Synthesis and Biological Activity of L-5-Deazafolic Acid and L-5-Deazaaminopterin: Synthetic Strategies to 5-Deazapteridines[1]

Edward C. Taylor,* David C. Palmer, Thomas J. George, Stephen R. Fletcher, Chi Ping Tseng, and Peter J. Harrington

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

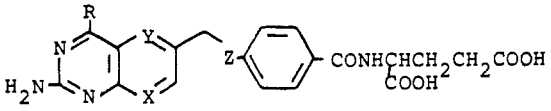
G. Peter Beardsley

Dana-Farber Cancer Institute, Boston, Massachusetts 02115

Received January 17, 1983

Condensation of 2,4-diamino-6(1*H*)-pyrimidinone with triformylmethane gives 6-formyl-5-deazapterin (**13**). Acetylation to **14**, followed by reductive amination with dimethyl *p*-aminobenzoyl-L-glutamate and saponification of the resulting acetylated dimethyl ester **16** then gives L-5-deazafolic acid (**12**). Condensation of α-cyanothioacetamide with 2-methyl-3-ethoxyacrolein gives 3-cyano-5-methyl-2(1*H*)-pyridinethione (**17**), which is converted to 2-[(*p*-nitrophenyl)thio]-3-cyano-5-methylpyridine (**18**) by arylation with *p*-nitrofluorobenzene. Free-radical bromination of **18** to the 5-bromomethyl derivative, conversion to the corresponding aldehyde **21** by the Kröhnke procedure, formation of the acetal **22**, and amination then gives 2-amino-3-cyano-5-(dimethoxymethyl)pyridine (**23**). This is condensed with guanidine and the product hydrolyzed selectively with formic acid to give 2,4-diamino-6-formyl-5-deazapteridine (**26**). Reductive amination of **26** with dimethyl *p*-aminobenzoyl-L-glutamate followed by saponification then gives L-5-deazaaminopterin (**6**). An alternative synthesis of **13** results from alkaline hydrolysis of **24** followed by acid cleavage of the resulting acetal **25**. Two syntheses of 2,4-diamino-6-methyl-5-deazapteridine (**32**) are described; functionalization of the C-6 methyl group, however, was not possible. Syntheses of 3-formylthietane (**45**) and its dimethyl and ethylene acetals (**44** and **46**, respectively) are described, and their utilization as synthons for the pyridine ring in the 5-deazapteridines **51** and **52** is explored. Difficulties militating against this alternate strategy for the preparation of **26** are discussed. L-5-Deazaaminopterin (**6**) is equipotent with methotrexate both as an inhibitor of bovine liver dihydrofolate reductase and of L1210 murine leukemia cells. It is also equipotent with methotrexate in vivo both against L1210 and P388 leukemia in BDF_1 mice.

Both methotrexate (MTX, **1**) and aminopterin (**2**) are classical antimetabolites which inhibit dihydrofolate reductase (DHFR). Because of the central importance of the folate coenzymes in the biosynthesis of both purine and pyrimidine nucleotides, inhibition of DHFR interrupts the cycling of dihydrofolate back to tetrahydrofolate and has a profoundly deleterious effect upon cell growth. As a consequence, both MTX and aminopterin are potent cytotoxic agents, although the latter is too toxic for clinical use.



1, R = NH_2, X = Y = N, Z = NCH_3
2, R = NH_2, X = Y = N, Z = NH
3, R = OH, X = CH, Y = N, Z = NH
4, R = OH, X = Y = N, Z = CH_2
5, R = NH_2, X = Y = N, Z = CH_2
6, R = NH_2, X = N, Y = CH, Z = NH
7, R = OH, X = Y = CH, Z = NH
8, R = NH_2, X = Y = CH, Z = NH
9, R = OH, X = CH, Y = N, Z = CH_2
10, R = OH, X = Y = CH, Z = CH_2
11, R = NH_2, X = Y = CH, Z = CH_2
12, R = OH, X = N, Y = CH, Z = NH

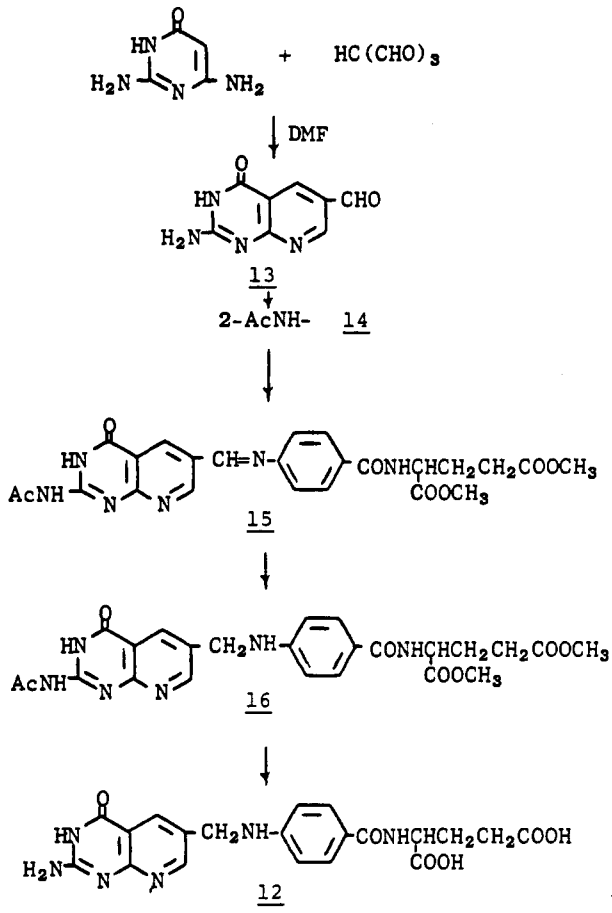
Among the most promising of modified folate derivatives intended as potential inhibitors of DHFR or thymidylate synthetase (TS) are various deaza derivatives of the pteridine ring system. 8-Deazafolic acid (**3**), for example, although inactive as an inhibitor of L1210 DHFR, shows significant activity against mouse L1210 leukemia and possesses better transport properties than folic acid itself.[2] Although 10-deazafolic acid (**4**) shows no significant in vitro activity against human epidermoid cells or in vivo activity against L1210 leukemia,[3] 10-deazaaminopterin (**5**) is an extremely promising compound which exhibits greater activity than methotrexate or aminopterin against a variety of solid and ascites tumors;[4-6] the enhanced in vivo antitumor activity of **5** was attributed to a more favorable interaction with the tumor transport system, compared with normal tissue, in the small intestine.[7] Furthermore, 5-deazaaminopterin (**6**) was reported to possess "phenomenal antimetabolite activity".[8] Both 5,8-dideazafolic acid (**7**) and 5,8-dideazaaminopterin (**8**) are effective inhibitors of TS from mouse neuroblastoma cells,[9-12] while the N-10 propargyl derivative of **7** appears to be the most potent inhibitor of TS yet discovered and is currently undergoing extensive clinical evaluation.[13] Although 8,10-dideazafolic acid (**9**) is only marginally effective as an inhibitor of bacterial DHFR[2] and although 5,8,10-tride-

(1) We are indebted both to F. Hoffmann-La Roche & Co., Ltd., Basel, and to the National Institutes of Health, National Cancer Institute (Grant No. R01 CA28351), for their generous support of this work.

(2) DeGraw, J. I.; Brown, V. H.; Kisliuk, R. L.; Gaumont, Y.; Sirotnak, F. M. In "Chemistry and Biology of Pteridines"; Elsevier/North-Holland: Limerick, Ireland, 1979, 229.
(3) Struck, R. F.; Shealy, Y. F.; Montgomery, J. A. *J. Med. Chem.* **1971**, *14*, 693.
(4) Sirotnak, F. M.; DeGraw, J. I.; Moccio, D. M.; Dorick, D. M. *Cancer Treat. Rep.* **1978**, *62*, 1047.
(5) DeGraw, J. I.; Brown, V. H.; Kisliuk, R. L.; Sirotnak, F. M. In "Chemistry and Biology of Pteridines"; Elsevier/North-Holland: Limerick, Ireland, 1979, 225.
(6) Piper, J. R.; Montgomery, J. A. *J. Med. Chem.* **1980**, *23*, 320.
(7) Sirotnak, F. M.; DeGraw, J. I.; Chello, P. L.; Moccio, D. M.; Dorick, D. M. *Cancer Treat. Rep.* **1982**, *66*, 351.
(8) Elslager, E. F.; Davoll, J. *Lect. Heterocycl. Chem.* **1974**, *2*, 5.
(9) Hutchinson, D. J. *Can. Chem. Rep.* **1968**, *52*, 697.
(10) Davoll, J.; Johnson, A. M. *J. Chem. Soc. C* **1970**, 997.
(11) Carlin, S. C.; Rosenberg, R. N.; Van de Venter, L.; Friedkin, M. *Mol. Pharmacol.* **1974**, *10*, 194.
(12) Acharya, S. P.; Hynes, J. B. *J. Heterocycl. Chem.* **1975**, *12*, 1283.
(13) Jones, T. R.; Calvert, A. H.; Jackman, A. L.; Brown, S. J.; Jones, M.; Harrap, K. R. *Eur. J. Cancer* **1981**, *17*, 11.

0022-3263/83/1948-4852$01.50/0

Scheme I



azafolic acid (**10**) shows marginal activity against mouse L1210 leukemia,[14] the corresponding 5,8,10-trideazaaminopterin (**11**) exhibits confirmed inhibitory activity against mouse L1210 leukemia.[15]

Encouraged by these results, we have embarked upon a synthetic program aimed at the development of new synthetic routes to deazapteridines and the synthesis of the missing deaza derivatives of folic acid, aminopterin, and methotrexate. This paper reports syntheses of 5-deazafolic acid (**12**) and 5-deazaaminopterin (**6**) and discusses our results with several alternative synthetic strategies.

