with 2 g of Zn dust. After 0.5 hr, an additional 7 g of Zn dust was added and the heating continued for 4 hr more. The mixture was filtered and the filtrate was diluted with H_2O. The product was extracted with C_6H_6 and chromatographed on Al_2O_3. The material eluted with hexane was essentially pure estra-1,3,5(10),16-tetraene (**8**) although it could not be induced to crystallize. A solution of 0.50 g of this material in 100 ml of Et_2O was treated with 0.50 g of OsO_4. After 18 hr at room temperature the mixture was diluted with 100 ml of EtOH and a solution of 1.0 g of $Na_2S_2O_3$ in 20 ml of H_2O. The mixture was heated at reflux for 1 hr and then filtered, using hot EtOH to wash the insoluble material. The filtrate was concentrated to dryness, diluted with H_2O, and extracted with C_6H_6. The resulting material (0.45 g), chromatographed on silica, was largely eluted with EtOAc. Crystallization of the eluates from Me_2CO–hexane gave 0.18 g of diol **9b**, mp 113–115°, ir 2.94 μ, $[\alpha]D$ +46°. *Anal.* ($C_{18}H_{24}O_2$) C, H.

16α-Iodoestra-1,3,5(10)-trien-17-one (2b).—Enol acetate **1b** (1.48 g) in 50 ml of AcOH containing 0.90 g of $Hg(OAc)_2$ was added to a stirred solution of 1.30 g of I_2 in 200 ml of AcOH. After 10 min the solution was poured into excess aqueous KI and extracted with C_6H_6. The extract was washed with aqueous $Na_2S_2O_3$, H_2O, and aqueous $KHCO_3$. The product obtained on concentration of the solvent was crystallized from CH_2Cl_2–MeOH to yield 0.70 g of pure iodo ketone **2b**, mp 190–193°, ir 5.76 μ, $[\alpha]D$ +85°. *Anal.* ($C_{18}H_{21}IO$) C, H.

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Biologically Oriented Organic Sulfur Chemistry. III. Formation of Mercaptals, Mercaptoles, an Orthothioformate, and Thiazolidines for the Latentiation of Thiols[1a-c]

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Mercaptals, mercaptoles, an orthothioformate, and thiazolidines are described. They were formed by the reaction of 2-aminoethanethiol hydrochloride with carbonyl compounds, several of which are reactive enough to form isolable hydrates. Most of the products had little or no activity as antiradiation drugs. D-5,5-dimethylthiazolidine-4-carboxylic acid did not reduce either the titer of rheumatoid factor *in vitro* or the skin-tensile strength of rats *in vivo*. The structural types mentioned thus seem less promising than α-hydroxy sulfides described previously for latentiating biologically active thiols, perhaps because of their greater stability *in vivo*.

The previous paper in this series[1a] reported that hemimercaptals, which can be derived from aldehydes sufficiently reactive to form isolable hydrates, afford a promising means of latentiating a typical radioprotective thiol (2-aminoethanethiol hydrochloride, **1**). The term "latentiation" simply is a convenient one for referring to the conversion of a biologically active compound to some derivative which will produce either the parent or a suitably active moiety of it *in vivo*.[1a] In order to explore the generality of this type of latentiation, it was important to learn whether formation of a mercaptal, a mercaptole, an orthothioformate, or a thiazolidine might be exploited similarly. Thiazolidines have been tested as antiradiation drugs; although many were inactive, some were active.[2] To the best of our knowledge, no reports have been published on antiradiation activity of the other types of structures.

Aldehydes or ketones usually react with thiols in the presence of acid catalyst to give mercaptals or mercaptoles, respectively (eq 1),[3] and with aminothiols in the absence of excess acid to give thiazolidines (eq 2).[3c,d,4] This paper describes derivatives of each kind.

$$2\ Cl^- H_3N^+(CH_2)_2SH + RR'CO \overset{H^+}{\rightleftharpoons} RR'C[S(CH_2)_2NH_3^+\ Cl^-]_2 + H_2O \quad (1)$$

