steadily. After 48 hr, the weight remained const at 0.365 g; the loss corresponded to 102% of expectation for a dihydrate. The strong ir absorption at 3440 cm^{-1} in the second sample had disappeared, but observations had to be made rapidly because H_2O soon was absorbed again.

References

(1) L. Field, W. S. Hanley, and I. McVeigh, *J. Org. Chem.*, 36, 2735 (1971) (paper 32).
(2) L. Field and R. B. Barbee, *ibid.*, 34, 1792 (1969).
(3) L. Field, B. J. Sweetman, and M. Bellas, *J. Med. Chem.*, 12, 624 (1969).
(4) J. D. Buckman and L. Field, *J. Org. Chem.*, 32, 454 (1967).
(5) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Amer. Chem. Soc.*, 83, 4414 (1961).
(6) L. Field and R. B. Barbee, *J. Org. Chem.*, 34, 36 (1969).
(7) R. Kuhn and G. Quadbeck, *Chem. Ber.*, 84, 844 (1951).
(8) R. E. Eibeck, *Inorg. Syn.*, 7, 128 (1963).

Insect Chemosterilants. 11. Substituted 3,5-Diamino-1,2,4-dithiazolium Salts and Related Compounds[1,†]

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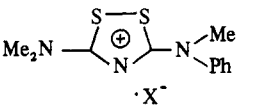
1,2,4-Dithiazolium salts substituted in 3 and 5 positions with Me_2N, pyrrolidinyl, or morpholino groups were active as chemosterilants in the male house fly. When combined with one of these substituents, Et_2N, piperidino, and substituted pyrrolidinyl groups also gave active compounds. Several other 3,5-disubstituted 1,2,4-dithiazolium salts were inactive. Analogs of dithiazolium compounds containing 1,2-dithiolium, 1,2,4-dithiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole, 1,2,4-triazole, 1,3,4-oxadiazole, 1,2,5-oxadiazole, and 1,2,5-thiadiazole rings substituted with Me_2N or other groups did not yield active sterilants. Analogs of the chemosterilant 1,1,5,5-tetramethyl-2,4-dithiobiuret were also inactive except for the moderately effective 1-(dimethylthiocarbamoyl)-2,3,3-trimethyl-2-thiopseudourea.

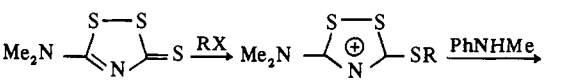
1,1,5,5-Tetramethyl-2,4-dithiobiuret (1) is an intermediate in the synthesis of 3,5-bis(dimethylamino)-1,2,4-dithiazolium chloride[2] (**10a**). Both compounds are effective as chemosterilants in house flies,[1,3a,5] *Musca domestica* L., and their activity in the male fly is comparable to that of the alkylating agent tepa[4] [tris(1-aziridinyl)phosphine oxide].

Because dithiazolium salts and dithiobiurets constitute new classes of insect chemosterilants, we have synthesized a number of their homologs and closely related compounds to explore the effects of structural changes on their sterilizing activity. We described the structure-activity relationships of a number of substituted dithiobiurets in a previous communication.[1] The present paper deals with the syntheses and activities of 32 3,5-disubstituted 1,2,4-dithiazolium salts, 14 related heterocyclic compounds, and 9 additional compounds related to the substituted dithiobiurets.

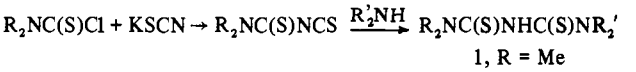
Chemistry. The general procedure for preparing substituted 3,5-diamino-1,2,4-dithiazolium salts (Table I) was that described by Diveley:[2] a dialkylthiocarbamoyl chloride was converted with KSCN to the corresponding thiocarbamoyl isothiocyanate and the latter, upon treatment with an amine, yielded a dithiobiuret. The dithiobiurets can be isolated,[1] but were more conveniently oxidized (H_2O_2 or I_2) *in situ* to dithiazolium salts when the latter were the desired products. An alternative synthesis is illustrated by the preparation of the dimethylamino *N*-methylanilino perchlorate 11 obtained by displacing MeSH from the dimethylamino, methylthio salt **27**. The *S*-alkyl salts **27–29** were obtained by alkylating 5-(dimethylamino)-1,2,4-dithiazolidine-3-thione[6] (**42**). 3-(Dimethylamino)-5-phenyl-1,2,4-dithiazolium perchlorate (**26**) was analogously prepared by treatment of the corresponding 3-(methylthio)-5-phenyl perchlorate (**30**) with Me_2NH.[7]



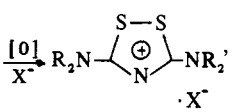
11



42 27, R = Me, X = ClO_4; 28, R = Et, X = ClO_4; 29, R = CH_2Ph, X = Cl



1, R = Me



10a, R = R' = Me, X = Cl; 10b, R = R' = Me, X = Br

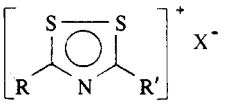
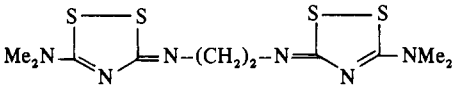
Compounds **48–50** were synthesized by treating **10b** with NaOH, NH_3, and NaOMe, respectively. Phenylhydrazone **43** was also prepared from **10b** by treating it with $PhNHNH_2$. 1-(Dimethylthiocarbamoyl)-2,3,3-trimethyl-2-thiopseudourea (**51**) was obtained by alkylating 1 with Me_2SO_4.

