Mass Spectra of Some 1,2,4-Thiadiazoles (1)

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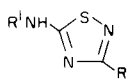
Substituted 1,2,4-thiadiazoles were found to undergo fragmentation by loss of RCN from the molecular ion with both 3- and 5-substituents being involved to some extent. This was followed by loss of sulfur to yield a nitrilium ion. With 5-hydrazino substituents, hydrogen transfer was observed from the substituent to a ring nitrogen atom.

Our interest in the 1,2,4-thiadiazole nucleus, particularly in ring-fused systems (2), required the synthesis of a variety of monocyclic derivatives. In this communication we described their synthesis and their mass spectral fragmentation patterns. A recent publication (3) described the mass spectra of a series of 3-substituted-5-amino-1,2,4-thiadiazoles (**1**) in which two major pathways controlled the fragmentation of the intense molecular ions. These pathways involved fission of the (3,4) and (5,1) bonds in one instance and the (1,2) and (3,4) [or alternatively the (2,3) and (4,5)] bonds in the other. The variety of substituents present in the 1,2,4-thiadiazoles examined in this present study (Table I) makes a useful complement to the above results and provides a more detailed description of the fragmentation patterns of the ring system. The mass spectra of derivatives of the 1,2,3-thiadiazole ring system (**2**) have recently been described (4), and a comparison of these data illustrate the effect of ring heteroatom position on the fragmentation pattern of small ring heterocycles.

The general fragmentation pathways are illustrated by the decomposition of 3-methylthio-1,2,4-thiadiazole (**3**; $R^1 = SCH_3$, $R^2 = H$) (Compound I), the simplest example of the ring system studied (Scheme 1). The molecular



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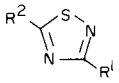


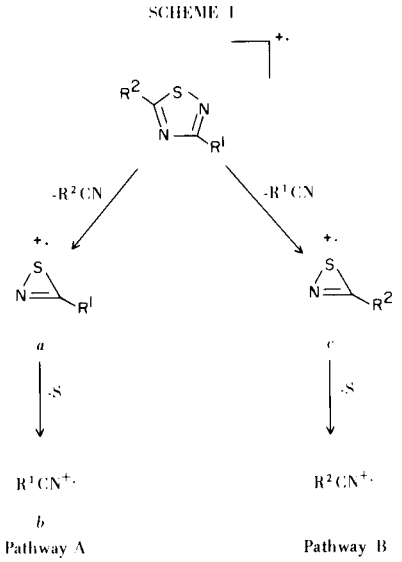
3

ion lost HCN to yield a thiazirenium ion *a* ($R^1 = SCH_3$) which then lost sulfur to yield ion *b* ($R^1 = SCH_3$) (Pathway A). This is similar to the well established loss of a nitrogen atom from the diazirenium ion observed in a series of *s*-triazoles (**5**). A similar loss of RCN has been observed in a series of thiazoles (6).

5-Chloro derivatives exhibited both of the general fragmentation pathways shown in Scheme 1. 5-Chloro-1,2,4-thiadiazole (**3**; $R^1 = H$, $R^2 = Cl$) (Compound II) lost both cyanogen chloride (Pathway A) and hydrogen cyanide (Pathway B) from the molecular ion. Similarly, 5-chloro-3-methylthio-1,2,4-thiadiazole (**3**; $R^1 = SCH_3$, $R^2 = Cl$) (Compound III) showed both fragmentation pathways, with ClCN and CH_3SCN being lost from the molecular ion. In the case of 5-chloro-3-phenyl-1,2,4-thiadiazole (**3**; $R^1 = C_6H_5$, $R^2 = Cl$) (Compound IV) only the loss of cyanogen chloride (Pathway A) was observed.

The spectrum of 5-mercapto-3-methyl-1,2,4-thiadiazole (**3**; $R^1 = CH_3$, $R^2 = SH$) (Compound V) exhibited Pathway B to a moderate extent with the loss of acetonitrile amounting to 21% of the base peak. The other fragmentation pathway in evidence was the loss of SCN· from the molecular ion. A similar loss from a series of 3-mercapto-

SCHEME I

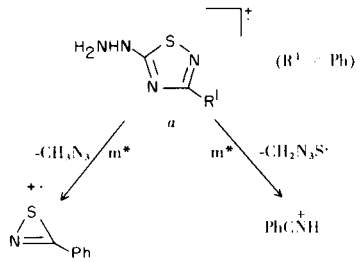


s-triazoles has been observed (5b). The fragmentation of 3-methyl-1,2,4-thiadiazol-5-ylthioacetic acid (**3**; R^1 = CH_3, R^2 = SCH_2CO_2H) (Compound VI) also followed Pathways A and B and, in addition, the molecular ion lost CO_2 to form the 3-methyl-5-methylthio-1,2,4-thiadiazolium ion (**3**; R^1 = CH_3, R^2 = SCH_3) which then lost acetonitrile *via* Pathway B.

