The Structure and Stereochemistry of the Products Derived from the Reaction of Halosulfenes with 1-(Morpholino)cyclohexene

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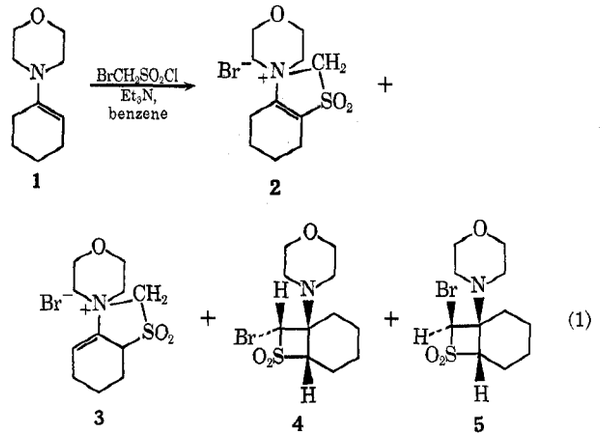
Received December 6, 1971

The reaction of 1-(morpholino)cyclohexene with chloro- and bromomethanesulfonyl chloride is described, and the nature and stereochemistry of the products are discussed. Detailed nmr analyses of the cycloadducts arising *via* halosulfene intermediates are presented.

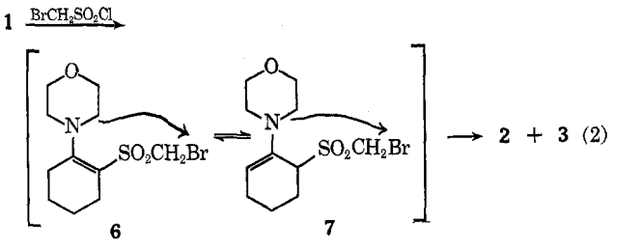
Recently the chemistry of sulfenes has received considerable attention, and several reviews have appeared.[1,2] Halogen-substituted sulfenes have, however, received only brief attention, the most detailed study being that of chlorosulfene by Paquette.[3] The present study deals with the nature and the stereochemistry of the products obtained by the reaction of halomethanesulfonyl chlorides with 1-(morpholino)-cyclohexene (1) in the presence of triethylamine.

The reaction of **1** with bromomethanesulfonyl chloride[4] in the presence of triethylamine (benzene) afforded four isolable products (eq 1). The salts **2** and **3** were



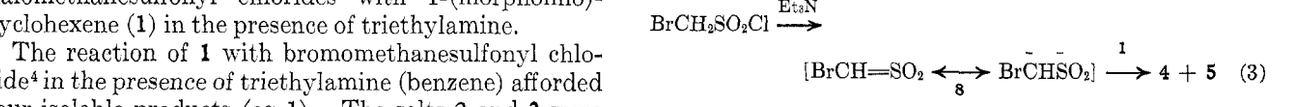
(1)

isolated as a 50:50 mixture of white, water-soluble crystals which could not be separated. These products are believed to arise *via* sulfonation of **1**, equilibration of the sulfonyl enamines **6** and **7**, and finally, intramolecular displacement by the tertiary nitrogen on the bromomethylsulfonyl group (eq 2).[5] The final displacement step in the formation of **2** and **3** represents the first known example of the displacement of a halogen α to a sulfonyl group by a "neutral" nitrogen nucleophile.[6]



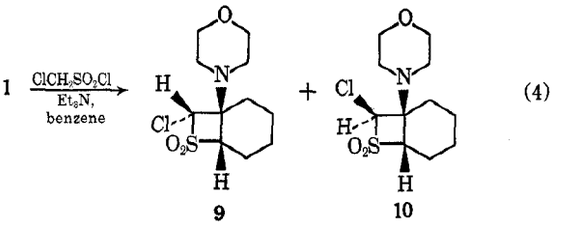
(2)

The cycloadducts **4** and **5** were isolated by fractional crystallization from ethanol, and arise *via* the cycloaddition of bromosulfene (**8**) to **1** (eq 3).[7]



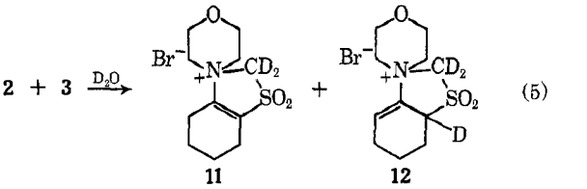
(3)

