

5-(Dialkylamino)-1,2,4-dithiazole-3-thiones and
3,5-Disubstituted-1,2,4-dithiazolium Salts

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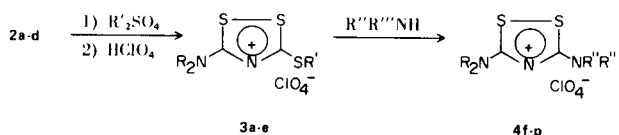
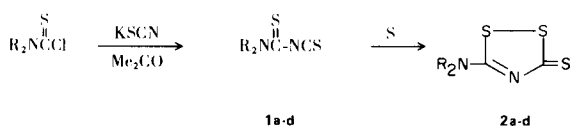
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Received October 8, 1971

3,5-Bis(dialkylamino)-1,2,4-dithiazolium salts (1) and 1,1,5,5-tetraalkyl-2,4-dithiobiurets (2) are chemosterilants against male house flies (*Musca domestica* L.). The dithiazolium salts are commonly prepared by oxidizing the corresponding dithiobiurets (1,3); however, tetraalkyldithiobiurets tend to be unstable (2), and we were unable to prepare certain amino-substituted dithiazolium salts by this method. Since we have converted 5-phenyl-3*H*-1,2,4-dithiazole-3-thione to 5-(dimethylamino)-3-phenyl-1,2,4-dithiazolium perchlorate (4), we felt that 5-(dialkylamino)-1,2,4-dithiazole-3-thiones might similarly be converted to bis(dialkylamino) dithiazolium salts and thus provide an alternate synthesis of these compounds. This report describes a new synthesis of the required 5-(dialkylamino)-3*H*-1,2,4-dithiazole-3-thiones and their conversion to some dithiazolium salts.

Clapp, Lies, and Lamb (5) recently prepared 5-(dimethylamino)-3*H*-1,2,4-dithiazole-3-thione (2a) by treating the adduct of *N,N,N',N'*-tetramethylguanidine with sulfur monochloride, and also obtained, in unspecified yields, 2a and several analogous thiones by reacting 1,1-dialkylthioureas with carbon disulfide in the presence of base and air. Although we were able to prepare 2a in an overall yield of 54% by the former procedure, neither method seemed ideal as a general thione synthesis since neither *N,N,N',N'*-tetraalkylguanidines nor 1,1-dialkylthioureas are readily available.

Goerdeler and Lüdke (6) have shown that *N,N*-dialkylthiocarbamoyl isothiocyanates (e.g., 1a) undergo a variety of 4+2 and 4+1 cycloadditions to provide 6- and 5-membered ring heterocycles. We felt that if elemental sulfur could be made to react with 1a-d, the desired thiones should result (7). Indeed, when an equivalent of sulfur was added to a solution of a thiocarbamoyl isothiocyanate in refluxing acetone, a rapid reaction occurred, and the corresponding thione separated from the solution.



The thiones were alkylated with dimethyl sulfate or diethyl sulfate to give the 3-(dialkylamino)-5-(alkylthio)-1,2,4-dithiazolium alkylsulfates, members of a previously unreported class of compounds. The alkyl sulfate salts were converted to perchlorates 3a-e with perchloric acid, and the dialkylamino alkylthio perchlorates were in turn reacted with amines to give the diamino dithiazolium perchlorates 4f-p. This final reaction did not always proceed smoothly, for example, when 3a was reacted with 1-methylpiperazine, 4i was obtained as its diperchlorate. Thus, a maximum yield of only 50% was possible; furthermore, 3,5-bis(dimethylamino)-1,2,4-dithiazolium perchlorate was also isolated from the reaction mixture. The reaction of 3d with *N*-methylaniline gave a syrup from which the only crystalline products obtained were the perchlorate salts of *N*-methylaniline and of morpholine. Also, in a few cases, thiones were isolated from the reaction mixtures, indicating that nucleophilic attack by the amines could occur at the S-alkyl group as well as at C₃ of the ring. In spite of these difficulties, however, the procedure does have merit, since several of the diamino dithiazolium salts (4g, 4h, 4i, 4k) prepared by this route were inaccessible by the dithiobiuret route.