Dimorpholinodithiomalonamide (**46**) and 3,5-dimorpholino-1,2-dithiolium iodide (**32**) were prepared as described.[9] *N,N,N',N'*-Tetramethyldithiomalonamide (**47**) was prepared from the corresponding malonamide[10] and P_2S_5, and was then oxidized with I_2 to 3,5-bis(dimethylamino)-1,2-dithiolium iodide; this compound was too insoluble in H_2O or DMSO-Me_2CO for testing by injection, and accordingly was converted to the nitrate salt **33** with $AgNO_3$.

The 1,2,4-thiadiazole **34** was obtained by H_2O_2 oxida-

†Mention of a pesticide does not constitute a recommendation by the U.S. Department of Agriculture.

Table I. Sterilizing Activity of 3,5-Disubstituted 1,2,4-Dithiazolium Salts in Male House Flies

No.	R	R'	X	Mp, °C	Formula	Analyses	Activity[a]
							
2	NH_2	NH_2	Cl	250 dec	$C_2H_4ClN_3S_2$	*b*	0
3	NH_2	$NHC_{12}H_{25}$	Cl	183–185	$C_{14}H_{28}ClN_3S_2$	*c*	0
4	NH_2	NMe_2	Br	219–220 dec	$C_4H_8BrN_3S_2$	C, H, N	0
5	NHMe	NMe_2	HSO_4	208–209 dec	$C_5H_{11}N_3O_4S_3$	C, H, N, S	0
6	NHEt	NMe_2	HSO_4	174–175	$C_6H_{13}N_3O_4S_3$	C, H, N, S	0
7	NHPr	NMe_2	HSO_4	152	$C_7H_{15}N_3O_4S_3$	C, H, N, S	0
8	NH-4-PhCl	NMe_2	HSO_4	180–182 dec	$C_{10}H_{12}ClN_3O_4S_3$	C, H, N, S	0
9	NH-1-Adamantyl	NMe_2	HSO_4	234 dec	$C_{14}H_{23}N_3O_4S_3$	C, H, N, S	0
10a	NMe_2	NMe_2	Cl	246 dec	$C_6H_{12}ClN_3S_2$	*c*	++
10b	NMe_2	NMe_2	Br	260 dec	$C_6H_{12}BrN_3S_2$	*d*	++
10c	NMe_2	NMe_2	HSO_4	218–222	$C_6H_{13}N_3O_4S_3$	C, H, N, S	++
11	NMe_2	NMe, Ph	ClO_4	167–168	$C_{11}H_{14}ClN_3O_4S_2$	C, H, N	0
12	NMe_2	$NMe(CH_2)_2$-2-pyridyl	I	159–160 dec	$C_{12}H_{17}IN_4S_2$	C, H, N	0
13	NMe_2	NEt_2	HSO_4	159–161	$C_8H_{17}N_3O_4S_3$	C, H, N, S	++
14	NMe_2	$N(CH_2CH_2OH)_2$	I	148–152 dec	$C_8H_{16}IN_3O_2S_2$	C, H, N	0
15	NMe_2	Pyrrolidinyl	Br	201–204 dec	$C_8H_{14}BrN_3S_2$	C, H, Br, N, S	++
16	NMe_2	Piperidino	Br	224–226 dec	$C_9H_{16}BrN_3S_2$	C, H, Br, N, S	++
17	NMe_2	Morpholino	HSO_4	194–195 dec	$C_8H_{15}N_3O_5S_3$	C, H, N, S	++
18	NMe_2	2-Methoxycarbonylpyrrolidinyl	Br	184–185 dec	$C_{10}H_{16}BrN_3O_2S_2$	C, H, N, S	+
19	NEt_2	NEt_2	HSO_4	113–116	$C_{10}H_{21}N_3O_4S_3$	C, H, N, S	0
20		Pyrrolidinyl	I	185–189 dec	$C_{10}H_{16}IN_3S_2$	C, H, N, S	+
21		Piperidino	HSO_4	161–162 dec	$C_{11}H_{19}N_3O_4S_3$	C, H, N, S	+
22		Morpholino	HSO_4	169–170 dec	$C_{10}H_{17}N_3O_5S_3$	C, H, N, S	++
23		Piperidino	HSO_4	192 dec	$C_{12}H_{21}N_3O_4S_3$	C, H, N, S	0
24		Morpholino	Br	256–256.5 dec	$C_{11}H_{18}BrN_3OS_2$	C, H, Br, N, S	0
25		Morpholino	HSO_4	197–198 dec	$C_{10}H_{17}N_3O_6S_3$	C, H, N, S	++
26	NMe_2	Ph	ClO_4	189–190	$C_{10}H_{11}ClN_2O_4S_2$	*e*	0
27	NMe_2	SMe	ClO_4	142–143	$C_5H_9ClN_2O_4S_3$	C, H, N, S	0
28	NMe_2	SEt	ClO_4	108–109	$C_6H_{11}ClN_2O_4S_3$	C, H, N, S	0
29	NMe_2	SCH_2Ph	Cl	150–152	$C_{11}H_{13}ClN_2S_3$	*f*	0
30	SMe	Ph	ClO_4	165–166	$C_9H_8ClNO_4S_3$	*g*	0
31			H_2SO_4	205 dec	$C_{10}H_{18}N_6O_4S_4$	*c*	0