The reaction of chloromethanesulfonyl chloride[8] with **1** was also investigated. In contrast to the results previously reported by Paquette,[3] **1** was found to react with chloromethanesulfonyl chloride to give both isomers of the sulfene cycloaddition product, **9** and **10** (eq 4).[9]



(4)

The structures of **2**–**5**, **9**, and **10** were established by nmr and mass spectroscopy. The nmr spectrum (60 MHz, CF_3CO_2H) of the mixture of **2** and **3** displays singlets at δ 5.32 and 5.46 for the $-SO_2CH_2N^+$ protons of the two isomers, and a multiplet centered at δ 7.08 for the vinyl proton of **3**. The $-SO_2CH_2N^+$ protons of **2** and **3**, as well as the methine proton α to the sulfonyl



(5)

(1) T. J. Wallace, *Quart. Rev., Chem. Soc.*, **20**, 67 (1966).

(2) P. N. Son, Ph.D. Thesis, Purdue University, 1967.

(3) L. A. Paquette, *J. Org. Chem.*, **29**, 2854 (1964).

(4) W. E. Truce, D. J. Abraham, and P. Son, *J. Org. Chem.*, **32**, 990 (1967).

(5) The mechanisms proposed for the reaction of **1** with cyanosulfene [M. P. Sammes, C. M. Wylie, and J. G. Hoggett, *J. Chem. Soc. C*, 2151 (1971)] might account for the formation of **3**, but not **2**.

(6) Displacement of halogen α to a sulfonyl group by nitrogen anions has been reported in the base-catalyzed decomposition of halomethanesulfonamides: T. B. Johnson and I. B. Douglass, *J. Amer. Chem. Soc.*, **63**, 1571 (1941); F. G. Bordwell and G. D. Cooper, *ibid.*, **73**, 5187 (1951); W. V. Farrar, *J. Chem. Soc.*, 3058 (1960).

(7) It has been established that products such as **4** and **5** do, in fact, arise *via* sulfene intermediates: I. J. Borowitz, *J. Amer. Chem. Soc.*, **86**, 1146 (1964).

(8) H. Brintzinger, H. Koddebusch, K. Kling, and G. Jung, *Chem. Ber.*, **85**, 455 (1952).

(9) Although the chloro analogs of **2** and **3** were not isolated from this reaction, their formation cannot be precluded, since a detailed material balance was not carried out.

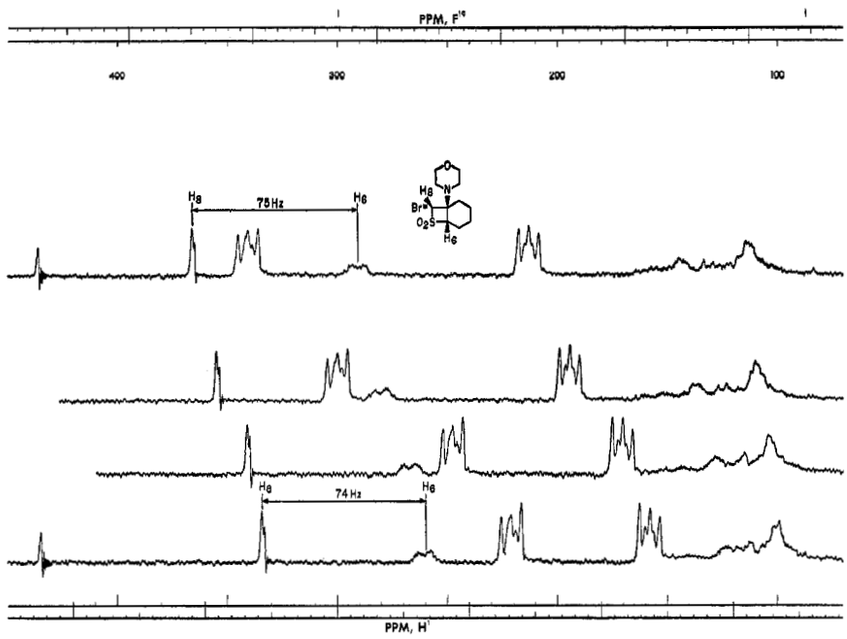


Figure 1.—Successive scans displaying the effect of the addition of incremental amounts of Eu(fod)$_3$ on the 60-MHz nmr spectrum of **4**.

