Synthesis and Reactions of 2,3-Diamino-4(3*H*)-pyrimidinones and 3-Amino-2-hydrazino-4(3*H*)-pyrimidinones. I.

Joseph J. Hlavka*, Panayota Bitha, Yang-i Lin and Timothy Strohmeyer

Medical Research Division, American Cyanamid Company,
Pearl River, New York 10965

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A series of new 2,3-diamino-4-pyrimidinones and 3-amino-2-hydrazino-4-pyrimidinones were synthesized by the reactions of β-ketoesters with amino or diaminoguanidines.

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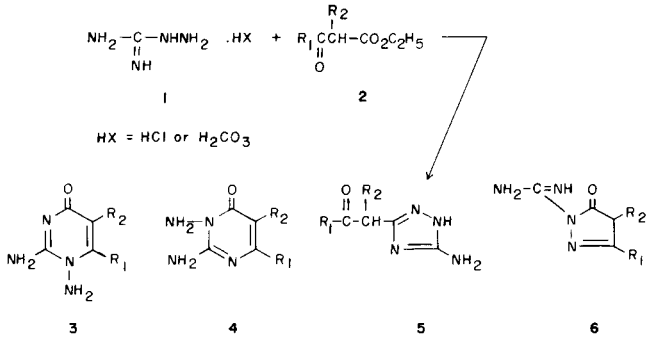
In our search for new pharmacologically useful drugs, we have been investigating the reaction of aminoguanidine **1** with β-ketoesters **2**. An inspection of this reaction suggests that at least 4 products are possible: the 1,2-diamino-4(1*H*)-pyrimidinones **3**, the 2,3-diamino-4(3*H*)-pyrimidinones [1] **4**, the 3-aminotriazoles [2] **5** and the 3-pyrazolones [3] **6**. We have found that the reaction of aminoguanidine bicarbonate, **1**, with ethyl trifluoroacetoacetate,

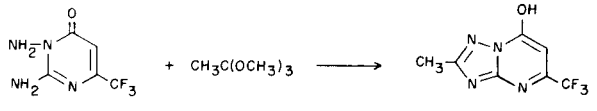


3 **4** **5** **6**

2 (R_1 = CF_3, R_2 = H) in refluxing butanol yielded only the 2,3-diamino-4(3*H*)-pyrimidinone, **4a** (R_1 = CF_3, R_2 = H). The high resolution mass spectrum of this material showed the highest mass ion at 194 m/e ($C_5H_5F_3N_4O$) and the fragmentation pattern was consistent with the assigned structure.

The ^1H nmr spectrum of this product in deuterated dimethyl sulfoxide contained the following peaks: δ 6.20 (s, 5-vinyl proton), δ 5.55 (s, N-NH_2) and δ 7.75 (s, C-NH_2).

Final resolution of the structure of this material **4a** was made by single crystal X-ray spectroscopy of the product **8** obtained by the reaction of **4a** with trimethylorthoacetate **7**. When other simple alkanoylacetates (**2**, R_1 = CH_3 or

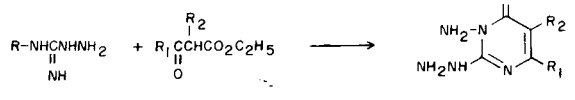


4a **7** **8**

C_2H_5, R_2 = H) were used we isolated the corresponding pyrazolones [2], **6** (R_1 = CH_3 or C_2H_5, R_2 = H). On the other hand, with most aryloylacetates **2**, (R_1 = phenyl or substituted phenyl; R_2 = H) a mixture of two products were isolated, the 2,3-diaminopyrimidinones, **4**, and the 3-aminotriazoles **5**. In one case, **2** R_1 = *o*-methylthiophenyl R_2 = H, the reaction yielded only the triazole derivative **5** (R_1 = *o*-methylthiophenyl R_2 = H). The initial asssignment of the triazole structures (*i.e.* **5**, R_1 = C_6H_5, R_2 = H) was based on ^1H nmr [δ 11.81 (s, NH); δ 4.12 (s, NH_2); δ 5.75 (s, NH)] and high resolution mass spectrometry (202 m/e) with final confirmation by single crystal X-ray spectroscopy.

