22°; $[\theta]_{281}$ $-85{,}000$; $[\theta]_{262}$ $+87{,}000$. Although less satisfactory, partial asymmetric catalytic hydrogenation of **4** could be accomplished using a soluble rhodium catalyst with chiral phosphine ligands. Hydrogenation of **4** (4 g) in the presence of (1,5-cyclooctadiene)-bis(*o*-anisylcyclohexylmethylphosphine)rhodium(I) tetrafluoroborate[9] and triethylamine (1 equiv) in methanol under 1 atm of hydrogen gave, by direct crystallization, 1.7 g of **5**: uv max (CH_3OH) 272 nm (ϵ 23,500); the CD spectrum ($[\theta]_{281}$ $-58{,}000$; $[\theta]_{262}$ $+60{,}000$) indicated this product to be *ca.* 68% optically pure. Unfortunately, the mother liquor exhibited no optical activity.

Two methods were devised for the transformation of **5** into **3a** without racemization.[10] Reaction of **5** with triethylamine and 0.95 equiv of benzoyl chloride at −15° afforded the enol benzoate **6a**[8] (70%)[11] as an oil: uv max (CH_3OH) 241 nm (ϵ 20,100); $[\alpha]^{24}\text{D}$ $+35.0°$ (*c* 2.0, $CHCl_3$). Reduction of **6a** by treatment with excess sodium bis(2-methoxyethoxy)aluminum hydride in tetrahydrofuran at −78°, followed by acidic hydrolysis (HOAc-H_2O 75:25, 37°, 26 hr), gave **3a** (60%): mp 60–61°; $[\alpha]^{24}\text{D}$ $+17.8°$ (*c* 0.49, CH_3OH); CD (*C* 1.37×10^{-4}, CH_3OH), 22°; $[\theta]_{321}$ -9900; uv max (CH_3OH) 222 nm (ϵ 8200). In the alternate approach **5** was alkylated by refluxing with isopropyl iodide and K_2CO_3 in acetone for 16 hr to give the isopropyl enol ether **6c**[8] (53% yield by direct crystallization):[12] mp 60–62°; $[\alpha]^{24}\text{D}$ $+35.1°$ (*c* 1.02, CH_3OH); uv max (CH_3OH) 259 nm (ϵ 20,600). Reduction with sodium bis(2-methoxyethoxy)aluminum hydride in tetrahydrofuran at −78°, followed by acidic hydrolysis (HCl–H_2O, pH 2.5, 25°, 1–2 hr), gave **3a** (60%): mp 60–61°; $[\alpha]^{24}\text{D}$ $+17.6°$ (*c* 0.71, CH_3OH); uv max (CH_3OH) 222 nm (ϵ 8400).

The following modified hydroalumination procedure[13] was employed for the synthesis of iodide **2a**. Triisobutylaluminum (1.5 equiv) was added to (3*S*)-1-octyn-3-ol[14] in heptane to complex the alcohol function; diisobutylaluminum hydride (1 equiv) was then added, and the reaction mixture was heated at 50–55° for 2 hr. After treatment with iodine in tetrahydrofuran at −50° and acidic work-up, the small amount of saturated alkyl iodide by-product was removed by heating (15 hr, 80–85°) with triethylamine. The crude iodide **2a** was purified by chromatography and vacuum distillation to afford a colorless liquid;[8,15] bp 70° (0.02 mm), $[\alpha]^{24}\text{D}$ $+9.52°$ (*c* 1.56, CH_3OH).

The iodo alcohol **2a**, protected as the *tert*-butyldimethylsilyl ether **2c**,[16] was treated with lithium powder in ether to give the vinyllithium reagent **2d** (>60% yield by the benzophenone method[4a]), which was added to 0.5 equiv of tri-*n*-butylphosphine-copper(I) iodide complex[17] to generate the cuprate **1b**. Protection of **3a** as the *tert*-butyldimethylsilyl ether **3c** and reaction with 1 equiv of cuprate **1b** (−15°, 0.5 hr) gave, after acidic hydrolysis of the protecting groups[16] and chromatography, PGE_1 methyl ester[18] (**7**, 65–70% yield based on **3a**). Hydrolysis of the methyl ester was effected by exposure of **7** to *Rhizopus oryzae* to yield PGE_1,[18] **8** (95% yield), mp 115–116°, $[\alpha]^{24}\text{D}$ $-54°$ (*c*, 0.7 THF). The synthetic product was found to be identical (infrared, nuclear magnetic resonance, and mass spectra) with an authentic specimen[19] of natural PGE_1.

