Pyrimido[4,5-*c*]pyridazines. 3. Preferential Formation of 8-Amino-1*H*-pyrimido[4,5-*c*]-1,2-diazepin-6(7*H*)-ones by Cyclizations with α,γ-Diketo Esters[1]

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6-(1-Methylhydrazino)isocytosine cyclizes with α,γ-diketo esters to give pyrimido[4,5-*c*]pyridazines and 1*H*-pyrimido[4,5-*c*]-1,2-diazepines, the latter being predominant in each case. The pyrimidodiazepines are susceptible to ring-opening/ring-closure rearrangement reactions leading to either pyrido[2,3-*d*]pyrimidines, pyrazolo[3,4-*d*]pyrimidines, or pyrimido[4,5-*c*]pyridazines.

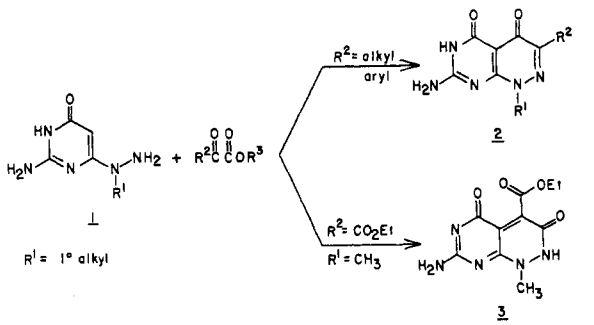
Reactions of 1a with α,γ-Diketo Esters

We previously reported[2] that simple α-keto esters cyclize straightforwardly with (1-alkylhydrazino)isocytosines **1** in methanol or water to give pyrimido[4,5-*c*]pyridazine-4,5-(1*H*,6*H*)-diones **2**. Only with diethyl oxomalonate was the product **3** of reversed orientation obtained (Scheme I).

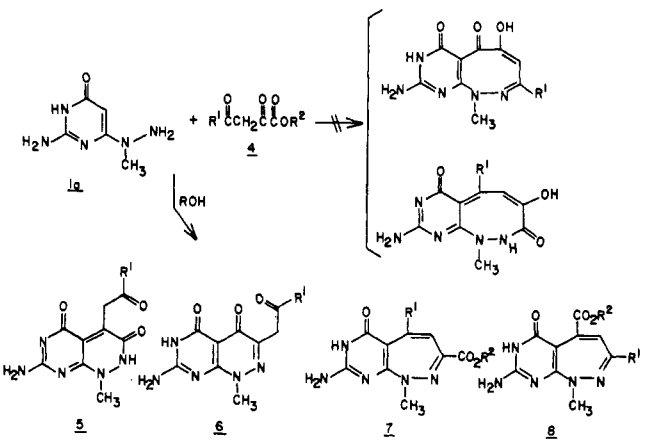
Extension of this synthesis by reaction of 6-(1-methylhydrazino)isocytosine **1a** and α,γ-diketo esters (**4**, Table I) in refluxing methanol (our preferred reaction medium for the production of **2** in high purity) has led to a more complex situation. We have observed four of the six possible types of cyclization products between our bisnucleophile **1a** and the carbonyl groups of the triselectrophiles **4** indicated in Scheme II. Neither of the two possible 1*H*-pyrimido[4,5-*c*]-1,2-diazocines from eight-membered-ring formation, nor products of cyclization onto the pyrimidine ring nitrogen, nor any products derived from Michael additions to enolic forms of the tricarbonyl reagents were observed.

The product distribution has varied according to the nature of the diketo ester γ-substituents, but in every case, cyclizations across the two ketone functions to produce 3-carbalkoxy-1*H*-pyrimido[4,5-*c*]-1,2-diazepines **7** were predominant (30–56% yield).[3] Compounds **7** are likely formed by an initial hydrazone formation at the most reactive (α-) ketone function of **4**. Under these reaction conditions, cyclization is favored at the γ-ketone function to give a seven-membered ring rather than at the terminal ester group to give a six-membered ring. The α,γ-diketo ester with the most reactive γ-carbonyl function, **4a** ($R^1 = CH_3$), produced the 3- and 5-carbalkoxypyrimidodiazepines **7a** and **8a** and no pyrimidopyridazines **5** and **6**. Compounds **4** with the least reactive γ-carbonyl functions (R^1 = di- and trimethoxyphenyl) allowed the production of the highly insoluble pyrimidopyridazines **5** and **6** (**e–g**) in low yield. The reactions to form the 3,5-diones **5** appeared to be complete before the 4,5-dione (**6**) cyclizations had finished since we were able to filter off an inseparable mixture of **5** and **6** after an overnight reflux and obtain a small amount of pure **6** by further refluxing of the filtrate. In addition, we isolated no 5-carbalkoxypyrimidodiazepines **8** from reactions with **4** having γ-aryl ketone functions (**4b–g**). Therefore, the reactivity of the γ-carbonyl group affected the production of 5-carbalkoxypyrimidodiazepines **8** directly and the production of pyrimidopyridazines **5** and **6** inversely.

Scheme I



Scheme II



With reactions as complex as those of **1a** with **4**, a change in reaction conditions could possibly alter the product distributions. Examination of this variation was not the goal of this present study. However, in the one case examined, a change of the reaction medium from refluxing methanol (bp 65 °C) to refluxing methyl Cellosolve (bp 124 °C) allowed production of the pure pyrimidopyridazine 3,5-dione **5g** in moderate yield (44%) with no contamination from the 4,5-dione **6g**. The ultraviolet spectrum of the reaction filtrate indicated that the chromophore for pyrimidodiazepine **7g** was not present to any noticeable extent, and we did not examine this filtrate further. Clearly, the production distribution was affected by the change in reaction conditions in this case.

The isomeric pyrimido[4,5-*c*]pyridazines were distinguished by comparisons of their spectral properties (proton NMR, mass, and UV) with those of known 4,5-diones **2** and the 3,5-dione **3**. Seven-membered-ring formation onto the pyrimidine ring nitrogen (N-1) rather than the C-5 position

(1) Presented at the 174th National Meeting of the American Chemical Society, Chicago, IL, Aug 29, 1977.

(2) Morrison, R. W., Jr.; Mallory, W. R.; Styles, V. L. *J. Org. Chem.* **1978**, *43*, 4844.

(3) Following our initial disclosure[1] of this previously unreported ring system, a related synthesis was described that involved reactions of 6-(1-methylhydrazino)uracil with substituted malondialdehydes or α,β-unsaturated aldehydes (Waid, K.; Breitmaier, E. *Synthesis*, **1978**, 748).

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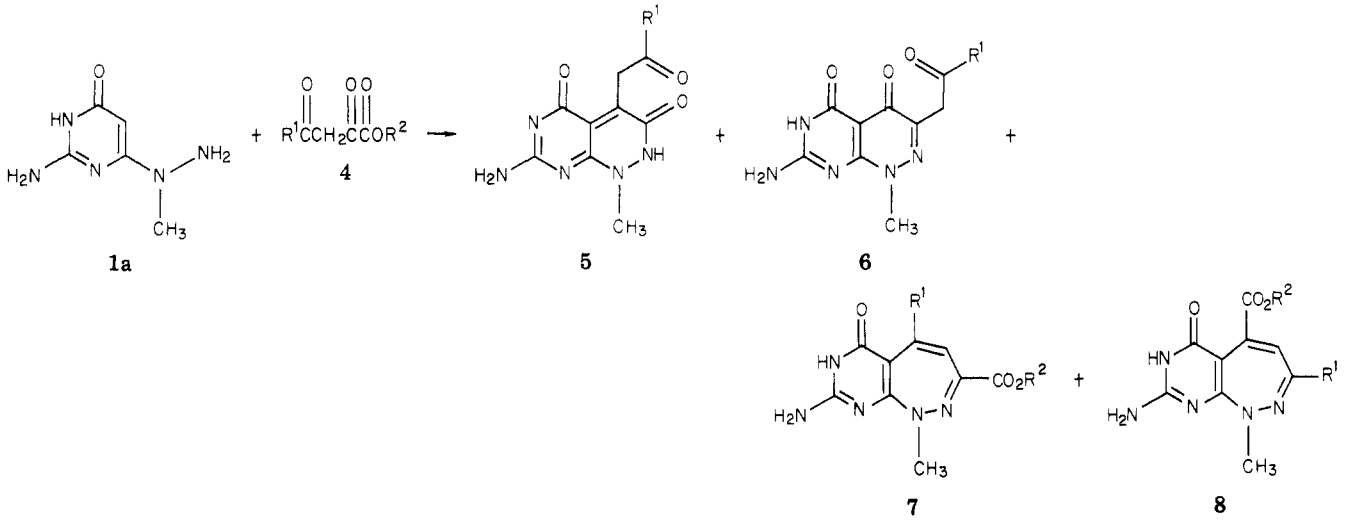
Table I. Fused Isocytosines

