Synthesis of Pyridazine Derivatives as Herbicides

Part I. Preparation of Pyridazyl Ethers

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Series of 3-chloro-6-phenoxy- and 3,6-bisphenoxy-pyridazines were prepared from 3,6-dichloropyridazine to be evaluated as herbicides. Certain thioethers were also prepared.

Physiological activity of substituted pyridazines has not been studied so extensively, as compared with those of pyridine, pyrimidine and *s*-triazine derivatives. Recently some interests have grown in this field and various pyridazine derivatives were synthesized for the examination of structure-activity relations by several workers. Fischer¹⁾ tested herbicidal property of pyridazone derivatives and showed that 5-amino-4-chloro-1,2-dihydro-6-oxo-1-phenyl-pyridazone (I) has the best activity. With relation to the effectiveness of (2,4-dichlorophenoxy) acetic acid as the herbicide, syntheses of (3-chloro-pyridaz-6-oxy) acetic acid (II) and related compounds have been disclosed in a German patent²⁾. Steck et al.^{3,4)} prepared a few 3-chloro-6-phenoxy-pyridazines substituted at their benzene rings, besides 3-chloro-6-alkoxy- and 3,6-dialkoxy-pyridazines, for eventual pharmaceutical trials. Few attempts have been made, however, for the

systematic evaluation of physiological activities of pyridazyl phenyl ethers, especially for the evaluation as herbicides. These situations led the authors to the serial synthesis of 3-chloro-6-phenoxy-pyridazines (III) and 3,6-bisphenoxy-pyridazines (IV) to find new herbicides among these compounds. Pyridazyl

ethers and thioethers prepared are shown in Tables I and II, along with some related compounds.

In syntheses of 3-chloro-6-alkoxy- and 3,6-dialkoxy-pyridazines, theoretical amounts of metallic sodium or sodium alkoxide and 3,6-dichloropyridazine are usually treated with large excess (usually fifteen to twenty folds as much as the theoretical amount) of corresponding alcohols, which are removed by distillation after completion of the reactions⁵⁻⁷⁾. In synthesis of phenoxy-ethers, how-

1) A. Fisher, *Weed Research*, **2**, 177 (1962).

2) L. Holzer and R. Schönbeck, Ger. Patent 1,099,544 (1961).

3) E.A. Steck and R.P. Brundage, *J. Am. Chem. Soc.*, **81**, 6511 (1959).

4) E.A. Steck, U.S. Patent 2,905, 672 (1959).

5) J. Druery, K. Meier and K. Bichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

6) T. Itai and H. Igeta, *J. Pharm. Soc. Japan*, **74**, 1195 (1954).

7) N. Takabayashi, *ibid.*, **75**, 778 (1955); **76**, 1296 (1956).