This short synthetic route (four integral steps from trione ester **4**) leads to natural PGE_1 in overall yields of 15% (not optimized). Further refinements of this approach and its extension to PGE_2 are currently in progress.[20,21]

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[9] W. S. Knowles, M. J. Sabacky, and B. D. Vineyard, *Chem. Commun.*, 10 (1972). We thank Dr. W. S. Knowles of the Monsanto Co. for a generous supply of this catalyst.

[10] Attempts to convert **5** into the methyl enol ether **6b** by refluxing with 2,2-dimethoxypropane and an acid catalyst as described by R. Pappo, P. Collins, and C. Jung, *Ann. N. Y. Acad. Sci.*, 180, 64 (1971), gave only totally racemic material.

[11] The major by-product (20%) was 2-(6-carbomethoxyhexyl)-4(*R*)-benzoyloxycyclopentane-1,3-dione.

[12] Two isomeric isopropyl enol ethers were formed in the reaction, but only the desired isomer was crystalline.

[13] G. Zweifel and C. C. Whitney, *J. Amer. Chem. Soc.*, 89, 2753 (1967).

[14] J. Fried, C. Lin, M. Mehra, W. Kao, and P. Dalven, *Ann. N. Y. Acad. Sci.*, 180, 38 (1971).

[15] The yield from (3*S*)-1-octyn-3-ol varied from 40 to 50%. Unreacted octynol (25–30%) could be recovered by fractional distillation.

[16] E. J. Corey and D. J. Beames, *J. Amer. Chem. Soc.*, 94, 7210 (1972).

[17] G. B. Kaufman and L. A. Teter, *Inorg. Syn.*, 7, 9 (1963).

[18] No stereoisomeric products were detected, thus indicating (1) the exclusive addition of the cuprate **1b** in a trans fashion to the C-4 substituent of **3c** and (2) the optical purity of the synthetic intermediates.

[19] C. Takeguchi, E. Kohno, and C. J. Sih, *Biochemistry*, 10, 2372 (1971).

[20] This investigation was supported in part by research grants from the Wisconsin Alumni Research Foundation and the National Institutes of Health (AM-4874 and AM-9688).

[21] NOTE ADDED IN PROOF. The conversion of **5** to **3a** has now been attained in 60% yield by a modified procedure, thus raising the overall yield of *nat*-PGE_1 to *ca.* 30% from **4** without chromatographic purification of intermediates. This work will be reported in detail at a later date.

Charles J. Sih,* J. B. Heather, George P. Peruzzotti
Philip Price, Rattan Sood, Lan-Fong Hsu Lee
School of Pharmacy, University of Wisconsin
Madison, Wisconsin 53706

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Stable Free Radicals. XII. Direct and Sensitized Nitronyl Nitroxide Photochemistry in Aprotic Solvent

Sir:

During the course of studies of nitronyl nitroxides,[1] nitroxide radical impurities were encountered with unusually large nitrogen coupling, a^N = ~25 G (three esr lines). These impurities were found to be formed by room light during tlc separations. Although a competing photochemical reaction of the nitronyl nitroxide **1** predominated in water,[2] irradiation in aprotic solvents yielded the new nitroxide as the major radical product. We describe here the course of this reaction and outline preliminary experiments which document the expected ability of triplet sensitizers to effect doublet–doublet excitation of organic radicals.

