Table I. Bacterial Growth Inhibition of 10-Deazaminopterin and Its Reduced Forms

	MIC (ng/ml) for 50% inhibition[a,g]				
	S. faecium[b] (ATCC 8043)	*S. faecium*[b] MTX resistant	*L. casei*[b] (ATCC 7649)	*L. casei* MTX resistant	*P. cerevisiae*[c]
10-Deazaminopterin (VI)	0.2	>2000	0.02	>2,000	86
VI-H_2[e]	0.01	200	0.002[d]	60	2.5
VI-H_4[f]	0.03	>2000	0.007	250	0.18
Methotrexate (MTX)	0.15	>6000	0.01	38,000	60
7,8-Dihydro-MTX[e]	0.01		0.009		
5,6,7,8-Tetrahydro-MTX[f]	0.05		0.06		
Aminopterin	1.0		0.03		210
7,8-Dihydroaminopterin[e]	0.01		0.01		
5,6,7,8-Tetrahydroaminopterin[f]	0.07		0.06		

[a]None of the compounds supported growth in the absence of folate at a level of 2000 ng/ml. [b]Folate, 1 ng/ml, growth inhibition reversed by added folate. *S. faecium:* medium of L. M. Flynn, V. B. Williams, B. L. O'Dell, and A. G. Hogan, *Anal. Chem.*, **23,** 180 (1951); *L. casei:* BBL folic acid assay broth. [c]5-Formyltetrahydrofolate, 1 ng/ml (Difco CF assay medium). [d]5×10^{-12} *M*. [e]From $Na_2S_2O_4$ reduction of parent compound: M. Friedkin, E. J. Crawford, and D. Misra, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **21,** 176 (1962). [f]From H_2–PtO_2 reduction in neutral aqueous solution: R. L. Blakley, *Biochem. J.*, **65,** 331 (1957). [g]All compounds were diluted in potassium ascorbate, 6 mg/ml (pH 6.0), and added to growth media aseptically after autoclaving: H. A. Bakerman, *Anal. Biochem.*, **2,** 558 (1961).

Table II. Enzyme Inhibition of 10-Deazaminopterin and Its Reduced Forms

	Molarity for 50% inhibition[c]	
	Dihydrofolic reductase[a]	Thymidylate synthetase[a]
VI	4.5×10^{-9}	$>1 \times 10^{-4}$
VI-H_2[b]	4.5×10^{-9}	1×10^{-5}
VI-H_4[b]	1.0×10^{-7}	5.7×10^{-6}
MTX	3.3×10^{-9}	$>1 \times 10^{-4}$

[a]Derived from *L. casei* (ATCC 7649). [b]Reduced forms were not active as substrates for either enzyme. [c]Conditions: DHF, 50 μM; NADPH,[f] 80 μM; Tris HCl, 0.05 *M*; 2-mercaptoethanol, 0.01 *M*; EDTA, 0.001 *M*; protein, 0.0012 mg; pH 7.4; 30°; reaction initiated with enzyme.

with *i*-BuOCOCl under controlled conditions. *tert*-Butyloxycarbonylglutamic acid α-benzyl ester was esterfied to Merrifield resin through the γ-COOH group.[4] After deprotection the amino group of resin-bound glutamate was then coupled with the mixed anhydride of V. Cleavage of coupled product from the resin with 2 *N* NaOH–dioxane at ambient temperature afforded VI in 70% yield.

Alternatively, the mixed anhydride of V was coupled with trimethylsilyl glutamate[5] and the silyl esters were cleaved with 1% Na_2CO_3 at room temperature. After chromatography on DEAE-cellulose the product was found to be identical with VI produced by the resin technique. Since prolonged treatment of V with 1% Na_2CO_3 did not cause deamination, the product obtained by the two different coupling procedures was established as the 2,4-diamino compound VI, as was also verified by elemental analysis.

Experimental Section

10-Deazaminopterin (VI). Method A. Compound V[3] (155 mg, 0.5 mmol) was dissolved in DMSO (15 ml) and 15 ml of dry THF was added. The solution was chilled and *N*-methylmorpholine (0.625 mmol) was added. The solution was kept at 0° for 15 min and *i*-BuOCOCl (0.5 mmol) was added with stirring. After 15 min this product was coupled with the NH_2 deprotected α-benzyl-γ-glutamyl resin ester.[4] The coupled product was cleaved from the resin by shaking for 1 hr at room temperature in a mixture of 20 ml of 2 *N* NaOH and 20 ml of dioxane under N_2.

