Synthesis of *cis*- and *trans*-2-(2′-Tetrahydropyranylthio)cyclopropylmethylamines

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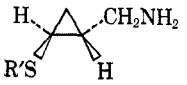
In connection with a program designed to synthesize conformationally rigid cyclopropane analogs of γ-mercaptopropylamine (2) reactions of ethyl diazoacetate (6) and diazoacetonitrile (7) with 2-vinylthiotetrahydropyran (8) were studied. The synthesized 2-(2′-tetrahydropyranylthio)-1-carbethoxy- and -cyanocyclopropanes (5a and 5b, respectively) are separated into cis and trans isomers and characterized by means of nmr spectroscopy. Conversion of *cis*- and *trans*-5a and -5b to *cis*- and *trans*-2-(2′-tetrahydropyranylthio)cyclopropylmethylamine (4) is discussed.

The relatively high radioprotective activity of β-mercaptoethylamine (1)[1] and γ-mercaptopropylamine (2)[2] is of considerable theoretical interest.[3] Rigid analogs,

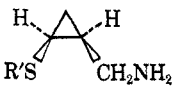
$$HS(CH_2)_nNH_2$$

1, $n = 2$
2, $n = 3$

cis- and *trans*-2-mercaptocyclopropylmethylamine (3) are related to respective eclipsed and staggered conformations of γ-mercaptopropylamine (2) whose radioprotective effectiveness is 2.5 times that of 1.[2] For purposes of comparatively investigating stereochemical requirements *in vivo* and *in vitro* for such activity, we initiated a program designed to synthesize cis and trans analogs 3. In this communication we report several routes to the preparation of the corresponding tetrahydropyranylthio derivatives 4 and an nmr analysis of selected cis and trans intermediates.

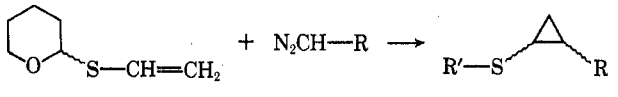


trans-3, R′ = H
trans-4, R′ = 2-tetrahydropyranyl



cis-3, R′ = H
cis-4, R′ = 2-tetrahydropyranyl

The method chosen for the synthesis of *cis*- and *trans*-3 necessitated construction of an appropriately substituted cyclopropane ring 5 where R′ represents a protecting function which when removed affords the free –SH group and R is a function potentially convertible to $-CH_2NH_2$. Further, 5 should readily be separable into pure cis and trans isomers. For these reasons reactions of both ethyl diazoacetate (6) and diazoacetonitrile (7) with 2-vinylthiotetrahydropyran (8) were studied.



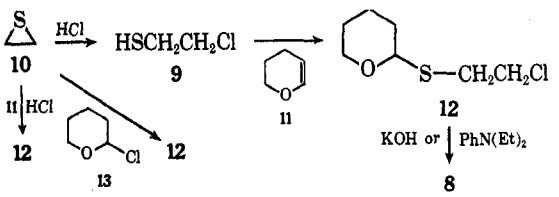
8

6, R = CO_2Et
7, R = C≡N

5a, R′ = 2-tetrahydropyranyl; R = CO_2Et
b, R′ = 2-tetrahydropyranyl; R = C≡N

Results and Discussion

2-Mercaptoethyl chloride (9) served as starting material and was readily prepared from ethylene sulfide (10) and gaseous HCl in 93% yield by a modification of the method of Meade and Woodward.[4] Reaction of 9 with 2,3-dihydropyran (11) on a steam bath for 3 hr afforded 2-(β-chloroethylthio)tetrahydropyran (12) in nearly quantitative yield. Alternatively, 12 was prepared directly from 10 in excellent yields and in a shorter time when 2,3-dihydropyran (11) was added to a saturated solution of ethylene sulfide (10) in HCl–ether. 2-(β-Chloroethylthio)tetrahydropyran (12) was also obtained in poor yield (with the formation of a large amount of polymeric product) from 2-chlorotetrahydropyran (13) and ethylene sulfide in the presence of $AlCl_3$. These data suggest 2-chlorotetrahydropyran (13) not be be an intermediate in the conversion of 10 to 12. The reaction most likely proceeds *via* protonation of ethylene sulfide (10) affording 9 which then reacts with 2,3-dihydropyran (11) yielding 12.



Base-catalyzed elimination of HCl from intermediate 12 in the presence of solid KOH in dry ether afforded the desired 2-vinylthiotetrahydropyran (8) in 83% yield. Elimination of HCl using *N*,*N*-diethylaniline afforded 8 in only 42% yield; the remainder of the product was starting 12.

Reaction of 2-vinylthiotetrahydropyran (8) with ethyl diazoacetate (6) was studied under a variety of reaction conditions with and without added solvent. Xylene is a most satisfactory solvent for this reaction; copper powder serves as a suitable catalyst. Reaction of 6 and 8 in the presence of anhydrous $CuSO_4$ (or without solvent) afforded much polymeric material along with numerous by-products as indicated by gas–liquid partition chromatography (glpc). With copper powder catalysis in xylene six products were detected gas chromatographically. The desired compounds, *cis*- and *trans*-2-(2′-tetrahydropyranylthio)-1-carbethoxycyclopropane (5a) were obtained in approximately 50% yield. Other reaction products detected and isolated were the isomeric tricarbethoxycyclopropanes (14) and 3-carbethoxypyrazole (15). Compounds 14 and

* To whom correspondence should be addressed.

(1) (a) Z. M. Bacq, A. Herve, J. Lecomte, P. Fischer, J. Blavier, G. Dechamps, H. LeBihan, and P. Rayet, *Arch. Int. Physiol.*, **59**, 442 (1951); (b) Z. M. Bacq and A. Herve, *Brit. J. Radiol.*, **24**, 617 (1951); (c) Z. M. Bacq and P. Alexander in "Fundamentals of Radiobiology," Butterworths, London, 1955, pp 290–327; (d) A. Hollaender and C. O. Doudney in "Radiobiology Symposium," Z. M. Bacq and P. Alexander, Ed., Butterworths, London, 1954, pp 112–115.

(2) (a) D. G. Doherty, W. T. Burnett, Jr., and R. Shapira, *Radiat. Res.*, **7**, 13 (1957); (b) R. Shapira, D. G. Doherty, and W. T. Burnett, Jr., *ibid.*, **7**, 22 (1957).

(3) For recent reviews, see W. O. Foy, *J. Pharm. Sci.*, **58**, 283 (1969); "Annual Reports in Medicinal Chemistry, 1965, 1966, 1967," C. K. Cain, Ed., Academic Press, New York, N. Y., 1966–1968.

(4) E. M. Meade and F. N. Woodward, *J. Chem. Soc.*, 1894 (1948).

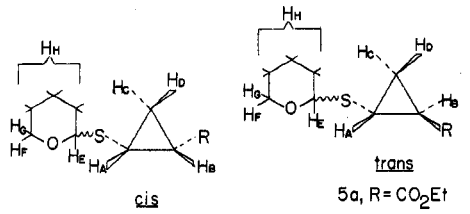
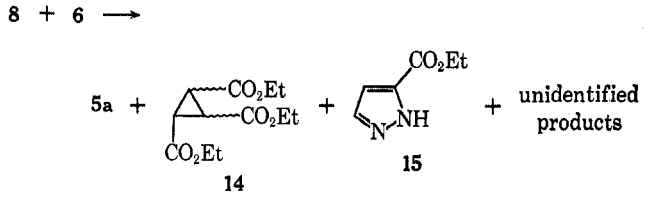


Figure 1.—Proton designations for *cis*- and *trans*-2-(2′-tetrahydropyranylthio)cyclopropyl esters (**5a**) and nitriles (**5b**).

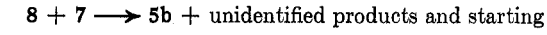
15 were isolated in less than 1% yield. The major by-products (28.5% of the reaction mixture as calculated from glpc analysis) were not characterized. Uncharacterized and characterized by-products were removed from the desired 2-(2′-tetrahydropyranothio)-1-carbethoxycyclopropane (**5a**) by distillation under reduced pressure. The crude ester **5a** remains undistilled and shows two major peaks (glpc) analyzing for a trans to cis ratio of 9:1.



Formation of ester **5a** in good yield is dependent upon the reaction conditions. When the reaction was carried out at a temperature of 120° considerable amounts of low boiling by-products and 3-carbethoxypyrazole (**15**) are formed. Increased formation of **15** at lower temperatures (120°) is most likely a result of increased concerted reaction of ethyl diazoacetate (**6**) with **8** affording an intermediate pyrazoline which gains aromatic stabilization upon elimination of the tetrahydropyranylthio group.[5] At temperatures of 160° tar formation was greatly increased. When this reaction was carried out at 140° with slow addition of ethyl diazoacetate (1 drop/20 sec) competing concerted addition of ethyl diazoacetate (**6**) to olefin **8** was minimized; the olefin reacts with carbethoxycarbene to a greater extent affording **5a** with the least amount of by product.[6]

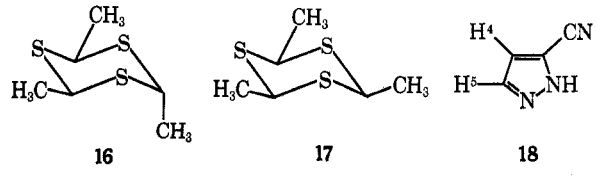
Repeated column chromatography of the crude ester **5a** on dry silicic acid with chloroform afforded pure *trans*-**5a**. Nmr analysis showed this to be a diastereoisomeric mixture owing to the asymmetry of the tetrahydropyranyl group, but only one peak was observed gas chromatographically. The cis isomer **5a** eluted last in the presence of a minor product (4.4%) believed to be one of the cis diastereoisomeric products. Attempts to further purify the cis ester **5a** were unsuccessful. The stereochemical assignment for cis and trans esters **5a** is based on nmr analysis which is discussed in a later section.

