).

To a suspension of sodium admide (prepared from 0.1 g.-atom of sodium in 80 ml. of liquid ammonia) was slowly added 0.1 mole of 4-methylpyrimidine (4). After one half-hour's stirring, a solution of 0.05 mole of ethyl picolinate (for IV) or ethyl pyrimidine-4-carboxylate (5) (for V), was gradually added. After one hour's stirring, 0.1 mole of ammonium chloride was added, and the ammonia allowed to evaporate overnight. The residual solid was dissolved in ice water, neutralized with hydrochloric acid and extracted with ether. The residue from removal of ether was crystallized from the solvent indicated in Table I. (For compound II, prepared by this method, a melting point of 100° was obtained; (lit. (1) gives 87.5°).

Preparation of Diazinyl 2-Pyridinylmethyl Ketones (VIII, IX).

To alcohol-free potassium ethoxide prepared from 0.08 g.-atom of potassium was added 100 ml. of benzene, 0.29 mole of 2-picoline, and 0.06 mole of ethyl pyrimidine-4-carboxylate or methyl pyrazinecarboxylate. The mixture was heated at reflux with stirring for 6 hours. After cooling, water was added and the benzene layer separated and dried over sodium sulfate. The aqueous layer was made neutral and extracted with ether. After removal of the two solvents, the combined liquid was heated *in vacuo* to remove unchanged reactants and the residue crystallized from the solvent indicated in Table I.

Preparation of Diazinyl Pyrazinyl or 4-Pyrimidinylmethyl Ketones. (VI, X, XI).

A mixture of 0.08 mole of potassium ethoxide, 100 ml. of benzene, 0.12 mole of methylpyrazine or 4-methylpyrimidine and 0.6 mole of methyl pyrazinecarboxylate or ethyl pyrimidine-4-carboxylate was heated at reflux for 6 hours, and then treated as in the previous directions. See Table I.

Preparation of Substituted Methyl Ketone Monoximes, ($R_1CH_2C(=NOH)R_2$. (B)

A mixture of 1 g. of ketone, 1 g. of hydroxylamine hydrochloride, 1 g. of sodium hydroxide, and 8 ml. of water was heated for 5 minutes on a steam bath. After cooling, the mixture was neutralized with acetic acid, the oxime separated by filtration, dried and crystallized from the solvent indicated in Table III. From ketones V and VI, no such oximes were obtained.

Preparation of Substituted Glyoxal Monoximes ($R_1C(=NOH)COR_2$). (A)

To 1 g. of the appropriate ketone dissolved in 20 ml. of 1.5*M* hydrochloric acid was added a solution of 0.4 g. of sodium nitrite in 4 ml. of water. After one hour's standing the solution was neutralized with ammonium hydroxide, and the resulting precipitate removed by filtration, dried and crystallized from the solvent indicated in Table II. From ketones VIII and X no oximes were obtained.

Preparation of Dioximes (XXX, XXXI, XXXII and XXXIII). (C)

These were prepared from monoximes (XIV, XVI, XVIII and XX) using hydroxylamine in the same manner as those described above. See Table IV.

Chelation Studies.

Procedures, reagents and standard solutions were similar to those described previously (7). Ascorbic acid was employed in place of hydroxylamine hydrochloride as the reductant in preparing complexes of the substituted glyoxal monoximes (Type A ligands in Table V) to avoid their possible conversion to dioximes. Solutions were adjusted to *p*H 7 by addition of 1 *M* ammonium acetate and to *p*H 11.5 with concentrated ammonia. A Cary Model 14 spectrophotometer was used to record spectra. Conformance to Beer's law and the necessity for use of excess ligand for quantitative formation of the iron (II) complexes were examined in addition to determination of wavelengths of maximum absorbance and molar absorptivities. See Table V.

REFERENCES AND NOTES

(1) J. D. Behun and R. Levine, *J. Am. Chem. Soc.*, **81**, 5157 (1959).

(2) C. Fauran, J. Eberle, J. F. Archer, M. Sergant and G. Raynoud, French Patent 2,077,856; *Chem. Abstr.*, **77**, 101,657 (1972).

(3) A. Dornow and K. Bruncken, *Chem. Ber.*, **83**, 189 (1950).

(4) "Organic Syntheses," **43**, 77 (1963).

(5) M. Robba, *Ann. Chim.* (Paris), **5**, 531 (1960).

(6) F. Case and P. McMenamin, *J. Heterocyclic Chem.*, **5**, 161 (1968).

(7) A. Schilt and P. Taylor, *Talanta*, **16**, 448 (1969).

(8) D. Zacharias, Institute for Cancer Research, Philadelphia, Pa. 19111.