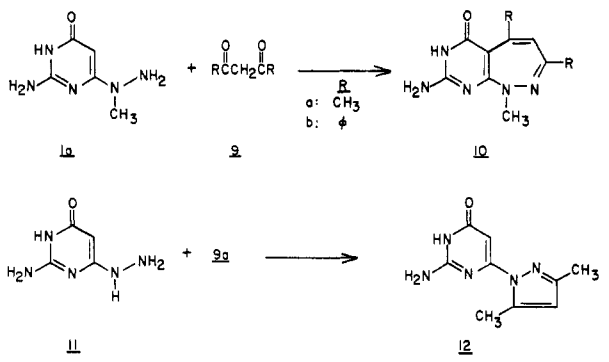


1a 4 5 6 7 8

	R^1	R^2	molar ratio 4/1a		yield of fused isocytosines,[b] % (mp, °C) 5	6	7	8
a	CH_3	C_2H_5	*c*	1.2:1	NI[cc]	NI	30[d] (237-238 dec)	11[e,f] (8a′) (196 dec)
b	3-pyridyl	CH_3	*g*	1.2:1	NI	NI	56[h] (258-272 dec)	NI
c	C_6H_5	C_2H_5	*i*	1.5:1	NI	7[j] (>300)	53[k] (228-230.5 dec)	NI
d	$C_6H_4(OH)$ (3)	CH_3	*l*	1.2:1	<1[m]	6[n] (290-295 dec)	49[o] (>275)	NI
e	$C_6H_3(OCH_3)_2$ (2,5)	CH_3	*p*	1.1:1	[3][q dd]	[3][q] + 1[r] (>300)	42[s] (201-202 dec)	NI
f	$C_6H_3(OCH_3)_2$ (2,4)	C_2H_5	*t*	1.5:1	[2][u]	[4][u] + 9[v] (290-300 dec)	49[w] (201.5-203 dec)	NI
g	$C_6H_2(OCH_3)_3$ (3,4,5)	CH_3	*x*	1.5:1	[5][y,z]	[5][y] + 2[aa] (>300)	48[bb] (258 dec)	NI

[a] Prepared from the methyl ketones and either methyl or ethyl oxalate in alcoholic sodium alkoxide solution. [b] Yields are based on the 6-(1-methylhydrazino)isocytosine used for the cyclizations. [c] Marvel, C. S.; Dreger, E. E. "Organic Syntheses", Collect. Vol. I; Wiley: New York, 1941; p 238. [d] Isolated from the concentrated reaction filtrate by column chromatography (silica gel) with a solvent gradient beginning with a 1:1 benzene/chloroform mixture, then chloroform, chloroform/ethyl acetate mixtures, ethyl acetate, and finally a 4:1 ethyl acetate/methanol mixture. Compound 7a was eluted with ethyl acetate and was subsequently recrystallized from ethyl acetate. [e] Subsequent fraction to 7a[d] eluted with ethyl acetate and the 4:1 ethyl acetate/methanol mixture and recrystallized (twice) from carbon tetrachloride. [f] The corresponding methyl ester 8a′ (contaminated with ~10% ethyl ester) was prepared in a yield of 42% from the reaction of 1a with ethyl 2,4-dioxopentanoate 4-ethylene ketal (Rossi, A.; Lauchenauer, A. *Helv. Chim. Acta*, **1947**, *30*, 1501) in refluxing methanol. Also obtained from this reaction was an inseparable mixture of 7-amino-3-[2-(ethylenedioxy)-*n*-propyl]-1-methylpyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-dione and the corresponding 3-methyl compound. [g] Walker, G. N., U.S. Patent 3 449 350, 1969; *Chem. Abstr.* **1969** *71*, 70595n. The procedure reported for synthesis of the ethyl ester was used to make the methyl ester: Gardner, T. S.; Wenis, E.; Lee, J. *J. Org. Chem.* **1961**, *26*, 1514. [h] Isolated by filtration of the hot reaction mixture after 17.5 h. [i] Beyer, C.; Claisen, L. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2078. [j] Isolated by filtration of the hot reaction mixture after 67 h. [k] Isolated by concentration (boiling) of the reaction filtrate to ~30% of its orginal volume, filtration of the cooled mixture, and recrystallization of collected solid from methanol. A solution of the recrystallized solid in absolute ethanol was refluxed for 17 days to reconvert some methyl ester which formed (~25% by NMR) back to ethyl ester. The solution was then concentrated to the pure orange solid 7c. [l] Hashimoto, S.; Shizu, M.; Takahashi, S. *Chem. Pharm. Bull.* **1976**, *24*, 1757. [m] Isolated from the filtrate of the pyrimidodiazepine. NMR showed that the 3,5-dione isomer was present in a trace amount. [n] This hygroscopic compound was isolated by filtration after 22 h and was obtained in anhydrous form by drying at 100 °C under high vacuum. Subsequent air equilibration afforded the pentahydrate. [o] Isolated by boiling down the reaction filtrate to ~40% of its original volume and filtration of the cooled mixture. [p] Novel compound, mp 94.5-95.5 °C. See supplementary data section for further data. [q] Isolated as a 1:1 mixture of 3,5-dione and 4,5-dione isomers by filtration of the hot reaction mixture after 19 h. [r] Isolated by filtration of the hot reaction mixture after 23.5 h of further reflux. [s] Isolated by filtration of the hot reaction mixture after 6.5 h of further reflux. Solid precipitated during heating back to reflux. [t] Perkin, W. H., Jr.; Robinson, R. *J. Chem. Soc.* **1908**, *93*, 489. [u] Isolated as a 1:2 mixture of 3,5-dione and 4,5-dione isomers, respectively, by filtration of the hot reaction mixture after 18 h. [v] Isolated by filtration of the hot reaction mixture after 46.5 h of further reflux. [w] Isolated from the concentrated reaction filtrate by column chromatography (silica gel) with eluting solvents consisting of a 1:1 chloroform/ethyl acetate mixture and ethyl acetate. Compound 7f was eluted with ethyl acetate. A solution of the concentrated column fraction of 7f in absolute ethanol was refluxed for 15 days to reconvert some methyl ester back to ethyl ester. It was then concentrated to a low volume, and the product crystallized during cooling and was collected by filtration. [x] Novel compound, mp 151-153 °C. See supplementary data section for further data. [y] Isolated as a 1:1 mixture of 3,5-dione and 4,5-dione isomers by filtration of the hot reaction mixture after 18.5 h. [z] Preparable in pure form (44%) by cyclization in refluxing methyl Cellosolve for 1 h 50 min. [aa] Isolated by filtration of the hot reaction mixture after 23 h of further reflux. [bb] Isolated from the concentrated reaction filtrate by column chromatography (silica gel) with a solvent gradient beginning with chloroform, then a 1:1 chloroform/ethyl acetate mixture, ethyl acetate, and finally a 9:1 ethyl acetate/methanol mixture. Compound 7g was eluted with the 9:1 ethyl acetate/methanol mixture and was subsequently recrystallized from methanol. [cc] Not isolated. [dd] Lines: isomeric mixtures, yields estimated from spectral data. We were unsuccessful in separating the 3,5-dione and 4,5-dione isomers due primarily to their insolubility in most common solvents.

Scheme III



was ruled out on the basis of proton NMR spectra. In each case the pyrimidine C-5 proton was absent, and the typical broad, low-field (exchangeable) ring NH proton (δ 10–11 in Me_2SO-d_6) was always present. Isomeric pyrimidodiazepines were distinguishable by their mass spectra; they readily lose either R^1CN or $R^2OC(O)CN$ from their molecular ions.

Reactions with 1,3-Diketones

Several structural variations were made for a partial assessment of the scope of the diazepine cyclizations. Reactions of **1a** with the symmetrical 1,3-diketones **9** produced the pyrimidodiazepines **10**, but 6-hydrazinoisocytosine (**11**)[4] cyclized with **9a** to give the 6-pyrazolylisocytosine **12** (Scheme III).

The 1,3-diketones reacted with 2,4-diamino-6-(1-methylhydrazino)pyrimidine (**13**) in a less straightforward manner (Scheme IV). Treatment of **13** with **9a** under the usual cyclization conditions (refluxing methanol) produced only the hydrazone **15a**.[5] Although **15a** could be made to cyclize slowly to **16** under more vigorous conditions (refluxing methyl Cellosolve, 4 days), 1-phenyl-1,3-butanedione (**14**) reacted with **13** in refluxing methyl Cellosolve only as far as the hydrazone stage **15b**.[5] Finally, both the isocytosine **1a** and the diaminopyrimidine **13** formed only the hydrazones **18**[5] and no cyclic products with ethyl 3-oxobutanoate (**17**).

Pyrimidodiazepine Rearrangement Reactions

We found the pyrimidodiazepines to be particularly susceptible to ring-opening/ring-closure rearrangement reactions. Depending on the nature of the substituents, their location, and reaction conditions, these compounds were converted into either pyrido[2,3-*d*]pyrimidines **21**, pyrazolo[3,4-*d*]pyrimidines **25**, or a pyrimido[4,5-*c*]-pyridazine **26**.

