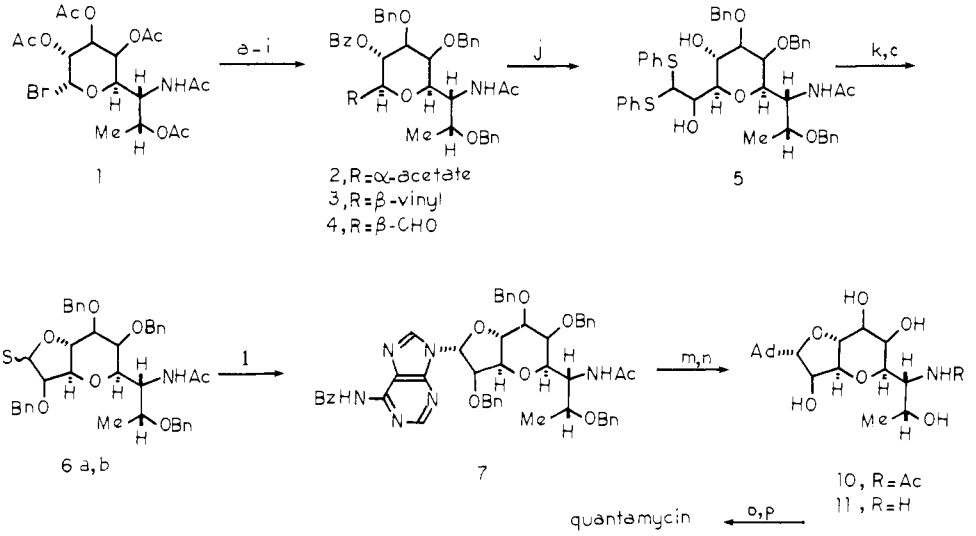
Scheme I[a]



[a] (a) Bu_3SnOMe, Bu_4NBr, $CHCl_3$, 98%; (b) NaOMe, MeOH; (c) BnBr, NaH, DMF; (d) aqueous HCl; (e) Ac_2O, pyr, 67% (4 steps); (f) HBr, AcOH; (g) vinyl MgBr, THF; (h) Bz_2O, DMAP, pyr, 66.8% (3 steps); (i) OsO_4–$NaIO_4$, aqueous acetone; (j) $(PhS)_2CH_2$, *n*-BuLi, −78 °C, 70% 7:1 ratio (2 steps); (k) $Me_2S^+Br\,Br^-$, CH_2Cl_2, 0 °C, 80% (2 steps); (l) *N*-benzoyladenine, Br_2, DMF, 62%; (m) 20% $Pd(OH)_2/C$, H_2, MeOH, 88% (2 steps); (n) aqueous 0.5 N $Ba(OH)_2$, reflux 30 min; (o) hexamethyldisilazane, DMF, 120 °C, 2 h, then add mixed anhydride from isobutyl chloroformate and *N*-propylhygric acid in the presence of *N*-methylmorpholine, −20 °C, 45 min; (p) chromatography, then Bu_4NF, THF.

of functional groups. The synthesis shown in Scheme I starts with **1**, which is readily available from lincomycin,[12] and proceeds to install a glycol aldehyde equivalent as in **5**, $[\alpha]_D$ +7.4°,[10] in a highly stereocontrolled manner. Treatment with bromodimethylsulfonium bromide, followed by benzylation led to a 3:1 mixture of anomeric α- and β-phenyl thioglycosides, **6a**, $[\alpha]_D$ +87.9°, *m/e* 561 ($M^+ - PhCH_2OH$), and **6b**, $[\alpha]_D$ −2°, respectively. In a unique ring-closure reaction, the mixture of glycosides **6a,b** was transformed into a 2:1 mixture of **7**, $[\alpha]_D$ +31.3°, *m/e* 797 ($M^+ - PhCH_2\cdot$), and the unwanted anomeric α-nucleoside, which could be recycled to the desired **7** by mercaptolysis to the diphenyl dithioacetal, $[\alpha]_D$ +30.93°, *m/e* 760 ($M^+ - PhS\cdot$), and subjecting it to cyclization as for **6**. It should be remarked that not only does this method produce the delicately balanced functionality in the intended target, but it also constitutes a novel way of forming cyclic nucleosides from acyclic dithioacetals and thioglycosides.[10,13] With the ring structure established, we proceeded to complete the synthesis of quantamycin. Deprotection of benzyl ethers gave the *N*-acetyl derivative **10** as an amorphous solid, $[\alpha]_D$ +23.1°. De-N-acetylation to quantamine **11** and coupling with *n*-propylhygric acid[14] gave quantamycin as a microcrystalline solid: mp 205–207 °C dec; $[\alpha]_D$ +4.5° (*c* 0.7, $CHCl_3$); M^+ 535.2721 (measured), 535.2754 (calcd).

