Pyridazines. VI. Some 6-Substituted 3(2*H*)pyridazinones (1)

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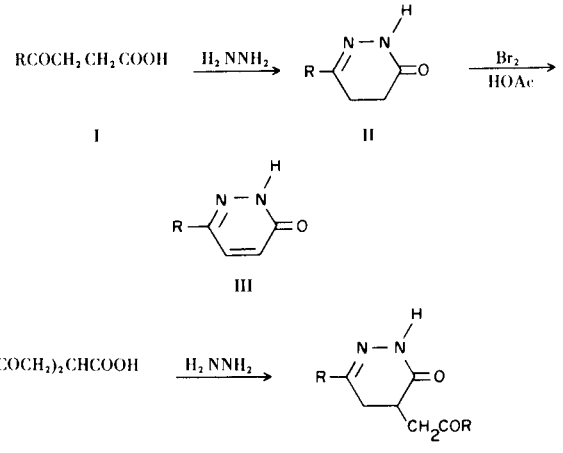
A series of 6-substituted 3(2*H*)pyridazinones was prepared. The 6-substituent was either aromatic of heter-aromatic in structure. A few basically-substituted representatives were also made.

Pyridazine derivatives have been the subject of detailed review (3,4), and clear evidence given that numerous representatives exhibit diverse and valuable effects upon biological systems. Very recently, attention has been drawn to the fact that various 4,5-dihydro-3(2*H*)pyridazinones have interesting levels of anti-hypertensive activity and depressant effects on the central nervous system (5-8). It is pertinent to report on some of our prior synthetic work (9) on related compounds, which had begun with studies on allied types (10-12) showing anti-protozoal effects.

Synthesis of the requisite 6-substituted 3(2*H*)pyridazinones was accomplished (*cf.* 3,4,10) by interaction of an appropriate γ-ketonic acid (I) with hydrazine hydrate to form a 6-substituted 4,5-dihydro-3(2*H*)pyridazinone (II), which was then dehydrogenated with bromine in acetic acid to give the desired product (III). The method was first used by Curtius (13), essentially based upon work of Emil Fischer (14). In some instances, a substituted hydrazine was employed to obtain a target compound having a functional grouping at position 2. As a variant on the γ-ketonic acid component used in the synthesis, a few of *bis*-(phenacyl)acetic acid types (IV) were interacted with hydrazine to give 6-aryl-4-phenacyl-4,5-dihydro-3(2*H*)-pyridazinones, V.



The majority of γ-ketonic acids were prepared by subjecting the parent type, RH (wherein R was either aromatic or heteraromatic in character), to Friedel-Crafts reaction (15,16) with succinic anhydride. The greater number of these intermediates was known, however a few new compounds have been listed in Table I. The *bis*-(phenyl)-acetic acid types, IV, required as intermediates for V were obtained by the action of alkali on the appropriate 4-oxo-4-phenylacrylic acid (*cf.* 17,18).

Table II summarizes the bulk of data on 6-substituted 4,5-dihydro-3(2*H*)pyridazinones formed by interaction of hydrazine with an appropriate 4-substituted 4-oxobutanoic acid. A few additional representatives were prepared from those tabulated, and also from the *bis*-(phenacyl)acetic acid type. The 2,6-disubstituted 4,5-dihydro-3(2*H*)pyridazinones prepared from reaction of a substituted hydrazine with a 4-substituted 4-oxobutanoic acid have been assembled in Table III.

6-Substituted 3(2*H*)pyridazinones in Table IV were obtained from the appropriate 4,5-dihydro compounds. In some instances, other products were also of interest, as resulting from bromination which occurred during dehydrogenation of the intermediate by use of bromine in acetic acid. Thus, both 6-(4-methoxyphenyl)-3(2*H*)pyridazinone and the related 6-(3-bromo-4-methoxyphenyl) compound were produced by the action of one equivalent of bromine with 6-(4-methoxyphenyl)-4,5-dihydro-3(2*H*)pyridazinone. Use of two equivalents of bromine gave only 6-(3-bromo-4-methoxyphenyl)-3(2*H*)pyridazinone (*cf.* 19), whose structure was proven by oxidation to 3-bromo-4-methoxybenzoic acid. Further, 6-(2-thienyl)-3(2*H*)pyridazinone and 6-(5-bromo-2-thienyl)-3(2*H*)pyridazinone were formed by the action of one equivalent of bromine upon 6-(2-thienyl)-4,5-dihydro-3(2*H*)pyridazinone. The structure of the latter product was proven by oxidation to 5-bromo-2-thenoic acid.

