2-Amino- and 2-Guanidino-4-thiazolylpyrimidines

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The synthesis of the four possible 2-amino- and 2-guanidino- 4-(2-amino- and 2-guanidinothiazolyl)pyrimidines is described and p*K*a values are calculated. Guanidinopyrimidines are more basic than guanidinothiazoles. However, the reverse is true of the corresponding amino heterocycles; the amino thiazole is more basic than the amino pyrimidine.

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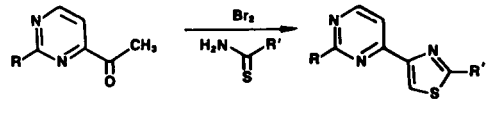
In connection with our interest in biaryl and guanidino thiazolyl heterocycles having hydrogen bonding and histamine H_2-receptor antagonist properties [1,2] we were interested in preparing four possible 2-amino- and 2-guanidino-4-(2-amino- and 2-guanidinothiazolyl)pyrimidines and determining the basicities of the amino and guanidinopyrimidine and thiazole moieties.

Although 4-substituted-2-amino- and 2-guanidinothiazoles are readily prepared by cyclization of thiourea or amidinothiourea with alpha-halo ketones, the precursor 2-amino- and 2-guanidino-4-acetylpyrimidines **1** and **2** (Scheme 1), which were projected as key intermediates to our targets **3**, **4**, **5** and **6** were unknown and proved difficult to prepare.

Scheme 1



1: R = NH_2

2: R = NH-C(=NH)-NH_2

3: R = NH_2; R' = NH_2

4: R = NH_2; R' = NH-C(=NH)-NH_2

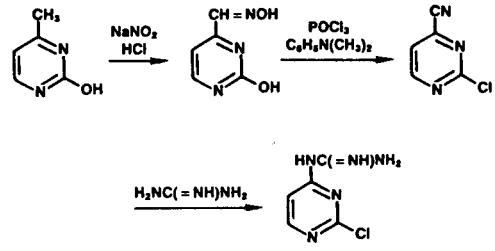
5: R = NH-C(=NH)-NH_2; R' = NH_2

6: R = NH-C(=NH)-NH_2; R' = NH-C(=NH)-NH_2

In a first approach towards the acetylpyrimidines **1** and **2** we sought to prepare a pyrimidine-4-carboxylic acid derivative which would serve as a precursor to **1** and **2**. The reaction of acetamidine with mucobromic acid has been reported to yield 5-bromo-2-methylpyrimidine-4-carboxylic acid which was subsequently debrominated with Raney nickel [3]. Attempts to prepare the analogous 5-bromo-2-guanidino pyrimidine-4-carboxylic acid by reaction of mucobromic acid with biguanide sulfate in aqueous sodium hydroxide resulted in isolation of a poorly soluble material in very low yield whose properties were most consistent with those of a Schiff base of mucobromic acid and biguanide.

A second approach was based on literature precedent indicating that guanidine can displace an appropriate leaving group in an electron deficient heterocycle [4]. In an attempt to prepare 4-cyano-2-guanidinopyrimidine which could serve as a 4-acetylpyrimidine precursor, we prepared 4-cyano-2-chloropyrimidine from 2-hydroxy-4-methylpyrimidine by a literature sequence [5] and combined this product with guanidine generated from guanidine nitrate and sodium hydride. The only product isolated in very low and not preparatively useful yield from this reaction was characterized by high resolution mass spectroscopy as the 2-chloro-4-guanidinopyrimidine (**7**) arising from loss of the 4-cyano group in preference to the 2-chloro group (Scheme 2).

Scheme 2



A third and successful approach relied on cyclization of biguanide with a β-dicarbonyl surrogate to give the required 2-guanidinopyrimidine. Although there are no literature examples of cyclization of biguanide to 2-guanidino-4-alkanoylpyrimidines, we felt that a reasonable precursor for the requisite 2-guanidino- and 2-amino-4-acetylpyrimidines would be an enone system **8** as shown in Scheme 3 in which Q is an appropriate leaving group.

