Synthesis of Some Substituted Guanidinopyrimidines and their Structural Assignment by ^{13}C and ^{1}H NMR

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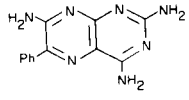
A series of substituted 2- and 4-guanidinopyrimidines were prepared by reaction of halopyrimidines with guanidine; alkylamino and amino substituents were introduced by subsequent halogen replacement by primary amines or ammonia or the catalytic reduction of nitro groups. Structural assignments were made on the basis of ^{13}C and ^{1}H nmr. A guanidinopteridine and a bispyrimidinylguanidine were also synthesized. Some unsuccessful reactions illustrated the low nucleophilic reactivity and thermal instability of the guanidine group.

J. Heterocyclic Chem., **19**, 917 (1982).

We wish to report the synthesis of a series of substituted 2-guanidinopyrimidines, 4-guanidinopyrimidines, a guanidinopteridine and a bispyrimidinylguanidine. These compounds are of interest as potential potassium-sparing diuretics. They possess some structural features of the known (1) potassium-sparing diuretic triamterene (**1**).



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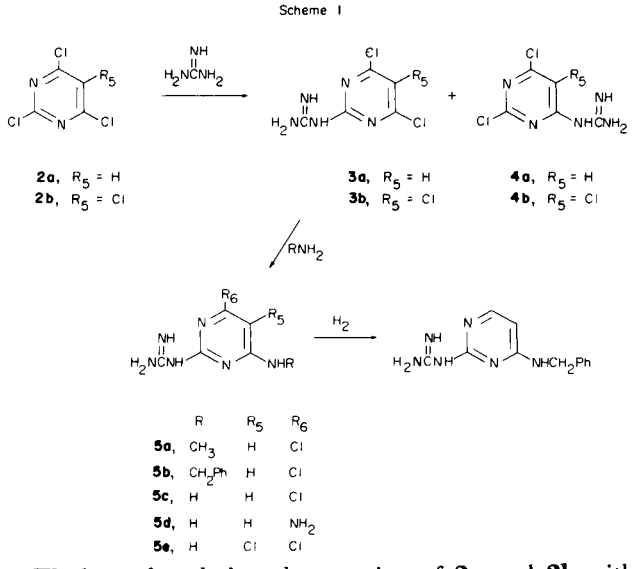
Intermediates **3a** and **3b** were required for the preparation of several guanidinopyrimidines. It has been reported (2) that 2,4,6-trichloropyrimidine (**2a**) reacts with guanidine to give exclusively **4a** (Scheme I).

Scheme I



	R	R_5	R_6
5a,	CH_3	H	Cl
5b,	CH_2Ph	H	Cl
5c,	H	H	Cl
5d,	H	H	NH_2
5e,	H	Cl	Cl

We have found that the reaction of **2a** and **2b** with guanidine gives a mixture of 2- and 4-guanidinopyrimidine. In addition, the product described by King and King (2) is **3a** and not **4a** as stated. The structural assignments were made unambiguously by ^{13}C-nmr (Table I).

Table I

^{13}C NMR Chemical Shifts of 2- and 4-Guanidinopyrimidines

Compound No.	C-5	Other C's
3a	108.6	164.9, 160.3, 159.8
4a	111.0	168.8, 160.2, 157.5, 157.3
5c (a)	98.6	164.7, 157.9, 156.6, 155.8
11a	101.6	169.4, 162.0, 160.1, 158.1
3b	112.3	161.4, 159.8, 156.9
4b	116.9	163.9, 160.6, 154.6, 154.0
5e (a)	106.0	161.4, 156.4, 155.8, 154.3

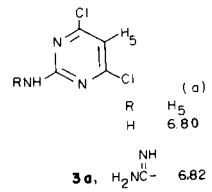
(a) Hydrochloride salt.

The symmetrically substituted pyrimidines (**3a, 3b**) showed only four types of carbon atoms, whereas the unsymmetrically substituted pyrimidines (**4a, 5c, 11a, 4b, 5e**) showed five types of carbon atoms. No attempt was made to assign the carbon resonances other than the obvious C-5 peaks.

The proton nmr spectra of **3a** and **4a** (Table II) provide additional support for these structural assignments. The ^{1}H nmr chemical shifts for the H_5-hydrogen in **3a** and **4a** compare favorably with the reported (3) chemical shifts for the analogous aminopyrimidines.

