23 (R = 8-CH_3), 70970-73-9; **23** (R = 8-CH_3) (alcohol), 2164-59-2; **24** (R = 6-$SO_2N(Me)_2$), 70918-64-8; **24** (R = 6-$SO_2N(Me)_2$) (alcohol), 70918-62-6; **24** (R = 7-$SO_2N(Me)_2$), 70918-65-9; **24** (R = 7-$SO_2N(Me)_2$) (alcohol), 70918-63-7; **25**, 70918-49-9; **25** (alcohol), 70918-48-8; **25** (methyl ester), 70918-50-2; **26**, 68281-27-6; **26**, 68281-27-6; **26** (alcohol), 16163-83-0; **27**, 70918-42-2; **27** (ethyl ester), 70918-41-1; **28**, 70918-52-4; **28** (methyl ester), 70918-51-3; **29** (R = 5-Pr-i), 70918-38-6; **29** (R = 5-Pr-*i*) (ethyl ester), 104808-40-4; **29** (R = 8-Pr-i), 70918-39-7; **29** (R = 8-Pr-i) (ethyl ester), 104808-39-1; **30**, 70918-43-3; **30** (ethyl ester), 16212-66-1; **31** (R = 6-Cl), 70918-58-0; **31** (R = 6-Cl) (ethyl ester), 51714-18-2; **31** (R = 7-Cl), 16212-69-4; **31** (R = 7-Cl) (ethyl ester), 16212-65-0; **34**, 104808-21-1; $BrCH_2CH(Br)CO_2Et$, 3674-13-3; 4,5-dimethylcatechol, 2785-74-2; 3,4-diacetoxybenzenesulfonic acid pyridinium salt, 70918-60-4; dimethylamine, 124-40-3; *N,N*-dimethyl-3,4-dihydroxybenzenesulfonamide, 70918-61-5; epichlorohydrin, 106-89-8; (+)-dehydroabietylamine, 99306-87-3; 2-methyl piperazine, 109-07-9; piperazine, 110-85-0; homopiperazine, 505-66-8; 4-acetylcatechol, 1197-09-7.

Supplementary Material Available: X-ray data are available for 6,7-dimethoxy-4-(dimethylamino)-2-[4-(1,4-benzodioxan-2-ylcarbonyl)piperazin-1-yl]quinazoline hydrochloride (**34**) (4 pages). Ordering information is given on any current masthead page.

Antiradiation Compounds. 20. 1-Methylquinolinium(and pyridinium)-2-dithioacetic Acid Derivatives

William O. Foye,* Robert W. Jones, Pallab K. Ghoshal, and Bijan Almassian

Department of Chemistry, Massachusetts College of Pharmacy and Allied Health Sciences, Boston, Massachusetts 02115.
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A new class of radiation-protective compounds has been found in the bis(methylthio) and methylthio amino derivatives of 1-methylquinolinium- and 1-methylpyridinium-2-dithioacetic acids. The compounds gave good protection to mice vs. 1000-rad γ-radiation in ip doses of 10 mg/kg or less, much lower than those required for the aminoalkyl thiols (~150–600 mg/kg). The dithioacetic acid zwitterions were prepared from the base-catalyzed reaction of carbon disulfide with quinaldine and picoline methiodides, and the bis(methylthio) derivatives resulted from reaction with methyl iodide at room temperature. Replacement of one methylthio moiety took place readily on reaction of the bis(methylthio) derivatives with 1 molar equiv of an amine. The best protective activity was found with the methylthio piperidino derivative in both the quinolinium and pyridinium series.

For good chemical radiation protection in the mammal, the mercaptoalkyl amines and mercaptoalkyl guanidines have constituted the most effective class of compounds.[1] After a sizable number of these compounds had been tested, it was apparent that a free or potentially free thiol group is required.[2,3] One of the mechanisms proposed by which radiation-produced radicals of cellular macromolecules may be repaired is hydrogen-atom transfer from thiols to radicals; repair of simple free radicals by hydrogen transfer from thiols has been observed.[4] According to Cohen, both mercaptans and disulfides may enter rapid, repetitive hydrogen atom transfer reactions, affecting radiation-induced free radicals.[5] These reactions proceed with rate constants of 10^3–10^6 M^{-1} s^{-1} and show very little free energy change, so they compete effectively with other reactions possible for free radicals.

Another functional group that should be capable of rapid hydrogen transfer is the dithio acid moiety. This type of compound has already shown some radioprotective properties but has not been systematically investigated. Table I summarizes results already obtained with dithio acids in a radiation-protective screen. The dithio acid derivatives in Table I do not have basic functions, but two have amide functions. Dithio acids with basic functions, analogous to the mercaptoalkyl amines, might be expected to confer greater protection.

