lithium in dry Et_2O under N_2 at −70°. After 2 hr the mixture was warmed to room temp and hydrolyzed (H_2O). The resulting α-(2-pyridyl) 6-methyl-2-trifluoromethyl-4-quinolyl ketone was recrystd from EtOH (30%) mp 155° (lit.[8] mp 153°). The results of these experiments are shown in Table II.

As might have been expected the reaction between 4-quinolyllithiums and pipecolenic acid which has two active hydrogens and would form a dianion with two proximate negative charges, failed to give the piperidyl ketone; in the case of the 6-Me derivative the corresponding parent quinoline was obtained in 55% yield.

The reaction of 4-cyano-6,8-dimethyl-2-trifluoromethylquinoline (13[8]) with 2-PyLi in Et_2O at −70° for 4 hr under N_2 and purification by column chromatography on silica gel ($CHCl_3$) gave 50% of 2-pyridyl 6,8-dimethyl-2-trifluoromethyl-4-quinolyl ketone, mp 94° (lit.[8] mp 98°).

Biologically Oriented Organic Sulfur Chemistry. 7. Carbonyl Disulfides as Inhibitory Agents for *Histoplasma capsulatum*[1a-d]

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Twenty-one unsymmetrical carbonyl disulfides, RC(O)SSR′, were synthesized by reaction of thio acids with thiolsulfonates (eq 1) or with sulfenyl chlorides (eq 2; usually preferred). Absence of symmetrical disulfides was demonstrated by tlc and occasionally by glpc also. Structures were confirmed by ir, nmr, and mass spectra, and by identity of 3 products synthesized using both eq 1 and 2. The reactivity of methyl acetyl disulfide (**1**) differed greatly under various conditions; for example, at 100°, half reacted during 78 days in dioxane but during only 0.2 day in the presence of thiolate ion and during only 0.3 day in 100% EtOH. The decomposition of **1** did not involve merely disproportionation to two symmetrical disulfides (eq 3), but was complex (eq 4). *In vitro* tests against *Histoplasma capsulatum* showed that minimum inhibitory concentrations ranged upward from 8 μg/ml (amphotericin B, **25**, showed 0.1 μg/ml; Table I), with best results when both R and R′ were short, unbranched alkyl or unsubstituted Ph moieties. The approximate LD_{50} ranged downward from *ca.* 430 mg/kg (LD_{50} for **25**, 280 mg/kg). Eight disulfides were unpromising *in vivo* in comparion with **25**, although 1 (the best) did result in approximately 17% prolongation of life, which was considered statistically significant. Several carbonyl disulfides afforded no protection against ionizing radiation.

An earlier paper reported the synthesis of carbonyl disulfides by the reaction of eq 1.[2] The compound in

$$RC(O)S^- + R'SSO_2R' \longrightarrow RC(O)SSR' + R'SO_2^- \quad (1)$$

which R = Me and R′ = Ph was considered "good" as an inhibitor of *Histoplasma capsulatum*, the causative organism of histoplasmosis; the compound in which R = R′ = Ph was "fair."[3] The present paper reports a structure–activity study of types of alkyl and aryl groups favorable as a backbone for carbonyl disulfides, onto which functional groups can be substituted later.

Chemistry.—The procedure of eq 1 (method A) was used to prepare several carbonyl disulfides, but purification proved to be difficult.[4]

An adaptation of a method of Hawley and Kittleson, shown in eq 2, gave a smoother preparation and was

$$R'SH \xrightarrow{0.5\ Cl_2} 0.5(R'S)_2 \xrightarrow{0.5\ Cl_2} R'SCl \xrightarrow{RC(O)SH} RC(O)SSR' \quad (2)$$

used in most instances (method B). Compounds prepared are shown in Table I. With **1**, **2**, and **19**, with which both methods A and B were used, A seemed to have an advantage only with **19** (with **1**, the seemingly higher yield by method A actually was offset by greater impurity).[4] In principle, however, method A does have an advantage over B if one wishes to vary the thio acid component (R) with R′ fixed, because the thiolsulfonate used in method A can be stored, whereas the sulfenyl chloride used in method B cannot. By circumstance, method A alone was used for **15** and **18**, but B probably would have served as well.

For method B, most sulfenyl chlorides were prepared by condensing an equivalent amount of Cl_2 and then allowing it to volatilize into a solution of the disulfide or thiol in CH_2Cl_2 at −20°; 2-methyl-2-propanesulfenyl chloride needed for the preparation of **6**, however, was prepared in hexane at room temp because a thiosulfenyl chloride, $(CH_3)_3CSSCl$, and *t*-BuCl form at low temp.[6] The solution of the sulfenyl chloride then was added to one of the thio acid at −20° (with **1**, when the solution

(1) (a) Paper VI, L. Field and P. M. Giles, Jr., *J. Org. Chem.*, **36**, 309 (1971); (b) this investigation was supported by Public Health Service Research Grants No. AM11685 from the National Institute of Arthritis and Metabolic Diseases (L. F.) and No. AI 08916 from the National Institute of Allergy and Infectious Diseases (I. M.), and by Biomedical Science Support Grant, National Institutes of Health Grant FR-07089 to Vanderbilt University (I. M.); (c) taken from part of the forthcoming Ph.D. dissertation of W. S. H., which may be consulted for greater detail; (d) reported in part at the Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 1968 (Abstracts, p 98), and at the Second National Conference on Histoplasmosis, Atlanta, Ga., Oct 6–9, 1969.

