The intensity data were corrected for Lorentz and polarization effects, but no absorption correction was made. The data set of **2a** was corrected for crystal deterioration.

The structures were solved by the heavy-atom method, and the refinement was carried out by the block-diagonal least-squares procedure.[23,24] Temperature factors were anisotropic for the nonhydrogen atoms and isotropic for the hydrogen atoms. In the refinement, the function minimized was $\Sigma\omega(|F_o| - |F_c|)^2$. For **3a** only nonzero reflections were included, and the temperature factors of the hydrogen atoms were held constant ($B = 3.8$ Å^2) in the refinement; the weight was $1/(\sigma^2|F_o| + a|F_o| + b|F_o|^2)$, and the final refinement ($a = -0.1297$, $b = 0.0140$) gave the $R(\Sigma||F_o| - |F_c||/\Sigma|F_o|)$ of 0.104. For **2a** the weighting scheme was $\omega = 1/2$ for $F_o = \theta$, $\omega = 1$ for $\theta < |F_o| < 2\theta$, and $\omega = (2\theta/|F_c|)^2$ for $|F_o| \geq 2\theta$, and the final R is 0.080 for 1854 nonzero reflections. The atomic scattering factors were taken from ref 24. All the calculations were carried out on FACOM 230-60 and 230-75 computers of Nagoya University.

Acknowledgment. The diffractometer intensity measurements were kindly made possible by Professor M. Kakudo of Osaka University, to whom our thanks are due. We thank Tomomitsu Ito, Yasuyuki Yamada, Hiromi Ito, and Tsuneo Yamamoto of the Faculty of Engineering, Nagoya University, for technical assistance.

Registry No.—**1,** 35211-83-7; **2a,** 64682-19-5; **2b,** 51425-75-3; **3a,** 64682-20-8; **3b,** 64682-21-9; **5,** 64682-22-0; **12,** 64682-23-1; **13,** 64682-24-2; **14,** 64682-25-3; **15,** 64682-26-4; **16,** 64728-31-0; **17,** 64682-27-5; bromine, 7726-95-6; iodine, 7553-56-2; Bu_3SnH, 688-73-3; azobis(isobutyronitrile), 764-28-3; *p*-chlorobenzenethiol, 106-54-7; methanesulfenyl chloride, 5813-48-8; thiocyanogen, 505-14-6.

Supplementary Material Available: Tables II–VI, positional and thermal parameters for the structures **2a** and **32** (7 pages). Ordering information is given on any current masthead page.

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Ring Expansion by [2,3]Sigmatropic Shift: Conversion of Five-Membered into Eight-Membered Heterocycles

E. Vedejs,* J. P. Hagen, B. L. Roach, and K. L. Spear

Department of Chemistry, University of Wisconsin, Madison, Wisconsin 53706

Received August 23, 1977

Syntheses of α-vinyltetrahydrothiophene and 2-vinyl-*N*-benzylpyrrolidine are described. Conversion of these heterocycles into ylides by an alkylation–deprotonation sequence results in rearrangement to eight-membered heterocycles. In the sulfur series, *cis*-thiacyclooctenes are formed preferentially, but a trans alkene has been isolated in one case. In the nitrogen series, comparable amounts of cis and trans alkenes are formed. The origin of olefin geometry is considered as a function of ylide geometry. In both the sulfur and the nitrogen series, the stereochemistry of ylides is subject to interconversion of diastereomers. Reversible deprotonation α to the vinyl group is a sufficient explanation for diastereomer interconversion in both heterocyclic series, but other mechanisms are not ruled out.

Synthetic approaches to macrocyclic natural products under way in our laboratory require the development of methodology for easily repeatable multicarbon ring expansion ("ring growing reactions"). A solution to this problem has been devised using the [2,3]sigmatropic rearrangement of ylides obtained from α-vinyl heterocycles, as described in a preliminary communication.[1] Assuming that techniques for heteroatom extrusion can be developed, these rearrangements provide rapid access to large rings with varying functionality. In this report we shall describe fundamental aspects of the most difficult ring expansion in terms of ring size, the conversion of five- to eight-membered heterocycles.

Preparation of α-Vinyl Heterocycles. Our synthesis of α-vinyltetrahydrothiophene (**3**) begins with the conversion of thietane into the allylic sulfide **2** via fragmentation of an unstable thietanium bromide (**1**, Scheme I). Similar frag-

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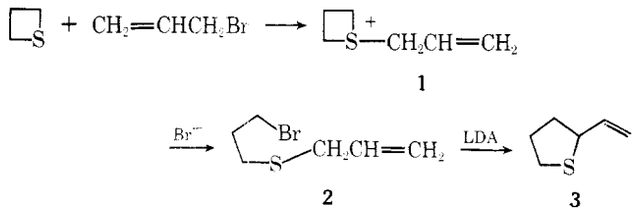
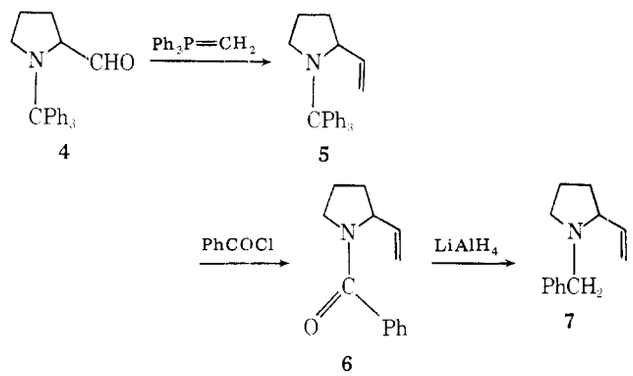
Scheme I