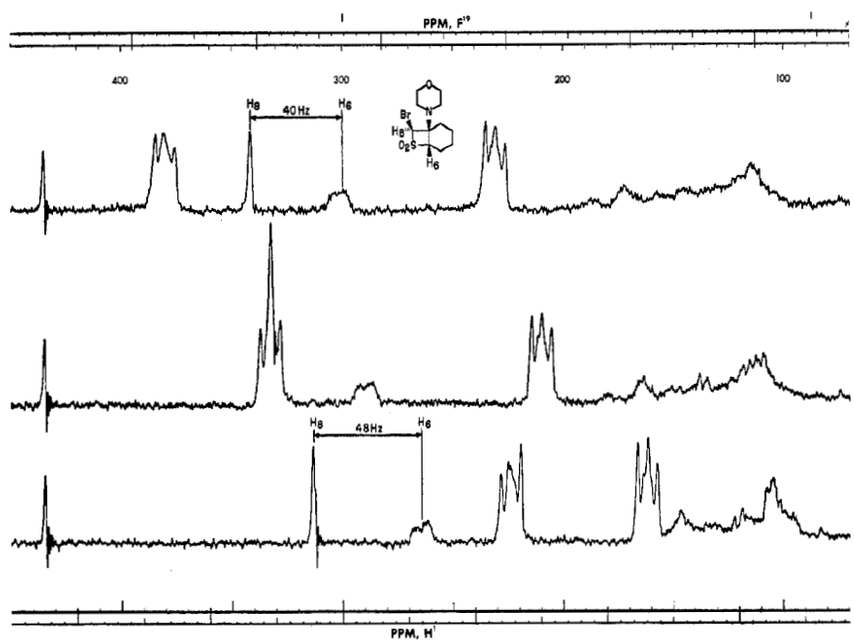
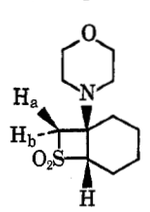


Figure 2.—Successive scans displaying the effect of the addition of incremental amounts of Eu(fod)$_3$ on the 60-MHz nmr spectrum of **5**.

group in **3**, are readily exchangeable, and are not seen when the nmr spectrum is run in D_2O (eq 5).

The exchange of **2** and **3** with D_2O to give **11** and **12** was confirmed by mass spectroscopy. The mass spectrum of the mixture of **2** and **3** gave a parent peak at *m/e* 323. The mass spectrum of the crystalline solid obtained by treatment of **2** and **3** with D_2O displayed parent peaks at *m/e* 325 and 326, corresponding to **11** and **12**.

The stereochemistry of compounds such as **4**, **5**, **9**, and **10** has not previously been determined in a definitive manner. Consideration of the nmr chemical shifts induced upon complexation with Eu(fod)$_3$, however, permits an unambiguous assignment of the stereochemistry. The results of the complexation studies are shown in Figures 1, 2, and 3 for **4**, **5**, and the unhalogenated analog, **13**, respectively.[10] The primary



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site of complexation in each case is the oxygen of the morpholine ring, since the largest shifts are induced

(10) Similar studies were carried out with the chloro analogs, **9** and **10**, with similar results.