Reaction of 2-Vinylthiotetrahydropyran (8) with Diazoacetonitrile (7).—Diazoacetonitrile (**7**) was prepared under N_2 in CH_2Cl_2 and was used without further purification.[7] This solution and xylene were simultaneously added dropwise under N_2 to a stirred mixture of copper powder in a solution of 2-vinylthiotetrahydropyran (**8**) in xylene at 120°. The rate of addition was such as to avoid a vigorous reaction. Yields of 10–30% 2-(2′-tetrahydropyranylthio)cyclopropylnitrile (**5b**) were obtained depending upon the rate of addition and the concentration of diazoacetonitrile (**7**) used (usually a two- to fourfold excess). At a faster rate of addition of a large excess of diazoacetonitrile the higher yield was obtained. Under these conditions a considerable amount of by-product believed to arise from the self condensation of **7** was obtained.[6] With a slower rate of addition the low yield of cyclopropylnitrile **5b** and more tar was obtained. During all experiments approximately 40% starting olefin **8** was recovered.



The reaction mixture containing *trans*- to *cis*-**5b** in a ratio of about 4:3 was chromatographed on silica gel G utilizing $CHCl_3$ as the eluting solvent. Most of the polymeric material was removed by this procedure; the eluate was fractionally distilled under reduced pressure to remove starting olefin **8** and low boiling by-products. The remaining undistilled residue was then chromatographed on silicic acid with chloroform with the aid of an automatic fraction collector. The mixture of cis and trans nitriles **5b** eluted first and was rechromatographed under similar conditions. Pure *trans*-**5b** eluted first, followed by pure cis and subsequently by a third unidentified product whose infrared spectrum is identical to the spectrum observed for *cis*-**5b**. The third compound had a different retention time in the gas chromatograph; nmr spectra analysis suggests the compound to be diastereoisomeric with *cis*-**5b**. Some polymeric by-product eluted last while some of the polymer remained adsorbed to the column. Like the trans ester **5a**, the trans nitrile **5b** showed only one peak in the gas chromatograph, but nmr analysis confirmed the nitrile to be a diastereoisomeric mixture as expected.

The isomeric α- and β-trithioacetaldehydes (**16** and **17**, respectively) were isolated on occasion when a higher reaction temperature ($\geq$160°) was used. Assignment of structures **16** and **17** was based on their physical properties as well as nmr data.[8] 3-Cyanopyrazole (**18**) was detected (but not isolated) by nmr



(5) (a) D. T. Witiak and M. C. Lu, *J. Org. Chem.*, **33**, 4451 (1968); (b) D. T. Witiak and B. K. Sinha, *ibid.*, **35**, 501 (1970).

(6) Other by-products likely result from sulfonium ylide intermediates. Such reactions will be discussed in a subsequent communication.

(7) (a) D. D. Phillips and W. C. Champion, *J. Amer. Chem. Soc.*, **78**, 5452 (1956); (b) M. J. S. Dewar and R. Pettit, *J. Chem. Soc.*, 2026 (1956); (c) M. Lesbre and R. Buisson, *Bull. Soc. Chim. Fr.*, 1204 (1957).

(8) For **16**, a pair of doublets centered at δ 1.49 and 1.83 and integrating for 6 and 3 protons, respectively, were observed. These proton resonance signals may be attributed to the two equatorial and one axial methyl group. The methine protons appear as a quartet at δ 4.32 and 4.42, integrating for 2 and 1 protons, respectively. The coupling constants for both equatorial methyl groups with the axial hydrogen atoms or axial methyl group with the equatorial hydrogen atom are identical ($J_{CH_3,H}$ = 7 Hz). With compound **17** all methyl groups are equivalent (equatorial) and the proton resonances are found as a doublet centered at δ 1.35 ($J_{CH_3,H}$ = 7 Hz); the methine protons exhibit resonance signals as a quartet at δ 3.97.

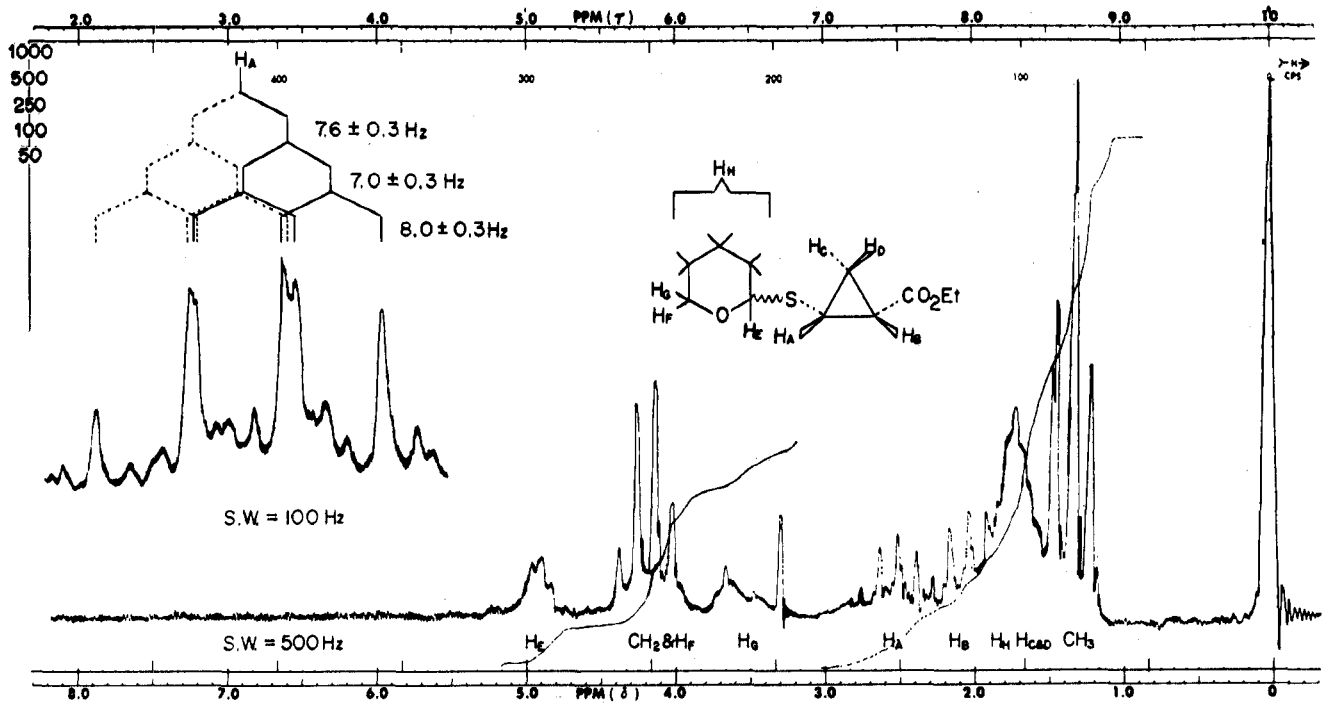


Figure 2.—Nmr spectrum of 20% *cis*-2-(2′-tetrahydropyranylthio)-1-carboethoxycyclopropane (**5a**) in $DCCl_3$. The H_A proton resonance signal is shown at 100-Hz sweep width.

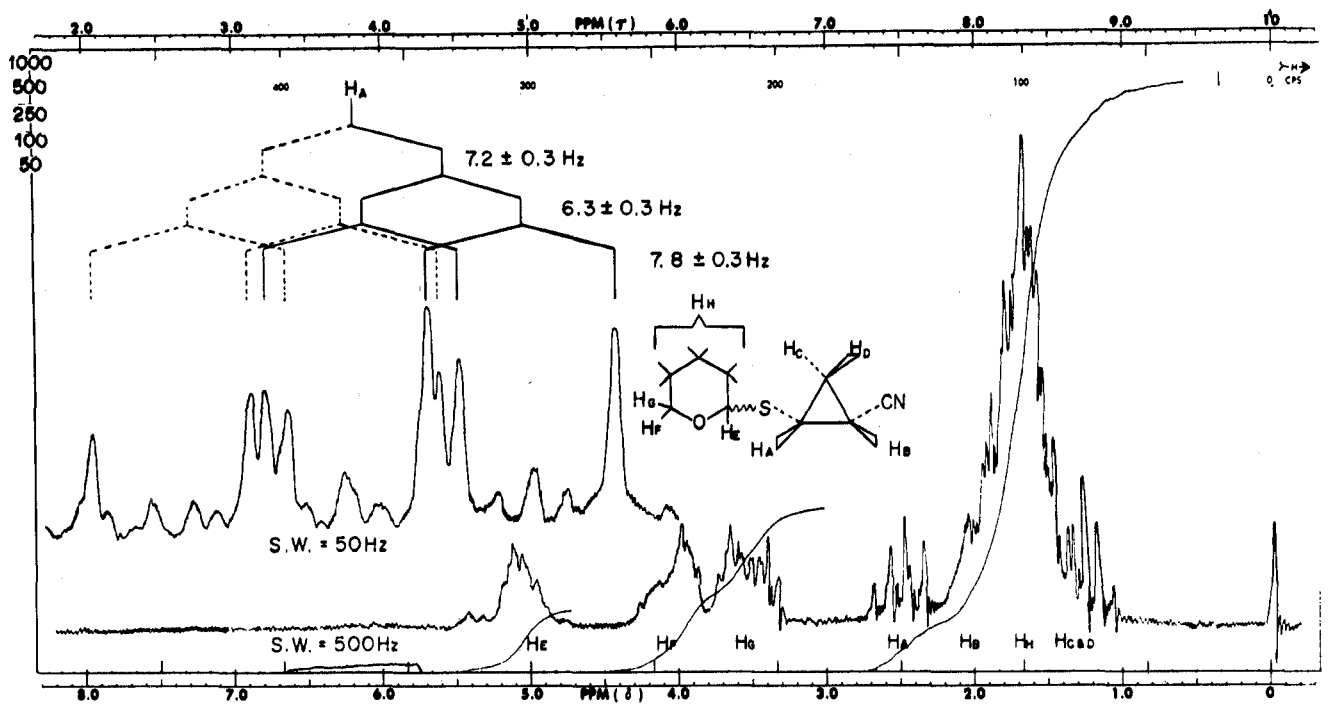


Figure 3.—Nmr spectrum of 50% *cis*-2-(2′-tetrahydropyranylthio)cyclopropylnitrile (**5b**) in $DCCl_3$. The H_A proton resonance signal is shown at 50-Hz sweep width.