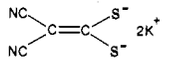
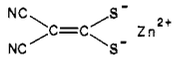
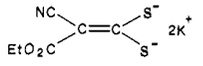
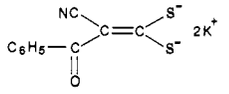
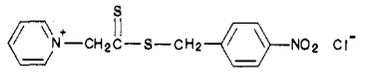
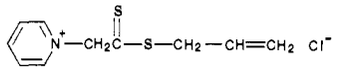
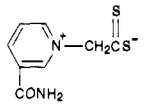
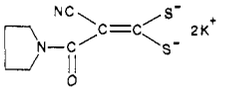
Dithio acids should be more effective agents for transferring hydrogen atoms at neutral or slightly acidic pH than mercaptans. The pH for maximum rate of hydrogen atom (free radical) extraction for mercaptans is around 10.[6] The rate of the reaction is pH dependent and is greatest at a pH roughly 1 pH unit greater than the pK_a of the thiol. Mercaptoethanol, for example, has a pK_a of 9.34, and its maximum rate of H-atom transfer was found at 10.30.[7] Dithio acids have pK_a values of 3–4. On the assumption that reaction rates for H-atom transfer will be around 1 pH unit higher, then the maximum rate for this reaction with dithio acids should be in the range of 4–5, closer to cellular values.

The 1-methyl-2-quinoliniumdithioacetic acids (1), already prepared in this laboratory,[8] appeared to be suitable candidates for radiation-protective tests. These compounds also have significant antileukemic activity and showed both DNA-binding ability and DNA polymerase inhibitory activity.[9] They were isolated as zwitterions, however, and were poorly soluble in either aqueous or organic media. Better solubility properties were found with bis(thiomethyl)[10] and thiomethyl amino derivatives,[11] and the antileukemic activities were improved as well. Accordingly, both types of acid derivatives (**2** and **3**) were

(1) Foye, W. O. In *Burger's Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; Wiley: New York, 1981; Part 3, Chapter 37, p 14.
(2) Bacq, Z. M. *Bull. Acad. R. Med. Belg.* **1966**, *6*, 115.
(3) Foye, W. O. *Int. J. Sulfur Chem.* **1973**, *8*, 161.
(4) Adams, G. E. In *Radiation Protection and Sensitization*; Moroson, H. L., Quintiliani, M., Eds.; Barnes and Noble: New York, 1970; p 3.
(5) Cohen, S. G. In *Organosulfur Chemistry*; Janssen, M. J., Ed.; Interscience: New York, 1967; p 33.
(6) Huyser, E. S.; Tang, H.-N. In *Organic Free Radicals*: Pryor, W. A., Ed.; ACS Symposium Series 69; American Chemical Society: Washington, DC, 1978; p 261.
(7) Kreevoy, M. M.; Harper, E. T.; Durall, R. E.; Wilgus, H. A.; Ditsch, L. T. *J. Am. Chem. Soc.* **1960**, *82*, 4899.
(8) Foye, W. O.; Lee, Y. J.; Shah, K. A.; Kauffman, J. M. *J. Pharm. Sci.* **1978**, *67*, 962.
(9) Foye, W. O.; Vajragupta, O.; Sengupta, S. K. *J. Pharm. Sci.* **1982**, *71*, 253.
(10) Foye, W. O.; Kauffman, J. M. *J. Pharm. Sci.* **1980**, *69*, 477.
(11) Foye, W. O.; Kim, Y. H.; Kauffman, J. M. *J. Pharm. Sci.* **1983**, *72*, 1356.

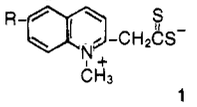
0022-2623/87/1830-0057$01.50/0

Table I. Dithio Acids and Derivatives as Radioprotectives

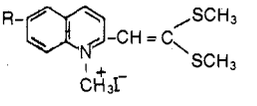
compound	dose, mg/kg	protective effect[a]	ref
	350	fair act. (>25% protn) vs. 825 rads (X-rays) in mice	15
	25	sl act. (<25% protn) vs. 1000 rads (γ-rays) in mice	15
	100	50% protn vs. 600-rad (γ-rays) in mice	15
	120	17% protn vs. 825 rads (X-rays) in mice	15
		33% protn vs. 825 rads (X-rays) in mice	16
		17% protn vs. 825 rads (X-rays) in mice	16
		good (>45%) protn to bacteria	16
		other derivatives gave poor protn to bacteria	
	600 (ip)	80% protn vs. 849 rads (γ-rays) in mice	17
	600 (po)	30% protn in mice vs. 849 rads (γ-rays)	

[a] Screening was done at the Walter Reed Army Institute of Reasearch.

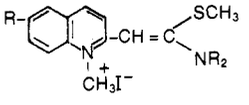
prepared as potential radiation-protection agents. The corresponding 2-pyridiniumdithioacetic acid derivatives (**5**, **6**) were prepared as well.



