4(And 5)-Cyclopropylamino-5(and 4)halo-3(2*H*)pyridazinones. Formation and Characterization of Isomers

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The reactions of 4,5-dihalo-3(2*H*)pyridazinones with ammonia and amines gave mixtures of 5-amino-4-halo- and 4-amino-5-halo-3(2*H*)pyridazinones separated by chromatography. Structures were elucidated by means of retention values (R_f) and confirmed by independent synthesis.

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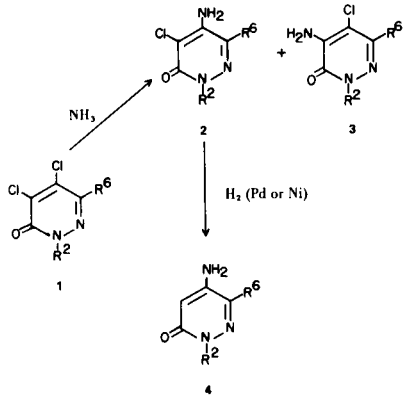
A general problem encountered in the study of reactions of 4,5-dihalo-3(2*H*)pyridazinones with ammonia and amines is the elucidation of the structure of the isomeric reaction products, that is the extent of formation of 5-amino-4-halo- or 4-amino-5-halo-3(2*H*)pyridazinones. Many investigators in this field left the question unanswered or predicted the structure on the basis of theoretical considerations. Although a large number of 5-amino-4-halo-3(2*H*)pyridazinones (**2**) have been reported in this way (1), the simultaneous formation and characterization of both isomers (**2** and **3**) appears to have been described in only two instances. In the cases of **2a** (1,2) and **2b** (3), the structures were confirmed by reductive dechlorination to the known 5-amino-3(2*H*)pyridazinones (**4a** and **4b**) (Scheme 1).

Scheme 1



a, $R^2 = C_6H_5$, $R^6 = H$
b, $R^2 = R^6 = CH_3$

We observed that the **2** and **3** compounds obtained from 4,5-dihalo-3(2*H*)pyridazinones with ammonia and primary amines produce two distinct retention values suggesting a convenient means for their separation and a reliable technique for structure assignment of isomeric 3(2*H*)pyridazinones. Some observations of chemical shift differences at position-6 of some isomeric 4(and 5)cyclopropylamino-5(and 4)halo-3(2*H*)pyridazinones are also presented.

EXPERIMENTAL

Materials and Methods

Chemical Methods

The compounds required for this study were prepared either by following standard literature procedures or as described below.

4,5-Dichloro-2-phenyl-3(2*H*)pyridazinone (**1a**) m.p. 163-164° (lit. (4) m.p. 163-164°); 4,5-dibromo-2-methyl-3(2*H*)pyridazinone (**1c**) m.p. 113-116° (lit. (5) m.p. 108-111°); 4,5-dichloro-2-methyl-3(2*H*)pyridazinone (**1d**) m.p. 87-88° (lit. (6) m.p. 90-91°); 4,5-dibromo-2-phenyl-3(2*H*)pyridazinone (**1e**) m.p. 142-143° (lit. (7) m.p. 145°); and 4,5-dichloro-2-(3-trifluoromethyl)phenyl-3(2*H*)-pyridazinone (8) (**1g**), m.p. 93-95°, were prepared by reactions of mucobromic or mucochloric acid with the respective hydrazine in dilute hydrochloric acid. 4-Bromo-5-chloro-2-phenyl-3(2*H*)-pyridazinone (**1f**), m.p. 147-148°, was prepared analogously from 3-bromo-4-chloro-5-hydroxy-2(5*H*)furanone (9) and phenylhydrazine.

Reactions of 4,5-dihalo-3(2*H*)pyridazinones (**1**) with ammonia were run in sealed glass cylinders on a steam bath. The following procedures are typical of the reactions of a primary amine with **1**.

