hr. It was acidified to pH 1 with 60 ml of 6 *N* HCl and the precipitated KCl (18.3 g) was removed by filtration. MeOH was distilled from the filtrate at reduced pressure, the remaining aqueous mixture was extracted with three 50-ml portions of CH_2Cl_2, and the combined extract was dried (Na_2SO_4). Distillation of solvent from the extract left 3.3 g of an amber oil which crystallized to an oily tan solid. One recrystallization from aqueous EtOH gave 1.0 g of white solid, mp 109–113°. Recrystallization of the product once again from aqueous EtOH and three times from 95% EtOH gave the analytical sample: $[\alpha]^{25}D$ −31° (c 3.99, $CHCl_3$); λ_{max}^{EtOH} 259 mμ (ε 403), $\lambda_{max}^{CHCl_3}$ 261 mμ (ε 506); ir, 1300 (broad), 1160, and 1140 cm^{-1} (sulfonamide).

b. From the Bis-Bunte Salt IIf.—The solution of the bis-Bunte salt IIf, prepared as described above, was added dropwise over a period of 35 min to a stirred solution of 159 g (2.41 moles) of 85% KOH in 3 l. of distilled H_2O, N_2 being bubbled through during this time. The solution was allowed to stand for 19 hr at room temperature and then stirred and heated at 85° under N_2 for 4 hr. After standing for 6 hr at room temperature, the solution was extracted with five 100-ml portions of CH_2Cl_2 and the combined extract was dried (Na_2SO_4). Distillation of solvent from the extract left 3 g of an orange solid, mp 99–110°. The aqueous phase was saturated with NaCl and extracted continuously with Et_2O for 5 days. After the extract had been dried over Na_2SO_4, distillation of solvent left 11.2 g of a white solid, mp 107–115°, giving a combined yield of 14.2 g. An ir spectrum of the crude solid obtained by Et_2O extraction was identical with that of authentic Ic prepared from IIe.

(*S*)-[4-Mercapto-1-(mercaptomethyl)butyl]methanesulfonamide (IIi). a.—Na (1.0 g, 0.0435 g-atom) was added in small pieces to a solution of 3.0 g (0.0132 mole) of Ic in 200 ml of liquid NH_3 until a permanent deep blue color was attained. The solution was stirred for 45 min, the blue color remaining during this time, and then solvent was removed at reduced pressure. EtOH (50 ml) was added to the gray solid residue and the mixture was stirred thoroughly. It was cooled in an ice bath and acidified to pH 1 with 125 ml of 6 *N* HCl. A solution of 8.4 g (0.026 mole) of $Hg(OAc)_2$ in 100 ml of distilled H_2O was added to the faintly yellow solution and the precipitated white mercury mercaptide was removed by filtration, washed (EtOH), and dried. A suspension of the mercaptide in 50 ml of absolute EtOH was treated with H_2S for 1 hr. The HgS precipitate was removed by filtration through Celite and washed with EtOH. Evaporation of the colorless filtrate to dryness in a vacuum desiccator left 2.2 g (73.4%) of a colorless oil: ir, 2560 (thiol), 1290, and 1150 cm^{-1} (sulfonamide).

b.—Concentrated HCl (28 ml) was added dropwise over a period of 1 hr to a stirred mixture of 5.1 g (0.0224 mole) of Ic, 30.4 g (0.465 g-atom) of Zn powder, and 84 ml of glacial HOAc. The mixture was heated under reflux with stirring for 12.5 hr. At the end of this time 84 ml of concentrated HCl was added over a period of 1.5 hr, and the mixture was heated under reflux for 1 hr until nearly all the Zn had dissolved. The solution was cooled and diluted with 200 ml of H_2O. A solution of 10.6 g of $Hg(OAc)_2$ in 100 ml of distilled H_2O was added and the precipitated mercury mercaptide was coagulated by warming on a steam bath, removed by filtration, and washed with EtOH. The mercaptide was dissolved in 100 ml of hot concentrated HCl and reprecipitated by dilution with 200 ml of H_2O. It was reprecipitated a second time from concentrated HCl, removed by filtration, washed with EtOH, and dried. A suspension of the solid in 50 ml of absolute EtOH was treated with H_2S for 0.5 hr. The precipitated HgS was removed by filtration through Celite, resuspended in 20 ml of absolute EtOH, and again treated with H_2S for 10 min. After filtration, the combined filtrate was evaporated to dryness in a vacuum desiccator and 3.5 g (68%) of a colorless oil was obtained. An ir spectrum of the oil was identical with that obtained from the Na–NH_3 reduction of Ic.

