to δ 6.62 in CD_3OD). The bromine atoms were assigned to the pyrrole ring of **5**, which is related to oroidin (**1**) by oxidative cyclization. The ^{13}C NMR spectrum contained 11 signals including key resonances occurring at δ 161.5 (amide carbonyl), 147.0, 126.0, and 111.6 (2-aminoimidazole ring) and was entirely consistent with this structural assignment.

Experimental Section

Extraction and Chromatography. The specimen was collected by hand (Scuba, −15 m) at Ponape, Carolina Islands. The sponge (76.1 g dry weight) was soaked in methanol at ca. 0 °C for ca. 6 months, after which the solvent was evaporated to leave of an amorphous light orange solid (18.7 g). This residue was sequentially extracted with 2 × 400 mL portions of hexane. CH_2Cl_2, EtOAc, and methanol. The methanol soluble material was chromatographed on Sephadex LH-20 using methanol as the eluant. The fractions were monitored by TLC on silica using a CH_3OH/CH_2Cl_2/concentrated NH_4OH (6:3:1) solvent system. Rechromatography of the active fractions (antimicrobial assay) gave sceptrin (**4**, 144 mg, 0.19% dry weight) and stevensine (**5**, 80 mg, 0.10% dry weight) as amorphous orange solids.

Stevensine (5): IR (film) 3400, 1650, 1450 cm^{-1}; UV (CH_3OH) 258 (ε 11 600), 220 (ε 17 200) nm; ^1H NMR (360 MHz, Me_2SO-d_6) δ 8.21 (br t, 1 H, amide N*H*), 7.43 (s, 1 H, pyrrole N–H), 6.90 (s, 1 H, H-10), 6.21 (t, J = 7 Hz, 1 H, H-7), 3.48 (br m, 2 H, $-CH_2-$); (CD_3OD) δ 6.81 (s, 1 H, H-10), 6.27 (t, J = 7 Hz, 1 H, H-7), 3.50 (d, J = 7 Hz, 2 H, $-CH_2-$); ^{13}C NMR (50 MHz, Me_2SO-d_6) δ 161.5 (s, C-5), 147.0 (s, C-11), 128.5 (s, C-4), 126.0 (s, C-9), 125.9 (d, C-7), 124.6 (s, C-3), 120.9 (s, C-8), 111.6 (d, C-10), 107.6 (s, C-1), 97.7 (s, C-2), 37.2 (t, C-6); high-resolution fast atom bombardment mass spectrum, obsd m/z 385.9248, $C_{11}H_{10}Br_2N_5O$ requires 385.9252.

Acknowledgment. This research was supported by grants from the National Institutes of Health (AI-11969 and CA07458 to K.F.A.).

(1) Christophersen, C. In "The Alkaloids"; Brossi, A., Ed.; Academic Press: Orlando, FL, 1985; Vol. 24.
(2) Fenical, W. H. In "Alkaloids, Chemical and Biological Perspectives"; Pelletier, S. W., Ed.; Wiley: New York; Vol. 4, in press.
(3) Forenza, S.; Minale, L.; Riccio, R.; Fattorusso, E. *Chem. Commun.* **1971**, 1129. Garcia, E. E.; Benjamin, L. E.; Fryer, R. I. *J. Chem. Soc., Chem. Commun.* **1973**, 78. The X-ray structure of oroidin is reported in ref 8.
(4) Sharma, G. M.; Buyer, J. S.; Pomerantz, M. W. *J. Chem. Soc., Chem. Commun.* **1980**, 435.
(5) Cimino, G.; De Rosa, S.; De Stefano, S.; Mazzarella, L.; Puliti, R.; Sodano, G. *Tetrahedron Lett.* **1982**, *23*, 767.
(6) Kitagawa, I.; Kobayashi, M.; Kitanaka, K.; Kido, M.; Kyogoku, Y., *Chem. Pharm. Bull.* **1983**, *31*, 2321.
(7) Attempts to identify this sponge were frustrated by the poor physical condition of the preserved specimens. The sponge is not a species of *Agelas* since the only spicule type observed were styles.
(8) Walker, R. P.; Faulkner, D. J.; Van Engen, D.; Clardy, J. *J. Am. Chem. Soc.* **1981**, *103*, 6772.