Scheme II



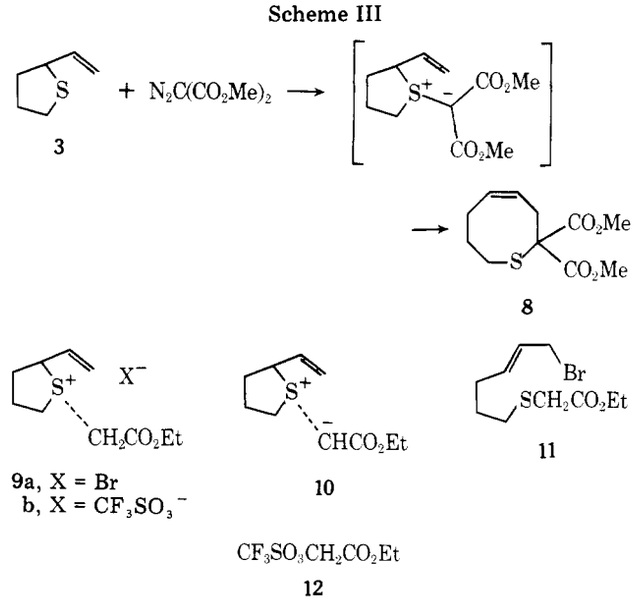
mentation of thietanium salts is well-known.[2] Cyclization to **3** can then be achieved by treatment of **2** with lithium diisopropylamide at −78 °C. An 85% isolated yield of **3** results if **2** is added slowly to the solution of LDA. An alternative route to **3** by Grignard displacement of α-chlorotetrahydrothiophene has also been examined, but it appears less suitable for preparation of reasonable amounts of material.[3]

The analogous nitrogen heterocycle **7** is available from the known *N*-tritylpyrrolidinecarboxaldehyde **4**[4] (Scheme II). The Wittig reaction can be used to convert **4** into the α-vinyl compound **5**, and heating the latter with benzoyl chloride results in **6**. Finally, lithium aluminum hydride reduction affords 2-vinyl-*N*-benzylpyrrolidine (**7**). Attempts to use 2-vinyl-*N*-tritylpyrrolidine (**5**) in ring expansion reactions failed because we were unable to isolate the corresponding *N*-tritylammonium precursors of ammonium ylides.

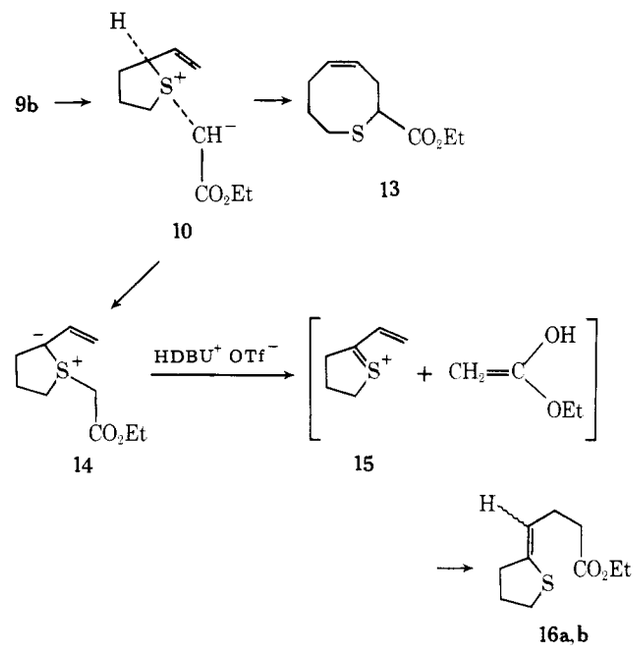
Ring Expansions in the Sulfur Series. A well-precedented approach to generation of sulfur ylides which might undergo ring expansion is to combine the sulfide with a diazocarbonyl compound under conditions of carbenoid generation.[5] Thus, treatment of **3** with dimethyl diazomalonate and copper bronze in toluene at 100 °C results in a single major product (53% isolated) which has all of the spectral characteristics expected for the *cis*-thiacyclooctene **8** (Scheme III). No other isomers can be isolated in significant quantity. Attempts to employ a similar carbenoid decomposition of ethyl diazoacetate for generation of ylide **10** proved unsatisfactory. At best, 15% of a ring expansion product, **13** (Scheme IV), was formed according to GLPC analysis, and numerous polar side products were also present.

An alternative approach to **10** was considered. Alkylation of **3** with ethyl bromoacetate should give the sulfonium bromide **9a**, and subsequent deprotonation would lead to **10**. However, it proved necessary to heat **3** in neat ethyl bromoacetate to achieve conversion of the starting material. Under these conditions no salts could be isolated at all. Instead, a neutral substance, **11**, was obtained; **11** is obviously derived from **9a** by nucleophilic attack of bromide ion at the vinyl terminus. In order to avoid this side reaction, an alkylating agent having a nonnucleophilic anion as the leaving group was necessary. The trifluoromethanesulfonate **12**[6] derived from ethyl glycolate proved ideal for the problem at hand. Thus, **3** affords crystalline triflate salt **9b** (86%) after

