tallized from H_2O, yield 145 mg (50% recovery), mp 144° dec with presoftening from 139°.

7-Amino-5-(benzylthio)pyrimido[5,4-*e*]-*as*-triazine (31).—To a suspension of **30** (5.0 g) in H_2O (250 ml) containing 1 *N* HCl (2.5 ml) was added $(EtO)_3CH$ (75 ml) with vigorous stirring. The mixture became oily and then resolidified. After 3 hr the crude product was collected by filtration and dried *in vacuo* over P_2O_5, yield 4.4 g (85%). For analyses a sample (860 mg) was recrystallized from MeCN, yield 650 mg (76% recovery), mp 226° dec.

5,7-Diaminopyrimido[5,4-*e*]-*as*-triazine (32).—Solid **31** (2.0 g) was added with stirring to 10% ethanolic ammonia (40 ml), which was cooled in an ice bath. After 30 min the ice bath was removed, and the reaction mixture was stirred at room temperature for 18 hr. The solid was collected by filtration, recrystallized from a large volume of H_2O, and dried *in vacuo* over P_2O_5 at 78°, yield 0.50 g (41%), mp >264°.

Registry No.—**1**, 31739-65-8; **5**, 31739-66-9; **7**, 31739-67-0; **9**, 31739-68-1; **10**, 31791-00-1; **13**, 31739-69-2; **14**, 31739-70-5; **15**, 31739-71-6; **16**, 31739-72-7; **17**, 31791-01-2; **20**, 31736-42-2; **21**, 31791-02-3; **22**, 31736-43-3; **24**, 31736-44-4; **26**, 23706-18-5; **28**, 31736-46-6; **30**, 31736-47-7; **31**, 31736-48-8; **32**, 31736-49-9.

Acknowledgments.—The authors are indebted to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Research Institute, who performed most of the microanalytical and spectral determinations reported.

Bridgehead Nitrogen Heterocycles. I. The 2*H*(and 4*H*)-Pyrimido[1,2-*b*]pyridazin-2(and 4)-one, 3*H*-Imidazo[1,2-*b*]pyridazin-2-one, and 7*H*-1,3,4-Thiadiazolo[3,2-*a*]pyrimidin-7-one Systems

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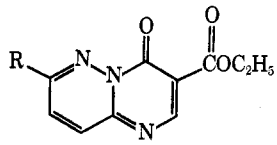
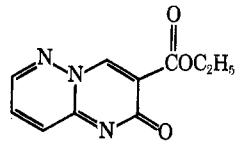
The title compounds have been synthesized by condensation of 3-amino-6-chloropyridazine and 2-amino-1,3,4-thiadiazole with several 3-chloroacrylic and atropic acids (and acid chlorides). Nucleophilic replacement reactions of some chloro-substituted 2*H*-pyrimido[1,2-*b*]pyridazin-2-ones are reported. Structural assignments are based on chemical evidence, ir, nmr, and mass spectral data. A brief analysis of the results is reported.

Of the isomeric pyrimido[1,2-*b*]pyridazinone and the 1,3,4-thiadiazolo[3,2-a]pyrimidone systems, only representatives of 4*H*-pyrimido[1,2-*b*]pyridazin-4-one[2] and 4*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-4-one[3,4] are known. The first report of the synthesis of the pyrimido[1,2-*b*]-pyridazinone ring system appeared in 1968 and came to our attention during the course of our own investigations. The condensation of 3-aminopyridazine with ethyl ethoxymethylenemalonate was reported by Stanovnik and Tišler[2] to afford ethyl 3-pyridazinylaminomethylenemalonate, which cyclized in refluxing diphenyl ether to give 3-ethoxycarbonyl-4*H*-pyrimido-[1,2-*b*]pyridazin-4-one (**1a**). The corresponding intermediate was prepared from 3-amino-6-chloropyridazine, but efforts to cyclize it to **1b** were unsuccessful. Structure **2**, resulting from initial condensation of 3-aminopyridazine with the ester carbonyl of ethyl ethoxymethylenemalonate, was rejected on the basis of the evidence for the intermediate and upon examination of spectroscopic data. An earlier report[3] describes a similar route to the 4*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-4-one system starting with 2-amino-5-methyl-1,3,4-thiadiazole and ethyl ethoxymethylenemalonate. Levin, *et al.*,[4] described these two reactants as yielding ethyl 5-methyl-1,3,4-thiadiazol-2-ylaminomethylenemalonate, which ring closed to the bicyclic product **3** on prolonged heating at elevated temperature under reduced pressure. Tišler and coworkers[5] have recently described the preparation of 6-chloro-2-hydroximidazo-[1,2-*b*]pyridazine (**4**) and 7-chloro-3,4-dihydropyrimido-[1,2-*b*]pyridazin-2-one (**5**) by fusion of 3-amino-2-(ethoxycarbonylalkyl)-6-chloropyridazinium bromides.