Biologically Oriented Organic Sulfur Chemistry. II. Formation of Hemimercaptals or Hemimercaptoles as a Means of Latentiating Thiols[1]

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Reactions of thiols with carbonyl compounds that form isolable hydrates led to hemimercaptals and hemimercaptoles. Hemimercaptals (**3** and **7**) of 2-aminoethanethiol hydrochloride (**1**), containing the groups Cl_3C-CH(OH), or $F_3CCH(OH)$, respectively, were active as antiradiation drugs, suggesting that these two groups (and similar ones) deserve a broader trial as latentiating groups for medicinally promising thiols. The hemimercaptal **3** reduced the titer of the rheumatoid factor *in vitro* but not the skin-tensile strength of rats *in vivo*.

The biochemical significance of the SH group and of moieties related to it is so well known as to require no comment. Medicinally, thiols have been of interest in a number of situations, among which the following may be mentioned illustratively: rheumatoid arthritis[2a–c,e] and rheumatoid lung disease,[2d] leprosy,[3a] Wilson's disease,[3b,c] heavy-metal antagonism,[3b] macroglobulinemia,[4] inflammation,[5] cystinuria[6a,b] and cystinosis,[6c] scleroderma,[7] idiopathic pulmonary fibrosis,[8] as a mucolytic agent,[9] and for protection against ionizing radiation.[10] Two of these applications particularly interest us: rheumatoid arthritis and protection against ionizing radiation.

In respect to the first, penicillamine (β,β-dimethylcysteine) produces a fall in titer of the rheumatoid factor, as well as a favorable effect on other parameters

(1) (a) Paper I: L. Field and B. J. Sweetman, *J. Org. Chem.*, **34**, 1799 (1969). (b) 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 Grant No. 1 RO1 AM11685 from the National Institute of Arthritis and Metabolic Diseases.

(2) (a) I. A. Jaffe and P. Merryman, *Ann. Rheumatic Diseases*, **27**, 14 (1968); (b) B. Lake and G. Andrews, *Am. J. Med.*, **44**, 105 (1968); (c) I. A. Jaffe, *Arthritis Rheumat.*, **8**, 1064 (1965); (d) A. Lorber, *Nature*, **210**, 1235 (1966); (e) I. A. Jaffe, *J. Lab. Clin. Med.*, **60**, 409 (1962).

(3) (a) L. S. Goodman and A. Gilman, Ed., "The Pharmacological Basis of Therapeutics," 3rd ed, The Macmillan Co., New York, N. Y., 1965, p 1312; (b) *ibid.*, p 940; (c) I. Sternlieb and I. H. Scheinberg, *J. Am. Med. Assoc.*, **189**, 748 (1964).

(4) (a) C. L. Edwards and N. Gengozian, *Ann. Internal Med.*, **62**, 576 (1965); (b) J. J. Costanzi, C. A. Coltman, Jr., D. A. Clark, J. I. Tennenbaum, and D. Criscuolo, *Am. J. Med.*, **39**, 163 (1965).

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(7) E. D. Harris, Jr., and A. Sjoerdsma, *Lancet*, 996 (1966).

(8) *Cf.* R. I. Henkin, H. R. Keiser, I. A. Jaffe, I. Sternlieb, and I. H. Scheinberg, *ibid.*, 1268 (1967).

(9) (a) W. T. Moreland in "Annual Reports in Medicinal Chemistry, 1966," C. K. Cain, Ed., Academic Press, Inc., New York, N. Y., 1967, p 83; (b) H. W. Reas, *J. Pediat.*, **62**, 31 (1963).

(10) (a) J. F. Thomson, "Radiation Protection in Mammals," Reinhold Publishing Corp., New York, N. Y., 1962, p 53; (b) V. G. Yakovlev in "Chemical Protection of the Body against Ionizing Radiation," V. S. Balabukha, Ed., The Macmillan Co., New York, N. Y., 1963, p 11.

of rheumatoid disease activity.[2c,d] Unfortunately, its use often results in side effects such that at this time "the drug should not be the subject of widespread clinical trial."[2c] An attractive approach thus seems to lie in the synthesis of relatives of penicillamine, which hopefully would be more effective and less toxic than penicillamine itself.

