Syntheses of Pyridazine Derivatives as Herbicides

Part II. Preparation of 3-Halo- and 3-Anilino-6-phenoxy-pyridazines

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Various 3-halo-6-phenoxy-pyridazines, with or without nitro groups on their benzene rings, and 3-anilino-6-phenoxy-pyridazines were prepared together with some related compounds to be evaluated as herbicides. Ultraviolet spectra of some nitrophenoxypyridazines thus obtained were also examined.

In the previous paper,¹⁾ it was reported that several pyridazyl phenyl ethers showed marked pre-emergent herbicidal activity to radish and millet. To extend the preceding studies on the structure-activity relationship of pyridazine derivatives, the authors prepared 3-halo-6-phenoxy-pyridazines, with or without nitro groups on their benzene rings, and 3-anilino-6-phenoxy-pyridazines. The compounds obtained are shown in Tables I and II.

For the syntheses of 3-bromo-6-phenoxy-pyridazines, various phenols were treated with 3, 6-dibromopyridazine²⁾ in the presence of metallic sodium in boiling benzene or toluene according to the procedure described earlier.³⁾ However, 3-bromo-6-(2', 4'-dichlorophenoxy)- and 3-bromo-6-(2', 6'-dichlorophenoxy)-pyridazines could not be obtained by this method, whereas the reaction in the presence of anhydrous potassium carbonate at 150~160°C without the solvent gave these compounds in fairly good yields respectively.

Syntheses of various anilino-pyridazines including 3-chloro-6-anilino- and 3-anilino-6-benzyloxy-pyridazines had been reported by Yoneda et al.⁴⁾ In the present study, several 3-anilino-6-phenoxy-pyridazines as well as 3-

bromo-6-anilino-pyridazines were prepared.

In syntheses of nitrophenoxypyridazines, the treatment of 6-chloro-3-(2H) pyridazone (I) with chloronitrobenzenes in the presence of the base was attempted at first, but this reaction did not occur and only starting materials were recovered. On the other hand, reaction of I with 2, 4-dinitro-chlorobenzene gave a product, which was supposed to be 6-chloro-2-(2', 4'-dinitrophenyl)-3-pyridazine having the structure II through the examination of infrared spectrum and elementary analysis.

Reaction of 3, 6-dihalopyridazines with nitrophenols in anhydrous condition gave the expected nitrophenoxypyridazines. Thus, equimolar amounts of the corresponding nitrophenol and halopyridazine were treated in the presence of anhydrous potassium carbonate at 150~160°C for about 15 min. After initial vigorous reaction had ceased, the

1) S. Tamura and T. Jojima, *This Journal*, **27**, 728 (1963).

2) J. Druey, Kd. Meier and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

3) S. Tamura and T. Jojima, *This Journal*, **27**, 653 (1963).

4) F. Yoneda, T. Ohtaka and Y. Nitta, *Chem. Pharm. Bull.*, **11**, 740 (1963).

reaction mixture usually became solid, which was cooled, washed with dilute aqueous alkali and recrystallized from appropriate solvent. Under this reaction condition, *m*-nitrophenol always gave expected mono-ethers in good yields, but *o*-nitrophenols reacted slowly to yield expected products in poor yields. Especially, the attempt to obtain ether from 2, 4-dinitro-6-methylphenol was unsuccessful. The difficulty of *o*-nitrophenols to react with dichloropyridazines may be partly due to steric hindrance by nitro groups in the benzene rings, as was previously observed in the reaction of *o*-chlorophenols with dichloropyridazine.²⁾

Recently, syntheses of 4- or 5-substituted pyridazines were reported by several workers, but none of corresponding phenoxypyridazines had been prepared. Kuraishi⁵⁾ obtained 4-ethoxy-3, 6-dichloropyridazine (III) and 4-hydrazino-3, 6-dichloropyridazine (IV), by the reaction of sodium ethoxide or hydrazine with 3, 4, 6-trichloropyridazine, and pointed out that the chlorine atom at 4-position of this trichloropyridazine is more reactive than those at 3- and 6-positions.