1a, R = H
b, R = Cl



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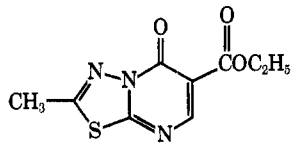

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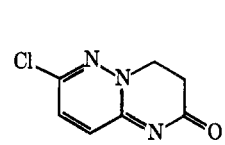

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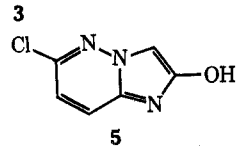


5

We wish to report the reaction of chlorinated acrylic and atropic acids (and acid chlorides) with 3-amino-6-chloropyridazine and 2-amino-5-(methylthio)-1,3,4-thiadiazole, which gave derivatives of 2*H*(and 4*H*)-pyrimido[1,2-*b*]pyridazin-2-(and 4)-one, 3*H*-imidazo-[1,2-*b*]pyridazin-2-one, and 7*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-7-one.

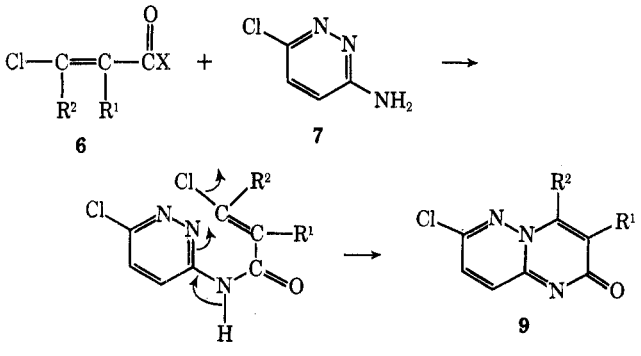
(1) To whom correspondence should be addressed.
(2) B. Stanovnik and M. Tišler, *Tetrahedron Lett.*, 33 (1968).
(3) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, I. F. Tinker, and J. A. Van Allan, *J. Org. Chem.*, **24**, 779 (1959).
(4) Ya. A. Levin, N. A. Shvink, and V. A. Kukhtin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **8**, 1481 (1964); *Chem. Abstr.*, **64**, 19595 (1966).
(5) S. Ostroversnik, B. Stanovnik, and M. Tišler, *Croat. Chem. Acta*, **41**, 135 (1969); *Chem. Abstr.*, **72**, 12684 (1970).

Results and Discussion

2*H*(and 4*H*)-Pyrimido[1,2-*b*]pyridazin-2(and 4)-one Systems.—A literature[6] synthesis of 2*H*-pyrido[1,2-*a*]pyrimidin-2-one suggested to us that entry into the desired pyrimido[1,2-*b*]pyridazinone system might be obtainable through a similar condensation involving a suitable substituted derivative of β-chloroacrylic or β-chloroatropic acid (**6**) and 3-amino-6-chloropyridazine (**7**). The reaction of heterocyclic amines having the amidine structure with derivatives of **6** is complicated by the presence in both molecules of two centers of similar reactivity, and it is frequently difficult to present unequivocal proof of structure of the reaction products.

The first β-chloroacrylic acid examined was the readiy available α,β-dichloroacrylic acid **6a** (X = OH). Fusion with **7** at 190° led to isolation of **9a** in 16% yield; when, however, the intermediate acrylamide **8a** was first prepared by conventional means and cyclization of the latter was carried out in refluxing xylene (2.5 hr), the yield of **9a** rose to 84%. Compound **9a** is colorless, melts at 277–278° with decomposition, is insoluble in hexane and benzene, and may be recrystallized from water. Analytical, spectroscopic, and mass spectral data (see Experimental Section) clearly establish that ring closure has occurred. Structures with NH or OH groups can be eliminated from consideration since bands for these groups are absent from both the ir and nmr spectra.

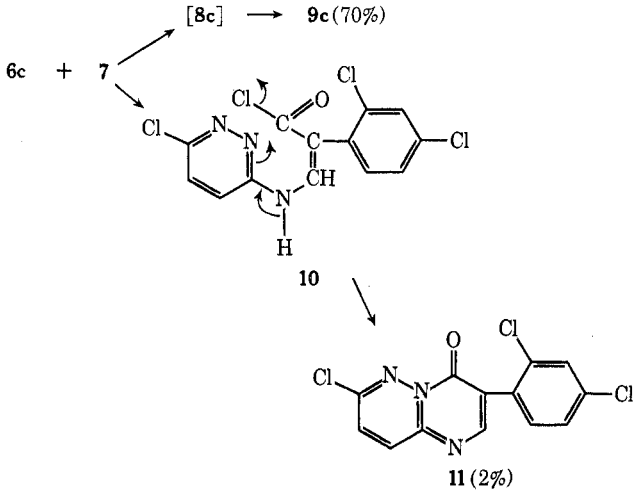
Fusion of the similarly constituted trichloroacrylamide **8b** proceeded more sluggishly (18 hr in refluxing xylene) to give the expected heterocycle **9b** in 69% yield. At higher temperature, cyclodehydrochlorination of **8b** took a different course, the results of which will be discussed in the next section.



