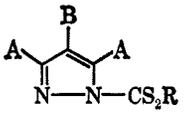
TABLE I

COMPOUNDS OF STRUCTURE



Method	A	B	R	Yield, %	Bp, °C (mm)	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found	S, % Calcd	S, % Found	Nmr[c]
A	H	H	CH_3	86	99 (3)	38.0	37.9	3.80	3.91			40.5	41.1	d (3.0) 1.54; d (1.6) 2.33; q (3.0 and 1.6) 3.70; s 7.47 (1:1:1:3)
A	H	H	Allyl	73	97 (1)[d]	45.6	46.2	4.35	4.55			34.8	34.8	d (3.0) 1.44; d (1.4) 2.25; q (3.0 and 1.4) 3.63, allyl H's 3.7–6.1 (1 1:1:5)
A	H	H	*n*-Butyl	16	131–150 (2)	48.0	48.3	6.00	6.26			32.0	33.5	
A	H	H	$-CH_2-$	86	182–184[a,b]	36.0	35.9	2.67	2.52			42.7	43.3	d (2.9) 1.39; d (2.4) 2.20; q (2.9 and 1.4); s 4.78 (1:1:1:1)
B	H	Cl	CH_3	54	113 (1.8) 45–50[b]	31.1	30.9	2.60	2.76	14.5	14.5	33.3	33.5	s 1.45; s 2.3; s 7.36 (1:1:3)
B	H	Br	CH_3	69	124 (1.7) 68–69[b]	25.3	25.3	2.11	2.17	11.6	11.6			s 1.48; s 2.26; s 7.33 (1:3:3)
B	CH_3	Br	CH_3	43	98–99[b]	31.7	32.1	3.40	3.53	10.6	10.6			s 7.29; s 7.40; s 7.70 (1:1:1)
A	CH_3	H	CH_3	94	125 (1.5) 31–32[b]	45.2	45.0	5.37	5.41	15.1	15.7	34.4	34.9	s 4.00; s 7.35; s 7.48; s 7.80 (1:3:3:3)

[a] Recrystallized from toluene. [b] Melting point. [c] The nmr spectra were taken in deuteriochloroform with tetramethylsilane as internal reference. Listed are multiplicity (coupling constant), chemical shift in τ, plus relative areas. [d] Values from the ultraviolet spectrum are 425 mμ (ε 60.5), 296 mμ (ε 22,100); sh 325 mμ (ε 9500).

Potassium 3,5-Dimethyl-1-pyrazoledithiocarboxylate.—Potassium metal (18.5 g, 0.475 g-atom) was added to 48 g (0.5 mole) of 3,5-dimethylpyrazole in 1 l. of tetrahydrofuran (under N_2) and the mixture was stirred under reflux until hydrogen ceased to be evolved. Excess carbon disulfide (>0.5 mole) was added. A yellow solid formed exothermally. The mixture was refluxed briefly and stirred overnight. The solid was filtered, washed with tetrahydrofuran, and air dried to give 98.6 g (98.6%) of dark yellow solid soluble in water and methanol. It decomposed above 200°.

Anal. Calcd for $C_6H_7KN_2S_2$: C, 34.3; H, 3.33; S, 30.5. Found: C, 35.9; H, 4.33; S, 26.0.

Transition Metal Bis(3,5-dimethyl-1-pyrazoledithiocarboxylates).—The compounds were prepared by mixing aqueous solutions of potassium 3,5-dimethylpyrazol-1-yldithiocarboxylate with the appropriate transition metal ions. The colors of the chelates are Mn(II), yellowish; Fe(II), black; Co(II), reddish; Ni(II), red-brown; Cu(II), black; Zn(II), yellow. The products derived from Co, Ni, Cu, and Zn could be extracted into methylene chloride.

Nickel Bis(3,5-dimethyl-1-pyrazoledithiocarboxylate).—Potassium 3,5-dimethylpyrazol-1-yldithiocarboxylate (14 g, 0.05 mole) was dissolved in 400 ml of water. The solution was stirred and 50 ml of 0.5 *M* nickel acetate solution was added. A red-brown solid precipitated. It was filtered and pressed dry. The crude product was dissolved in methylene chloride and purified by chromatography on alumina (packed and eluted with methylene chloride). The pure compound was obtained in a 4.0-g (40%) yield as shiny red-brown crystals. They slowly turn grey on heating above 300°.

