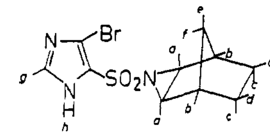
The mixture was heated at 200 °C until vapors of bromine were evolved (ca. 1 h) and then poured on crushed ice whereupon the 4-bromo-5-imidazolesulfonyl chloride precipitated. It was filtered, dried, and recrystallized from acetone/petroleum ether as chloroform/petroleum ether did not work. Yield: 6.8 g (41%) of **1**; mp 186-188 °C (decomp.)

4-Bromo-5-imidazolesulfonyl Azide (2). Compound **1** (2.0 g, 8.1 mmol) and sodium azide (0.7 g, 11 mmol) were stirred in acetone/water (95/5, v/v) at room temperature for 12 h. Solvent was removed and the resulting solid filtered, washed with water, and dried. Yield: 1.9 g of **2** (95.7%); mp 140 °C (evolution of nitrogen), 180-181 °C (decomp.)

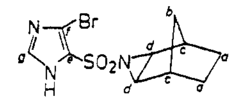
4-Bromo-5-imidazolesulfonamide (4). This compound was prepared from compound **1** and excess ammonium hydroxide as in ref *5*.

3-(4-Bromo-5-imidazolesulfonyl)-3-azatricyclo-[3.2.1.0^{2,4}]octane (3). 4-Bromo-5-imidazolesulfonyl azide (1.0 g, 10.7 mmol) and 2-norbornene (1.0 g, 10.7 mmol) were refluxed in dichloromethane/methyl *tert*-butyl ether (1/2, v/v) for 48 h. Solvent was removed and the resulting solid recrystallized from ethanol to give 450 mg of **3** (39.6%): mp 163-165 °C (Anal. Found: C, 37.75; H, 3.80; Br, 25.01; N, 13.20; S, 10.04. $C_{10}H_{12}BrN_3O_2S$ requires: C, 37.75; H, 3.80; Br, 25.11; N, 13.21; S, 10.08).

^{1}H NMR spectrum (270 MHz, DMSO-d_6, TMS): δ = 0.82 (1 H, d, J = 10.7 Hz, H_f); 1.25 (2 H, d, J = 9.6 Hz, $H_{c,d}$); 1.36 (1 H, d, J = 10.7 Hz, H_e); 1.49 (2 H, d, J = 9.6 Hz, $H_{c,d}$); 2.51 (2 H, s, H_b); 2.98 (2 H, s, H_a); 8.04 (1 H, s, H_g); 14.12 (1 H, bs, H_h).



^{13}C NMR spectrum (100.62 MHz, BB, DMSO-d_6): δ = 24.63 (s, C_a); 27.57 (s, C_b); 35.24 (t, C_c); 41.19 (t, C_d); 112.31 (q, $C_{e,f}$); 125.76 (q, $C_{e,f}$); 138.36 (t, C_g).



Abbreviations used for ^{13}C NMR spectrum: p = primary, s = secondary, t = tertiary, q = quaternary C atom.

Assignment was made by means of a DEPT spectrum.

Registry No. **1**, 99903-04-5; **2**, 99903-05-6; **3**, 115588-67-5; **4**, 34238-24-9; 4-bromoimidazole, 2302-25-2; 2-norbornene, 498-66-8.

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Synthesis of New Acylhydrazones as Iron-Chelating Compounds

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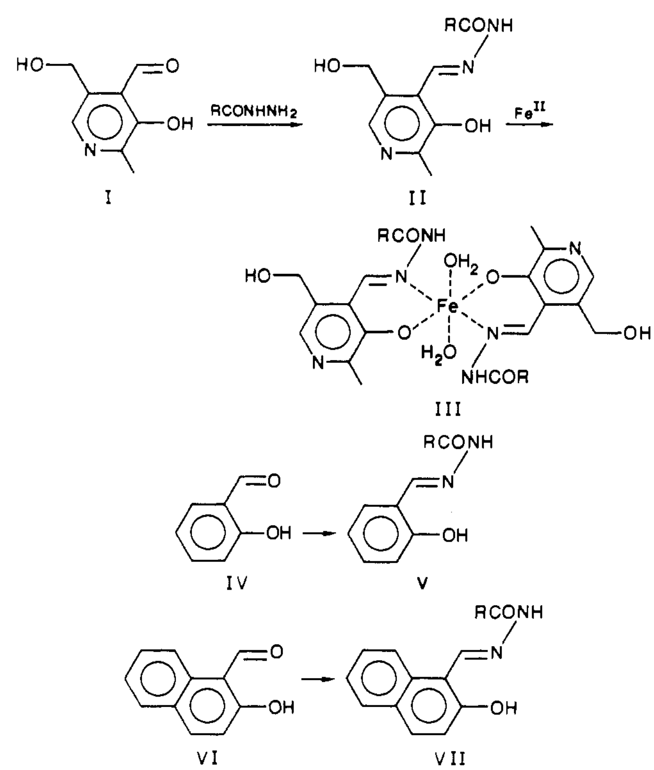
Fourteen acylhydrazides have been condensed with three aromatic *o*-hydroxy aldehydes (pyridoxal, salicylaldehyde, and 2-hydroxy-1-naphthaldehyde) to give 42 acylhydrazones, of which 38 are new. These compounds complex iron and have shown varying abilities to promote the movement of iron across biological membranes. Their infrared and nuclear magnetic resonance spectra support the structures assigned to them.