In the present study, 3, 4, 6-trichloropyridazine was heated with nitrophenols and anhydrous potassium carbonate as in the case of the corresponding reaction of 3, 6-dichloropyridazine. As shown in Table II, *m*-nitrophenoxy derivative was obtained in the best yield, whereas attempts to prepare 4-(2', 4'-dinitrophenoxy)-3, 6-dichloropyridazine gave merely intractable tars.

As described in the previous report,¹⁾ 3-chloro-6-phenoxypyridazines having methoxyl group at their benzene rings possess rather high herbicidal activity. 4-(2'-Methoxy-

phenoxy)-3, 6-dichloropyridazine (V) was prepared by treating 3, 4, 6-trichloropyridazine with guaiacol in the presence of metallic sodium in the molar ratio of 1:2:1 in refluxing benzene.

Then the ultraviolet spectra of pyridazines containing nitrophenoxy or methoxyphenoxy groups were examined in methanol and the results are shown in Figs. 1, 2 and 3. As shown in these figures, *p*-nitrophenoxypyridazines such as 3-chloro-6-(4'-nitrophenoxy)- and 4-(4'-nitrophenoxy)-3,6-dichloropyridazines exhibit large shifts of absorption maxima to longer wave length as compared with those of corresponding *o*- and *m*-nitrophenoxy derivatives. More-

FIG. 1. Ultraviolet Spectra of 3-Chloro-6-nitrophenoxypyridazines (in MeOH).

- 3-Chloro-6-(2'-nitrophenoxy)pyridazine
- - - 3-Chloro-6-(3'-nitrophenoxy)pyridazine
- 3-Chloro-6-(4'-nitrophenoxy)pyridazine
- · - · 3-Chloro-6-(2',4'-dinitrophenoxy)pyridazine

5) T. Kuraishi, *Chem. Pharm. Bull.*, **4**, 137 (1956); **5**, 376 (1957).

FIG. 2. Ultraviolet Spectra of 4-Nitrophenoxy-3,6-dichloropyridazines (in MeOH).

----- 4-(2'-Nitrophenoxy)-3,6-dichloropyridazine
 ————— 4-(3'-Nitrophenoxy)-3,6-dichloropyridazine
 4-(4'-Nitrophenoxy)-3,6-dichloropyridazine

FIG. 3. Ultraviolet Spectra of Methoxyphenoxy-pyridazines (in MeOH).

————— 3-Chloro-6-(2'-methoxyphenoxy)pyridazine
 4-(2'-Methoxyphenoxy)-3,6-dichloropyridazine

over, the former derivatives show stronger absorption intensity. Concerning the relation between absorption maxima and position of nitrophenoxy group in pyridazine ring, it was found that compounds of 6-substituted series show the maxima of a little longer wave length than those of 4-substituted series. Among 6-substituted compounds, 3-chloro-6-(2', 4'-dinitrophenoxy)pyridazine has no absorption maximum, showing only a shoulder at 240 mμ. As for methoxyphenoxy pyridazines, 3-chloro-6-(2'-methoxyphenoxy)pyridazine has a doublet with maxima at 273 mμ. and 277 mμ., one of which is observed as a shoulder in the case of 4-(2'-methoxyphenoxy)-3, 6-dichloropyridazine.

Herbicidal activities of these pyridazine derivatives will be reported later.

EXPERIMENTAL

Melting points are uncorrected. The ultraviolet absorption spectra were taken in methanol with Cary 14-PM spectrophotometer. For the preparation of compounds, only typical runs are described in this part.

3-Bromo-6-(2'-methoxyphenoxy)pyridazine.

