A Convergent Synthesis of 5,10-Dideaza-5,6,7,8-tetrahydrofolic Acid and 5,10-Dideaza-5,6,7,8-tetrahydrohomofolic Acid. An Effective Principle for Carbonyl Group Activation

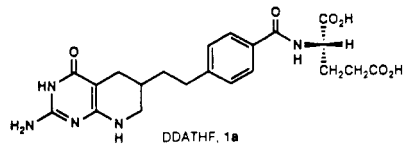
Edward C. Taylor* and Philip M. Harrington

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

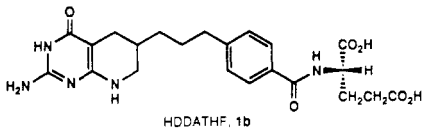
Received September 5, 1989

5,10-Dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF, **1a**) has been synthesized by a new convergent strategy that has also been applied to the preparation of a homologue, 5,10-dideaza-5,6,7,8-tetrahydrohomofolic acid (HDDATHF, **1b**). A key feature of these synthesis is the activation of carbonyl groups by aldol condensation with malononitrile. HDDATHF, like DDATHF, is an extremely potent cytotoxic agent whose mechanism of action involves inhibition of glycinamide ribonucleotide transformylase in the de novo purine biosynthetic pathway.

The discovery of 5,10-dideaza-5,6,7,8-tetrahydrofolic acid (DDATHF, **1a**), a folate antimetabolite with a novel mechanism of action, may represent a major breakthrough in antifolate cancer chemotherapy. DDATHF is the first



DDATHF, 1a

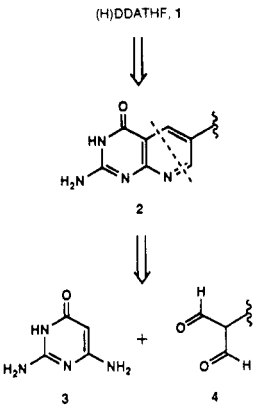


HDDATHF, 1b

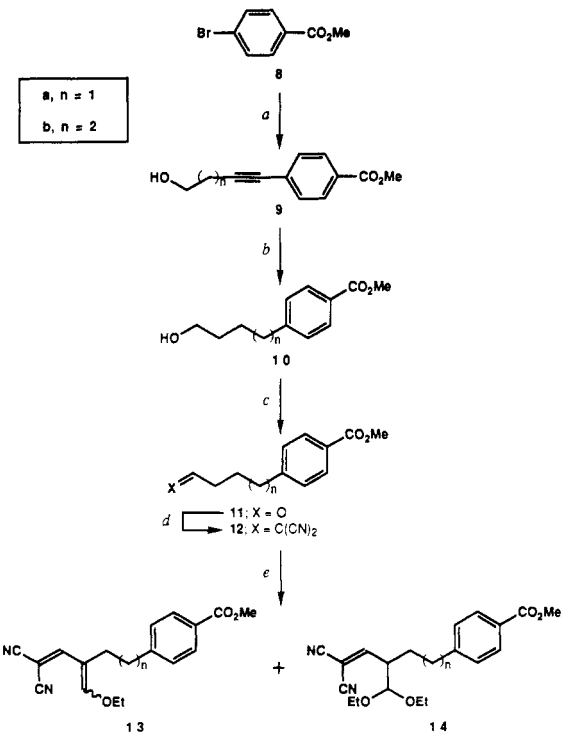
potent inhibitor of the folate cofactor-requiring enzyme glycinamide ribonucleotide transformylase (GAR TFase) in the purine de novo biosynthetic pathway.[1] DDATHF possesses extraordinary and selective antitumor activity; indeed, both its therapeutic index and its broad spectrum of activity against a variety of murine solid tumors and human colon xenografts in mice are unrivaled among known antitumor agents.[2-7] Since DDATHF is not an inhibitor of dihydrofolate reductase (DHFR), it is fully active against tumors that have developed resistance to DHFR inhibitors such as methotrexate. The 6*R* diastereomer (isomer B) of DDATHF (LY264618) is currently in phase I clinical trial as an antineoplastic agent.

Since homofolic acid, dihydrohomofolic acid, *dl*-tetrahydrohomofolic acid, and *dl*-5-methyltetrahydrohomofolic acid all show antitumor activity in the L1210 murine tumor system in vivo, we were interested in examining 5,10-dideaza-5,6,7,8-tetrahydrohomofolic acid (HDDATHF, **1b**), a homologue of DDATHF possessing one extra methylene group between the 5-deazatetrahydropterin and 4-aminobenzamide moieties. We describe herein a novel convergent strategy that provides access to both **1a** and **1b**, and potentially to other derivatives modified in the bridge region, and exploits a remarkably simple and effective principle for carbonyl group activation.

Scheme I



Scheme II[a]



[a] (a) 3-Butyn-1-ol (**7a**) or 4-pentyn-1-ol (**7b**), $(Ph_3)_2PdCl_2$, CuI, $HNEt_2$; (b) H_2, 5% Pd/C, EtOH; (c) PCC, NaOAc, CH_2Cl_2; (d) $NCCH_2CN$, DL-alanine, AcOH, benzene, $-H_2O$; (e) $HC(OEt)_3$, Ac_2O, $ZnCl_2$.

Several alternative syntheses of DDATHF have now appeared[8-11] since our original nonconvergent synthesis was

(1) Beardsley, G. P.; Moroson, B. A.; Taylor, E. C.; Moran, R. G. *J. Biol. Chem.* **1989**, *264*, 328.
(2) Taylor, E. C.; Wong, G. S. K.; Fletcher, S. R.; Harrington, P. J.; Beardsley, G. P.; Shih, C. J. In *Chemistry and Biology of Pteridines*; Cooper, B. A., Whitehead, V. M., Eds.; Walter de Gruyter: Berlin, 1986; p 61.
(3) Taylor, E. C.; Beardsley, G. P.; Grindey, G. B.; Moran, R. G. In *Chemistry and Biology of Pteridines*; Cooper, B. A., Whitehead, V. M., Eds.; Walter de Gruyter: Berlin, 1986; p 953.
(4) Moran, R. G.; Taylor, E. C.; Beardsley, G. P. *Proc. Am. Assoc. Cancer Res.* **1985**, *26*, 231.
(5) Beardsley, G. P.; Taylor, E. C.; Shih, C.; Poore, G. A.; Grindey, G. B.; Moran, R. G. *Proc. Am. Assoc. Cancer Res.* **1986**, *27*, 259.
(6) Moran, R. G.; Taylor, E. C.; Shih, C.; Beardsley, G. P. *Proc. Am. Assoc. Cancer Res.* **1987**, *28*, 274.
(7) Pizzorno, G.; Moroson, B. A.; Cashmore, A. R.; Taylor, E. C.; Beardsley, G. P. *Proc. Am. Assoc. Cancer Res.* **1988**, *29*, 281.