Anal. Calcd for $C_{12}H_{14}N_4NiS_4$: C, 35.9; H, 3.50; Ni, 14.6. Found: C, 35.8; H, 3.72; Ni, 14.4.

On prolonged standing this material decomposes in undetermined fashion. The infrared spectrum exhibits strong bands at about 1560, 1320, 1250, 1130, 1080, 1040, 980, and 880 cm^{-1}.

Alkylation of 1-Pyrazoledithiocarboxylates.—The alkylations of 1-pyrazoledithiocarboxylates were carried out by refluxing together equivalent quantities of the sodium or potassium 1-pyrazoledithiocarboxylate (or a substituted analog) and the alkyl halide. They are exemplified by the following typical procedures. The properties of the compounds are listed in Table I.

A. Methyl 1-Pyrazoledithiocarboxylate.—A mixture of 0.2 mole of potassium 1-pyrazoledithiocarboxylate and 0.2 mole of methyl iodide was refluxed for 8 hr in 250 ml of tetrahydrofuran. The reaction mixture was filtered, the filtrate was stripped, and the residue was distilled *in vacuo* to give 27 g (86%) of bright-yellow liquid, bp 93° (3 mm).

B. Methyl 4-Chloro-1-pyrazoledithiocarboxylate.—To 0.5 mole of sodium hydride (mineral oil suspension) in 200 ml of tetrahydrofuran was added dropwise a solution of 0.5 mole of 4-chloropyrazole in 200 ml of tetrahydrofuran. When the theoretical amount of hydrogen had been evolved, 38 g (0.5 mole) of carbon disulfide was added. The reaction mixture was stirred for 1 hr at room temperature, 0.55 mole of methyl iodide was added, and the mixture was refluxed for 1 hr. It was then filtered, and the filtrate was evaporated to leave a yellow oil. It was distilled *in vacuo* affording 52 g (54%) of methyl 4-chloro-1-pyrazoledithiocarboxylate as a yellow oil, bp 113° (1.8 mm). It solidified on standing, mp 49–50°.

Registry No.—III (M = Cu), 15376-60-0; IV, 15315-15-8; Va, 15315-17-0; Vb, 15315-08-9; Vc, 15315-09-0; VI, 15315-10-3; IX (M = Fe), 15336-50-2; X (A = CH_3, B = H, M = K), 15315-16-9; XI (A = H, B = Cl), 15315-11-4; XI (A = H, B = Br), 15315-12-5; XI (A = CH_3, B = Br), 15315-13-6; XI (A = CH_3, B = H), 15315-14-7; $C_{12}H_{14}N_4NiS_4$, 15336-51-3.

Reactions of Hydrazine and Methylhydrazine with Uracil-5-carboxaldehyde. An Unusual Pyrimidine into Pyrazole Conversion[1]

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Several substituted hydrazone derivatives, notably the methyl- and formylhydrazones of orotaldehyde and thymine-6-carboxaldehyde,[2] have recently been shown to possess tumor inhibitory activity against the Walker 256 (intramuscular) test system. In connection with our continued efforts in the investigation of hydrazone derivatives, the reactions of uracil-5-carboxaldehyde with hydrazines have been studied.

Phenylhydrazine and hydroxylamine were reported to give normal condensation products with uracil-5-carboxaldehyde[3] (I). When methylhydrazine was used in the condensation reaction, however, the resulting white product ($\lambda_{max}^{pH\ 1}$ 237 mμ; $\lambda_{max}^{pH\ 11}$ 239 mμ) failed to give a characteristic ultraviolet absorption spectrum for a pyrimidine hydrazone derivative (usually a maximum peak is seen at 310–320 mμ in alkali).

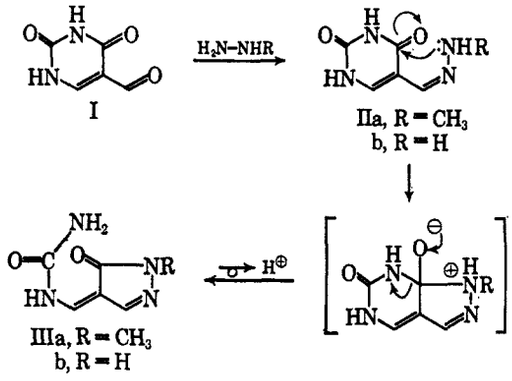
(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute, of the National Institutes of Health, Public Health Service, Contract PH-43-65-94.