Table II

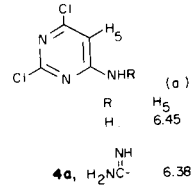
^{1}H NMR Chemical Shifts of Amino- and Guanidinodichloropyrimidines



(a)

R	H_5
H	6.80

3a, $H_2NC(=NH)-$ 6.82



(a)

R	H_5
H	6.45

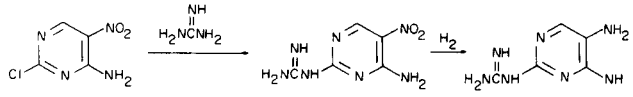
4a, $H_2NC(=NH)-$ 6.38

(a) Chemical shifts in ppm downfield from TMS (DMSO-d_6 solution).

Substituted 2-guanidinopyrimidines **5(a-e)** were prepared by the nucleophilic replacement (4) of chloropyrimidines **3a,b** by primary amines or ammonia (Scheme I). Interestingly, reductive dehalogenation of **5b** afforded **6** without causing debenzylation.

It is well known (5) in pyrimidine chemistry that amino groups have a deactivating effect toward nucleophilic replacement and that nitro groups provide activation. Therefore, synthesis of pyrimidine **9** (Scheme II) required starting with the more reactive 4-amino-2-chloro-5-nitropyrimidine (**7**) which was converted to **8** with guanidine, then catalytically reduced to 4,5-diamino-2-guanidinopyrimidine (**9**).

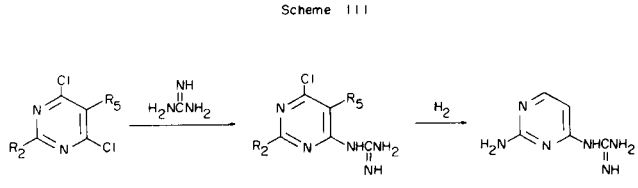
Scheme II



7 **8** **9**

Reaction of chloropyrimidines **10a** and **10b** with guanidine gave substituted 4-guanidinopyrimidines **11a,b** (Scheme III); **11a** was reductively dehalogenated to **12**.

Scheme III

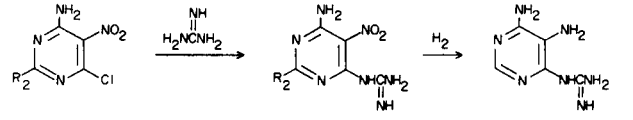


	R_2	R_5
10a,	NH_2	H
10b,	H	NH_2

Cpd	R_2	R_5
11a,	NH_2	H
11b,	H	NH_2

12

Scheme IV



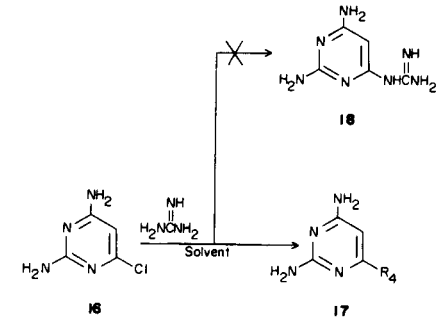
13a, R_2 = H
13b, R_2 = NH_2

14a, R_2 = H
14b, R_2 = NH_2

15

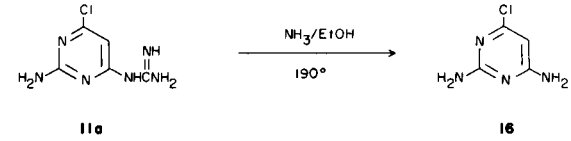
Scheme IV shows additional examples of the use of activated nitropyrimidines to prepare guanidinopyrimidines. The preparation of **14a** has been reported (6); catalytic reduction produced 4,5-diamino-6-guanidinopyrimidine (**15**).

During the preparation of the above compounds, some unsuccessful reactions illustrated the low nucleophilic reactivity and thermal lability of the guanidine group. For example, the highly deactivated 2,4-diamino-6-chloropyrimidine (**16**) preferred to react with solvent (presumably dimethylamine was present as an impurity in the DMF), to form **17 (a-c)** rather than the weakly reactive guanidine. Fusion with neat guanidine at 105° resulted in no reaction; at 135° the guanidine self-condensed to form melamine. In no case was any **8** observed. Reaction of guanidinopyrimidine (**11a**) with ammonia at 190° resulted in cleavage of the guanidine group to form **16**; at lower