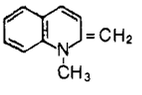
1



2



3



4

Discussion

Chemistry. The 1-methyl-2-quinoliniumdithioacetic acid zwitterions (1) were prepared by the reaction of carbon disulfide, generally with aqueous sodium hydroxide as base, with the 1-methylquinaldine iodides.[8] Reaction of the 1-methyl-2-quinoliniumdithioacetic acid zwitterions with excess iodomethane in dimethylformamide (DMF) gave the corresponding bis(2-methylthio) derivatives (**2**), as previously described.[10] The 2-[2-(methylthio)-2-aminovinyl]-1-methylquinolinium iodides (**3**) were prepared from the bis(2-methylthio) derivatives by reaction with the appropriate amine at 30–70 °C, according to the previous procedure.[11] For compounds of type **2**, a solution of the methylene base **4** in dry toluene was prepared with an appropriate base, followed by reaction with carbon disulfide in toluene and treatment with iodomethane in DMF. This procedure was superior to that in which the dithio acid zwitterion was isolated. Spectral characteristics of the quinolinium compounds prepared were described previously.[10,11] Physical characteristics of both series are listed in Table II.

Reaction of the bis(methylthio) compounds **2** with 1 mol of primary or secondary amine to form **3** generally resulted in replacement of only one thiomethyl function. Use of 2 mol of amine, as in the case of *N,N*-dimethylethylenediamine, resulted in replacement of both methylthio groups. The bis(methylthio) and methylthio amino derivatives were generally moderately soluble in both water and the polar organic solvents; the longer chain difunctional amino derivatives had generally good solubilities in alcohols and other polar solvents, as well as in water.

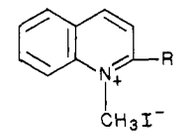
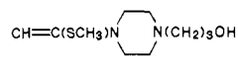
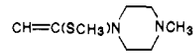
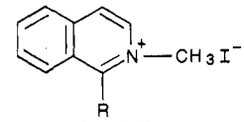
Condensation of 1-methylpicolinium iodide with carbon disulfide in the presence of aqueous sodium hydroxide resulted in replacement of the 2-methyl group to give the pyridinium dithio acid **7**.[8] Use of either butyllithium or potassium *tert*-butoxide as a base for this reaction, followed by conversion to the resultant bis(methylthio) derivatives **5** by iodomethane, yielded the desired dithioacetic acid derivatives. Attempts to isolate the dithio acid gave an unstable compound **8**, which was converted to the bis(methylthio) derivative **5** with iodomethane. Formation of the tetrakis(methylthio) derivative from the 2,6-dimethylpyridinium iodide required a two-step condensation with carbon disulfide in the presence of potassium *tert*-butoxide, followed by reaction with iodomethane. Conversion of the bis(methylthio) derivatives **5** to the methylthio amino compounds **6** took place as before (Scheme I).

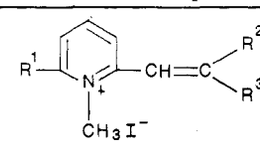
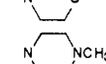
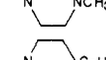
Further modification of the pyridinium derivatives was made in the thioether portion to increase lipophilicity. The methylthio functions were replaced by ethylthio, butylthio, and hexylthio groups, and the amine functions included both cyclic and open-chain amines, with the inclusion of additional amino, hydroxy, and alkoxy groups.

Radiation-Protective Test Results. Tests for radiation protection were supplied by the Walter Reed Army Institute of Research, and results were transmitted by H. A. Musallam. Tests were performed by whole-body γ-irradiation of mice using 1000 rads, generally 30 min after administration of the compound, either intraperitoneally or orally. Testing results are shown in Table III.

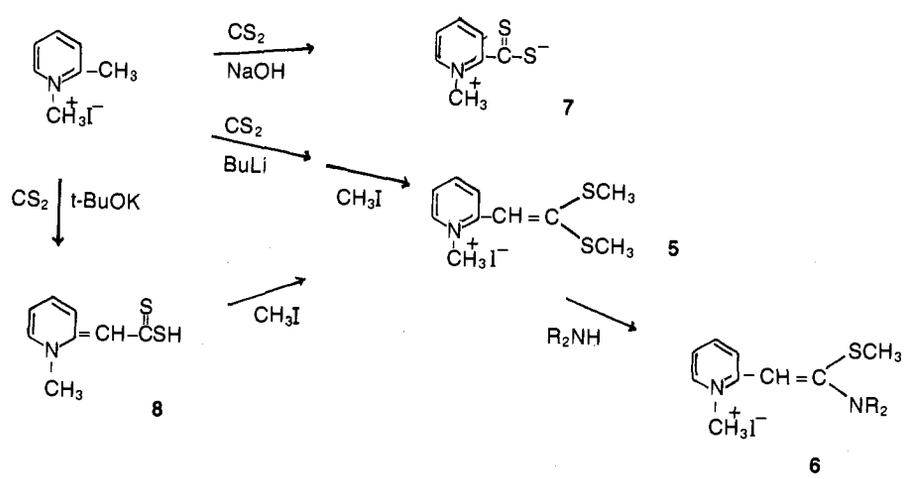
The most active compounds in both the quinolinium and pyridinium series gave good protection (>45% survival)

Table II. 1-Methylquinolinium(and pyridinium)-2-dithioacetic Acid Derivatives

no.	R	mp, °C	yield, %	formula	anal.
					