TABLE I. 3-CHLORO-6-PHENOXYPYRIDAZINES AND RELATED COMPOUNDS

R	Solvent ^{a)}	Time (hrs.)	Appearance	M.p. °C ^{b)}	Solvent of recrystallization	Yield (%)	Calcd.			Found		
							C	H	N	C	H	N
C ₆ H ₅	B	2	Needle	69~70 ^{c)}	Ethanol-water	36	58.13	3.41	13.56	58.52	3.74	13.51
"	B	5				54						
2-CH ₃ -C ₆ H ₄	T	2	Column	85~85.5	Ethanol-water	26	59.87	4.11	12.70	59.72	4.13	13.13
3-CH ₃ -C ₆ H ₄	T	2	"	71	"	50	"	"	"	59.83	4.08	13.07
4-CH ₃ -C ₆ H ₄	B	3	Leaflet	107~108	"	75	"	"	"	59.43	4.28	12.70
2,4-di-CH ₃ -C ₆ H ₃	T	2	"	96	"	81	61.80	4.72	11.94	62.26	4.88	11.84
3,4-di-CH ₃ -C ₆ H ₃	T	2	Needle	106	"	47	"	"	"	61.57	4.83	11.95
3,5-di-CH ₃ -C ₆ H ₃	T	2	Prism	132~133 ^{d)}	"	60	"	"	"	61.61	4.91	11.94
2,3,5-tri-CH ₃ -C ₆ H ₂	T	5	"	129~130	Ethanol	92	62.78	5.27	11.26	62.56	5.17	11.46
4-C ₂ H ₅ -C ₆ H ₄	T	5	Leaflet	75	Ligroin	82	61.41	4.72	11.94	61.22	4.88	11.94
2- <i>i</i> -C ₃ H ₇ -C ₆ H ₄	T	5	Column	77~77.5	Ethanol	43	62.78	5.27	11.26	62.75	5.42	11.09
2-C ₆ H ₅ -C ₆ H ₄	B	5	"	99.5	Ethanol-water	83	67.97	3.91	9.91	68.20	3.83	9.90
4-Cl-C ₆ H ₄	T	2	"	115~116 ^{e)}	"	35	49.82	2.51	11.62	50.14	2.65	11.50
4-Br-C ₆ H ₄	B	3	Leaflet	135~136	"	16	42.06	2.12	9.81	42.36	2.24	9.94
2,4-di-Cl-C ₆ H ₃	B	5	Needle	80~81	Ligroin	46	43.59	1.83	10.17	43.23	1.86	10.29
2,6-di-Cl-C ₆ H ₃	T	2	Leaflet	106~107	Ethanol-water	35	"	"	"	44.01	2.18	10.37
2,4,5-tri-Cl-C ₆ H ₂	B	5	Column	173~174	Ligroin	43	38.75	1.30	9.04	39.05	1.42	8.79
3-CH ₃ -4-Cl-C ₆ H ₃	B	5	Prism	92	"	65	51.79	3.16	10.98	51.34	3.06	11.29
2-CH ₃ O-C ₆ H ₄	T	5	Leaflet	98.5	Ethanol-water	48 ^{f)}	55.87	3.83	11.84	55.76	4.09	11.95
3-CH ₃ O-C ₆ H ₄	B	3	Needle	73.5	"	68	"	"	"	55.64	4.05	12.07
4-CH ₃ O-C ₆ H ₄	T	2	Column	98~99	Ethanol	62 ^{g)}	"	"	"	55.73	3.79	11.70
2-CH ₃ O-4-CH ₃ -C ₆ H ₃	T	5	Leaflet	105~106	"	51	57.49	4.42	11.18	57.59	4.76	11.21
C ₆ H ₅ CH ₂	T	5	Plate	77 ^{h)}	Ligroin	47	59.87	4.11	12.70	59.90	4.15	12.91
4-CH ₃ O-C ₆ H ₄ CH ₂	T	5	Blade	115	"	42	57.49	4.42	11.18	57.21	4.63	11.48
C ₆ H ₅ OCH ₂ CH ₂	T	5	Leaflet	74	"	86	"	"	"	57.73	4.61	11.24
2-Cl-C ₆ H ₄ OCH ₂ CH ₂	T	5	Needle	114~115	"	46	50.55	3.54	9.83	50.62	3.64	9.71
C ₆ H ₅ CH=CHCH ₂	T	5	Plate	118	Ethanol	36	63.29	4.49	11.36	63.04	4.59	11.26
C ₁₂ H ₁₁	T	5	Leaflet	107.5	Ligroin	43	56.47	6.16	13.17	56.49	6.31	13.14

a) B=Benzene, T=Toluene. b) Uncorrected. c) Reported m.p. 71°C³⁾. d) Reported m.p. 135.5°C⁴⁾. e) Reported m.p. 119.5~120°C.⁴⁾ f) When two equivalents of sodium were used, the yield increased to 65%, while bis-ether could not be obtained (see Experimental part). g) A small amount of bis-ether was obtained at the same time (12% yield), which was separated from mono-ether by crystallizing the crude mixture from ethanol. h) Reported m.p. 77°C³⁾.

ever, large excess of phenols must be avoided because of their high-boiling points and difficulties to be distilled off, and the use of appropriate solvents becomes necessary.