Scheme III



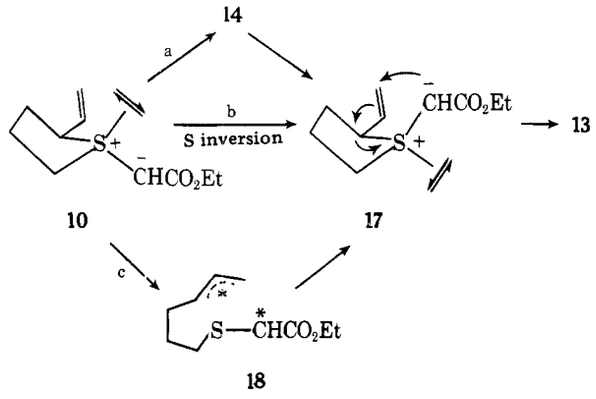
Scheme IV



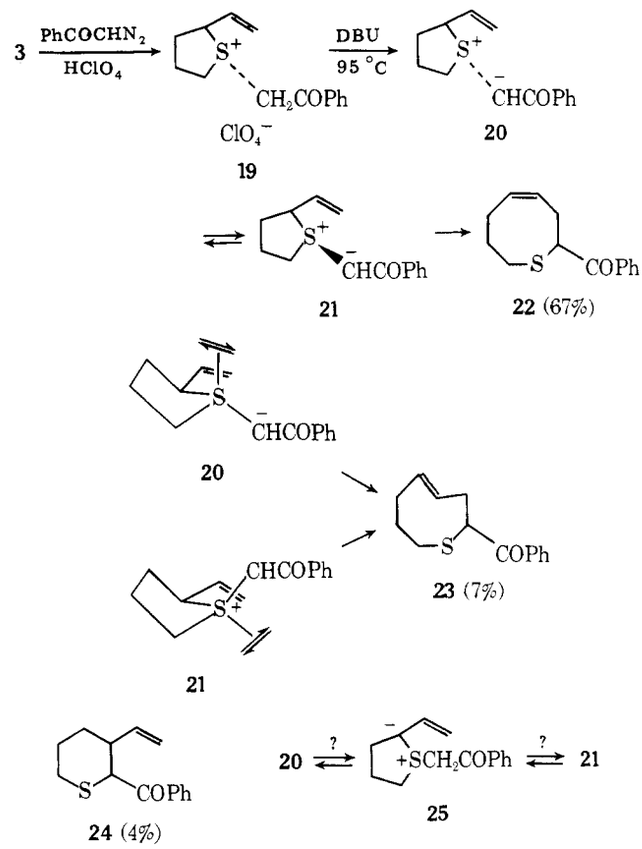
treatment with **12** at 0 °C. The crystalline salt is obviously homogeneous by NMR spectroscopy and is assigned the trans stereochemistry based on the assumption that least hindered approach by alkylating agent **12** occurs under the conditions used. On treatment with sodium bromide in a two-phase system of water–chloroform, **9b** is converted into **11** (77% isolated) after 2.5 h at room temperature. Thus, nucleophilic agents must be avoided in subsequent reactions of salts related to **9**.

Ring expansion of **9b** can be achieved with a variety of bases, including K_2CO_3, LDA, and DBU (1,5-diazabicyclo[5.4.0]undec-5-ene), but the highest yield (80%) of thiacyclooctene **13** (Scheme IV) is obtained using potassium *tert*-butoxide in acetonitrile (20 °C, 2 h). No other isomers can be found in sufficient quantity for characterization using this procedure. In contrast, DBU-induced rearrangement of **9b** gives comparable amounts of **13** and a mixture of isomeric vinyl sulfides **16a,b**. The isomers are extremely difficult to purify, and repeated preparative thin-layer chromatography is required for partial separation of one isomer (**16a**). By

Scheme V



Scheme VI



270-MHz spectroscopy it was found that **16a** contains no asymmetric carbons and retains one vinyl proton. All of the necessary coupling interactions were present as required for structure **16a**. An NMR spectrum of the enriched **16a,b** mixture after partial removal of **16a** can be interpreted to show that a second closely analogous set of signals is present which can only be due to the other geometrical isomer of the vinyl sulfide. It is obviously necessary to remove the allylic proton α to vinyl at some stage to account for the appearance of **16a,b**. We suggest that ylide **10** equilibrates with isomer **14**. In the presence of an acid catalyst such as protonated DBU ($HDBU^+ \cdot CF_3SO_3^-$), **14** might undergo cleavage to sulfonium ion **15** and the enol form of ethyl acetate. Recombination of these fragments by Michael addition would then lead to **16a,b**. The alternative of simple Stevens rearrangement by **14** would also give **16a,b**. However, this rationale fails to explain why **16a,b** is formed only in the DBU-induced rearrangement.

If the stereochemistry assigned to **9b** is correct, then formation of **13** requires interconversion of ylide diastereomers **10** and **17**. Only the cis diastereomer (**17**) can attain a reasonable geometry for a [2,3] shift via a cisoid vinyl rotamer, which would result in cis olefin **13** (Scheme V). Three reasonable mechanisms for this interconversion can be considered: (a) reversible deprotonation–reprotonation α to the vinyl group via ylide isomer **14**; (b) pyramidal inversion at sulfur in the ylide **10**;[7-9] (c) fragmentation of the allylic C–S bond and reclosure of an intermediate diradical or dipole (**18**).

Indirect evidence for the formation of **14** has already been presented, so path a would be a sufficient mechanism to account for the formation of **17**. Path b has some analogy in the facile inversion of a nonstabilized ylide,[9] but acyclic stabilized ylides invert slowly at 25 °C.[7] Furthermore, Fava et al. have pointed out that pyramidal inversion in a cyclic system should be slower for steric reasons.[8] Additional kinetic studies are required before the pyramidal inversion process can be proved or disproved in our system.[10] Path c appears less likely. The intermediate **18** should be capable of Stevens rearrangement[11] to form a six-membered ring, but no such product has been obtained from **9b**.

One additional example of tetrahydrothiophene ring expansion was examined. Treatment of **3** with diazoacetophenone and perchloric acid according to the method of Flower, Holt, and Hope[12] gives the phenacylsulfonium salt **19** in good yield (Scheme VI). In the presence of DBU at 20 °C, a slow rearrangement to thiacyclooctenes results (23% of cis alkene **22** and 2% of trans alkene **23** after 1.25 h). For efficient conversion and good product recovery it is necessary to heat the solution of salt and base. Thus, reaction of **19** and DBU at 95 °C in toluene (10 min) affords three products (ca. 80% recovery) consisting of **22** (67%), the trans isomer **23** (7%), and the Stevens product **24** (4%).