[a] See Biological Activity. [b] Ref 5. [c] Obtained from Agricultural Chemicals Laboratory, Hercules, Inc., Wilmington, Del. [d] Ref 2. [e] Ref 7. [f] C: calcd, 43.34; found, 42.23. H: calcd, 4.30; found, 4.21. N: calcd, 9.19; found, 9.04. S: calcd, 31.55; found; 31.77. [g] Ref 8.

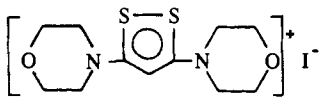
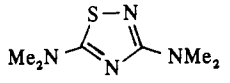
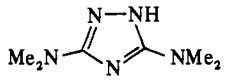
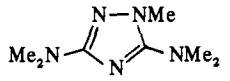
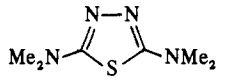
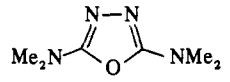
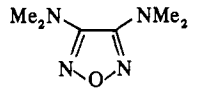
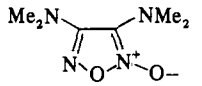
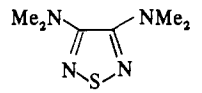
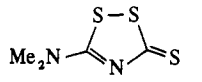
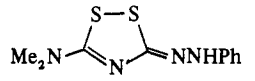
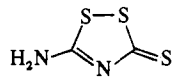
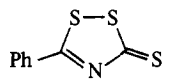
tion of **49**, but we subsequently found that **34** could be prepared more easily and in higher yield by treating **10b** with NaN_3 in DMF.[7] The 1,2,4-triazoles **35** and **36** were also prepared from **10b** by reaction with N_2H_4 and $MeNHNH_2$, respectively.

1,1,6,6-Tetramethyldithiobiurea **52** was obtained from the reaction of Me_2NCSCl with N_2H_4; cyclization of **52** with $POCl_3$ gave the 1,3,4-thiadiazole **37**. The corresponding 1,3,4-oxadiazole **38** was similarly prepared from 1,1,6,6-tetramethylbiurea[12] and $POCl_3$.

We were unable to cyclize bis(dimethylamino)glyoxime to the 1,2,5-oxadiazole **39** with any of several reagents; however the glyoxime was smoothly oxidized to the furoxan **40** with NaOCl, and **40** in turn was reduced with PCl_3 to **39**. The corresponding 1,2,5-thiadiazole **41** was obtained by treating 3,4-dichloro-1,2,5-thiadiazole[13] with Me_2NH in DMSO. 5-(Dimethylamino)-2,3-dihydro-3-methyl-4*H*-1,3,5-thiadiazine-4-thione (**54**) was prepared from 1,1,5-trimethyldithiobiuret[1] and CH_2O.

Biological Activity. The compounds were tested for sterilizing activity by injecting them into newly emerged male house flies that were subsequently mated to virgin female flies. Details of the testing procedure have been described by Chang and Bořkovec.[4] When activity was detected at a nontoxic level, the dose-response relationship was evaluated statistically by probit analysis, and sterilizing doses SD_{50} and SD_{95} were calcd in moles/male fly. The activity scale in Table I indicated high activity

Table II. Heterocyclic Compounds Related To Dithiazolium Chemosterilants

No.	Structure	Mp or bp, (mm)°C	Formula	Analyses
32		263–264 dec	$C_{11}H_{17}IN_2O_2S_2$	*a*
33		255 dec	$C_7H_{13}N_3O_3S_2$	C, H, N
34		87–89 (0.1)	$C_6H_{12}N_4S$	C, H, N
35		181–182	$C_6H_{13}N_5$	*b*
36		127–129 (14)	$C_7H_{15}N_5$	C, H, N
37		105	$C_6H_{12}N_4S$	C, H, N, S
38		50–51	$C_6H_{12}N_4O$	C, H, N
39		51.5–52	$C_6H_{12}N_4O$	C, H, N
40		46–48	$C_6H_{12}N_4O_2$	C, H, N
41		110–112 (20)	$C_6H_{12}N_4S$	C, H, N
42		175–176	$C_4H_6N_2S_3$	*c*
43		164–165	$C_{10}H_{12}N_4S_2$	C, H, N, S
44		194 dec	$C_2H_2N_2S_3$	*d*
45		136–137	$C_8H_5NS_3$	*e*

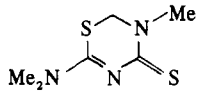
[a]Ref 16. [b]Ref 11. [c]Ref 6. [d]Ref 17. [e]Ref 18.