Degassed pentane solutions 2.8×10^{-3} *M* in **1** were irradiated with >410-nm light at 20° with a 300-W projector. The combined solutions from five runs (150 mg of **1**) were evaporated at −78° and purified by tlc at 4° to give two new radicals. The less stable of these, **5**, had a well-resolved 51-line esr spectrum (C_6H_6), $a^{N\text{-}1} = 12.25$ G, $a^{N\text{-}2} = 1.72$ G, a^H (6 H) = 0.50 G, $g = 2.0046$, similar to that of the structurally related nitroxide **6**, $a^{N\text{-}1} = 11.61$ G, $a^{N\text{-}2} = 1.67$ G,

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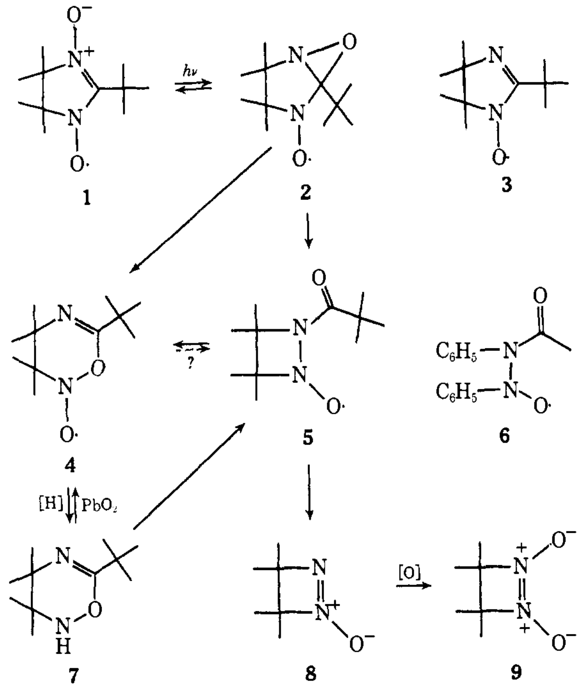
[1] E. F. Ullman, J. H. Osiecki, D. G. B. Boocock, and R. Darcy, *J. Amer. Chem. Soc.*, 94, 7049 (1972).

[2] L. Call and E. F. Ullman, *Tetrahedron Lett.*, in press.

$g = 2.0055$.[3] On standing for 15 min at 20°, **5** rearranged in part to its congener **4**, $a^{\mathrm{N\text{-}1}} = 25.1$ G, $g = 2.0056$ (C_6H_6), $\nu_{\mathrm{max}}^{\mathrm{CCl_4}}$ 1650 cm^{-1} (C═N). The large nitrogen coupling of **4** is highly characteristic of alkoxy nitroxides.[4]



Thermal decomposition of a mixture of **4** and **5** took place within a few minutes at 60° in benzene or 20° in ether. The mixture obtained from 150 mg of **1** in benzene contained 44 mg (49%) of the azo oxide **8**[5] [mp 170° (sublimes); $\nu_{\mathrm{max}}^{\mathrm{KBr}}$ 1540 cm^{-1} (N═N); $\lambda_{\mathrm{max}}^{\mathrm{CH_3OH}}$ 219 nm (ϵ 8200); nmr ($CDCl_3$) δ 1.47 (s, 6 H) and 1.52 (s, 6 H)], 15 mg (21%) of pivalamide, and small amounts of pivalic anhydride and the imino nitroxide **3**.[6] Positive identification of **8** was obtained by its conversion with *m*-chloroperbenzoic acid ($CHCl_3$, 25°, 6 weeks) to the known diazetine 1,2-dioxide (**9**).[7]

The esr spectra and thermal degradation products of **4** and **5** provide strong support for the proposed structures. Confirmatory evidence for these structures was obtained by catalytic hydrogenation (Pt and Pd/C) of a mixture of **4** and **5** at −70° in ether. The structure of the diamagnetic product **7**,[5] mp 98–100°, was deducible from its analytical and spectral data: nmr ($CDCl_3$) δ 1.02 (9 H), 1.33 (6 H), 1.52 (6 H), 5.0 (NH); $\nu_{\mathrm{max}}^{\mathrm{CHCl_3}}$ 3420 (NH), 1597 (C═N) cm^{-1}; *m/e* 198 (M^+), 84 ($C_6H_{12}^+$). Oxidation of **7** in benzene with excess lead dioxide for 2 min at 25° gave back **4** and **5**. This unexpected oxidation may involve initial attack by hydroxide on the imidate carbon followed by oxidation and cyclization of the resulting open chain hydroxylamine.

