Pyridazines I

4-Halo-5-hydrazino-3-pyridazone and Its Derivatives

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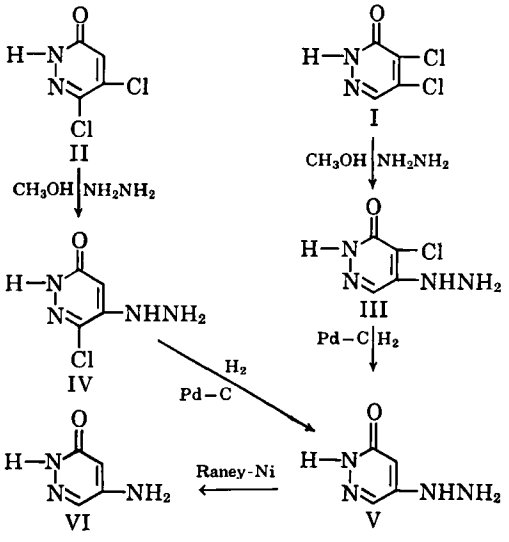
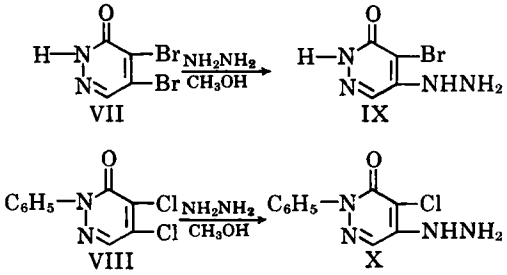
When 4,5-dichloro-3-pyridazone, 4,5-dibromo-3-pyridazone, or 4,5-dichloro-2-phenyl-3-pyridazone in methanol was allowed to react with 95% hydrazine, a mono-halo mono-hydrazino-3-pyridazone was obtained. An unequivocal proof of structure for 4-chloro-5-hydrazino-3-pyridazone is reported. Twenty-five hydrazones of 4-bromo-5-hydrazine-3-pyridazone and twenty-seven hydrazones of 4-chloro-5-hydrazino-3-pyridazone were prepared. One cyclized derivative of 4-chloro-5-hydrazino-2-phenyl-3-pyridazone is also reported.

DURING investigations in this laboratory of the relative reactivity of the chlorine atoms of 4,5-dichloro-3-pyridazone (I), the very facile reaction of this compound with hydrazine to yield a mono-halo mono-hydrazino-3-pyridazone was noted. The structure of 4-chloro-5-hydrazino-3-pyridazone (III) was determined by catalytic dechlorination followed by Raney-Ni cleavage of the hydrazino group to give the known 5-amino-3-pyridazone (VI) first prepared by Kuraishi (1).

Further confirmation was obtained by allowing 5,6-dichloro-3-pyridazone (II) to react with hydrazine. The product, compound IV, was catalytically dechlorinated to produce a compound (V) identical in all respects to that obtained from 4,5-dichloro-3-pyridazone under the same conditions.



4,5-Dibromo-3-pyridazone (VII) was also treated with hydrazine as was 4,5-dichloro-2-phenyl-3-pyridazone (VIII) and structures for the products—compounds IX and X, respectively—were assigned by analogy. The properties of compounds III through VI, IX, and X are listed in Table I.



The pyridazines have long been the subject of pharmacological studies, and the activities attributed to compounds of this ring system vary greatly (2–5). Similarly, the hydrazino group has frequently been found to confer activity upon a given structure. A complete review of hydrazine derivatives used as medicinals was published by Jucker in 1959 (6). With these facts in mind, it was deemed appropriate to prepare several carbonyl derivatives of both the bromo and chloro hydrazino compounds.

The properties of the derivatives are listed in Table II. Where a 1,3- or 1,4-dicarbonyl compound was employed, a cyclized derivative was obtained. Structures and properties for these products are given in Table III.

Infrared and ultraviolet absorption spectra of all the compounds prepared were recorded and contribute confirmatory evidence for the structure assigned.[1]

Data have been received concerning 23 of the compounds submitted to Cancer Chemotherapy National Service Center, National Cancer Insti-

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[1] The spectra appear in the doctoral dissertation by Winnifred M. Osner. Copies are available through University Microfilm, Inc., 313 N. First St., Ann Arbor, Mich.