1

2, R = R′ = H
3, R = H; R′ = CO_2H
4, R = H; R′ = $Cl^- H_3N^+(CH_2)_2S$
5, R = R′ = CH_3
6, R = H; R′ = C_6H_5
7, R = R′ = CO_2Et

$$1 + RR'CO \xrightarrow{-H_2O} \text{(thiazolidine)} \quad (2)$$

8, R = H; R′ = CCl_3
9, free base of **8**
10, R = R′ = CH
11, R = H; R′ = C_6H_5CO
12, RR′ = (oxindole)

Carbonyl compounds which are sufficiently reactive to form isolable hydrates, on the other hand, may give

(1) (a) Paper II: L. Field, B. J. Sweetman, and M. Bellas, *J. Med. Chem.*, **12**, 624 (1969). (b) Paper I: L. Field and B. J. Sweetman, *J. Org. Chem.*, **34**, 1792 (1969). (c) This investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2030, and by Public Health Service Research Grant No. 1 RO1 AM-11685 from the National Institute of Arthritis and Metabolic Diseases. (d) To whom correspondence should be addressed.

(2) (a) J. F. Thomson, "Radiation Protection in Mammals," Reinhold Publishing Corp., New York, N. Y., 1962, p 84; (b) F. Yu. Rachinskiĭ, A. S. Mozzhukhin, N. M. Slavachevskaya, and L. I. Tank, *Usp. Khim.*, **28**, 1488 (1959); *Chem. Abstr.*, **54**, 13424 (1960); (c) A. Kaluszyner, P. Czerniak, and E. D. Bergmann, *Radiation Res.*, **14**, 23 (1961); (d) V. G. Yakovlev in "Chemical Protection of the Body against Ionizing Radiation," V. S. Balabukha, Ed., Pergamon Press, New York, N. Y., 1963, p 11; (e) W. Shapiro, M. F. Tansy, and S. Elkin, *J. Pharm. Sci.*, **57**, 1725 (1968).

(3) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Chemical Publishing Co., Inc., New York, N. Y., 1960: (a) Vol. III, p 320; (b) Vol. II, p 205; (c) S. V. Tsukerman, *Ukr. Khim. Zh.*, **19**, 169 (1953); *Chem. Abstr.*, **49**, 5439 (1955); (d) S. V. Tsukerman, *ibid.*, **19**, 523 (1953); *Chem. Abstr.*, **49**, 8255 (1955).

(4) A. H. Cook and I. Heilbron in "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, p 921.

α-hydroxy sulfides with thiols[1a,b]; this paper reports conditions under which these can give mercaptals, mercaptoles, or thiazolidines.

The mercaptals **2**, **3**, and **6** were synthesized from trioxane, glyoxylic acid hydrate, and benzaldehyde, respectively. The mercaptoles **5** and **7** and the orthothioester **4** were synthesized from acetone, diethyl oxomalonate, and formic acid, respectively. With all six carbonyl compounds, the aminothiol salt **1** was used in the presence of excess HCl, with water as a solvent or with no solvent.

The mercaptole **7** from diethyl oxomalonate was best prepared, even though in low yield, by an alternative method (DMF as solvent, absence of HCl). Analytical data, as well as ir, nmr, and mass spectra, appear to be consistent with the assignment of structure **7** to this product. The isolation of the presumed mercaptole **7** instead of the hemimercaptole seems surprising, however, since diethyl oxomalonate reacted with 1-propanethiol to give the hemimercaptole, which could not be significantly converted to a mercaptole even with attempted acid catalysis.[1b]

The thiazolidine hydrochloride 8 was obtained in 93% yield by the reaction of chloral with **1** in DMF at *ca.* 65° It was also formed in other similar reactions by dehydration of the corresponding hemimercaptal,[1a] although the ease of this cyclization may be less than in those which lead to the thiazolidines **10**–**12**. A reduced propensity to cyclization of the chloral hemimercaptal seems likely to be a consequence of destabilization of an essential intermediary carbonium ion, owing to strong electron withdrawal by the trichloromethyl group (*cf.* ref 1b). Support for this view is that no thiazolidine formation at all could be observed under any conditions tried, using either a trifluoromethyl hemimercaptal (obtained from **1** and trifluoroacetaldehyde derivatives) or a bistrifluoromethyl hemimercaptole (from **1** and hexafluoroacetone).[1a] Addition of $NaHCO_3$ to 8 resulted in the crystalline free base **9**.