6 **7** **8** **9**

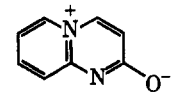
a, $R^1 = Cl; R^2 = H$
b, $R^1 = Cl; R^2 = Cl$
c, $R^1 = 2,4\text{-}Cl_2C_6H_3; R^2 = H$

Both (*Z*)-β-2,4-trichloroatropic acid **6c** (X = OH) and the corresponding atropoyl chloride **6c** (X = Cl) reacted with **7** to give the fused heterocycle **9c**. Thus, when **7** and **6c** (X = OH) were fused at 170–180° for 10 min, **9c** was obtained in 31% yield; intermediates such as **8c** and **10** could not be detected in the reaction mixture. When the reaction described above was carried out in polyphosphoric acid (3 hr at 170°), the only product obtained (34%) was **9c**. However, when **7** was allowed to react with **6c** (X = Cl) in tetrahydrofuran at 66° in the presence of triethylamine, reaction conditions which normally provided the intermediate amides **8**, the products isolated were **9c** (70%) and **11** (2%). The formation of **9c** from **6c** (X = Cl) and **7** indicates that



the fused ring system is most likely formed *via* intermediate **8c**. As **6c** (X = Cl) is an acid chloride, it would be expected to form the hypothetical amide **8c** first, followed by an extremely facile ring closure. The formation of **9c** from **6c** (X = OH) and **7** can also be rationalized as proceeding *via* intermediate **8c**.[7] The formation of **11** may involve nucleophilic displacement by the amino group of **7** of the β-chlorine atom in **6c** (X = Cl) to give the β-aminoatropic acid derivative **10**, which would cyclize to the 4*H*-pyrimido[1,2-*b*]pyridazin-4-one (**11**) system.

Both **9c** and **11** are colorless compounds. Compound **11**, the 4-one, melts at 195–198° with decomposition, has a high R_f value in nonpolar solvents, and may be recrystallized from benzene and hexane. Compound **9c**, the 2-one, on the other hand, melts at 240–243°, is only sparingly soluble in refluxing benzene, and has a low R_f value in polar solvents. Adams and Pachter[6] report similar differences in physical properties for the similarly constituted pyrido[1,2-*a*]pyrimidin-4-one and pyrido[1,2-*a*]pyrimidin-2-one; these authors suggest that fully aromatic structures such as **12** contribute



12

largely to the resonance hybrid of the 2-one. The structural dissimilarity of **9c** and **11** is also indicated by differences in their ir spectra. Ir absorption at $\nu_{C=O}$ 1643 cm^{-1} for **9c** and $\nu_{C=O}$ 1708 cm^{-1} for **11** is in agreement with and confirms[9] the expectation that the isomeric 2-one (**9c**) would be expected to absorb at a longer wavelength than the 4-one **11**.

(6) R. Adams and I. Pachter, *J. Amer. Chem. Soc.*, **74**, 5491 (1952).

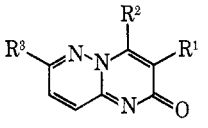
(7) In agreement with this mechanism it has been found[8] that carboxylic acids react with weakly basic amines in the presence of polyphosphoric acid to yield the corresponding amides.

(8) H. R. Snyder and C. T. Elston, *J. Amer. Chem. Soc.*, **76**, 3039 (1954).

(9) According to ref 3 members of the 2-one series have carbonyl absorption at 1667 cm^{-1}, whereas the 4-one series has a band at shorter wavelengths.

The displacement of chlorine in both the 4 and 7 positions of **9** was quite facile, and reactions of methylamine and sodium methylmercaptide with **9a–c** led to additional products **17–21** listed in Table I. Monosubstituted products of **9b** were not isolated and the 3-chlorine atom in **9a** and **9b** was inert under the conditions employed.

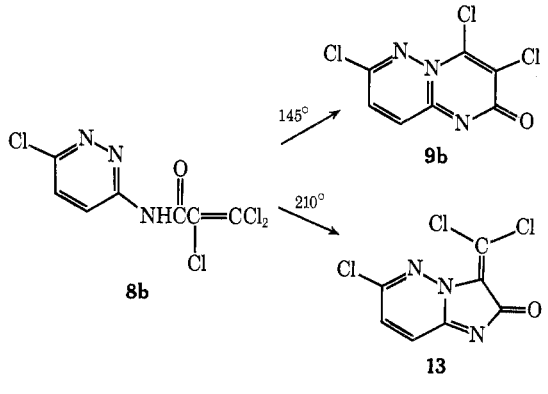
TABLE I
2*H*-PYRIMIDO[1,2-*b*]PYRIDAZIN-2-ONES[a]



Compd	R¹	R²	R³	Mp, °C	Ir data, $\nu_{C=O}$, cm⁻¹
9a	Cl	H	Cl	275–277[b]	1652
17	Cl	H	CH_3S[c]	240[b]	1645
9b	Cl	Cl	Cl	285–289[b]	1650
18	Cl	CH_3S	CH_3S[c]	203–206	1641
9c	2,4-$Cl_2C_6H_3$	H	Cl	235	1643
19	2,4-$Cl_2C_6H_3$	H	$NHCH_3$	>300	1635
20	2,4-$Cl_2C_6H_3$	H	CH_3S	192–194	1642
21	2,4-$Cl_2C_6H_3$	H	CH_3SO_2	130[b]	1650

[a] Satisfactory analytical data (±0.3% for C and H) were reported for all compounds in this table; Cl analyses were reported for all except **17**; N analyses for all except **21**; S analyses were reported for **18** and **20**: Ed. [b] With decomposition. [c] Oxidation with 33% H_2O_2 in CH_3CO_2H afforded water-soluble products from which sulfone could not be isolated.