Although quantamycin was found to have no antibacterial activity, *it exhibited anti-ribosomal activity in competitive binding tests of* ^{14}C *lincomycin to ribosomes from Streptomyces.*[15-17] Although somewhat weaker than anticipated,[18] the ribosomal binding activity of quantamycin constitutes an encouraging lead considering its mode of conception and genesis. The results could pave the way to designing potentially bioactive, new-generation drugs through further fine tuning of the original quantamycin model, or others based on the same concept.

Acknowledgment. We acknowledge generous financial assistance from The Upjohn Co. We are particularly indebted to Dr. E. C. Olson for his encouragement, vision, and commitment to the pursuit of pioneering projects such as quantamycin. We also are grateful to Dr. L. Baczynskyj for his help in mass spectrometric analyses,Dr. G. Slomp for high-resolution NMR, and Dr. B. Bannister for most helpful discussions. We are also greatly indebted to Prof. E. Cundliffe, University of Leicester, U.K., for the ribosomal binding studies.

Registry No. **1**, 6991-36-2; **2**, 91899-81-9; **3**, 91899-82-0; **4**, 91899-83-1; **5**, 91899-84-2; **6a**, 91899-85-3; **6b**, 91899-86-4; **7**, 91899-87-5; **10**, 91899-88-6; **11**, 91899-89-7; quantamycin, 91899-90-0; *N*-benzoyladenine, 4005-49-6; *N*-propylhygric acid, 20488-28-2.

Supplementary Material Available: NMR spectra of **4**, **5**, **6** (α and β anomers), **7**, **10**, and quantamycin and IR spectrum of **4** (10 pages). Ordering information is given on any current masthead page.

(12) Bannister, B. *J. Chem. Soc., Perkin Trans. 1* **1972**, 3025–3036.
(13) Pedersen, C.; Fletcher, H. G., Jr. *J. Am. Chem. Soc.* **1960**, *82*, 5210–5211. Wolfrom, M. L.; McWain, P.; Thompson, A. *J. Org. Chem.* **1962**, *27*, 3549–3554; *Synth. Proced. Nucleic Acid Chem.* **1968**, *1*, 219–223. Horton, D. *Pure Appl. Chem.* **1975**, *42*, 301–325.
(14) Magerlein, B. J.; Birkenmeyer, R. D.; Herr, R. R.; Kagan, F. *J. Am. Chem. Soc.* **1967**, *89*, 2459–2464.
(15) Chang, F. N.; Weisblum, B. *Biochemistry* **1967**, *6*, 836–843. Pestka, S. *Antimicrob. Agents Chemother.* **1974**, *6*, 474–480.
(16) Cundliffe, E. *Mol. Gen. Genet.* **1984**, in press.
(17) While the observed activity with quantamycin may be partly due to "residual" lincomycin-like features, the drastic alteration of the aglycone portion producing a novel structural entity should not be overlooked. This feature is presently under active study.
(18) The extent of inhibition of binding was 8–10% that of unlabeled lincomycin or erythromycin and 15–20% that of chloramphenicol at the same concentration. The lack of in vitro antibacterial activity and the weak inhibition of protein biosynthesis in cell-free systems (*Streptomyces lividans*)[16] may be due to a pharmacodynamic (e.g., partitioning) behavior.

