Synthesis of 2,4-Diamino-5,10-dideaza Nonclassical Antifolates

Aleem Gangjee* and Rajesh Devraj

Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, PA 15282

Fu-Tyan Lin

Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260

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Condensation of 2,4,6-triaminopyrimidine (**8**) with bromomalonaldehyde (**9**) afforded, after pivaloylation, 2,4-dipivaloyl-6-bromopyrido[2,3-*d*]pyrimidine (**11**). This 6-bromo derivative served as a key intermediate for the synthesis of 2,4-diamino-6-[2-(3',4'-dimethoxyphenyl)ethenyl]pyrido[2,3-*d*]pyrimidine (**5**) *via* a palladium catalyzed carbon-carbon coupling with 3,4-dimethoxystyrene (**12**). Compound **5**, its 9,10-dihydro analogue **6** and the 5,6,7,8,9,10-hexahydro analogue **7** were of interest as potential inhibitors of dihydrofolate reductase. Compounds **6** and **7** were synthesized from **5** by catalytic hydrogenation over 5% Pd-C.

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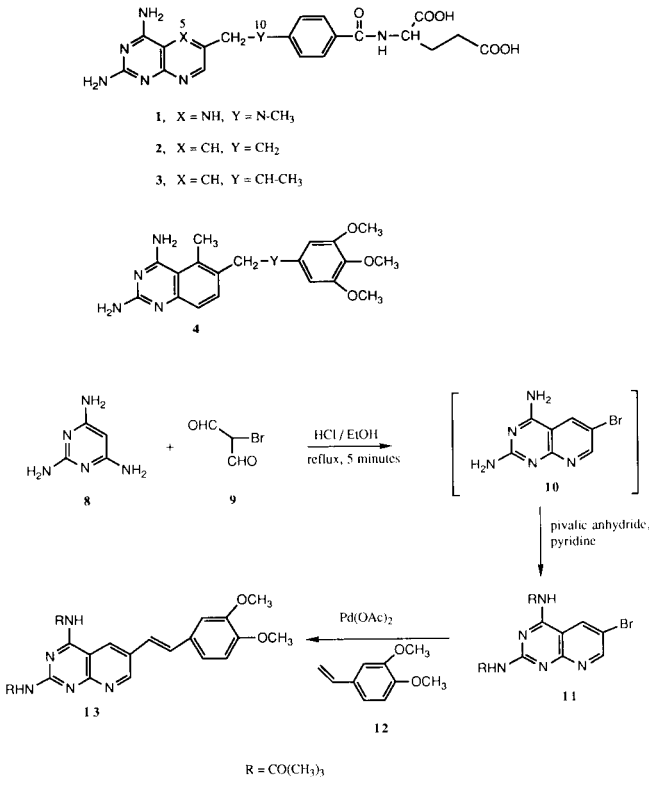
Methotrexate (MTX) **1** has served as a lead compound for structural modification since its introduction as an anticancer agent. The 2,4-diamino substitutions on MTX are crucial for its biological action as a potent inhibitor of dihydrofolate reductase. One modification of substituting carbon for nitrogen in MTX has been particularly fruitful. Thus, the synthesis of 5,10-dideazaaminopterin (DDAMT) **2** [1], 5,10-dideaza MTX **3** [2] and 5 and 10-alkyl substituted derivatives [3] have been reported, and the compounds have shown significant antitumor activity. A disadvantage of classical folate analogues is that they require a transport mechanism into the cell. Cells which lack this transport mechanism are not susceptible to the action of classical antifolates. In an attempt to circumvent this transport, nonclassical antifolates have been developed such a trimetrexate **4**, which lack the L-glutamate portion [4]. These nonclassical analogues are highly lipophilic and are transported into cells by passive diffusion and have a broad range of activity. This report consists of a general synthesis of 2,4-diamino-5,10-dideaza nonclassical antifolates **5-7** as potential antitumor, antibacterial and antiprotozoal agents as an extension of our continuing interest in deazafolate analogues [5-8].