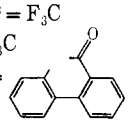
Our work in the second area of interest, antiradiation drugs, suggested one means of attacking the first area. For several years we have sought to form derivatives which would modify radioprotective thiols in such a way as to reduce their toxicity and improve their activity.[11] Unsymmetrical disulfides[11-15] and thiolsulfonates[16] have proved to be promising combinations of protective thiols with the groups RS and RSO_2, respectively. Study of modifying groups thus seems worthwhile, not only in relation to antiradiation drugs but also in relation to use of penicillamine and its congeners with rheumatoid arthritis (and hopefully to other uses of pharmacologically active thiols as well). Essentially this approach is one of "latentiation," which has been defined as "the chemical modification of a biologically active compound to form a new compound, which upon *in vivo* enzymatic attack will liberate the parent compound."[17] Our view has been rather broader than this, our feeling being that an active moiety of a latentiated drug might react directly at a biologically important site without liberation of the parent compound as such, but the terms "latentiation" and "latentiating group" are convenient expressions of the idea and will be used henceforth. Latentiation of a drug by its conversion in this way may provide means of favorably influencing absorption, transport, distribution, localization, metabolism, and toxicity,[17] as well as stability.

This paper describes the use of aldehydes and ketones for latentiating aminothiols by reaction with the thiol function. The aldehydes and ketones used were chosen on the basis of high reactivity, as suggested largely by a capacity for forming isolable hydrates. 2-Aminoethanethiol hydrochloride (**1**) was selected as a model thiol because of its ready availability and its well-known properties as an antiradiation drug.[10a]

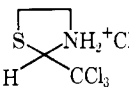
We reasoned that carbonyl groups which could form hydrates might form stable hemimercaptals or hemimercaptoles (α-hydroxy sulfides), which then could regenerate the thiol *in vivo*, as suggested by eq 1. Further selection was made from among possible carbonyl compounds in such a way as to afford a range of equilibrium constants (K) for eq 1; K values were determined previously with this selection in mind.[1a] Yakovlev tested two presumed α-hydroxy sulfides involving a cysteine moiety as antiradiation drugs but was seeking a correlation with a tendency to form stable complexes with metals; both were completely inactive.[10b]

General procedures for synthesis were sought first,

$$R^1SH + R^2COR^3 \rightleftarrows R^1SC(OH)R^2R^3 \quad (1)$$

1, $R^1 = Cl^-H_3N^+(CH_2)_2$
2, $R^1 = H_3CC(O)NH(CH_2)_2$
3, $R^1 = Cl^-H_3N^+(CH_2)_2$; $R^2 = Cl_3C$; $R^3 = H$
4, $R^1 = CH_3C(O)NH(CH_2)_2$; $R^2 = Cl_3C$; $R^3 = H$
5, $R^1 = Cl^-H_3N^+(CH_2)_2$; $R^2 = Br_3C$; $R^3 = H$
6, $R^1 = CH_3C(O)NH(CH_2)_2$; $R^2 = Br_3C$; $R^3 = H$
7, $R^1 = Cl^-H_3N^+(CH_2)_2$; $R^2 = F_3C$; $R^3 = H$
8, $R^1 = Cl^-H_3N^+(CH_2)_2$; $R^2 = R^3 = F_3C$
9, $R^1 = H_2N(CH_2)_2$; $R^2 = R^3 = F_3C$
10, $R^1 = Cl^-H_3N^+(CH_2)_2$; $R^2R^3 =$ 
11, $R^1 = Cl^-H_3N^+(CH_2)_2$; $R^2R^3 =$ 

with the formation of **3** from chloral and the thiol **1** as a model (Table I). Procedures developed proved somewhat less general than hoped, with carbonyl compounds markedly different from chloral, but should be useful for many latentiating groups more like chloral with many thiols. The best procedures were no. 7, 1, and 4. Number 7 is the one of choice with chloral, and perhaps with other carbonyl compounds sufficiently soluble in *i*-PrOH; however, the isopropyl hemiacetal may sometimes be so stable that *i*-PrOH is inappropriate. Number 1 was developed for water-soluble hydrates, and no. 4 for compounds soluble only in DMF (the DMF experiments other than no. 4 gave **3** that was harder to purify). If the temperature rose to 30–50° in the presence of excess chloral in DMF (*cf.* no. 3, 4) some cyclization of **3** occurred to give **12** (eq 2); indeed, no. 5 affords a useful preparation of **12**.[18] Some reactions

$$\underset{\mathbf{3}}{Cl_3CCH(OH)S(CH_2)_2NH_3^+Cl^-} + Cl_3CCHO \longrightarrow \underset{\mathbf{12}}{\text{  }} + Cl_3CCH(OH)_2 \quad (2)$$

(*e.g.*, no. 2, 9, 10) with equimolar amounts in DMF or *i*-PrOH gave products which were hard to purify.

Methods were desired for preparing stable crystalline derivatives of α-hydroxy sulfides involving the OH group, since some of the products to be sought seemed likely to be liquid, unstable, or difficult to crystallize. Such derivatives also might be of medicinal interest, since the *in vivo* action might be usefully different. However, despite the success of others with rather similar reactions,[19] efforts with a number of reagents failed to provide useful derivatives of **3** or **4** (see Experimental Section). Whatever the cause, it seems certain that the presence of the powerful electron-withdrawing trichloromethyl group leads to a carbinol group of a highly unusual type (*cf.* ref 19).