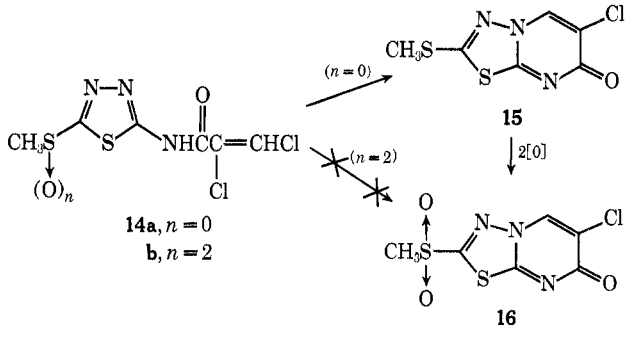
The 3*H*-Imidazo[1,2-*b*]pyridazin-2-one System.—Entry into the 3*H*-imidazo[1,2-*b*]pyridazin-2-one system was obtained unexpectedly when it was discovered that fusion of **8b** led to cyclization involving either the α or β chlorine atom, depending upon the reaction temperature. Thus, when **8b** was refluxed in xylene at 140° for a period of 6 hr, the heterocycle **9b** described above was obtained. However, when the cyclization was carried out in 1,2,4-trichlorobenzene at 210° for 20 min, **9b** could not be isolated from the reaction mixture. Instead, 6-chloro-3-dichloromethylene-3*H*-imidazo[1,2-*b*]pyridazin-2-one (**13**) was formed.



Since **9b** and **13** are not in practice thermally interconvertible (at 210°), it is concluded that the former is not a precursor in the formation of **13**. The structural dissimilarity of **9b** and **13** is indicated by differences in melting point, R_f value, and ir and mass spectrum. The 1700-cm⁻¹ region in the ir spectra proved to be of analytical interest. From the location of the carbonyl absorption bands, it was possible to characterize the ring size. For example, ir absorption at $\nu_{C=O}$ 1650 cm⁻¹ for **9b** and $\nu_{C=O}$ 1710 cm⁻¹ for **13** is in agreement[10] with the expectation that an increased ring strain will result in a shift toward higher frequencies as one proceeds from a six-membered ring such as **9b** to a more strained five-membered ring structure such as **13**.

The nmr spectrum of **13** is simple, showing the expected proton count and shifts of two aromatic protons at 7.9 and 8.15 ppm. Mass spectra were shown to be a valuable and reliable tool in the deduction of the structures of the isomers **9b** and **13**. The fragmentation patterns are in accord with their structural assignment and indicate the molecular arrangement of the respective C_2Cl_2 fragments in both isomers. For example, the prominent ion *m/e* 94 (C_2Cl_2) from **13** is not observed in the mass spectrum of **9b**. Because of its high degree of symmetry, dichloroacetylene (ClC≡CCl) may leave the ionization chamber without apparent ionization. This is no doubt due to the higher ionization potential and the reluctance of this molecule to hold a formal positive charge.

The 7*H*-1,3,4-Thiadiazolo[3,2-*a*]pyrimidin-7-one System.—5*H*-1,3,4-Thiadiazolo[3,2-*a*]pyrimidin-5-ones have previously been synthesized from a 5-substituted 2-amino-1,3,4-thiadiazole and ethyl ethoxymethylenemalonate.[3,11] We have now investigated an approach which builds up the 7-one system from a β-chloro-*N*-1,3,4-thiadiazol-2-ylacrylamide. 2-Amino-5-(methylthio)-1,3,4-thiadiazole (mp 174–178°) is readily prepared from 2-amino-5-mercapto-1,3,4-thiadiazole[12] by methylation and yielded the acrylamide **14a** on treatment with 2,3-dichloroacryloyl chloride in 96% yield. When **14a** was heated for 45 min in refluxing 1,2,4-trichlorobenzene, **15** was obtained in 35% yield; oxidation gave the corresponding sulfone **16** (62%). All efforts to achieve cyclization of sulfone **14b** to the corresponding heterocycle **16** directly were unfruitful. The failure of **14b** to cyclize is presumably due to the electronegativity of the methylsulfonyl group, which prevents the development of a negative charge on the hetero amidine nitrogen atom, whereas the methylthio group does not prevent this cyclization.