Scheme 3

8 Z = $CO_2C_2H_5$; Q = OC_2H_5

9 Z = $CH(OCH_3)_2$; Q = $N(CH_3)_2$

10 Z = $C(OCH_3)_2CH_3$; Q = $N(CH_3)_2$

11 R = NH_2

12 R = NH-C(=NH)-NH_2

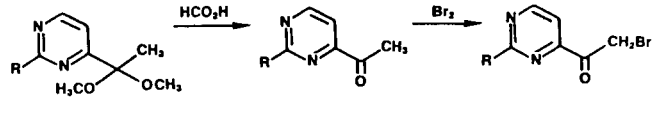
Initially our attention was focused on the known [6] intermediate **8** since a related intermediate is reported to cyclize with acetamidine to 2-methyl-4-benzoylpyrimidine [7]. However, reaction of **8** with biguanide sulfate in sodium ethoxide-ethanol failed to afford a pyrimidine adduct. Instead, there was obtained what appeared by nmr to be a Michael adduct which failed to cyclize thermally in ethanol or isopropanol or by refluxing in acetic acid or by heating neat to the melting point. Attempts to cyclize **8** with urea, guanidine or thiourea to gain an entry into the pyrimidine ring also failed.

Attention then turned to the known intermediate **9** related to **8** in which the Z group is a diethylacetal moiety. This intermediate is reported to cyclize with acetamidine or guanidine to a 2-methyl- or 2-aminopyrimidine-4-carboxaldehyde diethylacetal [8]. We prepared the related homologous dimethylketal **10** in 65% yield by heating the known 3,3-dimethoxybutan-2-one [9] neat with dimethylformamide dimethylacetal at 110° for 19 hours. Unlike **8** ketal **10** cyclized smoothly with guanide hydrochloride in ethanolic sodium ethoxide to give aminopyrimidine ketal **11** in good yield. A similar cyclization with biguanide sulfate also proceeded fairly cleanly to afford guanidinopyrimidine ketal **12** in 71% yield.

As shown in Scheme 4, the aminopyrimidine ketal **11** was converted to the ketone **1**. In a similar procedure the guanidino pyrimidine ketal **12** was smoothly converted to the guanidino ketone **2**; however, this product was isolated as the analytically pure formate salt.

The nmr pilot experiments indicated that the formic acid cleavage method was superior to a cleavage using 1*N* hydrochloric acid and is an improvement over literature methods since related pyrimidine-4-carboxaldehyde dimethylacetal cleavages using 1*N* hydrochloric acid or sulfuric acid proceed in less than 50% yield [8,10]. Both ketones were brominated uneventfully under slightly different conditions and the resultant bromoketones **13** and **14** were, as anticipated, converted readily to the desired products **3, 4,** which were isolated as monohydrobromides and **5, 6,** which were isolated as dihydrobromides.

Scheme 4



11 R = NH_2 1 R = NH_2 13 R = NH_2

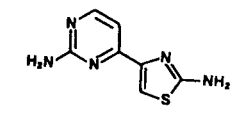
12 R = NH-C(=NH)-NH_2 2 R = NH-C(=NH)-NH_2 14 R = NH-C(=NH)-NH_2

HCO_2H HBr

Compounds **3, 4, 5** and **6** are ideally suited for studying the basicity of the respective amino- and guanidinothiazole rings as measured by the p*K*a of the conjugate acids since the complete set of 4 compounds provides internal cross comparisons. As depicted in Table 1, p*K*a values in water were determined by plotting the shift in ultraviolet absorbance as a function of p*H* at multiple wavelengths.

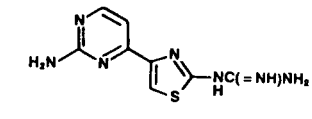
The method of Ang [11], which relies on a symmetrical maximum or minimum in the absorbance *versus* p*H* curve, was used to determine the two closely related p*K*a values for **3** and was also in good agreement with directly measured values for **4**. The two p*K*a values in **3** were unambiguously assigned in part by correlations of the spectral shift of **3** at 330 nm with the shifts observed for **5** at 330 nm (which are entirely due to change in protonation state of the aminothiazole moiety) and by the consistency of the pattern of spectral shifts among all 4 compounds when the higher p*K*a value in **3** was assigned to the aminothiazole moiety. The observed p*K*a values of guanidinopyrimidine and guanidinothiazole moieties are consistent with reported values [12,13]. It is particularly interesting that the guanidinopyrimidine moiety is more basic than the guanidinothiazole moiety while the reverse is true for the corresponding amino moieties, where the aminothiazole is more basic than the aminopyrimidine.