analysis of impure cyclopropylnitrile **5b**; a pair of characteristic downfield doublets at δ 7.01 and 8.42 ($J_{4,5}$ = 2.2 Hz) are most likely due to the presence of trace amounts of this compound.[5a]

Nmr Analysis of *cis*- and *trans*-2-(2′-Tetrahydropyranylthio)-1-carbethoxycyclopropane (5a) and 2-(2′-Tetrahydropyranylthio)cyclopropylnitrile (5b).—Nmr studies of the cis and trans cyclopropyl esters **5a** and nitriles **5b** supplied valuable evidence to support the stereochemical assignment for these compounds. Proton designations are found in Figure 1. In Table I are found the δ for the center of the multiplet attributed to the proton resonance signal labeled H_A; calculated and observed bandwidths are also listed. Tetrahydropyranyl protons (H_F, H_G, and H_H) and other proton resonances are listed under individual compounds in the Experimental Section. The nmr spectra for the cis ester **5a** and nitrile **5b** are shown in Figures 2 and 3, respectively. The spectra for the trans ester **5a** and nitrile **5b** are similar. However, the cyclopropyl proton designated H_A exhibits a considerably different splitting pattern; the resonance signal is shown in Figures 4

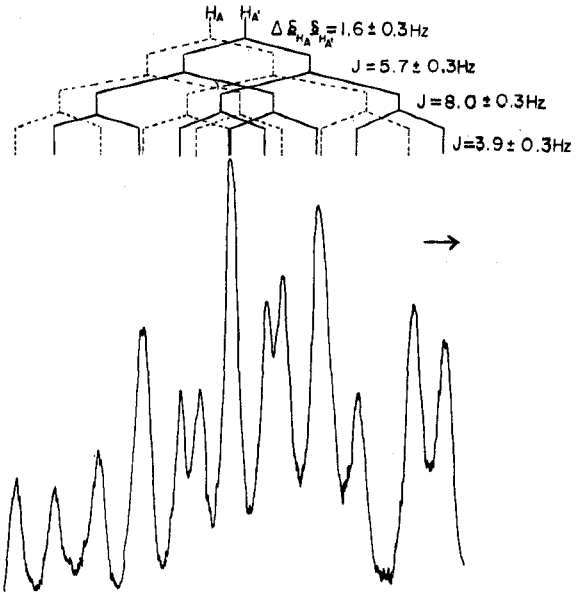


Figure 4.—Nmr spectrum of the H_A resonance signal for 20% *trans*-2-(2′-tetrahydropyranylthio)-1-carbethoxycyclopropane (**5a**) in $DCCl_3$. Sweep width = 50 Hz.

and 5 for the trans ester **5a** and trans nitrile **5b**, respectively.

TABLE I

MULTIPLET CENTER AND THE SUM OF THE COUPLING CONSTANTS FOR THE H_A RESONANCE SIGNAL

Compd	Multiplet center for H_A, δ	$\lvert J_{AB} + J_{AC} + J_{AD}\rvert$,[a] Hz
trans-**5a**	2.55, 2.49	17.6 (19.0)[b]
cis-**5a**	2.48	22.6 (26.0)[b]
trans-**5b**	2.60, 2.56	19.1 (21.0)[b]
cis-**5b**	2.54	21.3 (23.0)[b]

[a] Calculated from the sum of the apparent coupling constants. [b] Observed bandwidth at the base of the peaks for one of the diastereoisomers.

Presence of the tetrahydropyranyl protons and methyl protons of the esters complicates the nmr analysis; H_B, H_C, and H_D resonance signals of the cyclopropane ring are under the broad multiplet owing to the proton resonance signals of the tetrahydropyranyl group (H_H resonance signals). The methyl triplet of the ethyl esters is also superimposed on the H_C and H_D cyclopropyl proton resonance signals. For these reasons the spectra for the H_A resonance signal may be analyzed only by first-order approximations. In actuality the spectra may be second order.[9] Analysis using computers may be desirable, but would contribute little additional information since H_B, H_C, and H_D resonance signals cannot be observed. Their presence was determined by integration and spin tickling in the δ range listed for these protons (Figures 2 and 3) while observing the H_A resonance signals. The stereochemical relationship between the tetrahydropyranylthio and carbethoxy or nitrile functions was determined using the first-order approximation for the H_A resonance signal which appears downfield to the resonance signals of H_B, H_C, H_D, and H_H. This downfield shift of the

(9) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, Chapter 2-3.

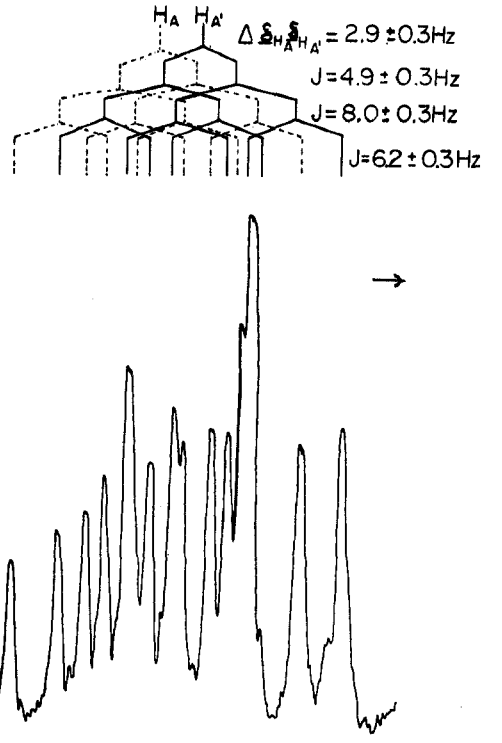


Figure 5.—Nmr spectrum of the H_A resonance signal for 50% *trans*-2-(2′-tetrahydropyranylthio)cyclopropylnitrile (**5b**) in $DCCl_3$. Sweep width = 100 Hz.

H_A signal is attributable to the deshielding effect of the S atom.

In the cis series (Figures 2 and 3), the H_A resonance signal was observed as an eight-line pattern. Low intensity signals observable in the expanded spectra for the H_A resonance signal of the cis ester **5a** are likely due to a small amount of diastereoisomer. First-order analysis of the major signals reveals J_{AD} = 8.0 ± 0.3 Hz, J_{AC} = 7.0 ± 0.3 Hz, and J_{AB} = 7.6 ± 0.3 Hz. These data are in accord with nmr studies of other substituted cyclopropanes which confirm $J_{cis} > J_{trans}$.[10] The eight-line H_A resonance signal for the cis nitrile **5b** is also most reasonably interpreted as J_{AD} = 7.8 ± 0.3 Hz, J_{AC} = 6.5 ± 0.3 Hz, and J_{AB} = 7.2 ± 0.3 Hz.

In the trans series, the H_A resonance signal (Figures 4 and 5 for ester **5a** and nitrile **5b**, respectively) is most satisfactorily interpreted as a sixteen-line pattern. This results from the overlapping of two eight-line spectra separated by 1.6 ± 0.3 Hz for the ester and 2.9 ± 0.3 Hz for the nitrile. These two (H_A and H_A') signals are attributable to the diastereoisomeric nature of the product, which, on the basis of this analysis, consists of 50% each. First-order analysis of the H_A (or H_A') resonance signal for the trans ester **5a** reveals coupling constants of 8.0, 5.7, and 3.9 ± 0.3 Hz. J_{AC} and J_{AD} are assigned the respective values of 5.7 and 8.0 Hz since J_{AD} is expected to be larger than J_{AC} and $\lvert J_{AC} + J_{AD}\rvert$ for *trans*- and *cis*-**5a** should be approximately the same. In this case $\lvert J_{AC} + J_{AD}\rvert_{trans}$ = 13.7 ± 0.6 Hz, $\lvert J_{AC} + J_{AD}\rvert_{cis}$ = 15.0 ± 0.6 Hz. A

(10) (a) J. D. Graham and M. T. Rogers, *J. Amer. Chem. Soc.*, **84**, 2249 (1962); (b) H. M. Hutton and T. Schaefer, *Can. J. Chem.*, **40**, 875 (1964); (c) T. Shiono, T. Morikawa, A. Oku, and R. Oda, *Tetrahedron Lett.*, 791 (1964); (d) K. B. Wiberg and B. J. Nist, *J. Amer. Chem. Soc.*, **85**, 2788 (1963); (e) K. L. Williamson, C. A. Lanford and C. R. Nicholson, *ibid.*, **86**, 762 (1964).

similar analysis for the H_A (or H_A') resonance signal for the trans nitrile **5b** reveals $J_{AD} = 8.0 \pm 0.3$ Hz, $J_{AC} = 6.2 \pm 0.3$ Hz, and $J_{AB} = 4.9 \pm 0.3$ Hz. For nitrile **5b** $|J_{AC} + J_{AD}|_{trans} = 14.2 \pm 0.6$ Hz, $|J_{AC} + J_{AD}|_{cis} = 14.3 \pm 0.6$ Hz.

