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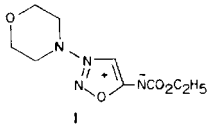
Received December 3, 1980

The synthesis of some novel anhydro-3-mercapto-5-pyrazinyl-1,2,4-triazolium hydroxides **5** is described. The appropriate 1-methylhydrazides **3** were condensed with isothiocyanates to give the thiosemicarbazides **4** which were cyclized to **5** under mildly basic conditions. A few 1,2,4-triazole-3-thiones **8** were synthesized for comparison, starting with the 2-methylhydrazides **6** and then carrying out analogous synthetic transformations.

J. Heterocyclic Chem., **18**, 1017 (1981).

As part of a general program of exploring the biological activity of novel heterocycles, we were interested in the class of chemical compounds known as "mesoionic". These compounds have been reviewed by Potts (1) and by Ollis and Ramsden (2) and have been defined as "five- or six-membered heterocyclic compounds which cannot be represented satisfactorily by any one covalent or polar structure and possess a sextet of electrons in association with the atoms comprising the ring. The ring bears a fractional positive charge balanced by a corresponding negative charge located on a covalently attached atom or group of atoms (2)." Many mesoionic compounds display biological activity (2) and one in particular, molsidomine, **1** (a sydnone imine), is marketed in Europe as an antianginal (3) and is undergoing clinical trials in the United States. We were particularly interested in compounds **5**, anhydro-3-mercapto-5-pyrazinyl-1,2,4-triazolium hydroxides, which would bear a resemblance to the aminotriazoles **2**, reported to be moderate diuretics in normal rats (4).



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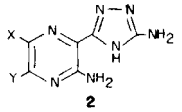

2

These compounds were synthesized by a modification of the methods described by Ollis and Ramsden (2) and indicated in Scheme 1. The appropriate 1-methylhydrazides **3** were reacted with isothiocyanates to give the acylthiosemicarbazides **4**. These were either isolated and characterized or reacted without isolation. Cyclization under mildly basic conditions gave the mesoionic compounds **5**. The 3-acetamido derivatives **4b** and **4c** were subjected to mild acid hydrolysis prior to ring closure, giving the 3-amino compounds, **5e** and **5g**. These reactions were straightforward and went in uniformly good yields; however, the synthesis of the precursor 1-methylhydrazides **3** proved to be more challenging (Scheme 2).

The reaction of the esters **9** (Scheme 2) with methylhydrazine gave the 2-methylhydrazides **6a** (5), **6b**, and **6c** (6). The desired 1-methylhydrazides **3a-d** were obtained from the reaction of methylhydrazine with more reactive acylating reagents, *i.e.*, **10**, **12**, and **13**. The acetylation of methylhydrazine shows this same selectivity and has been studied in detail by Condon (7). Heindel (8) has also noted the selectivity of acylation of alkylhydrazines and obtained only the 1-methylhydrazide from the reaction of methylhydrazine with isatoic anhydrides. Peet (9) however, obtained an 85:15 mixture of 1- and 2-methylhydrazides from the reaction of isatoic anhydride with methylhydrazine in DMF.

The required pyrazinecarboxylic acid 1-methylhydrazide **3a** was obtained in 26% from methyl hydrazine and pyrazine carbonyl chloride **10** (10). The principle side product was the diacylated product **11**. Compound **3b**, 3-acetamidopyrazinecarboxyic acid 1-methylhydrazide, was obtained in somewhat better yield from the reaction of methylhydrazine with 2-methylpyrazine[2,3-*d*][1,3]oxazin-4-one, **12** (11). Errede (12) has discussed the reaction of analogous acylanthranils with amines and detailed some side reactions. Acid hydrolysis of **3b** gave the 3-amino derivative, **3c**, in poor yield. The *N,N*-diphenylcarbamic anhydride **13** was synthesized in a variation of a literature procedure (13). It led to 3,5-diamino-6-chloropyrazinecarboxylic acid 1-methylhydrazide **3d** in good yield.

The 1-methylhydrazides **3a-d** were distinguished from the 2-methylhydrazides **6a-c** by proton nmr. The NCH_3 of **3a-d** absorbed at 3.12-3.51 ppm in deuteriochloroform or DMSO-d_6 while the NCH_3 of **6a-c** absorbed at 2.52-2.88 ppm. The NCH_3 absorptions reported by Peet (9) for the 85:15 mixture of 2-aminobenzoic acid 1- and 2-methylhydrazides and by Ainsworth (14) for benzoic acid 1- and 2-methylhydrazides fall within these ranges. The structure of 1-methylhydrazide **3a** was also established by the synthesis of thiosemicarbazide **4a**, which was identical to the **4a** obtained from the reaction of pyrazine carbonyl chloride (**10**) and 4-cyclohexyl-1-methylthiosemicarbazide (15) (Scheme 2). Compounds **3b** and **3d** were characterized by their ability to form hydrazone derivatives **14a** and **14b** respectively (see Experimental).