Additionally, compounds listed in Table IV were used as intermediates for various desired 6-substituted-3(2*H*)-pyridazinones. The following substituted-phenyl types

TABLE I

4-Substituted 4-Oxobutanoic Acids

4-Substituent	Appearance	M.p. °C, (a)	Solvent (b)	Yield, %	Formula	Analyses Calcd. Neut. eq.	Calcd. Br (c)	Found Neut. eq.	Found Br
4-(2-Bromoethoxy)phenyl	Prismatic needles	137-138	P	54	$C_{12}H_{13}BrO_4$	301.1	26.54	301.1	26.38
3,4-Ethylenedioxyphenyl	Needles	139.5-140	W	89	$C_{12}H_{12}O_5$	236.2	(d)	230.4	(d)
8-Bromo-2-dibenzofuryl	Needles	198.5-199	A	71	$C_{16}H_{11}BrO_4$	347.2	23.02	349	23.28
8-Bromo-2/3-phenoxathiinyl	Yellowish platelets	214-215	A	16 (f)	$C_{16}H_{11}BrO_4S$	379.2	8.45 (e)	375.0	8.54 (e)
8-Bromo-3/2-phenoxathiinyl	Yellowish platelets	188-189 (D.)	T	5 (f)				359.9	8.19 (e)

(a) D. signifies decomposition. (b) Legend: A, ethanol: Ac, acetic acid; Bl, butanol; C, diethylene glycol monoethyl ether; Di, dioxane; Ea, ethyl acetate; H, hexane; P, pentanol; Pg, propylene glycol; T, toluene; W; a, aqueous. (c) In all cases, except one, carbon and hydrogen values were not concordant. (d) *Anal.* Calcd. for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 61.31; H, 5.00. (e) Sulfur. (f) See text.

TABLE II

6-Substituted 4,5-Dihydro-2(2*H*)pyridazinones

6-Substituent	Appearance	M.p. °C.	Solvent (a)	Yield, %	Formula	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
3-Nitrophenyl	Dull yellow microcryst	238-240	aAc	88	$C_{10}H_9N_3O_3$	54.80	4.14	6.39 (b)	55.16	4.16	6.34 (b)
4-Methoxyphenyl	Platelets	150.5-151 (c)	aDi	91	$C_{11}H_{12}N_2O_2$	64.69	5.92	13.72	64.90	5.75	13.57
4-(2-Bromoethoxy)phenyl	Creamy tablets	167.5-168.5	aAc	95	$C_{12}H_{13}BrN_2O_2$	26.89 (d)		9.43	26.41 (d)		9.55
4-Acetamidophenyl	Leaflets	251-252 (g)	Bl	88	$C_{12}H_{13}N_3O_2$	62.33	5.67	18.17	62.25	5.56	18.31
4-Chloro-3-methylphenyl	Stout prisms	171.5-172.5	aDi	89.5	$C_{11}H_{12}ClN_2O$	59.34	4.98	12.58	59.52	5.00	12.50
3,4-Ethylenedioxyphenyl	Needles	217-218	aA	97	$C_{12}H_{12}N_2O_3$	62.06	5.21	12.06	62.21	4.89	11.41 (e)
2-Thienyl	Spears	126-127	W	96.5	$C_8H_8N_2OS$	53.31	4.47	15.55	53.44	4.26	15.56
8-Bromo-2-dibenzofuryl	Creamy needles	258-260	Bl	87	$C_{16}H_{11}BrN_2O_2$	55.99	3.23	8.16	56.10	3.15	8.05
8-Bromo-2/3-phenoxthiinyl	Yellow leaflets	220-220.5	Ac	90.5	$C_{16}H_{11}BrN_2O_2S$	51.21	2.95	8.54 (f)	51.42	2.92	8.18 (f)

(a) Legend: see TABLE I, Footnote (b). (b) Nitro nitrogen. (c) Reported melting points: 147-148° (19); 146-147° (48); 153-154° (49). (d) Bromine. (e) Average of 3 Dumas determinations. (f) Sulfur. (g) Reported (40) m.p. 252°.

