

Terminal Dicarboximido Analogs of *S*-2-(ω -Aminoalkylamino)ethyl Dihydrogen Phosphorothioates and Related Compounds as Potential Antiradiation Agents. 1. Phthalimides and Saccharins¹

JAMES R. PIPER, CARL R. STRINGFELLOW, JR., ROBERT D. ELLIOTT, AND THOMAS P. JOHNSTON*

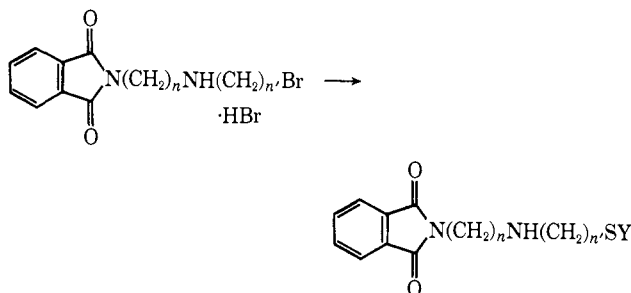
Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

Received September 26, 1970

A number of *S*-2-(ω -phthalimidoalkylamino)ethyl and *S*-3-(ω -phthalimidoalkylamino)propyl phosphorothioates, thiosulfates, and related compounds were prepared for evaluation as radioprotective agents. Of 31 compounds of this type tested only one, *S*-2-(2-phthalimidoethylamino)ethyl sodium hydrogen phosphorothioate (**2b**·6H₂O), gave fair protection in mice; 8 were slightly protective and all others nonprotective. *S*-2-Phthalimidoethyl thioacetate, an intermediate in the synthesis of the inactive *S*-2-(ω -(2-phthalimidoethylthio)alkylamino)ethyl thiosulfates **26a,b** and phosphorothioates **26c,d**, was the most active phthalimide tested. Rearrangement was noted in the last step of the conversion of 5-methyl-2-oxazolidinone into *S*-2-(3-phthalimido-propylamino)propyl hydrogen thiosulfate (**12**), and phthalimide ring opening precluded the conversion of *N*-(2-bromo-1,1-dimethylethyl)phthalimide to the corresponding tertiary-branched congeners of the title compounds.

The *N*-[ω -(2-bromoethylamino)alkyl]phthalimide hydrobromides **1a-g** (Scheme I), which were inter-

SCHEME I



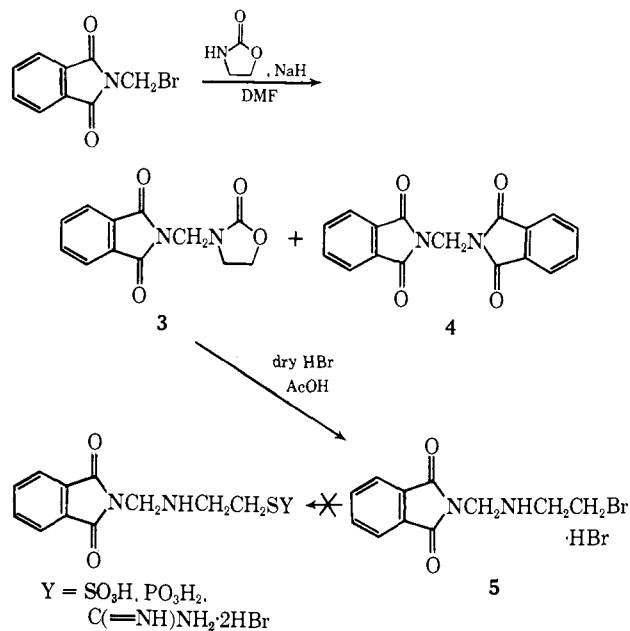
1a, $n = 2$; $n' = 2$
1b, $n = 3$; $n' = 2$
1c, $n = 4$; $n' = 2$
1d, $n = 5$; $n' = 2$
1e, $n = 3$; $n' = 3$
1f, $n = 4$; $n' = 3$
1g, $n = 5$; $n' = 3$

2a, $n = 2$; $n' = 2$; Y = SO₃H
2b, $n = 2$; $n' = 2$; Y = PO₃HNa
2c, $n = 2$; $n' = 2$; Y =
 C(=NH)NH₂·2HBr
2d, $n = 3$; $n' = 2$; Y = SO₃H
2e, $n = 3$; $n' = 2$; Y = PO₃H₂
2f, $n = 4$; $n' = 2$; Y = SO₃H
2g, $n = 4$; $n' = 2$; Y = PO₃HNa
2h, $n = 5$; $n' = 2$; Y = SO₃H
2i, $n = 5$; $n' = 2$; Y = PO₃H₂
2j, $n = 3$; $n' = 3$; Y = SO₃H
2k, $n = 3$; $n' = 3$; Y = PO₃H₂
2l, $n = 3$; $n' = 3$; Y =
 C(=NH)NH₂·2HBr
2m, $n = 4$; $n' = 3$; Y = SO₃H
2n, $n = 4$; $n' = 3$; Y = PO₃H₂
2o, $n = 5$; $n' = 3$; Y = SO₃H
2p, $n = 5$; $n' = 3$; Y = PO₃H₂

mediates in one of the two routes developed for the synthesis of a series of radioprotective *S*- ω -(ω -aminoalkylamino)alkyl dihydrogen phosphorothioates and related compounds having terminal amino groups,² were converted into thiosulfates (**2a,d,f,h,j,m,o**), phosphorothioates (**2b,e,g,i,k,n,p**), and isothiuronium salts (**2c,l**) for evaluation as radioprotective agents. The development of this route, which involved the HBr cleavage of 3-substituted 2-oxazolidinones³ and tetrahydro-2*H*-1,3-oxazin-2-ones,² was the basis for subsequent syn-

theses of a number of congeners in which the terminal dicarboximido group has been widely varied (see Schemes VII and VIII and the succeeding paper⁴ on this subject). An application of the general scheme to phthalimidomethyl analogs, however, was thwarted by reagent and/or product decomposition in attempted conversions of the intermediate bromide **5** (Scheme II)

SCHEME II



into the corresponding thiosulfate, phosphorothioate, and isothiuronium salt. Moreover, the preparation of the intermediate oxazolidinone **3** was complicated by the formation in appreciable yield of *N,N'*-methylene-diphthalimide (**4**) as a by-product, whose origin, possibly dependent on the liberation of phthalimide during the reaction, remains obscure.

