activity is due to steric factors is strengthened by the moderately high activity of the smaller fluoro derivative.

With the exception of IX, the five-membered ring dioxaphospholanes were poor anticholinesterases, probably due in part to their rapid breakdown in water. The I_{50} value of IX, a liquid, must be taken with caution since its instability to heat and moisture made purification difficult.

None of the compounds in Table II showed topical toxicity at 500 γ/g. to house flies, *Musca domestica*, or at 10 p.p.m. in water to mosquito larvae, *Culex pipiens quinquefasciatus*.

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Potential Antiradiation Drugs. II.[1] 2-Amino-1-alkanethiols, 1-Amino-2-alkanethiols, 2-Thiazolines, and 2-Thiazoline-2-thiols[2]

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Syntheses and radioprotective properties are described for 21 compounds drawn from the title classes. With few exceptions all compounds studied showed some protective activity in either mice or bacteria. The best protection was shown by 2-amino-1-pentanethiol (**24**), 2-amino-3-methyl-1-butanethiol (**25**), and 1-amino-2-propanethiol (**27**). Three thiazolines offering good protection (**15**, **16**, and **10**) are the precursors of these same aminothiols. Radioprotective activities observed in the present work are compared with those observed in other laboratories with the same or analogous compounds.

The purpose of the present work was to continue the preparation of pure organic compounds which might protect against the lethal effects of ionizing radiation.[3] As part of an extensive program directed by the sponsoring agency,[4] we prepared 10 g.–1 kg. of the aminoalkanethiol hydrochlorides shown in Table III. The radioprotective activities of some of these substances had been reported previously by several investigators, but we felt it desirable to re-examine these substances, along with new compounds, using a standard testing technique.

When radioprotective activity was observed with some of the 2-thiazoline intermediates isolated during the aminothiol syntheses, all such intermediates (Table II) were purified and tested.

Chemistry.—We chose to prepare aminoalkanethiols from the related amino alcohols because of the availability of the latter. From among a variety of routes that have been devised for the replacement of an alcohol function by a thiol function, that involving a 2-thiazoline intermediate[5,6] proved to be completely satisfactory, not only with respect to yield but particularly with respect to purity of product. At the beginning of our work we prepared **21** and **27** by way of appropriate 2-thiazoline-2-thiol intermediates (**19** and **20**) but abandoned this route when a repetition of the synthesis of **27** by way of a 2-thiazoline showed clearly the superiority of this latter route.

Amino alcohols were acetylated effectively by reaction with ethyl acetate[7] (method A). In early work we sought to acetylate by heating the acetate salt of the amino alcohol[5] (method B) but found that yields were low and that the desired amide was difficult to separate from unreacted acetate salt. In addition, we observed that at the temperature needed for this reaction the amide sometimes cyclized to the oxazoline. In the case of the acetate salt of 2-amino-2-methyl-1-propanol, 2,4,4-trimethyl-2-oxazoline was the only product formed; this facile cyclization, noted by others with the benzoyl derivatives,[8] appears to be another example of the so-called *gem*-dimethyl effect.[9] When acetylation was effected with acetic anhydride (method C), the acetate salt of the amino alcohol interfered with the isolation and purification of the amide (as in method B) and diacetylation of the amino alcohol also occurred.

The hydroxyalkylacetamides (Table I) were converted smoothly to the 2-thiazolines (Table II) when heated with phosphorus pentasulfide.[5,6] An important modification of the published procedures, introduced in our work, was the use of mineral oil as a diluent to moderate the otherwise violent reaction. This modification permitted us to carry out large-scale runs. The mechanism of this cyclization reaction has been studied recently.[10]

Hydrolysis of the 2-thiazolines by boiling overnight with dilute HCl[11] gave the desired aminoalkanethiol

(1) Paper I: E. R. Atkinson, G. R. Handrick, R. J. Bruni, and F. E. Granchelli, *J. Med. Chem.*, **8**, 29 (1965).

(2) Reported at the Division of Medicinal Chemistry at the 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1965.

(3) (a) J. F. Thomson, "Radiation Protection in Mammals," Reinhold Publishing Corp., New York, N. Y., 1962; (b) S. Fallab and H. Erlenmeyer, *Experientia*, **19**, 374 (1963); (c) F. Yu. Rachinskii, A. S. Mozzhukin, N. M. Slavachevskaya, and L. I. Tank, *Usp. Khim.*, **28**, 1488 (1959).

(4) This work was performed under contract DA-49-193-MD-2071 with the U. S. Army Medical Research and Development Command, Office of the Surgeon General, during the period 1959–1962.

(5) H. Wenker, *J. Am. Chem. Soc.*, **57**, 1079 (1935).

(6) G. Bach and M. Zahn, *J. prakt. Chem.*, **8**, 68 (1959).

