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.

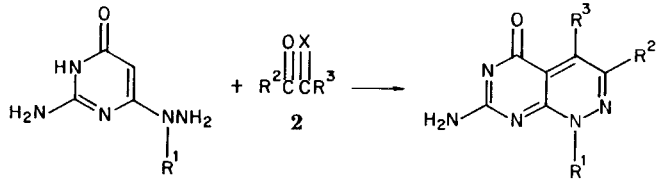
Selectivity was also obtained for cyclizations of **1a** with an alkyl and an aryl α-keto aldoxime. With pyruvaldoxime (**2f**) and ω-isonitrosoacetophenone (**2g**) only the 3-substituted compounds **3h** and **3i**, respectively, were obtained. These cyclizations provide an additional exploitation 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

(1) This work was presented, in part, at the 29th Southeast Regional Meeting of the American Chemical Society, Tampa, FL, Nov 1977.
(2) Morrison, R. W., Jr.; Mallory, W. R.; Styles, V. L. *J. Org. Chem.* **1978**, *43*, 4844.
(3) Mallory, W. R.; Morrison, R. W., Jr.; Styles, V. L. *J. Org. Chem.* **1982**, *47*, 667.
(4) Styles, V. L.; Morrison, R. W., Jr. *J. Org. Chem.* **1982**, *47*, 585.
(5) Mallory, W. R.; Morrison, R. W., Jr. *J. Org. Chem.* **1980**, *45*, 3919.
(6) Billings, B. K.; Wagner, J. A.; Cook, P. D.; Castle, R. N. *J. Heterocycl. Chem.* **1975**, *12*, 1221.
(7) Pfleiderer, W.; Ferch, H. *Justus Liebigs Ann. Chem.* **1958**, *615*, 48.
(8) Taylor, E. C.; Kobayashi, T. *J. Org. Chem.* **1973**, *38*, 2817.
(9) Hurlbert, B. S.; Ledig, K. W.; Stenbuck, P.; Valenti, B. F.; Hitchings, G. H. *J. Med. Chem.* **1968**, *11*, 703.

0022-3263/82/1947-0674$01.25/0

Table I. 7-Aminopyrimido[4,5-*c*]pyridazin-5(1*H*)-ones (3)[a]



1 + 2 → 3

1	R^1	2	X	R^2	R^3	molar ratio 2:1	rctn solvent (time, h)	3	% yield[b] (mp, °C)	^{1}H NMR (δ in CF_3COOH) R^1	R^2	R^3
a	CH_3	a[c]	O	CH_3	CH_3	2.0:1	CH_3OH[d] (19)	a	95[e] (>300)	4.42 (s, 3 H)	2.78 (s, 3 H)	3.09 (s, 3 H)
a	CH_3	b[f]	O	C_6H_5	C_6H_5	1.1:1[g]	CH_3OH[d] (30)	b	20[h] (>300)	4.57 (s, 3 H)	7.1-7.5 (m, 10 H)	
a	CH_3	c[i]	O	H	C_6H_5	1.5:1	CH_3OH[d] (4)	c	50[j] (262.5-264 dec)	4.49 (s, 3 H)	8.72 (s, 1 H)	7.60 (s, 5 H)
a	CH_3	d[i]	O	[H / CH_3]	[CH_3 / H]	3.0:1	CH_3OH[d] (1.5)	d	84[k] (>300)	4.43 (s, 3 H) 4.46 (s, 3 H)	8.64 (s, 1 H) 2.80 (s, 3 H)	3.04 (s, 3 H) 8.60 (s, 1 H)
a	CH_3	e[l]	O	[H / *m*-HOC_6H_4]	[*m*-HOC_6H_4 / H]	1.1:1	CH_3OH[d] (3)	e	86[m] (>300)	4.49 (s, 3 H) 4.58 (s, 3 H)	8.69 (s, 1 H) 7.1-7.7 (m, 4 H)	7.18-7.68 (m, 4 H) 9.15 (s, 1 H)
b	H	d	O	CH_3	H	1.5:1	H_2O[d] (1)	f	40[n] (>300)		3.12 (s, 3 H)	8.98 (s, 1 H)
b	H	c	O	C_6H_5	H	1.5:1	H_2O[d,o] (1)	g	49[p] (>300)		7.63-7.92 (m, 3 H) 8.00-8.22 (m, 2 H)	9.33 (s, 1 H)
a	CH_3	f[q]	NOH	CH_3	H	2.2:1	CH_3COOH[r] (44)	h	23[s] (>300)	4.46 (s, 3 H)	2.80 (s, 3 H)	8.60 (s, 1 H)
a	CH_3	g[q]	NOH	C_6H_5	H	1.1:1	CH_3COOH[r] (20)	i	58[t] (>300)	4.58 (s, 3 H)	7.58-7.77 (m, 3 H) 8.00-8.22 (m, 2 H)	9.18 (s, 1 H)
b	H	h[i]	(O)[u]	H	H	2:1	H_2O[d] (1)	j	49[v,w] (>300)		9.40 (d,[x] 1 H)	8.97 (d,[x] 1 H)

