Phosphorus–Nitrogen Compounds. VII.[1,2] Urea, Aziridinecarboxamide, and Semicarbazide Derivatives

LINDLEY A. CATES

College of Pharmacy, University of Houston, Houston, Texas 77004

Received February 17, 1967
Revised Manuscript Received May 15, 1967

A series of thirteen phosphinyl- and phosphinylidynenreas, -aziridinecarboxamides, and -semicarbazides were synthesized as potential oncolytic agents and screened in one or more tumor test systems. Selected derivatives were investigated for chelating properties, monoamine oxidase inhibitions, and antimalarial activity.

Since previous studies[2,3] have indicated that direct phosphorylation of physiologically active amines results in a reduction of activity and toxicity, it was considered advisable to separate the phosphorus and nitrogen atoms by a carbamoyl grouping in an attempt to produce agents with antineoplastic activity *per se* or as a result of bioconversion. Derivatives of this nature were prepared by condensation of phosphorisocyanatidic dichloride or phosphinylidyne trisisocyanate with amines or hydrazines to yield phosphorylated ureas or semicarbazides.

The reaction between phosphorisocyanatidic dichloride and amines proceeded in good yield with formation of dichlorophosphinylureas. These fairly reactive and deliquescent materials are not normally isolated; however, by means of washing and *in vacuo* drying, it was possible to obtain pure products in the two cases attempted. Amidation of the dichlorophosphinylureas using excess amine or equimolar amounts of amine and triethylamine afforded the corresponding diaminophosphinylureas.

Condensations of isocyanates with aryl- or acyl-substituted hydrazines are reported to yield 1-substituted semicarbazides.[4] On this basis, as well as failure to detect primary amine groups by chemical means, the structures for IX and XIII are proposed. Reaction between monoalkylhydrazines and an isocyanate moiety, however, produces 2-alkylsemicarbazides,[5] presumably due to the greater nucleophilic character of the secondary amine groups. Nmr spectroscopic examination of XI in dry DMSO-d_6[6] revealed a single, intense peak at 2.95 ppm which is assigned to the protons of a methyl group attached to N^2 of the semicarbazide. The low-field site of the methyl resonance peak indicates its apparent increased deshielding by the carbonyl group. In addition, XI gave a positive ninhydrin test and an aqueous solution reacted with excess benzaldehyde to form a white, water-insoluble product. The instability of this material precluded its analysis; however, assuming it to be the trissemicarbazone derivative a yield of 84% was obtained. Semicarbazides IX, XII, and XIII gave negative results in similar testing. Attempts to crystallize the urea and carboxamide products from different systems apparently resulted in occlusion of solvent molecules while heating invariably led to decomposition. This latter effect has been observed in related compounds and referred to as an undetermined change.[7] The phosphinylidynetrissemicarbazides are subject to oxidation, rapidly decolorizing potassium permanganate solution with hydrogen peroxide formation.

Several of the compounds reported herein are structurally related to agents possessing anticancer activity: VI, VII, VIII, and XIII can be compared to bis(ethylenimido)phosphorourethans,[8] triethylenephosphoramide, 3-diethyl-1-methoxyurea,[9] and methylglyoxalbis-N-methylthiosemicarbazone,[10] respectively. In view of the high antineoplastic activity shown by methylhydrazine derivatives, a phosphinylidynetrissemicarbazide incorporating this group (XI) as well as two homologs (X and XII) were prepared. Methylhydrazines are a new class of oncolytic agents markedly suppressing the mitotic cycle by producing a high per cent of chromatid breaks during or after DNA synthesis.[11] This fragmentation of DNA takes place only in the presence of oxygen and the degradation is considered to be due to the formation of H_2O_2. 1-Methyl-2-benzylhydrazine[12] was the first member of this class to be synthesized for possible monoamine oxidase inhibition and later shown to produce pronounced inhibition of several transplanted tumors. Similarly, N-isopropyl-α-(2-methylhydrazino)-*p*-toluamide is very active against Hodgkin's disease[13] and produced psychic reactions in clinical trial and potentiated sleeping time of barbiturates in a manner similar to MAO inhibitors.[14] Bollag[11] indicates that only the methylhydrazine compounds are active antitumor agents, whereas other hydrazine compounds, *e.g.*, ethylhydrazine, are inactive. He relates this difference to the slower rate of autoxidation of the methyl derivatives, allowing time for the compound to reach the tumor before being oxidized.