Reaction of **3** with $NaHCO_3$ gave the unstable free base of **3**, which apparently underwent cyclization during a few days to form the free base of the thiazolidine **12**. Another interesting reaction of **3** was with

(11) See the series entitled Organic Disulfides and Related Substances. Paper XXVII: L. Field and R. B. Barbee, *J. Org. Chem.*, **34**, 1792 (1969).
(12) (a) L. Field and J. D. Buckman, *ibid.*, **32**, 3467 (1967); (b) L. Field, H. K. Kim, and M. Bellas, *J. Med. Chem.*, **10**, 1166 (1967); (c) L. Field and J. D. Buckman, *J. Org. Chem.*, **33**, 3865 (1968).
(13) M. Bellas, D. L. Tuleen, and L. Field, *ibid.*, **32**, 2591 (1967).
(14) L. Field and H. K. Kim, *J. Med. Chem.*, **9**, 397 (1966).
(15) R. R. Crenshaw and L. Field, *J. Org. Chem.*, **30**, 175 (1965).
(16) L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).
(17) N. J. Harper, *ibid.*, **1**, 467 (1959); see also N. J. Harper, *Progr. Drug. Res.*, **4**, 221 (1962).
(18) Details on **12** will be reported in paper III of this series.
(19) H. Böhme, H.-D. Lohmeyer, and J. Wickop, *Ann. Chem.*, **587**, 51 (1954).

Table I
Reaction of Chloral with 1

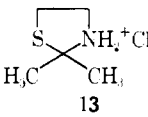
Procedure no.	1, mmoles	Chloral, mmoles	Solvent	Temp, °C	Time, hr	Hemimercaptal (3) Yield, %	Hemimercaptal (3) Mp, °C	Yield of 12, %
1	150	150[a]	H_2O	0	48	65	123–124	*b*
2	25	25	DMF	*Ca.* 25	4	61	114–122	*b*
3	25	75	DMF	*c*	1.5	0		56
4	25	75	DMF	*d*	19	44	123.5–125.5	25
5	25	75	DMF	65	1	0		93
6	25	25	DMF	65	1	78	120–122	*b*
7	25	75	*i*-PrOH	*e*	18	72	123–124	10
8	25	25	*i*-PrOH	*e*	18	56	124–124.5	*b*
9	25	25	*i*-PrOH	*e*	46	69	105–121	*b*
10	25	25	*i*-PrOH	*e*	3.5	43	70–80	*b*

[a] Used as chloral hydrate. [b] Not isolated. [c] At 40–50° briefly, then at 25°. [d] At 30° briefly, then below 0°. [e] Temperature at 0° during addition of chloral, then later at *ca.* 25°.

acetone, which at room temperature gave 2,2-dimethylthiazolidine hydrochloride **13** (eq 3). This reaction probably involved displacement of the usual equilibria,

$$\mathbf{3} + (CH_3)_2CO \rightleftarrows [(CH_3)_2C(OH)S(CH_2)_2NH_2^+Cl^-] \xrightarrow{-H_2O}$$

14



(3)

13

involving the intermediary hemimercaptole **14** (*cf.* eq 1), because of cyclization to the relatively more stable thiazolidine **13** and because of loss of water.

Reaction of chloral with 2-acetamidoethanethiol (**2**) was achieved in the neat state, since both reactants were liquids. It led to the presumed hemimercaptal **4**, which could not be distilled; crystalline derivatives of **4** could not be obtained. The ir spectrum of **4** met expectations.

Reaction of bromal with **1** using methods of Table I led to good yields of colorless hemimercaptal **5** (consistent ir spectrum; *cf.* ref 1a), but the **5** was impure (mp ~90–110°) and decomposed on attempted recrystallization or storage. Similarly, reaction with the acetamidothiol **2** led apparently (ir spectrum) to the hemimercaptal **6**, which unlike the chloral adduct **4** was unstable and soon gave HBr and colored tars; no crystalline derivative could be obtained. Neither **5** nor **6** seemed stable enough to warrant further interest in them as practical drugs. Decomposition of the hemimercaptals of bromal evidently involves an oxidation, since in several instances the principal product isolated during attempted recrystallizations was a salt of cystamine.

Fluoral hydrate, used in a method similar to that of no. 1 of Table I (because fluoral itself is a gas) gave only very low yields of the hemimercaptal (**7**), perhaps because of the high stability of fluoral hydrate. However, an efficient synthesis of **7** was achieved by reaction of fluoral ethyl hemiacetal with **1** in a strongly acidic medium (which might be effective with the hydrate as well).