9	$CH{=}C(SCH_3)NH(CH_2)_2OCH_3$	143–145	58	$C_{16}H_{21}IN_2OS$	C, H, N
10	$CH{=}C(SCH_3)NH(CH_2)_3OH$	135–138	40	$C_{16}H_{21}IN_2OS$	C, H, N
11	$CH{=}C[NHCH_2CH_2N(CH_3)_2]_2$	148–150	39	$C_{20}H_{32}IN_5$	C, H, N
12	$CH{=}C(SCH_3)NHCH_2CH(OCH_3)_2$	142–143	58	$C_{17}H_{23}IN_2O_2S$	C, H, N
13		173–174	31	$C_{20}H_{28}IN_3OS$	C, H, N
14		125–126	54	$C_{18}H_{24}IN_3S$	C, H, N
					
15	$CH{=}C(SCH_3)_2$	204–205	70	$C_{14}H_{16}INS_2$	C, H, N

no.	R^1	R^2	R^3	mp, °C	yield, %	formula	anal.
							
5	H	SCH_3	SCH_3	134–135	53	$C_{10}H_{14}INS_2$	C, H, N
16	CH_3	SCH_3	SCH_3	165–166	68	$C_{11}H_{16}INS_2$	C, H, N
17	H	SC_2H_5	SC_2H_5	143–145	77	$C_{12}H_{18}INS_2$	C, H, N
18	H	SC_4H_9	SC_4H_9	105–106	79	$C_{16}H_{26}INS_2$	C, H, N
19	H	SC_6H_{13}	SC_6H_{13}	86–88	58	$C_{20}H_{34}INS_2$	C, H, N
20	H	SCH_3		143–144	66	$C_{14}H_{21}IN_2S$	C, H, N
21	H	SCH_3		154–157		$C_{13}H_{19}IN_2OS$	C, H, N
22	H	SCH_3		173–174	69	$C_{14}H_{22}IN_3S$	C, H, N
23	H	SCH_3		189–190	35	$C_{20}H_{25}IN_2S$	C, H, N
24	$(CH_3S)_2C{=}CH$	SCH_3	SCH_3	205–206	82	$C_{14}H_{20}INS_4$	C, H, N

Scheme I



at dose levels of less than 10 mg/kg. This is in contrast to the effective dose levels of the mercaptoamines; 2-aminoethanethiol (MEA), for instance, is most active at a dose range of 150–250 mg/kg,[12] and 2-[(3-aminopropyl)amino]ethyl dihydrogen phosphorothioate (WR2721) is most active at a dose range of 300–600 mg/kg.[13] The two most active compounds are the 2-

(12) Klayman, D. L.; Copeland, E. S. In *Drug Design*; Ariens, E. J., Ed.; Academic: New York, 1975; Vol. 6, p 94.

(13) Piper, J. R.; Stringfellow, C. R., Jr.; Elliott, R. D.; Johnston, T. P. *J. Med. Chem.* **1969**, *12*, 236.

(14) Foye, W. O.; Kauffman, J. M. *J. Pharm. Sci.* **1979**, *68*, 336.

(15) Foye, W. O.; Kauffman, J. M. *J. Pharm. Sci.* **1968**, *57*, 1611.

Table III. Radiation-Protective Properties in Mice[a]

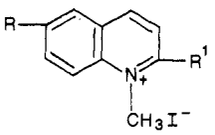
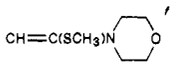
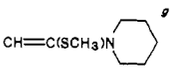
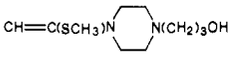
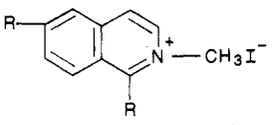
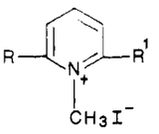
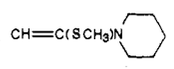
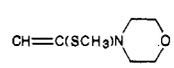
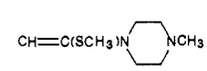
R	R^1	LD_{50},[b] mg/kg	route	dose, mg/kg	survival,[c] %
					