A search of the literature showed that a similar compound was reported by Hurlbert and Valenti [9]. However, the reported synthetic method was not adaptable for the synthesis of a common intermediate, from which the 6-position could be exploited to afford series of 6-substituted 2,4-diamino classical and nonclassical antifolate analogues which was our goal. Our synthetic method was suggested by the report of Bernetti *et al.* [10] and Taylor and Cheol-Min [11], who had synthesized 2-amino-4-oxo-6-bromopyrido[2,3-*d*]pyrimidine from 2,6-diamino-4-oxopyrimidine and bromomalonaldehyde, this was followed by a palladium catalyzed coupling with styrene of the 6-bromopyrido[2,3-*d*]pyrimidine in a modification of similar couplings in carbocyclic systems reported by Heck and Nolley [12].

The synthesis of 2,4-diamino substituted analogues *via* Taylor's method would necessitate a conversion of the 4-oxo system to a 4-amino system. In order to directly afford 2,4-diamino analogues, we decided to start with 2,4,6-triaminopyrimidine, which would incorporate the 2,4-diamino system, desired in our final compounds, **5-7**. Initial attempts to condense 2,4,6-triaminopyrimidine (**8**) with bromomalonaldehyde (**9**) under neutral [13] or mildly acidic conditions [14] (*eg.* glacial acetic acid) failed and the starting pyrimidine was recovered unreacted. This necessitated the use of a stronger acid (hydrochloric acid) in order to affect the condensation. We were aware that the hydrolysis of the 4-amino group to the 4-oxo moiety during the condensation in mineral acid was a significant possibility [15]. However, condensation of **8** and **9** proceeded smoothly in concentrated hydrochloric acid-ethanol, 3:2 (v/v) and the product 2,4-diamino-6-bromopyrido-[2,3-*d*]pyrimidine (**10**) falls out of solution within five minutes. Thin layer chromatography indicated the disappearance of both starting materials and the formation of a major product spot. The fast reaction time with 2,4,6-triaminopyrimidine was in contrast to the literature report [11] for the 2,6-diamino-4-oxopyrimidine which takes a much longer time (24 hours).

The product **10**, was resistant to purification due to its poor solubility in a variety of solvents. Pivaloylation of the 2- and 4-amino moieties was anticipated to increase the solubility of **10**. Thus **10** was heated under nitrogen at reflux with pivaloyl anhydride and pyridine to afford the more soluble 2,4-dipivaloylamino-6-bromopyrido[2,3-*d*]-pyrimidine (**11**) in 39% yield from **8**. The ^{1}H nmr of **11** in deuterated dimethyl sulfoxide, indicated the presence of the two aromatic protons H_5 and H_7 at δ 8.42 and δ 8.94 re-



spectively and the absence of the pyrimidine H_5 proton at δ 4.90, confirming the formation of the pyrido[2,3-*d*]pyrimidine system. In addition a large peak at δ 1.33 integrating for eighteen protons and the presence of two exchangeable amide protons at δ 11.88 supported the dipivaloylation. The mass spectrum of **11** shows the (M^+) peak at 407 (calculated m/e = 407) and a (M + 2) peak of equal intensity which confirms the presence of bromine.

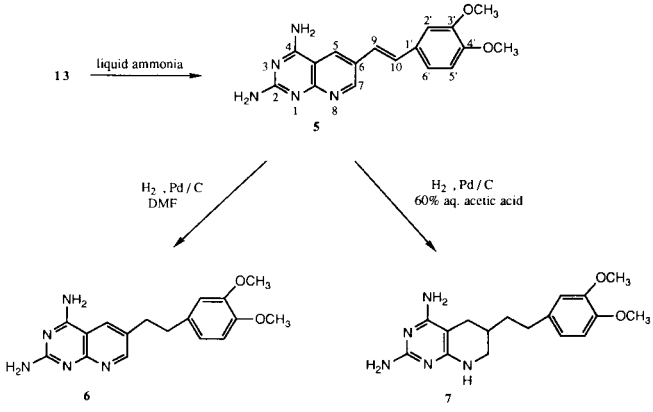
Palladium catalyzed carbon-carbon coupling of **11** was carried out with 3,4-dimethoxystyrene (**12**), under nitrogen, in the presence of palladium acetate, tri-*o*-tolylphosphine, a hindered base, triethylamine and catalytic amount of cuprous iodide, in a modification of that reported by Taylor and co-workers [11,16] to obtain, after purification, the coupled product 2,4-dipivaloylamino-6-[2-(3',4'-dimethoxyphenyl)ethenyl]pyrido[2,3-*d*]pyrimidine (**13**) in 55% yield.

