Pteridines. 48. Utilization of 3,3-Dimethoxy-2-pyrrolidinopropene for the Synthesis of Folic Acid, $N^{2'}$-Acetyl-7-folic Acid, and 5-Deaza-7-folic Acid[1a,b]

Edward C. Taylor*[1c] and Donald J. Dumas[1d]

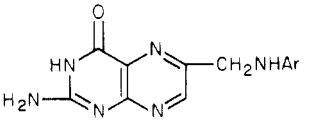
Department of Chemistry, Princeton University, Princeton, New Jersey 08544

Received October 28, 1980

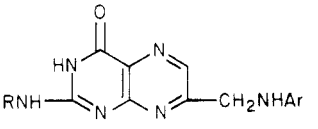
3,3-Dimethoxy-2-pyrrolidinopropene (**7**) is shown to be a useful intermediate for the synthesis of 6-formylpterin (**1**), 7-formylpterin (**8**), and 5-deaza-7-formylpterin (**9**). Thus, treatment of **7** with nitrosyl chloride followed by hydrolysis gives 1,1-dimethoxy-3-oximino-2-propanone (**3**) which with aminomalononitrile (**13**) provides 2-amino-3-cyano-5-(dimethoxymethyl)pyrazine 1-oxide (**14**), an established precursor of **1**, by way of its deoxygenation product, 2-amino-3-cyano-5-(dimethoxymethyl)pyrazine (**4**). Reaction of **7** first with *O*-tosyloximinomalononitrile (**15**) and then with ammonia furnishes 2-amino-3-cyano-6-(dimethoxymethyl)pyrazine (**17**), which is converted to **8** by guanidine cyclization to 2,4-diamino-7-(dimethoxymethyl)pteridine (**18**), alkaline hydrolysis to 7-(dimethoxymethyl)pterin (**19**), and acidic cleavage of the acetal grouping. Reaction of **7** with (methoxymethylene)malononitrile (**20a**) followed by cyclization with ammonia gives 2-amino-3-cyano-6-(dimethoxymethyl)pyridine (**22**); guanidine cyclization followed by successive treatment with aqueous base and aqueous acid then furnishes **9**. Aldehydes **8** and **9** are converted to $N^{2'}$-acetyl-7-folic acid (**10a**) and 5-deaza-7-folic acid (**11**), respectively. Nitrosation of 3,3-dimethoxy-1-pyrrolidinopropene (**38**), followed by hydrolysis and reaction with **13**, gives 2-amino-3-cyano-6-(dimethoxymethyl)pyrazine 1-oxide (**43**) in low yield. Reaction of **38** with **15** followed by treatment with ammonia provides an alternative route to **4**, while condensation of **38** with (ethoxymethylene)malononitrile (**20b**) followed by treatment with ammonia leads to 2-amino-3-cyanopyridine (**45**) by means of an unusual deformylation reaction.

Our continuing interest in the synthesis of 6-formylpterin (**1**),[1a,2,3] a useful precursor to folic acid (**2**)[4-6] and related pteridines,[4-11] led us to seek a convenient route to 1,1-dimethoxy-3-oximino-2-propanone (**3**). Utilization of this α-oximino ketone in our unequivocal pteridine synthesis[12-14] would provide direct access to 2-amino-3-cyano-5-(dimethoxymethyl)pyrazine (**4**), which may be readily converted to **1**[3] (see Scheme I). Since α-oximation of methyl ketones (e.g., pyruvaldehyde dimethyl acetal, **5**) is not a facile process,[15] some means of activation of the methyl ketone is required. A commonly employed approach to this problem involves conversion to the corresponding β-keto ester followed by oximation and decarboxylation, but previous efforts to convert the readily available β-keto ester **6**[16] to **3** failed.[1a]

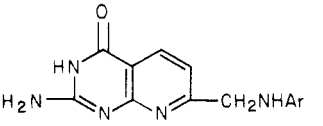
We describe in this paper the preparation of **3** from 3,3-dimethoxy-2-pyrrolidinopropene (**7**, the pyrrolidine enamine of pyruvaldehyde dimethyl acetal), the utilization of **3** and **7** for the synthesis of 6-formylpterin (**1**), 7-formylpterin (**8**), and 5-deaza-7-formylpterin (**9**), and the conversion of aldehydes **8** and **9** to the isomerically pure, stable folic acid analogues $N^{2'}$-acetyl-7-folic acid (**10a**) and



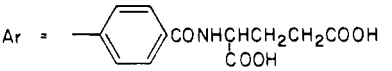
2



10a, R = $COCH_3$
b, R = H



11



5-deaza-7-folic acid (**11**), respectively. 7-Folic acid (**10b**) has been claimed[17] to be a folate antagonist and described[18] as "very unstable both in the solid state as the free acid or in an alkaline solution". 5-Deaza-7-folic acid (**11**) is unexpectedly stable and is of particular interest in the light of the attention which has recently been given to the biological properties of 5-deazapteridines.[19-24]

(1) (a) For the previous paper in this series, see: Taylor, E. C.; Dumas, D. J. *J. Org. Chem.* **1980**, *45*, 2485-2489. (b) We are indebted to F. Hoffmann-La Roche & Co., Ltd., and to the National Cancer Institute, National Institutes of Health (Grant 1 R01 CA28351-01), for support of this work. (c) John Simon Guggenheim Memorial Fellow, 1979-1980. (d) Recipient of an American Can Company Predoctoral Fellowship.

(2) Taylor, E. C.; Lenard, K. *Justus Liebigs Ann. Chem.* **1969**, *726*, 100-102.

(3) Taylor, E. C.; Henrie R. N., II; Portnoy, R. C. *J. Org. Chem.* **1978**, *43*, 736-737.

(4) Sletzinger, M.; Reinhold, D.; Grier, J.; Beachem, M.; Tishler, M. *J. Am. Chem. Soc.* **1955**, *77*, 6365-6367.

(5) Khalifa, E.; Sengupta, P. K.; Bieri, J. H.; Viscontini, M. *Helv. Chim. Acta* **1976**, *59*, 242-247.

(6) Bieri, J. H.; Viscontini, M. *Helv. Chim. Acta* **1973**, *56*, 2905-2911.

(7) Plante, L. T. *J. Org. Chem.* **1971**, *36*, 860-861.

(8) Viscontini, M.; Bieri, J. *Helv. Chim. Acta* **1971**, *54*, 2291-2297.

(9) Khalifa, E.; Bieri, J. H.; Viscontini, M. *Helv. Chim. Acta* **1973**, *56*, 2911-2919.

(10) Sengupta, P. K.; Bieri, J. H.; Viscontini, M. *Helv. Chim. Acta* **1975**, *58*, 1374-1379.

(11) Nakahara, Y.; Sekikawa, I.; Kakimoto, S. *J. Heterocycl. Chem.* **1975**, *12*, 1073-1076.

(12) Taylor, E. C.; Lenard, K. *J. Am. Chem. Soc.* **1968**, *90*, 2424-2425.

(13) Taylor, E. C.; Perlman, K. L.; Sword, I. P.; Sequin-Frey, M.; Jacobi, P. A. *J. Am. Chem. Soc.* **1973**, *95*, 6407-6412.

(14) Taylor, E. C.; Perlman, K. L.; Kim, Y.-H.; Sword, I. P.; Jacobi, P. A. *J. Am. Chem. Soc.* **1973**, *95*, 6413-6418.

(15) Touster, O. *Org. React.* **1953**, *7*, 330-336.

(16) Secrist, J. A., III; Hickey, C. J.; Norris, R. E. *J. Org. Chem.* **1977**, *42*, 525-527.

(17) Avakian, S.; Martin, G. J. U.S. Patent 2620340; *Chem. Abstr.* **1953**, *47*, 10014.

(18) Waller, C. W.; Fahrenbach, M. J.; Boothe, J. H.; Angier, R. B.; Hutchings, B. L.; Mowat, J. H.; Poletto, J. F.; Semb, J. *J. Am. Chem. Soc.* **1952**, *74*, 5405-5407.

(19) Hurlbert, B. S.; Ferone, R.; Herrmann, T. A.; Hitchings, G. H.; Barnett, M.; Bushby, S. R. M. *J. Med. Chem.* **1968**, *11*, 711-717.

(20) Elslager, E. F.; Davoll, J. *Lect. Heterocycl. Chem.* **1974**, *2*, 120-121.

(21) Rosowsky, A.; Papathanasopoulos, N. *J. Med. Chem.* **1974**, *17*, 1272-1276.

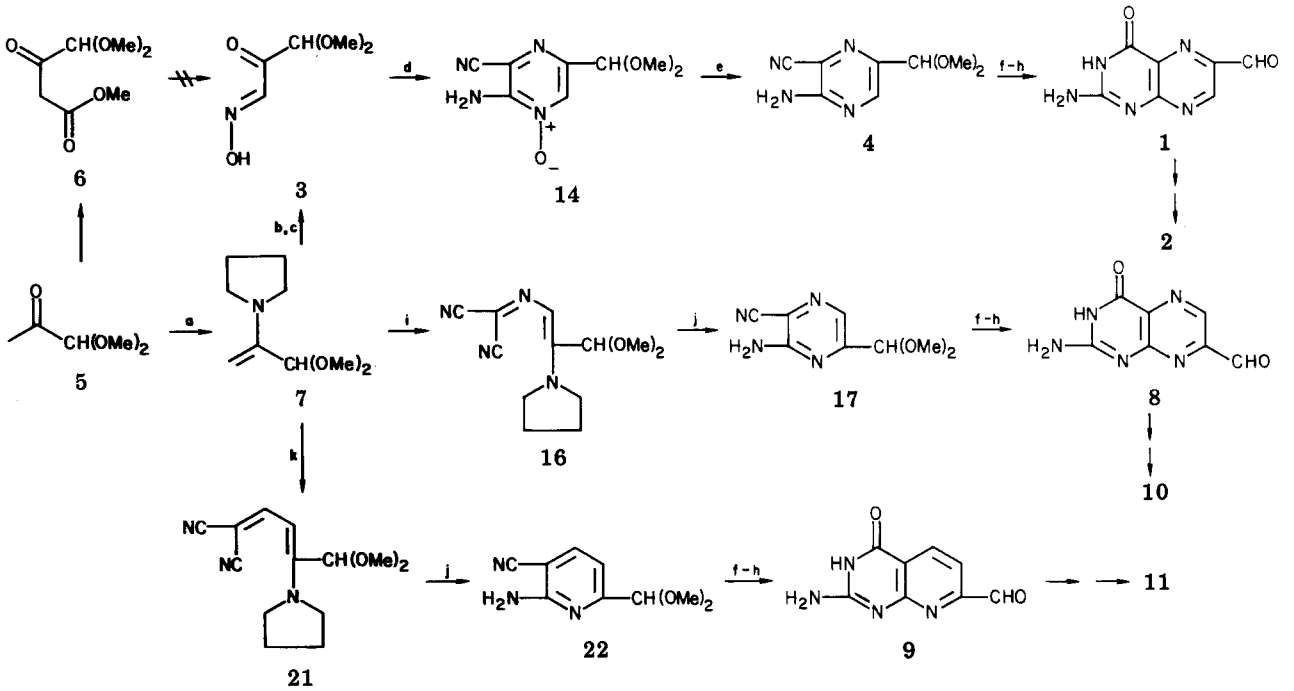
(22) Srinivasan, A.; Fagerness, P. E.; Broom, A. D. *J. Org. Chem.* **1978**, *43*, 828-834.