(7) G. F. D'Alelio and E. E. Reid, *J. Am. Chem. Soc.*, **59**, 111 (1937).

(8) R. N. Boyd and R. C. Rittner, *ibid.*, **82**, 2032 (1960).

(9) N. I. Allinger and V. Zalkow, *J. Org. Chem.*, **25**, 701 (1960).

(10) J. Roggero and J. Metzger, *Bull. soc. chim. France*, 2533 (1963).

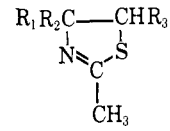
(11) An extensive study of this reaction has been made by R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *J. Am. Chem. Soc.*, **81**, 5089 (1959); R. B. Martin, R. I. Hedrick, and A. Parcell, *J. Org. Chem.*, **29**, 3197 (1964); G. L. Schmir, *J. Am. Chem. Soc.*, **87**, 2743 (1965).

TABLE I
N-(HYDROXYALKYL)ACETAMIDES

No.	R_1	R_2	B.p., °C. (mm.)	M.p., °C.	Yield, %	Method[a]	Formula	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
			N-(1-Alkyl-2-hydroxyethyl)acetamide				$CH_3CONHCR_1R_2CH_2OH$						
1[b]	C_2H_5	H	146–148 (1)	...	62	B	$C_6H_{13}NO_2$	54.94	9.99	10.68	54.65	9.73	10.38
2	CH_3	CH_3	>118 (0.6)	87.5–88	49	C	$C_6H_{13}NO_2$	54.94	9.99	10.68	55.21	9.89	10.71
3	n-C_3H_7	H	127–132 (0.3)	63–64	79	A	$C_7H_{15}NO_2$	57.90	10.41	9.65	58.51	10.38	9.74
4	i-C_3H_7	H	135–138 (1.2)	84–85	96	A	$C_7H_{15}NO_2$	57.90	10.41	9.65	58.65	10.81	9.99
5	n-C_6H_{13}	H	...	82.5–83	90	A	$C_{10}H_{21}NO_2$	64.13	11.30	...	63.73	11.13	...
			N-(2-Alkyl-2-hydroxyethyl)acetamide				$CH_3CONHCH_2CHR_1OH$						
6	CH_3	...	131 (0.1)[c]	...	97	A	$C_5H_{11}NO_2$	51.26	9.47	11.96	50.72	9.09	11.92
7	C_2H_5	...	133–134 (0.1)[d]	...	90	A	$C_6H_{13}NO_2$	54.94	9.99	10.68	54.77	9.87	10.62
8	n-C_6H_{13}	...	...	76.5–77	93	A	$C_{10}H_{21}NO_2$	64.13	11.30	7.48	63.54	11.02	7.31
			N-(1,2-Dialkyl-2-hydroxyethyl)acetamide				$CH_3CONHCHR_1CHR_2OH$						
9[e]	CH_3	CH_3	103–104 (0.2)	...	99	A	$C_6H_{13}NO_2$	54.94	9.99	10.68	54.83	9.93	10.65.

[a] See Experimental Section for details. [b] $n^{25}D$ 1.4687; mentioned but not described by A. W. Campbell and P. F. Tryon, *Ind. Eng. Chem.*, **45**, 125 (1953). [c] $n^{25}D$ 1.4654. [d] $n^{25}D$ 1.4660. [e] $n^{25}D$ 1.4665; B. T. Gillis [*J. Org. Chem.*, **24**, 1027 (1959)] used another synthesis and reported b.p. 112–115° (0.3 mm.), n_D 1.4664.

TABLE II
THIAZOLINES AND THIAZOLINETHIOLS



No.	R_1	R_2	R_3	B.p., °C. (mm.)	$n^{22}D$	Yield, %	Formula	% calcd. C	% calcd. H	% calcd. N	% found C	% found H	% found N
10[a]	H	H	CH_3	51 (20)	1.4977	50	C_5H_9NS	52.13	7.87	12.16	52.28	8.11	12.20
11	C_2H_5	H	H	67 (20)	1.4960	59	$C_6H_{11}NS$	55.76	8.58	10.84	55.6	8.4	10.9
12	H	H	C_2H_5	62–63 (16)	1.4939	34	$C_6H_{11}NS$	55.76	8.58	10.84	55.79	8.59	9.90
13[b]	CH_3	H	CH_3	57–58 (20)	1.4900	40	$C_6H_{11}NS$	55.76	8.58	10.84	55.56	8.60	11.2
14[c]	CH_3	CH_3	H	67 (49)	1.4862	65	$C_6H_{11}NS$	55.76	8.58	10.84	55.21	8.40	10.92
15	n-C_3H_7	H	H	78–79 (20)	1.4920	59	$C_7H_{13}NS$	58.69	9.15	9.78	59.22	9.03	9.84
16	i-C_3H_7	H	H	74–75 (20)	1.4918	79	$C_7H_{13}NS$	58.69	9.15	9.78	60.1	9.42	10.1
17	n-C_6H_{13}	H	H	92–93 (2)	1.4853	67	$C_{10}H_{19}NS$	64.81	10.33	7.56	65.0	10.14	7.41
18	H	H	n-C_6H_{13}	82–84 (1.2)	1.4847	54	$C_{10}H_{19}NS$	64.81	10.33	7.56	64.75	10.26	7.8
19	4-Methyl-2-thiazoline-2-thiol			98.5–99[d]	...	50	$C_4H_7NS_2$	...	...	...	...	...	...
20	5-Methyl-2-thiazoline-2-thiol[e]			92–93[d]	...	60	$C_4H_7NS_2$	...	...	...	...	...	...

