the aqueous phase was concentrated in vacuo until salts began to crystallize. Enough water was added to complete solution, the pH was adjusted to 6–7, and then the solution was applied to a column containing Dowex 1 × 2 (100–200 mesh, formate form, 40 ml). The resin was washed with water (2 l.) to remove unreacted **13** and the inorganic salts. The compound was obtained by gradient elution (0.1 *M* formic acid to H_2O). The eluent containing the compound was pooled, frozen, and lyophilized to yield 0.24 g (23.5%) of **14**, mp >169° dec. This was slightly impure, so 0.17 g of this product was passed through a column containing the same resin as above (15 ml), to give 0.11 g of pure (**14**) after work-up as above: mp >172° dec; $[\alpha]^{25}D$ −62.9° (*c* 1.0, H_2O); ^1H NMR (D_2O) δ 5.71 (d, *J* = 5.5 Hz, $C_{1'}H$), 7.50 (s, 2 H, C_2H and C_3H); uv λ_{max} (pH 1) 265 nm (ε 8.4), 302 (19.4); λ_{max} (pH 7) 293 nm (ε 19.9); λ_{max} (pH 11) 292 nm (ε 20.3).

Anal. Calcd for $C_{11}H_{15}N_4O_8P \cdot 1.5H_2O$ (389.25): C, 33.94; H, 4.66; N, 14.39. Found: C, 34.14; H, 4.38; N, 14.54.

Acknowledgment. The authors wish to thank Dr. Mason G. Stout for helpful discussions relative to this work.

Registry No.—**1**, 1074-41-5; **2**, 3289-35-8; **3**, 56817-09-5; **4**, 55662-66-3; **5**, 56817-10-8; **6**, 13035-61-5; **7**, 56817-11-9; **9**, 56817-12-0; **10**, 56817-13-1; **11**, 56817-14-2; **β-12**, 56817-10-8; **α-12**, 56817-15-3; **13**, 56817-16-4; **14**, 56817-17-5; **15**, 56817-18-6; **16**, 56817-19-7; **17**, 56817-20-0; **18**, 56817-21-1; **19**, 56817-22-2; 2,2-dimethoxypropane, 77-76-9; phosphorus oxychloride, 10025-87-3; 7-chloroimidazo[1,2-*c*]pyrimidin-5-one anion, 56817-23-3.

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Pyrimido[4,5-*b*][1,4]oxazines, 8-Oxadihydropteridines[1]

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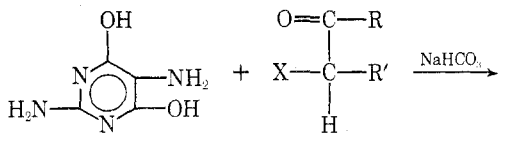
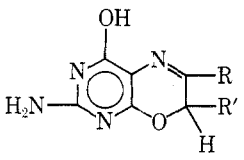
Received May 15, 1975

The synthesis and characterization of several 2-amino-4-hydroxy-6- and/or -7-(substituted)pyrimido[4,5-*b*]-[1,4]oxazines (8-oxadihydropteridines) have been accomplished. These compounds are homeosteric analogues of the 7,8-dihydropteridine moiety and were produced by the condensation of 2,5-diamino-4,6-pyrimidinediol and an α-halo ketone. Hydrogenation of the N_5–C_6 double bond in formic acid produced a mixture of cis and trans isomers when both the 6 and 7 positions were substituted. An analysis of their NMR spectra indicated a preference for cis isomer formation.

Homeosteric[2] replacement of the N_8 nitrogen in the pteridine nucleus by oxygen has not been widely studied. However, synthesis of the pyrimido[4,5-*b*][1,4]oxazine (8-oxadihydropteridine) ring system has been accomplished by cyclization of 5-(chloroacetamido)-4-methyl-2,6-pyrimidinediol to give 2,6-dihydroxy-4-methyl-8-oxadihydropteridine.[3,4] More recently, another route has been reported by the reaction of an α-halo ketone and 2,4,5-triamino-6-pyrimidinol to yield 2,4-diamino-8-oxadihydropteridine derivative.[5] Unfortunately, this method often yielded a pteridine as the major product in preference to a 8-oxadihydropteridine derivative. A synthesis of the 8-oxadihydropteridine ring system was then attempted by the condensation of an α-halo ketone and 2,5-diamino-4,6-pyrimidinediol.[1] In con-

trast to previous reported procedures,[5] this route yields unambiguous products, and the physical and spectral proper-





