using a Packard 7201 scanner. UV spectra were measured on a Beckman Model 25 spectrophotometer and optical rotations were obtained on a Perkin-Elmer 141 polarimeter. The IR spectrum was measured on a Perkin-Elmer Model 700 spectrophotometer. The proton and triton magnetic resonance spectra were obtained on a Bruker WP 200-MHz NMR. Chemical shift values are expressed in parts per million downfield from internal $(CH_3)_4Si$. The high-resolution mass spectrum was performed by Shrader Analytical Laboratories, Detroit, MI, and the elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Preparative and analytical high-performance LC were run on a Waters instrument, using μ-Bondapak CN and μ-Bondapak C_{18} columns (Waters) eluted with S_3 (5% EtOH in 0.01 N KH_2PO_4 (pH 3) buffer). Peak detection was performed at 280 nm with a Waters 440 UV detector.

(−)-8,9-Dibromoapomorphine Hydrobromide (2). To a solution of 100 mg (0.33 mmol) of apomorphine hydrochloride **1** (Merck) in 30 mL of TFA was added dropwise at room temperature over 20 min 35 μL (0.678 mmol) of bromine in 7 mL of TFA with rapid stirring in the dark. A crystalline precipitate was observed to form several minutes after completion of the addition of bromine. After the mixture was stirred for a total of 1.5 h, the precipitate was filtered, washed with a few mL of cold TFA, and dried under vacuum to yield 100 mg (60%) of **2** as an off-white solid, mp 281–283 °C dec. TLC of **2** on silica gel eluted with S_1 yielded a single spot (R_f 0.39) which turned only light green when visualized with iodine vapors. Apomorphine **1** in the same TLC system (R_f 0.49) turned emerald green with iodine visualization. High-performance LC of **2** on a μ-Bondapak CN column eluted with S_3 at 2 mL/min yielded a single peak (retention time = 27 min; whereas the retention time of **1** in this system is 7 min) by UV detection. Spectral and analytical data for **2** now follow: ^1H NMR (CD_3OD) δ 8.40 (d, 1, J = 8.07 Hz, H-1), 7.40 (t, 1, J = 8.07 Hz, H-2), 7.25 (d, 1, J = 7.80 Hz, H-3) (the two proton singlet (δ 6.70) for H-8 and H-9 was absent); IR (KBr) 3700–2900 (br), 2700, 1590, 1470, 1410, 1375, 1150 cm^{-1}; UV (EtOH) λ max 220 (log ε 4.48), 272 (4.22), 320 (3.55); $[\alpha]^{25}_D$ −131.4° (c 0.59, CH_3OH); exact mass calcd for $C_{17}H_{14}NBr_2O_2$ (M^+ − 423.9368, found 423.9377.

Anal. Calcd for $C_{17}H_{15}NBr_2O_2$·HBr: C, 40.35; H, 3.19; N, 2.71. Found C, 40.28; H, 3.23; N, 2.63.

(−)-[8,9-^{3}H]Apomorphine (3). Dibromide **2** (13 mg, 0.026 mmol) was reduced with tritium (100 Ci) in 10 mL of EtOH, using 26 mg of 10% Pd/C at room temperature in the dark for 2 h with stirring. After catalyst removal, excess solvent was evaporated and the crude residue was taken up in 20 mL of CH_3OH (total radioactivity = 804 mCi; a 94% crude yield of **3** based on dibromide **2**). TLC (silica gel eluted with S_1 or S_2) of crude **3** underspotted with **1** showed the reduction to consist of **3** at 95% radiochemical purity. Final purification of **3** was performed by high-performance LC using a μ-Bondapak CN column eluted with S_3 (1 mL/min). Typically, 804 mCi of crude **3** yielded 100 mCi (a 12% overall yield of pure **3** based on dibromide **2**) of **3** (retention time = 12 min) at 98% radiochemical purity (silica gel TLC eluted with S_1 or S_2; μ-Bondapak CN and C_{18} high-performance LC eluted with S_3).[10] Compound **3** cochromatographed (TLC, high-performance LC) with **1** and afforded a UV spectrum superimposable on that of **1**. The specific activity of **3** was determined to be 33 Ci/mmol by UV spectroscopy (272 nm (ε 17 000) for **1**). A sample of **3** (free base) for the triton magnetic resonance spectrum was obtained by silica gel TLC (S_1).