(23) Moad, G.; Luthy, C. L.; Benkovic, P. A.; Benkovic, S. J. *J. Am. Chem. Soc.* **1979**, *101*, 6068-6076.

(24) Vargo, D.; Jorns, M. S. *J. Am. Chem. Soc.* **1979**, *101*, 7623-7626 and references cited therein.

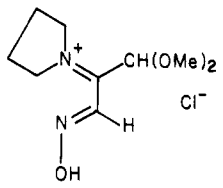
0022-3263/81/1946-1394$01.25/0

Scheme I[a]



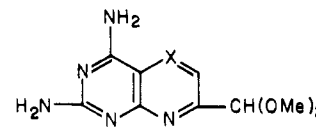
[a] a, pyrrolidine, $MgSO_4$, Et_2O; b, NOCl, THF; c, H_2O; d, $(NC)_2CHNH_2 \cdot TsOH$ (13); e, $P(OMe)_3$, Δ; f, $(H_2N)_2C=NH$, RONa, ROH, Δ; g, NaOH, H_2O, Δ; h, HCl, H_2O, Δ; i, $(NC)_2C=NOTs$ (15), pyr.; j, NH_3, MeOH; k, $(NC)_2C=CHOMe$ (20a).

The pyrrolidine enamine 7 was readily prepared in 70% yield by treatment of 5 with an excess of pyrrolidine in the presence of $MgSO_4$ or K_2CO_3.[25,26] Treatment of a solution of 7 in dry tetrahydrofuran with nitrosyl chloride at −50 °C led to the immediate formation of a white precipitate, presumably the chloride salt 12, which on careful hydrolysis provided 1,1-dimethoxy-3-oximino-2-propanone (3) in 47% yield as a golden oil. Addition of 3 to an ice-cold, concentrated solution of aminomalononitrile tosylate[27] (13) in methanol led to the direct separation of crystalline 2-amino-3-cyano-5-(dimethoxymethyl)pyrazine 1-oxide (14) in 57% yield. Since this compound has previously been converted to pyrazine 4 on heating with trimethyl phosphite,[1a] its preparation formally completes a new and abbreviated synthesis of 6-formylpterin (1).

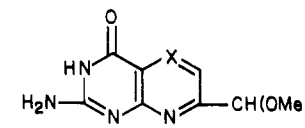


12

Reaction of enamine 7 with the *O*-tosyl derivative of oximinomalononitrile[28,29] (15) provided (*Z*)-azadiene 16 in 44% yield as a yellow, crystalline solid.[30] Brief treatment of 16 with methanolic ammonia[31] gave 2-amino-3-cyano-6-(dimethoxymethyl)pyrazine (17) in 85% yield. Conversion of 17 to 7-formylpterin (8) was then carried out by using standard procedures.[3] Thus, guanidine cyclization to 2,4-diamino-7-formylpteridine dimethyl acetal (18, 71% yield), hydrolysis with aqueous sodium hydroxide to 7-formylpterin dimethyl acetal (19, 90% yield), and treatment with 1 N hydrochloric acid gave 8 in quantitative yield. This synthesis represents the first unequivocal preparation of 7-formylpterin[32] (8).



18, X = N
23, X = CH

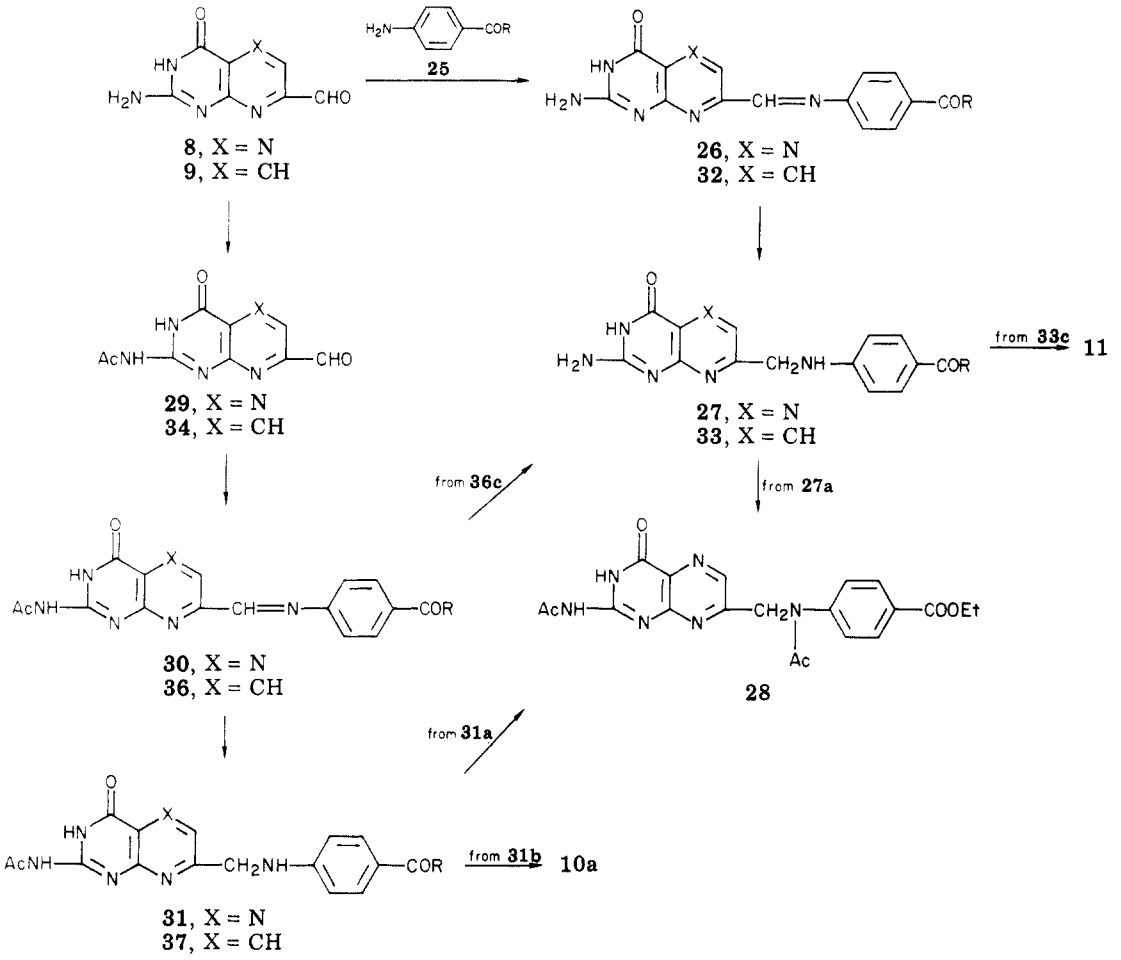


19, X = N
24, X = CH

Efforts were then directed toward an analogous synthesis of 5-deaza-7-formylpterin (9). Reaction of enamine 7 with (methoxymethylene)malononitrile (20a) according to the procedure of Kurihara and Mishima[33] provided butadiene 21 in 80% yield.[34] Reaction of this material with methanolic ammonia furnished 22 (93% yield) which, however, proved to be surprisingly unreactive with guanidine under normal conditions (refluxing in methanolic sodium methoxide). However, the successful conversion of 22 to 23 (65% yield) was achieved by refluxing for 24 h in 1-butanol. Compound 23 was then converted in a straight-

(25) Cook, A. G., Ed. "Enamines: Synthesis, Structure and Reactivity"; Marcel Dekker: New York, 1969; p 56–59.
(26) Zoretic, P. A.; Barcelos, F.; Branchard, B. *Org. Prep. Proced. Int.* **1976**, *8*, 211–214.
(27) Ferris, J. P.; Sanchez, R. A.; Mancuso, R. W. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 32–35.
(28) Biehler, J.-M.; Perchais, J.; Fleury, J.-P. *Bull. Soc. Chim. Fr.* **1971**, 2711–2716.
(29) Schoeni, J. P.; Fleury, J.-P. *Tetrahedron* **1975**, *31*, 671–678.
(30) Schoeni and Fleury[29] observed that the IR spectra of azadienes which were constrained to exist in the *Z* configuration always displayed an absorption band below 1590 cm^{-1}, while those in the *E* configuration (usually because of steric considerations) displayed an absorption band above 1610 cm^{-1}. The corresponding IR absorption band of compound 16 is at 1568 cm^{-1}.
(31) Lang, M.; Fleury, J.-P. *Tetrahedron Lett.* **1974**, 3967–3970.
(32) For previous syntheses of this material by ambiguous condensation reactions, see: (a) Petering, H. G.; Weisblat, D. I. *J. Am. Chem. Soc.* **1947**, *69*, 2566–2567; (b) Petering, H. G. U.S. Patent 2541717; *Chem. Abstr.* **1951**, *45*, 6224.
(33) Kurihara, H.; Mishima, M. *J. Heterocycl. Chem.* **1977**, *14*, 1077–1079.
(34) A five-step synthesis of a similar butadiene derivative, 1,1-dicarbethoxy-4-(dimethoxymethyl)-4-(dimethylamino)butadiene, from pyruvaldehyde dimethyl acetal has recently been reported: Gompper, R.; Sobotta, R. *Tetrahedron Lett.* **1979**, 921–924.

Scheme II



a, R = OEt; b, R = L-NHCH(CO$_2$-*t*-Bu)CH$_2$CH$_2$CO$_2$-*t*-Bu; c, R = L-NHCH(CO$_2$Me)CH$_2$CH$_2$CO$_2$Me

forward manner to 5-deaza-7-formylpterin (**9**) in 85% overall yield by treatment with 5% sodium hydroxide to give 7-(dimethoxymethyl)-5-deazapterin **24**, followed by acid hydrolysis.

With aldehydes **8** and **9** now in hand, attention was turned to the synthesis of the corresponding folic acid analogues by pathways patterned after the well-studied conversion of 6-formylpterin (**1**) to folic acid (**2**).[4-6] In each case, the desired reaction sequence was first examined by using the condensation of the appropriate aldehyde with ethyl *p*-aminobenzoate (**25a**) as a model.