The fate of the 3-carbalkoxypyrimidodiazepines **7** was found to vary as a function of reaction conditions. For example, saponification of **7g** at room temperature followed by acidification effected a clean conversion to the acid **19g** (Scheme V). When a solution of **19g** in Me_2SO-d_6 was allowed to stand overnight at 35 °C, complete conversion to the nitrile **20g** occurred ($\gamma_{C\equiv N}$ 2225 cm^{-1}, $NHCH_3$ in Me_2SO-d_6 at δ 2.71, a doublet which collapses to a singlet with addition of D_2O or CF_3COOH). This cleavage is reminiscent of Yoneda and Nagamatsu's pyrolytic decomposition of aldehyde hydrazones prepared from 1,3-dimethyl-6-(1-methylhydrazino)uracil to give nitriles[6] and Garanti and Zecchi's[7] thermal rearrangement of 1*H*-1,2-benzodiazepine-3-carboxylic acid to give 2-aminoquinoline. On the other hand, Nastasi and Streith[8] showed the thermal rearrangement of simple (nonfused) 1*H*-1,2-diazepines to 2-aminopyridine derivatives to proceed via diazanorcaradienes and not by ring closure of an acyclic dieneaminonitrile.[9] Further heating of **20g** at 125 °C caused the methylamino group to add across the nitrile to give, ultimately, what we propose to be the 2,7-diaminopyrido[2,3-*d*]pyrimidine **21g**. ^1H NMR, UV, IR, and mass spectra appeared to be consistent with this structural assignment, particularly when compared with those of the 2,7-diamino-5-(unsubstituted) analogue **21h** prepared unambiguously[10] in two steps from 6-(methylamino)isocytosine (**22**)[11] and 3-(dimethylamino)acrylonitrile (**23**). For preparative purposes, rearrangements of **19** to **21** were conveniently carried out by addition of **19** to refluxing methyl Cellosolve.

Heating **7g** in aqueous acid produced the pyrazolo[3,4-*d*]pyrimidine **25d** (Scheme VI), most likely by hydrolytic ring opening at the "hydrazone" bond followed by a retroaldol reaction and ring closure. No suggestion is made as to the sequence of the last two steps. Similar products were also prepared from the 3,5-dimethyl- and 3,5-diphenylpyrimidodiazepines **10** and the 3-carbalkoxy derivatives **7c,d**. Again, spectral characteristics were consistent with the pyrazolopyrimidine structures. Pyrazole formation by ring opening/ring closure of 1,2-diazepines has been reported by Snieckus et al.,[12] who were able to convert 3,5,7-triphenyl-1,2-diazepine into 3,5-diphenylpyrazole with refluxing 5 N ethanolic HCl.

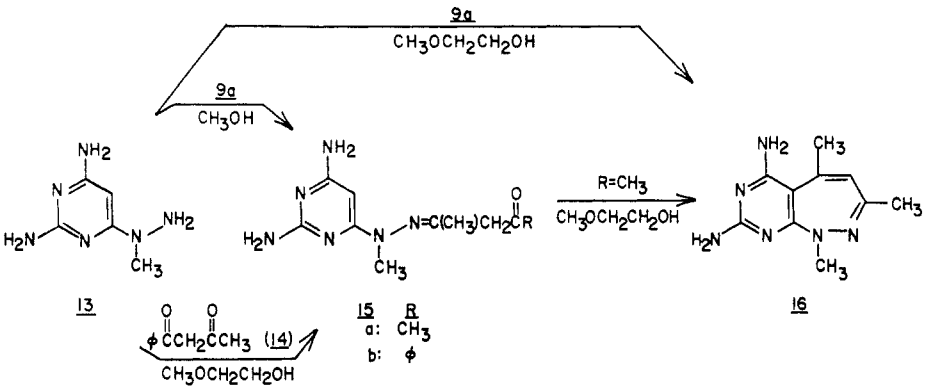
Finally, the 5-(carbomethoxy)pyrimidodiazepine **8a′** when treated with aqueous acid at room temperature underwent hydrolytic ring opening, presumably at the hydrazone linkage, followed by ring closure with the unchanged ester to give a pyrimido[4,5-*c*]pyridazine in moderate yield. This intermediate is proposed to be the 4-acetonyl derivative **26** (Scheme VII) on the basis of its NMR and UV spectra. Attempts to purify **26** by recrystallization from methyl Cellosolve caused a solvolytic cleavage to the 4-methyl derivative **27**. Pyrazolopyrimidine formation did not appear to occur to any appreciable extent under this mild hydrolytic treatment. A preferred synthesis of **27** entails the treatment of the (trimethoxyphenacyl)pyrimidopyridazine **5g** with 1 N NaOH at room temperature.

Conclusions on Rearrangements

The 3-carbalkoxypyrimidodiazepines **7** can be converted into the pyridopyrimidines **21** if first converted to the acids and subsequently heated or into the pyrazolopyrimidines **25** if heated directly in strong acid. Hot acid treatment also converts the 3,5-dialkyl- or 3,5-diarylpyrimidodiazepines **10** into **25**. Finally, mild acid treatment of the 5-(carbomethoxy)pyrimidodiazepine **8a′** effects rearrangement to a pyrimidopyridazine **26**. The reactions to give the pyridopyrimidines and pyrazolopyrimidines are synthetically useful. However, the rearrangement to give the pyrimidopyridazine suffers limited synthetic utility

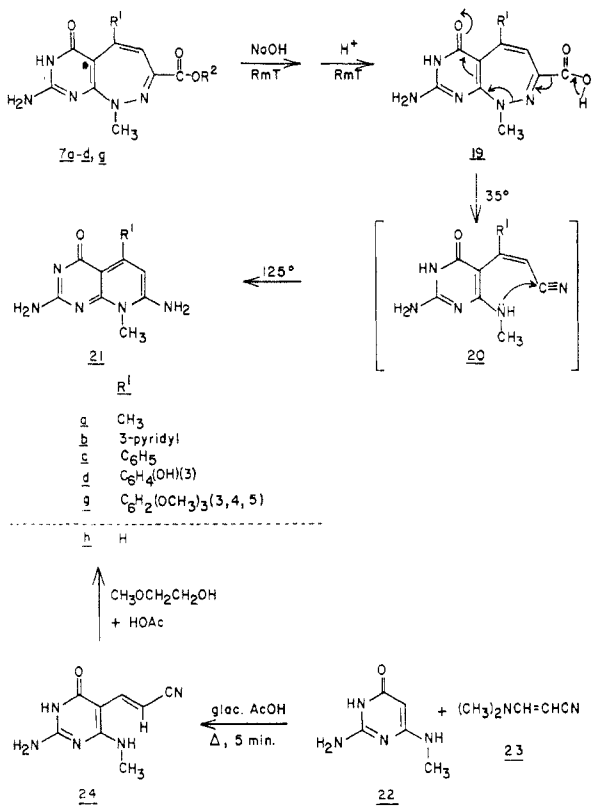
(4) Laird, A. H.; Landquist, J. K.; Langley, B. W. British Patent 876601, 1961; *Chem. Abstr.* **1962**, *56*, 4781f.
(5) An NMR spectrum in Me_2SO-d_6 suggested an isomeric mixture.
(6) Yoneda, F.; Nagamatsu, T. *Heterocycles* **1974**, *2*, 153.
(7) Garanti, L.; Zecchi, G. *J. Heterocycl. Chem.* **1979**, *16*, 1061.
(8) Nastasi, M.; Streith, J. *Bull. Soc. Chim. Fr.* **1973**, 635.
(9) An extensive review of 1,2-diazepine rearrangement reactions was reported by M. Nastasi in *Heterocycles* **1976**, *4*, 1509.
(10) This method is similar to that reported for a related compound by E. E. Garcia in *Synth. Commun.* **1973**, *3*, 397.
(11) Fidler, W. E.; Wood, H. C. S. *J. Chem. Soc.* **1957**, 4157.
(12) Harris, D. J.; Thomas, M. T.; Snieckus, V.; Klingsberg, E. *Can. J. Chem.* **1974**, *52*, 2805.