The solution was adjusted to pH 7.5, diluted to 1 l., and chromatographed on a DEAE Cl column (20 × 3 cm) with elution by 0.15 *M* NaCl. The peak fractions were concentrated to 250 ml *in vacuo*, acidified to pH 4.5 (HOAc), and chilled 15 hr. The pale yellow product was collected by filtration (154 mg, 70%): $\lambda^{pH\ 13}$ 256 nm (32,500), 372 (7475); $\lambda^{pH\ 1}$ 243 (26,800), 340 (8800); chromatography on analytical DEAE column, single uv-absorbing band. *Anal.* ($C_{20}H_{21}N_7O_5 \cdot H_2O$) C, H, N.

Method B. A mixture of glutamic acid (147 mg, 1 mmol), hexamethyldisilazane (10 ml), and 30 mg of H_2SO_4 was stirred at reflux until solution was complete. The solvent was removed *in vacuo* and the residual silyl ester dissolved in 15 ml of DMSO–THF (1:1) and coupled with the mixed anhydride of V. After 15 hr the solution was concentrated to 15 ml *in vacuo* and treated with 100 ml of 1% Na_2CO_3 for 2 hr. The solution was adjusted to pH 7 (1 *N* HCl), diluted to 700 ml, and chromatographed on DEAE as above. Only two peaks were eluted—one corresponded with starting material V and the other was identical with product VI obtained by method A. A control experiment where V was exposed to similar treatment with 1% Na_2CO_3 gave no deamination to 10-deazapteroic acid (III)[1] as shown by analytical DEAE chromatography.

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Synthesis of 1-Deaza-N^{10}-methylfolic Acid and Related Compounds

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Recent tests showed that 3-deazamethotrexate was more effective against leukemia L1210 in mice, more cytotoxic in cell culture, and a better inhibitor of the dihydrofolate reductase enzyme (pigeon liver) than 1-deazamethotrexate. These results indicated that the 1-nitrogen contributed more to activity than the 3-nitrogen in these ring systems.[1] In contrast, a dihydro-1-deazapteridine† precursor of 1-deazamethotrexate showed activity against leukemia L1210 in mice,[2] and the preparation of a number of 1-deazapteridines is currently being investigated. In

†Compound **10a**, ref 2. Preliminary results indicated that this compound gave a 30% (qd 1–9) increase in lifespan against leukemia L1210 in mice at a dose of 25 mg/kg.

this paper, we wish to report the unambiguous synthesis and some biological properties of 1-deaza-N^{10}-methylfolic acid‡ and its precursors.

Previously, the interaction of 2,3,6-triaminopyridin-4(1*H*)-one, 2,3-dibromopropionaldehyde, and *p*-aminobenzoyl-L-glutamic acid was reported to give 3-deazafolic acid.[3] To circumvent the possible difficulties in assigning the position of the side chain in the pyrazine ring, we selected the method of Boon and Leigh[4,5] for the preparation of 1-deaza-N^{10}-methylfolic acid. Treatment of the 6-aminopyridine (**1**)[6] with isoamyl nitrite and sulfuric acid gave the pyridin-6-one **2**, which was allowed to react with methyl *p*-[(3-aminoacetonyl)methylamino]benzoate oxime[4] to give the nitropyridine intermediate **3**. Reductive cyclization of **3** to give **4** was effected in the presence of Raney nickel and hydrogen. Presumably this conversion involves the reduction of the nitro group of **3** to give the corresponding 3-aminopyridine, the amino group of which undergoes a transamination type of reaction with the oxime function of the side chain to give **4**.[2] Oxidation of **4** with $KMnO_4$ gave the heteroaromatic system **5**, which was treated with refluxing ethanolic KOH to hydrolyze both the urethane and ester moieties to give the 1-deazapteroic acid **6**. Acylation of **6** with Ac_2O gave **7**. The resulting blocked 1-deazapteroic acid was treated with diethyl L-glutamate and *N,N'*-dicyclohexylcarbodiimide in pyridine to give **8**, which was saponified with aqueous NaOH in ethanol to give the 1-deazafolic acid **9**. A solution of the corresponding 1-deazadihydrofolic acid **10** was prepared by hydrogenation of **9** in the presence of a palladium catalyst (Scheme I).