[a] P. A. S. Smith and J. M. Sullivan [*J. Org. Chem.*, **26**, 1132 (1961)] used an alternative synthesis and reported b.p. 48° (22 mm.). [b] Lit.[a] b.p. 55–56° (25 mm.). [c] A. I. Meyers and J. J. Ritter [*J. Org. Chem.*, **23**, 1918 (1958)] used an alternative synthesis and reported b.p. 146–148°, $n^{25}D$ 1.4825. [d] Melting point. [e] Prepared by a procedure similar to that of P. A. S. Smith and J. M. Sullivan[a] who reported m.p. 93–95°.

hydrochlorides (Table III) in high yield. In contrast, the hydrolysis of two 2-thiazoline-2-thiols (**19** and **20**) required 150 hr. for complete hydrolysis to the aminothiol. In one such hydrolysis we detected the presence of a partially hydrolyzed intermediate (see Experimental Section).

Radioprotective Activities.—The results tabulated in Tables IV and V were obtained exactly as described in our first paper.[1] The same standards for rating the compounds were used.

Our results with 1-amino-2-propanethiol (**27**) in rodents confirmed the observation of earlier workers[3c,12,13] that this is an effective radioprotective substance. Its prophylactic range is said[12] to be superior to those of all other aminothiol derivatives. Its distribution and elimination and its metabolism products have been studied[14] and papers describing its protective action on lysogenic bacteria[15] and yeast[16] have appeared. We also confirmed the earlier observation[12] that the isomeric 2-amino-1-propanethiol (**21**) is inferior in the dose range studied.

The isomeric aminobutanethiols **22** and **28** have been reported previously[3c,13] to offer only fair protection in rodents, and other structural variants in this group (**23** and **30**) produced no striking changes in protective activity. Among the higher homologs described here only **24** and **25** are of continuing interest. An isomer of **25**, 1-amino-3-methyl-2-butanethiol, was reported[3c,13] to have fair protective activity. The octanethiols **26** and **29** are not protective even in bacteria. An earlier preparation of **29** was reported to have no protective activity.[17]

In earlier work[18] no significant relationship was found between the radioprotective activity of certain amino-

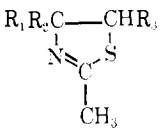
(12) D. W. van Bekkum and H. T. M. Nieuwerkerk, *Intern. J. Radiation Biol.*, **7**, 473 (1964).
(13) L. I. Tank, *Med. Radiol.*, **5**, No. 9, 34 (1960).
(14) G. V. Kalistratov and E. F. Romantsev, *Farmakol. i Toksikol.*, **27**, 364 (1964).
(15) M. N. Zhukov-Verezhnikov, I. N. Maiskii, A. P. Pekhov, N. I. Rybakov, P. P. Saksonov, B. A. Mishchenko, V. A. Kozlov, K. D. Rybakova, and E. D. Aniskin, *Radiobiologiya*, **4**, 738 (1964).
(16) J. Judis, *J. Pharm. Sci.*, **50**, 221 (1961).
(17) F. I. Carroll, J. D. White, and M. E. Wall, *J. Org. Chem.*, **28**, 1236 (1963).
(18) V. Wolf and W. Braun, *Arzneimittel-Forsch.*, **10**, 304 (1960).