Anomalous Rearrangement in the Hydrolysis of Diazotized *syn*-4-Amino[2.2](1,4)naphthalenoparacyclophane

Nobuo Mori* and Tamon Tachibana

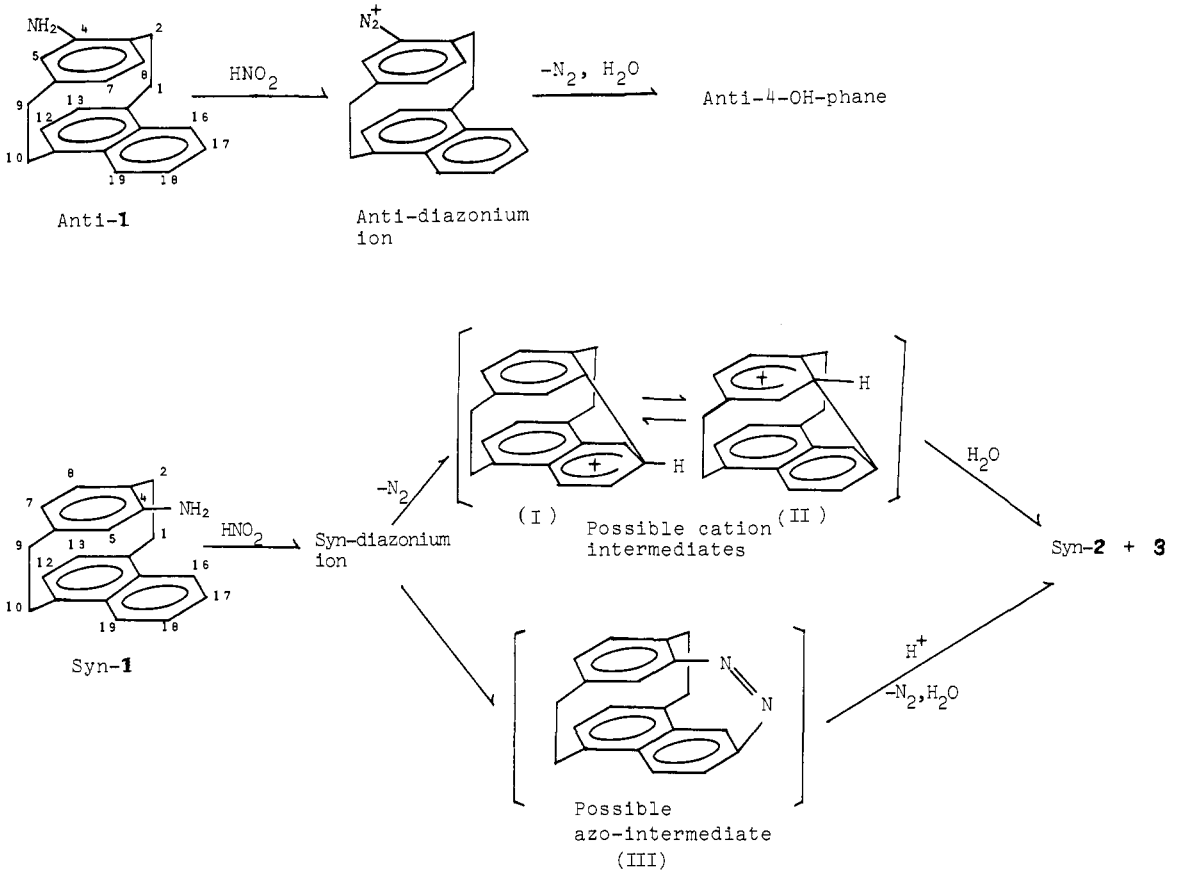
Department of Chemistry
Science University of Tokyo
Kagurazaka, Shinjuku-ku, Tokyo 162, Japan

Received April 23, 1984

The anomalous rates and products of electrophilic substitutions of layered aromatics such as [2.2]paracyclophanes have been generally accepted as being due to transannular electronic in-

0002-7863/84/1506-6115$01.50/0

Scheme I



teraction between the aromatic rings,[1] but it is not yet known whether such interaction exerts its influence on nucleophilic substitutions. We report here the anomalous rearrangement in the hydrolysis of the diazonium ion from *syn*-4-amino[2.2]-(1,4)naphthalenoparacyclophane (*syn*-**1**). No similar rearrangement occurred in the case of the isomeric *anti*-4-amino phane (*anti*-**1**) and is also unknown in the cyclophane chemistry (Scheme I).

Both *syn*- and *anti*-**1** were prepared by catalytic reduction of the corresponding *syn*- and *anti*-4-nitro phanes,[2] which had been obtained by the usual method[3] using 1,4-bis(sulfhydrylmethyl)-naphthalene and 2,6-bis(bromomethyl)nitrobenzene as starting materials.