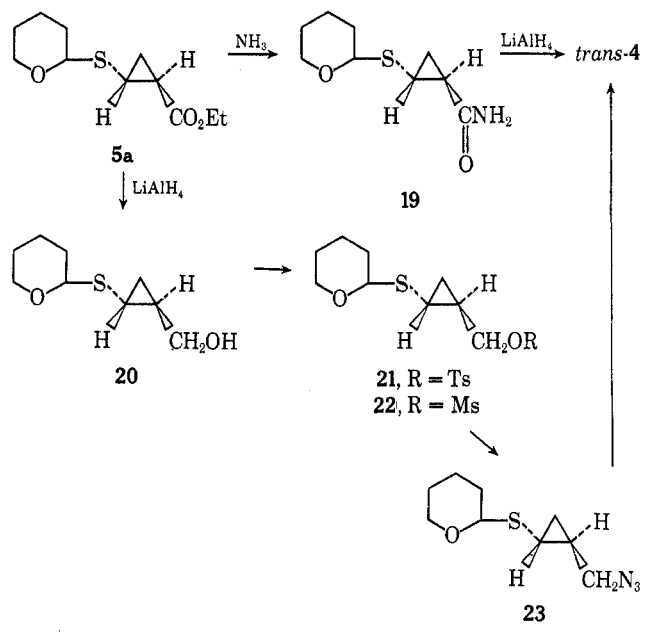
The stereochemical assignment of functional groups in **5a** and **5b** is confirmed by the observation $|J_{AB} + J_{AC} + J_{AD}|_{trans} < |J_{AB} + J_{AC} + J_{AD}|_{cis}$ (Table I). This difference in the ΣJ values for the H_A resonance signals is attributed to the difference in coupling constants between the cyclopropyl protons on the substituted carbon atoms. Since $J_{cis} > J_{trans}$, compounds of the cis configuration should have the larger ΣJ for the H_A resonance signal.

***cis*- and *trans*-2-(2′-Tetrahydropyranylthio)cyclopropylmethylamines (4).**—Geometrically pure *cis*- and *trans*-2-(2′-tetrahydropyranylthio)cyclopropylmethylamines (**4**) are most conveniently prepared from the respective pure cis and trans nitriles **5b**. Lithium aluminum hydride ($LiAlH_4$) reduction of nitriles **5b** afforded the aminomethyl compounds **4** in greater than 60% isolated yield. Esters **5a** may also be converted to **4** by two different routes. Since ester **5a** is formed in an approximate geometrical ratio of 9 parts trans to 1 part cis, ester **5a** to methylamine **4** conversion is most applicable for the trans isomer.

Ammonolysis of trans esters **5a** is dependent upon the catalytic effect of the solvent and the length of the reaction time.[11] When H_2O or methanol were employed as a solvent a 30% conversion of *trans*-**5a** to amide **19** was observed after 14 days in a pressure bottle. When the reaction time was extended to 2 months and solvent methanol was used, amide **19** was obtained in >95% yield. However, with ethylene glycol as solvent, a greater than 60% conversion of trans ester **5a** to amide **19** was obtained in 18 days.

Attempts to crystallize trans amide **19** after column chromatography and under a variety of conditions always afforded a gummy semisolid. The purity of **19** was confirmed by glpc and characterized by the absence of ester carbonyl absorption at 1750 cm^{-1} and the presence of amide carbonyl absorption (1675 cm^{-1}), plus NH stretching (3350 and 3200 cm^{-1}) and bending (1620 cm^{-1}) absorption bands.[12] $LiAlH_4$ reduction of amide **19** affords 2-(2′-tetrahydroxypyranylthio)cyclopropylmethylamine (**4**) identical with the amine prepared by $LiAlH_4$ reduction of trans nitrile **5b**.

Alternatively, *trans*-**4** may be prepared from *trans*-**5a** by the following sequence: $LiAlH_4$ reduction of *trans*-**5a** afforded the *trans*-cyclopropylcarbinol **20**. If the 9:1 trans–cis ratio of esters **5a** was employed as starting material a similar ratio of trans–cis carbinol **20** was obtained. For convenience, this ratio of geometrical isomers was used to explore subsequent reaction steps. The tosylate **21** prepared from trans–cis carbinol **20** is unstable and was used without further purification. Reaction of tosylate **21** with 10 molar excess NaN_3 in DMF afforded azide **23** in approximately 90% yield. $LiAlH_4$ reduction of azide **23** afforded *trans–cis*-**4** in a ratio of 9:1. Similarly, mesylate **22** was prepared from carbinol **20** in 39% yield.



Displacement with azide ion followed by $LiAlH_4$ reduction afforded trans–cis amine **4** in 89% overall yield. The ratio of geometrical isomers was the same as the ratio found in starting ester **5a**.

Conversion of *trans*-**4** to *trans*-**3** was unsuccessful. Under conditions utilizing gaseous HCl or various concentrations of aqueous HCl in Et_2O, MeOH, EtOH, or *i*-PrOH a hygroscopic brown solid was obtained which failed to crystallize even after cation exchange resin chromatography. Infrared analysis (KBr) of this solid showed the absence of characteristic bands for the tetrahydropyranyl group at 1100, 1080, 1035, and 1010 cm^{-1} and the presence of a strong cyclopropane ring signal at 1045 cm^{-1}. Bands owing to NH stretching (3380, 3000 cm^{-1}, broad) and NH bending (strong, 1600 and 1490 cm^{-1}) were also present. These data are in agreement with structure **3**. However, nmr analysis of this solid showed extra protons to be present where the protecting group proton resonances are found. While the tetrahydropyranyl group may have been removed, fragments resulting from its cleavage were apparently still present in solution. Attempts to remove the impurities from this reaction product by cation exchange resin chromatography or by continued ether extraction resulted in no change in the product spectral analysis. However, preliminary results indicated that the best conditions for converting amine **4** to amine HCl **3** is the one which utilizes *i*-PrOH as solvent and gaseous HCl (10 min). A white crystalline solid was obtained which is stable under solvent (*i*-PrOH–Et_2O), but which rapidly decomposes (turns black) upon solvent removal. Attempts to work up the reaction product under N_2 also resulted in product decomposition.

Experimental Section[13]

2-Mercaptoethyl chloride (**9**) was prepared by a modification of the method of Meade and Woodward.[4] In a 500-ml three-necked flask provided with a magnetic stirrer, thermometer, gas-inlet

(11) M. Gordon, J. G. Miller, and A. R. Day, *J. Amer. Chem. Soc.*, **71**, 1245 (1949).

(12) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," K. L. Rinehart, Jr., Ed., Prentice-Hall, Englewood Cliffs, N. J., 1965, p 36.

(13) Nmr spectra were recorded utilizing a Varian A-60A spectrometer. Infrared spectra was recorded utilizing Perkin-Elmer 237 and 257 spectrophotometers. Gas–liquid chromatographs were obtained using an F & M Model 402 gas chromatograph equipped with flame ionization detector and glass columns. Melting points were taken on a calibrated Thomas–Hoover melting point apparatus. Analyses were determined by Clark Microanalytical Laboratory, Urbana, Ill.

and drying tubes was placed 12.0 g (0.2 mol) of ethylene sulfide (10) in 300 ml of dry ether. The ether solution was chilled to −10°, and, with rapid stirring, HCl gas, generated from NaCl (reagent grade) and H_2SO_4, was bubbled through the solution for 3 hr. The ether was removed under reduced pressure and the residue fractionally distilled affording 17.7 g (93.3%) of 9: bp 50–51° (95 mm) [lit.[4] bp 113–113.5° (760 mm)]; ir (liquid film) 2570 cm^{-1} (sh stretch).

2,3-Dihydropyran (11) was purchased from Aldrich Chemical Co., Milwaukee, Wis., and was freshly distilled.

2-(β-Chloroethylthio)tetrahydropyran (12) **from 2-Mercaptoethyl Chloride** (9).—2-Mercaptoethyl chloride (9, 19.2 g, 0.2 mol), and 16.8 g (0.2 mol) of 2,3-dihydropyran (11) with a few crystals of *p*-toluenesulfonic acid were placed in a 100-ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser. The mixture was heated on a steam bath for approximately 3 hr. The reaction mixture was fractionally distilled affording 34.3 g (90%) of 2-(β-chloroethylthio)tetrahydropyran (12): bp 72° (0.35 mm); ir (liquid film) 2850 and 2940 (CH_2 stretch), 995, 1025, 1070, and 1090 $cm.^{-1}$ (cyclic ether); nmr (neat) δ 1.42–1.92 [broad, 6 H, $-(CH_2)_3-$], 2.7–3.0 (multiplet, 2 H, $-SCH_2-$), 3.52 and 3.62 (doublet, 2 H, $-CH_2Cl$), 4.98 (multiplet, 1 H, –O—CH—S–), and 3.38–4.3 (broad, multiplet, 2 H, $-OCH_2-$).

Anal. Calcd for $C_7H_{13}OSCl$: C, 46.52; H, 7.25; S, 17.74; Cl, 19.62. Found: C, 46.40; H, 7.44; S, 18.28; Cl, 20.77.