EXPERIMENTAL (8)

Melting points are uncorrected. Dimethylthiocarbamoyl chloride was purchased; the pyrrolidine-, piperidine-, and morpholine-carbothiyl chlorides were prepared from thiophosgene and the appropriate secondary amine (9). Commercial diethyl sulfate was distilled, and a fraction boiling at 98-100° (20 mm.) was used. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

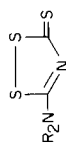
5-(Dialkylamino)-3*H*-1,2,4-dithiazole-3-thiones (2a-d).

A mixture of a thiocarbamoyl chloride (0.1 mole) and potassium thiocyanate (0.1 mole) in acetone (100 ml.) was refluxed 20-30 minutes, then was cooled to room temperature and filtered

TABLE I
5-(Dialkylamino)-1,2,4-dithiazole-3-thiones

Number	R ₂	Formula	M.p., °C	Yield %	Recrystallization Solvent	Elemental Analyses					
						Calcd., %	Found, %				
						C	H	N	S		
2a	CH ₃ , CH ₃	C ₄ H ₆ N ₂ S ₃	176.5-177.5 (a)	71	MeCN	35.27	3.95	13.71	3.92	13.69	47.12
2b	-(CH ₂) ₄ -	C ₆ H ₈ N ₂ S ₃	188-189	56	MeCN	38.50	4.62	12.83	4.73	12.98	43.82
2c	-(CH ₂) ₅ -	C ₇ H ₁₀ N ₂ S ₃	145-146	70	Benzene	32.71	3.66	12.71	3.63	12.64	43.51
2d	-(CH ₂) ₂ O(CH ₂) ₂ -	C ₆ H ₈ N ₂ OS ₃	217 (dec.)	42	Pyridine						

(a) Reported (5) m.p. 175-177.5°.



to remove potassium chloride. Sulfur (0.1 mole) was added to the yellow filtrate and the mixture was refluxed 15-45 minutes. The sulfur was quickly consumed; the thione separated from solution and was collected by filtration and recrystallized (see Table I for yields, m.p.'s, and crystallization solvents).

Alkylation of Thiones **2a-d** with Dialkylsulfates.

A mixture of the thione and dimethyl sulfate or diethyl sulfate (ca. 3 g. per g. of thione) was heated with stirring until a homogeneous solution resulted (usually 80-100°). The solution was cooled to room temperature and was then treated with 70% perchloric acid (ca. 1 ml. per g. of thione). The resulting mixture was diluted with ether and the solid perchlorate salt was collected by filtration and washed with ether (see Table II for yields, m.p.'s, and crystallization solvents).




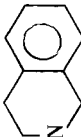




Treatment of 3-(Dialkylamino)-5-(alkylthio)-1,2,4-dithiazolium Perchlorates with Amines.

A 3-(dialkylamino)-5-(alkylthio)-1,2,4-dithiazolium perchlorate and an equivalent of an amine were combined in glacial acetic acid (the ethylthio salts were usually used to minimize attack at the S-alkyl group). The mixture was refluxed 10-30 minutes, then cooled to room temperature. In some cases the product crystallized as the solution cooled. If no solid separated, the solution was diluted with ether to precipitate a crude product that was purified by crystallization (**4g** was obtained as an oil that crystallized on standing). In several cases oils were obtained from which no pure dithiazolium salts could be isolated (e.g., the reactions of **3d** with *N*-methylaniline, and of **3a** with dibutylamine, or of **3a** with tetrahydroquinoline), and thione **2a** was the only solid product obtained from an attempted reaction of **3a** with *N*-methylethanolamine.