TABLE III

2,6-Disubstituted 4,5-Dihydro-3(2*H*)pyridazinones

2-Substituent	6-Substituent	Appearance	M.p., °C.	Solvent (a)	Yield, %	Formula	Analyses Calcd. C	H	N	Found C	H	N
Methyl	Phenyl	Prisms	107.5-108	H	96	$C_{11}H_{12}N_2O$	70.19	6.43	14.89	70.48	6.51	14.85
	4-Chlorophenyl (c)	Prisms	79-79.5	H	91	$C_{11}H_{11}ClN_2O$	59.33	4.98	12.59	59.61	4.88	12.63
4-Chlorophenyl	Phenyl (d)	Blades	113-114	aA	72	$C_{16}H_{13}ClN_2O$	67.49	4.60	12.45 (b)	67.80	4.30	12.20 (b)
	4-Chlorophenyl	Tablets	95-96	aA	78	$C_{16}H_{12}Cl_2N_2O$	22.23 (b)		8.78	22.50 (b)		8.77
	2-Thienyl	Prisms	119-119.5	aA	63	$C_{14}H_{11}ClN_2OS$	12.19 (b)		9.64	12.28 (b)		9.63

(a) Legend: see TABLE I, Footnote (b). (b) Chlorine. (c) Compound in reference 50; not characterized in abstract. (d) Compound in reference 51; not characterized in abstract.

TABLE IV

6-Substituted 3(2*H*)pyridazinones

6-Substituent	Appearance	M.p., °C.	Solvent (a)	Yield, %	Formula	Analyses Calcd. C	H	N	Found C	H	N
3-Nitrophenyl	Creamy tablets	275-276	A	85.5	$C_{10}H_7N_3O_3$	55.30	3.25	6.45	55.31	3.57	6.38
4-Methoxyphenyl	Prismatic needles	191-191.5	aA	56 (b)	$C_{11}H_{10}N_2O_2$	65.35	4.99	13.86	65.55	4.75	13.79
3-Bromo-4-methoxyphenyl	Leaflets	282-283 (c)	C	31 (b)	$C_{11}H_9BrN_2O_2$	46.99	3.22	9.97	47.19	3.22	9.77
4-(2-Bromoethoxy)phenyl	Creamy needles	183.5-184 (g)	aA or aAc	68		27.08 (d)		9.49	27.08 (d)		9.39
4-Acetamidophenyl	Needles	298.5-299.5	aA	89	$C_{12}H_{11}N_3O_2$	69.20	4.84	6.11	62.77	4.87	6.15 (e)
4-Chloro-3-methylphenyl	Microcrystals	236-237	C	93	$C_{11}H_{10}ClN_2O$	59.87	4.11	12.70	59.51	4.34	12.91
3,4-Ethylenedioxyphenyl	Platelets	253-255 (dec.)	aA	92	$C_{12}H_{10}N_2O_3$	62.63	4.38	12.17	62.35	4.44	12.30
2-Thienyl	Microcrystals	181-181.5	aA	52 (b)	$C_8H_6N_2OS$	53.92	3.39	15.72	53.67	3.37	15.85
5-Bromo-2-thienyl	Creamy platelets	249-251	aC	29 (b)	$C_8H_5BrN_2OS$	12.47 (f)		10.90	12.40 (f)		10.81
8-Bromo-2-dibenzofuryl	Fine needles	321-322	Pg	89.5	$C_{16}H_9BrN_2O_2$	56.32	2.66	8.21	56.51	2.44	8.23

(a) Legend: see TABLE I, Footnote (b). (b) See text. (c) Reported m.p. 263° (reference 19). (d) Bromine. (e) Dumas values were not concordant. Nitrogen assay accomplished by hydrolysis, followed by estimation of amino nitrogen by diazotization. (f) Sulfur. (g) Sulfur. (g) Reported in reference 52; not characterized in abstract.

were made: 3- and 4-aminophenyl; 3-amino-4-bromophenyl; 4-chloro-3-nitrophenyl; 4-sulfamylphenyl; 4-hydroxyphenyl; and 4-(2-diethylaminoethoxy)phenyl. Further, 6-(4-aminophenyl)-3(2*H*)pyridazinone was interacted with 4,7-dichloroquinoline in phenol to form 6-[4-(7-chloro-4-quinolylamino)phenyl]-3(2*H*)pyridazinone.

EXPERIMENTAL (20)

Intermediates.

The 4-substituted 4-oxobutanoic acids were generally prepared by the Friedel-Crafts reaction (15,16), with published procedures available for application to anisole (21), acetanilide (22,23), *o*-chlorotoluene (24), and thiophene (25). 4-(3-Nitrophenyl)-4-oxobutanoic acid was made by nitration (26,27) of the 4-phenyl compound.