Thus, 7-formylpterin (**8**) was condensed with **25a** in refluxing dimethylformamide to give the Schiff base **26a** in 93% yield (see Scheme II). Sodium borohydride reduction of **26a** gave ethyl 7-pteroate (**27a**) as a bright yellow solid which decomposed rapidly on exposure to air. This instability of **27a** is consistent with the reported instability of 7-folic acid (**10b**, vide supra). However, immediate treatment of **27a** with acetic anhydride provided the colorless, air-stable diacetyl derivative **28** in 38% yield.

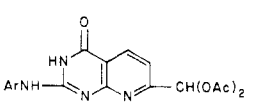
An attempted condensation of di-*tert*-butyl *p*-aminobenzoyl-L-glutamate (**25b**) with **8** in refluxing dimethylformamide led to decomposition of **25b** rather than imine formation, while the use of milder conditions (refluxing ethanol) gave no reaction. Since the failure of **8** to react under these conditions appeared to be a result of its insolubility, it was converted to $N^{2'}$-acetyl-7-formylpterin (**29**) with refluxing acetic anhydride (88% yield). This latter compound readily condensed with ethyl *p*-aminobenzoate (**25a**) to give the Schiff base **30a** (78% yield), which was smoothly reduced with sodium borohydride to ethyl $N^{2'}$-acetyl-7-pteroate (**31a**) (76% yield). Treatment of this material with acetic anhydride provided an alternate route to the diacetate **28**.

The L-glutamate side chain was then successfully carried through this latter sequence. Thus, condensation of **25b** with aldehyde **29** in refluxing ethanol to the Schiff base **30b** (76% yield), sodium borohydride reduction to **31b** (50% yield), and cleavage of the *tert*-butyl ester groupings with trifluoroacetic acid provided $N^{2'}$-acetyl-7-folic acid (**10a**) in a nonoptimized yield of 37%.[35]

Heating 5-deaza-7-formylpterin (**9**) with ethyl *p*-aminobenzoate (**25a**; see Scheme II) at 150 °C furnished the imine **32a** (86% yield). Sodium borohydride reduction of this compound provided ethyl 5-deaza-7-pteroate (**33a**) in 88% yield as an air- and base-stable, pale yellow solid. Acetylation of **9** gave the $N^{2'}$-acetyl derivative **34** (80% yield),[36] which was heated with ethyl *p*-aminobenzoate

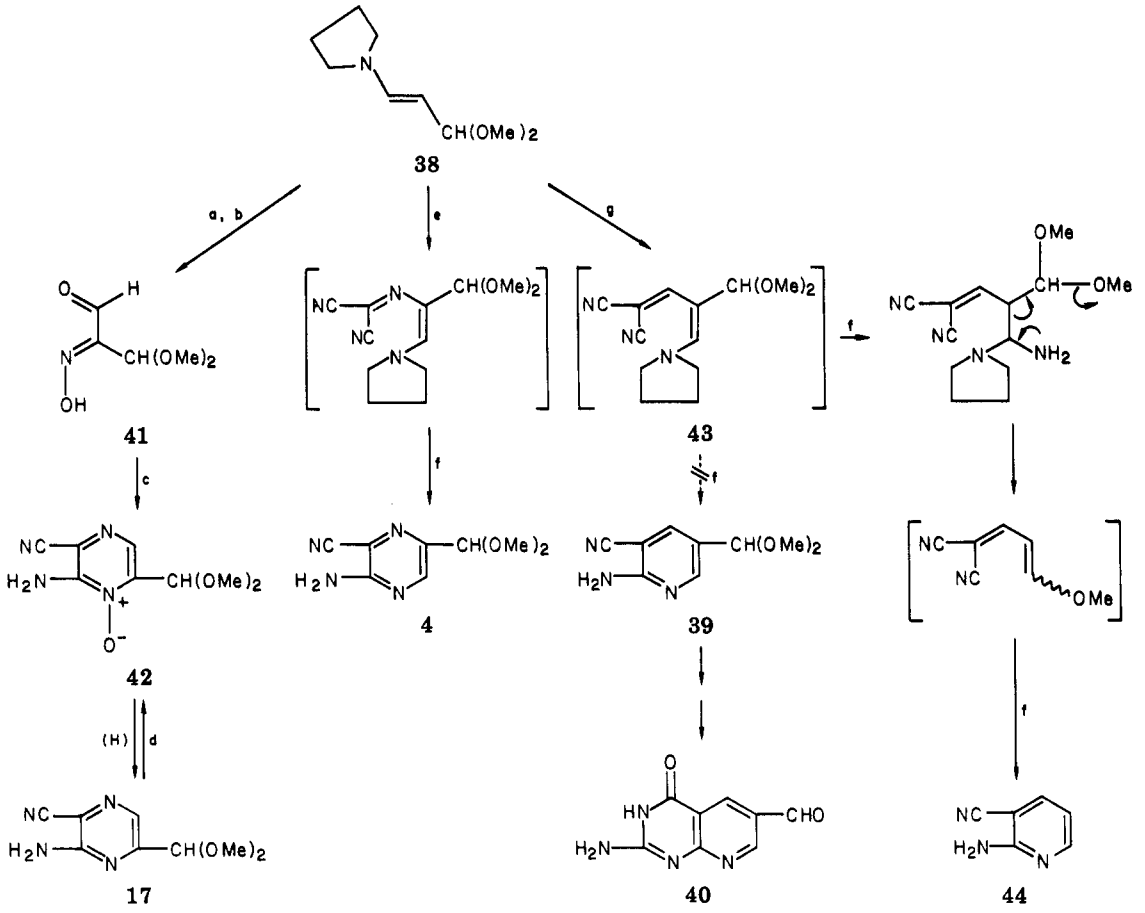
(35) Taylor, E. C.; Henrie, R. N., II; Dumas, D. J. "Chemistry and Biology of Pteridines"; Kisliuk, R. L., Brown, G. M., Eds.; Elsevier North Holland, Inc.: New York, 1979; p 71–75.

(36) Heating **9** with acetic anhydride under reflux led to the formation in significant amounts (up to 17% after 2 h of reflux) of $N^{2'}$-acetyl-5-deaza-7-(diacetoxymethyl)pterin (**i**) [mp (acetonitrile) 246–248 °C. Anal. Calcd for $C_{14}H_{14}N_4O_6$: C, 50.30; H, 4.22; N, 16.76. Found: C, 50.20; H, 4.02; N, 16.71]. However, the formation of this byproduct could be almost completely repressed by carrying out the acetylation at 100 °C for 1.5 h.



i

Scheme III[a]



[a] a, NOCl, THF; b, H_2O; c, $(NC)_2CHNH_2 \cdot TsOH$ (13); d, MCPBA, CH_2Cl_2; e, $(NC)_2C{=}NOTs$ (15); f, NH_3, MeOH; g, $(NC)_2C{=}CHOEt$.

(25a) in dimethyl sulfoxide at 100 °C to afford the Schiff base 36a (84% yield). Sodium borohydride reduction of this material then gave ethyl N^2-acetyl-5-deaza-7-pteroate (37a) in 75% yield.

This procedure was then utilized for the synthesis of 5-deaza-7-folic acid (11). Reaction of aldehyde 34 with dimethyl *p*-aminobenzoyl-L-glutamate (25c) in refluxing methanol gave 36c in 41% yield. Sodium borohydride reduction of 36c was unusual in that reduction of the imine bond was accompanied by cleavage of the N^2-acetyl group. Thus, addition of 36c to a methanolic solution of sodium borohydride under a continuous flow of nitrogen and stirring for 3 h at room temperature gave the dimethyl ester of 5-deaza-7-folic acid (33c) in 82% yield as a pale yellow powder. Finally, heating a slurry of 33c in 0.1 N sodium hydroxide to 80 °C under nitrogen, followed by acidification to pH 1.7 with 6 N hydrochloric acid and cooling,[6] gave 5-deaza-7-folic acid (11) in 66% yield.

These successful applications of enamine 7 to the synthesis of 7-substituted pteridines and 7-substituted 5-deazapteridines prompted us to examine the isomeric enamine, 3,3-dimethoxy-1-pyrrolidinopropene (38),[37,38] for its possible utility as an intermediate for the preparation of 4 and 17, as well as for the preparation of 2-amino-3-cyano-5-(dimethoxymethyl)pyridine (39), a potential precursor to 5-deaza-6-formylpterin (40; see Scheme III). Reaction of 38 with nitrosyl chloride in tetrahydrofuran, followed by hydrolysis and extraction, gave an impure light yellow oil whose NMR spectrum (δ 9.7 and 10.0) showed it to contain, inter alia, a mixture of the syn and anti isomers of the desired α-oximino aldehyde 41. Treatment of this crude oil with aminomalononitrile tosylate (13) gave a complex mixture of products which did, however, contain the desired 2-amino-3-cyano-6-(dimethoxymethyl)pyrazine 1-oxide (42; by TLC comparison with authentic material prepared by oxidation of 17 with *m*-chloroperbenzoic acid). However, no further effort was expended on this approach to 17, since a more satisfactory route from the enamine 7 was already available.

Reaction of 2 equiv of enamine 38 with the *O*-tosyl derivative of oximinomalononitrile (15), followed by treatment with ammonia, provided 2-amino-3-cyano-5-(dimethoxymethyl)pyrazine (4) in 31% yield. Finally, condensation of enamine 38 with (ethoxymethylene)malononitrile (20b) to 43, followed by addition of methanolic ammonia, surprisingly gave 2-amino-3-cyanopyridine (44), with (apparent) loss of the 5-dimethoxymethyl substituent, rather than the anticipated 2-amino-3-cyano-5-(dimethoxymethyl)pyridine[39] (39). A possible mechanism for this unexpected transformation is outlined in Scheme III.

These studies demonstrate the versatility of the simple enamines 7 and 38 for the unequivocal synthesis of pteridines and 5-deazapteridines. Further synthetic applications of this methodology are under investigation.

(37) Bredereck, H.; Effenberger, F.; Zeyfang, D.; Hirsch, K.-A. *Chem. Ber.* **1968**, *101*, 4036–4047.
(38) Brit. Patent 769,652; *Chem. Abstr.* **1957**, *51*, P12986.
(39) The synthesis of a similar compound, 2-bromo-3-cyano-5-formylpyridine ethylene glycol acetal, has recently been reported: Ponticello, G. S.; Baldwin, J. J. *J. Org. Chem.* **1979**, *44*, 2702–2704.

Experimental Section

Melting points are uncorrected and were recorded on a Thomas-Hoover apparatus. Infrared spectra were recorded on a Perkin-Elmer 467 grating spectrometer. NMR data were obtained on a Varian A-60A or Perkin-Elmer R32 instrument, using Me_4Si as internal standard. Optical rotations were determined by using a Perkin-Elmer 141 polarimeter with an operating temperature of 31 °C. UV spectra were recorded on a Cary 11 spectrophotometer.