Preparation of 2-(β-Chloroethylthio)tetrahydropyran (12) **from Ethylene Sulfide** (10). **An Alternative Method.**—In a 500-ml three-necked flask fitted with a dropping funnel (equipped with a drying tube), thermometer, gas inlet tube, and magnetic stirrer was placed 30.0 g (0.5 mol) of freshly distilled ethylene sulfide (10) in 400 ml of anhydrous ether. The solution was chilled to −10°, and, with rapid stirring, gaseous HCl was bubbled into the mixture for 3 hr. The gas flow was stopped and 42 g (0.5 mol) of 2,3-dihydropyran (11) was added dropwise along with 100 mg of *p*-toluenesulfonic acid. The reaction mixture was further stirred for 2 hr at −10 to 0°. After removal of the solvent, the residual liquid was fractionally distilled affording 85.0 g (94.5%) of 2-(β-chloroethylthio)tetrahydropyran (12).

2-Chlorotetrahydropyran (13) was prepared by the method of Eliel and Daignault,[14] bp 40° (15 mm) [lit.[14] bp 40–42° (16 mm)].

Reaction of 2-Chlorotetrahydropyran (13) **with Ethylene Sulfide** (10).—To a solution of 30 g (0.5 mol) of ethylene sulfide in 50 ml of CCl_4 was added 60.0 g (0.5 mol) of 2-chlorotetrahydropyran dropwise with stirring at −15°. The reaction mixture was kept in a cold room overnight. Under these conditions, the infrared spectrum of the crude reaction mixture indicated no reaction took place. $AlCl_3$ (0.1 g) was added and the reaction mixture was heated on steam bath for 10 min. After removal of the solvent (CCl_4), the residue was distilled affording 44.6 g (49.6%) of 2-(β-chloroethylthio)tetrahydropyran (12) whose infrared spectra is identical in all respects with compound 12 obtained from 10 and 11.

2-Vinylthiotetrahydropyran (8) **from 2-(β-Chloroethylthio)-tetrahydropyran** (12). **KOH Method.**—In a 100-ml two-necked flask provided with a dropping funnel, distilling head, and condenser was placed 3.0 g of finely powdered KOH suspended in 5 ml of dry ether. To this was added 9.0 g (0.05 mol) of 2-(β-chloroethylthio)tetrahydropyran (12) in small portions. The mixture was heated to 130° and the 2-vinylthiotetrahydropyran (8) mixed with H_2O was removed by distillation (60 mm). A reduced pressure of 20 mm was applied to remove residual amounts of 8 from the reaction mixture. After distillation the crude distillate was treated with 10 ml of saturated NaCl and extracted with several 20-ml portions of ether. The combined ether extracts were dried (Na_2SO_4), filtered, and distilled under reduced pressure affording 6.0 g (83.3%) of 2-vinylthiotetrahydropyran (8): bp 74–75° (10 mm), 78° (11 mm); ir (liquid film) 3095 ($C=CH_2$, stretch), 2850 and 2940 (CH_2, stretch), 1590 and 960 ($-SCH=CH_2$), 1000, 1030, 1075, and 1100 cm^{-1} (tetrahydropyranyl group); nmr (neat) δ 1.42–1.92 [broad, 6 H, $-(CH_2)_3-$], 3.5–4.05 (broad, multiplet, 2 H, $-OCH_2-$), 4.98 (multiplet, 1 H, –S—CH—O–), vinyl protons ($-SCH=CH_2$), absorption at 5.0–5.4 (AB) and 6.42 (X) with $|J_{cis} + J_{trans}| = 27$ Hz.

Anal. Calcd for $C_7H_{12}OS$: C, 57.29; H, 8.39; S, 22.22. Found: C, 57.57; H, 8.25; S, 22.30.

2-Vinylthiotetrahydropyran (8) **from 2-(β-Chloroethylthio)tetrahydropyran** (12). ***N,N*-Diethylaniline Dehydrochlorination.**—Nine grams (0.05 mol) of 2-(β-chloroethylthio)tetrahydropyran and 16.3 g (0.1 mol) of *N,N*-diethylaniline was heated at 150° under reflux for 10 hr. After cooling, the solid *N,N*-diethylaniline HCl was filtered and washed with dry ether. The combined filtrates were fractionally distilled affording 3.0 g (41.7%) of 2-vinylthiotetrahydropyran (8), bp 78–79° (11 mm), whose properties were identical in all respects with compound 8 described above.

Reaction of 2-Vinylthiotetrahydropyran (8) **with Ethyl Diazoacetate** (6). **Copper Catalyst. Anhydrous Xylene Method.**—In a 500-ml three-necked flask provided with a reflux condenser (drying tube), two dropping funnels, and a magnetic stirrer is placed 25 g (0.175 mol) of 2-vinylthiotetrahydropyran (8) in 25 ml of dry xylene containing 200 mg of copper powder. The xylene solution was taken to 140° and by means of the dropping funnels the remaining 25.0 g (0.175 mol) of 8 and 39.6 g (0.35 mol) of ethyl diazoacetate (6) were simultaneously added (1 drop/20 sec). When the addition was completed and evolution of N_2 stops, the reaction mixture was refluxed for 2 hr. The crude reaction mixture was filtered and the solvent xylene and volatile products were removed under reduced pressure. The residual oil, analyzed by gas–liquid partition chromatography [3.8% silicone gum rubber (UC-W98)[15] on Chromosorb W (80–100 mesh), 4 ft × 0.25 in. glass column, temperature 175°, injection port temperature 290°, detector (flame) temperature 275°, inlet pressure of 40 psi, and carrier gas (He) flow rate of 40 ml/min], shows 15.4% at 24 sec (starting 8), 35.3% unidentified product at 1 min, 1.2 min, and 1.4 min, 5.4% unidentified compound at 2 min, and 42.5% at 3 min with a shoulder peak at 3.2 min [2-(2′-tetrahydropyranylthio)-1-carbethoxycyclopropanes, 5a]. The crude reaction mixture was fractionally distilled employing a 10-cm micro-Vigreux column. The following fractions were obtained: fraction I, 10.0 g [bp 23–24° (0.05 mm), glpc 1 peak at 24 sec]; fraction II, 5.4 g [bp 65–69° (0.05 mm), glpc 3 peaks at 1.0, 1.2, and 1.4 min with 3 minor <1% contaminants]; fraction III, 5.0 g [bp 88–100° (0.06 mm), glpc 3 peaks at 1.2, 1.4, and 3.0 min]; fraction IV, 10.0 g [bp 100–110° (0.06–0.16 mm), glpc 2 peaks at 1.4 and 3.0 min with 2 minor peaks (attributed to tricarbethoxycyclopropane, 14)]; fraction V, 17.7 g [bp 115–130° (0.2 mm), glpc 1 peak at 3.0 min with 1 minor peak at 2.2 min (attributed to 14)]; fraction VI, undistilled material. Infrared analysis shows the presence of cyclopropane derivatives (bands at 1005, 1035, 1075, and 1100 cm^{-1}, attributed to tetrahydropyranyl and cyclopropane rings) in fraction VI. Infrared spectra of fraction III, IV, and V prove these fractions all contain the desired cyclopropane derivatives 5a. On standing, a small amount of solid (approximately 200 mg) was isolated from these fractions (III, IV, and V) whose infrared spectrum is identical in all respects with an authentic sample of 3-carbethoxypyrazole (15): mp 158–159° (lit.[16] mp 160°); nmr ($DCCl_3$) δ 1.31 (triplet, 3 H, CH_3), 2.52 (broad, 1 H, NH), 4.30 (quartet, 2 H, OCH_2), 6.79 (doublet, 1 H, H^4), and 7.82 (doublet, 1 H, H^5), $J_{4,5} = 2.2$ cps.

Anal. Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.71; N, 20.00. Found: C, 51.16; H, 5.55; N, 19.46.

In a similar reaction 72.0 g (0.5 mol) of 8 and 57.0 g (0.5 mol) of 7 afforded a reaction mixture (121.7 g) after removal of most of the xylene. Glpc analysis of the reaction mixture showed the same ratio of products formed as above. The reaction mixture was fractionated by spinning-band distillation affording 17.0 g (14.0%) of starting material 8 [bp 23–25° (0.05 mm), glpc 1 peak], 25.8 (21.5%) of by-products [bp 35–70° (0.05 mm), glpc 4 peaks], and 78.9 g (65%) of undistilled material whose infrared spectrum showed the presence of desired cyclopropane derivatives 5a (liquid film, at 2970, 2940, 2860, 1725, 1465, 1445, 1400, 1380, 1355, 1340, 1290, 1265, 1205, 1180, 1100, 1080, 1040, 1010, 905, 885, 875, 840, 820, 770, and 730 cm^{-1}). Glpc analysis on 3.8% silicone gum rubber (UC-W98)[15] on Chromosorb W (80–100 mesh), 4 ft × 0.25 in. glass column with column temperature 195°, injection port temperature 265°, detector temperature 225°, inlet pressure 40 psi, and carrier gas (He) flow rate at 60 ml/min shows a single peak for *cis-trans*-5a (1.8 min, >90%) with 2 minor impurities (2.6 and 3.3 min). Tlc analysis on silica gel G with $CHCl_3$ showed two migrating spots. This crude ester 5a was then chromatographed on silica gel–charcoal

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(15) Hewlett-Packard, Mosely Division, Pasadena, Calif.

(16) R. I. Meltzer, A. D. Lewis, F. H. McMillan, J. D. Genzer, F. Leonard, and J. A. King, *J. Amer. Pharm. Ass.*, **42**, 594 (1953).

(80–20) to remove any polymeric tar. The $CHCl_3$ eluate containing 70.6 g of **5a** was either separated into pure cis and trans isomers or used as such in subsequent reactions.