Each amino phane was diazotized in dilute sulfuric acid with aqueous sodium nitrite, treated with urea, and then stirred at room temperature until the diazonium ion disappeared on TLC. The solution was extracted with ether, and the extract was subjected to preparative TLC on silica gel using ether–hexane (1:1). In this general manner, *anti*-**1** (88 mg) gave the corresponding *anti*-4-hydroxy phane (16 mg):[4] colorless needles, mp 135–138 °C (from benzene–hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.62 (m, 1 H), 2.82 (m, 1 H), 3.00 (m, 2 H), 3.23 (m, 2 H), 3.76 (m, 2 H), which are due to four methylenes, 4.40 (s, OH), 5.26 (dd, J = 7.8, 1.7 Hz, H-7), 5.46 (d, J = 7.6 Hz, H-8), 5.59 (d, J = 1.5 Hz, H-5), 6.69 (d, J = 7.3 Hz, H-12 or -13), 7.16 (d, J = 7.3 Hz, H-13 or -12), 7.38 (m, H-17 and -18), 7.66 (dd, J = 7.2, 2.3 Hz, H-16 or -19), 7.73 (dd, J = 7.2, 2.3 Hz, H-19 or -16); MS, *m/e* (relative intensity, fragment) 274 (45, M^+), 154 (100, $C_{12}H_{10}$), 120 (76, C_8H_8O); M_r by high-resolution MS 274.1349 (calcd for $C_{20}H_{18}O$ 274.1358); IR (dilute solution in CCl_4) ν_{OH} 3607 cm^{-1}.

On the other hand, the diazonium ion from *syn*-**1** (97 mg) gave suprisingly two hydroxy phanes:[4] one was the corresponding *syn*-4-hydroxy phane (*syn*-**2**) (16 mg), as expected: colorless needles, mp 164–168 °C (from benzene–hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.70 (m, 1 H), 2.81 (m, 1 H), 3.04 (m, 2 H), 3.20 (m, 1 H), 3.46 (m, 1 H), 3.87 (m, 2 H), which are due to four methylenes, 3.19 (s, OH), 4.87 (d, J = 1.5 Hz, H-5), 6.22 (dd, J = 7.8, 1.7 Hz, H-7), 6.41 (d, J = 7.8 Hz, H-8), 6.69 (d, J = 7.3 Hz, H-12 or -13), 6.73 (d, J = 7.1 Hz, H-13 or -12), 7.31 (m, H-18), 7.43 (m, H-17), 7.76 (d, J = 8.1 Hz, H-19), 8.06 (d, J = 8.3 Hz, H-16); MS, *m/e* (relative intensity, fragment) 274 (50, M^+), 154 (100, $C_{12}H_{10}$), 120 (74, C_8H_8O); M_r by high-resolution MS 274.1364; IR (dilute solution in CCl_4) ν_{OH} 3598 cm_2^{-1}. The other was the 17-hydroxy phane **3** (17 mg): colorless plates, mp 171–173 °C (from benzene–hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.88 (m, 2 H), 3.06 (m, 4 H), 3.68 (m, 2 H), which are due to four methylenes, 4.88 (s, OH), 5.63 (dd, J = 7.7, 1.7 Hz, H-7 or -8), 5.75 (dd, J = 7.6, 1.7 Hz, H-8 or -7), 6.42 (dd, J = 7.0, 1.7 Hz, H-4 or -5), 6.46 (dd, J = 6.7, 1.7 Hz, H-5 or -4), 6.63 (d, 7.3 Hz, H-12 or -13), 6.69 (d, J = 7.3 Hz, H-13 or -12), 6.99 (dd, J = 8.8, 2.7 Hz, H-18), 7.04 (d, J = 2.5 Hz, H-16), and 7.57 (d, J = 8.8 Hz, H-19); MS, *m/e* (relative intensity, fragment) 274 (23, M^+), 170 (100, $C_{12}H_{10}O$), 104 (18, C_8H_8); M_r by high-resolution MS 274.1352; IR (dilute solution in CCl_4) ν_{OH} 3608 cm^{-1}.