It can be postulated that hydrazides may also undergo *in vivo* oxidation forming hydroxamic acids which in

(1) This investigation was supported by Grant CA-08711 from the National Cancer Institute, U. S. Public Health Service.

(2) For the previous paper of this series see L. A. Cates, W. D. Lawrence, and R. J. McClain, *J. Pharm. Sci.*, **55**, 1400 (1966).

(3) L. A. Cates and N. M. Ferguson, *ibid.*, **55**, 966 (1965).

(4) C. Pacilly, *Rec. Trav. Chim.*, **55**, 101 (1936).

(5) I. D. Morton and E. Hoggarth in "Chemistry of Carbon Compounds," E. H. Rodd, Ed., Elsevier Publishing Co., New York, N. Y., 1952, p 919.

(6) Performed by Southwest Research Institute, San Antonio, Texas, and Purdue University, Lafayette, Ind.

(7) A. A. Kropasheva, G. I. Derkach, L. P. Zhuravleva, N. V. Sazonov, and A. V. Kirsanov, *Zh. Obshch. Khim.*, **32**, 1540 (1962); *Chem. Abstr.*, **58**, 3375*d* (1963).

(8) T. J. Bardos, Z. B. Papanastassiou, A. Segaloff, and J. L. Ambrus, *Nature*, **183**, 390 (1959).

(9) Olin Mathieson Corp., British Patent 920,814 July 10, 1963.

(10) E. Mihich and C. A. Nichol, *Cancer Res.*, **25**, 1410 (1965).

(11) W. Bollag in "Chemotherapy of Cancer," P. A. Plattner, Ed., Elsevier Publishing Co., New York, N. Y., 1964, p 191.

(12) W. Bollag and E. Grunberg, *Experientia*, **19**, 130 (1963).

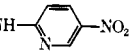
(13) G. Mathe, M. Schneider, A. Cattan, J. L. Amiel, and L. Schwarzenberg, ref 11, p 201.

(14) H. Gerhartz, ref 11, p 215.

TABLE I

PHOSPHINYL- AND PHOSPHINYLIDYNEUREAS, -AZIRIDINECARBOXAMIDES, AND -SEMICARBAZIDES

$R_2P(O)NHCOR'$

No.	R	R'	Mp, °C[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
I	Cl	$NHOCH_3$	91–92 dec	$C_2H_5Cl_2N_2O_3P$	11.6	2.4	13.5	11.7	2.5	13.5
II	Cl		70 dec	$C_3H_5Cl_2N_2O_2P$	17.7	2.5	13.8	17.8	2.7	13.6
III	C_6H_5NH		150–152	$C_{15}H_{17}N_4O_2P$	57.0	5.4	17.7	56.7	5.3	17.4
IV	C_6H_5NH		295–297	$C_{18}H_{17}N_6O_4P$	52.4	4.2	20.4	52.5	4.2	20.2
V	C_6H_5NH	NHC_6H_4Br-*p*	206–208	$C_{19}H_{18}BrN_4O_2P$	51.3	4.1	12.6	51.6	3.8	12.5
VI		$NHOCH_3$	99–101	$C_6H_{13}N_4O_3P$	32.7	6.0	25.4	32.7	6.0	25.5
VII			285–287 dec	$C_9H_{15}N_6O_3P$	35.8	5.0	27.8	35.8	5.3	27.6
VIII	$CH_3ONHCONH$	$NHOCH_3$	181–182 dec	$C_6H_{15}N_6O_7P$	22.9	4.8	26.7	22.8	4.7	26.4
IX	$C_6H_5NHNHCONH$	$NHNHC_6H_5$	211–212 dec	$C_{21}H_{24}N_6O_4P$	50.7	4.9	25.3	50.6	4.9	25.1
X	$NH_2NHCONH$	$NHNH_2$	138–140 dec	$C_3H_{12}N_7O_4P$	13.4	4.5	46.8	13.3	4.6	46.2
XI	$NH_2NH(CH_3)CONH$	$N(CH_3)NH_2$	126–129 dec	$C_6H_{18}N_6O_4P$	23.1	5.8	40.5	23.0	5.8	40.3
XII	$(CH_3)_2NNHCONH$	$NHN(CH_3)_2$	160–161 dec	$C_9H_{24}N_9O_4P$	30.6	6.8	35.7	30.3	6.7	35.6
XIII	$CH_3NHCSNHNHCONH$	$NHNHCSNHCH_3$	205 dec	$C_9H_{21}N_{12}O_4PS_3$	22.1	4.3	34.4	22.1	4.2	34.2