2-Phenoxyethyl bromide (28) was interacted with succinic anhydride and aluminum chloride in nitrobenzene to obtain 4-[4-(2-bromoethoxy)phenyl]-4-oxobutanoic acid. Data concerning that and other new intermediates have been assembled in Table I. 1,2-Ethylenedioxybenzene was made from catechol (29) and subjected to Friedel-Crafts reaction with succinic anhydride in a mixture of *sym*-tetrachloroethane and nitrobenzene (*cf.* 21,30). 2-Bromodibenzofuran (31) was converted into 4-(8-bromo-2-dibenzofuryl)-4-oxobutanoic acid after the manner used for the parent substance (32). 2-Bromophenoxathiin (33,34) was treated as described for phenoxathiin (35). The resultant mixture of 4-(8-bromo-2/3-phenoxathiinyl)-4-oxobutanoic acids was fractionally crystallized from ethanol, and the lower-melting, more soluble isomer then crystallized from cyclohexane or toluene. Structure proof was not done for these intermediates, of which only one was at hand in amount adequate for conversion to the 6-substituted 4,5-dihydro-3(2*H*)-pyridazinone type.

bis-(4-Bromophenacyl)acetic Acid.

This compound was prepared from 4-bromobenzoyl acrylic acid (36) essentially after that employed for conversion of benzoyl acrylic acid into *bis*-phenacyl acetic acid (17,18). A solution of 34.5 g. (0.136 mole) of 4-bromobenzoyl acrylic acid in 400 ml. of 10% sodium hydroxide was warmed on the steam bath for one hour. A small amount of gum was left upon decantation, and the liquors were treated with charcoal, clarified, cooled, washed with ether to remove 4-bromo acetophenone, then acidified. The crude product separated as an oily solid which crystallized well from ethanol (charcoal) as fine white needles. Two further crystallizations afforded 15.2 g. (49% yield) pure *bis*-(4-bromophenacyl)acetic acid, m.p. 176.3-177.5°. When later prepared by a different method (37) the compound had m.p. 174°.[5]

Anal. Calcd. for $C_{18}H_{14}Br_2O_4$: C, 47.60; H, 3.11; Neut. Equiv., 450. Found: C, 47.83; H, 3.17; Neut. Equiv., 440.

bis-(3,4-Dichlorophenacyl)acetic Acid.

This compound was prepared from 3,4-dichlorobenzoylacrylic acid (36) much as described above, and a 30.5% yield of thrice-crystallized (propanol) product resulted. The fine, white needles had m.p. 212-212.5°.

Anal. Calcd. for $C_{18}H_{12}Cl_4O_4$: C, 49.80; H, 2.79; Cl, 32.67; Neut. Equiv., 434.1. Found: C, 49.77; H, 2.83; Cl, 32.80; Neut. Equiv., 435.

Methyl hydrazine sulfate was prepared from benzalazine (38) and 4-chlorophenyl hydrazine hydrochloride (39) was made from 4-chloroaniline.

4,5-Dihydro-3(2*H*)pyridazinones.

The γ-keto acids were interacted with hydrazine after the manner we have described previously (10,12). In some instances, it was necessary to concentrate the reaction liquors and extract with ethanol to isolate the product from residual solids. The 6-substituted 4,5-dihydro-3(2*H*)pyridazinones listed in Table II were prepared by this method.

6-(3-Aminophenyl)-4,5-dihydro-3(2*H*)pyridazinone.

This compound was obtained from the related nitro compound (Table II) by reduction in methanol at 3 atmospheres hydrogen pressure using Adams' catalyst. It was isolated in the form of the hydrochloride in 81% yield as a creamy microcrystalline solid (ethanol-ether); m.p. 265.4-267° dec. The corresponding base has been reported recently (40).

Anal. Calcd. for $C_{10}H_{11}N_3O \cdot HCl$: C, 53.22; H, 5.36; N, 18.62. Found: C, 53.31; H, 5.30; N, 18.83.

6-(4-Aminophenyl)-4,5-dihydro-3(2*H*)pyridazinone.

This compound was isolated in 83.5% yield by hydrolysis of the acetamido compound (Table II) with 6*N* hydrochloric acid in ethanol. The hydrochloride separated from ethanol-ether as a pale yellow microcrystalline solid; m.p. 261-262° dec. The base has been reported (40).