(2) K. Y. Zee-Cheng and C. C. Cheng, *J. Heterocyclic Chem.*, **4**, 163 (1967).

(3) R. H. Wiley and Y. Yamamoto, *J. Org. Chem.*, **25**, 1906 (1960).

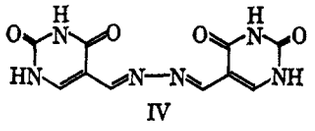
A closer examination of the data suggested that a rearrangement reaction had occurred and that the product is a derivative of pyrazole (IIIa). Elemental analysis and the nmr spectrum of this product were found to be in accordance with the structural assignment. In addition, the product gave a positive *p*-dimethylaminobenzaldehyde–HCl test for a ureido group.[4,5] Similarly, when hydrazine was caused to react with I, a homologous pyrazole derivative, IIIb, was obtained.

The fact that this rearrangement was not observed when less basic hydrazines (such as formyl- or phenylhydrazine, etc.) or N,N-dimethylhydrazine[3] were used in the condensation reaction suggests that the following reaction sequence might be a possible mechanism for the rearrangement.



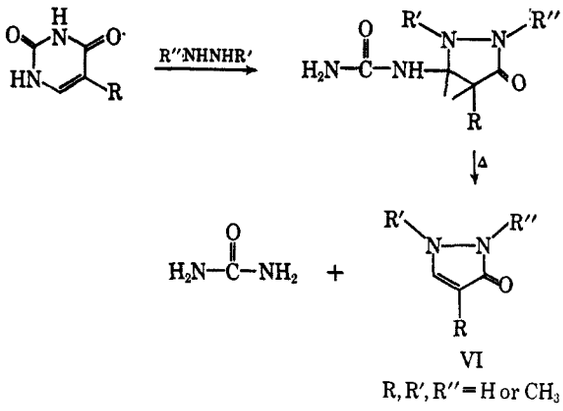
When the reaction of methylhydrazine and I was carried out in the presence of acetic acid and a shorter reaction time, the normal methylhydrazone derivative, IIa, could be isolated as an orange-yellow solid ($\lambda_{max}^{pH\ 11}$ 239, 315 mμ), along with the rearranged product IIIa. A small amount of the hydrazone derivative IIb ($\lambda_{max}^{pH\ 11}$ 234, 311 mμ), could also be obtained under similar reaction conditions.

Attempts to obtain IIb by the treatment of I with equimolar or lesser amounts of hydrazine resulted in the formation of the azine IV.



A slow conversion of IIa into IIIa (also IIb into IIIb) was observed in either neutral or slight basic aqueous media (such as recrystallization of II from boiling water, which accounts for the fact that it was difficult to obtain a purified, unrearranged sample, or treatment of II with methylhydrazine at room temperature). The course of this rearrangement can be followed by observing the shift of the major peak of the ultraviolet absorption spectra.

A related rearrangement has been observed in the reaction of uracil or thymine with excess hydrazine, methylhydrazine or N,N′-dimethylhydrazine; the intermediate 3-ureido-5-pyrazolinone (V) further decomposed to



yield urea and a 5-pyrazolone VI.[6,7] The present rearrangement differs in that condensation of the pyrimidine-5-carboxaldehyde group with hydrazine takes place initially (which excludes the participation of N,N′-disubstituted hydrazines), followed by an intramolecular nucleophilic attack at the pyrimidine-carbonyl-C_4 rather than intermolecular nucleophilic attack at the pyrimidine-C_6.[6,7]

Experimental Section[8]