Preparation of a hemimercaptole (**8**) was achieved in high yields by reaction of the thiol **1** with hexafluoroacetone trihydrate (neat), or by suspending **1** in condensed hexafluoroacetone at −78°. The first procedure is easier and more convenient, but the second has the advantage that excess ketone volatilizes readily and leads easily to a pure product. The hemimercaptole **8**, although quite stable as a solid, decomposes much more readily in solution than the analogous hemimercaptole of fluoral (**7**) and must be recrystallized cautiously. For example, when **8** was suspended in boiling toluene it dissociated completely to the ketone and thiol **1** in less than 16 hr. Reaction of **8** with aqueous $NaHCO_3$ gave the free base **9**. Spectra of **9** did not permit distinction between the structural alternatives of an amino compound and the corresponding zwitterion, but the possibility of a zwitterionic structure for **9** is intriguing.

Hexachloroacetone did not react with **1** (it also does not react with H_2S[20] or with 1-propanethiol[1a]). With DMF as a solvent, **1** was oxidized to cystamine dihydrochloride.

Previous work indicated that **1** might form hemimercaptoles with quinones, as do various other thiols.[21] When **1** was used with 9,10-phenanthrenequinone, the hemimercaptole **10** crystallized from the mixture. This direct separation of pure **10** was fortunate, because **10** could not be recrystallized. It rapidly dissociated to the quinone and **1** either in solution or (apparently) when heated; the analogous hemimercaptole with ethanethiol decomposes partially even at room temperature.[21]

The well-known stability of ninhydrin (indan-1,2,3-trione hydrate) suggested that the parent triketone might give a stable hemimercaptole with **1**. Preparation of this hemimercaptole **11** was achieved essentially by procedure 2 of Table I; **11** seemed rather more stable than **10** and could be purified by careful recrystallization.

A guide to the relative ease of biological dissociation of the α-hydroxy sulfides described may be afforded by the relative equilibrium constants (K); where known,[1a] these are included in Table II. A more qualitative but still pertinent estimate was sought by testing with nitroprusside at *ca.* pH 8.5; however, no useful distinction was possible since tests were positive with all of the compounds (**1**–**10** and **13**; **11** and **12** gave dubious results).

Antiradiation activities are summarized in Table II for all of the α-hydroxy sulfides which seemed worth testing. Compounds were administered intraperitoneally to mice using as vehicles either a suspension or solution of the compound in 0.3% carboxymethylcellu-

(20) J. F. Harris, Jr., *J. Org. Chem.*, **30**, 2190 (1965).
(21) A. Schönberg, O. Schütz, G. Arend, and J. Peter, *Ber.*, **60**, 2344 (1927).

TABLE II

ANTIRADIATION ACTIVITIES OF α-HYDROXY SULFIDES[a]

Cmpd	K[b]	ALD_{50}, mg/kg[c]	Drug dose, mg/kg	Vehicle[d]	pH of soln admind	Survival, 30 days, %
			Hemimercaptals			
3[e-g]	5×10^2	740	100	CMCTw	5.5	50
			200	CMCTw	5.5	33
			300	CMCTw	5.5	33
			600	CMCTw	5.5	83
4[h-i]	5×10^2	800	250	CMCTw	2.0	0
			500	CMCTw	2.0	27
7[e-g]		430	160	CMCTw	5.5	33
7[h,f,i]			160	CMCTw	6.1	67
7[e-g]			200	CMCTw	5.5	17
7[e-g]			320	CMCTw	5.5	83
7[h,f,i]			320	CMCTw	6.1	67
7[e-g]			400	CMCTw	5.5	83
			Hemimercaptoles			
8[h-i]	10^3–10^5	250	75	NaCl	3.4	0
			150	NaCl	3.4	13
10[h-i]		240	37.5	CMCTw	6.0	0
			75	CMCTw	6.0	0
11[h,f,i]	$>10^3$	93	8.7	NaCl	4.8	0
			17.4	NaCl	4.8	0
			20	NaCl	4.8	0
			40	NaCl	4.8	0

[a] For details, see the text or other footnotes. [b] Approximate equilibrium constant for the reaction of 1-propanethiol and the carbonyl component, giving an α-hydroxy sulfide, as determined by ir or uv absorption of the carbonyl compound.[1a] [c] Approximate LD_{50} for the compound in mice; see text. [d] See text. [e] Six mice tested, with six controls. [f] Drug administered 15 min prior to irradiation. [g] X-Ray irradiation. [h] Fifteen mice tested, with ten controls. [i] Drug administered 30 min prior to irradiation. [j] ^{60}Co γ irradiation.