(2) (a) L. Field and J. D. Buckman, *J. Org. Chem.*, **32**, 3467 (1967); (b) *Chem. Abstr.* has named such compounds as *SS*-dithioperoxy esters. Thus MeC(O)SSPh is named "dithioperoxyacetic acid, *SS*-phenyl ester" [*cf. Chem. Abstr.*, **68**, 2763 (1968)]. However, nomenclature as disulfides has precedent in simple systems and is clearer for purposes of this paper.

(3) I. McVeigh and Z. Evans, *Mycopathol. Mycol. Appl.*, **35**, 313 (1968).

(4) Method A was much less satisfactory than method B with RC(O)SSR, when R and R′, respectively, were Me, Me; Me, Et; 1-adamantyl, Et; and *p*-$MeOC_6H_4$, Et. Crude yields were 34–89%, but none of these disulfides could be purified readily to the point of giving one spot by tlc.

(5) R. S. Hawley and A. R. Kittleson, U. S. Patent 2,553,777 (1951); *Chem. Abstr.*, **45**, 7742 (1951).

(6) W. A. Schulze, G. H. Short, and W. W. Crouch, *Ind. Eng. Chem.*, **42**, 916 (1950).

TABLE I

SYNTHESIS AND INHIBITORY ACTIVITY OF CARBONYL DISULFIDES

$$RC(O)SH + R'SY^{a} \longrightarrow RC(O)SSR' + HY$$

Compd	RC(O)SSR' R	R'	Method	Product Yield,[d] %	Bp (mm) or mp, °C	Purified bp (mm) or mp, °C; $n^{25}D$ or solv[e]	Formula[b]	MIC, μg/ml[c] H-7	H-25	Highest concn tested, μg/ml	Toxicity Mouse, mg/kg[f]	ALD_{50}, mg/kg[g]
1	Me	Me	A	89	42–45 (5)	45 (5); 1.5308[h]		10	8	20	>50	130
			B	75	40–42 (4)							
2	Me	Et	A	59	40–76 (6)	55 (3);[i] 1.5232		10	10	20		
			B	100	48–60 (3)							
3	Me	*p*-CH_3Ph	B	65	110–114 (0.4)	114 (0.4); 1.5958	$C_9H_{10}OS_2$	8	8	15	200	240
4	Me	*o*-CH_3Ph	B	89	92–125 (0.1)	105 (0.1); 1.6068	$C_9H_{10}OS_2$	20	15	20	>50	
5	Me	CH_2CH_2Cl	B	91	46–62 (0.3)	61 (0.3); 1.5506[j]		8	8	15	200	
6	Me	*t*-Bu	B	68	45–65 (3)	60 (3); 1.5052	$C_6H_{12}OS_2$	30	20	20		
7	Me	3,4-Cl_2Ph	B	89	70–80 (0.2)	*k*; 1.6328	$C_8H_6Cl_2OS_2$	15	8	20		430
8	Me	*n*-$C_{12}H_{25}$	B	95	140–160 (0.2)	150 (0.2); 1.4907	$C_{14}H_{28}OS_2$	50	50	20		
9	Et	Me	B	76	45–60 (0.4)	52 (0.4); 1.5235	$C_4H_8OS_2$	20	10	20	100	
10	Et	Ph	B	75	95–105 (0.1)	99 (0.1); 1.5950	$C_9H_{10}OS_2$	10	10	20	>50	
11	*t*-Bu	Ph	B	84	77–114 (0.2)	114 (0.2); 1.5664	$C_{11}H_{14}OS_2$	15	10	20	100	74
12	*t*-Bu	*n*-$C_{12}H_{25}$	B	75	155–162 (0.2)	155 (0.2); 1.4834	$C_{17}H_{34}OS_2$	50	20	15	>50	
13	*t*-Bu	Me	B	90	55–65 (3)	60 (3); 1.5044	$C_6H_{12}OS_2$	30	20	20		
14	*t*-Bu	Et	B	92	66–75 (4)	69 (0.3); 1.5005	$C_7H_{14}OS_2$	30	20	20		
15	3,4,5-$(MeO)_3Ph$	Et	A	75	44–48	51.5–52.5; E–W	$C_{12}H_{16}O_4S_2$	30	20	25		
16	2,4,6-Me_3Ph	Ph	B	79	42–45	46–47; Hp	$C_{16}H_{18}OS_2$	20	15	20		
17	3,4-Cl_2Ph	Ph	B	85	52–55	58–59; Hx	$C_{13}H_8Cl_2OS_2$	50	30	20		
18	*n*-$C_{17}H_{35}$	Me	A	39	39–43	45–45.5; E–W	$C_{19}H_{38}OS_2$	50	50	20		
19	*n*-$C_{17}H_{35}$	Et	A	72[l]	35–40	42–42.5; E	$C_{20}H_{40}OS_2$	50	50	20		
			B	55	36–40							
20	*n*-$C_{17}H_{35}$	*n*-$C_{12}H_{25}$	B	90	46–50	51–52; E	$C_{30}H_{60}OS_2$	*m*	*m*	10		
21	*n*-$C_{17}H_{35}$	Ph	B	67	55–60	62–63; E	$C_{24}H_{40}OS_2$	*m*	*m*	10		
22	1-$C_{10}H_{15}$	1-$C_{10}H_{15}C(O)$	*n*	75	175–180	186–188; E	$C_{22}H_{30}O_2S_2$	*m*	*m*	10		
23	Me	Ph	*o*					8	5	20		
24	Ph	Ph	*o*					10	15	20		
25	Amphotericin B							0.2	0.1	0.3		(280)[p]