A few 1,2,4-triazole-3-thiones **8a-e** were synthesized from the 2-methylhydrazides for comparison with the corresponding mesoionic compounds (Scheme 1). It was

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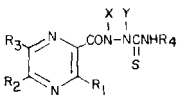
Table 1

Physical Properties of Some Pyrazinoylthiosemicarbazides

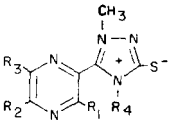


Compound No.	X	Y	R_1	R_2	R_3	R_4	Recrystallization Solvent (a)	Yield	M.p., (°C)	Molecular Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
4a	CH_3	H	H	H	H	c-C_6H_{11}	A + D	58	196-197	$C_{13}H_{19}N_5OS$	53.22	6.53	23.87	53.18	6.60	23.92
4b	CH_3	H	$NHCOCH_3$	H	H	C_6H_5	A	96	190-192	$C_{15}H_{16}N_6O_2S$	52.31	4.68	24.40	52.02	4.60	24.60
4c	CH_3	H	$NHCOCH_3$	H	H	C_2H_5	A	92	181-183	$C_{11}H_{16}N_6O_2S$	44.58	5.44	28.36	44.90	5.40	28.30
4d	CH_3	H	NH_2	NH_2	Cl	CH_3	B + C	96	240-241	$C_8H_{12}ClN_7OS$	33.16	4.18	33.84	32.99	4.16	33.74
4e	CH_3	H	NH_2	NH_2	Cl	$CH_2C_4H_3O$	E	85	220-221	$C_{12}H_{14}ClN_7O_2S$	40.51	3.97	27.56	40.68	4.00	27.57
4f	CH_3	H	NH_2	NH_2	Cl	C_6H_5	B + C	98	210-212	$C_{13}H_{14}ClN_7OS$	44.38	4.01	27.87	44.56	4.05	27.86
4g	CH_3	H	NH_2	NH_2	Cl	C_2H_5	B + C	82	240-242	$C_9H_{14}ClN_7OS$	35.58	4.64	32.28	35.55	4.61	32.19
4h	CH_3	H	NH_2	NH_2	Cl	$CH_2CH=CH_2$	B + C	89	238-240	$C_{10}H_{14}ClN_7OS$	38.03	4.47	31.05	37.88	4.46	30.83
4i	CH_3	H	NH_2	NH_2	Cl	4-FC_6H_4	B + C	97	220-221	$C_{13}H_{13}ClFN_7OS$	42.22	3.54	26.52	42.45	3.63	26.34
7a	H	CH_3	H	H	H	C_6H_5	A	71	170-172	$C_{12}H_{13}N_5OS$	54.34	4.56	24.38	54.07	4.74	24.64
7b	H	CH_3	H	H	H	C_2H_5	A	85	176-178	$C_9H_{13}N_5OS$	45.17	5.47	29.27	45.12	5.52	29.73

(a) A = methanol, B = water, C = DMSO, D = acetone, E = acetonitrile.

Table 2

Physical Properties of Anhydro-3-mercapto-1,2,4-triazolium Hydroxides

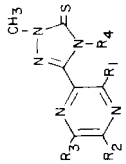


Compound No.	R_1	R_2	R_3	R_4	Synthetic Method	Recrystallization Solvent (a)	Yield	M.p., (°C)	Molecular Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
5a	H	H	C_2H_5		A	B	71	219-221	$C_9H_{11}N_5S$	48.85	5.01	31.65	48.92	5.01	31.48
5b	H	H	H	C_6H_5	A	B	58	232-234	$C_{13}H_{11}N_5S$	57.97	4.12	26.01	57.91	4.20	25.98
5c	H	H	H	c-C_6H_{11}	B	A	84	247-250	$C_{13}H_{17}N_5S$	56.70	6.22	25.43	56.74	6.17	25.48
5d	$NHCOCH_3$	H	H	C_6H_5	B	A	96	292-295	$C_{15}H_{14}N_6OS$	55.20	4.32	25.75	55.13	4.39	25.73
5e	NH_2	H	H	C_6H_5	C	A	80	323-326	$C_{13}H_{12}N_6S$	54.91	4.26	29.56	54.78	4.39	29.39
5f	$NHCOCH_3$	H	H	C_2H_5	D	A	79	272-274	$C_{11}H_{14}N_6OS$	47.47	5.07	30.20	47.30	5.04	30.25
5g	NH_2	H	H	C_2H_5	C	A	66	300-302	$C_9H_{12}N_6S$	45.74	5.12	35.57	45.62	5.08	35.65
5h	NH_2	NH_2	Cl	CH_3	E	D + A	93 (b)	279-280	$C_8H_{10}ClN_7S \cdot \frac{1}{2}H_2O$	34.22	3.92	34.92	34.57	3.80	34.81
5i	NH_2	NH_2	Cl	$CH_2C_4H_3O$	E	C	94	237-238	$C_{12}H_{12}ClN_7OS$	42.66	3.58	29.03	42.79	3.52	28.82
5j	NH_2	NH_2	Cl	$CH_2CH=CH_2$	E	D + A	89	268-270	$C_{10}H_{12}ClN_7S$	40.33	4.06	32.93	40.29	4.01	32.76
5k	NH_2	NH_2	Cl	C_2H_5	E	D + A	68	295-297	$C_9H_{12}ClN_7S$	37.82	4.23	34.31	37.80	3.96	34.36
5l	NH_2	NH_2	Cl	4-FC_6H_4	E	D + A	95	289-291	$C_{13}H_{11}ClFN_7S$	44.38	3.15	27.87	44.41	3.21	27.94
5m	NH_2	NH_2	Cl	C_6H_5	E	D + A	99	298-299	$C_{13}H_{12}ClN_7S$	46.77	3.62	29.38	46.86	3.75	29.31

(a) A = water, B = methanol, C = acetonitrile, D = DMSO. (b) Calculated for the hemihydrate.