A synthesis of 5-deazafolic acid (**12**) has recently been described[16] which involves condensation of 2,4-diamino-6(1*H*)-pyrimidinone with triformylmethane,[17] followed by elaboration of the requisite side-chain substituent. We independently developed[18] an analogous route to **12** which is summarized in Scheme I. 6-Formyl-5-deazapterin (**13**), which is obtained analytically pure from triformylmethane and 2,4-diamino-6(1*H*)-pyrimidinone in dry DMF, was acetylated under nitrogen to give the 2-acetyl derivative **14**. This was then condensed with dimethyl *p*-aminobenzoyl-L-glutamate in glacial acetic acid at room temperature, and the resulting imine **15** was reduced with borane triethylamine to **16**. Saponification of the 2-acetamido and methyl ester groupings then gave optically active 5-deazafolic acid (**12**) in 62% overall yield from **13**.

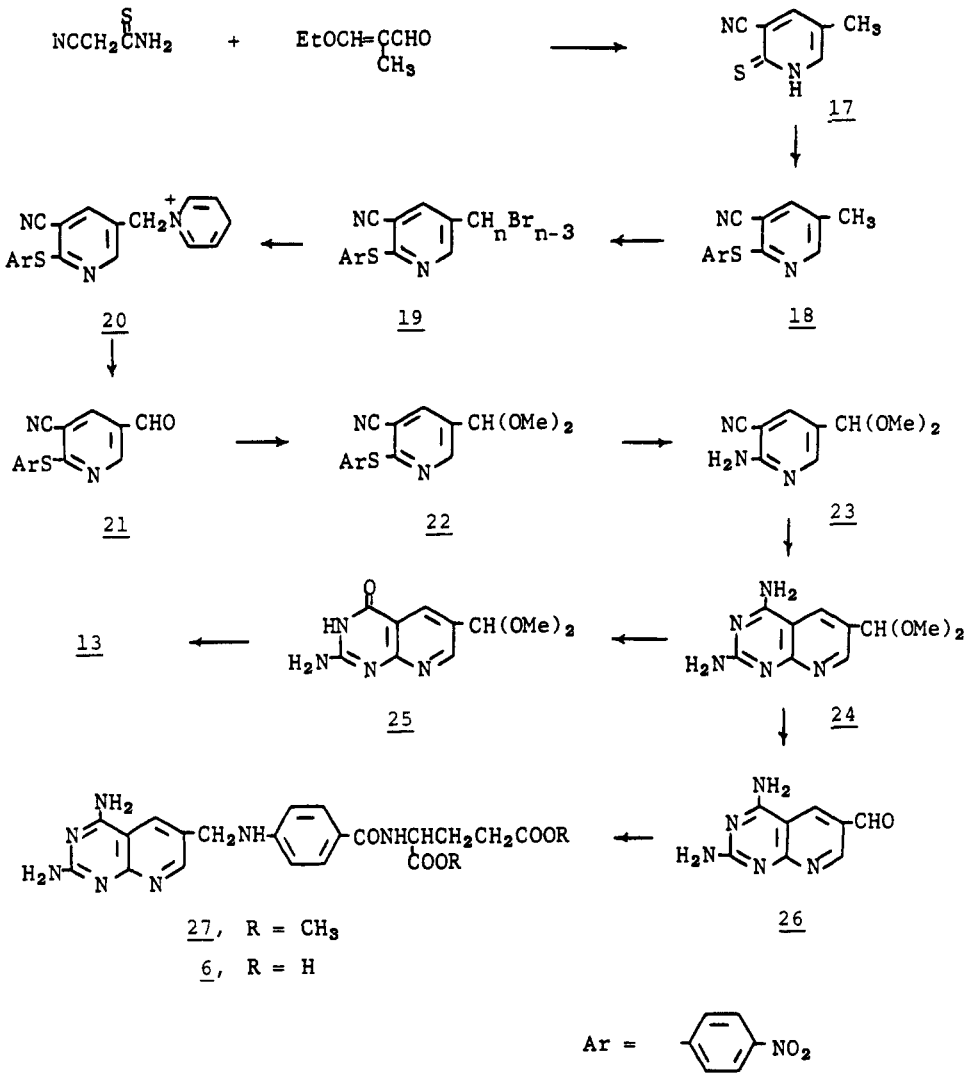
A synthesis of L-5-deazaaminopterin (**6**) patterned after the above route to L-5-deazafolic acid would require the intermediacy of 2,4-diamino-6-formyl-5-deazapteridine (**26**). Attempts to prepare this critical intermediate by the condensation of 2,4,6-triaminopyrimidine with pure triformylmethane met with failure, although, curiously enough, this condensation has recently been reported to be successful when *impure* triformylmethane (i.e., the crude reaction mixture from DMF/$POCl_3$/bromoacetic acid) was used.[16] We therefore developed an alternate synthesis of **26** which has led not only to another synthesis[16] of L-5-deazaaminopterin (**6**), as described below in Scheme II, but also to useful intermediates for the preparation of other types of MTX analogues. Condensation of α-cyanothioacetamide with 2-methyl-3-ethoxyacrolein (a methylmalondialdehyde equivalent) proceeded in excellent yield to give 3-cyano-5-methyl-2(1*H*)-pyridinethione (**17**). This was readily arylated on sulfur with *p*-nitrofluorobenzene, and the resulting arylthio intermediate **18** was brominated with NBS and benzoyl peroxide in benzene. Although the resulting mixture of mono-, di- and tribromomethyl derivatives **19** could be separated by tedious silica gel chromatography, it proved to be much more convenient to retrieve the desired monobromomethyl derivative as its pyridinium salt (**20**) by addition of pyridine directly to the crude reaction mixture.[19] Application of the Kröhnke procedure to this crystalline pyridinium salt then gave the pyridine-5-carboxaldehyde **21**, which was converted in quantitative yield to its dimethyl acetal (**22**) with methanol in the presence of a cation-exchange resin.

Aminolysis of **22** was accomplished in >90% yield with liquid ammonia in the presence of cupric bromide. Condensation of the resulting *o*-amino nitrile **23** with guanidine in anhydrous methanol in the presence of sodium methoxide then gave 2,4-diamino-6-(dimethoxymethyl)-5-deazapteridine (**24**). Alkaline hydrolysis of **24** (to remove the 4-amino grouping), followed by acidic hydrolysis of the acetal **25**, gave 6-formyl-5-deazapterin (**13**), identical in every respect with the material prepared as described above by condensation of 2,4-diamino-6(1*H*)-pyrimidinone with triformylmethane. Formic acid hydrolysis of **24**, on the other hand, led in quantitative yield to 2,4-diamino-6-formyl-5-deazapteridine (**26**). Reductive amination of **26** with dimethyl *p*-aminobenzoyl-L-glutamate, followed by saponification of the resulting dimethyl ester, then provided L-5-deazaaminopterin (**6**).[20]

A number of alternative strategies designed to lead to **6** and **12** were also investigated which, although ultimately unsuccessful in permitting elaboration of the final target compounds, led to the synthesis of a number of intriguing intermediates and the development of some novel thietane chemistry. For example, 2,4-diamino-6-methyl-5-deazapteridine (**32**), on the basis of previous syntheses of folic acid,[21,22] aminopterin,[22-24] and methotrexate,[22-26] appeared

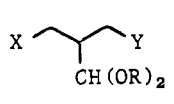
(14) Oatis, J. E., Jr.; Hynes, J. B. *J. Med. Chem.* **1977**, *20*, 1393.
(15) Yan, S. J.; Weinstock, L. T.; Cheng, C. C. *J. Heterocycl. Chem.* **1979**, *16*, 541.
(16) Temple, C., Jr.; Elliott, R. D.; Montgomery, J. A. *J. Org. Chem.* **1982**, *47*, 761.
(17) (a) Arnold, A. *Collect. Czech. Chem. Commum.* **1961**, *26*, 3051. (b) Arnold, A.; Zemlicka, J. *Ibid.* **1960**, *25*, 1318.
(18) Our synthesis of 5-deazafolic acid was first presented in detail in a Plenary Lecture delivered at the Spring Meeting of the Royal Society (London) in Cardiff, Wales, in March 1979.
(19) A forthcoming publication will describe the utilization of the triphenylphosphonium salt derived from the monobromomethyl component of this bromination mixture as an intermediate for the preparation of 5,10-dideazaaminopterin and related compounds.
(20) This synthesis of 5-deazaaminopterin was first presented in detail at the 8th International Congress of Heterocyclic Chemistry in Graz, Austria, in August 1981.
(21) Bieri, J. H.; Viscontini, M. *Helv. Chim. Acta* **1973**, *56*, 2905.
(22) Montgomery, J. A.; Rose, J. D.; Temple, C., Jr.; Piper, J. R. In "Chemistry and Biology of Pteridines"; Pfleiderer, W., Ed.; Walter de Gruyter: West Berlin, 1976; p 485.
(23) Piper, J. R.; Montgomery, J. A. *J. Heterocycl. Chem.* **1974**, *11*, 279.
(24) Piper, J. R.; Montgomery, J. A. *J. Org. Chem.* **1977**, *42*, 208.
(25) Catalucci, E. Ger. Offen. 2 741 383, 1977.

Scheme II

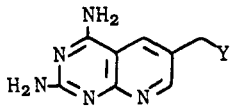


to be an attractive and versatile synthetic precursor to a variety of C-6 substituted intermediates. Two independent syntheses of **32** have been developed which are summarized in Scheme III. Unfortunately, all attempts to convert **32** either to **26** or to a halomethyl derivative were unsuccessful. Mild reaction conditions resulted in recovery of starting material, whereas more harsh conditions consumed **32** but gave no identifiable products. The unreactivity of the C-6 methyl group in **32** is reminiscent of the unreactivity of 3-picoline, even under forcing conditions;[27] the problem is certainly compounded in the present case by the extreme insolubility of **32** in organic solvents.