3,3-Dimethoxy-2-pyrrolidinopropene (7). A mixture of 23.6 g (0.2 mol) of pyruvaldehyde dimethyl acetal, 28.4 g (0.4 mol) of pyrrolidine, 6 g of anhydrous magnesium sulfate, and 90 mL of anhydrous ethyl ether was stirred mechanically at room temperature. Two-gram portions of magnesium sulfate were added at 1 h intervals for the next 7 h. The mixture was stirred an additional 5 h and then allowed to stand overnight. The magnesium sulfate was filtered off and rinsed thoroughly with ether. The solvent and excess pyrrolidine were then removed in vacuo and the residue was distilled to give 24.2 g (70%) of a colorless oil: bp 45–48 °C (0.3 mm); NMR ($CDCl_3$) δ 1.68–2.00 (m, 4 H, CH_2CH_2), 3.00–3.42 (m, 4 H, $N(CH_2)_2$), 3.30 (s, 6 H, $(OCH_3)_2$), 3.58 (s, 1 H, vinyl H), 3.87 (s, 1 H, vinyl H), 4.68 (s, 1 H, CH); IR (neat) 2950, 2890, 2840, 2820, 1608, 1440 cm^{-1}.

1,1-Dimethoxy-3-oximino-2-propanone (3). A solution of 5.1 g (30 mmol) of **7** in 50 mL of dry THF was cooled to −50 °C and 1.9 mL (33 mmol) of condensed nitrosyl chloride added dropwise with mechanical stirring. After 5 min the mixture was diluted with 75 mL of anhydrous ethyl ether and allowed to warm to 0 °C. The solid product was filtered off and rinsed with ether. The filter cake, which was always kept wet with ether, was transferred to a beaker and covered with 150 mL of ether. Water (10 mL) was added with stirring until all of the solid dissolved. The ether layer was decanted and the residue extracted with ether (50 mL followed by 25 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed in vacuo to leave 2.1 g (47%) of a golden oil which was suitable for use in the next step. Refrigeration of this material resulted in the crystallization of a white solid. Drying on a clay plate gave 0.4 g (10%) of analytically pure white needles: mp 49–52 °C; NMR ($CDCl_3$) δ 3.46 (s, 6 H, $(OCH_3)_2$), 5.22 (s, 1 H, CH), 7.71 (s, 1 H, CH=NOH), 10.15 (br s, 1 H, NOH); IR (KBr) 3310, 2930, 2815, 1698, 1590, 1440 cm^{-1}.

Anal. Calcd for $C_5H_9NO_4$: C, 40.81; H, 6.17; N, 9.52. Found: C, 40.56; H, 5.97; N, 9.52.

2-Amino-3-cyano-5-(dimethoxymethyl)pyrazine 1-Oxide (14). A slurry of 3.04 g (12 mmol) of aminomalononitrile tosylate (**13**) in 15 mL of dry methanol was cooled in an ice bath and 1.6 g (11 mmol) of **3** was added with stirring and rinsed in with 5 mL of methanol. Once all of the material was in solution the stirring bar was removed and crystallization induced with scratching. The mixture was refrigerated for 3 h, and the product was filtered off and rinsed with a minimum of cold methanol to leave 1.33 g (57%) of fluffy white needles, mp 91.5–94 °C (lit.[1a] mp 93.5–94.5 °C), identical with authentic material.

(*Z*)-(3,3-Dimethoxy-2-pyrrolidino-1-propenyl)iminopropanedinitrile (16). A solution of 5.92 g (20 mmol) of *O*-tosyloximinomalononitrile (**15**) and 1.8 mL of pyridine in 200 mL of ethyl ether was cooled to −30 °C and a solution of 3.76 g (22 mmol) of **7** in 40 mL of ether added dropwise, with stirring, over a period of 5 min. The reaction mixture was allowed to warm to −20 °C, 100 mL of water was added, and the organic layer was separated and washed successively with 60-mL portions of cold 1 N HCl, cold 10% NaOH, and cold water. After being dried ($MgSO_4$), the solution was concentrated to 50 mL and refrigerated overnight to give 2.22 g (44%) of bright yellow, chunky crystals, mp 125–127 °C. A second crystallization from ether provided the analytical sample with no change in melting point: NMR ($CDCl_3$) δ 2.00 (m, 4 H, CH_2CH_2), 3.47 (s, 6 H, $(OCH_3)_2$), 3.58 and 4.00 (m, 4 H, $N(CH_2)_2$), 6.10 (s, 1 H, CH), 7.10 (s, 1 H, vinyl CH); IR (KBr) 2180, 2175, 1568 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}N_4O_2$: C, 58.05; H, 6.50; N, 22.57. Found: C, 58.10; H, 6.50; N, 22.35.

2-Amino-3-cyano-6-(dimethoxymethyl)pyrazine (17). Method A. A solution of 14.8 g (0.05 mol) of *O*-tosyloximinomalononitrile (**15**) and 4.5 mL (0.055 mol) of pyridine in 500 mL of anhydrous ethyl ether was cooled under nitrogen to −25 °C and a solution of 9.4 g (0.055 mol) of **7** in 100 mL of ether was added dropwise over 20 min, with the temperature being kept below −20 °C. After addition was complete the mixture was stirred at −20 °C for an additional 5 min and 200 mL of saturated methanolic ammonia then added. The mixture was allowed to stir overnight with gradual warming to room temperature and filtered, the filtrate concentrated in vacuo, and the red residue partitioned between 100 mL of saturated $NaHCO_3$ and 150 mL of ether. The layers were separated, the aqueous layer was extracted with ether (2 × 50 mL), the combined organic extracts were washed with 150 mL of 1 N HCl, and the aqueous layer was backwashed with ether (2 × 50 mL). The combined organic extracts were then washed with 150 mL of 10% NaOH and dried ($MgSO_4$). The solvent was removed in vacuo to leave a light orange solid which was recrystallized from 75 mL of toluene to give 2.53 g of fine white needles, 119–121.5 °C. Treatment of the mother liquors with carbon followed by concentration to 20 mL and refrigeration provided a second crop of 1.69 g (43% total yield), mp 113–119 °C. One further recrystallization from toluene provided the analytical sample: mp 122–123 °C; NMR ($CDCl_3$) δ 3.41 (s, 6 H, $(OCH_3)_2$), 5.28 (s, 1 H, CH), 5.45 (br, 2 H, NH_2), 8.26 (s, 1 H, C-5 H); IR (KBr) 3425, 3280, 3160, 2205, 1635 cm^{-1}.

Anal. Calcd for $C_8H_{10}N_4O_2$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.18; H, 5.26; N, 28.95.

Method B. A solution of 0.25 g (1 mmol) of **16** in 5 mL of saturated methanolic ammonia was stirred at room temperature for 45 min. The solvent was then removed in vacuo, and the residue was slurried with 5 mL of toluene, heated on a steam bath for 5 min, and allowed to cool to give 0.165 g (85%) of white needles, mp 121–122 °C, identical with the material prepared by method A.

2,4-Diamino-7-formylpteridine Dimethyl Acetal (18). A solution of guanidine in methanol was prepared by dissolving 0.49 g (21 mmol) of sodium in dry methanol, followed by the addition of 2.0 g (21 mmol) of guanidine hydrochloride. To this solution was added 3.10 g (16 mmol) of **17** in 300 mL of methanol and the solution heated to reflux for 15 h. The solution was then concentrated in vacuo to approximately 25 mL and cooled to 0 °C. The product was filtered off and washed successively with cold methanol, water, methanol, and finally ether to leave 2.68 g (71%) of a yellow powder, mp 208–209.5 °C. The analytical sample was prepared by recrystallization from methanol with no change in melting point: NMR (Me_2SO-d_6) δ 3.40 (s, 6 H, $(OCH_3)_2$), 5.23 (s, 1 H, CH), 6.60 (br s, 2 H, NH_2), 7.65 (br s, 2 H, NH_2), 8.33 (s, 1 H, C-6 H); IR (KBr) 3320, 3110, 1625 cm^{-1}.

Anal. Calcd for $C_9H_{12}N_6O_2$: C, 45.76; H, 5.12; N, 35.58. Found: C, 45.68; H, 4.94; N, 35.89.

7-Formylpterin Dimethyl Acetal (19). A slurry of 2.36 g (10 mmol) of **18** and 90 mL of 5% sodium hydroxide was heated to reflux until all the starting material went into solution (approximately 5 min). The solution was then allowed to cool to room temperature and neutralized with acetic acid. The product was collected and washed successively with water, ethanol, and ether to leave 2.14 g (90%) of a pale yellow powder, mp >330 °C. The analytical sample was prepared by recrystallization from DMF: NMR (Me_2SO-d_6) δ 3.38 (s, 6 H, $(OCH_3)_2$), 5.35 (s, 1 H, CH), 6.95 (br s, 2 H, NH_2), 8.44 (s, 1 H, C-6 H); IR (KBr) 3320, 3190, 1725, 1692, 1660 cm^{-1}.

Anal. Calcd for $C_9H_{11}N_5O_3$: C, 45.57; H, 4.67; N, 29.53. Found: C, 45.44; H, 4.60; N, 29.30.

7-Formylpterin (8). A slurry of 2.14 g (9 mmol) of **19** in 54 mL of 1 N HCl was heated slowly in an oil bath to an external temperature of 110 °C and then allowed to cool slowly back to room temperature. When the solution had reached 90 °C most of the starting material had passed into solution and a bright yellow precipitate had begun to form. On cooling the yellow solid was collected, washed with water followed by ethanol, and dried in vacuo to leave 1.88 g (100%) of 7-formylpterin monohydrate, mp >330 °C. This material analyzed correctly after block drying at 130 °C: NMR (Me_2SO-d_6) δ 6.85 (br s, 2 H, NH_2), 8.55 (s, 1 H, NH), 8.75 (s, 1 H, C-6 H), 10.0 (s, 1 H, CHO); IR (KBr) 3240, 2700, 1715, 1680 cm^{-1}.

Anal. Calcd for $C_7H_5N_5O_2$: C, 43.98; H, 2.64; N, 36.64. Found: C, 43.73; H, 2.89; N, 36.45.