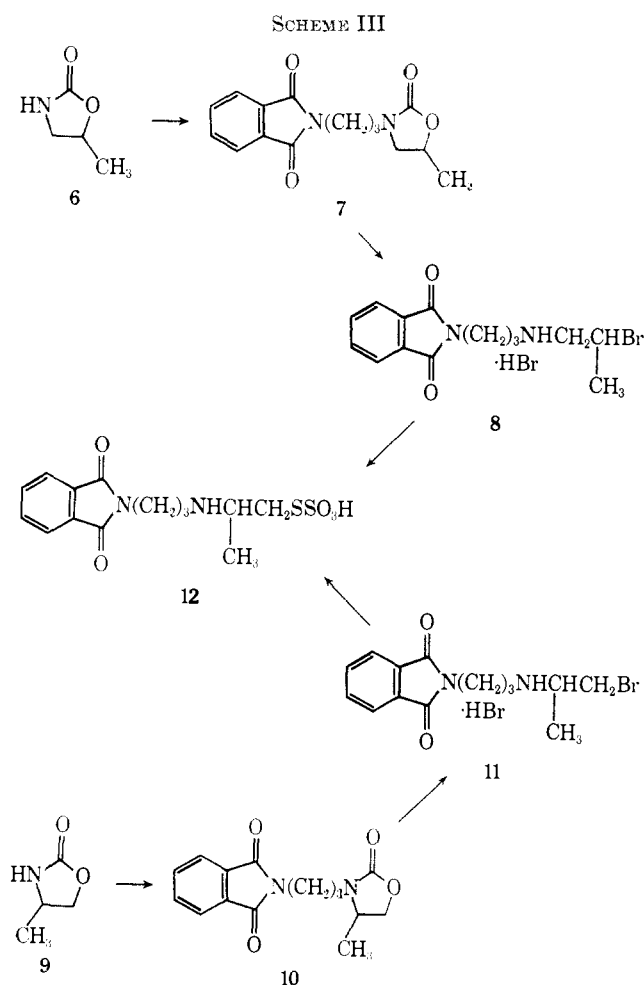
Me branching was introduced by routes indicated in Schemes III and IV. Spectral evidence suggested that the product of the sequence beginning with 5-methyl-2-oxazolidinone (**6**) was the thiosulfate **12**, which would be

(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contracts No. DA-49-193-MD-2028 and DADA17-69-C-9033.

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

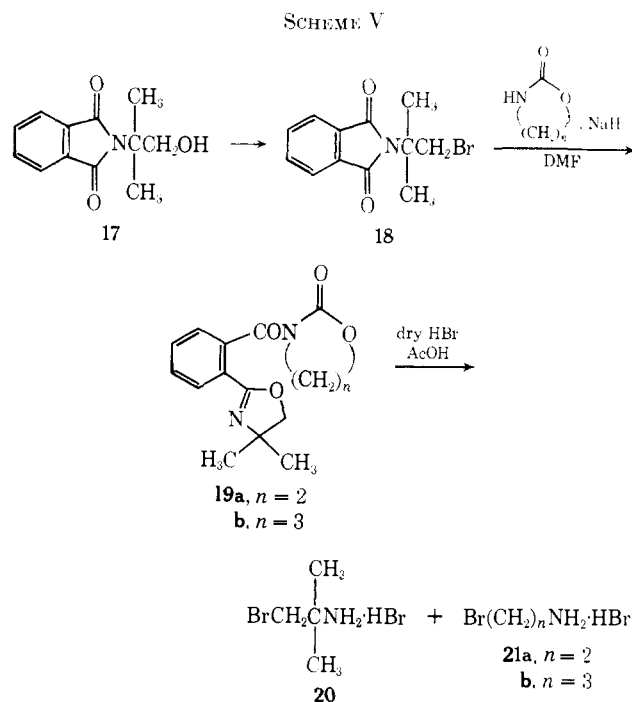
(3) J. R. Piper, R. D. Elliott, C. R. Stringfellow, Jr., and T. P. Johnston, *Chem. Ind. (London)*, 2010 (1966).

(4) J. R. Piper, C. R. Stringfellow, Jr., and T. P. Johnston, *J. Med. Chem.*, **14**, 350 (1971).



expected if rearrangement due to aziridinium ion formation had occurred in the displacement step.⁵ This speculation was confirmed by a synthesis of **12** from 4-methyl-2-oxazolidinone (**9**). The 3-step conversions of 4,4-dimethyl-2-oxazolidinone (**13**) into the tertiary-branched thiosulfates **16a,b** and the phosphorothioate **16c** (Scheme IV) proceeded as planned, but the attempted conversion of *N*-(2-hydroxy-1,1-dimethylethyl)phthalimide (**17**) into other tertiary-branched

congeners was frustrated by phthalimide-ring openings as shown in Scheme V. The identity of the unexpected



oxazolidinone **19a** and its homolog **19b** was first suggested by differences seen in ir spectral comparisons with nonbranched analogs of the expected products, particularly in the CO region. Supporting evidence for these structural assignments was found in the pmr spectra and in the cleavage products of **19a** and **19b** with dry HBr in AcOH. As judged by ir absorption and elemental analysis, **19a** gave a nearly equimolar mixture of 2-bromo-1,1-dimethylethylamine·HBr (**20**, from the oxazoline moiety) and 2-bromoethylamine·HBr (**21a**, from the oxazolidinone moiety); similar treatment of **19b** gave **20**, but apparently the tetrahydro-2*H*-1,3-oxazin-2-one moiety was not cleaved to an appreciable extent. The formation of **19a,b**, undoubtedly favored by tertiary branching, is somewhat analogous to the reported conversion of *N*-(2-bromoethyl)phthalimide into *o*-2-oxazolin-2-ylbenzoic acid.⁶