[a] For method A, Y = SO_2R'; for method B, Y = Cl. [b] All new compds gave analyses for C, H, and S within 0.4% of theory (**3**, **4**, **6–22**), as did **1**, **2**, and **5** previously prepared by other methods. [c] MIC = minimum inhibitory concentration. Numerals through 20 indicate the lowest concn in μg/ml which led to complete inhibition of growth of *H. capsulatum* during a 7-day incubation period. As an aid to comparison of activities, compds that showed activity at the 4th day, but not thereafter, were arbitrarily assigned a MIC of 30 and those that were inactive on the 4th day a MIC of 50; *such compounds were not actually tested at 30 and 50 μg/ml.* H-7 and H-25 are strains of *H. capsulatum* used earlier (*cf.* ref 3 and 12). Compds tested were dissolved in MeOH, and the solns then were dild with H_2O (**1** only) or with an aq soln of Tween 80, so that the final concns in the medium did not exceed 0.25% for MeOH or 0.008% for Tween 80. [d] Sulfenyl chlorides were not isolated. Yields reported are based on thiol or disulfide used. [e] Solvents used for recrystg solids: E, 95% EtOH; Hex, hexane; Hp, heptane; W, H_2O. All melting points reported were after recrystn to constant melting point. [f] Lowest single dose which resulted in deaths. (Tests were kindly arranged by Dr. W. B. Lacefield and carried out under the supervision of Dr. R. S. Gordee of Eli Lilly and Co.) The value >50 was from sc injection of the toxicity controls in *in vivo* testing against *H. capsulatum*. The other values were after ip injection. [g] For the method of determination see L. Field, B. J. Sweetman, and M. Bellas, *J. Med. Chem.*, **12**, 624 (1969). [h] Lit. bp 55–56° (12 mm), n^{20} D 1.5353 [from MeSH and AcSCl; H. Böhme and G. Zinner, *Justus Liebigs Ann. Chem.*, **585**, 142 (1954)]. [i] Lit. bp 70–71° (11 mm) [from AcSCl and EtSH; H. Böhme and M. Clement, *ibid.*, **576**, 61 (1952)]. [j] Lit. bp 118–120° (19 mm) [from AcSSCl and ethylene; H. Böhme and M. Clement, *ibid.*, **576**, 61 (1952). [k] Compd decompd partly on distn. The anal. sample was obtained by drying the initial product for 24 hr at 0.005 mm. The sample thus obtained exhibited all criteria for purity (tlc, ir, and nmr). [l] Prepd by an improvement in method A; see Experimental Section. [m] Sparing solubility prevented tests above 10 μg/ml. At 10 μg/ml the compd was completely inactive. [n] $C_{10}H_{15}$ = 1-adamantyl. Compd **22** was synthesized by oxidn of 1-adamantanecarbothioic acid with 0.1 *N* aq I_2–KI. [o] Previously reported (*cf.* ref 2a). [p] See Discussion.

of the thio acid was added to that of the sulfenyl chloride, a complicated mixture of products resulted).

Most of the thio acids used were unavailable commercially and were synthesized essentially as reported.[7,8] They were characterized by their ir spectra (SH absorption at 2530 to 2580 cm^{-1}), by titration with I_2, and occasionally by nmr. They were then used without purification, since the disulfide products could be purified without great difficulty.

