and neutralized by dropwise addition of HOAc to pH 6–7. The precipitated product was collected by filtration, washed (H_2O), dried (P_2O_5) at reduced pressure, and recrystallized as summarized in Table II.

2,4-Dioxo-1H-3-(N-*p*-nitrophenyl)-5-phenyl-6,6-dimethyl-5,6-dihydrofuro[2,3-*d*]pyrimidine (6e).—A solution of 3.85 g (0.0093 mole) of **5e** and 0.4 g (0.0075 mole) of $NaOCH_3$ in 150 ml of anhydrous MeOH was refluxed for 24 hr, concentrated at reduced pressure to one-tenth its initial volume, and hydrolyzed in H_2O (200 ml). The aqueous solution was neutralized by dropwise addition of HOAc causing the precipitation of a pale yellow solid which was subsequently collected by vacuum filtration, washed well (H_2O), dried (P_2O_5) at reduced pressure, and recrystallized twice from EtOAc affording 1.0 g (28%) of colorless crystals, mp 217–219°. *Anal.* ($C_{20}H_{17}N_3O_5$) C, H, N.

α-Carbomethoxy-β-phenyl-γ,γ-dimethylbutyrolactone (7).—A solution of 1.0 g (0.004 mole) of **4a** in 25 ml of $CHCl_3$ was refluxed for 10 hr with HCl gas bubbling through the solution continuously. After cooling to room temperature, the solution was washed (H_2O, 5% $NaHCO_3$, H_2O) and dried ($MgSO_4$). Concentration at reduced pressure yielded 970 mg of crude product which was recrystallized from 95% EtOH affording 790 mg (80%) of white crystalline product, mp 113.5–115°. *Anal.* ($C_{14}H_{16}O_4$) C, H.

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ω-Dithiolano Amino Acids[1]

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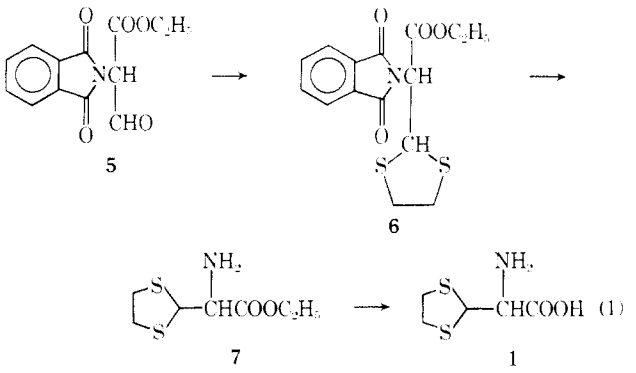
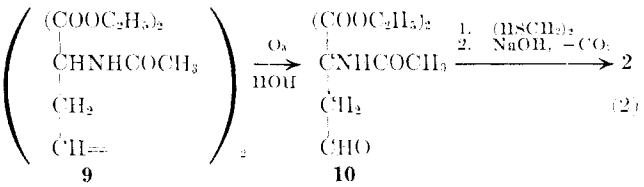
Many theories have been forwarded to explain the destructive action of ionizing radiation on the cell.[2] Although the chemical theories include a wide array of target molecules as the primary reaction in the cell, common agreement points to either a direct ionizing action on a cellular constituent or an indirect action mediated by peroxides formed in the cell. Based on the radioprotection afforded by cysteine and cysteamine many related aminothiols have been synthesized and examined. In this investigation interest was focused on the 1,3-dithiolane ring. The ease of chemical oxidation of this system to a disulfonyl would make it a likely candidate for radioprotection. Three 1,3-dithiolano amino acids were prepared for biological evaluation as radioprotective agents: 2-amino-2-[2-(1,3-dithiolano)]acetic (**1**), -propionic (**2**), and -butyric acids (**3**).

Ethyl phthalimidoacetate[3] (**4**) was treated with ethyl formate and NaOEt in xylene to give ethyl 2-phthalimidomalonaldehydate[4] (**5**). The 1,3-dithiolane derivative **6** was prepared by an HCl-catalyzed reaction of **5** with ethanedithiol. Hydrazine cleavage of **6** gave the intermediate amino ester **7** which was saponified by treatment with KOH in aqueous dioxane to give **1** (eq 1).