(++) when SD_{50} was less than 10^{-8} mole/male, moderate activity (+) when SD_{50} was larger than 10^{-8} mole/male, and no activity (0) when subtoxic doses of the candidate compounds did not reduce the fertility of treated males. Because most of the active compounds were to some extent toxic at SD_{95}, the latter was not a suitable parameter for comparative studies in this class of chemosterilants. As indicated in Table I, the Me_2N, pyrrolidinyl, or morpholino substituents appeared to be required for activity of 3,5-substituted 1,2,4-dithiazolium salts. Activity was also found in compounds containing Et_2N, piperidino, and substituted pyrrolidinyl groups, but only when these were in combination with one of the "activating" substituents. In general, the sterilizing activities of the dithiazolium salts paralleled those of the corresponding dithiobiurets.[1]

Since the dithiobiurets are easily oxidized to dithiazolium salts, and, in principle, dithiazolium salts could be reduced to dithiobiurets, it is quite conceivable that only one biologically active form is responsible for the activities observed with the two classes of compounds. Whatever the active species may be, the only active compounds were those with two dialkylamino or cyclic amino groups, *i.e.*, 3,5-bis(dialkylamino)dithiazolium salts and 1,1,5,5-tetrasubstituted dithiobiurets. To some extent the patterns of activity observed here parallel those observed in the melamines[14] and phosphoramides:[15] the highest male-sterilizing activity seemed to be associated with the Me_2N substituent; the activity decreased or disappeared when methyls were replaced with other groups or with H, and when dialkylamino groups were replaced with SR or Ph groups (Table I).

Because of the activity associated with the dimethyl-

Table III. Compounds Related to Dithiobiuret Chemosterilants

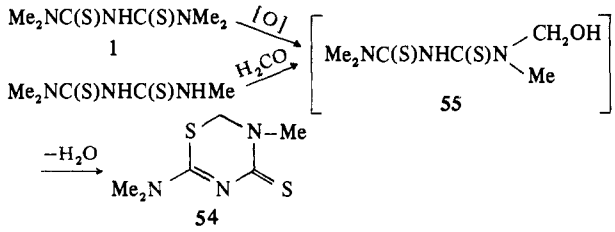
No.	Structure	Mp, °C	Formula	Analyses
46	$CH_2(CSN(CH_2CH_2)_2O)_2$[c]	210	$C_{11}H_{18}N_2O_2S_2$	*a*
47	$Me_2NCSCH_2CSNMe_2$	106	$C_7H_{14}N_2S_2$	C, H, N
48	$Me_2NCSNHCONMe_2$	119-119.5	$C_6H_{13}N_3OS$	C, H, N, S
49	$Me_2NCSNHC(=NH)NMe_2$	105-106	$C_6H_{14}N_4S$	C, H, N, S
50	$Me_2NCSN=C(OMe)NMe_2$	75-76	$C_7H_{15}N_3OS$	C, H, N, S
51	$Me_2NCSN=C(SMe)NMe_2$	85.5-86	$C_7H_{15}N_3S_2$	C, H, N, S
52	$Me_2NCSNHNHCSNMe_2$	163	$C_6H_{14}N_4S_2$	C, H, N, S
53	$Me_2NCSSCSNMe_2$	105-106	$C_6H_{12}N_2S_3$	*b*
54		169-171	$C_6H_{11}N_3S_2$	C, H, N, S

[a] Ref 9. [b] Ref 19. [c] $N(CH_2CH_2)_2O$ is morpholino.

amino dithiazolium salts, and with similarly substituted melamines and phosphoramides, we prepared the bis(dimethylamino) heterocyclic compounds shown in Table II. These were mainly unchanged, 5-membered ring compounds with 3 heteroatoms; several (**34**, **35**, **37**, **38**) were geometrically quite similar to the bis(dimethylamino)-dithiazolium system. It was thus disappointing that none of these compounds showed any activity against male house flies.

Nor was any activity found for the 3,5-disubstituted 1,2-dithiolium salts **32** and **33** (Table II) or for the dithiomalonamides **46** and **47** (Table III). These compounds differ from the active dithiazolium salts and dithiobiurets, respectively, only in that the central N has been replaced by CH. Other compounds in Table III represent further variations in the structure of 1,1,5,5-tetramethyl-2,4-dithiobiuret (**1**) by replacement of the central NH with S (**53**) or NHNH (**52**), or by replacement of a C=S by C=O (**48**) or C=NH (**49**). All of these modifications completely eliminated the sterilizing activity.