A mixture of 26.0 g (0.21 mole) of guaiacol 1.15 g (0.50 mole) of metallic sodium and 40 ml of toluene was heated to reflux. After the phenolate was formed, 10.0 g (0.04 mole) of 3,6-dibromopyridazine was added to the mixture, and refluxing continued for additional 4 hrs. After cooling, the reaction mixture was transferred into a 1 l. separating funnel along with ca. 600 ml of 2N aqueous sodium hydroxide and 160 ml of toluene, and the funnel was shaken vigorously. The toluene layer separated was washed with three portions of 300 ml of water and dried over anhydrous potassium carbonate. After removal of toluene under reduced pressure, the oily residue was dried in a vacuum desiccator. The crude crystalline solid was recrystallized from ethanol to yield 11.0 g of colorless prisms, m.p., 121~122°C.

3-Bromo-6-(2',6'-dichlorophenoxy)pyridazine.

Five grams (0.02 mole) of 3,6-dibromopyridazine, 3.4 g (0.02 mole) of 2,6-dichlorophenol and 2.9 g (0.02 mole) of anhydrous potassium carbonate were thoroughly mixed and heated at 150~160°C in an oil

TABLE I. BROMO- AND ANILINO-PHENOXYPYRIDAZINES

X ₁	X ₂	Solvent ^{a)}	Appearance	M.p., recrystallization °C ^{b)}	Solvent of recrystallization	Yield (%)	Formula	Calcd.			Found		
								C	H	N	C	H	N
Br	C ₆ H ₅ O	B	Plate	71	Ligroin	87	C ₁₀ H ₇ BrN ₂ O	47.83	2.81	11.16	48.06	2.90	11.54
Br	2-CH ₃ O-C ₆ H ₄ O	T	Prism	121~122	Ethanol	93	C ₁₁ H ₉ BrN ₂ O ₂	47.00	3.23	9.97	47.39	3.33	10.07
Br	4-CH ₃ -C ₆ H ₄ O	B	Leaflet	96~98	"	96	C ₁₁ H ₉ BrN ₂ O	49.83	3.42	10.57	49.93	3.45	10.54
Br	2-C ₆ H ₅ -C ₆ H ₄ O	B	Needle	112	"	65	C ₁₆ H ₁₁ BrN ₂ O	58.73	3.39	8.56	58.77	3.42	8.60
Br	3-CH ₃ -4-Cl-C ₆ H ₃ O	B	Leaflet	94~95	"	23	C ₁₁ H ₈ BrClN ₂ O	44.10	2.69	9.35	44.03	2.64	9.39
Br	2,4-di-Cl-C ₆ H ₃ O	—	Rod	88~89	"	65	C ₁₀ H ₅ BrCl ₂ N ₂ O	37.53	1.58	8.76	38.29	1.60	8.60
Br	2,6-di-Cl-C ₆ H ₃ O	—	"	126	Ligroin	78	"	"	"	"	37.72	1.62	8.72
Br	C ₆ H ₅ NH	M	Prism	186~187	Methanol	52	C ₁₀ H ₈ BrN ₃	48.02	3.22	16.80	48.21	3.24	17.39
C ₆ H ₅ NH	C ₆ H ₅ O	—	Leaflet	133~136	Ethanol	67	C ₁₆ H ₁₃ N ₃ O	72.99	4.98	15.96	72.53	5.02	15.98
3-Cl-C ₆ H ₄ NH	C ₆ H ₅ O	—	—	150~151	"	44	C ₁₆ H ₁₂ ClN ₃ O	64.54	4.06	14.11	64.31	4.14	14.39
4-Cl-C ₆ H ₄ NH	C ₆ H ₅ O	—	—	182~183	"	27	"	"	"	"	64.23	3.88	14.34
C ₆ H ₅ NH	2-CH ₃ O-C ₆ H ₄ O	—	Prism	175~176	"	60	C ₁₇ H ₁₅ N ₃ O ₂	69.61	5.15	14.33	69.33	5.09	14.60
3-Cl-C ₆ H ₄ NH	2-CH ₃ O-C ₆ H ₄ O	—	Rod	139~140	"	31	C ₁₇ H ₁₄ ClN ₃ O ₂	62.29	4.31	12.82	61.97	4.54	13.31

a) B: Benzene, T: Toluene, M: Methanol. The symbol— means that the reaction has been conducted without any organic solvent.
b) Uncorrected.