Table 3

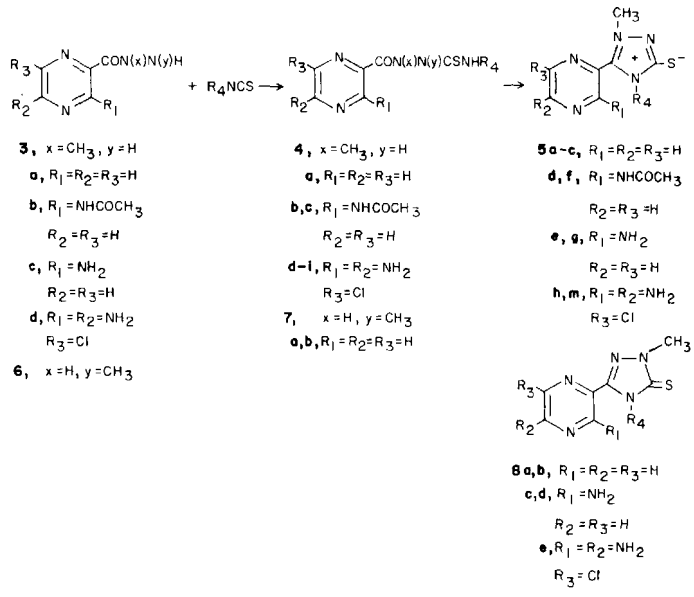
Physical Properties of 1,2,4-Triazole-3-thiones



Compound No.	R_1	R_2	R_3	R_4	Synthetic Method	Recrystallization Solvent (a)	Yield	M.p., (°C)	Molecular Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
8a	H	H	H	C_2H_5	F	D + E	89	93-95	$C_9H_{11}N_5S$	48.85	5.01	31.65	48.73	4.96	31.76
8b	H	H	H	C_6H_5	F	A	99	135-137	$C_{13}H_{11}N_5S$	57.97	4.12	26.00	57.94	4.19	26.22
8c	NH_2	H	H	C_2H_5	G	A	88	161-163	$C_9H_{12}N_6S$	45.74	5.12	35.57	45.58	5.14	35.73
8d	NH_2	H	H	C_6H_5	G	B	59	198-200	$C_{13}H_{12}N_6S$	54.91	4.26	29.56	54.80	4.34	29.79
8e	NH_2	NH_2	Cl	C_6H_5	H	C	65	236-237	$C_{13}H_{12}ClN_7S$	46.77	3.62	29.38	46.62	3.71	29.47

(a) A = water, B = methanol, C = acetonitrile, D = benzene, E = hexane.

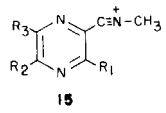
SCHEME I



thought that the proton nmr absorption of the triazole ring methyl group might be generally characteristic of the mesoionic compounds but it was not. The methyl absorptions of the following pairs of compounds, for example, were nearly identical: **5a** and **8a**, **5b** and **8b**, and **5m** and **8e** (see Table 4). In fact, the apparent differences in the methyl absorptions in Table 4 are due for the most part to solvent effects. For example, the methyl absorption of **8d** at 4.12 ppm in deuteriochloroform containing a drop of DMSO-d_6 shifted to 3.88 ppm in pure DMSO-d_6. On the other hand, the methyl absorption of **5e**, which was originally measured at 3.70 ppm in DMSO-d_6, shifted to 3.80 ppm in deuteriochloroform containing several drops of DMSO-d_6. The values in Table 4 bracket that reported by Ollis (16) for anhydro-1-methyl-3-mercapto-5-phenyl-4-*p*-tolyl-1,2,4-triazolium hydroxide at 3.84 ppm in deuteriochloroform.

Infrared spectroscopy was not generally characteristic of these classes of compounds either. In the compounds where the C=S absorption (16) was prominent (*e.g.*, **5b** and **8b**) it was nearly identical (1330 cm^{-1} and 1335 cm^{-1}, respectively).

