was stirred for 48 hr at room temp. The pptd hydrazine hydrochloride was filtered off, the solvent evapd, and the residue chromatogd on silica gel in PhH, after elution with PhH. The product was eluted with PhH–EtOAc (9:1). The oily product was crystd from hexane and recrystd from EtOAc–hexane to give colorless crystals (140 mg), mp 103–104°.

1-*N*-(4-*n*-Pentyloxyphenyl)-2-(*N,N*-dimethylcarbamoyl)hydrazine (18). A mixt of 4-*n*-pentyloxyphenylhydrazine hydrochloride (1.153 g) and dimethylcarbamoyl chloride (0.538 g) in pyridine (20 ml) was allowed to stand at room temp for 24 hr, the solvent evapd *in vacuo*, and H_2O added. The ppt was filtered off, washed (H_2O), and dried. Recrystn from Et_2O gave colorless crystals (542 mg), mp 135–136°.

4-*n*-Pentyloxyphenyldiazenecarboxylic Acid Thioamide (23). *p*-Benzoquinone (54 mg) in MeOH (5 ml) was added at room temp to a soln of 12 (127 mg) in MeOH (20 ml). The mixt was stirred for 30 min and poured into ice water, and the ppt (125 mg) was collected, mp 100–101°. Recrystn from PhMe at −78° gave red crystals, mp 100–101°. The *N,N*-dimethylthioamide (21), orange crystals from hexane, mp 83–84° (80% yield), was obtained in a similar manner.

4-*n*-Pentyloxyphenyldiazenecarboxylic Acid *N,N*-Dimethylamide (18). *N*-Bromosuccinimide (239 mg) in CH_2Cl_2 (20 ml) was added with cooling in Dry Ice–acetone bath to a soln of 14 (356 mg) and pyridine (110 mg) in CH_2Cl_2 (10 ml). The mixt was stirred for 30 min and for an addl hr after Dry Ice–acetone bath was removed. The reaction mixt was washed (H_2O) and dried (Na_2SO_4), and the solvent was evapd. The residue was recrystd from Et_2O (below −70°) to give orange crystals (263 mg), mp 56–57°.

1-*N*-(3-*n*-Hexylphenyl)-2-(*N,N*-dimethylcarbamoyl)hydrazine (13). A soln of *m*-*n*-hexylphenylhydrazine (762 mg) and dimethylcarbamoyl chloride (213 mg) in Et_2O (10 ml) was stirred for 20 hr at room temp. The solvent was evapd, PhH added, and the insol *m*-*n*-hexylphenylhydrazine hydrochloride filtered off. The filtrate was concd and the product recrystd from the soln to give colorless crystals (160 mg), mp 156–157°. The corresponding diazene (10) was generated from 9 by a procedure like that used for 18. Chromatography on silica gel in hexane and elution with PhH gave a reddish oil, which was shown to be a pure sample of the expected product (13) by tlc and nmr.

Acknowledgments. The authors are grateful to the Army Research Office (Durham, N. C.) and the National Institutes of Health for support.