The purity of disulfides **1–22** was assured by observation of only single spots after tlc (in several instances the symmetrical disulfides were easily resolved), and with **1**,**2**,**5**,**6**,**9**,**10**,**13**, and **14** as typical products, also by only single peaks after glpc. Accordingly, none of the products contained either of the two symmetrical disulfides that might result from disproportionation (eq 3).

$$2RC(O)SSR' \rightleftharpoons [RC(O)S]_2 + (R'S)_2 \qquad (3)$$

The structures of the disulfides were confirmed in several ways: by ir spectra (loss of absorption associated with the SH moiety, with retention of that associated with the CO moiety); by nmr spectra (loss of the peak at about δ 4–5 for thio acids with presence of the correct number and relationship of protons); by elemental analysis; by mass spectrometry (molecular ions and consistent fragmentations were seen for **1**, **2**, **4**, **9**, and **14**); and, by the fact that when both methods A and B were used the products were identical (by ir; **1**, **2**, **19**); furthermore, **1**, **2**, and **5** had been prepared previously by still other methods (see Table I).

The reactivity of carbonyl disulfides under various circumstances was studied because of its relevance to synthesis, purification, and storage, to reactions during testing, and to possible correlation of chemical reactivity with biological activity. In seeking such information, we used as examples one of the compounds which proved most active biologically (*vide infra*), methyl acetyl disulfide (**1**), along with one of the least so, methyl pivaloyl disulfide (**13**). The effects of heat, light,

(7) P. Noble, Jr. and D. S. Tarbell, *Org. Syn.*, **32**, 101 (1952).
(8) Y. Hirabayashi, M. Mizuta, and T. Mazume, *Bull. Chem. Soc. Jap.*, **37**, 1002 (1964).

solvents, and catalysts are shown in Table II, in order of increasing reactivity of **1** and **13**, as reflected by "t_{50}," the time estimated for reaction of half of **1** or **13**.

TABLE II

REACTIVITY OF MeC(O)SSMe (**1**) and *t*-BuC(O)SSMe (**13**)[a]

Expt	Temp, °C	Solvent	Other variables	Estd t_{50}, days[b]
1	100	Dioxane		78[c]
2	25	Neat	Uv	42
3	25	H_2O–Me_2CO		44
4	100	Neat		33
5	25	Dioxane	Uv	22[d]
6	100	Dioxane	RSH[e]	13
7	100	Neat	RSH[e]	5
8	100	H_2O–Me_2CO (1:1)		0.6
9	100	EtOH (100%)		0.3
10	100	Dioxane	RSNa[e]	0.2

[a] Disulfide **1** was used except where **13** is specified (footnotes c and *d*). Kept in the dark unless uv light is specified. See Experimental Section for details. [b] Estimated from plots of % remaining *vs.* time (see Experimental Section for data). [c] With **13**, after 78 days 84% remained and decompn was so slow that t_{50} was not estimated. [d] Estimated t_{50} for **13**, 10 days. [e] As a catalyst, 11 mole % of a thiol or thiolate was added.

When heated, simple unsymmetrical disulfides are known to disproportionate to give equilibrium mixtures of the unsymmetrical and the two symmetrical disulfides, as illustrated for a carbonyl disulfide in eq 3; equilibrium ordinarily can be approached from either side.[9] In contrast, disproportionation of a disulfide having the general structure of **26** went essentially to

$$\text{X-C}_6\text{H}_4\text{CH}_2\text{SS(CH}_2)_2\text{NH}_2^+\text{-}n\text{-C}_{10}\text{H}_{21}\ \text{Cl}^-$$
26

$$\text{CH}_3\text{C(O)SS(CH}_2)_2\text{NHAc}$$
27

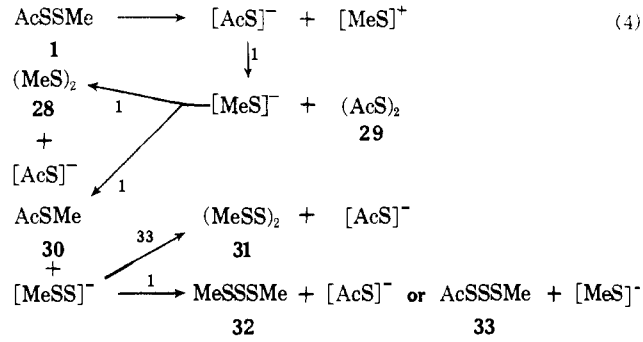
completion.[10] The aspect of equilibrium was of interest, therefore, as well as that of resistance to disproportionation.