TABLE III
AMINOALKANETHIOLS

No.	R_1	R_2	M.p., °C.	Recrystn. solvent[a]	Yield, %	Formula	% calcd. C	H	N	SH	% found C	H	N	SH[b]
2-Amino-1-alkanethiol Hydrochloride $R_1R_2CCH_2SH$														
										$NH_2 \cdot HCl$				
21[c]	CH_3	H	97–98	D	64	$C_3H_{10}ClNS$	...	...	...	25.9	...	...	...	25.8
22[d]	C_2H_5	H	149–150	A	95	$C_4H_{12}ClNS$	33.91	8.54	9.89	23.34	34.10	8.50	9.70	23.18
23[e]	CH_3	CH_3	188–188.5	D	90	$C_4H_{12}ClNS$	33.91	8.54	9.89	23.34	34.01	8.58	9.96	23.21
24	n-C_3H_7	H	164–165	A	77	$C_5H_{14}ClNS$	38.57	9.06	9.00	21.24	38.60	9.20	8.90	21.28
25	i-C_3H_7	H	161–162	B	71	$C_5H_{14}ClNS$	38.57	9.06	9.00	21.24	38.17	8.85	9.02	21.33
26	n-C_6H_{13}	H	59–60	C	80	$C_8H_{20}ClNS$	48.58	10.19	7.08	16.72	49.04	10.11	7.45	16.79
1-Amino-2-alkanethiol Hydrochloride $R_1CH(SH)CH_2NH_2 \cdot HCl$														
27[f]	CH_3	...	85–87	A, D 10:1	90	$C_3H_{10}ClNS$	...	...	...	25.9	...	...	...	25.8
28[g]	C_2H_5	...	159–160	A	94	$C_4H_{12}ClNS$	33.91	8.54	9.89	23.24	34.04	8.46	10.00	23.35
29[h]	n-C_6H_{13}	...	90.5–100.5	B	90	$C_9H_{20}ClNS$	48.58	10.19	7.08	16.72	48.60	10.20	7.10	16.71
3-Amino-2-alkanethiol Hydrochloride R_2CHCHR_1SH														
										$NH_2 \cdot HCl$				
30[i]	CH_3	CH_3	103–104	A	83	$C_4H_{12}ClNS$	33.91	8.54	9.89	23.34	33.82	8.47	9.73	23.32

[a] A = acetonitrile, B = ethyl acetate, C = ether, D = 2-propanol containing a few drops of HCl. [b] Iodimetric in dilute HCl. [c] Prepared by the hydrolysis of 4-methyl-2-thiazoline-2-thiol; see Experimental Section. Lit.[30] m.p. 94°. [d] R. G. Lawton, H. Saltzman and W. R. Martin (Report on Anti-Radiation Drug Program, Division of Nuclear Medicine, Walter Reed Army Institute of Research, April 1959) used another synthesis but did not describe the product. [e] R. G. Lawton, *et al.*,[d] used another synthesis and reported m.p. 186–188°. [f] In early work we also used the procedure of S. Gabriel and E. Leupold [*Ber.*, **31**, 2832 (1898)] who hydrolyzed 5-methyl-2-thiazoline-2-thiol and reported m.p. 87–88°; the optical resolution of this substance was reported by J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **29**, 1657 (1964); for commercial synthesis and isolation see U. S. Patent 3,165,451 (1965). [g] S. D. Turk, R. P. Louthan, R. L. Cobb, and C. R. Bresson [*J. Org. Chem.*, **27**, 2852 (1962)] used another synthesis and reported m.p. 154–157°. [h] Prepared but not described in ref. 17. [i] Free base, m.p. 82–86°; E. D. Bergmann and A. Kalnszyner [*Rec. trav. chim.*, **78**, 289 (1959)] used another synthesis and reported m.p. 78–80° for the free base.

TABLE IV
PROTECTIVE ACTIVITIES OF THIAZOLINES AND THIAZOLINETHIOLS



No.	R_1	R_2	R_3	Radiation protection: Rodent drug dose, mg./kg.	Rodent test	Bacteria test (*E. coli*)
10	H	H	CH_3	151–350	Good	...
11	C_2H_5	H	H	51–150	Fair	None
12	H	H	C_2H_5	51–150	None	...
13	CH_3	H	CH_3	151–350	Fair	...
14	CH_3	CH_3	H	151–350	Slight	...
15	n-C_3H_7	H	H	51–150	Good	...
16	i-C_3H_7	H	H	51–150	Good	...
17	n-C_6H_{13}	H	H	>750	Slight	...
18	H	H	n-C_6H_{13}	>750	Slight	...
19	4-Methyl-2-thiazoline-2-thiol			50	None	Fair
20	5-Methyl-2-thiazoline-2-thiol			151–350	None	Good