Depivaloylation of similar systems have been reported with aqueous sodium hydroxide [16,17]. This method was not suitable for **13** due to the prolonged reaction time required which would increase susceptibility of the 4-amino group to hydrolysis. Another report in the literature suggested the use of liquid ammonia in methanol [18] as a method of deprotection. However, using the reported reaction conditions, the di-depivaloylation of **13** essentially remained incomplete even after prolonged reaction periods (five days). Reports of deacetylations of related pyrido[2,3-*d*]pyrimidines with liquid ammonia in a sealed vessel [19,20] suggested an alternate method of depivaloylation. Thus **13** was stirred in a sealed vessel with liquid ammonia which afforded the deprotected compound 2,4-diamino-6-[2(3',4'-dimethoxyphenyl)ethenyl]pyrido[2,3-*d*]pyrimidine (**5**). Optimal conditions for the di-depivaloylation were found to be the use of liquid ammonia and methylene chloride-methanol, 3:1 (v/v) as a solvent for sixty-six hours. This allowed the precipitation of the less soluble deprotected product **5** which was obtained in 78% yield. The 300 MHz ^{1}H nmr spectrum of **5** in deuterated dimethyl sulfoxide indicated the presence of an AB system for the H_9 and H_{10} protons with a J_{AB} = 16.5 Hz which indicated an E configuration of the C_9-C_{10} double bond. The aromatic protons H_5 and H_7 occur at δ 8.65 and δ 8.78 respectively.

Having synthesized **5**, we were interested in obtaining the partially saturated (9,10-dihydro) analogue 2,4-diamino-6-[2-(3',4'-dimethoxyphenyl)ethyl]pyrido[2,3-*d*]pyrimidine (**6**) as well as the hexahydro analogue 2,4-diamino-6-[2-(3',4'-dimethoxyphenyl)ethyl]-5,6,7,8-tetrahydro-1*H*-pyrido[2,3-*d*]pyrimidine (**7**). Hydrogenation of **5** with 5% Pd-C in 60% aqueous acetic acid at 50 psi for 24 hours afforded **7** in 67% yield after column chromatographic purification on silica gel. The poor solubility of compound **7** required that it be chromatographed as a solid dispersion on silica gel. Subsequent elution with a gradient solvent system, chloroform-methanol, 99:1 (v/v) to 80:20 (v/v) afforded analytically pure **7** as a white powder. Compound **7** was homogenous on tlc in three different solvent systems. The 300 MHz ^{1}H nmr of **7** in deuterated dimethyl sulfoxide showed the presence of the 8-NH proton as a broad singlet at δ 6.08, (exchanged with deuterium oxide). The presence of eight methylene protons together with the absence of aromatic protons H_5 and H_7 and that of the vinylic protons, H_9 and H_{10} further supported the structure of **7**. Proton assignments for compound **7** was accomplished with the help of spin-spin decoupling experiments and by homonuclear shift correlated two-dimensional nmr spectroscopy. The results indicated that the C-6 methine proton is shielded by anisotropy of the dimethoxyphenyl ring and occurs as a multiplet at δ 1.49-1.63 along with the C-9 methylene protons. The conformation of compound **7** which provided the sheilding of the C-6 proton by the dimethoxyphenyl ring was also found to be the minimum energy conformation generated by molecular modeling (Tripos Associates Inc., SYBYL 4.1).