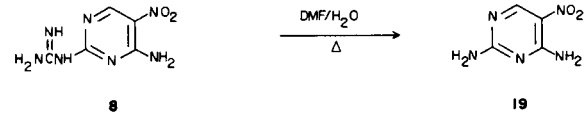
16 **17** **18**

Solvent	Temp	R_4	
2-methoxyethanol	reflux	$-O(CH_2)_2OCH_3$,	**17a**
toluene/methanol (trace)	reflux	$-OCH_3$,	**17b**
DMF	110°	$-N(CH_3)_2$,	**17c**



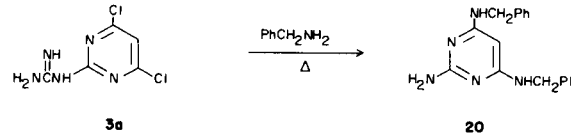
11a **16**

temperatures **11a** was recovered. Recrystallization of **8** from DMF/water caused it to decompose to **19**. Heating



8 **19**

3a with excess benzylamine also caused cleavage of the

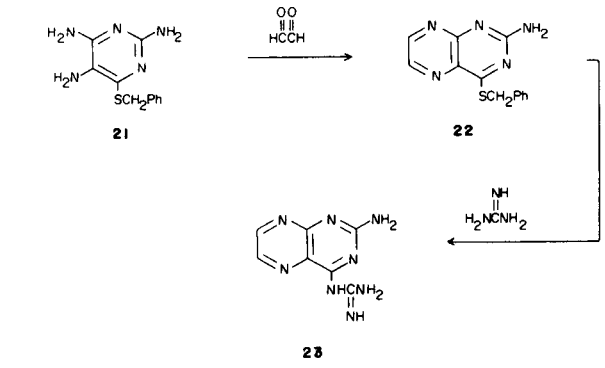


3a **20**

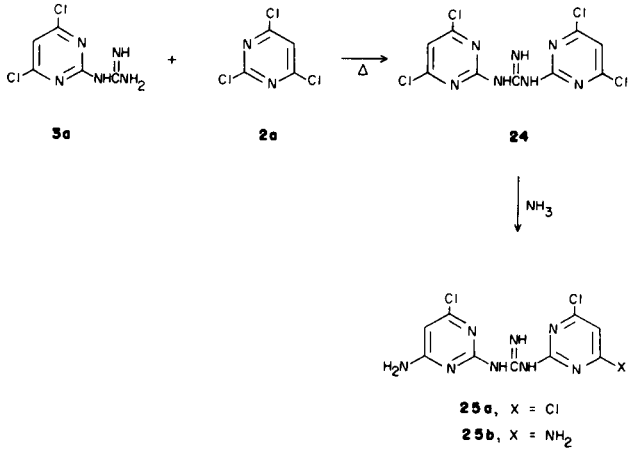
guanidine group to produce **20**.

The last two examples of guanidinopyrimidines, 2-amino-4-guanidinopteridine (**23**) and 1,3-bis(4-amino-6-chloro-2-pyrimidinyl)guanidine (**25b**) were prepared as outlined in Schemes V and VI.

Scheme V



Scheme VI



Pteridine **22** was prepared from **21** by a modification (7) of the literature procedure (8) and the benzylthio group displaced with guanidine. Bis compound **(24)** was prepared as shown; reaction of **24** with ammonia yielded initially the monoamine **25a** which on further reaction with ammonia yielded the symmetrical diamino compound **25b**. That **25b** is symmetrically substituted is not surprising in view of the deactivating effect of the amino group toward additional displacement. The structural assignments for **24, 25a** and **25b** were made on the basis of the ^{1}H nmr and mass spectra (see Experimental).

EXPERIMENTAL

Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Elemental analyses were performed by the analytical department of Smith Kline and French Laboratories. Mass spectra were obtained with either a Hitachi Perkin Elmer RMU 6E Spectrometer (electron impact) or a Varian MAT CH-5 DF Spectrometer (field desorption). The ^{13}C nmr spectra were recorded in DMSO-d_6 solution with tetramethylsilane as internal standard at 20 MHz using a Varian CFT-20 Fourier-Transform Spectrometer; ^{1}H nmr spectra were obtained on a Varian T60 spectrometer using tetramethylsilane as internal standard. Intermediates and final products were routinely checked for purity by reverse phase hplc.

Guanidine free base was prepared by stirring a solution of guanidine hydrochloride (0.5 mole) in 500 ml of methanol with sodium hydroxide pellets (0.5 mole) for 3½ hours, filtered and concentrating at 50°. Residual methanol was removed by slurrying in toluene and stripping at 70° to give a mushy white solid.