Anal. $C_{10}H_{11}N_3O \cdot HCl$: C, 53.22; H, 5.36; N, 18.62; Cl, 15.71. Found: C, 53.36; H, 5.29; N, 18.79; Cl, 15.87.

6-(5-Iodo-2-thienyl)-4,5-dihydro-3(2*H*)pyridazinone.

This compound was prepared by iodination of 48.0 g. (0.268 mole) of 6-(2-thienyl)-4,5-dihydro-3(2*H*)pyridazinone - Table II - in 200 ml. of glacial acetic acid with 48.0 g. (0.296 mole) of iodine monochloride below 40°. The reaction mixture was stirred for 1 hour after addition of the reagent, chilled, and the brown product collected. It was triturated with ethyl acetate, filtered, and then slurried with cold acetone prior to treating a dilute acetone solution of the crude yellowish solid with charcoal. The solvent was removed *in vacuo* and the residue crystallized twice from ethanol to give dull white needles, m.p. 198.5-199°. The yield was 83%.

Anal. Calcd. for $C_8H_7IN_2OS$: C, 31.38; H, 2.31; N, 9.13. Found: C, 31.67; H, 2.14; N, 9.26.

6-[4-(2-Dibutylaminoethoxy)phenyl]-4,5-dihydro-3(2*H*)pyridazinone Nitrate.

A mixture of 23.8 g. (0.08 mole) of 6-[4-(2-bromo-ethoxy)-phenyl]-4,5-dihydro-3(2*H*)pyridazinone and 31.0 g. (0.24 mole) of di-*n*-butylamine was heated under reflux at 130-180° for 3 hours, and then at 180° for 3 hours. The cooled material was admixed with 10 volumes of absolute ether, the di-*n*-butylamine hydrobromide removed, and the filtrates concentrated. The viscous brown residue readily yielded a nitrate when treated with 3 *N* nitric acid, and the salt was crystallized from water (charcoal) to afford 19.3 g. (59% yield) of white blades, m.p. *ca.* 190°. Further crystallizations from ethanol and from water gave the pure nitrate, which required prolonged drying to free it of solvents, m.p. 195.5-196.5°.

Anal. Calcd. for $C_{20}H_{31}N_3O_2 \cdot HNO_3$: C, 58.80; H, 7.90; N, 13.73; (total) N, 3.42 (basic). Found: C, 58.97; H, 7.61; N, 13.24 (total); N, 3.24 (basic).

4-(4-Bromophenacyl)-6-(4-bromophenyl)-4,5-dihydro-3(2*H*)pyridazinone.

This compound resulted from the interaction of *bis*-(4-bromophenacyl)acetic acid with hydrazine in the usual manner (10,12). A somewhat gummy, yellow solid was obtained in quantitative yield, however the pure compound was isolated in only 42% yield.

The crude material was extracted with boiling ethanol, then crystallized repeatedly from aqueous dioxane after treatment with charcoal in dioxane to give pale yellow needles, m.p. 202.5-203.5°.

Anal. Calcd. for $C_{18}H_{14}Br_2N_2O_2$: C, 48.03; H, 3.13; N, 6.23. Found: C, 48.21; H, 2.87; N, 6.31.

4-(3,4-Dichlorophenacyl)-6-(3,4-dichlorophenyl)-4,5-dihydro-3(2*H*)-pyridazinone.

This compound was prepared from *bis*-(3,4-dichlorophenacyl)-acetic acid and hydrazine. The crude product was isolated as a sticky yellow solid, which was purified after the manner used for the bromine-containing analogue. A 45% yield of glistening white leaflets resulted; m.p. 195.5-196.5°.

Anal. Calcd. for $C_{18}H_{12}Cl_4N_2O_2$: C, 50.26; H, 2.81; Cl, 32.97; N, 6.51. Found: C, 49.99; H, 2.54; Cl, 32.74; N, 6.53.

2,6-Disubstituted 4,5-dihydro-3(2*H*)pyridazinones listed in Table III were prepared by reaction of the appropriate benzoyl propionic acids with a substituted hydrazine after the general scheme used for hydrazine.

3(2*H*)Pyridazinones.

Conversion of 4,5-dihydro-3(2*H*)pyridazinones into 3(2*H*)pyridazinones was conveniently accomplished by treatment with bromine in glacial acetic acid at 60-70° by a well known procedure (*cf.* 3,4, 10,12). Most of the 6-substituted 3(2*H*)pyridazinones in Table IV were prepared by that method, or resulted as by-products consequent to bromination which does occur at times during dehydrogenation of the dihydro compounds.