References

(1) T. Zehavi-Wilner, E. M. Kosower, T. Hunt, and N. S. Kosower, *Biochim. Biophys. Acta*, 228, 245 (1971) (part 5); N. S. Kosower, *et al.*, *ibid.*, 192, 1, 8, 15, 23 (1969).
(2) H. G. Mautner and W. D. Kumler, *J. Amer. Chem. Soc.*, 78, 97 (1956).
(3) (a) C. W. Pluijgers, J. Berg, A. Kaars Sijpesteijn, A. Tempel, and A. Verloop, *Recl. Trav. Chim. Pays-Bas*, 87, 833 (1968); (b) A. Fuchs, A. L. Homans, and F. W. DeVries, *Ann. Appl. Biol.*, 65, 489 (1970).
(4) E. M. Kosower and N. S. Kosower, *Nature (London)*, 224, 117 (1969).
(5) N. S. Kosower, E. M. Kosower, B. Wertheim, and W. Correa, *Biochem. Biophys. Res. Commun.*, 37, 593 (1969).
(6) D. Weinman, E. Galun, N. S. Kosower, and E. M. Kosower, *Experientia*, 26, 40 (1970).
(7) R. Wax, E. Rosenberg, N. S. Kosower, and E. M. Kosower, *J. Bacteriol.*, 101, 1092 (1970).
(8) E. L. Wang, M. Hamada, Y. Okami, and H. Umezawa, *J. Antibiot., Ser. A.*, 19, 216 (1966).
(9) H. Naganawa, T. Takita, K. Maeda, and H. Umezawa, *ibid.*, 21, 241 (1968).
(10) R. G. Herrman and K. P. DuBois, *J. Pharmacol. Exp. Ther.*, 95, 262, 272 (1949).
(11) E. Urbschat and P. E. Frohberger, U. S. Patent 2,911,336; *Chem. Abstr.*, 54, 20056 (1960).
(12) G. C. Papavizas, *Plant Dis. Rep.*, 51, 125 (1967); W. Krueger, *Phytopathol. Z.*, 62, 174 (1968); J. T. Mills and H. A. Wallace, *Can. J. Plant Sci.*, 48, 587 (1968); H. Cole, D. Mackenzie, and C. B. Smith, *Bull. Environ. Contam. Toxicol.*, 3, 116 (1968); N. H. Peck, B. E. Clark, and J. J. Natti, *Agron. J.*, 59, 78 (1967).
(13) T. Miyadera and E. M. Kosower, *J. Med. Chem.*, 15, 339 (1972).
(14) P.-K. C. Huang and E. M. Kosower, *J. Amer. Chem. Soc.*, 90, 2354 (1968).
(15) E. M. Kosower, *Accounts Chem. Res.*, 4, 193 (1971).
(16) R. C. Neuman, Jr., and L. B. Young, *J. Phys. Chem.*, 69, 1777 (1965).
(17) M. R. Siegel, *J. Agr. Food Chem.*, 18, 819 (1970); E. Somers, Abstracts, 156th Meeting of the American Chemical Society, Atlantic City, N. J., AGFD 72 (1968).
(18) N. S. Kosower and E. M. Kosower, *Lancet*, ii, 1343 (1970).
(19) N. S. Kosower, G. Vanderhoff, B. Benerofe, T. Hunt, and E. M. Kosower, *Biochem. Biophys. Res. Commun.*, 45, 816 (1971).
(20) D. V. Richmond and E. Somers, *Biochem. Biophys. Res. Commun.*, 25, 657 (1966).
(21) Cf., J. Buechi, H. Muehle, H. Braunschweiger, and P. Fabiani, *Helv. Chim. Acta*, 45, 449 (1962).
(22) Cf., Th. Pyl, K. H. Scheel, and H. Beyer, *J. Prakt. Chem.*, 20, 255 (1963).

Organic Disulfides and Related Substances. 33. Sodium 4-(2-Acetamidoethyldithio)butanesulfinate and Related Compounds as Antiradiation Drugs[1,†]

Lamar Field* and Yong H. Khim

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37203. *Received September 6, 1971*

The compound $AcNH(CH_2)_2SS(CH_2)_4SO_2Na$ (**1**), a promising antiradiation drug, disproportionates far more rapidly in solution to the symmetrical disulfides **2** (the amide) and **3** (the sulfinate) than would be expected from behavior of analogous compounds having no SO_2Na moiety; solid **1** is stable. The disproportionation is reversible. An improved preparation of **1** minimizes disproportionation by use of lower temperatures, precipitation instead of concentration, and minimum contact with polar solvents. Radioprotective activity of improved **1** confirms earlier results; **3** is active as well, but **2** is inactive. The trisulfide $[NaO_2S(CH_2)_4S]_2S$ (**9**) was prepared in 80% yield from 1,2-dithiane 1,1-dioxide (**6**) using Na_2S. Thus far, **9** has shown $ALD_{50} > 900$ mg/kg (ip or po) and 73–100% protection of mice at doses of 38 (ip)–300 (po) mg/kg in mice. The promising activity of **3** and (especially) **9** is noteworthy since neither contains a nitrogen function.

Sodium 4-(2-acetamidoethyldithio)butanesulfinate (**1**) has given promising results as an antiradiation drug.[2] However, difficulties were encountered in the large-scale preparation of pure **1** and in reproducing the promising protective activity using **1** that was obtained.‡ Disproportionation of **1** seemed

†This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DADA17-69-C-9128.

‡Discussion with Dr. E. A. Steck of the Walter Reed Army Institute of Research, Washington, D. C.