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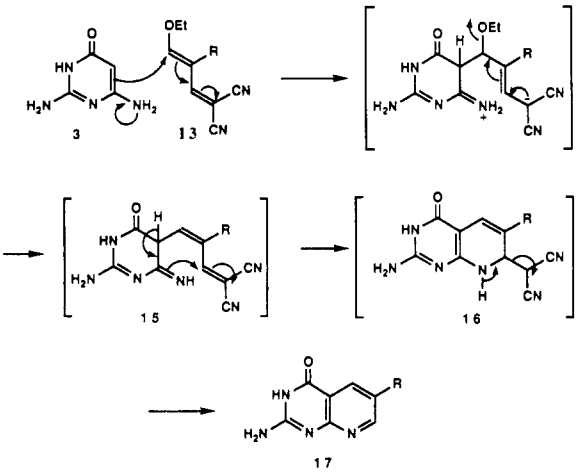
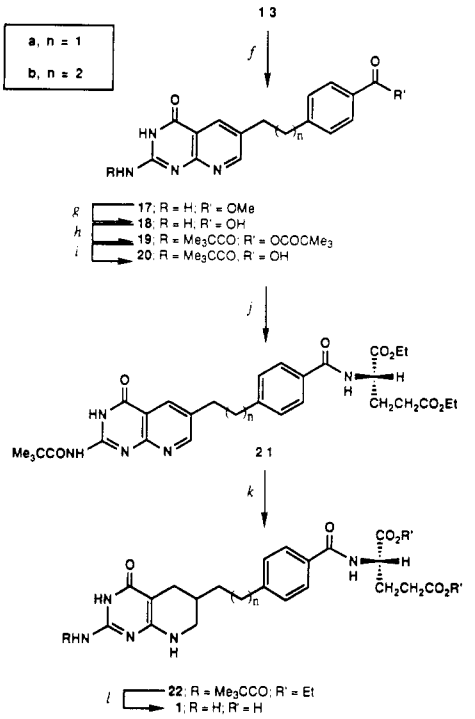
Scheme III



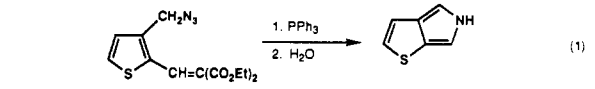
Scheme IV[a]



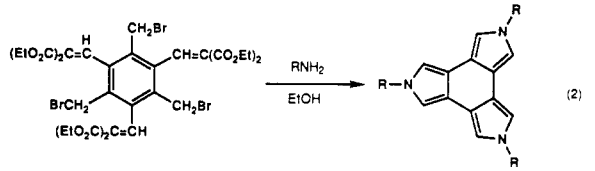
[a] (f) **3**, 60% AcOH; (g) 1 N NaOH; (h) $(Me_3CCO)_2O$, 4-DMAP; (i) ~0.1 N NaOH; (j) diethyl L-glutamate hydrochloride, phenyl *N*-phenylphosphoramidochloridate, *N*-methylmorpholine, NMP; (k) H_2, 5% Pd/C, TFA; (l) 1 N NaOH.

published in 1985.[12] The most efficient of these alternative routes is a convergent one involving two successive palladium-mediated carbon–carbon coupling reactions.[9] We now describe a new DDATHF synthesis that evolved from the retrosynthetic analysis outlined in Scheme I whereby the pentultimate aromatic pyrido[2,3-*d*]pyrimidine ring system found in **2** is formed by condensation of 2,4-diamino-6(1*H*)-pyrimidone (**3**) with the appropriately substituted malondialdehyde derivative **4**.[13] The latter, in principle, could be formed by α-formylation of the 4-arylbutyraldehyde derivative **11a** (see Scheme II). However, a model experiment with 4-phenylbutyraldehyde revealed that the required α-formylation reaction could not be satisfactorily effected under a broad variety of conditions (DMF–DMA, triethyl orthoformate/$ZnCl_2$, acetic formic anhydride, the Vilsmeier reagent, prepared either from $POCl_3$/DMF or from oxalyl chloride/DMF). Formylation of the pyrrolidine enamine of 4-phenylbutyraldehyde was likewise unsuccessful.

Two recent papers by Sha and co-workers suggested a possible solution both to the above formylation problem and to the contemplated ring annulation reaction leading to **2**.[14,15] The cyclization reactions described by Sha in eq 1 and 2 both involve Michael addition of a nucleophile

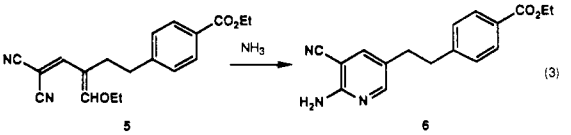


(1)



(2)

to the Knoevenagel product of an aldehyde and diethyl malonate, followed by aromatization through elimination of diethyl malonate anion as a leaving group. Several years ago we showed[12] that the conversion of the ethyl ester corresponding to **11a** (see Scheme II) to its Knoevenagel condensation product with malononitrile resulted in substantial acidification of the α-methylene group, permitting facile formylation with triethyl orthoformate to yield **5** (this is the ethyl ester corresponding to **13a**, Scheme II). This intermediate was then utilized by us for the synthesis of the 2-amino-3-cyanopyridine intermediate **6** by reaction with ammonia (eq 3). (An analogous synthesis of a 5-substituted 2-amino-3-cyanopyridine from a similar intermediate was later described by DeGraw and co-workers.[16])



(3)

However, condensation of **5** or **13a** *as a malondialdehyde equivalent* with 2,4-diamino-6(1*H*)-pyrimidone (**3**) might be expected to take place more readily than with the elusive malondialdehyde **4** itself, *since the initial Michael condensation of* ***13a*** *with* ***3*** *to give* ***15*** *(see Scheme III), the second Michael ring closure of* ***15*** *to give* ***16***, *and the final aromatization step leading to* ***17*** *should all be facilitated by the greater electrophilicity of* $C{=}C(CN)_2$ *as compared with* $C{=}O$. These expectations were fully realized in the DDATHF synthesis summarized below in Schemes II–IV.

As an improved route to the requisite starting methyl 4-(formylpropyl)benzoate (**11a**),[12,16] we initially considered

(8) Taylor, E. C.; Harrington, P. M.; Warner, J. C. *Heterocycles* **1988**, *27*, 1925.
(9) Taylor, E. C.; Wong, G. S. K. *J. Org. Chem.* **1989** *54*, 3618.
(10) Boschelli, D. H.; Webber, S.; Whiteley, J. M.; Oronsky, A. L.; Kerwar, S. S. *Arch. Biochem. Biophys.* **1988**, *265*, 43.
(11) Piper, J. R.; McCaleb, G. S.; Montgomery, J. A.; Kisliuk, R. L.; Gaumont, Y.; Thorndike, J.; Sirotnak, F. M. *J. Med. Chem.* **1988**, *31*, 2164.
(12) Taylor, E. C.; Harrington, P. J.; Fletcher, S. R.; Beardsley, G. P.; Moran, R. G. *J. Med. Chem.* **1985**, *28*, 914.
(13) The condensation of 6-aminopyrimidines with 1,3-dicarbonyl compounds to give pyrido[2,3-*d*]pyrimidines is well known: (a) Robins, R. K.; Hitchings, G. H. *J. Am. Chem. Soc.* **1958**, *80*, 3449. (b) Bernetti, R.; Mancini, F.; Price, C. C. *J. Org. Chem.* **1962**, *27*, 2863.
(14) Sha, C.-K.; Tsou, C.-P. *J. Chem. Soc., Chem. Commun.* **1986**, 310.
(15) Sha, C.-K.; Tsou, C.-P.; Li, Y.-C.; Lee, R.-S.; Tsai, F.-Y.; Yeh, R.-H. *J. Chem. Soc., Chem. Commun.* **1988**, 1081.
(16) DeGraw, J. I.; Tagawa, H.; Christie, P. H.; Lawson, J. A.; Brown, E. G.; Kisliuk, R. L.; Gaumont, Y. *J. Heterocycl. Chem.* **1986**, *23*, 1.