The origin of photoproducts **4** and **5** became apparent on irradiation of **1** in deoxygenated pentane at −70°. The esr spectrum of **1** disappeared more rapidly than at room temperature and its five-line pattern was replaced by a three-line spectrum, $a^{\mathrm{N}} = 12.10$ G, suggestive of a nitroxide flanked by electron withdrawing substituents. On warming to room temperature 68% of the original **1** was gradually formed with the simultaneous appearance of **4** and **5**. These observations strongly suggest that the primary photoproduct is the oxaziridine nitroxide **2**. The formation of **2** finds ample precedent in the photochemistry of nitrones and aza aromatic *N*-oxides[8] and its rearrangements to **4** and **5** can be viewed as orbital symmetry allowed ${}_{\sigma}2_{\mathrm{a}} + {}_{\sigma}2_{\mathrm{s}}$ rearrangements.

The quantum yields for the disappearance of **1** in benzene at 25° were $\phi_{578\ \mathrm{nm}} = 0.0098$ and $\phi_{313\ \mathrm{nm}} = 0.013$. The reaction could not be quenched by 1×10^{-3} *M* di-*tert*-butyl nitroxide (DTBN) or 2×10^{-3} *M* diazetine 1,2-dioxide (**9**) ($E_{\mathrm{T}} \approx 43$ kcal/mol),[7b] but sensitization of **1** (2×10^{-5} *M*) was observed by benzophenone ($\phi = 0.022$), fluorenone ($\phi = 0.008$), pyrene ($\phi = 0.0041$), and benzanthrone ($\phi = 0.004$, $E_{\mathrm{T}} = 47.0$ kcal/mol).[9] Anthracene ($E_{\mathrm{T}} = 42.4$ kcal/mol) sensitization was, however, very inefficient. Photoreaction of a solution of **1** contained in a tube immersed in a separate anthracene solution demonstrated that this sensitization was due primarily to trivial energy transfer. The relative ratios for the initial rates of appearance of **4** to the rates of disappearance of **1** demonstrate that the reaction proceeds in somewhat lower yields when sensitized: direct irradiation (1), benzophenone ($\gtrsim 0.08$), fluorenone ($\gtrsim 0.77$), pyrene ($\gtrsim 0.15$), benzanthrone ($\gtrsim 0.82$).

Since the lowest energy doublet–doublet transition of **1** lies between 49.4 (structureless n,π^* maximum at 579 nm) and ~44 kcal/mol (absorption onset ~650 nm), the observed sensitizer triplet energy dependence is consistent with the spin-allowed excitation process (1). However the spin-allowed, doublet–quartet sensitization process (2) must also be considered. The more efficient disappearance of **1** by benzophenone sensitization than by direct irradiation would support the latter process were it not that product formation is actually *less* efficient. Moreover, the major pathway for benzophenone sensitized disappearance of **1** does not even involve energy transfer from benzophenone triplets, since the calculated energy transfer rate for this process would be impossibly high

$$ {}^3S^* + {}^2A_0 \longrightarrow {}^1S_0 + {}^2A^* \tag{1} $$

$$ {}^3S^* + {}^2A_0 \longrightarrow {}^1S_0 + {}^4A^* \tag{2} $$

$$ {}^3S^* + {}^2A_0 \longrightarrow {}^1S_0 + {}^2A_0 \tag{3} $$

(3.6×10^{11} l. mol^{-1} sec^{-1} estimated from the rate of disappearance of **1** as a function of concentration). The predominant reaction of **1** on irradiation with benzophenone must therefore involve a longer lived intermediate, possibly benzophenone ketyl, and postulation of process 2 is unnecessary.

Inefficiency in sensitized process 1 is expected because of competition with the allowed process 3.[10] The reason that process 1 is predominant in sensitiza-

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(3) (a) G. Binsch, E. Merz, and C. Rüchardt, *Chem. Ber.*, **100**, 247 (1967); (b) G. R. Chalfont and M. J. Perkins, *J. Amer. Chem. Soc.*, **89**, 3054 (1967).

(4) A. Mackor, Th. A. J. W. Wajer, and Th. J. de Boer, *Tetrahedron Lett.*, 385 (1967).

(5) Satisfactory elemental and molecular weight analyses.

(6) E. F. Ullman, L. Call, and J. H. Osiecki, *J. Org. Chem.*, **35**, 3623 (1970).