6-(3-Bromo-4-methoxyphenyl)- and 6-(4-Methoxyphenyl)-3(2*H*)-pyridazinone.

These compounds were formed by action of one equivalent of bromine in 6-(4-methoxyphenyl)-4,5-dihydro-3(2*H*)pyridazinone. It had been reported (19) that two compounds were produced under such conditions, and but one substance resulted from use of two equivalents of bromine, yet structures were not determined. The crude mixture was fractionally crystallized from diethylene glycol monomethyl ether. The more soluble fraction was isolated from liquors by concentration and precipitation, then crystallized from ethanol (charcoal) to give white needles, m.p. 191-192°. This was 6-(4-methoxyphenyl)-3(2*H*)pyridazinone (analyses). The less soluble fraction contained bromine, and melted 282-283° after further crystallization from diethylene glycol monoethyl ether. Poppenberg (19) had reported m.p. 263° for a compound considered to be 6-(3-bromo-4-methoxyphenyl)-3(2*H*)pyridazinone. That assessment of structure was here established for the less soluble fraction by oxidation with alkaline permanganate (*cf.* 41), followed by vacuum sublimation and crystallization of the crude acid from aqueous ethanol to obtain needles of 3-bromo-4-methoxybenzoic acid, m.p. 220.5-221.5 [reported (42), m.p. 218-218.5]. Data on both products have been listed in Table IV.

Anal. Calcd. for $C_8H_7BrO_3$: C, 41.58; H, 3.05; Neut. Equiv., 231.1. Found: C, 41.73; H, 3.01; Neut. Equiv., 232.0.

6-(4-Hydroxyphenyl-3(2*H*)pyridazinone.

This compound was formed from 6-(4-methoxyphenyl)-3(2*H*)-pyridazinone, (7.07 g., 0.035 mole) by heating it with concentrated hydrochloric acid (30 ml.) at 125-130° during 5 hours. Following the customary isolation procedure (*cf.* 43), the crude compound was sublimed at 270° (0.1 mm) and crystallized repeatedly from aqueous propylene glycol to give the desired compound in 64% yield. The white, microcrystalline solid had m.p. >300°. 6-(4-Hydroxyphenyl)-3(2*H*)pyridazinone was previously (19) made from 6-(3-bromo-4-methoxyphenyl-3(2*H*)pyridazinone.

Anal. Calcd. for $C_{10}H_8O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.94; H, 4.21; N, 15.11.

6-(3-Aminophenyl)-3(2*H*)pyridazinone Hydrochloride.

This compound was prepared by catalytic reduction of the corresponding nitro compound, essentially as described for the dihydropyridazinone. A crude yield of 78% (m.p. *ca.* 290°) resulted, from which the pure product was obtained by multiple crystallizations from ethanol-ether. The fine, creamy-white needles had m.p. 307-309°.

Anal. Calcd. for $C_{10}H_9N_3O$·HCl: C, 53.70; H, 4.51; N, 18.79; Cl, 15.85. Found: C, 53.74; H, 4.73; N, 18.94; Cl, 16.12.

6-(4-Aminophenyl)-3(2*H*)pyridazinone Hydrochloride.

This compound was obtained from the corresponding acetamido compound (Table IV) by hydrolysis following the method used for the related dihydropyridazinone. The crude product (89% yield, m.p. 290-293°, dec.) was treated in methanol solution with charcoal, precipitated with ether and recrystallized from methanol-ether to give white microcrystals. It melted 207.5-309° with decomposition accompanied by intumescence (in bath at 290°). The base has been reported in the patent literature (44,45) and also seems to be part of more detailed report recently made (8) of work in the area.

Anal. Calcd. for $C_{10}H_9N_3O$·HCl: C, 53.70; H, 4.51; N, 18.79. Found: C, 54.00; N, 4.68; N, 18.58.

6-(3-Aminophenyl-4-bromophenyl)-3(2*H*)pyridazinone.