Initial attempts to selectively reduce the 9-10 double bond using lower hydrogen pressure and decreased reaction times in aqueous acetic acid or aqueous trifluoroacetic acid failed, and a mixture of products was indicated by tlc. Selective hydrogenation was accomplished in dimethylformamide using a modification of a procedure reported

by Piper *et al.* [21]. Due to the insolubility of the acetate salt of **5** in dimethylformamide, the trifluoroacetate salt was used which was readily soluble in dimethylformamide. Thus hydrogenation of **5**, as a trifluoroacetate salt, in dimethylformamide using 5% Pd-C as catalyst at 25 psi for fifteen minutes followed by chromatographic purification, as described above for **7**, afforded the product **6** (51% yield). This product was homogenous on tlc in three different solvent systems.



The 300 MHz ^{1}H nmr spectrum of **6** in deuterated dimethyl sulfoxide indicated that the H_9 and H_{10} methylene hydrogens resonated at δ 2.87 as a singlet integrating for four protons. The phenyl proton $H_{2'}$, occurs as a singlet at δ 6.81 whereas the $H_{5'}$ and $H_{6'}$ form part of an AB system each occurring as a doublet at δ 6.81-6.84 and δ 6.68-6.71 with a coupling constant J_{ortho} = 8.1 Hz. The aromatic protons H_5 and H_7 occur as doublets at δ 8.27 and δ 8.47 respectively with a coupling constant J = 2.1 Hz, indicating a 2,4 relationship in the pyridine ring system.

Three model 2,4-diamino-5,10-dideaza nonclassical antifolates have been synthesized *via* a common 6-bromo-2,4-diaminopyrido[2,3-*d*]pyrimidine intermediate **11**. This intermediate **11** can be readily utilized for structural variation at the 6-position to afford a variety of 2,4-diamino classical and nonclassical antifolates which can be obtained in reasonable yields *via* a relatively short synthetic sequence. This work is currently in progress.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra (ir) were recorded with a Perkin Elmer Model 1430, in Nujol Mulls. Nuclear magnetic resonance spectra for proton (^{1}H nmr) were recorded on a Varian EM-360 (60 MHz) or a Brucker WH-300 (300 MHz). The data was accumulated by 16k size with 0.5 second delay time and 70° tip angle with internal standard TMS; s = singlet, d = doublet, t = triplet, m = multiplet. Low-resolution mass spectra were obtained on an LKB-9000 instrument. High-resolution mass spectra were obtained by peak matching on a Varian MATCH-5DF instrument. Thin layer chromatography (tlc) was performed on silica gel plates and cellulose plates with flourescent indicator and were visualized with light at 254 nm and 366 nm. Column chromatography was performed on 230-400 mesh silica gel purchased from Aldrich, Milwaukee, Wisconsin. Samples for micro analysis were dried *in vacuo* over phosphorus pentoxide at 70° or 110°. Microanalysis were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee or Atlantic Microlabs, Norcoss, Georgia. Fractional moles of water or organic solvents in some analytical samples frequently found in such systems could not be prevented in spite of vigorous drying *in vacuo* (see for example, references [22] and [23]) and was confirmed by their presence in the nmr.

2,4-Dipivaloylamino-6-bromopyrido[2,3-*d*]pyrimidine (**11**).