The successful synthesis of **32** from **33** as outlined in Scheme III suggested an alternative approach to a 2,4-diamino-6-(substituted methyl)-5-deazapteridine (i.e., **39**) by utilization of a suitably functionalized isobutyraldehyde acetal (**38**). In this projected synthetic sequence, X would



38



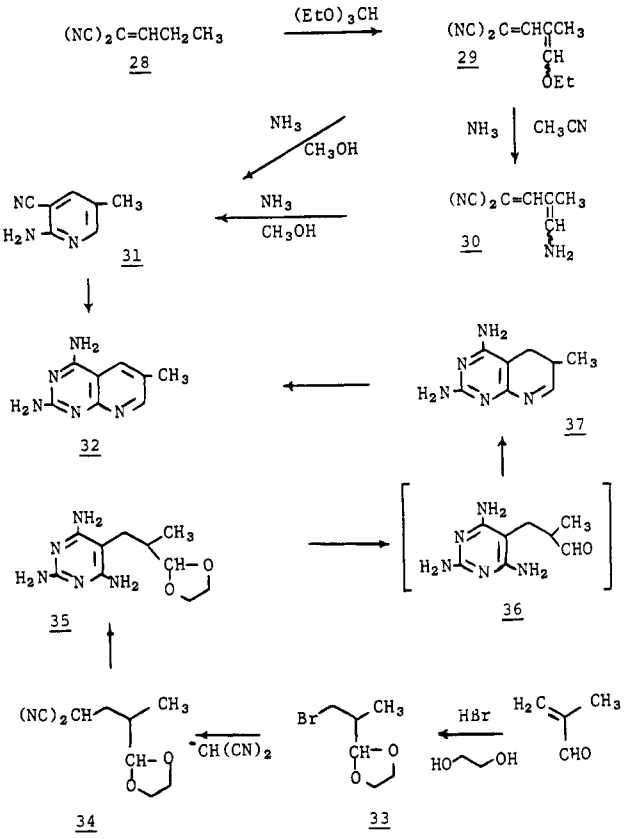
39

have to be a leaving group capable of displacement by the monoanion of malononitrile (analogous to the conversion of **33** to **34**, Scheme III), while Y should be a functional group stable to displacement, base-catalyzed elimination, and the dehydrogenation conditions, but still capable of serving as a latent halomethyl or aldehyde functionality. All of these requirements would be met if X were halogen and Y were an aralkylthio group.

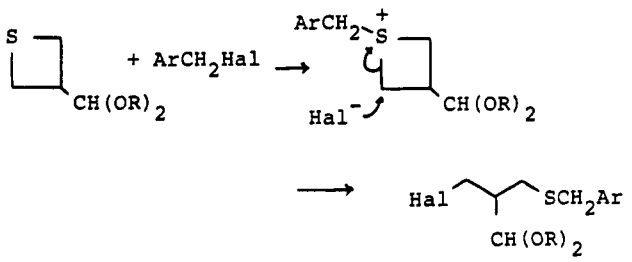
Our strategy for the preparation of **38** (X = Hal, Y = SCH_2Ar) involved alkylative ring opening of an appropriate acetal of 3-formylthietane (Scheme IV). Since the latter compound was unknown, however, we investigated a number of procedures for its preparation; the best one is outlined in Scheme V. α-(*N*-Pyrrolidino)acrolein dimethyl acetal (**40**)[28] was converted in excellent (65–75%) yield to 3-(*N*-pyrrolidino)-3-formylthietane 1,1-dioxide dimethyl acetal (**41**) by cycloaddition with sulfene (formed in situ from mesyl chloride and triethylamine in methylene chloride). Quaternization of **41** with methyl fluorosulfonate (Magic Methyl, Aldrich), followed by elimination of *N*-methylpyrrolidine with triethylamine, then furnished 3-formylthiete 1,1-dioxide dimethyl acetal (**42**) in 87% yield. After considerable experimentation, it was found that reduction of the thiete sulfone **42** to the thietane sulfone **43** could best be accomplished by catalytic reduction with 30% by weight palladium-on-charcoal catalyst in ethanol at 50 psi and at room temperature. After 46 h, the re-

(26) Portnoy, R. C. Ph.D. Thesis, Princeton University, 1974.
(27) Kutney, J. P.; Cretney, W.; Tabata, T.; Frank, M. *Can. J. Chem.* **1964**, *42*, 698.
(28) Taylor, E. C.; Dumas, D. J. *J. Org. Chem.* **1981**, *46*, 1394.

Scheme III



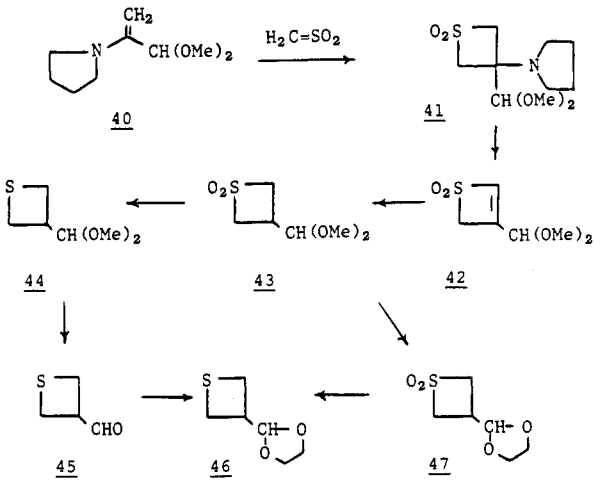
Scheme IV



duction mixture was filtered, an additional 20% by weight of catalyst added, and hydrogenation continued for 54 h. This process was then repeated again with addition of 10% by weight of catalyst and subsequent reduction for an additional 32 h. This laborious, expensive, but effective procedure produced **43** in an optimum yield of 97%; some contamination of the product with dimethyl sulfone could not be avoided. Reduction of **43** to **44** was best carried out with 2.5 equiv of LAH in diethyl ether. The 1,3-dioxolane **46** (which proved to be preferable to **44** in subsequent ring-opening reactions because of its greater hydrolytic stability) was then prepared by (a) hydrolysis of **44** with 0.5 N HCl at room temperature for 3 h to 3-formylthietane (**45**), which was then treated with ethylene glycol in the presence of *p*-toluenesulfonic acid, and (b) transacetalization of 3-formylthietane 1,1-dioxide dimethyl acetal with ethylene glycol/*p*-toluenesulfonic acid to give **47**, followed by Dibal reduction.

Treatment of **46** with 1 equiv of freshly prepared *p*-methoxybenzyl bromide in acetonitrile at room temperature gave a quantitative yield of the ring-opened primary bromide **48** (Scheme VI), which was condensed with the sodium salt of malononitrile in Me_2SO in the presence of a small amount of NaI to give the monoalkylated malononitrile **49**. Cyclization of **49** with ethanolic guanidine then gave the triaminopyrimidine **50**, which was heated

Scheme V



in 1 N HCl; neutralization of the acidic reaction mixture with ammonium hydroxide then gave a mixture of the dihydro-5-deazapteridine **51** and the fully aromatized 5-deazapteridine **52**. However, despite extensive experimentation with this crude reaction mixture, we were unable either to effect separation of **51** and **52** or to dehydrogenate **51** cleanly to **52**. The extraordinary insolubility of these compounds precluded TLC monitoring, reliable spectroscopic identification of intermediates or products, and chromatographic separation. It was thus apparent that, although the overall synthetic strategy leading from 3-formylthietane to 2,4-diamino-6-[(aralkylthio)methyl]-5-deazapteridines has been vindicated, the complexity and moderate yields, coupled with difficulties in adequate characterization of the pentultimate intermediate **52**, led us to abondon further efforts in this direction.

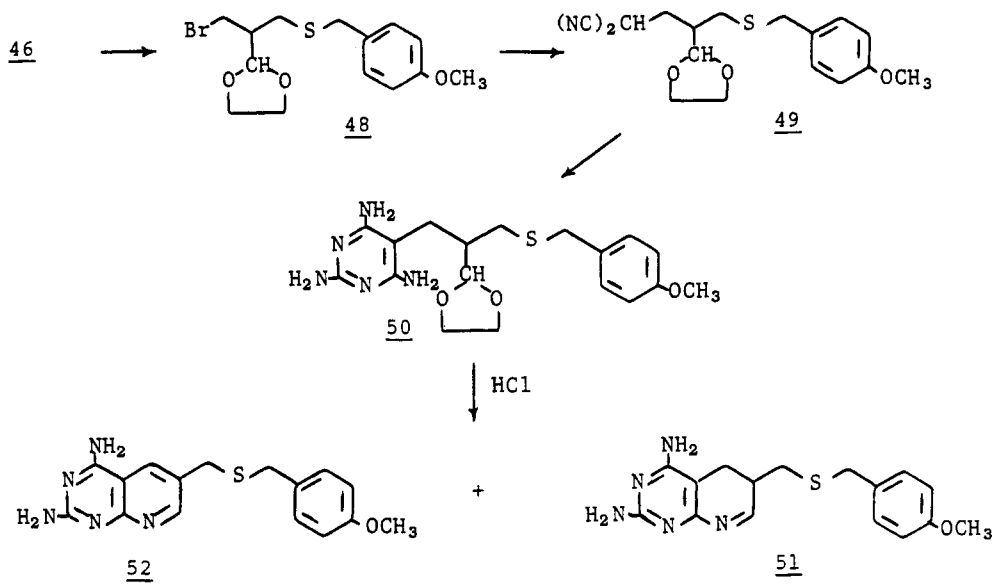
Biological determinations were carried out as follows. Both **12** and **6** were evaluated as inhibitors of beef liver DHFR by using the assay described by Friedkin et al.[29] Compound **6** is a potent inhibitor of DHFR with an IC_{50} of 7.1×10^{-9} M, which is close to that of aminopterin (IC_{50} 5×10^{-9} M); **12** is much less potent (IC_{50} 8.0×10^{-7} M).

These compounds were also evaluated as inhibitors of *L. casei* thymidylate synthetase by using the assay described by Kisliuk and Levine.[30] Neither **12** nor **6** is a strong inhibitor of this enzyme, both having IC_{50} values $>10^{-4}$M. Both compounds were also studied as inhibitors of the growth of L1210 murine leukemia cells in vitro.[31] Briefly, the L1210 cells in the log phase were exposed to varying concentrations of the drug, and the cell number was counted after 48 h. The concentration required for a reduction in cell number to 50% of that of the control is obtained by extrapolation over the concentration range. This simple method is particularly valid for making comparisons among a series, and for this reason aminopterin and MTX were studied concurrently as controls. Compound **6** (IC_{50} 3.8×10^{-8} M) is nearly equipotent with MTX (IC_{50} 5.9×10^{-9} M). As expected on the basis of the enzyme studies described above, **12** is only weakly cytotoxic (IC_{50} 8.8×10^{-6} M).