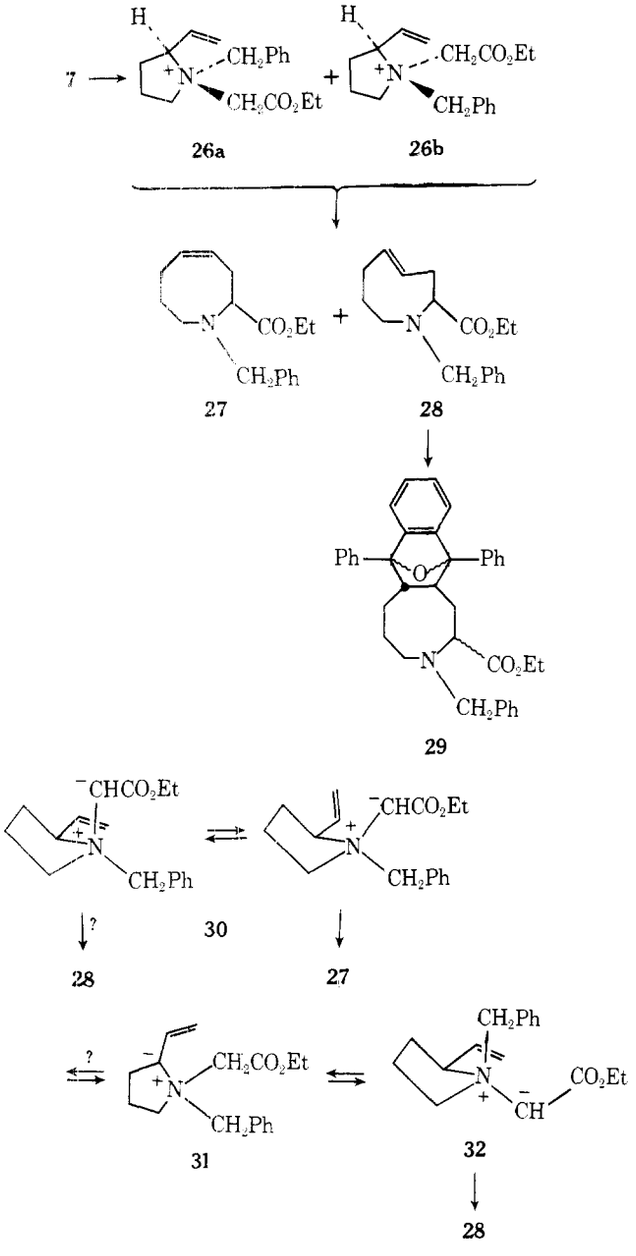
As before, sulfonium salt formation gives a homogeneous crystalline isomer which is assumed to be the trans diastereomer. Therefore, it again is necessary to postulate interconversion of diastereomers to explain the appearance of cis alkene **22**. However, the thermal barrier for ring expansion shows that the process which interconverts ester-stabilized ylides **10** and **17** is considerably less effective for the phenacyl ylides **20** and **21**. It is reasonable to argue that interconversion of the highly stabilized phenacyl ylide **20** with **25** would be more difficult than the analogous process **10** ⇌ **14** in the ester series and might not in fact take place. Although we cannot prove that **25** is not formed, we note that products analogous to **16a,b** are not observed in the phenacyl series whether or not DBU is used as the base. In any event, pyramidal inversion at sulfur must be regarded as a realistic alternative for diastereomer interconversion at 95 °C, pending kinetic studies in more closely related ylide systems. Also, the S–C fragmentation–recombination process might be considered since a Stevens product **24** is formed to a significant extent.

In contrast to the ester-stabilized system, the phenacyl ylide is capable of rearrangement to a trans double-bond isomer **23**. As shown in Scheme VI, either ylide diastereomer **20** or **21** can attain the necessary transoid geometry with reasonable five-center overlap for a [2,3] shift. Since the trans olefin constitutes an asymmetric center in an eight-membered ring, two geometric isomers of **23** are possible.[13] However, we have observed only one diastereomer in the product mixture.

Nitrogen Ring Expansions. Alkylation of 2-vinyl-*N*-benzyl-pyrrolidine (**7**) with the triflate reagent **12** affords a mixture of diastereomers **26** (Scheme VII). One of the two ammonium salts can be crystallized efficiently as the bromide. The other isomer has not been obtained pure, but NMR analysis indicates less that 10% residual crystalline isomer in the oily salt.

Treatment of either diasteromer **26a** or **26b** with potassium *tert*-butoxide at 20 °C gives a mixture of two ring expansion products (ca. 2-h reaction time). One of the products can be

Scheme VII



isolated by chromatography and is clearly the cis olefin according to the NMR spectrum. The second product decomposes on silica gel and has not been purified or fully characterized. However, a 270-MHz NMR spectrum of the crude mixture of ring expansion products shows, in addition to signals from **27**, a highly characteristic doublet of doublets of doublets at δ 5.45 (J = 15.5, 11.8, and 3.7 Hz) identical in appearance with the upfield olefin signal of **23** and other trans cyclooctene derivatives. The infrared spectrum of the mixture contains a typical *trans*-cyclooctene absorption at 971 cm^{-1} which disappears on attempted chromatography, acid treatment, or prolonged manipulation at ambient temperatures.

Based on this evidence, structure **28** can be assigned to the unstable product. In confirmation of the *trans*-azacyclooctene structure, the mixture of **27** and **28** reacts with diphenylisobenzofuran at 20 °C to give adduct **29** (mixture of at least three diastereomers) together with unreacted cis olefin **27**. Adduct **29** is characterized by the correct molecular ion and the absence of vinylic hydrogens in the NMR spectrum.

The ratio of **27**/**28** is 3:2 starting from the crystalline salt, while a slight preference for trans olefin **28** is observed from the oily salt. We suggest therefore that **26b** is the oily salt and that rearrangement to **28** occurs competitively with interconversion of ylides **32** and **30**. Due to the geometrical requirements for cis olefin formation as discussed in the sulfur series, ylide **32** cannot give **27** without prior stereochemical change. The most reasonable mechanism for interconversion of **32** and **30** involves the ylide **31**. According to molecular models, ylide **30** could conceivably rearrange to either **27** or **28**. Thus, it is clear that **32** must lose stereochemistry competitively with ring expansion, but there is not sufficient evidence to show whether **30** likewise equilibrates with **31** under the conditions employed.

Conclusion

Ring expansion of five-membered sulfur or nitrogen heterocycles by a [2,3]sigmatropic shift is a viable method for synthesis of eight-membered heterocycles. Interconversion of ylide diastereomers is necessary for rearrangement in the sulfur series and also plays a role in the nitrogen series. In several of the examples studied diastereomer interconversion is probably the slowest step in the overall reaction and accounts for the relatively slow rates for 2,3 shifts. In subsequent publications we will show that rearrangement of ylides derived from larger, more flexible rings is much more facile and does not require interconversion of diastereomers.

Experimental Section

Allyl 3-Bromopropyl Sulfide(2). To thietane[1] (7.9 g, 0.107 mol) in acetonitrile (40 mL, Aldrich, used without further purification) was added allyl bromide (12.84 g, 0.107 mol) at room temperature. The mixture was stirred overnight. The solvent was removed at reduced pressure, and the residue was distillad to give **2** (17.4 g, 0.0893 mol, 85%): bp 43–44 °C (0.5 Torr); IR (neat) 1635 m cm^{-1}; NMR ($CDCl_3$) δ 5.8 (1 H, ddt, J = 17, 10, 7 Hz), 5.15 (2 H, m), 3.5 (2 H, t, J = 8 Hz), 3.18 (2 H, d, J = 7 Hz), 2.64 (2 H, t, J = 8 Hz), 2.1 (2 H, quintet, J = 8 Hz); *m/e* 196 (M + 2), 194 (M), 154, 152, 74, 63; exact mass, 193.97675; calcd for $C_6H_{11}SBr$, 193.97654.