Separation of *cis*- and *trans*-2-(2′-Tetrahydropyranylthio)-1-carbethoxycyclopropane (5a).—The crude ester (**5a**, 10.0 g) was chromatographed (2 times) on dry silicic acid (65 × 5.0 cm column) utilizing $CHCl_3$ as the eluting solvent. The pure trans ester **5a** eluted first, followed by a mixture of cis and trans esters **5a**. The cis ester **5a** eluted last and was contaminated with an unidentified minor impurity. The pure trans ester **5a** obtained [bp 95–98° (0.03 mm)] exhibited an infrared spectrum similar to that of crude ester **5a** with major bands assigned to the tetrahydropyranyl group (2940, 2860, 1100, 1080, 1040, and 1010 cm^{-1}), carbonyl group (1725 cm^{-1}), and cyclopropane ring (2980, 1040 cm^{-1}); nmr ($DCCl_3$, 20%), δ 1.27 (triplet, 3 H, CH_3), 1.00–2.15 [broad, 9 H, $-(CH_2)_3-$ and $-CH_2-$ of cyclopropane and >CH of cyclopropane α to CO_2Et group], 2.52 (multiplet, 1 H, >CH of cyclopropane proton α to S), 4.15 (quartet, 2 H, CH_2 of ethyl group), 3.3–4.4 (broad, multiplet, 2 H, $-OCH_2-$), and 4.98 (unresolved quartet, 1 H, –O—CH—S–).

Anal. Calcd for $C_{11}H_{18}O_3S$: C, 57.39; H, 7.82; S, 13.91. Found: C, 56.81; H, 7.70; S, 13.86.

cis-**13** eluted in the presence of an unidentified minor impurity [glpc analysis on 3.8% silicone gum rubber (UC-W98)[15] on Chromosorb W (80–100 mesh), 4 ft × 0.25 in. glass column with column temperature 180°, injection port temperature 285°, detector temperature 240°, inlet pressure of 40 psi, and carrier gas (He) flow rate of 60 ml/min, 2 peaks at 3 min 3 sec (95.6%, *cis*-**5a**) and 3 min 10 sec (4.4%, impurity)]. The infrared spectrum of impure *cis*-**5a** was nearly identical with that of *trans*-**5a** with a few minor differences [absence of bands at 1205 cm^{-1} and the presence of additional bands at 1240, 1290, and 1300 cm^{-1}]: nmr ($DCCl_3$, 20%) δ 1.28 (triplet, 3 H, CH_3), 1.00–2.10 [broad, 9 H, $-(CH_2)_3-$ and $-CH_2-$ and >CH of cyclopropane α to CO_2Et], 2.48 (multiplet, 1 H, >CH of cyclopropane proton α to S), 4.15 (quartet, 2 H, $-CH_2-$ of ethyl group), 3.3–4.4 (broad, multiplet, 2 H, $-OCH_2-$), and 4.90 (unresolved quartet, 1 H, –O—CH—S–).

Anal. Calcd for $C_{11}H_{18}O_3S$: C, 57.39; H, 7.82; S, 13.91. Found: C, 55.81; H, 7.67; S, 13.54.

Diazoacetonitrile (7).—In a 1-l. three-necked round bottom flask provided with a mechanical stirrer, dropping funnel, gas inlet and outlet, and a thermometer was placed 69 g (0.45 mol) of finely powdered α-aminoacetonitrile bisulfite suspension in 400 ml of CH_2Cl_2. The solution was chilled to −10°. Under N_2 atmosphere and with rapid stirring, 94.2 g (1.35 mol) of $NaNO_2$ in a minimum amount of H_2O (nearly saturated) was added dropwise to the reaction flask at such a rate that the temperature of the solution did not rise above 0°. After addition, the mixture was further stirred at 0° for 30 min and then was transferred to a dry 2-l. separatory funnel; the yellow-green CH_2Cl_2 layer was separated and washed with 200 ml of 1% aqueous Na_2CO_3. The aqueous layers are backwashed with CH_2Cl_2 The combined CH_2Cl_2 solutions were dried over anhydrous $CaCl_2$; this solution was utilized in subsequent reactions.

Reaction of 2-Vinylthiotetrahydropyran (8) with Diazoacetonitrile (7) in the Presence of Copper Powder and Anhydrous Cupric Sulfate.—A solution of 26.0 g (0.18 mol) of 2-vinylthiotetrahydropyran (**8**) in 40 ml of dry xylene and 200 mg of Cu powder were placed in a 1-l. three-necked flask provided with a magnetic stirrer, nitrogen inlet, dropping funnel, and a distillation apparatus. Under N_2, with rapid stirring, was added a solution of diazoacetonitrile in CH_2Cl_2 [approximately 47.69 g (0.71 mol) in about 3 l. CH_2Cl_2]. This solution was added dropwise with 100 ml of dry xylene at such a rate as to avoid a vigorous reaction. The temperature of the oil bath was maintained at 120°; the solvent CH_2Cl_2 was continuously removed by distillation. After CH_2Cl_2 removal, 100 mg of anhydrous $CuSO_4$ was added to the reaction mixture. Refluxing was continued for an additional 2 hr at 130°. The solvent xylene was distilled under reduced pressure. Glpc of the crude residue on 3.8% silicone gum rubber (UC-W98)[15] on Chromosorb W (80–100 mesh), 4 ft × 0.25 in. glass column with column temperature 200°, injection port temperature 305°, detector (flame) temperature 245°, inlet pressure of 40 psi, and carrier gas (He) flow rate of 40 ml/min shows 17.0% at 20 sec (starting **8**), 56.3% at 26.5, 30.0, 31.2, and 39.0 sec (unidentified by-products believed to be formed from selfcondensation of diazoacetonitrile), 11.6% at 55.2 sec (*trans*-**5b**), 8.9% at 1.1 min (*cis*-**5b**), and 6.2% at 12.5 min (diastereoisomer **5b**). The crude residue was chromatographed through a 30 × 15 cm silica gel–$CHCl_3$ column (100–200 mesh) to remove tar. The crude eluate (containing 46.5 g product) was fractionally distilled using a micro-Vigreux column affording fraction I, 7.0 g, bp 28° (0.06 mm) representing starting olefin; fraction II, 8.2 g, bp 46–55° (0.025 mm), glpc 4 peaks (one major) of unidentified products. Fraction III remains undistilled. This residue was twice chromatographed on silicic acid with $HCCl_3$ (42 × 5.5 cm column) affording 6.98 g (21.2%) of an impure product **5b**. This impure material (glpc 3 peaks calculates for 43.4% *trans*-**5b**, 33.3% *cis*-**5b**, and 23.3% cis diastereoisomer **5b**) was further chromatographed on silicic acid–$HCCl_3$ affording pure *trans*-2-(2′-tetrahydropyranylthio)cyclopropylnitrile (**5b**) followed by a mixture of cis and trans isomers and pure *cis*-**5b** and then the diastereoisomeric cis product: ir *trans*-**5b** (liquid film) 2860, 2940, and 3010 (CH_2 stretch), 2250 (CN), 1010, 1040, 1080, and 1110 cm^{-1} (tetrahydropyranol and cyclopropane rings); nmr ($DCCl_3$, 50%) δ 1.25 (multiplet, 2 H, $-CH_2-$ of cyclopropane ring), 1.68 [broad, 7 H, $-(CH_2)_3-$ and >CH of cyclopropane α to CN), 2.58 (multiplet, 1 H, >CH of cyclopropane α to S), 3.48 and 4.05 (multiplet, 2 H, $-OCH_2-$), 5.02 (unresolved quartet, 1 H, –OCHS–).

Anal. Calcd for $C_9H_{13}OSN$: C, 58.98; H, 7.20; S, 17.54; N, 7.70. Found: C, 58.64; H, 7.09; S, 17.96; N, 7.65.

The infrared spectrum of pure *cis*-**5b** was essentially identical with that of the trans isomer: nmr ($DCCl_3$, 50%) δ 1.25 (multiplet, 2 H, $>CH_2$ of cyclopropane), 1.70 [broad, 7 H, $-(CH_2)_3-$ and >CH of cyclopropane α to CN], 2.54 (octet, 1 H, with J = 7.8, 7.2, 6.3 ± 0.3 Hz, >CH of cyclopropane α to S), 3.55 and 4.08 (multiplet, 2 H, $-OCH_2-$), 5.18 (unresolved quartet, 1 H, –OCHS–).

Anal. Calcd for $C_9H_{13}OSN$: C, 58.98; H, 7.20; S, 17.54; N, 7.70. Found: C, 59.01; H, 7.19; S, 16.95; N, 8.01.

The infrared spectrum of pure diastereoisomeric product **5b** was essentially identical with that of the trans isomer **5b**: nmr ($DCCl_3$, 50%) δ 1.15 (multiplet, 2 H, $>CH_2$ of cyclopropane), 1.70 [broad, 7 H, $-(CH_2)_3-$ and CH of cyclopropane α to CN], 2.46 (multiplet, 1 H, >CH of cyclopropane α to S), 3.55 and 4.08 (multiplet, 2 H, $-OCH_2-$), 5.05 (unresolved quartet, 1 H, –OCHS–).