Because of the possibility that these compounds might possess a therapeutic advantage against MTX-resistant cells, similar studies were carried out against the highly MTX-resistant human melanoma line G361. Compound **6** is less potent (IC_{50} 2.7×10^{-5} M) than either MTX (IC_{50}

(29) Friedkin, M.; Crawford, E. J.; Humphreys, S. R.; Goldin, A. *Cancer Res.* **1962**, *22*, 600.
(30) Kisliuk, R. L.; Levine, M. D. *J. Biol. Chem.* **1964**, *239*, 1900.
(31) Foley, G. E.; Lazarus, H. *Biochem. Pharm.* **1967**, *16*, 659.

Scheme VI



5.5 × 10^{-6} M) or aminopterin (IC_{50} 5.0 × 10^{-7} M) as an inhibitor of the growth of this cell line.

Since pharmacokinetic differences such as tissue distribution or rates of metabolism can produce in vivo therapeutic advantages, the effectiveness of **6** against L1210 and P388 leukemia was studied in BDF_1 mice by using standard methods.[32] A dose of 2 mg/kg daily for 9 days produced a 77% increase in lifespan (ILS). Toxicity was observed at 8 mg/kg against P388 leukemia by using this same schedule. There was a 100% ILS at 1 mg/kg, again with toxicity at 8 mg/kg. These values are all similar to those found with MTX.

Experimental Section

2-Amino-6-formyl-4(3*H*)-pyrido[2,3-*b*]pyrimidinone (6-Formyl-5-deazapterin, 13). Method A. 2,4-Diamino-6(1*H*)-pyrimidinone monohydrate (1.4 g, 9.3 mmol) was added to 140 mL of dry DMF. The mixture was warmed to 57 °C until complete solution had been achieved and cooled to 35 °C, and 0.933 g (9.3 mmol) of triformylmethane[17] in 50 mL of dry DMF was added. The reaction mixture was then stirred at 55 °C for 24 h, cooled to room temperature, and filtered. The collected solid was washed well with ethanol and dried to give 1.36 g (77%) of **13** as an amorphous, colorless solid, mp >350 °C.

This compound was characterized as its 2-acetyl derivative, prepared as described below.

2-Acetamido-6-formyl-4(3*H*)-pyrido[2,3-*b*]pyrimidinone (2-Acetyl-6-formyl-5-deazapterin, 14). A mixture of 1.36 g of **13** in 240 mL of acetic anhydride was heated under reflux under nitrogen for 12 h, cooled to room temperature, and filtered. The collected solid was washed with methylene chloride and dried to give 1.07 g of **14**, mp >300 °C. An additional 0.36 g of **14** could be obtained by evaporation of the above filtrate (combined yield, 1.43 g, 86%). The analytical sample was prepared by recrystallization from acetonitrile: NMR (TFA) δ 2.08 (s, 3 H), 8.93 (br s, 1 H), 9.17 (br s, 1 H), 9.68 (s, 1 H). Anal. Calcd for $C_{10}H_8N_4O_3$: C, 51.73; H, 3.47; N, 24.13. Found: C, 51.84; H, 3.34; N, 24.01.

Dimethyl *N*-[4-[[[2-(Acetylamino)-4(3*H*)-oxopyrido[2,3-*d*]pyrimidin-6-yl]methyl]amino]benzoyl]-L-glutamate (16). A mixture of 0.53 g (1.8 mmol) of dimethyl *p*-aminobenzoyl-L-glutamate and 0.35 g (1.5 mmol) of 2-acetamido-6-formyl-4-(3*H*)-pyrido[2,3-*b*]pyrimidinone in 24 mL of glacial acetic acid was stirred under nitrogen with exclusion of moisture for 6 h. Borane–triethylamine (0.56 mmol) was then added, and the solution was stirred at room temperature for an additional 40 min and then warmed to 60 °C. After 10 min, the reaction mixture was cooled and concentrated to near dryness under reduced pressure, and 45 mL of dry methanol was added. The mixture was then filtered and the collected solid washed first with 10 mL of methanol and then with 180 mL of ether. The filtrates were combined, refrigerated overnight, and filtered, and the combined solids were recrystallized from methanol to give **16**: 0.474 g (62%); mp 244 °C dec; $[\alpha]^{22}_{589}$ −7.0 ± 0.6° (*c* 0.5, 4:1 methanol/Me_2SO); NMR (TFA-*d*) δ 2.06–2.91 (m, 7 H), 3.91 (s, 3 H), 4.02 (s, 3 H), 4.9–5.15 (m, 1 H,), 5.21 (s, 2 H), 7.77 (d, 2 H), 8.17 (d, 2 H), 9.3 (br s, 1 H), 9.47 (br s, 1 H). Anal. Calcd for $C_{24}H_{26}N_6O_7$: C, 56.46; H, 5.13; N, 16.46. Found: C, 56.55; H, 5.02; N, 16.66.

L-5-Deazafolic Acid (12). To a 0.1 N sodium hydroxide solution (160 mL) deaerated with nitrogen was added 0.4 g of **16**. The solution was then heated to 80 °C under nitrogen, cooled to room temperature, and filtered, and the pH of the filtrate was adjusted to 3 by addition of 3 N HCl with cooling (0 °C). The resulting solution was refrigerated overnight, and the precipitated solid was collected by filtration, washed well with water, ethanol, ether, and methylene chloride, and purified by dissolution in 0.1 N sodium hydroxide, filtration, and acidification to pH 3. The collected solid was washed and dried in vacuo to give L-5-deazafolic acid: 0.254 g (80%); mp >300 °C. $[\alpha]^{22}_{589}$ +14.0 ± 2° (*c* 0.5, 0.1 N NaOH); NMR (TFA-*d*) δ 2.0–3.2 (m, 4 H), 4.6–5.06 (t, 1 H), 5.25 (s, 2 H), 7.92 (d, 2 H), 8.28 (d, 2 H), 9.12 (s, 1 H), 9.24 (s, 1 H); UV (0.1 N HCl) λ_{max} nm ($10^{-3}\epsilon$) 212 (40.4), 278 (22.9), 295 (sh, 19.8), 350 (6.73); UV (0.1 N NaOH) λ_{max} nm ($10^{-3}\epsilon$) 240 (23.3), 275 (24.0), 292 (sh, 22.0), 340 (sh). Anal. Calcd for $C_{20}H_{20}N_6O_6$: C, 54.54; H, 4.58; N, 19.08. Found: C, 54.30; H, 4.42; N, 18.86.

3-Cyano-5-methyl-2(1*H*)-pyridinethione (17). A mixture of 95.4 g (0.84 mol) of 2-methyl-3-ethoxyacrolein, 83.7 g (0.84 mol) of cyanothioacetamide, 2.9 mL of 2-(dimethylamino)ethanol, and 850 mL of anhydrous ethanol was stirred at room temperature for 15 min and then heated under reflux for 24 h. The resulting suspension was cooled to 0 °C and filtered, and the collected solid was washed with anhydrous ethanol and dried to give 101.1 g (81%) of **17** as a yellow microcrystalline solid, mp 216–221 °C. Recrystallization from acetonitrile raised the melting point to 220–227 °C: NMR (Me_2SO-d_6) δ 2.18 (s, 3 H), 7.83–7.97 (m, 1 H), 8.04–8.13 (m, 1 H); IR (KBr) 2231, 1592, 1564, 1331, 1323, 1161 cm^{-1}. Anal. Calcd for $C_7H_6N_2S$: C, 55.98; H, 4.03; N, 18.65; S, 21.34. Found: C, 55.81; H, 4.06; N, 18.58; S, 21.39.

3-Cyano-5-methyl-2-[(*p*-nitrophenyl)thio]pyridine (18). A mixture of 10.0 g (0.067 mol) of **17**, 9.4 g (0.067 mol) of *p*-nitrofluorobenzene, 21.2 g (0.2 mol) of anhydrous sodium carbonate, and 100 mL of DMF was heated at 100 °C for 6 h, cooled to room temperature, poured into 800 mL of water, and filtered. The collected solid was washed thoroughly with water and dried in vacuo to afford 17.4 g (97%) of crude **18**, mp 136–139 °C. Recrystallization from anhydrous ethanol then gave pure **18**: yellow needles; mp 138–141 °C; NMR ($CDCl_3$) δ 2.42 (s, 3 H), 7.67

(32) USA/USSR Monograph "Methods of Development of New Anti-Cancer Drugs"; *Nat. Cancer Inst. Monogr.* **1977**, *No 45*, 45.

(d, J = 9 Hz, 2 H), 7.80 (d, J = 3.6 Hz, 1 H), 8.23 (d, J = 9 Hz, 2 H), 8.46 (br d, 1 H). IR (KBr) 2225, 1511, 1344, 847 cm^{-1}. Anal. Calcd for $C_{13}H_8N_4O_4S$: C, 57.56; H, 3.34; N, 15.49; S, 11.82. Found: C, 57.29; H, 3.57; N, 15.44; S, 12.01.

1-[[3-Cyano-2-[(*p*-nitrophenyl)thio]-5-pyridinyl]-methyl]pyridinium Bromide (20). A mixture of 100.0 g (0.37 mol) of **18**, 65.6 g (0.37 mol) of freshly recrystallized *N*-bromosuccinimide, 4.0 g of benzoyl peroxide, and 1 L of benzene was heated under reflux with irradiation from a 275-W sunlamp for 16 h. The dark reaction mixture was then cooled to room temperature and evaporated under reduced pressure to dryness, and the residual solid was shaken with a mixture of 1 L of methylene chloride and 1 L of water. The organic layer was separated, washed twice with water, and dried over anhydrous magnesium sulfate, and 29.2 g (0.37 mol) of dry pyridine (from storage over anhydrous potassium hydroxide followed by distillation from calcium oxide) was added. The mixture was then heated under reflux for 24 h, cooled, and filtered, and the collected solid was washed with methylene chloride and dried to give **20**: 87.8 g (55%); beige solid; mp 237–243 °C dec; NMR (Me_2SO-d_6) δ 6.02 (s, 2 H), 7.86 (d, J = 9.9 Hz, 2 H), 8.10–8.36, 8.69 (m, 6 H), 8.94 (d, J = 1.8 Hz, 1 H), 9.33 (d, J = 7.2 Hz, 2 H); IR (KBr) 3025, 2985–2920, 2230, 1630, 1510, 1493, 1348 cm^{-1}.