Table I. Antiradiation Activities of Sodium 4-(2-Acetamidoethyldithio)butanesulfinate and Related Compounds

Compd	RSSR′ R	RSSR′ R′	ALD_{50},[a] mg/kg	Drug[b] dose, mg/kg	pH of soln admin	Survival, 30 days,[c,d] %
1,[e] prev	$AcNH(CH_2)_2$	$(CH_2)_4SO_2Na$	694 ip	370 ip	7.1	47
				185 ip	7.1	67
				47 ip (NaCl)	7.0–7.1	87–100
1,[d,f] new	$AcNH(CH_2)_2$	$(CH_2)_4SO_2Na$	800 ip	343 ip	~7.0	80
				172 ip	~7.0	93
			1050 po	556 po	7.0	100
				278 po	7.0	100
2	$AcNH(CH_2)_2$	$(CH_2)_2NHAc$	425 ip	350 ip	7.2	0
3[d]	$NaO_2S(CH_2)_4$	$(CH_2)_4SO_2Na$	800 ip	400 ip	8.5	7
				200 ip	8.5	73
9[d]	$NaO_2S(CH_2)_4$	$S(CH_2)_4SO_2Na$	>900 ip	300 ip	7.5	100
				150 ip	7.5	93
				75 ip	7.0	87
				38 ip	7.0	73
			>900 po	600 po	7.5	100
				300 po	7.5	100

[a] Approximate LD_{50} for the compound in nonirradiated mice; ip = intraperitoneal admin, po = oral admin. [b] Vehicle: solution of the compd in H_2O or (NaCl) in physiological saline soln. [c] Usually 15 mice with 10 controls to permit comparison. Test compds were admin 15–30 min before the animals were exposed to radiation. Protective activities based on per cent survival of irradiated mice may be correlated as follows: good, >45%; fair, 25–44%; slight, 1–24%; none, 0%. For comparison, 2-mercaptoethylamine had ALD_{50} = 250 mg/kg and afforded 100% survival at dose levels of 150 mg/kg. [d] Except for 1, prev and 2, mice were tested for 30-day survival against lethal radiation usually of 975 rads (1023R) (230 rads/min) from a ^{60}Co source. [e] Sample of 1 and procedures as described in ref 2. [f] New sample of 1 prepared as described in the Experimental Section.

a possible cause of the difficulties (eq 1). Surprisingly, further studies have now shown that disproportionation of **1** does indeed occur far more rapidly with **1** in H_2O or MeOH than has been observed for compounds assumed to be quite similar but that have no sulfinate moiety.

$$2\,\underset{1}{AcNH(CH_2)_2SS(CH_2)_4SO_2Na} \rightleftharpoons \underset{2}{[AcNH(CH_2)_2S]_2} + \underset{3}{[NaO_2S(CH_2)_4S]_2} \quad (1)$$

Thus **4** gave 2 symmetrical disulfides in 79% yield only after 72 hr in H_2O at 100%,[2] but **1** gives **2** and **3** in ~50–55% yield after only ~0.5 hr in H_2O or 8 hr in MeOH at only 61°.

$R(CH_2)_2SS(CH_2)_4SO_2CH_2Ph$
4, R = $N^+H_3 \cdot Cl^-$
5, R = AcNH

The results with **1** were obtained by analytical tlc (which showed 55% of **3**) and were checked approximately by isolation of **2** (50% yield). Compounds **4** and **5** were found to disproportionate much more slowly than **1** under the same conditions (disproportionation at 61°, of **5**, 0% in MeOH for 8 hr; of **4**, 0% in H_2O for 0.5 hr or in MeOH for 8 hr, trace in H_2O for 8 hr).

The level of ~55% for **1** is an equilibrium value. Evidence for this conclusion is that the same level can be reached by heating **2** and **3** for ~0.5 hr in H_2O or ~8 hr in MeOH. Details of these reactions and of the probable involvement of the sulfinate moiety (*i.e.*, of SO_2Na) in accelerating the disproportionation of **1** relative to **4** and **5** will be discussed in a later paper, but an example of the disproportionation of **1** in MeOH is given in the Experimental Section.