Acknowledgment. We gratefully acknowledge the technical assistance of K. Bradley (NEN) in the tritiation of **2** to **3** and the help of Professor L. J. Altman (Stony Brook) in obtaining the triton magnetic resonance spectrum of **3**. A stimulating discussion with Dr. C. Kelley (Massachusetts College of Pharmacy) is also acknowledged.

Registry No. **1**, 314-19-2; **2**, 40609-52-7; **3**, 74467-14-4.

(10) The loss of product **3** attending this stage of the purification is undoubtedly due to product decomposition during rotary evaporator concentration of crude **3** in CH_3OH to a volume suitable for high-performance LC injection, as well as peak shaving during the high-performance LC of **3**.

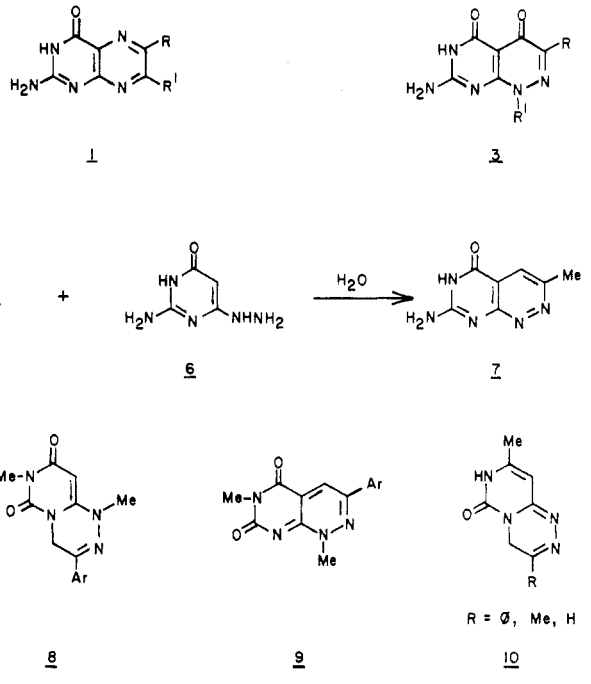
Pyrimido[4,5-*c*]pyridazines. 2. Preferential Formation of Pyrimido[6,1-*c*][1,2,4]triazines by Cyclizations with Simple and Complex α-Halo Ketones

W. Revill Mallory and Robert W. Morrison, Jr.*

The Wellcome Research Laboratories, Burroughs Wellcome Co., Research Triangle Park, North Carolina 27709

Received March 31, 1980

Our search for analogues of the naturally occurring pterins (**1**) led us initially to successful cyclizations of 6-(1-alkylhydrazino)isocytosines (**2**, Table I) with α-keto esters to give pyrimido[4,5-*c*]pyridazine-4,5-diones (**3**).[1] We now report that **2** cyclizes with one simple and two complex α-halo ketones (**4**) under acidic conditions to give pyrimido[6,1-*c*][1,2,4]triazines (**5**) and that we did not isolate any pyrimidopyridazines from these reactions. In contrast, the reaction between bromoacetone (**4a**) and 6-hydrazinoisocytosine[2] (**6**) under similar conditions afforded pyrimidopyridazine **7** in low yield with no evidence of pyrimidotriazine formation.

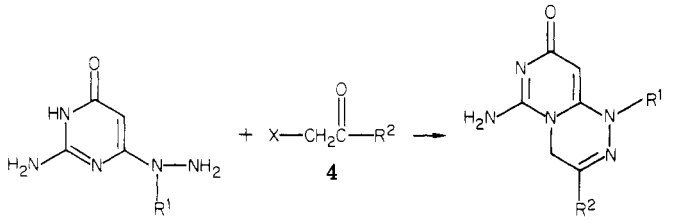


The pyrimido[6,1-*c*][1,2,4]triazine ring system has been reported only twice in the literature. Yoneda[3] isolated both pyrimidotriazines **8** and pyrimidopyridazines **9** from reactions of phenacyl bromides with 3-methyl-6-(1-methylhydrazino)uracil, and La Noce reported[4] the exclusive formation of pyrimidotriazines **10** by reaction of simple α-halo ketones with 4-hydrazino-2-hydroxy-6-methylpyrimidine. In contrast with La Noce's results, Senga[5] obtained only pyrimido[4,5-*c*]pyridazines from the reaction of another unsubstituted hydrazinopyrimidine (6-hydrazino-3-methyluracil) with phenacyl bromides.