***N*-[*p*-(Dimethylamino)phenyl]-*C*-[3-cyano-2-[(*p*-nitrophenyl)thio]-5-pyridinyl]nitrone.** A mixture of 26.3 g (0.17 mol) of *p*-nitroso-*N*,*N*-dimethylaniline, 72.5 g (0.17 mol) of **20**, and 133.7 g (0.97 mol) of potassium carbonate in 450 mL of water and 800 mL of ethanol was stirred at room temperature for 1 h, cooled to 5 °C, and filtered. The collected solid was washed thoroughly with water, with ethanol, and then with ether and dried to give 67.0 g (95%) of the nitrone as an orange solid, mp 180–184 °C dec. Recrystallization from acetonitrile gave orange plates: mp 197–207 °C dec; IR (KBr) 2233, 1608, 1584, 1580, 1510, 1371, 1345, 1341 cm^{-1}. Anal. Calcd for $C_{21}H_{17}N_5O_3S$: C, 60.13; H, 4.09; N, 16.70; S, 7.64. Found: C, 59.90; H, 3.96; N, 16.60; S, 7.54.

3-Cyano-5-formyl-2-[(*p*-nitrophenyl)thio]pyridine (21). A mixture of 30.0 g of the above nitrone, 1250 mL of 6 N HCl (cooled to 0 °C), and 1200 mL of ethyl acetate was shaken for 3 min in a separatory funnel and then filtered to remove a small amount of insoluble material. The aqueous layer was separated and extracted twice with 200 mL of ethyl acetate. Saturated aqueous sodium chloride (1 L) was added to the aqueous layer which was extracted once again with a 200-mL portion of ethyl acetate. The combined organic extracts were washed with 500 mL of saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness to give **21**: 18.4 g (90%); tan powder; mp 142.5–147.5 °C. The analytical sample was obtained as a beige powder; mp 157–158 °C (by recrystallization from heptane); NMR (Me_2SO-d_6) δ 7.95 (d, J = 9 Hz, 2 H), 8.35 (d, J = 9 Hz, 2 H), 8.79 (d, J = 2.7 Hz, 1 H), 9.04 (d, J = 2.7 Hz, 1 H), 10.06 (s, 1 H); IR (KBr) 2237, 1700, 1600, 1578, 1537, 1510, 1350–1340 cm^{-1}. Anal. Calcd for $C_{13}H_7N_3O_3S$: C, 54.73; H, 2.47; N, 14.73; S, 11.24. Found: C, 54.62; H, 2.43; N, 14.52; S, 11.06.

3-Cyano-5-(dimethoxymethyl)-2-[(*p*-nitrophenyl)thio]-pyridine (22). A mixture of 23.4 g of **21** and 25.5 g of Dowex 50W-X4 ion-exchange resin in 750 mL of anhydrous methanol was stirred at room temperature for 24 h and poured into 4 L of anhydrous diethyl ether, and 40 g of 3-Å molecular sieves was added. The mixture was allowed to stand for 4 h and filtered. Evaporation of the solvent afforded 23.6 g (88%) of **22** as a beige solid (mp 98–102.5 °C) which was obtained as colorless crystals: mp 103–109 °C (recrystallization from hexane); NMR ($CDCl_3$) δ 3.36 (s, 6 H), 5.45 (s, 1 H), 7.75 (d, J = 9 Hz, 2 H), 8.14 (d, J = 1.8 Hz, 1 H), 8.27 (d, J = 9 Hz, 2 H), 8.59 (d, J = 1.8 Hz, 1 H); IR (KBr) 2223, 1600, 1580–1574, 1518, 1375, 1075 cm^{-1}. Anal. Calcd for $C_{15}H_{13}N_3O_4S$: C, 54.37; H, 3.95; N, 12.68; S, 9.68. Found: C, 54.58; H, 3.81; N, 12.61; S, 9.67.

2-Amino-3-cyano-5-(dimethoxymethyl)pyridine (23). A suspension of 2.14 g (6.5 mmol) of **22** and 1.59 g (7.1 mmol) of cupric bromide in 50 mL of liquid ammonia in a sealed pressure reaction vessel was stirred at 70 °C for 44 h. It was then cooled to room temperature, the ammonia was allowed to evaporate, and the residual solid was dissolved in methylene chloride and passed through a short column of Florisil. The methylene chloride was removed by evaporation, and the residual solid was chromatographed on silica gel; impurities were eluted with benzene, and the product was then eluted with ethyl acetate. Evaporation of the ethyl acetate eluate gave 1.14 g (91%) of crude **23** which was obtained as pale yellow needles: mp 87.5–91 °C (recrystallization from hexane); NMR ($CDCl_3$) δ 3.31 (s, 6 H), 5.34 (s, 1 H), 5.99 (br, 2 H), 7.79 (d, J = 1.8 Hz, 1 H), 8.29 (d, J = 1.8 Hz, 1 H); IR (KBr) 3415, 3325, 3150, 2225, 1650, 1042 cm^{-1}. Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 56.06; H, 5.74; N, 21.59.

2,4-Diamino-6-(dimethoxymethyl)pyrido[2,3-*d*]pyrimidine [2,4-Diamino-6-(dimethoxymethyl)-5-deazapteridine, 24]. A mixture of 3.88 g (0.02 mol) of **23** and 0.04 mol of guanidine (from 3.86 g, 0.04 mol, of guanidine hydrochloride and 1.02 g, 0.044 mol, of sodium in 70 mL of anhydrous methanol, filtered to remove precipitated NaCl) was heated under reflux for 99 h. It was then cooled to room temperature, concentrated under reduced pressure to a small volume, cooled to −20 °C, and filtered. The collected solid was washed with water, 10 mL of cold (−20 °C) methanol, and ether: yield 3.72 g (79%); yellow microcrystalline solid; mp >350 °C. The analytical sample of **24** was obtained by recrystallization from anhydrous methanol: NMR (Me_2SO-d_6) δ 3.30 (s, 6 H), 5.45 (s, 1 H), 6.33 (br, 2 H), 7.55 (br, 2 H), 8.38 (d, J = 1.8 Hz, 1 H), 8.61 (d, J = 1.8 Hz, 1 H); IR (KBr) 3400, 3320, 3120–3080, 1650–1640, 1618, 1580, 1550–1540, 1338 cm^{-1}. Anal. Calcd for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57; N, 29.77. Found: C, 51.06; H, 5.62; N, 29.48.

2-Amino-6-(dimethoxymethyl)-4(3*H*)-pyrido[2,3-*d*]pyrimidinone [6-(Dimethoxymethyl)-5-deazapterin, 25]. A suspension of 0.50 g (2.67 mmol) of **24** in 20 mL of 5% aqueous sodium hydroxide was heated under reflux for 2.5 h, cooled to room temperature, and filtered through sintered glass. The filtrate was carefully neutralized with glacial acetic acid, and the precipitated solid was collected by filtration and washed thoroughly with water followed by acetone and methanol to give 0.50 g (100%) of a pale yellow powder, mp >350 °C. The analytical sample was obtained by recrystallization from DMF: IR (KBr) 3600–3300, 1720, 1674, 1600, 1565–1560, 1110, 1048, 806 cm^{-1}. Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.65; H, 4.93; N, 23.62.

2-Amino-6-formyl-4(3*H*)-pyrido[2,3-*d*]pyrimidinone (6-Formyl-5-deazapterin, 13). Method B. A solution of 0.15 g (0.64 mmol) of **25** in 10 mL of 88% formic acid was stirred at room temperature for 1 h, poured into 15 mL of water, and neutralized with concentrated ammonium hydroxide. The precipitated solid was collected by filtration, washed thoroughly with water, ethanol, and then ether, and dried in vacuo to give **13**: 0.12 g (97%); light yellow microcrystalline solid; mp >350 °C; NMR (TFA-*d*, internal Me_4Si) δ 9.34 (d, 1 H), 9.45 (d, 1 H), 10.18 (s, 1 H); IR (KBr) 3500–2500, 1690–1670, 1590, 1560–1550, 1510, 1410, 1260, 1195 cm^{-1}.

2,4-Diamino-6-formylpyrido[2,3-*d*]pyrimidine (2,4-Diamino-6-formyl-5-deazapteridine, 26). A solution of 2,4-diamino-6-(dimethoxymethyl)pyrido[2,3-*d*]pyrimidine (**24**) in 15 mL of 88% formic acid was stirred at room temperature for 30 min, poured into water, and neutralized with concentrated ammonium hydroxide. The resulting precipitate was collected by filtration and washed thoroughly with water, 15 mL of cold (−20 °C) anhydrous ethanol, and ether to give **26**: 0.24 g (100%); light yellow microcrystalline solid; mp >350 °C; NMR (Me_2SO-d_6) δ 6.95 (br, 2 H), 7.93 (br, 2 H), 8.91–8.94 (br d, 1 H), 9.18–9.21 (br d, 1 H), 9.99 (s, 1 H); IR (KBr) 3350–3310, 3260–3160, 1672–1660, 1600, 1540, 1460–1450, 1342 cm^{-1}. Anal. Calcd for $C_8H_7N_5O$: C, 50.79; H, 3.73; N, 37.02. Found: C, 51.09; H, 3.54; N, 36.91.

L-5-Deazaaminopterin Dimethyl Ester (27). To a suspension of 2.03 g (11 mmol) of **26** and 3.24 g (11 mmol) of dimethyl *p*-aminobenzoyl-L-glutamate in 450 mL of methanol containing 9.2 mL of 2.0 N HCl in methanol was added 0.33 g (5.2 mmol) of sodium cyanoborohydride. The mixture was stirred at room temperature under dry nitrogen for 9.5 days. The solvent was then removed under reduced pressure, 500 mL of 1 N sodium carbonate added to the residue, the mixture filtered, and the collected solid washed with water followed by ether to give 3.58 g of a light yellow solid. This crude product was then recrystallized from methanol followed by recrystallization from acetonitrile to give **27**: 1.72 g (33%); light yellow solid; mp 226 °C; NMR (Me_2SO-d_6) δ 1.90–2.30 (br m, 2 H), 2.39–2.54 (br m, 2 H), 3.60 (s, 3 H), 3.66 (s, 3 H), 4.33 (br, 3 H), 6.33 (br, 2 H), 6.67 (d, J =

8.1 Hz, 2 H), 7.53 (br, 2 H), 7.69 (d, J = 8.1 Hz, 2 H), 8.27 (br d, 1 H), 8.43 (d, 1 H), 8.68 (d, 1 H). IR (KBr) 3400–3100, 1731, 1632, 1603, 1570, 1550–1540, 1500–1495, 1447 cm^{-1}. Anal. Calcd for $C_{22}H_{25}N_7O_5$: C, 56.52; H, 5.39; N, 20.97. Found: C, 56.57; H, 5.22; N, 20.70.