Previously, 3-deazafolic acid was reported to be a growth inhibitor of *Lactobacillus casei* 7469 (ED_{50} 0.15 μM) but not of *Streptococcus faecium* 8043.[3] In contrast, 1-deaza-N^{10}-methylfolic acid (**9**) was an inhibitor of both *L. casei* (ED_{50} 0.72 μM) and *Strept. faecium* (ED_{50} 0.11 μM). The dihydro derivative **10** (ED_{50} 2.0 μM) was less effective against the latter bacterium. Compound **9** is a poor inhibitor of the dihydrofolate reductase enzyme from pigeon liver,[7] and presumably this compound is inhibiting at another site in the bacteria described above. In addition, compounds **4**–**6** and **8** were ineffective against the reductase enzyme from pigeon liver. No significant cytotoxicity was observed for **4**–**6** and **8**–**10** in the KB cell culture screen, and no significant activity was observed for **4** and **9** when tested against leukemia L1210 in mice.

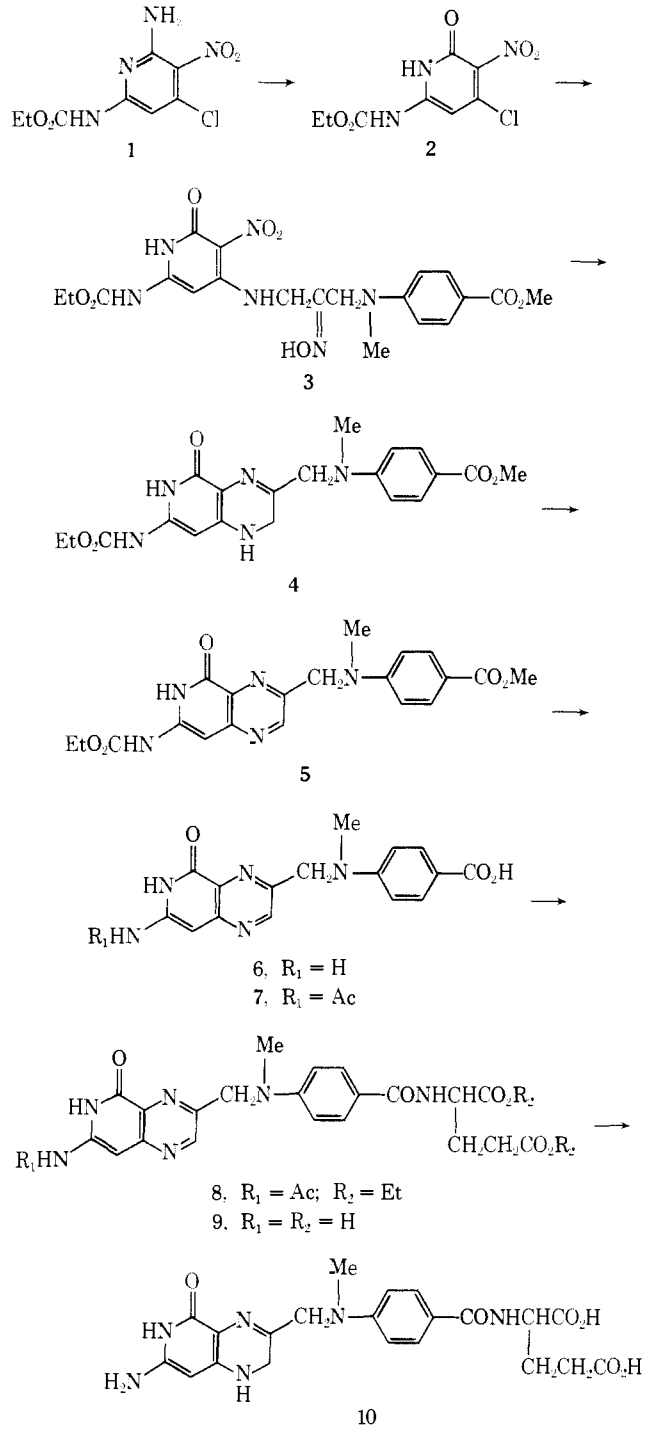
Experimental Section§

Ethyl 4-Chloro-5-nitro-6(1*H*)-oxo-2-pyridinecarbamate (2). A stirred solution of **1** (15.0 g, 57.8 mmol)[6] and isoamyl nitrite (10.8 g, 92.4 mmol) in DMAC (200 ml) at 0° was treated dropwise with 2 *N* H_2SO_4 (57.8 ml, 57.8 mmol) and refrigerated for 16 hr. The resulting solution was heated gradually (1 hr) to 100° and maintained at this temperature for 1 hr. Dropwise addition of H_2O (200 ml) gave a crystalline precipitate of **2**, which was collected by filtration, washed successively with DMAC–H_2O (1:1), H_2O, and cold EtOH, and dried *in vacuo* (P_2O_5): yield 9.96 g (66%); mp ~235° dec (Mel-Temp apparatus); λ_{max} nm ($\epsilon \times 10^{-3}$), pH 7, 233 (9.90), 265 (sh, 5.68), 303 (4.47), 400 (4.35). *Anal.* ($C_8H_8ClN_3O_5$) C, H, N.

‡Chemical Abstracts name: *N*-[*p*-[[(7-amino-5,6-dihydro-5-oxopyrido[3,4-*b*]pyrazin-3-yl)methyl]methylamino]benzoyl]-L-glutamic acid.