To a stirred solution of 10 g (80 mmoles) of 2,4,6-triaminopyrimidine (**8**) in 15 ml of concentrated hydrochloric acid and 10 ml of absolute ethanol at 80° was added 12.06 g (80 mmoles) of bromomalonaldehyde (**9**) [24] (freshly prepared). The solution was brought to reflux for 5 minutes, when an orange colored solid falls out of solution. This thick suspension was cooled rapidly to $<5°$ and diluted with water (30 ml). The mixture was basified with concentrated ammonium hydroxide to *p*H 8, with the temperature maintained at below 10°. The precipitate was filtered, washed with water until neutral, air dried, and further dried *in vacuo* over phosphorus pentoxide at 70°. To the crude dried precipitate (16.0 g) was added 25 ml of pyridine and 50 ml (240 mmoles) of pivaloyl anhydride. The mixture was refluxed under nitrogen for 8 hours. The reaction mixture was cooled to room temperature, and the excess pyridine and pivaloyl anhydride were removed under reduced pressure (oil-pump). To the dark brown sticky residue was added 500 ml of methylene chloride. The suspension was stirred overnight and the undissolved material filtered. The filtrate was evaporated to ~50 ml and chromatographed on a wet (methylene chloride) silica gel column (2.4 x 38 cm). The column was eluted with methylene chloride, collecting 10 ml fractions. Fractions showing a single spot on tlc, were pooled and evaporated to afford a white residue which was recrystallized from acetone to give 10.1 g (39%) of **11** as small needles, tlc; silica gel, methylene chloride-methanol, 15:1 (v/v), R_f = 0.67, mp 212-214°; ir (nujol): 3240 (NH), 1680 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): 60 MHz δ 1.33 (s, 18H, 2 x $COC(CH_3)_3$), 8.42 (s, 1H, 5-H), 8.94 (s, 1H, 7-H), 11.88 (br s, 2H, 2 and 4-NH, deuterium oxide exchangeable); ms: (m/e) 407 (M^+), 409 (M + 2); hrms: Calcd. for $C_{13}H_{13}N_5O_2Br$: 350.0253. Found: 350.0253.

2,4-Dipivaloylamino-6-[2-(3',4'-dimethoxyphenyl)ethenyl]pyrido-[2,3-*d*]pyrimidine (**13**).

To a mixture of 1.94 g (6 mmoles) of **11**, 15 mg (0.06 mmole, 1% w/w) of palladium acetate, 38 mg (0.12 mmole) of tri-*o*-tolylphosphine, 7 mg (0.03 mmole) of cuprous iodide and 5 ml of triethylamine was added 30 ml of acetonitrile and the solution brought to reflux under nitrogen. To the solution, under reflux, was added 1.97 g (12 mmoles, 2 equivalents) of 3,4-dimethoxystyrene (**12**). The progress of the reaction was followed by tlc (silica gel, methylene chloride:methanol, 15:1 v/v) for formation of product (R_f = 0.56). Following 18 hours of reflux the mixture was cooled to 5°. The precipitate formed was filtered, washed with cold acetonitrile and air dried. The solid was dissolved in a mixture of methylene chloride-methanol, 9:1 (v/v) (~30 ml) and passed through a short column of silica gel (2.4 x 10 cm), using 10% methanol in methylene chloride as eluent. The eluate was evaporated under reduced pressure to a small volume (~30 ml).

This solution was left overnight at 0° to deposit a solid which was filtered, washed with ice-cold methanol and dried to afford 1.55 g (53%) of **11** as a bright-orange solid, tlc; silica gel, methylene chloride:methanol, 15:1 (v/v), R_f = 0.56, mp 297-299° dec; ir (nujol): 3450 (NH), 1720 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 300 MHz δ 1.27-1.30 (s, 18H, 2 x $COC(CH_3)_3$), 3.78 (s, 3H, 3'-OCH_3), 3.84 (s, 3H, 4'-OCH_3), 6.97-7.41 (m, 5H, 9-, 10-, 2'-, 5'- and 6'-H), 8.53-8.54 (d, 1H, 5-H, J = 2.1 Hz), 9.06-9.07 (d, 1H, 7-H, J = 2.1 Hz), 11.40 (br s, 2H, 2 and 4-NH).

Anal. Calcd. for $C_{27}H_{33}N_5O_4 \cdot 0.5\ CH_3OH$: C, 65.07; H, 6.95; N, 13.80. Found: C, 64.69; H, 7.00; N, 14.01.

2,4-Diamino-6-[2-(3',4'-dimethoxyphenyl)ethenyl]pyrido[2,3-*d*]-pyrimidine (**5**).