(*Z*)-1,1-Dicyano-4-(dimethoxymethyl)-4-pyrrolidinobutadiene (21). A solution of 10.8 g (0.10 mol) of (methoxymethylene)malononitrile (**20a**) in 100 mL of dry THF was cooled to −20 °C and a solution of 17.1 g (0.10 mol) of **7** in 100 mL of THF added dropwise over 0.5 h, with the temperature being held at −20 °C. After addition was complete the mixture was allowed to warm to 0 °C, and the yellow precipitate collected, washed with ether, and dried in vacuo to give 17.0 g of a yellow powder, mp 156–158 °C. The mother liquors were concentrated in vacuo and the residue was triturated with ether to give a dark red powder which was collected and recrystallized from methanol to give an additional 2.9 g (80% total yield) of dark yellow crystals, mp 156–158 °C. The analytical sample was prepared by recrystallization from methanol: mp 157–159 °C; NMR ($CDCl_3$) δ 1.85–2.10 (m, 4 H, CH_2CH_2), 3.42 (s, 6 H, $(OCH_3)_2$), 3.52–3.94 (m, 4 H, $N(CH_2)_2$), 5.13 (s, 1 H, CH), 5.45 (d, J = 13.5 Hz, 1 H, C-3 H), 7.75 (d, J = 13.5 Hz, 1 H, C-2 H); IR (KBr) 2202, 2195, 1565, 1443 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.14; H, 6.93; N, 16.99. Found: C, 63.06; H, 7.02; N, 16.78.

2-Amino-3-cyano-6-(dimethoxymethyl)pyridine (22). Method A. A solution of 10.8 g (0.10 mol) of (methoxymethylene)malononitrile (**20a**) in 100 mL of dry THF was cooled to −20 °C and a solution of 17.1 g (0.10 mol) of 3,3-dimethoxy-2-pyrrolidinopropene (**7**) in 90 mL of THF was added dropwise over 1 h, with the temperature being held at −20 °C. After addition was complete the mixture was allowed to warm slowly to 0 °C and 100 mL of saturated methanolic ammonia added, with the temperature being kept between 0 and −5 °C. The mixture was then allowed to stir at room temperature for 18 h. The resulting dark green solution was concentrated in vacuo, and the residue slurried with an additional 100 mL of saturated methanolic ammonia and allowed to stir at room temperature for an additional 20 h. The solvent was then removed in vacuo, the residue was warmed in 25 mL of 1-propanol and allowed to cool, and the product was collected and washed thoroughly with 1-propanol to give 14.3 g of a faintly green powder which turned light yellow on drying in vacuo at 60 °C, mp 136–139 °C. On standing the mother liquors provided an additional 0.30 g (75% total yield) of a yellow powder, mp 136–139 °C. The analytical sample was prepared by recrystallization from toluene (carbon) to give white needles: mp 137–138 °C; NMR ($CDCl_3$) δ 3.38 (s, 6 H, $(OCH_3)_2$), 5.20 (s, 1 H, CH), 5.62 (br s, 2 H, NH_2), 6.98 (d, J = 8 Hz, 1 H, C-5 H), 7.75 (d, J = 8 Hz, 1 H, C-4 H); IR (KBr) 3400, 3325, 3185, 2210, 1650, 1568 cm^{-1}.

Anal. Calcd for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 56.10; H, 5.93; N, 21.54.

Method B. A slurry of 15.7 g (63 mmol) of **21** in 100 mL of saturated methanolic ammonia was stirred at room temperature for 11 h. The solvent was then removed in vacuo, and the residue was slurried with 100 mL of 1-propanol and warmed on a steam bath for a few minutes to break up the solid product. The mixture was allowed to cool and refrigerated overnight. The product was then collected, washed with cold 1-propanol and dried in vacuo to give 11.45 g (93%) of a white powder, mp 135–137 °C, identical with the material prepared by method A.

2,4-Diamino-7-(dimethoxymethyl)-5-deazapteridine (23). A solution of guanidine in 1-butanol was prepared by dissolving 0.89 g (38.5 mmol) of sodium in 200 mL of 1-butanol followed by the addition of 3.35 g (35 mmol) of guanidine hydrochloride. After the mixture was stirred for 3 h the precipitated sodium chloride was removed by filtration and rinsed with 50 mL of 1-butanol. To this solution was then added 3.86 g (20 mmol) of **22** along with an additional 150 mL of 1-butanol. The mixture was then heated to reflux for 24 h under nitrogen, filtered hot, allowed to cool to room temperature, and then refrigerated to give 3.08 g (65%) of fine white needles, mp 223–224 °C. Recrystallization from 1-butanol provided the analytical sample without any change in the melting point: NMR (Me_2SO-d_6) δ 3.33 (s, 6 H, $(OCH_3)_2$), 5.18 (s, 1 H, CH), 6.25 (br s, 2 H, NH_2), 7.10 (d, J = 8 Hz, 1 H, C-6 H), 7.50 (br s, 2 H, NH_2), 8.42 (d, J = 8 Hz, 1 H, C-5 H); IR (KBr) 3380, 3320, 3150, 1632, 1602 cm^{-1}.

Anal. Calcd for $C_{10}H_{13}N_5O_2$: C, 51.05; H, 5.57; N, 29.77. Found: C, 51.03; H, 5.53; N, 29.78.

5-Deaza-7-(dimethoxymethyl)pterin (24). A slurry of 2.35 g (10 mmol) of **23** in 90 mL of 5% sodium hydroxide was heated at reflux until all of the starting material passed into solution. The solution was then allowed to cool to room temperature and 7 mL of acetic acid added in one portion with stirring. Once the mixture had cooled back to room temperature, the precipitate was collected, washed thoroughly with water, and dried in vacuo to give 2.27 g (96%) of a white solid. The analytical sample was prepared by recrystallization from DMF to give a white powder which slowly decomposed on heating above 300 °C; IR (KBr) 3230, 3190, 3050, 1675, 1590 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.72. Found: C, 50.58; H, 5.37; N, 24.00.

5-Deaza-7-formylpterin (9). A slurry of 2.25 g (9.5 mmol) of **24** in 120 mL of 1 N HCl was heated to 85 °C (bath temperature). The resulting yellow solution was then allowed to cool to room temperature and cooled in an ice bath and 100 mL of saturated sodium bicarbonate was added. The resulting voluminous precipitate was collected by filtration, washed with water followed by ethanol, and dried in vacuo to give 1.77 g (89%; monohydrate) of a yellow solid. The compound slowly decomposed on heating above 300 °C and was block dried prior to analysis. NMR (Me_2SO-d_6) δ 7.75 (d, J = 8 Hz, 1 H, C-6 H), 8.48 (d, J = 8 Hz, 1 H, C-5 H), 9.89 (s, 1 H, CHO); IR (KBr) 3300, 3250, 3100, 1680, 1580 cm^{-1}.

Anal. Calcd for $C_8H_6N_4O_2 \cdot 0.12H_2O$: C, 49.96; H, 3.21; N, 29.13; H_2O, 1.10. Found: C, 49.85; H, 3.47; N, 29.38; H_2O, 1.09.

7-[[(4-Carbethoxyphenyl)imino]methyl]pterin (26a). A slurry of 0.10 g (0.48 mmol) of 7-formylpterin monohydrate (**8**) and 0.17 g (1 mmol) of ethyl *p*-aminobenzoate in 5 mL of DMF was heated slowly to reflux and then allowed to cool slowly back to room temperature. The product was collected by filtration, washed with DMF followed by ethanol, and dried in vacuo (110 °C) to leave 0.15 g (93%) of a yellow powder, mp >400 °C. This material analyzed correctly without further purification. Its NMR (TFA, external Me_4Si) spectrum revealed that this material consisted of a 1:3.7 mixture of the syn and anti imines:[40] δ 1.00 (br t, J = 6.5 Hz, 3 H, CH_3), 4.03 (br q, J = 6.5 Hz, 2 H, OCH_2), 6.90, 7.16 (A_2B_2, J = 8 Hz, syn) and 7.50, 7.82 (A_2B_2, J = 9 Hz, anti, 4 H, aryl), 8.72 (s, syn) and 9.10 (s, anti, 1 H, C-6 H), 9.35 (s, anti) and 9.45 (s, syn, 1 H, CH=N); IR (KBr) 3240, 3100, 1702, 1680, 1608, 1588 cm^{-1}.

Anal. Calcd for $C_{16}H_{14}N_6O_3$: C, 56.80; H, 4.17; N, 24.84. Found: C, 56.68; H, 4.09; N, 24.96.

$N^{2'}$,N^{10}-Diacetyl-7-[[(4-carbethoxyphenyl)amino]methyl]pterin (28). Method A. Ethanol (25 mL) was flushed with nitrogen and 0.06 g (1.5 mmol) of sodium borohydride added. Once all of the borohydride was in solution, 0.10 g (0.3 mmol) of **26a** was added and rinsed in with 5 mL of ethanol. The mixture was stirred under nitrogen until all of the starting material passed into solution (24 h). A solution of 1 mL of acetic acid in 9 mL of ethanol was then added dropwise to give a bright yellow precipitate, and the mixture was refrigerated overnight and then centrifuged. The supernatant was decanted and the product, which darkened on exposure to air, was washed twice with ethanol and once with acetic anhydride. The material was then slurried with acetic anhydride and heated to reflux for 0.5 h. The solvent was removed in vacuo, and the residue was triturated with ethanol, collected, and dried in vacuo to give 0.048 g (38%) of a dark yellow solid. Recrystallization from acetonitrile (carbon) provided yellow microcrystals, mp 281–282 °C. A second recrystallization from acetonitrile provided the analytical sample as a colorless solid: mp 286–287 °C; NMR (Me_2SO-d_6) δ 1.33 (t, J = 7 Hz, 3 H, CH_3), 1.98 (s, 3 H, $COCH_3$), 2.25 (s, 3 H, $COCH_3$), 4.37 (q, J = 7 Hz, 2 H, OCH_2), 5.18 (s, 2 H, CH_2N), 7.66, 8.08 (A_2B_2, J = 8.5 Hz, 4 H, aryl), 8.75 (s, 1 H, C-6 H); IR (KBr) 3140, 1698, 1658, 1598 cm^{-1}.

Anal. Calcd for $C_{20}H_{20}N_6O_5$: C, 56.60; H, 4.75; N, 19.80. Found: C, 56.76; H, 4.69; N, 19.76.

Method B. A slurry of 0.10 g (0.26 mmol) of **31a** in 10 mL of acetic anhydride was heated to reflux for 15 min. The yellow solution was allowed to cool, the solvent removed in vacuo, and the yellow solid residue recrystallized from acetonitrile to give 0.073 g (66%) of compact yellow crystals, mp 284–285 °C, identical

(40) For further examples of this type of isomerism see ref 5, 6, 8, and 9.

with the material prepared by method A.

N^2-Acetyl-7-formylpterin (29). A slurry of 0.63 g (3 mmol) of 7-formylpterin monohydrate (**8**) in 30 mL of acetic anhydride was heated under nitrogen at reflux until all of the starting material went into solution (30 min). The solution was allowed to cool to room temperature and was filtered, the filtrate was concentrated in vacuo, and the residue was triturated with ethanol to give 0.62 g (88%) of a tan solid which darkened slowly on standing at room temperature: NMR (Me_2SO-d_6) δ 2.26 (s, 3 H, $COCH_3$), 9.13 (s, 1 H, C-6 H), 10.17 (s, 1 H, CHO); IR (KBr) 3600–3040, 1650 cm^{-1}.