L-5-Deazaaminopterin (6). A solution of 0.65 g of L-5-deazaaminopterin dimethyl ester (**27**) in 325 mL of methanol and 6.5 mL of 0.47 M sodium hydroxide (4.2 mmol) was stirred for 72 h at room temperature. The methanol was then removed under reduced pressure and 6.5 mL of 0.47 M HCl (4.2 mmol) added to the residue. The precipitated solid was collected by filtration, washed with acetone followed by ether, and dried under reduced pressure to give **6**: 0.53 g (86%); microcrystalline yellow solid: mp >200 °C dec; $[\alpha]^{22}_{589}$ +14.0 ± 2° (c 0.5, 0.1 N NaOH); NMR (TFA-d) δ 2.3–2.8 (m, 2 H), 2.8–3.0 (m, 2 H), 5.0–5.3 (m, 3 H), 7.85 and 8.25 (AB q, 4 H, J = 9 Hz), 9.25 (s, 2 H); UV (0.1 N NaOH) λ_{max} nm ($10^{-3}\epsilon$) 247 (21.2), 278 (23.8), 290 (sh, 22.5), 342 (sh, 7.5). Anal. Calcd for $C_{20}H_{21}N_7O_5 \cdot 2.5H_2O$: C, 49.59; H, 5.37; N, 20.25. Found: C, 49.26; H, 4.93; N, 20.41.

4-Amino-1,1-dicyano-3-methyl-1,3-butadiene (30). Ammonia was bubbled through a solution of 1.62 g (10 mmol) of 1,1-dicyano-4-ethoxy-3-methyl-1,3-butadiene[33] in 16 mL of acetonitrile for 30 min. The resulting solution was then refluxed for 5 h and cooled to room temperature, and the solvent was removed by evaporation under reduced pressure. Recrystallization of the residual solid from toluene/1-butanol provided 0.42 g (69%) of **30** as an orange solid which was recrystallized from toluene/1-butanol (Norite) to give yellow crystals: mp 166–167 °C; NMR (Me_2SO-d_6) δ 1.83 (s, 3 H, CH_3), 7.20 (s, 1 H, C-2(H)), 7.38 (br s, 1 H, C-4(H)), 8.13 (br, 2 H, NH_2); IR (KBr) 3340, 3180, 2200, 1670, 1530 cm^{-1}. Anal. Calcd for $C_7H_7N_3$: C, 63.14; H, 5.30; N, 31.56. Found: C, 62.90; H, 5.29; N, 31.33.

2-Amino-3-cyano-5-methylpyridine (31). A solution of 1.0 g of 1,1-dicyano-4-ethoxy-3-methyl-1,3-butadiene (**29**) in 50 mL of saturated methanolic ammonia was stirred at room temperature for 15 h. The solvent was then removed under reduced pressure and the residue partitioned between 40 mL of 1 N HCl and 40 mL of ethyl acetate. The aqueous layer was separated and poured over 40 mL of saturated sodium bicarbonate solution. The pale yellow solid which separated was collected, washed with water, and dried to give 0.42 g (51%) of **31**, mp 162–163 °C. Recrystallization from 1-propanol provided white needles, mp 166–167 °C (lit.[33,34] mp 166–168 °C). The same compound was prepared in comparable yield by treating 4-amino-1,1-dicyano-3-methyl-1,3-butadiene (**30**) with saturated methanolic ammonia under the same conditions. All properties of the product obtained by the above procedures were identical with those reported.

2,4-Diamino-6-methyl-5-deazapteridine (2,4-Diamino-6-methylpyrido[2,3-d]pyrimidine, 32). Method A. A solution of guanidine in 1-butanol was prepared by dissolving 0.03 g (1.3 mmol) of sodium in 10 mL of 1-butanol, followed by addition of 0.11 g (1.13 mmol) of guanidine hydrochloride. The mixture was stirred for 30 min, the precipitated sodium chloride was removed by filtration and rinsed with 2 mL of 1-butanol, and to the combined filtrates were added 0.10 g (0.75 mmol) of 2-amino-3-cyano-5-methylpyridine and an additional 8 mL of 1-butanol. The resulting solution was refluxed for 36 h. Cooling resulted in the separation of 0.06 g of a microcrystalline white solid which was collected by filtration, washed with water followed by methanol, and dried: mp 289–290 °C dec. An additional 0.01 g (46% total yield) of product slowly separated from the mother liquors upon standing: NMR (TFA) δ 2.70 (s, 3 H, CH_3), 8.80 and 9.22 (AB, 2 H, J = 2 Hz, C-5 H and C-7 H); IR (KBr) 3415, 3290, 3220, 3100, 1650–1610, 1555, 1415 cm^{-1}. Anal. Calcd for $C_8H_9N_5$: C, 54.84; H, 5.18; N, 39.98. Found: C, 54.64; H, 4.91; N, 39.75.

2-(1-Bromo-2-propyl)-1,3-dioxolane (33). Hydrogen bromide gas was slowly bubbled with stirring through 130 g (2.1 mol) of ethylene glycol until 80 g (1 mol) had been absorbed. To this mixture was then added slowly 50 g (0.64 mol) of methacrolein (90% technical) while the temperature was maintained between 5 and 10 °C. After the addition was complete, the mixture was stirred for 1 h at room temperature and extracted twice with pentane, and the pentane extracts were washed with 5% aqueous sodium bicarbonate solution and dried over anhydrous Na_2SO_4; evaporation yielded **33**: 78 g (62%); bp 70–78 °C (9 mm); NMR (neat) δ 1.10 (d, 3 H, J = 6.5 Hz), 2.0 (m, 1 H), 3.45 (m, 2 H), 3.90 (m, 4 H), 4.78 (d, 1 H, J = 4.5 Hz).

2-(1,1-Dicyano-2-propyl)-1,3-dioxolane (34). To a slurry of 11.45 g (0.272 mol) of sodium hydride (57% oil dispersion) and 200 mL of Me_2SO was added, with stirring and occasional cooling, 87 g (1.32 mol) of malononitrile in 200 mL of Me_2SO. After the addition was complete, the mixture was stirred for 10 min, the temperature raised to 80 °C, and 51.5 g (0.264 mol) of **33** rapidly added. There was a vigorous exothermic reaction, and the temperature rose to 100 °C. The reaction mixture was stirred until the temperature dropped to 80 °C; heating was then reapplied to maintain this temperature for a period of 3 h. The reaction mixture was cooled and poured into water and the product extracted with ether. The ether extracts were washed well with water to remove excess malononitrile and dried over anhydrous Na_2SO_4, and the product was distilled at 95–110 °C (0.03 torr) to give 23.3 g (49%) of **34**.

2-[1-(2,4,6-Triamino-5-pyrimidinyl)-2-propyl]-1,3-dioxolane (35). A solution of guanidine in ethanol was prepared by addition of 12.4 g (0.13 mol) of guanidine hydrochloride to sodium ethoxide in ethanol [prepared from 3.22 g (0.14 mol) of sodium and 60 mL of absolute ethanol], followed by filtration of the precipitated sodium chloride. To this solution was added 23.4 g (0.13 mol) of **34**, and the reaction mixture was refluxed overnight. It was then cooled and diluted with an equal volume of petroleum ether (bp 30–60 °C). The dark brown crystals which separated were removed by filtration; a second crop could be obtained by evaporation of the filtrate, followed by further addition of petroleum ether. The combined solids were then recrystallized from Me_2SO/acetone to give **35**: 24.9 g (89%); colorless crystals: mp 180–181 °C; NMR (Me_2SO-d_6) δ 0.75 (d, 3 H, J = 6.5 Hz), 2.1 (m, 3 H), 3.2 (s, 2 H, NH_2), 3.75 (m, 4 H), 4.55 (d, 1 H, J = 4 Hz), 5.2 (d, 4 H, NH_2). Anal. Calcd for $C_{10}H_{17}N_5O_2$: C, 50.21; H, 7.11; N, 29.29. Found: C, 50.06; H, 6.91; N, 29.25.

2,4-Diamino-6-methyl-5-deazapteridine (32). Method B. A solution of 7.26 g of the pyrimidine **35** in 100 mL of 10% aqueous HCl was heated to boiling on a hot plate for 15 min, cooled to room temperature for 30 min, and then adjusted to pH 7 by addition of concentrated aqueous sodium hydroxide. The neutral solution was cooled to 0 °C, and the milky-white precipitate which had separated was collected by filtration and dried to give 4.14 g (77%) of a 1:1 mixture (NMR) of 2,4-diamino-6-methyl-5-deazapteridine (**32**) and the corresponding 5,6-dihydro derivative **37**. This mixture was dissolved in 50 mL of trifluoroacetic acid, 12.2 g of triphenylcarbinol was added, and the dark red solution was heated at 60 °C for 4 h and then stirred at room temperature overnight. It was poured into a mixture of 200 mL of diethyl ether and 200 mL of petroleum ether (bp 30–60 °C). The resulting mixture was cooled to 0 °C and filtered, and the collected solid was triturated with 100 mL of hot (90 °C) water. Filtration removed a small amount of suspended solid; the filtrate was adjusted to neutrality by addition of aqueous sodium hydroxide, and the milky-white precipitate which separated was collected by filtration and dried to give 3.52 g (66%) of **32**, identical in every respect with the material prepared by method A.