Iron overload, a consequence of long-term transfusion therapy in the disease thalassemia major, may be relieved by oral administration of such iron-chelating compounds as pyridoxal isonicotinoylhydrazone (PIH; II, R = 4-pyridyl) (*1-3*), which forms a complex with Fe^{II} to which the structure III (R = 4-pyridyl) has been assigned (*4*). It complexes also with Fe^{III} (*1*). Although most biological studies have employed PIH, three other hydrazones (II, R = phenyl), (V, R = phenyl), and (V, R = 4-pyridyl) are also effective (*3*). Accordingly, for systematic study of the effect of substituents on biological activity, we have synthesized these and 38 other hydrazones having the general structures II, V, and VII by reaction of the aldehydes I, IV, and VI with 14 acylhydrazides $RCONHNH_2$ (R = methyl, phenyl, *p*-hydroxyphenyl, *p*-methylphenyl, *p*-nitrophenyl, *p*-aminophenyl, *p*-*tert*-butylphenyl, *p*-methoxyphenyl, *m*-chlorophenyl, *m*-fluorophenyl, *m*-bromophenyl, 4-pyridyl, 2-furyl, 2-thienyl).



Ten of the acylhydrazides were commercially available; the other four (*p*-*tert*-butylphenyl, *p*-methoxyphenyl, *m*-chloro-

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Table I. Melting Points and Infrared Characteristics of Hydrazones II, V, and VII

compd	R	mp, °C	amide bands, cm^{-1} C=O	amide bands, cm^{-1} N–H
II	CH_3	245–247	1680	3190
	C_6H_5	210–213	1635	3220
	p-HO–C_6H_4	274–276	1645	3220
	p-$CH_3C_6H_4$	207–209	1640	3160
	p-O_2N–C_6H_4	255–257	1667	3230
	p-H_2N–C_6H_4	205–210	1590	3220
	p-t-C_4H_9–C_6H_4	235–237	1640	3220
	p-CH_3O–C_6H_4	199–202	1605	3180
	m-Cl–C_6H_4	232–234	1645	3230
	m-F–C_6H_4	223–225	1640	3220
	m-Br–C_6H_4	235–237	1655	3260
	4-C_5H_4N	253–255	1600	3190
	2-C_4H_3O	202–205	1640	3180
	2-C_4H_3S	224–227	1620	3140
V	CH_3	197–198	1675	3180
	C_6H_5	163–164	1630	3220
	p-HO–C_6H_4	255–256	1605	3140
	p-$CH_3C_6H_4$	192–194	1620	3220
	p-O_2N–C_6H_4	280–283	1663	3225
	p-H_2N–C_6H_4	216–217	1655	3280
	p-t-C_4H_9–C_6H_4	190–191	1640	3210
	p-CH_3O–C_6H_4	175–177	1620	3210
	m-Cl–C_6H_4	191–192	1620	3230
	m-F–C_6H_4	178–179	1645	3210
	m-Br–C_6H_4	193–194	1630	3220
	4-C_5H_4N	145–147	1675	3200
	2-C_4H_3O	168–169	1635	3200
	2-C_4H_3S	174–175	1615	3215
VII	CH_3	248–249	1652	3278
	C_6H_5	205–207	1642	3250
	p-HO–C_6H_4	279–281	1610	3240
	p-$CH_3C_6H_4$	244–245	1628	3250
	p-O_2N–C_6H_4	309–310	1646	3208
	p-H_2N–C_6H_4	220–221	1628	3250
	p-t-C_4H_9–C_6H_4	246–248	1638	3210
	p-CH_3O–C_6H_4	236–238	1638	3160
	m-Cl–C_6H_4	250–252	1640	3170
	m-F–C_6H_4	223–225	1640	3190
	m-Br–C_6H_4	250–252	1640	3180
	4-C_5H_4N	252–255	1675	3230
	2-C_4H_3O	194–195	1638	3220
	2-C_4H_3S	220–221	1635	3210