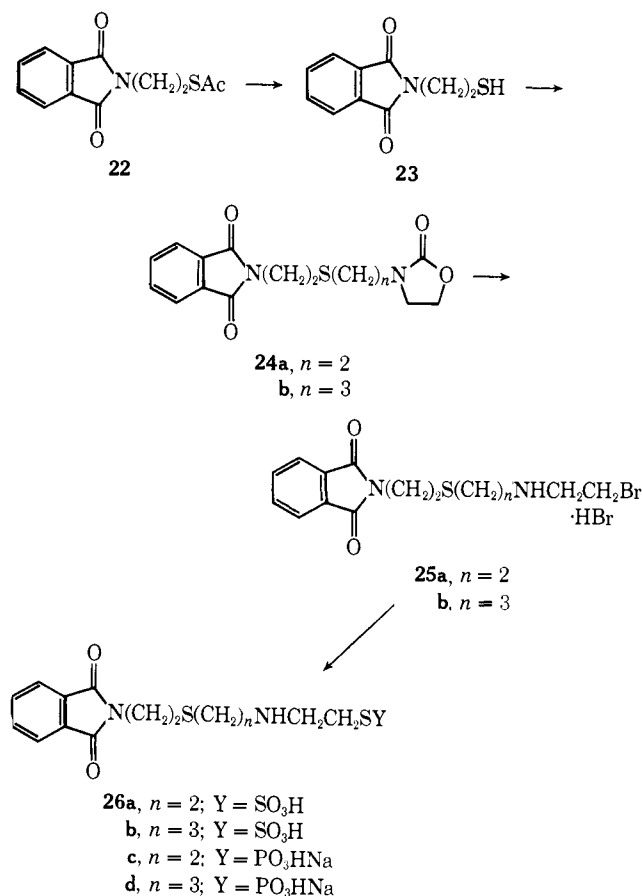
Application of the general scheme to *N*-(2-mercaptoethyl)phthalimide (**23**) led to the (phthalimidoethylthio)alkyl analogs **26a-d** as shown in Scheme VI; ethanolsis of the thioacetate **22** provided a convenient method for the preparation of **23**. The thiosulfate **29** (Scheme VII) was the only aza congener derived from 2,3-pyridinedicarboximide that could be isolated and characterized, whereas application of the general scheme to saccharin (**32a-e** and **33a,b**) produced several congeners as shown in Scheme VIII. (The reaction of the bromide **31a** with Na₃SPO₃ was an inexplicable exception, however, in that elemental S was deposited and none of the desired product could be isolated.) Alkylations promoted by KI enabled the preparation of the requisite oxazolidinones **30a-c**.

The candidate compounds described above were evaluated at the Walter Reed Army Institute of Re-

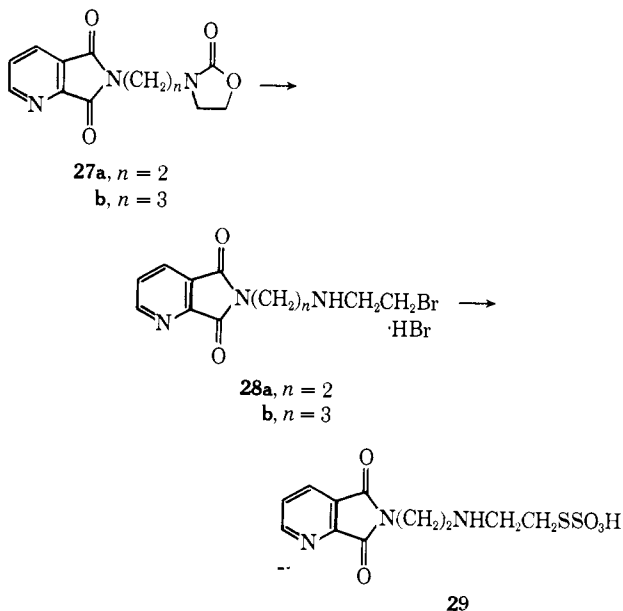
(5) Cf. D. L. Klayman, L. W. Lown, and T. R. Sweeney, *J. Org. Chem.*, **30**, 2275 (1965); J. R. Piper, C. R. Stringfellow, Jr., and T. P. Johnston, *J. Med. Chem.*, **9**, 911 (1966).

(6) K. Kormendy and J. Volford, *Acta Chim. Acad. Sci. Hung.*, **32**, 115 (1962).

SCHEME VI



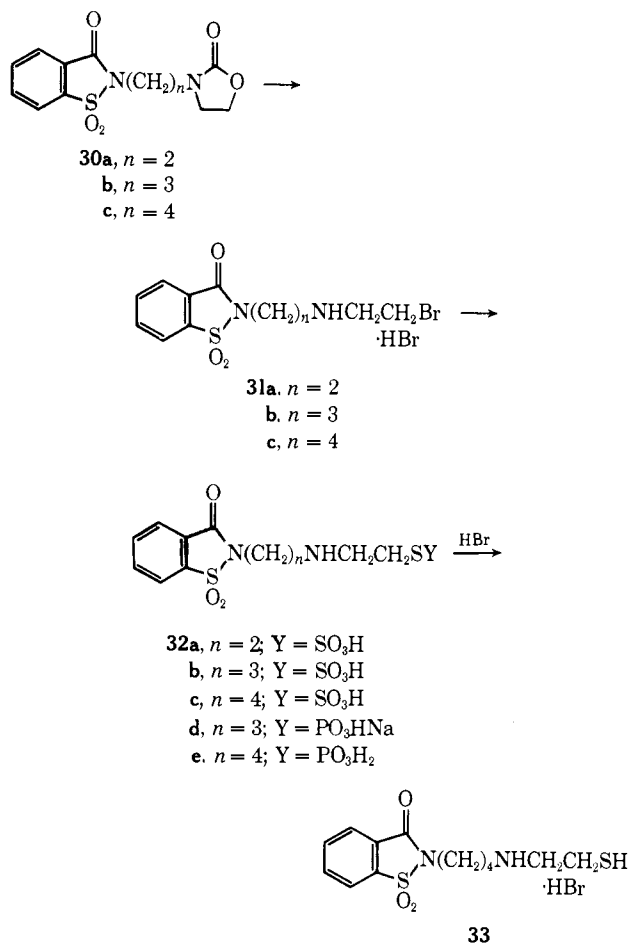
SCHEME VII



search as radioprotective agents in mice by a previously described method.⁷ Initial observations of good radioprotection (>45% survival) with **2a**, **2b**, and **2d** were not confirmed in subsequent tests; but the initial results prompted the extensive congener synthesis reported here, a number of intermediates for which were available from the previously reported² introduction of alkyl

(7) L. Field, A. Ferretti, R. Crenshaw, and T. Owen, *J. Med. Chem.*, **7**, 39 (1964).

SCHEME VIII



substituents having terminal amino groups. Radioprotective data are given in Table I for those compounds that gave some degree of protection, but most were nonprotective at the doses tested, which were usually the maximum tolerated dose and one-half that dose. In no instance did the observed activity approach that of the phosphorothioates having dephthaloylated amino groups;² the only activity in the phthaloyl series that could perhaps be rated good belonged to the thioacetate **22**, a fully acylated form of radioprotective 2-aminoethanethiol and an intermediate in the synthesis of the inactive thiosulfates **26a,b** and phosphorothioates **26c,d**.