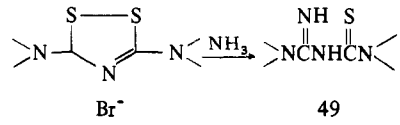
Hexamethylmelamine[20] and hexamethylphosphoric triamide[15a,21] are metabolized in house flies and in other organisms by oxidative demethylation, and the metabolic intermediates, *i.e.*, the *N*-(hydroxymethyl) derivatives, may be the actual species responsible for the sterilizing activity. The bis(dimethylamino)dithiazolium salts, on the other hand, are already in a high oxidation state and their oxidative demethylation is expected to be quite difficult. Tetramethyldithiobiuret could conceivably be demethylated, but the ease of ring closure to dithiazolium salts might make this the preferred oxidation course. To investigate whether the activity of **1** is associated with *in vivo* oxidation to 1-(hydroxymethyl)-1,5,5-trimethyl-2,4-dithiobiuret **55**, we attempted to synthesize the



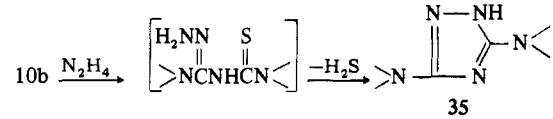
latter from 1,1,5-trimethyldithiobiuret[1] and H_2CO. The only product we were able to isolate, however, was the cyclodehydrated compound **54**. This compound had no activity, and although **54** might also be formed if a CH_2OH group resulted from *in vivo* oxidation, we cannot draw any definite conclusions concerning this possible mode of action.

In addition to their presumed resistance to oxidation, the chemical properties of the dithiazolium salts are distinctly different from those of the rather stable melamine and phosphoramide chemosterilants. The bis(dialkylamino)dithiazolium salts are usually highly crystalline compounds with long shelf lives, and do not decompose appreciably in H_2O or alcohols; however, they react readily with a variety of nucleophiles including hydrazines, amines, NaOH, NaOMe, NaSH, NaN_3, and KNCO. The course of these reactions[7] is nucleophilic attack at a ring C, ring opening with loss of elemental S, and then tautomerization or further reaction depending upon the nature of the nucleophile. Many of the reactions proceed smoothly and have useful synthetic applications; they have been particularly useful in this study for preparing **48-50** and **34-36** in one step from bis(dimethylamino)dithiazolium bromide **10b** (see Chemistry). Phenylhydrazone **43** was also obtained directly from **10b**; however, in this case the usual ring opening was not observed.

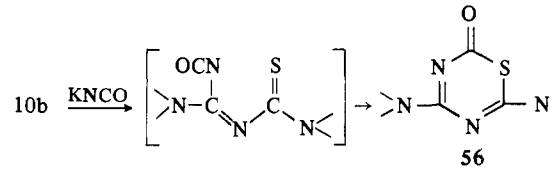
Biologically active compounds that are capable of reacting with nucleophiles are often referred to as alkylating agents regardless of the exact nature of the moiety that is ultimately bound to the nucleophile.[22] We have observed at least 3 minor variations in the reactions of **10b** with



(1)



(2)



(3)

nucleophiles; (1) ring opening by a simple nucleophile exemplified by the reaction with NH_3 to give **49**; (2) ring opening and reclosing in the addition of a bifunctional nucleophile, *e.g.*, the reaction with N_2H_4 to give the 1,2,4-triazole **35**; (3) ring opening and reclosing at an electrophilic center originally present in the nucleophile, *e.g.*, the reaction of **10b** with KNCO to give 4,6-bis(dimethylamino)-1,3,5-thiadiazine-2-one[23] (**56**). Thus, if we accept the rather loose definition of "alkylating agent" as any electrophile that is capable of reacting with an undefined nucleophile, it may be possible to include the dithiazolium salts in this biologically important class of compounds. Since alkylating agents constitute one of the most important general classes of chemosterilants of male insects,[24] the activity of these compounds in male house flies is also consistent with such a hypothesis. To gain additional evidence, we prepared 1-(dimethylthiocarbamoyl)-2,3,3-trimethyl-2-thiopseudourea (**51**). The methylthio function provides a rather good leaving group, and nucleophilic attack at the 2 position (with displacement of MeSH) should give the same products obtained from the reactions of **10b** with nucleophiles. Indeed, **51** was active as a chemosterilant, although the level of activity (+) was somewhat lower than that of either **10b** or tetramethyldithiobiuret (**1**). We have not determined the relative reactivities of **51** and **10b** with nucleophiles but we did observe that **51** was recovered unchanged

from an attempted reaction with NaN_3 under conditions that smoothly converted **10b** to **34**.

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. $MgSO_4$ was employed as a drying agent. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.; where analyses are indicated by the symbols of the elements, analytical results for these elements were within ±0.3% of the theoretical values. Ir and nmr spectra of all compds were consistent with the assigned structures.

Preparation of Dithiazolium Salts (4-10c, 12-25). The general procedure was that described by Diveley.[2] A mixt of a dialkylthiocarbamoyl chloride‡ (0.1 mole) and KSCN (0.1 mole) in Me_2CO (90 ml) was refluxed 15 min, then cooled, and filtered. The desired amine (0.1 mole, usually neat or in Me_2CO; $MeNH_2$ and NH_3 were added in H_2O) was added dropwise to the yellow soln at or below room temp. The resulting dithiobiuret was usually oxidized without isolation as follows: H_2SO_4 or HBr (0.1 mole) and 30% H_2O_2 (0.1 mole) were added dropwise in that order to the chilled Me_2CO soln. The product was collected by filtration, was washed with Me_2CO, and recrysd (usually EtOH, EtOH–H_2O, or MeCN). The yields were normally 40–60% from the thiocarbamoyl chloride. In a few cases the dithiobiurets were isolated and subsequently oxidized, either as described above or with an equiv of I_2 in EtOH. In general, H_2O_2 appears to be the preferred oxidant. The amines were all commercially available except for proline methyl ester which was prepd from L-proline and CH_2N_2 and was used without purification.