phenyl, *m*-fluorophenyl) were synthesized by the general method of Sah (*5*). All had the melting points (*5–11*) and physical properties reported in the literature.

The condensation of the acylhydrazides with the aldehydes I, IV, and VI gave the acylhydrazones II, V, and VII, usually in yields of 80–95%. The hydrazones crystallizing directly from the reaction mixture were usually essentially pure, and their melting points (given in Table I) were not raised by recrystallization. However, several of the hydrazones retained water or ethanol of crystallization which could not be removed by heating to 110 °C at a pressure of 3 mm.

The infrared spectra of acylhydrazides are reported to show peaks at about 1620 and 1650 cm^{-1} (*12*) due to C=O stretching (*13*) and at about 3200 and 3300 cm^{-1} (*12*) due to N–H stretching (*13*). These peaks were present in the spectra of all the acylhydrazides prepared by us. Condensation with the aldehydes I, IV, and VI shifted the C=O peaks to slightly higher wavenumbers, with the peak at higher frequency having diminished intensity and often appearing only as a shoulder to the peak at lower frequency. The latter peaks are given in Table II. The frequencies of the N–H peaks are less affected; the peak at lower frequency is given in Table II.

The proton magnetic resonance spectra of all the hydrazones II and V were determined, and the important peaks are given in Tables II and III; however, most of the hydrazones VII proved to be too insoluble, and the spectral peaks of only two hydrazones of this series are given in Table III. The numbers of protons obtained by integration of the peaks, and the splitting patterns of the peaks, were in all cases in agreement with the expected structures. For compounds of the series V and VII the aromatic protons of the aldehyde moiety overlapped with protons of the R group of the hydrazide, when this was also aromatic, and complex multiplets were shown which are not given in Table III; however, the integration showed the expected total of aromatic protons. Peaks due to OH and NH could be identified by exchange with D_2O. Changes in R of II, V, and VII would be expected to affect the chemical shift of amide NH more than that of phenolic OH, and explain our assignment of NH and OH peaks in Tables II and III.

Experimental Section

Satisfactory elemental analyses were obtained for all new compounds and were submitted for review. These analyses were done by Galbraith Laboratories, Knoxville, TN, and are available as supplementary material. Melting points were taken in open capillary tubes by using a Gallenkamp apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer 257 spectrometer. NMR spectra were obtained with a Varian C-60 spectrometer using tetramethylsilane as an internal standard. Acylhydrazides were prepared from the acid or ester by the method of Sah (*5*) or were used as received from Aldrich Chemical Co. or Eastman Co.

Preparation of Acylhydrazones

A. From Pyridoxal Hydrochloride. The acylhydrazide (0.01 mol) was dissolved in 100 mL of water or ethanol by heating,

Table II. Proton Magnetic Resonance Peaks of Hydrazones II Derived from Pyridoxal

R	solvent	peaks (δ) CH_3[b]	CH_2OH[c]	CH_2OH[d]	CH=N	OH[b]	NH[b]	others
CH_3	d	2.40	4.57	5.27	8.57	11.97		2.02 (CH_3), 7.87[e]
C_6H_5	d	2.43	4.63	5.34	9.07	12.37	12.63	7.28–8.15[e,f]
p-HO–C_6H_4	d	2.45	4.65	5.38	8.90	10.25	12.28	6.92,[f] 7.88[e,f]
p-$CH_3C_6H_4$	d	2.47	4.68	5.43	9.00	12.52		2.47 (CH_3), 7.43,[f] 7.97[e,f]
p-O_2N–C_6H_4	t	2.47	4.12		8.93			7.53–8.17[e,f]
p-H_2N–C_6H_4	d	2.47	4.65	6.03	8.93	12.23		6.03 (OH and NH_2), 6.97,[f] 7.78,[f] 7.95[e]
p-(t-C_4H_9)C_6H_4	d	2.45	4.65	5.38	8.95	12.38		1.33 (t-Bu), 7.55,[f] 7.95[e,f]
p-CH_3O–C_6H_4	d	2.45	4.67		9.03	12.53		3.90 (OMe), 7.12,[f] 7.98,[e] 8.03[f]
m-Cl–C_6H_4	d	2.43	4.65	5.40	9.05	12.70		7.77–8.23,[f] 7.97[e]
m-F–C_6H_4	d	2.45	4.67	5.43	9.03	12.27	12.67	7.37–8.08[e,f]
m-Br–C_6H_4	d	2.27	4.47		8.93			6.22,[f] 6.65–8.28[e,f]
4-C_5H_4N	t	2.50	4.80		8.95			7.80,[e] 8.30,[e] 8.72[e]
2-C_4H_3O	d	2.45	4.65	5.40	9.05	12.27	12.63	6.73–6.87,[g] 7.87,[g] 8.07[e]
2-C_4H_3S	d	2.45	4.65	5.42	8.92	12.18	12.52	7.28,[h] 7.98[e,h]