Reactions of Uracil-5-carboxaldehyde and Methylhydrazine. Experiment A.—To a warm (50–60°) solution of 2.8 g (0.020 mole) of uracil-5-carboxaldehyde[9] (I) in 160 ml of water containing 0.2 g of acetic acid was added dropwise a solution of 1.2 g (0.026 mole) of methylhydrazine in 12 ml of water, with stirring. The resulting solution was then heated on a steam bath for 1 hr with stirring. On cooling, 3.1 g (90% yield) of **1-methyl-4-ureidomethylene-1H-5-pyrazolone** (IIIa) was isolated as white needles: mp 250–251° (recrystallization from water raised its melting point to 251–252°); $\lambda_{max}^{pH\ 1}$ 237 mμ (ε 16,100); $\lambda_{max}^{pH\ 11}$ 239 mμ (ε 16,800). The nmr spectrum (CF_3COOH) showed absorption for three protons (s) at 3.84 ($N-CH_3$), one proton (s) at 8.50 and one proton (s) at 8.55 ppm (CH=C and CH=N). The product gave a light yellow coloration with acidified *p*-dimethylaminobenzaldehyde (positive test for $RNHCONH$[4,5]).

Anal. Calcd for $C_6H_8N_4O_2$: C, 42.86; H, 4.79; N, 33.32. Found: C, 42.84; H, 4.74; N, 33.52.

Experiment B.—To a warm (50–60°) solution of 500 mg (0.0035 mole) of uracil-5-carboxaldehyde (I) in 40 ml of water containing 200 mg of acetic acid was added dropwise a solution of 230 mg (0.0050 mole) of methylhydrazine in 5 ml of water and 600 mg of acetic acid, with stirring. The resulting solution was heated on a steam bath for 15 min and then stirred at room temperature for an additional 15 min. On cooling, 320 mg of IIIa (54% yield), mp 250°, was collected by filtration. The filtrate was then concentrated under reduced pressure to 5 ml and 160 mg (17% yield) of the **methylhydrazone of uracil-5-carboxaldehyde** (IIa), mp 240–242°, was obtained on cooling: $\lambda_{max}^{pH\ 1}$ 237 (ε 13,200) and 277 mμ (ε 3700); $\lambda_{max}^{pH\ 11}$ 239 (ε 12,100) and 312 mμ (ε 3400).

Anal. Calcd for $C_6H_8N_4O_2$: C, 42.86; H, 4.79; N, 33.32. Found: C, 43.19; H, 4.76; N, 32.91.

When 50 mg of IIa in 5 ml of warm (40–50°) water was added to 30 mg of methylhydrazine and the solution was allowed to stand at room temperature overnight, 40 mg of white needles, mp 251–252°, were obtained, which was shown to be identical (uv and ir) with IIIa prepared previously. This orange-yellow hydrazone IIa also gradually rearranged to IIIa when boiled with water.

Reactions of Uracil-5-carboxaldehyde and Hydrazine. Experiment A.—To a solution of 1.4 g (0.020 mole) of hydrazine

(4) J. J. Fox, N. C. Miller, and R. J. Cushley, *Tetrahedron Letters*, 4927 (1966).

(5) R. M. Fink, R. E. Cline, C. McGaughey, and K. Fink, *Anal. Chem.*, 28, 4 (1956).

(6) R. Fosse, A. Hieulle, and L. W. Bass, *Compt. Rend.*, 178, 811 (1924).

(7) (a) F. Lingens and H. Schneider-Bernlöhr, *Angew. Chem.*, 76, 379 (1964); *Ann. Chem.*, 686, 134 (1965). (b) D. H. Hayes and F. Hayes-Baron, *J. Chem. Soc., cf.* 1528 (1967), and references cited therein.

(8) All melting points (corrected) were taken on a Thomas-Hoover melting point apparatus. The ultraviolet absorption spectra were determined with a Beckman DK-2 spectrophotometer. The infrared spectra were taken with a Perkin-Elmer Infracord, and the nmr spectrum was determined with a Varian A-60 spectrometer.

(9) R. Brossmer and D. Ziegler, *Tetrahedron Letters*, 5253 (1966).

monohydrochloride in 100 ml of water was added dropwise a warm solution of 1.4 g (0.01 mole) of uracil-5-carboxaldehyde in 200 ml of water. The mixture was heated on a steam bath for 1 hr and stirred for an additional hour at room temperature. The white solid was collected by filtration and washed with ethanol and ether to give 1.4 g (quantitative yield) of the **azine of uracil-5-carboxaldehyde** (IV), mp >360°. An analytical sample was obtained by dissolving the product in dilute KOH, filtering, and acidifying the filtrate to pH 5 with dilute HCl: $\lambda_{max}^{pH\ 1}$ 229 (ε 20,200), 274 (ε 24,000), and 358 mμ (ε 3600); $\lambda_{max}^{pH\ 11}$ 280 (ε 13,500) and 357 mμ (ε 38,800).