1

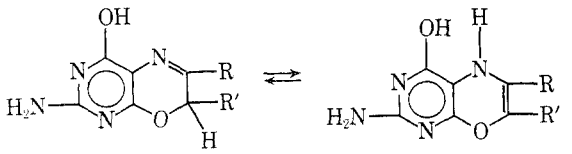
ties of a number of 6- and/or 7-(substituted) analogues have been examined. Since characteristic reactions of this ring system are of interest, several 8-oxadihydropteridines were hydrogenated, and the stereochemistry of the resulting derivatives identified.

Results and Discussion

2-Amino-4,6-pyrimidinediol was produced by the reaction of guanidine with diethyl malonate.[6] Nitrosation of the 5 position under acidic conditions followed by reduction with dithionite gave 2,5-diamino-4,6-pyrimidinediol.[7,8] Condensation of an α-halo ketone and 2,5-diamino-4,6-pyrimidinediol in the presence of sodium bicarbonate yielded 2-amino-4-hydroxy-8-oxadihydropteridine derivatives. Yields varied between 52 and 70%. All of the compounds decomposed around 250°C and were only sparingly soluble in common solvents. The analogues were characterized through elemental analyses, ultraviolet spectra, and nuclear magnetic resonance studies.

Characteristic uv spectra for acid solutions of the 8-oxadihydropteridines possess two major maximum absorption peaks at 264 and 361 nm. Substituent groups at either the 6 or 7 positions did not affect the uv spectra significantly. However, reduction to the corresponding 8-oxatetrahydropteridine resulted in loss of the absorption peak at 361 nm. This is analogous to the spectral properties of 2,6-diamino-4-hydroxy-7,8-dihydropteridine in acid solutions, where maximum absorption peaks at 280 and 330 nm were reported. The corresponding tetrahydropteridine has only one absorption at 280 nm.[9]

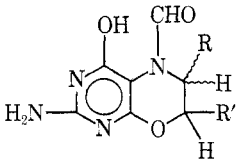
8-Oxadihydropteridines which possess a hydrogen in the 7 position can exist in two tautomeric forms. It has been re-



2 3

ported that form 2 is most favored by 2,4-diamino-8-oxadihydropteridines[5] and the structurally similar pyrimido[4,5-*b*][1,4]thiazines (8-thiodihydropteridines).[10] Both 2-amino-4-hydroxy-6,7-dimethyl-8-oxadihydropteridine (**1a**) and 2-amino-4-hydroxy-6-phenyl-7-methyl-8-oxadihydropteridine (**1e**) possess NMR spectra showing the 7 hydrogen split into a quartet by the adjacent methyl group, and the 7 methyl split into a doublet by the adjacent hydrogen (Table II). Thus, in this case structure **2** also appears to be the preferred isomer at least in trifluoroacetic acid solutions.

The N_5–C_6 double bond readily underwent hydrogenation, and if formic acid was used as a solvent, the N_5 position was concurrently formylated to produce 5-formyl-8-oxatetrahydropteridines.[4]



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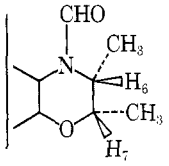
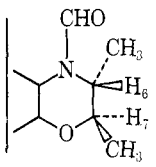
Theoretically, hydrogenation of a 6,7-disubstituted 8-oxadihydropteridine should produce a mixture of cis and trans isomers. If the hydrogen atoms come in from the same side as the 7 substituent, then the trans isomer will be produced, and if they come in from the opposite side, the cis isomer will be produced. However, reaction from the same side should be sterically more difficult and approach from the opposite side might be preferred. Thus, the majority of the hydrogenated product should be cis isomer.



cis

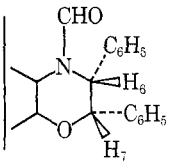


trans

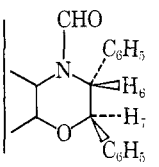
The NMR spectra of 2-amino-4-hydroxy-5-formyl-6,7-dimethyl-8-oxatetrahydropteridine (**4a**) shows four peaks for the 6 and 7 hydrogens. The cis isomer has two at δ 4.16 and 4.84, and the trans isomer has two at δ 3.68 and 4.56. A cis to trans ratio of 70:30 was estimated from the peak areas. For both isomers, the 7 hydrogen, which is closer to the more electronegative oxygen, appears downfield from the 6 hydrogen.