4-Chloro-5-(cyclopropylamino)-2-phenyl-3(2*H*)pyridazinone (**2i**) and 5-Chloro-4-(cyclopropylamino)-2-phenyl-3(2*H*)pyridazinone (**3i**).

(a) A solution containing 241 g. (1.0 mole) of **1a** and 125 g. (2.19 moles) of cyclopropylamine in 2.4 l. of ethanol was refluxed for 4.5 hours. Fractional crystallization of the reaction mixture gave 202 g. (77%) of **2i**, m.p. 168-170°. The combined mother liquors were evaporated to dryness. The residual solid, which consisted of **2i** and **3i**, was resolved by column chromatography using solvent system No. 1. The first fraction consisted of 16.5 g. (6.3%) of **3i**, m.p. 86-87° (from hexane). The second fraction consisted of 14.5 g. of **2i**, bringing the yield to a total of 83%.

(b) A solution containing 24.1 g. (0.1 mole) of **1a**, 7.0 g. (0.127 mole) of cyclopropylamine and 11.2 g. (0.11 mole) of triethylamine in 250 ml. of tetrahydrofuran was refluxed for 54 hours. The solvent was removed under reduced pressure and the residual solid was washed well with water. Column chromatography of the crude reaction mixture gave 10.5 g. (40%) of **3i** and 11.5 g. (44%) of **2i**.

Physical-Chemical Methods.

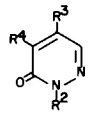
Column chromatography was run using "Grace" silica gel (grade 62, mesh size 60-200) and solvent system No. 1 (see below). Retention values (R_f) were obtained using pre-coated tlc glass plates (20 x 20 cm) with layers of silica gel F-254 (layer thickness 0.25 mm). The spots were detected by uv absorbance.

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Molecular weights were determined with a vapor pressure osmometer. Nmr spectra were recorded on a Varian A-60 spectrometer and chemical shifts are expressed in parts per million (δ) downfield from internal tetramethylsilane. Infrared absorption was measured with a Perkin-Elmer Model 21 spectrometer.

Results and Discussion

Table I

3(2*H*)pyridazinones, **2** and **3**



Compound	R^2	R^4	R^5	% Yield	M.p., °C	Formula	Nitrogen Calcd.	Nitrogen Found	Halogen Calcd.	Halogen Found
2c	CH_3	Br	NH_2	34	215-217	$C_5H_6BrN_3O$ (a)	20.6	20.3	–	–
3c	CH_3	NH_2	Br	19.5	126-127	$C_5H_6BrN_3O$ (b)	20.6	20.6	–	–
2a	C_6H_5	Cl	NH_2	84	203-204 (c)	$C_{10}H_8ClN_3O$	19.0	19.0	16.1	15.8
3a	C_6H_5	NH_2	Cl	6	141-142 (d)	$C_{10}H_8ClN_3O$	19.0	18.9	16.1	16.1
2d	C_6H_5	Cl	NHC_2H_5	32	154-156	$C_{12}H_{12}ClN_3O$	16.8	17.0	14.2	13.9
3d	C_6H_5	NHC_2H_5	Cl	30	77-78	$C_{12}H_{12}ClN_3O$	16.8	17.1	14.2	14.0
2e	C_6H_5	Cl	$NHC(CH_3)_3$	8	161-162	$C_{14}H_{16}ClN_3O$	15.2	15.4	12.8	13.0
3e	C_6H_5	$NHC(CH_3)_3$	Cl	18	50-51	$C_{14}H_{16}ClN_3O$	15.2	14.8	12.8	13.0
2f	CH_3	Br	NH-cyclopropyl	36.4	123-125	$C_8H_{10}BrN_3O$	17.2	17.0	32.8	32.8
3f	CH_3	NH-cyclopropyl	Br	16.8	69-70	$C_8H_{10}BrN_3O$	17.2	16.8	32.8	32.9
2g	CH_3	Cl	NH-cyclopropyl	33.9	133-134	$C_8H_{10}ClN_3O$	21.1	20.7	17.8	17.8
3g	CH_3	NH-cyclopropyl	Cl	8	76-78	$C_8H_{10}ClN_3O$	21.1	10.9	17.8	17.5
2h	C_6H_5	Br	NH-cyclopropyl	83.5	164-165	$C_{13}H_{12}BrN_3O$	13.7	13.5	26.1	26.5
3h	C_6H_5	NH-cyclopropyl	Br	7.2	79-80	$C_{13}H_{12}BrN_3O$	13.7	13.5	26.1	26.3
2i	C_6H_5	Cl	NH-cyclopropyl	44	168-170	$C_{13}H_{12}ClN_3O$	16.0	15.8	13.6	13.5
3i	C_6H_5	NH-cyclopropyl	Cl	40	86-87	$C_{13}H_{12}ClN_3O$	16.0	16.2	13.6	13.6
2j	3-CF_3-C_6H_4	Cl	NH-cyclopropyl	42	148-149	$C_{14}H_{11}ClF_3N_3O$	12.8	13.1	10.8	11.2
3j	3-CF_3-C_6H_4	NH-cyclopropyl	Cl	32	65-66	$C_{14}H_{11}ClF_3N_3O$	12.8	12.4	10.8	11.0