Experimental Section⁸

3-(5-Phthalimidopentyl)-2-oxazolidinone and 3-(5-Phthalimidopentyl)tetrahydro-2H-1,3-oxazin-2-one.—The Na derivs of 2-oxazolidinone and tetrahydro-2H-1,3-oxazin-2-one were alkylated with *N*-(5-bromopentyl)phthalimide⁹ in a manner like that described for the prepn of homologous compds.² The residue from removal of the reaction solvent was distributed between C₆H₆ and H₂O, and evapn of the H₂O-washed and dried

(8) Unless noted otherwise, melting points were determined with a Mel-Temp apparatus. Ir spectra were determined with Perkin-Elmer Models 521 and 621 spectrophotometers, pmr spectra with a Varian A-60A spectrometer (Me₄Si). Chemical shifts for complex multiplets are recorded as the approx centers. Microanalyses were performed for the most part by Galbraith Laboratories, Knoxville, Tenn. Where anal. are indicated only by symbols of the elements, analytical results obtained for these elements were within 0.4% of the calcd values.

(9) Prepd by an adaptation of the procedure of H. B. Donahoe, R. J. Seiwald, M. M. C. Neuman, and K. K. Kimura [*J. Org. Chem.*, **22**, 68 (1957)] for the prepn of a homologous compd. The material used had mp 58–61° [lit. mp 61°, A. W. Baldwin, *J. Chem. Soc.*, 2959 (1929)].

TABLE I

RADIOPROTECTIVE ACTIVITY OF SOME PHTHALOYLATED ANALOGS OF *S*-2-(ω -AMINOALKYLAMINO)ETHYL DIHYDROGEN PHOSPHOROTHIOATES AND RELATED COMPOUNDS^a

Compd	Approx LD ₅₀ , mg/kg	Drug dose, mg/kg ^b	Vehicle of admn	30-day survival, % ^c
2a · H ₂ O	1800	1000	MC-Tw ^d	13
		500	MC-Tw	7
2b · 6H ₂ O	625	400	Water	40
		200	Water	13
2e	187	100	MC-Tw	7
		50	MC-Tw	0
2h	250	100	MC-Tw	7
2i	150	70	MC-Tw	7
		35	MC-Tw	0
2l · 2HBr · H ₂ O	160	70	Saline ^e	20
		35	Saline	0
16c	160	37.5	MC-Tw	7
26c	250	120	Saline	0
		60	Saline	7
22	680	200	MC-Tw	13
		100	MC-Tw	47
23	500	300	MC-Tw	40
		150	MC-Tw	0
33	80	30	Saline	0
		15	Saline	13

^a Compds tested in mice against lethal radiation (950 R, γ rays). ^b Compds injected ip as 0.7–5% soln or suspension, pH unadjusted, 15 min before irradiation. ^c No 30-day survival among control mice. ^d Physiological saline soln contg methylcellulose (0.3%) and Tween-80 (0.1%). ^e Physiological saline soln.

(MgSO₄) C₆H₆ solns gave the products as oils, which were not characterized but were used successfully in conversions into 1d and 1g.

3-(Phthalimidomethyl)-2-oxazolidinone (3).—A soln of 10.0 mmoles each of *N*-(bromomethyl)phthalimide (2.40 g, Frinton Laboratories) and 2-oxazolidinone (871 mg) in DMF (15 ml) was added dropwise to a stirred mixt of NaH (400 mg of 60% dispersion in oil, 10.0 mmoles) and DMF (5 ml) at 0°. The resulting soln was stirred at 25° for 16 hr. DMF was removed by distn *in vacuo* (bath up to 100°), and the residue was stirred with H₂O (25 ml). The remaining solid was collected, washed (H₂O), dried *in vacuo* (25–30°, P₂O₅), and recrystd from EtOAc (55 ml) to give **3**, mp¹⁰ 180°, in 36% yield (890 mg). *Anal.* (C₁₂H₁₀N₂O₄) C, H, N. The EtOAc filtrate coned to 25 ml deposited 370 mg (24%) of *N,N'*-methylenebipthalimide (**4**), mp¹⁰ 228°. A scaled-up run (0.287 mole) gave **3**, mp¹⁰ 180°, and **4**, mp¹⁰ 230°, in resp yields of 27 and 31%. The sample of **4** thus obtained was identical (mp, mmp, ir and pmr spectra) with the sample of authentic **4** whose prepn is described below.

N,N'-Methylenebipthalimide (**4**).—A soln of *N*-(bromomethyl)phthalimide (1.20 g, 5.00 mmoles) in DMF (5 ml) was added dropwise to a stirred mixt of K phthalimide (925 mg, 5.00 mmoles) and DMF (5 ml). The resulting mixt was stirred for 24 hr, then poured into H₂O (50 ml) to ppt cryst **4** in 80% yield (1.22 g); mp¹⁰ 230° (lit.¹¹ mp 232°).

4,4-Dimethyl-2-oxazolidinone (13) was prepd by treatment of 2-amino-2-methyl-1-propanol with (EtO)₂CO in the presence of NaOMe as described in a reported procedure.¹² Adaptations of this method also sufficed for the prepn of **5-methyl-2-oxazolidinone (6)** and **4-methyl-2-oxazolidinone (9)** from 1-amino-2-propanol and 2-amino-1-propanol, resp. The yield of **6**, bp 107–113° (0.5 mm) and *n*_D²⁰ 1.4603, was 55% [lit.¹³ bp 111–113° (1 mm) and *n*_D²⁰ 1.4592]. *Anal.* (C₄H₇NO₂) C, H, N. Compd **9** was obtained as a colorless oil, bp 120–125° (2.3 mm), in 24% yield. *Anal.* (C₄H₇NO₂) C, H, N.

(10) Taken on a Mettler FP1 mp apparatus.

(11) G. Vanags, *Ber.*, **75B**, 719 (1942).

(12) A. H. Homeyer, U. S. Patent 2,399,118 (1946); *Chem. Abstr.*, **40**, 4084 (1946).

(13) J. B. Bell, Jr. and J. D. Malkemus, U. S. Patent 2,755,286 (1956); *Chem. Abstr.*, **51**, 2871 (1957).