[a] VII–XIII at 4°/min.

turn cleave yielding hydroxylamines, credence being lent to this hypothesis by the work of Boyland, *et al.*,[15] which indicated that the alkylating hydroxamic acid, N-hydroxyurethan, is the active metabolite formed from urethan which is responsible for chromosome breaks. These authors concluded that these radiomimetic effects may be caused by some simple hydroxylamine derivative released in the tissue. In an earlier study of urethan, Berenblum, *et al.*,[16] mentioned the possibility that the carcinogenic activity of this drug is due to formation of an effective metabolite through some oxidative mechanism. Hydrazides IX–XIII may, therefore, allow for an appropriate rate of autoxidation and incorporation in tumor cells prior to bioconversion to cytotoxic products. This rationale is essentially that offered for hydrazide MAO inhibitors whereby these acyl derivatives serve as "carrier" moieties to produce peripherally inactive agents relying on metabolic degradation to release the active compounds in the brain.[17]

In consideration of these data, an estimation of the degree of MAO inhibition by certain of the semicarbazide derivatives was considered worthy of determination. None of the compounds produced reversal of reserpine-induced blepharoptosis; however, central stimulation of some nature occurred upon administration of XI as indicated by the convulsion induced by this compound. Semicarbazides of certain hydrazines are known to possess potent MAO inhibition;[18] however, phosphorylated semicarbazides may not provide for tissues selectivity and, in view of their lack of stability toward oxidation *in vitro*, it is likely that they may undergo oxidative biodegradation with cleavage to an active moiety prior to distribution to the target organ.

Preliminary antitumor screening indicates that VI may be the most promising of the series, giving a T/C (%) of 68 against Walker 256 subcutaneous at a dose of 1 mg/kg. Subsequent testing at higher dose levels and against other systems may afford greater activity. X gave the most favorable response, T/C (%) = 27, against Walker 265 subcutaneous at a dose of 80 mg/kg.

Five compounds were incidentally screened for antimalarial properties; none extended survival time sufficiently to be classified as being active under the test conditions.

Phosphorylation of ureas and semicarbazides results in the formation of compounds containing a large number of donor atoms, particularly in the case of the phosphinylidynetrissemicarbazides (IX–XIII) and 1,1′,-1″-phosphinylidynetris-3-methoxyurea (VIII) which may be considered to be tridecadentate ligands. Upon potentiometric titration to determine their approximate ability to chelate, three derivatives complexed with cupric ion and two with zinc in a 2:1 ratio. Only XI was examined with vanadium ion which it sequestered in a ratio of 2:1.

Experimental Section

Chemistry.—Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Coleman carbon, hydrogen, and nitrogen analyzers were used for the elemental analyses. Infrared spectra of all starting materials, intermediates, and products were taken in a Nujol mull on a Beckman IR-8 spectrophotometer and gave the expected absorptions. A Corning Model 12 pH meter was used in the potentiometric titration and a Varian A-60 spectrometer for the nmr spectra. The experimental procedures given below refer to the compounds listed in Table I.

Synthesis. 1-Dichlorophosphinyl-2-methoxyurea (I) and N-Dichlorophosphinyl-1-aziridinecarboxamide (II).—A solution of phosphorisocyanatidic dichloride[19] (80 mmoles) in 100 ml of ether was cooled to 5–10°, and an equimolar amount of aziridine or methoxyamine[20] in 50 ml of ether was added dropwise. Following filtration the residues were washed with ether and placed in a vacuum desiccator.

N-Dianilinophosphinyl-1-aziridinecarboxamide (III).—Compound II (25 mmoles) was added in portions to aniline (100

(15) E. Boyland, R. Nery, K. S. Peggie, and K. Williams, *Biochem. J.*, **89**, 113*p* (1963).

(16) I. Berenblum, D. Ben-Ishai, N. Haran-Ghera, A. Lapidot, E. Simon, and N. Trainin, *Biochem. Pharmacol.*, **2**, 168 (1959).

(17) J. H. Biel, A. Horita, and A. E. Drukker in "Psychopharmacological Agents," M. Gordon, Ed., Academic Press Inc., New York, N. Y., 1964, p 359.

(18) Reference 17, p 414.

(19) Z. B. Papanastassious and T. J. Bardos, *J. Med. Pharm. Chem.*, **5**, 1000 (1962).

(20) T. C. Bissot, R. W. Parry, and D. H. Campbell, *J. Am. Chem. Soc.*, **79**, 796 (1957).