(a) Carbon, Calcd: 29.4. Found: 29.8. Hydrogen, Calcd: 2.9. Found: 3.0. (b) Carbon, Calcd: 29.4. Found: 29.8. Hydrogen, Calcd: 2.9. Found: 2.9. (c) Lit. (11) m.p. 205-206°. (d) Lit. (12) m.p. 142-143.5°.

A summary of the reaction products of 4,5-dihalo-3-(2*H*)pyridazinones (**1**) with ammonia and primary amines is presented in Table I. An interesting feature of the reaction of **1** with an amine is that the ratio of products formed, **2** to **3**, appears to depend upon the nature of the solvent used in the reaction. For example, replacement of chlorine in **1a** by cyclopropylamine in ethanol takes place largely at position 5 (83% of **2i**) and only to a small extent at position 4 (6.3% of **3i**). With **1a**, cyclopropylamine and triethylamine (molar ratio 1:1.3:1.1) in tetrahydrofuran under reflux conditions, it was found that chlorine replacement was relatively slow. The reaction was complete after 64 hours to give 44% of **2i** and 40% of **3i**. The considerable spread in product ratio and reaction time suggests that nucleophilic attack on the 5-position of **1** is favored over attack at position 4 in solvents having high dielectric constants such as water (ϵ *ca* 80) and ethanol (ϵ *ca* 25), whereas in tetrahydrofuran ($\epsilon < 10$) both positions appear nearly equally susceptible to nucleophilic attack. In tertiary-butylamine ($\epsilon < 5$), attack by the nucleophile on the 4-position is favored (18% of **3e**) over attack at position 5 (8% of **2e**). A steric effect is clearly operating in this reaction as evidenced by the low overall yields in the very slow reaction (50 hours) of **1a** with *t*-butylamine.

Retention values for compound classes, **1**, **2**, and **3** are summarized in Table II. The structure assignments of several pairs of isomeric 3(2*H*)pyridazinones, **2** and **3**, are based upon the following: a) The configurations of **2a** (major isomer, higher melting) and **3a** (minor isomer, lower melting) are known (see above and reference 1). b) Inasmuch as the most reactive halogen of a 4,5-dihalo-3(2*H*)pyridazinone (a cyclic vinylog of an acid chloride), **1**, is at position-5, the more abundant isomer is considered to have its amino group in that position (1,10). c) In all cases and in a number of solvent systems, the minor (lower melting) isomer, **3**, has a considerably higher retention value in thin layer chromatography than the corresponding major (higher melting) isomer, **2**, as illustrated in Table II. d) The apparent molecular weights for **2f** and **2i** in carbon tetrachloride and chloroform were higher than theoretical and increased with increasing concentration. On the other hand, **3f** and **3i** gave almost theoretical molecular weights and showed no variation with increasing concentration (Table III).