Anal. Calcd for $C_{10}H_8N_6O_4$: C, 43.48; H, 2.92; N, 30.43. Found: C, 43.68; H, 2.96; N, 30.15.

Experiment B.—To a stirred solution of 1.28 g (0.04 mole) of 97% hydrazine in 50 ml of water and 0.6 g of acetic acid was added dropwise a warm solution of 2.8 g (0.02 mole) of uracil-5-carboxaldehyde in 180 ml of water. The resulting solution was heated with stirring on a steam bath for 1 hr. On cooling, a light yellow solid (2.0 g) was separated, which consisted of a mixture of azine (IV) and the rearranged product (**4-ureidomethylene-1H-5-pyrazolone**, IIIb). These were separated by recrystallizing the crude product from 800 ml of water. The azine IV, which was quite insoluble in water, was isolated first to yield 1 g (36%), mp >360°. The rearranged product IIIb was obtained from the concentrated filtrate to give 0.8 g (25% yield), mp 289–290° dec. Further recrystallization from water yielded an analytically pure sample as white needles: mp 290° dec; $\lambda_{max}^{pH\ 1}$ 231 mμ (ε 13,700); $\lambda_{max}^{pH\ 11}$ 234 mμ (ε 12,200). The product gave a yellow coloration with acidified *p*-dimethylaminobenzaldehyde (positive test for R-NHCONH$_2$[4,5]).

Anal. Calcd for $C_5H_6N_4O_2$: C, 38.96; H, 3.92; N, 36.35. Found: C, 38.87; H, 3.89; N, 36.03.

Experiment C.—To a solution of 1.6 g (0.05 mole) of 97% hydrazine in 100 ml of water was added a warm solution of 1.4 g (0.01 mole) of uracil-5-carboxaldehyde in 300 ml of water containing 0.2 g of acetic acid. The resulting mixture was heated on a steam bath for 1 hr. On cooling, 0.32 g (20.8% yield) of white solid, mp 280–282°, was collected (impure IIIb). The filtrate was concentrated to 30 ml under reduced pressure and a light orange solid separated. This was collected by filtration and washed with a small amount of ethanol and ether to give 0.5 g (32.4% yield) of the **hydrazone of uracil-5-carboxaldehyde** (IIb): mp 275–276°; $\lambda_{max}^{pH\ 1}$ 230 (ε 12,400), 274 mμ (ε 3400); $\lambda_{max}^{pH\ 11}$ 234 (ε 9700), 311 mμ (ε 3000).

Anal. Calcd for $C_5H_6N_4O_2$: C, 38.96; H, 3.92; N, 36.35. Found: C, 38.16; H, 3.49; N, 36.63.

Attempted further purification of this product from boiling water resulted in its conversion to IIIb.

Uracil-5-carboxaldehyde Formylhydrazone.—To 5.0 g (0.08 mole) of formylhydrazine in 400 ml of water was added dropwise, with stirring, a warm (60–70°) solution of 5.7 g (0.04 mole) of uracil-5-carboxaldehyde in 1 l. of water and 2 ml of acetic acid. The mixture was heated on a steam bath for 1 hr and cooled. The resulting white solid was collected by filtration and recrystallized from dimethylformamide to give 7.2 g (97% yield) of the formylhydrazone, which darkened at 350° and decomposed at 360°: $\lambda_{max}^{pH\ 1}$ 231 (ε 9500) and 268 mμ (ε 11,800); $\lambda_{max}^{pH\ 11}$ 272 (ε 14,000) and 320 mμ (ε 19,000).

Anal. Calcd for $C_6H_6N_4O_3$: C, 39.56; H, 3.32; N, 30.76. Found: C, 39.51; H, 3.28; N, 30.55.