(1) Morrison, R. W., Jr.; Mallory, W. R.; Styles, V. L. *J. Org. Chem.* **1978**, *43*, 4844.
(2) Laird, A. H.; Landquist, J. K.; Langley, B. W. British Patent 876 601, 1961; *Chem. Abstr.* **1962**, *56*, 4781[f].
(3) Yoneda, F.; Higuchi, M.; Kawamura, M.; Nitta, Y. *Heterocycles* **1978**, *9*, 1571.
(4) La Noce, T.; Bellasio, E.; Vigevani, A.; Testa, E. *Ann. Chim. (Rome)* **1972**, *62*, 647; *Chem. Abstr.* **1973**, *79*, 78750.
(5) Senga, K.; Sato, J.; Kanamori, Y.; Ichiba, M.; Nishigaki, S.; Noguchi, M.; Yoneda, F. *J. Heterocycl. Chem.* **1978**, *15*, 781.

0022-3263/80/1945-3919$01.00/0

Table I. 6-Amino-1,4-dihydro-8*H*-pyrimido[6,1-*c*][1,2,4]triazin-8-ones[a] (5)



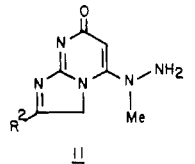
2 4 5

compd	R^1	R^2	X	4	molar ratio 4:2	reaction solvent (time, h)	exceptions to general workup procedures	recrystallization solvent	5, % yield[b] (mp, °C)
a	CH_3	CH_3	Br	*c*	1.3:1	H_2O (3)		$CH_3CH(OH)CH_3$	63 (280–288 dec)
b	n-C_4H_9	CH_3	Br	*c*	1.3:1	H_2O (3)		95% C_2H_5OH	69 (240–242 dec)
c	$CH_2C_6H_5$	CH_3	Br	*c*	1.3:1	95% C_2H_5OH (23)		95% C_2H_5OH	47[d] (258–261 dec)
d	CH_3	CHNOH	Cl	*e*	1.1:1	CH_3CO_2H (21)	*f*	$CH_3OCH_2CH_2OH$	44 (>300)
e	CH_3	$CO_2C_2H_5$	Br	*g*	1.3:1	H_2O (2)	*h*	absolute C_2H_5OH	26 (236–240 dec)
f	CH_3	CO_2H						H_2O	53[i] (>300)

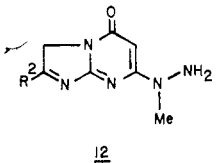
[a] These compounds were prepared according to the general example in the experimental section. [b] Yields are based on the (alkylhydrazino)isocytosines used for the cyclizations. Yields are reported after one recrystallization. [c] Levene, P. A. "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. II, p 88. [d] Yield after three recrystallizations. [e] Taylor, E. C.; Portnoy, R. C. *J. Org. Chem.* **1973**, *38*, 806. [f] The reaction mixture was filtered, and collected solid was dissolved in 15 mL of 1 N NaOH/g of crude product. The solution was brought to pH 8–9 with concentrated HCl, and precipitated solid was collected by filtration, washed with water, and recrystallized. [g] Aldrich Chemical Co. [h] The slightly cloudy reaction solution was filtered and adjusted carefully to neutral pH with concentrated NH_4OH. Solid was collected, washed with water, and recrystallized. [i] Prepared by saponification of e.

While the production of pyrimido[6,1-*c*][1,2,4]triazines from reactions of **2** with bromoacetone (**4a**) was not surprising in view of the reports of Yoneda and La Noce, their exclusive formation was not predicted. Furthermore, the products from cyclizations of **2a** with the more complex α-halo ketones chloropyruvaldoxime (**4d**) and ethyl bromopyruvate (**4e**) (each with three adjacent functional groups as potential points for cyclization) were even less predictable. In both cases cyclization occurred as if the trifunctional reagent were a simple α-halo ketone to give pyrimidotriazines **5d** and **5e**, respectively. No products resulting from cyclization across the oximino or ester groups were isolated.

