(13) D. Greco, F. Olmsted, M. G. N. Masson, and A. C. Corcoran, *J. Lab. Clin. Med.*, **41**, 729 (1953); D. M. Green, F. J. Saunders, N. Wahlgren, and R. L. Craig, *Amer. J. Physiol.*, **170**, 94 (1952).
(14) C. W. Muth, N. Abraham, M. L. Linfield, R. B. Wotring, and E. A. Pacofsky, *J. Org. Chem.*, **25**, 736 (1960).
(15) (a) S. R. Aspinal and E. J. Bianco, *J. Amer. Chem. Soc.*, **73**, 602 (1951); (b) Netherlands Application, 6,510,117 (1966); *Chem. Abstr.*, **65**, 3791*f* (1966).

Notes

Radioprotective Thiazolidines from β-Keto Esters†

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Antiradiation activity has been reported for a variety of thiazolidines,[1-7] although the absence of significant protection in certain other derivatives led Sweetman, *et al.*,[8] to conclude that a thiazolidine "ordinarily is likely to lock an aminothiol too firmly into a stable structure to afford a promising means of latentiating biologically active aminothiols."

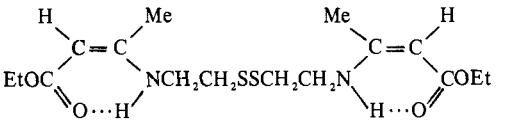
We have latentiated the well-known radioprotective 2-mercaptoethylamine (MEA) in the form of 2,2-disubstituted thiazolidine derivatives of some β-keto esters. The results of preliminary screening of these compounds for antiradiation activity in mice have been presented elsewhere.[9]

Results and Discussion

Data for the compounds prepared are shown in Table I. The synthesis of the thiazolidine bases **1-4** from MEA by a procedure similar to that used by Tondeur, *et al.*,[10] was straightforward. With the exception of **5**, the corresponding hydrochloride salts could not be obtained in an analogous manner from MEA hydrochloride. They were instead prepared from the parent bases and hydrogen chloride in anhydrous ether.

The carbamates **9-12** were prepared from equimolar quantities of ethyl chloroformate and the thiazolidine bases. In each instance, about half of the base was converted into its hydrochloride which was isolated and purified with little loss. The theoretic yield of carbamate, calculated from the thiazolidine, was thus reduced by *ca.* 50%, making the obtained yields (Table I) virtually quantitative. The use of tertiary bases to trap the hydrogen chloride generated by the condensation of the chloroformate and thiazolidine did not produce satisfactory yields of the carbamates.

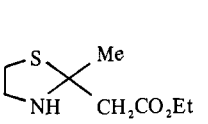
Neither the free bases nor the hydrochloride salts of these disubstituted heterocycles proved to be particularly stable. The thiazolidine bases decomposed on standing over a period of a few weeks. The acetoacetate condensation product **1** apparently underwent aerial oxidation to the disulfide **13** of ethyl 3-(2-mercaptoethylamino)crotonate. The ir spectrum (in KBr) of this substance shows weak N-H absorption at 3250 cm^{-1} and strong bands at 1645 and 1600 cm^{-1} for the intramolecularly hydrogen bonded carbonyl and the C=C stretching mode of the 3-aminocrotonate moiety.[11,12] Similarly, the pmr spectrum (in $CDCl_3$) supports structure **13**.



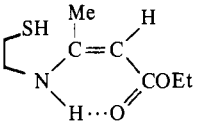
13

The low-field position (8.75 ppm) of the enamine NH proton is apparently due to the paramagnetic effect produced by intramolecular hydrogen bonding; the corresponding signal in related *trans*-enamines is near 5.5 ppm.[13]

Both the ir and pmr spectral data suggest that the four bases **1-4** themselves exist in tautomeric equilibria with the corresponding β-aminocrotonates (*e.g.*, **14**). These proto-



1

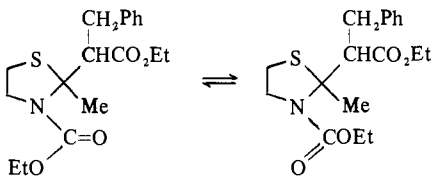


14

tropic reactions are interesting since they illustrate the lability of the C(2)-S(1) bond and therefore the reversibility of this form of latentiation. It seems that, while 2,2 disubstitution reportedly decreases the stability of thiazolidines,[10] further destabilization may occur in the β-keto ester derivatives, due to *stabilization* of the open chain tautomers (**14**) by the ester carbonyl, both through conjugation with the double bond and through hydrogen bonding with the amine proton.