[a] d = DMSO-d_6, t = trifluoroacetic acid-*d*. [b] Singlet. [c] Doublet, $J \approx 5$ Hz, or broad singlet. [d] Triplet, $J \approx 5$ Hz, or broad singlet. [e] Pyridine CH. [f] Benzene CH. [g] Furan CH. [h] Thiophene CH.

Table III. Proton Magnetic Resonance Peaks of Hydrazones V and VII in DMSO-d_6

compd	R	peaks (δ)			
		CH=N	OH	NH	R
V	CH_3	8.30	11.15	12.20	2.01, 2.20[a]
	C_6H_5	8.60	11.25	12.03	
	p-HO-C_6H_4	8.55	11.27	11.80	10.13 (OH)
	p-$CH_3C_6H_4$	8.57	11.27	11.92	2.37 (CH_3)
	p-O_2N-C_6H_4[b]	8.37			
	p-H_2N-C_6H_4	8.55	11.50	11.68	5.78 (NH_2)
	p-t-C_4H_9-C_6H_4	8.63	11.38	12.00	1.33 (t-Bu)
	p-CH_3O-C_6H_4	8.67	11.48	12.00	3.88 (OCH_3)
	m-Cl-C_6H_4	8.62	11.18	12.08	
	m-F-C_6H_4	8.67	11.23	12.10	
	m-Br-C_6H_4	8.60	11.17	12.08	
	4-C_5H_4N	8.68	11.15	12.20	8.78 (2H, pyridyl)
	2-C_4H_3O	8.60	11.50		
	2-C_4H_3S	8.60	11.13	11.98	
VII	C_6H_5	9.45	12.10	12.73	
	p-HO-C_6H_4	9.50	12.00	12.93	10.30 (OH)

[a] Two singlet peaks integrate to three H, indicating compound to be mixture of geometrical isomers. [b] Solvent: trifluoroacetic acid-d.

and to this was added a solution of pyridoxal hydrochloride (2.04 g, 0.01 mol) and anhydrous sodium acetate (0.90 g, 0.11 mol) in water (100 mL). The mixture was boiled under reflux for 30 min, cooled, and filtered. The solid hydrazone was washed in the filter with water and dried in a vacuum desiccator overnight. The hydrazone was essentially pure, neither melting point nor NMR spectrum showing any change when the compound was recrystallized from 95% ethanol.

B. From Salicylaldehyde or 2-Hydroxy-1-naphthaldehyde. A solution of the aldehyde (1.22 g, 0.01 mol) and acetic acid (2 mL) in 95% ethanol (50 mL) was added to a solution of the acylhydrazide (0.01 mol) in 50% aqueous ethanol (125 mL). The mixture was boiled under reflux, concentrated, cooled, and filtered, and the solid hydrazone dried for 3 days in a vacuum desiccator. The melting point and NMR spectrum of the hydrazone were not altered by recrystallization from 95% ethanol.

