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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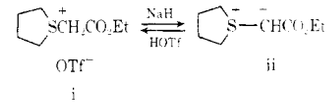

i ii

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Nucleophilic Substitution of Dihalopyridazines by Pyridazinethiones

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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

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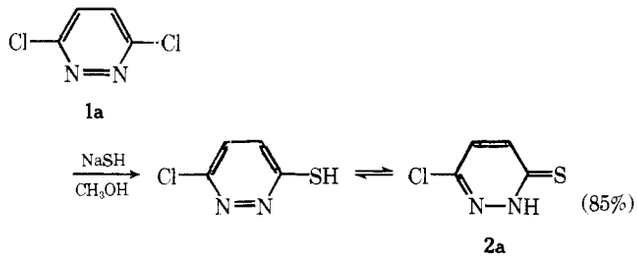
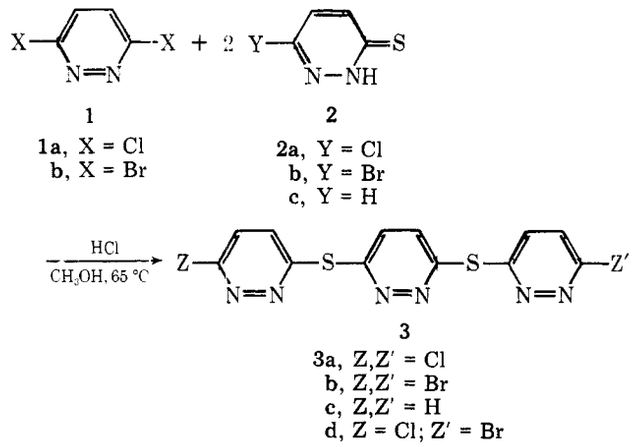


1a

2a

acidic, refluxing methanol with 6-halo-3(2*H*)-pyridazinethiones (**2**) to yield the double-substitution product 3,6-bis(6-halo-3-pyridazinethio)pyridazine (**3**).



1
1a, X = Cl
b, X = Br

2
2a, Y = Cl
b, Y = Br
c, Y = H

3
3a, Z,Z′ = Cl
b, Z,Z′ = Br
c, Z,Z′ = H
d, Z = Cl; Z′ = Br

Depending upon the substitution patterns of **1** and **2**, either **3a**, **b**, **c**, or **d** may be formed as the major product.

1a + 2 **2a** → **3a**

1b + 2 **2a** → **3a**

1b + 2 **2b** → **3b**

1a + 2 **2c** → **3c**

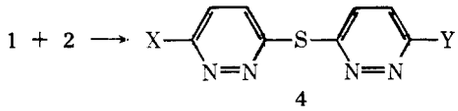
1b + 2 **2c** → **3c**

1a + 2 **2b** → **3d**

The release of halide ion as a product of the reaction was detected by potentiometric titration; yields were always 95–100% of theoretical.

Results and Discussion

We consider that the mechanism involves two successive displacements of halide ion by the nucleophilic sulfur of **2**.

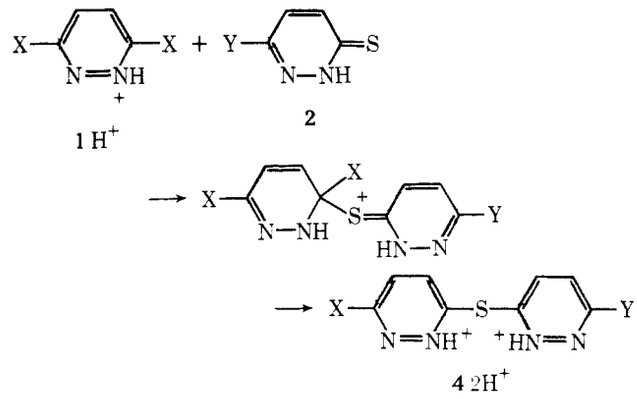


4

4 + 2 → **3**

Since the reaction does not take place under basic conditions (e.g., the conditions for synthesis of **2a** from **1a**) and since a slightly acidic medium is required, we expect that the nucleophilic attack occurs upon protonated **1**. However, the reaction cannot be run under strongly acidic conditions because **2** precipitates. The attacking nucleophile is probably the thione, rather than the thiol, tautomer of **2**, since the parent compound, 3(2*H*)-pyridazinethione,[3] and other derivatives[4,5] have been shown to exist predominantly in the thione form. The two-step mechanism shown below is typical for acid-catalyzed heterocyclic nucleophilic substitution.[6]