α-Vinyltetrahydrothiophene (3). To diisopropylamine (Aldrich, 5.76 mL, 41.30 mmol, distilled from BaO) was added dropwise a hexane solution of n-butyllithium (25 mL, 41.30 mmol) at −70 °C. A nitrogen stream was maintained throughout the experiment. Dry tetrahydrofuran (50 mL, distilled from sodium benzophenone) was added. To this rapidly stirred solution allyl 3-bromopropyl sulfide (4.6 mL, 31 mmol) was then added dropwise over a 0.5-h period. Stirring was continued at −70 °C for 1 h, and then the mixture was quenched with water. After the mixture had warmed to room temperature it was washed with 10% HCl and then 10% $NaHCO_3$ solution, dried over Na_2SO_4, and filtered. The solvent was removed at atmospheric pressure using a fractionating column. The residue was distilled under reduced pressure to give **3** (2.99 g, 85%): bp 55–56 °C (16 Torr); IR (neat) 1630 m cm^{-1}; NMR ($CDCl_3$) δ 5.8 (1 H, ddd, J = 15, 10, 8 Hz), 5.08 (1 H, dd, J = 15, 2 Hz), 4.9 (1 H, dd, J = 10, 2 Hz), 3.9 (1 H, m), 2.85 (2 H, m), 1.4–2.3 (4 H, m); *m/e* 114 (M), 87, 85, 81, 71; exact mass, 114.05026; calcd for $C_6H_{10}S$, 114.05032.

***N*-Trityl-2-vinylpyrrolidine (5).** Methyltriphenylphosphonium bromide (0.564 g, 1.59 mmol) in dry THF (15 mL) was stirred at −78 °C under nitrogen. A solution of n-butyllithium in hexane (2.38 mmol) was added dropwise with stirring over 2 min and the mixture stirred for 2.5 h at −78 °C. A solution of *N*-trityl-2-formylpyrrolidine[4] (0.27 g, 0.793 mmol) in THF (4 mL) was added dropwise by syringe at −78 °C. After 40 min the mixture was warmed to 0 °C (0.5 h), quenched with water, and partitioned between ether–water. After extracting with 3 × 15 mL of ether, the combined organic layers were dried ($MgSO_4$) and evaporated (aspirator). The brown oil was separated by preparative layer chromatography (PLC) over silica gel (ether–hexane, 1:4) to give a major band, R_f 0.56. Extraction with ether and crystallization from hexane gave **5** as a white solid (73%), mp 94.5–95 °C, sufficiently pure for the next step; NMR ($CDCl_3$) δ 6.9–7.7 (15 H, m), 5.8 (1 H, ddd, J = 4.8, 8.9, 15.6 Hz), 5.29 (1 H, dd, J = 1.9, 15.6 Hz), 5.05 (1 H, dd, J = 1.9, 8.9 Hz), 3.77 (1 H, m), 3.25 (1 H, m), 2.85 (1 H, m), 0.7–1.7 (4 H, m).

***N*-Benzoyl-2-vinylpyrrolidine (6).** Benzoyl chloride (27 μL, 0.23 mmol) was refluxed with *N*-trityl-2-vinylpyrrolidine (71 mg, 0.21 mmol) in methylene chloride (5 mL) for 3.5 h. Evaporation of solvent gave an orange residue, and separation by PLC (silica gel, 10% ether–hexane) gave two major bands. The less polar (R_f 0.66) was

trityl chloride, while the more polar (R_f 0.32) was the desired *N*-benzoyl derivative **6** (35 mg, 82%). The oily product was used in the next step without further purification.

***N*-Benzyl-2-vinylpyrrolidine (7).** A solution of *N*-benzoyl-2-vinylpyrrolidine (33 mg, 0.165 mmol) in dry ether (2 mL) was added to a stirred mixture of $LiAlH_4$ (9 mg, 0.25 mmol) and ether (3 mL) at 20 °C. The mixture was then refluxed for 3 h and cooled to 0 °C, and solid $Na_2SO_4 \cdot 10H_2O$ was added slowly until frothing ceased. After extraction of ether-soluble products from the salts and evaporation of ether, a yellow oil was obtained (32 mg). Separation by PLC (silica gel, 1:1 ether–hexane) gave a major zone at R_f 0.5, and extraction with ether gave **7** as an oil, 21.4 mg (69%); NMR ($CDCl_3$) δ 7.32 (5 H, br s), 5.82 (1 H, ddd, J = 8, 9.5, 17.5 Hz), 5.12 (1 H, dd, J = 2, 17.5 Hz), 5.07 (1 H, dd, J = 2, 9.5 Hz), 4.03 and 3.09 (2 H, AB q, J = 13 Hz), 2.9 (2 H, m), 1.6–2.3 (5 H, m); exact mass, 187.13610; calcd for $C_{13}H_{17}N$, 187.13597.

Ring Expansion of 3 with Dimethyl Diazomalonate: Preparation of 8. In a 5-mL flask were mixed dimethyl diazomalonate (250 μL, 2.1 mmol), toluene (1 mL, distilled from $LiAlH_4$), copper bronze (161 mg, U.S. Bronze Powder Works), and α-vinyltetrahydrothiophene (**3**) (0.114 g, 1 mmol). The flask was fitted with a condenser and heated at 100 °C without stirring for 5 h under a slight positive pressure of nitrogen. The mixture was filtered and subjected to separation by LC (silica gel, 35% ether in hexane) to give **8** (0.13 g, 53%; oil): IR (neat) 1635 w, 1740 s cm^{-1}; NMR ($CDCl_3$) δ 5.9 (1 H, td, J = 8, 7 Hz), 5.45 (1 H, td, J = 8, 7 Hz), 3.8 (6 H, s), 2.9 (4 H, m), 2.25 (2 H, m), 1.8 (2 H, m); *m/e* 244 (M), 203, 185, 180, 157, 153, 144, 132, 125, 113, 100, 87; exact mass, 244.07905; calcd for $C_{11}H_{16}O_4S$, 244.07693.