a palladium-catalyzed coupling of a methyl 4-halobenzoate with 3-buten-1-ol, to be followed by reduction of the olefinic double bond and final oxidation of the primary alcohol. This approach was abandoned when it was found that, under standard coupling conditions, methyl 4-bromobenzoate (**8**) and 3-buten-1-ol gave a complex mixture of coupled products arising from addition of the aryl–palladium complex both to the terminal and to the internal positions of the double bond. However, the closely related acetylene **9a** was readily obtained by coupling of 3-butyn-1-ol (**7a**) with **8** using bis(triphenylphosphine)-palladium chloride and copper(I) iodide in diethylamine as solvent. Reduction of the acetylenic triple bond with H_2/Pd–C gave the primary alcohol **10a**, which was oxidized with PCC to the aldehyde **11a**. Knoevenagel condensation of **11a** with malononitrile, by the procedure previously described,[12] then gave **12a**, which was readily formylated with triethyl orthoformate/acetic anhydride and a catalytic amount of zinc chloride. The major formylation product was the ethoxymethylene derivative **13a**, which crystallized directly from the reaction mixture as a yellow solid.[17] The acetal **14a**, formed concomitantly as a byproduct in the formylation reaction, proved to be difficult to isolate and also unreactive in an attempted condensation reaction with 2,4-diamino-6(1*H*)-pyrimidone (**3**). On the other hand, the malondialdehyde equivalent **13a** condensed readily with **3** upon heating in refluxing 60% acetic acid to give the desired pyrido[2,3-*d*]pyrimidine intermediate **17a** as an analytically pure solid in 68% yield.

A possible mechanism for this extremely facile ring annulation reaction is indicated in Scheme III. Initial Michael condensation (**3** to **15**) presumably takes place as shown, since 2,4-diamino-6(1*H*)-pyrimidone is known to undergo Michael reactions as a primary enamine by reaction at C-5, not at the 6-amino group.[18,19] Every one of the steps from **3** to **17**—the initial Michael reaction at C-5 of **3**, the second Michael condensation that results in ring annulation (**15** to **16**), and the terminal aromatization step (**16** to **17**)—appears to be facilitated by replacement of C=O by $C=C(CN)_2$.

Separation of **17a** in a pure state from the above reaction mixture proved to be most fortunate, since **17a** is extraordinarily insoluble (it could be neither chromatographed nor recrystallized). Heating this compound with 1 N sodium hydroxide, however, resulted in smooth hydrolysis of the methyl ester, and the resulting free acid **18a** was then heated in refluxing pivalic anhydride in the presence of 4-(dimethylamino)pyridine as catalyst (Scheme IV). The resulting 2-pivaloylated mixed anhydride **19a** when stirred with dilute sodium hydroxide gave the free acid **20a**, which, because of the 2-pivaloyl grouping, was sufficiently soluble for further functionalization.[20-22] An alternate strategy, which involved initial pivaloylation of the methyl ester **17a**, followed by attempted selective saponification in 0.1 N NaOH, failed to give **20a**, but instead (after only 20 min at room temperature) cleanly regenerated the starting methyl ester **17a**. This perhaps surprising greater lability of the amide grouping at position 2 compared with the methyl benzoate functionality is presumably due to the weak basicity of the 2-amino group in **17a**, i.e., the electron-deficient deazapterin moiety is an excellent leaving group in weakly basic solution.

The glutamate side chain was introduced by using phenyl *N*-phenylphosphoramidochloridate as the coupling reagent in *N*-methylpyrrolidinone as solvent, and the resulting **21a** was reduced catalytically to the tetrahydro derivative **22a**. Since DDATHF has already been prepared from this intermediate by hydrolysis of the ester functions and the pivaloyl protecting group,[9] this malononitrile-facilitated synthesis of **22a** constitutes a new synthetic route to DDATHF (**1a**).

An appealing feature of the preceding methodology is the ease with which the nature and length of the bridging unit between the pyridine and aryl rings can be varied. As an example, we have prepared homoDDATHF (HDDATHF, **1b**) starting with methyl 4-(4-formylbutyl)benzoate (**11b**), obtained by coupling methyl 4-bromobenzoate (**8**) with 4-pentyn-1-ol (**7b**) in the presence of a palladium catalyst, followed by reduction of the triple bond and oxidation of the primary hydroxyl group. All of the succeeding steps in the synthesis of **1b** parallel the reactions described previously for the synthesis of DDATHF itself; the final hydrolysis steps (**22b** to **1b**) parallel the conditions previously utilized for the preparation of DDATHF from **22a**.[9] HomoDDATHF is a potent cytotoxic agent, with an IC_{50} value of 0.009 μg/mL against human T-cell-derived lymphoblastic leukemia cells (CCRF-CEM) (cf. DDATHF, with an IC_{50} of 0.007 μg/mL). Full details on the pharmacology of this new DDATHF analogue will be published independently.

This new methodology represents a versatile addition to previously available synthetic methods in this field of folate antimetabolites, and it provides potential access to compounds unavailable by routes previously developed for the preparation of DDATHF itself. Applications to the preparation of additional DDATHF-based antitumor agents will be described in due course.

Experimental Section

General. Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1320 instrument and are reported in cm^{-1}. ^1H NMR data were obtained with a General Electric QE 300-MHz instrument using residual solvent as an internal standard and chemical shifts are reported in ppm downfield from TMS. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, and b = broad), coupling constant (in hertz), integration, and assignment. Mass spectral data were obtained by Dr. Dorothy Little on AEI MS-902 and Kratos MS50TC spectrometers. Elemental analyses were performed by Eli Lilly and Co., Indianapolis, IN. Column chromatography was performed on Merck silica gel 60 (240–400 mesh). Analytical thin layer chromatography (TLC) analyses were carried out on Bakerflex IB2-F plates utilizing UV visualization.

Materials. Commercial reagents were utilized without further purification. Anhydrous solvents were distilled before use.

Methyl 4-(4-Hydroxybutynyl)benzoate (9a). A 500-mL round-bottomed flask, equipped with a magnetic stirrer and gas inlet, was charged with a mixture of 0.082 g (0.005 equiv) of palladium chloride, 0.244 g (0.01 equiv) of triphenylphosphine, and 300 mL of a diethylamine solution of 20.00 g (1.0 equiv) of methyl 4-bromobenzoate (**8**).[23] To the stirred mixture, under a nitrogen atmosphere, was added 0.178 g (0.01 equiv) of copper(I) iodide and 6.52 g (1.0 equiv) of 3-butyn-1-ol (**5**), and the reaction

(17) An alternative synthesis of the closely related enamine has been achieved (ref 16) in low yield by condensation of the enamine derived from **11a** (itself prepared in low yield from *p*-toluic acid) with (ethoxymethylene)malononitrile; this compound was subsequently utilized for the synthesis of a 2-amino-3-cyanopyridine derivative by reaction with ammonia (cf. **5** to **6**).