TABLE I.—HYDRAZINO AND AMINO-3-PYRIDAZONES

Compound	M.p., °C.	Formula	Analysis C Calcd.	C Found	H Calcd.	H Found
III	195 dec.	$C_4H_5N_4OCl$	29.92	30.27	3.14	3.22
IV	268 dec.	$C_4H_5N_4OCl$	29.92	30.29	3.14	3.19
V	259 dec.	$C_4H_6N_4O$	38.09	38.16	4.79	4.59
VI	289 dec.	$C_4H_5N_3O$	43.24	42.94	4.54	4.10
IX	180 dec.	$C_4H_5N_4OBr$[a]	23.43	23.78	2.46	2.14
X	164 dec.	$C_{10}H_9N_4OCl$[a]	50.75	50.47	3.83	3.51

[a] Inactive in first stage of screening.

tute, for tissue culture screening. Though it is in no way complete or conclusive, this information as indicated in the tables is included here for consideration.

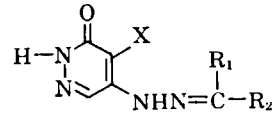
EXPERIMENTAL

All melting points were determined with a Vanderkamp Melt-Pointer and are uncorrected.

4 - Chloro - 5 - hydrazino - 3 - pyridazone (III).—Thirty-three Gm. (0.2 mole) of 4,5-dichloro-3-pyridazone (I) prepared by the method of Mowry (7) were dissolved in 560 ml. of boiling methanol. To this solution 19 Gm. (0.6 mole) of 95% hydrazine was added portionwise, and a yellow precipitate appeared after 10 minutes. The mixture was allowed to reflux a total of 1.5 hours; then it was cooled and filtered. Recrystallization from water afforded 20 Gm. (62%) of pale yellow needles, m.p. 195° dec.

4 - Bromo - 5 - hydrazino - 3 - pyridazone (IX).—4,5-Dibromo-3-pyridazone prepared by the method

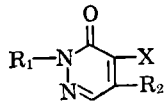
TABLE II.—DERIVATIVES OF 4-HALO-5-HYDRAZINO-3-PYRIDAZONE

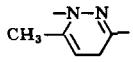
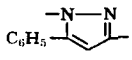
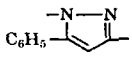
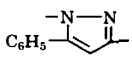