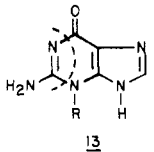
The structures of the pyrimido[6,1-*c*][1,2,4]triazines were confirmed by NMR and mass spectrometry. The two possible isomeric pyrimido[4,5-*c*]pyridazines were ruled out due to the presence of the pyrimidine C-5 proton in the NMR spectra. The isomeric pyrimido[6,1-*c*][1,2,4]-triazines that would result from hydrazino attack at the α-halo carbon atoms instead of the carbonyl groups were eliminated since methylene singlets appear in the NMR spectra. Structures such as **11** and **12** that could result



11



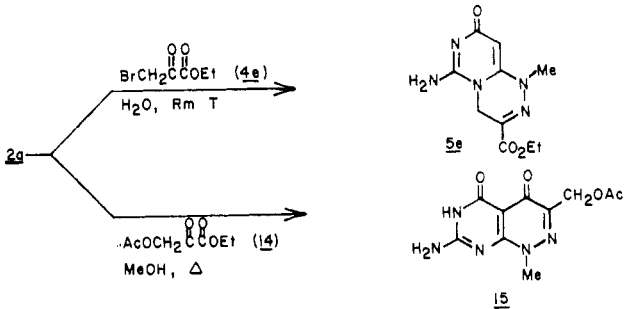
12



13

from consecutive ring-opening/ring-closure reactions (or less likely from direct cyclization) of the pyrimido[6,1-*c*][1,2,4]triazines were eliminated due to the loss of H_2NCN (M – 42) in representative mass spectra. This loss follows the fragmentation pattern observed for substituted guanines (**13**) that cleave as indicated below.[6] Structures **11** and **12** would be unlikely to lose this fragment, but structures **5** could lose it readily. Additional support for structures **5** lies in the failure of **5a** to react with benzaldehyde when refluxed in 95% ethanol overnight. Structures **11** and **12** would each be expected to form a hydrazone derivative under these conditions.

Attention is called to the contrasting cyclization behavior of **2a** in this present report with ethyl bromopyruvate (**4e**) in water at room temperature to give pyrimidotriazine **5e** and with ethyl acetoxypyruvate (**14**) in refluxing methanol (as reported previously)[1] to give pyrimidopyridazinedione **15**. Enhancement of leaving ability for the substituent



15

β to the ester carbonyl in the present case and/or (less likely) the change in reaction conditions affected not only the points of cyclization on the three-carbon backbone but also the position of cyclization onto the pyrimidine ring (N-1 for the bromo ketone **4e**, C-5 for the α-keto ester **14**).

Experimental Section

Melting points were run on a Thomas-Hoover capillary melting-point apparatus and are corrected. Quantitative UV spectra were recorded on a Varian Superscan 3, Cary 118, or Unicam SP 800A spectrophotometer. NMR spectra were determined with a Varian T-60 spectrometer with tetramethylsilane as the internal standard. Low-resolution mass spectra were obtained with a Varian MAT CH5 DF double-focusing spectrometer at 70 eV, and probe temperatures were noted. Accurate masses

(6) Rice, J. M.; Dudek, G. O. *J. Am. Chem. Soc.* **1967**, *89*, 2719.

were determined by peak matching at 10 000 resolution, 10% valley definition. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and Galbraith Laboratories, Inc., Knoxville, TN. All C, H, N analyses not reported here were acceptable (±0.3%) and can be found with other physical data in the supplementary material.[7] The 6-(1-alkylhydrazino)isocytosines (**2a–c**) were prepared as described previously.[1]

Cyclizations to 6-Amino-1,4-dihydro-8*H*-pyrimido[6,1-*c*][1,2,4]triazin-8-ones (5a–e) The appropriate α-halo ketone was added all at once to a stirred mixture of (alkylhydrazino)-isocytosine **2** and solvent at room temperature in the proportion of 0.009 75 mol in 100 mL. An exception to this proportion was the preparation of **4d** (0.009 75 mol in 130 mL). At the end of the reaction time, the acidic solution or mixture was brought to pH 8–9 with 10% (w/w) aqueous NaOH equimolar with the α-halo ketone used. The mixture was concentrated under vacuum to a solid residue that was stirred with water,[8] collected by filtration, washed with a little fresh reaction solvent, dried at 70 °C in a vacuum oven, and recrystallized. A specific example is described below for the preparation of **5a**.