4,6-Dichloro-2-guanidinopyrimidine (**3a**).

A solution of 141.8 g (1.48 moles) of guanidine hydrochloride, 59.3 g (1.48 moles) of sodium hydroxide and 709 ml of water was added to a solution of 183.4 g (0.74 mole) of 2,4,6-trichloropyrimidine (**2a**) in 2127 ml of acetone causing a mild exotherm. After stirring for 1 hour at room temperature a mixture of solid and oil had formed. Refrigeration caused complete crystallization. The crystals were filtered, then suspended in 1200 ml of water and stirred for 1 hour, filtered, washed with water, then acetone and air dried to give 53.0 g (35%) of product, mp >360°; nmr (DMSO-d_6): δ 6.82 (s, 1, ArH), 7.17 (br s, 4, -NHC(NH)NH$_2$); ms: (electron impact) m/e 207, 205 (M+), 172, 170, 165, 163, 130, 128.

Anal. Calcd. for $C_5H_3Cl_2N_5$: C, 29.15; H, 2.45; N, 33.99. Found: C, 29.42; H, 2.43; N, 33.75.

4,5,6-Trichloro-2-guanidinopyrimidine (**3b**).

A solution of 19.1 g (0.20 mole) of guanidine hydrochloride, 8.0 g (0.20 mole) of sodium hydroxide and 50 ml of water was added to a solution of 21.8 g (0.10 mole) of 2,4,5,6-tetrachloropyrimidine (**2b**) in 300 ml of acetone causing a mild exotherm. Initially a mixture of oil and solid formed; after stirring for 1 ½ hours at room temperature only solid was pesent. The mixture was diluted with water to a volume of 1500 ml and two crops of precipitate collected. The combined precipitated solids were boiled with 250 ml of acetone and the insoluble material (0.6 g, crop I) filtered off; the mother liquor was cooled, then concentrated until precipitation starts to give 2.6 g of crop II. Tlc (2 methanol:8 chloroform, silica gel) of crops I and II shows them to be contaminated with a small amount of higher R_f material (**4b**); they were combined in 250 ml boiling acetone and sufficient methanol added to give a solution. The solution was reduced by ½ volume by concentrating on a rotavap, then cooled. Some insoluble matter was filtered off and the mother liquor was chromatographed on 100 g of silica gel eluting with dichloromethane with a 50-100% acetone gradient. The purified fractions were recrystallized from acetone/methanol to give 0.65 g (2.7%) of product, mp >360°; ms: (electron impact) m/e 243, 241, 239 (M+), 226, 224, 222, 206, 204, 201, 199, 197, 189, 187, 164, 162.

Anal. Calcd. for $C_5H_4Cl_3N_5 \cdot 0.10\ C_3H_6O$ (acetone): C, 25.85; H, 1.88; N, 28.44. Found: C, 25.78; H, 1.87; N, 28.41.

2,6-Dichloro-4-guanidinopyrimidine (**4a**).

The mother liquor from the preparation of **3a** was diltued with water to give a second crop of solid [tlc (2 methanol:8 chloroform, silica gel) shows two spots, the lower R_f spot corresponds to **3a**]. A 10.54 g sample of this material was slurried with 77 g of dry-column silica gel in acetone, concentrated to a powder and packed on top of a column pre-packed with 500 g of dry-column silica gel. The column was eluted with acetone; the initial fractions contained the desired material and were concentrated to 3.07 g. Recrystallization from acetone followed by recrystallization from methanol gave 0.58 g of product, mp, liquified and turned orange at 225°, then quickly resolidified, partially melted at 360°; nmr (DMSO-d_6): δ 6.38 (s, 1, ArH), 7.22 (br s, 4, NHC(NH)NH$_2$); ms: (electron impact) m/e 207, 206, 205 (M+), 204, 172, 170, 153, 128.

Anal. Calcd. for $C_5H_3Cl_2N_5$: C, 29.15; H, 2.45; N, 33.99. Found: C, 29.08; H, 2.59; N, 34.37.

2,5,6-Trichloro-4-guanidinopyrimidine (**4b**).