Awareness of the facile disproportionation of **1** made it possible to improve the preparation. The key proved to be to minimize disproportionation during preparation, rather than to attempt the extremely difficult separation of the salt **3** from the salt **1**. This minimization was achieved by conducting the reaction at 0–5° instead of at ~25°,[2] by precipitating **1** from the reaction mixture rather than by concg it to dryness,[2] and by precipitating **1** from MeOH for purification only twice instead of repeatedly.[2] The much greater rapidity of disproportionation of **1** in H_2O than in MeOH mentioned above suggests that the disproportionation is favored by more polar solvents, but that contact even with MeOH should be minimized. Although the stability of **1** as a dry solid seems good, storage at low temperature seems a wise precaution; tlc showed however that **1** could be heated dry at 61° for up to 72 hr with insignificant formation of **2** and **3**.

Table I shows that the activity of the newly prepared **1** confirms that reported earlier,[2,§] so that the anomalies mentioned‡ must have been associated with the difficulties of large-scale preparation.

The ease of disproportionation of **1** made it desirable to determine the antiradiation activities of the disproportionation products **2** and **3**. Table I shows the results. 2-Acetamidoethyl disulfide (**2**) is readily obtainable; it is inactive. Isolation of the symmetrical salt **3** from a mixt produced according to eq 1 in a state pure enough for analyses proved to be possible, although it was difficult because the chemical and physical properties of the symmetrical salt **3** and the unsymmetrical disulfide salt **1** are so similar. The sample of **3** that could be obtained from a disproportionation mixture was free enough of the other two possible compounds (**1** and **2**) to make the 73% survival found with it a significant result (Table I).

In order to obtain **3**, after **1** had been heated in MeOH for 8 hr for disproportionation (eq 1), the solution was concd until pptn began, and pptn then was completed by adding Me_2CO. The ppt was washed well with Me_2CO and EtOH and was subjected to the same treatment four more times. Since **2** (unlike **1** and **3**) is soluble in Me_2CO and EtOH, eq 1 thus could be forced nearly entirely to the product side. Tlc of the final residue showed a single large spot for **3**, only a trace of **1**, and no **2**. Ir spectra of the salt **3** showed a strong sulfinate anion absorption, but only very weak amide absorption. The high degree of radioprotective activity in **3**, a compound that contains *no N*, seems to be an ex-

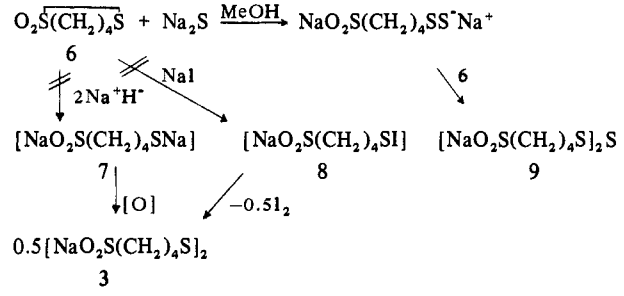
§ For these and other activities reported we are indebted to M. M. Grenan, and also to D. P. Jacobus, T. R. Sweeney, E. A. Steck, and D. L. Klayman; for helpful discussion, Walter Reed Army Institute of Research, Washington, D. C.; for details of testing not given in the footnotes to Table I see ref 3.

cellent lead that should be pursued further (Table I), since lack of N in such compounds might obviate side effects associated with the amine function present in nearly all promising antiradiation drugs.

Several efforts were made to obtain pure **3** by a simpler means. We hoped that "oxodisulfide cleavage," which occurs with 1,2-dithiane 1,1-dioxide (**6**) upon attack by certain nucleophiles,[2] might be used to convert **6** to **7** with a metal hydride, after which oxidation might give **3** (Scheme I). However, NaH in benzene or xylene failed to cleave **6** to **7**, and **6** was quantitatively recovered after 21-24 hr of reflux. Similarly, NaI (or LiCl) with **6** gave no **8**, which hopefully would lose I_2 (or Cl_2) to give **3** (Scheme I); after reaction for 20-70 hr in Me_2CO, Me_2CO-H_2O, DMSO, or DMF at 90°, 53-100% of **6** was recovered.

Since **3** proved so difficult to obtain, it occured to us that the corresponding trisulfide **9** might be active as well and hence would be an attractive alternative to the disulfide **3**. Smooth preparation of trisulfides was achieved earlier by thioalkylating S^{-2} ion with acyclic thiolsulfonates.[4]

Scheme I



For such a synthesis of **9** (Scheme I), a soln of Na_2S was added slowly to a soln of the dioxide (**6**) until the pH became ~7. Addition of Me_2CO then pptd **9** (80%), which was purified by repptn (**9** actually was obtained as the dihydrate, and prolonged heating was necessary to obtain anhydrous **9**). The structure **9** for the product was confirmed by elemental analysis and by consistency of the ir and nmr spectra with expectation. Preliminary biological results for **9** are exciting (Table I), particularly so since **9** contains *no N*. These preliminary results show excellent protection at doses well below the toxic level, and it is noteworthy that **9** is active when administered *orally* as well as ip. At this time, **9** appears to be fully as active as **1**, either ip or po, and may prove to be more so; a characteristic thiol-like odor respired from mice dosed with **1** seems to be less noticeable with **9**.