Scheme IV

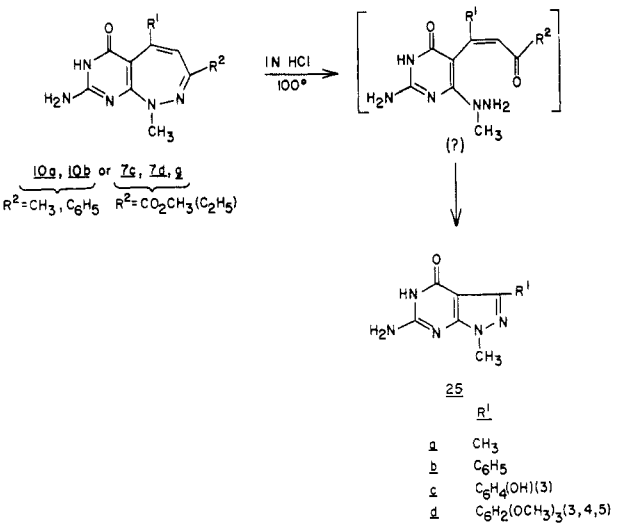


Ar
1a: 6-isocytosinyl
13: 2,4-diamino-6-pyrimidinyl

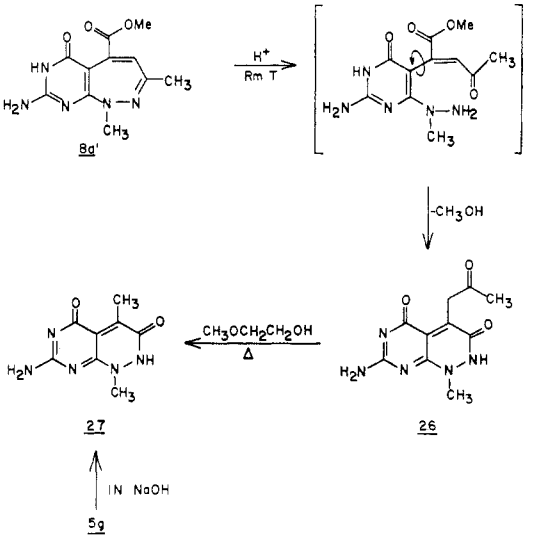
Scheme V



Scheme VI



Scheme VII



because of the lability of the functionality at the 4-position of the pyridazine ring.

Experimental Section

Melting points were run on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra (Nujol) were recorded on Beckman IR 8 and Perkin-Elmer 267 spectrophotometers, and quantitative ultraviolet spectra were recorded on Cary 15, Cary 118, and Varian Superscan 3 instruments. NMR spectra were determined with Varian T-60, XL-100, and CFT-20 and Hitachi Perkin-Elmer R-24 A spectrometers with tetramethylsilane as the internal standard. Fourier transform was utilized in cases of poor solubility. Nuclear Overhauser and

decoupling experiments were run on a Varian XL-100 spectrometer. Nuclear Overhauser effect (NOE) is expressed as $f_I(S)$ = fractional enhancement of nucleus I due to saturation of nucleus S. Low-resolution mass spectra were obtained with a Varian MAT CH5 DF double-focusing mass spectrometer at 70 eV, and probe temperatures are noted; accurate masses were determined by peak matching at 10000 resolution, 10% valley definition; the MIKES technique (mass analzyed ion kinetic energy spectrometry)[13] was employed for metastable analysis. Field-desorption data were determined with a Varian MAT 731 spectrometer. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA. All C, H, N analyses not reported here were acceptable (±0.4%) and can be found along with other physical data in the supplementary data section.[14] 6-(1-Methylhydrazino)isocytosine (**1a**) and 2,4-diamino-6-(1-methylhydrazino)pyrimidine (**13**) were prepared as described previously.[2] 2,4-Pentanedione and ethyl 3-oxobutanoate were obtained from Fisher Scientific Co. 1,3-Diphenyl-1,3-propanedione was obtained from Eastman Organic Chemicals. 1-Phenyl-1,3-butanedione and 3-(dimethylamino)acrylonitrile were obtained from Aldrich Chemical Co. Silica gel was obtained from E. Merck (silica gel 60, 70–230 mesh).

Special Note. Many of the ring-fused pyrimidines in this work crystallized with nonstoichiometric amounts of solvents that proved to be resistant to removal under vacuum. In those cases additional evidence (usually NMR or halogen analysis in the case of CCl_4) for the presence of organic solvent was obtained.

Cyclizations to 5, 6, 7, and 8. The appropriate α,γ-diketo ester was added to a refluxing mixture prepared from very pure 6-(1-methylhydrazino)isocytosine **1a** and filtered methanol[15] in the proportion of 1 g in 100 mL. Precipitated **6** or a mixture of **5** and **6** was collected by filtration from the hot reaction mixture. In cases in which a mixture of **5** and **6** was isolated, the filtrate was refluxed further, and pure **6** was collected by filtration from the hot reaction mixture. Products **7** were isolated either by concentration of the reaction filtrate to a low volume and collection of the precipitated solid, by heating the reaction filtrate back to reflux and filtration of the solid that had begun to precipitate even before reflux was reached, or by concentration of the reaction filtrate onto silica gel and subsequent column chromatography. Exceptions to this procedure were **7a** and **8a** which were the only cyclized products isolated from their reaction solution by column chromatography and **7b** which was the sole product collected by filtration of its hot reaction mixture. Specific examples are described below for the preparations of **7a** and **8a** and for the preparations of **5g** and **6g** (as isomeric mixtures), **6g** (isomer free), and **7g**. A preparation of **5g** in pure form is also included.

8-Amino-3-carbethoxy-1,5-dimethyl-1*H*-pyrimido[4,5-*c*]-1,2-diazepin-6(7*H*)-one (7a). To a stirred, refluxing mixture of 5.00 g (0.0305 mol) of 6-(1-methylhydrazino)isocytosine hemihydrate (**1a**) in 500 mL of methanol was added 5.78 g (0.0365 mol) of ethyl 2,4-dioxopentanoate (**4a**). After 65 h the solution was concentrated by boiling to 40 mL and was allowed to stand overnight. The solution was concentrated under vacuum onto 10 g of silica gel that was added to a column of 400 g of silica gel in hexane. Elution of the column with a 1:1 benzene/chloroform mixture, then chloroform, chloroform/ethyl acetate mixtures, ethyl acetate, and a 4:1 ethyl acetate/methanol mixture effected separation of **7a** in the earlier ethyl acetate fractions; yield, 3.95 g. Orange crystals were obtained after recrystallization from ethyl acetate: yield, 2.52 g (30%); mp 237–238 °C dec; NMR (Me_2SO-d_6) δ 1.24 (t, J = 7.5 Hz, 3 H), 2.12 (d, J = 1 Hz, 3 H),[16] 3.03 (s, 3 H), 4.22 (q, J = 7.5 Hz, 2 H), 6.18 (q, J = 1 Hz, 1 H), 6.83 (br s, 2 H), 10.8 (br s, 1 H), NOE/$f_{6.18}$ (2.12) = 32%; UV (CH_3OH) λ_{max} 244.5 nm (ε 17300), 279 (sh, 11200), 306 (14100), 413 (600); mass spectrum (155 °C), m/e 277 (M, 29), 248 (2), 232 (2), 204 (13), 187 (5), 179 (12), 178 (M – $H_5C_2O_2CCN$, 100),[17] 177 (17), 162 (10), 161 (37), 136 (24). The following selected accurate masses were determined: 277.1163 ($C_{12}H_{15}N_5O_3$), 178.0843 ($C_8H_{10}N_4O$). Anal. Calcd for $C_{12}H_{15}N_5O_3$: C, 51.98; H, 5.45; N, 25.26. Found: C, 51.91; H, 5.45; N, 25.18.

The isolation of the 5-carbethoxy isomer of **7a** from this reaction mixture is described below.

8-Amino-5-carbethoxy-1,3-dimethyl-1*H*-pyrimido[4,5-*c*]-1,2-diazepin-6(7*H*)-one (8a). This product was found in the later ethyl acetate and the 4:1 ethyl acetate/methanol eluates (see **7a** above); yield, 3.13 g. Pale yellowish-orange crystals of **8a** were obtained after two recrystallizations from carbon tetrachloride: yield, 0.942 g (11%); mp 196 °C dec; NMR (Me_2SO-d_6) δ 1.17 (t, J = 7 Hz, 3 H), 1.95 (s, 3 H), 2.92 (s, 3 H), 4.08 (q, J = 7 Hz, 2 H), 6.42 (s, 1 H), 6.89 (br s, 2 H), 10.8 (br s, 1 H); UV (CH_3OH) λ_{max} 240 nm (ε 14100), 295 (13700), 306.5 (sh, 12600), 386 (900); mass spectrum (160 °C), m/e 277 (M, 70), 236 (M – CH_3CN, 100). The following selected accurate masses were determined: 277.1170 ($C_{12}H_{15}N_5O_3$), 236.0902 ($C_{10}H_{12}N_4O_3$). Anal. Calcd for $C_{12}H_{15}N_5O_3 \cdot 0.45CCl_4$:[18] C, 43.15; H, 4.36; N, 20.21; Cl, 18.42. Found: C, 42.87; H, 4.38; N, 20.43; Cl, 18.23.