Organic Disulfides and Related Substances. 44. Preparation and Characterization of 1-Adamantyl Hydrodisulfide as a Stable Prototype of the Series[1a]

Norman E. Heimer*

Department of Chemistry, University of Mississippi, University, Mississippi 38677

Lamar Field and John A. Waites[1b]

Department of Chemistry and Center in Molecular Toxicology, Vanderbilt University, Nashville, Tennessee 37235

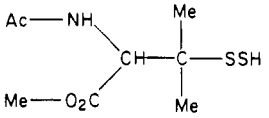
Received April 8, 1985

Two recent papers have described the preparation and characterization of hydrodisulfide derivatives of penicillamine.[2,3] Reasons were outlined in these papers for interest in hydrodisulfides as a class and, in particular, for seeking especially stable hydrodisulfides. The present paper reports the preparation and characterization of 1-adamantyl hydrodisulfide and compares the shelf life with that reported for the penicillamine derivatives **1**[2] and **2**.[3]

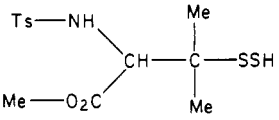
Table I. ^{13}C Chemical Shifts (δ) of 1-Adamantane Derivatives[a]

compd	C-1	C-2	C-4	C-3
AdSH	47.56	43.18	35.79	30.11
AdSSAd	47.32	43.10	36.20	30.11
AdCl	68.74	47.72	35.63	31.73
AdSCl	51.05	40.74	36.04	29.46
AdSSAc	50.16	42.11	35.80	29.79
AdSSH	46.73	41.56	36.16	29.82
AdSS-2,4-DNP	52.98	42.77	35.84	30.04
AdSSSSAd	50.73	42.93	36.13	30.03

[a] Ad = 1-adamantyl (tricyclo[3.3.1.1]decan-1-yl).

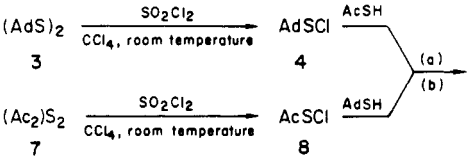


1

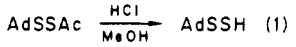


2

The preparation of 1-adamantyl hydrodisulfide was achieved by acid-catalyzed methanolysis[4] of the acetyl disulfide derivative **5** (eq 1). The required acetyl disulfide derivative **5** should be available by two routes, by the

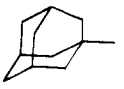


3 4 7 8



5 6

Ad =



reaction of adamantanesulfenyl chloride with thioacetic acid (eq 1a) or by the reaction of 1-oxoethanesulfenyl chloride with 1-adamantanethiol (eq 1b). We examined both of these routes and found the second more satisfactory.

Attempts to convert 1-adamantyl disulfide (**3**) to sulfenyl chloride **4** followed by reaction of the sulfenyl chloride with thioacetic acid gave product mixtures from which it was difficult to separate the desired product. Efforts were made to improve the preparation of **4** by a study of the chlorinolysis of **3** by both Cl_2 and SO_2Cl_2, since it had been reported earlier that the chlorinolysis of another tertiary disulfide, *tert*-butyl disulfide, gave different products at −20 and 45 °C.[5] Initially, a GC method was used to assess S–S vs. S–C cleavage under various conditions by determining the amount of the S–C bond cleavage product, 1-chloroadamantane. However, we found that the GC method could not be used because 1-adamantanesulfenyl

(1) (a) Paper 43: Field, L.; Bowen, G. T. *J. Org. Chem.* **1981**, *46*, 2771–2775. (b) Stephen Harris Cook Memorial Fellow, Summer, 1983.
(2) Heimer, N. E.; Field, L.; Neal, R. A. *J. Org. Chem.* **1981**, *46*, 1374–1377.
(3) Heimer, N. E.; Field, L. *J. Org. Chem.* **1984**, *49*, 1446–1449.
(4) Field, L. In "Organic Chemistry of Sulfur"; Oae, S., Ed.; Plenum Press: New York, 1977; pp 307–309.
(5) Schulze, W. A.; Short, G. H.; Crouch, W. W. *Ind. Eng. Chem.* **1950**, *42*, 916–921.