Registry No. I·HCl, 65-22-5; II (R = CH_3), 15871-96-2; II (R = C_6H_5), 72343-06-7; II (R = p-HO-C_6H_4), 116324-84-6; II (R = p-CH_3-C_6H_4), 116324-85-7; II (R = p-O_2N-C_6H_4), 116324-86-8; II (R = p-H_2N-C_6H_4), 116324-87-9; II (R = p-t-C_4H_9-C_6H_4), 116324-88-0; II (R = p-CH_3O-C_6H_4), 116324-89-1; II (R = m-Cl-C_6H_4), 116324-90-4; II (R = m-F-C_6H_4), 116324-91-5; II (R = m-Br-C_6H_4), 116324-92-6; II (R = 4-C_5H_4N), 737-86-0; II (R = 2-C_4H_3O), 105402-29-7; II (R = 2-C_4H_3S), 96712-66-2; IV, 90-02-8; V (R = CH_3), 5941-05-9; V (R = C_6H_5), 3232-37-9; V (R = p-HO-C_6H_4), 82859-76-5; V (R = p-CH_3-C_6H_4), 82859-74-3; V (R = p-O_2N-C_6H_4), 50366-20-6; V (R = p-H_2N-C_6H_4), 50366-22-8; V (R = p-t-C_4H_9-C_6H_4), 82859-75-4; V (R = p-CH_3O-C_6H_4, 100969-61-7; V (R = m-Cl-C_6H_4), 116324-93-7; V (R = m-F-C_6H_4), 116324-94-8; V (R = m-Br-C_6H_4), 116324-95-9; V (R = 4-C_5H_4N), 495-84-1; V (R = 2-C_4H_3O), 92982-43-9; V (R = 2-C_4H_3S), 96818-57-4; VI, 708-06-5; VII (R = CH_3), 34334-87-7; VII (R = C_6H_5), 15017-21-7; VII (R = p-HO-C_6H_4), 69733-97-7; VII (R = p-CH_3-C_6H_4), 82859-80-1; VII (R = p-O_2N-C_6H_4), 95523-63-0; VII (R = p-H_2N-C_6H_4), 116324-96-0; VII (R = p-t-C_4H_9-C_6H_4), 68758-85-0; VII (R = p-CH_3O-C_6H_4), 40111-51-1; VII (R = m-Cl-C_6H_4), 116324-97-1; VII (R = m-F-C_6H_4), 116324-98-2; VII (R = m-Br-C_6H_4), 116324-99-3; VII (R = 4-C_5H_4N), 796-42-9; VII (R = 2-C_4H_3O), 60947-25-3; VII (R = 2-C_4H_3S), 116325-00-9; $CH_3CONHNH_2$, 1068-57-1; $C_6H_5CONHNH_2$, 613-94-5; p-HO-$C_6H_4CONHNH_2$, 5351-23-5; p-CH_3-$C_6H_4CONHNH_2$, 3619-22-5; p-O_2N-$C_6H_4CONHNH_2$, 636-97-5; p-H_2N-$C_6H_4CONHNH_2$, 5351-17-7; p-t-C_4H_9-$C_6H_4CONHNH_2$, 43100-38-5; p-CH_3O-$C_6H_4CONHNH_2$, 3290-99-1; m-Cl-$C_6H_4CONHNH_2$, 1673-47-8; m-F-$C_6H_4CONHNH_2$, 499-55-8; m-Br-$C_6H_4CONHNH_2$, 39115-96-3; 4-$C_5H_4NCONHNH_2$, 54-85-3; 2-$C_4H_3OCONHNH_2$, 3326-71-4; 2-$C_4H_3SCONHNH_2$, 2361-27-5; Fe, 7439-89-6.

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Supplementary Material Available: Elemental analyses (C, H, N) for all compounds (3 pages). Ordering information given on any current masthead page.

Cycloaddition Reactions of 2,4,6-Trimethoxybenzonitrile Oxide with Disubstituted Acetylenes. 3

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Cycloaddition reactions of 2,4,6-trimethoxybenzonitrile oxide with dimethyl acetylenedicarboxylate, diethyl acetylenedicarboxylate, di-*tert*-butyl acetylenedicarboxylate, and diphenylacetylene were used for the synthesis of polyfunctional isoxazole ring systems.

One of the most general methods for the preparation of various isoxazole and 2-isoxazoline derivatives is the cycloaddition reaction of nitrile oxide with substituted acetylenes (*3-7*) and substituted ethylenes (*8-10*), respectively. In connection with our continuing interest in the synthesis of polyfunctional heterocyclic compounds such as isoxazole and 2-isoxazolines (*1, 2*), we have examined herein the cycloaddition reactions of 2,4,6-trimethoxybenzonitrile oxide (**1**) with disubstituted acetylenes which provide polyfunctional isoxazoles as shown in Scheme I. This type of synthesis is the first example using a benzonitrile oxide bearing a substitutent more