Thus, both retention value and molecular weight measurements indicate that **2f** and **2i** have more intermolecular hydrogen bonding than **3f** and **3i**. The structures having the amino group in the 4-position (α to carbonyl, as in **3a-3j**) would allow for intramolecular hydrogen bonding, whereas the structures with the amino group in the 5-position preclude intramolecular bonding, but would allow intermolecular hydrogen bonding. Therefore, the isomers with lower retention values are considered to have the amino group in position-5.

The nmr spectra of 3(2*H*)pyridazinones, **1**, **2** and **3**, in deuteriochloroform, and in several instances, in dimethyl sulfoxide-d6, are included in Table II. The heteroaromatic proton (H-6) has a relatively constant value (δ 7.5-8.3), not greatly influenced by the nature of the solvent. Among pairs of isomers a simple correlation is not apparent. For example, **2a** (major isomer, higher melting) shows a signal for H-6 at 7.80 ppm, whereas for **3a** (minor isomer, lower melting) the corresponding signal is shifted downfield by 0.1 ppm. By analogy, the bands appearing at lower field in the cyclopropylamino-3(2*H*)pyridazinones, **2f-2j** and **3f-3j**, are attributed to the 4-cyclopropylamino isomer, and consequently, the bands appearing at higher field are assigned to the 5-cyclopropylamino isomer. This is in obvious conflict with the physical behavior of these compounds as discussed above.

Structure and assignment of configuration for the isomeric pairs, **2h** and **3h** and **2i** and **3i**, obtained by reaction of **1e** and **1a** with cyclopropylamine (CPA), have been confirmed through a rational synthesis of **2h** and **3i** (Scheme 2). The method described by Hachihama, *et al.* (9), of treating freshly distilled furfural with concentrated hydrochloric acid and manganese dioxide to give 4-chloro-5-hydroxy-2(5*H*)furanone (**4**) followed by bromination of

Scheme 2

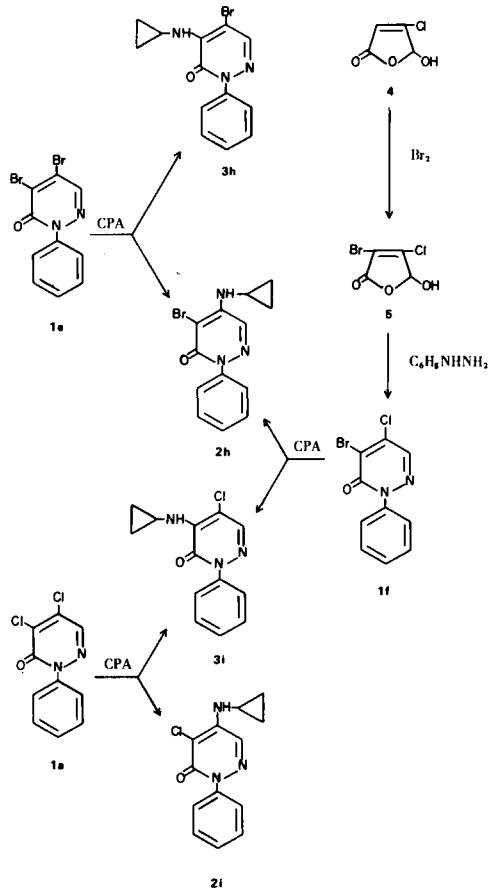
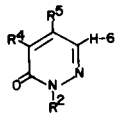
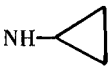
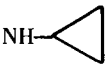
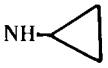
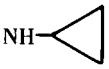
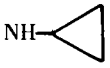
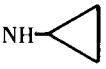
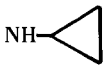
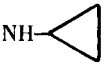


Table II

R_f-Values and Nuclear Magnetic Resonance Positions for 3(2*H*)pyridazinones

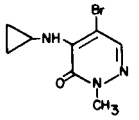
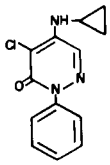
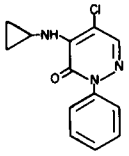