Experimental Section#

Starting Materials. 2-Acetamidoethyl disulfide (2),[5] 1,2-dithiane 1,1-dioxide (6),[6] 2-acetamidoethanethiol,[7] and sodium sulfide[8,**] were prepared according to reported procedures.

Experiments in Disproportionation. A solution of 1 (0.300 g, 1.02 mmoles) in 50 ml of spectroquality MeOH was heated at 61° for 8 hr. Solvent was removed, and the residue was washed with dry Me_2CO several times. Removal of Me_2CO left 0.060 g (50%) of 2, which had an ir spectrum identical with that of authentic 2[5] and mp 92-93° (lit.[5] mp 92-93°). Tlc showed that the residue was a mixture of 1 and 3 which was insoluble in Me_2CO. Tlc and comparison with an area plot based on standards (to be detailed in a later paper) showed the yield of 3 to be ~55% when a similar expt was done with 1 in H_2O (30 min, 61°). The disproportionation of 4 was 0% when it was heated at 61° for 30 min in H_2O; after 8 hr at 61° in H_2O, only a trace of the symmetrical disulfide 1,14-diphenyl-2,7,8,-13-tetrathiatetradecane 2,2,13,13-tetroxide was isolated (mp 117-118°, lit.[2] mp 118-118.5°). Compound 5 was quantitatively recovered after being heated at 61° for 8 hr in MeOH.

The reverse reaction of eq 1 was proved by a tlc method, through checking formation of 1 from a mixt of 2 and 3 in both H_2O and MeOH; the conversion to 1 of 2 and 3 stopped at ~55% over varied reaction times. Further details on disproportionation reactions will be published elsewhere.

Sodium 4-(2-Acetamidoethyldithio)butanesulfinate (1). Methanolic NaOMe (2 *N*, 33.3 mmoles) was added dropwise to 6 (5.00 g, 32.9 mmoles) and 2-acetamidoethanethiol (3.92 g, 32.9 mmoles) in 75 ml of absolute EtOH with stirring at 0-5° until the solution became just neutral to pHydrion pH test paper (pH ~6.5-7). After the addition was complete (~10 min), dry Et_2O was added to the reaction mixt until no more ppt appeared. After decantation to remove Et_2O, the white ppt was dissolved in MeOH at 0-5° and as quickly as possible dry Me_2CO was slowly added until no more ppt could be obtained. This solid was separated, washed with Me_2CO, and purified by adding dry Et_2O to a soln in MeOH at 0-5° until no more white ppt formed; yield of 1, 6.8 g (71%); tlc in 1:2 MeOH-Me_2CO showed a single spot (R_f 0.66). Insofar as possible throughout, contact time with MeOH was minimized and solns were kept at ~0-5°. The 1 then was dried at ~25° *in vacuo*. The dry 1 then could be kept at ~25° indefinitely (although low temp storage in the dark where feasible seems a wise precaution). The ir and nmr spectra of this 1 met expectation and were identical with those of authentic 1.[2]

Disodium 4,4'-Dithiobis(butanesulfinate) (3) from the Disproportionation of 1. A soln of 6.00 g (20.5 mmoles) of 1 in 300 ml of MeOH was heated at the reflux temp for 8 hr. The mixt then was concd under reduced pressure using a rotary evaporator until white ppt began to appear. Dry Me_2CO was added until no more ppt appeared. The ppt was removed by filtn and was washed with dry Me_2CO and EtOH. The white solid then was subjected to the same treatment 4 more times. The white solid 3 which then remained showed one tlc spot of R_f 0.33 (3), a trace spot at R_f 0.66 (1), and no spot at R_f 0.69 (2) (1:1 Me_2CO-MeOH). It also showed strong sulfinate anion ir absorption (SO_2^-, 1030 and 1000 cm^{-1}) but very weak amide absorption (1550, 1650 cm^{-1}); amide absorptions for 1 and 2 are strong at 1650 and 1550 cm^{-1}. Therefore the product 3 isolated from the disproportionation of 1 was nearly all 3 but did contain a trace amount of 1; yield, 1.5 g (42%), mp 296° dec. *Anal.* ($C_8H_{16}Na_2O_4S_4$) C, H, Na, S.