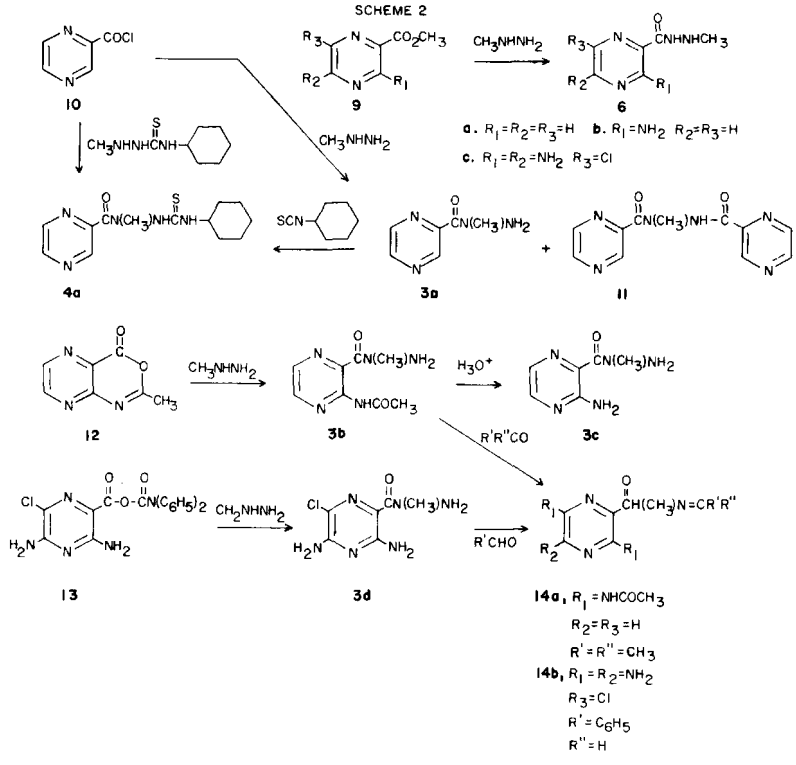
The mass spectra of these compounds were more diagnostic. In each case, the mesoionic compounds **5a-m** exhibited a fragment due to the *N*-methylpyrazinylnitrilium ion **15** (described by Potts (17)) that was absent in the fragmentation patterns of four out of five of the corresponding triazole-3-thiones **8a-e** (Table 4). Even mass spectra were not completely suitable for distinguishing between these two types of compounds, since **8d** showed a peak at m/e 135 due to the fragment containing the elements of phenyl isothiocyanate (17) (Table 4). The ^{13}C nmr spectra showed consistent differences between these compound types and are discussed in the succeeding paper.



15

These compounds were tested in saline loaded rats and in conscious dogs, but displayed only weak diuretic activity.

SCHEME 2



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover or Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 grating spectrophotometer. Nuclear magnetic resonance spectra were taken on a Jeol C-60HL instrument. Chemical shifts are reported as δ units with tetramethylsilane as an internal standard. The mass spectra were obtained from a Finnigan Model 4000 spectrophotometer operating in the electron impact mode with an INCOS data system at 70 eV by direct insertion. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

Isothiocyanates were purchased from either Aldrich Chemical Company or Trans World Chemicals.

Pyrazinecarboxylic Acid 2-Methylhydrazide (**6a**).

Methyl pyrazinoate (**9a**) (Columbia Organics) (13.10 g., 0.095 mole) was refluxed overnight in 90 ml. of absolute ethanol containing 8.75 g. (0.19 mole) of methylhydrazine. The solvent was evaporated and the residue recrystallized from benzene to give a total of 11.72 g. (81.1%), m.p. 94-96° (lit. m.p. 99-100° (5)); nmr (deuteriochloroform): δ2.88 (s, 3H, NCH_3), 4.70 (broad s, 1H, $NHCH_3$), 8.44 (m, 1H, H-5), 8.68 (d, 1H, J = 3 Hz, H-6), 8.82 (d, 1H, J = 1.5 Hz, H-3), 10.10 (broad s, 1H, CONH).

3-Aminopyrazinecarboxylic Acid 2-Methylhydrazide (**6b**).

Methyl 3-aminopyrazine-3-carboxylate (**9b**) (18) (15.3 g., 0.10 mole) was suspended in 200 ml. of sieve-dried dimethoxyethane and refluxed for 24 hours with 9.2 g. of methylhydrazine (0.20 mole). The solvent was evaporated to dryness and the residue recrystallized from methanol to give 11.80 g. of product (71%), m.p. 105-107°; nmr (deuteriochloroform): δ 2.82 (s, 3H, NCH_3), 4.75 (broad s, 1H, $NHCH_3$), 7.15 (broad s, 2H, NH_2), 8.10 (d, 1H, J = 2 Hz, H-6), 8.52 (d, 1H, J = 2 Hz, H-5), 9.30 (broad s, 1H, CONH).

Anal. Calcd. for $C_6H_9N_5O$: C, 43.11; H, 5.43; N, 41.90. Found: C, 43.31; H, 5.43; N, 42.03.

3,5-Diamino-6-chloropyrazinecarboxylic Acid 2-Methylhydrazide (**6c**).