Metastable ions were observed in all cases for the above transitions and these are shown in Table II.

A series of 5-hydrazino derivatives was found to fragment by the above two general pathways in addition to a significant new fragmentation (Scheme 2). 5-Hydrazino-3-phenyl-1,2,4-thiadiazole (**3**; R^1 = C_6H_5, R^2 = $NHNH_2$) (Compound XIII) showed the loss of CH_3N_3 from the molecular ion *a* (Scheme 2, Pathway A), with the appropriate metastable ion being present. Exact

SCHEME 2



b, m/e 135.0143 *c*, m/e 104.0231

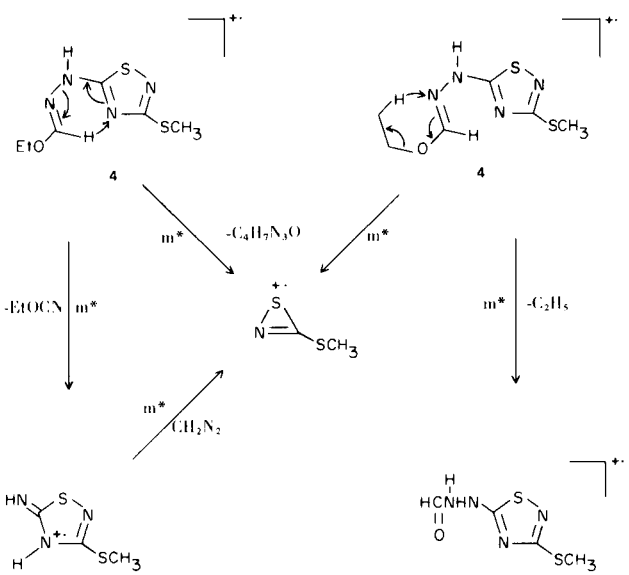
mass determination in a high resolution spectrum confirmed that this elimination resulted in an ion *b*, $[C_7H_5NS]^+$, m/e 135.0143 (5%)[‡] most likely the 3-phenylthiazirenium ion. The alternative fragmentation pathway gave rise to a $[C_7H_6N]^+$ ion, m/e 104.0231 (6.7%)[‡], most likely the protonated benzonitrilium ion *c*, resulting from the breaking of the (1-2) and (3-4) bonds with the concomitant transfer of a hydrogen atom to N_2.

5-Hydrazino-3-methyl-1,2,4-thiadiazole (**3**; R^1 = CH_3, R^2 = $NHNH_2$) (Compound VII) and 5-hydrazino-3-methylthio-1,2,4-thiadiazole (**3**; R^1 = SCH_3, R^2 = $NHNH_2$) (Compound X) both followed the two general fragmentation Pathways A and B as well as exhibiting the loss of CH_2N_3S as discussed for the 3-phenyl derivative. These data are shown in Table I.

1-Methyl-(3-methylthio-1,2,4-thiadiazol-5-yl)hydrazine (**3**; R^1 = SCH_3, R^2 = NCH_3NH_2) (Compound XI) exhibited the loss of $C_2H_5N_3$ *via* pathway A, giving an ion $[C_2H_3NS_2]^+$, m/e 104.9716 (55.8%)[‡]. In addition, the loss of CH_2N_3S, which again involved hydrogen transfer from the exocyclic moiety to N_1, was observed to a significant extent. Both of these fragmentations were substantiated by the appropriate metastable ion (Table II) and the high resolution spectrum.

‡ Relative Intensity

SCHEME 3



1-Methyl-(3-methyl-1,2,4-thiadiazol-5-yl)hydrazine (**3**; R^1 = CH_3, R^2 = NCH_3NH_2) (Compound VIII) fragmented by Pathways A and B as well as by the proton transfer pathway with loss of CH_2N_3S. All transitions were accompanied by the appropriate metastable ions (Table II).