The above-described results for *anti*-**1** are similar to those for ordinary aromatic amines, but the results for *syn*-**1** are anomalous and cannot be explained by the well-known transannular interaction in [2.2]paracyclophanes since this interaction is operative between the facing pseudogeminal sites.[5] We have no convincing explanation, but at least two different mechanisms would be suggested, as shown in the scheme. One involves loss of N_2 and

(1) Cram, D. J.; Cram, J. M. *Acc. Chem. Res.* **1971**, *4*, 204.
(2) All new intermediates and products were confirmed as to their structure by ^{1}H NMR and MS.
(3) Sherrod, S. A.; da Costa, R. L.; Barnes, R. A.; Boekelheide, V. *J. Am. Chem. Soc.* **1974**, *96*, 1565.
(4) According to TLC and GC, the ether extract of the reaction mixture contained, apart from the hydroxy phane(s), minor amounts of several unidentified substances, which contained no OH group, as confirmed by IR spectroscopy.
(5) For example, see: Cram, D. J.; Wechter, W. J.; Kierstead, R. W. *J. Am. Chem. Soc.* **1958**, *80*, 3126.

formation of a bond between C-4 and C-17, followed by H migration. The resulting two cation intermediates I and II are in equimolar equilibrium and open with aqueous acid to give equal amounts of the 4- and the 17-hydroxy phane (*syn*-**2** and **3**). An alternative mechanism involves intramolecular diazo coupling to form a nonionic azo intermediate (III), which could undergo ring protonation on either ring with loss of N_2 and addition of H_2O to give equal amounts of *syn*-**2** and **3**. This mechanism does not involve the transannular H migration. In order to make a choice between these possible explanations, a further study is in progress.

Failure To Confirm Our Observations of Reactivity of Triose-P Isomerase, Methylglyoxal Synthase, and Ferricyanide with Triose-P Enediol

Irwin A. Rose

Institute for Cancer Research
Fox Chase Cancer Center
Philadelphia, Pennsylvania 19111

Received June 4, 1984

It has been reported[1] that the enzymes methylglyoxal synthase and triose-P isomerase make use of different stereoisomers of enediol-3-P. This conclusion was based on the finding that as the *cis*- and *trans*-enediol-Ps were generated in dilute alkaline solution from L-glyceraldehyde 3-phosphate one of them could be diverted from its rapid β-elimination to P_i and methylglyoxal by added triose-P isomerase and the other isomer by oxidation with 1 mM $K_3Fe(CN)_6$. It was reported that methylglyoxal synthase, an enzyme that normally converts dihydroxyacetonephosphate to P_i and methylglyoxal, restored the β-elimination reaction in competition with the ferricyanide but not the isomerase.

These observations cannot be reproduced: no effect of 2 μM triose-P isomerase on the rate of P_i formation from L-glyceraldehyde 3-phosphate can be shown. Furthermore, the effect of ferricyanide is now found to be much less than was reported. Table I compares the earlier and present results.

Evidence that the P_i is formed by β-elimination of $-OPO_3^{2-}$ from enediol-P derives from the observation (Table I) of the complete diversion of the intermediate to an alkaline-stable species by I_2. The failure of isomerase to trap any of the intermediate was surprising in view of our earlier reports that fresh isomerase can trap an intermediate generated by acid denaturation of an isomerase–DHAP equilibrium mixture.[2,3] However, recent experiments have failed to confirm these observations. Ferricyanide was expected to oxidize the enediol-P by analogy with its oxidation of dihydroxyacetone phosphate to phosphopyruvaldehyde with aldolase of yeast.[4] Evidently, unlike I_2, ferricyanide does not compete well with the β-elimination reaction. Moreover, since we are unable to confirm the high equilibrium concentration of enzyme-bound D-glyceraldehyde 3-phosphate, reported earlier,[2,3] a second paper[5] purporting to explain a D_2O effect on the partition of this bound substrate must also be retracted. A separate report indicating our inability to reproduce observations on complexes present on triose-P isomerase is to appear elsewhere.[6]

I deeply regret the misinformation resulting from these reports.