Although the hydrochlorides were reasonably stable in the dry crystalline state, their hygroscopicity led to eventual acid hydrolysis of the thio-aminal linkage, so rapidly in the case of **5** that it was unsuited for biological evaluation.[9] The carbamates were much more stable.

Restricted rotation about the amide C-N bond of **12**, resulting in the presence of pseudo-geometric isomers **12a** and



12a 12b

12b, was evidenced in the pmr spectrum by the marked splitting of the singlet for the 2-methyl group and, to a lesser extent, of the triplet and quartet for the carbamate

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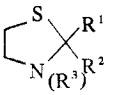
Table I. Physical Data for Thiazolidines Prepared



Compd	R^1	R^2	R^3	Yield, %	Bp (mm) or mp, °C	Formula	Analyses
1	Me	CH_2CO_2Et	H	69[a]	73-74 (0.1)[a]	$C_8H_{15}NO_2S$	
2	Pr	CH_2CO_2Et	H	58	77-78 (0.1)	$C_{10}H_{19}NO_2S$	C, H, N, S
3	Ph	CH_2CO_2Et	H	54	68-70[b]	$C_{13}H_{17}NO_2S$	C, H, N, S
4	Me	$CH(CH_2Ph)CO_2Et$	H	67	137-138 (0.2)	$C_{15}H_{21}NO_2S$	C, H[c]
5	Me	CH_2CO_2Et	H·HCl	100	112-114[d]	$C_8H_{16}ClNO_2S$	
6	Pr	CH_2CO_2Et	H·HCl	100	115-117	$C_{10}H_{20}ClNO_2S$	C, H, Cl, N, S
7	Ph	CH_2CO_2Et	H·HCl	100	127-128	$C_{13}H_{18}ClNO_2S$	C, H, Cl, N[e]
8	Me	$CH(CH_2Ph)CO_2Et$	H·HCl	100	147-149	$C_{15}H_{22}ClNO_2S$	C, H, Cl
9	Me	CH_2CO_2Et	CO_2Et	48	94-95 (0.1)	$C_{11}H_{19}NO_4S$	C, H, N, S
10	Pr	CH_2CO_2Et	CO_2Et	60	103-104 (0.1)	$C_{13}H_{23}NO_4S$	C, H, S[f]
11	Ph	CH_2CO_2Et	CO_2Et	46	158-159 (0.1)	$C_{16}H_{21}NO_4S$	g
12	Me	$CH(CH_2Ph)CO_2Et$	CO_2Et	51	162-163 (0.1)	$C_{18}H_{25}NO_4S$	C, H, S[h]

[a] Lit.[10] 60%, bp 154-155° (20 mm). [b] From Et_2O. [c] N: calcd, 5.01; found, 5.56. S: calcd, 11.47; found, 11.88. [d] Lit.[10] mp 118°. [e] S: calcd, 11.14; found, 11.61. [f] N: calcd, 4.84; found, 5.28. [g] C: calcd, 59.42; found, 61.56, 58.81. H: calcd, 6.54; found, 5.43, 5.52. N: calcd, 4.33; found, 4.73, 4.60. S: calcd, 9.91; found, 9.54, 11.07. [h] N: calcd, 3.99; found, 4.44.

Table II. Effect of Temperature on Signals Assigned to the 2-Methyl Group in the 100-MHz Spectrum of 12 in DMF-d_7

Temp, °C	Signal 1, ppm	Signal 2, ppm	Δδ, ppm
28	1.79	1.94	0.15
70	1.79	1.92	0.13
100	1.80	1.91	0.11

ethyl protons. These chemical shift differentials decreased in spectra obtained at higher temperatures, as expected, in response to an increased rate of bond rotation (*cf.* Table II).