Methyl 3,5-diamino-6-chloropyrazinecarboxylate (**9c**) (19) (4.0 g., 0.020 mole) was heated 16 hours on a steam bath in 30 ml. of diglyme containing 8.0 g. of methylhydrazine (0.134 mole). The solvent was removed under reduced pressure and the residue was taken up in hot methanol. Ethyl acetate was added to cloudiness and 0.6 g. of material crystallized that was identical to 3,5-diamino-6-chloropyrazinecarboxylic acid by tlc (20% methanol/ethyl acetate). The mother liquor was concentrated and the residue triturated with isopropyl alcohol to give 3.0 g. of product (70%), m.p. 160-163°. After one recrystallization from isopropyl alcohol the melting point was raised to 166-168° (lit. m.p. 176-177.5° (6)); nmr (DMSO-d_6): δ 2.52 (s, 3H, NCH_3), 4.95 (broad s, 1H, $NHCH_3$), 7.00 (broad s, 2H, NH_2), 7.25 (broad s, 2H, NH_2), 9.15 (broad s, 1H, CONH).

Pyrazinecarboxylic Acid 1-Methylhydrazide (**3a**).

Methylhydrazine (30.0 g.; 0.65 mole) was dissolved in 1 l. of anhydrous ether, chilled to −35°, and a solution of pyrazine carbonyl chloride (**10**) (10) (17.0 g., 0.12 mole) in 300 ml. of ether was added dropwise. After the addition was complete the reaction was allowed to warm to room temperature and the ether was decanted from the gummy residue on the sides of the flask. Concentration of the ether phase, followed by crystallization from benzene gave colorless crystals of the 1-methylhydrazide (6.5 g., 36%), m.p. 58-60°. The analytical sample was recrystallized an additional time from benzene and had m.p. 59-60°; nmr (deuteriochloroform): δ 3.51 (s, 3H, NCH_3), 4.80 (broad s, 2H, NH_2), 8.98

(m, 2H, H-5 and H-6), 9.36 (m, 1H, H-3).

Anal. Calcd. for $C_6H_8N_4O$: C, 47.36; H, 5.30; N, 36.83. Found: C, 47.22; H, 5.25; N, 36.78.

The ether insoluble residue was washed with water and then recrystallized from methanol to give 1-methyl-1,2-dipyrazinoylhydrazine (**11**), m.p. 176-178°; nmr (DMSO-d_6): δ 3.60 (s, 3H, NCH_3), 8.65-9.60 (m, 6H, ArH), 10.60 (broad s, 1H, NH).

Anal. Calcd. for $C_{11}H_{10}N_6O_2$: C, 51.16; H, 3.90; N, 32.55. Found: C, 51.12; H, 3.96; N, 32.66.

4-Cyclohexyl-1-methyl-1-pyrazinoylthiosemicarbazide (**4a**).

To a stirring solution of 4-cyclohexyl-1-methylthiosemicarbazide (15) (3.9 g., 0.021 mole) in 15 ml. of dry tetrahydrofuran containing 2.0 g. (0.020 mole) of triethylamine was added a solution of pyrazine carbonyl chloride (**10**) (2.80 g., 0.020 mole) in 15 ml. of tetrahydrofuran. After 30 minutes a precipitate had developed which was filtered off and washed well with water. It was then suspended in 150 ml. of boiling methanol and acetone was added to effect dissolution (total volume 300 ml.). This solution was then concentrated to 125 ml. by distillation at atmospheric pressure and the product was allowed to crystallize upon chilling. Analytically pure material was obtained in this manner, m.p. 196-197°, amounting to 3.44 g. (58%); nmr (deuteriochloroform + DMSO-d_6): δ 0.85-2.10 (m, 10H, cyclohexyl CH_2's), 3.32 (s, 3H, NCH_3), 4.10 (m, 1H, cyclohexyl CH), 8.5 (broad m, 1H, 4-NH), 8.85-9.05 (m, 2H, H-5 and H-6), 9.10 (d, 1H, J = 1.5 Hz, H-3), 9.90 (broad s, 1H, 2-NH).

This material was identical in all respects to the compound prepared from the reaction of **3a** with cyclohexylisothiocyanate (see preparation of **4d**).

3-Acetamidopyrazinecarboxylic Acid 1-Methylhydrazide (**3b**).

Methylhydrazine (50.0 g., 1.1 moles) was dissolved in 2 l. of anhydrous ether, chilled to 5° and 2-methylpyrazine[2,3-*d*][1,3]oxazine-4-one (**12**) (11) (35.4 g., 0.22 mole) was added in 2 g. portions while the reaction was stirred vigorously. After the addition was complete the reaction was allowed to stir for an additional 45 minutes and then the ether was decanted from the thick gum which had formed. The gum was dissolved in a minimum of chloforoform and chromatographed over 350 g. of activated alumina, eluting with 30% methanol/benzene. Concentration of the eluate and trituration with ethyl acetate gave 20.8 g. of **3b** (45%), m.p. 150-152°; nmr (deuteriochloroform): δ 2.22 (d, 3H, $COCH_3$), 3.50 (d, 3H, NCH_3), 4.75 (broad s, 2H, NH_2), 8.72 (m, 2H, H-5 and H-6), 9.90 (broad s, 1H, N*H*CO).

Anal. Calcd. for $C_6H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 45.75; H, 5.31; N, 33.48.