§Melting points were determined on a Kofler Heizbank apparatus unless otherwise indicated. The uv absorption spectra of solutions were determined with Cary Model 14 and 17 spectrophotometers, whereas the ir absorption spectra were determined in pressed KBr disks with Perkin-Elmer Models 521 and 621 spectrophotometers. The pmr spectra were obtained on DMSO-d_6 solutions with a Varian XL-100 spectrometer with tetramethylsilane as an internal reference. Chemical shifts quoted in the case of multiplets are measured from the approximate center, and the relative peak areas are given to the nearest whole number. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Scheme I



Ethyl 4-[[3-(*p*-Methoxycarbonyl-*N*-methylanilino)acetonyl]-amino]-5-nitro-6(1*H*)-oxo-2-pyridinecarbamate Oxime (3). A stirred solution of **2** (7.96 g, 30.4 mmol), methyl *p*-[(3-aminoacetonyl)methylamino]benzoate oxime (7.65 g, 30.4 mmol),[4] and triethylamine (3.07 g, 30.4 mmol) in CH_3OH (200 ml) was refluxed under N_2 for 19 hr and cooled to 25°. The yellow crystalline product was collected by filtration, washed with CH_3OH, and dried *in vacuo* (P_2O_5): yield 11.4 g (79%); mp ~206° dec; λ_{max} nm ($\epsilon \times 10^{-3}$), pH 7, 233 (26.3), 315 (29.4), 353 (sh, 13.4). *Anal.* ($C_{20}H_{24}N_6O_8$) C, N; H: calcd, 5.08; found, 4.60.

Ethyl 1,2-Dihydro-3-[(*p*-methoxycarbonyl-*N*-methylanilino)-methyl]-5(6*H*)-oxopyrido[3,4-*b*]pyrazine-7-carbamate (4). A suspension of finely powdered **3** (10.0 g, 21.0 mmol) in EtOH (1.25 l.) at 49° was hydrogenated in the presence of Raney nickel (8.7 g, weighed wet with EtOH). After 48 hr, the mixture had absorbed 89.4 mmol of hydrogen. The reaction mixture was evaporated to dryness *in vacuo*, and the residue was triturated with EtOH (4 × 50 ml) under N_2. A mixture of the residue with DMAC (100 ml)

was heated at 85° under N_2 for 3 min and filtered through Celite under N_2. The filtrate was diluted with H_2O (200 ml) and refrigerated. The resulting orange crystalline precipitate was collected by filtration, washed successively with cold H_2O–DMAC (2:1) and H_2O, and dried at 65° *in vacuo* (P_2O_5): yield 5.19 g (60%); mp ~161° dec (Mettler FP1 apparatus); λ_{max} nm ($\epsilon \times 10^{-3}$), pH 7, 244 (29.2), 312 (30.5). *Anal.* ($C_{20}H_{23}N_5O_5$) C, H, N.