Guanidine and 2,4,5,6-tetrachloropyrimidine (**2b**) were reacted as described for **3b** on 0.010 mole scale. The solid (sodium chloride) was removed by filtration and discarded. The acetone filtrate was diluted with water and the resultant solid was collected [tlc (2 methanol:8

chloroform, silica gel) shows two spots of which the lower R_f one corresponds to **3b** plus a trace of bis(trichloropyrimidinyl)guanidine (9) near solvent front]. The solid was further purified by precipitation from methanol with water; it was then dissolved in warm acetone, diluted with dichloromethane and chromatographed on 30 g of silica gel eluting with 1:1 dichloromethane/acetone to give 0.42 g (17%) of product corresponding to the higher R_f spot, mp >300°; ms: (electron impact): 243, 241, 239 (M+), 226, 224, 222, 206, 204, 199, 197, 189, 187, 164, 162.

Anal. Calcd. for $C_5H_4Cl_3N_5$: C, 24.97; H, 1.68; N, 29.12. Found: C, 25.35; H, 1.54; N, 28.94.

4-Chloro-2-guanidino-6-methylaminopyrimidine Hydrochloride (**5a**).

Methylamine was bubbled into a refluxing mixture of 1.92 g (9.32 mmoles) of **3a** and 100 ml of methanol for 1.5 hours. The mixture was concentrated to a white foam which was recrystallized twice from ethanol/ether to give 0.77 g (35%) of product, mp 260-264°; nmr (DMSO-d_6): δ 2.78 (s, 3, CH_3), 6.37 (br s, 1, ArH), 8.50 (br s, 6); ms: (electron impact) m/e 202, 200 (M+), 183, 171, 160, 158.

Anal. Calcd. for $C_6H_6ClN_6 \cdot HCl$: C, 30.40; H, 4.25; N, 35.45. Found: C, 30.27; H, 4.35; N, 35.36.

4-Benzylamino-6-chloro-2-guanidinopyrimidine Hydrochloride (**5b**).

A solution containing 2.0 g (9.71 mmoles) of **3a**, 1.17 ml (10.7 mmoles) of benzylamine and 100 ml of methanol was refluxed overnight, filtered, then concentrated to a white foam which was recrystallized from ethanol/ether followed by recrystallization from ethanol/methanol/-ether to give 1.84 g (61%) of product, mp 246-250° dec; nmr (DMSO-d_6): δ 4.43 (d, 2, CH_2Ph), 6.40 (s, 1, ArH), 7.25 (s, 5, Ph), 8.48 (br m, 5), 10.73 (s, 1); ms: (electron impact) m/e 278, 276 (M+), 261, 259, 234, 106.

Anal. Calcd. for $C_{12}H_{13}ClN_6 \cdot HCl$: C, 46.02; H, 4.50; N, 26.83. Found: C, 46.06; H, 4.84; N, 26.56.

4-Amino-6-chloro-2-guanidinopyrimidine Dihydrochloride (**5c**).

A slurry of 20.0 g (0.0971 mole) of 4,6-dichloro-2-guanidinopyrimidine (**3a**) in 1000 ml of absolute ethanol was prepared in a stainless steel bomb. The slurry was then cooled to 0° and saturated with ammonia; the bomb was sealed, then heated and stirred at 115° for 16 hours. After cooling, the reaction mixture was concentrated to a dark viscous oil. The oil was dissolved in a small volume of hot methanol; then chilled to give 6.5 g of tan precipitate. The precipitate was recrystallized twice from methanol giving 1.95 g which was dissolved in warm methanol, diluted with ether, acidified with ethereal hydrogen chloride and more ether added. The precipitated white solid was filtered, washed with ether and vacuum dried giving 2.03 g (8.1%) of product, mp 241-245°; nmr (DMSO-d_6): δ 6.28 (s, 1, ArH), 8.32 (br m, 8); ms: (electron impact) m/e 188, 186 (M+), 171, 170, 169, 151, 146, 144, 109.

Anal. Calcd. for $C_5H_6N_6 \cdot 2HCl$: C, 23.14; H, 3.50; N, 32.31. Found: C, 23.51; H, 3.58; N, 32.00.

4,6-Diamino-2-guanidinopyrimidine Hydrochloride (**5d**).

The combined methanol mother liquors from the recrystallization of 4-amino-6-chloro-2-guanidinopyrimidine (**5c**) were concentrated to a small volume, then diluted with ether, acidified with ethereal hydrogen chloride, more ether added and chilled. The tan precipitate was collected, then triturated with 500 ml of boiling ethanol, filtered while hot and vacuum dried giving 2.05 g (9.0%) of light gray product, mp 274° dec; nmr (DMSO-d_6): δ 5.43 (s, 1, ArH), 8.57 (br m, 10); ms: (electron impact) m/e 167 (M+), 150, 125.