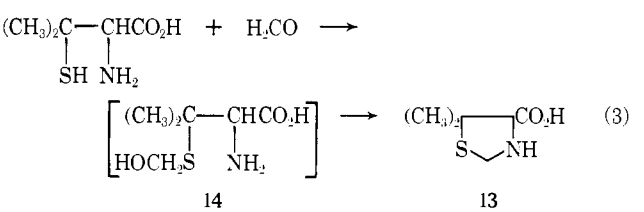
Acetone reacted with **1** to give the thiazolidine salt **10**, apparently in a purer state than previously reported.[3d] In an analogous reaction at room temperature, isatin reacted with the thiol **1** giving the spirothiazolidine salt **12**, reaction at the 3 position being presumed. Apparently, the 3-keto group of isatin is at least comparable in reactivity to that of acetone in this reaction. Schubert reported formation of an adduct (which we presume to be the 3-hemimercaptole) from the reaction of isatin with mercaptoacetanilide,[5] and Schönberg, *et al.*,[6] reported that hemimercaptoles are formed at the 3 position in reactions of isatin with ethanethiol and phenylmethanethiol. Formation of the thiazolidine **12** with the aminothiol **1**, instead of hemimercaptole, seems explained best by a very facile cyclization of a hemimercaptole because of the presence of the amino group; formation of water would drive the reaction toward completion, of course.

The antiradiation activities of the mercaptals (**2**, **3**, and **6**) the orthothioformate (**4**), the mercaptole (**7**), and the thiazolidines (**8**–**12**) are listed in Table I. These were determined as described previously,[1a] through the kindness of Drs. D. P. Jacobus, T. R. Sweeney, and E. A. Steck of the Walter Reed Army Institute of Research, Washington, D.C.

The results can be oriented in a context of earlier work, since one compound (**10**) has been tested previously. The data of Table I might result (barely) in a rating[1a] of "good" for the thiazolidine **10** (at the highest dose used, administered 30 min prior to irradiation), a result which confirms an earlier report of "+" activity.[2a] With the possible exception of the presumed oxomalonate mercaptole (**7**), the other compounds in Table I showed slight to no activity, in contrast to hemimercaptals reported previously.[1a]

We have outlined our interest in development of latentiating groups for penicillamine and related thiols, which might be useful in connection with rheumatoid arthritis (or other medicinal uses of penicillamine).[1a] Hence, attention also was given to penicillamine in the context of the types of potential latentiating groups discussed in the present paper.

The reaction of penicillamine hydrochloride with formaldehyde leading to the thiazolidine **13** has been reported.[4] The present paper describes the synthesis of **13** from D-penicillamine directly (eq 3). An interesting fact, which seems to have gone unnoticed before,[4] was that very shortly after the dissolution of the penicillamine in formalin, a product (**14**, mp **111**–**112**°) precipitated which did not have a melting point consistent with **13** (mp 195–195.5°). This intermediate, formulated as **14**, was stable for at least **1** week, but when it was dissolved in H_2O, addition of EtOH precipitated only the thiazolidine **13**. Formulation of **14** as the S-hydroxymethyl compound (eq 3) is suggested by earlier work. Levi[7a] and Milligan and Swan[7b] have described the formation of S-hydroxymethyl derivatives of alkanethiols. Ratner and Clarke suggested the formation of S-hydroxymethyl derivatives of cysteine and N-acetylcysteine,[7c] and Sweetman has suggested that S-hydroxymethylcysteinyl residues are formed in the reaction of formaldehyde with reduced keratin.[7d] The thiazolidine **13** was inactive in protecting against radiation (Table I).