As we have reported elsewhere,[9] three of these thiazolidines have significant antiradiation activity in mice, measured as per cent survival for 30 days against 800 rads of X-radiation (133 rads/min), which was lethal to 96% of the control animals. Administered intraperitoneally (ip) 15 min prior to irradiation, 6 (300 mg/kg) gave 62% survival, 8 (600 mg/kg) 81%, and 9 (600 mg/kg) 77%, while MEA hydrochloride (150 mg/kg) gave 87% survival. The salts 6 and 8 now have also been tested against γ-radiation from a ^{134}Cs source (95 rads/min). The compounds, emulsified in aqueous 0.3% carboxymethylcellulose plus 0.1% Tween 80, and adjusted to pH 7.0, were administered ip to SPF COBS white female mice. It was noted that the emulsified 8 was somewhat unstable, with some yellowing; no thiol odor was detected. The 30-day LD_{50} values and other statistical parameters were calculated with a computer program for probit analysis. At 300 mg/kg, 15 min prior to irradiation, 6 raised the $LD_{50/30}$ from 790 (740-881) rads for the untreated controls to 1069 (1032-1138) rads (95% fiducial limits) with a slope function of 7.86 ± 1.57. At 500 mg/kg, 30 min prior to irradiation, 8 resulted in an $LD_{50/30}$ value of 1160 (1106-1281) rads (95% fiducial limits) with a slope function of 8.27 ± 2.02. Since the response curves for the test groups were nearly parallel with that of the control (slope 9.97 ± 3.03), dose reduction factors (DRF) were approximated at 1.35 and 1.47, respectively, for 6 and 8.

These results indicate that, on a molar basis, the active thiazolidines examined exert radioprotection comparable with that of MEA itself. The less stable 8 protected better than 6. The implication is that they function by releasing MEA *in vivo*. Certainly, the spectroscopic data obtained on the free bases **1-4** illustrate the lability of the 2,2-disubstituted thiazolidine ring. This appears to be at variance with the findings of Granger, *et al.*,[14] who attribute the radioprotection activity of certain other thiazolidines to the intact ring.

In any case, we cannot report any superiority of the thiazolidines **1-12** over MEA. Derivatives of thiazolidines have not yet been found in which the pharmacokinetics of MEA have been suitably modulated to improve the radioprotection/toxicity ratio.

Experimental Section[#]

2-Mercaptoethylamine was prepared in quantitative yield from ethyleneimine and H_2S, as described by Mills and Bogert,[15] mp 97° (lit.[15] mp 97-98.5°).

2-Ethoxycarbonylmethyl-2-methylthiazolidine (1). Ethyl acetoacetate (254 g, 1.95 mol) was stirred with MEA (30 g, 0.39 mol) in the presence of molecular sieve (Type 4A, 15 g) at 60-70° for 24 hr. The mixture was filtered and excess ester was removed under reduced pressure. Distillation of the residue gave a colorless oil (51 g, 69%): bp 73-74° (0.1 mm); ir (film) 3300 (m, N-H), 1725 (vs, C=O), 1645 (m, C=O), 1600 cm^{-1} (s, C=C) [lit.[10] 60% yield; bp 154-155° (20 mm)].

The pmr spectrum ($CDCl_3$) is treated as two separate spectra, the first (interpreted as that of **1**) being about four times as intense as the second (considered to be due to **14**): δ 1.28 (t, 3, J = 7 Hz, CH_3CH_2O), 1.63 (s, 3, CH_3C), 2.80 (s, 2?, CH_2CO), 2.40-3.73 (m, 5?), 4.10 ppm (q, 2, J = 7 Hz, CH_3CH_2O); and δ 1.21 (t, 3, J = 7 Hz, CH_3CH_2O), 1.96 (s, 3, CH_3C=C), 2.40-3.73 (m, 5?), 4.06 (q, 2, J = 7 Hz, CH_3CH_2O), 4.48 (s, 1, CH=C), 8.80 ppm (broad, 1?, NH).

The other bases **2-4** were prepared in a similar manner. Their absorption spectra showed similar features.

The **hydrochlorides 5-8** were obtained by stirring the respective bases for 2 hr with ice-cooled anhydrous Et_2O previously saturated with HCl. They were recrystallized to constant melting point from EtOH-Et_2O. 2-Ethoxycarbonylmethyl-2-methylthiazolidine hydrochloride (**5**) was also prepared from ethyl acetoacetate (9.1 g, 70 mmol) and anhydrous MEA hydrochloride (7.9 g, 70 mmol): yield, 3.9 g (25%); mp 111-113° (lit.[10] mp 118°). Attempts to prepare the other salts by this route failed.