An isopropylidene derivative (**14a**) was obtained cleanly by refluxing **3b** overnight in acetone, followed by chilling and filtration of the crystalline product, m.p. 159-162°; nmr (deuteriochloroform): δ 1.96-2.05 and 2.20-2.35 (m, 9H total, $COCH_3$ and $=C(CH_3)_2$); 3.25-3.38 (m, 3H, NCH_3), 8.30-8.50 (m, 2H, H-5 and H-6), 9.80 (broad s, 1H, N*H*CO).

Anal. Calcd. for $C_{11}H_{15}N_5O_2$: C, 53.00; H, 6.07; N, 28.10. Found: C, 52.78; H, 6.02; N, 27.94.

3-Aminopyrazinecarboxylic Acid 1-Methylhydrazide (**3c**).

Compound **3b** (19.1 g., 0.09 mole) was dissolved in 300 ml. of 5% hydrochloric acid and heated for 30 minutes on a steam bath. Concentration under reduced pressure gave a residue that was treated with concentrated aqueous ammonia and then concentrated again. This gummy residue was suspended in methanol and applied to a column containing 300 g. of activated alumina. Elution with 30% methanol/benzene gave, upon concentration and trituration with ethyl acetate, 2.5 g. of **3c** (16%), m.p. 155-157° after recrystallization from methanol; nmr (DMSO-d_6): δ 3.34 (s, 3H, NCH_3), 5.25 (broad s, 2H, NNH_2), 6.60 (broad s, 2H, $ArNH_2$), 8.08 (m, 1H, H-6), 8.84 (m, 1H, H-5).

Anal. Calcd. for $C_6H_9N_5O$: C, 43.11; H, 5.43; N, 41.90. Found: C, 43.06; H, 5.40; N, 41.65.

3,5-Diamino-6-chloropyrazinecarboxylic Acid 1-Methylhydrazide (**3d**).

3,5-Diamino-6-chloropyrazinecarboxylic acid (4) (10.9 g., 0.058 mole) was suspended in 120 ml. of water and dissolved with the addition of 9.1 ml. of triethylamine (6.61 g., 0.065 mole). This solution was added dropwise to a cold solution of *N,N*-diphenylcarbamoylpyridinium chloride (20 (21.2 g., 0.068 mole) in 150 ml. of ethanol. After 15 minutes the precipitate was filtered off and washed three times with acetonitrile, then ether, to give 18.3 g. of crude product. Recrystallization from acetonitrile gave 14.0 g. (62.8%) of *N,N*-diphenylcarbamic 3,5-diamino-6-chloropyrazinecarboxylic anhydride, m.p. 215-218° (lit. m.p. 228-230° (13)).

This mixed anhydride (0.036 mole) was dissolved in 350 ml. of tetrahydrofuran. To this was added a solution of methylhydrazine (3.50 g., 0.076 mole) in 70 ml. of tetrahydrofuran. After 30 minutes the solvent was evaporated and the resulting solid triturated with ether to give 6.7 g. of the 1-methylhydrazide **3a** (85%), m.p. 160-161° (lit. m.p. 173-174.5° (6)); nmr (DMSO-d_6): δ 3.12 (s, 3H, NCH_3), 5.00 (broad s, 2H, NNH_2), 6.48 (broad s, 2H, $ArNH_2$), 6.55 (broad s, 2H, $ArNH_2$).

The benzylidene derivative **14b** was obtained cleanly by refluxing **3d** overnight in ethanol with benzaldehyde. Evaporation and recrystallization from methanol gave material of m.p. 205-207° (lit. m.p. 208-209.5° (6c)): nmr (DMSO-d_6): δ 3.45-3.48 (d, 3H, NCH_3), 6.46 (broad s, 2H, NH_2), (6.88 (broad s, 2H, NH_2), 7.42-7.85 (m, 5H, ArH), 8.15 (s, 1H, CH).

1-(3,5-Diamino-6-chloropyrazinoyl)-1,4-dimethylthiosemicarbazide (**4d**).

The 1-methylhydrazide **3d** (4.0 g., 0.018 mole) was suspended in 70 ml. of dimethoxyethane and then methyl isothiocyanate (1.7 g., 0.023 mole) was added. The reaction was refluxed for 45 minutes and then chilled and the product filtered off. After washing with ether and drying, 5.16 g. (96%) of **4d** were obtained, m.p. 240-242°. The analytical sample was recrystallized from aqueous DMSO and had m.p. 240-241°; nmr (DMSO-d_6): δ 2.88 (d, 3H, 4-CH_3), 3.00 (s, 3H, 1-CH_3), 6.60 (broad s, 2H, NH_2), 6.75 (broad s, 2H, NH_2), 7.90 (broad q, 1H, 4-NH), 9.20 (broad s, 1H, 2-NH).

The other pyrazinoylthiosemicarbazides were prepared in an analogous manner. The physical constants and analytical data are given in Table 1.

Anhydro-3-mercapto-5-pyrazinyl-1,2,4-triazolium Hydroxides (**5a-m**).

Method A.