Dr. I. A. Jaffe, of the New York Medical College and Flower and Fifth Avenue Hospitals (New York, N. Y.), using means referred to previously,[1a] kindly tested the thiazolidine **13** for its effect in reducing the titer of the rheumatoid factor *in vitro* and for its effect *in vivo* on the skin-tensile strength and soluble-collagen fraction of rats. Although penicillamine is active in both respects,[8] **13** was inactive in both. This result seems significant in the dual implication that formation of the thiazolidine **13** may lock penicillamine into too stable a form for activity *in vivo* (at least over the 14-day feeding period used), and that the NH_2 and SH func-

(5) M. P. Schubert, *J. Biol. Chem.*, **114**, 341 (1936).

(6) A. Schönberg, O. Schütz, G. Arend, and J. Peter, *Ber.*, **60**, 2344 (1927).

(7) (a) T. G. Levi, *Gazz. Chim. Ital.*, **62**, 775 (1932); *Chem. Abstr.*, **27**, 268 (1933); (b) B. Milligan and J. M. Swan, *J. Chem. Soc.*, 6008 (1963); (c) S. Ratner and H. T. Clarke, *J. Amer. Chem. Soc.*, **59**, 200 (1937); (d) B. J. Sweetman, *Textile Res. J.*, **36**, 1096 (1966).

(8) *Cf.* ref 1a.

TABLE I

ANTIRADIATION ACTIVITIES OF COMPOUNDS TESTED[a]

Compd	K[b]	MLD$_{50}$, mg/kg[c]	Drug dose, mg/kg	Vehicle[d]	pH of soln admnd	Survival, 30 days, %
2[e,m]		700	500	H_2O	6.2	0
3[h,i,k]		1800	1000	CMCTw	5.5[j]	17
			500	CMCTw	5.5[j]	17
4[h,i,l]		320	180	CMCTw	5.5	17
6[h,i,k]	5×10^6	240	56	CMCTw	7.0	17
7[f,g,i]	$>10^3$	360	150	CMCTw	3.3	73
8[h,i,k]	5×10^2	560	200 or 100	CMCTw	5.5[j]	0
9[h,i,k]	5×10^7	740	560	CMCTw	7.0	33
10[g,i]	0	300	150	NaCl	4.6	47[j]
			150	NaCl	1.5	0[m]
11[f,g,i]	$>10^3$	500	125	H_2O	2.6	0
12[f,g,i]		480	250	H_2O	1.9	13
			125	H_2O	1.9	7
13[f,g,i]		>800	600 or 300	CMCTw	4.3	0

[a] Several active compounds led to 0% survival when the dose was cut in half: **4**, **6**, **7**, **9** (0% at doses of 280 or 140), and **10**. For details of testing not given in other footnotes, see ref 1a. [b] Approximate equilibrium constant for the reaction of the carbonyl component with 1-propanethiol, giving an α-hydroxy sulfide, as determined by ir or uv absorption of the carbonyl compound.[1b] [c] Approximate LD$_{50}$ for the compound in mice; *cf.* ref 1a. [d] CMCTw = suspension or solution in 0.3% carboxymethylcellulose plus 0.1% Tween 80; NaCl = suspension or solution in physiological saline solution. [e] Twenty mice tested, with twenty controls. [f] Drug administered 30 min prior to irradiation. [g] ^{60}Co γ irradiation. [h] Six mice tested, with six controls. [i] Adjusted pH value. [j] Drug administered 15 min prior to irradiation. [k] X-Ray irradiation. [l] Fifteen mice tested, with ten controls. [m] Drug administered 60–90 min prior to irradiation (900 R, γ).

tions of penicillamine probably must not be covered simultaneously if it is to be active in the respects mentioned.

The general conclusion drawn from the compounds studied, as a whole, is that a mercaptal, a mercaptole, an orthothioformate, or a thiazolidine, in contrast to a hemimercaptal, ordinarily is likely to lock an aminothiol too firmly into a stable structure to afford a promising means of latentiating biologically active aminothiols.

Experimental Section[9]

Bis(2-aminoethylthio)methane Dihydrochloride (2).—s-Trioxane (3.0 g, 33.3 mmoles) and **1** (23.0 g, 202 mmoles) were heated together at *ca.* 100°, while dry HCl was passed into the mixture for *ca.* 30 min. The mixture then was triturated with EtOH, and a colorless solid was separated. Recrystallization (H_2O–EtOH) gave **2** as prisms (10.0 g, 42%), mp 184–186°. Further recrystallization gave **2** with a constant melting point of 186°. *Anal.* ($C_5H_{16}Cl_2N_2S_2$) C, H, N, S.