3-(*N*-Pyrrolidino)-3-formylthietane 1,1-Dioxide Dimethyl Acetal (41). A solution of 49.2 g (0.43 mol) of methanesulfonyl chloride in 100 mL of anhydrous ether was added dropwise over a period of 60 min to a solution of 67 g (0.39 mol) of α-pyrrolidinoacrolein dimethyl acetal (**34**)[28] and 42.4 g (0.42 mol) of triethylamine in 200 mL of diethyl ether. Addition was carried out so that the temperature of the reaction mixture was maintained below 5 °C. After the addition was complete, the mixture was brought to room temperature, stirred for 1 h, and poured into 200 mL of water. The ether layer was separated, and the aqueous layer was extracted with portions of methylene chloride (3 × 50 mL). The extracts and the above ether layer were combined, dried over anhydrous $MgSO_4$, and evaporated to give a brown oil which, upon trituration with a mixture of ether/pentane, yielded 3-(*N*-pyrrolidino)-3-formylthietane 1,1-dioxide dimethyl acetal (**41**): 84 g (86%); mp 81–84 °C; NMR ($CDCl_3$) δ 1.7–2.0 (m, 4 H), 2.6–3.0

(33) Baldwin, J. J.; Raab, A. W.; Ponticello, G. S. *J. Org. Chem.* **1978**, *43*, 2529.

(34) El-Haj, M. J. A.; Dominy, B. W. U.S. Patent 3917624 **1975**; *Chem. Abstr.* **1976**, *84*, *P*105635, U.S. Pat. 3950160 **1976**; *Chem. Abstr.* **1977**, *85*, *P*29577*j*, U.S. Pat. 3962164 **1976**; *Chem. Abstr.* **1977**, *85*, *P*123967*h*.

(m, 4 H), 3.6 (s, 6 H), 4.25, 4.35 (2 s, 4 H), 4.6 (s, 1 H). Anal. Calcd for $C_{10}H_{19}NO_4S$: C, 48.17; H, 7.68; N, 5.62; S, 12.86. Found: C, 47.83; H, 7.42; N, 5.77; S, 12.89.

3-Formylthiete 1,1-Dioxide Dimethyl Acetal (42). A solution of 8.8 mL (0.11 mol) of methyl fluorosulfonate in 30 mL of anhydrous methylene chloride was added dropwise at 5 °C to a solution of 24.9 g (0.1 mol) of **41** in 170 mL of methylene chloride. Addition was carried over a period of 15 min. The mixture was stirred at room temperature for 18 h, and over this period an orange solid separated from the reaction mixture. A solution of 15.3 mL (0.11 mol) of triethylamine in 50 mL of methylene chloride was added dropwise at 5 °C to the above mixture, and the resulting suspension was stirred at reflux for 1 h to give a homogeneous orange solution. This was washed sequentially with 100 mL of water, 20 mL of 1 N hydrochloric acid, 20 mL of 5% sodium bicarbonate solution, and 50 mL of water and then dried over anhydrous $MgSO_4$. Evaporation gave 15.4 g (86.5%) of a pale yellow crystalline solid (mp 49–51 °C) which was purified for analysis by distillation at 92–96 °C (0.05 mm): NMR ($CDCl_3$) δ 3.42 (s, 6 H), 4.53 (m, 2 H), 5.22 (m, 1 H, J = 1.5 Hz), 6.82 (d, 1 H, J = 1.5 Hz). Anal. Calcd for $C_6H_{10}SO_4$: C, 40.44; H, 5.66; S, 17.99. Found: C, 40.48; H, 5.79; S, 18.07.

3-Formylthietane 1,1-Dioxide Dimethyl Acetal (43). A solution of 10 g of 3-formylthiete 1,1-dioxide dimethyl acetal (**42**) in 200 mL of absolute ethanol was hydrogenated in a Parr rocking hydrogenator at 55 psi for 24 h in the presence of 3 g of 5% palladium-on-carbon catalyst. The catalyst was removed by filtration through Celite, and the resulting green ethanolic solution was evaporated to dryness under reduced pressure. The residual oil was taken up in 100 mL of ethanol, an additional 1 g of catalyst added, and the hydrogenation repeated for an additional 24 h. The catalyst was again removed by filtration, and the colorless filtrate was evaporated to leave an oil which, upon trituration with hexane, yielded **43**: 9.6 g (95%); mp 57–59 °C; NMR ($CDCl_3$) δ 2.6–3.0 (m, 1 H), 3.45 (s, 6 H), 4.08, 4.18 (2 s, 4 H), 4.56 (d, 1 H, J = 8 Hz). Anal. Calcd for $C_6H_{12}O_4S$: C, 39.99; H, 6.71; S, 17.79. Found: C, 40.23; H, 6.53; S, 17.50.

3-Formylthietane Dimethyl Acetal (44). A 250-mL three-necked flask was equipped with a magnetic stirring bar, a nitrogen inlet, a mercury bubbler, and an addition funnel, and the system was flame-dried under nitrogen. A suspension of 3.60 g (20.0 mmol) of **43** in 100 mL of anhydrous diethyl ether was cooled to −13 °C and treated dropwise with 30 mL of 1.15 M ethereal lithium aluminum hydride. The addition required 30 min, while the temperature was maintained between −10 and −13 °C. As the reduction proceeded, a white solid began to precipitate. The reaction mixture was stirred at <−10 °C for 2 h, excess lithium aluminum hydride destroyed by cautious addition of 12 mL of 10 N NaOH, and the mixture stirred for 2.75 h while being allowed to slowly warm to room temperature. The resulting suspension was filtered through Celite to remove precipitated aluminum salts, and the Celite pad was washed with portions (6 × 25 mL) of diethyl ether. Evaporation of the filtrate and ether washings left **44** as a vile-smelling light yellow oil: 1.46 g (49%, and pure by NMR); NMR ($CDCl_3$) δ 3.00 (m, 4 H), 3.20 (s, 6 H), 3.30 (m, 1 H), 4.44 (d, 1 H, J = 8 Hz). Anal. Calcd for $C_6H_{12}O_2S$: C, 48.62; H, 8.16; S, 21.63. Found: C, 48.89; H, 8.08; S, 21.67.

3-Formylthietane (45). A heterogeneous mixture of 2.965 g of 3-formylthietane dimethyl acetal (**44**) and 25 mL of 1 N HCl was stirred vigorously at room temperature for 5 h. Over this period of time **44** dissolved, and a turbid solution resulted. A saturated brine solution (25 mL) was then added, and the mixture was extracted with portions (4 × 50 mL) of methylene chloride. The combined methylene chloride extracts were then passed through Whatman phase-separating paper and evaporated to give crude **45** as a vile-smelling pale yellow oil: 1.63 g (79%); IR (neat) 2720, 1720 cm^{-1}; NMR ($CDCl_3$) δ 3.33 (m) and 3.47 (s) (4 H), 3.82 (m, 1 H), 9.85 (s, 1 H). 3-Formylthietane was characterized as its 2,4-dinitrophenylhydrazone, mp (ethanol) 184–185.5 °C. Anal. Calcd for $C_{10}H_{10}N_4O_4S$: C, 42.55; H, 3.57; N, 19.85; S, 11.36. Found: C, 42.76; H, 3.52; N, 19.94; S, 11.40.

2-(3-Thietanyl)-1,3-dioxolane (46). Method A. A solution of 3.22 g of 3-formylthietane (**45**), 4.0 mL of ethylene glycol, and 0.05 g of *p*-toluenesulfonic acid monohydrate in 140 mL of benzene was refluxed (Dean–Stark trap) for 20 h. The benzene solution was washed with portions (3 × 40 mL) of water, dried ($MgSO_4$), and evaporated to leave 4.23 g of an oil which was distilled in vacuo to give **46**: 4.00 g (87%); colorless oil: bp 29–30 °C (0.01 mm); IR (neat) 2950, 2890, 1115 cm^{-1}; NMR ($CDCl_3$) δ 3.23 (m, 5 H), 3.95 (m, 4 H), 4.95 (d, 1 H, J = 4 Hz). Anal. Calcd for $C_6H_{10}O_2S$: C, 49.29; H, 6.89; S, 21.93. Found: C, 49.22; H, 6.51; S, 21.77.

Method B. A suspension of 33 g of 3-formylthietane 1,1-dioxide dimethyl acetal (**43**) in 20 mL of ethylene glycol containing 0.5 g of *p*-toluenesulfonic acid monohydrate was heated with stirring in a 50-mL pear-shaped flask equipped for downward distillation. At 50 °C a homogeneous solution was obtained, and at ~120 °C distillation of methanol commenced. The external bath temperature was raised to 150 °C, and 12.5 mL (90%) of methanol was collected. The flask was then cooled and the residual material partitioned between dichloromethane and 5% aqueous sodium bicarbonate. The organic phase was separated, the aqueous phase was extracted with methylene chloride (3 × 50 mL), and the combined organic extracts were dried ($MgSO_4$) and evaporated to yield **2-(1,1-dioxo-3-thietanyl)-1,3-dioxolane (47)**: 25.8 g (78%); NMR ($CDCl_3$) δ 2.6–3.1 (m, 1 H), 4.0–4.1 (m, 4 H), 4.15 (d, 4 H, J = 9 Hz), 5.08 (d, 1 H, J = 4 Hz).

A solution of Dibal in toluene (25%, 40 mL, 0.067 mol) was added dropwise with cooling to a suspension of 3.0 g (0.017 mol) of **47** in 50 mL of dry toluene under nitrogen, while the temperature was maintained below 20 °C. The reaction mixture was stirred at room temperature overnight, and then water (2 mL), 10 N sodium hydroxide (2 mL), and water (2 mL) were added sequentially. The resulting precipitate was collected by filtration, and the mother liquors were evaporated (<50 °C) under reduced pressure to give 2.4 g of a pale yellow oil. Distillation at 29–30 °C (0.01 mm) gave 1.6 g (64%) of 2-(3-thietanyl)-1,3-dioxolane (**46**), identical in every respect with the material prepared by method A.

1-Bromo-2-(1,3-dioxolan-2-yl)-3-[(*p*-methoxybenzyl)thio]propane (48). Freshly prepared 4-methoxybenzyl bromide[35] (6.88 g, 0.034 mol) was added in one portion to a solution of 5.0 g (0.034 mol) of **46** in dry acetonitrile under N_2 and at room temperature. A mildly exothermic reaction ensued, and the solution became pale yellow. It was stirred at room temperature overnight and the solvent removed under reduced pressure to give pure **48**, as judged by NMR and microanalysis: IR (neat) 1610, 1590 cm^{-1}; NMR ($CDCl_3$) δ 1.9–2.5 (m, 1 H), 2.6–2.7 (m, 2 H), 3.6–3.8 (m, 2 H), 3.7 (s, 2 H), 3.8 (s, 3 H), 3.9 (m, 4 H), 4.95 (d, 1 H, J = 6 Hz), 6.85 and 7.25 (AB q, 4 H, J = 10 Hz). Anal. Calcd for $C_{14}H_{19}BrO_3S$: C, 48.42; H, 5.52; Br, 23.01; S, 9.23. Found: C, 48.49; H, 5.53; Br, 23.21; S, 8.95.

