Substituted 2,4,6-Triamino-1,3,5-Thiadiazinium Salts. A New Heteroaromatic System.

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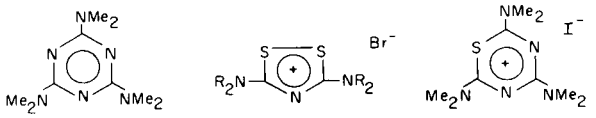
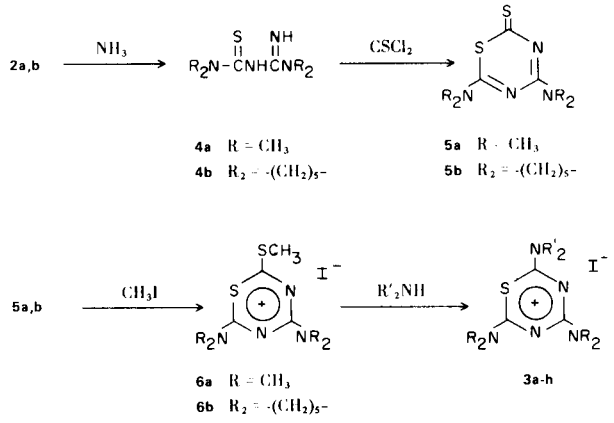
Hexamethylmelamine (**1**) (1) and 3,5-bis(dimethylamino-1,2,4-dithiazolium bromide (**2a**) (2) are effective chemosterilants against male house files, *Musca domestica* L. As part of our continuing search for new classes of insect sterilants, we wished to prepare a thia-analog of **1**, 2,4,6-tris(dimethylamino)-1,3,5-thiadiazinium iodide (**3a**). This report describes a successful synthesis of **3a** and some other symmetrically and unsymmetrically substituted 1,3,5-thiadiazinium salts, representatives of a previously undescribed ring system (3).



1 **2a** R = CH_3; **2b** R_2 = $-(CH_2)_5-$ **3a**

We have recently reported (2,4) the utility of **2a** in the synthesis of a variety of heterocyclic and open chain compounds; for example, **2a** reacted with ammonia to give the amidinothiourea **4a** in 89% yield (2). Condensation of **4a** with thiophosgene or with 1,1-thiocarbonyldiimidazole provided the thiadiazine-2-thione **5a** which was readily alkylated with methyl iodide to give the methylthio salt **6a**. Dimethylamine readily displaced methyl mercaptan from **6a** to give **3a**.



4a R = CH_3; **4b** R_2 = $-(CH_2)_5-$ **5a** R = CH_3; **5b** R_2 = $-(CH_2)_5-$

6a R = CH_3; **6b** R_2 = $-(CH_2)_5-$ **3a-h**

Pyrrolidine and morpholine also reacted smoothly with **6a** to give the unsymmetrical salts **3b** and **3c** (Table I), respectively.

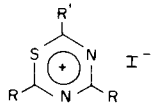
The piperidino analogs **3d-3f** (Table I) were prepared by the same sequence of reactions starting from 3,5-dipiperidino-1,2,4-dithiazolium bromide (**2b**) (4). Since 3,5-bis(dialkylamino)-1,2,4-dithiazolium halides are easily prepared (2,4,5), and since all the yields in the reaction sequence are good to excellent, this method appears to constitute a general and useful synthesis of substituted triamino-1,3,5-thiadiazinium iodides. Although our main objective was the synthesis of the tris(dialkylamino) salts, we have found that methylamine and aniline also displace methyl mercaptan from **6a** to give the methylamino and anilino iodides **3g** and **3h** (Table I). Thus the reaction is not restricted to secondary amines.

The nmr spectrum (chlorobenzene) of thione **5a** consists of two doublets centered at δ = 2.63 and 2.93. Each doublet coalesces to a singlet as the temperature is increased (*ca.* 50° and 110°, respectively). This undoubtedly represents an example of the familiar phenomenon of splitting of dialkylamide signals because of restricted rotation around an N-C bond (6).

The nmr spectrum of **3a** is also interesting. The deuteriochloroform spectrum consists of two sharp peaks at δ = 3.37 and 3.49 with relative intensities of 1:2. The spectrum of **3a** in hexafluoroacetone deuterate ($(CF_3)_2CO \cdot 1.6D_2O$, HFD) however, consists of a singlet (6H, δ = 3.32) and a doublet (12H, centered at δ = 3.30). Two noteworthy results of the symmetry of **3a** are: (1) the 2- and 6-dimethylamino groups are identical, and (2) the 4-dimethylamino will be represented by a singlet whether or not that group is rotating freely. Since a doublet (12H) is observed, rotation must be restricted for the 2- and 6-dimethylamino groups. The deuteriochloroform spectrum of the bis(dimethylamino)morpholino salt **3c** contains, in addition to the morpholino signals, a singlet (δ = 3.37) and a doublet (δ = 3.47 and 3.50). In the HFD spectrum, on the other hand, both dimethylamino groups appear as doublets (δ 3.26 and 3.38; δ 3.31 and 3.35). The spectrum of the bis(dimethylamino)pyrrolidinyl salt **3b** also