TABLE II. NITROPHENOXYPYRIDAZINES

X ₁	X ₂	X ₃	Appearance	M.p., °C ^{a)}	Solvent of recrystal- lization	Yield (%)	Formula	Calcd.			Found		
								C	H	N	C	H	N
Cl	H	2-NO ₂ -C ₆ H ₄ O	Leaflet	95	Ethanol	13	C ₁₀ H ₆ ClN ₃ O ₃	47.73	2.40	16.70	47.98	2.43	16.64
Cl	H	3-NO ₂ -C ₆ H ₄ O	"	114~115	"	82	"	"	"	"	48.18	2.49	16.58
Cl	H	4-NO ₂ -C ₆ H ₄ O	Rod	125~126	"	52	"	"	"	"	47.84	2.35	17.32
Cl	H	2,4-di-NO ₂ -C ₆ H ₃ O	Needle	151~152	"	13	C ₁₀ H ₅ ClN ₄ O ₅	40.49	1.70	18.89	40.54	1.88	18.74
Br	H	2-NO ₂ -C ₆ H ₄ O	Leaflet	100~102	"	18	C ₁₀ H ₆ BrN ₃ O ₃	40.56	2.04	14.19	40.29	2.12	14.11
Br	H	3-NO ₂ -C ₆ H ₄ O	Rod	125~126	"	95	"	"	"	"	40.86	2.32	14.37
Br	H	4-NO ₂ -C ₆ H ₄ O	"	124~125	"	36	"	"	"	"	40.91	2.30	14.31
Br	H	2,4-di-NO ₂ -C ₆ H ₃ O	Leaflet	165~166	"	52	C ₁₀ H ₅ BrN ₄ O ₅	35.21	1.48	16.43	35.30	1.59	16.82
Br	H	2-NO ₂ -4-Cl-C ₆ H ₃ O	Rod	168	"	29	C ₁₀ H ₅ BrClN ₃ O ₃	36.34	1.52	12.71	36.35	1.54	12.83
C ₆ H ₅ O	H	4-NO ₂ -C ₆ H ₄ O	Prism	180	"	44	C ₁₆ H ₁₁ N ₃ O ₄	62.13	3.59	13.69	62.03	3.53	13.49
C ₆ H ₅ O	H	2,4-di-NO ₂ -C ₆ H ₃ O	Leaflet	141	Ethanol-Acetone	32	C ₁₆ H ₁₀ N ₄ O ₆	54.24	2.85	15.81	54.09	2.85	15.59
2-CH ₃ O-C ₆ H ₄ O	H	2,4-di-NO ₂ -C ₆ H ₃ O	Rod	146	Ethanol	39	C ₁₇ H ₁₂ N ₄ O ₇	53.13	3.15	14.58	53.13	3.35	14.55
Cl	2-NO ₂ -C ₆ H ₄ O	Cl		164	Ethanol-Acetone	42	C ₁₀ H ₅ Cl ₂ N ₃ O ₃	41.98	1.76	14.69	42.12	1.79	14.68
Cl	3-NO ₂ -C ₆ H ₄ O	Cl	Needle	173~175	"	99	"	"	"	"	42.53	1.83	14.28
Cl	4-NO ₂ -C ₆ H ₄ O	Cl	Leaflet	173	"	33	"	"	"	"	41.95	1.79	14.68
Cl	2-CH ₃ O-C ₆ H ₄ O	Cl	Needle	151	Ethanol	31	C ₁₁ H ₅ Cl ₂ N ₂ O ₂	48.73	2.97	10.33	48.64	2.97	10.39

a) Uncorrected.

bath for 15 mins. After cooling, the residue was washed with dilute sodium hydroxide solution and water successively, and then recrystallized from ligroin to yield colorless rods, m.p. 126°C.