To a solution of 500 mg (1.01 mmoles) of **13** in 15 ml of methylene chloride and 5 ml of methanol was added 40 ml of liquid ammonia. This solution was sealed and stirred in a Parr acid digestion bomb for a period of 66 hours. The liquid ammonia was allowed to evaporate and the suspension filtered. The yellow solid residue was extracted with 100 ml of boiling methanol followed by 100 ml of boiling acetone, and air dried. For purification, the solid was dissolved in 15% aqueous acetic acid and clarified through a thick pad of glass wool. The solution was evaporated under reduced pressure to dryness and the residue stirred overnight in the dark in a mixture of methanol:ethyl acetate, 1:1 (v/v) and filtered. The solid was dried *in vacuo* at 70° to afford 216 mg of **5** (78%) as a yellowish-orange solid, mp >300°. The compound was homogenous on tlc; a) cellulose, 50% aqueous acetic acid, R_f = 0.45, b) silica gel, chloroform-methanol-ammonium hydroxide, 14:2:1, R_f = 0.18; ir (nujol): 3350, 3180 (NH_2) cm^{-1}; ^1H nmr (DMSO-d_6): 300 MHz δ 3.78 (s, 3H, 3'-OCH_3), 3.84 (s, 3H, 4'-OCH_3), 6.45 (br s, 2H, 4-NH_2), 6.96-6.99 (d, 1H, 5'-H, J = 8.3 Hz), 7.05-7.08 (d, 1H, 6'-H, J = 8.4 Hz), 7.10-7.16 (d, 1H, H_9 or H_{10} $J_{9,10}$ = 16.5 Hz), 7.18-7.22 (d, 1H, H_9 or H_{10} $J_{9,10}$ = 16.5 Hz), 7.21 (s, 1H, 2'-H), 7.59 (br s, 2H, 2-NH_2), 8.66 (s, 1H, 5-H), 8.79 (s, 1H, 7-H).

Anal. Calcd. for $C_{17}H_{17}N_5O_2 \cdot 0.5\ CH_3COOH \cdot 0.5\ H_2O$: C, 59.66; H, 5.56; N, 19.33. Found: C, 59.58; H, 5.57; N, 19.34.

2,4-Diamino-6-[2-(3',4'-dimethoxyphenyl)ethyl]pyrido[2,3-*d*]pyrimidine (**6**).

In order to increase solubility of **5** in dimethylformamide it was first converted to the triflouroacetate salt. Compound **5**, 100 mg (0.3 mmole), was dissolved in 20 ml of triflouroacetic acid and the solution was evaporated to dryness (<30°) with an oil pump. The residue was dissolved in 20 ml of dimethylformamide and 200 mg of 5% Pd-C was added to the solution. The suspension was hydrogenated at 25 psi for fifteen minutes in a Parr apparatus. Tlc (cellulose, 10% aqueous acetic acid v/v) of the reaction mixture showed two spots, the desired product **6** (R_f = 0.5) and unreacted **5** (R_f = 0.01). The reaction mixture was filtered through Celite and the Celite washed with 20 ml of dimethylformamide. The filtrate was evaporated under reduced pressure (<50°) to dryness. The residue was dissolved in 30 ml of methanol-glacial acetic acid (95:5 v/v) mixture. To this solution was added 0.5 g of silica gel, and the solvent was removed under reduced pressure. This solid dispersion was loaded on a dry silica gel column (35 g, 2.4 x 20 cm). The column was flushed with 500 ml chloroform, and then eluted stepwise with 100 ml portions of 99:1, (v/v) chloroform-methanol to 80:20, (v/v) chloroform-methanol collecting 10 ml fractions. Fractions showing a single spot on tlc corresponding to the product were pooled and evaporated to dryness. (The product elutes in fractions corresponding to 85:15 to 81:19 (v/v) chloroform-methanol). The residue was stirred overnight in ethyl acetate in the dark and filtered. The filtered solid was dried *in vacuo* at 70° over phosphorus pentoxide to afford 51 mg (51%) of a pale yellow solid, mp >300°. The compound was homogenous on tlc; a) cellulose, 10% aqueous acetic acid, R_f = 0.5, b) silica gel, chloroform-methanol-ammonium hydroxide, 14:2:1, R_f = 0.22, c) silica gel, ethyl acetate-methanol, 2:1, R_f = 0.41; ir (nujol): 3350, 3200 (NH_2) cm^{-1}; ^1H nmr (DMSO-d_6): 300 MHz δ 2.87 (s, 4H, 9 and 10-CH_2), 3.69-3.70 (2s, 6H, 3 and 4-OCH_3), 6.22 (br s, 2H, 4-NH_2), 6.69-6.72 (d, 1H, 6'-H, J = 8.1 Hz), 6.81 (s, 1H, 2'-H), 6.81-6.84 (d, 1H, 5'-H, J = 8.1 Hz), 7.44 (br s, 2H, 2-NH_2), 8.27 (d, 1H, 5-H, J = 2.1 Hz), 8.45 (d, 1H, 7-H, J = 2.1 Hz).