The spectrum of 1-formyl-2-(3-methylthio-1,2,4-thiadiazol-5-yl)hydrazine (**3**; R^1 = SCH_3, R^2 = NHNHCHO) (Compound XII) gave a moderately strong molecular ion with the first fragment being the loss of carbon monoxide. As expected, the rest of the spectrum was essentially that of 5-hydrazino-3-methylthio-1,2,4-thiadiazole (**3**; R^1 = SCH_3, R^2 = $NHNH_2$) (Compound X). A direct loss of $C_2H_2N_3OS$, analogous to the loss of CH_2N_3S *via* a hydrogen transfer, as was observed with the hydrazines above, was not detected.

Ethyl formate (3-methylthio-1,2,4-thiadiazol-5-yl)hydrazone (**4**) (Compound XV) and ethyl formate (3-methyl-1,2,4-thiadiazol-5-yl)hydrazone (**5**) (Compound XIV) exhibited several new fragmentations due to the hydrazone moiety as well as following the general Pathway A already discussed. The molecular ion of the 3-methylthio derivative (**4**) was observed to undergo two competing McLafferty rearrangements (Scheme 3). In one of these rearrangements, the formyl proton migrated to N_4 while losing EtOCN to give ion m/e 129 which then fragmented by Pathway A. The other hydrogen transfer reaction involved migration of hydrogen to the imino nitrogen atom with the loss of ethylene and formation of the 1-formyl-2-(3-methylthio-1,2,4-thiadiazol-5-yl)hydrazinium ion discussed previously.

Ethyl formate (3-methyl-1,2,4-thiadiazol-5-yl)hydrazone (**5**) fragmented by the general Pathway A. In addition, a hydrogen transfer to N_4 with the loss of

TABLE I

Mass Spectral Fragmentation of Some 1,2,4-Thiadiazoles (3)

Compound Number	Substituents R_2	R_1														
I	H	SCH_3	m/e	134	133	132	107	105	93	79	78	73	62	61	47	46
			Rel. Int.	10	6	100	7	50	14	10	9	9	20	27	11	12
II	Cl	H	m/e	122	121	120	95	93	81	79	73	61	59	58	47	46
			Rel. Int.	25	4	67	23	53	9	26	9	9	100	24	10	10
			m/e	43	41											
			Rel. Int.	40	32											
III	Cl	SCH_3	m/e	168	167	166	133	131	128	126	120	107	106	105	98	97
			Rel. Int.	29	5	71	5	19	8	5	12	14	5	100	14	32
			m/e	96	95	94	93	92	90	85	81	80	79	78	76	73
			Rel. Int.	42	8	6	7	7	65	38	14	13	8	10	27	63
			m/e	72	70	64	61	60	59	58	48	47	46	45	44	43 41
			Rel. Int.	15	15	21	21	16	21	26	12	60	8	8	21	21 10
IV	Cl	Ph	m/e	198	197	196	137	136	135	108	104	103	91	77	76	75 63
			Rel. Int.	15	4	39	5	9	100	5	6	34	7	30	22	8 8
			m/e	51	50	43	39	36								
			Rel. Int.	23	20	9	14	25								
V	HS	CH_3	m/e	134	133	132	91	77	76	74	73	72	66	64	59	47
			Rel. Int.	7	4	80	22	9	5	100	4	5	5	35	12	13
			m/e	46	42											
			Rel. Int.	10	72											
VI	SCH_2CO_2H	CH_3	m/e	190	149	148	147	146	145	105	104	92	91	90	89	78 76
			Rel. Int.	21	31	10	7	100	5	20	20	15	21	33	16	7 8
			m/e	75	74	73	72	64	61	60	59	58	47	46	45	44 43
			Rel. Int.	14	24	83	15	9	6	10	16	16	26	61	55	11 17
			m/e	42	41											
			Rel. Int.	49	28											

TABLE I (continued)