CH_3	$CH_2CS_2^-$[d,e]	~225	IP	150	10
				75	20
				37.5	10
H	$CH{=}C(SCH_3)_2$	~300	IP	150	60
				75	0
				37.5	0
		>300	PO	300	0
				150	10
				75	10
CH_3		~15	IP	9.38	60
				4.69	0
				2.34	0
H		~5	IP	4.69	10
				2.34	70
				1.17	30
CH_3O	$CH{=}C(SCH_3)_2$	~30	IP	9.4	0
				4.7	0
				2.3	0
H	$CH{=}C(SCH_3)NHCH_2CH_2OCH_3$	~50	IP	37.5	0 (9 tox)
				18.8	0
				9.4	0
H	$CH{=}C(SCH_3)NH(CH_2)_3OH$	~50	IP	37.5	0
				18.8	0
				9.4	0
H		>10	IP	9.4	30
				4.7	0
				2.3	0
H	$CH{=}C(SCH_3)NHCH_2CH(OCH_3)_2$	~30	IP	18.8	30
				9.4	0
				4.7	0
H	$CH{=}C(NHCH_2CH_2N(CH_3)_2)_2$	~90	IP	75	0 (1 tox)
				37.5	0
				18.8	0
					
H	$CH{=}C(SCH_3)_2$	~15	IP	9.4	20
				4.7	0
				2.3	0
					
H	$CH{=}C(SCH_3)_2$	~30	IP	18.8	50
				9.4	0
				4.7	0
CH_3	$CH{=}C(SCH_3)_2$	~50	IP	18.8	40 (1 tox)
				9.4	0
				4.7	0
$^-S_2CCH_2$	$CH_2CS_2^-Na^+$[d,h]	>600	IP	1200	0 (2 tox)
				600	0
				300	0
$(CH_3S)_2C{=}CH$	$CH{=}C(SCH_3)_2$	~25	IP	9.4	30
				4.7	10
				2.3	10
H		~25	IP	9.4	80
				4.7	20
				2.4	30
H		~50	IP	18.8	0
				9.4	0
				4.7	0
H		~60	IP	18.8	10
				9.4	0
				4.7	0

Table III (Continued)

R	R^1	LD_{50},[b] mg/kg	route	dose, mg/kg	survival,[c] %
H	$CH{=}C(SC_2H_5)_2$	~20	IP	9.4	20
				4.7	0
H	$CH{=}C(SC_4H_9)_2$	~3	IP	2.3	30 (3 tox)
				1.2	10 (1 tox)
				0.6	0
H	$CH{=}C(SC_6H_{13})_2$	~5	IP	4.7	0 (8 tox)
				2.3	0 (4 tox)
				1.2	0

[a] Groups of 10 mice were exposed to 1000-rad γ-radiation 30 min after dosing. [b] Toxic doses were generally determined in 10–20% ethanol by ip administration in mice; animals were observed for 20 days. [c] Percent survival was determined over a 30-day period. Deaths due to toxicity of drug (shown in parentheses) appeared before 5 days. [d] No I^- present. [e] Oral doses up to 600 mg/kg gave no protection. [f] Oral doses up to 75 mg/kg gave no protection. [g] Oral doses up to 18.75 mg/kg gave no protection. [h] Oral doses up to 1200 mg/kg gave no protection.

(methylthio)-2-piperidino derivative of the 1-methyl-2-vinylpyridinium iodide **20**, which gave an 80% survival rate at a dose of 9.4 mg/kg, and the 2-(methylthio)-2-piperidino derivative of the 1-methyl-2-vinylquinolinium iodide **3**, which provided 70% survival, at a dose of 2.34 mg/kg. The bis(methylthio) derivative of the 6-methylquinolinium compound **2**, however, provided 60% protection, but at a dose of 150 mg/kg, more comparable to that of the mercapto amines. The bis(methylthio) derivative of the pyridinium analogue **5** gave 50% protection at a dose of 18.8 mg/kg.

Other substitutions in the molecules either lowered or removed activity. The 1-methylpyridinium methylpyridinium bis(ethylthio) and bis(butylthio) derivatives **17** and **18** gave 20% and 30% protection, respectively. The bis(hexylthio) derivative **19** was inactive. Incorporation of alkoxy or hydroxy groups in the amine moiety resulted in fair (25–45% protection) or no activity. Inclusion of the morpholino moiety in the 1,6-dimethylquinolinium bis(methylthio) compound **3** provided 60% protection, but in the *N*-methylpyridinium bis(methylthio) compound **21**, inclusion of morpholine resulted in loss of activity. The only quinolinium dithio acid zwitterion tested, the 1,6-dimethylquinolinium derivative[8] **1**, gave only 20% protection at a dose of 75 mg/kg. The bis(dithio acid dianion) of the pyridinium compound[8] was inactive, but the corresponding tetrakis(methylthio) derivative **24** gave fair (30%) protection.

Because of the much lower dose levels at which these compounds provide protection, as compared to the aminoalkanethiols, it is possible that they are acting through a different mechanism than the one proposed. In addition, the methylthio ether function would be required to undergo hydrolysis or enzymatic demethylation to provide a free thiol group for H-atom transfer. Laboratory attempts to hydrolyze the methylthio function in acidic solutions resulted in decomposition with liberation of hydrogen sulfide, as indicated by moist lead acetate paper.