[a] These compounds were prepared according to the general example in the Experimental Section. [b] Yields are based on the amount of 1 used. [c] Fisher Scientific Co., freshly distilled. [d] Heated at reflux. [e] After recrystallization from glacial acetic acid; solvated with 2.5 mol of acetic acid. [f] Eastman Kodak Co. [g] Increasing the molar ratio of 2:1 to 2:1 and reaction time to 6 days did not appreciably increase product formation, and unreacted 1 remained in the reaction mixture in both cases. [h] After removal of unreacted 1 by subsequent dissolution of the crude product in glacial acetic acid, removal of the solvent under vacuum, trituration with hot water, recovery by filtration, and recrystallization from methanol. [i] Aldrich Chemical Co. [j] Recrystallized from methanol. [k] An acceptable elemental analysis was not obtained for the crude product (a 1:1 mixture of isomers), and attempts to purify it by chromatography (silica gel) and recrystallization from alcohol and acetic acid failed. Instability of the 4-methyl isomer is suspected. Structures are proposed on the basis of NMR comparisons with 3h and other models within the series. [l] Fodor, G.; Kovács, Ö. *J. Am. Chem. Soc.* **1949**, *71*, 1045. [m] Separated pure (as the isomeric mixture) from the reaction medium. The 4-aryl isomer represented >80% of the mixture and was isolated in pure form by fractional crystallization from methanol. [n] After one recrystallization from glacial acetic acid and another from water; isolated as the hemihydrate. [o] When methanol was used as the solvent, the analytically pure product separated from the reaction mixture; yield, 33%. [p] After recrystallization from glacial acetic acid. The yield of crude product was 84%. The hydrochloride monohydrate was obtained in 99% yield as yellow crystals from 1.0 N HCl. Anal. ($C_{13}H_{11}N_5O \cdot HCl \cdot H_2O$); mass spectrum (field desorption) 253 (M); NMR (Me_2SO-d_6) δ 4.33 (s, 3 H), 7.55-7.70 (m, 3 H), 8.05-8.28 (m, 2 H), 8.68 (br d, 1 H), 8.99 (s, 1 H), 9.30 (br d, 1 H); note the nonequivalence of amino protons as evidenced by the broad doublets at δ 8.68 and 9.30. [q] Life Science Division of ICN Pharmaceuticals, Inc. [r] Heated by an oil bath at 55 °C. [s] After evaporation of the acetic acid under vacuum and removal of byproducts (including methyl glyoxime) from the residue by extraction with ether, then ethyl acetate and, subsequently, two fractional crystallizations from methanol. [t] Crystallized in analytically pure form from the reaction medium. [u] As the disodium bisulfite addition compound. [v] The insoluble byproduct was removed by filtration of hot mixture and washed with hot water. The combined filtrates were then acidified with concentrated HCl and concentrated under vacuum to precipitate 3j. [w] The byproduct (22% yield) was the bishydrazone. For related reaction, see Pfleiderer, W; Ferch, H. *Justus Liebigs Ann. Chem.* **1958**, *615*, 48. [x] J = 5 Hz.

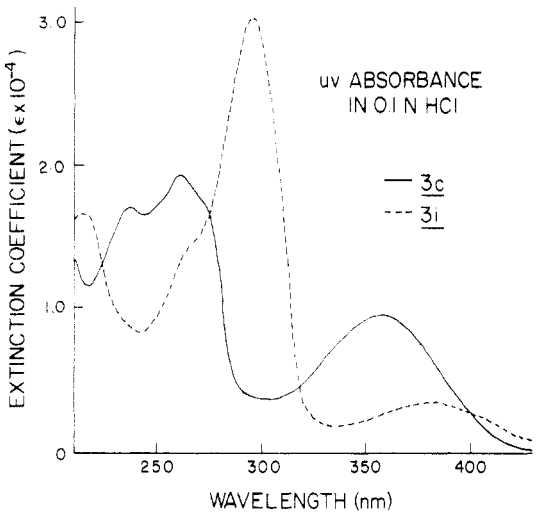


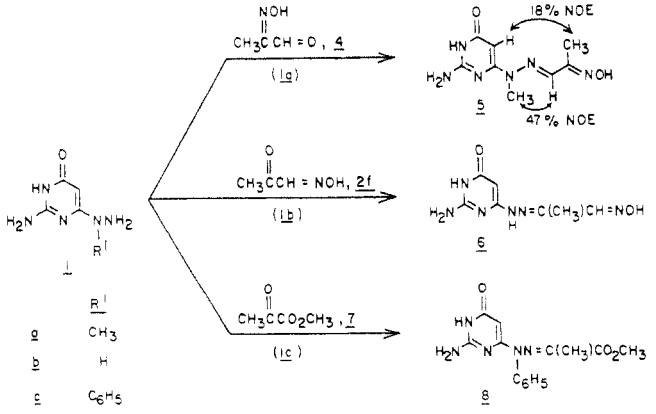
Figure 1.

diamagnetic anisotropy allowed by the more coplanar geometry of this compound.[10,11]

By analogy, useful structural information was obtained from the relative chemical shifts of the vinyl protons of the pyridazine moieties of **3**. For the 3-aryl compounds **3e** (as determined from the isomeric mixture), **3g**, and **3i**, the vinyl signals appeared significantly downfield (below δ 9.1 in CF_3CO_2H) from those of the 4-aryl compounds **3c** and **3e** (Table I). Note also the additional deshielding (ca. 0.1 ppm) of the NCH_3 protons for the 3-aryl compounds **3b**, **3e**, and **3i**.

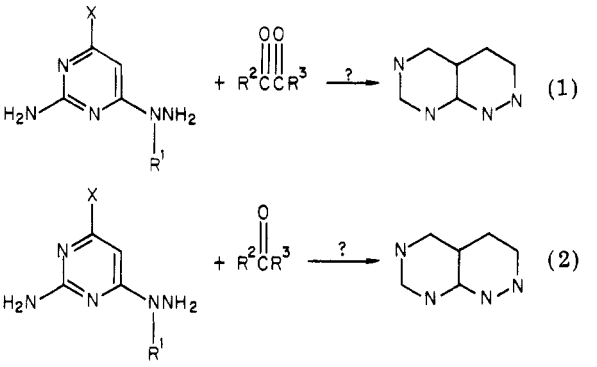
Further substantiation of these structural assignments was provided by the reduction products (below) and by ^{13}C NMR spectroscopy. In general terms, C_3H (adjacent to the ring nitrogen) was found at a lower field (greater shift from tetramethylsilane) than C_4H; these absorptions appear as doublets in the proton-coupled spectra of the phenyl compounds **3c** and **3i**. A detailed discussion of these ^{13}C NMR studies is to be found in a subsequent paper.[12]

In contrast to the α-keto aldoxime case above, α-oximidopropionaldehyde (**4**) reacted with **1a** to give hydrazone **5**, and pyruvaldoxime (**2f**) reacted with **1b** to give hydrazone **6**, neither of which showed any tendency to cyclize. On the basis of the nuclear Overhauser effect