Table 1



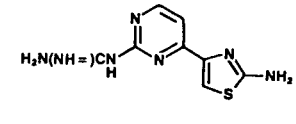
3

pKa = 2.6(a) pKa = 4.0(a)



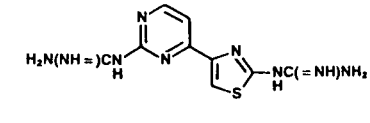
4

pKa = 3.3(a) = 3.4(b) pKa = 6.1(a) = 6.1(b)



5

pKa = 9.2(b) pKa = 2.7(b)



6

pKa = 9.2(b) pKa = 5.8(b)

(a) Calculated by the method of Ang [11].

(b) Calculated directly from plot of Absorbance vs pH.

These results suggest that the guanidinopyrimidine and guanidinothiazole derivatives are not both ring protonated and that it may be possible to achieve marked differences in a heteroaromatic guanidine p*K*a value by modification of the heterocyclic ring structure. This latter point may be important in a biological sense because an increase in charged species at physiological *p*H generally decreases membrane penetration but conversely also increases hydrogen bonding ability [14]. Compounds **3, 4, 5** and **6** were tested for histamine H_2-receptor antagonist activity on isolated guinea-pig atria and did not exhibit competitive antagonism. This is in contrast to 2-amino-4-(2-guani-

dino-4-thiazolyl)thiazole which is a potent competitive histamine H_2-receptor antagonist [2].

EXPERIMENTAL

4-Acetyl-2-aminopyrimidine (**1**).

A solution of **11** (1.5 g, 8.2 mmoles) in 50 ml of 88% formic acid was kept at 23° for 2 hours and then was concentrated *in vacuo* to nearly white solid which was recrystallized from ethanol to give, after filtration and washing with ethanol and ether, 0.88 g (78%), mp 148-149°; nmr (DMSO-d_6): δ 8.47 (d, 1H, J = 5 Hz), 6.90 (broad s, 2H), 6.92 (d, 1H, J = 5 Hz), 2.57 (s, 3H).

Anal. Calcd. for $C_6H_7N_3O$: C, 52.55; H, 5.14; N, 30.64. Found: C, 52.31; H, 5.21; N, 30.41.

4-Acetyl-2-guanidinopyrimidine Formate (**2**).

A solution of **12** (900 mg, 4 mmoles) in 20 ml of 88% formic acid was kept at 23° for 3 hours and then was concentrated *in vacuo* to a white solid which was dissolved in 1:1 ethyl acetate-ethanol, filtered and evaporated to 30 ml. On cooling, white crystals formed and were collected by filtration, washed with ethyl acetate, and then ether, and dried to give 0.68 g (76%), mp 173-769° dec; nmr (DMSO-d_6): δ 9.43 (very broad s, 5H), 8.90 (d, 1H, J = 6 Hz), 8.45 (broad s, 1H), 7.50 (d, 1H, J = 6 Hz), 2.68 (s, 3H).

Anal. Calcd. for $C_7H_9N_5O{\cdot}HCO_2H$: C, 42.67; H, 4.92; N, 31.10. Found: C, 42.71; H, 4.82; N, 31.15.

2-Amino-4-(2-amino-4-thiazolyl)pyrimidine Hydrobromide (**3**).

A suspension of **13** (2.16 g, 10 mmoles) in 100 ml of ethanol was heated to reflux and thiourea (760 mg, 10 mmoles) was added and heating at reflux was continued for 30 minutes. The reaction was cooled and concentrated *in vacuo* to a volume of 20 ml. The crude solid was triturated with ethyl acetate and the resulting solid was collected by filtration and washed with ethyl acetate, then ether, to give after drying *in vacuo*, 2.41 g of a tan powder. This was slurried in 100 ml of ethanol at reflux, decolorized with activated charcoal, concentrated to dryness and triturated with ethyl acetate to give 1.45 g (51%), mp (by differential thermal analysis-endotherms) 253° and 262° followed by decomposition; nmr (DMSO-d_6): δ 8.53 (d, 1H, J = 6 Hz), 8.30 (broad s, 5H), 7.83 (s, 1H), 7.32 (d, 1H, J = 6 Hz).