Alkylation of 3 with Triflate 12: Isolation of 9b. Neat α-vinyltetrahydrothiophene (**3**, 0.52 g, 4.56 mmol) was added dropwise via syringe to a solution of triflate **12**[6] (1.19 g, 5.07 mmol) in acetonitrile (8 mL, distilled from P_2O_5) at 0 °C under nitrogen flow. The mixture was allowed to stir for 2 h and then warmed to room temperature. The acetonitrile was removed (aspirator, there is a tendency for bumping) to give a slightly red solid. Recrystallization in ethyl acetate gave needles of **9b** (1.47 g, 86%): mp 99–101 °C; IR (KBr) 1025 s, 1155 broad, 1250 broad, 1632 w, 1730 s cm^{-1}; NMR (CD_3CN) δ 5.88–6.24 (1 H, ddd, J = 18, 10, 8 Hz), 5.48 (1 H, d, J = 18 Hz), 5.40 (1 H, d, J = 10 Hz), 4.54–4.76 (1 H, m), 4.30 (2 H, s), 4.20 (2 H, q, J = 7 Hz), 3.40–3.80 (2 H, m), 2.0–2.6 (4 H, m), 1.24 (3 H, t, J = 7 Hz).

Conversion of Sulfonium Triflate 9b into Sulfide 11 by Bromide Ion. A solution of **9b** (0.1 g, 0.286 mol) in $CHCl_3$ (3 mL) was stirred with saturated aqueous NaBr (5 mL) at 20 °C for 2.5 h. After separation of layers, the aqueous phase was diluted 5-fold with water and extracted with $CHCl_3$ (3 × 10 mL). The combined organic phase was dried (Na_2SO_4) and evaporated (aspirator) to yield **11** (0.063 g, 77%) as a colorless oil, homogeneous by TLC (10% ether–hexane); NMR ($CDCl_3$) δ 5.72 (2 H, m), 4.18 (2 H, br q, J = 7 Hz), 3.94 (2 H, m), 3.20 (2 H, s), 2.64 (2 H, t, J = 8 Hz), 2.18 (2 H, br q, J = 7 Hz), 1.72 (2 H, br q, J = 7 Hz), 1.30 (3 H, t, J = 7 Hz); IR ($CHCl_3$) 1725 cm^{-1}; exact mass, 282.01188; calcd for $C_{10}H_{17}O_2SBr$, 282.01134.

Ring Expansion of 9b to 2-Carboethoxythiacyclooct-4-ene (13). Sulfonium salt **9b** (37 mg, 0.106 mmol) was dissolved in acetonitrile (0.5 mL, distilled from P_2O_5) under nitrogen flow at room temperature. To this solution was added solid potassium *tert*-butoxide (12.5 mg, 0.111 mmol), and it was allowed to stir for 2 h. Hexane was added to the mixture, and the reaction was quenched with 1 N HCl (1 mL) and washed twice with water (1 mL). The water washes were combined and back-extracted with ether. The organic layers were combined, and the solvents were removed (aspirator). Preparative layer chromatography (3 elutions in 10% ether–90% hexane) gave pure **13** (17.5 mg, 80%; oil), R_f = 0.6; IR (neat) 1650 w, 1710 s cm^{-1}; NMR ($CDCl_3$) δ 5.7 (2 H, m), 4.2 (2 H, q, J = 6 Hz), 3.35 (1 H, dd, J = 10, 4 Hz), 2.2–3.1 (6 H, m), 1.7 (2 H, m), 1.3 (3 H, t, J = 6 Hz); *m/e* = 200 (M), 159, 127, 125, 100, 93, 87; exact mass, 200.08748; calcd for $C_{10}H_{16}O_2S$, 200.08709.

Ring Expansion of 9b Using DBU as Base. A solution of **9b** (160 mg, 0.46 mmol) in acetonitrile (1.5 mL, distilled from P_2O_5) was treated with DBU (142 mg, 0.93 mmol) at 20 °C for 2 h. Partitioning between pentane and water gave an organic layer which was dried (Na_2SO_4), evaporated (aspirator), and separated by PLC (silica gel, 10% ether–hexane). A lead zone, R_f 0.6, was isolated to give **13** (30 mg, 33%). A slightly more polar zone, R_f 0.5, gave a mixture containing **16a, 16b,** and traces of a third, unidentified contaminant (43 mg, 47%). The more polar zone was chromatographed a second time (6% ether–hexane, 4 developments) and was partially resolved into a lead zone and a trailing zone. The upper half of the lead zone was carefully separated and recovered to give **16a,** containing ca. 10% **16b** and ca. 5% of the contaminant. An NMR study at 270 MHz with spin decoupling established the following characteristics of **16a:** ($CDCl_3$) δ 5.28 (1 H, br t, J = 6 Hz), 4.13 (2 H, q, J = 7 Hz), 3.01 (2 H, t, J = 6.4 Hz), 2.54 (2 H, br t, J = 6.8 Hz), 2.36 (4 H, m), 2.06 (2 H, m), 1.26 (3 H, t, J = 7 Hz). Decoupling at δ 5.28 caused simplification at δ 2.36 and sharpening of the triplet at δ 2.54. Decoupling at δ 3.01 collapsed the δ 2.06 signal to a triplet, J = 6.8 Hz, and decoupling at δ 2.54 sharpened the olefinic triplet and collapsed the δ 2.06 signal to a triplet with some off-resonance interference by the decoupler frequency. Irradiation at δ 2.36 collapsed the vinyl proton to a broad singlet.

An NMR spectrum of the remaining PLC zone enriched in **16b** revealed additional signals at δ 5.39 (1 H, t, J = 6.6 Hz), 3.23 (2 H, t, J = 8.5 Hz), 2.73 (2 H, br t, J = 8.4 Hz), 2.4 (overlapping signals with **18a**), 1.84 (2 H, m), and 1.3 (partially resolved methyl triplet overlapping **16a** signal).

Further characterization of **16a:** IR (CCl_4) 1730 s, 1637 m cm^{-1}; exact mass, 200.08700; calcd for $C_{10}H_{16}O_2S$, 200.08709.

Rearrangement of **9b** was performed in the same way using toluene as the solvent. After the usual workup, 39% of **13** and 33% of the zone containing **16a,b** resulted.