(NOE) measurements on **5**, we suggest that this molecule, even when in solution, must be rigidly flat and linear. Particularly striking was the 18% NOE between the pyrimidine C-5 proton and those of the methyl group at the terminus of the side chain at position 6. A comparison of molecular models showed the distance between these two positions to be similar to the distance between the C-8 and C-1′ protons of nucleosides (which are also known to show weak NOE effects).[13] Since **1a** *does* cyclize with α-keto esters and aldoximes but **1b** does not,[2] a *steric inhibition* of this stabilized form of hydrazone intermediate is probably necessary for successful cyclization when the

Table II. Summary: Pyrimidopyridazine Formation from 2-Amino-4-hydrazinopyrimidines and Vicinal Difunctional Reagents[a]



X	R^1	R^2	R^3	% yield
		Reaction 1		
OH	H	H	H	49
OH	H	alkyl, aryl	H	40, 49
OH	alkyl	alkyl, aryl	alkyl, aryl	95, 20
OH	alkyl	alkyl, aryl	H	50-86
OH	alkyl	alkyl, aryl, CO_2Et	O-alkyl	11-87[2]
NH_2	alkyl	alkyl, CO_2Et	O-alkyl	50-76[2]
SH	alkyl	alkyl	O-alkyl	8[2]
OMe	alkyl	alkyl	O-alkyl	7[2]
OH	alkyl	alkyl, aryl	OH	48, 56[4]
OH	alkyl	H	O-alkyl	*b*
OH	alkyl	aryl-C(O)CH_2	O-alkyl	1-4[3]
OH	alkyl	MeC(O)CH_2	O-alkyl	NI[c,3]
OH	aryl	alkyl	O-alkyl	NI
OH	H	alkyl	O-alkyl	NI[2]
Cl	alkyl	alkyl	O-alkyl	NI[2]
H	alkyl	alkyl	O-alkyl	NI[2]
		Reaction 2		
OH	alkyl	alkyl, aryl	-HC(=NOH)	23, 58
OH	H	alkyl	CH_2Br	8[5]
OH	alkyl	alkyl	CH_2Br	NI[5]
OH	alkyl	H	-C(=NOH)alkyl	NI

[a] In general, the term alkyl in this table refers to primary alkyl groups. [b] Unpublished results. Microanalysis and NMR indicated that cyclization does occur to give a pure mixture of pyrimidopyridazine **12a** and the stable ethyl glyoxylate hydrazone which we could neither cyclize further nor separate. We did not consider this reaction to be synthetically useful. [c] Not isolated.

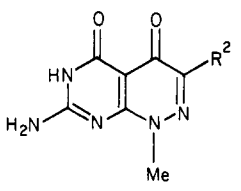
(10) Bovey, F. A. In "Nuclear Magnetic Resonance Spectroscopy"; Academic Press: New York, 1969; Chapter 3, Section 6; discusses shielding in aromatic rings.

(11) We have also noted a downfield shift (ca. 0.3 ppm) of the ortho protons of benzaldehyde methylhydrazone.

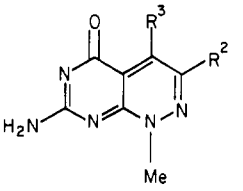
(12) Hurlbert, B. S.; Morrison, R. W., Jr.; Styles, V. L., manuscript in preparation. See also the Supplementary Material section of this paper.

(13) Davies, D. B. In "Progress in NMR Spectroscopy"; Emsley, J. W.; Feeney, J.; Sutcliffe, L. H.; Ed., Pergamon Press: Oxford, 1978; Vol. 12, p 135.

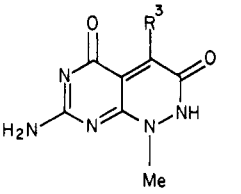
Table III. Orientation Selectivity for Pyrimido[4,5-c]pyridazines Prepared from 1a and Vicinal Difunctional Reagents



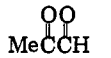
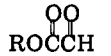
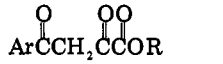
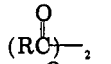
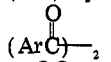
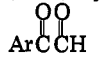
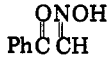
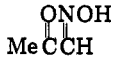
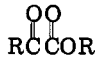
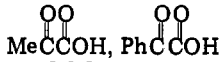
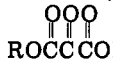
A



B



C

selectivity	difunctional reagent	reaction conditions	product type(s)
random		MeOH, Δ	B (1:1 R^2 = H/R^3 = H)
random		MeOH, Δ	C (+ uncyclized hydrazone)[a]
random		MeOH, Δ	A + C[3]
good		$MeOCH_2CH_2OH$, Δ	C[3]
		MeOH, Δ	B
		MeOH, Δ	B
very good		MeOH, Δ or HOAc, Δ	B (R^2 = H)
very good		HOAc, Δ	B (R^3 = H)
best		HOAc, Δ	B (R^3 = H)
best		MeOH, Δ	A[2]
best		H_2O, Δ	A[4]
best		EtOH, Δ or H_2O, Δ or glacial HOAc, room temp	C[2]

[a] See Table II, footnote *b*.

vicinal difunctional reagent is less reactive than an α-keto aldehyde (see Summary, Table II). The only exception to this generalization may be hydrazone 8, prepared from 6-(1-phenylhydrazino)isocytosine (1c) and methyl pyruvate. Its failure to cyclize was likely due to a combination of steric and electronic (deactivating) effects.

An analysis of the structural requirements for cyclization (Table II) and the control of substituent orientation for cyclizations of **1a** (Table III) suggests the probability of alternate cyclization mechanisms (initial reaction at C-5 vs. initial hydrazone formation), the choice of which depends on the type of substitution on N-1 of the hydrazino group at pyrimidine position 6, the degree of activation at C-5, and the relative differences in reactivity for the vicinal functional groups of the condensing agent.