Methyl acetyl disulfide (**1**) was surprisingly unreactive when heated at 100° in dioxane in the dark (expt 1; t_{50} 78 days). It reacted much more readily when heated without solvent (expt 4; t_{50} 33 days); the pivaloyl disulfide **13** reacted less readily than **1** in dioxane, 84% remaining after 78 days. A plot of the per cent remaining of **1** indicates that the respective times after which 78% and 68% remained were 32 and 43 days (expt 1); since the respective times after which 78% and 68% of the 2-acetamidoethyl disulfide **27** remained were only 1 and 2 days,[2a] a neighboring group participation of AcNH may be involved in the much more facile decomposition of **27**; such participation was suggested for the amino group of **26**.[10] The decomposition of **1** was greatly accelerated by the presence of a thiol as a catalyst (expt 6, 7); again, **1** was less reactive in solution than neat. With thiolate ion as a catalyst, t_{50} was only 0.2 day (expt 10).

In light, the reactivity of **1** in dioxane increased greatly (*cf.* expt 5 *vs.* 1); **1** was more stable to light in the absence of dioxane (*cf.* expt 2 *vs.* 5). In another series of unsymmetrical disulfides, disproportionation seemed to be largely by a heterolytic process when induced thermally and by a homolytic process when induced photochemically,[11] and a similar duality of mechanisms seems likely in the present series as well. The t_{50} was less for **13** exposed to uv than for **1**. Exposure to light during tlc of **27** led to partial disproportionation,[2a] but ambient light seemed to cause no problems with the isolation or tlc of the present carbonyl disulfides; one wonders here again if this difference may not point to a neighboring group effect of the acetamido moiety of **27**.

Hydrolysis or ethanolysis of **1** was rapid in comparison with most of the other conditions of Table II, but even so t_{50} reflected considerable resistance of **1** (0.3–0.6 day at 100° in expt 8 and 9, and 44 days at 25° in expt 3).

It should be emphasized that the products of decomposition of **1** and **13** were not merely the simple symmetrical disulfides predicted by eq 3 but rather a complicated mixture that reflects reactions concurrent with disproportionation. Indeed, glpc and mass spectrometric analysis of **1** that had been heated neat at 100° for 9.5 days gave evidence for the seven compounds shown in eq 4: unchanged **1**, **28**, and **29** (the products of disproportionation), and **30**–**33**. Formation of these



(4)

products can be envisioned as a consequence of initial heterolytic S–S bond cleavage as shown in eq 4 (or, alternatively, to give $[AcS]^+$ and $[MeS]^-$), followed by attack of the cleavage fragments on the starting material **1**. It was no surprise, in view of the several concurrent reactions which seem to occur, that attempts to equilibrate the two symmetrical disulfides **28** and pivaloyl disulfide gave a complicated mixture. However, use of these disulfides in 1:1 mole ratio at 100° did result in the sole formation of **13** in about 9% yield during the first 5 days; the amount rose to 15–18%, which later decreased.

Biological Activity.—Table I shows the results of *in vitro* tests of the carbonyl disulfides **1**–**24** and of amphotericin B, a standard drug used against histoplasmosis. The procedure for testing has been reported.[3,12] The highest level actually tested was 25 μg/ml. Those compounds that caused partial inhibition of growth at the highest concentration tested were assigned *arbitrarily* an MIC value of 30 μg/ml to distinguish them from completely inactive ones, which were assigned *arbitrarily* an MIC value of 50 μg/ml. The results with variation of R in $RC(O)SSCH_3$ suggest the following approximation for decreasing effectiveness of R(compound compared; *average* MIC *vs.*

(9) *Cf.* footnotes 8 and 9 given in ref 10.

(10) M. Bellas, D. L. Tuleen, and L. Field, *J. Org. Chem.*, **32**, 2591 (1967).

(11) L. Field, T. F. Parsons, and D. E. Pearson, *J. Org. Chem.*, **31**, 3550 (1966).

(12) I. McVeigh, Z. Evans, L. Field, and W. S. Hanley, *Mycopathol. Mycol. Appl.*, **37**, 349 (1969).

H-7 and H-25): Me(**1**, 9) > Et(**9**, 15) > Ph[13] > *t*-Bu (**13**, 25) > *n*-$C_{17}H_{35}$ (**18**, 50). *t*-Bu was anomalous with R′ = Ph (**11**, 13) but was typically poor again with R′ = Et(**14**, 25). Ph seemed to be adversely influenced by either electron withdrawal (**17**, 40) or donation (**15**, 25; **16**, 18). Generally, therefore, the most favorable R group seems to be a short unbranched alkyl or unsubstituted phenyl group. The variations of R′ in $CH_3C(O)SSR'$ suggest the following approximation: Ph (**23**, 7) ~ *p*-MePh (**3**, 8) ~ CH_2CH_2Cl (**5**, 8) ~Me(**1**, 9) ~ Et(**2**, 10) > *t*-Bu (**6**, 25) > *n*-$C_{12}H_{25}$ (8, 50). As before, Ph was adversely influenced by other types of substitution (*e.g.*, with the *o*-CH_3 of **4**, 18; and with the 3,4-Cl_2 of **7**, 12). The most favorable R′ groups thus seem to be Ph, para-substituted Ph, or short, unbranched alkyl groups. That these results are meaningful is supported by the marked drop in activity with compounds which would be predicted to be poor by the foregoing generalization; thus **12** and **19–22** were either completely inactive or nearly so. It is noteworthy that in earlier tests of alkanethiols and thio acids *per se*, lengthening or branching of chains led to low activity.[12]