(18) Taylor, E. C.; Sowinski, F. *J. Org. Chem.* **1974**, *39*, 907.

(19) The initial condensation of 1,3-dicarbonyl compounds with 6-aminopyrimidines also takes place at the 5-position: see ref 13a.

(20) Taylor, E. C.; Ray, P. S. *J. Org. Chem.* **1987**, *52*, 3997.

(21) Taylor, E. C.; Ray, P. S. *J. Org. Chem.* **1988**, *53*, 35.

(22) Taylor, E. C.; Yoon, C.-M. *Synth. Commun.* **1988**, *18*, 1187.

(23) *Dictionary of Organic Compounds*, Oxford University Press: New York, 1965.

mixture was stirred under nitrogen at room temperature for 18 h. Diethylamine was removed under reduced pressure, water was added, and the mixture was extracted with benzene. The benzene extract was passed over a short silica gel pad to remove the catalyst, the filtrate was concentrated under reduced pressure, and the residue was recrystallized from benzene–hexanes to give 14.40 g (76%) of pure **9a** as white flakes: mp 95.5–96.0 °C; ^{1}H NMR ($CDCl_3$) δ 7.98, 7.49 (AA'BB', 4 H, Ar), 3.93 (s, 3 H, CH_3), 3.87 (m, 2 H, CH_2OH), 2.74 (t, J = 6.2 Hz, 2 H, propargyl), 1.88 (m, 1 H, OH). Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.36; H, 5.68.

Methyl 4-(4-Hydroxybutyl)benzoate (10a). A Parr flask was charged with 2.55 g of **9a** dissolved in 200 mL of ethanol and 0.26 g (10% wt equivalent) of 5% palladium on carbon catalyst suspended in 25 mL of ethanol. Hydrogenation was carried out at 50 psi of hydrogen for 12 h. The reaction mixture was filtered through a silica gel pad, which was washed with ethanol, and the filtrate was concentrated under reduced pressure to give 2.60 g (quantitative) of pure **10a** as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.95, 7.25 (AA'BB', 4 H, Ar), 3.89 (s, 3 H, CH_3), 3.65 (t, J = 6.3 Hz, 2 H, CH_2OH), 2.69 (t, J = 7.5 Hz, 2 H, benzyl), 1.85 (b s, 1 H, OH), 1.57–1.78 (m, 4 H, 2° aliphatic). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 68.97; H, 7.92.

4-(4'-Carbomethoxyphenyl)butyraldehyde (11a). A 500-mL two-necked round-bottomed flask, equipped with a magnetic stirrer, reflux condenser, and gas inlet, was charged with 4.19 g (1.5 equiv) of pyridinium chlorochromate and 1.06 g (1.0 equiv) of sodium acetate in 100 mL of dry methylene chloride. To this stirred solution was added 2.70 g (1.0 equiv) of **10a** in 50 mL of dry methylene chloride, and the reaction mixture was stirred at room temperature under a nitrogen atmosphere for 12 h, diluted with diethyl ether, and filtered through a silica gel pad. The filtrate was concentrated under reduced pressure and the residue was distilled to give 1.59 g (60%) of pure **11a** as a colorless oil: bp 131 °C at <1 Torr; ^{1}H NMR ($CDCl_3$) δ 9.77 (m, 1 H, CHO), 7.98, 7.24 (AA'BB', 4 H, Ar), 3.90 (s, 3 H, CH_3), 2.72 (t, J = 7.5 Hz, 2 H, benzyl), 2.47 (m, 2 H, CH_2CHO), 1.95 (m, 2 H, CH_2). 2,4-DNP of **11a** (from ethanol): mp 114–116 °C (lit.[16] mp 122–123 °C); IR (KBr) 3295, 1720, 1615, 1510, 1340, 1284 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.80 (m, 1 H, CH=N), 8.29 (dd, J = 2.7, 9 Hz, 1 H, CH ortho-para to two NO_2), 7.90–7.93 (m, 4 H, CH meta to two NO_2, CH ortho-ortho to two NO_2, Ar), 7.38 (AA'BB', 2 H, Ar), 3.88 (s, 3 H, CH_3), 2.79 (t, J = 7.5 Hz, 2 H, benzyl), 2.45 (m, 2 H, CH_2CH=N), 1.97 (m, 2 H, CH_2). Anal. Calcd for $C_{18}H_{18}N_4O_6$: C, 55.96; H, 4.70; N, 14.50. Found: C, 55.91; H, 4.43; N, 14.57.

Methyl 4-(5,5-Dicyano-4-pentenyl)benzoate (12a). A 100-mL round-bottomed flask, equipped with a magnetic stirrer, Dean–Stark trap, reflux condenser, heating mantle, and drying tube, was charged with 3.36 g (1.0 equiv) of **11a**, 1.29 g (1.2 equiv) of malononitrile, 0.05 g of DL-alanine, 1 mL of glacial acetic acid, and 60 mL of benzene. The reaction mixture was refluxed with stirring and azeotropic removal of water for 3 h (theoretical yield of water, 0.29 mL; collected yield, 0.25 mL). The mixture was cooled to room temperature and poured over water. The aqueous layer was extracted (2×) with benzene, and the organic extracts were combined, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification was carried out by column chromatography, eluting with 50% ethyl acetate/hexanes. Fractions homogeneous by TLC for the major component were combined and concentrated under reduced pressure to give 3.12 g (75%) of **12a** as a light yellow oil:[24] ^{1}H NMR ($CDCl_3$) δ 7.99 (AA'BB', 2 H, Ar), 7.26–7.30 (m, 3 H, Ar, vinyl), 3.90 (s, 3 H, CH_3), 2.79 (t, J = 7.5 Hz, 2 H, benzyl), 2.62 (m, 2 H, CH_2CH=C), 1.95 (m, 2 H, CH_2).

Methyl 4-(5,5-Dicyano-3-(ethoxymethylidene)-4-pentenyl)benzoate (13a). A 100-mL round-bottomed flask, equipped with a magnetic stirrer, reflux condenser, heating mantle, and drying tube, was charged with 5.59 g (22.0 mmol) of **12a**, 29.3 mL (176 mmol) of triethyl orthoformate, 33.2 mL (352 mmol) of acetic anhydride, and 0.08 g of zinc chloride.[25] The reaction mixture was refluxed with stirring and exclusion of moisture at 145 °C for 18 h. The suspension was cooled and the volatiles were removed by distillation at atmospheric pressure up to 100 °C. Triethyl orthoformate (14.7 mL, 88.0 mmol) and acetic anhydride (16.6 mL, 176 mmol) were added, and the reaction mixture was refluxed with stirring and exclusion of moisture at 150 °C for 12 h. The suspension was cooled, poured over water, and extracted with chloroform. The extracts were combined, dried (sodium sulfate), filtered, and concentrated under reduced pressure. The residue was dissolved in chloroform and passed through a short silica gel pad to remove base-line material. Ethanol was added to the filtrate, and the solution was concentrated under reduced pressure until a solid crystallized. This solid was collected by filtration and recrystallized from ethanol to yield 3.66 g (54%) of pure **13a** as long rust-colored needles: mp 136–137 °C; ^{1}H NMR ($CDCl_3$) δ 7.96, 7.33(AA'BB', 4 H, Ar), 7.06 (s, 1 H, CH=C$(CN)_2$), 6.95 (s, 1 H, vinyl), 4.10 (q, J = 7.1 Hz, 2 H, OCH_2), 3.92 (s, 3 H, CH_3), 2.86–3.00 (m, 4 H, $ArCH_2CH_2$) 1.30 (t, J = 7.1 Hz, 3 H, CH_3CH_2O). Anal. Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H8 5.85; N, 9.03. Found: C, 69.47; H, 5.68; N, 8.86.