TABLE V
PROTECTIVE ACTIVITIES OF AMINOTHIOLS

No.	R_1	R_2	Radiation protection: Rodent drug dose, mg./kg.	Rodent test	Bacteria test (*E. coli*)
2-Amino-1-alkanethiol Hydrochloride $R_1R_2CCH_2SH$					
				$NH_2 \cdot HCl$	
21	CH_3	H	151–350	Slight[a]	Fair
22	C_2H_5	H	51–150	Fair[a]	Fair
23	CH_3	CH_3	51–150	None	Good
24	n-C_3H_7	H	51–150	Good	Good
25	i-C_3H_7	H	51–150	Good	Good
26	n-C_6H_{13}	H	50	None	None
1-Amino-2-alkanethiol Hydrochloride $R_1CH(SH)CH_2NH_2 \cdot HCl$					
27	CH_3	...	151–350	Good[a]	Good
28	C_2H_5	...	151–350	None[a]	Good
29	n-C_6H_{13}	...	50	Slight[a]	None
3-Amino-2-alkanethiol Hydrochloride R_2CHCHR_1SH					
				$NH_2 \cdot HCl$	
30	CH_3	CH_3	151–350	Fair	None

[a] In the text this radioprotective activity is compared with that observed in other laboratories.

thiol precursors and the ease of conversion to aminothiols *in vitro*. In a recent study[19] the failure of 22 thiazolines to protect rodents was reported and similar failures with thiazolines have been reported previously.[3a] We have observed protective activity with eight of nine thiazolines studied (**10**–**18**). Of particular interest was the observation that the three thiazolines offering good protection (**10**, **15**, and **16**) are the precursors of the three aminothiols (**27**, **24**, and **25**) found to provide the best protection in the present work. This suggests that there may be a mechanism by which thiazoline is hydrolyzed in the mouse.

The two thiazolinethiols (**19** and **20**) provided no protection in rodents, a result noted earlier[3a] with 2-thiazoline-2-thiol. These results are not surprising, for these compounds are not only very difficult to hydrolyze but also have very little thiol function, being primarily thiones.[20,21]

(19) V. S. Shashkov, V. M. Fedoseev, T. E. Burkovskaya, P. P. Saksonov, V. V. Antipov, and Y. N. Evdokimov, *Radiobiologiya*, **6**, 927 (1964).

(20) L. B. Clapp and J. W. Watjen, *J. Am. Chem. Soc.*, **75**, 1470 (1953).

(21) M. G. Ettlinger, *ibid.*, **72**, 4699 (1950).

Experimental Section[22]

1-Amino-2-propanol was Eastman material and 2-amino-2-methyl-1-propanol was a gift from the Commercial Solvents Corp. 1-Amino-2-butanol,[23] 3-amino-2-butanol,[24] 2-amino-3-methyl-1-butanol,[25a] 2-amino-1-octanol,[25b,26] and 1-amino-2-octanol[27] were prepared either by catalytic reduction of the appropriate nitro alcohol or by reduction of α-amino acids by the activated $NaBH_4$ reagent of Brown and Subba Rao.[28] Analogous reductions of amino acids by $LiAlH_4$ have been described previously.[25]

2-Amino-1-pentanol.—A solution of 83.6 g. (0.625 mole) of anhydrous $AlCl_3$ in 270 ml. of dry diglyme was added to a solution of 71.3 g. (1.88 moles) of $NaBH_4$ in 550 ml. of dry diglyme. The mixture was stirred at 70° while 117.1 g. (1.0 mole) of solid 2-aminopentanoic acid (Mann Research Laboratories) was added in portions during 2 hr. The reaction mixture was then heated on a steam bath for 3.5 hr. The pasty mass was poured onto crushed ice and acidified with concentrated HCl to dissolve all solids. The solution was evaporated to dryness under reduced pressure, the residual solid was dissolved in water, and the solution was treated with excess 30% NaOH solution and finally saturated with potassium carbonate to cause the separation of 2-amino-1-pentanol as a supernatant layer; additional product was obtained by extracting the aqueous phase with *n*-butyl alcohol. The organic layers were combined, dried ($MgSO_4$), and distilled to yield 82.4 g. (80%), b.p. 96–98° (19 mm.), set point about 23°, $n^{21}D$ 1.4508.

Anal. Calcd. for $C_5H_{13}NO$: C, 58.21; H, 12.70; N, 13.58. Found: C, 58.25; H, 12.63; N, 13.50.

2-Amino-1-pentanol is very soluble in water. It forms a **hydrochloride salt,** m.p. 90.5–91.5° (acetone–acetonitrile).

A dibenzoyl derivative, **2-benzamido-1-pentyl benzoate**, was prepared by the Schotten–Baumann procedure and obtained as colorless needles, m.p. 136.5–137.5° (ethanol).

Anal. Calcd. for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.44; H, 6.84; N, 4.43.

This latter compound was refluxed for 5 min. in 2 *N* NaOH in 50% aqueous alcohol. The solution was allowed to cool and deposited the monobenzoyl derivative, **N-[(1-hydroxymethyl)-butyl]benzamide,** m.p. 96–97°, needles from CCl_4.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27. Found: C, 69.88; H, 8.64.