TABLE II
CHELATION STUDIES

Compd	0.03 *M* ligand	pH ligand:metal(a) 1:1 Moles of base:moles of ligand	2:1
VIII	2.9	2.8 (1:1 Cu[c])	5.2 (1:1 Cu) +[b]
		2.5 (2:1 Cu)	5.3 (2:1 Cu) 7.0 (2:1 Cu[e] dark green
		2.6 (2:1 Zn)	6.6 (1:1 Zn) +
			6.5 (2:1 Zn) +
			6.5 (3:1 Zn) +
XI	6.6	1.9 (1:1 Cu)	4.2 (1:1 Cu) +[d]
		2.6 (2:1 Cu)	9.8 (2:1 Cu) 11.9 (2:1 Co) dark blue-green
		3.7 (1:1 Zn)	5.8 (1:1 Zn) +[d]
		4.0 (2:1 Zn)	9.6 (2:1 Zn)
XII	5.4	2.5 (1:1 Cu)	6.8 (1:1 Cu) +
		3.6 (2:1 Cu)	6.5 (2:1 Cu) 9.8 (2:1 Cu[e] dark brown
		4.3 (1:1 Zn)	7.1 (1:2 Zn) +[d]
		4.5 (2:1 Zn)	7.7 (1:1 Zn) 11.8 (1:1 Zn)
			10.0 (2:1 Zn) 12.0 (2:1 Zn)

[a] Cu^{2+}. [b] + indicates precipitation. [c] pH 11.0 after 3 moles of base/mole of ligand (2:1 Cu). [d] After 1.5 moles of base/mole of ligand. [e] pH 11.8 after 3 moles of base/mole of ligand (2:1 Cu).

TABLE III
MAO INHIBITION

Compd	Dose, mmoles/kg	Mean protic score 2.5 mg/kg reserpine	5 mg/kg reserpine
IX	1.1	3.2	3.2
X	1.1	2.4	3.6
XI	1.1	Toxic[a]	Toxic[b]
	0.825		Toxic[c]
	0.550		3.3[d]
	0.275		3.2[e]
XII	1.1	3.2	3.2
XIII	1.1	3.6	3.8
Vehicle		2.6	3.4
Isocarboxazide	1.1	0.0	0.0

[a] No survivors. [b] Two survivors convulsed to death upon being disturbed. [c] Two survivors, one of which died of convulsions while being observed. The last survivor gave a score of 4.0. [d] Mean score of three survivors. [e] All survived.

TABLE IV
ANTICANCER AND ANTIMALARIAL SCREENING

Compd	Anticancer test results: Test system	Dose, mg/kg[a]	Stage index T/C, %	Rodent antimalaria test results Δ survival time, days[b]
I	LE	200	93	1.3
II	WA	25[c]	82	0.5
III	WA	12[c]	88	
IV	LE	200	95	
	WM	170[c]	67	
V	LE	400	87	
VI	WA	1[c]	68	
VII	WA	5[c]	145	0.7
VIII	LE	400	90	1.4
	WM	400[c]	87	
IX	LE	400	94	0.3
	WM	400[c]	52	
X	LE	200	92	0.3
	WM	80[c]	27	
XI	LE	100	100	
XII	LE	400	87	0.1
	WM	400[c]	72	

[a] Highest dose allowing all test animals to survive. [b] At 640 mg/kg, the highest dose with 5/5 survivors. [c] Only dose level administered.

mmoles) in 50 ml of acetonitrile, previously dried (CaH_2). The white mass thus formed was crystallized from ethanol–water.

1-Dianilinophosphinyl-3-(5-nitro-2-pyridyl)urea (IV) and 1-Dianilinophosphinyl-3-(4-bromophenyl)urea (V).—Equimolar amounts of phosphorisocyanatidic dichloride and 2-amino-5-nitropyridine (dioxane) or *p*-bromoaniline (benzene) reacted in the manner described for I and II. Aniline (4 moles) was added to the reaction mixture, the solvents were removed by spin evaporation, and the residues were washed with dilute HCl. The remaining materials were extracted with 100-ml portions of 10% NaOH and filtered, and the filtrates were acidified with dilute HCl to yield yellow precipitates. This process was repeated until no clouding occurred upon filtrate acidification. The precipitates were crystallized from ethanol–water (IV) or dioxane–water (V).