Anal. Calcd. for $C_5H_9N_7 \cdot 1.85HCl$: C, 25.60; H, 4.66; N, 41.79. Found: C, 25.37; H, 4.71; N, 41.98.

4-Amino-5,6-dichloro-2-guanidinopyrimidine Hydrochloride (**5e**).

A slurry of 2.25 g (9.31 mmoles) of **3b** and 112 ml of absolute ethanol was prepared in a stainless steel bomb. The slurry was cooled in an ice bath and ammonia bubbled in for 20 minutes, then sealed and heated at 65° for 17 hours. The resultant solution was concentrated to a white foam which was dissolved in hot water, filtered, acidified with concentrated hydrochloric acid and chilled. An additional 5 ml of concentrated hydrochloric acid caused precipitation of the product, 1.65 g (69%), mp 319° dec; ms: (electron impact) m/e 222, 220 (M+), 205, 203, 180, 178, 168.

Anal. Calcd. for $C_5H_6Cl_2N_6 \cdot HCl$: C, 23.32; H, 2.74; N, 32.64. Found: C, 23.57; H, 3.07; N, 32.56.

4-Benzylamino-2-guanidinopyrimidine Dihydrochloride (**6**).

A solution of 0.50 g (1.60 mmoles) of **5b**·HCl in 50 ml of 50% aqueous ethanol containing 1.0 g of magnesium oxide and 0.15 g of 10% Pd/C was hydrogenated at room temperature for 5 ½ hours at 50 psi. The mixture was heated on a steam bath, filtered and concentrated to an oil. The oil was converted to the dihydrochloride in methanol/ether giving 0.23 g (46%) of white crystalline solid with mp 217-223°; nmr (DMSO-d_6): δ 4.50 (br s, 2, CH_2Ph), 6.47 (d, 1, ArH), 7.27 (s, 5, Ph), 7.93 (d, 1, ArH); ms: (elecron impact) m/e 242 (M^+), 225, 200, 106, 91.

Anal. Calcd. for $C_{12}H_{14}N_6 \cdot 2HCl$: C, 45.73; H, 5.12; N, 26.66; Cl, 22.50. Found: C, 45.70; H, 4.89; N, 26.55; Cl, 22.20.

4-Amino-2-guanidino-5-nitropyrimidine Hydrochloride (**8**).

A mixture of 6.25 g (0.0358 mole) of 4-amino-2-chloro-5-nitropyrimidine (**7**), a large excess of guanidine free base and 200 ml of absolute ethanol was refluxed for 1 ½ hours. The ethanol was evaporated and the residue was treated with water giving a solid which was collected, washed with water and air-dried. The solid was slurried in methanol and treated with excess ethereal hydrogen chloride. After stirring for 1 hour the solid was collected and air-dried to 5.20 g (62%) of product. Attempted recrystallization of this material from DMF/water caused it to rapidly decompose to starting material upon heating. A small sample was purified by slurrying in methanol, filtering and concentrating without heat to give product of mp 303° dec; nmr (DMSO-d_6): δ 3.20 (methanol impurity), 8.50 (br s), 8.67 (br s), 9.00 (s, ArH), 9.17 (br s); ms: (electron impact) m/e 197 (M+), 155, 111.

Anal. Calcd. for $C_5H_7N_7O_2 \cdot HCl \cdot 1/6\ CH_3OH$: C, 25.97; H, 3.66; N, 41.03. Found: C, 25.57; H, 3.82; N, 41.21.

4,5-Diamino-2-guanidinopyrimidine Dihydrochloride (**9**).

A suspension of 0.98 g (4.19 mmoles) of **8** was treated with sufficient water and ethereal hydrogen chloride to cause complete solution to occur. This solution was hydrogenated over Raney nickel at room temperature on a Parr shaker at 45 psi for 20 minutes; filtering and removing the solvent at 45° gave 0.70 g (68%) of product, mp 225° dec; nmr (DMSO-d_6): δ 6.97 (br s), 8.23 (br s); ms: (electron impact) m/e 167 (M+), 150, 125.

Anal. Calcd. for $C_5H_9N_7 \cdot 2HCl \cdot \frac{1}{3}H_2O$: C, 24.20; H, 4.78; N, 39.84. Found: C, 24.09; H, 4.32; N, 40.17.

2-Amino-4-chloro-6-guanidinopyrimidine (**11a**).