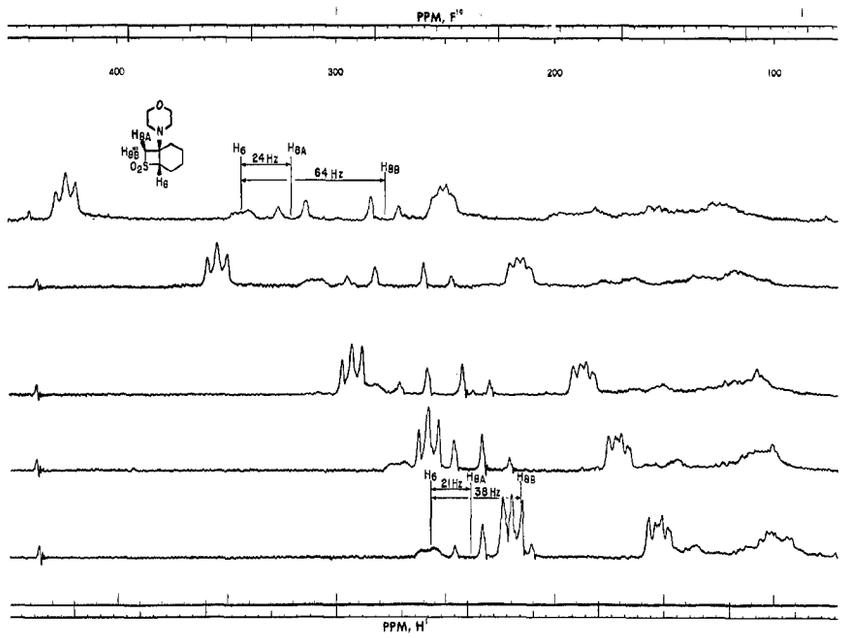

Figure 3.—Successive scans displaying the effect of the addition of incremental amounts of Eu(fod)$_3$ on the 60-MHz nmr spectrum of **13**.

in the protons vicinal to the oxygen. The Eu(fod)$_3$ was added in several small quantities, and the spectrum was recorded after each addition so that spectral bands could be assigned even if two adjacent bands crossed.

In Figure 1, the difference in chemical shift between H_6 and H_8 remains essentially constant (within approximately 2%), whereas in Figure 2 the same chemical shift difference has decreased by approximately 20% at a comparable ratio of complex to substrate. Thus, in **5** H_8 is deshielded less than H_6, whereas in **4** H_8 and H_6 are deshielded to approximately the same extent. Similar behavior is observed in **13** (Figure 3); *i.e.*, one of the H_8 protons is deshielded at approximately the same rate as H_6, whereas the other H_8 proton is deshielded more slowly.

An examination of Dreiding models of **4**, **5**, and **13** indicates that for a complexation site near the morpholine oxygen, H_6 and H_8 (in **4** and **5**) and H_6, H_{8a}, and H_{8b} (in **13**) all have about the same angular dependence with respect to the paramagnetic chelate. Thus, the only reasonable explanation for the observed differences in induced shifts must lie in the distance from the chelate to the protons,[11] establishing that H_6 and H_8 are *cis* to each other in **4** and *trans* to each other in **5**. This distance dependence also permits the unambiguous assignment of the downfield signal of the AB pattern in **13** to H_{8a}, and the upfield signal to H_{8b} (see Table I for a summary).

Since the signal for H_8 of **9** had previously been reported to be a triplet (J = 1.5 Hz)[3] and no reasonable explanation had been proposed, the signals due to H_6 and H_8 in **4**, **5**, **9**, and **10** were studied in detail. The signal due to H_8 is a doublet in each case, and the coupling constants are summarized in Table I. That

(11) An examination of Dreiding models also shows that if complexation occurred at the sulfonyl group, H_6 and H_8 (in **4** and **5**) and H_6, H_{8a}, and H_{8b} (in **13**) are symmetrically disposed with respect to the complexation site. Consequently, complexation at the sulfonyl group cannot account for the differential shifts which are observed.

TABLE I

100-MHz NMR SPECTRAL DATA FOR THIETANE DIOXIDES ($CDCl_3$)

Compd	H_6, δ	H_8, δ	$J_{6,8}$, Hz
4	4.35	5.59	1.1
5	4.42	5.26	0.9
9	4.28	5.49	1.1
10	4.42	5.12	0.9
13	4.36	*a*	*b*

[a] The signals for the geminal protons H_{8a} (δ 4.04) and H_{8b} (δ 3.73) appear as the AB portion of an ABX pattern with $J_{a,b} = -12.6$ Hz. [b] $J_{6,8a} = 0.8$ Hz and $J_{6,8b} = 0.9$–1.0 Hz.

the large coupling to H_8 was, in fact, due to H_6 was established in each case by selective decoupling.[12]

Similar studies of the couplings to H_{8a} and H_{8b} in **13** were also conducted. An INDOR experiment demonstrated that $J_{6,8a}$ and $J_{6,8b}$ are of opposite sign, but the signs could not be related to the sign of the geminal coupling constant, $J_{8a,8b}$, since the H_6 signal is very broad owing to strong coupling of H_6 with protons of the carbocyclic ring.

Experimental Section

All reactions were run in a nitrogen atmosphere. The nmr spectra were recorded on a Varian HA-100 spectrometer with an internal lock on tetramethylsilane (TMS = 0) unless otherwise indicated. The infrared spectra were recorded on a Perkin-Elmer Infracord. All melting points and boiling points are uncorrected.