REFERENCES

- (1) J. E. Oliver, S. C. Chang, R. T. Brown, J. B. Stokes, and A. B. Borkovec, *J. Med. Chem.*, **15**, 315 (1972).
- (2) J. E. Oliver, S. C. Chang, R. T. Brown, and A. B. Borkovec, *ibid.*, **14**, 772 (1971).
- (3) W. R. Diveley, U. S. Patent, 3,166,564, Jan. 19, 1865; *Chem. Abstr.*, **62**, 9145g (1965).
- (4) J. E. Oliver, *J. Org. Chem.*, **36**, 3465 (1971).
- (5) J. W. Clapp, T. A. Lies, and G. Lamb, U. S. Patent, 3,520,897, July 21, 1970; *Chem. Abstr.*, **73**, 120636r (1970).
- (6) J. Goerdeler and H. Lüdke, *Chem. Ber.*, **103**, 3393 (1970).
- (7) Goerdeler and Weiss have reported a similar reaction that they consider to be a cycloaddition of elemental sulfur. J. Goerdeler and R. Weiss, *ibid.*, **100**, 1627 (1967).
- (8) Mention of a proprietary product or company does not imply endorsement by the U. S. Department of Agriculture.
- (9) W. Ried, H. Hillenbrand, and G. Oertel, *Ann. Chem.*, **590**, 123 (1954).

TABLE II
3,5-Disubstituted 1,2,4-Dithiazolium Salts

No.	R ₁	R ₂	X	Formula	M.p., °C	Yield %	Recrystl. Solvent	Elemental Analyses							
								Calcd., %	Found, %						
								C	H	N	S	C	H	N	S
3a	(CH ₃) ₂ N	SC ₂ H ₅	ClO ₄	C ₆ H ₁₁ ClN ₂ O ₄ S ₃	108-109	53	HOAc	23.49	3.61	9.13	31.35	23.24	3.56	9.09	31.38
3b		SC ₂ H ₅	ClO ₄	C ₈ H ₁₃ ClN ₂ O ₄ S ₃	114-115	65	iPrOH	28.87	3.94	8.42	28.90	28.79	4.02	8.42	28.87
3c		SC ₂ H ₅	ClO ₄	C ₉ H ₁₅ ClN ₂ O ₄ S ₃	97-98	84	HOAc/EtOAc	31.16	4.36	8.08	27.73	31.21	4.40	7.97	27.88
3d		SC ₂ H ₅	ClO ₄	C ₈ H ₁₃ ClN ₂ O ₅ S ₃	222 (dec.)	77	MeCN	27.54	3.76	8.03	27.57	27.64	3.90	7.73	27.26
3e	(CH ₃) ₂ N	SCH ₃	ClO ₄	C ₅ H ₉ ClN ₂ O ₄ S ₃	142-143	46	MeCN	20.51	3.10	9.57	32.85	20.44	3.09	9.38	32.79
4f	(CH ₃) ₂ N	NHPh	ClO ₄	C ₁₀ H ₁₂ ClN ₃ O ₄ S ₂	186-187	65	HOAc	35.56	3.58	12.44		35.51	3.60	12.70	
4g	(CH ₃) ₂ N	N(CH ₃)Ph	ClO ₄	C ₁₁ H ₁₄ ClN ₃ O ₄ S ₂	167-168	55	HOAc	37.55	4.01	11.95		37.61	4.16	11.71	
4h	(CH ₃) ₂ N		ClO ₄	C ₁₃ H ₁₆ ClN ₃ O ₄ S ₂	158.5-159	41	EtOH	41.32	4.27	11.12	16.97	41.16	4.39	11.05	17.19
4i	(CH ₃) ₂ N		2 ClO ₄	C ₉ H ₁₈ Cl ₂ N ₄ O ₈ S ₂	248-250	26	EtOH/H ₂ O	24.27	4.07	12.58		23.95	4.08	12.26	
4j		NHPh	ClO ₄	C ₁₂ H ₁₄ ClN ₃ O ₄ S ₂	223.5-224	60	HOAc/H ₂ O	39.61	3.88	11.55		40.03	4.08	11.68	
4k		N(CH ₃)Ph	ClO ₄	C ₁₃ H ₁₆ ClN ₃ O ₄ S ₂	177-178	78	HOAc	41.32	4.27	11.12		41.27	4.31	11.30	
4l		NHPh	ClO ₄	C ₁₂ H ₁₄ ClN ₃ O ₅ S ₂	217 (dec.)	31	HOAc	37.94	3.71	11.06		37.88	3.94	11.08	