Disodium 4,4'-Trithiobis(butanesulfinate) (9). A soln of Na_2S (0.05 mole) in MeOH (60 ml) was added slowly to the dioxide 6 (15.2 g, 0.10 mole) in MeOH (60 ml) at 0-5° with good stirring under dry N_2 during 2 hr. After the addn was complete (the pH then was 7), the reaction mixt showed only one spot (R_f 0.69) for 9 by tlc (1:1 MeOH-Me_2CO) and none for 6. Addition of a large amount of Me_2CO (~500 ml) and then of Et_2O (~300 ml) at 0° gave white ppt (each was added until pptn seemed complete). Most of the solvent was decanted, after which drying *in vacuo* gave 15 g (80%) of white 9, mp 252° dec. This 9 was dissolved in a little MeOH and a small amount of dry Me_2CO was added until cloudy ppt began to appear. A colorless clean soln then resulted upon removal of the small amount of ppt by a centrifuge as quickly as possible. Dry Me_2CO again was added to this soln until appearance of white ppt was complete. Decantation and drying at 0.1 mm for 20 hr at 56° gave 13.0 g (69%) of anhydrous white 9, mp 254° dec. Tlc showed one spot (R_f 0.69, 1:1 MeOH-Me_2CO), ir 2940, 1460, 1420, 1190, 1070, 1000, and 980 cm^{-1}; nmr (D_2O), δ 2.82 (t), 2.39 (t), 1.80 (m). *Anal.* ($C_8H_{16}Na_2O_4S_5$) C, H, S.

The salt 9 ordinarily is obtained as a dihydrate (the anhydrous form reported above is highly hygroscopic). In order to confirm that the undried 9 contains 2 H_2O, 0.400 g was placed in a tube and another sample was prepd in KBr for ir observation. Both samples then were heated simultaneously at 110° and 0.1 mm. From time to time the weight of the first sample and the ir spectrum of the second were detd. The weight and OH peak (3440 cm^{-1}) decreased

#Melting points, detd in capillary tubes using a Mel-Temp apparatus, are corrected. Ir spectra were obtained using KBr pellets and a Beckman Model IR 10 spectrophotometer; bands reported were at least of medium intensity. Nmr spectra were obtained using a Varian Model A-60 spectrometer (Me_4Si). Tlc spots were obtained using Brinkman F-254 precoated sheets of silica gel (0.25 mm) on Al and were developed by exposure to I_2 vapor in a sealed container. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Where analyses are indicated only by symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values.

**The NaSH thus prepared was not isolated but was treated with 1 equiv of NaOEt in EtOH before pptn with Et_2O. Since both NaSH and Na_2S are very hygroscopic, and since NaSH is hydrolyzed easily to H_2S and NaOH, materials were handled under N_2 as quickly as possible.

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,†]

J. E. Oliver,* S. C. Chang, R. T. Brown, J. B. Stokes, and A. B. Bořkovec

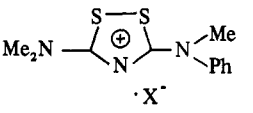
Entomology Research Division, U. S. Department of Agriculture, Beltsville, Maryland 20705. *Received July 30, 1971*

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.

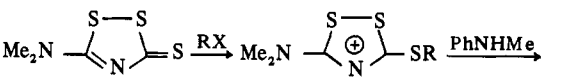
1,1,5,5-Tetramethyl-2,4-dithiobiuret (**1**) is an intermediate in the synthesis of 3,5-bis(dimethylamino)-1,2,4-dithiazolium chloride[2] (**10a**). Both compounds are effective as chemosterilants in house flies,[1,3a,b] *Musca domestica* L., and their activity in the male fly is comparable to that of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



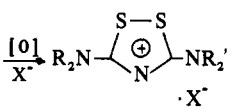
11



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

$R_2NC(S)Cl + KSCN \rightarrow R_2NC(S)NCS \xrightarrow{R'_2NH} R_2NC(S)NHC(S)NR'_2$

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.