Anal. Calcd. for $C_7H_7N_5S{\cdot}HBr{\cdot}.5H_2O$: C, 29.69; H, 3.20; N, 24.73. Found: C, 29.40; H, 2.98; N, 24.40.

2-Amino-4-(2-guanidino-4-thiazolyl)pyrimidine Hydrobromide (**4**).

A suspension of **13** (2.16 g, 10 mmoles) in 100 ml of ethanol was warmed at 40° and amidinothiourea (1.18 g, 10 mmoles) was added in one portion. A clear solution resulted and the reaction was heated at reflux for 2 hours during which time a precipitate formed. The reaction was filtered while still hot and the filtrate was concentrated to 30 ml and cooled to give a yellow powder. This was collected by filtration, washed with cold ethanol, followed by ether, and dried to give 1.65 g (53%), mp 272° dec; nmr (DMSO-d_6): δ 8.35 (d, 1H, J = 6 Hz), 8.23 (broad s, 6H), 7.97 (s, 1H), 7.30 (d, 1H, J = 6 Hz); ms: Calcd. $C_7H_7N_5S$: 235.0652. Found: 235.0646.

Anal. Calcd. for $C_8H_9N_7S{\cdot}HBr$: C, 30.39; H, 3.19; N, 31.01. Found: C, 30.40; H, 3.32; N, 30.76.

2-Guanidino-4-(2-amino-4-thiazolyl)pyrimidine Dihydrobromide (**5**).

To a solution of thiourea (76 mg, 1 mmole) in 0.5 ml of water at 40° was slowly added **14** (340 mg, 1 mmole). Solution occurred and then a thick precipitate was formed. After stirring 1 hour the reaction was diluted with 1 ml of ethanol and 1 ml of ethyl acetate and after stirring briefly the resulting precipitate was isolated by filtration and washed with ethyl acetate and then ether. After drying *in vacuo* there was obtained 390 mg (98%) of a yellow powder, mp >300°; nmr (DMSO-d_6): δ 8.63 (d, 1H, J = 5 Hz), 8.17 (broad s, 6H), 7.77 (s, 1H), 7.56 (d, 1H, J = 5 Hz).

Anal. Calcd. for $C_8H_9N_7S{\cdot}2HBr$: C, 24.18; H, 2.79; N, 24.69. Found: C, 24.60; H, 2.91; N, 24.83.

2-Guanidino-4-(2-guanidino-4-thiazolyl)pyrimidine Dihydrobromide (**6**).

A solution of amidinothiourea (120 mg, 1 mmole) in 0.5 ml of water at 40° was slowly added **14** (340 mg, 1 mmole). A clear solution resulted followed by formation of a precipitate. After 1 hour at 40°, the reaction mixture was diluted with 1 ml ethanol and 1 ml ethyl acetate and was stirred briefly. The resulting precipitate was collected by filtration, washed with ethyl acetate, then ether, to give 400 mg of crude product, mp >300°. A portion (300 mg) of this material was slurried in 5 ml hot ethanol and cooled slowly to 23°. A fine yellow powder formed and was collected by filtration, washed with ethanol and dried to give, after drying *in vacuo* at 110°, 200 mg (60%) of yellow powder, mp >300°; nmr (DMSO-d_6): δ 8.76 (d, 1H, J = 6 Hz), 8.35 (s, 1H), 8.26 (broad s, 8H), 8.00 (d, 1H, J = 6 Hz); ms: Calcd. $C_9H_{11}N_9S$: 277.0858. Found: 277.0857.

Anal. Calcd. for $C_9H_{11}N_9S{\cdot}2HBr$: C, 24.61; H, 2.98; N, 28.71. Found: C, 24.89; H, 3.34; N, 28.52.

2-Chloro-4-guanidinopyrimidine (**7**).