A mixture of 12.0 g (0.0732 mole) of 2-amino-4,6-dichloropyrimidine (**10a**) and 55.0 g (0.931 mole) of guanidine free base was heated at 80° for 1.5 hours. The mixture was cooled to room temperature and diluted with water; the white crystalline precipitate was filtered, washed with water then air dried giving 7.22 g (53%) of product, mp 220° dec; nmr (DMSO-d_6): δ 5.70 (s, 1, ArH), 6.55 (br s, 6); ms: (electron impact) m/e 188, 187, 186 (M+), 185, 171, 169, 151, 144, 134, 128, 109, 92.

Anal. Calcd. for $C_5H_7ClN_6$: C, 32.18; H, 3.78; N, 45.04. Found: C, 32.08; H, 3.97; N, 45.43.

5-Amino-4-chloro-6-guanidinopyrimidine Hydrochloride (**11b**).

A solution of 6.87 g (0.0419 mole) of 4,6-dichloro-5-aminopyrimidine (**10b**) in absolute ethanol containing a large excess of guanidine free base was refluxed overnight. The solution was cooled to room temperature, filtered and the filtrate concentrated to an orange oil which was triturated with water giving a solid which was filtered and dried to 0.74 g (9.5%) of product. The hydrochloride salt was prepared in methanol-ether, mp 230° dec; ms: (electron impact) m/e 188, 186 (M^+), 171, 169, 151, 146, 144, 134, 119, 117.

Anal. Calcd. for $C_5H_7ClN_6 \cdot 0.9HCl$: C, 27.37; H, 3.63; N, 38.30. Found: C, 27.35; H, 3.69; N, 38.61.

2-Amino-4-guanidinopyrimidine Hydrochloride (**12**).

A solution of 3.0 g (0.0161 mole) of 2-amino-4-chloro-6-guanidinopyrimidine (**11a**) in a mixture of 100 ml of ethanol and 100 ml of water containing 3.0 g of magnesium oxide and 0.5 g of 10% Pd/C was hydrogenated at room temperature for 2.5 hours at 50 psi. The mixture was filtered, concentrated and the residue converted to the hydrochloride in methanol-ether giving 2.32 g (66%). Recrystallization from a mixture of methanol-ethanol gave product with mp 290° dec; nmr (DMSO-d_6/deuterium oxide): δ 6.48 (d, 1, ArH), 8.10 (d, 1, ArH); ms: (electron impact) m/e 152 (M+), 151, 135, 110, 94.

Anal. Calcd. for $C_5H_8N_6 \cdot 1.8HCl$: C, 27.58; H, 4.54; N, 38.59. Found: C, 27.44; H, 4.58; N, 38.48.

2,4-Diamino-6-guanidino-5-nitropyrimidine Hydrochloride (**14b**).

Guanidine hydrochloride (1.51 g, 15.8 mmoles) was suspended in 40 ml of dry DMF and 0.76 g (15.8 mmoles) of 50% sodium hydride in oil was added and stirred for 2 hours under nitrogen; 1.50 g (7.91 mmoles) of 2,4-diamino-5-nitro-6-chloropyrimidine (**13b**) (10) was then added. The yellow suspension was stirred at room temperature for 1 hour, heated at 55° for 1 hour, then stood overnight at room temperature. The mixture was filtered and the precipitate washed with ethanol. The combined filtrate and washing was diluted with water giving a yellow precipitate which was removed by filtration and discarded; the filtrate was concentrated to an oil which was boiled with 35 ml of ethanol; filtered while hot and allowed to cool to room temperature; some yellow precipitate was removed and the ethanol filtrate treated with ethereal hydrogen chloride to give 0.50 g (23%) of product, mp 324° dec; ms: (electron impact) m/e 212 (M+), 195, 182, 170, 166.

Anal. Calcd. for $C_5H_8N_8O_2 \cdot 1\ ⅔HCl$: C, 22.00; H, 3.57; N, 41.05. Found: C, 22.03; H, 3.48; N, 40.87.

4,5-Diamino-6-guanidinopyrimidine Sulfate (**15**).

A solution of 5.70 g (0.0289 mole) of 4-amino-6-guanidino-5-nitropyrimidine (**14a**) (6) in 500 ml 2-methoxyethanol was hydrogenated over Raney nickel at 60° for 20 minutes at 60 psi. The warm mixture was filtered, and concentrated; the brown residue was slurried in a warm mixture of 2-methoxyethanol and water, then made acidic with 10% sulfuric acid. The cooled mixture was filtered, then washed with water and ethanol giving 6.2 g (81%) of product. A purified sample was prepared by hot trituration of the crude product with 50% aqueous 2-methoxyethanol followed by methanol to give product of mp 305° dec; ms: (field desorption) m/e 168, 167 (M+), 151, 150.