Experimental Section

Reaction of 3-Amino-6-chloropyridazine (7) with 2,3-Dichloroacrylic Acid 6a (X = OH).—An intimate mixture of **6a** (6.5 g,

(10) L. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 213.
(11) L. B. Dashkevich and E. S. Korbelainen, *Khim. Geterotsikl. Soedin.*, 441 (1968); *Chem. Abstr.*, **69**, 96645 (1968).
(12) T. Sandstrom, *Acta Chem. Scand.*, **15**, 1295 (1961).

46 mmol) and **7** (2.6 g, 20 mmol) was heated with stirring in an oil bath at 150°. When the temperature of the melt reached 140°, an exothermic reaction accompanied by evolution of hydrogen chloride took place and the internal temperature rose rapidly to 190°. The reaction was complete within 10 min and the temperature dropped to 160°, at which point gas evolution ceased. The cooled reaction mixture was extracted with 150 ml of boiling benzene, and the extract was dried ($MgSO_4$) and decolorized (Norit). Evaporation of the solvent provided 2 g of an oil. Trituration with 5 ml of methanol gave 0.7 g (16%) of **9a**, a brown solid melting at 271–272° dec. Recrystallization from boiling water gave **9a** as a colorless solid melting at 277–278° dec: ir (KBr) 3050 (CH=), 1652 (C=O), and 1631 cm^{-1} (C=N); nmr (DMSO-d_6) δ 7.75 (s, 2, CH=CH) and 9.0 ppm (s, 1, NCH=); nmr (CF_3CO_2H) δ 8.30 (d, 2, J = 9 Hz, CH=CH) and 8.93 ppm (s, 1, NCH=); mass spectrum (70 eV) m/e 215 and 217 (M^+).

2,3-Dichloro-*N*-(6-chloropyridazin-3-yl)acrylamide (8a).—A solution of 6.5 g (46 mmol) of **7** in 50 ml of DMF, prepared by warming to 50°, was added dropwise during an interval of 15 min to a stirred solution of **6a** (X = Cl) (4.0 g, 25 mmol) in 25 ml of DMF. The addition was exothermic, the temperature rising rapidly to 65°. Heating at 70° was continued for 15 min, whereupon the reaction mixture was poured into 150 ml of cold water with brisk agitation. The solid was collected by filtration and washed with cold water. The crude product was recrystallized from benzene to give 6.0 g (95%) of **8a**, yellow solid melting at 161–163°.

Compound **8a** was also prepared in 64% yield using a 2:1 molar ratio of **7** and **6a** (X = Cl), and in 71% yield from equimolar amounts of the reagents in DMF in the presence of triethylamine as an acid acceptor: ir (KBr) 3440, 3375 (NH), 3085 (CH=), 1690 (C=O), 1640 (C=, weak), 1590, 1575 cm^{-1} (amide II); nmr ($CDCl_3$) δ 7.5 (d, 1, J = 9 Hz, CH=), 8.5 (d, 1, J = 9 Hz, CH=), and 7.8 (s, 1, CHCl=).

Anal. Calcd for $C_7H_4Cl_3N_3O$: C, 33.3; H, 1.6; Cl, 42.2; N, 16.6 Found: C, 33.1; H, 1.7; Cl, 42.6; N, 16.7.

Fusion of 8a. A. With 1,2,4-Trichlorobenzene as Solvent.—A solution of **8a** (10.0 g, 39.6 mmol) in 75 ml of 1,2,4-trichlorobenzene was heated to 200–210° for 1 hr. Evolution of HCl was detected. The dark reaction mixture was cooled to 20° and filtered. The filter cake (6.5 g) was recrystallized from boiling water to give 6.0 g (70.5%) of **9a** melting at 277–278° dec. The identity of this product with that described above was confirmed by tlc (different solvent systems) and a mixture melting point and verified by identical mass and ir spectra.

B. With Xylene as Solvent.—A suspension of **8a**, 45.0 g (0.178 mol), in 250 ml of xylene was heated to reflux for 2.5 hr. The mixture became increasingly darker as HCl evolved. The reaction mixture was cooled to 20°, filtered, and washed with hexane, yield 32 g (84%) of tan solid melting at 275–277°. This product was identical (tlc, mixture melting point, ir) with **9a**.

3-Chloro-7-(methylthio)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (17).—To a solution of 9.0 g (41.6 mmol) of **9a** in 100 ml of dimethylsulfoxide containing 5.0 g (104 mmol) of methyl mercaptan sodium methoxide (2.4 g, 44.5 mmol) in 25 ml of dimethyl sulfoxide was added dropwise within 10 min, causing an exothermic reaction which was controlled at 30° with an ice bath. The mixture was stirred at 25–30° for 1.5 hr and then poured over ice water and filtered. The solid was recrystallized from methanol to yield 3.0 g (32%) of **17**, tan crystalline solid, mp 240° dec.