The following derivatives of I were prepared in a similar fashion. **Uracil-5-carboxaldehyde phenylhydrazone** showed mp 309–310° (lit.[3] mp 298–300°) and ultraviolet bands were at λ_{max}^{EtOH} 290 (ε 16,300) and 365 mμ (ε 14,000). **Uracil-5-carboxaldehyde oxime** had mp 290° dec (lit.[3] mp 260° dec) and ultraviolet bands were at $\lambda_{max}^{pH\ 1}$ 238 (ε 10,700) and 281 mμ (ε 9400) and $\lambda_{max}^{pH\ 11}$ 257 (ε 11,400) and 307 mμ (ε 11,200). **Uracil-5-carboxaldehyde thiosemicarbazone** had mp >360° (lit.[7] mp 320° dec) and ultraviolet bands were at $\lambda_{max}^{pH\ 1}$ 270 (ε 17,200) and 315 mμ (ε 22,900) and $\lambda_{max}^{pH\ 11}$ 283 (ε 17,000) and 328 mμ (ε 31,000).

Registry No.—I, 1195-08-0; IIa, 15352-84-8; IIb, 15352-85-9; IIIa, 15352-86-0; IIIb, 15352-87-1; IV, 14684-66-3; hydrazine, 302-01-2; methylhydrazine, 60-34-4; uracil-5-carboxaldehyde formylhydrazone, 15352-89-3; uracil-5-carboxaldehyde phenylhydrazone, 14859-92-8; uracil-5-carboxaldehyde oxime, 14859-93-9; uracil-5-carboxaldehyde thiosemicarbazone, 13545-08-9.

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Twofold Aroylations of Certain Amides by Means of Sodium Hydride[1]

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Recent publications[2,3] describing 1,3-diaroylations of acetone and dimethyl sulfone with aromatic esters by means of sodium hydride prompt us to report the results of a study in which acetamide and certain other primary amides were found to undergo related twofold aroylations in the presence of these reagents.

Treatment of acetamide with excess sodium hydride and 2.5 mol equiv of the appropriate aromatic ester in refluxing 1,2-dimethoxyethane (monoglyme) afforded β-keto imides **1a–c** in yields of 62–100% (eq 1). Simi-

$$CH_3CONH_2 \xrightarrow[2.\ \text{acid}]{1.\ \text{ArCOOR, NaH}} \text{ArCOCH}_2\text{CONHCOAr} \quad (1)$$

1a, Ar = C_6H_5
b, Ar = $C_6H_4OCH_3$-*p*
c, Ar = C_6H_4Cl-*p*

larly, phenylacetamide gave the products **2a–d** in yields of 27–92%. That the method was general for higher primary amides was demonstrated by twofold benzoylation of butyramide and hexanamide to produce **3a** and **3b** in yields of 68 and 65%, respectively. The results of these experiments are summarized in Table I.

ArCOCHCONHCOAr
|
C_6H_5

2a, Ar = C_6H_5
b, Ar = $C_6H_4OCH_3$-*p*
c, Ar = C_6H_4Cl-*p*
d, Ar = 3-pyridyl

$C_6H_5COCHCONHCOC_6H_5$
|
R

3a, R = C_2H_5
b, R = *n*-C_4H_9

The identity of **1a** was established by comparison with an authentic sample, which was prepared from dipotassio N-acetylbenzamide.[4] The structural assignments for **1b**, **1c**, **2a–d**, **3a**, and **3b**, all of which appear to be new compounds, were based on analyses and nmr spectra (Table II). Further confirmation of structures **2a** and **2b** was provided by their acid-catalyzed hydrolysis to form, in the case of **2a**, benzoic acid and deoxybenzoin, and in the case of **2b**, anisic acid and 2-phenyl-4′-methoxyacetophenone. Acidic hydrolysis of **3a** afforded benzoic acid and butyrophenone, while that of **3b** gave benzoic acid and caprophenone. β-

(1) Supported by the Public Health Service, Research Grant No. GM 14340 from the National Institute of General Medical Sciences.

(2) M. L. Miles and C. R. Hauser, *J. Org. Chem.*, **29**, 2329 (1964).

(3) M. L. Miles, T. M. Harris, and C. R. Hauser, *ibid.*, **30**, 1007 (1965).

(4) S. D. Work, D. R. Bryant, and C. R. Hauser, *J. Am. Chem. Soc.*, **86**, 872 (1964).