6-Amino-1,3-dimethyl-1,4-dihydro-8*H*-pyrimido[6,1-*c*]-[1,2,4]triazin-8-one (5a). To a stirred mixture of 1.60 g (0.009 75 mol) of 6-(1-methylhydrazino)isocytosine hemihydrate (**2a**) and 100 mL of water was added all at once 1.80 g (0.0131 mol) of bromoacetone. After 3 h the mixture was adjusted to pH 8–9 with 5.30 g of 10% (w/w) aqueous NaOH and was then concentrated under vacuum to dryness. The residue was stirred for 10 min with 15 mL of water, and a light gray solid was collected by filtration, washed with water (2 × 5 mL), and dried under vacuum at 70 °C to yield 1.414 g. A 0.500-g sample of this solid was recrystallized from 2-propanol to give 0.418 g of light green, fine crystals: mp 280–288 °C dec; NMR (CF_3COOH) δ 2.22 (s, 3 H), 3.55 (s, 3 H), 4.60 (s, 2 H), 5.60 (s, 1 H), 8.3 (br s, 2 H); UV λ_{max} (CH_3OH) 253.5 nm (sh, ε 4700), 300 (13 700), 312.5 (sh, 9700); mass spectrum (175 °C), *m/e* 193 (M, 91%), 178 (10), 152 (3), 151 (M − CH_2N_2, 27), 150 (27), 149 (2), 136 (16), 82 (100). The following selected accurate masses were determined: 151.0741 ($C_7H_9N_3O$), 150.0668 ($C_7H_8N_3O$), 136.0508 ($C_6H_6N_3O$). Anal. Calcd for $C_8H_{11}N_5O$: C, 49.73; H, 5.74; N, 36.25. Found: C, 49.58; H, 5.77; N, 36.15.

Hydrolysis of Ester 5e. 6-Amino-3-carboxy-1,4-dihydro-1-methyl-8*H*-pyrimido[6,1-*c*][1,2,4]triazin-8-one (5f). A mixture of 0.108 g (0.000 378 mol) of crude **5e**[9] in 3 mL of water was stirred while 10% (w/w) aqueous NaOH was added until pH 11–12 was reached. The resulting solution was allowed to stand, and solid slowly precipitated. After 22 min the mixture was brought to pH 5 with glacial acetic acid. Precipitated solid was collected by filtration, washed with 0.5 mL of water, and dried under vacuum at 70 °C to yield 0.089 g of pale yellow solid. Recrystallization of this solid from water afforded 0.046 g (53%) of off-white solid: mp >300 °C; NMR (CF_3COOH) δ 3.69 (s, 3 H), 4.90 (s, 2 H), 5.80 (s, 1 H), 8.4 (br s, 2 H); UV λ_{max} (0.1 N NaOH) 330 nm (ε 16 100). Anal. Calcd for $C_8H_9N_5O_3 \cdot 0.4H_2O$: C, 41.70; H, 4.29; N, 30.40. Found: C, 41.57; H, 4.00; N, 30.37.

7-Amino-3-methylpyrimido[4,5-*c*]pyridazin-5(6*H*)-one (7).[10] To a stirred mixture of 2.00 g (0.0142 mol) of 6-hydrazinoisocytosine (**6**) in 140 mL of water was added all at once 2.57 g (0.0188 mol) of bromoacetone. After 1 h the mixture was adjusted to pH 8–9 with 7.53 g of 10% (w/w) aqueous NaOH (0.0188 mol) and was concentrated under vacuum to a solid that was stirred for 20 min with 20 mL of water, collected by filtration, rinsed with 5 mL of ethanol, and dried under vacuum at 70 °C to yield 2.01 g of a very crude product.[11]

A 1.00-g sample of solid was suspended in 3 L of boiling methanol. Some undissolved solid was removed by filtration. The filtrate was concentrated by boiling to 500 mL whereupon a solid began to precipitate. The mixture was allowed to cool slowly to room temperature and was refrigerated overnight. Solid was collected by filtration, washed with 10 mL of methanol, and dried under vacuum at 70 °C to yield 0.302 g. Three recrystallizations of this solid from water afforded 0.103 g of a brown solid: mp >300 °C; NMR (CF_3COOH) δ 3.13 (s, 3 H), 8.99 (s, 1 H); UV λ_{max} (0.1 N NaOH) 252 nm (ε 21 600), 270 (sh, 7700), 362 (4200); mass spectrum (300 °C), *m/e* 177 (M, 100%), 149 (18), 148 (3), 136 (M − CHN_2 and M − CH_3CN, 1), 133 (10), 132 (5), 122 (13), 121 (7), 120 (5), 109 (7), 107 (12). The following selected accurate masses were determined: 136.0517 ($C_6H_6N_3O$), 136.0388 ($C_5H_4N_4O$). Anal. Calcd for $C_7H_7N_5O$: C, 47.45; H, 3.98; N, 39.53; O, 9.03. Found: C, 47.73; H, 3.70; N, 39.50; O, 9.25.