Table I. Trapping of Triose-P Enediol, Failure To Substantiate Our Earlier Report

addn	$[^{32}P]P_i$, % of total ^{32}P			
	Iyengar and Rose[1]	current expts		
none	62[a]	19.4[b]	41[c]	53[d]
TIM	24	19.1	39	
TIM + $K_3Fe(CN)_6$	8.4	14.1		
$K_3Fe(CN)_6$			28	49
I_2 (1.5 mM), KI (12 mM)				0

[a] From Table II of Iyengar and Rose.[1] The incubation mixture contained in 0.5 mL: Gly·NaOH (80 mM, pH 9.5), $[^{32}P]$-L-G3P (~5 pm, 4.5 × 10^5 cpm), NADH (0.4 mM), α-glycerol-phosphate dehydrogenase (7 units), noted additions of triose-P isomerase, TIM (2 μM), and $K_3Fe(CN)_6$ (0.8 mM). After 1 h at 25 °C the $[^{32}P_i]P_i$ formed was determined as the molybdate complex extracted into 2-butanol. [b] Same as *a*. [c] L-G3P increased to 0.1 mM, α-glycerol-phosphate dehydrogenase only present with TIM. [d] Same as *c*. With I_2/KI present the $[^{32}P]$-L-glyceraldehyde 3-phosphate disappeared as expected from the formation of P_i in the control.

Acknowledgment. This work was supported by United States Public Health Service Grants GM-20940 (IAR), CA-06927, and RR-05539 (ICR) and also by an appropriate from the Commonwealth of Pennsylvania.

(1) Iyengar, R.; Rose, I. A. *J. Am. Chem. Soc.* **1983**, *105*, 3301.
(2) Iyengar, R.; Rose, I. A. *Biochemistry* **1981**, *20*, 1223.
(3) Iyengar, R.; Rose, I. A. *Biochemistry* **1981**, *20*, 1229.
(4) Riordan, J. F.; Christen, P. *Biochemistry* **1969**, *8*, 2381.
(5) Rose, I. A.; Iyengar, R. *J. Am. Chem. Soc.* **1983**, *105*, 295.
(6) Rose, I. A. *Biochemistry*, submitted for publication.

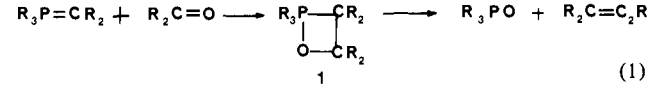
Theoretical Study of the Reactivity of Phosphonium and Sulfonium Ylides with Carbonyl Groups

F. Volatron[†] and O. Eisenstein*[‡]

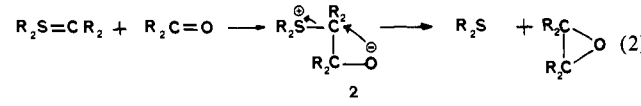
Laboratoire de Chimie Théorique
CNRS, UA 506 Bâtiment 490
Université de Paris-Sud, 91405 Orsay Cédex, France
Department of Chemistry, University of Michigan
Ann Arbor, Michigan, 48109
Institut of Molecular Science, Okazaki, Japan 444

Received September 23, 1983

The ylides form a class of nucleophilic reactants that have been extensively used in organic synthesis. The nature of the atom linked to the nucleophilic carbon is important in determining the course of the reaction. Phosphonium,[1] sulfonium,[2] and oxosulfonium[3] ylides react differently with carbonyl groups. While in the Wittig reaction an olefin and a phosphine oxide are the products of the reaction,[1] oxirane is exclusively formed in the reaction of sulfur ylides, as shown primarily by Corey and Chaykovsky.[2-4] Different mechanisms have been proposed to account for the different products: (a) a phosphonium ylide adds to the carbonyl group to form a four-membered ring, oxaphosphetane **1**, which decomposes into an olefin and a phosphine oxide (eq 1); (b) a sulfonium ylide adds to the carbonyl group to give



(1)



(2)

[†] Université de Paris-Sud.
[‡] University of Michigan and Institut of Molecular Science. Present address: Université de Paris-Sud.

(1) Wittig, G. *Pure Appl. Chem.* **1964**, *9*, 255.
(2) Trost, B. M.; Melvin, Jr., L. S. "Sulfur Ylides"; Academic Press: New York, 1975; p 51.
(3) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353. Johnson, C. R.; Schroeck, C. W.; Shanklin, J. R. *Ibid.* **1973**, *95*, 7424.
(4) For a recent review on this subject, see: Morris, D. G. *Surv. Prog. Chem.* **1983**, *10*, 189.

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