3-Ethoxycarbonyl-2-ethoxycarbonylmethyl-2-methylthiazolidine (9). Ethyl chloroformate (21.7 g, 0.2 mol) was added dropwise through 2 hr to a stirred, ice-cooled solution of **1** (37.8 g, 0.2 mol) in anhydrous Et_2O, and stirring was continued for 24 hr. The hydrochloride **5** produced (22.0 g, 0.1 mol) was filtered off and washed with Et_2O. The filtrate and washings were combined and the Et_2O

[#] Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are reported uncorrected. The ir spectra were recorded with a Perkin-Elmer Model 237 spectrophotometer and the pmr spectra with Varian Models T-60 and HA-100 spectrometers using tetramethylsilane as internal reference. Elemental analyses were performed by the Organisch-Chemisches Institut, Vienna. Analytical results for those elements indicated only by their symbols were within ±0.4% of the theoretical values.

was removed under reduced pressure. Distillation gave a colorless oil: 25 g (48%); bp 94–95° (0.1 mm). *Anal.* ($C_{11}H_{19}NO_4S$) C, H, N, S.

The other carbamates **10–12** were prepared in a similar manner. Their absorption spectra were consistent with the assigned structures.

Bis[2-(1-ethoxycarbonylprop-1-en-2-yl)aminoethyl] Disulfide (13). On overnight exposure to the atmosphere, or on standing in a closed container for a longer period of time, 1 gave 13 which was recrystallized from ligroine (bp 66–75°): mp 81–82.5°; ir (KBr) 3250 (w, N-H), 1645 (s, C=O), 1600 cm^{-1} (vs, C=C); pmr ($CDCl_3$) δ 1.24 (t, 6, J = 7.2 Hz, CH_3CH_2O), 1.96 (s, 6, CH_3C=C), 2.82 ("A_2B_2" m, 4, SCH_2CH_2N), 3.59 ("A_2B_2X" m, 4, SCH_2CH_2NH), 4.12 (q, 4, J = 7.2 Hz, CH_3CH_2O), 4.50 (s, 2, CH=C), 8.75 ppm (broad, 2, NH). *Anal.* ($C_{16}H_{28}N_2O_4S_2$) C, H.

13 gave the 2,4-dinitrophenylhydrazone of ethyl acetoacetate, mp 94°, mmp (with an authentic sample) 93°.

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References

(1) V. G. Yakovlev in "Chemical Protection of the Body Against Ionizing Radiation," V. S. Balabukha, Ed., Pergamon Press, New York, N. Y., 1963, p 11.
(2) F. Yu. Rachinskii, A. S. Mozzhukhin, N. M. Slavachevskaya, and L. I. Tank, *Usp. Khim.*, **28**, 1488 (1959); *Chem. Abstr.*, 54, 13424 (1960).
(3) A. Kaluszyner, P. Czerniak, and E. D. Bergmann, *Radiat. Res.*, 14, 23 (1961).
(4) J. F. Thomson, "Radiation Protection in Mammals," Reinhold, New York, N. Y., 1962, p 84.
(5) D. V. Mangind, *Radiobiologiya*, **3**, 240 (1963); *Chem. Abstr.*, 59, 11860 (1963).
(6) F. Yu. Rachinskii, M. S. Kushakovskii, B. V. Matveev, N. M. Slavachevskaya, and L. I. Tank, *Radiobiologiya*, 4, 266 (1964); *Chem. Abstr.*, 61, 4677 (1964).
(7) W. Shapiro, M. F. Tansy, and S. Elkin, *J. Pharm. Sci.*, 57, 1725 (1968).
(8) B. J. Sweetman, M. Bellas, and L. Field, *J. Med. Chem.*, 12, 888 (1969).
(9) P. S. Farmer, C.-C. Leung, and P. J. Foreman, *Progr. Antimicrob. Anticancer Chemother., Proc. Int. Congr. Chemother., 7th*, 1971, in press.
(10) R. Tondeur, R. Sion, and E. Deray, *Bull. Soc. Chim. Fr.*, **10**, 2493 (1964).
(11) G. DeStevens, B. Smolinski, and L. Dorfman, *J. Org. Chem.*, 29, 1115 (1964).
(12) F. Korte and K. Trautner, *Chem. Ber.*, **95**, 295 (1962).
(13) A. G. Sanchez and M. T. Aldava, *J. Chem. Soc. C*, 2570 (1968).
(14) R. Granger, H. Orzalesi, Y. Robbe, J. P. Chapat, A. Terol, M. Randon, J. Bitoun, and F. Simon, *Bull. Chem. Ther.*, 439 (1971).
(15) E. J. Mills and M. T. Bogert, *J. Amer. Chem. Soc.*, 62, 1173 (1940).