***trans*-2-(2′-Tetrahydropyranylthio)cyclopropylmethylamine (4).**—A solution of 442.7 mg (2.42 × 10^{-3} mol) of *trans*-2-(2′-tetrahydropyranylthio)cyclopropylnitrile (**5b**) in 10 ml of dry ether was added dropwise to a suspension of 736 mg (2.15 × 10^{-2} mol) of $LiAlH_4$ in 40 ml of dry ether. After addition, the mixture was refluxed for 1 hr and cooled and 15 ml of ethanol followed by 20 ml of ice–water was added. The solution was filtered and both the solid aluminum hydroxide and filtrate were extracted with three 30-ml portions of ether. The combined ether extracts were dried (Na_2SO_4), filtered, and removed under reduced pressure. The residual amine was distilled affording 297 mg (66.0%) pure *trans*-**4**. Glpc analysis on 3.8% silicone gum rubber (UC-W98)[15] on Chromosorb W (80–100 mesh), 4 ft × 0.25 in. glass column with column temperature 180°, injection port temperature 285°, detector temperature 245°, inlet pressure of 40 psi, and carrier gas (He) flow rate of 60 ml/min, shows 1 peak at 1.35 min (99.1%) with 1 minor peak at 0.9 min (0.9%): ir (liquid film) 3280 and 3360 (broad, NH_2 stretch), 3000, 2940 and 2860 (CH_2 stretch), 1590 (broad, NH bending), 1015, 1045, 1085, and 1110 cm^{-1} (tetrahydropyranyl and cyclopropane rings); nmr ($DCCl_3$, 20%) δ 0.74 (multiplet, 2 H, $-CH_2-$ of cyclopropane ring), 1.30 (multiplet, 1 H, >CH of cyclopropane proton α to CH_2), 1.40–2.10 [broad, 7 H, $-(CH_2)_3-$ plus >CH of cyclopropane α to S], 2.39 (singlet, 2 H, NH_2), 2.73 (multiplet, 2 H, $-CH_2N$), 3.54 and 4.05 (multiplet, 2 H, $-OCH_2-$), 4.94 (unresolved quartet, 1 H, –OCHS–).

Anal. Calcd for $C_9H_{17}OSN$: C, 57.71; H, 9.14; S, 17.11; N, 7.47. Found: C, 58.26; H, 9.17; S, 16.64; N, 6.58.

***cis*-2-(2′-Tetrahydropyranylthio)cyclopropylmethylamine (4).**—A procedure identical with the preparation of the trans isomer was utilized. Thus, 250 mg (1.38 × 10^{-3} mol) of *cis*-**5b** was reduced by 420 mg (1.1 × 10^{-2} mol) of $LiAlH_4$ to yield 160 mg (62.5%) of *cis*-**4**. Glpc analysis on 3.8% silicone gum rubber (UC-W98)[15] on Chromosorb W (80–100 mesh), 4 ft × 0.25 in. glass column with column temperature 180°, injection port temperature 285°, detector temperature 245°, inlet pressure of 40 psi, and carrier gas (He) flow rate of 60 ml/min, shows 1 peak at 1.50 min (99.5%) with 1 minor peak at 1.2 min (0.5%): ir (liquid film) 3200–3350 (broad, NH_2 stretch), 2940 and 2860 (CH_2 stretch), 1590 (weak, broad, NH bending), 1015, 1045, 1085, and 1100 cm^{-1} (tetrahydropyranyl and cyclopropane rings); nmr ($DCCl_3$, 20%) δ 0.43 (octet, 1 H, >CH of cyclopropane), 1.02 (multiplet, 2 H,

CH_2 of cyclopropane), 1.68 [broad, 6 H, $-(CH_2)_3-$], 2.21 (unresolved peak, 1 H, >CH of cyclopropane), 2.43 (singlet, 2 H, NH_2), 2.89 (doublet, $J_{CH_2,H}$ = 6.5 Hz, 2 H, CH_2N), 3.55 and 4.08 (multiplet, 2 H, $-OCH_2-$), 4.94 (unresolved quartet, 1 H, -OCHS-).

Anal. Calcd for $C_9H_{17}OSN$: C, 57.71; H, 9.14; S, 17.11; N, 7.47. Found: C, 57.94; H, 9.23; S, 15.82; N, 6.71.

Ammonolysis of *trans*-2-(2′-Tetrahydropyranylthio)-1-carbethoxycyclopropane (5a).—The preparation of 2-(2′-tetrahydropyranylthio)cyclopropanecarboxamide (19) was studied under a variety of conditions: *i.e.*, at room temperature in concentrated NH_4OH, NH_3 in methanol or ethylene glycol, and under pressure in liquid NH_3. The best result was obtained when ethylene glycol is employed as solvent. Thus, 1.7 g (7.4×10^{-3} mol) of ester **5a** dissolved in 50 ml of saturated ethylene glycol–ammonia solution was placed in a pressure bottle and allowed to stand for 18 days at room temperature. A small amount of black precipitate was observed on standing for 1 day but redissolves after 3 days. After 18 days the bottle was cooled and opened; the NH_3 was removed by gentle warming on a steam bath. The ethylene glycol was removed under reduced pressure (0.02 mm). The concentrated solution was extracted with ether affording 0.87 g (58%) of gummy amide **19**: ir (liquid film) 3200 and 3320 (NH_2 stretch), 1670 (broad, C=O), 1615 (NH bending), 1010, 1040, 1080, and 1108 cm^{-1} (tetrahydropyranyl ring); nmr (CD_3OD, 20%) δ 1.05 (multiplet, 2 H, $>CH_2$ of cyclopropane ring), 1.68 [broad, 7 H, $-(CH_2)_3-$ and >CH of cyclopropane ring α to $CONH_2$ group], 2.43 (multiplet, 1 H, >CH of cyclopropane proton α to S), 3.64 and 4.09 (multiplet, 2 H, $-OCH_2-$), 5.01 (unresolved quartet, 1 H, -OCHS-). Attempts to crystallize this compound failed even after column chromatography. Alternatively, a 95% conversion of ester **5a** to amide **19** was obtained when 4.2 g (1.9×10^{-2} mol) of ester **5a** in 50 ml of MeOH and 14.5 g of NH_3 in a pressure bottle was allowed to stand for 67 days at room temperature. Amide **19** prepared by either method was not further purified.

***trans*-2-(2′-Tetrahydropyranylthio)cyclopropylmethylamine (4) from 2-(2′-Tetrahydropyranylthio)cyclopropylcarboxamide (19).**—A solution of 954.3 mg (4.2×10^{-3} mol) of amide **19** in 40 ml of Et_2O was added dropwise to a stirred suspension of 0.4 g (1.25×10^{-2} mol) of $LiAlH_4$ in 20 ml of Et_2O. The mixture was refluxed on steam bath for 2 hr. While cooling, 10 ml of absolute ethanol followed by 10 ml of ice–water was added. The mixture was filtered and extracted with Et_2O, dried (Na_2SO_4), filtered, and removed under reduced pressure affording trans amine **4** (395 mg, 50.3%) whose physical and spectral properties were identical in all respects with those of trans amine **4** obtained from lithium aluminum hydride reduction of the trans cyclopropylnitrile **5b**.

***trans*-2-(2′-Tetrahydropyranylthio)cyclopropylcarbinol (20).**—A solution of 2.0 g (8.7×10^{-3} mol) of trans cyclopropyl ester **5a** in 20 ml of anhydrous ether was added dropwise to a stirred suspension of 0.6 g (1.6×10^{-2} mol) of $LiAlH_4$ in 20 ml of anhydrous ether. After completion of the addition, the reaction mixture was refluxed (steam bath) for 1 hr. The mixture was cooled and the excess $LiAlH_4$ was decomposed by addition of 10 ml of ethanol followed by 30 ml of ice–water. The mixture was filtered, extracted with ether, dried (Na_2SO_4), filtered, and fractionally distilled affording 1.4 g (85.4%) of *trans*-**20**: bp 100–103° (0.05 mm); ir (liquid film) 3320–3420 (broad, OH), 2940 and 2860 (CH_2 stretch), 3000 (weak, >CH stretch of cyclopropane), 1010, 1035, 1080, and 1106 (tetrahydropyranyl group), 1035 cm^{-1} (strong, cyclopropane ring); nmr ($DCCl_3$, 20%) δ 0.84 (multiplet, 2 H, $-CH_2-$ in cyclopropane ring), 1.18 (multiplet, 1 H, >CH of cyclopropane proton α to CH_2OH), 1.20–2.30 [broad, 7 H, $-(CH_2)_3-$ in tetrahydropyranyl group, >CH of cyclopropane proton α to S], 3.27 (singlet, 1 H, OH), 3.05–4.32 (broad, multiplet, 2 H, $-CH_2O-$), 4.98 (unresolved quartet, 1 H, -OCHS-).

Anal. Calcd for $C_9H_{16}O_2S$: C, 57.41; H, 8.57; S, 17.03. Found: C, 57.01; H, 8.68; S, 16.70.

2-(2′-Tetrahydropyranylthio)cyclopropylcarbinol *p*-Toluenesulfonate (21) from Alcohol 20.—For convenience and to facilitate investigation of the reaction sequence (**20** → **4** conversion) alcohol **20** was prepared from the mixture of *cis*- and *trans*-**5a** present in a ratio of 1 part cis to 9 parts trans. 2-(2′-Tetrahydropyranylthio)cyclopropylcarbinol (**20**, 2.6 g, 1.26×10^{-2} mol) in 50 ml of dry pyridine was cooled on an ice bath. With rapid stirring a solution of 7.23 g (3.78×10^{-2} mol) of *p*-toluenesulfonyl chloride in 20 ml of dry pyridine was added. The reaction mixture was allowed to stand at −5° overnight, poured into 500 ml of ice–water, and extracted (Et_2O). The ether layer was washed with two 50-ml portions of ice cold 10% HCl followed by 50 ml of 10% $NaHCO_3$ and two 50-ml portions of H_2O. The ether extract was dried (Na_2SO_4), filtered, and removed under reduced pressure affording 978 mg (23%) of a colorless oil (tosylate **21**): ir (liquid film) 2940 and 2860 (CH_2 stretch), 1595 and 1490 (aromatic), 1360 (SO_2 asymmetric stretching), 1185 and 1175 (SO_2 symmetric stretching), 1100, 1075, 1030, and 1005 cm^{-1} (tetrahydropyranyl and cyclopropane rings); nmr ($DCCl_3$) δ 1.21 (multiplet, 2 H, $>CH_2$ of cyclopropane), 1.62 [broad, 7 H, $-(CH_2)_3-$ and >CH of cyclopropane proton α to CH_2], 2.42 (singlet, 3 H, CH_3), 2.56 (multiplet, 1 H, >CH of cyclopropane proton α to S), 3.46 (doublet, 2 H, $-CH_2S$), 3.20–4.35 (multiplet, 2 H, $-OCH_2-$), 4.90 (broad, 1 H, -OCH—S-), and a pair of doublets ($A_2'B_2'$) at 7.31 and 7.76 (J = 8.0 Hz) characteristic of para aromatic substitution. Owing to the instability of this compound it was not further purified.