lose plus 0.1% Tween 80 (CMCTw), or a suspension or solution in physiological saline solution (NaCl). The mice were tested for 30-day survival against lethal radiation (midline dose) of 950 R (100 R/min) from a ^{60}Co source or 825 R (35 R/min) from an X-ray source (G.E. 300-kV Maxitron, filtered through Cu, 2 mm, and Al, 0.25 mm); these are considered of comparable biological effectiveness. The ALD_{50} is the approximate dose of drug lethal to 50% of nonirradiated mice; mortality was determined 10 days after graded doses of compound had been administered to each of ten animals at each dose level. 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%. We are indebted both for the results and for helpful discussions to Drs. D. P. Jacobus, T. R. Sweeney, and E. A. Steck of the Walter Reed Army Institute of Research, Washington, D. C.; in comparison, they have found that **1** as its free base has an ALD_{50} of 250 mg/kg and affords 100% survival at dose levels of 150 mg/kg.

The most promising compounds seem to be the hemimercaptals of chloral and of fluoral, **3** and **7**, respectively. These also are the compounds of lowest toxicity, thus enabling testing at higher levels than the more toxic hemimercaptoles **8**, **10**, or **11** (which had slight or no activity). The acetyl derivative of **3** (*i.e.*, **4**) seems significantly less active than **3**. It may be significant that the derivatives which seemed more stable during handling (**7**, **3**) also appear to be the most promising. The latentiating groups $Cl_3CCH(OH)$– and $F_3CCH(OH)$– deserve trial with a wider variety of biologically active thiols; obviously such thiols should include radioprotective ones which are more effective than the prototypes **1** and **2**. Furthermore, the two covering groups themselves should serve as prototypes for the design of better ones [$R^1(CR^2R^3)_nCCl_2CH(OH)$–, etc.].

Other Biological Activities.—Treatment of patients having rheumatoid arthritis with penicillamine causes a fall in titer of the rheumatoid factor (RF) and causes some clinical improvement in most cases but, as mentioned, use of penicillamine often is associated with problems of toxicity.[2c] A number of thiols other than penicillamine also cause a fall in the titer of RF *in vitro*.[2e] In collaboration with I. A. Jaffe of the New York Medical College and Flower and Fifth Avenue Hospitals (New York, N. Y.), we have commenced a study of compounds related to penicillamine to examine their effects on RF *in vitro* and their effects on the skin-tensile strength of rats.

The hemimercaptal **3** of chloral with the aminothiol **1** proved to be somewhat more effective than penicillamine in its effect on RF *in vitro* (+++ on a scale where penicillamine was rated ++).[2e] However, **3** had no effect on the skin-tensile strength of rats or on the soluble collagen fraction of the skin, where penicillamine is known to have an effect.[22] We are indebted to Dr. Jaffe for these evaluations and for much helpful discussion. Reported methods were used by Dr. Jaffe in evaluating the effect on RF[2c,e] and on skin-tensile strength and soluble collagen.[22]

Efforts to use some of the aldehydes and ketones mentioned to form α-hydroxy sulfides with penicillamine itself have been rather unpromising so far. For example, intractable products in low yields, gums, etc., have resulted from use of penicillamine or its hydrochloride with chloral, ninhydrin, or hexafluoroacetone trihydrate. Limited solubility of penicillamine

(22) (a) M. E. Nimni and L. A. Bavetta, *Science*, **150**, 905 (1965); (b) M. E. Nimni, *Biochim. Biophys. Acta*, **111**, 576 (1965).

itself in organic solvents is a considerable complication, suggesting that better results may be obtained by using penicillamine derivatives in these procedures.

Experimental Section[23]

1-(2-Aminoethylthio)-2,2,2-trichloroethanol Hydrochloride (3) and Its Amide (4). A. Procedure 7 (Table I).—2-Aminoethanethiol hydrochloride (1, 2.84 g) in *i*-PrOH (50 ml) was cooled with stirring in ice–salt, and (anhydrous) chloral (11.04 g) was added below 0°. After the mixture had been stirred (18 hr *ca.* 25°), solvent was evaporated and $CHCl_3$ (25 ml) was added to give **3** (4.7 g, 72%), mp 123–124° dec. *Anal.* ($C_4H_9Cl_4NOS$) C, H, Cl, N, S. Thiazolidine **12** was obtained by concentrating the mother liquor and adding ether; mp 173–178° dec.[18]

B. Procedure 1.—Chloral hydrate (24.75 g) was added to the thiol **1** (17.04 g) in H_2O (12.0 ml) containing HCl (12 *N*, 0.30 ml). Storage for 48 hr at 0° gave **3** (25.5 g, 65%), mp 123–124° dec, unchanged by cautious crystallizations from cold MeOH by adding $CHCl_3$.