Reaction of 1 with Bromomethanesulfonyl Chloride.—In a 250-ml, three-neck flask equipped with a magnetic stirrer, a nitrogen inlet, a thermometer, a calcium chloride drying tube, and an addition funnel were placed 16.72 g (0.10 mol) of 1-(morpholino)cyclohexene, 10.0 g (0.10 mol) of triethylamine, and 100 ml of dry benzene. The flask was flushed with nitrogen, and the contents were cooled to 2°. To the cooled solution, a solution of 19.3 g (0.10 mol) of bromomethanesulfonyl chloride in 20 ml of benzene was added dropwise, with stirring, over 1.25 hr. After the addition was complete, the reaction mixture was

(12) Any further coupling to H_8 was not resolved, and would be estimated to be less than 0.2 Hz.

stirred at 2–5° for an additional 0.5 hr. The reaction mixture was filtered to remove the triethylamine hydrochloride produced. The triethylamine hydrochloride was washed with several portions of benzene. The benzene was removed *in vacuo* from the combined filtrates, leaving a heavy, orange oil. A small amount of absolute ethanol was added to the oil, and after standing for 3 days, orange-brown crystals separated. The crystals were filtered, washed with acetone, and vacuum dried to give 9.30 g (29% yield) of crude **2** and **3**, mp 165–166°. The solid was recrystallized from aqueous ethanol to give 7.03 g of a mixture of 4,5,6,7-tetrahydrospiro[benzothiazoline-3,4′-morpholinium] bromide 1,1-dioxide (**2**) and 5,6,7,7a-tetrahydrospiro-[benzothiazoline-3,4′-morpholinium] bromide 1,1-dioxide (**3**), mp 175–177°.

Anal. Calcd for $C_{11}H_{18}BrNO_3S$: C, 40.75; H, 5.59; Br, 24.65; N, 4.32; S, 9.89. Found: C, 40.90; H, 5.51; Br, 24.65; N, 4.42; S, 10.25. Mass spectrum (intense ions): *m/e* 325, 323 (molecular ion), 261, 259 (1 Br), 180, 166, 136, 109, 95, 87.

The combined filtrate and acetone washings from the isolation of **2** and **3** were treated with 25 ml of 10% sodium hydroxide solution and then extracted with methylene chloride. The methylene chloride extracts were washed with water and dried, and the methylene chloride was removed *in vacuo*, leaving 13.85 g of a viscous, yellow-brown oil. The oil was treated with approximately 50 ml of absolute ethanol, and a crystalline solid separated. The solid was filtered and vacuum dried to give 5.44 g (17% yield) of crude **4**, mp 166–168°. The solid was recrystallized from approximately 150 ml of aqueous ethanol to give 3.81 g of 4-(*trans*-8-bromo-7-thiabicyclo[4.2.0]oct-1-yl)-morpholine *S,S*-dioxide (**4**) as fine, white crystals, mp 172–174°.

Anal. Calcd for $C_{11}H_{18}BrNO_3S$: C, 40.75; H, 5.59; Br, 24.65; N, 4.32; S, 9.89. Found: C, 41.06; H, 5.57; Br, 24.81; N, 4.28; S, 9.81. Mass spectrum (intense ions): *m/e* 325, 323 (molecular ion), 244, 180, 167, 166, 152, 139, 138, 137, 136, 124, 123, 122, 110, 109, 108, 95, 94, 93, 91, 86, 81, 79, 77, 67, 66, 65, 56, 55, 54, 53, 42, 41, 39, 30, 29, 27.

The filtrate from the isolation of **4** was refrigerated and, after standing for 30 days, yielded 3.20 g (10% yield) of crude **5** as a slightly orange solid, mp 120–129°. The solid was recrystallized from approximately 50 ml of ethanol (with decolorization) to give 1.20 g of 4-(*cis*-8-bromo-7-thiabicyclo[4.2.0]oct-1-yl)-morpholine *S,S*-dioxide (**5**) as white needles, mp 129.5–131.5°.

Anal. Calcd for $C_{11}H_{18}BrNO_3S$: C, 40.75; H, 5.59; Br, 24.65; N, 4.32; S, 9.89. Found: C, 40.67; H, 5.46; Br, 24.60; N, 4.44; S, 10.00.