7-Amino-3-(3,4,5-trimethoxyphenacyl)-1-methylpyrimido[4,5-*c*]pyridazine-4,5(1*H*,6*H*)-dione (6g). To a stirred, refluxing mixture of 5.00 g (0.0305 mol) of **1a** in 500 mL of methanol was added 13.50 g (0.0457 mol) of **4g**. After 18.5 h an orange solid was collected by filtration of the hot mixture, washed with 50 mL of methanol, and dried under vacuum at 80 °C; yield, 1.30 g. This solid was an inseparable 1:1 mixture of the 4,5-dione **6g** and its 3,5-dione isomer **5g** (as indicated by an acceptable microanalysis for $C_{18}H_{19}N_5O_6$ and its NMR spectrum in CF_3CO_2H which represented a composite of the spectra for pure **5g** and pure **6g**). The filtrate was refluxed an additional 23 h, and the pale yellow solid **6g** was collected from the hot mixture, washed with 35 mL of methanol, and dried under vacuum at 80 °C: yield, 0.195 g (2%); mp >300 °C; NMR (CF_3COOH) δ 4.07 (s) and 4.13 (s, 9 H), 4.30 (s, 3 H), 4.86 (s, 2 H), 7.18 (br s, 2 H), 7.54 (s, 2 H); UV (CH_3OH) λ_{max} 258.5 nm (ε 43700), 297 (sh, 17200), 310 (sh, 13700); mass spectrum (250 °C), m/e 401 (M, 7), 196 (11), 195 (100), 181 (2), 167 (2), 166 [M – $(CH_3O)_3C_6H_2COCH_2CN$, 2], 165 (2), 152 (7), 137 (6), 122 (5), 111 (10). The following selected accurate mass was determined: 166.0488 ($C_6H_6N_4O_2$). Anal. Calcd for $C_{18}H_{19}N_5O_6$: C, 53.86; H, 4.77; N, 17.45. Found: C, 53.82; H, 4.85; N, 17.55.

The isolation of **7g** from this reaction mixture is described below.

8-Amino-3-(carbomethoxy)-1-methyl-5-(3,4,5-trimethoxyphenyl)-1*H*-pyrimido[4,5-*c*]-1,2-diazepin-6(7*H*)-one (7g). The filtrate from the collection of pure **6g** was concentrated under vacuum to 14.6 g of orange solid. A 5-g sample in methanol was concentrated onto 25 g of silica gel that was added to a column consisting of 200 g of silica gel in toluene. Elution of the column successively with chloroform, a 1:1 chloroform/ethyl acetate mixture, ethyl acetate, and a 9:1 ethyl acetate/methanol mixture effected separation of **7g** in the last solvent mixture; yield, 2.5 g. Orange needles were obtained after recrystallization from methanol: yield, 2.07 g (48%);[19] mp 258 °C dec; NMR (Me_2SO-d_6) δ 3.10 (s, 3 H), 3.67 (s), 3.75 (s), and 3.77 (s, 12 H), 6.47 (s, 2 H), 6.51 (s, 1 H), 6.86 (br s, 2 H), 10.79 (br s, 1 H); UV (CH_3OH) λ_{max} 237 nm (sh, ε 19400), 305 (24000), 425 (800); mass spectrum (210 °C), m/e 415 (M, 56), 414 (4), 371 (4), 357 (9), 356 (5), 331 (11), 330 (57), 329 (10), 317 (5), 316 (19), 315 (100). Anal. Calcd for $C_{19}H_{21}N_5O_6$: C, 54.93; H, 5.10; N, 16.86. Found: C, 54.86; H, 5.14; N, 16.84.

Preparation of a Pure Pyrimido[4,5-*c*]pyridazine-3,5-dione. 7-Amino-1-methyl-4-(3,4,5-trimethoxyphenacyl)pyrimido[4,5-*c*]pyridazine-3,5(1*H*,2*H*)-dione (5g). To a stirred, refluxing solution of 4.00 g (0.0244 mol) of **1a** in 400 mL of methyl Cellosolve was added 8.64 g (0.0292 mol) of **4g**. After 1 h 50 min the reddish-orange solid **5g** was collected by filtration of the hot mixture, washed 3 times with 50 mL of methanol, and dried under vacuum at 75 °C: yield, 4.29 g (44%); mp >300 °C; NMR (CF_3COOH) δ 4.08 (s) and 4.13 (s, 9 H), 4.33 (s, 3 H), 5.39 (s, 2 H), 6.96 (br s, 2 H), 7.54 (s, 2 H); UV ($CH_3OCH_2CH_2OH$)[20] λ_{max} 248.5

(13) Beynon, J. H.; Cooks, R. G. *Res/Dev.* 1971, *22*, 26.
(14) See paragraph on supplementary material at end of paper.
(15) Refluxing methanol was chosen as the preferred reaction medium because it afforded higher yields of pyrimidopyridazines **6** than did ethanol (either at reflux or at 65 °C) or methyl Cellosolve even though in some cases minor problems with transesterification occurred.
(16) A decoupling experiment showed that the CH_3 at δ 2.12 is coupled to the CH at δ 6.18.
(17) A metastable ion for this fragmentation was detected by the MIKES[13] technique.
(18) Drying to constant weight at 100 °C under high vacuum failed to remove the carbon tetrachloride.
(19) This yield is extrapolated.

nm (ε 18 700), 268 (sh, 18 300), 271.5 (18 500), 317.5 (8900), 388.5 (sh, 4400), 413 sh (6800), 464 (33 300), 486 (42 500); mass spectrum (field desorption), *m/e* 401 (M). Anal. Calcd for $C_{18}H_{19}N_5O_6$: C, 53.86; H, 4.77; N, 17.45. Found: C, 53.75; H, 4.80; N, 17.65.

8-Amino-1,3,5-trimethyl-1*H*-pyrimido[4,5-*c*]-1,2-diazepin-6(7*H*)-one (10a). To a stirred, refluxing mixture of 1.00 g (0.00609 mol) of **1a** in 100 mL of methanol was added 0.913 g (0.009 12 mol) of 2,4-pentanedione (**9a**). After 48 h the resulting orange solution was allowed to cool to room temperature and stand overnight. The solution was concentrated by boiling to 25 mL and was allowed to cool to room temperature. After 2 h the slightly cloudy solution was filtered, and the clear filtrate was concentrated by boiling to 15 mL when it was once again allowed to cool to room temperature and stand overnight. No crystallization occurred until after 24 h when the solution was suddenly jarred. After an additional 2 h yellow crystals of **10a** were collected by filtration, washed quickly with 5 mL of methanol and 10 mL of hexane, and dried under vacuum at 75 °C: yield, 0.541 g (41%); mp 250–253 °C dec; NMR (Me_2SO-d_6) δ 1.84 (s, 3 H), 2.06 (d, J = 1 Hz, 3 H),[21] 2.88 (s, 3 H), 5.89 (q, J = 1 Hz, 1 H), 6.67 (br s, 2 H), 10.58 (br s, 1 H), NOE/$f_{5.89}$ (2.06) = 25%, NOE/$f_{5.89}$ (1.84) = 19%; UV (CH_3OH) λ_{max} 233.5 nm (sh, ε 11 400), 267 (17 900), 302 (9900), 348 (1300); pK_a 9.1 and 3.3; mass spectrum (160 °C), *m/e* 219 (M, 43), 191 (2), 179 (13), 178 (100), 177 (29), 174 (3), 163 (4), 162 (10), 161 (53), 151 (16), 136 (37). Anal. Calcd for $C_{10}H_{13}N_5O$: C, 54.78; H, 5.98; N, 31.95. Found: C, 54.96; H, 5.99; N, 31.72.

8-Amino-3,5-diphenyl-1-methyl-1*H*-pyrimido[4,5-*c*]-1,2-diazepin-6(7*H*)-one (10b). To a stirred, refluxing mixture of 1.00 g (0.006 09 mol) of **1a** in 100 mL of methanol was added 2.05 g (0.009 13 mol) of 1,3-diphenyl-1,3-propanedione (**9b**). After 236 h the orange solution was concentrated under vacuum onto 5 g of silica gel that was added to a column of 90 g of silica gel in hexane. Successive elution of the column with benzene, a 3:1 benzene/chloroform mixture, chloroform, and ethyl acetate effected separation of **10b** (found in all but the benzene eluates); yield, 1.005 g. A yellow solid was obtained after recyrstallization from carbon tetrachloride: yield, 0.64 g (29%); mp 205–220 °C dec; NMR (Me_2SO-d_6) δ 3.12 (s, 3 H), 6.69 (s, 1 H), 6.77 (br s, 2 H), 7.2–7.6 (m, 8 H), 7.6–8.0 (m, 2 H), 10.65 (br s, 1 H); UV (CH_3OH) λ_{max} 255.5 nm (ε 22 200), 285 (26 400), 385 (700); mass spectrum (285 °C), *m/e* 343 (M, 15), 241 (17), 240 (100), 223 (28), 198 (11). The following selected accurate mass was determined: 343.1437 ($C_{20}H_{17}N_5O$). Anal. Calcd for $C_{20}H_{17}N_5O$·0.022CCl_4:[18] C, 69.35; H, 4.94; N, 20.20; Cl, 0.90. Found: C, 69.43; H, 5.09; N, 20.15; Cl, 0.90.