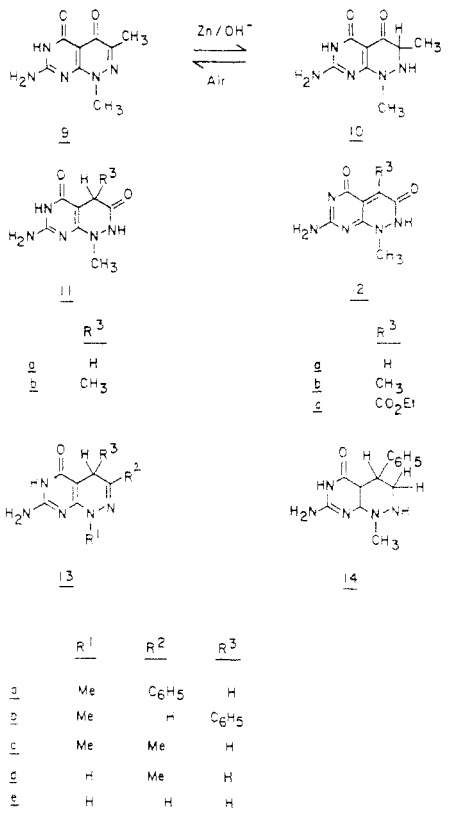
Note the enhanced substituent selectivity when pyruvaldehyde reacted with **1a** and **1b** (Table I, **3d** and **3f**, respectively). When the approach to C-5 was less crowded (**1b**, R^1 = H), the only pyrimidopyridazine isolated was the one derived from exclusive reaction of the more reactive aldehyde group at pyrimidine C-5. With the more crowded situation around C-5 (**1a**, R^1 = CH_3), no selectivity was observed. However, decreasing the reactivity of the α-ketone function by changing from an aliphatic to an aromatic substituent enhanced selectivity (**3c,e**), but this time with preferential reaction of the aldehyde with the hydrazino group.

Reductions

Representative pyrimidopyridazines were cleanly reduced with zinc and aqueous sodium hydroxide[14a] to the corresponding dihydro compounds, and their proton NMR spectra confirmed the original structural assignments by showing the expected splitting patterns (Table IV). The 3-methyl 4-one **9**[2] provided the 2,3-dihydro derivative **10** which was unstable in the presence of air, particularly when in solution, and readily reverted to the oxidized form. Conversely, the 4,6-reduced 3-ones **11** were stable at ambient conditions but regenerated their oxidized counterparts **12a** and **12b** when treated with permanganate. Zinc/base treatment of the 4-carbethoxy 3-one **12c**[2] effected ring reduction, saponification, and decarboxylation to give the 1,4-dihydro-4-unsubstituted compound **11a**.

Zinc/base reduction of four pyrimidopyridazines lacking carbonyl functionality in the pyridazine ring afforded analogues (**13**) of the generally unstable[14b,15] 5,8-dihydropterins. In this series only the 3-phenyl compound **13a** was unstable to air; its 4-phenyl isomer **13b** required permanganate for reversion to the oxidized form. The 4-phenyl compound **13b** was also prepared by catalytic hydrogenation. It was then further reduced to the tetrahydro derivative **14** with sodium and liquid ammonia. Other stable 1,4-dihydropyrimido[4,5-c]pyridazines are reported to have been synthesized directly from 5-acetonyl-6-chloropyrimidines and hydrazine.[16,17]

(14) (a) Blakely, R. L. "The Biochemistry of Folic Acid and Related Pteridines"; Wiley: New York, 1969; p 73. (b) *Ibid.*, p 75.
(15) Mengel, R.; Pfleiderer, W.; Knappe, W. R. *Tetrahedron Lett.* 1977, 2817.
(16) Bisagni, E.; Marquet, J. P.; Andre-Luisfert, J. *Bull. Soc. Chim. Fr.* 1972, 1483.
(17) Wolfers, H.; Kraatz, U.; Korte, F. *Heterocycles* 1975, *3*, 187.



	R^1	R^2	R^3
3	Me	C_6H_5	H
5	Me	H	C_6H_5
c	Me	Me	H
d	H	Me	H
e	H	H	H

The somewhat surprising stability of some of these reduced pyrimidopyridazines may be associated with their resemblance to either substituted hydrazides (the reduced 3-ones, 11) or arylhydrazones (the 1,4-dihydro compounds 13).

Experimental Section

Melting points were run on a Thomas-Hoover capillary melting point apparatus. NMR spectra were determined with Varian T-60 and XL-100 spectrometers with tetramethylsilane as the internal standard and Fourier transform was utilized in cases of poor solubility. Nuclear Overhauser effect (NOE) is expressed as $f_I(S)$ = fractional enhancement of nucleus I due to saturation of nucleus S. Quantitative ultraviolet spectra were recorded on a Cary 118 spectrophotometer. Low-resolution mass spectra were obtained with a Varian MAT CH5 DF double-focusing mass spectrometer at 70 eV, and probe temperatures were noted. Field-desorption data were determined with a Varian MAT 731 spectrometer. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and were acceptable (±0.4%). Methyl pyruvate (7) was obtained from Aldrich Chemical Co.; phenylhydrazine was obtained from Mallinckrodt Chemical Co.

6-(1-Phenylhydrazino)isocytosine (1c). Under nitrogen, a mixture of 2.91 g (0.02 mol) of 6-chloroisocytosine,[18] 11.03 g of 98% phenylhydrazine, and 100 mL of water was heated at reflux for 17 h. A considerable amount of dark red oil was removed by filtration (gravity) of the hot mixture. As the solution cooled under a stream of nitrogen, more oil separated and was removed by filtration, (gravity, paper filter). The solution deposited crystals on standing at ambient temperature under nitrogen for 5 h. The yellow solid was collected by filtration, washed with water, and dried under vacuum at 70 °C; yield, 1.03 g of a mixture (based on NMR) of **1c** and its 2-phenylhydrazino isomer[19] (4:5). Pure **1c** was obtained in low yield by repeated fractional crystallization from 95% EtOH, **1c** tending to crystallize first: mp >258 °C dec; NMR (Me_2SO-d_6) δ 5.06 (br s,[20] 2 H), 5.17 (s, 1 H), 6.19 (br s,[20] 2 H), 7.00–7.40 (m, 5 H), 9.90 (br s,[20] 1 H); UV (MeOH) λ_{max} 224 nm (ε 19 900), 256 (11 300), 284 (15 400); mass spectrum (170 °C), *m/e* 217 (M, 100), 200 (6), 175 (20), 159 (7), 158 (6), 131 (11), 111 (11), 77 (50). Anal. Calcd for $C_{10}H_{11}N_5O$: C, 55.29; H, 5.10; N, 32.24. Found: C, 55.03; H, 5.17; N, 32.09.