Methyl 4-[2-(2-Amino-3,4-dihydro-4-oxo-5-deazapteridin-6-yl)ethyl]benzoate (Methyl 5,10-Dideazapteroate) (17a). A 50-mL round-bottomed flask equipped with a magnetic stirrer, reflux condenser, and heating mantle was charged with 2.00 g (1.0 equiv) of **13a**, 0.93 g (1.0 equiv) of 2,4-diamino-6(1*H*)-pyrimidone monohydrate and 30 mL of 60% acetic acid. The reaction mixture was refluxed with stirring for 4 h and allowed to cool to room temperature, and the suspended solid was collected by filtration, washed with water and diethyl ether, and dried to give 1.41 g (68%) of pure **17a** as a white powder: mp >300 °C; ^{1}H NMR (TFA-*d*, DMSO-d_6) δ 8.38 (s, 1 H, (7)-H), 7.99 (s, 1 H, (5)-H), 7.55, 6.82 (AA'BB', 4 H, Ar), 6.87 (s, 1 H, (3)-H), 3.56 (s, 3 H, CH_3), 2.79 (m, 2 H, (6)-CH_2), 2.70 (m, 2 H, benzyl). Anal. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 62.65; H, 5.03; N, 17.06.

4-[2-(2-Amino-3,4-dihydro-4-oxo-5-deazapteridin-6-yl)-ethyl]benzoic Acid (5,10-Dideazapteroic Acid) (18a). A 100-mL round-bottomed flask equipped with a magnetic stirrer was charged with 0.46 g of **17a** in 30 mL of 1 N NaOH. The reaction mixture was stirred at room temperature for 36 h, and the homogeneous solution was acidified with glacial acetic acid to ca. pH 4. The resulting suspension was centrifuged with fresh water several times and transferred to a round-bottomed flask with methanol. Concentration under reduced pressure gave 0.44 g (quantitative) of **18a** as a white powder: mp >300 °C; ^{1}H NMR (TFA-*d*, DMSO-d_6) δ 8.38 (s, 1 H, (7)-H), 8.02 (s, 1 H, (5)-H), 7.62, 6.82 (AA'BB', 4 H, Ar), 6.87 (s, 1 H, (3)-H), 2.79 (m, 2 H, (6)-CH_2), 2.73 (m, 2 H, benzyl); HRMS m/z calcd for $C_{16}H_{15}N_4O_3$ (MH^+) 311.1144, found 311.1153.

4-[2-[2-(Pivaloylamino)-3,4-dihydro-4-oxo-5-deazapteridin-6-yl]ethyl]benzoic Acid (2-Pivaloyl-5,10-dideazapteroic Acid) (20a). A 50-mL round-bottomed flask equipped with a magnetic stirrer, reflux condenser, heating mantle, and gas inlet was charged with 0.40 g (1.0 equiv) of **18a**, 0.02 g (0.1 equiv) of 4-(*N*,*N*-dimethylamino)pyridine, and 10 mL of pivalic anhydride. The reaction mixture was refluxed with stirring under a nitrogen atmosphere for 6 h and cooled to room temperature, 50 mL of diethyl ether was added, and the light brown solid was collected by filtration. This solid was triturated with water and 1 N NaOH was added dropwise until a homogeneous solution resulted (to hydrolyze the intermediate mixed anhydride **19a**). The resulting precipitate was collected by vacuum filtration and washed sequentially with water, methanol, acetone, and diethyl ether. A solid formed in the filtrate, which was collected by vacuum filtration and washed with diethyl ether to give 0.19 g (37%) of **20a** as a pale yellow powder: mp >300 °C; ^{1}H NMR (TFA-*d*, $CDCl_3$) δ 9.03 (s, 1 H, (7)-H), 8.73 (s, 1 H, (5)-H), 8.14, 7.37 (AA'BB', 4 H, Ar), 3.36 (t, J = 7.4 Hz, 2 H, (6)-CH_2), 3.24 (t, J = 7.2 Hz, 2 H, benzyl), 1.46 (s, 9 H, $C(CH_3)_3$); HRMS m/z calcd for $C_{21}H_{22}N_4O_4$ (M^+) 394.1641, found 394.1649.

Diethyl *N*-[4-[2-[2-(Pivaloylamino)-3,4-dihydro-4-oxo-5-deazapteridin-6-yl]ethyl]benzoyl]-L-glutamate (Diethyl 2-Pivaloyl-5,10-dideazafolate) (21a). A 50-mL round-bottomed

(24) Neither satisfactory elemental analyses nor a high resolution mass spectrum could be obtained for this compound, since it underwent extensive decomposition upon standing. However, the identity of **12** was fully confirmed by its conversion to **13**, which was fully characterized.

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

flask equipped with a magnetic stirrer and gas inlet tube was charged with 0.19 g (1.0 equiv) of **20a**, 0.19 g (1.5 equiv) of phenyl *N*-phenylphosphoramidochloridate, 0.24 g (5.0 equiv) of *N*-methylmorpholine, and 20 mL of *N*-methylpyrrolidinone. The mixture was stirred at room temperature under a nitrogen atmosphere for 1 h. To the resulting homogeneous solution was added 0.23 g (2.0 equiv) of diethyl L- glutamate hydrochloride, and stirring under nitrogen was continued for 24 h. The solvent was removed by vacuum distillation and chloroform was added to the residue. The chloroform solution was washed with water, and the organic extracts were combined, dried (magnesium sulfate), filtered, and concentrated under reduced pressure. Purification was carried out by column chromatography, eluting with 2% methanol/chloroform. Fractions homogeneous by TLC for the major component were combined and concentrated under reduced pressure to give 0.12 g (43%) of **21a** as a pale yellow solid: mp >250 °C; ^{1}H NMR ($CDCl_3$) δ 8.63 (s, 1 H, (7)-H), 8.33 (s, 1 H, (5)-H), 7.74, 7.21 (AA'BB', 4 H, Ar), 7.19 (d, J = 6.9 Hz, 1 H, NH), 4.80 (m, 1 H, CH), 4.24 (q, J = 7.8 Hz, 2 H, CO_2CH_2), 4.12 (q, J = 7.8 Hz, 2 H, CO_2CH_2), 3.05 (s, 4 H, 2° aliphatic), 1.97–2.61 (m, 4 H, 2° aliphatic), 1.34 (s, 9 H, $C(CH_3)_3$), 1.29 (t, J = 7.8 Hz, 3 H, CH_3), 1.22 (t, J = 7.8 Hz, 3 H, CH_3). Anal. Calcd for $C_{30}H_{37}N_5O_7$: C, 62.16; H, 6.43; N, 12.08. Found: C, 61.91; H, 6.44; N, 11.84.