The methyl-3-(ω -phthalimidoalkyl)-2-oxazolidinones, **7**, **10**, **14a**, and **14b**, were prepd by NaH-promoted alkylations of **6**, **9**, and **13** with the appropriate *N*-(ω -bromoalkyl)phthalimide in DMF as described for the prepn of related compds.² The yield of pure **7**, mp 90–91°, was 65% after recrystn from PhMe–ligroin (bp 30–60°). *Anal.* (C₁₅H₁₈N₂O₄) C, H, N. Isomeric **10** was obtained as an uncharacterized oil, which was successfully used for the conversion into **11**. Compds **14a**, mp 100–101°, and **14b**, mp 163–165°, were obtained in resp yields of 37 and 42% after recrystn from C₆H₆–ligroin (bp 30–60°). *Anal.* (C₁₆H₁₈N₂O₄, **14a**) C, H, N. (C₁₇H₂₀N₂O₄, **14b**) C, H, N.

N-(2-Bromo-1,1-dimethylethyl)phthalimide (**18**) via *N*-(2-Hydroxy-1,1-dimethylethyl)phthalimide (**17**).—A mixt of 2-amino-2-methyl-1-propanol (44.5 g, 0.500 mole) and phthalic anhydride (74.0 g, 0.500 mole) in EtOH (200 ml) was stirred until soln occurred and then heated gradually under a distn apparatus until the bath (silicone oil) temp reached 200°. The distn head was removed, and the viscous oil was heated with stirring in an open flask at 208–210° for 1 hr. The stirred oil (crude **17**) was then allowed to cool to approx 45°. (In an earlier run the oil set to a waxy solid when cooled to 25–30°.) PBr₃ (53 ml, 0.56 mole) was added in a thin stream to the stirred oil, and the mixt was gradually heated to 100°, kept at 100° for 2 hr, cooled, and poured into rapidly stirred ice slush (1 l.). The ppt that formed was collected, pulverized under cold H₂O, pressed as dry as possible on a filter, and recrystd from MeOH to give **18**, mp 67–69°, in 60% overall yield (84.5 g). An analytical sample, mp 67.5–68.5°, was obtained from a pilot run. *Anal.* (C₁₂H₁₂BrNO₂) C, H, N.

3-[*o*-(4,4-Dimethyl-2-oxazolin-2-yl)benzoyl]-2-oxazolidinone (19a).—A soln of 0.100 mole each of **18** (28.2 g) and 2-oxazolidinone (8.71 g) in DMF (250 ml) was added dropwise to a stirred mixt of NaH (4.00 g of 60% dispersion in oil, 0.100 mole) and DMF (50 ml) with the temp maintained at 25°. Stirring at 25–30° over a weekend led to complete soln. After removal of DMF by distn *in vacuo*, the solid residue was stirred with H₂O (60 ml), collected, and dried *in vacuo* (78°, P₂O₅). The crude product (23.7 g) was recrystd from C₆H₆–ligroin (bp 30–60°) to give **19a**, mp 166–168°, in 60% yield (19.8 g): ir (KBr) 1785 (2-oxazolidinone C=O), 1670 (benzamide C=O), and 1645 cm⁻¹ (oxazoline C=N);¹⁴ pmr (CDCl₃) δ 1.28 (s, 6, CH₃), 4.03 [s, 2, OCH₂C(Me)₂], ca. 4.3 (m, 4, CH₂CH₂), and ca. 7.5 (m, 4, C₆H₄). *Anal.* (C₁₅H₁₆N₂O₄) C, H, N.

3-[*o*-(4,4-Dimethyl-2-oxazolin-2-yl)benzoyl]tetrahydro-2H-1,3-oxazin-2-one (19b).—Dropwise addn of a soln of 0.100 mole each of **18** (28.2 g) and tetrahydro-2H-1,3-oxazin-2-one (10.1 g) in DMF (250 ml) to a stirred mixt of NaH (4.00 g of 60% dispersion in oil, 0.100 mole) and DMF (50 ml) at 25° was followed by a 64-hr stirring period at 25–30°. Insol **19b** was collected, and the filtrate was set aside for further work-up. The ppt was washed successively with C₆H₆ and EtOH, then dried *in vacuo* (78°, P₂O₅); wt 11.7 g, mp 201–203°. Removal of the DMF from the filtered reaction mixt left a sticky yellow residue, which was stirred with H₂O (60 ml), collected, and washed successively with EtOH, C₆H₆, and again with EtOH. White cryst **19b** remained, which, after being dried *in vacuo* (78°, P₂O₅), amounted to 8.2 g, mp 201–203°. The total yield of **19b** with mp 201–203° was 66% (19.9 g). An analytical sample (recrystd from EtOH) had the same mp: ir (KBr) 1740 (tetrahydro-2H-1,3-oxazin-2-one C=O), 1660 (benzamide C=O) and 1640 cm⁻¹ (oxazoline C=N);¹⁴ pmr (CDCl₃) δ 1.28 (s, 6, CH₃), ca. 2.1 (m, 2, CH₂CH₂CH₂), 4.01 [s, 2, OCH₂C(Me)₂], ca. 3.93 (m, 2, NCH₂CH₂ or OCH₂CH₂), ca. 4.3 (m, 2, OCH₂CH₂ or NCH₂CH₂), and ca. 7.5 (m, 4, C₆H₄). *Anal.* (C₁₅H₁₈N₂O₄) C, H, N.

HBr Cleavage of 19a.—A soln of **19a** (19.8 g, 68.7 mmoles) in 30% dry HBr–AcOH (160 ml) was stirred at 25–30° for 48 hr, then heated during 1.5 hr to boiling, refluxed 30 min, and finally left at 25–30° over a weekend. Addn of Et₂O gave a cryst ppt (18.5 g), which was recrystd from EtOH–Et₂O; yield 12.7 g. Elemental anal. and comparisons of ir spectra showed this material to be a mixt of **20**¹⁵ and **21a** in a ratio of approx 1:1. *Anal.* (C₄H₁₀BrN · HBr and C₂H₆BrN · HBr, 1:1) C, H, Br, N.

HBr Cleavage of 19b.—A soln of **19b** (18.6 g, 61.5 mmoles) in 30% dry HBr–AcOH (150 ml) was heated during 1.5 hr to boiling, refluxed 30 min, cooled, and diild with Et₂O. The ppt was

(14) Cf. V. Rosnati and D. Misiti, *Gazz. Chim. Ital.*, **90**, 584 (1960).