When the reaction conditions were modified by reacting aminoguanidine free base with β-ketoesters at room temperature, only the 2,3-diamino derivatives, **4**, were obtained. In no case, either using aminoguanidine bicarbonate or its free base, did we isolate any of the 1,2-diamino derivative, **3**.

The reaction was extended to include the reaction of diaminoguanidine, **9**, with β-ketoesters, **2**, which yielded the 3-amino-2-hydrazino-4(3*H*)-pyrimidinones **10**. Table III gives a listing of these derivatives. Chart I gives a survey of the wide variety of β-ketoesters that have been used



9 (R = NH_2) **2** **10**

in this reaction along with the new heterocyclic systems that have been synthesized. The use of dione-diester **25** yields the novel tricyclic system **26**. With the proper choice of cyclic ketoesters we could synthesize bicyclic systems containing sulfur **19** or nitrogen **22** in the additional ring. Additional novel heterocyclic systems were synthesized (*i.e.* **4r** and **17**) when we used the lactone **20** or the salicylate **16** as the β-ketoester. In all cases the product was isolated, purified and identified by ^1H nmr, elemental analysis and high resolution mass spectrometry.

Halogenation of the monocyclic 2,3-diaminopyrimidinones, **4a,c,t** with *N*-halosuccinimides afforded the 5-halo products, **4s,d,p**. On the other hand, when the bicyclic diaminopyrimidinones, *i.e.* **12** or **14**, were brominated

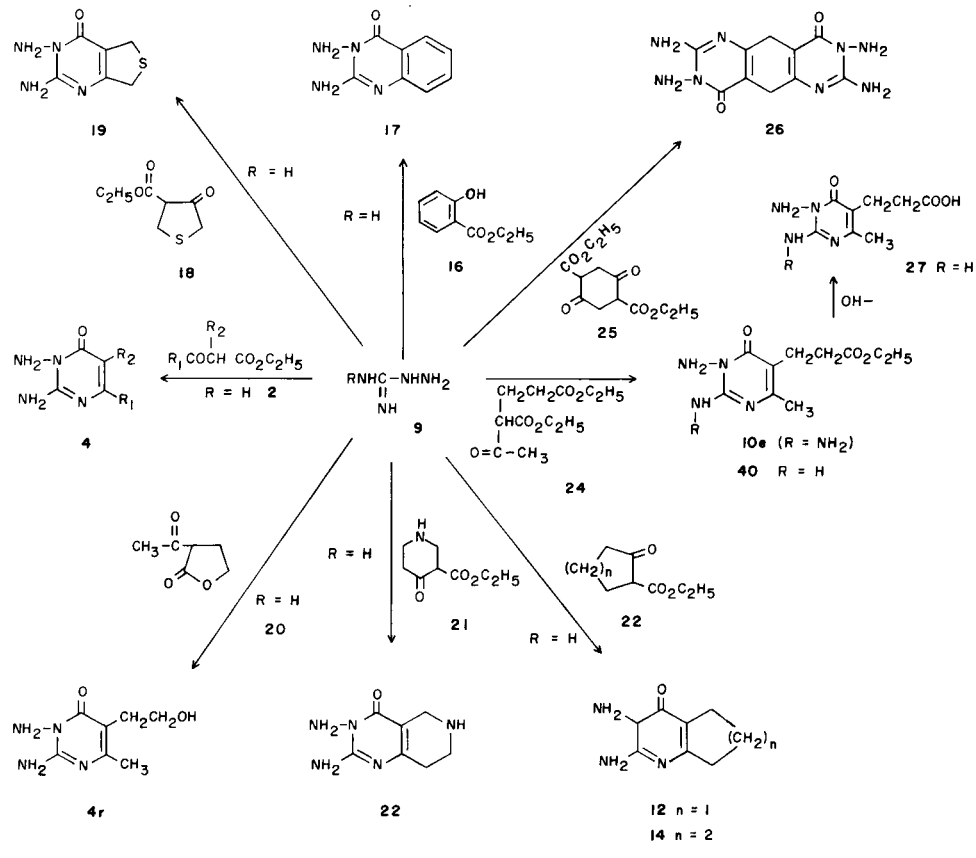
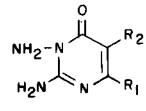