At least two alternative mechanisms involving neutral substrates may be envisioned.[7] One possibility is a preequilibrium between the slightly acidic **2** and the slightly basic **1**,



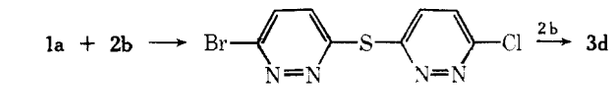
1 H^+ **2**

4 $2H^+$

followed by a rapid reaction of the resulting ion pair, as has been observed for arylthiol reactions with chloroquinoline.[8] Alternatively, **2** may act as a bifunctional nucleophile, involving H bonding to the ring N of **1** to enhance reactivity.[9] In the absence of any specific kinetic data, we cannot rule out these mechanistic possibilities.

We have never been able to isolate the expected intermediate **4**. Apparently, the initial substitution greatly increases the reactivity toward further nucleophilic substitution. Thus, **4** must be much more reactive toward **2** than **1** is and goes on to product **3** rapidly. Reactions run to partial completion and reactions with up to a tenfold excess of **1** over **2** gave only **3** and no evidence for **4**. A possible explanation is that the intermediate **4** is doubly protonated, which would be expected to enhance its reaction toward nucleophiles. In fact, the initial reaction between 1 H^+ and **2**, followed by halide ion loss, leads directly to doubly protonated **4**. Still further substitutions, after the second rapid substitution, are not observed, simply because the product **3** precipitates from solution. If the reaction is run in hot DMF, in which **3** is soluble, the only product observed is intractable polymeric material, suggesting that further substitution apparently can occur while **3** remains in solution.

The formation of a bromochloro derivative **3d** from **1a** plus **2b** is taken as evidence that the reaction must go through a bromochloro intermediate **4a** from which Br is a better leaving group than Cl. The nucleophile can only displace Cl from **1a**,



4a

but from **4a** displacement of Br is apparently preferred over displacement of Cl. The release of 1 equiv of Cl^-, followed by 1 equiv of Br^-, was monitored by potentiometric titration. This reactivity order is relatively unusual for activated aromatic or heterocyclic nucleophilic substitution, where the normal order of halogen reactivity is F ≫ Cl ≈ Br ≥ I.[10] In some cases, however, Br has been found to be a better leaving group than Cl in activated aromatic nucleophilic substitution[11] and in heterocyclic nucleophilic substitution.[12] The reversal of order of leaving-group activity indicates that carbon–halogen bond cleavage is significant in the rate-determining step.[10] Thus, the addition of **2** to **4** must involve a rapid initial attack followed by a rate-determining loss of halide ion.

Experimental Section

3,6-Dichloropyridazine (1a) and 3,6-dibromopyridazine (1b) were prepared from maleic hydrazide and $POCl_3$ or PBr_5.[13]

6-Chloro-3(2*H*)pyridazinethione (2a) and 6-bromo-3(2*H*)-pyridazinethione (2b) were prepared from **1a** or **1b** by refluxing with NaSH in methanol.[2]

3(2*H*)-Pyridazinethione (2c) was prepared from 3(2*H*)-pyridazinone by treatment with P_2S_5 in pyridine.[14] The pyridazinone was

prepared from **1a** by treatment with hot 3 N NaOH,[15] followed by hydrogenolysis.[16]

3,6-Bis(6-chloro-3-pyridazinethio)pyridazine (3a) was prepared by the reaction of either **1a** or **1b** with 2 equiv of **2a** in refluxing methanol. Inclusion of two drops of concentrated HCl improved the yields somewhat. During 3 h at reflux, a green solid precipitated. The reaction mixture was reduced to about half-volume by distillation at atmospheric pressure, cooled, and filtered. The solid residue was washed with hot methanol and recrystallized from DMF, mp 205–207 °C. The yield of purified product was 68% from **1a** and 75% from **1b.** The identity of the products from the two precursors was verified by the identity of the infrared spectra (see below) and the absence of a mixture melting point depression.