Initial efforts of the authors were directed to synthesis of 3-chloro-6-phenoxy-pyridazines; and phenol, 3,6-dichloropyridazine and metallic sodium in 5:1:1 molar ratio were treated in boiling toluene for 2~5 hrs. When phenols containing lower alkyl groups, such as cresols,

xenols, 2,3,5-trimethylphenol and *p*-ethylphenol were treated in this condition, they usually gave the expected mono-ethers. On the other hand, phenols other than alkylphenols often yielded bis-ethers in boiling toluene even though they were treated in the presence of one equivalent of sodium, and mono-ethers were obtained only when the reactions were carried out under 100°C using such a solvent as benzene. As expected, if these phenols

TABLE II. PYRIDAZINE 3,6-BIS-ETHERS

R ₁	R ₂	Times ^{a)} (hrs.)	Appearance	M.p. °C ^{b)}	Solvent of recrystallization	Yield ^{c)} (%)	Calcd.			Found		
							C	H	N	C	H	N
C ₆ H ₅ O	C ₆ H ₅ O	5	Needle	140~141 ^{d)}	Ethanol	52	72.71	4.58	10.60	72.26	4.61	10.44
4-CH ₃ -C ₆ H ₄ O	4-CH ₃ -C ₆ H ₄ O	3	Column	169~170	"	31	73.95	5.52	9.58	73.51	5.46	9.88
2-Cl-C ₆ H ₄ O	2-Cl-C ₆ H ₄ O	3	"	208~209	"	28	57.68	3.03	8.41	57.52	3.10	8.74
3-Cl-C ₆ H ₄ O	3-Cl-C ₆ H ₄ O	5	Needle	126.5	"	(61)	"	"	"	57.89	2.94	8.50
2-Br-C ₆ H ₄ O	2-Br-C ₆ H ₄ O	5	"	196~197	"	16	45.53	2.39	6.64	45.92	2.63	6.80
4-Br-C ₆ H ₄ O	4-Br-C ₆ H ₄ O	5	Column	198~201	"	28	"	"	"	45.35	2.52	6.84
2,4-di-Cl-C ₆ H ₃ O	2,4-di-Cl-C ₆ H ₃ O	3	Needle	205	Ethanol-water	16	47.79	2.01	6.97	47.37	2.11	6.90
2,6-di-Cl-C ₆ H ₃ O	2,6-di-Cl-C ₆ H ₃ O	5	Leaflet	238~240	Ethanol	22	"	"	"	48.09	2.43	6.92
3-CH ₃ -4-Cl-C ₆ H ₃ O	3-CH ₃ -4-Cl-C ₆ H ₃ O	5	Column	152	"	36 ^{e)}	59.85	3.91	7.76	59.77	4.02	8.18
2-CH ₃ O-C ₆ H ₄ O	2-CH ₃ O-C ₆ H ₄ O	10	"	171	"	(13)	66.66	4.97	8.64	66.58	4.92	8.61
3-CH ₃ O-C ₆ H ₄ O	3-CH ₃ O-C ₆ H ₄ O	5	"	112~114	"	65	"	"	"	66.50	5.23	8.95
4-CH ₃ O-C ₆ H ₄ O	4-CH ₃ O-C ₆ H ₄ O	5	Prism	176~177	"	(57)	"	"	"	66.53	5.07	8.65
2-C ₆ H ₅ -C ₆ H ₃ O	2-C ₆ H ₅ -C ₆ H ₃ O	5	Leaflet	137	Ligroin-ethanol	20	80.74	4.84	6.73	80.26	4.87	6.87
2-Cl-4-C ₆ H ₃ -C ₆ H ₃ O	2-Cl-4-C ₆ H ₃ -C ₆ H ₃ O	5	Column	198	Acetone-ethanol	36	69.30	3.72	5.77	69.38	3.84	5.81
CH ₃ O	2,4-di-Cl-C ₆ H ₃ O	3	Leaflet	145	Ethanol	46	48.72	2.97	10.33	48.94	3.15	10.31
CH ₃ O	2-CH ₃ O-C ₆ H ₄ O	10	Needle	92.5	Ligroin	38	62.06	5.21	12.06	61.87	5.38	11.91
CH ₃ S	C ₆ H ₅ O	5	"	99 ^{f)}	"	49	60.53	4.62	12.83	60.50	4.74	12.77
CH ₃ S	2-CH ₃ O-C ₆ H ₄ O	10	"	133	Ethanol	48	58.05	4.87	11.28	58.38	5.23	11.28