3-(Dimethylamino)-5-(alkylthio)-1,2,4-dithiazolium Salts 27-29. A mixt of 3-(dimethylamino)-1,2,4-dithiazolidine-5-thione 42[6] (8.6 g) and Me_2SO_4 (26 g) was gradually heated until a homogeneous soln resulted (*ca.* 80°). The soln was cooled to room temp and treated with 70% $HClO_4$ (5 ml). The resulting mixt was dild with Et_2O, and 3-(dimethylamino)-5-(methylthio)-1,2,4-dithiazolium perchlorate (27) was collected and washed with Et_2O (7.3 g, 52%, mp 138–142°). The anal. sample was recrystd from MeCN.

3-(Dimethylamino)-5-(ethylthio)-1,2,4-dithiazolium perchlorate (28) was similarly prepd from 42 and Et_2SO_4 (53%, recrystd from HOAc).

3-(Dimethylamino)-5-(benzylthio)-1,2,4-dithiazolium chloride 29 was prepd by refluxing 42 and $PhCH_2Cl$ in HOAc 4 hr, then evapg the soln to dryness. Trituration of the residue with MeCN gave essentially pure 29 (47%) that was recrystd from 1:1 EtOAc–HOAc.

***N,N,N',N'*-Tetramethyldithiomalonamide (47).** A mixt of *N,N,N',N'*-tetramethylmalonamide[10] (35 g) and P_4S_{10} (30 g) in PhMe (300 ml) was refluxed 2 hr. Filtration and evapn of the filtrate gave 5.1 g of 47 that could be purified by recrystn from hexane–EtOAc or Et_2O–THF, mp 106°.

3,5-Bis(dimethylamino)-1,2-dithiolium Nitrate (33). A soln of 47 in CH_2Cl_2 was treated dropwise with a soln of I_2 in CH_2Cl_2 at room temp. A dark solid sepd immediately that was suspended in H_2O and treated with $NaHSO_3$ until the color was discharged. The solid 3,5-bis(dimethylamino)-1,2-dithiolium iodide was collected (3.76 g, mp 300°), suspended in H_2O, and treated with aq $AgNO_3$ (2.1 g). The AgI was removed by filtration and the filtrate was evapd at reduced pressure. Recrystn of the residue from Me_2CO–EtOH gave 2.1 g of 33, mp 248° dec. A second crop (0.2 g) had mp 255° dec.

3-(Dimethylamino)-5-(*N*-methylanilino)-1,2,4-dithiazolium Perchlorate (11). A mixt of 27 (3.00 g) and PhNHMe (2.5 g) in HOAc (40 ml) was heated to boiling. A clear soln resulted that was cooled to room temp and dild with Et_2O (150 ml). A yellow oil separated and then solidified. The solid (2.70 g, 75%, mp 139–159°) was collected and washed with Et_2O, then was recrystd from HOAc contg a small amount of EtOAc (1.96 g, mp 166°).

1,1,5,5-Tetramethyl-2-thiobiuret (48). A soln of 3,5-bis(dimethylamino)-1,2,4-dithiazolium bromide (10b, 2.50 g) in H_2O (10 ml) was treated dropwise with NaOH (372 mg) in H_2O (10 ml). A milky white suspension formed immediately, it was stirred for 1 hr at room temp, then warmed on a steam bath, and filtered to remove S. Evapn of the filtrate and extn of the residue with C_6H_6 gave 1.12 g (70%) of 48 as a clear oil that solidified on standing. Recrystn from cyclohexane–C_6H_6 gave 0.68 g, mp 119–119.5°. The same compd could be prepd less efficiently from dimethylcarbamoyl isothiocyanate[17] and $MeNH_2$.

3-(*N,N*-Dimethylamidino)-1,1-dimethylthiourea (49). A soln of 10b (16.9 g) in EtOH (500 ml) under a Dry Ice condenser was treated with an excess of anhyd NH_3 at room temp. The mixt was stirred 1 hr, filtered to remove S, and evapd to dryness. CH_2Cl_2 was added to the residue and the soln was filtered, washed with H_2O and with NaCl, and dried. Evapn of the solvent gave 9.70 g (89%) of 49, mp 101–104°. Recrystn from cyclohexane–EtOAc gave the pure material, mp 105–106°. Poorer yields of 49 were obtained if aqueous NH_3 was used.

1-(Dimethylthiocarbamoyl)-2,3,3-trimethylpseudourea (50). A soln of 10b (10.8 g, 0.04 mole) in cold NaOMe (from 0.92 g, 0.04 g-atom of Na) in MeOH (50 ml) was stirred at room temp 1 hr and filtered to remove sulfur, and the filtrate was evapd. The residue was extd with several portions of warm C_6H_6; filtration and evapn of the C_6H_6 gave 7.39 g (98%) of 50 as an oil. Crystn from hexane–EtOAc gave the pure material (6.33 g, 85%), mp 75–76°.