Diethyl *N*-[4-[2-[2-(Pivaloylamino)-3,4,5,6,7,8-hexahydro-4-oxo-5-deazapteridin-6-yl]ethyl]benzoyl]-L-glutamate (22a). A Parr flask was charged with 0.05 g of **21a** and 0.15 g (3.0 wt equivalent) of 5% palladium on carbon in 20 mL of trifluoroacetic acid. Hydrogenation was carried out at 50 psi of hydrogen for 24 h. The reaction mixture was diluted with methylene chloride and filtered through a Celite pad, and the filtrate was concentrated under reduced pressure. The residue was redissolved in methylene chloride and extracted with a saturated sodium bicarbonate solution. The organic extracts were combined, dried (sodium sulfate), filtered, and concentrated under reduced pressure. Purification was carried out by subjecting the residue to column chromatography, eluting with 4% methanol/methylene chloride. Fractions homogeneous by TLC for the major component were combined and concentrated under reduced pressure to give 0.05 g (quantitative) of **22a** as a white solid: mp >250 °C; ^{1}H NMR ($CDCl_3$) δ 8.56 (b s, 1 H, (3)-NH), 7.73, 7.23 (AA'BB', 4 H, Ar) 7.17 (d, J = 7.5 Hz, 1 H, NH), 5.15 (b s, 1 H, (8)-H), 4.80 (m, 1 H, $CHCO_2Et$), 4.23 (q, J = 7.2 Hz, 2 H, CO_2CH_2), 4.11 (q, J = 7.2 Hz, 2 H, CO_2CH_2), 1.61–3.35 (m, 13 H, 2° aliphatic), 1.30 (t, J = 7.2 Hz, 3 H, CH_3), 1.29 (s, 9 H, $C(CH_3)_3$), 1.22 (t, J = 7.2 Hz, 3 H, CH_3). Anal. Calcd for $C_{30}H_{41}N_5O_7$: C, 61.73; H, 7.08; N, 12.00. Found: C, 61.49; H, 6.94; N, 12.04.

Methyl 4-(5-Hydroxypentynyl)benzoate (9b). This compound was prepared from 0.021 g (0.005 equiv) of palladium chloride, 0.061 g (0.01 equiv) of triphenylphosphine, 5.00 g (1.0 equiv) of **8**, 0.044 g (0.01 equiv) of copper(I) iodide, and 1.96 g (1.0 equiv) of 4-pentyn-1-ol (**7b**) as described previously for the preparation of **9a**. The product was obtained as lime-green needles after recrystallization from benzene/hexanes to give 4.21 g (83%): mp 69–70 °C; ^{1}H NMR ($CDCl_3$) δ 7.96, 7.45 (AA'BB', 4 H, Ar), 3.92 (s, 3 H, CH_3), 3.84 (m, 2 H, CH_2OH), 2.58 (t, J = 7.0 Hz, 2 H, propargyl), 1.89 (qn, J = 6.6 Hz, 2 H, 2° aliphatic), 1.63 (b s, 1 H, OH); HRMS m/z calcd for $C_{13}H_{14}O_3$ (M^+) 218.0943, found 218.0936. Anal. Calcd for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.26; H, 6.38.

Methyl 4-(5-Hydroxypentyl)benzoate (10b). This compound was prepared from 14.60 g of **9b** and 1.46 g (10% wt equivalent) of 5% palladium on carbon as described previously for the preparation of **10a**, yield 14.84 g (quantitative) of pure **10b** as a light yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.94, 7.23 (AA'BB', 4 H, Ar), 3.89 (s, 3 H, CH_3), 3.62 (t, J = 6.5 Hz, 2 H, CH_2OH), 2.66 (t, J = 7.7 Hz, 2 H, benzyl), 1.86 (b s, 1 H, OH), 1.53–1.71, (m, 4 H, 2° aliphatic), 1.40 (m, 2 H, 2° aliphatic). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 70.05; H, 8.17.

4-(4′-Carbomethoxyphenyl)valeraldehyde (11b). This compound was prepared from 20.50 g (1.5 equiv) of pyridinium chlorochromate, 5.20 g (1.0 equiv) of sodium acetate, and 14.09 g (1.0 equiv) of **10b** as described previously for the preparation of **10a**, yield 8.34 g (60%) of pure **11b** as a clear colorless liquid: bp 133–134 °C; ^{1}H NMR ($CDCl_3$) δ 9.73 (t, J = 1.9 Hz, 1 H, CHO), 7.94, 7.22 (AA'BB', 4 H, Ar), 3.88 (s, 3 H, CH_3), 2.67 (t, J = 6.9 Hz, 2 H, benzyl), 2.44 (m, 2 H, CH_2CHO), 1.62–1.68, (m, 4 H, 2° aliphatic); FDMS m/z 220 (M^+). 2,4-DNP of **11b** (from ethanol): mp 130–132 °C; IR (KBr) 3275, 3090, 3010, 2970, 2915, 2835, 1709, 1608, 1582, 1500, 1425, 1411, 1322, 1298, 1277, 1210, 1132, 1100, 1066, 909, 824, 736, 715 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.13 (m, 1 H, CH=N), 8.30 (dd, J = 2.4, 9.6 Hz, 1 H, Ar ortho-para to two NO_2), 7.98, 7.38 (AA'BB', 4 H, Ar), 7.89 (d, J = 9.6 Hz, 1 H, Ar ortho-ortho to two NO_2), 7.52 (t, J = 5.2 Hz, 1 H, Ar meta to two NO_2), 3.92 (s, 3 H, CH_3), 2.75 (t, J = 7.2 Hz, 2 H, benzyl), 2.48 (m, 2 H, CH_2CH=N), 1.65–1.80 (m, 6 H, 2° aliphatic); HRMS m/z calcd for $C_{19}H_{20}N_4O_6$ (M^+) 400.1382, found 400.1354. Anal. Calcd for $C_{19}H_{20}N_4O_6$: C, 57.00; H, 5.03; N, 14.00. Found: C, 57.21; H, 5.14; N, 14.24.

Methyl 4-(6,6-Dicyano-5-hexenyl)benzoate (12b). This compound was prepared from 4.87 g (1.0 equiv) of **11b**, 1.75 g (1.2 equiv) of malononitrile, 0.10 g of DL-alanine, and 1.5 mL of glacial acetic acid as described previously for the preparation of **12a**, yield 4.28 g (72%) of **12b** as a light yellow oil:[24] ^{1}H NMR ($CDCl_3$) δ 7.98, 7.25 (AA'BB', 4 H, Ar), 7.31 (t, J = 8.0 Hz, 1 H, vinyl), 3.91 (s, 3 H, CH_3), 2.72 (t, J = 7.4 Hz, 2 H, benzyl), 2.62 (m, 2 H, allyl), 1.56–1.79 (m, 6 H, 2° aliphatic).