The structure of **3a** was deduced from the common method of synthesis (from **1a** or **1b**); from sodium fusion tests which indicated N, S, and Cl, but no Br; and from infrared, mass spectral, and elemental analyses: IR (KBr pellet): 3000, 1650, 1550, 1380, 1280, 1210, 1130, 1030, 1000, 840, and 770 cm^{-1}; mass spectrum[17] parent peaks at 368, 370, and 372 in the expected 9:6:1 ratio; M − Cl peaks at 333 and 335; other major fragments were at 223 and 225. Molecular weight was determined by the Rast method: 391 (calculated: 369). Anal.[18] Calcd for $C_{12}H_6Cl_2N_6S_2$: C, 39.0; H, 1.6; N, 22.8. Found: C, 39.20; H, 1.9; N, 22.0.

3,6-Bis(6-bromo-3-pyridazinethio)pyridazine (3b) was prepared similarly to **3a,** using 2 equiv of **2b** and 1 equiv of **1b.** Yields of the green product were typically 50%, after recrystallization from DMF: mp 216–217 °C (dec); IR (KBr pellet) 3000, 1630, 1510, 1440, 1370, 1260, 1120, 1030, 1000, 840, and 710 cm^{-1}; mass spectrum parent peaks at about 456, 458, 460 (very low intensities made accurate mass counting difficult; however, the expected 1:2:1 ratio was evident); M − Br peaks at 377 and 379; other major fragments were at 267 and 269. Anal.[19] Calcd for $C_{12}H_6Br_2N_6S_2$: C, 31.5; H, 1.3; N, 18.3. Found: C, 29.7; H, 2.0; N, 17.5.

3,6-Bis(3-pyridazinethio)pyridazine (3c) was prepared similarly, by the reaction of 2 equiv of **2c** with 1 equiv of either **1a** or **1b.** The dark-blue product was recrystallized from DMF, washed with acetone until the filtrate was clear, and dried in vacuo. The yield was 53%: mp 250 °C; IR (KBr pellet) 3060, 1533, 1400, 1340, 1280, 1240, 1110, 975 cm^{-1}. Anal.[19] Calcd for $C_{12}H_8N_6S_2$: C, 48.0; H, 2.7; N, 28.0. Found: C, 41.4; H, 2.6; N, 23.8.

3-(6-Bromo-3-pyridazinethio)-6-(6′-chloro-3′-pyridazinethio)pyridazine (3d) was prepared similarly to **3a** or **3b** using 1 equiv of **1a** and 2 equiv of **2b.** Recrystallization from DMF gave 41% of the green product: mp 194–196 °C (dec); IR (nujol mull) 1690, 1560, 1520, 1300, 1130, 1030, 840, 775, 765, 710 cm^{-1}; mass spectrum parent peaks at 412, 414, 416 (very weak; the expected 3:4:1 ratio was unconfirmed); peaks common to the spectrum of **3a** were observed at 333 and 335 (M − Br) and at 223 and 225; peaks common to the spectrum of **3b** were observed at 377 and 379 (M − Cl) and at 267 and 269. Anal.[18] Calcd for $C_{12}H_6BrClN_6S_2$: C, 34.8; H, 1.5; N, 20.3. Found: C, 38.3; H, 2.0; N, 19.5

Potentiometric Titrations. The release of halide ion was monitored by potentiometric titrations with standardized $AgNO_3$ solution. Standardizations were performed against KCl and KBr, including mixtures, such that both Cl^- and Br^- could be determined independently. Since the reactions were run in refluxing acidic methanol, the HX was trapped as a gas, entrained in a stream of nitrogen, and bubbled through an aqueous solution. An aliquot of this solution was then titrated with $AgNO_3$. Yields of halide were 2.0 equiv (±5%) based upon starting **1.**

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Registry No.—**1a,** 141-30-0; **1b,** 17973-86-3; **2a,** 3916-78-7; **2b,** 65027-58-9; **2c,** 28544-77-6; **3a,** 65027-59-0; **3b,** 65027-60-3; **3c,** 65027-48-7; **3d,** 65027-49-8; maleic hydrazide, 123-33-1; $POCl_3$, 10025-87-3; PBr_5, 7789-69-7; NaSH, 16721-80-5; 3(2*H*)-pyridazinone, 504-30-3; P_2S_5, 1314-80-3.

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(18) Elemental analyses performed by Truesdail Laboratories, Los Angeles, Calif.
(19) Elemental analyses performed by Caltech Analytical Facility, Pasadena, Calif.