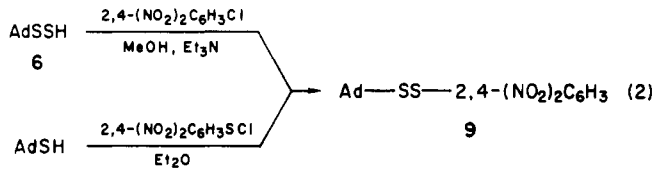
0022-3263/85/1950-4164$01.50/0 © 1985 American Chemical Society

chloride decomposed under the conditions of the GC analysis to give 1-chloroadamantane. The product distribution in the chlorinolysis reaction could be determined by examination of the ^{13}C NMR spectrum of the reaction mixture, since the chemical shift of C-1 and to a lesser extent the chemical shifts of the other carbon atoms were characteristic of the products present (Table I). By measurement of the intensities of the ^{13}C NMR peaks of the product mixture, it was determined that chlorinolysis of **3** with Cl_2 in CCl_4 consistently gave a product mixture that consisted of unreacted disulfide, sulfenyl chloride, and 1-chloroadamantane. The maximum yield of **4** was 70% at room temperature but was nearly quantitative at −24 °C. Chlorinolysis by sulfuryl chloride at room temperature, on the other hand, provided the desired sulfenyl chloride as the only product of the reaction (along with SO_2). Solutions of sulfenyl chloride **4** decomposed at room temperature to 1-chloroadamantane during time intervals ranging from several minutes to several hours; for example, one preparation was 50% converted to 1-chloroadamantane in 45 min while another showed only 25% conversion in 1 h. Therefore, solutions of the 1-adamantanesulfenyl chloride should be used soon after preparation to provide products that are essentially free of 1-chloroadamantane.

An alternate route, the reaction of acetylsulfenyl chloride with 1-adamanthiol (eq 1b), also provided the unsymmetrical disulfide **5** in good yield and was the more convenient method. As determined by ^1H NMR, the reaction of sulfuryl chloride with diacetyl sulfide required 0.5 h at room temperature for complete conversion to the sulfenyl chloride, whereas the reaction of 1-adamantyl disulfide with sulfuryl chloride is complete in less than 2 min. The product mixture from the chlorinolysis of **7** can be used without distillation to remove acetyl chloride, since, under the reaction conditions, acetyl chloride does not react with 1-adamantanethiol.

Crude acetyl adamantyl disulfide (**5**) from the reaction of 1-oxoethanesulfenyl chloride with 1-adamantanethiol was obtained from the reaction mixture as a mobile liquid that crystallized upon standing. Purified **5** then was converted to hydrodisulfide **6** in 92% yield by acid-catalyzed methanolysis. Molecular distillation of **6** at a bath temperature of 45 °C and a pressure of 50 mtorr gave **6** as a colorless liquid with only a mildly disagreeable odor that had a melting point below 25 °C. The ^1H NMR spectrum of **6** showed a single line at δ 2.58, which was lost upon shaking with D_2O, for the proton on sulfur with a relative area of 1 when compared to that of the 15 hydrogens of the adamantane nucleus. The ^{13}C NMR spectrum (Table I) showed four lines consistent with a 1-substituted adamantane. A solution of purified **6** in $CDCl_3$ at room temperature in a tightly capped NMR sample tube was analyzed by ^{13}C NMR and showed no decomposition for 3 weeks. Titration of a sample of freshly distilled **6** with standard I_2 resulted in the consumption of 98% of the theoretical amount of I_2, and a sample of neat **6** that had been stored in a sealed ampule under ambient conditions for 4 months consumed 95% of the theoretically required volume of I_2 and showed no significant change in the ^{13}C NMR. Derivatization of **6** was accomplished by conversion to the 2,4-dinitrophenyl disulfide derivative by reaction with 2,4-dinitrochlorobenzene and Et_3N in MeOH. The same dinitrophenyl disulfide derivative also was prepared from 2,4-dinitrobenzenesulfenyl chloride and 1-adamantanethiol (eq 2).