Table I [a]

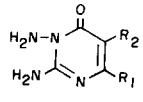


	R_1	R_2	mp °C	Elemental Analysis Calcd. (Found) C	H	N	X(Cl, Br, I)	F
4a	$-CF_3$	H	217-219	30.94 (30.90)	2.60 (2.49)	28.86 (29.24)		29.36 (29.50)
4b	$-C(CH_3)_3$	H	165-167	52.73 (52.86)	7.74 (7.78)	30.75 (30.86)		
4c	$-C_6H_5$	H	125-128	59.40 (59.16)	4.98 (4.98)	27.71 (28.00)		
4d	$-C_6H_5$	Br	280-282	42.73 (42.50)	3.23 (3.21)	19.93 (19.90)	28.43 (28.01)	
4e	$-C_6H_5$	Et	180-183	62.59 (62.35)	6.13 (6.13)	24.33 (24.10)		
4f	$-C_6H_5$	$-N=N-C_6H_5$	241 Dec	62.74 (62.52)	4.61 (4.77)	27.43 (27.03)		
4g	$-C_6H_5$	NH_2	185-190	55.29 (55.81)	5.10 (5.01)	32.24 (32.28)		
4h	$-C_6H_4F(p)$	H	160-162	54.54 (54.30)	4.12 (4.14)	25.44 (25.76)		8.63 (8.69)
4j	$-C_6H_4Cl(p)$	H	247-250	50.75 (51.07)	3.82 (3.98)	23.67 (23.31)	14.98 (14.90)	

4k	-$C_6H_4NO_2$(*p*)	H	261-264	48.59 (48.27)	3.67 (3.81)	28.33 (28.52)		
4l	-$C_6H_4CH_3$(*p*)	H	244-246	61.10 (61.10)	5.59 (5.47)	25.91 (26.01)		
4m	-$C_6H_4OCH_3$(*m*)	H	193-195	56.89 (56.86)	5.21 (5.00)	24.12 (24.34)		
4n	Adamantyl	H	230-236	64.59 (64.84)	7.74 (7.73)	21.52 (21.71)		
4o	CH_3	$CH_2CH_2CO_2C_2C_5$	92-95	49.99 (49.94)	6.71 (6.52)	23.32 (22.98)		
4p	CH_3	Cl	302-305	34.40 (34.51)	4.04 (4.06)	32.09 (32.07)	20.31 (20.16)	
4q	CH_3	CH_2CH_2COOH	121-122	45.28 (45.58)	5.70 (5.59)	26.0 (26.02)		
4r	CH_3	CH_2CH_2OH	109-111	45.65 (45.38)	6.57 (6.40)	30.42 (30.21)		
4s	CF_3	Br	225-228	21.99 (21.89)	1.48 (1.39)	20.52 (20.44)	29.2 (29.07)	20.73 (20.77)
4t	CH_3	H	282-285	42.85 (42.84)	5.75 (5.69)	39.88 (40.36)		

[a] Compounds **4d**, **4p** and **4s** were prepared by Experimental Procedure B. Compounds **4a**, **4o** and **4r** were prepared by Experimental Procedure A. Compound **4q** was prepared by hydrolysis of **4p** (see Experimental for details). All other compounds in the Table were prepared by Experimental Procedure C.