3-Anilino-6-phenoxy pyridazine.

A mixture of 50 g (about nine times of the theoretical amount) of phenol, and 1.5 g (0.07 mole) of metallic sodium was heated in an oil bath to give the phenolate, to which was added 10.0 g (0.05 mole) of 3-chloro-6-anilino pyridazine. The heating was further continued at 180~200°C for 4 hrs. After removal of excess phenol under reduced pressure, the residue was extracted with three portions of 200 ml of ether. The combined ether solution was washed with dilute sodium hydroxide solution and water successively, and dried over anhydrous potassium carbonate. After evaporation of ether, the residue was recrystallized from ethanol giving colorless needles, m.p. 149°C.

3-Chloro-6-(3'-nitrophenoxy)- and 3,6-Bis(3'-nitrophenoxy)-pyridazines.

A mixture of 20.0 g (0.13 mole) of 3,6-dichloropyridazine, 28.1 g (0.13 mole) of *m*-nitrophenol and 17.9 g (0.13 mole) of anhydrous potassium carbonate was treated as described for the preparation of 3-bromo-6-(2',6'-dichlorophenoxy)pyridazine. After recrystallization from ethanol, there was obtained 26.8 g of colorless leaflets, m.p. 114~115°C.

The mixture was heated for 1 hr to give the bis-ether, 3,6-bis(3'-nitrophenoxy)pyridazine, along with the mono-ether. Thus, starting from 20.0 g of 3,6-dichloropyridazine, 7 g of bis-ether and 8 g of mono-ether were obtained. The bis-ether melts at 162°C, after repeated recrystallization from ethanol-acetone. *Anal.* Found: C, 54.16; H, 2.81; N, 15.97. Calcd. for $C_{16}H_{10}N_4O_6$: C, 54.24; H, 2.85; N, 15.82%.

3-Phenoxy-6-(4'-nitrophenoxy)pyridazine, 4-(3'-nitrophenoxy)-3,6-dichloropyridazine and related compounds were prepared by the same procedure as described for the synthesis of 3-bromo-6-(2',6'-dichlorophenoxy)pyridazine.

6-Chloro-2-(2',4'-dinitrophenyl)-3-pyridazone.

A mixture of 5.0 g (0.04 mole) of 6-chloro-3-(2H)-

pyridazone, 7.7 g (0.04 mole) of 2,4-dinitro-chloro-benzene, and 23 ml of 10% aqueous potassium hydroxide solution was heated at 80°C for 5 hrs with stirring. The resulted yellowish crystals were washed with water and dried. Recrystallization from ethanol gave 2 g of slightly yellowish fine needles, m.p. 167°C. The infrared spectrum shows strong C=O band at 1680 cm^{-1} as well as strong NO_2 bands at 1351 and 1551 cm^{-1} . *Anal.* Found: C, 40.46; H, 1.91; N, 19.01. Calcd. for $C_{10}H_5ClN_4O_5$: C, 40.49; H, 1.70; N, 18.89%. From these results this product was proved to be 6-chloro-2-(2',4'-dinitrophenyl)-3-pyridazone.

4-(2'-Methoxyphenoxy)-3,6-dichloropyridazine.

A mixture of 22.1 g (0.18 mole) of guaiacol, 2.1 g (0.09 mole) of metallic sodium and 40 ml of benzene was heated to reflux. After phenolate was formed, 15 g (0.08 mole) of 3,4,6-trichloropyridazine was added to the mixture, and refluxing continued for additional 2 hrs. After cooling, the crystalline solid separated were filtered off and washed with ether. After recrystallization from ethanol, there was obtained 2.0 g of fine needles. The benzene filtrate was washed with dilute aqueous sodium hydroxide and water successively, and dried over anhydrous sodium sulfate. Benzene was removed under reduced pressure, and the crude residue recrystallized from ethanol. There was obtained 4.8 g of the product. The total yield was 31%. After repeated recrystallization from ethanol, it melted at 151°C.

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