Bis(2-aminoethylthio)acetic Acid Dihydrochloride (3).—Glyoxylic acid hydrate (4.60 g, 50 mmoles) and **1** (11.36 g, 100 mmoles) were stirred together at *ca.* 145–150° for *ca.* 3 min under HCl. The residue was then triturated with EtOH, after which colorless **3** was separated by filtration. Recrystallization from H_2O–AcOH gave **3** as needles (8.3 g, 59%), mp 180–182° dec. Further recrystallization gave **3** having a constant melting point of 184° dec. *Anal.* ($C_6H_{16}Cl_2N_2O_2S_2$) C, H, N, S.

Tris(2-aminoethylthio)methane Trihydrochloride (4).—HCO_2H (1.5 ml, 80–90%, *ca.* 31 mmoles) and **1** (10.1 g, 89 mmoles) were heated together at 100° under HCl for *ca.* 45 min. The residue was recrystallized from H_2O–EtOH and gave **4** as colorless needles (4.7 g, 45%), mp 202–203° dec. *Anal.* ($C_7H_{22}Cl_3N_3S_3$) C, H, N, S.

2,2-Bis(2-aminoethylthio)propane Dihydrochloride (5).—Thiol **1** (2.84 g, 25 mmoles) was dissolved in 12 *N* HCl (2.0 ml) and a mixture of $CHCl_3$ (2.0 ml) and Me_2CO (3.90 g, 67.2 mmoles) was added. After 24 hr at 0°, filtration separated colorless hygroscopic needles of **5** (3.0 g, 90%), mp 175–177°. Three recrystallizations of this product from MeOH–Et_2O, gave a sample having mp 178.5–179°, which was dried to constant weight under reduced pressure at 100° (lit.[3a] mp 195–196°). *Anal.* ($C_7H_{20}Cl_2N_2S_2$) C, H, N.

α,α-Bis(2-aminoethylthio)toluene Dihydrochloride (6).—Thiol **1** (17.04 g, 150 mmoles) was dissolved in 3 *N* HCl (12 ml), benzaldehyde (15.93 g, 150 mmoles) was added, and the mixture was stirred for *ca.* 45 min; the precipitate which resulted was separated and recrystallized from hot MeOH by adding Et_2O to give colorless **6** (7.2 g, 30%), mp 199–201°. *Anal.* ($C_{11}H_{20}Cl_2N_2S_2$) C, H, N, S.

Diethyl Bis(2-aminoethylthio)malonate Dihydrochloride (7).—Thiol **1** (14.2 g, 125 mmoles) was dissolved in DMF (25 ml), and to the stirred solution diethyl oxomalonate (21.8 g, 125 mmoles) was added dropwise. The mixture initially became warm, and thereafter it was stirred at *ca.* 25° for 17 hr and then concentrated under reduced pressure at 90°. Addition of EtOAc to the residue gave colorless material (12.8 g, 54%), mp 136–139° dec. This was recrystallized four times from MeOH or EtOH, by adding ether, to give **7** (0.7 g, 3%) having a constant melting point of 154.5–155°; ir (KBr), 3420 (b), 3200–2300 (complex), 1735 cm^{-1} (ester C=O); nmr (D_2O), τ 8.63 (t, 6, J = 7 Hz), 7.25–6.09 (m, 9?), 5.52 (q, 4, J = 7 Hz), 5.23 (s, 6); mass spectrum (**7** was introduced as the dihydrochloride), *m/e* (relative intensity, assignment) 310 [0.7, $(EtO_2C)_2C(SCH_2CH_2NH_2)_2$], 293 (0.1), 267 (0.2), 234 [14, $(EtO_2C)_2CSCH_2CH_2NH_2$], 202 (19), 188 (52), 162 (20), 160 [100, $(EtO_2C)_2CH_2$], 132 [44, $(HO_2C)(EtO_2C)CH_2$], 114 (32), 102 (15), 88 (30), 82 (22), 74 (10), 61 (30). *Anal.* Calcd for $C_{11}H_{24}Cl_2N_2O_4S_2$: C, 34.46; H, 6.31; N, 7.31; S, 16.73; mol wt (0.33$C_{11}H_{24}Cl_2N_2O_4S_2$ for three particles), 128. Found (separate preparations): C, 34.96, 34.07; H, 6.73, 6.31; N, 7.50, 7.60; S, 17.21, 17.30; mol wt (MeOH), 159.