Ethyl 3-[(*p*-Methoxycarbonyl-*N*-methylanilino)methyl]-5(6*H*)-oxopyrido[3,4-*b*]pyrazine-7-carbamate (5). A stirred suspension of finely powdered 4 (100 mg, 0.242 mmol) in H_2O (10 ml), EtOH (1 ml), and 1 *N* NaOH (0.32 ml, 0.32 mmol) was treated dropwise with a 0.27% solution of $KMnO_4$ (9.44 ml, 0.161 mmol) in H_2O. After filtration, the filtrate was neutralized with 1 *N* HCl. The resulting yellow precipitate was collected by centrifugation, washed with H_2O, and dried at 65° *in vacuo* (P_2O_5): yield 81 mg (81%); mp ~225° dec; λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 253 (17.4), 313 (39.9), 375 (5.25). *Anal.* ($C_{20}H_{21}N_5O_5$) C, H, N.

***p*-[[(7-Amino-5(6*H*)-oxopyrido[3,4-*b*]pyrazin-3-yl)methyl]-methylamino]benzoic Acid (6).** A stirred solution of 5 (2.23 g, 5.43 mmol) and KOH (11.2 g) in EtOH (200 ml) was refluxed under N_2 for 16 hr and evaporated to dryness *in vacuo*. A solution of the residue in H_2O (100 ml) was filtered and acidified with 6 *N* HCl to pH 3.5. The precipitate of 6, containing partially hydrolyzed 5, was retreated with KOH in EtOH as described above to give pure 6 as an orange precipitate. This solid was collected by filtration, washed with water, and dried at 100° *in vacuo* (P_2O_5): yield 1.61 g (91%); melting point indefinite, turned black at ~220°; λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 252 (17.1), 316 (28.7), 417 (3.57); 0.1 *N* NaOH, 273 (30.0), 433 (4.32); ν_{max}, 1673, 1660, 1650 (C=O and NH_2), 1604, 1564, 1512 cm^{-1} (C=C, C=N); pmr δ 3.21 (3, NCH_3), 4.77 (2, NCH_2), 5.59 (1, 8-CH), 6.22 (2, NH_2), 6.82, 7.76 (m, 4, C_6H_4), 8.42 (1, 2-CH), ~10 (br, CO_2H, NH). *Anal.* ($C_{16}H_{15}N_5O_3$) C, H, N.

***p*-[[(7-Acetamino-5(6*H*)-oxopyrido[3,4-*b*]pyrazin-3-yl)methyl]methylamino]benzoic Acid Hydrochloride (2:1) (7).** A solution of 6 (1.27 g, 3.91 mmol) in Ac_2O (127 ml) was refluxed under N_2 for 1 hr and evaporated to dryness *in vacuo*. The residual gum was stirred with H_2O (50 ml) for 2 days until a homogeneous powder formed. The resulting suspension was treated with concentrated NH_4OH (3 ml) to give a solution, which was immediately filtered and acidified to pH 3 with 6 *N* HCl. The brown precipitate was collected by centrifugation, washed with H_2O (pH 3), and dried *in vacuo* (P_2O_5): yield 1.39 g (92%); melting point indefinite; λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 256 (19.0), 300 (25.8). *Anal.* ($C_{18}H_{17}N_5O_4 \cdot 0.5HCl$) C, H, N.

Diethyl *N*-[*p*-[[(7-Acetamido-5(6*H*)-oxopyrido[3,4-*b*]pyrazin-3-yl)methyl]methylamino]benzoyl]-L-glutamate Hydrate (5:4) (8). A suspension of 7 (1.01 g, 2.62 mmol) and *N,N'*-dicyclohexylcarbodiimide (540 mg, 2.62 mmol) in anhydrous pyridine (50 ml) was treated with diethyl-L-glutamiate hydrochloride (628 mg, 2.62 mmol), stirred at 25° for 44 hr, filtered to remove *N,N'*-dicyclohexylurea, and evaporated to dryness *in vacuo*. A solution of the residue in $CHCl_3$ (20 ml) was filtered and washed successively with 0.3 *N* HCl (2 × 20 ml), H_2O (10 ml), saturated $NaHCO_3$ solution (10 ml), and H_2O (2 × 10 ml). The resulting solution was dried over $MgSO_4$ and evaporated *in vacuo* to give a brown foam (1.05 g). A solution of the foam in $CHCl_3$ (5 ml) was adsorbed on a short column (28 mm diameter) containing 30 g of silica gel[a] equilibrated with $CHCl_3$. The column was developed with $CHCl_3$ (50 ml) followed by 98:2 $CHCl_3$–MeOH (50 ml) and 96:4 $CHCl_3$–MeOH. The major yellow fraction was evaporated *in vacuo* to give 524 mg (35%) of yellow product: melting point indefinite with softening at ~97°; λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 254 (16.2), 311 (32.7), 374 (br, 4.85). *Anal.* ($C_{27}H_{32}N_6O_7 \cdot 0.8H_2O$) C, H, N.