Acknowledgment. We thank Dr. B. S. Hurlbert, Mr. A. Ragouzeous, and Mrs. C. A. Jenkins for the NMR spectra, Dr. D. A. Brent, Ms. D. Rouse, and Mr. R. L. Johnson, Jr. for the mass spectra, and Miss S. Wrenn and Mrs. J. Miller for technical assistance.

Registry No. 2a, 67873-21-6; **2b**, 67873-24-9; **2c**, 67873-25-0; **5a**, 74467-08-6; **5b**, 74467-09-7; **5c**, 74467-10-0; **5d**, 74467-11-1; **5e**, 74467-12-2; **5f**, 74467-13-3; **6**, 6298-85-7; **7**, 74482-47-6; 1-bromo-2-propanone, 598-31-2; 3-chloro-2-oxopropanal 1-oxime, 14337-41-8; 3-bromo-2-oxopropanoic acid ethyl ester, 70-23-5.

Supplementary Material Available: Full data available include the microanalyses, UV data, and NMR data on compounds **5b–e** and mass spectral data on **5d** and **5e** (5 pages). Ordering information is given on any current masthead page.

(7) See paragraph on supplementary material at end of paper.
(8) A minimum of water should be used in order to maximize the yield of crude product.
(9) Shown by microanalysis to be a 1.9 hydrate.
(10) V. L. Styles in our laboratory also prepared this compound by a preferred procedure from 6-hydrazinoisocytosine and pyruvaldehyde in refluxing water.
(11) No pyrimidotriazine was indicated by NMR or UV data.

Methanolysis of a Phosphate Triester: A Change in Mechanism with Acidity

Stevin H. Gehrke and William S. Wadsworth, Jr.*

Department of Chemistry, South Dakota State University, Brookings, South Dakota 57007

Received May 19, 1980

In previous publications, we have pointed out the utility of the 2-substituted-5-methyl-2-oxo-1,3,2-dioxaphosphorinan system in determining stereochemistry of substitutions at phosphorus in phosphate triesters.[1] We reported that for aprotic media, substitutions at phosphorus occur by both inversion and retention, with the former favored by good leaving groups, i.e., Cl^-, while retention is favored by nucleophiles which can backbond to phosphorus, i.e., RO^-. Retention can be made the only pathway by employing conditions under which the attacking nucleophile is highly associated with its counterion.[2]

Our initial success has dictated employment of the same system in protic media, specifically acid-catalyzed methanolysis. Due to ease of handling and lack of side reactions,[3] we selected the 2-(*p*-nitrophenyl) esters as model substrates. As pointed out in previous publications, the cyclic esters strongly prefer that conformation with the phosphoryl oxygen equatorial.[1,4] As a consequence, and

(1) W. W. Wadsworth, Jr., S. Larson, and H. L. Horton, *J. Org. Chem.*, **38**, 256 (1973); W. S. Wadsworth, Jr., *ibid.*, **38**, 2921 (1973).
(2) M. Bauman and W. S. Wadsworth, Jr., *J. Am. Chem. Soc.*, **100**, 6388 (1978).
(3) An insignificant amount of ring-opened methyl ester is also obtained which becomes a problem only in those cases where a poor leaving group, i.e., phenol, is employed.
(4) R. J. P. Corriu, J. P. Dutheil, G. F. Lanneau, and S. Ould-Kada, *Tetrahedron*, **35**, 2889 (1979).
(5) T. Koisumi and P. Haake, *J. Am. Chem. Soc.*, **95**, 8073 (1973); D. A. Tysee, L. P. Bausher, and P. Haake, *ibid.*, **95**, 8066 (1973); M. J. Harger, *J. Chem. Soc., Perkin Trans. 1*, 1294 (1979).

0022-3263/80/1945-3921$01.00/0