Anal. Calcd. for $C_{17}H_{19}N_5O_2 \cdot CF_3COOH \cdot 2.2\ H_2O$: C, 47.64; H, 5.13; N, 14.62. Found: C, 47.86; H, 5.04; N, 14.22.

2,4-Diamino-6-[2-(3',4'-dimethoxyphenyl)ethyl]-5,6,7,8-tetrahydro-1*H*-pyrido[2,3-*d*]pyrimidine (**7**).

To a solution of 280 mg (0.87 mmole) of **5** in 40 ml of 60% aqueous acetic acid was added 435 mg of 5% Pd-C, and the suspension was hydrogenated in a Parr apparatus at 50 psi for 24 hours. The catalyst was filtered through Celite and washed with 60% aqueous acetic acid. The filtrate and washings were evaporated to dryness under reduced pressure (<35°). The residue was taken up in methanol (20 ml) and dissolved with a drop of glacial acetic acid. To this solution was added 1 g of silica gel and the suspension evaporated under reduced pressure to dryness. This silica gel plug (with product evenly dispersed in it) was loaded on a dry silica gel column (31 g, 2.4 x 18 cm). The column was first flushed with chloroform (500 ml) and then eluted stepwise with 100 ml portions of 99:1 to 89:11 (v/v) of chloroform-methanol, collecting 10 ml fractions. (The product elutes in fractions corresponding to 93:7 to 90:10 (v/v) chloroform-methanol). Fractions showing a single spot were pooled, filtered through a pad of glass wool and evaporated under reduced pressure to give a residue which was re-evaporated twice with 30 ml portions of diethyl ether. The solid obtained was triturated with anhydrous ether in the dark overnight, filtered and dried *in vacuo* over phosphorus pentoxide at 70° to give 190 mg (67%) of a white solid, mp 180-182° dec. The compound was homogenous on tlc in three different solvent systems; a) cellulose, 10% aqueous acetic acid, R_f = 0.45, b) silica gel, chloroform-methanol-ammonium hydroxide, 14:2:1, R_f = 0.43, c) silica gel, ethyl acetate-methanol, 2:1, R_f = 0.45; ir (nujol): 3180, 3360 (NH_2) cm^{-1}; ^1H nmr (DMSO-d_6): 300 MHz δ 1.49-1.63 (m, 3H, 6-H and 9-CH_2), 1.84-1.92 (q, 1H, 5-H, $J_{5,5}$ = 15.03 Hz, $J_{5,6}$ = 7.06 Hz), 2.44-2.49 (q, 1H, 5-H, $J_{5,5}$ = 15.03 Hz), 2.57-2.64 (q, 2H, 10-CH_2), 2.76-2.82 (q, 1H, 7-H, $J_{7,7}$ = 11.8 Hz, $J_{7,6}$ = 7.68 Hz), 3.16-3.20 (q, 1H, 7-H, $J_{7,7}$ = 11.8 Hz), 5.27 (br s, 2H, 4-NH_2), 5.56 (br s, 2H, 2-NH_2), 6.08 (br s, 1H, 8-NH), 6.70-6.73 (q, 1H, 6'-H), 6.81-6.85 (m, 2H, 2'-H and 5'-H).

Anal. Calcd. for $C_{17}H_{23}N_5O_2 \cdot 0.5\ H_2O$: C, 60.34; H, 7.15; N, 20.69. Found: C, 60.61; H, 6.86; N, 20.32.

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