(7) (a) P. Singh, D. G. B. Boocock, and E. F. Ullman, *Tetrahedron Lett.*, 3935 (1971); (b) E. F. Ullman and P. Singh, *J. Amer. Chem. Soc.*, **94**, 5077 (1972).

(8) G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, 70, 23 (1970).

(9) The observation of **2** at −70° confirmed that a similar reaction pathway was followed.

(10) G. J. Hoytink, *Accounts Chem. Res.*, **4**, 114 (1969).

tion of **1**, particularly by fluorenone, whereas only process 3 is observed in triplet quenching by DTBN,[11] is uncertain. Possibly energy transfer to **1** is favored by better steric accessibility. On the other hand, failure to observe process 2 was predictable. Unlike nitric oxide which is excited to a quartet by sensitization,[12] **1** lacks the singly occupied pair of degenerate orbitals present in nitric oxide and must therefore have a relatively high energy quartet state.

(11) R. E. Schwerzel and R. A. Caldwell, *J. Amer. Chem. Soc.*, in press. We thank these authors for providing a copy of their manuscript prior to publication.

(12) J. Heicklen and N. Cohen, *Advan. Photochem.*, 5, 268 (1968).

(13) Syva Postdoctoral Fellow, 1969–1970.

(14) Syva Postdoctoral Fellow, 1970–1972.

Edwin F. Ullman,* Ludwig Call,[13] S. S. Tseng[14]
Contribution No. 46, Syva Research Institute
Palo Alto, California 94304

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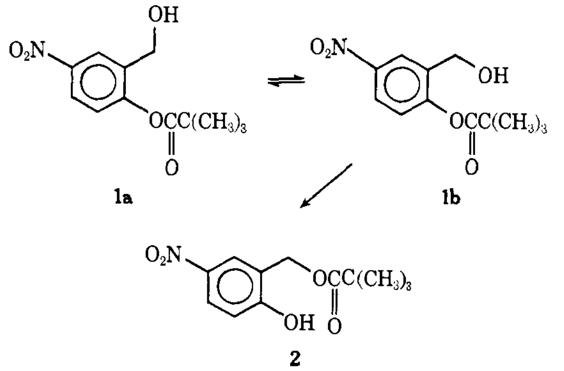
Orientational Catalysis by Cyclohexaamylose

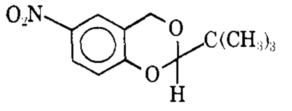
Sir:

We wish to report that inclusion of 2-hydroxymethyl-4-nitrophenyl trimethylacetate (**1**) within the cavity of cyclohexaamylose produces a sixfold acceleration in the rate of conversion of **1** to **2**. In contrast, formation of the inclusion complex of **1** with cycloheptaamylose decelerates the rate of this intramolecular transesterification by a factor of 5. We suggest that these cycloamyloses, by virtue of their ability to include organic materials within rigid binding sites,[1] perturb the equilibrium between orientational conformers **1a** and **1b**, and, thereby, force the reacting groups of **1** to assume either a mutually favorable or unfavorable orientation with respect to the activated complex. We further suggest that binding forces between cycloamylose and **1** are utilized to effect these orientational restrictions.