To 25 ml of dimethylformamide was added sodium hydride (150 mg, 6.3 mmoles) and guanidine nitrate (1.2 g, 10 mmoles) at 0°. After gas evolution ceased, 2-chloro-4-cyanopyrimidine [5] (1.4 g, 10 mmoles) dissolved in 10 ml of dimethylformamide was added dropwise and the reaction was maintained at 0°. A white precipitate quickly formed and then the reaction became orange and then purple. After 30 minutes at 0°, tlc examination (silica gel, 25% methanol, 75% chloroform) showed multiple spots with one somewhat stronger than others with an Rf of 0.5. The reaction was diluted with water, extracted with ethyl acetate, backwashed with dilute hydrochloric acid and the acid layer neutralized with sodium hydroxide. The aqueous layer was concentrated to dryness, the residue extracted with ethyl acetate and, after concentration, the residue was chromatographed on silica gel with 10% methanol-chloroform as eluent to isolate the material with Rf 0.5 as essentially a single spot by tlc. There was obtained 139 mg (9%) of a solid, mp 160-165°; nmr (DMSO-d_6): δ 8.86 (d, 1H, J = 5 Hz), 8.10 (d, 1H, J = 5 Hz), 7.33 (broad s, 4H); ms: Calcd.$C_5H_6N_5Cl$ Cl-35 and 37 isotopes: 171.0312 and 173.0282. Found: 171.0306 and 173.0289. No peak attributable to 4-cyano-2-guanidinopyrimidine was observed.

Anal. Calcd. for $C_5H_6N_5Cl$: C, 35.00; H, 3.52; N, 40.82. Found: C, 35.47; H, 4.31; N, 30.67. The grossly low N analysis may be due either to analysis problems or to lack of analytical purity, especially in view of the broad mp.

5-Dimethylamino-3-oxo-4-penten-2-one-3-dimethylketal (**10**).

A solution of 3,3-dimethoxybutan-2-one [9] (13.2 g, 0.1 mole) and dimethylformamide dimethylacetal (11.9 g, 0.1 mole) was heated at 110° for 29 hours. Methanol was removed by distillation at atmospheric pressure and then the product was isolated by distillation (bp 106°, 0.5 mm Hg). The resultant orange oil solidified to give 12.17 g (65%) of solid, mp 54-59°. A 1 gram sample was recrystallized from 5 ml of cyclohexane to give 700 mg as light yellow flakes, mp 57-59°; a second recrystallization raised the mp to 59-60°; nmr (DMSO-d_6): δ 7.53 (d, 1H, J = 13 Hz), 5.38 (d, 1H, J = 13 Hz), 3.13 (s, 6H), 2.92 (s, 3H).

Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.77; H, 8.85; N, 7.44.

4-Acetyl-2-aminopyrimidine Dimethylketal (**11**).

To a solution of sodium ethoxide prepared from 0.575 g (25 mmoles) of sodium in 75 ml of ethanol was added guanidine hydrochloride (2.39 g, 25 mmoles). To the resultant slurry was added **10** (4.67 g, 25 mmoles) and the reaction was heated at reflux for 20 hours. The reaction was cooled and filtered and the precipitate was washed well with ethanol. The combined ethanol filtrates were evaporated to dryness. The residue was taken up in 200 ml of boiling ethyl acetate and insoluble material was removed by filtration. On cooling, a small amount of amorphous solid formed and was removed by filtration. On standing, fluffy white needles formed and on drying gave 3.47 g (76%), mp 150-151°; nmr (DMSO-d_6): δ 8.22 (d, 1H,

J = 5 Hz), 6.70 (d, 1H, J = 6 Hz), 5.17 (very broad s, 2H), 3.12 (s, 6H), 1.47 (s, 3H).

Anal. Calcd. for $C_8H_{13}N_3O$: C, 52.45; H, 7.15; N, 22.94. Found: C, 52.49; H, 7.33; N, 22.97.

4-Acetyl-2-guanidinopyrimidine Dimethylketal (**12**).