In the cis isomer, the 6 and 7 hydrogens are in an equatorial, axial conformation. The typical coupling constants of cyclohexane hydrogens in this conformation are usually small (i.e., 2–3 Hz).[11] Repulsion between the cis 6 and 7 methyl groups could cause an even greater dihedral angle between the 6 and 7 hydrogens, and from the Karplus relation, coupling constants even smaller than those in cyclohexane could result.[12] Indeed, it appears that the 6 and 7 hydrogens couple to a small degree (ca. <2 Hz) as only quartets were observed at δ 4.16 and 4.84.

In the trans isomer, the 6 and 7 methyls are probably in an equatorial, equatorial conformation, and this means that the 6 and 7 hydrogens will be axial, axial. Cyclohexane axial, axial hydrogens have a large average coupling of about 8–10 Hz,[11] and the 8-oxatetrahydropteridine 6 and 7 hydrogens also exhibit a large coupling (ca. 8–10 Hz) which produces pentuplets at δ 3.68 and 4.56.



cis



trans

The NMR spectra of 5-formyl-6,7-diphenyl-8-oxatetrahydropteridine (**4c**) is much simpler because only two doublets are observed. The 7-hydrogen doublet is at δ 6.10 and the 6-hydrogen doublet is at δ 5.82. Apparently, only cis isomer is formed since the coupling constant observed for each of the doublets was 3.5 Hz. This is consistent with the 6 and 7 hydrogens being in an equatorial, axial conformation, but not the axial, axial arrangement required by the trans isomer.

In a similar manner, the 6-phenyl-7-methyl derivative (**4e**) was found to possess a cis to trans ratio of 60:40, and the 6-methyl-7-phenyl analogue (**4f**) was found to consist

Table I[a]
2-Amino-4-hydroxy-7*H*-pyrimido[4,5-*b*][1,4]oxazines (1)

Compd	No.	Yield, %	Mp, °C	Formula	Uv spectrum: 2 *N* HCl λ_{max}, nm	Log ϵ	2 *N* NaOH λ_{max}, nm	Log ϵ
6,7-Dimethyl-	1a	70	>320	$C_8H_{10}N_4O_2 \cdot H_2O$	267	4.35	268	3.99
					341	4.47	311	3.94
6-Methyl-	1b	65	>320	$C_7H_8N_4O_2 \cdot 2H_2O$	266	3.87	267	3.77
					347	4.05	311	3.71
6,7-Diphenyl-	1c	69	294–296 dec	$C_{18}H_{14}N_4O_2$	258	4.32	279	3.82
					353	4.13	366	3.92
6-Phenyl-	1d	64	303–305 dec	$C_{12}H_{10}N_4O_2$	258	4.16	275	3.71
					391	4.07	361	4.01
6-Phenyl-7-methyl-	1e	59	298–299 dec	$C_{13}H_{12}N_4O_2$	272	4.27	279	3.84
					384	4.37	362	4.32
6-Methyl-7-phenyl-	1f	52	314–316 dec	$C_{13}H_{12}N_4O_2 \cdot {}^1/_2H_2O$	262	4.11	264	3.63
					351	3.87	319	3.46

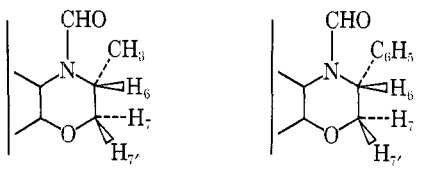
[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all compounds listed in this table.