N^2-Acetyl-7-[[(4-carbethoxyphenyl)imino]methyl]pterin (30a). A slurry of 0.23 g (1 mmol) of **29** and 0.165 g (1 mmol) of ethyl *p*-aminobenzoate in 50 mL of ethanol was heated to reflux under nitrogen for 3.5 h. The solvent was then removed in vacuo and the residue dissolved in 25 mL of methylene chloride and allowed to stand overnight to give 0.25 g of a yellow powder, mp 280 °C dec. Concentration of the mother liquors provided a second crop of 0.05 g (78% total yield). The analytical sample was prepared by recrystallization from acetonitrile: mp 290–293 °C dec; NMR (Me_2SO-d_6) δ 1.35 (t, J = 7 Hz, 3 H, CH_3), 2.23 (s, 3 H, $COCH_3$), 4.33 (q, J = 7 Hz, 2 H, OCH_2), 7.47, 8.00 (A_2B_2, J = 8 Hz, 4 H, aryl), 8.67 (s, 1 H, C-6 H), 9.25 (s, 1 H, CH=N); IR (KBr) 3270, 3120, 1730, 1685, 1600, 1585, 1530 cm^{-1}.

Anal. Calcd for $C_{18}H_{16}N_6O_4$: C, 56.84; H, 4.24; N, 22.10. Found: C, 56.56; H, 4.16; N, 22.36.

N^2-Acetyl-7-[[(4-carbethoxyphenyl)amino]methyl]pterin (31a). Ethanol (60 mL) was flushed with nitrogen and 0.15 g (4 mmol) of sodium borohydride added. Once all the borohydride was in solution, 0.25 g (0.65 mmol) of **30a** was added. The mixture was allowed to stir at room temperature for 4 h, and the off-white precipitate was collected and washed with ethanol. The solid was then slurried with 50 mL of water and acidified with a few drops of acetic acid to give a voluminous precipitate which was collected, washed thoroughly with water, and dried in vacuo to leave 0.19 g (76%) of an off-white solid. Recrystallization from acetonitrile provided the analytical sample which slowly decomposed on heating above 185 °C: NMR (Me_2SO-d_6) δ 1.25 (t, J = 7 Hz, 3 H, CH_3), 2.22 (s, 3 H, $COCH_3$), 4.20 (q, J = 7 Hz, 2 H, OCH_2), 4.64 (br d, J = 6 Hz, 2 H, CH_2NH), 6.67, 7.67 (A_2B_2, J = 8.5 Hz, 4 H, aryl), 8.63 (s, 1 H, C-6 H); IR (KBr) 3520, 3385, 3145, 1680, 1605 cm^{-1}.

Anal. Calcd for $C_{18}H_{18}N_6O_4$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.77; H, 4.57; N, 21.64.

$N^{2'}$-Acetyl-7-L-[[[4-[[[1,3-bis(*tert*-butoxycarbonyl)-propyl]amino]carbonyl]phenyl]imino]methyl]pterin (30b). A slurry of 0.23 g (1 mmol) of **29** and 0.38 g (1 mmol) of di-*tert*-butyl *p*-aminobenzoyl-L-glutamate (**25b**) in 50 mL of ethanol was heated to reflux under nitrogen for 2 h. The resulting yellow solution was allowed to cool and was concentrated in vacuo, and the residue was dissolved in 10 mL of acetonitrile and refrigerated to give 0.06 g of a dark yellow solid. Concentration of the mother liquors provided another 0.39 g of yellow solid (76% total yield). Recrystallization from acetonitrile provided the analytical sample which decomposed slowly on heating above 225 °C: NMR (Me_2SO-d_6) δ 1.50 (s, 9 H, *tert*-butyl), 1.52 (s, 9 H, *tert*-butyl), 2.23 (s, 3 H, $COCO_3$), 2.25 (m, 4 H, CH_2CH_2), 4.35 (m, 1 H, CH), 7.48, 7.98 (A_2B_2, J = 8 Hz, 4 H, aryl), 8.72 (s, 1 H, C-6 H), 9.23 (s, 1 H, CH=N); IR (KBr) 3360 (br), 1730, 1685, 1625 cm^{-1}.

Anal. Calcd for $C_{29}H_{35}N_7O_7$: C, 58.67; H, 5.94; N, 16.52. Found: C, 58.49; H, 5.93; N, 16.77.

$N^{2'}$-Acetyl-7-L-[[[4-[[[1,3-bis(*tert*-butoxycarbonyl)-propyl]amino]carbonyl]phenyl]amino]methyl]pterin (31b). Ethanol (20 mL) was flushed with nitrogen and 0.23 g (0.6 mmol) of sodium borohydride added. Once all the borohydride was in solution, 0.12 g (0.2 mmol) of **30b** was added and the solution allowed to stir for 1 h. The solvent was then removed in vacuo, the residue slurried with 10 mL of water and neutralized with acetic acid, and the precipitate collected and washed with water. The product was taken up in hot ethyl acetate and refrigerated to give 0.09 g (75%) of a tan powder.

Higher quality material could be obtained in 50% overall yield in the following manner. The crude product was dissolved in 10 mL of acetonitrile and some dark orange solid which precipitated on standing removed by filtration. The filtrate was then concentrated in vacuo and the residue recrystallized from ethyl acetate to give 0.06 g (50%) of a yellow solid. Two recrystallizations from ethyl acetate provided the analytical sample which slowly decomposed and melted on heating above 135 °C: NMR (Me_2SO-d_6) δ 1.35 (s, 18 H, *tert*-butyls), 2.18 (s, 3 H, $COCH_3$), ~1.75–2.35 (m, 4 H, CH_2CH_2) ~4.40–4.75 (m, 3 H, NHCH and $NHCH_2$), 7.58, 7.73 (br A_2B_2, J = 8.5 Hz, 4 H, aryl), 8.65 (s, 1 H, C-6 H); IR (KBr) 3400, 1720, 1685, 1605 cm^{-1}.

Anal. Calcd for $C_{29}H_{37}N_7O_7 \cdot H_2O$: C, 56.76; H, 6.41; N, 15.98; H_2O, 2.93. Found: C, 57.11; H, 6.19; N, 16.14; H_2O, 2.65.

$N^{2'}$-Acetyl-7-L-[[[4-[[[1,3-dicarboxypropyl]amino]-carbonyl]phenyl]amino]methyl]pterin ($N^{2'}$-Acetyl-7-folic Acid, 10a). A solution of 65 mg (0.11 mmol) of **31b** in 1.3 mL of TFA was allowed to stand at room temperature for 0.5 h. The deep purple solution was then diluted with 13 mL of ether and neutralized with approximately 13 mL of saturated sodium bicarbonate. The ether was decanted and the yellow solution refrigerated. Addition of a few drops of acetic acid resulted in the slow precipitation of a yellow solid which was collected, washed with ethanol, and recrystallized from aqueous ethanol containing a few drops of acetic acid to give 0.21 g (37%) of a yellow powder which decomposed slowly on heating but remained solid even at 330 °C: IR (KBr) 3600–2300, 1680, 1620, 1600 cm^{-1}; $[\alpha]^{31}_D$ +6° (*c* 0.2, HOAc).

Anal. Calcd for $C_{21}H_{21}N_7O_7 \cdot 2H_2O$: C, 48.55; H, 4.85; N, 18.88; H_2O, 6.93. Found: C, 48.54; H, 4.68; N, 18.69; H_2O, 10.04.

The disodium salt of **10a** was prepared as follows. A solution of 50 mg (0.09 mmol) of **31b** in 0.5 mL of TFA was allowed to stand at room temperature for 0.5 h. The deep purple solution was then diluted with 10 mL of ether and centrifuged, the supernatant decanted, and the purple solid rinsed with ether. The product was then dissolved in a minimum amount of sodium bicarbonate to give a dark red solution which faded to a dark yellow within a few minutes. This solution was acidified with acetic acid and refrigerated to give a yellow gel which was collected and recrystallized immediately from ethanol–water to give 0.017 g (28%) of a fluffy yellow solid which became off-white on exposure to air. This compound slowly darkened on heating but remained a solid even at 330 °C: NMR (TFA) δ 1.87–2.46 (m, 4 H, CH_2CH_2), 2.05 (s, 3 H, $COCH_3$), 4.55 (m, 1 H, CH), 4.95 (br s, 2 H, CH_2N), 7.55 (m, 4 H, aryl), 9.65 (s, 1 H, C-6 H); IR (KBr) 3400, 1670, 1600 cm^{-1}.

Anal. Calcd for $C_{21}H_{19}N_7O_7Na_2 \cdot 9\ H_2O$: C, 36.62; H, 5.41; N, 14.22; H_2O, 23.50. Found: C, 36.78; H, 5.20; N, 14.28; H_2O, 19.30.

5-Deaza-7-[[(4-carbethoxyphenyl)imino]methyl]pterin (32a). A slurry of 0.10 g (0.48 mmol) of 5-deaza-7-formylpterin monohydrate (**9**) and 0.165 g (1.0 mmol) of ethyl *p*-aminobenzoate (**25a**) in 5 mL of Me_2SO was heated to 150 °C (oil bath temperature) and then allowed to cool back to room temperature. The yellow solid product was collected, washed with ethanol, and dried in vacuo to give 0.14 g (86%), mp >400 °C. The NMR (TFA, external Me_4Si) spectrum indicated that the product consisted of a mixture of syn and anti isomers:[40] NMR δ 1.00 (br t, J = 7 Hz, 3 H, CH_3), 4.03 (br q, J = 7 Hz, 2 H, OCH_2), 7.00 (br d, J = 9 Hz, 1 H, C-6 H), 7.40–8.00 (m, 4 H, aryl), 8.58 (br d, J = 9 Hz, 1 H, C-5 H), 9.33 (br s, 1 H, CH=N); IR (KBr) 3220–3070, 1712, 1675, 1590, 1570 cm^{-1}.

Anal. Calcd for $C_{17}H_{15}N_5O_3 \cdot 0.5\ H_2O$: C, 58.95; H, 4.66; N, 20.22. Found: C, 58.95; H, 4.44; N, 20.11.

Ethyl 5-Deaza-7-pteroate (33a). Ethanol (25 mL) was flushed with nitrogen and 0.06 g (1.6 mmol) of sodium borohydride added followed by 0.09 g (0.27 mmol) of **32a**. The mixture was stirred at room temperature for 24 h, and the product was collected by filtration, washed with ethanol, and dried in vacuo to give 0.08 g (88%) of a light yellow solid: mp >330 °C; NMR (TFA, external Me_4Si) δ 1.00 (t, J = 6.5 Hz, 3 H, CH_3), 4.03 (q, J = 6.5 Hz, 2 H, OCH_2), 4.63 (s, 2 H, CH_2N), 6.98 (d, J = 8 Hz, 1 H, C-6 H), 7.18, 7.72 (A_2B_2, J = 8 Hz, 4 H, aryl), 8.15 (d, J = 8 Hz, 1 H, C-5 H); IR (KBr) 3390, 3240, 3190, 1685, 1670, 1605, 1570, 1525 cm^{-1}.