(15) Compd **20** was prepd by the procedure of J. E. Earley, C. E. O'Rourke, L. B. Clapp, J. O. Edwards, and B. C. Lawes, *J. Amer. Chem. Soc.*, **80**, 3458 (1958).

collected and recrystd from EtOAc to give 8.00 g of product, which was found through elemental anal. and its ir spectrum to be almost entirely **20**.¹⁵ *Anal.* (C₄H₁₀BrN·HBr) C, H, N; Br: calcd 68.60; found 69.64. In a later expt **19b** (1.00 g) was subjected to the condns described above for cleavage of **19a** and recrystn was omitted. The Et₂O-pptd product (0.61 g) gave an ir spectrum nearly identical with that of **20**.

S-2-Phthalimidoethyl Thioacetate (22).—Solid *N*-(2-bromoethyl)phthalimide (98.4 g, 0.387 mole) was added to a cooled (20–25° H₂O bath), stirred soln of KSAc (44.1 g, 0.387 mole) in DMF (160 ml). The soln was kept at 25° for 1 hr, then poured into cold H₂O (1 l.). Cryst **22** sepd readily. After refrign, the ppt was collected, washed (H₂O), and dried *in vacuo* (25–30°, P₂O₅): yield 93.3 g (97%); mp 115° (Kofler Heizbank). An anal. sample (from EtOH) had mp 114–115°. *Anal.* (C₁₂H₁₁NO₃S) C, H, N, S.

2-Phthalimidoethanethiol (23).—A soln of **22** (91.6 g, 0.367 mole), EtOH (600 ml), and dry HCl-satd (at 25–30°) EtOH (375 ml) was refluxed for 18 hr. Cryst **23** sepd from the cooled soln; a second crop was collected after concn of the filtrate, and the total yield of **23**, mp 73–74°, was 97% (74.1 g). Recrystn from EtOH gave **23**, mp 75–77° (lit. mp of **23** prepd by other methods: 77–78°, 78–79°¹⁷) in 74% yield (56.1 g).

3-[ω-(2-Phthalimidoethylthio)alkyl]-2-oxazolidones 24a and 24b.—A mixt of **23** (28.0 g, 0.135 mole), the 3-(ω-chloroalkyl)-2-oxazolidinone (0.138 mole), K₂CO₃ (26.1 g, 0.189 mole), and DMF (100 ml) was stirred at 80–85° for 2.5 hr, cooled, and poured into H₂O (300 ml).

Isolation of 24a.—The oily ppt was caused to crystallize by chilling and scratching. The collected solid was dried *in vacuo* (25–30°, P₂O₅): crude yield 85%; mp 88–91°. Recrystn from PhMe-ligroin (bp 30–60°) gave pure **24a**, mp 93–94°, in 70% yield. *Anal.* (C₁₅H₁₆N₂O₄) C, H, N.

Isolation of 24b.—The clear aq phase was decanted from the oily ppt, and the oil was stirred with five 300-ml portions of cold H₂O, each portion being removed by decantation. The oil was then dissolved in PhMe (400 ml), and addn of ligroin (bp 30–60°) to the dried (MgSO₄) soln caused sepn of cryst **24b**: yield 51% (23.1 g); mp 55–56°. *Anal.* (C₁₆H₁₈N₂O₄S) C, H, N.

N-[ω-(2-Oxo-3-oxazolidinyl)alkyl]-2,3-pyridinedicarboximides 27a and 27b.—A soln of 2,3-pyridinedicarboximide¹⁸ (14.8 g, 0.100 mole) and the appropriate 3-(ω-chloroalkyl)-2-oxazolidinone (0.100 mole) in DMF (140 ml) was added dropwise during 1 hr to a stirred mixt of NaH (4.00 g of 60% dispersion in oil, 0.100 mole) and DMF (30 ml). The stirred mixt was then kept at 90–95° for 1 hr, cooled, and filtered. Solvent was removed *in vacuo* (pressure <1 mm, rotary evap, bath up to 75°), and the residual gum was dissolved in the min vol of hot H₂O. Cryst product sepd from the refrigd soln. The yield of pure **27a**, mp 145–147°, was 45% and that of pure **27b**, mp 106–108°, was 67%. *Anal.* (C₁₂H₁₁N₃O₄, **27a**) C, H, N. (C₁₃H₁₃N₃O₄, **27b**) C, H, N.

2-[ω-(2-Oxo-3-oxazolidinyl)alkyl]-1,2-benzothiazolin-3-one 1,1-Dioxides (30a-c).—Anhyd K₂CO₃ (19.0 g, 0.137 mole) was added in portions to a stirred soln of saccharin (25.0 g, 0.137 mole) in DMF (125 ml) at 25–30°. After CO₂ evoln had subsided, the appropriate 3-(ω-chloroalkyl)-2-oxazolidinone (0.150 mole) was added along with KI (22.7 g, 0.136 mole). The mixt was stirred at 110–120° for 1 hr, cooled, and poured into H₂O (750 ml). The cryst ppt was collected, washed (H₂O), and dried *in vacuo* (78°, P₂O₅). The products thus obtained in the yields listed in Table II were of satisfactory purity for conversion into **31a-c**. Samples recrystd once from EtOH gave satisfactory anal. for C, H, N.

TABLE II

No.	Yield, %	Mp. °C	Formula
30a	67	204–207	C ₁₂ H ₁₂ N ₂ O ₅ S
30b	74	103–105	C ₁₃ H ₁₄ N ₂ O ₅ S
30c	41	124–126	C ₁₄ H ₁₆ N ₂ O ₅ S

N-Substituted bromoalkylamine hydrobromides (Table III) were prepd by adaptations of reported procedures. The compds

(16) R. O. Clinton, C. M. Suter, S. C. Lackowski, M. Jackman, and W. Huber, *J. Amer. Chem. Soc.*, **67**, 594 (1945).

(17) S. Gabriel, *Ber.*, **24**, 1110 (1891).

(18) C. H. Fuchsmann, Ph.D. Thesis, Western Reserve University, Cleveland, Ohio (1965); *Diss. Abstr. B*, 749 (1966); E. Sucharda, *Ber.*, **58**, 1727 (1925).