1-(Dimethylthiocarbamoyl)-2,3,3-trimethyl-2-thiopseudourea (51). A soln of Me_2SO_4 (4.14 g, 0.033 mole) in Me_2CO (25 ml) was added dropwise to a stirred mixt of 1,1,5,5-tetramethyldithiobiuret (1, 5.74 g, 0.03 mole), K_2CO_3 (4.55 g, 0.033 mole), and Me_2CO (100 ml) at room temp under N_2. The mixt was stirred 20 hr and filtered, and the filtrate was evapd *in vacuo*. The residue was chromatogd on silica gel; elution with $CHCl_3$ gave 6.3 g of an oily solid. Recrystn from Et_2O gave 2.67 g (44%) of 51, mp 82–85°. Two recrystns from ether provided an analytical sample, mp 85.5–86°.

1,1,6,6-Tetramethyl-2,5-dithiobiurea (52). A soln of anhyd N_2H_4 (8.7 g) in CH_2Cl_2 (50 ml) was added dropwise to a stirred soln dimethylthiocarbamoyl chloride (62 g) and Et_3N (72 ml) in CH_2Cl_2 (50 ml). An exothermic reaction occurred, and the rate of addn was controlled to maintain gentle refluxing. After the addn the mixt was refluxed 2 hr, the solvent was stripped, and the residue was made slightly alk with Na_2CO_3. Evapn of the H_2O, repeated extn of the residue with THF, and evapn of the THF gave 50.7 g of an oily solid that was crystd from Me_2CO to give 16 g (31%) of 52, mp 169–70°. Another recrystn from Me_2CO gave an analytical sample, mp 163°.

5-(Dimethylamino)-3*H*-1,2,4-dithiazol-3-one Phenylhydrazone (43). A soln of $PhNHNH_2$ (2.3 g, 0.0212 mole) in EtOH (25 ml) was added to a soln of 10b in EtOH (100 ml). The mixt was then refluxed 1 hr, cooled, and filtered, and the filtrate was concd *in vacuo*. Recrystn of the residue from THF, then from $CHCl_3$, gave 43 (0.50 g, 20%, mp 162–164°). The analytical sample was recrystd again from $CHCl_3$, mp 164–165°.

3,5-Bis(dimethylamino)-1,2,4-thiadiazole (34). A cold, stirred soln of 49 (8.7 g, 0.05 mole) in 2 *N* HCl (250 ml) was treated dropwise with H_2O_2 (20 ml, 30%). The mixt was stirred at room temp 1 hr, made basic with Na_2CO_3, and extd with $CHCl_3$ (3 × 250 ml). Distn of the $CHCl_3$ ext afforded 5.4 g (63%) of 34, bp 87–89° (0.1 mm) (mp *ca.* 20°). The same compd could be obtained in 76% yield by heating 10b with NaN_3 in DMF.[7]

3,5-Bis(dimethylamino)-1*H*-1,2,4-triazole (35). A soln of anhyd N_2H_4 (14.4 g, 0.46 mole) in CH_2Cl_2 (250 ml) was added dropwise to a stirred soln of 10b (40.5 g, 0.15 mole) in CH_2Cl_2 (3 l). The mixt was warmed at reflux 3 hr and filtered, the CH_2Cl_2 was evapd *in vacuo*, and then the residue was extd with H_2O (250 ml). The aqueous ext was treated with charcoal and Celite, filtered, satd with NaCl, and extd with EtOAc (3 × 500 ml). Evapn of the solvent and recrystn of the residue from EtOAc–Et_2O gave 14.6 g (64%) of 35, mp 181–182° (lit.[11] mp 182–183°).

3,5-Bis(dimethylamino)-1-methyl-1*H*-1,2,4-triazole (36). A soln of $MeNHNH_2$ (13.8 g, 0.30 mole) in CH_2Cl_2 (250 ml) was added dropwise to a stirred soln of 10b (27.0 g, 0.10 mole) in CH_2Cl_2 (2.5 l). The mixt was refluxed 2 hr, then the solvent was stripped, and the residue was extd with Et_2O (500 ml). Distn of the dried Et_2O ext provided 5.60 g (33%) of 36, bp 127–129° (14 mm). The same compd was obtained in 52% yield by methylation of 35 with NaH and MeI in xylene–THF.

2,5-Bis(dimethylamino)-1,3,4-thiadiazole (37) was prepd from 52 following the procedure for the synthesis of 38. Recrystn from hexane–C_6H_6 gave 37 in 71% yield, mp 101–103°. Recrystn from hexane gave the analytical sample, mp 105°,

2,5-Bis(dimethylamino)-1,3,4-oxadiazole (38). A soln of 1,1,6,6-tetramethylbiurea[12] (10.2 g) in $POCl_3$ (60 ml) was refluxed

‡ Dimethylthiocarbamoyl chloride was purchased from the Aldrich Chemical Company. The pyrrolidinyl, piperidino, morpholino, and diethylamino thioacid chlorides were prepd from $CSCl_2$ and the appropriate amine; see ref 25.