2,3,3-Trichloro-*N*-(6-chloropyridazin-3-yl)acrylamide (8b).—A suspension of **7** (32.4 g, 0.25 mol) and triethylamine (25.3 g, 0.25 mol) in 500 ml of tetrahydrofuran was stirred and controlled at 30° during the dropwise addition of **6b** (X = Cl). After completion of the addition, the mixture was heated to 60° for 1 hr and then poured into ice water. The products were extracted into methylene chloride, dried ($MgSO_4$), filtered, and concentrated to dryness. Recrystallization from methanol afforded 48.4 g (66%) of **8b**, colorless crystalline solid melting at 124–126°: ir (KBr) 3380, 3200 (NH), 1705 (C=O), and 1510 cm^{-1} (amide II).

Anal. Calcd for $C_7H_3Cl_4N_3O$: Cl, 49.5; N, 14.6. Found: Cl, 49.5; N, 14.6.

Fusion of 8b. A. With Xylene as Solvent.—A solution of **8b** (14.0 g, 0.05 mol) in 100 ml of xylene was heated at reflux for 6 hr. The mixture was cooled and filtered. Recrystallization from methanol afforded 3.0 g (24%) of **9b**, white crystalline solid melting at 285–289°: ir (KBr) 3080, 3050 (CH=), 1650 (C=O), 1609, 1585 cm^{-1} (C=); nmr (CF_3CO_2H) δ 8.28 ppm (q, J = 9 Hz, CH=CH), very similar to that of **9a**; mass spectrum (70 eV) (ions with a relative abundance of >5%) 249, 221, 214, 186, 155, 108, 99, 73, 64.

B. With 1,2,4-Trichlorobenzene as Solvent.—A solution of 13.0 g (45 mmol) of **8b** in 50 ml of 1,2,4-trichlorobenzene was heated at reflux for 20 min. Acidic gases evolved and the mixture became a dark solution. The mixture was cooled to 25° and diluted with 50 ml of hexane. The resultant precipitate (9.5 g) was filtered and recrystallized from methanol to yield 6.5 g (59%) of **13**, tan crystalline solid melting at 207–210°: ir (KBr) 1710 cm^{-1} (C=O); nmr (CF_3CO_2H) δ 7.8 (d, 1, J = 9.5 Hz, CH=) and 8.15 ppm (d, 1, J = 9.5 Hz, CH=); mass spectrum (70 eV) (ions with a relative abundance >5%) 249, 221, 214, 186, 108, 94, 73, 64.

Anal. Calcd for $C_7H_2Cl_3N_3O$: Cl, 42.5; N, 16.8. Found: Cl, 42.3; N, 16.5.

3-Chloro-4,7-bis(methylthio)-2*H*-pyrimido[1,2-*b*]pyridazin-2-one (18).—A solution of 12.5 g (0.05 mol) of **9b** in 150 ml of methanol was stirred during the dropwise addition of a previously prepared solution of 2.3 g of metallic sodium in 100 ml of methanol and 6 g (0.125 mol) of methyl mercaptan. The addition was exothermic to 45° and the reaction mixture was heated to 60° for 1.5 hr. The product was chilled to 5° and filtered. The filter cake was recrystallized from methanol to yield 12.0 g (88%) of **18**, tan crystalline solid melting at 203–206°: ir (KBr) 1641 (C=O), 1610, 1557 cm^{-1}; (C=); nmr (CF_3CO_2H) δ 2.8, 2.9 (s, 3, SCH_3), and 8.0 ppm (s, 1, CH=).

2,4-Dichloro-α-(chloromethyl)mandelonitrile.—A 105-g portion (0.47 mol) of 2,2′,4′-trichloroacetophenone (mp 56–59°) and approximately 0.5 ml of saturated, aqueous potassium cyanide were placed in a 1-l. three-necked flask equipped with a water-cooled dropping funnel and efficient reflux condenser. Liquid hydrogen cyanide (50 ml) was added rapidly producing almost immediate solution of the solid ketone. A mild exothermic reaction occurred and the HCN refluxed gently at 32°. After about 15 min, the reaction subsided, and external warming was provided to maintain reflux at 30–32° for 30 min longer. The colorless solution was cooled at 25° and a few drops of concentrated sulfuric acid were added to stabilize the cyanohydrin. Excess HCN was removed under reduced pressure into a KOH trap, causing the residual cyanohydrin to solidify. The product was triturated with hexane to remove traces of unreacted ketone and used without further purification after being dried *in vacuo*. The yield was 113 g (96%), mp 97–98°.

Anal. Calcd for $C_9H_6Cl_3NO$: Cl, 42.5. Found: Cl, 42.9.

(*Z*)-β,2,4-Trichloroatropamide.—2,4-Dichloro-α-(chloromethyl)-mandelonitrile (15 g, 0.05 mol) was suspended in 100 ml of concentrated sulfuric acid and heated on the steam bath, causing the solid to dissolve rapidly. After 30 min at 95°, the dark colored, opaque solution was collected by filtration and recrystallized from CCl_4, yielding 12 g (96%): mp 101–102°; ir (KBr) 3450, 3220 (NH), and 1669 cm^{-1} (C=O); nmr ($CDCl_3$) δ 6.2, 7.2 (s, 2, NH), 6.55 (s, 1, CH=), and 7.3 ppm (m, 3, C_6H_3).