From the data presented here, it is apparent that 1-adamantyl hydrodisulfide (**6**) decomposes more slowly than



either of the previously studied penicillamine derivatives, one of which completely decomposed in less than 18 h when stored as a neat sample at −20 °C (**1**) and the other which was 40% decomposed after being stored at room temperature for 18 h (**2**). In earlier work it was found that *tert*-butyl hydrodisulfide[6] is a distillable material, which is presumably comparable in stability to **6**. Compounds **1**,[2] **2**,[3] and 2-hydroxyethyl hydrodisulfide[7] have been reported to be observable but not with a long enough half-life to allow for acceptable combustion analysis. It seems therefore that the presence of the OH or NH functional group in the molecule near the hydrodisulfide functional group results in the hydrodisulfide being more labile than in the present simple tertiary derivative. Adamantyl hydrodisulfide thus promises to be a valuable tool for investigation of the little known chemistry of hydrodisulfides, since it is rather easily prepared and can be stored without extensive decomposition for long periods of time.

Experimental Section

Melting points were determined by using a Thomas-Hoover stirred-liquid apparatus and are corrected. NMR spectra were recorded on either a JEOL FX-60Q or 90Q spectrometer in $CDCl_3$ using Me_4Si as the internal standard, and chemical shifts are reported in parts per million (δ). IR spectra were obtained on KBr pellets or on $CHCl_3$ solution with a Perkin-Elmer Model 521 spectrophotometer. GC/MS analyses were done with a Hewlett-Packard Model 5985 system using a 50-m capillary column. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Moist extracts were dried with $MgSO_4$ or Na_2SO_4. Thioacetic acid, 2,4-dinitrobenzenesulfenyl chloride, 1-bromoadamantane, and 1-chloroadamantane were purchased from Aldrich Chemical Co. Diacetyl sulfide,[8] 1-adamantanethiol,[9] and 1-adamantyl disulfide[10] were prepared by published procedures.

Acetyl Adamantyl Disulfide (5). A solution of 8.9 g (66 mmol) of SO_2Cl_2 in 50 mL of CCl_4 was added rapidly to a solution of 7.8 g (66 mmol) of diacetyl sulfide in 10 mL of CCl_4 at ca 25 °C, and the resulting yellow solution was allowed to stand for 0.5 h. [The progress of the chlorinolysis reaction can be followed conveniently by ^1H NMR since the spectrum of diacetyl sulfide (δ 2.52) is replaced by that of acetyl chloride (δ 2.68) and acetyl sulfenyl chloride (δ 2.43)]. The solution of 1-oxoethanesulfenyl chloride then was poured slowly into a solution of 10.0 g (59 mmol) 1-adamantanethiol until the yellow color of the sulfenyl chloride just persisted (HCl is evolved). The yellow solution was allowed to stand for 10 min, and then a small crystal of 1-adamantanethiol was added to just remove the yellow color of the excess sulfenyl chloride. Removal of the solvent under reduced pressure gave 15.4 g (96%) of crude **5**, n^{27}_D 1.5747. An 8-g portion of crude **5** was dissolved in MeOH (70 mL) and the insoluble portion discarded. The MeOH was removed under reduced pressure, and the resulting oil was dissolved in Et_2O, washed with 5% $NaHCO_3$, and dried. Removal of the Et_2O under reduced pressure yielded **5** as an oil that crystallized upon standing. Four recrystallizations from MeOH (ice bath) provided **5** with a constant mp of 53.5–54.5 °C; mass spectrum, 242 ($M^{+\cdot}$) [calcd 242], 135 (base peak).

Anal. Calcd for $C_{12}H_{18}SO_2$: C, 59.46; H, 7.48. Found: C, 59.24; H, 7.29.

(6) Aycock, D. F.; Jurch, G. R. *J. Org. Chem.* **1979**, *44*, 569–572.
(7) Tsurugi, J.; Abe, Y.; Kawamura, S. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1890–1892.
(8) Böhme, H. In "Methoden der Organischen Chemie (Houben-Weyl)"; Müller, E., Ed.; Georg Thieme Verlag: Stuttgart, Vol. 9, p 53.
(9) Khuller, K. K.; Bauer, L. *J. Org. Chem.* **1971**, *36*, 3038–3040.
(10) Jorgensen, F. S.; Snyder, J. P. *J. Org. Chem.* **1980**, *45*, 1015–1020.