N-(Hydroxyalkyl)acetamides (**Table** I) are high-boiling viscous liquids which usually crystallize on standing. They are insoluble in ether or benzene but dissolve readily in water and alcohols. Solid substances were recrystallized from ethyl acetate in our work but we made no attempt to achieve a high degree of purity.

Method A.—Acetylation of the amino alcohol by ethyl acetate involved a modification of the procedure of D'Alelio and Reid.[7] The amino alcohol was refluxed with 2 equiv. of ethyl acetate for 75–90 hr. and the mixture was then fractionally distilled, except in the case of **5** and **8** where the amide solidified in the pot and was then recrystallized from ethyl acetate.

Method B.—Dehydration of the acetate salt of the amino alcohol, as described by Wenker,[5] was used to prepare N-[(1-hydroxymethyl)propyl]acetamide (**1**). Equimolar amounts of 2-amino-1-butanol and glacial acetic acid were stirred and gradually heated while water escaped through a simple still head. When the reaction mixture reached 205°, the product was collected by fractional distillation at reduced pressure. When the temperature was allowed to exceed 205°, increased amounts of 4-ethyl-2-methyl-2-oxazoline (see below) were obtained as a forerun in the distillation. When this procedure was used for the acetylation of 2-amino-2-methyl-1-propanol, the oxazoline was the only product isolated (see below).

Method C.—Acetylation of the amino alcohol by acetic anhydride was used to prepare N-(1,1-dimethyl-2-hydroxyethyl)-acetamide (**2**). 2-Amino-2-methyl-1-propanol was stirred at 80–90° while an equimolecular quantity of acetic anhydride was added during 15 min. The reaction mixture was distilled at reduced pressure. The material which did not distil below 118° (0.6 mm.) solidified on standing in the pot and was then recrystallized. During the distillation a fraction b.p. 92–97° (1 mm.) deposited a 12% yield of the **acetate salt of 2-amino-2-methyl-1-propanol**, m.p. 109°; the same substance was prepared independently by the neutralization of the amino alcohol with acetic acid in acetonitrile solution.

Anal. Calcd. for $C_6H_{15}NO_3$: C, 48.30; H, 10.13; N, 9.39. Found: C, 48.32; H, 10.15; N, 9.25.

When this method of acetylation was applied to 2-amino-3-methyl-1-butanol both N- and O-acetylation occurred to give **2-acetamido-3-methyl-1-butyl acetate,** b.p. 111–114° (0.2 mm.), $n^{25}D$ 1.4528.

Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 58.35; H, 9.21; N, 6.95.

4-Ethyl-2-methyl-2-oxazoline.[29]—As mentioned above this substance was formed when mixtures of 2-amino-1-butanol and acetic acid were heated above 205°. In a separate experiment N-[(1-hydroxymethyl)propyl]acetamide (65 g., 0.5 mole, prepared above) was heated to 230°. Crude oxazoline, b.p. 100–160°, escaped when the temperature exceeded 205°. The crude product was dried and redistilled to give 25 g. (44%), b.p. 73–76° (155 mm.), $n^{25}D$ 1.4315.

Anal. Calcd. for $C_6H_{11}NO$: C, 63.68; H, 9.80; N, 12.38. Found: C, 63.85; H, 10.00; N, 12.36.

2,4,4-Trimethyl-2-oxazoline.[29]—Equimolar amounts of 2-amino-2-methyl-1-propanol and glacial acetic acid were heated gradually to 165–170° while volatile material, b.p. 107–130°, amounting to 80% of the reactants charged, escaped during 4 hr. The crude distillate was redistilled and an azeotrope of oxazoline and water was collected at 93–105°. This was dried over solid KOH and redistilled to give the pure oxazoline, b.p. 112–113°, $n^{25}D$ 1.4195.

Anal. Calcd. for $C_6H_{11}NO$: C, 63.68; H, 9.80; N, 12.38. Found: C, 63.31; H, 9.72; N, 12.25.

2-Methyl-2-thiazolines (**Table** II).—The general procedure developed by us is illustrated by the synthesis of 2-methyl-4-isopropyl-2-thiazoline (**16**). The reaction was carried out in a 500-ml. flask equipped with a stirrer, thermometer, simple still head, and condenser. To 60 ml. of mineral oil was added 28 g. (0.193 mole) of N-2-(1-hydroxy-3-methylbutyl)acetamide, followed by 25.7 g. (0.116 mole, 50% excess) of P_2S_5. The mixture was stirred until well mixed and then was heated gradually to 130° during **1** hr. A vigorous evolution of gas occurred at 90–105° and the reaction mixture was held at 110° until this subsided. The reaction mixture was cooled to 80° and 40 ml. of water was added to prevent the mixture from solidifying. About 100 ml. of 20% aqueous NaOH was added to bring the reaction mixture to pH 10 or higher, and the mixture was then steam distilled until collection of the thiazoline became quite slow. The crude thiazoline was extracted from the distillate by ether, the extract was dried (KOH), and the product was recovered by distillation under the conditions stated in Table II.