X	R_1	R_2	M.p., °C.	Formula	Analysis C Calcd.	C Found	H Calcd.	H Found	Prepn.
Br	Hydrogen	Phenyl	241 dec.	$C_{11}H_9N_4OBr$[b]	45.07	44.93	3.09	3.01	A
Cl	Hydrogen	Phenyl	304 dec.	$C_{11}H_9N_4OCl$[b]	53.11	53.30	3.65	3.57	A
Br	Hydrogen	*m*-Hydroxyphenyl	267 dec.	$C_{11}H_9N_4O_2Br$	42.74	42.49	2.93	2.86	A
Cl	Hydrogen	*m*-Hydroxyphenyl	300 dec.	$C_{11}H_9N_4O_2Cl$	49.91	49.73	3.42	3.21	A
Br	Hydrogen	3,4-Dimethoxyphenyl	248 dec.	$C_{13}H_{13}N_4O_3Br$	44.20	44.19	3.71	3.29	A
Cl	Hydrogen	3,4-Dimethoxyphenyl	276 dec.	$C_{13}H_{13}N_4O_3Cl$[c]	50.57	50.55	4.24	4.11	A
Br	Methyl	Phenyl	220 dec.	$C_{12}H_{11}N_4OBr$[c]	46.92	46.96	3.61	3.40	A
Cl	Methyl	Phenyl	255 dec.	$C_{12}H_{11}N_4OCl$[d]	54.88	54.66	4.22	3.99	A
Br	Methyl	*p*-Methylphenyl	224 dec.	$C_{13}H_{13}N_4OBr$	48.61	48.70	4.08	3.92	A
Cl	Methyl	*p*-Methylphenyl	280 dec.	$C_{13}H_{13}N_4OCl$	56.42	56.29	4.73	4.64	A
Br	Methyl	3,4-Dimethylphenyl	220 dec.	$C_{14}H_{15}N_4OBr$	50.16	50.29	4.51	4.44	A
Cl	Methyl	3,4-Dimethylphenyl	263 dec.	$C_{14}H_{15}N_4OCl$	57.83	57.81	5.20	4.78	A
Br	Methyl	*o*-Hydroxyphenyl	234 dec.	$C_{12}H_{11}N_4OBr$	44.60	44.79	3.43	3.50	A
Cl	Methyl	*o*-Hydroxyphenyl	289 dec.	$C_{12}H_{11}N_4O_2Cl$	51.71	51.58	3.98	3.84	A
Br	Methyl	3,4-Dichlorophenyl	240 dec.	$C_{12}H_9N_4OBrCl_2$	38.32	38.72	2.41	2.41	A
Cl	Methyl	3,4-Dichlorophenyl	314 dec.	$C_{12}H_9N_4OCl_3$	43.46	43.70	2.74	2.68	A
Br	Ethyl	Phenyl	182	$C_{13}H_{13}N_4OBr$	48.61	48.67	4.03	3.83	A
Cl	Ethyl	Phenyl	209–210	$C_{13}H_{13}N_4OCl$[b]	56.43	56.38	4.74	4.49	A
Br	*n*-Propyl	Phenyl	175–176	$C_{14}H_{15}N_4OBr$	50.16	50.14	4.51	4.21	A
Cl	*n*-Propyl	Phenyl	217–218	$C_{14}H_{15}N_4OCl$[a]	57.84	57.57	5.20	4.90	A
Br	Isopropyl	Phenyl	221 dec.	$C_{14}H_{15}N_4OBr$[a]	50.16	49.75	4.51	4.25	A
Cl	Isopropyl	Phenyl	251	$C_{14}H_{15}N_4OCl$[c]	57.83	57.56	5.20	4.95	A
Br	*n*-Butyl	Phenyl	151	$C_{15}H_{17}N_4OBr$	52.90	52.72	5.27	4.97	A
Cl	*n*-Butyl	Phenyl	190	$C_{15}H_{17}N_4OCl$	60.27	60.15	6.01	5.68	A
Br	2-Carboxyvinyl	Phenyl	233 dec.	$C_{14}H_{11}N_4O_3Br$[a]	46.30	46.36	3.05	2.78	A
Cl	2-Carboxyvinyl	Phenyl	255 dec.	$C_{14}H_{11}N_4O_3Cl$[c]	52.76	52.62	3.47	3.44	A
Br	Methyl	Styryl	207 dec.	$C_{14}H_{13}N_4OBr$	50.46	51.02	3.93	3.85	A
Cl	Methyl	Styryl	214 dec.	$C_{14}H_{13}N_4OCl$	58.34	58.96	4.54	4.47	A
Br	Phenyl	Phenyl	299 dec.	$C_{17}H_{13}N_4OBr$	55.30	55.46	3.54	3.32	B
Cl	Phenyl	Phenyl	304 dec.	$C_{17}H_{13}N_4OCl$	62.87	62.87	4.03	4.02	B
Br	Phenyl	*p*-Methoxyphenyl	232	$C_{18}H_{15}N_4O_2Br$	54.15	54.23	3.79	3.52	A
Cl	Phenyl	*p*-Methoxyphenyl	252	$C_{18}H_{15}N_4O_2Cl$	61.11	61.11	4.27	4.29	A
Br	Benzyl	*p*-Methylphenyl	236 dec.	$C_{19}H_{17}N_4OBr$[a]	57.44	57.25	4.31	4.09	A
Cl	Benzyl	*p*-Methylphenyl	276 dec.	$C_{19}H_{17}N_4OCl$	64.68	64.41	4.86	4.73	A
Br	Benzyl	Benzyl	192 dec.	$C_{19}H_{17}N_4OBr$[a]	57.44	57.33	4.31	4.30	A
Cl	Benzyl	Benzyl	207	$C_{19}H_{17}N_4OCl$	64.68	64.53	4.86	4.41	A
Br	Phenyl	Phenylhydroxymethyl	240 dec.	$C_{18}H_{15}N_4O_2Br$	54.15	53.69	3.79	3.31	A
Cl	Phenyl	Phenylhydroxymethyl	259 dec.	$C_{18}H_{15}N_4O_2Cl$	60.93	60.81	4.26	3.93	A
Br	Phenyl	Benzoyl	225	$C_{18}H_{13}N_4O_2Br$	54.42	54.11	3.30	3.06	A
Cl	Phenyl	Benzoyl	220 dec.	$C_{18}H_{13}N_4O_2Cl$[d]	61.28	61.43	3.71	3.55	A
Cl	Hydrogen	2-Furyl	259 dec.	$C_9H_7N_4O_2Cl$[b]	45.30	45.05	2.96	2.78	A
Br	Methyl	3-Pyridyl	267 dec.	$C_{11}H_{10}N_5OBr$[a]	42.87	43.05	3.27	3.19	B
Cl	Methyl	3-Pyridyl	280 dec.	$C_{11}H_{10}N_5OCl$	50.10	49.80	3.82	3.69	A
Br	Methyl	2-Pyridyl	251 dec.	$C_{11}H_{10}N_5OBr$[a]	42.87	42.81	3.27	3.18	B
Cl	Hydrogen	3-Pyridyl	287 dec.	$C_{10}H_8N_5OCl$	48.11	47.63	3.23	3.11	A
Br	Phenyl	*p*-Dimethylaminophenyl	213 dec.	$C_{19}H_{18}N_5OBr$	55.35	55.34	4.40	4.66	A
Cl	Phenyl	*p*-Dimethylaminophenyl	258 dec.	$C_{19}H_{18}N_5OCl$	62.04	61.53	4.93	4.68	A
Cl	*p*-Dimethylaminophenyl	*p*-Dimethylaminophenyl	253 dec.	$C_{21}H_{23}N_6OCl$[c]	61.38	61.10	5.64	5.18	A
Cl	Hydrogen	*p*-Dimethylaminophenyl	252 dec.	$C_{13}H_{14}N_5OCl$	53.52	53.54	4.84	4.64	A