1-Adamantyl Hydrodisulfide (6). A 30-mL portion of 2.4 M HCl in MeOH was added to a solution of 2.1 g (8.7 mmol) of acetyl adamantyl disulfide (5) in 60 mL of MeOH, and the total volume then was brought to 100 mL with MeOH. The resulting solution was allowed to stand at room temperature for 16 h. The MeOH was removed under reduced pressure, the residue dissolved in hexane, washed four times with water, and dried. The hexane was removed under reduced pressure, yielding 1.6 g (92%) of crude 1-adamantyl hydrodisulfide (6). Molecular distillation at 50 mtorr with a bath temperature of 45 °C gave 1.0 g of 6 (58%) as a colorless liquid: n^{27}_D 1.5824; mp below 25 °C; mass spectrum (direct probe), 200 ($M^{+\cdot}$) [calcd 200]; 135 (base peak); IR 2500 cm^{-1} (S-H); ^1H NMR δ 2.58 (1 H, s, H-S), 1.7-1.0 (15 H, H of adamantyl group); ^{13}C NMR δ 46.73 (s, C-1), 41.56 (t, C-2), 36.16 (t, C-4), 29.82 (d, C-3). Titration of a 28.3-mg portion of 6 with 0.100 N I_2 required 1.45 mL of titrant; equiv wt 195 (calcd 200; 98% purity).

Anal. Calcd for $C_{10}H_{16}S_2$: C, 59.95; H, 8.05. Found: C, 59.77; H, 8.32.

1-Adamantyl 2,4-Dinitrophenyl Disulfide (9). A solution of 0.236 g (1.00 mmol) of 2,4-dinitrobenzenesulfenyl chloride in Et_2O was added to a solution of 0.168 g (1.00 mmol) of 1-adamantanethiol in Et_2O. Crystals of 9 precipitated from the reaction mixture, and three recrystallizations from MeOH gave 0.23 g (63% yield) of 9 that had a constant melting point of 162-163 °C.

Anal. Calcd for $C_{16}H_{18}N_2O_4S_2$: C, 52.44; H, 4.95; S, 17.50. Found: C, 52.57; H, 5.03; S, 17.61.

The same material (9) could be obtained from the reaction of crude samples of 6 with 2,4-dinitrochlorobenzene in methanol and a drop of Et_3N in yields of ca. 50%, mp 161-162 °C. The identity of the materials was determined by identity of the IR spectra, melting points, and an undepressed mixture melting point.

NMR Studies of Chlorinolysis Reactions. To solutions of 1-adamantyl disulfide (6; 0.17 g, 0.50 mmol in 1.5 mL of $CDCl_3$) was added 0.5 mL of 1.0 M solutions of either Cl_2 or SO_2Cl_2 in CCl_4 in one portion. Solutions of Cl_2 were prepared by bubbling Cl_2 gas into CCl_4 at ca. 0 °C and were analyzed by iodometric titration. Solutions of SO_2Cl_2 in CCl_4 were prepared by dissolving the required amount of freshly distilled SO_2Cl_2 in dry CCl_4 and were not analyzed. The resulting solutions then were subjected to either analysis by GC or by NMR.

Acknowledgment. This investigation was supported by PHS Grant CA 30321 awarded by the National Cancer Institute, DHHS.

Heteroatom Cyclopentene Annulation. Synthesis of Guaiane Ring System

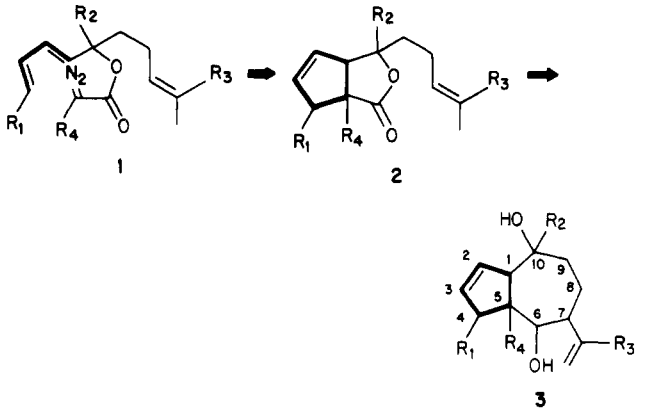
Tomas Hudlicky,*[1] Serengulam V. Govindan, and James O. Frazier