Naphthothiophenes. 2. Benzo[1,2-*b*:4,3-*b'*]dithiophenemethanols as Isosteres of Naphthothiophenes

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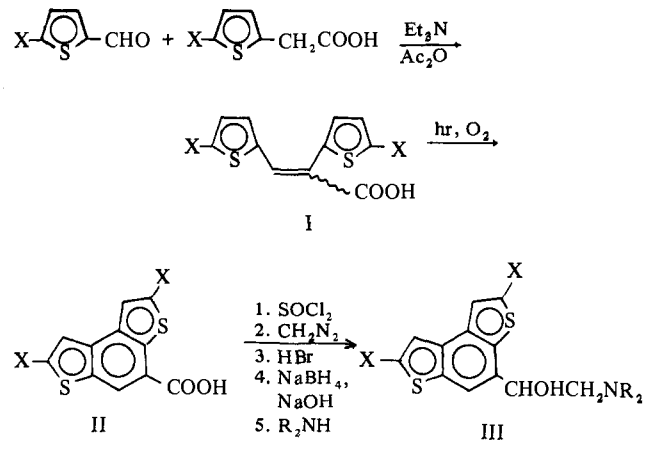
Recently we have been engaged in the synthesis of naphthothiopheneethanolamines for evaluation as antimalarial agents.[1] In connection with this program we have also prepared some closely related isosteric benzo[1,2-*b*:4,3-*b'*]dithiopheneethanolamines and this report deals with the synthesis and antimalarial activity of these compounds.

Scheme I



The synthesis of the benzodithiophenes is similar to that described for the naphthothiopheneethanolamines[1] and is outlined in Scheme I. The key step in this synthesis involves the photooxidative cyclization of dithienylethylenes to the benzodithiophenes. This method has been reported previously for the cyclization of dithienylethylenes in which the thiophene rings were unsubstituted.[2,3] The dithienylacrylic acids (I) were obtained by condensation of thiophene-2-carboxaldehydes and thiophene-2-acetic acids under modified Perkin reaction conditions.[4] No attempt was made to isolate the geometric isomers from the Perkin reaction since it was found that either isomer 1 or 2 underwent photooxidative cyclization upon exposure to 2537-Å light to yield the desired benzodithiophenecarboxylic acid. The structure of the photocyclization product was demonstrated by combustion analysis, by characteristic uv absorptions,[2] and by decarboxylation to yield a compound which has the properties reported in the literature for benzo[1,2-*b*:4,3-*b'*]dithiophene.[2,5] Photocyclization of the dithienylacrylic acids was achieved with **1**, **2**, and with **3** in poor yields. This observation may be worthy of note in view of the continuing interest in cyclization of stilbene analogs, particularly those which fail to cyclize.[6,7] The classical five-step procedure described by Lutz, *et al.*,[8] was employed to convert the benzo[1,2-*b*:4,3-*b'*]dithiophenecarboxylic acids (II) into the desired ethanolamines III.

The antimalarial activity of the benzodithiopheneethanolamines was assessed against *Plasmodium berghei* in mice by the method of Rane, *et al.*,[9] and the results are given in Table I. Table I also contains, for comparison, test data on selected isosteric phenanthreneethanolamines and quinine sulfate. Among the compounds tested 2-chloro-α-(*n*-dibutylaminomethyl)-4-benzo[1,2-*b*:4,3-*b'*]dithiophenemethanol hydrochloride (**9**) showed the most significant activity effecting cures at a dosage of 160 mg/kg. As noted upon comparison with **11**, **12**, and **13**, the activity of these benzodithiophenes is considerably superior to that of quinine but they are not superior to their phenanthrene isosteres. In addition to their *in vivo* antimalarial activity, these benzodithiophenes have been shown to bind *in vitro* to calf thymus DNA.†

Experimental Section

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were per-

†J. W. Panter, D. W. Boykin, Jr., and W. D. Wilson, unpublished results.