Several of the more promising disulfides were tested *in vivo* for prolongation of the life of mice that had been given 4–8 LD_{50} doses of *H. capsulatum iv* 24 hr after they had been exposed to 400 R of X-rays.[14] Doses in the range of 6.3–100 mg/kg were either injected sc at the time of infection and again after 4 hr or twice daily at 2-hr intervals for 2 days; 6 mice were used for each of several dose levels; amphotericin B, similarly given, afforded >60% prolongation of life at a dose of 50 mg/kg. Compounds **1**, **3–5**, and **9–12** did not show interesting activity compared with amphotericin B, although **1** (the best) did lead to 17% prolongation of life, which was considered statistically significant.

2-Acetamidoethyl acetyl disulfide (**27**) earlier showed "good" activity as an antiradiation drug;[2a] however, a recent check using independently synthesized **27** gave an ALD_{50} of 280 mg/kg and only 7% protection at 50 mg/kg ("slight protection"). Disulfides **1**, **3**, **7**, and **11** were inactive in tests for antiradiation activity,[15a] but the values of ALD_{50} determined[15b] are included in Table I, along with "Toxicity, mouse,"[14a] as indications of relative toxicity; amphotericin B has an LD_{50} of 280 mg/kg (ip, mice).[16]

Experimental Section[17]

Thio Acids.—Commercial thioacetic acid was used as received. Where R of eq 5 was *n*-$C_{17}H_{35}$, essentially the method of Hirabayashi, *et al.*, was used.[8] With all other thio acids, essentially the method of Noble and Tarbell was used.[7] Both methods are based on eq 5; acid chlorides were prepd using $SOCl_2$ (but other

$$RCOCl + 2KSH \longrightarrow RC(O)SK + KCl + H_2S \quad (5)$$

methods should be better in prepg CH_3CH_2COCl). The results, along with deviations from these procedures, are shown in Table III. All thio acids were used without further purification for synthesis of the carbonyl disulfides, since the latter then could be purified without great difficulty.

TABLE III

SYNTHESIS OF THIO ACIDS

RC(O)SH (of eq 1, 2), R =	Yield, %[a]	SH, %[b]	Ir, cm^{-1}[c]
p-CH_3OPh	77	88	2540 (N)
Et	43	94	2560 (N)
t-Bu	75	100	2570 (N)
3,4,5-$(MeO)_3Ph$	62	72	2530 (Nj)
2,4,6-$(Me)_3Ph$	74[d]	80	2530 (N)
3,4-Cl_2Ph	80[e]	95	2580 (KBr)
n-$C_{17}H_{35}$	50	85	2560 (Nj)
1-Adamantyl	51[f]	75	2570 (N)

[a] Based on the weight of product isolated after the reaction of eq 5. [b] By titration of the product isolated with aq KI_3. [c] Determined neat (N), in Nujol (Nj), or in KBr pellets (KBr). [d] Stirred at *ca.* 25° for 8 hr. [e] Stirred at *ca.* 25° for 5 hr. [f] The soln of KSH was warmed to 40° during addition of the acid chloride and was stirred for 1.5 hr at 40° after addition was complete.

Unsymmetrical Carbonyl Disulfides. Method A. Using Thiolsulfonates.—The prepn of methyl stearoyl disulfide (**18**) illustrates method A. Et_3N (1 g, 9.9 mmoles) was added (*ca.* 25°) during *ca.* 2 min to a stirred soln of thiostearic acid (2.35 g, 6.7 mmoles, 85% SH) and methyl methanethiosulfonate (0.84 g, 6.7 mmoles) in 30 ml of $CHCl_3$. The reaction mixt was stirred for 2 hr. The soln was washed with H_2O, cold 3% NaOH, and again with H_2O to neutrality. It then was dried over anhyd $MgSO_4$. Evapn of solvent left 0.90 g (39%) of **18**, mp 39–43°. Recrystn from EtOH–H_2O gave **18** with constant mp 45–45.5°.

An improvement used for the prepn of **19** probably would give better results with **1**, **2**, **15**, and **18** also. After a stirring period of 2 hr at *ca.* 25°, the reaction mixt was heated to 50°, more Et_3N was added (1.41 g), and stirring at 50° was continued for 1.5 hr. Isolation as before afforded **19** (72%), mp 35–40°. Recrystn from EtOH gave **19** with constant mp 42–42.5°.