Table II
NMR Spectra[a] of 2-Amino-4-hydroxy-7*H*-pyrimido[4,5-*b*][1,4]oxazines (1)

Compd	
6,7-Dimethyl- (1a)	δ 1.92 (d, 3 H, 7-CH_3), 2.82 (s, 3 H, 6-CH_3), 5.88 (q, 1 H, –H), 7.90 (s, 2 H, $-NH_2$)
6-Methyl- (1b)	δ 2.70 (s, 3 H, $-CH_3$), 5.62 (s, 2 H, $-CH_2-$), 7.68 (s, 2 H, $-NH_2$)
6,7-Diphenyl- (1c)	δ 2.78 (s, 1 H, –H), 7.82 [m, 12 H, 2($-C_6H_5$), $-NH_2$]
6-Phenyl- (1d)	δ 6.08 (s, 2 H, $-CH_2-$), 7.78 (m, 7 H, $-C_6H_5$, $-NH_2$)
6-Phenyl-7-methyl- (1e)	δ 1.88 (d, 3 H, $-CH_3$), 6.70 (q, 1 H, –H), 8.16 (m, 7 H, $-C_6H_5$, $-NH_2$)
6-Methyl-7-phenyl- (1f)	δ 2.66 (s, 3 H, $-CH_3$), 6.64 (s, 1 H, –H), 7.68 (m, 7 H, $-C_6H_5$, $-NH_2$)

[a] Solvent CF_3COOH.

only of cis isomer. These observed isomer distributions do not appear to have resulted from acid-catalyzed ring opening and ring closing of the reduced product. A sample of 5-formyl-6,7-diphenyl-8-oxatetrahydropteridine (**4c**) dissolved in 97% formic acid showed no appearance of trans isomer over a 24-hr period.



No geometrical isomers are possible in the case of the 6-methyl- or 6-phenyl-5-formyl-8-oxatetrahydropteridines (**4b, 4d**), but the NMR spectra are still informative. The 6, 7, and 7′ hydrogens in the 6-methyl analogue (**4b**) form an $ABCX_3$ system. LAOCOON III computer analysis[13] of the resulting NMR patterns gave the following coupling constants: $J_{6,7} = 8.80$, $J_{6,7'} = 0.01$, $J_{7,7'} = -12.00$, and $J_{6\text{-}CH_3} = 2.40$ Hz.

The 6, 7, and 7′ hydrogens in the 6-phenyl derivative (**4d**) form an ABX system. Computer analysis[13] gave the following coupling constants: $J_{6,7} = 10.00$, $J_{6,7'} = 1.10$, and $J_{7,7'} = -13.10$ Hz. These results support the previous NMR assignments, as the trans 6 and 7 hydrogens have much larger coupling constants than the cis 6 and 7′ hydrogens.

Experimental Section

Melting points were determined in a capillary melting point apparatus and are uncorrected. Uv spectra were determined with a Beckman DB-GT grating spectrophotometer. NMR spectra were carried out on a Jeol PS-100 high-resolution NMR at 100 MHz using tetramethylsilane as internal standard. Microanalyses were performed either by Heterocyclic Chemical Co., Harrisonville, Mo., or Midwest Microlab, Indianapolis, Ind.

α-Halo Ketones. These compounds were purchased from commercial sources except for α-chloro-α-phenylacetophenone, which was synthesized by the procedure of Ward,[14] and 1-chloro-1-phenyl-2-propanone, which was prepared by the procedure of Bordwell and Scamehorn.[15]

2-Amino-4,6-pyrimidinediol. The following synthesis is a modification of a previously reported procedure.[6] Sodium (12.0 g, 0.52 mol) was dissolved in 300 ml of ethanol, guanidine hydrochloride (48.0 g, 0.50 mol) was added, and the solution was filtered. Another sodium ethoxide solution was prepared by dissolving sodium (23.0 g, 1.0 mol) in 500 ml of ethanol, to which was added diethyl malonate (80.0 g, 0.50 mol) and the guanidine solution prepared above. The resulting reaction mixture was heated under reflux for 1 hr. After evaporation to dryness in vacuo, the residue was taken up in water, and the pH adjusted to 6 with acetic acid. The precipitate which formed was filtered, washed with ethanol and ether, and finally dried for 12 hr at 60°C in vacuo: yield 58.0 g, 91.3%; mp >300°C; uv (0.1 *N* HCl) λ_{max} 255 nm (log ϵ 4.03) [Davoll and Laney[16] give uv (0.1 *N* HCl) λ_{max} 256 nm (log ϵ 3.98)].