Attempts to carry out the above reaction were unpromising using *i*-PrOH or H_2O as solvents (in general procedures as described in ref 1a), or using $CHCl_3$–HCl. When **1** (1.13 g, 10 mmoles) and diethyl oxomalonate (2.0 g, 11.5 mmoles) were heated together for *ca.* 20 sec, with shaking, over an open flame and EtOH (2 ml), followed by EtOAc to incipient turbidity, was added, crude **7** (0.57 g, 30%) resulted; recrystallization (H_2O–Me_2CO, dioxane–EtOH) gave **7** with mp 152–153° dec.

2-(Trichloromethyl)thiazolidine Hydrochloride (8).—Chloral (11.04 g, 75 mmoles) was added to the thiol **1** (2.84 g, 25 mmoles) in DMF (5 ml) and the mixture was stirred at *ca.* 65° for 1 hr, when addition of Et_2O to incipient turbidity and chilling gave colorless **8** (5.65 g, 93%), mp 182° dec, unchanged by three recrystallizations from MeOH by addition of Et_2O. *Anal.* ($C_4H_7Cl_4NS$) C, H.

For conversion of the hydrochloride **8** to its free base (**9**), **8** was treated with $NaHCO_3$ and the mixture was extracted by CCl_4; the residue after evaporation crystallized from hexane to

(9) Mass spectra were kindly determined by C. T. Wetter using an LKB Model 9000 instrument at 70-eV electron energy with a direct inlet system. Where analyses are indicated only by symbols of the elements, results of analyses for those elements were within ±0.4% of the theoretical values (Galbraith Microanalytical Laboratories, Knoxville, Tenn.). All other details were as described in footnote 22 of ref 1a.

give colorless needles of **9**, mp 73–74°, nmr consistent. *Anal.* ($C_4H_6Cl_3NS$) C, H, N, S.

2,2-Dimethylthiazolidine Hydrochloride (10).—Thiol 1 (16.84 g, 148 mmoles) was dissolved in MeOH (25 ml) and excess Me_2CO (300 ml), and the mixture was heated under reflux for 8.5 hr. Evaporation of solvent gave a residue (20.3 g), mp 162–166°, which was crystallized three times from MeOH by addition of Et_2O to give **10** as colorless needles (8.6 g, 38%), having constant mp 170–171.5° (lit.[3d] 164–165°). *Anal.* ($C_5H_{12}ClNS$) C, H, S.

2-Benzoylthiazolidine Hydrochloride (11).—Thiol 1 (5.50 g, 48.5 mmoles) and phenylglyoxal hydrate (7.60 g, 50 mmoles) were heated together at *ca.* 85° for *ca.* 5 min; the mixture then was dissolved in MeOH (30 ml) and Et_2O (120 ml) was added to incipient turbidity. Cooling gave colorless **11** (4.4 g, 39%), mp 151–153° dec. Recrystallization three times from MeOH by addition of Et_2O gave **11** with a melting point of 151.5–152.5° dec, nmr consistent. *Anal.* ($C_{10}H_{12}ClNOS$) C, H, N, S.

Spiro[2,3-dihydroindole-3,2′-thiazolidine]-2-one Hydrochloride (12).—Finely powdered isatin (10.95 g, 75 mmoles) was slowly added to thiol 1 (8.5 g, 75 mmoles) in *i*-PrOH (80 ml) to give a red mixture which, after being stirred for 24 hr at *ca.* 25°, became pale brown. Filtration separated pale brown **12** (15.4 g, 85%), mp 200–203° dec. A sample was recrystallized three times from MeOH by addition of Et_2O and had a constant melting point of 203–204° dec; ir (KBr), 2370, 1735 (amide C=O) cm^{-1}. *Anal.* ($C_{10}H_{11}ClN_2OS$) C, H, N, S.