Anhydro-4-ethyl-1-methyl-3-mercapto-5-pyrazinyl-1,2,4-triazolium Hydroxide (**5a**).

The 1-methylhydrazide **3a** (1.85 g., 0.012 mole) was refluxed for 4 hours in 25 ml. of THF containing 1.60 g. (0.018 mole) of ethyl isothiocyanate. At the end of this time 20 ml. of 10% aqueous potassium carbonate was added and the solution boiled on a hot plate for 20 minutes. The crystalline product which separated upon chilling was filtered and washed with anhydrous ether, giving 1.91 g. (71%) of **5a**, m.p. 219-221°. The melting point was unchanged after recrystallization from methanol; nmr (deuteriochloroform + DMSO-d_6): δ 1.40 (t, 3H, CH_2CH_3), 4.10 (s, 3H, CH_3), 4.42 (q, 2H, CH_2CH_3), 9.38 (s, 2H, H-5 and H-6), 9.62 (s, 1H, H-3).

Analytical data for this and analogous compounds are given in Table 2.

Method B.

Anhydro-4-cyclohexyl-1-methyl-3-mercapto-5-pyrazinyl-1,2,4-triazolium Hydroxide (**5c**).

The pyrazinoylthiosemicarbazide **4a** (2.0 g., 6.8 moles) was suspended in 50 ml. of 10% aqueous potassium carbonate and heated for 5 minutes on a steam bath. The suspension dissolved and was rapidly replaced with a slightly yellow precipitate. Filtration, followed by washing with anhydrous ether gave 1.58 g. (84%) of pale yellow product, m.p. 247-250°; nmr (deuteriochloroform): δ 1.20-2.15 (m, 10H, c-C_6H_{11}), 3.88 (s, 3H, CH_3), 4.80-5.30 (broad s, 1H, c-C_6H_{11}), 9.26 (m, 2H, H-5 and H-6), 9.50 (d, 1H, J = 1.5 Hz, H-3).

Method C.

Anhydro-1-methyl-3-mercapto-4-phenyl-5-(3-aminopyrazinyl)-1,2,4-triazolium Hydroxide (**5e**).

The appropriate pyrazinoylthiosemicarbazide **4b**, (3.0 g., 8.7 mmoles) was refluxed for 10 minutes in a solution of 15 ml. of 5% hydrochloric acid and 20 ml. of methanol. At the end of this time the reaction mixture was chilled and made basic by the careful addition of 50% sodium hydroxide. The desired **5e** crystallized from the aqueous solution and was filtered off. After washing successively with water, methanol, and ether, 2.0 g. (80%), were obtained, m.p. 323-326°; nmr (DMSO-d_6): δ 3.70 (s, 3H, CH_3), 7.00 (s, 2H, NH_2), 7.30-7.50 (m, 5H, C_6H_5), 7.82 (d, 1H, J = 2.3 Hz, H-6), 8.12 (d, 1H, J = 2.3 Hz, H-5).

Method D.

Anhydro-4-ethyl-1-methyl-3-mercapto-5-(3-acetamidopyrazinyl)-1,2,4-triazolium Hydroxide (**5f**).

The appropriate pyrazinoylthiosemicarbazide **4c**, (5.0 g., 0.017 mole) was dissolved in 30 ml. of 5% aqueous sodium hydroxide, chilled, and then neutralized with 5% aqueous hydrochloric acid. The precipitated **5f** was filtered and washed with methanol and then ether, giving 3.7 g. (79%), m.p. 272-274°; nmr (DMSO-d_6): δ 1.22 (t, 3H, CH_2CH_3), 2.10 (s, 3H, $COCH_3$), 3.62 (s, 3H, CH_3), 3.70-4.40 (m, 2H, CH_2CH_3), 8.80-8.95 (m, 2H, H-5 and H-6), 13.35 (broad s, 1H, NH).

Method E.

Anhydro-1,4-dimethyl-3-mercapto-5-(3,5-diamino-6-chloropyrazinyl)-1,2,4-triazolium Hydroxide (**5h**).

The appropriate pyrazinoylthiosemicarbazide **4d** (4.90 g., 0.017 mole) was dissolved in 25 ml. of warm DMSO and 150 ml. of 5% aqueous sodium hydroxide was added. The solution was chilled and the resulting pale yellow **5h** was filtered off and washed as for the previous compounds to give 4.0 g. (83%) as the hemihydrate, m.p. 279-280°; nmr (DMSO-d_6): δ 3.44 (s, 3H, 4-CH_3), 3.70 (s, 3H, 1-CH_3), 6.20 (broad s, 2H, NH_2), 7.32 (broad s, 2H, NH_2).

5-Pyrazinyl-1,2,4-triazole-3-thiones (**8a-e**).

Method F.

4-Ethyl-2-methyl-5-pyrazinyl-1,2,4-triazole-3-thione (**8a**).