2-(2′-Tetrahydropyranylthio)-1-azidomethylcyclopropane (23) from Tosylate 21.—A solution of 778.0 mg (2.3×10^{-3} mol) of tosylate **21** in 20 ml of DMF was placed in a 100-ml erlenmeyer flask provided with a reflux condenser and a magnetic stirrer. To this solution, 1.495 g (2.3×10^{-2} mol) of sodium azide was added. The reaction was heated to 120° for 20 hr. The reaction mixture was then poured into ice–water and extracted with ether, dried (Na_2SO_4), filtered, and removed under reduced pressure affording 440.0 mg (90.5%) of azide **23**. Infrared absorption shows bands (liquid film) at 2095 (N≡N), 2940, 2860, 1100, 1075, 1035, and 1005 cm^{-1} (tetrahydropyranyl and cyclopropane rings). This compound could not be crystallized and was not further purified.

$LiAlH_4$ Reduction of 2-(2′-Tetrahydropyranylthio)-1-azidomethylcyclopropane (23).—A solution of 1.20 g (5.6×10^{-3} mol) of azide **23** in 50 ml of dry ether was added dropwise to a suspension of 851.2 mg (2.24×10^{-2} mol) of $LiAlH_4$ in 100 ml of dry ether. The reaction mixture was refluxed on a steam bath for 30 min after completion of the addition. While cooling, 20 ml of absolute ethanol was added followed by 10 ml of ice–water. The reaction mixture was filtered and extracted with ether, dried (Na_2SO_4), filtered, and removed under reduced pressure affording 1.0 g (95.0%) of 2-(2′-tetrahydropyranylthio)cyclopropylmethylamine (**4**) in a cis to trans ratio, determined by glpc, identical with the ratio in the starting ester. The infrared spectrum was identical with the trans amine **4** prepared from 2-(2′-tetrahydropyranylthio)cyclopropylnitrile (**5b**).

2-(2′-Tetrahydropyranylthio)cyclopropylcarbinol Methanesulfonate (22) from Alcohol 20.—Carbinol **20** was prepared from the mixture of *cis*- and *trans*-**5a** present in a ratio of 1 part cis to 9 parts trans. 2-(2′-Tetrahydropyranylthio)cyclopropylcarbinol (**20**, 3.76 g, 2.0×10^{-2} mol) in 100 ml of dry pyridine was stirred and cooled on an ice bath. Methanesulfonyl chloride (6.96 g, 6.0×10^{-2} mol) in 10 ml of dry pyridine was added dropwise. The reaction mixture was allowed to stand at 5° overnight, poured into ice–water, and extracted (Et_2O). The ether layer was washed with water, dried (Na_2SO_4), filtered, and removed under reduced pressure affording 2.12 g (39.0%) of mesylate **22**: ir 1360 (SO_2 asymmetric stretching), 1175 and 1195 (SO_2 symmetric stretching), 1110, 1080, 1040, and 1015 cm^{-1} (tetrahydropyranyl and cyclopropane rings). The mesylate was isolated as a brown oil and was used without further purification.

2-(2′-Tetrahydropyranylthio)cyclopropylmethylamine (4) from Mesylate 22.—A solution of 1.6 g (6.0×10^{-3} mol) of mesylate **22** in 50 ml of DMF and 3.90 g (6.0×10^{-2} mol) of NaN_3 was heated under reflux for 12 hr. The products were isolated according to the procedure described for the conversion of tosylate **21** to azide **23**. An azide (1.20 g, 93.7%) exhibiting an infrared spectrum identical with that of the product obtained from the tosyl derivative was obtained. This azide was characterized by reduction to the corresponding amine **4** utilizing the procedure previously described. Amine **4** was obtained from mesylate **22** in 89.0% overall yield in a ratio of geometrical isomers identical with those observed in starting ester **5a**.

Registry No.—*trans*-**4**, 26310-64-5; *cis*-**4**, 26310-65-6; *trans*-**5a**, 26310-66-7; *cis*-**5a**, 26310-67-8; *trans*-**5b**, 26310-68-9; *cis*-**5b**, 26310-69-0; **8**, 26315-66-2; **12**,

26315-67-3; **15**, 21056-77-9; **19**, 26310-70-3; *trans*-**20**, 26310-71-4; **21**, 26310-72-5.

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The Copper-Catalyzed Addition of Arenesulfonyl Chlorides to Conjugated Dienes, Trienes, and Phenylacetylene[1]

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The copper-catalyzed addition of arenesulfonyl chlorides to 2-methyl-1,3-butadiene (isoprene), 1,3-cyclohexadiene, 1,3-cyclooctadiene, bicyclo[2.2.1]hepta-2,5-diene (norbornadiene), cycloheptatriene, and phenylacetylene to give 1:1 adducts is described. The adducts with 2-methyl-1,3-butadiene and 1,3-cyclohexadiene were dehydrohalogenated to the corresponding acyclic and cyclic 1,3-unsaturated sulfones, respectively.

The copper-catalyzed addition (Asscher–Vofsi reaction) of alkane- and arenesulfonyl chlorides to simple olefins[2] and substituted styrenes[3] has been described previously. This paper presents the results of our studies of the copper-catalyzed addition of arenesulfonyl chlorides to conjugated dienes and trienes.

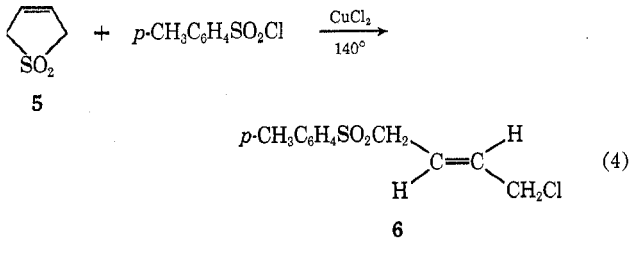
In their original paper, Asscher and Vofsi[2] reported that the reaction of benzenesulfonyl chloride with 1,3-butadiene gave the 1,4-monoadduct (**1**, eq 1). Similarly, we have found that treatment of 2-methyl-1,3-butadiene (**2**) with benzenesulfonyl chloride in the presence of cuprous chloride afforded a good yield of the 1,4 adduct **3** (eq 2). The stereochemistry about the double bond in **3** is uncertain from the 100-MHz nmr spectrum.[4] Treatment of **3** with triethylamine in benzene resulted in dehydrohalogenation to the corresponding diene **4** in 93% yield (eq 3).

$$CH_2{=}CH{-}CH{=}CH_2 + C_6H_5SO_2Cl \xrightarrow{CuCl_2} C_6H_5SO_2CH_2CH{=}CHCH_2Cl \quad (1)$$
1

$$CH_2{=}C(CH_3){-}CH{=}CH_2 + C_6H_5SO_2Cl \xrightarrow{CuCl} C_6H_5SO_2CH_2C(CH_3){=}CHCH_2Cl \quad (2)$$
2 → **3**

$$C_6H_5SO_2CH_2C(CH_3){=}CHCH_2Cl \xrightarrow[C_6H_6]{Et_3N} C_6H_5SO_2CH{=}C(CH_3){-}CH{=}CH_2 \quad (3)$$
3 → **4**

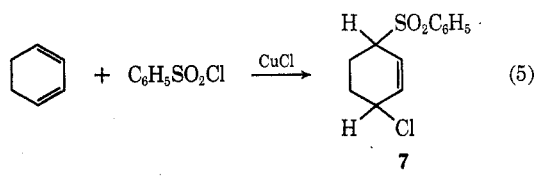
In continuing our investigations of free-radical additions to unsaturated sulfones,[5] the copper-catalyzed addition of benzenesulfonyl chloride to 3-sulfolene (**5**) was also studied. Treatment of **5** with benzenesulfonyl chloride for 2 hr at 108–110° under Asscher–Vofsi conditions resulted in no reaction. When the reaction was repeated with *p*-toluenesulfonyl chloride at 135–140° a vigorous evolution of sulfur dioxide was observed, and the monoadduct with butadiene, 1-chloro-4-(*p*-toluenesulfonyl)-2-butene (**6**), was isolated in 67% yield (eq 4). In view of the known ability of 3-sulfolenes to serve as *in situ* sources of dienes,[6] it is reasonable to assume that butadiene was formed smoothly from 3-sulfolene (which itself is apparently inert to addition under these conditions) and subsequently underwent addition of *p*-toluenesulfonyl chloride to give **6**. The use of 3-sulfolenes as an *in situ* source of dienes in the Asscher–Vofsi reaction thus represents a convenient laboratory method of obtaining 1-chloro-4-(arenesulfonyl)-2-butenes, and avoids the need for employing sealed tube or bomb reactions with the highly volatile dienes.



(4)

5 → **6**

The reaction of sulfonyl chlorides with cyclic conjugated dienes was also investigated. Reaction of benzenesulfonyl chloride with 1,3-cyclohexadiene afforded the 1,4 monoadduct **7** (eq 5). The 100-MHz nmr spectrum of **7** is consistent with a time average conformation in which both substituents are equatorial, indicating a trans addition of the sulfonyl chloride, and in which the molecule is in the half-chair conformation.[4] Treatment of **7** with triethylamine in benzene gave an



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