2-Amino-6-(3,5-dimethylpyrazoloyl)pyrimidin-4(3*H*)-one (12). A mixture of 5.65 g (0.040 mol) of 6-hydrazinoisocytosine (**11**),[4] 5.00 g (0.050 mol) of 2,4-pentanedione, and 200 mL of methyl Cellosolve was heated under reflux for 59 h and was then filtered while hot to remove a small amount of unchanged **11**. The pale orange filtrate deposited 3.70 g of colorless crystals after standing overnight at room temperature. Additional crystals were obtained from the mother liquor after concentration to 65 mL; total yield, 5.02 g; mp 303–304 °C. Recrystallization from 75 mL of methyl Cellosolve afforded analytically pure, colorless crystals of **12**: yield, 3.70 g (45%); mp 305–306 °C; NMR (Me_2SO-d_6) δ 2.14 (s, 3 H), 2.56 (s, 3 H), 5.86 (s, 1 H), 6.04 (br s, 1 H), 6.71 (br s, 2 H), 10.72 (br s, 1 H); UV (CH_3OH) λ_{max} 235 nm (sh, ε 16 300), 252.5 (25 300), 301.5 (12 000); mass spectrum (210 °C), *m/e* 205 (M, 100), 190 (35), 164 (11), 110 (8), 95 (3). The following selected accurate masses were determined: 205.0960 ($C_9H_{11}N_5O$), 164.0693 ($C_7H_8N_4O$), 110.0346 ($C_4H_4N_3O$), 95.0613 ($C_5H_7N_2$). Anal. Calcd for $C_9H_{11}N_5O$: C, 52.67; H, 5.40; N, 34.13. Found: C, 52.68; H, 5.43; N, 34.19.

6-Pyrimidinylhydrazones. 2,4-Pentanedione (2,4-Diamino-6-pyrimidinyl)methylhydrazone (15a). A mixture of 2.0 g (0.013 mol of 2,4-diamino-6-(1-methylhydrazino)pyrimidine (**13**) and 1.95 g (0.0195 mol) of 2,4-pentanedione in 100 mL of methanol was stirred at reflux for 23 h. The solution was concentrated under vacuum to a partially solid residue which was triturated with hexanes. The solid was collected by suction filtration, washed with hexanes, and dried under vacuum (70 °C): yield, 3.0 g (98%) of the crude hydrazone; mp 184–189 °C. Recrystallization from benzene afforded straw-colored crystals of **15a**: yield, 2.4 g (78%); mp 197–198 °C; NMR (Me_2SO-d_6) isomer A, δ 1.83 (s, 3 H), 1.97 (s, 3 H), 3.13 (s, 3 H), 5.00 (s, 1 H), 5.15 (s, 1 H), 5.68 (br s, 2 H), 5.92 (br s, 2 H), 11.25 (br s, 1 H); NMR (Me_2SO-d_6) isomer B, δ 1.90 (s, 3 H), 2.20 (s, 3 H), 3.10 (s, 3 H), 5.08 (s, 1 H), 5.20 (s, 1 H), 5.68 (br s, 2 H), 5.92 (br s, 2 H); UV (CH_3OH) λ_{max} 272 nm (ε 16 400), 299 (17 900). Anal. Calcd for $C_{10}H_{16}N_6O$: C, 50.83; H, 6.83; N, 35.57. Found: C, 50.82; H, 6.88; N, 35.66.

The following hydrazones were prepared and purified in a similar manner except for the noted variations: (pyrimidine, ketone, reaction medium, reflux time, trituration solvent, recyrstallization solvent, yield).

1-Phenyl-1,3-butanedione (2,4-Diamino-6-pyrimidinyl)methylhydrazone (15b): [**13**, 1-phenyl-1,3-butanedione, methyl Cellosolve, 25 h,[22] ether, benzene (once), and methanol (once), 40%]; mp 187–188 °C. Anal. ($C_{15}H_{18}N_6O$·CH_3OH).

Ethyl 3-Oxobutanoate (2-Amino-4-oxo-3,4-dihydro-6-pyrimidinyl)methylhydrazone (18a): (**1a**, ethyl 3-oxobutanoate, 95% ethanol, 43 h,[22] ether, benzene, 63%); mp 172–182 °C. Anal. ($C_{11}H_{17}N_5O_3$).

Ethyl 3-Oxobutanoate (2,4-Diamino-6-pyrimidinyl)methylhydrazone (18b): (**13**, ethyl 3-oxobutanoate, 95% ethanol, 21 h,[22] hexanes, benzene, 58%); mp 148–150 °C. Anal. ($C_{11}H_{18}N_6O_2$).

6,8-Diamino-1,3,5-trimethyl-1*H*-pyrimido[4,5-*c*]-1,2-diazepine (16).[23] A mixture of 1.54 g (0.01 mol) of **13** and 1.50 g (0.015 mol) of 2,4-pentanedione in 50 mL of methyl Cellosolve was heated at reflux for 4 days. The resulting greenish-red solution was concentrated under vacuum to a partially solid residue which was triturated with hexanes and dried under vacuum (70 °C): yield, 1.85 g of very crude product from which 0.28 g (13%) of analytically pure **16** was obtained by subsequent fractional crystallizations from *n*-propanol and benzene; mp 267–269 °C dec; NMR (Me_2SO-d_6) δ 1.86 (s, 3 H), 2.02 (d, J = 1 Hz, 3 H), 2.90 (s, 3 H), 5.97–6.03 (br m, 5 H); UV (CH_3OH) λ_{max} 275.5 nm (ε 13 500), 295 (sh, 8500), 350 (1400). Anal. Calcd for $C_{10}H_{14}N_6$: C, 55.03; H, 6.47; N, 38.51. Found: C, 55.13; H, 6.56; N, 38.37.

Rearrangements of Pyrido[2,3-*d*]pyrimidin-4(8*H*)-ones (21). 2,7-Diamino-8-methyl-5-(3,4,5-trimethoxyphenyl)-pyrido[2,3-*d*]pyrimidin-4(8*H*)-one (21g). To 1.00 g (0.00241 mol) of **7g** was added 15 mL of 10% (w/w) aqueous NaOH, and a solution resulted after the mixture was stirred. After 1 h the orange solution was acidified with concentrated HCl until pH 2–3 was reached. The precipitated yellow solid **19g** was collected by filtration, washed twice with 10 mL of water, and dried under vacuum at 75 °C; yield, 0.91 g (90%). A microanalysis of this compound indicated the corresponding carboxylic acid of starting ester.[24] The acid was dissolved in 200 mL of boiling methyl Cellosolve, and the orange solution became pale yellow. The solution was concentrated by boiling to 20 mL whereupon a solid precipitated. The mixture was allowed to cool to room temperature and stand for 5 days. The pale yellow solid **21g** was collected, washed with 15 mL of water and 10 mL of methanol, and dried under vacuum at 75 °C: yield, 0.470 g (55%); mp >300 °C; NMR (CF_3COOH) δ 4.00 (s, 6 H), 4.09 (s, 6 H), 6.73 (s, 1 H), 6.76 (s, 2 H), 7.26 (br s, 2 H); NMR (Me_2SO-d_6) δ 3.64 (s, 3 H), 3.72 (s), and 3.76 (s, 9 H), 6.00 (s, 1 H), 6.53 (s, 2 H), 6.86 (br s, 2 H), 8–9 (br s, 2 H); NOE/$f_{6.00}$ (3.64) = 0, NOE/$f_{6.00}$ (3.72) = 0; UV (CH_3OH) λ_{max} 261.5 nm (ε 10 400), 293 (14 000), 339 (sh, 16 900), 348 (18 800); UV (0.1 N HCl) λ_{max} 291 nm (ε 17 300), 333 (sh, 17 600), 340.5 (18 600); UV (0.1 N NaOH) λ_{max} 253.5 nm (ε 16 100), 288 (sh, 12 200), 292 (12 300), 346.5 (15 000); mass spectrum (260 °C), *m/e* 357 (M, 100), 356 (3), 343 (6), 342 (M − CH_3, 16), 327 (M− CH_2O and M − C_2H_6, 4), 326 (4), 325 (4), 317 (M − C_2H_2N, 1), 316 (M − C_2H_3N, 1). The following selected accurates masses

(20) The sample should be dissolved as quickly as possible with the aid of a steam bath and cooled back to room temperature where it is much more stable.

(21) A decoupling experiment showed that the CH_3 at δ 2.06 is coupled to the CH at δ 5.89.

(22) UV was unchanged after 3 h or less.

(23) Alternatively prepared by refluxing a solution of **15a** in methyl Cellosolve for 3 days.

(24) Calcd for $C_{18}H_{19}N_5O_6$: C, 53.86; H, 4.77; N, 17.45. Found: C, 53.90; H, 4.80; N, 17.34 (after 4.13% weight loss during drying to constant weight at 100 °C under high vacuum).

were determined: 357.1432 ($C_{17}H_{19}N_5O_4$), 342.1203 ($C_{16}H_{16}N_5O_4$), 327.1333 ($C_{16}H_{17}N_5O_3$), 327.0969 ($C_{15}H_{13}N_5O_4$), 317.1265 ($C_{15}H_{17}N_4O_4$), 316.1164 ($C_{15}H_{16}N_4O_4$). Anal. Calcd for $C_{17}H_{19}N_5O_4$: C, 57.13; H, 5.36; N, 19.60. Found: C, 57.15; H, 5.41; N, 19.52.