Experimental Section

Melting points were determined in capillaries with a Mel-Temp block and are uncorrected. ^1H NMR spectra were obtained with a Varian T-60 spectrometer, using tetramethylsilane as internal standard. IR spectra were obtained with a Perkin-Elmer Model 457A spectrophotometer using KBr pellets. Elemental analyses were done by Multi Chem Laboratories, Lowell, MA, and are within ±0.4% of theoretical values. TLC was carried out with use of silica gel plates with fluorescent indicator. Organic reagents were supplied by Aldrich Chemical Co. or Eastman Organic Chemicals.

1-Methyl-2-(dithiocarboxymethylene)-1,2-dihydropyridine (8). To a suspension of 1,2-dimethylpyridinium iodide (2.35 g, 10 mmol) in dry toluene (15 mL) were added potassium *tert*-butoxide (2.4 g, 20 mmol) and 5 drops of 95% EtOH. The mixture was stirred under N_2 for 15 min, and the yellow solution was decanted into a dry flask. The process was repeated, and the solution was dried (Na_2SO_4) and filtered. To the filtrate was added a large excess of CS_2, and the orange-red solid was stirred for 10 min, collected by filtration, and washed with toluene. It was dried under vacuum; mp 130–135 °C; ^1H NMR (Me_2SO-d_6) δ 3.33 (s, 3 H, NCH_3), 4.23 (s, 1 H, CH), 7.8–8.4 (m, 4 H, ring H). Reaction of the product with iodomethane in CH_2Cl_2 gave **5**. Anal. ($C_{10}H_{14}INS_2$) C, H, N.

1-Methyl-2-[2,2-bis(methylthio)vinyl]pyridinium Iodide (5). To a stirred solution of picoline (0.97 g, 10 mmol) in dry THF (20 mL) under N_2 at −5 to −10 °C was added *n*-butyllithium (4.4 mL, 2.5 M) in hexane dropwise. To the red solution was added CS_2 (1.2 mL, 20 mmol) in THF (5 mL) dropwise at −5 to −10 °C. The mixture was stirred for 30 min at this temperature, and an excess of iodomethane (4 mL, 64 mmol) was added. The resulting mixture was stirred overnight at room temperature and filtered. The residue was washed with CH_2Cl_2 (40 mL) and repeatedly with water until the aqueous layer was colorless. The combined washings were condentrated to 10–15 mL in a rotary evaporator at 50–60 °C. The solution was stored at 0 °C, and the resulting crystals were filtered and recrystallized (H_2O), giving 1.8 g (53%) of yellow crystals: mp 134–135 °C; IR ν 1630 (C=C), 1175 (CH_2S), 800 (C=C); ^1H NMR ($CDCl_3$) δ 2.57 (s, 3 H, SCH_3), 2.67 (s, 3 H, SCH_3), 4.57 (s, 3 H, NCH_3), 6.53 (s, 1 H, CH=C), 7.63–9.0 (m, 4 H, arom H). Anal. ($C_{10}H_{14}INS_2$) C, H, N.

1,6-Dimethyl-2-[2,2-bis(2-methylthio)vinyl]pyridinium Iodide. To a suspension of 1,2,6-trimethylpyridinium iodide (7.5 g, 30 mmol) in toluene (50 mL) was added potassium *tert*-butoxide (3.5 g) in one portion. The mixture was stirred at room temperature, and 10–15 drops of 95% EtOH were added. The yellow solution was stirred for 20 min, the supernatant liquid was decanted, and to the residue was added toluene (50 mL), followed by potassium *tert*-butoxide (1 g) and 95% EtOH (10–15 drops). This process was repeated with use of the same quantities of reagents. To the combined toluene solutions was added an excess of CS_2 (7.2 mL, 120 mmol), and the mixture was stirred for 30 min. The red solid was filtered and suspended in $CHCl_2$ (100 mL), and iodomethane (7.4 mL, 120 mmol) was added. The mixture was stirred overnight at room temperature and was filtered. The residue was washed with CH_2Cl_2 and the organic extract was evaporated to dryness. The residue was recrystallized (H_2O) to give 7.3 g (68%) of yellow needles: mp 165–166 °C; IR ν 1620 (C=C), 1190 (CH_2S), 830 (C=C); ^1H NMR ($CDCl_3$) δ 2.53 (s, 3 H, SCH_3), 2.67 (s, 3 H, SCH_3), 3.00 (s, 3 H, CH_3), 4.35 (s, 3 H, NCH_3), 6.63 (s, 1 H, CH=C), 7.67–8.41 (m, 3 H, arom H). Anal. ($C_{11}H_{16}INS_2$) C, H, N.