Anal. Calcd for $C_9H_6Cl_3NO$: Cl, 42.5; N, 5.6. Found: Cl, 42.8; N, 5.2.

(*Z*)-β,2,4-Trichloroatropic Acid (6c, X = OH).—To a solution of 25.1 g (0.1 mol) of β,2,4-trichloroatropamide in 95 ml of concentrated sulfuric acid was added gradually at 0–15° a solution of 9.0 g of sodium nitrite in 30 ml of water. The mixture was then heated over the steam bath at 95° for 4 hr until gas evolution ceased. The cooled solution was poured over ice and the solid product was recrystallized from CCl_4. The colorless crystalline acid, 15.1 g (60%), melted at 94–97°: nmr ($CDCl_3$) δ 6.83 (s, 1, CH=) and 7.25 and 7.43 ppm (m, 3, C_6H_3).

Anal. Calcd for $C_9H_5Cl_3O_2$: Cl, 42.3; acid equiv, 250.5. Found: Cl, 42.4; acid equiv, 226.

Reaction of 3-Amino-6-chloropyridazine (7) with (*Z*)-β,2,4-Trichloroatropic Acid (6c, X = OH). A. Without Solvent.—An intimate mixture of **6c** (X = OH) (5.0 g, 0.02 mol) and **7** (2.6 g, 0.02 mol) was heated in an oil bath at 170–180° for 10 min, the solid mass melting with evolution of gas to form a dark liquid melt. The product was extracted with boiling benzene, dried ($MgSO_4$), and concentrated to dryness. Trituration with hexane gave 2.0 g (31%) of **9c**, yellow solid melting sharply at 235° (238–239° dec): ir (KBr) 3090, 3055 (CH=), 1643 (C=O), 1601, 1590 cm^{-1} (C=); nmr (DMSO-d_6) δ 7.3–7.7 (m, 3, C_6H_3), 7.73 (s, 2, CH=), and 8.62 ppm (s, 1, CH=).

B. With Polyphosphoric Acid as Solvent.—When the reaction described above was carried out in 30 ml of polyphosphoric acid

at 170° over a period of 3 hr, the only product isolated (34%) was **9c**.

Reaction of 3-Amino-6-chloropyridazine (7) with β-2,4-Trichloroatropoyl Chloride (6c, X = Cl).—A solution of 16.0 g (0.059 mol) of **6c**[13] (X = Cl) in 50 ml of tetrahydrofuran was added dropwise with stirring to a slurry of 8.0 g (0.061 mol) of **7** and 6.0 (0.061 mol) of triethylamine in 350 ml of tetrahydrofuran at 55°. During the period of addition (30 min), the temperature was maintained at 55°. Heating was then resumed at reflux (66°) for 2.5 hr. Triethylamine hydrohloride was removed by filtration, and the residual solution was concentrated and poured into water. The product was extracted with cold benzene; the insoluble solid, 13.6 g (70%) of **9c**, melted at 238–241° dec. Evaporation of the benzene provided 2 g of a brown solid which was purified by column chromatography over silica gel using acetone as eluent: yield 0.4 g (2%) of **11**; pale yellow solid melting at 195–198° dec; ir (KBr) 3095 (CH=) and 1708 cm^{-1} (C=O); nmr (DMSO-d_6) δ 7.5, 7.7 (m, 3, C_6H_3), 8.0 (d, 2, J = 9 Hz, CH=CH) and 8.35 ppm (s, 1, CH=).

Anal. Calcd for $C_{13}H_6Cl_3N_3O$: Cl, 32.7. Found: Cl, 32.5.

The reaction repeated at a lower temperature (30°) on a larger scale (0.1 mol) gave 15 g (46%) of **9c**, mp 240–243° dec. No other product was isolated. The identity of this product and **9c** (see above) was confirmed by tlc (different solvent systems) and mixture melting point and verified by identical ir spectra.

3-(2,4-Dichlorophenyl)-7-(methylamino)-2*H*-pyrimido[1,2-*b*]-pyridazin-2-one (19).—A suspension of **9c** (0.5 g, 1.5 mmol in 70 ml of 40% aqueous methylamine was heated on a water bath at 60–82° (final temperature) for 1 hr. The product was filtered and washed successively with water and acetone to give 0.45 g (94%) of **19**, tan solid melting at >300°: ir (KBr) 3240 (NH), 3060 (CH=), 1635 (C=O), 1600, 1580 cm^{-1} (C=).

3-(2,4-Dichlorophenyl)-7-(methylthio)-2*H*-pyrimido[1,2-*b*]-pyridazin-2-one (20).—A solution of **9c** (3.0 g, 12.7 mmol), 50 ml of dimethyl sulfoxide, and methyl mercaptan (2.0 g 41.6 mmol) was stirred at 25–30° during the dropwise addition of 0.6 g of sodium hydroxide in 5 ml of water. The mixture was stirred at ambient temperature for 1 hr and then poured into 400 ml of ice water. The precipitate was filtered and recrystallized from benzene–hexane to yield 2.5 g (80%) of yellow-brown crystalline solid, mp 192–194°.