2,5-Diamino-4,6-pyrimidinediol. The following synthesis is a combination of two previously reported procedures[7,8] with modifications. Finely ground 2-amino-4,6-pyrimidinediol (25.4 g, 0.2 mol) was suspended in a mixture of 300 ml of water, 300 ml of ethanol, and 20 ml of acetic acid. Sodium nitrite (13.8 g, 0.2 mol), dissolved in 50 ml of water, was added in several portions with stirring. The resulting mixture was stirred for an additional 0.5 hr at room temperature, and the reddish nitrosopyrimidine which formed was filtered. The solid was suspended in 400 ml of warm water, heated to 75°C, and sodium dithionite added in small portions until the color of the reaction mixture changed to a light yellow. The suspension was maintained at 70–80°C for 20 min and then cooled in an ice bath. Concentrated sulfuric acid (50 ml) was carefully added and the mixture again cooled. The precipitated pyrimidine hemisulfate was filtered and dried in vacuo overnight. The crude solid was suspended in 100 ml of water, the pH was adjusted to 8 with 2 *N* sodium hydroxide, and the free base was filtered and added immediately to 300 ml of 6 *N* hydrochloric acid. The resulting solution was treated with charcoal and filtered, ethanol (600 ml) was added to the filtrate, and the solution was cooled overnight. 2,5-Diamino-4,6-pyrimidinediol hydrochloride crystallized as white needles which were filtered and dried in vacuo: yield 23.3 g, 59.0%; mp >300°C; uv (2 *N* HCl) λ_{max} 256 nm (log ϵ 4.03) [Bendrich and Clements[17] give uv (0.25 *N* HCl) λ_{max} 253 nm (ϵ not reported)]. The compound gave a strongly positive alkaline phosphomolybdate test, confirming that a 5-amino group was present.[17]

Table III[a]
2-Amino-4-hydroxy-5-formyl-6,7-dihydro-5*H*-pyrimido[4,5-*b*][1,4]oxazines (4)

Compd	No.	Yield, %	Mp, °C	Formula	Uv spectrum: 2 *N* HCl λ_{max}, nm	2 *N* HCl Log ϵ	2 *N* NaOH λ_{max}, nm	2 *N* NaOH Log ϵ
6,7-Dimethyl	4a	89	272–274 dec	$C_9H_{12}N_4O_3$	259	4.01	253	4.31
6-Methyl[b]	4b	85	286–288 dec	$C_8H_{10}N_4O_3 \cdot {}^1/_2H_2O$	258	3.82	249	4.35
6,7-Diphenyl-	4c	86	315–318 dec	$C_{19}H_{16}N_4O_3$	266	3.87	253	4.21
6-Phenyl-	4d	92	273–274 dec	$C_{13}H_{12}N_4O_3 \cdot 2H_2O$	255	4.06	256	4.35
6-Phenyl-7-methyl-	4e	84	310–313 dec	$C_{14}H_{14}N_4O_3 \cdot {}^1/_2H_2O$	261	3.86	256	4.19
6-Methyl-7-phenyl-	4f	85	>320	$C_{14}H_{14}N_4O_3 \cdot {}^1/_2H_2O$	258	4.10	260	4.33

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all compounds listed in this table. [b] Analytical sample obtained after recrystallization from boiling water.

Table IV
NMR Spectra of 2-Amino-4-hydroxy-5-formyl-6,7-dihydro-5*H*-pyrimido[4,5-*b*][1,4]oxazines (4)

6,7-Dimethyl-[a] (4a)	δ 1.46 [m, 6 H, 2(−CH_3)]; 3.68 (p, trans isomer), and 4.16 (q, cis isomer) (1 H, 6 hydrogen); 4.56 (p, trans isomer) and 4.84 (q, cis isomer) (1 H, 7 hydrogen); 7.15 (sharp s overlapping broad s, 3 H, −NH_2, −CHO)
6-Methyl-[b,c] (4b)	δ 1.65 (d, 3 H, −CH_3); 4.20 (m, 1 H, 6 hydrogen), 4.61 (t, 1 H, 7 hydrogen trans to 6 hydrogen); 4.87 (d, 1 H, 7 hydrogen cis to 6 hydrogen); 7.32 (sharp s overlapping broad s, 3 H, −NH_2, −CHO)
6,7-Diphenyl-[a] (4c)	δ 5.82 (d, 1 H, 6 hydrogen); 6.10 (d, 1 H, 7 hydrogen); 7.12 [m, 13 H, 2(−C_6H_5), −NH_2, −CHO]
6-Phenyl-[b,c] (4d)	δ 4.90 (AB portion of ABX pattern, 2 H, 7 and 7′ hydrogen); 5.94 (X portion of ABX pattern, 1 H, 6 hydrogen); 7.29 (m, 8 H, −C_6H_5, −NH_2, −CHO)
6-Phenyl-7-methyl- (4e)[b]	δ 1.08 (m, 3 H, −CH_3); 4.26 (m, trans isomer) and 4.59 (m, cis isomer) (1 H, 7 hydrogen); 4.78 (d, trans isomer) and 5.55 (s, cis isomer) (1 H, 6 hydrogen); 7.10 (m, 8 H, −C_6H_5, −NH_2, −CHO)
6-Methyl-7-phenyl- (4f)[b]	δ 0.92 (d, 3 H, −CH_3); 5.00 (m, 1 H, 6 hydrogen); 5.43 (d, 1 H, 7 hydrogen); 7.21 (m, 8 H, −C_6H_5, −NH_2, −CHO)