6-(4-Bromophenyl)-3(2*H*)pyridazinone (142.4 g., 0.573 mole) was dissolved in 170 ml. of concentrated sulfuric acid, chilled to -5°, and stirred at -5° to 0° while to it there was added a mixture of concentrated nitric acid (82 g.) and concentrated sulfuric acid (245 g.). Addition required 2 hours; thereafter, the mixture was stirred at 0° for 2 hours prior to quenching it in several kilos of ice-water slurry. The yellow solid was collected, washed free of acid, and crystallized twice from diethylene glycol monethyl ether, with liberal use of charcoal. It was washed with cold ethanol by decantation, boiled with ether, and dried *in vacuo* to obtain 129.0 g. (75.5%) of 6-(4-bromo-3-nitrophenyl)-3(2*H*)pyridazinone. The yellowish needles had m.p. 175.176.5°.

Anal. Calcd. for $C_{10}H_6BrN_3O_3$: C, 40.29; H, 2.03; Br, 26.99; N, 14.17. Found: C, 40.39; H, 2.06; Br, 27.15; N, 13.94.

Reduction of the foregoing bromonitro compound was done in methanol at 50° with use of Raney nickel catalyst, under hydrogen pressure of 75 atm. The crude compound (78% yield) was crystallized from ethylene glycol, then from dilute acetic acid, each time with charcoaling, to give the pure product in 63% yield. The 6-(3-amino-4-bromophenyl)-3(2*H*)pyridazinone was a pale yellow microcrystalline solid, m.p. 290-292° dec.

Anal. Calcd. for $C_{10}H_8BrN_3O$: C, 45.13; H, 3.03; Br, 30.03. Found: C, 45.40; H, 3.00; Br, 30.00.

6-(5-Bromo-2-thienyl)- and 6-(2-Thienyl)-3(2*H*)pyridazinone.

Both of the compounds resulted from dehydrogenation of 4,5-dihydro-6-(2-thienyl)-3(2*H*)pyridazinone with bromine in glacial acetic acid. Fractional crystallization from propylene glycol achieved satisfactory separation, and the less soluble portion was leached well with boiling ethanol. All liquors were concentrated, precipitated with water, and the resultant crude 6-(2-thienyl-3(2*H*)-pyridazinone crystallized from ethanol (charcoal) to give the pure compound. The less soluble fraction was purified from aqueous diethylene glycol monoethyl ether and the structure proven to be 6-(5-bromo-2-thienyl)-3(2*H*)pyridazinone by oxidation with aqueous alkaline permanganate solution (*cf.* 41). The crude product from the oxidation was sublimed and crystallized from water to give fine

needles of 5-bromo-2-thenoic acid, m.p. 140.5-141.5° [lit. (46), m.p. 141-142°]. Data on the two pyridazinones are given in Table IV.

6-(4-Sulfamylphenyl)-3(2*H*)pyridazinone.

Thirty five ml. of chlorosulfonic acid was stirred at 20° during addition (1-1/2 hours) of 17.2 g. (0.1 mole) powdered 6-phenyl-3(2*H*)pyridazinone. The golden mixture was kept at 20-25° for 1 hour and at 58-60° for 2 hours, then chilled to 0° prior to quenching it in ice. The gummy white product was washed be decantation, covered with ice, and basified with concentrated ammonium hydroxide. A friable solid was obtained by trituration with ice water. That crude product had 228-231° (22.2 g.; 88.5% yield). It separated from water as white needles, m.p. 238-240°.

Anal. Calcd. for $C_{10}H_9N_3O_3S$: N, 16.73; S. 12.76. Found: N, 16.91; S, 12.56.

6-(4-Chloro-3-nitrophenyl)-3(2*H*)pyridazinone.

A solution of 20.7 g. (0.1 mole) of 6-(4-chlorophenyl)-3(2*H*)-pyridazinone (10,12) in 35 ml. of concentrated sulfuric acid was stirred well at 8° to 10° while in a mixture of 25 ml. of concentrated sulfuric acid and 12 ml. of nitric acid was added during 2 hours. At the end of the addition, the entire mixture was stirred for 2 hours at 0° to 10° while a mixture of 25 ml. of concentrated sulfuric acid and 12 ml. of nitric acid was added during 2 hours. At the end of the addition, the entire mixture was stirred for 2 hours at 0° to 5° for 2 hours before it was quenched in ice. The cream colored solid was collected, washed well with water, and dried to give a quantitative yield (25.2 g.) of product, m.p. *ca.* 250° dec. Three crystallizations from 2-methoxy ethanol afforded 20.8 g. (82.5%) of yellowish, felted needles of 6-(4-chloro-3-nitrophenyl)-3(2*H*)pyridazinone; m.p. 271.5-272.5° dec. (immersed at 265°).