D-5,5-Dimethylthiazolidine-4-carboxylic Acid (13).—D-Penicillamine (35 g, 235 mmoles)[10] was dissolved in 45% aqueous HCHO (200 ml, 3.0 moles). Within *ca.* 5 min, solid started to separate. The mixture was stirred for *ca.* 20 hr. Filtration then removed the colorless intermediate **14** (29 g, 69%), mp 111–112°, after a wash with dioxane then Et_2O and drying over silica gel; ir (KBr), 3420, 2990, 2750, 1635, 1475, 1400, 1380, 1360, 1340, 1135 (s), 1105, 1010, 830, and 705 cm^{-1}. Conversion to the thiazolidine **13**, generally in *ca.* 75% yields, was achieved by dissolving the intermediate **14** in H_2O (10 ml/g of **14**) and adding EtOH (4 vol) to incipient turbidity, then cooling. The thiazolidine **13** had mp 195–195.5° dec,[11] ir and nmr consistent.

(10) Kindly supplied by Dr. Elmer Alpert, Merck Sharp and Dohme Research Laboratories, West Point, Pa.

(11) Reference 4, p 958, reports mp 196–197° dec. The melting point reported there for the L form was 193–194°; a later patent abstract indicates this preparation was from L-penicillamine rather than the hydrochloride, but the identity of the procedures suggests an error in the abstract [J. H. Hunter and B. E. Leach, U. S. Patent 2,480,079 (1949); *Chem. Abstr.*, **44**, 2569 (1950)].

Quaternary Thiazolylpyridinium Salts. Oral Hypoglycemic Agents

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A series of quaternary 4-(thiazolyl)pyridinium salts has been synthesized. Blood glucose concentration of normal mice was decreased following oral administration of these compounds.

A number of azolylpyridinium salts, including members of the pyrazolyl-,[1] isoxazolyl-,[2–4] 1,2,4-oxadiazolyl-,[5] and oxazolylpyridinium[6] salt families, have been found to induce hypoglycemia in laboratory animals. As a further development of this series, we have investigated the replacement of the five-membered ring with still other heterocycles. We describe herein the synthesis of some novel 4-(thiazolyl)pyridinium salts. The choice of substituents was influenced by structure–activity correlations developed in the pyrazolylpyridinium salt series.[1]

The 4-(thiazolyl)pyridinium salts **10–29** were prepared from the thiazolylpyridine bases **4–9** by quaternization with the appropriate alkyl halide. The base **4** was prepared as described by Wallenfels and Gellrich.[7] The bases **5**, **7**, and **8** were prepared by modification of this procedure. Thus, reaction of thioisonicotinamide with 3-bromo-2-butanone gave **5**, reaction of thioacetamide with **1**[8] gave **7**, and reaction of cyclopropanethiocarboxamide with **1** gave **8**. The bases **6** and **9** were prepared by fusion of the amido ketones **2**[5] and **3**,[9] respectively, with P_2S_5 using a modification of the procedure of Gabriel[10] as described by Ott, *et al.*,[11] for the preparation of arylthiazoles.

In the nmr spectra of the 4-(thiazolyl)pyridine bases **4–9**, the pyridyl protons appear as two doublets at δ 7.73–7.76 and 8.60–9.01. Upon quaternization, these signals shift to new values of δ 8.33–8.53 and 8.83–9.18. These changes, a downfield displacement of both doublets, as well as a smaller separation between chemical shifts, were found to be diagnostic of pyridine quaternization in our earlier study of pyrazolylpyridinium salts.[1,12] Spin-decoupling experiments demonstrate that the quaternary methyl of **11** is coupled with the α-pyridyl protons, further confirming that alkylation has occurred on the pyridyl nitrogen.

Hypoglycemic Activity.[13]—Saline solutions or 0.5% aqueous carboxymethylcellulose suspensions of test compounds were administered by gavage to male CF-1 mice (Carworth Farms, 25–30 g) at doses of 0.5–1.5 mmol/kg; controls received an equal volume of vehicle.

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