Cyclizations to 7-Aminopyrimido[4,5-*c*]pyridazin-5-(1*H*)-ones (3a–j). A stirred mixture of the 6-(hydrazino)isocytosine (1), the appropriate vicinally functionalized reagent (**2a–h**), and solvent was heated as indicated in Table I. At the end of the reaction period, the crude product was collected by suction filtration of the reaction mixture. Purification procedures and two exceptions to the isolation procedure (**3h** and **3j**) are indicated in Table I. As a specific example, the preparation of **3g** is described below.

7-Amino-3-phenylpyrimido[4,5-*c*]pyridazin-5(6*H*)-one (3g). To a solution of 0.70 g (5.0 mmol) of **1b**[2] in 100 mL of water was added 1.14 g (7.5 mmol) of phenylglyoxal hydrate. Refluxing was carried out for 1 h before the resulting pale yellow solid was collected by filtration, washed with water, and dried under vacuum (70 °C); yield, 1.0 g. Recrystallization from glacial acetic acid provided 0.59 g (49%) as yellow crystals: mp >300 °C; NMR (CF_3COOH) δ 7.63–7.92 (m, 3 H), 8.00–8.22 (m, 2 H), 9.33 (s, 1 H); NMR (Me_2SO-d_6) δ 7.10 (br s, 2 H), 7.49–7.60 (m, 3 H), 8.12–8.22 (m, 2 H), 8.34 (s, 1 H), 11.58 (br s, 1 H); UV (CH_3OH) λ_{max} 291 nm (ε 27 500), 366 (2900); UV (0.1 N NaOH) λ_{max} 265.5 (26 100), 289 (sh, 19 200), 374 (3400); mass spectrum (290 °C), *m/e* 239 (M, 100), 211 (36), 169 (32), 142 (18), 141 (41), 140 (53). Anal. Calcd for $C_{12}H_9N_5O$: C, 60.24; H, 3.79; N, 29.28. Found: C, 60.01; H, 3.83; N, 29.31.

Stable Hydrazones 5, 6, and 8. The appropriate hydrazinopyrimidine, vicinal difunctional reagent, and solvent were stirred and heated for the specified time period before the products were isolated by filtration of the reaction mixture. Details for specific reactions are described below (molar ratio of carbonyl reagent to starting pyrimidine, reaction medium, reaction time, temperature, yield).

1-[*N*-(2-Amino-4-oxo-3,4-dihydro-6-pyrimidinyl)-*N*-methylhydrazono]-2-(hydroxyimido)propane (5): (1.1:1 of 4[21]:**1a**[2], glacial acetic acid, 0.5 h,[22] 55 °C, 74% after recrystallization from MeOH); mp >300 °C; NMR (Me_2SO-d_6) δ 2.01 (s, 3 H), 3.41 (d, J = 0.6 Hz, 3 H), 5.50 (s, 1 H), 6.51 (br s, 2 H), 7.41 (d, J = 0.6 Hz, 1 H), 10.8 (v br, 2 H); NOE/$f_{5.50}$ (2.00) = 18%, NOE/$f_{7.41}$ (3.41) = 47%; UV (CH_3OH) λ_{max} 246 nm (ε 19 500), 275 (34 200), 317 (24 200). Anal. ($C_8H_{12}N_6O_2$).

2-[*N*-(2-Amino-4-oxo-3,4-dihydro-6-pyrimidinyl)-hydrazono]propionaldoxime (6): (2:1 of **2f**:**1b**[2], glacial acetic acid, 23 h, 56 °C, 67% isolated in pure form from the reaction medium); mp 285 °C dec; NMR (Me_2SO-d_6) δ 2.05 (s, 3 H), 5.24 (s, 1 H), 6.30 (br s, 2 H), 7.69 (s, 1 H), 9.36 (br s, 1 H), 11.28 (br 2 H); UV λ_{max} (pH 7.2) 246 nm (ε 13 300), 269 (19 000), 313 (27 200). Anal. ($C_7H_{10}N_6O_2$).

Methyl 2-[*N*-(2-amino-3,4-dihydro-4-oxo-6-pyrimidinyl)-*N*-phenylhydrazono]propionate (8): (2.6:1 of 7:**1a**[2], methanol, 20 h,[23] reflux, 46% by concentrating and chilling the mother liquor to induce crystallization); mp >150 °C dec; NMR (Me_2SO-d_6) δ 1.52 (s, 3 H), 3.75 (s, 3 H), 5.22 (s, 1 H), 6.32 (br s, 2 H), 7.06–7.45 (m, 5 H), 10.30 (br s, 1 H); NMR (MeOH) δ 3.15 (d), 4.04 (q), (0.5 mol); UV (CH_3OH) λ_{max} 221.5 nm (ε 20 600), 249 (15 900), 272 (17 300) 309 (sh, 8500). Anal. ($C_{14}H_{15}N_5O_3$·0.5C-H_3OH).