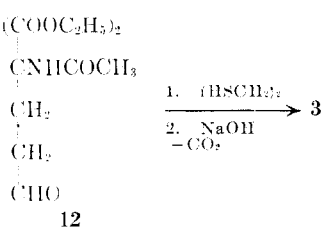


Unsuccessful approaches to the synthesis of the aldehyde **10** were made by alkylation of diethyl acetamidomalonate with chloroacetaldehyde diethyl acetal and through ozonolysis and reduction of diethyl allylacetamidomalonate (**8**). The synthesis of **2** (eq 2)



was accomplished *via* alkylation of diethyl acetamidomalonate using 1,4-dibromo-2-butene to give 1,1,6,6,-tetracarbethoxy-1,6-diacetamido-3-hexene (**9**).[5] Ozonolysis of **9** to **10** was followed by treatment with ethanedithiol to give the amido ester **11**. Alkaline saponification and decarboxylation in acid gave the intermediate amido acid; subsequent refluxing in 1 *M* H_2SO_4 yielded **2**.

Using the procedure of Warner and Moe[6] 4,4-dicarbethoxy-4-acetamidobutyraldehyde (**12**) was prepared. Treatment with ethanedithiol and HCl yielded the product 2-(3,3-dicarbethoxy-3-acetamidopropyl)-1,3-dithiolane (**13**); hydrolysis and decarboxylation of **13** proceeded with ease. Amide hydrolysis, unsuccessful using 2.5 *M* NaOH, was accomplished in 1 *M* H_2SO_4 to give 2-amino-4-[2-(1,3-dithiolano)]butyric acid (**3**).



Biological Results.—The radioprotective ability of 2-amino-2-[2-(1,3-dithiolano)]acetic acid (**1**) and 2-amino-4-[2-(1-3-dithiolano)]butyric acid (**3**) against radiation was tested in mice at Walter Reed Army Institute of Research. Neither of the compounds tested at 400 mg/kg afforded survival or protection in mice exposed to 950 R (cobalt-60, γ rays).

(1) This work was supported by Grant GM-1341, Division of General Medical Sciences, and by Grant 1K3-CA-10739 from the National Cancer Institutes, National Institutes of Health. Taken in part from the dissertation presented by A. A. Ramsey, May 1968, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

(2) (a) A. Pihl and T. Sanner, *Progr. Biochem. Pharmacol.*, **1**, 85 (1965); (b) Z. M. Bacq, "Chemical Protection Against Ionizing Radiation," Charles C Thomas, Publisher, Springfield, Ill., 1965, p 147.

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(4) J. C. Sheehan and D. A. Johnson, *J. Amer. Chem. Soc.*, **76**, 158 (1954).

(5) K. Schöpf, *Monatsh. Chem.*, **89**, 377 (1958).

(6) D. Warner and O. Moe, *J. Amer. Chem. Soc.*, **74**, 2690 (1952).

Experimental Section[7]

Ethyl 2-Phthalimido-2-[2-(1,3-dithiolano)]acetate (6).—To a stirred solution of ethyl α-phthalimidomalonaldehydate (**5**)[4] (0.02 mole) in 160 ml of dry $CHCl_3$ was added ethanedithiol (23.5 g, 0.25 mole); the solution was saturated with dry HCl and stirred at 25° for 12 hr. It was neutralized with 10% Na_2CO_3 solution, washed (H_2O), dried ($MgSO_4$), and filtered and most of the solvent was removed at 100° under N_2. The oily yellow residue was dissolved in EtOAc and treated with 5% NaOH solution. The aqueous portion was extracted again with EtOAc and the combined EtOAc solutions were washed (H_2O), dried, and evaporated to give a thick red syrup. An orange solid which was produced by standing overnight at 25° was recrystallized from EtOH to yield 40.6 g (60%) of **6**. An analytical sample recrystallized several times from C_6H_6 and from EtOH melted at 118°. The nmr spectra were as expected. *Anal.* ($C_{15}H_{15}NO_4S_2$) C, H, N, S.

Ethyl 2-Amino-2-[2-(1,3-dithiolano)]acetate (7).—Compound **6** (20.0 g, 0.066 mole) was dissolved in 500 ml of EtOH, 5.4 ml of 85% $(H_2N)_2 \cdot H_2O$ (0.09 mole) was added, and the solution was heated under reflux for 2.5 hr. The reaction mixture was cooled and the solid was removed by filtration. EtOH was removed, and the remaining liquid was dissolved in $CHCl_3$ and MeOH. This was chromatographed on 130 g of silica gel using hexane–$CHCl_3$ (1:1) as the eluent followed by $CHCl_3$ to give 8.0 g (59%) of the liquid amino ester **7**.