TABLE III
N-SUBSTITUTED BROMOALKYLAMINE HYDROBROMIDES

No.	Recrystn solvent ^a	Yield, %	Mp. °C dec	Formula ^b
1d	A	63 ^c	193–195	C ₁₅ H ₁₉ BrN ₂ O ₂ ·HBr
1g	A	55 ^c	169–170	C ₁₆ H ₂₁ BrN ₂ O ₂ ·HBr
5		97	~190 ^d	C ₁₁ H ₁₁ BrN ₂ O ₂ ·HBr
8	B, C	46	220–221	C ₁₄ H ₁₇ BrN ₂ O ₂ ·HBr
11	B, C	52 ^c	210–213	C ₁₄ H ₁₇ BrN ₂ O ₂ ·HBr
15a	B	41	214–216	C ₁₅ H ₁₉ BrN ₂ O ₂ ·HBr
15b	B	53	210–212	C ₁₆ H ₂₁ BrN ₂ O ₂ ·HBr
25a	A	90	152–153	C ₁₄ H ₁₇ BrN ₂ O ₂ S·HBr
25b	A	93	174–175	C ₁₅ H ₁₉ BrN ₂ O ₂ S·HBr
28a	C	73	~200 ^e	C ₁₁ H ₁₂ BrN ₃ O ₂ ·HBr
28b	C	62	~210 ^e	C ₁₂ H ₁₄ BrN ₃ O ₂ ·HBr
31a	B	79	~226 ^e	C ₁₁ H ₁₃ BrN ₂ O ₂ S·HBr
31b	B	93	208–210	C ₁₂ H ₁₅ BrN ₂ O ₂ S·HBr
31c	B	90	215–216	C ₁₃ H ₁₇ BrN ₂ O ₂ S·HBr

^a A, EtOH; B, MeOH–Et₂O; C, MeOH. ^b *Anal.* C, H, and N for all compds; Br for **1g**, **8**, and **11**. ^c Overall yield for 2 steps. ^d Taken on Mettler FP1 app. ^e Melted indefinitely.

derived from methyl-2-oxazolidinones and compd **1g** were prepd by a procedure like that described for the prepn of *N*-[4-(3-bromopropylamino)butyl]phthalimide·HBr.² The other compds listed (**1d**, **5**, **28a**, **28b**, **31a-c**) were obtained in essentially the same manner as that described for *N*-[2-(2-bromoethylamino)ethyl]phthalimide·HBr.²

S-Substituted hydrogen thiosulfates (Table IV) were prepd by one of the two general procedures designated in the table and described below.

TABLE IV

S-SUBSTITUTED HYDROGEN THIOSULFATES

No.	Method	Yield, %	Mp. °C dec	Formula ^a
2a	A	69	213–214	C ₁₂ H ₁₄ N ₂ O ₅ S ^b
2d	A	79	209–210	C ₁₃ H ₁₆ N ₂ O ₅ S ₂
2f	A	88	205–206	C ₁₄ H ₁₈ N ₂ O ₅ S ₂
2h	A	80	197–199	C ₁₅ H ₂₀ N ₂ O ₅ S ₂
2j	A	82	202–204	C ₁₄ H ₁₈ N ₂ O ₅ S ₂
2m	A	82	220–221	C ₁₅ H ₂₀ N ₂ O ₅ S ₂
2o	A	71	198–200	C ₁₆ H ₂₂ N ₂ O ₅ S ₂
12	B	88 ^c	208–210	C ₁₄ H ₁₈ N ₂ O ₅ S ₂
16a	A	69	237–239	C ₁₅ H ₂₀ N ₂ O ₅ S ₂
16b	B	80	238–239	C ₁₆ H ₂₂ N ₂ O ₅ S ₂
26a	A	77	205–206	C ₁₄ H ₁₈ N ₂ O ₅ S ₃
26b	A	92	198–199	C ₁₅ H ₂₀ N ₂ O ₅ S ₃
29	B	70	218–220	C ₁₁ H ₁₃ N ₃ O ₅ S ₂
32a	B	31	~221	C ₁₁ H ₁₄ N ₂ O ₆ S ₃
32b	B	76	~210	C ₁₂ H ₁₆ N ₂ O ₆ S ₃
32c	B	83	~211	C ₁₃ H ₁₈ N ₂ O ₆ S ₃

^a *Anal.* C, H, N, and S for all compds. ^b Crystd from H₂O as monohydrate and air-dried; a cryst sample dried *in vacuo* collapsed to hygroscopic powder. ^c Prepd from **11** and is identical (mp, mmp, and ir spectrum) with a sample prepd in 85% yield from **8**.

Procedure A.—Equimolar amts of Na₂S₂O₃·5H₂O and the appropriate *N*-substd bromoalkylamine·HBr were dissolved in slightly more than the required vol of hot H₂O, and the soln was refluxed for 30 min. Cryst product, which sepd from the cooled soln, was recrystd from H₂O and then dried *in vacuo* (25–30°, P₂O₅).

Procedure B.—Equimolar amts of MgS₂O₃·6H₂O and the appropriate *N*-substd bromoalkylamine·HBr were dissolved in MeOH (2.5 ml/mole of MgS₂O₃·6H₂O), and the soln was refluxed for ~15 min. Product which sepd was collected, washed (MeOH), and dried *in vacuo* (25–30°, P₂O₅). Compds **32a-c** were recrystd from H₂O before characterization.

S-Substituted sodium hydrogen phosphorothioates and dihydrogen phosphorothioates (Table V) were prepd by the following general procedure. Na₃PSO₃ was dissolved with stirring in H₂O (see Table V) at 40–45° (bath temp). The soln was cooled

TABLE V
S-SUBSTITUTED SODIUM HYDROGEN PHOSPHOROTHIOATES AND
DIHYDROGEN PHOSPHOROTHIOATES

No.	ml of H ₂ O/ mmole of Na ₂ PSO ₃	Yield, %	Mp, °C dec	Formula ^a
2b	1.5	45		C ₁₂ H ₁₄ N ₂ NaO ₃ PS·6H ₂ O
2c	1.5	93	131-132	C ₁₃ H ₁₇ N ₂ O ₃ PS·H ₂ O
2g	5.0	77		C ₁₄ H ₁₈ N ₂ NaO ₃ PS·5H ₂ O
2i	4.2	45	148-150	C ₁₅ H ₂₁ N ₂ O ₃ PS
2k	2.3	44	158-160	C ₁₄ H ₁₉ N ₂ O ₃ PS·1.3H ₂ O
2n	3.5	56	151-152	C ₁₅ H ₂₁ N ₂ O ₃ PS
2p	3.5	43	179-180	C ₁₆ H ₂₃ N ₂ O ₃ PS
16c ^b	1.0	59	184-186	C ₁₆ H ₂₃ N ₂ O ₃ PS
26c	2.0	55		C ₁₄ H ₁₅ N ₂ NaO ₃ PS ₂ ·4.5H ₂ O
26d	2.0	70		C ₁₅ H ₂₀ N ₂ NaO ₃ PS ₂ ·5H ₂ O
32d	2.0	65		C ₁₂ H ₁₆ N ₂ NaO ₃ PS ₂ ·6.5H ₂ O
32e	2.0	89	182-183	C ₁₃ H ₁₉ N ₂ O ₃ PS ₂ ·0.5H ₂ O