[a] Solvent CF_3COOH. [b] Solvent 97% HCOOH. [c] Second-order patterns subjected to LAOCOON III computer analysis.[13]

Anal. Calcd for $C_4H_6N_4O_2 \cdot HCl \cdot 1{}^1/_2H_2O$: C, 23.35; H, 4.90; N, 27.24. Found: C, 23.37; H, 4.70; N, 27.55.

7*H*-Pyrimido[4,5-*b*][1,4]oxazines (8-Oxadihydropteridines) (1). All of these derivatives were synthesized by comparable procedures. Individual physical data and uv spectra are summarized in Table I. 2,5-Diamino-4,6-pyrimidinediol hydrochloride (2.06 g, 0.01 mol) was suspended in a solvent containing 250 ml of water and 250 ml of ethanol. The resulting mixture was heated to reflux and the appropriate α-halo ketone (0.02 mol), dissolved in 25 ml of ethanol, was added dropwise. After 10–15 min sodium bicarbonate (1.68 g, 0.02 mol), dissolved in 25 ml of water, was added dropwise with continued heating. After 6 hr, heating was discontinued and the mixture was cooled overnight. A precipitate formed which was filtered and dried in vacuo. In those instances where no precipitate formed, the reaction mixture was reduced in volume in vacuo to produce a solid product. Ir spectra obtained for the various 8-oxadihydropteridines are all very similar and showed typical maximum absorptions at (Nujol) 3390, 1650, 830, 770, and 660 cm^{-1}. NMR spectra are given in Table II.

Hydrogenation of the 7*H*-Pyrimido[4,5-*b*][1,4]oxazines (4). The reduction procedures used for all of the analogues studied are comparable. Individual physical data and uv spectra are summarized in Table III. The appropriate 8-oxadihydropteridine (0.5 g) was dissolved in 150 ml of 88% formic acid, platinum oxide (10 mg) was added, and the reaction mixture was shaken under hydrogen pressure (50 lb) for 2 hr at room temperature. The catalyst was filtered, the filtrate was concentrated in vacuo, and ether was added. After cooling overnight, the resulting precipitate was filtered and dried in vacuo to give the corresponding 6,7-dihydro-5-formyl-5*H*-pyrimido[4,5-*b*][1,4]oxazine (4). NMR spectra are given in Table IV.

Acknowledgment. This study was supported in part by the Robert A. Welch Foundation (B-342) and the North Texas State University Faculty Research Fund. D.L.D. holds the Samuel R. Noble Foundation Fellowship, 1974–1975. We are indebted to Gary P. Holmes for technical assistance in the preparation of some compounds used in this study.

Registry No.—**1a,** 56830-44-5; **1b,** 56830-45-6; **1c,** 56830-46-7; **1d,** 56830-47-8; **1e,** 56830-48-9; **1f,** 56830-49-0; *cis*-**4a,** 56830-50-3; *trans*-**4a,** 56830-51-4; **4b,** 56830-52-5; **4c,** 56830-53-6; **4d,** 56830-54-7; *cis*-**4e,** 56830-55-8; *trans*-**4e,** 56830-56-9; **4f,** 56830-57-0; 2-amino-4,6-pyrimidinediol, 56-09-7; guanidine hydrochloride, 50-01-1; diethyl malonate, 105-53-3; 2,5-diamino-4,6-pyrimidinediol hydrochloride, 56830-58-1.

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