To a solution of sodium ethoxide prepared from 0.23 g (10 mmoles) of sodium in 20 ml of ethanol was added biguanide sulfate (3.36 g, 10 mmoles). To this was added **10** (1.87 g, 10 mmoles) and the reaction was heated at reflux for 20 hours. The reaction was cooled and filtered and the ethanol filtrate was concentrated *in vacuo* to a solid which was triturated with ethyl acetate and collected by filtration to give 1.6 g (71%) of crude product. This solid was purified by dissolving in a mixture of 150 ml of ethyl acetate and 50 ml of ethanol at the reflux temperature, filtering and concentrating to a final volume of 50 ml. On cooling, fluffy white crystals formed which were collected by filtration, washed with ethyl acetate, then ether and dried *in vacuo* to give 1.15 g (51%) of a white solid, mp 213° dec; nmr (DMSO-d_6): δ 8.50 (d, 1H, J = 6 Hz), 7.43 (broad s, 4H), 6.93 (d, 1H, J = 6 Hz), 3.20 (s, 6H), 1.53 (s, 3H).

Anal. Calcd. for $C_9H_{15}N_5O_2$: C, 47.99; H, 6.71; N, 31.09. Found: C, 48.15; H, 6.51; N, 30.96.

2-Amino-4-bromoacetylpyrimidine (**13**).

The hydrobromide of **1** was preformed by dissolving **1** in warm ethyl acetate and precipitating the hydrobromide salt by addition of concentrated hydrobromic acid. To **1** hydrobromide (12.7 g, 58 mmoles) in 200 ml of acetic acid containing 2 ml of 48% hydrobromic acid was added bromine (9.3 g, 58 mmoles). The reaction was stirred at 23° for 20 hours and the resulting red solid was collected by filtration and slurried in 75 ml of water. Sodium bicarbonate was added until the mixture was just neutral. The solid was collected by filtration, washed well with water and dried *in vacuo* to give 10.4 g (83%) of a brown powder, blackens at 100° no melt <300°. The material appeared to decompose on attempting to obtain an nmr spectrum in DMSO-d_6; ms: Calcd.: $C_6H_6BrN_3O$, Br 79 and 81 isotopes: 214.9694 and 216.9674. Found: 214.9676 and 216.9686.

2-Bromoacetyl-2-guanidinopyrimidine Hydrobromide (**14**).

To 130 ml of 48% hydrobromic acid was added **2** (5.0 g, 22.2 mmoles) and after foaming stopped, bromine (3.4 g, 19 mmoles) was added and the reaction was stirred at 23° for 4 hours. A precipitate began to form after 30 minutes and at 4 hours the mixture had decolorized. Light pink crystals were isolated by filtration, washed with 48% hydrobromic acid, followed by ethanol, and then ether, to give after drying *in vacuo* 4.23 g (56%), mp 231° dec; nmr (DMSO-d_6): δ 9.82 (broad s, 1H), 8.98 (d, 1H, J = 6 Hz), 8.23 (broad s, 4H), 7.66 (d, 1H, J = 6 Hz), 5.03 (s, 2H).

Anal. Calcd. for $C_7H_8N_5OBr{\cdot}HBr$: C, 24.80; H, 2.68; N, 20.66; Br, 47.14. Found: C, 24.89; H, 2.80; N, 20.55; Br, 46.76.

p*K*a Determinations.

A 2 to 3 mg sample of material is dissolved in 100 ml distilled water at 23° and the solution filtered and the initial *p*H is measured. A uv scan between 190-360 nm is taken at 23° by transfering an aliquot from the 100 ml solution to a quartz uv cell zeroed agains a water blank. The contents of the uv cell are returned to the 100 ml volume and the *p*H is adjusted to an arbitrary basic value by addition of 6*N* sodium hydroxide *via* a micropipette. The scan is retaken and the uv cell contents are returned to the 100 ml volume. The procedure is repeated with 6*N* hydrochloric acid. Based on these curves, readings are taken at multiple wavelengths following arbitrary adjustment of solution *p*H by micropipette addition of acid or base. In this way, absorbance readings as a function of *p*H are obtained at selected wavelengths. These are plotted and the apparent p*K*a is obtained graphically. The changes in volume due to micropipette addition are minimal relative to the total 100 ml volume and ionic strength corrections need not be made because of the low concentration (about $10^{-4}M$). The assumption that volume changes are minimal can be verified by the reproducibility of the initially obtained base and acid scans. Reproducibility of isobestic points and initial scan reproducibility confirms compound aqueous stability under test conditions. Absorption of carbon dioxide and slight sodium chloride content increase do not affect absorbance under typical test conditions at wavelengths of 240 nm or greater.

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