4-Ethyl-2-methyl-1-pyrazinoylthiosemicarbazide **7b**, (2.0 g., 8.4 moles) was suspended in 50 ml. of 10% aqueous potassium carbonate and heated for 10 minutes on a steam bath. The suspension first dissolved, then was replaced with a milky emulsion. Upon chilling this emulsion coagulated into solid lumps which were pulverized under the solvent and then filtered and dried. In this way 1.65 g. (89%) of **8a** were obtained, m.p. 92-95°. The analytical sample was recrystallized from benzene/hexane and had m.p. 93-95°; nmr (deuteriochloroform): δ 1.42 (t, 3H, CH_2CH_3), 4.12 (s, 3H, CH_3), 4.88 (q, 2H, CH_2CH_3), 9.20 (m, 2H, H-5 and H-6), 9.78 (m, 1H, H-3).

Analytical data for this and analogous compounds are given in Table 3.

Method G.

4-Ethyl-2-methyl-5-(3-aminopyrazinyl)-1,2,4-triazole-3-thione (**8c**).

The 2-methylhydrazide **6b**, (2.0 g., 0.012 mole) was refluxed for 20 minutes in 25 ml. of THF containing 1.50 g. (0.018 mole) of ethyl isothiocyanate. Heating was continued as 50 ml. of methanol and 25 ml. of 10% aqueous potassium carbonate were added. After an additional 15 minutes the reaction mixture was poured into 500 ml. of water and heated on a hot plate to drive off the organic solvents. The product crystallized upon chilling and was filtered off and washed with methanol, giving 2.20 g. (83%) of **8c**, m.p. 161-163°; nmr (deuteriochloroform): δ 1.40 (t, 3H, CH_2CH_3), 4.10 (s, 3H, CH_3), 4.98 (q, 2H, CH_2CH_3), 6.70 (broad s, 2H, NH_2), 8.36 (d, 1H, J = 2.3 Hz, H-6), 8.50 (d, 1H, J = 2.3 Hz, H-5).

Method H.

2-Methyl-4-phenyl-5-(3,5-diamino-6-chloropyrazinyl)-1,2,4-triazole-3-thione (**8e**).

The 2-methylhydrazide **6c**, (1.13 g., 5.2 mmoles) was suspended in 20 ml. of dimethoxyethane and phenyl isothiocyanate (0.74 g., 5.5 mmoles) was added. After 15 minutes at reflux a little gummy material was filtered off (Celite) and the solvent was removed under reduced pressure. Trituration of the residue with ethyl acetate gave 1.5 g. of crude thiosemicarbazide. This was dissolved in 25 ml. of hot methanol, 50 ml. of 10% aqueous sodium hydroxide was added, and the product was allowed to crystallize. Filtration and drying gave 1.10 g. of **8e** (65%), m.p. 235-238°. The analytical sample was recrystallized from acetonitrile and had m.p. 236-238°; nmr (DMSO-d_6): δ 3.82 (s, 3H, CH_3), 6.82 (broad s, 4H, NH_2), 7.10-7.62 (m, 5H, C_6H_5).

Table 4

Comparison of Anhydro-3-mercapto-1,2,4-triazolium Hydroxides and 1,2,4-Triazole-3-thiones

Compound No.	^{1}H-NMR CH_3, ppm (solvent)(a)	Mass Spectrum M$^+$ (%)	Mass Spectrum ArC≡N-CH_3 (%)
5a	4.10 (C + D)	221 (100)	120 (38)
5b	4.20 (C + D)	269 (100)	120 (20)
5c	3.88 (C)	275 (44)	120 (11)
5d	3.80 (D)	326 (16)	177 (9) 135 (24) (b)
5e	3.70 (D), 380 (C + D)	284 (80)	134 (45)
5f	3.62 (D)	278 (77)	177 (17) 135 (25) (b)
5g	3.70 (D)	236 (100)	135 (6)
5h	3.70 (D)	271 (100)	184 (20)
5i	3.70 (D)	337 (4)	184 (2)
5j	3.66 (D)	297 (100)	184 (48)
5k	3.76 (D)	285 (100)	184 (5)
5l	3.82 (D)	351 (100)	184 (5)
5m	3.82 (D)	333 (76)	184 (72)
8a	4.12 (C)	221 (100)	---
8b	4.16 (C)	269 (100)	---
8c	4.10 (C)	236 (100)	---
8d	4.12 (C + D), 3.88 (D)	284 (100)	135 (41) (c)
8e	3.82 (D)	333 (100)	---

(a) C = deuteriochloroform, D = DMSO-d_6. (b) Corresponds to A-C≡N-CH_3 with the loss of ketene from the acetamido group. (c) Phenyl isothiocyanate, see text.

Acknowledgement.

The author wishes to thank Marc N. Agnew and Peter Kranack for spectral data and Rose Marie Boysen for typing this manuscript.

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expeiments showed, however, that these conditions gave a good yield of the 2-methylhydrazide (see experimental). A later report (6c) indicates the preparation of the 1-methylhydrazide (m.p. 173-174.5°l) in a manner similar to that described in this paper; (b) E. J. Cragoe, Jr., German Offen. 1,808,677 (1970); *Chem. Abstr.*, **72**, 90516m (1970); (c) K. L. Shepard and E. J. Cragoe, Jr., U. S. Patent 3,573,306 (1971).

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