Anal. Calcd for $C_{17}H_{17}N_5O_3$: C, 60.17; H, 5.05; N, 20.64. Found: C, 59.98; H, 4.90; N, 20.71.

$N^{2'}$-Acetyl-5-deaza-7-formylpterin (34). A slurry of 0.50 g (2.6 mmol) of finely powdered **9** in 25 mL of acetic anhydride was heated at 100 °C (bath temperature) for 1.5 h. The reaction mixture was allowed to cool and the tan, fluffy solid product carefully decanted from some granular, dark yellow solid, and collected by filtration. The product was washed with ethyl ether

and dried in vacuo to give 0.49 g (80%) of a tan powder which slowly decomposed on heating above 290 °C. Recrystallization from acetonitrile (carbon) provided the analytical sample as fine white needles with no change in melting characteristics: NMR (Me_2SO-d_6) δ 2.25 (s, 3 H, $COCH_3$), 7.83 (d, J = 8 Hz, 1 H, C-6 H), 8.60 (d, J = 8 Hz, 1 H, C-5 H), 10.02 (s, 1 H, CHO); IR (KBr) 3310, 3180, 1710, 1678, 1612, 1582, 1562, 1498 cm^{-1}.

Anal. Calcd for $C_{10}H_8N_4O_3$: C, 51.72; H, 3.47; N, 24.13. Found: C, 51.57; H, 3.26; N, 24.11.

$N^{2'}$-Acetyl-5-deaza-7-[[(4-carbethoxyphenyl)imino]methyl]pterin (36a). A slurry of 0.12 g (0.50 mmol) of **34**, 0.91 g (0.55 mmol) of ethyl *p*-aminobenzoate (**25a**) and 5 mL of Me_2SO was warmed to 100 °C (oil bath temperature) and allowed to cool back to room temperature. The product crystallized out and was collected, washed with ethanol, and dried in vacuo to give 0.16 g (84%) of an off-white, fluffy solid, mp 288–289 °C dec. The analytical sample was prepared by recrystallization from Me_2SO, mp 290–291 °C dec. Its NMR (TFA) spectrum indicated that the product consisted of an approximately 1:1 mixture of syn and anti isomers:[40] NMR δ 1.54 (br t, J = 8 Hz, 3 H, CH_3), 2.30 (s) and 2.55 (s, 3 H, $COCH_3$), 4.59 (br q, J = 8 Hz, 2 H, OCH_2), 7.60–8.40 (m, 6 H, C-5 H, C-6 H, aryl), 8.88 (s) and 8.96 (s, 1 H, CH=N); IR (KBr) 3390, 3152, 1706, 1610, 1580, 1565 cm^{-1}.

Anal. Calcd for $C_{19}H_{17}N_5O_4$: C, 60.15; H, 4.52; N, 18.46. Found: C, 60.06; H, 4.57; N, 18.81.

$N^{2'}$-Acetyl-5-deaza-7-[[(4-carbethoxyphenyl)amino]methyl]pterin (37a). Ethanol (25 mL) was flushed with nitrogen and 0.03 g (0.78 mmol) of sodium borohydride added. Once all of the borohydride was in solution, 0.10 g (0.26 mmol) of **36a** was added in one portion. The mixture was stirred at room temperature for 3 h. The cream colored, fluffy product was decanted from some yellow, granular solid which had also formed. The product was collected, washed with ethanol, and dried in vacuo to give 0.075 g (75%), mp 174 °C dec. The analytical sample was prepared by recrystallization from acetonitrile: mp 205–210 °C; NMR (Me_2SO-d_6) δ 1.27 (t, J = 7 Hz, 3 H, CH_3), 2.25 (s, 3 H, $COCH_3$), 4.17 (q, J = 7 Hz, 2 H, OCH_2), 4.49 (br d, J = 6 Hz, 2 H, CH_2N), 6.65, 7.68 (A_2B_2, J = 8 Hz, 4 H, aryl), 7.10 (br, 1 H, NH), 7.20 (d, J = 8 Hz, 1 H, C-6 H), 8.28 (d, J = 8 Hz, 1 H, C-5 H) (on addition of D_2O the signal at δ 4.49 coalesced to a sharp singlet); IR (KBr) 3365, 3200, 1700, 1690, 1670, 1625, 1595, 1560, 1525 cm^{-1}.

Anal. Calcd for $C_{19}H_{19}N_5O_4 \cdot 0.7\ H_2O$: C, 57.91; H, 5.21; N, 17.78. Found: C, 57.81; H, 5.19; N, 17.99.

$N^{2'}$-Acetyl-5-deaza-7-L-[[[4-[[[1,3-bis(methoxycarbonyl)propyl]amino]carbonyl]phenyl]imino]methyl]pterin (36c). A slurry of 0.70 g (3 mmol) of **34** and 0.97 g (3.3 mmol) of dimethyl *p*-aminobenzoyl-L-glutamate (**25c**) in 75 mL of methanol was heated to reflux under nitrogen for 3 h. Ten minutes before the end of the reflux period activated carbon was added. The mixture was filtered hot, the filtrate concentrated in vacuo, and the residue taken up in 225 mL of hot ethyl acetate which was filtered hot from some insoluble solid, chilled, and filtered. The collected solid was washed with cold ethyl acetate and dried in vacuo to give 0.63 g (41%) of a bright yellow solid, mp 160–162 °C. The analytical sample was prepared by recrystallization from ethyl acetate: mp 162–164 °C; NMR (Me_2SO-d_6) δ 1.95–2.80 (m, 4 H, CH_2CH_2), 2.28 (s, 3 H, $COCH_3$), 3.65 (s, 3 H, CO_2CH_3), 3.74 (s, 3 H, CO_2CH_3), 4.50–4.72 (m, 1 H, CH), 7.53, 8.07 (A_2B_2, J = 8.5 Hz, 4 H, aryl), 8.14 (d, J = 8 Hz, 1 H, C-6 H), 8.56 (d, J = 8 Hz, C-5 H), 8.67 (s, 1 H, CH=N); IR (KBr) 3400–3000, 1730, 1685, 1560 cm^{-1}.

Anal. Calcd for $C_{24}H_{24}N_6O_7$: C, 56.69; H, 4.76; N, 16.53. Found: C, 56.61; H, 4.69; N, 16.88.

5-Deaza-7-L-[[[4-[[[1,3-bis(methoxycarbonyl)propyl]amino]carbonyl]phenyl]amino]methyl]pterin (33c). Methanol (50 mL) was flushed continuously with nitrogen and after 5 min 0.05 g (1.3 mmol) of sodium borohydride was added. After an additional 5 min 0.25 g (0.5 mmol) of **36c** was added. The starting material went quickly into solution and within a few minutes a precipitate began to form. The mixture was allowed to stir for 3.5 h at room temperature, and the product was collected, washed with methanol, and dried in vacuo to give 0.19 g (82%) of a pale yellow powder. This material analyzed correctly without further purification and decomposed slowly on heating above 190 °C: NMR (TFA) δ 2.25–2.95 (m, 4 H, CH_2CH_2), 3.88 (s, 3 H, CO_2CH_3), 3.99 (s, 3 H, CO_2CH_3), 5.03 (m, 1 H, CH), 5.18 (s, 2 H, CH_2N), 7.61 (d, J = 9 Hz, 1 H, C-6 H), 7.90, 8.20 (A_2B_2, J = 9 Hz, 4 H, aryl), 8.75 (d, J = 9 Hz, 1 H, C-5 H); IR (KBr) 3500–2500, 1720, 1665, 1590, 1505, 1430 cm^{-1}.

Anal. Calcd for $C_{22}H_{24}N_6O_6 \cdot 0.5H_2O$: C, 55.34; H, 5.28; N, 17.60; H_2O, 1.88. Found: C, 55.42; H, 5.16; N, 17.30; H_2O, 2.15.

5-Deaza-7-folic Acid (11). A slurry of 0.10 g (0.19 mmol) of **33c** in 40 mL of 0.1 N sodium hydroxide was flushed with nitrogen and emersed in an oil bath preheated to 100 °C. Once the internal temperature reached 80 °C the pale yellow solution was acidified to pH 1.7 with 6 N HCl. The clear yellow solution was filtered hot, allowed to cool to room temperature, and refrigerated overnight The product was then collected by filtration and washed successively with 5-mL portions of cold water, ethanol, and ether. The product was dried in vacuo to give 0.061 g (66%) of a yellow powder which slowly decomposed on heating above 150 °C: NMR (TFA) δ 2.10–3.00 (m, 4 H, CH_2CH_2), 5.09 (m, 1 H, CH), 5.19 (s, 2 H, CH_2N), 7.62 (d, J = 9 Hz, 1 H, C-6 H), 7.86, 8.14 (A_2B_2, J = 9 Hz, 4 H, aryl), 8.75 (d, J = 9 Hz, 1 H, C-5 H); IR (KBr) 3600–2200, 1710, 1600, 1505 cm^{-1}; $[\alpha]^{31}_D$ +18.4° (c 1.0, 0.1 N NaOH).

Anal. Calcd for $C_{20}H_{20}N_6O_6 \cdot 1.2H_2O$; C, 52.00; H, 4.89; N, 18.18; H_2O, 4.67. Found: C, 51.91; H, 4.45; N, 18.30; H_2O, 5.56.

3,3-Dimethoxy-1-pyrrolidinopropene (38). To a solution of 12.25 g (0.098 mol) of 3-pyrrolidinoacrolein[38] in 30 mL of toluene was added 9.9 mL (0.108 mol) of dimethyl sulfate, and the slightly exothermic reaction was controlled by the use of a room-temperature water bath. After 0.5 h a red oil began to separate. After a total reaction time of 1.75 h, the toluene was decanted and the product was washed with toluene (3 × 5 mL) followed by ether (3 × 10 mL) to give a red waxy solid. This was then combined with 5.6 g (0.104 mol) of sodium methoxide and 120 mL of anhydrous ethyl ether and heated to reflux for 17 h with vigorous stirring. The mixture was then allowed to cool, the salts were removed by filtration, washed thoroughly with ether, the filtrate was concentrated in vacuo, and the residue was distilled to give 11.9 g (71%) of a colorless liquid, bp 70–79 °C (0.55 mm). The product quickly yellowed on standing and was best stored (−5 °C) under nitrogen: NMR ($CDCl_3$) δ 1.7–2.0 (m, 4 H, CH_2CH_2), 2.95–3.40 (m, 4 H, $N(CH_2)_2$), 3.25 (s, 6 H, $(OCH_3)_2$), 4.06 (dd, J = 6, 13.5 Hz, 1 H, C-2 H), 4.73 (d, J = 6 Hz, 1 H, C-3 H), 6.49 (d, J = 13.5 Hz, 1 H, C-1 H); IR (KBr) 2960, 2940, 2870, 2820, 1650 cm^{-1}.