2-Amino-2-[2-(1,3-dithiolano)]acetic Acid (1).—The ester **7** (8.50 g, 0.041 mole) was added to a solution of 3.10 g (0.055 mole) of KOH in 100 ml of H_2O. Dioxane (15 ml) was added to effect partial solution and this mixture was refluxed for 2.5 hr. The solvent was removed under reduced pressure leaving an orange solid which was dissolved (H_2O), filtered, and neutralized by passing through an ion-exchange column of 12 g of Amberlite IRC-50 (H^+ form). The H_2O in the eluate was evaporated with a stream of air to leave 4.64 g (63%) of amino acid **1**, which was heated with activated charcoal and recrystallized from H_2O and EtOH to yield white crystals, mp 209° dec. *Anal.* ($C_5H_9NO_2S_2 \cdot 0.5H_2O$) C, H, N.

1,1,6,6-Tetracarbethoxy-1,6-diacetamido-3-hexene (9).[5]—NaOEt [from 2.3 g (0.1 g-atom) of Na in dry EtOH (225 ml)] was mixed with 21.7 g (0.1 mole) of diethyl acetamidomalonate and the stirred solution was heated to reflux for 30 min. A solution of 10.70 g (0.05 mole) of 1,4-dibromo-2-butene in 50 ml of dry EtOH was added dropwise over 30 min. The solution was refluxed for 6 hr, the NaBr was removed by filtration, and the EtOH was evaporated *in vacuo*. The residue was partitioned between $CHCl_3$ and H_2O, and the $CHCl_3$ extract was dried ($MgSO_4$) and evaporated *in vacuo* to yield 24.7 g (0.05 mole) of crude **9** (quantitative yield). Recrystallization from C_6H_6–C_6H_{14} produced white crystals, mp 118–119° (lit.[5] mp 112–114°). *Anal.* ($C_{22}H_{34}N_2O_{10}$) C, H, N.

3,3-Dicarbethoxy-3-acetamidopropionaldehyde (10).—Compound **9** (2.43 g, 0.005 mole) was treated with O_3 for 1 hr (60 mg/min) in 25 ml of EtOAc at −80°. The solution was warmed to 25° and N_2 was passed through for 30 min. EtOAc (75 ml) and 0.25 g of 5% Pd-C were added; the mixture was hydrogenated at 2 atm for 1.5 hr. The catalyst was removed by filtration and the EtOAc solution was stored at 4° for 12 hr. The solvent was removed giving **10** as a thick liquid which was not purified.

2-(2,2-Dicarbethoxy-2-acetamidoethyl)-1,3-dithiolane (11).—The yellow oil **10** (0.01 mole) was dissolved in 25 ml of AcOH and 3.0 g (0.03 mole) of ethanedithiol and 5 ml of freshly distilled $BF_3 \cdot Et_2O$ was added. This solution was stirred for 12 hr, neutralized with 16.6 g of aqueous NaOH, and extracted ($CHCl_3$). The extract was dried ($MgSO_4$), filtered, and evaporated *in vacuo* to produce a solid which was recrystallized from H_2O–EtOH to yield 1.16 g of **11** (0.0037 mole, 37% from **9**). An analytical sample, mp 112°, was prepared by sublimation at 95–100° (0.3 mm). *Anal.* ($C_{13}H_{21}NO_5S_2$) H, N, S; C: calcd, 46.53; found, 46.99.

2-Amino-3-[2-(1,3-dithiolane)]propionic Acid (2).—A solution of 0.5 g (1.5 mmoles) of **11** in 1.3 ml of EtOH and 0.53 g of Na_2CO_3 in 3.75 ml of H_2O was refluxed for 20 hr. The solution was cooled and partitioned between EtOAc and the basic aqueous solution. The aqueous extract was acidified with dilute HCl to pH 3 and extracted with three 75-ml portions of EtOAc. The combined extracts were dried (Na_2SO_4) and evaporated *in vacuo* to yield 0.27 g (1.15 mmoles, 78%) of the intermediate amido acid, mp 189.5–190.5°. The 2-acetamido-3-[2-(1,3-dithiolano)]-propionic acid (0.27 g, 1.15 mmoles) was refluxed in 5 ml of 1 *M* H_2SO_4 for 4.5 hr. The reaction mixture was cooled and neutralized by stirring with 40 g of Dowex 3 (OH^- form) ion-exchange resin in 50 ml of H_2O. The H_2O solution was filtered off and the resin was washed with 50 ml of H_2O. The obtained extracts were combined and the H_2O was evaporated with a stream of air to yield 0.17 g (0.9 mmole, 78%) of relatively pure amino acid **2**, which was recrystallized from H_2O–EtOH, mp 246°. *Anal.* ($C_6H_{11}NO_2S_2$) C, H.