TABLE I

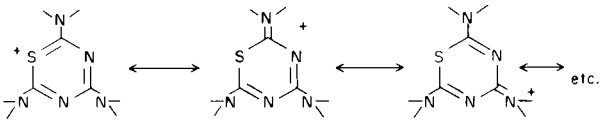
1,3,5-Thiadiazinium Iodides



No.	R	R′	Formula	M.p., °C	Yield %	Recryst. Solvent	Elemental Analyses % Calcd. C	H	N	S	% Found C	H	N	S
3a	$N(CH_3)_2$	$N(CH_3)_2$	$C_9H_{18}IN_5S$	>335	88	aq EtOH	30.43	5.11	19.72	9.03	30.27	5.25	19.53	9.21
3b	$N(CH_3)_2$		$C_{11}H_{20}IN_5S$	267-269	100	EtOH	34.64	5.28	18.37		34.50	5.30	18.20	
3c	$N(CH_3)_2$		$C_{11}H_{20}IN_5OS$	238-239	95	EtOH	33.24	5.07	17.63	8.07	33.12	5.11	17.73	8.22
3d			$C_{18}H_{30}IN_5S$	254-255	95	EtOAc-EtOH	45.48	6.36	14.73	6.74	45.76	6.52	14.59	6.90
3e		$N(CH_3)_2$	$C_{15}H_{26}IN_5S$	245-246	99	EtOAc-EtOH	41.38	6.02	16.08		41.56	6.08	16.14	
3f			$C_{17}H_{28}IN_5OS$	254-256	97	EtOAc-EtOH	42.77	5.91	14.67		42.69	6.15	14.49	
3g	$N(CH_3)_2$	$NHCH_3$	$C_8H_{16}IN_5S$	243-248	48	EtOAc-EtOH	28.16	4.73	20.52	9.39	27.97	4.73	20.34	9.34
3h	$N(CH_3)_2$		$C_{13}H_{18}IN_5S$	294-296	81	aq EtOH	38.71	4.50	17.36	7.96	38.69	4.29	17.44	7.83
6a	$N(CH_3)_2$	SCH_3	$C_8H_{15}IN_4S_2$	229-234 dec.	95	EtOH	26.82	4.22	15.63	17.89	26.65	4.36	15.61	17.94
6b		SCH_3	$C_{14}H_{23}IN_4S_2$	163-165	81	Me_2CO	38.37	5.29	12.78		38.49	5.30	12.91	

varies with the solvent; in deuteriochloroform, both dimethylamino signals are singlets (δ 3.35 and 3.46) whereas in HFD a singlet (δ 3.32) and a doublet (δ 3.25 and 3.37) are observed. In contrast, both of the dimethylamino signals of the methylthio- salt **6a** appear as doublets at room temperature in deuteriochloroform.

The restricted rotation observed with the salts results from charge delocalization from the ring onto the exocyclic amino groups as represented by the imminium resonance structures shown (7).



The reason for the variations between the spectra in deuteriochloroform and in HFD is uncertain. Solvent dependant rotation barriers and/or shift differences may be responsible, and a more detailed study involving other solvents and variable temperatures will be required to answer this question.

EXPERIMENTAL (8,9)

1-Piperidino-*N*-(piperidinoformimido)thioformamide (**4b**).

A solution of 3,5-dipiperidino-1,2,4-dithiazolium bromide (**2b**, 14.2 g.) (4) in absolute ethanol (350 ml.) was treated with excess anhydrous ammonia at room temperature. The mixture was stirred 0.5 hour under a carbon dioxide condenser, then filtered and evaporated. The residue was taken up in chloroform, the chloroform solution was washed with water and with brine, and then was filtered and evaporated. Recrystallization from methanol-water gave 7.4 g. of **4b** (72%), m.p. 132-135°. Recrystallization from cyclohexane-ethyl acetate gave an analytical sample, m.p. 136-137°.

Anal. Calcd. for $C_{12}H_{22}N_4S$: C, 56.65; H, 8.72; N, 22.02. Found: C, 56.80; H, 8.78; N, 22.28.

4,6-Bis(dimethylamino)-2*H*-1,3,5-thiadiazine-2-thione (**5a**).