2-Oximino-3,3-dimethoxypropanal (41). A solution of 1.71 g (10 mmol) of **38** in 17 mL of dry THF was cooled under nitrogen to −50 °C and a solution of 0.72 g (11 mmol) of nitrosyl chloride in 8.6 mL of THF added dropwise with stirring to give a voluminous white precipitate. After addition was complete the mixture was stirred an additional 5 min at −50 °C, diluted with 25 mL of anhydrous ethyl ether, allowed to warm to 5 °C, and filtered, and the collected solid was rinsed thoroughly with ether in such a manner that the filtercake was always wet with ether. The product was then covered with ether and hydrolyzed by the addition of 5 mL of water. Once all of the solid had dissolved, the ether was decanted and the aqueous layer was extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed in vacuo to leave 0.27 g (18%) of a golden oil. Its NMR ($CDCl_3$) spectrum (singlets at δ 3.40, 3.46, 3.55, 5.02, 5.55, 5.88, 6.97, 9.71, 10.00; ratio of signals at δ 3.40–3.55 to all other signals of 3:1) showed that it contained, as two of three components, a mixture of the syn and anti isomers of **41**.

2-Amino-3-cyano-6-(dimethoxymethyl)pyrazine 1-Oxide (42). Method A. A solution of 0.10 g (0.51 mmol) of 2-amino-3-cyano-6-(dimethoxymethyl)pyrazine (**17**) and 0.60 g (2.8 mmol) of MCPBA in acetone was allowed to stand at room temperature for 9 days. The solvent was removed under reduced pressure and the yellow residue partitioned between 15 mL of methylene chloride and 15 mL of 10% aqueous sodium bisulfite. The organic layer was separated and the aqueous layer was washed with methylene chloride (2 × 15 mL). The combined organic extracts were then washed with 15 mL of saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and evaporated and the residual yellow solid was recrystallized from 2-propanol to give 0.55 g (51%) of yellow plates, mp 175.5–176.5 °C. A second recrystallization from chloroform provided the analytical sample: mp 176–177 °C; NMR (Me_2SO-d_6) δ 3.42 (s, 6 H, $(OCH_3)_2$), 5.74 (s, 1 H, CH), 7.92 (s,

1 H, C-5 H), 7.96 (br s, 2 H, NH_2); IR (KBr) 3370, 3265, 3215, 2230, 1620 cm^{-1}.

Anal. Calcd for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.80; N, 26.66. Found: C, 45.38; H, 4.80; N, 26.42.

Method B. A solution of 0.50 g (2 mmol) of aminomalononitrile tosylate in 3 mL of methanol was cooled in an ice bath and a solution of 0.27 g of crude **41** in 1 mL of methanol added in one portion. TLC (10% MeOH, 90% $CHCl_3$) examination of the resulting dark red solution indicated that a complex mixture of products had formed, but comparison with authentic **42** indicated its presence in the reaction mixture. This reaction was not investigated further.

2-Amino-3-cyano-5-(dimethoxymethyl)pyrazine (4). A solution of 1.48 g (5 mmol) of *O*-tosyloximinomalononitrile in 50 mL of anhydrous ethyl ether was cooled to −20 °C under nitrogen and a solution of 1.71 g (10 mmol) of 3,3-dimethoxy-1-pyrrolidinopropene in 12 mL of ether was added dropwise. The mixture was then allowed to warm to 0 °C and kept at 0 °C for 1 h. Saturated methanolic ammonia (20 mL) was then added and the resulting mixture kept at 0 °C for an additional h. The mixture was filtered and the filtrates were concentrated in vacuo to give a brown gum which was partitioned between 50 mL of ether and 25 mL of water. The layers were separated, the aqueous layer was extracted with ether (3 × 25 mL), and the combined ether extracts were dried ($MgSO_4$) and evaporated in vacuo to leave a brown oil in which crystals formed on standing. The product was filtered off and rinsed with cold toluene to give 0.23 g of light golden crystals, mp 94–95 °C (lit.[3] mp 91–93 °C), identical with authentic material. The filtrates were stirred overnight with activated carbon and concentrated to a small volume to give a second crop of 0.07 g (31% total yield).

2-Amino-3-cyanopyridine (44). A solution of 1.22 g (10 mmol) of (ethoxymethylene)malononitrile (Aldrich) in 10 mL of dry THF was cooled to −25 °C and a solution of 1.71 g (10 mmol) of **38** in 10 mL of THF added dropwise. The resulting solution was allowed to warm to 10 °C and 10 mL of saturated methanolic ammonia added. The reaction mixture was then stirred overnight with gradual warming to room temperature. The solvent was removed in vacuo, the residue was taken up in 25 mL of ethyl acetate and extracted with 25 mL of 1 N HCl, and the aqueous layer added carefully to 25 mL of saturated sodium bicarbonate. It was then extracted with methylene chloride (2 × 20 mL), the extracts were dried ($MgSO_4$) and evaporated under reduced pressure, and the residue was chromatographed (silica gel, ether) to give 0.020 g (1.7%) of a white solid, mp 129–130 °C (lit.[41] mp 131–133 °C), identical with an authentic sample of **44**.

Registry No. 3, 76282-54-7; **4**, 6440-77-3; **5**, 6342-56-9; **7**, 76282-55-8; **8**, 76282-56-9; **9**, 76282-57-0; **10a**, 76282-58-1; **10a**·2Na, 76282-59-2; **11**, 76282-60-5; **13**, 5098-14-6; **14**, 73198-29-5; **15**, 20893-01-0; **16**, 76282-61-6; **17**, 76282-62-7; **18**, 76299-37-1; **19**, 76299-38-2; **20a**, 672-81-1; **20b**, 123-06-8; **21**, 76282-63-8; **22**, 76282-64-9; **23**, 76299-39-3; **24**, 76282-65-0; **25a**, 94-09-7; **25b**, 76282-66-1; **25c**, 52407-60-0; **26a**, 76282-67-2; **28**, 76282-68-3; **29**, 76282-69-4; **30a**, 76282-70-7; **30b**, 76282-71-8; **31a**, 76282-72-9; **31b**, 76282-73-0; **32a** (isomer 1), 76282-74-1; **32a** (isomer 2), 76282-75-2; **33a**, 76299-40-6; **33c**, 76282-76-3; **34**, 76319-72-7; **36a** (isomer 1), 76282-77-4; **36a** (isomer 2), 76282-78-5; **36c**, 76282-79-6; **37a**, 76282-80-9; **38**, 76282-81-0; **41** (isomer 1), 76282-82-1; **41** (isomer 2), 76282-83-2; **42**, 76282-84-3; **44**, 24517-64-4; pyrrolidine, 123-75-1; nitrosyl chloride, 2696-92-6; guanidine, 113-00-8; 3-pyrrolidinoacrolein, 30545-31-4; N^2-acetyl-5-deaza-7-(diacetoxymethyl)pterin, 76282-85-4.

(41) Taylor, E. C.; Crovetti, A. J. *J. Org. Chem.* **1954**, *19*, 1633–1644.

Intramolecular 1,1-Cycloaddition of Nitrilimines as a Route to Benzodiazepines and Cyclopropa[*c*]cinnolines

Albert Padwa* and Steven Nahm

Department of Chemistry, Emory University, Atlanta, Georgia 30322

Received November 19, 1980

Treatment of *o*-vinylphenyl-substituted chloroglyoxylate phenylhydrazones with base leads to nitrilimines. These reactive 1,3-dipoles undergo intramolecular 1,1-cycloaddition with complete retention of configuration to give cyclopropa[*c*]cinnolines. When the nitrilimine was generated in the presence of an added dipolarophile, bimolecular 1,3-dipolar cycloaddition was the exclusive reaction observed. Thermolysis of the cyclopropa[*c*]cinnoline ring resulted in the formation of benzodiazepines. This thermal rearrangement is readily explicable in terms of an electrocyclic ring opening followed by a 1,5-sigmatropic shift of the transient ring-opened diazanorcaradiene intermediate. The ring-opened species can be trapped with added dipolarophiles to give 5-substituted 4,5-dihydrobenzodiazepines. Treatment of the homologous *o*-allylphenyl chlorohydrazone with base results in a 1,3-dipolar cycloaddition. With this system, the transition state for cycloaddition allows easy attainment of the parallel plane approach of the dipole and dipolarophile.

Nitrilimines are a long known and thoroughly investigated class of 1,3-dipoles.[1] Access to this group of dipoles can be realized by (a) treatment of hydrazonyl halides with base,[2] (b) thermal or photochemical decomposition of tetrazoles,[3,4] (c) photolysis of sydnones,[5] and (d) thermal elimination of carbon dioxide from 1,3,4-oxadiazolin-5-ones.[6,7] 1,3-Dipolar cycloaddition of this class of 1,3-dipoles has been widely investigated[8] and in many cases has led to the synthesis of a variety of interesting heterocyclic compounds,[9] some of which would be tedious to synthesize by other routes. The mechanism of the reaction of alkenes

(1) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2**, 565, 633 (1963).
(2) R. Huisgen, M. Seidel, G. Wallbillich, and H. Knupfer, *Tetrahedron*, **17**, 3 (1962).
(3) R. Huisgen, M. Seidel, J. Sauer, J. W. McFarland and G. Wallbillich, *J. Org. Chem.*, **24**, 892 (1959); J. S. Clover, A. Eckell, R. Huisgen, and R. Sustmann, *Chem. Ber.*, **100**, 60 (1967).
(4) P. Scheiner and J. F. Dinda, Jr., *Tetrahedron*, **26**, 2619 (1970); P. Scheiner and W. M. Litchman, *J. Chem. Soc., Chem. Commun.*, 781 (1972).
(5) M. Marky, H. Meier, A. Wunderli, H. Heimgartner, H. Schmid, and H. J. Hansen, *Helv. Chim. Acta.*, **61**, 1477 (1978).
(6) C. Wentrup, A. Damerius, and W. Richen, *J. Org. Chem.*, **43**, 2037 (1978).
(7) A. Padwa, T. Caruso, and S. Nahm, *J. Org. Chem.*, **45**, 4065 (1980).
(8) R. Huisgen, R. Grashey, and J. Sauer in the "The Chemistry of Alkenes", S. Patai, Ed., Interscience, New York, 1964, p 806.
(9) A. Padwa, *Angew. Chem., Int. Ed. Engl.*, **15**, 123 (1976).

0022-3263/81/1946-1402$01.25/0