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

Received January 29, 1985

While the intramolecular cyclopentene annulation of dienic diazo ketones has proven very useful in the synthesis of cyclopentanoid terpenes,[2,3] it has not been possible to extend this process to the preparation of bicyclo[5.3.0]-decanones due to the interfering *inter*molecular reactions of the conformationally mobile precursory diazo ketones.[4]

Scheme I



R_1 = H or CH_3; R_2 = H or CH_3; R_3 = H or CH_3 or CO_2R; R_4 = H or CH_3 or CO_2R

In order to establish this methodology as a tool in the synthesis of perhydroazulene sesquiterpenes of both guaiane or pseudoguaiane types, we sought a reaction sequence that would bypass the formation of a seven-membered ring during the cyclopropanation and, at the same time, allow a facile elaboration of any intermediate to the required bicyclo[5.3.0]decane ring system (Scheme I).

A solution to this problem was envisioned in the combination of the [4 + 1] annulation methodology which incorporates a heteroatom tether (e.g., 1 → 2) with the ene reaction or an equivalent closure[5] between an aldehyde generated from 2 and an appropriate olefinic appendage. This sequence, described herein, proceeds with reasonable steric control of all six chiral centers in 3: the ring junction, controlled by the fusion of two five-membered rings, remains cis; the stereochemistry at C6-C7 is dictated by the transition state of the olefin-aldehyde closure; the C4 center is controlled during the cyclopentene formation *or* by isomerization of the olefin, and the C10 center is controlled by oxidative manipulations at a more advanced stage of synthesis. Additionally, based on the selection of substituents in 1 (R_1 or R_4), the *regiochemistry* of 3 and thus the structural type of either guaianes or pseudoguaianes can be entered selectively (Scheme I).

Following the completion of a model study dealing with the synthesis of simple bicyclic lactones of type 2,[6] we prepared diazo ester 6 in three steps from readily available sorbyl aldehyde and the Grignard reagent derived from 4-methylpent-3-enyl bromide,[7] followed by esterification and diazo transfer reaction[8] (Scheme II). The exposure of 6 to $CuSO_4$ in refluxing benzene gave cyclopropanes **7a** and **7b** (1.7:1) in excellent yield after chromatography. The major isomer was subjected to thermolysis (Vycor, 600 °C) and subsequent decarbomethoxylation to give **9a** and **9b** (1.7:1). It should be noted that both cyclopropanes **7a** and **7b** can *eventually* be used in the synthesis of the same target molecule since the incipient C10 stereocenter will

(1) Fellow of the Alfred P. Sloan Foundation, 1981-1985; Research Career Development Award recipient, 1984-1989 (NIH, AI-00564).
(2) Hudlicky, T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1980**, *102*, 6351.
(3) Hudlicky, T.; Short, R. P.; Ranu, B. C.; Revol, J. M. *J. Org. Chem.* **1983**, *48*, 4453. Ranu, B. C.; Kavka, M.; Higgs, L. A.; Hudlicky, T. *Tetrahedron Lett.* **1984**, 2447.
(4) Hudlicky, T.; Sheth, J. P.; Barnvos, D.; Gee, V. *Tetrahedron Lett.* **1979**, 4889. Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020.
(5) We have not established whether the cyclization of olefin-aldehyde system in 2 is a true ene reaction or simply a Lewis acid catalyzed cationic closure. For simplicity the term ene, as used in this paper, refers to the *product* of a formal ene reaction.
(6) Hudlicky, T.; Govindan, S. V.; Reddy, D. B.; Kulp, T.; Still, B. *J. Org. Chem.* **1983**, *48*, 3422. Govindan, S. V.; Hudlicky, T.; Koszyk, F. J. *J. Org. Chem.* **1983**, *48*, 3581.
(7) Prepared from ethyl cyclopropylcarboxylate (i, MeMgI; ii, HBr, 48%). Oppolzer, W., private communication.
(8) Ledon, H. T. *Org. Synth.* **1979**, *59*, 66.

0022-3263/85/1950-4166$01.50/0 © 1985 American Chemical Society