1-Methyl-2,6-bis[2,2-bis(2-methylthio)vinyl]pyridinium Iodide. The foregoing procedure was repeated on the previous compound, and an 82% yield of yellow crystals was obtained: mp 205–206 °C; IR ν 1605 (C=C), 1190 (CH_2)S), 820 (C=C); ^1H NMR

(16) Foye, W. O.; Cho, Y. J.; Oh, K. H. *J. Pharm. Sci.* **1970**, *59*, 114.
(17) Foye, W. O.; Lowe, Y. H.; Lanzillo, J. J. *J. Pharm. Sci.* **1976**, *65*, 1247.

($CDCl_3$) δ 2.53 (s, 6 H, SCH_3), 2.68 (s, 6 H, SCH_3), 4.33 (s, 3 H, NCH_3), 6.55 (br s, 2 H, CH=C), 7.73–8.33 (m, 3 H, arom H). Anal. ($C_{14}H_{20}INS_4$) C, H, N.

The following procedure is representative of the formation of the *S*-alkyl derivatives (larger than methyl).

1-Methyl-2-[2,2-bis(2-ethylthio)vinyl]pyridinium Iodide. To a stirred suspension of picolinium methiodide (3.5 g, 15 mmol) in toluene (100 mL) were added potassium *tert*-butoxide (2 g) and 10–15 drops of 95% EtOH. The mixture was stirred 20 min, and the clear supernatant liquid was decanted. This process was repeated five times with 50 mL of toluene, 0.5 g of potassium *tert*-butoxide, and 5–10 drops of 95% EtOH. To the combined toluene solutions was added CS_2 (5 mL, 83 mmol), and the mixture was stirred for 30 min at room temperature. It was filtered, and the residue was taken up in DMF (20 mL). An excess of iodoethane (6 mL, 75 mmol) was added, and the mixture was stirred overnight at room temperature. The solvent was removed in vacuo at 60–70 °C, and the residue was recrystallized (H_2O), giving 4.2 g (77%) of yellow needles: mp 143–145 °C; IR ν 1620 (C=C), 1165–1175 (CH_2S), 800 (C=C); ^1H NMR ($CDCl_3$) δ 1.10–1.60 (m, 6 H, C_2H_5), 2.77–3.43 (m, 4 H, C_2H_5), 4.50 (s, 3 H, NCH_3), 6.67 (s, 1 H, CH=C), 7.63–9.07 (m, 4 H, arom H). Anal. ($C_{12}H_{18}INS_2$) C, H, N.

The following procedure is representative of the synthesis of compounds of type **6**.

1-Methyl-2-[2-(methylthio)-2-piperidinovinyl]pyridinium Iodide. 1-Methyl-2-[2,2-bis(2-methylthio)vinyl]pyridinium iodide (3.0 g, 9 mmol) and piperidine (1.53 g, 18 mmol) were added to 20 mL of DMF, and the mixture was heated at 70 °C for 2 h and at 50 °C for 4 days with stirring. After being cooled, the solution was added to 150 mL of ether and swirled, and the ethereal layer was decanted. Ethyl acetate (150 mL) was added to the residual syrup, and after it was chilled, yellow crystals separated and were filtered and recrystallized from 1:1 EtOH/2-PrOH, giving 2.19 g (66%): mp 143–144 °C; IR ν 1630 (C=C), 1160–1170 (CH_2S), 780 (C=C); ^1H NMR ($CDCl_3$) δ 1.40–1.70 (m, 6 H, piperidine), 2.40 (s, 3 H, SCH_3), 3.20–3.60 (d, 4 H, CH_2N), 4.0 (s, 3 H, NCH_3), 5.2 (s, 1 H, CH=C), 7.2–8.6 (m, 4 H, arom H). Anal. ($C_{14}H_{21}IN_2S$) C, H, N.

The following procedure is representative of the synthesis of compounds of type **3**.

1-Methyl-2-[2-(methylthio)-2-[bis(methoxyethyl)amino]-vinyl]quinolinium Iodide. 1-Methyl-2-[2,2-bis(methylthio)-vinyl]quinolinium iodide[14] (4.0 g, 10 mmol) and aminoacetaldehyde dimethyl acetal (1.05 g, 10 mmol) were added to 40 mL of Me_2SO. The solution was stirred at room temperature for 4 days and mixed with 300 mL of ether, and the ethereal layer was decanted. The solvent was evaporated and 50 mL of 2-PrOH was added to the residue. A solid was filtered and recrystallized (2-PrOH) to give 2.48 g (58%) of yellow crystals: mp 142–143 °C; IR ν 3200 (NH), 1610 (C=C), 820 (C=C); ^1H NMR (Me_2SO-d_6) δ 2.60 (s, 3 H, SCH_3), 3.36 (d, 6 H, OCH_3), 4.0 (s, 3 H, NCH_3), 4.40 (s, 2 H, CH_2N), 5.50 (s, 1 H, CH=C), 7.8–8.6 (m, arom H). Anal. ($C_{17}H_{23}IN_2O_2S$) C, H, N.