a) Solvent used was toluene in every case. b) Uncorrected. c) Since these experiments have been conducted originally to get mono-ethers using equimolecular amounts of dichloropyridazine and sodium, the yields of bisethers in this table are generally rather low. Improvement of yields may be expected if the reactions were carried out in the presence of more than one equivalent of sodium. The numbers parenthesized show the yields when two equivalents of sodium were used. d) Reported m.p. 140°C⁶. e) Mono-ether was obtained in a 47% yield along with bis-ether (see Experimental part). f) Reported m.p. 100.5°C⁷.

were treated with 3,6-dichloropyridazine and sodium in boiling toluene by the molar ratio of 5:1:2, yields of bis-ethers considerably increased as compared with the former case.

Sometimes mixtures of mono- and bis-ethers were obtained. For instance, when guaia-col, 3,6-dichloropyridazine and metallic sodium were treated by the molar ratio of 5:1:2 in boiling toluene for 10 hrs., corresponding mono- and bis-ethers were obtained in yields of 47 and 13% respectively based on dichloropyridazine, although only mono-ether was obtained by 5-hrs. refluxing in the same condition. Anyhow, mono- and bis-ethers can be easily separated from each other because mono-ethers dissolve in ethyl ether and ethanol more easily than bis-ethers do.

It is very interesting that in the case of *o*-halophenols, such as *o*-chlorophenol, *o*-bromophenol and 2-chloro-4-phenylphenol, the corresponding mono-ethers could not be obtained in any experimental conditions, and only bis-ethers were obtained in boiling toluene though the yields were rather poor. As for *o*-chlorophenol, the formation of a trace amount of mono-ether among the product was confirmed with the infrared spectrum when metallic sodium was replaced by 10% aqueous sodium hydroxide and excess of the phenol was used. The difficulty of *o*-halophenols to react with 3,6-dichloropyridazine may be due to steric hindrance by halogen atoms in the *ortho* position of benzene ring, but the reason why the second chlorine atom of 3,6-dichloropyridazine became so reactive for nucleophilic attack of *o*-halophenolate anions to give bis-ethers has not been elucidated.

In order to examine the effect of reaction conditions on the type of pyridazyl ethers produced, phenol without any substituent was treated with 3,6-dichloropyridazine in various ways. The results are shown in Table III. When phenol, 3,6-dichloropyridazine and

TABLE III. THE REACTION OF 3,6-DICHLOROPYRIDAZINE AND PHENOL IN VARIOUS CONDITIONS

Solvent	Base	Time (hrs.)	Yield ^a (%)	
			Mono-ether	Bis-ether
Toluene	Na (1 equiv.)	2	17	20
"	"	5	—	23
Benzene	"	2	35	—
"	"	5	47	—
Toluene	" (2 equiv.)	5	—	64
Water	NaOH ^b	5	—	—
Water	NaOH ^c	5	70	23

a) The yields were calculated based on 3,6-dichloropyridazine. b) Five g. (0.034 mole) of 3,6-dichloropyridazine and 3.5 g. (0.037 mole) of phenol were refluxed in 40 ml. of 10% NaOH. c) Five g. (0.034 mole) of 3,6-dichloropyridazine, 16.0 g. (0.17 mole) of phenol and 14.8 g. (0.037 mole) of 10% NaOH were refluxed without organic solvent.