Compound Number	Substituents R_2	Substituents R_1														
VII	$NHNH_2$	CH_3	m/e	132	131	130	115	89	88	76	74	73	72	60	59	47	46
			Rel. Int.	5	5	100	10	33	7	9	31	83	12	15	11	12	21
			m/e	43	42	41	40										
			Rel. Int.	97	79	18	13										
VIII	$N(CH_3)NH_2$	CH_3	m/e	144	129	128	115	103	78	77	74	73	60	57	56	55	46
			Rel. Int.	56	10	8	5	10	12	15	27	39	10	100	7	7	26
			m/e	45	43	42	41	40									
			Rel. Int.	17	15	57	25	17									
IX	N(COPh)NHCOPh	CH_3	m/e	338	216	106	105	103	78	77	51						
			Rel. Int.	4	3	21	75	11	7	100	25						
X	$NHNH_2$	SCH_3	m/e	164	163	162	160	146	145	132	131	129	128	116	106	105	96
			Rel. Int.	11	8	100	20	10	7	5	9	7	22	16	10	59	8
			m/e	91	90	85	81	79	76	74	73	64	60	59	47	46	
			Rel. Int.	7	26	15	8	7	11	57	11	39	12	31	21	23	
			m/e	45	43												
			Rel. Int.	19	38												
XI	$N(CH_3)NH_2$	SCH_3	m/e	178	177	176	160	132	131	107	106	105	99	90	87	85	83
			Rel. Int.	11	8	100	10	15	8	7	17	64	6	17	9	13	21
			m/e	76	74	73	72	60	59	57	47	46	45				
			Rel. Int.	6	25	9	6	7	8	59	15	19	18				
XII	NHNHCHO	SCH_3	m/e	192	191	190	162	161	146	145	143	142	117	116	107	106	105
			Rel. Int.	9	8	100	27	20	7	6	8	13	34	6	8	26	78
			m/e	99	90	89	85	83	79	76	73	72	69	60	59	58	48
			Rel. Int.	14	29	8	29	6	12	7	14	10	27	18	18	9	10
			m/e	47	46												
			Rel. Int.	39	38												
XIII	$NHNH_2$	Ph	m/e	194	193	192	135	105	104	103	89	77	76	60	51	50	
			Rel. Int.	3	11	78	47	9	100	33	8	35	14	6	18	10	

TABLE I (continued)

Compound Number	Substituents R_2	Substituents R_1																					
XIV	$C_3H_7N_2O$	CH_3	m/e	188	187	157	141	130	129	117	116	115	92	91	89	76	75						
			Rel. Int.	3	6	7	57	14	14	17	7	72	12	17	10	7	6						
			m/e	74	73	72	71	67	60	59	47	46	45	44	43	42							
			Rel. Int.	30	100	18	10	16	25	14	17	35	13	9	22	100							
			m/e	41	40																		
			Rel. Int.	25	15																		
XV	$C_3H_7N_2O$	SCH_3	m/e	219	218	190	189	161	147	146	145	127	117	107	106	105	101						
			Rel. Int.	12	100	4	3	6	40	10	9	6	9	9	19	90	9						
			m/e	100	99	90	88	85	79	74	73	72	69	60	59	47	46						
			Rel. Int.	8	16	19	9	24	13	28	16	12	16	22	16	28	53						
			m/e	45	43																		
			Rel. Int.	24	33																		

EtOCN occurred. However, no loss of ethylene from the molecular ion was observed.

EXPERIMENTAL

The 1,2,4-thiadiazoles were prepared by methods described in the literature (7,8,9) and by those outlined below. All compounds were of analytical purity.

The mass spectra were determined with an Hitachi Perkin-Elmer RMU-6E mass spectrometer operating at an ionizing voltage of 70 eV using the direct insertion probe technique with a source temperature of *ca.* 120°. The indirect inlet was utilized for those compounds with low melting points and high volatility.

Ethyl formate (3-methyl-1,2,4-thiadiazol-5-yl)hydrazone (XIV).

3-Methyl-5-hydrazino-1,2,4-thiadiazole (8) (1.3 g.) was refluxed in pure, dry triethylorthoformate (50 ml.) for 24 hours. The solution was cooled and the precipitate recrystallized from toluene-petroleum ether from which it separated as colorless needles: 0.28 g. (15%), m.p. 129-130°; ir (potassium bromide) 3200, 3100, 2980, 2870, 1610, 1500, 1450, 1270, 1290, 1250, 1145, 1110, 1021, 995, 938, 847, 811, 778, 710, 665, 610 cm^{-1}; uv max (methanol) 275 nm (log ϵ 4.12), 203 (4.13).

Anal. Calcd. for $C_6H_{10}N_4OS$: C, 38.70; H, 5.41; N, 30.08. Found: C, 38.97; H, 5.34; N, 29.88.

1,2-Dibenzoyl-1-(3-methyl-1,2,4-thiadiazol-5-yl)hydrazine (IX).