1,1-Dicyano-3-(1,3-dioxolan-2-yl)-4-[(*p*-methoxybenzyl)thio]butane (49). A solution of 8.42 g (0.023 mol) of 1-bromo-2-(1,3-dioxolan-2-yl)-3-[(*p*-methoxybenzyl)thio]propane in 5 mL of Me_2SO was added at room temperature to a freshly prepared solution of sodiomalononitrile and malononitrile in Me_2SO (from 3.2 g, 0.048 mol, of malononitrile and 1.04 g, 0.026 mol, of sodium hydride in 20 mL of Me_2SO). Potassium iodide (0.5 g) was added, and the mixture was heated under nitrogen at 80 °C for 3 h. It was then cooled to room temperature, diluted with 50 mL of water, and extracted with portions (3 × 25 mL) of 1,1,1-trichloroethane. The combined extracts were washed with 10 mL of 1 N HCl, dried ($MgSO_4$), and evaporated to give a viscous orange oil which was used directly for the synthesis of **50**, as described below.

Distillation (Kugelrohr) at 190–200 °C (0.05 mm) gave material which showed a single spot (R_f 0.7) on TLC chromatography (silica; methylene chloride/methanol, 97:3): NMR ($CDCl_3$) δ 2.0–2.8 (m, 5 H), 3.7 (s, 2 H), 3.82 (s, 3 H), 3.8–4.05 (m, 4 H), 4.1–4.4 (q, 1 H), 4.8 (d, 1 H), 6.88 and 7.25 (AB q, 4 H, J = 9 Hz); mass spectrum, calcd for $C_{17}H_{20}N_2O_3S$ m/e^+ 332, found m/e^+ 332.

1-(2,4,6-Triamino-5-pyrimidinyl)-2-(1,3-dioxolan-2-yl)-3-[(*p*-methoxybenzyl)thio]propane (50). The crude sample of **49** prepared as described above (1.17 g, 0.0035 mol) was added in one portion to a freshly prepared solution of guanidine in ethanol (from 0.37 g, 0.0039 mol, of guanidine hydrochloride, 0.13 g, 0.0058 mol, of sodium, and 25 mL of anhydrous ethanol), and the resulting mixture was refluxed for 20 h. The reaction mixture was evaporated to dryness, and the yellow residual solid was partitioned between water and dichloromethane. The organic

(35) Rzeszotarska, B.; Weber, K. *Org. Prep. Proceed. Int.* **1974**, *6*, 211.

phase was separated, dried ($MgSO_4$), and evaporated to dryness, and the residual yellow foam was chromatographed on silica gel (60–200 mesh, 20 g). Methylene chloride removed the remaining starting material; the column was then eluted sequentially with methylene chloride/methanol (98:2 and 97:3). Finally, the desired product (**50**) was eluted with methylene chloride/methanol (9:1). This material was homogeneous on TLC, and its NMR spectrum was compatible with the assigned structure: yield 0.6 g (44%); IR (Nujol) 3320, 3200, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.8–2.9 (m, 5 H), 3.7 (s, 2 H), 3.8 (s, 3 H), 3.85–3.95 (m, 4 H), 4.8 (d, 1 H, J = 4 Hz), 5.3–5.7 (br, 6 H), 6.85 and 7.2 (AB q, 4 H, J = 9 Hz).

2,4-Diamino-6-[[(*p*-methoxybenzyl)thio]methyl]-5,6-dihydro-5-deazapteridine (51) and 2,4-Diamino-6-[[(*p*-methoxybenzyl)thio]methyl]-5-deazapteridine (52). A mixture of 1.7 g of **50** and 25 mL of 1 N HCl was refluxed for 15 min, and the mixture was cooled and neutralized with ammonium hydroxide. The resulting white precipitate was collected by filtration; yield 0.7 g (49%). The NMR spectrum [(TFA-*d*) δ 2.2–4.0 (m), 4.0 (s), 7.0 and 7.25 (AB q, J = 9 Hz), 9.1 (m)] was indicative of a mixture of **51** and **52**. An unsuccessful attempt was made to dehydrogenate **51** to give homogeneous **52** by heating a sample of this material in TFA with 2 equiv of triphenylcarbinol. No way could be found to recrystallize the resulting white deazapteridine to homogeneity, although its mass spectrum indicated that dehydrogenation had indeed been accomplished: calcd for $C_{16}H_{17}N_5OS$ m/e^+ 327, found m/e^+ 327.

Registry No. **6**, 80360-09-4; **12**, 85597-17-7; **13**, 80360-03-8; **14**, 87373-56-6; **15**, 87373-57-7; **16**, 87373-58-8; **17**, 87373-59-9; **18**, 87373-60-2; **19** (n = 1), 87373-61-3; **20**, 87373-62-4; **21**, 87373-63-5; **22**, 87373-64-6; **23**, 87373-65-7; **24**, 87373-66-8; **25**, 87373-67-9; **26**, 80360-04-9; **27**, 87373-68-0; **29**, 65995-93-9; **30**, 87373-69-1; **31**, 38076-78-7; **32**, 85147-10-0; **33**, 87373-70-4; **34**, 87373-71-5; **35**, 87373-72-6; **36**, 87373-73-7; **37**, 87373-74-8; **40**, 76282-55-8; **41**, 87373-75-9; **42**, 87373-76-0; **43**, 87373-77-1; **44**, 87373-78-2; **45**, 87373-79-3; **46**, 87373-80-6; **47**, 87373-81-7; **48**, 87373-82-8; **49**, 87373-83-9; **50**, 87373-84-0; **51**, 87373-85-1; **52**, 87373-86-2; 2,4-diamino-6(1*H*)-pyrimidinone, 56-06-4; triformylmethane, 18655-47-5; dimethyl *p*-aminobenzoyl-L-glutamate, 52407-60-0; 2-methyl-3-ethoxyacrolein, 42588-57-8; cyanothioacetamide, 110-86-1; *p*-nitrofluorobenzene, 350-46-9; pyridine, 7357-70-2; *p*-nitroso-*N*,*N*-dimethylaniline, 138-89-6; quanidine, 113-00-8; ethylene glycol, 107-21-1; methacrolein, 78-85-3; malononitrile, 4341-85-9; dihydrofolate reductase, 9002-03-3; 4-methoxybenzyl bromide, 2746-25-0; *N*-[*p*-(dimethylamino)phenyl]-*C*-[3-cyano-2-[(*p*-nitrophenyl)thio]-5-pyridinyl]nitrone, 87373-87-3.

Competitive Reactions of Alkylidenetriphenylphosphoranes and Methylsulfinyl Carbanion with 3-Methylenespiro[5.5]undeca-1,4-diene

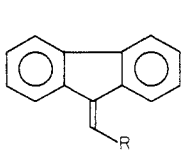
Diane F. Murray*

Department of Chemistry, Princeton University, Princeton, New Jersey 08544

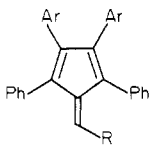
Received December 7, 1982

Treatment of 3-methylenespiro[5.5]undeca-1,4-diene (**3**) with methylenetriphenylphosphorane in Me_2SO provides 3-ethylidenespiro[5.5]undeca-1,4-diene (**4**) as the major product in 33% yield. The expected cyclopropane product dispiro[2.2.5.2]trideca-4,12-diene is obtained in only 1–2% yield. Control experiments show that **4** arises from the reaction of **3** with the methylsulfinyl carbanion. Indeed, when **3** is treated with a Me_2SO solution of the methylsulfinyl carbanion, multiple additions of the methylsulfinyl carbanion occur. The competition between the Wittig reagent and the methylsulfinyl carbanion in reaction with **3** can be shifted to favor the formation of cyclopropane products by increasing the nucleophilicity of the Wittig reagent by alkyl substitution at the carbanionic center. Thus, treatment of **3** with ethylidenetriphenylphosphorane in Me_2SO gives **4** and 1-methyldispiro[2.2.5.2]trideca-4,12-diene in yields of 28% and 17%, respectively, and reaction of **3** with isopropylidenetriphenylphosphorane in Me_2SO gives 1,1-dimethyldispiro[2.2.5.2]trideca-4,12-diene in 64% yield and less than a 1% yield of **4**.

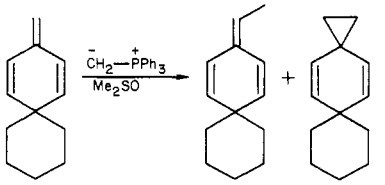
Previous reports of the reactions of alkylidenetriphenylphosphoranes with carbon–carbon double bonds unactivated by heteroatoms have been limited to the 9-alkylidenefluorenes[1] (**1**) and aryl-substituted 1-alkylidene-2,4-cyclopentadienes[2] (**2**). In each of these cases, the observed product is the corresponding spirocyclopropane. In striking contrast to these results, I have observed that treatment of 3-methylenespiro[5.5]undeca-1,4-diene (**3**) with 1.3 equiv of methylenetriphenylphosphorane in dimethyl sulfoxide (Me_2SO) proceeds with 80% conversion to give 3-ethylidenespiro[5.5]undeca-1,4-diene (**4**, eq 1) as the major product and only trace amounts of the cyclopropane product, dispiro[2.2.5.2]trideca-4,12-diene (**5**). A justification of this unexpected behavior forms the basis for this report.



1



2



(1)

3 4 5

* Present address: Research Center, Hercules Inc., Wilmington, DE 19894.

(1) (a) Mechoulam, R.; Sondheimer, F. *J. Am. Chem. Soc.* **1958**, *80*, 4386–4388. (b) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128–1129. (c) Bestmann, H. J.; Denzel, T.; Kunstmann, R.; Lengyel, J. *Tetrahedron Lett.* **1968**, 2895–2898.

(2) (a) Ried, W.; Herrmann, H. J. *Justus Liebigs Ann. Chem.* **1974**, 1239–1247. (b) Ried, W.; Knorr, H.; Gürcan, H. *Ibid.* **1976**, 1415–1420.

0022-3263/83/1948-4860$01.50/0