metallic sodium were treated by the molar ratio of 5:1:1 in toluene, 2-hrs. refluxing gave a mixture of mono- and bis-ethers and 5-hrs. refluxing, bis-ether exclusively. On the other hand, when the reaction was carried out in boiling benzene in the same condition, only mono-ether was obtained irrespective of refluxing period. If excess of 10% aqueous sodium hydroxide was used in place of metallic sodium, and phenol and 3,6-dichloropyridazine in a 1:1 molar ratio were treated without the organic solvent, only a trace amount of product was obtained which could not be identified. On the contrary, when a 1:1 molar ratio was adopted for aqueous sodium hydroxide and 3,6-dichloropyridazine in the presence of excess of phenol, a mixture of mono- and bis-ethers was obtained. Thus, types and yields of pyridazyl ethers largely depend on experimental conditions, and it is necessary to choose appropriate conditions in accordance with the kind of phenols reacted and the type of ethers desired.

For synthesis of 3-methylthio-6-phenoxy-pyridazines, 3-chloro-6-mercaptopyridazine must be prepared at first. This thiol compound was synthesized according to the method of Kumagai⁸⁾ by decomposing the

adduct from 3,6-dichloropyridazine and thio-urea. For the decomposition, he used aqueous sodium carbonate at room temperature, but the procedure described in his report was often unsuccessful for the present authors and the yield was very poor even when the product was obtained. Therefore, in this experiment, the adduct was decomposed with 10% aqueous sodium hydroxide at 100°C. The product thus obtained melted at 100°C, though reported melting point is 140°C⁸⁾ or 130~140°C (dec.)⁵⁾. As shown in the Experimental part, analytical data of this thiol compound coincided with calculated values for $C_4H_3ClN_2S$ and, moreover, methylation with methyl iodide gave 3-chloro-6-methylthiopyridazine, which has the same melting point, 101~102°C, as reported one⁹⁾. The cause for this curious disagreement in the melting points of 3-chloro-6-mercaptopyridazine has not been clarified. 3-Methylthio-6-phenoxy- and 3-methylthio-6-(2-methoxyphenoxy)-pyridazines were prepared by the reaction of 3-chloro-6-methylthiopyridazine with the corresponding phenol in the same procedure as those for 3-chloro-6-phenoxy-pyridazines.

Herbicidal activities of these pyridazyl ethers will be reported elsewhere in the near future.

EXPERIMENTAL

Typical runs are described in this part.

3-Chloro-6-(4-methylphenoxy)-pyridazine. A mixture of 18.4 g. (0.17 mole) of *o*-cresol, 0.86 g. (0.037 mole) of metallic sodium and 40 ml. of benzene was heated to reflux. After the formation of phenolate was complete, 5.0 g. (0.34 mole) of 3,6-dichloropyridazine was added to the mixture along with a small amount of copper powder as a catalyst, and refluxing was continued for additional 3 hrs. After removal of the solvent under reduced pressure, the residue was transferred into a 1 l. separating funnel with about

800 ml. of 2 N sodium hydroxide and extracted repeatedly with ether. The ether extract was dried over anhydrous potassium carbonate and evaporated under reduced pressure. The residue was recrystallized from ethanol-water to give 5.6 g. (75%) of colorless leaflets, m.p. 107~108°C.

3,6-Bis(3-chlorophenoxy)-pyridazine. A mixture of 21.8 g. (0.17 mole) of *m*-chlorophenol, 1.7 g. (0.074 mole) of metallic sodium and 40 ml. of toluene was heated to reflux to give the phenolate. Then, 5.0 g. (0.034 mole) of 3,6-dichloropyridazine was added and refluxing was continued for 5 hrs. The subsequent procedure was the same as that for 3-chloro-6-(4-methylphenoxy)-pyridazine. After recrystallization from ethanol, there was obtained 6.9 g. (61%) of colorless needles, m.p. 126.5°C.