3-Methyl-5-hydrazino-1,2,4-thiadiazole (6.3 g.) was dissolved in pyridine (100 ml.) and benzoyl chloride (8.5 g.) was added to the rapidly stirred solution at 0°. The reaction mixture was poured over ice and a white solid collected. It crystallized from benzene-petroleum ether as colorless needles: 8.1 g. (65%), m.p. 214-215°; ir (potassium bromide) 3300, 3200, 3040, 2975, 1650, 1490, 1440, 1350, 1310, 1140, 1090, 1038, 1012, 990, 940, 920, 855, 815, 799, 731, 723, 710, 620, 565, 535 cm^{-1}; uv max (methanol) 263 nm (log ϵ 3.96), 225 (4.30); nmr (DMSO-d_6) δ 2.48 (s, 3, CH_3), 7.50 (m, 5, C_6H_5), 7.80 (m, 5, C_6H_5).

Anal. Calcd. for $C_{17}H_{14}N_4O_2S$: C, 60.36; H, 4.17; N, 16.55. Found: C, 59.16; H, 4.17; N, 16.30.

Ethyl Formate (3-Methylthio-1,2,4-thiadiazol-5-yl)hydrazone (XV).

3-Methylthio-5-hydrazino-1,2,4-thiadiazole (9) (2.2 g.) and triethylorthoformate (7.1 g.), were refluxed in 95% ethanol (75 ml.) for 24 hours. After ½ hour the solution started to turn blue. Upon cooling with dry ice, a white solid separated which recrystallized from benzene forming colorless needles: 0.63 g. (15%), m.p. 159-160°; ir (potassium bromide) 3200, 3100, 2980, 1610, 1460, 1450, 1340, 1250, 1140, 1100, 1020, 950, 853, 798, 683, 560, 505 cm^{-1}; uv max (methanol) 277 nm (log ϵ 4.04), 220 (3.88); nmr (deuteriochloroform) δ 6.67 (s, 1, H-C=N-), 4.19 (q, 2, J = 7.0 Hz, CH_3CH_2), 2.60 (s, 3, SCH_3), 1.85 (t, 3, J = 7.0 Hz, CH_2CH_3), 0.8 (s, 1, NH).

Anal. Calcd. for $C_6H_{10}N_4OS_2$: C, 33.03; H, 4.62; N, 25.68. Found: C, 32.68; H, 4.61; N, 25.66.

1-Methyl-1-(3-methylthio-1,2,4-thiadiazol-5-yl)hydrazine (XI).

3-Methylthio-5-chloro-1,2,4-thiadiazole (9) (8.8 g.) was added dropwise with rapid stirring to a solution of methyl hydrazine (6.3 g.) in methanol (50 ml.) at 0°. Addition of water and cooling gave a colorless solid which crystallized from methanol-water as colorless rhombs: 6.1 g. (65%), m.p. 134-135°; ir (potassium bromide) 3320, 3240, 2940, 1645, 1540, 1450, 1325, 1305, 1270, 1240, 1125, 950, 890, 785, 738, 718, 680, 595, 563, 505 cm^{-1}; uv max (methanol) 256 nm (log ϵ 3.59), 237

TABLE II

Metastable Ions Present in the Mass Spectra of Some 1,2,4-Thiadiazoles (3)