Reaction of 1 with Chloromethanesulfonyl Chloride.—In a 250-ml, three-neck flask equipped with a magnetic stirrer, a nitrogen inlet, a thermometer, a calcium chloride drying tube, and an addition funnel were placed 12.00 g (0.072 mol) of 1-(morpholino)cyclohexene, 7.30 g (0.072 mol) of triethylamine, and 150 ml of benzene. The flask was swept with nitrogen and cooled in an ice bath. To the cooled solution, a solution of 10.96 g (0.072 mol) of chloromethanesulfonyl chloride in 20 ml of benzene was added dropwise, with stirring, over a period of 50 min. After the addition was complete, the reaction mixture was stirred with ice-bath cooling for an additional 0.5 hr. The reaction mixture was filtered to remove the triethylamine hydrochloride produced. The triethylamine hydrochloride was washed with several portions of benzene. The benzene was removed *in vacuo* from the combined filtrates, leaving a yellow oil. The oil was mixed with a small amount of absolute ethanol and allowed to stand at room temperature. After 3 days some small crystals formed. The crystals were filtered to give 0.65 g of crude **9**. The solid was recrystallized from 15 ml of absolute ethanol to give 0.35 g of 4-(*trans*-8-chloro-7-thiabicyclo[4.2.0]oct-1-yl)morpholine *S,S*-dioxide (**9**) as colorless crystals, mp 139–140.5° (lit.[3] mp 155–157°). This material is apparently a different crystalline modification of **9** than that isolated by Paquette,[3] since it has the same nmr spectrum as a sample of **9** with mp 155–157° which we later isolated (*vide infra*).

Anal. Calcd for $C_{11}H_{18}ClNO_3S$: C, 47.23; H, 6.48; Cl, 12.67; N, 5.00; S, 11.46. Found: C, 47.26; H, 6.50; Cl, 12.69; N, 4.90; S, 11.66. Mass spectrum (intense ions): *m/e* 279 (molecular ion), 244, 180, 168, 167, 166, 152, 139, 138, 137, 136, 124, 123, 122, 110, 109, 108, 96, 95, 94, 93, 91, 86, 82, 81, 80, 79, 78, 77, 68, 67, 66, 65, 64, 58, 57, 56, 55, 54, 53, 52, 49, 46, 45, 44, 43, 42, 41, 40, 37, 33, 31, 30, 29, 28, 27.

The filtrate was refrigerated to give another crop of 1.26 g of crude **9**. This solid was recrystallized from approximately 25 ml of ethanol to give 0.67 g of **9** as fine, white crystals, mp 155–157° (the same as that reported by Paquette[3]). The ethanol was removed *in vacuo* from the filtrate from the isolation of crude **9**, leaving an orange oil. The oil was treated with 100 ml of ether. Not all of the oil dissolved in the ether. The ether solution was separated and the ether was removed *in vacuo*, leaving another orange oil. The oil was diluted with a small amount of absolute ethanol, seeded with a crystal of **9**, and refrigerated to give an additional 0.44 g of **9**. The ethanol was again removed from the crystallization liquor, leaving an orange oil. A 4.50-g sample of this oil was placed on a silica gel column (neutral, 100–200 mesh) and eluted with ether. In this manner we obtained three fractions (total 1.95 g) of a pale yellow oil consisting of approximately 84% **10** and 16% **9**. The yellow oil slowly crystallized under refrigeration, but several attempts to get a pure (isomerically) sample of **10** were unsuccessful, the recrystallizations always leading again to a yellow oil.

4-(7-Thiabicyclo[4.2.0]oct-1-yl)morpholine *S,S*-Dioxide (13).—This compound was prepared by a modification of the procedure described by Borowitz (see ref 7) in which benzene was substituted for dioxane as solvent. Small, white prisms were obtained after recrystallization, mp 137–139° (lit. mp 139–140°).

Registry No.—**1**, 670-80-4; **2**, 34368-08-6; **3**, 34368-09-7; **4**, 34314-94-8; **5**, 34314-95-9; **9**, 34314-96-0; **10**, 34314-97-1; **13**, 34314-98-2.

Acknowledgment.—We wish to thank Drs. Jerry P. Heeschen (Chemical Physics Research) and Francis Johnson (Eastern Research Laboratory) for helpful discussions and suggestions. We also wish to thank Mr. George Kallos for obtaining and interpreting the mass spectra.