***N*-[*p*-[[(7-Amino-5,6-dihydro-5-oxopyrido[3,4-*b*]pyrazin-3-yl)methyl]methylamino]benzoyl]-L-glutamic Acid Hydrate (9).** A stirred solution of 8 (500 mg, 0.883 mmol) in EtOH (20 ml) and 1 *N* NaOH (8.50 ml, 8.50 mmol) was refluxed for 1 hr under N_2 and evaporated to dryness *in vacuo*. A solution of the residue in H_2O (12 ml) was filtered and acidified with 1 *N* HCl to pH 3. The red precipitate was collected, washed with H_2O at pH 3, and dried *in vacuo* (P_2O_5) at 100°: yield 340 mg (82%); melting point indefinite, darkens above 188°; λ_{max}, nm ($\epsilon \times 10^{-3}$), 0.1 *N* HCl, 262 (16.2), 329 (30.2), 495 (br, 4.81); pH 7, 225 (18.4), 255 (sh, 16.8), 318 (36.0), 413 (br, 3.73); 0.1 *N* NaOH, 272 (28.1), 309 (28.3), 432 (br, 3.90); ν_{max} 1710 (sh), 1640 (C=O and NH_2), 1598, 1565, 1500 cm^{-1} (C=C, C=N); pmr δ 1.8–2.5 (m, 4, CH_2CH_2), 3.19 (3, NCH_3), 4.36 (m, 1, NCH), 4.74 (2, NCH_2), 5.56 (8-CH), 6.18 (2, NH_2), 6.81, 7.75 (m, 4, C_6H_5), 8.18 (d, 1, NHCO), 8.40 (1, 2-CH), ~11 (br, CO_2H, NH). *Anal.* ($C_{21}H_{22}N_6O_6 \cdot H_2O$) C, H, N.

***N*-[*p*-[[(7-Amino-1,2,5,6-tetrahydro-5-oxopyrido[3,4-*b*]pyrazin-3-yl)methyl]methylamino]benzoyl]-L-glutamic Acid (10).** A solution of 9 (24 mg, 0.06 mmol) in 1 *N* NaOH (8 ml) was hydrogenated for 80 min at 25° in the presence of 5% palladium on charcoal (25 mg) to absorb 1.2 ml (0.05 mmol) of hydrogen. An aliquot portion (1 ml) of the filtered solution was treated with 1 *M* 2-mercaptoethanol (2.5 ml) and 1 *N* HCl (0.9 ml) for ultraviolet spectral determination: λ_{max}, nm ($\epsilon \times 10^{-3}$), pH 7, 309 (~24). The remaining solution of 10 was treated with ascorbic acid (70 mg) and tested in the KB cell culture screen.

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[a] SilicAR TLC-7 (fines removed), Mallinckrodt Chemical Works.

Ethambutol. Synthesis of an Unsaturated Analog

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We have recently[1] reported a new synthesis of ethambutol (**5**) based on the key intermediate **1**, easily obtainable in high yield by the reaction of phosgene on 3,4-epoxy-1-butene. The same intermediate has now been employed for the synthesis of (+)-2,2'-(ethylenediimino)di-3-buten-1-ol (**4b**), an unsaturated analog of ethambutol. Although the biological activity of this compound has been found inferior to that of the parent compound, its potential use in the preparation of tritium-labeled ethambutol warrants in our opinion the report of the details of its synthesis.†

2-Chloro-3-buten-1-yl chloroformate (1) was condensed in chloroform solution with ethylenediamine to give the symmetric bisurethane 2 that, by treatment with KOH, yielded a 50:50 mixture of meso and DL forms of 3,3'-ethylene-di(4-vinyl-2-oxazolidone) (**3**). Separation of the two forms was achieved by fractional crystallization from cyclohexylamine, in which the meso form is less soluble, and from pyridine, in which on the contrary the DL form is less soluble.

Alkaline hydrolysis of 3 (DL form) gave (±)-2,2'-(ethy-

†We are indebted to Dr. A. Sanfilippo of these laboratories for the biological data.