Table II [a]

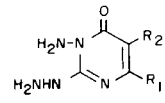


[R_1 and R_2 are connected in this Table]

	R_1 R_2	mp °C	Elemental Analysis Calcd. (Found) C	H	N	X(Cl, Br, I)	S
12	-$CH_2CH_2CH_2$-	246-248	50.59 (50.59)	6.07 (6.02)	33.71 (34.09)		
14	-$CH_2CH_2CH_2CH_2$-	215-218	53.32 (53.04)	6.71 (6.71)	31.09 (30.80)		
28	-$CH_2N(CH_2C_6H_5)CH_2CH_2$-	200-202	61.98 (61.59)	6.32 (6.21)	25.81 (25.66)		
29	1-,4-piperidyl	300 dec	52.16 (51.98)	6.32 (6.39)	33.79 (33.61)		
19	-CH_2S-CH_2-	285-287	39.12 (38.84)	4.38 (4.03)	30.41 (30.25)		17.41 (17.44)
22	-$CH_2CH_2NHCH_2$-	262.5-263.5	46.40 (46.0)	6.12 (6.19)	38.65 (38.20)		
17	-CH=CH-CH=CH-	175-176	54.54 (54.17)	4.58 (4.41)	31.80 (31.95)		
15	-CH(Br)-CH_2CH_2-CH_2-	155-157	34.31 (34.52)	3.70 (4.01)	22.86 (22.52)	32.60 (32.30)	
13	-CH(Br)-CH_2-CH_2-	88-90	34.31 (34.31)	3.70 (3.66)	22.86 (22.95)	32.6 (32.40)	

[a] Compounds **14**, **19**, **17**, and **22** were prepared by Experimental Procedure A, compounds **13** and **15** were prepared by Experimental Procedure B and **12**, **28**, and **29** by Experimental Procedure C.

Table III [a]



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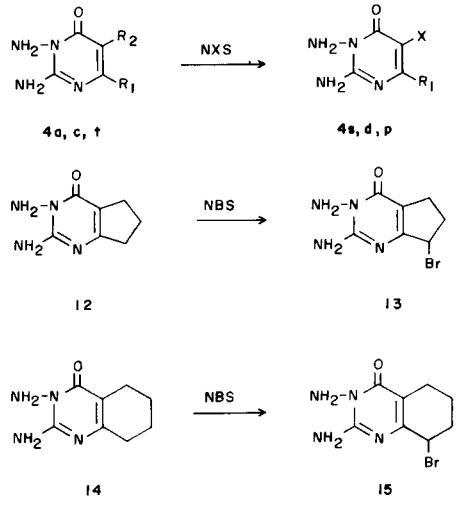
	R_1	R_2	mp °C	Elemental Analysis Calcd. (Found) C	H	N
10a	CH_3	H	207-210	38.71 (38.46)	5.85 (5.62)	45.11 (45.42)
10b	CH_3	CH_3	137-140	42.60 (42.44)	6.55 (6.17)	41.39 (41.73)
10c	Pr	H	155-157	45.89 (45.61)	7.15 (7.11)	38.22 (38.57)
10d	Et	H	144-145	42.60 (42.30)	6.55 (6.31)	41.39 (41.68)
10e	CH_3	$-CH_2CH_2COOEt$	107-109	47.05 (47.01)	6.71 (6.59)	27.43 (27.59)
10f	C_6H_5	H	192-Dec	55.29 (55.65)	5.10 (5.20)	32.24 (32.19)
10g	$C_6H_4Cl(p)$	H	235-238	47.72 (48.12)	4.01 (4.20)	27.83 (27.78)
10h	$C_6H_2(OCH_3)_3(3,4,5)$	H	200-201	50.81 (50.67)	5.58 (5.29)	22.79 (22.85)
10h	CH_3	CH_3	172-174	58.76 (58.57)	6.16 (6.26)	28.55 (28.35)
10i	CH_3	Et	175-177	45.89 (45.69)	7.15 (7.15)	38.22 (38.24)
10j	C_6H_5	Et	176-177	58.76 (58.49)	6.16 (6.01)	28.55 (28.85)
10k	*t*-Bu	H	228-230	48.72 (48.35)	7.67 (7.28)	35.51 (35.80)
10l	CH_3	Pr	166-168	48.72 (48.88)	7.67 (7.41)	35.51 (35.86)