Oxidation of 20.—To a solution of **20** (2.0 g, 6 mmol) in 50 ml of chloroform was added a solution of 2.5 g (12 mmol) of 85% *m*-chloroperbenzoic acid in 25 ml of chloroform. The mixture was stirred at ambient temperature for 18 hr and then extracted with 10% sodium carbonate solution. The chloroform layer was dried ($MgSO_4$), filtered, and concentrated. The residue was washed well with ether to give 1.0 g (45%) of **21**, brown crystalline solid melting at 130° dec.

2,3-Dichloro-*N*-[5-(methylthio)-1,3,4-thiadiazol-2-yl]acrylamide (14a).—To a solution of 29.4 g (0.2 mol) of 2-amino-5-(methylthio)-1,3,4-thiadiazole and 20.2 g (0.2 mol) of triethylamine in 200 ml of tetrahydrofuran was added dropwise, with stirring, 31.9 g (0.2 mol) of **6a** (X = Cl). The addition was exothermic to 50°. After completion of the addition, the mixture was heated to 66° for 1 hr and then drowned in ice water and filtered to yield 52 g (96%) of **14a**, cream-colored crystalline solid: mp 198–200°; ir (KBr) 3140 (NH), 1668 (C=O), 1532 cm^{-1} (amide II); nmr (DMSO-d_6) δ 2.8 (s, 3, SCH_3), 8.0 (s, 1, CHCl=), and 12.5 ppm (s, 1, NH).

Anal. Calcd for $C_6H_5Cl_2N_3S_2O$: Cl , 26.3; S, 23.7. Found: Cl, 26.6; S, 23.4.

Fusion of 14a.—A suspension of 30.0 g (11.1 mmol) of **14a** in 100 ml of 1,2,4-trichlorobenzene was heated to 210° for 45 min. The mixture was cooled and filtered. The filter cake was dissolved in hot dimethylformamide and allowed to cool to 25°. Filtration yielded 9 g (35%) of **15**, yellow-green crystalline solid: mp >320°; ir 3075 (C=), 1615 cm^{-1} (C=O).

Anal. Calcd for $C_6H_4ClN_3S_2O$: Cl, 15.2; N, 18.0. Found: Cl, 15.4; N, 17.8.

Oxidation of 15.—A mixture of 11.6 g (0.05 mol) of **15** in 100 ml of glacial acetic acid was treated with 25 ml of 30% hydrogen peroxide at 90° for 2 hr. The product was poured over ice water, filtered, and dried to yield 8.0 g (62%) of **16**, colorless crystalline solid: mp 235–238° dec; ir (KBr) 1680 (C=O), 1630 (C=), 1330, 1155 cm^{-1} (SO_2); nmr (DMSO-d_6) δ 3.65 (d, 3, CH_3), 6.9, 7.2 ppm (s, 1, CH=).

Anal. Calcd for $C_6H_4ClN_3S_2O_3$: N, 15.8; S, 24.1. Found: N, 15.6; S, 24.4.

2,3-Dichloro-*N*-[5-(methylsulfonyl)-1,3,4-thiadiazol-2-yl]acrylamide (14b).—A solution of 5.0 g (18.5 mmol) of **14a** in 30 ml of glacial acetic acid was treated with 20 ml of 30% hydrogen peroxide at 90° for 15 min. This solution was left standing for 2 hr, poured over ice water, and filtered to yield 4.0 g (72%) of **14b**, colorless crystalline solid: mp 217–220°; ir (KBr) 3450, 3250 (NH), 1675 (C=O), 1520 (amide II), 1315, 1155 cm^{-1} (SO_2); nmr (DMSO-d_6) δ 3.6 (s, 3, CH_3), 8.15 (s, 1, CHCl=), and 12.75 ppm (s, 1, NH).

Anal. Calcd for $C_6H_5Cl_2N_3S_2O_3$: Cl, 23.5; N, 21.2. Found: Cl, 23.1; N, 21.1.

Registry No.—**6c** (X = OH), 31579-71-2; **6c** (X = NH_2), 31579-72-3; **8a**, 31578-98-0; **8b**, 31578-99-1; **9a**, 31579-00-7; **9b**, 31579-01-8; **9c**, 31579-02-9; **11**, 31579-03-0; **13**, 31615-25-5; **14a**, 31568-46-4; **14b**, 31568-47-5; **15**, 31568-48-6; **16**, 31568-49-7; **17**, 31568-50-0; **18**, 31568-51-1; **19**, 31568-52-2; **20**, 31568-53-3; **21**, 31568-54-4; 2,4-dichloro-α-(chloromethyl)mandelonitrile, 24123-74-8.

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(13) Prepared from **6c** (X = OH) and thionyl chloride in the presence of catalytic amounts of dimethylformamide. The crude acid chloride was used without purification.