Phenacylsulfonium Salt 19. This material was made by analogy to a published procedure.[12] In a 50-mL flask were placed acetonitrile (6 mL, Aldrich, distilled from CaH_2), perchloric acid (61%, 1.84 g, 10.5 mmol), sulfide **3** (0.598 g, 0.725 mL, 5.25 mmol), and a magnetic stirring bar. To this rapidly stirred solution was added dropwise over a 25-min period diazoacetophenone (1.177 g, 8.06 mmol) in dry acetonitrile (8 mL). After addition was complete, the solvent was evaporated in vacuo at room temperature. The residue was recrystallized from 100% ethanol; yield 71%. The salt melts with decomposition at 158–159 °C; IR (CH_3CN) 1595 m, 1630 w, 1680 s cm^{-1}; NMR (CD_3CN) δ 7.95 (2 H, m), 7.6 (3 H, m), 6.05 (1 H, ddd, J = 17, 10, 8 Hz), 5.55 (1 H, d, J = 17 Hz), overlapping with 5.45 (1 H, d, J = 10 Hz), 4.2 (2 H, s), 4.65 (1 H, m), 3.6 (2 H, m), 2.0–2.6 (4 H, m).

Ring Expansion of 19. To the sulfonium salt **19** (253 mg, 0.762 mmol) was added toluene (20 mL, Mallinckrodt, distilled from LAH), and the flask was fitted with a condenser and a nitrogen stream was introduced. At 95 °C DBU (118.5 mg, 0.778 mmol) was added dropwise. The mixture was stirred rapidly during the addition. After 10 min at 95 °C the flask was allowed to cool to room temperature. After 1-h total elapsed time the reaction was quenched with 60% $HClO_4$. The toluene layer was washed with 10% K_2CO_3 solution, and the carbonate layer was back-extracted with pentane. The combined pentane–toluene layer was dried (Na_2SO_4) and filtered, and the solvent was evaporated to give a crude weight of 172 mg. Thin-layer silica gel chromatography (10% ether in hexane) yielded a major band (R_f 0.4, 119 mg) of cis alkene **22,** yield 67%; IR (neat) 690 m, 760 m, 1450 m, 1585 w, 1680 s cm^{-1}; NMR ($CDCl_3$) δ 7.96 (2 h, dd, J = 8, 2 Hz), 7.3–7.5 (3 H, m), 5.8 (2 H, m), 4.25 (1 H, dd, J = 10, 4 Hz), 2.1–3.1 (6 H, m), 1.75–2.1 (2 H, m); *m/e* 232 (M), 127, 105, 87, 85, 84; exact mass, 232.09216; calcd for $C_{14}H_{16}OS$, 232.09219.

A minor zone at R_f 0.35 (12 mg, 7%) proved to be trans alkene **23:** IR (neat) 685 m, 715 m, 750 m, 840 w, 880 w, 970 m, 1450 s, 1575 m, 1590 m, 1670 s cm^{-1}; NMR ($CDCl_3$) δ 8.0 (2 H, dd, J = 8, 2 Hz), 7.4–7.7 (3 H, m), 6.1 (1 H, m), 5.35 (1 H, ddd, J = 16, 12, 4 Hz), 4.42 (1 H, dd, J = 12, 4 Hz), 1.8–3.3 (8 H, m); *m/e* 232 (M), 157, 145, 127, 105, 77; exact mass, 232.09219; calcd for $C_{14}H_{16}OS$, 232.09218.

A third band was the Stevens product, 2-benzoyl-3-vinylthiacyclohexane (**24,** 7 mg, 4%), R_f 0.25; IR ($CHCl_3$) 910 m, 990 m, 1000 m, 1250 m, 1448 m, 1580 w, 1595 w, 1635 w, 1670 s cm^{-1}; NMR ($CDCl_3$) δ 7.96 (2 H, dd, J = 8, 2 Hz), 7.3–7.7 (3 H, m), 5.9 (1 H, ddd, J = 17, 10, 7.5 Hz), 5.05 (2 H, m), 4.35 (1 H, d, J = 4 Hz), 1.5–3.0 (7 H, m); *m/e* 232 (M), 127, 105, 77; exact mass, 232.09219; calcd for $C_{14}H_{16}OS$, 232.09218.

***N*-Benzyl-*N*-carboethoxymethyl-2-vinylpyrrolidinium Bromide (26a and 26b).** Carboethoxymethyl trifluoromethanesulfonate (**12**,[6] 0.791 g, 2.89 mmol) was dissolved in acetonitrile (4 mL) and added dropwise to a stirred solution of *N*-benzyl-2-vinylpyrrolidine (**7,** 0.512 g, 2.73 mmol) in acetonitrile (10 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated (aspirator), and the residue was washed with ether. Decantation of the ether left a yellow oil (1.362 g) which could not be crystallized. This crude product was stirred for 5 min in a methanolic solution of sodium bromide (12 g). The solvent was evaporated, and the residue was taken up in water (30 mL) and extracted with chloroform (3 × 25 mL). The combined organic layers were dried over sodium sulfate, filtered, and evaporated to a yellow oil. Crystallization from tetrahydrofuran left a white solid (0.518 g) with a melting point of 143.5–144 °C and a yellow oil (0.457 g). The two fractions proved to be the expected diastereomers **26a** and **26b;** yield of the solid isomer 53%, yield of impure liquid isomer 47%. Solid isomer (**26a**): NMR ($CDCl_3$) δ 7.4 (5 H, m), 5.95–6.35 (1 H, m), 5.3–5.7 (2 H, m), 4.75–5.2 (3 H, m), 3.8–4.5 (6 H, m), 2.1–2.8 (4 H, m),

1.28 (3 H, t, J = 6.3 Hz); IR ($CHCl_3$) 2940 s, 2450 m, 1749 s cm^{-1}. Anal. Calcd for $C_{17}H_{24}NO_2Br$: C, 57.63; H, 6.82; N, 3.95. Found: C, 57.47; H, 6.74; N, 3.92.

Liquid isomer (**26b**): NMR ($CDCl_3$) δ 7.5 (5 H, pseudo s), 5.75–6.4 (1 H, m), 5.4–5.7 (2 H, m), 4.6–5.1 (3 H, m), 4.28 (2 H, q, J = 7 Hz), 4.0 (4 H, pseudo s), 2.0–2.28 (4 H, m), 1.35 (3 H, t, J = 7 Hz); IR ($CHCl_3$) 3020 s, 2397 m, 1749 w cm^{-1}.