7-Amino-2,3-dihydro-1,3-dimethylpyrimido[4,5-*c*]-pyridazine-4,5(1*H*,6*H*)-dione (10). Under nitrogen, a mixture of 0.50 g (2.4 mmol) of **9**[2] and 1.0 g of purified zinc dust[24] in 100 mL of 2 N NaOH was stirred and heated to reflux during a 10-min period. Reflux was continued for 1 h before insoluble inorganic solids were removed by filtration. While hot, the filtrate was quickly adjusted to pH 4.0 with concentrated HCl to precipitate the product as a white solid. The mixture was allowed to cool to room temperature under nitrogen before the white solid was collected by filtration, washed with water, and dried under vacuum

(18) Aldrich Chemical Co.; purified by dissolution in dilute NH_4OH, treatment with charcoal, and reprecipitation with acetic acid.
(19) Langley, B. W. British Patent 875 717, 1961; *Chem. Abstr.* **1962**, *56*, 4780e, by an alternative method.
(20) Exchanges with D_2O.
(21) Newbold, G. T.; Sharp, W.; Spring, F. S. *J. Chem. Soc.* **1951**, 2679.
(22) No cyclic product was obtained when the reaction time was increased to 23 h.
(23) The UV spectrum of the reaction solution did not change substantially after 1 h.
(24) Purified by sequentially washing with dilute NaOH, H_2O, dilute acetic acid, H_2O, ethyl alcohol, acetone, and ether and drying under vacuum.

Table IV. ^{1}H NMR Data for Dihydropyrimidopyridazines[a]

compd	solvent	δ from Me_4Si		
		NCH_3	R^2	CHR^3
10	CF_3COOH	3.58 (s, 3 H)		1.54 (d, J = 7, 3 H)
				4.18 (q, J = 7, 1 H)
	Me_2SO-d_6	3.20 (s, 3 H)		1.04 (d, J = 7, 3 H)
11a	CF_3COOH	3.60 (s, 3 H)		3.3 (m, 1 H)
	Me_2SO-d_6	3.10 (s, 3 H)		3.70 (s, 2 H)
11b	CF_3COOH	3.60 (s, 3 H)		3.00 (s, 2 H)
				1.57 (d, J = 7, 3 H)
	Me_2SO-d_6	3.11 (s, 3 H)		3.98 (q, J = 7, 1 H)
				1.13 (d, J = 7, 3 H)
13a	CF_3COOH	3.78 (s, 3 H)	7.43-7.67 (m, 3 H), 7.73-7.93 (m, 2 H)	3.25 (q, J = 7, 1 H)
	Me_2SO-d_6	3.42 (s, 3 H)	7.40-7.50 (m, 3 H), 7.72-7.82 (m, 2 H)	3.85 (s, 2 H)
13b	CF_3COOH	3.76 (s, 3 H)	7.42 (d, J = 4, 1 H)	3.46 (s, 2 H)
				4.87 (d, J = 4, 1 H)
	Me_2SO-d_6	3.35 (s, 3 H)	6.92 (d, J = 4, 1 H)	7.37 (s, 5 H)
				4.58 (d, J = 4, 1 H)
13c	CF_3COOH	3.67 (s, 3 H)	2.27 (s, 3 H)	7.25 (s, 5 H)
	Me_2SO-d_6	3.23 (s, 3 H)	1.85 (s, 3 H)	3.52 (s, 2 H)
13d	CF_3COOH		2.38 (s, 3 H)	2.97 (s, 2 H)
	Me_2SO-d_6		1.82 (s, 3 H)	3.67 (s, 2 H)
13e	CF_3COOH		7.43 (t, J = 3, 1 H)	2.92 (s, 2 H)
	Me_2SO-d_6		6.70 (t, J = 3, 1 H)	3.58 (d, J = 3, 2 H)
				2.96 (d, J = 3, 2 H)

[a] Coupling constants given in hertz.

(70 °C): yield, 0.45 g (90%); mp >300 °C; NMR (CF_3COOH) δ 1.54 (d, J = 7 Hz, 3 H), 3.58 (s, 3 H), 4.18 (q, J = 7 Hz, 1 H); UV (1 N NaOH) λ_{max} 238 nm (ε 23 700), 285 (sh, 11 800), 297 (13 600); mass spectrum (235 °C), m/e 209 (M, 30), 194 (6), 168 (4), 167 (45), 166 (27), 165 (11), 111 (100). Anal. Calcd for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48. Found: C, 45.77; H, 5.39; N, 33.58.

This compound readily reoxidized to the parent compound on standing at room temperature in the presence of air for 3 days.

Reduction conditions for the other pyrimidopyridazines: (starting pyrimidopyridazine, moles of pyrimidopyridazine per gram of zinc dust, reaction medium, reflux time, yield).

7-Amino-1,4-dihydro-1-methylpyrimido[4,5-c]pyridazine-3,5(2*H*,6*H*)-dione (11a):[25] (**12c**, 0.0019:1, 2 N NaOH, 2.5 h, 65% after recrystallization from water); mp >300 °C. Anal. ($C_7H_9N_5O_2$).

7-Amino-1,4-dihydro-1,4-dimethylpyrimido[4,5-c]pyridazine-3,5(2*H*,6*H*)-dione monohydrate (11b):[25] (**12b**, 0.0024:1, 1 N NaOH, 4 h, 66% after recrystallization from water); mp > 300 °C. Anal. ($C_8H_{11}N_5O_2 \cdot H_2O$).

7-Amino-1,4-dihydro-1-methyl-3-phenylpyrimido[4,5-c]pyridazin-5(6*H*)-one (13a):[26] (**3i**, 0.0013:1, 2 N NaOH, 1 h, 100%); mp > 300 °C.

7-Amino-1,4-dihydro-1-methyl-4-phenylpyrimido[4,5-c]pyridazin-5(6*H*)-one (13b).[25] **Method A:** (**3c**, 0.0020:1, 2 N NaOH, 1 h, 70% after recrystallization from MeOH); mp > 300 °C. Anal. ($C_{13}H_{13}N_5O$).

Method B. A yellow solution of 1.00 g (3.95 mmol) of **3c** in 150 mL of glacial acetic acid and 300 mg of 10% palladium on charcoal in a 500-mL bottle was shaken in a Parr hydrogenation apparatus with the initial pressure of hydrogen at 34 psi. After 18 h the catalyst was removed by filtration through Celite and the solvent by evaporation under reduced pressure (50 °C). Recrystallization of the white solid residue from MeOH afforded 0.64 g (63%); identical in every respect with that prepared in method A.