Compound	R^2	R^4	R^5	δ (ppm) for H-6	Solvent (a)	Retention Value (100 x R_f) in System Indicated (b) 1	2	3
1c	CH_3	Br	Br	7.80	C	23	32	44
1d	CH_3	Cl	Cl	7.80	C	22	32	43
1e	C_6H_5	Br	Br	7.90	C	30	40	47
1f	C_6H_5	Br	Cl	7.83	C	29	39	49
				8.25	D			
1a	C_6H_5	Cl	Cl	7.90	C	30	40	44
1g	3-CF_3-C_6H_4	Cl	Cl	(c)	C	39	49	57
2c	CH_3	Br	NH_2	7.50	D	0	4	11
3c	CH_3	NH_2	Br	7.68	C	8	14	19
				7.72	D			
2a	C_6H_5	Cl	NH_2	7.80	D	3	8	25
3a	C_6H_5	NH_2	Cl	7.90	D	18	30	49
2d	C_6H_5	Cl	NHC_2H_5	(c)	C	5	14	34
3d	C_6H_5	NHC_2H_5	Cl	(c)	C	40	49	58
2e	C_6H_5	Cl	$NHC(CH_3)_3$	7.65	C	14	28	46
3e	C_6H_5	$NHC(CH_3)_3$	Cl	7.65	C	49	55	60
2f	CH_3	Br		7.83	C	6	10	30
3f	CH_3		Br	7.62	C	28	34	51
2g	CH_3	Cl		7.92	C	4	9	53
3g	CH_3		Cl	7.50	C	30	37	51
2h	C_6H_5	Br		7.95	C	3	12	30
				8.10	D			
3h	C_6H_5		Br	7.75	C	33	45	53
				7.55	D			
2i	C_6H_5	Cl		7.88	C	7	17	38
3i	C_6H_5		Cl	7.44	C	41	48	56
2j	3-CF_3-C_6H_4	Cl	NH	8.15	C	8	19	41
				8.30	D			
3j	3-CF_3-C_6H_4	NH	Cl	7.66	C	43	54	59
				7.85	D			

(a) Solvent: C = deuteriochloroform, D = dimethylsulfoxide-d6. (b) Solvent system (by volume): 1; hexane (80), ethyl acetate (16), tetrahydrofuran (4). 2; hexane (66), ethyl acetate (30), tetrahydrofuran (4). 3; hexane (50), ethyl acetate (25), tetrahydrofuran (25). (c) H-6 appears in the same position as H's of the phenyl group.

Table III

Molecular Weights of Isomeric 3(2*H*)pyridazinones

Compound	Structure	Apparent Molecular Weight (a) (Weight of Sample in mg./10 ml.)	Solvent
2f		266 (480) 278 (880)	Carbon tetrachloride
3f		245 (370) 250 (660) 253 (1100) 253 (1450)	Carbon tetrachloride
2i		272 (200) 283 (565)	Chloroform
3i		268 (180) 270 (550)	Chloroform

(a) Determined osmometrically. Molecular weight calculated for **2f** and **3f** ($C_8H_{10}BrN_3O$): 244.1; calculated for **2i** and **3i** ($C_{13}H_{12}ClN_3O$): 261.6.

4 was used for the preparation of the required 3-bromo-4-chloro-5-hydroxy-2(5*H*)furanone (**5**). In chemical respects, **5** showed no differences when compared with mucobromic and mucochloric acid. For example, reaction of **5** with phenylhydrazine in dilute hydrochloric acid gave exclusively **1f**. Compound **3i**, obtained from **1f**, proved to be identical (m.p., mixed m.p., R_f-value, mass spectrum) with the isomer from the reaction of **1a** with CPA having the higher R_f-value and lower melting point. Compound **2h**, on the other hand, was identical with the major isomer formed in the reaction of **1e** with CPA having the lower R_f-value and higher melting point.

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