3-Chloro-6-(2-methoxyphenoxy)-pyridazine and 3,6-Bis(2-methoxyphenoxy)-pyridazine. In 40 ml. of toluene, 21.1 g. (0.17 mole) of guaiacol, 5.0 g. (0.034 mole) of 3,6-dichloropyridazine and 1.7 g. (0.074 mole) of metallic sodium were treated in the same manner as that for 3,6-bis(3-chlorophenoxy)-pyridazine. After refluxing for 10 hrs., the reaction mixture was evaporated under reduced pressure and the residue was transferred into a 1 l. separating funnel with 800 ml. of 2 N aqueous sodium hydroxide and 150 ml. of ether successively. After the funnel was shaken vigorously and left to stand for about 30 min., the ether layer, in which dark-brown crystalline solids suspended, was filtered. The solid thus obtained was recrystallized from ethanol to give 1.4 g. of colorless columns, m.p. 171°C. Analysis indicated that this was the bis-ether. Its yield was 13% based on 3,6-dichloropyridazine. The aqueous layer in the separating funnel was further extracted repeatedly with ether, and these extracts were combined with the ether filtrate from which bis-ether had been removed. The ether was dried over anhydrous potassium carbonate, filtered, and evaporated under reduced pressure, leaving crude 3-chloro-6-(2-methoxyphenoxy)-pyridazine. Crystallization from ethanol-water gave fine colorless leaflets in 47% yield. After repeated crystallization from ethanol-water, it melted at 98.5°C.

When the initial refluxing was conducted for 5 hrs., only mono-ether was obtained in a 65% yield, though the subsequent procedure was the same as that described above.

3-Chloro-6-mercaptopyridazine. A mixture of 16.0 g.

8) M. Kumagai, *J. Chem. Soc. Japan*, **81**, 1604 (1960).

9) S. Sato, *J. Pharm. Soc. Japan*, **82**, 1085 (1962).

(0.107 mole) of 3,6-dichloropyridazine, 8.0 g. (0.105 mole) of thiourea and 135 ml. of ethanol was heated at 60~70°C for 25 min. After cooling, the resulted pyridazine-3,6-bis(thiuronium chloride) was removed by filtration. The filtrate was concentrated under reduced pressure to give 9.8 g. of S-(6-chloro-3-pyridazolyl) thiuronium chloride, which was dissolved in 500 ml. of water. The solution thus obtained was made alkaline with 40 ml. of 10% sodium hydroxide solution and heated to reflux. After cooling, it was filtered and the filtrate was acidified with dilute hydrochloric acid to precipitate 8.3 g. of crude 3-chloro-6-mercaptopyridazine, m.p. 98°C (dec.).

The mother liquor was extracted with chloroform repeatedly and the combined extracts were concentrated in vacuo, affording 1.6 g. of the thiol compound. The total yield of crude product was 62% based on 3,6-dichloropyridazine. Crystallization from benzene-hexane gave yellow needles, m.p. 100°C (dec.). Reported m.p. 140°C, 130~140°C (dec.).

Anal. Found: C, 32.81; H, 2.01; N, 18.96. Calcd. for $C_4H_3ClN_2S$: C, 32.55; H, 2.05; N, 18.98%.

3-Chloro-6-methylthiopyridazine. According to the method of S. Sato⁹⁾, 5.5 g. (0.038 mole) of 3-chloro-6-

mercaptopyridazine was treated with 5.4 g. (0.038 mole) of methyl iodide in 85 ml. of methanol to give a 66% yield of methylmercapto compound, which was recrystallized from benzene. Colorless columns, m.p. 101~102°C. Reported m.p. 101~102°C⁹⁾.

3-Methylthio-6-(2-methoxyphenoxy)-pyridazine. A mixture of 5.4 g. of 3-chloro-6-methylthiopyridazine (0.034 mole), 21.1 g. (0.17 mole) of guaiacol and 0.86 g. (0.037 mole) of metallic sodium was heated in 40 ml. of boiling toluene for 10 hrs. The subsequent procedure was the same as that for 3-chloro-6-pyridazolyl ethers. Recrystallization from ethanol gave colorless needles, m.p. 133°C.

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