When the mineral oil was omitted and the flask was heated by a free flame, the exothermic reaction that occurred was usually too difficult to control.

In large-scale runs the reaction was controlled by withholding much of the P_2S_5 until the reaction was proceeding smoothly at 100–110° and then adding the balance in portions.[6] In these large runs a 20% excess of the pentasulfide was adequate. It was convenient to separate the bulk of the mineral oil layer by decantation and pour the black tarry product layer directly into cold 20% aqueous NaOH, in which it dissolved, then to carry out the steam distillation.

The higher molecular weight thiazolines **17** and **18** steam distilled slowly and so were conveniently removed from the alkaline solution by extraction with ether. When mineral oil was present after the reaction mixture was made strongly basic, some thiazoline escaped into it; this was easily removed from the mineral oil solution by extraction with cold dilute HCl.

The thiazolines are all unpleasant smelling, colorless, water-insoluble, mobile liquids, whose boiling points and refractive

(22) All melting points and boiling points are corrected; analyses were performed by S. M. Nagy (Massachusetts Institute of Technology) or by C. K. Fitz (Needham, Mass.).

(23) R. Ghirardelli and H. J. Lucas, *J. Am. Chem. Soc.*, **79**, 734 (1957).

(24) C. A. Vander Werf, R. Y. Heisler, and W. E. McEwen, *ibid.*, **76**, 1231 (1954).

(25) (a) O. Vogl and M. Pöbm, *Monatsh.*, **83**, 541 (1952); (b) *ibid.*, **84**, 1097 (1953).

(26) R. J. Dummel and E. A. Garlock, *J. Org. Chem.*, **27**, 1049 (1962).

(27) W. C. Gakenheimer and W. H. Hartung, *ibid.*, **9**, 85 (1944).

(28) H. C. Brown and B. C. Subba Rao, *J. Am. Chem. Soc.*, **78**, 2582 (1956).

(29) Mentioned but not described by P. F. Tryon, U. S. Patent 2,372,409 (1945).

indices are considerably higher than those of the analogous oxazolines. Their neutralization equivalents can be determined by dissolving in excess 0.1 *N* HCl and back-titrating with 0.1 *N* NaOH to a potentiometric end point.

4-Methyl-2-thiazoline-2-thiol (19).—The route used was described by Böse.[30] A solution of 22.8 g. (0.4 mole) of 2-methylaziridine (Chemirad Corp.) in ethyl alcohol was added slowly to a solution of 48 g. (0.62 mole) of CS_2 in 120 ml. of ethyl alcohol. The addition was made at such a rate that the exothermic reaction caused the CS_2 to reflux moderately; in runs involving ten times the amounts specified above this addition was completed in 1.5 hr. The reaction mixture was refluxed for an additional hour, excess CS_2 was distilled, and the residual alcohol solution was stored at 0° to yield 31 g. (58%) of crude product. Two recrystallizations from CH_2Cl_2–CCl_4 (1:4) gave 23 g. (44%), m.p. 98.5–99°, lit.[29] m.p. 99–99.5°. This compound and the analogous 5-methyl compound (**20**) are almost colorless, water-insoluble, weakly basic solids which do not reduce iodine. The 2-thione structure is preferred[29,31] on the basis of infrared spectra.

Aminoalkanethiols (Table III).—With the exception of **21**, which was prepared by the hydrolysis of a thiazoline thiol (see below), all compounds described in Table III were prepared by acid hydrolysis of the appropriate 2-thiazoline. In a typical procedure a solution of 15.8 g. (0.122 mole) of 5-ethyl-2-methyl-2-thiazoline in 100 ml. of 2.5 *N* HCl was refluxed under nitrogen for 17 hr., then evaporated to dryness under vacuum. The residue was recrystallized from acetonitrile, washed on the filter with ether, and dried *in vacuo* to give 16.2 g. (94%) of 1-amino-2-butanethiol hydrochloride, m.p. 159–160°.

2-Amino-1-propanethiol hydrochloride (**21**) was prepared by the hydrolysis of 4-methyl-2-thiazoline-2-thiol (**19**).[30] In a typical run a solution of 250 g. (1.88 moles) of the thiazolinethiol in 2500 ml. of 6 *N* HCl was refluxed for 140 hr. Iodimetric assay of aliquots had shown that at this time the hydrolysis to aminothiol was 95% complete. The analogous hydrolysis of 2-thiazoline-2-thiol[31] had required 336 hr. The product was isolated as described in the preceding paragraph.