Migration of the trimethylacetyl group[2] can be conveniently followed by measuring the increase in uv absorption at 349 nm, the isosbestic wavelength for ionization of **2**. In aqueous solutions of dilute buffers containing from 0 to 0.02 *M* cycloamylose, the acyl migration obeys a first-order rate law. The only product of the migration is **2**, as indicated by the identity of the spectra of the reaction product and analytically pure **2**.[3] Values of k_2, the maximal first-order rate constant for conversion of **1** to **2** in the presence of a saturating amount of cycloamylose, and K_d, the dissociation constant of the cycloamylose-**1** inclusion complex, have been calculated from the dependence of k_{obsd} on cycloamylose concentration.[1] At 25.2°, within the pH range 4.95–7.60, the rate of conversion of **1** to **2** displays a linear dependence on hydroxide ion activity: in the absence of added cycloamylose, $k_{obsd} = [(3.41 \pm 0.14) \times 10^5]a_{OH}$; in the presence of cyclohexaamylose, $k_2 = [(25 \pm 10) \times 10^5]a_{OH}$; and, in the presence of cycloheptaamylose, $k_2 = [(0.64 \pm 0.05) \times 10^5]a_{OH}$. Unlike the maximal rate constants, the dissociation constants of the inclusion complexes of **1** with these two cycloamyloses are pH independent: at 25.2°, $K_d = (4.78 \pm 0.25) \times 10^{-2}$ *M* for the cyclohexaamylose complex of **1** and $(9.60 \pm 0.75) \times 10^{-4}$ *M* for the cycloheptaamylose complex of **1**. At pH 6.81, in the absence of added cycloamylose, the temperature dependence of k_{obsd} implies $\Delta H^{\neq} = 12.9 \pm 0.2$ kcal/mol and $\Delta S^{\neq} = -22.6 \pm 0.3$ gibbs; in the presence of cyclohexaamylose, the temperature dependence of k_2 implies $\Delta H^{\neq} = 13.1 \pm 0.5$ kcal/mol and $\Delta S^{\neq} = -18.3 \pm 1.8$ gibbs.

The suggestion that catalysis by cyclohexaamylose arises from the selection of a "reactive" ground state orientational conformer of **1** in a prior equilibrium binding process is supported by the following observations. (1) The reversal in the effects of cyclohexaamylose and cycloheptaamylose, which differ only in the sizes of their binding sites,[4] is indicative of a mechanism in which reactivity is determined by the geometry of the fit of the reactant to the binding site. (2) Orientational restriction in the ground state of **1** is equivalent to the freezing of an internal rotational degree of freedom, a process which involves an entropy change of about 4.5 gibbs.[5] The cyclohexaamylose-induced rate acceleration is entirely entropic in origin with $\Delta\Delta S^{\neq} = 4.3 \pm 2.0$ gibbs. (3) The inclusion complex of cyclohexaamylose with **3**[6] ($K_d = (1.22 \pm 0.15) \times 10^{-2}$ *M*) is more stable than the cyclohexaamylose-**1** inclusion complex by a factor which agrees, within experimental error, with the observed rate acceleration. Hence, to the extent that **3** accurately simulates the activated complex for the conversion of **1** to **2**,[7] the driving force for catalysis can be attributed



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[1] D. W. Griffiths and M. L. Bender, *Advan. Catal. Relat. Subj.*, 23, 209 (1973).

[2] A detailed investigation of this intramolecular transesterification is in progress; several similar transacylations have been previously described: M. Wakselman, *C. R. Acad. Sci., Ser. C*, **262**, 770 (1966); B. Helferich and H. Liesen, *Chem. Ber.*, **83**, 567 (1950); B. Helferich and H.-O. Muller von Blumencron, *ibid.*, **86**, 1058 (1953); W. Korytnyk and B. Paul, *J. Org. Chem.*, **32**, 3791 (1967).

[3] Mp 140–141°; nmr (acetone-d_6) δ 1.10 (s, 9), 5.21 (s, 2), 7.05–8.25 (m, 3). *Anal.* Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.73; H, 6.01; N, 5.49.

[4] Whereas the diameter of the cyclohexaamylose cavity is 4.5 Å, the diameter of the cycloheptaamylose cavity is more than 2 Å larger.[1]

[5] M. I. Page and W. P. Jencks, *Proc. Nat. Acad. Sci. U. S.*, **68**, 1678 (1971).

[6] Mp 82–83°; nmr (acetone-d_6) δ 1.05 (s, 9), 4.87 (s, 1), 5.07 (s, 2), 6.83–8.07 (m, 3). *Anal.* Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.89; H, 6.43; N, 5.94.

[7] A large difference between the values of K_d for the two enantiomers of **3** is unlikely since previous investigations of the association of the cycloamyloses with chiral materials have failed to reveal a significant dependence of K_d on the chirality of the substrate: H. P. Benschop and G. R. Van den Berg, *Chem. Commun.*, 1431 (1970); K. Flohr, R. M. Paton, and E. T. Kaiser, *ibid.*, 1621 (1971); C. van Hooidonk and C. C. Groos, *Recl. Trav. Chim. Pays-Bas*, **89**, 845 (1970).