[a] Inactive in first stage of screening. [b] Active in first stage; inactive in second stage. [c] Active in first stage; no data on second stage. [d] Active through first and second stages.

TABLE III.—CYCLIC DERIVATIVES OF 4-HALO-5-HYDRAZINO-3-PYRIDAZONE



X	R_1	R_2	M.p., °C.	Formula	Analysis C Calcd.	C Found	H Calcd.	H Found	Prepn.
Br	Hydrogen		264 dec.	$C_{10}H_{11}N_4OBr$[a]	42.42	42.49	3.92	3.39	A
Br	Hydrogen		211–213	$C_{19}H_{13}N_4OBr$	58.03	58.14	3.33	2.99	A
Cl	Hydrogen		209	$C_{19}H_{13}N_4OCl$[b]	65.44	65.51	3.76	3.64	A
Cl	Phenyl		176–178	$C_{25}H_{17}N_4OCl$	70.67	70.42	4.03	3.80	A

[a] Active in first stage; inactive in second stage. [b] Active in first stage; no data on second stage.

of Bistrzycki (9) was treated with hydrazine as described above for compound III. Recrystallization from water produced dark yellow needles, m.p. 180° dec.

4-Chloro-5-hydrazino-2-phenyl-3-pyridazone (X)—4,5-Dichloro-2-phenyl-3-pyridazone (VIII) prepared by the method of Mowry (7), when allowed to react with hydrazine as described above, gave a 75% yield of fine yellow needles, m.p. 164° dec.

6-Chloro-5-hydrazino-3-pyridazone (IV).—5,6-Dichloro-3-pyridazone (II), prepared by the method of Kuraishi (8), was similarly treated with hydrazine. The product (94%) was recrystallized from water to yield white crystals, m.p. 268° dec.

5-Hydrazino-3-pyridazone (V).—4-Chloro-5-hydrazino-3-pyridazone (III) (4.8 Gm., 0.05 mole) dissolved in 200 ml. of 1% sodium hydroxide was treated with hydrogen in the presence of 1.2 Gm. of 5% Pd-C catalyst at atmospheric pressure and room temperature. Following absorption of the theoretical amount of hydrogen, the catalyst was separated and washed with 50 ml. of 1% sodium hydroxide followed by methanol until washings were no longer basic. The filtrate and washings were neutralized with glacial acetic acid and the solution concentrated on a steam bath under reduced pressure. After cooling 48 hours, 2.8 Gm. (74%) of a dark orange solid was collected. Recrystallization from 95% ethanol (norite) afforded pale yellow needles, m.p. 267° dec.

5-Amino-3-pyridazone (VI).—A mixture of 1.75 Gm. (0.014 mole) of 5-hydrazino-3-pyridazone (V) dissolved in 85% ethanol and Raney-Ni W-2 (prepared from 15 Gm. of Raney-Ni alloy) was allowed to reflux 2 hours. The catalyst was removed and the filtrate evaporated on a steam bath under reduced pressure to approximately one-half volume. After cooling overnight, 0.9 Gm. (60%) of gray plates was collected and recrystallized from water (Norite) to yield white crystals, m.p. 288° dec.

General Procedure A.—One-tenth mole of the appropriate halo-hydrazino-pyridazone was treated with 8 ml. concentrated sulfuric acid followed by 70 ml. water and the mixture heated gently just until the solid dissolved, at which time the hot solution was poured into a second flask containing 1 ml. of carbonyl compound dissolved in 40–80 ml. 95% ethanol. After standing 12 to 48 hours, the solid was filtered and recrystallized usually from 95% ethanol.

General Procedure B.—To one-tenth mole of the halo-hydrazino-pyridazone were added 10 ml. concentrated hydrochloric acid in 10 ml. water and 15 ml. 95% ethanol. The mixture was heated then added to 1 Gm. of the carbonyl compound dissolved in 10 ml. of ethanol. After cooling 24 hours, the precipitate was filtered and recrystallized from an appropriate solvent.

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