[a] All compounds in Table III were prepared by Experimental Procedure D.

with *N*-bromosuccinimide (Procedure B in Experimental), allylic bromination occurred to yield **13** or **15**.



EXPERIMENTAL

All melting points were taken on a Mel-Temp apparatus. Samples for elemental analysis were dried at 50-60° for 1-24 hours under high vacuum. The ^1H nmr measurements were obtained on a Varian Model HA-100 spectrometer, and chemical shift values are reported in δ downfield from tetramethylsilane internal standard.

2,3-Diamino-6-(trifluoromethyl)-4(3*H*)-pyrimidinone, **4a**. Procedure A.

A suspension of 40.8 g (0.30 mole) of aminoguanidine bicarbonate and 55.2 g (0.30 mole) of ethyl 4,4,4-trifluoroacetoacetate in 250 ml of normal butanol was refluxed for 5 hours and then cooled to ice bath temperature. Crystalline precipitate was collected, washed with 1-butanol, then with water and dried to give 26 g (45%) of **4a** as white crystals.

2,3-Diamino-5-bromo-6-(trifluoromethyl)-4-(3*H*)-pyrimidinone (**4s**). Procedure B.

Typical Example for 5-Halopyrimidinones.

A solution of 3.0 g (0.0154 mole) of 2,3-diamino-6-(trifluoromethyl)-(3*H*)pyrimidinone, (**4a**) and 2.74 g (0.0154 mole) of *N*-bromosuccinimide in 50 ml of glacial acetic acid was stirred at room temperture for 30 minutes (to one hour). The crystalline precipitate was collected, washed

with water and then recrystallized from hot water to give 2.37 g (56%) of **4s** as white crystals.

2,3-Diamino-6-methyl-4(3*H*)-pyrimidinone, (**4t**). Procedure C. Typical Example of 6-Alkyl (other than CF_3)-pyrimidinones.

To a suspension of 11.0 g (0.1 mole) of aminoguanidine hydrochloride in 100 ml absolute ethanol was added 5.4 g (0.1 mole) of sodium methoxide. Suspension was stirred for 30 minutes at room temperature and filtered. The ethyl acetoacetate (6.5 g, 0.05 mole) was added to the filtrate and solution stirred at room temperature for 3 hours (to 24 hours depending on the ester). Crystalline precipitate was collected, washed with ethanol and dried to give 2.83 g (40%) of **4t**.

3-Amino-2-hydrazino-6-methyl-4(3*H*)-pyrimidinone, (**10a**. Procedure D. Typical Example of the 2-Hydrazino Series.

To a suspension of 13.22 g (0.1 mole) of 95% *N,N'*-diaminoguanidine hydrochloride in 100 ml of absolute alcohol was added 5.4 g (0.1 mole) of sodium methoxide. Suspension stirred at room temperature for 30 minutes and filtered. To the filtrate was added 6.5 g (0.05 mole) of ethyl acetoacetate and the reaction mixture was stirred at room temperature for 30 minutes (to 24 hours depending on the ester). Crystalline precipitate was collected, washed with ethanol and dried to give 2.58 g (37%) of **10a**.

2,3-Diamino-6-phenyl-4(3*H*)-pyrimidinone, **4c** and **5a**. Typical example of aryl pyrimidinones.