Method B. Using Sulfenyl Chlorides.—The prepn of methyl acetyl disulfide (**1**) illustrates method B. Methanesulfenyl chloride was prepared by condensing Cl_2 (5.8 g, 82 mmoles) using Dry Ice–Me_2CO and then allowing the Cl_2 to volatilize spontaneously (*ca.* 15 min), upon removal of cooling, into a stirred soln of Me_2S_2 (7.7 g, 82 mmoles) in 50 ml of CH_2Cl_2 maintained at −20° with Dry Ice–Me_2CO. The resulting soln, typically red-brown, was added (*ca.* 5 min) to a stirred soln of thioacetic acid (12.9 g, 170 mmoles) in 75 ml of CH_2Cl_2 at −20°. The mixt was allowed to warm to *ca.* 25° with stirring (1–2 hr) and then was washed with H_2O, 5% aq $NaHCO_3$, and again with H_2O to neutrality. The soln was dried ($MgSO_4$) and solvent was evapd to leave 15.0 g (75%) of **1**. Distn gave pure **1**, bp 45° (5 mm), $n^{25}D$ 1.5308.

Reactivity of Unsymmetrical Carbonyl Disulfides.—The

(13) Ranked below Me and Et by comparing RC(O)SSPh where R = Me (**23**, 7), Et (**10**, 10), and Ph (**24**, 13).

(14) (a) Tests kindly arranged by Dr. W. B. Lacefield and carried out under the supervision of Dr. R. S. Gordee of Eli Lilly and Company; (b) *cf.* R. S. Gordee and T. R. Matthews, *Bacteriol. Proc.*, **69**, 114 (1969).

(15) (a) Tested as described previously,[15b] through the kindness of Drs. D. P. Jacobus, T. R. Sweeney, and E. A. Steck, and of Miss Marie Grenan, of the Walter Reed Army Institute of Research, Washington, D. C.; (b) L. Field, B. J. Sweetman, and M. Bellas, *J. Med. Chem.*, **12**, 624 (1969).

(16) "The Merck Index," P. G. Stecher, Ed., 8th ed, Merck and Co. Inc., Rahway, N. J., 1968, p 75.

(17) Melting points, taken in capillary tubes using a Hershberg-type, stirred-liquid apparatus, are corrected; boiling points are uncorrected. Elemental analyses were done by Galbraith Microanalytical Laboratories, Knoxville, Tenn.; results for C, H, and S analysis (and Cl for **17**) of all new compds (those with mol formulas shown in Table I) were within 0.4% of theory, as were those for **1**, **2**, and **5** (and Cl for **5**). Mass spectra were kindly determined by C. T. Wetter at 70 eV using a chromatographic column (SE-30) inlet system on an LKB Model 9000 instrument, which was obtained through NSF Science Development Program Grant GU-2057. Moist extracts were dried using anhyd $MgSO_4$, and solvents then were removed at *ca.* 25 mm using a rotating-flask evaporator. Ir spectra were obtained using a Beckman Model IR 10 spectrophotometer and nmr spectra with a Varian Model A-60 spectrometer (Me_4Si). Glpc was performed on a Beckman Model GC-5 gas chromatograph (flame-ionization detector; detection and injection temps, 250°; flow rate (ml/min), 40 for H_2, 250 for air, and 20 for He; column, 6 ft × 0.13 in. 5% SE-30 on Chromosorb P). Peak areas were determined by an Infotronics Model CRS-100 electronic integrator. With **1** and **13**, there was a linear relation between peak area and amount. The unsym disulfides in general did not appear to decompose on the glpc column. All distns were performed using a Nester-Faust NFT-50 (5 mm × 61 cm) annular Teflon spinning-band column. Tlc of disulfides usually was performed on Eastman Chromagram No. 6060 sheets (silica gel) using PhH or Me_2CO, with development by I_2 vapor and with observation of spots after 10–15 min; in 5 instances where symmetrical disulfides were added to the unsymmetrical, they were clearly resolved.

resistance of disulfides **1** and **13** under the circumstances reported in Table II was determined by the general procedure below, the per cent remaining being determined by glpc analysis for **1** among the reaction products. Glpc was performed much as usual (oven temp for 1, 92°; for **13**, 122°).[17] Typical retention times for various components, given in sec for 92 or 122° (*) were: dioxane 29, 21*; 1,2,4-trichlorobenzene *ca.* 319, 116*; **1**, 86; **13**, 92*.

Disulfide **1** (1.0013 g) and 1,2,4-trichlorobenzene (0.5103 g) were dissolved in 4 ml of dioxane and 0.3-ml aliquots were sealed in each of several ampules; the same concns were used where other solvents are specified. The ampules were wrapped in Al foil for protection against light and, unless otherwise stated, were heated at 100° in **A**, **B**, **D**, and **E**; in **C**, for light-induced decompn, the samples were placed in 15 × 240 mm Pyrex tubes, which were stoppered and irradiated simultaneously at *ca.* 25° (H_2O cooling) in an Aminco constant-temp apparatus (Cat. No. 4-8600) at a radial distance of 15 cm from a Sylvania 400-W uv lamp. After the time (t) reported, 0.3–1.0 μl from an ampule or from the Pyrex tubes, was injected onto the glpc column. The per cent remaining of **1** or of **13** was calcd from the automatic peak-area output of the instrument by using the expression [(**1** or **13** at time t)/($Cl_3C_6H_3$ at time t)] (100)/[(**1** or **13** at t_0)/($Cl_3C_6H_3$ at t_0)]. The data given below are in order of compd no., per cent of 1 or **13** which remained, and time in days (in parentheses).