1 hr, then excess $POCl_3$ was stripped *in vacuo*. A little ice was added and the residue was neutralized with Na_2CO_3. Evapn of the H_2O, extn of the residue with warm EtOAc, and evapn of the EtOAc gave 6.5 g of a slightly orange oil that crystd on standing. Treatment with charcoal in Et_2O gave, after filtration and evapn of Et_2O, 5.8 g (64%) of 38, mp 49–50°. The analytical sample (hexane) had mp 50–51°.

3,4-Bis(dimethylamino)-1,2,5-thiadiazole (41). An autoclave was charged with 3,4-dichloro-1,2,5-thiadiazole[13] (15.5 g, 0.10 mole), anhyd Me_2NH (45 g, 1.0 mole), and DMSO (150 ml), then was heated at 120° for 5 hr. The dark mixt was poured into $CHCl_3$ (600 ml), and the soln was washed with several portions of dil NaCl. The NaCl washings were again extd with $CHCl_3$, and the combined $CHCl_3$ portions were again washed with dil NaCl (2 × 500 ml) and with H_2O (2 × 500 ml). Distn of the org phase yielded 8.5 g (49%) of 41, bp 110–112° (20 mm).

3,4-Bis(dimethylamino)-1,2,5-oxadiazole 2-Oxide (40). A soln of dichloroglyoxime diacetate[2b] (68.4 g) in CH_2Cl_2 (1 l) was added dropwise to a cold (0–5°) soln of anhyd Me_2NH (90 g) in CH_2Cl_2 (600 ml). After the addn the soln was refluxed 1 hr, then the solvent was stripped and the residue was extd with 3 portions of 2:1 Et_2O–hexane to remove dimethylacetamide. The residue was then extd with several portions of hot EtOAc, and finally with 1:1 THF–EtOH; the combined exts were filtered and evapd, and the resulting solid was made slightly alk with Na_2CO_3. H_2O was stripped and the residue was again extd with hot EtOAc to give 33.5 g of crude bis(dimethylamino)glyoxime, mp 125–145°. Recrystn from EtOAc–hexane gave a first crop of 20.8 g (mp 163–165°, 42%) and a second crop of 9 g (mp 166–169°, 18%). The analytical sample (EtOAc–hexane) had mp 169–170°. *Anal.* C, H, N.

A soln of bis(dimethylamino)glyoxime (14.6 g) in 0.5 *N* NaOH (150 ml) at 0–5° was treated dropwise with 5.25% NaOCl (145 g). A white solid separated that was collected by filtration and washed with cold H_2O; the yield of 3,4-bis(dimethylamino)-1,2,5-oxadiazole 2-oxide (40) was 11.3 g (79%, mp 45–46°). A second crop (0.9 g, 6%) was recrystd 3 times from pentane, mp 46–48°.

3,4-Bis(dimethylamino)-1,2,5-oxadiazole (39). A soln of 40 (0.38 g) in $CHCl_3$ (5 ml) and PCl_3 (0.5 ml) was refluxed 1 hr. The red soln was poured onto ice and neutralized with Na_2CO_3, then the aq phase was extd thoroughly with $CHCl_3$. The dried $CHCl_3$ exts were evapd to give 0.26 g (75%) of 39 as an oil that solidified on cooling. Recrystn from MeOH–H_2O, then from pentane at −20°, gave pure 39, mp 51.5–52°,

5-(Dimethylamino)-2,3-dihydro-3-methyl-4*H*-1,3,5-thiadiazine-4-thione (54). A mixt of 1,1,5-trimethyl-2,4-dithiobiuret[1] (1.0 g) and aqueous H_2CO (1 g, 40%) in H_2O (7 ml) was refluxed 1 hr then was stirred overnight at room temp. A cryst white solid and a sticky yellow solid separated from soln; the white solid (0.22 g, mp 167–171°) was separated mechanically and recrystd from MeOH to give pure 54, mp 169–171°.

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Molecular Weight Studies on the Active Constituents of Compound 48/80

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Compound 48/80 was studied for its behavior during dialysis and gel filtration. The dialysis results indicate that there is a mixture of substances possessing histamine-liberating activity which has an average HCl salt molecular weight of 1300. The gel filtration data are in agreement with the dialysis results and further indicate that the active constituents range in free base molecular weight approximately from 700 to 1400. These molecular weights suggest that the degree of polymerization of the active constituents ranges from the tetramer to the octamer, with the average being the hexamer.

In 1949, Baltzly, *et al.*,[1] described a family of long-acting blood pressure depressing substances obtained by reacting equimolar concentrations of formaldehyde and *p*-methoxy-*N*-methylphenethylamine. They proposed that the products have the structure shown in Figure 1. By countercurrent distribution they separated them into fractions which appeared to contain the dimer, trimer, tetramer, and higher oligomers. They associated the hypotensive activity with the trimeric and tetrameric members of the family. They also reported that the *p*-methoxy-*N,N*-dimethylphenethylamine family was quite active.

In 1966, DeGraw, *et al.*,[2] confirmed the presence of the dimer in the reaction mixture by isolating it, converting it to the *N,N*-dimethyl derivative, and showing it to be identical with the *N,N*-dimethyl dimer synthesized by an alternate route. This compound had no depressor activity, in agree-