7-Amino-1,4-dihydro-1,3-dimethylpyrimido[4,5-c]pyridazin-5(6*H*)-one (13c):[25] (**3h**, 0.0015:1, 2 N NaOH, 2 h, 52% after recrystallization from MeOH); mp >300 °C. Anal. ($C_8H_{11}N_5O$).

7-Amino-1,4-dihydro-3-methylpyrimido[4,5-c]pyridazin-5(6*H*)-one (13d):[25] (**3f**, 0.0016:1, 2 N NaOH, 2 h, 61% after recrystallization from MeOH): mp >300 °C. Anal. ($C_7H_9N_5 \cdot 0.25H_2O$).

7-Amino-1,4-dihydropyrimido[4,5-c]pyridazin-5(6*H*)-one (13e):[25] (**3j**, 0.0019:1, 2 N NaOH, 1 h, 87%); mp > 300 °C. Anal. ($C_6H_7N_5O$).

Oxidation of 11b to 12b. To a suspension of 53 mg (0.25 mmol) of **11b** and 1 mL of water was added 3 mL of 0.1 M potassium permanganate. After 20 min the dark mixture was treated with gaseous sulfur dioxide to break up the brown residue. The remaining yellow solid was collected by filtration, washed with a small amount of water, and dried under vacuum (70 °C); yield, 26 mg (50%), identified as **12b** by comparison (NMR, UV, TLC) with an authentic sample.[3]

Oxidation of 13b to 3c. To a solution of 128 mg (0.50 mmol) of **13b** and 3 mL of 1 N NaOH was added 7 mL of aqueous 0.1 M potassium permanganate. The resulting mixture was stirred at room temperature for 0.5 h and filtered. The residue, a mixture of brown and yellow solids, was subsequently washed with 1 mL of water and mixed with 50 mL of boiling MeOH. After removal of the insoluble inorganic matter by filtration, the yellow filtrate was concentrated to a volume of 15 mL and allowed to stand at room temperature. The resulting yellow crystals were collected, washed with a small volume of MeOH, and dried under vacuum (70 °C); yield 65 mg (51%) of **3c**, identical (by UV, NMR, and TLC comparison) with the authentic sample prepared by direct cyclization (Table I).

7-Amino-1-methylpyrimido[4,5-c]pyridazine-3,5-(1*H*,2*H*)-dione (12a). Method A. To a suspension of 0.200 g (1.00 mmol) of **11a** in 5 mL of water was added 15 mL of aqueous 0.1 M potassium permanganate. The resulting dark mixture was stirred at room temperature for 0.25 h before sufficient sulfur dioxide was added to effect a colorless solution. The solution was adjusted to pH 6 with 1 N NaOH and allowed to stand at room temperature. The slightly pink crystals that separated were collected by filtration, washed with a small volume of water, and dried under vacuum (70 °C); yield, 0.13 g: mp >300 °C. Anal. Calcd for $C_7H_7N_5O_2 \cdot NaHSO_3 \cdot 0.5H_2O$: C, 27.45; H, 2.96; N, 22.87; S, 10.47; Na, 7.51. Found: C, 27.29; H, 3.27; N, 22.75; S, 10.30; Na, 7.42.

A bisulfite-free sample of the **12a** was obtained after the sequential dissolution of a portion of the solid (60 mg) in boiling CF_3COOH (4 mL), removal of the solvent under reduced pressure, trituration of the residue with water (1 mL), isolation of the orange crystals (46 mg; analyzed as $C_7H_7N_5O_2 \cdot 0.9CF_3COOH$), and recrystallization from methanol containing triethylamine to give a yellow solid; yield, 20 mg: mp >300 °C; NMR (CF_3COOD) δ 4.32 (s, 3 H), 8.37 (s, 1 H); UV (1 N NaOH) λ_{max} 260 nm (ε 32 500), 414 (5800); mass spectrum (field desorption, 23 MA) m/e 193 (M). Anal. Calcd for $C_7H_7N_5O_2 \cdot 0.4H_2O$: C, 41.96; H, 3.92; N, 34.95. Found: C, 42.12; H, 3.96; N, 34.79.

Method B. To a solution of 40 mg (0.20 mmol) of **11a** and 1 mL of 1 N NaOH was added 3 mL of aqueous 0.1 M potassium

(25) The product appeared to be stable toward oxidation at ambient conditions.

(26) An elemental analysis was not obtained for this product, which rapidly reoxidized on exposure to air.

permanganate. After 0.25 h, the resulting dark mixture was filtered, and the residue was washed with a tiny portion of water. The filtrate was adjusted to pH 4 with 6 N HCl, and a greenish solid precipitated. This solid was collected by filtration, washed with a small amount of water, and dried under vacuum (70 °C); yield 25 mg (65%), identified by direct comparison (UV, IR, NMR, and TLC) with the sample prepared above in method A.

7-Amino-1,2,3,4-tetrahydro-1-methyl-4-phenylpyrimido[4,5-*c*]pyridazin-5(6*H*)-one (14). To a stirred mixture of 0.51 g (2.0 mmol) of **13b** and 15 mL of liquid ammonia contained in a 50-mL round-bottomed flask equipped with a Dewar condenser containing dry ice/isopropyl alcohol was added 0.14 g (0.006 mol) of sodium as small chunks during a 45-min period. The solution was allowed to decolorize before each successive piece was added, and a water bath was used to ensure the continuous ebullition of ammonia. After all of the blue color had dissipated, the ammonia was evaporated with a continuous flow of nitrogen. The solid residue was dissolved in 30 mL of water, and the resulting alkaline solution was washed with ether (2 × 20 mL) and, subsequently, adjusted to pH 5 with glacial acetic acid. The precipitate was collected by suction filtration, washed with water and dried under vacuum (70 °C); yield, 0.44 g. An analytical sample was prepared by recrystallization from methanol/water: mp >260 °C dec; NMR (Me_2SO-d_6) δ 2.94 (m,[27] 2 H), 3.14 (s, 3 H), 3.88 (m,[27] 1 H), 4.42 (m,[20] 1 H), 6.16 (br s,[20] 2H), 7.15–7.25 (m, 5 H), 9.90 (br s,[20] 1 H); UV (CH_3OH) λ_{max} 225 nm (ε 20600), 282 (13400). Anal. Calcd for $C_{13}H_{15}N_5O$: C, 60.68; H, 5.88; N, 27.22. Found: C, 60.67; H, 5.91; N, 27.15.