A. Thermolysis (100°).—For **1** and **13** in dry dioxane the data are: **1**, 88%(21), 59%(53), and 37%(114); **13**, 93%(21), 88%(53), and 78%(114); without solvent: **1**, 91%(12), 66%(25), and 52%(32).

In the analysis of the reaction mixt from the 9.5-day thermolysis (100° neat) of **1**, an ampule was cooled and its contents were analyzed by glpc–mass spectrometry. Compounds **1** and **29–33** were identified by their molecular ions and by seemingly consistent fragmentations, and **28** was identified by glpc-peak augmentation with authentic **28**.

B. Hydrolysis and Ethanolysis (100°).—For **1** in 100% EtOH the data are: 70%(0.12), 47%(0.33), and 17%(0.87); for 1:1 H_2O–Me_2CO: 93%(0.12), 62%(0.5), and 14%(1.0); for **1** in 1:1 H_2O–Me_2CO at *ca.* 25°: 82%(8), 67%(17), and 63%(24).

C. Irradiation.—In dioxane at *ca.* 25° the data are: **1**, 70%(7), 54%(18), and 40%(32); **13**, 54%(7), 41%(18), and 31%(32). Values for **1** at *ca.* 25° without solvent were: 83%(8), 74%(16), and 59%(32).

D. Catalyzed by Thiol or by Thiolate Ion (100°).—Catalyzed decomps of **1** were done as usual except that 0.0480 g (10 mole %) of thioacetic acid or 0.0618 g (10 mole %) of sodium thioacetate (from thioacetic acid and Na in dry dioxane; the soln remained homogeneous) was added to the proper amts of 1 and internal standard. For thiol-catalyzed decomps of **1** in dioxane the results were: 100%(2.2), 87%(6), and 49%(13); without solvent: 69%(2.2), 41%(6), and 12%(13). For thiolate-catalyzed reactions in dioxane the results were: 23%(0.3) and 13%(0.8).

E. Equilibria.—Reactions and analyses were done as before. Standard solns were prepd by dissolving equimolar portions of pivaloyl disulfide and **28** in dioxane. The per cent survival of pivaloyl disulfide (days) at 100° was: 85%(17), 49%(52), and 29%(114). For irradiated samples the per cent survival was: 95%(7), 72%(18), and 52%(32). The per cent formation of **13** was determined as follows: %**13** = (mole of **13** at time t/2) (100)/(mole of pivaloyl disulfide at time t_0). The per cent formation of **13** (days) in dioxane at 100° was: 4%(1.6), 5%(3), 9%(4.6), 12%(9), 12%(17), 18%(52), 17%(84), and 14%(114). For irradiated samples the per cent formation was: 3%(2), 7%(3), 8%(5), 11%(7), 13%(14), 13%(18), 15%(24), and 10%(32).

2-Amino-4-hydroxy-6-arylaminoethylpteridines as Potential Antimalarial Agents

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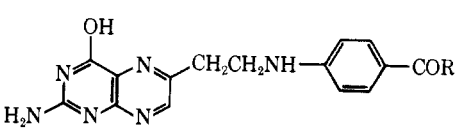
The synthesis of several 2-amino-4-hydroxy-6-arylaminoethylpteridines is described. These compounds, all analogs of homopteroic acid (II), were found to be ineffective in the standard antimalarial screen against *Plasmodium berghei* in rodents.

In recent years there has been a demand for new antimalarial agents to combat resistant strains of the disease. It was of especial interest to develop entirely new classes of compounds to help counteract this resistance problem.

The antifolate and other properties of homofolic acid (I) and its tetrahydro derivative have been reported.[1] We have also found that homopteroic acid (II), an intermediate in the synthesis[2] of I, and its tetrahydro derivative were potent growth inhibitors of *Streptococcus faecium*, a folate-dependent organism. These data, coupled with the observation of Kisliuk, *et al.*,[3] that tetrahydrohomopteroate displayed activity against a pyrimethamine-resistant strain of *Plasmodium cynomolgi* in monkeys, suggested that this area should be further studied in the hope of developing a new type of antimalarial agent.



I, R = NHCH(COOH)CH_2CH_2COOH
II, R = OH

A number of substituted 2-amino-4-hydroxy-6-anilinoethylpteridines related to homopteroic acid (II) were synthesized. These structures, represented in Table

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