Compound Number	R_2	R_1	Transition	Found m*	Calcd. m*	Fragment Expelled
I	H	SCH_3	132 → 105	83.5	83.5	HCN
			105 → 73	50.9	51.0	S
II	Cl	H	120 → 93	72.0	72.1	HCN
			120 → 59	29.5	29.0	ClCN
III	Cl	SCH_3	166 → 131	103.5	103.5	Cl
			166 → 105	66.5	66.5	ClCN
			105 → 73	51.0	50.8	S
			73 → 47	31.0	30.5	CN
IV	Cl	Ph	196 → 135	93.0	93.0	ClCN
			135 → 103	79.0	78.6	S
V	SH	CH_3	132 → 91	62.8	62.8	CH_3CN
			132 → 74	41.5	41.5	SCN
VI	SCH_2CO_2H	CH_3	190 → 146	112.5	112.5	CO_2
			146 → 105	75.5	75.5	CH_3CN
VII	$NHNH_2$	CH_3	130 → 115	103.5	103.7	CH_3
			130 → 89	61.0	61.0	CH_3CN
			130 → 73	41.0	41.0	CH_3N_3
VIII	$N(CH_3)NH_2$	CH_3	144 → 128	114.0	113.8	NH_2
			144 → 103	74.0	73.8	CH_3CN
			144 → 57	22.8	22.6	$C_2H_3N_2S$
			144 → 73	37.2	37.2	$C_2H_5N_3$
IX	N(COPh)NHCOPh	CH_3	105 → 77	56.5	56.5	CO
X	$NHNH_2$	SCH_3	162 → 146	131.7	131.5	NH_2
			162 → 105	68.5	68.3	CH_3N_3
			162 → 74	33.9	33.9	CH_2N_3S
			146 → 105	76.3	76.0	CHN_2
			105 → 73	51.0	50.8	S
XI	$N(CH_3)NH_2$	SCH_3	176 → 160	145.5	145.3	NH_2
			176 → 105	62.6	62.5	$C_2H_5N_3$
			176 → 74	31.6	31.3	CH_2N_3S
			160 → 105	69.5	69.0	$C_2H_3N_2$
XII	NHNHCHO	SCH_3	190 → 162	138.5	138.2	CO
			162 → 146	131.7	131.5	NH_2
			162 → 105	68.8	68.3	CH_3N_3
XIII	$NHNH_2$	Ph	192 → 135	95.0	95.0	CH_3N_3
			192 → 104	56.3	56.2	CH_2N_3S
XIV	$C_3H_7N_2O$	CH_3	186 → 141	107.0	106.8	C_2H_5O
			186 → 115	71.3	71.2	C_3H_5NO
			115 → 73	46.3	46.4	CH_2N_2
XV	$C_3H_7N_2O$	SCH_3	218 → 190	165.5	165.5	C_2H_4
			218 → 173	137.0	137.0	C_2H_5O
			218 → 147	99.1	99.0	C_3H_5NO
			218 → 105	51.0	50.5	$C_3H_7N_2O$
			147 → 105	75.0	74.8	CH_2N_2

(3.91), 220 (3.97); nmr (methanol) δ 2.50 (s, 3, SCH_3), 2.83 (s, 3, NCH_3).

Anal. Calcd. for $C_4H_8N_4S_2$: C, 27.21; H, 4.57; N, 31.90. Found: C, 27.09; H, 4.52; N, 31.73.

3-Methyl-1,2,4-thiadiazol-5-ylthioacetic Acid (VI).

3-Methyl-5-mercapto-1,2,4-thiadiazole (9) (3.0 g.) and chloroacetic acid (2.8 g.) were heated to 50° in a sodium hydroxide solution (25 ml., 10%) for 1 hour. Addition of concentrated hydrochloric acid precipitated a white product which crystallized from toluene as colorless irregular sheafs: 1.1 g. (25%), m.p. 122-124°; ir (potassium bromide) 2700, 1690, 1470, 1410, 1390, 1280, 1060, 1025, 840, 713, 650, 475, 443 cm^{-1}; uv max (methanol) 268 nm (log ε 3.92), 230 (3.58); nmr (DMSO-d_6) δ 2.60 (s, 3, CH_3), 4.20 (s, 2, CH_2).

Anal. Calcd. for $C_5H_6N_2O_2S_2$: C, 31.57; H, 3.17; N, 14.72. Found: C, 31.75; H, 3.06; N, 14.74.

Acknowledgment.

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REFERENCES

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(2) K. T. Potts and R. Armbruster, *J. Org. Chem.*, **35**, 1965 (1970).

(3) A. H. Miller and R. J. Pancirov, *J. Heterocyclic Chem.*, **8**, 163 (1971).

(4) B. J. Millard and D. L. Pain, *J. Chem. Soc. (C)*, 2042 (1970).

(5a) P. R. Briggs, N. L. Parker and T. W. Shannon, *Chem. Commun.*, 727 (1968); (b) K. T. Potts, R. Armbruster and E. Houghton, *J. Heterocyclic Chem.*, submitted for publication.

(6) B. J. Millard, *J. Chem. Soc. (C)*, 1231 (1969).

(7) J. Goerdeler, K. Wember and G. Worsch, *Chem. Ber.*, **87**, 57 (1954); J. Goerdeler, H. Groschopp, and U. Sommerbad, *ibid.*, **90**, 182 (1957).

(8) E. Bulka, F. Sommer and H. Beyer, *ibid.*, **95**, 1983 (1962).

(9) J. Goerdeler and G. Sperling, *ibid.*, **90**, 892 (1957).