2-Methyl-1-[2,2-bis(methylthio)vinyl]isoquinolinium Iodide. To a suspension of 1,2-dimethylisoquinolinium iodide (2.5 g, 8.8 mmol) in 50 mL of toluene were added 1.0 g (8 mmol) of potassium *tert*-butoxide and 5–10 drops of 95% EtOH. The mixture was stirred for 20 min, and the clear supernatant liquid was decanted. To the residue were added toluene (35 mL), potassium *tert*-butoxide (0.5 g), and 95% EtOH (5–10 drops). The mixture was stirred for 20 min, and the supernatant liquid was decanted. The process was repeated, and to the combined toluene solutions was added CS_2 (3 mL, 50 mmol). The solution was stirred at room temperature for 30 min, iodomethane (3 mL, 48 mmol) was added, and the mixture was stirred overnight. Toluene was removed in a rotary evaporator at 50–60 °C, and the residue was recrystallized from water, giving 2.4 g (70%) of yellow needles: mp 204–205 °C; IR ν 1630 (C=C), 1155 (CH_2)S), 815 (C=C); ^1H NMR ($CDCl_3$) δ 2.37 (s, 3 H, SCH_3), 2.80 (s, 3 H, SCH_3), 4.65 (s, 3 H, NCH_3), 7.03 (s, 1 H, CH=C), 7.80–9.10 (m, 6 H, arom H). Anal. ($C_{14}H_{16}INS_2$) C, H, N.

Test for Radiation Protection. Compounds were administered to groups of 10 mice at each dose level 30 min prior to whole-body irradiation with 1000 rads with a ^{60}Co source. Female C57 B16 mice, 18–20 g, were used. Compounds were generally injected intraperitoneally in water or 10–20% aqueous ethanol; in some cases Klucel or a Tween was also required. Animals surviving beyond 30 days were considered protected.

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Registry No. 1 (R = CH_3), 67943-66-2; 2 (R = H), 21804-67-1; 3 (R = CH_3, R_2 = $(CH_2)_2O(CH_2)_2$), 74020-12-5; 3 (R = H, R_2 = $(CH_2)_5$), 88973-10-8; 3 (R = CH_3O, R_2 = SCH_3), 74020-11-4; 5, 56185-70-7; 7·Na(6-$CH_2CS_2^-$), 67943-63-9; 8, 21695-44-3; 9, 104664-33-7; 10, 104664-34-8; 11, 104664-35-9; 12, 104664-36-0; 13, 104664-37-1; 14, 88973-11-9; 15 (R = CH=C$(SCH_3)_2$), 104664-38-2; 15 (R = CH_3), 51843-14-2; 16, 104664-39-3; 17, 104664-40-6; 18, 104664-41-7; 19, 104664-42-8; 20, 104664-43-9; 21, 54254-80-7; 22, 110-89-4; 23, 104692-93-5; 24, 104664-44-0; CS_2, 75-15-0; CH_3I, 74-88-4; H_3CCH_2I, 75-03-6; $H_2NCH_2CH(OCH_3)_2$, 22483-09-6; 1,2-dimethylpyridinium iodide, 872-73-1; picoline, 1333-41-1; 1,2,6-trimethylpyridinium iodide, 2525-19-1; picolinium methiodide, 930-73-4; piperidine, 110-89-4.

Synthesis and Antilipolytic Activities of Quinolyl Carbanilates and Related Analogues

John H. Musser,*[1] Utpal Chakraborty, Kevin Bailey, Stan Sciortino, Carol Whyzmuzis, Dilip Amin, and Charles A. Sutherland*

William H. Rorer, Inc., Fort Washington, Pennsylvania 19034. *Received March 31, 1986*

A series of quinolyl carbanilates was prepared and tested as antilipolytic agents. These compounds inhibited production of glycerol from rat adipocytes and inhibited liberation of free fatty acids from triolein by canine cardiac triglyceride lipases. An extensive structure–activity relationship study indicated that 8-quinolyl 4-methoxycarbanilate (1) contained features necessary for maximum potency in vitro. Substituting a benzofuranyl group for the quinolyl group of 1 provided the most interesting compound on the basis of both potency and structural novelty. 7-Benzofuranyl 4-methoxycarbanilate (44) has IC_{50}'s of 16 and 0.3 μM in the myocardial lipase and rat adipocyte assays, respectively. In vivo, compound 44 was orally active as an inhibitor (97% at 25 mg/kg) of lipolysis in the rat.

There is much evidence that free fatty acid (FFA) has a detrimental effect on the ischemic heart by disrupting electrical conduction, decreasing myocardial efficiency, and preventing the transfer of ADP and ATP, in and out, respectively, of the mitochondria. It has been shown that interventions which depress myocardial FFA accumulation

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