The following pyrido[2,3-*d*]pyrimidines were prepared in a manner similar to that of **21g**: (starting pyrimidodiazepine, yield).

2,7-Diamino-5,8-dimethylpyrido[2,3-*d*]pyrimidine-4-(8*H*)-one (21a): (**7a**, 68%); mp >300 °C; pK_a = 8.4. Anal. ($C_9H_{11}N_5O$).

2,7-Diamino-8-methyl-5-(3-pyridyl)pyrido[2,3-*d*]pyrimidin-4(8*H*)-one (21b):[25] (**7b**, 27%); mp 301–304 °C dec. Anal. ($C_{13}H_{12}N_6O$·0.24$CH_3OCH_2CH_2OH$·0.18H_2O).[26]

2,7-Diamino-8-methyl-5-phenylpyrido[2,3-*d*]pyrimidin-4-(8*H*)-one (21c): (**7c**, 49%); mp >300 °C. Anal. ($C_{14}H_{13}N_5O$·0.08$CH_3OCH_2CH_2OH$·0.20H_2O).[26]

2,7-Diamino-5-(3-hydroxyphenyl)-8-methylpyrido[2,3-*d*]-pyrimidin-4(8*H*)-one (21d):[27] (**7d**, 70%); mp >300 °C. Anal. ($C_{14}H_{13}N_5O_2$).

***trans*-(2-Amino-4-(methylamino)-6-oxo-1,6-dihydro-5-pyrimidinyl)acrylonitrile (24).** To a solution of 0.70 g (0.0050 mol) of 6-(methylamino)isocytosine (**22**)[11] in 12 mL of refluxing glacial acetic acid protected with a drying tube was added 0.50 g (0.0050 mol) of 3-(dimethylamino)acylonitrile (**23**). After 5 min the resulting mixture was allowed to cool to room temperature and stand for 2 days. The precipitated solid **24** was collected by filtration, washed with glacial acetic acid, and dried under vacuum at 70 °C: yield, 0.45 g (47%); mp >300 °C; IR $\nu_{C\equiv N}$ 2209 cm^{-1}; NMR (Me_2SO-d_6) δ 2.83 (d, *J* = 4 Hz, 3 H), 6.40 (d, *J* = 16 Hz, 1 H), 6.78 (br s, 2 H), 7.43 (br m, 1 H), 7.47 (d, *J* = 16 Hz, 1 H), 10.23 (br s, 1 H); UV (CH_3OH) λ_{max} 248 nm (ε 12 000), 278 (3900), 338 (16 600), 347 (sh, 15 900). Anal. Calcd for $C_8H_9N_5O$: C, 50.25; H, 4.74; N, 36.63. Found: C, 50.05; H, 4.83; N, 36.47.

2,7-Diamino-8-methylpyrido[2,3-*d*]pyrimidin-4(8*H*)-one (21h). After a solution of 0.37 g (0.0019 mol) of **24** in 100 mL of methyl Cellosolve containing two drops of glacial acetic acid had been refluxed for 19 h, the resulting mixture was allowed to cool to room temperature. The yellow solid **21h** was collected by filtration, washed 3 times with 1 mL of methanol, and dried under vacuum at 70 °C: yield, 0.24 g (66%); mp > 300 °C; NMR (CF_3COOH) δ 4.03 (s, 3 H), 6.85 (d, *J* = 9 Hz, 1 H), 7.26 (br s, 2 H), 8.37 (d, *J* = 9 Hz, 1 H); NMR (Me_2SO-d_6) δ 3.61 (s, 3 H), 6.18 (d, *J* = 11 Hz, 1 H), 6.57 (br s, 2 H), 7.78 (d, *J* = 11 Hz, 1 H), 8.30 (br s, 2 H); UV (CH_3OH) λ_{max} 214.5 nm (ε 27 900), 255.5 (7800), 289 (6100), 347.5 (19 400); UV (0.1 N HCl) 289 nm (ε 9800), 332 (sh, 17 200), 337 (17 400); UV (0.1 N NaOH) 245.5 nm (sh, ε 8800), 292 (7900), 326.5 (sh, 13 300), 338 (15 800), 349 (sh, 12 600); pK_a = 7.5. Anal. Calcd for $C_8H_9N_5O$: C, 50.25; H, 4.74; N, 36.63. Found: C, 50.18; H, 4.81; N, 36.57.

Rearrangements to Pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-ones (22). 6-Amino-1,3-dimethyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (25a). When a mixture of 0.219 g (0.000 999 mol) of **10a**[28] and 3 mL of 1 N HCl was heated by a hot water bath (>85 °C) for 2 h, a homogeneous solution formed from which crystals gradually began to separate. After standing at room temperature overnight, the mixture was filtered, and the straw-colored crystals of **25a** were washed with water and dried under vacuum at 70 °C: yield, 0.140 g (78%); mp >300 °C; NMR (Me_2SO-d_6) δ 2.28 (s, 3 H), 3.60 (s, 3 H), 6.52 (br s, 2 H), 10.30 (br s, 1 H); UV (CH_3OH) λ_{max} 217 nm (ε 26 800), 254 (13 000); mass spectrum (120 °C), *m/e* 179 (M, 100). Anal. Calcd for $C_7H_9N_5O$: C, 46.92; H, 5.06; N, 39.09. Found: C, 46.68; H, 5.11; N, 38.94.

The following pyrazolo[3,4-*d*]pyrimidines were prepared in a manner similar to that of **25a**: (starting pyrimidodiazepine, reaction time in hot water bath, yield).

6-Amino-1-methyl-3-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (25b): (**7c**, 3 h, 43%[29]); mp >300 °C. Anal. ($C_{12}H_{11}N_5O$). (**10b**, 3 h, 29%[30]); physical data same as those of product from **7c**.

6-Amino-3-(3-hydroxyphenyl)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (25c): (**7d**, 2 h,[31] 21%[32]); mp > 300 °C. Anal. ($C_{12}H_{11}N_5O_2$·0.55CH_3OH·0.16H_2O).[33]

6-Amino-1-methyl-3-(3,4,5-trimethoxyphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one (25d): (**7g**, 3 h, 40%[34]); mp 183–184 °C. Anal. ($C_{15}H_{17}N_5O_4$·CH_3OH).[35]

7-Amino-1,4-dimethylpyrimido[4,5-*c*]pyridazine-3,5-(1*H*,2*H*)-dione (27). Method A. A 1-g (0.00249 mol) sample of **5g** was dissolved in 40 mL of 1 N NaOH. After 17.5 h the green solution was brought to neutrality with concentrated HCl. A yellowish-green solid was collected by filtration, washed with two portions of water totalling 40 mL, and dried under vacuum at 75 °C; yield, 0.500 g. The solid **27** stood for 3 days under 60 mL of ether in order to remove a trace of 3,4,5-trimethoxybenzoic acid and was pulverized, collected by filtration, and dried under vacuum at 75 °C: yield, 0.488 g (85%); mp >300 °C; NMR (CF_3COOH) δ 3.03 (s, 3 H), 4.27 (s, 3 H), 6.85 (br s, 2 H); UV (1 N NaOH) λ_{max} 258.5 nm (ε 32 800), 282.5 (sh, 7500), 402 (5100); mass spectrum (310 °C), *m/e* 207 (M, 100), 206 (M – H, 7) 194 (18), 193 (M – CH_2, 5), 192 (3), 179 (M– CO, 26), 178 (M – COH or CHO, 16), 166 (6), 165 (15), 164 (M – C_2H_3O, 17), 163 (12), 162 (11). The following accurate masses were determined: 207.0772 ($C_8H_9N_5O_2$), 206.0701 ($C_8H_8N_5O_2$), 193.0603 ($C_7H_7N_5O_2$), 179.0811 ($C_7H_9N_5O$), 178.0727 ($C_7H_8N_5O$), 164.0571 ($C_6H_6N_5O$). Anal. Calcd for $C_8H_9N_5O_2$·0.75H_2O: C, 43.53; H, 4.80; N, 31.73. Found: C, 43.61; H, 4.72; N, 31.59.

Method B. A solution of 0.300 g (0.00113 mol) of **8a′** in 170 mL of 0.1 N HCl was allowed to stand for 76 h. The solution was then brought to pH 3.0–3.5 with 1 N NaOH, and precipitated solid was collected by filtration, washed twice with 5 mL of water, and dried under vacuum at 80 °C: yield, 0.107 g of greenish-yellow solid; NMR (CF_3COOH) δ 2.60 (s, 3 H), 4.27 (s, 3 H), 4.85 (s, 2 H), 6.94 (br s, 2 H) (impurity peaks were present also); UV (1 N NaOH after 5 min) λ_{max} 259 nm, 286 (sh), 403. The NMR spectrum was consistent with the proposed 4-acetonyl 3,5-dione **26**. The UV spectrum was qualitatively similar to that of **27** above and indicated a hydrolysis of **26** to **27** in a manner similar to the hydrolysis of **5g** to **27** in method A. Attempts to recrystallize **26** from methyl Cellosolve resulted in a solvolytic cleavage to **27**.[36] An attempted recrystallization is described in the paragraph below.