During the recrystallization of 95% pure 2-amino-1-propanethiol hydrochloride obtained by the hydrolysis of 700 g. of 4-methyl-2-thiazoline-2-thiol, we isolated 10 g. of a substance, m.p. 208–211°, insoluble in boiling isopropyl alcohol, which proved to be **bis(2-amino-1-propyl) dithiolcarbonate dihydrochloride,** $(CH_3CHNH_2CH_2S)_2CO\cdot 2HCl$.

Anal. Calcd. for $C_7H_{18}Cl_2N_2OS_2$: C, 29.89; H, 6.45; Cl, 25.21; N, 9.96; S, 22.80; neut. equiv., 140. Found: C, 30.40; H, 6.68; Cl, 24.86; N, 9.89; S, 23.21; neut. equiv., 136.

As analogous intermediate had been isolated during the incomplete hydrolysis of 2-thiazoline-2-thiol.[31] When the substance was refluxed with 6 *N* HCl for 150 hr. it was converted to 2-amino-1-propanethiol hydrochloride.

All of the aminoalkanethiol hydrochlorides prepared by us were colorless crystalline solids. Some were quite hygroscopic, but all were reasonably resistant to oxidation by air and required no extraordinary precautions in handling and storage.

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(30) M. Böse, *Ber.*, **53** 2000 (1920).

(31) R. J. Gaul and W. J. Fremuth, *J. Org. Chem.*, **25**, 869 (1960).

Sulfamylurea Hypoglycemic Agents. I. Synthesis and Screening

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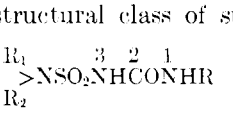
A number of sulfamylureas of general structure $R_1R_2NSO_2NHCONHR$ have been prepared and screened for hypoglycemic activity in the rat. The more promising variations in the R_1R_2N portion of the molecule were those derived from heterocyclic amines, especially piperidines and morpholines. In these series, activity was maximal when R was cyclohexyl, cycloheptyl, or bicycloalkyl. Several analogs, notably certain 4,4-disubstituted piperidine derivatives, were comparable in hypoglycemic potency to chlorpropamide. Structure–activity relationships are discussed, and a brief discussion is given of the use in synthetic planning of certain physical and chemical parameters that appear to be important determinants of drug dynamics in this class of compounds.

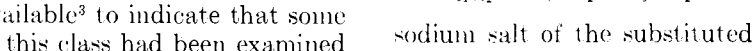
Previous publications from these laboratories[1] have indicated our interest in seeking more effective oral hypoglycemic agents; this interest has now led us to investigate the structural class of sulfamylureas (I).



I

Although clearly related to the well-studied sulfonylureas, very little was known about this class of compounds when we began our work; very few such compounds had been described chemically,[2] and only a general statement was available[3] to indicate that some members (I, R_1 = H) of this class had been examined and found to be inactive as hypoglycemic agents. While our work was in progress, however, some additional sulfamylureas were disclosed and stated to have hypoglycemic activity.[4] In this paper the synthesis and hypoglycemic screening of the more important groups of compounds that were investigated are reported, and structure–activity relationships are discussed. In paper II[5] a study of the drug dynamics of the more promising analogs is described.

Synthetic Methods.—The synthetic approach consisted essentially of the following. An amine was condensed with sulfamide to give a N-substituted or N,N-disubstituted sulfamide (Tables I and II)[6]; the



sodium salt of the substituted sulfamide was then allowed to react with the appropriate 3-substituted 1,1-diphenylurea (Table III) to produce a sulfamylurea and diphenylamine. This latter reaction was developed

(1) (a) W. M. McLamore, G. M. Fanelli, S. Y. P'an, and G. D. Laubach, *Ann. N. Y. Acad. Sci.*, **74**, 443 (1959); (b) G. F. Holland, D. A. Jaeger, R. L. Wagner, G. D. Laubach, W. M. McLamore, and S. Y. P'an, *J. Med. Pharm. Chem.*, **3**, 99 (1961); (c) G. F. Holland, *J. Org. Chem.*, **26**, 1662 (1961).

(2) S. Petersen, *Chem. Ber.*, **83**, 551 (1950).

(3) H. Ruschig, G. Korger, W. Aumüller, H. Wagner, and R. Weyer, *Arzneimittel-Forsch.*, **7A**, 453 (1958).

(4) Ciba, S. A., Belgian Patent 594,041 (1960); Ciba Ltd., British Patent 896,455; *Chem. Abstr.*, **57**, 1250i (1962).

(5) E. H. Wiseman, J. N. Pereira, K. F. Finger, and E. R. Pinson, Jr., *J. Med. Chem.*, **8**, 777 (1965).

(6) K. Hamann, German Patent 869,065 (1953); *Chem. Abstr.*, **48**, 1112*i* (1954).