Methyl 4-(6,6-Dicyano-4-(ethoxymethylidene)-5-hexenyl)benzoate (13b). This compound was prepared from 8.23 g (30.7 mmol) of **12b**, 76.5 mL (461 mmol) of triethyl orthoformate, 86.8 mL (922 mmol) of acetic anhydride, and 0.10 g of zinc chloride followed by 51.0 mL (307 mmol) of triethyl orthorformate and 57.9 mL (614 mmol) of acetic anhydride as described previously for the preparation of **13a**, yield 4.22 g (42%) of pure **13b** as long rust-colored needles after recrystallization from ethanol: mp 82–83 °C; ^{1}H NMR ($CDCl_3$) δ 7.96, 7.28 (AA'BB', H, Ar), 7.04 (s, 1 H, CH=C(CN)$_2$), 6.97 (s, 1 H, vinyl), 4.20 (q, J = 7.2 Hz, 2 H, OCH_2), 3.92 (s, 3 H, CH_3), 2.76 (t, J = 8.0 Hz, 2 H, benzyl), 2.62 (t, J = 7.9 Hz, 2 H, allyl), 1.80 (m, 2 H, 2° aliphatic), 1.39 (t, J = 7.0 Hz, 3 H, OCH_2CH_3); HRMS m/z calcd for $C_{19}H_{20}N_2O_3$ (M^+) 324.1474, found 324.1468. Anal. Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.10; H, 6.34; N, 8.47.

Methyl 4-[3-(2-Amino-3,4-dihydro-4-oxo-5-deazapteridin-6-yl)propyl]benzoate (17b). This compound was prepared from 1.71 g (1.0 equiv) of **13b**, 0.76 g (1.0 equiv) of 2,4-diamino-6-(1*H*)-pyrimidone monohydrate, and 40 mL of 60% acetic acid as described previously for the preparation of **17a**, yield 1.05 g (59%) of analytically pure **17b** as a white powder: mp 250 °C; ^{1}H NMR (TFA-*d*, DMSO-d_6) δ 8.48 (s, 1 H, (7)-H), 8.16 (s, 1 H, (5)-H), 7.53, 6.87 (AA'BB', 4 H, Ar), 3.56 (s, 3 H, CH_3), 2.38–2.49 (m, 4 H, benzyl, (6)-CH_2), 1.68 (m, 2 H, 2° aliphatic). Anal. Calcd for $C_{18}H_{18}N_4O_3$: C, 63.88; H, 5.36; N, 16.56. Found: C, 64.13; H, 5.46; H, 16.38.

4-[3-(2-Amino-3,4-dihydro-4-oxo-5-deazapteridin-6-yl)-propyl]benzoic Acid (18b). This compound was prepared from 0.39 g of **17b** in 30 mL of 1 N sodium hydroxide as described previously for the preparation of **18a**, yield 0.37 g (quantitative) of **18b** as a white powder: mp >300 °C; ^{1}H NMR (TFA-*d*, DMSO-d_6) δ 8.52 (s, 2 H, (7)-H, (5)-H), 7.72, 7.08 (AA'BB', 4 H, Ar), 2.48–2.56 (m, 4 H, benzyl), (6)-CH_2), 1.79 (m, 2 H, 2° aliphatic). Anal. Calcd for $C_{17}H_{16}N_4O_3$: C, 62.94; H, 4.98; N, 17.28. Found: C, 61.54; H, 4.99; N, 16.55.

4-[3-[2-(Pivaloylamino)-3,4-dihydro-4-oxo-5-deazapteridin-6-yl]propyl]benzoic Acid (20b). This compound was prepared from 0.50 g (1.0 equiv) of **18b**, 0.03 g (0.1 equiv) of 4-(*N*,*N*-dimethylamino)pyridine, and 10 mL of pivalic anhydride as described previously for the preparation of **20a**, yield 0.46 g (73%) of **20b** as a pale yellow powder: mp 257–258 °C; ^{1}H NMR (TFA-*d*, DMSO-d_6) δ 8.64 (s, 1 H, (7)-H), 8.27, (s, 1 H, (5)-H), 7.59, 6.91 (AA'BB', 4 H, Ar), 2.41–2.56, (m, 4 H, benzyl, (6)-CH_2), 1.72 (m, 2 H, 2° aliphatic), 0.95 (s, 9 H, $C(CH_3)_3$); HRMS m/z calcd for $C_{22}H_{24}N_4O_4$ (M^+) 408.1797, found 408.1805. Anal. Calcd for $C_{22}H_{24}N_4O_4$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.79; H, 5.74; N, 13.80.

Diethyl *N*-[4-[3-[2-(Pivaloylamino)-3,4-dihydro-4-oxo-5-deazapteridin-6-yl]propyl]benzoyl]-L-glutamate (21b). This compound was prepared from 1.00 g (1.0 equiv) of **20b**, 0.98 g (1.5 equiv) of phenyl *N*-phenylphosphoramidochloridate, 1.24 g (5.0 equiv) of *N*-methylmorpholine, and 1.17 g (2.0 equiv) of diethyl L-glutamate hydrochloride as described previously for the preparation of **21a**, yield 0.50 g (35%) of **21b** as a pale yellow solid: mp 203–204 °C; ^{1}H NMR ($CDCl_3$) δ 8.82 (s, 1 H, (7)-H), 8.36 (s,

1 H, (5)-H), 7.77, 7.27, (AA'BB', 4 H, Ar), 7.06 (d, J = 7.5 Hz, 1 H, NH), 4.80 (m, 1 H, CH), 4.26 (q, J = 7.3 Hz, 2 H, CO_2CH_2), 4.13 (q, J = 7.3 Hz, 2 H, CO_2CH_2), 2.73-2.82, (m, 4 H, 2° aliphatic), 2.03-2.57, (m, 6 H, 2° aliphatic), 1.62 (s, 9 H, $C(CH_3)_3$), 1.32 (t, J = 7.3 Hz, 3 H, CH_3), 1.24 (t, J = 7.3 Hz, 3 H, CH_3); HRMS m/z calcd for $C_{31}H_{40}N_5O_7$ (MH^+) 594.2927, found 594.2932.

Diethyl *N*-[4-[3-[2-(Pivaloylamino)-3,4,5,6,7,8-hexahydro-4-oxo-5-deazapteridin-6-yl]propyl]benzoyl]-L-glutamate (22b). This compound was prepared from 0.15 g of **21b** and 0.45 g (3.0 wt equivalent) of 5% palladium on carbon as described previously for the preparation of **22a**, yield 0.15 g (quantitative) of **22b** as a white microcrystalline solid: mp 196-197 °C; ^1H NMR ($CDCl_3$) δ 8.67 (b s, 1 H, (3)-H), 7.73, 7.25 (AA'BB', 4 H, Ar), 7.09 (d, J = 7.5 Hz, 1 H, NH), 4.94 (b s, 1 H, (8)-NH), 4.82 (m, 1 H, $CHCO_2Et$), 4.25 (q, J = 4.1 Hz, 2 H, CO_2CH_2), 4.12 (q, J = 7.1 Hz, 2 H, CO_2CH_2), 1.71-3.36 (m, 13 H, 2° aliphatic), 1.62 (s, 9 H, $C(CH_3)_3$), 1.32 (t, J = 7.1 Hz, 3 H, CH_3), 1.23 (t, J = 7.1 Hz, 3 H, CH_3); HRMS m/z calcd for $C_{31}H_{43}N_5O_7$ (M^+) 597.3162, found 597.2816. Anal. Calcd for $C_{31}H_{43}N_5O_7$: C, 62.29; H, 7.25; N, 11.72. Found: C, 62.07; H, 7.07; N, 11.48.