A 0.054-g sample of impure **26** was dissolved in 1 L of boiling methyl Cellosolve, and the solution was boiled down to 40 mL whereupon precipitated solid was noticed to be present. The mixture was allowed to cool to room temperature and stand overnight. Yellowish-green solid was collected by filtration, washed with 10 mL of methyl Cellosolve and 2 mL of methanol, and dried under vacuum at 75 °C; yield, 0.018 g. An NMR spectrum of this solid was identical with that of **27** prepared in method A.

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(25) The acid was heated in refluxing methyl Cellosolve for 1 h 45 min, and the cloudy solution was allowed to cool to room temperature. After 1 h a small amount of precipitated solid was removed by filtration and discarded. The filtrate was concentrated by boiling until a quite cloudy solution was present. Precipitated solid was collected by filtration after the mixture had reached room temperature and was dried under vacuum at 75 °C.

(26) Drying to constant weight at 100 °C under high vacuum failed to remove the methyl Cellosolve and water. The presence of methyl Cellosolve was confirmed by NMR.

(27) The acid was heated in refluxing methyl Cellosolve for 2.5 h, and precipitated solid was collected by filtration from a hot mixture, washed with methyl Cellosolve and methanol, and dried under high vacuum at 135 °C.

(28) NMR studies indicated that treatment of this compound with 10% (w/w) aqueous NaOH under otherwise similar conditions effected a partial conversion (<25%) to the same product.

(29) Yield after recrystallization from ethanol.

(30) Yield after ether wash to remove 1,3-diphenyl-1,3-propanedione, a product of a competing reaction, which was isolated in 50% yield.

(31) A solid impurity was removed by filtration before the crude product was subsequently precipitated form the mother liquor by adjustment to pH 3.5 with 4 N NaOH, collected by filtration, washed with water, and dried under vacuum at 70 °C.

(32) Yield after two recrystallizations from methanol and drying under vacuum at 70 °C.

(33) Drying to constant weight at 75 °C under high vacuum failed to remove the methanol and water. The presence of methanol was confirmed by NMR.

(34) Yield after ether wash, neutralization of the collected crude product with 1 N NaOH, recrystallization from methanol, and drying under vacuum at 70 °C.

(35) Drying to constant weight at 70 °C under high vacuum failed to remove the methanol. The presence of methanol was confirmed by NMR.

(36) Solvolytic cleavage to **24** has also been detected after prolonged reflux of **5g** in methyl Cellosolve.

NMR spectra, Dr. D. A. Brent, Ms. D. Rouse, and R. L. Johnson, Jr. for the mass spectra, and Mrs. P. Baker, Miss N. T. Rodgers, Miss S. Wrenn, Mrs. J. Miller, Miss J. Emery, and Mrs. C. A. Jenkins for technical assistance.

Registry No. **1a**, 67873-21-6; **4a**, 615-79-2; **4b**, 23424-36-4; **4c**, 6296-54-4; **4d**, 60640-63-3; **4e**, 70935-15-8; **4f**, 80081-75-0; **4g**, 70311-74-9; **5d**, 80081-76-1; **5e**, 80081-77-2; **5f**, 80081-78-3; **5g**, 80081-79-4; **6c**, 80081-80-7; **6d**, 80081-81-8; **6e**, 80081-82-9; **6f**, 80081-83-0; **6g**, 80081-84-1; **7a**, 80081-85-2; **7b**, 70311-79-4; **7c**, 80081-86-3; **7d**, 70311-78-3; **7e**, 80081-87-4; **7f**, 80081-88-5; **7g**, 70311-81-8; **8a**, 80081-89-6; **8a'**, 80081-90-9; **9a**, 123-54-6; **9b**, 120-46-7; **10a**, 70311-77-2; **10b**, 70311-76-1; **11**, 6298-85-7; **12**, 80081-91-0; **13**, 67873-55-6; **14**, 93-91-4; **15a**, 80081-92-1; **15b**, 80081-93-2; **16**, 80081-94-3; **17**, 141-97-9; **18a**, 80081-95-4; **18b**, 80081-96-5; **19g**, 80081-97-6; **21a**, 80081-98-7; **21b**, 80081-99-8; **21c**, 80082-00-4; **21d**, 80082-01-5; **21g**, 80082-02-6; **21h**, 80082-03-7; **22**, 54004-20-5; **23**, 2407-68-3; **24**, 80082-04-8; **25a**, 80082-05-9; **25b**, 80082-06-0; **35c**, 80082-07-1; **25d**, 80082-08-2; **26**, 70311-95-4; **27**, 70311-96-5.

Supplementary Material Available: Full data available include the following: microanalyses, UV data, and NMR data on compounds **4e,g**, **6c-f**, **7b-f**, **15b**, **18a,b**, **21a-d**, **25b** (from **7c**), **25c,d**; and mass spectral data on **6c**, **7c**, **15b**, **21a-c**, **25b** (from **7c**), **25c,d** (9 pages). Ordering information is given on any current masthead page.

Pyrimido[4,5-*c*]pyridazines. 5. Summary of Cyclizations with Vicinally Functionalized Reagents and Studies of the Reductive Behavior of the Ring System[1]

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New syntheses of pyrimido[4,5-*c*]pyridazines from 6-hydrazinoisocytosines and vicinal carbonyl reagents and reduction studies with selected members of this compound series are reported. Structural features required for pyrimidopyridazine formation from reactions of 2-amino-4-hydrazinopyrimidines with vicinal difunctional reagents and selectivity with respect to product substituent orientations are summarized.

In previous publications, we described the synthesis of pyrimido[4,5-*c*]pyridazines by cyclizations of appropriately substituted 6-hydrazinopyrimidines with α-keto esters,[2,3] pyruvic acid,[4] and in one case an α-halo ketone.[5] We now report additional syntheses from cyclizations of 6-hydrazinoisocytosines with reagents of other vicinal carbonyl functionality and studies of reductions of selected pyrimidopyridazines within our series.

Synthesis

Symmetrical α-dicarbonyl reagents such as glyoxal (either as the hydrate or bisulfite addition product), biacetyl, and benzil are known to cyclize with 3-methyl- and 1,3-dimethylhydrazinouracil derivatives,[6,7] but there are no reports of analogous reactions with isocytosines to give pyrimidopyridazine analogues of the naturally occurring pterins. We examined cyclizations of symmetrical and unsymmetrical vicinal dicarbonyl reagents (**2**) with 6-hydrazinoisocytosines (**1**) and found the chemistry to be particularly interesting when **2** was unsymmetrical (Table I). Structural assignments for the products in Table I were based on a combination of physical techniques.

Only the 4-phenyl compound (**3c**) was isolated from the reaction of **1a**[2] with phenylglyoxal (**2c**), but pyruvaldehyde (**2d**), with its more reactive aliphatic ketone function, provided a synthetically useless and inseparable mixture of roughly equivalent amounts of the 3- and 4-methyl isomers (**3d**; based on NMR interpretation). With (*m*-hydroxyphenyl)glyoxal, both isomers (**3e**) formed, but the 4-aryl compound predominated at a ratio of 5:1. The pure 4-(*m*-hydroxyphenyl) isomer was obtained from the mixture by fractional crystallization. Analogous reactions of **2d** and **2c** with **1b**[2] afforded only the 3-methyl- and 3-phenylpyrimidopyridazines **3f** and **3g**, respectively. In neither case was there evidence of the 4-substituted isomer.

Selectivity was also obtained for cyclizations of **1a** with an alkyl and an aryl α-keto aldoxime. With pyruvaldoxime (**2f**) and ω-isonitrosoacetophenone (**2g**) only the 3-substituted compounds **3h** and **3i**, respectively, were obtained. These cyclizations provide an additional exploitation of the inherent reactivity differences of these two functional groups implied in Taylor's unequivocal pteridine synthesis.[8] Note also that this change from the vicinal dicarbonyl **2c** to its monoxime derivative **2g** provided a shift in orientation for the phenyl substituent from position 4 (**3c**) to position 3 (**3i**) of the product.

Structures for the phenyl compounds **3c** and **3i** were initially assigned on the basis of differences in their UV and ^{1}H NMR spectra. The longer wavelength UV absorbance (Figure 1) for the compound which we assign as the 3-phenyl isomer (**3i**) may be rationalized on the basis of extended conjugation through the attached benzene ring. The nonplanar geometry required for the 4-phenyl isomer (**3c**) because of interaction with the 5-oxo substituent would minimize this conjugation effect. Similar phenomena have been reported for 5- vs. 6- and 7-phenylpyrido[2,3-*d*]pyrimidines.[9] Furthermore, deshielding of the ortho protons was seen in the NMR spectrum of the 3-phenyl isomer only (Table I). A similar deshielding effect was also noted for the ortho protons of its N^1-*unsubstituted* analogue **3g**. This downfield shift is explained as an effect of

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