1-Diaziridinylphosphinyl-2-methoxyurea (VI).—Aziridine (50 mmoles) and triethylamine (50 mmoles) in 100 ml of acetone were treated with II (22 mmoles) in the same manner as described for III. Following solvent removal the residue was extracted with ether and concentration of the ether extract produced the water-soluble product which gave a negative test with 0.1 *N* $AgNO_3$.

N,N',N''-Phosphinylidynetris-1-aziridinecarboxamide (VII). 1,1',1''-Phosphinylidynetris-3-methoxyurea (VIII). and Phosphinylidynetrissemicarbazides (IX–XIII).—Phosphinylidyne trisisocyanate (phosphoryl isocyanate, Alfa Inorganics, Inc.) (30 mmoles) in 50 ml of acetonitrile was added to a cooled (5–10°) solution of 100 mmoles of phenylhydrazine, hydrazine, methylhydrazine, 1,1-dimethylhydrazine, or 4-methyl-3-thiosemicarbazide in 200 ml of acetonitrile as described for I and II. XIII was further purified by stirring with dilute HCl and with ethanol to remove the unreacted semicarbazide.

XI gave an nmr peak (DMSO-d_6), δ 2.95 (N^2CH_3). To 2.9 g (6.4 mmoles) of this product in 100 ml of water was added 2.12 g (20 mmoles) of benzaldehyde with stirring at room temperature for 2 hr. The precipitate was collected on a filter and washed repeatedly with ether. All operations were conducted under N_2. The residue was crystallized from DMF–ether to yield 3.1 g of white, crystalline product weighing 3.1 g (84% calculated as benzaldehyde phosphinylidynetris-2-methylsemicarbazone) which on exposure to air converted to a yellow mass.

Chelation Studies.—Three phosphinylidynetrissemicarbazides (X–XII) and one phosphinylidynetrisurea (VIII) were potentiometrically titrated with 0.1 *N* KOH. These water-soluble, triprotic derivatives were combined with varying amounts of $CuSO_4$ and $ZnSO_4$ prior to titration and the results are given in Table II. Compound X (0.03 *M* = pH 7.4) gave an immediate precipitate upon addition of base. In addition a XI:$V^{(IV)}$ (as vanadyl sulfate dihydrate) ratio of 2:1 gave a clear, amber solution upon the addition of 2 moles of base/mole of ligand (pH 11.9), whereas a ligand:vanadium ratio of 1:1 gave a precipitate after introduction of 1 mole of base/mole of XI (pH 4.6). This precipitate disappeared at pH 8.2 upon continued titration and remained a clear, amber solution at pH 11.7.

Pharmacological Studies. MAO Inhibition.—Compounds IX–XIII were evaluated for possible monoamine oxidase inhibitory

activity by a procedure similar to that of Aceto and Harris[21] as modified by Nematollahi, *et al.*[22] A dose of 1.1 mmoles/kg was administered orally to groups of ten mice (male, strain C_3H 20 ± 1 g). Since IX and XIII are insoluble in water, a 3% suspension of acacia in distilled water was used as the vehicle in all cases except where otherwise noted. After 2 hr, five mice in each group were challenged with a 2.5-mg/kg ip dose of reserpine; the other five being given 5 mg/kg ip of reserpine. The animals were left undisturbed for 3 hr then evaluated as to degree of blepharoptosis by two individuals. Ten control mice received only vehicle and reserpine (2.5 and 5 mg/kg for each half) as a control while isocarboxazide, administered in the same manner as the test compounds at a dose of 0.275 mmole/kg, served as a standard. The following ptotic scoring system of Aceto and Harris[21] was used: 4 = complete, 3 = three-fourths, 2 = one-half, 1 = one-fourth closure of the eyelids and 0 = open eyelids. Since the administration of XI resulted in convulsive death of all animals at the 1.1-mmoles/kg level, the test was repeated using 0.275, 0.55, and 0.825-mole/kg doses (aqueous solutions) in a group of five mice with a challenging dose of 5 mg/kg ip of reserpine. The results of the testing are given in Table III.

(21) M. D. Aceto and L. P. Harris, *J. Toxicol. Appl. Pharmacol.*, **7**, 329 (1952).

(22) J. Nematollahi, W. Guess, and J. Autian, *J. Med. Chem.*, **9**, 660 (1966).

Anticancer Screening.—Derivatives containing aziridinyl moieties were tested against Walker 256 subcutaneous (WA); the remaining compounds against Walker 256 intramuscular (WM) and/or lymphoid leukemia L1210 (LE).[23] Screening results are presented in Table IV.