***N*-[4-[3-(2-Amino-3,4,5,6,7,8-hexahydro-4-oxo-5-deazapteridin-6-yl)propyl]benzoyl]-L-glutamic Acid (HDDATHF) (1b).** This compound was prepared from 0.16 g of **22b** and 40 mL of 1 N sodium hydroxide as described previously for the preparation of **1a** from **22a**,[9] yield 0.09 g (75%) of **1b** as a white solid: mp >250 °C; ^1H NMR (TFA-*d*, DMSO-d_6) δ 7.31, 6.93 (AA'BB', 4 H, Ar), 4.58 (m, 1 H, $CHCO_2H$), 3.19 (m, 1 H, (6)-H), 2.68 (t, J = 9.5 Hz, 2 H, benzyl), 1.47-2.48 (m, 8 H, 2° aliphatic), 1.35 (m, 2 H, 2° aliphatic), 1.04 (m, 2 H, 2° aliphatic); HRMS m/z calcd for $C_{22}H_{28}N_5O_6$ (MH^+) 458.1961, found 458.2011. Anal. Calcd for $C_{22}H_{27}N_5O_6$: C, 57.76; H, 5.95; N, 15.31. Found: C, 57.87; H, 5.94; N, 15.12.

Acknowledgment. We are indebted to Eli Lilly & Company both for financial support and for the in vitro cytotoxicity studies cited.

Registry No. **1a**, 95693-76-8; **1b**, 124018-99-1; **3**, 56-06-4; **7a**, 927-74-2; **7b**, 5390-04-5; **8**, 619-42-1; **9a**, 123910-86-1; **9b**, 123910-87-2; **10a**, 123910-88-3; **10b**, 123910-89-4; **11a**, 106200-41-3; **11b**, 123910-90-7; **12a**, 123910-83-8; **12b**, 126295-73-6; **13a**, 123910-84-9; **13b**, 123910-85-0; **14a**, 126295-74-7; **14b**, 126295-75-8; **17a**, 123910-81-6; **17b**, 123910-82-7; **18a**, 123910-91-8; **18b**, 123910-92-9; **19a**, 126295-76-9; **19b**, 126295-77-0; **20a**, 123910-93-0; **20b**, 123910-94-1; **21a**, 123910-95-2; **21b**, 123910-96-3; **22a**, 116387-28-1; **22b**, 123910-97-4; GAR TFase, 9032-02-4; $CH_2(CN)_2$, 109-77-3; $HC(OEt)_3$, 122-51-0; H-Glu(OEt)-OEt·HCl, 1118-89-4; pivalic anhydride, 1538-75-6.

Reactions of Oximes with Thianthrene Cation Radical in Nitrile Solvents. Cycloaddition To Form Oxadiazoles and Deoxygenation To Form Nitriles

Shishue Chiou, A. K. M. M. Hoque, and Henry J. Shine*

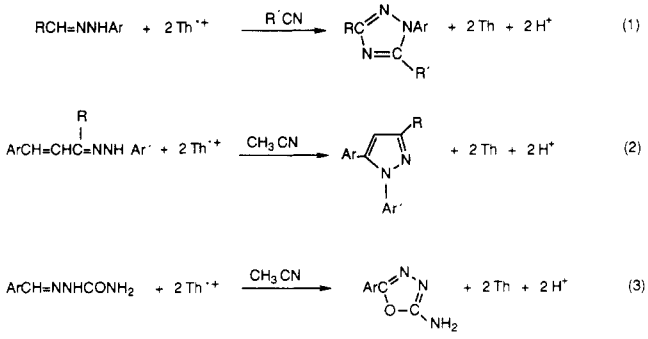
Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409

Received October 31, 1989

Reactions of eight oximes, RCH=NOH (**1a**, R = C_6H_5; **1b**, R = 4-$CH_3C_6H_4$; **1c**, R = 4-$NO_2C_6H_4$; **1d**, R = 4-$CH_3OC_6H_4$; **1e**, R = 2-$CH_3OC_6H_4$; **1f**, R = 1-naphthyl; **1g**, R = C_5H_{11}; **1h**, R = C_4H_9), with thianthrene cation radical perchlorate ($Th^{\bullet+}ClO_4^-$) in acetonitrile under argon were studied. The major product from the oxime in all cases, but of **1d**, was the nitrile, RCN. The anticipated product of oxidative cycloaddition, namely, a 3-R-5-methyl-1,2,4-oxadiazole (**2**), was obtained in substantial yield (**2d**, 66%) only in the case of **1d**. An isomeric 5-R-3-methyl-1,2,4-oxadiazole (**3**) was obtained from some reactions, that is, **3c** alone from **1c**, and a mixture of **2a** and **3a** from **1a**. Neither **2** nor **3** was obtained in measurable amounts from reactions of **1g** and **1h**. The aldehyde (RCHO) was obtained in small yields from each reaction. Thianthrene (Th) and thianthrene 5-oxide (ThO) were also major products. Studies with [^{18}O]-**1b** and [^{18}O]-**1d** showed that the oxygen atom in **2** came entirely and in ThO primarily from the oxime. Studies of workup with $H_2{}^{18}O$ showed that the workup water was the source of the oxygen atom in RCHO and to a small extent in ThO. Explanations are given for the formation of **2** by a stepwise addition of $RCH{=}NOH^{\bullet+}$ ($\mathbf{1}^{\bullet+}$) to solvent nitrile and of **3** by the reaction of solvent nitrile with an oxaziridine cation radical (**7**, obtained from $\mathbf{1}^{\bullet+}$).

Introduction

Earlier reports from this laboratory have described oxidative cycloadditions of aldehyde arylhydrazones to nitrile solvents, and oxidative intramolecular cyclizations of arylhydrazones of chalcones and benzalacetones, achieved by reaction with thianthrene cation radical ($Th^{\bullet+}$). Products of these reactions, obtained in excellent yields, were 1,2,4-triazoles (eq 1)[1-3]and pyrazoles (eq 2).[4] The cation radical was reduced to thianthrene (Th). Cyclizations of araldehyde semicarbazones into (mainly) 2-amino-1,3,4-oxadiazoles (eq 3) have been similarly achieved.[5] In each of these reactions the presence of a pyridine base, either 2,6-di-*tert*-butyl- or 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), enhanced the reaction but did not change its course. We report now the reactions of some aldoximes (**1**, RCH=NOH) in acetonitrile. Cycloaddition, with formation of oxadiazoles, is by no means the rule. The major trend is toward the formation of nitriles (RCN), a trend which is magnified by carrying out reaction in the presence of DTBMP.



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0022-3263/90/1955-3227$02.50/0