Anal. Calcd. for $C_5H_9N_7 \cdot H_2SO_4$: C, 22.64; H, 4.18; N, 36.96. Found: C, 23.04; H, 4.11; N, 37.33.

2-Amino-4-benzylthiopteridine (**22**).

A mixture of 12.35 g (0.050 mole) of 2,5,6-triamino-4-benzylthiopyrimidine (**21**) (11), 7.60 ml (0.0525 mole) of 40% aqueous glyoxal, 5.45 g (0.0525 mole) of sodium bisulfite and 250 ml of 50% aqueous ethanol was heated at 55° for 2 hours. The reaction mixture was cooled to room temperature, the precipitate filtered, washed with water and air-dried to 10.27 g (76%) of product, mp 179° dec, [lit (8) mp 182-183°]; nmr (DMSO-d_6): δ 4.50 (s, 2, CH_2Ph), 7.35 (br m, 5, Ph), 8.40 (d, 1, ArH), 8.83 (d, 1, ArH); ms: (electron impact) m/e 269 (M+), 236, 91.

Anal. Calcd. for $C_{13}H_{11}N_5S \cdot ¼H_2O$: C, 57.02; H, 4.23; N, 25.58; S, 11.71. Found: C, 56.84; H, 4.43; N, 25.62; S, 11.98.

2-Amino-4-guanidinopteridine (**23**).

A mixture of 6.00 g (22.3 mmoles) of **22**, 4.26 g (44.6 mmoles) of guanidine hydrochloride, 1.80 g (45.0 moles) of sodium hydroxide and 210 ml of ethanol was refluxed for 30 minutes. The warm reaction mixture was filtered, concentrated to a small volume and the solid collected. The solid was triturated with 300 ml of boiling ethanol, then vacuum dried to give 2.37 g (52%) of product. A purified sample was obtained by recrystallization from water, mp 222° dec; nmr (DMSO-d_6): δ 6.87 (br s, 2), 7.83 (br s, 4), 8.32 (d, 1, ArH), 8.60 (d, 1, ArH); ms: (electron impact) m/e 204 (M+), 187, 162.

Anal. Calcd. for $C_7H_8N_8 \cdot 0.85NaCl$: C, 33.12; H, 3.18; N, 44.14. Found: C, 33.10; H, 3.43; N, 43.76.

1,3-Bis(4-amino-6-chloro-2-pyrimidinyl)guanidine Hydrochloride (**25b**).

A mixture of 8.20 g (0.040 mole) of **3a**, 11.40 g (0.062 mole) of **2a** and 500 ml of diethyl ketone was refluxed ovrnight, cooled, filtered and concentrated to a solid. The solid was triturated with two 75 ml portions of boiling acetone to give 3.86 g (14%) of **24** [nmr (DMSO-d_6): δ 7.28 (s, ArH); ms: (electron impact) m/e 355, 353, 351 (M+), 316, 314, 191, 189, 165, 163, 130, 128].

A slurry of 3.12 g (8.84 mmoles) of **24** in 150 ml of absolute ethanol in a glass bomb was cooled in an ice bath and ammonia bubbled in for 15 minutes; the bomb was sealed and heated and stirred at 80° for 2 hours. The slurry cooled and 1.73 g (59%) of **25a** was collected as a white solid; a sample was purified by trituration with warm aqueous methanol [nmr (DMSO-d_6): δ 6.17 (s, 1, ArH), 7.13 (s, 1, ArH); ms: (electron impact) m/e 336, 334, 332 (M+), 191, 189, 172, 170, 146, 144, 130, 128, 109].

A slurry of 0.95 g (2.85 mmoles) of **25a** in 200 ml of ethanol was reacted with ammonia in a glass bomb at 80° for 42 hours, cooled, and some unreacted **25a** removed by filtration. The ethanol filtrate was concentrated to 0.70 g (69%), mp >360°; nmr (DMSO-d_6): δ6.26 (s, 2, ArH), 7.67 (br s, 9); ms: (electron impact) m/e 315, 313 (M+).

Anal. Calcd. for $C_9H_9Cl_2N_9 \cdot HCl \cdot ¼H_2O$: C, 30.44; H, 2.98; N, 35.50. Found: C, 30.78; H, 3.24; N, 35.18.

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