A suspension of 40.8 g (0.30 mole) of aminoguanidine bicarbonate and 57.6 g (0.3 mole) of ethyl benzoylacetate in 250 ml normal butanol was refluxed for 5 hours and then cooled to room temperature. It was stored in the refrigerator overnight. Crystals filtered, washed with butanol, water and dried to give 13 g (22%) of white crystals: mp 195-198°.

Anal. Calcd. for $C_{10}H_{10}N_4O$: C, 59.40; H, 4.98; N, 27.71. Found: C, 59.39; H, 5.02; N, 27.89.

The 3-aminotriazole **5a** was isolated pure from the above mixture by suspending 5 g of it in 50 ml of *N,N*-dimethylformamide and stirring for 30 minutes at room temperature. The white crystals filtered, washed with dimethylformamide and dried to give 1.75 g of the pure product **5a** (37%)

The R_f values for the 2,3-diamino derivative, **4c**, and the triazole, **5a**, isomers were 0.4 and 0.06, respectively, using silica gel plates and chloroform/methanol (95:5) as the elution solvent.

3-Amino-5-(*o*-methylthiobenzoylmethyl)-1,2,3-triazole (**5b**).

Using the procedure described above, 7.0 g (0.051 moles) of aminoguanidine bicarbonate was reacted with 12.25 g (0.051 mole) of ethyl (*o*-methylthiobenzoyl)acetate. The solid that crystallized on cooling weighed 2.7 g, mp 205-207°. The structure was confirmed by mass spectrometry (m/e = 248).

Anal. Calcd. for $C_{11}H_{12}N_4SO$: C, 53.21; H, 4.87; N, 22.56; S, 12.91. Found: C, 52.89; H, 4.62; N, 22.33; S, 12.59.

2-Methyl-5-(trifluoromethyl)-1,2,4-triazolo[1,5-*a*]pyrimidine-7-ol (**8**).

A solution of 2,2-diamino-6-(trifluoromethyl)-4(3*H*)-pyrimidinone (**4a**) (2.91 g), triethyl orthoacetate (10 ml) and glacial acetic acid (20 ml) was refluxed for 15-20 hours. Solution cooled to room temperature and white crystalline solid filtered, washed with acetic acid, ether and dried to afford 1.2 g of 2-methyl-5-(trifluoromethyl)-1,2,4-triazolo[1,5-*a*]pyrimidine-7-ol (**8**) (56%), mp 346-348°.

Anal. Calcd. for $C_7H_5F_3N_4O$: C, 38.54; H, 2.31; N, 25.68; F, 26.13. Found: C, 38.23; H, 2.29; N, 25.60; F, 26.08.

1,2-Diamino-1,6-dihydro-4-methyl-6-oxo-5-pyrimidinepropanoic Acid (**27**).

A solution of 2.8 g (0.01 mole) of 1,2-diamino-1,6-dihydro-4-methyl-6-oxo-5-pyrimidinepropanoic acid ethyl ester in 80 ml of 1*N* sodium hydroxide was stored at room temperature overnight. The *p*H of the solution was adjusted to 6.8 with 6*N* hydrochloric acid with cooling. A solid crystallized, yield 1.5 g, mp 121-122°.

Anal. Calcd. for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.7; N, 26.4. Found: C, 45.58; H, 5.59; N, 26.0.

2,3,7,8-Tetraamino-3,5,8,10-tetrahydropyrimidine[4,5-*g*]-quinazoline-4,9-dione (**26**).

A mixture of 12.8 g (0.05 mole) of diethyl 1,4-cyclohexanedione-2,5-dicarboxylate and 13.6 g (0.1 mole) of aminoguanidine bicarbonate in 100 ml of 1-butanol was heated at reflux for nine hours. The resulting solution was cooled to room temperature and a solid crystallized, yield, 17 g, mp, 152-155°.

Anal. Calcd. for $C_{10}H_{12}N_8O_2$: C, 43.38; H, 4.38; N, 40.56. Found: C, 42.99; H, 4.21; N, 40.32.

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