Antimalarial Screening.—Five mice were infected with a lethal dose of *Plasmodium berghei* 3 days prior to administration of I, II, VII–X, and XII in doses of 40, 160, and 640 mg/kg sc in oil.[24] The mean survival time of infected control mice was 6.1 days. The changes in survival time are given as the mean survival time of the treated group minus the mean survival time of the control group. The results of the rodent antimalarial tests are given in Table IV.

Acknowledgments.—The author wishes to thank M. M. Clay for his assistance in the MAO inhibition study. The author is also indebted to D. A. Montalvo, Southwest Research Institute, San Antonio, Texas, M. R. Willcott, School of Chemistry, University of Houston, and J. E. Robbers, Purdue University, for recording and interpreting the nmr spectra.

(23) Test results furnished by the Cancer Chemotherapy National Service Center, Bethesda, Md.

(24) Test results furnished by Walter Reed Army Medical Center, Washington, D. C.

Alkylating Agents Related to 2,2′-Biaziridine. II.[1] N,N′-Dicarbethoxy-2,2′-biaziridine

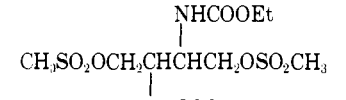
Peter W. Feit and Ole Tvaermose Nielsen

Leo Pharmaceutical Products, Ballerup, Denmark

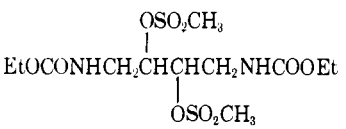
Received December 17, 1966
Revised Manuscript Received April 17, 1967

DL- and (2*R*:2′*R*)-N,N′-dicarbethoxy-2,2′-biaziridine (**3**) and the bismethanesulfonates of the symmetrical position isomers of DL- and (2*S*:3*S*)-N,N′-dicarbethoxydiaminobutanediols (**1** and **2**) were synthesized. Unsuccessful attempts to prepare the corresponding 1,4-dihalogeno-2,3-diaminobutanes are mentioned. As far as they are available the anticancer screening data for the compounds are summarized.

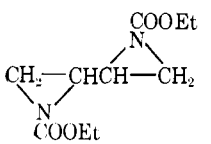
For reasons already discussed[1] the present communication concerns the synthesis of DL- and (2*S*:3*S*)-N,N′-dicarbethoxy-2,3-diamino-1,4-butanediol 1,4-bismethanesulfonate [DL-**1**, (*S*:*S*)-**1**], (2*S*:3*S*)-N,N′-dicarbethoxy-1,4-diamino-2,3-butanediol 2,3-bismethanesulfonate [(*S*:*S*)-**2**], and DL- and (2*R*:2′*R*)-N,N′-dicarbethoxy-2,2′-biaziridine [DL-**3**, (*R*:*R*)-**3**].



1



2



3

(1) Paper I: P. W. Feit and O. Tvaermose Nielsen, *J. Med. Chem.*, **10**, 697 (1967).

The biaziridine derivatives **3** might act *in vivo* as alkylating agents *per se*, or alternatively after being metabolized to the corresponding unsubstituted 2,2′-biaziridine, inasmuch as James[2] has proved aziridine formation from N-carboalkoxyaziridines *in vitro* after incubation with rat plasma.

For the N,N′-dicarbethoxydiaminobutanediol bismethanesulfonates **1** and **2** a ring closure to the biaziridine **3** seems unlikely under physiological pH as this reaction proceeds *in vitro* under strong alkaline conditions only. However, there might be a possibility of metabolizing to the unsubstituted amino compounds which are considered *in vivo* precursors of the corresponding 2,2′-biaziridine.

Chemistry.—The synthetic route for the preparation of DL-**1** and (*S*:*S*)-**1** and the corresponding biaziridines DL-**3** and (*R*:*R*)-**3** is summarized for the optically active compounds in Scheme I.[3] Ring closure to the biaziridine (*R*:*R*)-**3** could be performed by treatment of (*S*:*S*)-**1** with KOH in methylene chloride. Examination of the infrared spectrum established the structure since a strong carbonyl absorption is present while

(2) R. M. James, *Biochem. Pharmacol.*, **14**, 915 (1965).

(3) The reaction from **6** to **7** proceeds under Walden inversion at C-2 and -3. The prefix (*S*:*S*) is not changed in this special case due to the rules of the Cahn–Ingold–Prelog system: R. S. Cahn, C. K. Ingold, and V. Prelog, *Angew. Chem.*, **78**, 413 (1966), and preceding papers.