Anal. Calcd. for $C_{10}H_6ClN_3O_3$: C, 47.73; H, 2.40; Cl, 14.09; N, 16.70; N (nitro), 5.57. Found: C, 48.16; H, 2.16; Cl, 14.48; N, 17.06; N (nitro), 5.52.

6-[4-(2-Diethylaminoethoxy)phenyl]-3(2*H*)pyridazinone.

6-[4-(2-Bromoethoxy)phenyl]-3(2*H*)pyridazinone (14.7 g., 0.05 mole) and diethylamine (14.6 g., 0.2 mole) were placed in an autoclave and shaken at 128-130° for 7 hours. The volatile material was evaporated with nitrogen, then the residue was taken up in ethanol, filtered, and concentrated *in vacuo*. The dark oil was mixed with dilute sodium hydroxide solution, extracted well with ether, dried (sodium sulfate), and the solvent removed. The residual solid was taken up in benzene and then chromatographed on alumina with benzene-hexane (3:7) as eluant. It was necessary to crystallize the substance from cyclohexane, and then thrice from benzene-hexane to obtain 3.0 g. (21%) of pure compound as creamy white platelets, m.p. 146-147.5°.

Anal. Calcd. for $C_{16}H_{21}N_3O_2$: C, 66.87; H, 7.37; N, 14.62. Found: C, 66.82; H, 7.65; N, 14.69.

6-[4-(7-Chloro-4-quinolylamino)phenyl]-3(2*H*)pyridazinone.

A solution of 9.3 g. (0.047 mole) of 4,7-dichloroquinoline in 20 g. of molten phenol was stirred at 100°, and 0.2 g. powdered potassium iodide added. The mixture was kept at 100-110° for 10 minutes, and then 8.0 g. (0.043 mole) of 6-(4-aminophenyl)-3(2*H*)-pyridazinone added in one portion. The entire mixture was heated to 170° during 1 hour, then held at 170-172° for 10 hours. Thereafter, the cooled, viscous material was mixed with an excess of 35% sodium hydroxide solution and crushed ice. The purplish solid was collected, washed well with water and cold ethanol, and dried *in vacuo*. The brownish product (14.0 g., 86% crude yield) melted above 300°. It was crystallized twice from pyridine acetate, then boiled in 80% ethanol to free it of solvent. The 6-[4-(7-chloro-4-quinolylamino)phenyl]-3(2*H*)pyridazinone was a bright yellow, microcrystalline solid of m.p. >315°.

Anal. Calcd. for $C_{19}H_{13}ClN_3O$: C, 65.43; H, 3.76; N, 16.07. Found: C, 65.64; H, 3.70; N, 16.21.

2-Methyl-6-phenyl-3(2*H*)pyridazinone.

Five g. (0.029 mole) of 6-phenyl-3(2*H*)pyridazinone and 5 ml. of methyl iodide in 35 ml. of methanol in a sealed tube were heated at 100° for 6 hours. The resultant mixture was taken to dryness, leached with cold, dilute ammonium hydroxide, then crystallized from water containing a trace of sodium bisulfite. White prismatic needles (4.5 g., 83.5%) resulted from an additional crystallization from water; m.p. 113-113.5° [reported (47), m.p. 105-106°].

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 71.22; H, 5.10; N, 14.96.

2-(4-Chlorophenyl)-6-phenyl-4(2*H*)pyridazinone.

2-(4-Chlorophenyl)-4,5-dihydro-6-phenyl-3(2*H*)pyridazinone (14.2 g., 0.05 mole) was dissolved in glacial acetic acid (75 ml.) and kept at 65° (stirring) during addition of iodine monochloride 16.6 g., 0.102 mole) in glacial acetic acid (25 ml.) in 1 hour. Thereafter, it was heated at 70-75° for 2-1/2 hours, cooled, and the brownish solid collected. It was washed with cold glacial acetic acid, triturated with carbon disulfide, and then crystallized from dilute acetone which contained a trace of sodium bisulfite and charcoal. The iodine-free compound was crystallized twice from ethyl acetate to obtain felted white needles (10.0 g., 70% yield); m.p. 164-164.4°. A trace of greenish substance was insoluble in ethyl acetate.

Anal. Calcd. for $C_{16}H_{11}ClN_2O$: Cl, 12.54; N, 9.91; Mol. wt., 282.7. Found: Cl, 12.83; N, 9.81; Mol. wt., 278.5 (in dioxane).

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