A solution of thiophosgene (21.2 g., 0.184 mole) in dichloromethane (420 ml.) was added over 7 minutes to a stirred solution of **4a** (31.1 g., 0.179 mole) and triethylamine (36.2 g., 0.357 mole) in dichloromethane (480 ml.) at room temperature. After stirring 38 hours, the solution was washed with water, dried (magnesium sulfate), and evaporated. Recrystallization (95% ethanol) of the residue gave **5a** as light tan needles (24.7 g., 64%, m.p. 180.5-181.5°).

Anal. Calcd. for $C_7H_{12}N_4S_2$: C, 38.87; H, 5.59; N, 25.90; S, 29.64. Found: C, 38.90; H, 5.69; N, 25.81; S, 29.65.

A 45% yield of **5a** was obtained from the reaction of **4a** and thiocarbonyldiimidazole in refluxing toluene (6 hours).

4,6-Dipiperidino-2*H*-1,3,5-thiadiazine-2-thione (**5b**).

The reaction between thiophosgene and **4b** was run as described for the preparation of **5a**. The crude product upon evaporation of the dichloromethane was triturated with hot ethanol; the mixture was cooled and **5b** was collected by filtration (58%, m.p. 211-214°). The analytical sample was recrystallized from 95% ethanol, m.p. 216.5-218.5°.

Anal. Calcd. for $C_{13}H_{20}N_4S_2$: C, 52.65; H, 6.80; N, 18.90. S, 21.65. Found: C, 52.89; H, 6.81; N, 18.92; S, 21.41.

2,4-Bis(dimethylamino)-6-(methylthio)-1,3,5-thiadiazinium Iodide (**6a**).

Thione **5a** (21.6 g., 0.1 mole) was treated with methyl iodide (15.6 g., 0.11 mole) in refluxing acetone (650 ml.) for 15 minutes. The mixture was chilled and **6a** was collected by filtration (33.7 g., 95%), m.p. 229-234°; nmr (deuteriochloroform) δ = 2.88 (3H, S-CH_3), 3.38, 3.47, 3.55, and 3.58 (combined total 12H).

2-(Methylthio)-4,6-dipiperidino-1,3,5-thiadiazinium Iodide (**6b**).

The same procedure was used as for the preparation of **6a** except that the product was collected (81%, m.p. 163-165°) after diluting the acetone solution with hexane. An analytical sample was recrystallized from acetone, m.p. 163-165°.

2,4,6-Tris(substituted amino)-1,3,5-thiadiazinium Iodides (**3a-3h**).

A secondary amine (1.05 equivalent) or a primary amine (1.0 equivalent) in ethanol was added in one portion to a solution or suspension of **6a** or **6b** in absolute ethanol (dimethylamine and methylamine were used as 40% and 30% aqueous solutions, respectively). The total solvent volume was *ca.* 75 ml. per 0.01 mole of **6a** or **6b**. The reactions were stirred at room temperature for 2-4 hours. Insoluble products were isolated by chilling the mixtures and collecting the products by filtration. The more soluble products were obtained by removing the solvent and recrystallizing the residue. Recrystallization solvents, melting points, and yields are included in Table I.

Acknowledgment.

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REFERENCES

(1) A. B. Borkovec and A. B. DeMilo, *J. Med. Chem.*, **10**, 457 (1967).

(2) J. E. Oliver, S. C. Chang, R. T. Brown, J. B. Stokes, and A. B. Borkovec, *ibid.*, in press.

(3) The 1,3,5-thiadiazine system is known. For example, 4,6-diamino-1,3,5-thiadiazine-2-thione, the unsubstituted counterpart of **5a** and **5b** has been prepared from dicyandiamide and carbon disulfide: D. W. Kaiser and R. L. Sperry, U. S. Patent 2,397,421 (1946); *Chem. Abstr.*, **40**, 4089^8 (1946). Tetrahydro-1,3,5-thiadiazine-2-thiones can be prepared from amines, carbon disulfide, and formaldehyde: I. D. Shah and J. P. Trivedi, *J. Indian Chem. Soc.*, **41**, 225 (1964).

(4) J. E. Oliver, *J. Org. Chem.*, **36**, 3465 (1971).

(5) W. R. Diveley, U. S. Patent 3,166,564 (1965); *Chem. Abstr.*, **62**, 9145g (1965).

(6) W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970).

(7) The 1,2-dithiolium cation is considered to be aromatic, but amino-substituted 1,2-dithiolium cations are best represented as iminium salts with most of the positive charge on the exocyclic nitrogen. H. Prinzbach and E. Futterer in "Advances in Heterocyclic Chemistry," Vol. VII, A. R. Katritzky and A. J. Boulton, Eds., Academic Press, New York, N. Y., 1966, pp. 90-100.

(8) Melting points are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian Model T-60 or on Varian Model A-60 spectrometers. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

(9) Mention of a proprietary product or company does not imply endorsement by the U. S. Department of Agriculture.