C. Procedure 4.—Chloral (11.04 g) was slowly added to a stirred solution of **1** (2.84 g) in DMF (5 ml) at *ca.* 0° (the temperature rose to *ca.* 30°). The mixture was kept for 19 hr at 0° and then was added to $CHCl_3$ (400 ml). Vigorous stirring gave **3** (2.9 g, 44%), mp 123.5–125.5° dec. Concentration provided the thiazolidine **12** (1.5 g, 25%), mp 182–183.5° dec.[18]

D. Other Aspects.—Attempts failed to effect reaction of the OH group of **3** with various reagents (phenyl isocyanate, *p*-toluenesulfonyl isocyanate, 3,5-dinitrobenzoyl chloride, *S*-benzylthiouronium chloride, $SOCl_2$ in C_6H_6 followed by 2,4,6-tribromoaniline, and *p*-bromophenacyl bromide).

Attempts also failed to obtain a crystalline derivative of the hemimercaptal **4**. Although **4** could not be crystallized or distilled, its identity seems assured from the preparation: thiol **2** (2.41 g) was stirred vigorously at 5° and chloral (2.95 g) was added dropwise; the viscous product, 1-(2-acetamidoethylthio)-2,2,2-trichloroethanol (**4**), was stable on storage. Furthermore, the ir spectrum (thin film) was consistent with structure **4** (no bands attributable to the CO of chloral; bands at 3330, 1640, 1550, 1445, 1385, 1300, 1090, 820, 730, and 620 cm^{-1}).

In the reaction of **3** with base, aqueous 5% $NaHCO_3$ (19.33 ml, 0.966 g, 11.5 mmoles) was added dropwise over *ca.* 10 min to **3** (3.00 g, 11.5 mmoles) in H_2O (10 ml) at 0° with rapid stirring. After *ca.* 20 min, the solution was extracted with three 50-ml portions of $CHCl_3$. The extract was dried (Na_2SO_4) and evaporated to give an oily residue (2.0 g). After 2 weeks at 0°, the residue had become insoluble in $CHCl_3$. Addition of HCl gave orange, semicrystalline **12** (2.9 g, 104% on the basis of pure **12**), identified[18] by its ir spectrum.

In studying the reaction of **3** with Me_2CO, a suspension of finely powdered **3** (12.0 g, 46 mmoles) in excess Me_2CO (250 ml) was stirred at *ca.* 25° for 42 hr. The insoluble residue (4.1 g), mp 163–165°, was recrystallized from MeOH by adding Et_2O to give the thiazolidine **13** (2.9 g, 41%), mp 169–172°, identified by comparison with the melting point of authentic **13** (mp 170–171.5°, lit.[24] mp 164–165°) and by ir and nmr spectra. The Me_2CO filtrates gave a residue (10.7 g), which appeared to be crude **3**.

1-(2-Aminoethylthio)-2,2,2-trifluoroethanol Hydrochloride (7).—The thiol **1** (8.52 g, 75 mmoles) and fluoral ethyl hemiacetal (10.80 g, 75 mmoles) were stirred together in 12 *N* HCl (6 ml) for *ca.* 5 min at *ca.* 25°, when crystallization commenced. After *ca.* 20 min, colorless **7** (11.0 g, 69%), mp 121.5–122.5°, was removed by filtration. *Anal.* ($C_4H_9ClF_3NOS$) C, H, N, S.

Attempts to prepare **7** using fluoral hydrate by essentially procedure 1 (Table I), as used for **3** with chloral hydrate, led to **7** in yields of less than 10%. EtOAc, with subsequent addition of $CHCl_3$, was suitable for recrystallization of **7**.

1,1,1,3,3,3-Hexafluoro-2-(2-aminoethylthio)-2-propanol Hydrochloride (8).—A homogeneous syrup of $(CF_3)_2CO \cdot 3H_2O$ (46 g, 245 mmoles) and the thiol **1** (22.6 g, 199 mmoles) was heated for *ca.* 5 min at 100° and then was kept at *ca.* 25° for 48 hr. Evaporation under reduced pressure gave colorless **8** (46 g, 83%), mp 140° dec. Careful recrystallization from EtOAc–$CHCl_3$ (Celite) and then from MeOH–$CHCl_3$ gave colorless needles, mp 151–152° dec. Ir and nmr spectra were consistent with structure **8**. *Anal.* ($C_5H_8ClF_6NOS$) C, H, N, S.