^a Anal. C, H, N, P, and S for all compds except **2n**, which gave satisfactory results for C, H, N, and S. ^b The Na salt from which **16c** was prep'd was ppt'd from the reaction soln with Me₂CO instead of EtOH.

to room temp, and DMF (one-half the vol of H₂O used) was added. Pulverized N-subst'd bromoalkylamine·HBr (equimolar with Na₂PSO₃) was added, and the mixt was stirred until the AgNO₃ test for PSO₃²⁻ was negative.¹⁹ Except for the preps which led to **2e**, **2k**, and **2n**, the addn of EtOH (to cause pptn of the desired Na salt) followed, although **2b**, **2g**, **26c**, **26d**, **32d**, and the Na salt from which **32e** was derived had partially sep'd from the reaction mixt. The ppt was collected, washed (EtOH, then Et₂O), and suction dried. The Na salts **2b**, **2g**, **26c**, **26d**, and **32d** were dissolved in the required vol of H₂O at 25°, then reppt'd by addn of EtOH, collected, washed as above, and air-dried. Compds

(19) S. Åkerfeldt, *Acta Chem. Scand.*, **16**, 1897 (1962).

2e, **2k**, and **2n** crystd directly from the reaction soln after the addn of AcOH in small excess (approx 1 ml in a 10-nmole run). The collected products were washed (cold H₂O, EtOH, then Et₂O) and dried *in vacuo* (25-30°, P₂O₅). Compds **2i**, **2p**, **16c**, and **32e** were similarly obtained after H₂O solns of the EtOH-pptd Na salts were treated with AcOH.

2-[2-(2-Phthalimidoethylamino)ethyl]-2-thiopseudourea (2c)·2HBr.—A soln of 15.0 mmoles each of **1a** (5.67 g) and thiourea (1.14 g) in EtOH was refluxed 30 min. A test portion of the soln dild with EtOAc was chilled, stirred, and scratched to give seed crystals, which, when added to the reaction soln, caused crystn of pure **2c**·2HBr, mp 220-222° dec, in 44% yield (3.02 g). Anal. (C₁₃H₁₆N₄O₂S·2HBr) C, H, N, S.

2-[3-(3-Phthalimidopropylamino)propyl]-2-thiopseudourea (21)·2HBr·H₂O.—A stirred mixt of 12.3 mmoles each of **1e** (5.00 g) and thiourea (0.940 g) in EtOH (150 ml) was refluxed until soln occurred (15 min), then dist'd until 100 ml had been collected. The cooled residual soln deposited cryst product, which was collected and recryst'd from EtOH. The dried (*in vacuo*, 77°, P₂O₅) sample underwent a wt increase when exposed to ambient condns of the lab (~60% rel humidity) and eventually came to const wt; yield 62% (3.84 g), mp 98-100°. Anal. (C₁₅H₂₀N₄O₂S·2HBr·H₂O) C, H, N, S.

2-[4-(3-Oxo-1,2-benzisothiazolin-2-yl)butylamino]ethanethiol S,S-Dioxide·HBr (33).—A mixt of **32e**·0.5H₂O (4.24 g, 10.5 mmoles) and 3 N HBr (50 ml) was stirred at 70° until soln occurred. The soln was allowed to cool, and **33** sep'd as long colorless needles. The collected material was washed (Et₂O), air-dried, and recryst'd from MeOH-Et₂O to give **33**·0.5H₂O, mp 185-187°, in 76% yield (3.04 g). Anal. (C₁₃H₁₈N₂O₃S₂·HBr·0.5H₂O) C, H, N, S, SH.

Acknowledgments.—The authors are indebted to Dr. D. P. Jacobus and Dr. T. R. Sweeney for antiradiation data and to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Research Institute for spectral data.

Terminal Dicarboximido Analogs of S-2-(ω-Aminoalkylamino)ethyl Dihydrogen Phosphorothioates and Related Compounds as Potential Antiradiation Agents. 2. Succinimides, Glutarimides, and *cis*-1,2-Cyclohexanedicarboximides¹

JAMES R. PIPER, CARL R. STRINGFELLOW, JR., AND THOMAS P. JOHNSTON*

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

Received September 26, 1970

Terminal dicarboximido analogs of highly radioprotective S-2-(ω-aminoalkylamino)ethyl dihydrogen phosphorothioates and related compounds were prepared from succinimide, glutarimide, glutethimide, and *cis*-1,2-cyclohexanedicarboximide *via* 3-substituted 2-oxazolidinones. A novel method was developed for the preparation of thiosulfates in this series in which N-substituted 2-bromoethylamine intermediates were treated with MgS₂O₃ in MeOH, but such treatment of N-[2-(2-bromoethylamino)ethyl]glutarimide·HBr (**5a**) resulted in an unexpected condensation and formation of the bicyclic betaine thiosulfate **7**. A departure from the general reaction scheme was also encountered in the formation of N,N'-(iminodiethylene)bis(*cis*-1,3-cyclohexanedicarboximide) (**14**) in the preparation of 3-[2-(*cis*-1,2-cyclohexanedicarboximido)ethyl]-2-oxazolidinone (**11a**). Of the series of thiosulfates and phosphorothioates prepared, only S-2-(2-succinimidoethylamino)ethyl sodium hydrogen phosphorothioate (**3b**) trihydrate and S-2-[2-(*cis*-1,2-cyclohexanedicarboximido)ethylamino]ethyl sodium hydrogen phosphorothioate (**13b**) tetrahydrate showed good radioprotective activity in mice.

Terminal substitution by aliphatic dicarboximido groups in the synthesis of analogs of a radioprotective series of S-2-(ω-aminoalkylamino)ethyl dihydrogen phosphorothioates² was accomplished by methods based

on those described in the preceding paper³ for the introduction of phthalimido and related groups. The key reaction was again the selective HBr cleavage of 3-substituted 2-oxazolidinones.

In the preparation of succinimido analogs (Scheme I), conversions of the bromides **2a,b,c** into the corresponding thiosulfates **3a,c,e** were effected in MeOH at room

(1) This investigation was supported by the U. S. Army Medical Research and Development Command under Contracts Nos. DA-49-193-MD-2028 and DADA17-69-C-9033.

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

(3) J. R. Piper, C. R. Stringfellow, Jr., R. D. Elliott, and T. P. Johnston, *ibid.*, **14**, 345 (1971).