***N*-Benzyl-2-carboethoxyazacyclooct-4-ene (27 and 28).** *N*-Benzyl-*N*-carboethoxymethyl-2-vinylpyrrolidinium bromide (**26a,** solid isomer; 62.3 mg, 0.175 mmol) was dissolved in acetonitrile (2 mL). Solid, finely ground potassium carbonate (27.7 mg, 0.200 mmol) was quickly added, and the resulting heterogeneous mixture was stirred at room temperature for 3.5 h. The solvent was evaporated by a stream of nitrogen, and the residue was taken up in water (2 mL) and extracted with hexane (4 × 7 mL). The combined organic layers were dried over sodium sulfate, filtered, and evaporated to give a colorless oil (44.5 mg). Preparative layer chromatography on silica gel (EM Reagents, 60P-254) using a 1:1 ether–hexane mixture as the eluent left a colorless oil (22.9 mg) at an R_f of 0.65, which proved to be the cis isomer **27,** yield 48%; IR ($CHCl_3$) 2942 s, 1725 s, 701 m cm^{-1}; NMR ($CDCl_3$) δ 7.32 (5 H, m), 5.84 (1 H, ddd, J = 10.5, 9, 8 Hz), 5.69 (1 H, ddd, J = 9, 8, 8 Hz), 4.20 (2 H, q, J = 7 Hz), 3.94 (2 H, AB, J = 14 Hz), 3.41 (1 H, dd, J = 8.6, 5 Hz), 2.0–3.3 (6 H, m), 1.2–1.7 (2 H, m), 1.30 (3 H, t, J = 7 Hz); m/e 273, (base 200; exact mass, 273.17271; calcd for $C_{17}H_{23}NO_2$, 273.17288.

Analysis (NMR and IR) of the crude product after hexane extraction but prior to chromatography showed the presence of the unstable trans isomer **28,** which decomposed on silica gel. Additional absorbtions in the mixture were as follows: IR ($CHCl_3$) 1732 s, 971 m cm^{-1}; NMR ($CDCl_3$) δ 5.90 (1 H, m), 5.45 (1 H, ddd, J = 15.5, 11.8, 3.7 Hz), 4.22 (2 H, q), 1.33 (3 H, t), and additional unresolved signals overlapping those of **27.** Comparison of the peak heights of the methyl triplets at δ 1.33 and 1.30 in the NMR indicates the ratio of cis to trans isomers from the solid isomer **26a** is approximately 3:2.

The above procedure is somewhat modified for rearrangement of the liquid isomer **26b.** Potassium *tert*-butoxide (30.4 mg, 0.261 mmol) in dry tetrahydrofuran (1 mL, distilled from sodium benzophenone) was added dropwise to a stirred solution of *N*-benzyl-*N*-carboethoxymethyl-2-vinylpyrrolidinium bromide (liquid isomer **26b;** 87.5 mg, 0.247 mmol) in dry THF (3 mL). The resulting solution was stirred at room temperature for 2 h. Workup as before left a colorless oil (19.2 mg) after preparative layer chromatography which proved to be identical with the product **27** obtained from the solid isomer **26a,** 28% yield. In addition, the crude material from the hexane extraction contained both **27** and **28** in a ratio varying from 45:55 to 40:60, depending on the experiment.

An aliquot containing both the cis and trans isomers **27** and **28** was stirred with excess 1,8-diphenylisobenzofuran in methylene chloride for 3 h. Isolation of the products by preparative layer chromatography on silica gel (EM Reagents, 60P-254) using a 1:1 ether–hexane mixture as eluent gave recovered **27** (R_f 0.67) as well as a noncrystalline mixture of several diastereomers of the Diels–Alder adduct **29** (R_f 0.57), in which no olefinic protons were observed; NMR (CCl_4) δ 7.0–7.8 (19 H, m), 3.2–4.3 (5 H, m), 2.5–3.0 (1 H, m), 1.0–2.4 (11 H, m); m/e 543, 91 (base); exact mass, 543.27619; calcd for $C_{37}H_{37}NO_3$, 543.27734.

Acknowledgment. This work was supported by grants from the National Institutes of Health (CA17918-02) and the National Science Foundation (GD43891 X).

Registry No.—**2,** 64871-50-7; **3,** 57565-42-1; **4,** 64871-54-1; **5,** 64871-51-8; **6,** 64871-52-9; **7,** 64871-53-0; **8,** 64871-35-8; **9b,** 64871-37-0; **11,** 64871-38-1; **12,** 61836-02-0; **13,** 64871-39-2; (*Z*)-**16,** 64871-40-5; (*E*)-**16,** 64871-41-6; **19,** 64871-43-8; **22,** 57565-37-4; **23,** 57565-38-5; **24,** 64871-45-0; **26a,** 64871-46-1; **26b,** 64871-47-2; **27,** 64871-48-3; **28,** 64871-49-4; **29,** 64900-49-8; thietane, 287-27-4; allyl bromide, 106-95-6; benzoyl chloride, 98-88-4; dimethyl diazomalonate, 6773-29-1; diazoacetophenone, 3282-32-4.

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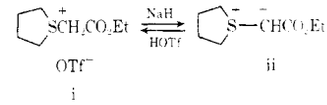

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Nucleophilic Substitution of Dihalopyridazines by Pyridazinethiones

Richard B. Phillips and Carl C. Wamser*

Department of Chemistry, California State University at Fullerton, Fullerton, California 92634

Received November 8, 1977

The reaction of 1 equiv of 3,6-dihalopyridazine (1) with 2 equiv of 6-halo-3(2*H*)-pyridazinethione (2) in slightly acidic, refluxing methanol yields the double-substitution product 3,6-bis(6-halo-3-pyridazinethio)pyridazine (3). The mechanism of the reaction is viewed as successive nucleophilic displacements upon protonated 1 by the thione tautomer of 2.

The pyridazine ring system is highly resistant to electrophilic substitution, but for pyridazines substituted with appropriate leaving groups nucleophilic substitution is a facile process.[1] The conversion of **1a** to **2a** is a rather typical example.[2]

It was during the synthesis of **2a** from **1a,** inadvertently run under acidic rather than basic conditions, that we noted the formation of a new product (**3a**). This product was found to be the result of further reaction of **1a** with **2a.** In general, we have found that 3,6-dihalopyridazines (1) react in slightly

0022-3263/78/1943-1190$01.00/0