(27) These protons exhibited a distinct ABX pattern after D_2O exchange. J_{AB}(gem) was measured as 13.5 Hz after decoupling at δ 3.88. The other coupling constants and chemical shifts for the geminal protons were determined by spin simulation to be δ 2.84 (J_{AX} = 2.2 Hz) and 3.04 (J_{BX} = 3.8 Hz).

Acknowledgment. We thank Dr. B. S. Hurlbert, Mr. A. Ragouzeos, and Mr. R. Crouch for NMR studies, Dr. D. A. Brent and Mr. R. Johnson for mass spectra data, and Ms. J. Miller and Ms. S. Wrenn for technical assistance.

Registry No. **1a**, 67873-21-6; **1b**, 6298-85-7; **1c**, 80082-11-7; **1c** (2-phenylhydrazino isomer), 80082-33-3; **2a**, 431-03-8; **2b**, 134-81-6; **2c**, 1074-12-0; **2d**, 78-98-8; **2e**, 70935-14-7; **2f**, 306-44-5; **2g**, 532-54-7; **2h**, 52143-74-5; **3a**, 70935-27-2; **3b**, 80082-12-8; **3c**, 70935-17-0; **3d** (R_3 = Me; R_2 = H), 80082-13-9; **3d** (R_2 = Me; R_3 = H), 80082-14-0; **3e** (R_3 = *m*-HO-C_6H_4; R_2 = H), 70935-18-1; **3e** (R_2 = *m*-HO-C_6H_4; R_3 = H), 80082-15-1; **3f**, 74482-47-6; **3g**, 80082-34-4; **3g**·HCl, 80082-16-2; **3i**, 80082-17-3; **3j**, 80082-18-4; **4**, 52764-58-6; **5**, 80082-19-5; **6**, 80082-20-8; **7**, 600-22-6; **8**, 80082-21-9; **9**, 67873-29-4; **10**, 80082-22-0; **11a**, 80082-23-1; **11b**, 80082-24-2; **12a**, 80082-25-3; **12a**·$NaHSO_3$, 80082-26-4; **12b**, 70311-96-5; **12c**, 67873-68-1; **13a**, 80082-27-5; **13b**, 80082-28-6; **13c**, 80082-29-7; **13d**, 80082-30-0; **13e**, 80082-31-1; **14**, 80082-32-2; 6-chloroisocytosine, 1194-21-4; phenylhydrazine, 100-63-0.

Supplementary Material Available: Full data available include the following: microanalyses on compounds **3a–c**, **3e–j**, **5**, **6**, **8**, **11a,b**, and **13b–e**; UV data on compounds **3a–c**, **3e** (4-aryl isomer), **3f**, **3h–j**, **11a,b**, and **13b–e**; ^1H NMR data on compounds **3a–j**, **10**, **11a,b**, and **13a–e**; ^{13}C NMR data on compounds **3a,-c,d,f–j**; and mass spectral data on **3a–c,g–j**, **11a,b**, and **13b,d** (8 pages). Ordering information is given on any current masthead page.

Synthesis and Reactions of 2,6-Diphenyl-4-(trimethysilyl)-4*H*-thiopyran[1]

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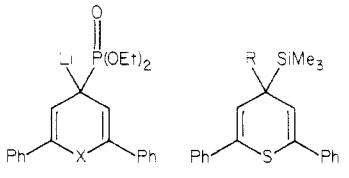
The title compound **3** was synthesized by trimethylsilyl chloride quenching of 2,6-diphenyl-4-lithio-4*H*-thiopyran (**7**), which was obtained by direct lithiation (*n*-BuLi) of either the 4*H*-thiopyran **10** or the 2*H* isomer **6**. Compound **6** was readily prepared in one step from the reaction of 2,6-diphenyl-4-hydroxy-4*H*-thiopyran (**5**) with NCS in 74% yield. Compound **3** was metalated to give **12** in 80–85% yield by using a combination of *n*-BuLi and *t*-BuOK in THF at an internal temperature slightly below -20 °C. The successful reaction of **12** with a variety of ketones and aldehydes provides an alternative synthesis of the Δ[4]-2,6-diphenyl-4*H*-thiopyrans **16**. The scope and limitation of this Peterson-type reaction of **12** is compared with those of the corresponding Wittig–Horner reagent **2**.

Recently we reported the synthesis of the Wittig–Horner reagents of 2,6-diphenyl-4*H*-pyran **1**[2] and thiopyran **2**[3] and



1, X = O
2, X = S

3, R = H
4, R = M

their uses in the preparation of various *unsymmetrical* Δ[4,4']-bi-4*H*-thiopyrans and *polyene-separated* Δ[4,4']-bi-4*H*-pyrans and bithiopyrans.[4,5] The thio analogue **2**, however, is less stable than the pyran **1** and in many cases gives poorer yields in condensation reactions with aldehydes or ketones.[3–5] Since most of the interesting organic dark conductors of the bithiopyran class[6] are derived from **2**, an alternative reagent is desired to complement **2** in the synthesis of *unsymmetrical* bithiopyrans. One interesting modification is the Peterson type of reagent[7] **4** in which a trimethylsilyl group is substituted for the diethylphosphonyl group in **2**. This paper describes our synthesis of 2,6-diphenyl-4-(trimethylsilyl)-4*H*-thiopyran (**3**) and the generation of its metalated anion **4** from which a variety of *unsymmetrical* bithiopyrans were prepared in good yields. The scope and limitations of this reaction are

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