In an alternative method for **8**, $(CF_3)_2CO$ (*ca.* 25 ml) was added to thiol **1** (8.00 g, 70 mmoles), and the mixture was saturated with dry HCl and stirred vigorously at *ca.* −70° for 6 hr. The excess $(CF_3)_2CO$ then was allowed to evaporate at *ca.* 25°. The colorless residue was washed with a little *i*-PrOH to remove excess **1** and was dried under reduced pressure to give **8** (15.2 g, 79%), mp 150.5–153° dec.

Compound **8** could be kept as a solid for up to 2 years without decomposition; since it is sensitive in solution, however, it is best recrystallized rapidly at *ca.* 25° or lower.

Dissociation of **8** in boiling toluene was shown to go to completion by heating a suspension of **8** (3.0 g, 10.7 mmoles) in PhMe (110 ml) under reflux for 16 hr; the PhMe-insoluble residue was shown to be solely **1** by comparison of melting point, mixture melting point, and ir spectra, using an authentic sample.

For conversion to its free base, **1,1,1,3,3,3-hexafluoro-2-(2-aminoethylthio)-2-propanol (9)**, a solution of **8** (6.2 g, 22.2 mmoles) in H_2O (10 ml) was basified using excess aqueous $NaHCO_3$. The solution was extracted immediately with four 25-ml portions of C_6H_6, two 50-ml portions of $CHCl_3$, and C_6H_6 (100 ml), and the extracts were combined and dried. Removal of solvent gave a crude product which was recrystallized twice from C_6H_6–hexane to give **9** (1.2 g, 23%): mp 112.5–114.5°; ir (KBr) 3600–2200 (b, complex), 1610 (sh), 1570, 1265, 1210 (sh), 1170, 1140, 1120 (sh), 930, 870, and 700 cm^{-1}; nmr (DMSO-d_6), τ 7.14 (singlet, 4), 3.94 (singlet, 3; OH, NH_2 or O^-, NH_3^+). *Anal.* ($C_5H_7F_6NOS$) C, H, N; S: calcd, 13.19; found, 13.70.

9-Hydroxy-9-(2-aminoethylthio)-9,10-dihydrophenanthren-10-one Hydrochloride (10).—9,10-Phenanthrenequinone (7.6 g, 36.5 mmoles) was added to a solution of **1** (5.7 g, 50 mmoles) in MeOH (30 ml). The mixture was kept at 100° for 10 min, then at *ca.* 25° for 16 hr. Precipitate was removed and briefly washed with MeOH, Et_2O, and $CHCl_3$ to give pale yellow **10** (8.5 g, 72%), mp 139–140° dec. *Anal.* ($C_{16}H_{16}ClNO_2S$) C, H, N, S.

The hemimercaptole **10** is rather unstable in solution and could not be recrystallized from any solvent or combination of solvents tried; upon extraction of 7.0 g (21.8 mmoles) with boiling MeOH (100 ml) and cooling, 9,10-phenanthrenequinone (1.3 g, 29%) crystallized from the extract.

2-Hydroxy-2-(2-aminoethylthio)indan-1,3-dione Hydrochloride (11).—Indan-1,2,3-trione was prepared by heating ninhydrin (23.5 g) with excess $SOCl_2$ (150 ml) for 4 hr under reflux; removal of $SOCl_2$ under reduced pressure gave the trione in 100% yield, mp 256° (lit.[25] mp 255°). A suspension of the trione (10.0 g, 62.5 mmoles) in DMF (15 ml) was added during 30 min to a stirred, ice-cooled solution of the thiol **1** (7.1 g, 62.5 mmoles) in DMF (13 ml). The mixture became progressively browner. After *ca.* 40 min, $CHCl_3$ (200 ml) was added, giving almost colorless **11** (12.3 g, 72%), mp 138–139° dec (appears to liberate the trione above *ca.* 100°; **11** slowly turns purple). A portion of **11** (1.0 g) was dissolved in MeOH (10 ml) at *ca.* 25°, Et_2O (10 ml) immediately was added to incipient turbidity, and the solution was chilled to 0° for *ca.* 16 hr, giving pale yellow plates of **11** (0.6 g, 43% over-all), mp 139–140° dec. *Anal.* ($C_{11}H_{12}ClNO_3S$) C, H, N, S.

(23) Melting points, determined in capillary tubes using a Hershberg-type stirred-liquid apparatus, are corrected. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Ir spectra were obtained using a Beckman Model IR10 spectrophotometer, with films of liquids and KBr pellets of solids (sh signifies shoulder, b, broad); bands reported were of at least medium intensity. Nmr spectra were obtained using a Varian Model A-60 spectrometer (Me_4Si); purchase of the instrument was assisted by Departmental National Science Foundation Grant GP-1683. Solvents were evaporated under reduced pressure using a rotary evaporator. Where analyses are indicated only by symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values.

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