2-(3,3-Dicarbethoxy-3-acetamidopropyl)-1,3-dithiolane (13).—The crude yellow syrup (0.50 mole) of **12**[6] was dissolved in $CHCl_3$ (200 ml) and 47.0 g (42.7 ml, 0.50 mole) of $(HSCH_2)_2$ was added. The solution was saturated with dry HCl, and the flask was stoppered and stirred for 12 hr. The $CHCl_3$ solution was washed to neutrality (H_2O), the solution was dried (Na_2SO_4), and most of the solvent was removed at 100° with N_2. The slightly viscous solution yielded 121 g (76%) of **13**. Recrystallization (Et_2O, aqueous EtOH) produced a white solid, mp 92–93°. *Anal.* ($C_{14}H_{23}NO_5S_2$) C, H, N, S.

2-Amino-4-[2-(1,3-dithiolano)]butyric Acid (3).—Compound **13** (17.1 g, 0.05 mole) was dissolved in 45 ml of EtOH. A solution of 125 ml of 1.25 *M* Na_2CO_3 was added and refluxed for 20 hr. The solution was cooled and extracted with two 75-ml portions of EtOAc. The aqueous solution was separated and the EtOAc extract was evaporated *in vacuo*. This residue again was treated with 25 ml of EtOH and 50 ml of 1.25 *M* Na_2CO_3 and refluxed for 24 hr. The combined aqueous solutions were acidified to pH 3, extracted with two 75-ml portions of EtOAc, dried (Na_2SO_4), and evaporated *in vacuo*. The residue, a brown liquid, was chromatographed on a silicic acid column and eluted with 2% MeOH in $CHCl_3$ to yield 7.25 g (0.035 mole, 70%) of 2-acetamido-4-[2-(1,3-dithiolano)]butyric acid. Recrystallization from $CHCl_3$ produced a white solid, mp 156.5–157°. The intermediate, 2-acetamido acid (7.25 g, 0.035 mole), and 100 ml of 1 *M* H_2SO_4 were refluxed for 5 hr. The orange solution was extracted with two portions of $CHCl_3$. The aqueous solution was neutralized to pH 6 with $Ba(OH)_2$ solution, $BaSO_4$ was removed by filtration, and the aqueous solution was concentrated *in vacuo* to 150 ml, which yielded 2.5 g of crude amino acid **3** upon standing. The mother liquor was evaporated to dryness and the residue was dissolved in a small amount of H_2O to yield an additional 1.52 g of **3**. The total yield of **3** was 0.019 mole (56%) which was dissolved in boiling H_2O, heated with activated charcoal, and filtered to give **3**, mp 262–263° dec. *Anal.* ($C_7H_{13}NO_2S_2$) C, H, N, S.

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(7) All melting points were taken on a calibrated Thomas-Hoover capillary melting point apparatus. Analyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England, by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M Model 185, University of Kansas. Spectral data were obtained using Beckman IR-8, IR-10, Varian A-60, and A-60A spectrometers. The latter used Me_4Si as an internal standard except in D_2O where 3-trimethylpropanesulfonic acid sodium salt was employed. The nmr spectra were as expected. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements are within 0.4% of the theoretical values.

Antimicrobial Activity of a Series of Aminoalkyl Esters of Benzyldithiocarbamic Acids

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In continuation of our previous work[1] on the preparation of water-soluble antimicrobial agents, we have prepared a number of 2-aminoethyl esters of N-benzyldithiocarbamic acids, in an effort to combine water solubility with the known activity of benzyl

(1) R. C. Tweit, R. D. Muir, S. Mizuba, and W. R. Crowley, Jr., *J. Med. Chem.*, **8**, 374 (1965).