Syntheses of Pyridazine Derivatives as Herbicides

Part III. Preparation of 3- and 4-Phenoxypyridazines

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Various 3-phenoxypyridazines were prepared by either catalytic dehalogenation of corresponding 3-phenoxy-6-chloropyridazines or reaction of 3-chloropyridazine with phenols in the presence of base. Syntheses of certain 4-phenoxypyridazines are also described.

In the course of our search for new series of herbicides, we discovered a group of halogeno-pyridazyl phenyl ethers with marked biological activity, such as 3-phenoxy-6-chloropyridazine (I) and 3-(2,6-dichlorophenoxy)-6-chloropyridazine (II).^{1,2)}

Further, we have recently found that 3-phenoxypyridazine (III) without a chlorine atom on its pyridazine ring was by far the stronger herbicide than I and II in paddy field condition.³⁾ This prompted us to prepare various 3-phenoxypyridazines along with certain 4-phenoxypyridazines containing respectively no substituents on their heterocyclic rings to be evaluated their herbicidal effects.

	X	Y
I:	Cl	H
II:	Cl	Cl
III:	H	H

Concerning the synthesis of 3-phenoxypyridazines, only one example has been reported by Itai and Igeta,⁴⁾ who prepared III by catalytic dehalogenation of I. In this paper syntheses of 3-phenoxypyridazines containing lower alkyl, phenyl, chlorine, nitro and methoxyl groups on their benzene rings are described. These compounds except nitrophenoxypyridazines were prepared by catalytic reduction of corresponding 3-phenoxy-6-chloropyridazines over palladium on carbon or Raney nickel in ammoniacal methanol at room temperature and ordinary pressure. In a large-scale preparation, hydrogenation was carried out in an autoclave at 50~60°C, initial pressure of hydrogen being 10~20 kg/cm². Interestingly the chlorine atom attached to the benzene ring was never attacked during this process. On the other hand, all attempts to dehalogenate 3-phenoxy-6-chloropyridazines with zinc dust or iron powder in ethanol or acetic acid were unsuccessful, resulting in cleavage of the ether linkage.

Another synthetic route, in which 3-chloropyridazine (IV) and phenol are treated in the presence of base, was adopted to obtain

1) S. Tamura and T. Jojima, *Agr. Biol. Chem.*, **27**, 728 (1963).

2) T. Jojima and S. Tamura, *ibid.*, **29**, 157 (1965).

3) S. Tamura, T. Jojima, K. Kawakubo, K. Nakamura and T. Takematsu, *ibid.*, **30**, 423 (1966).

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

TABLE I. 3-PHENOXYPYRIDAZINES

R	Method ^{a)}	mp, ^c or bp, °C	Solvent for recrystn.	Yield, %	Molecular formula	Calcd, %			Found, %		
						C	H	N	C	H	N
H	A	76 ^{b)}	Ligroin	80	—	—	—	—	—	—	—
H	B	"	"	13	—	—	—	—	—	—	—
2-CH ₃	A	78	"	88	C ₁₁ H ₁₀ N ₂ O	70.95	5.41	15.04	71.35	5.51	15.08
3-CH ₃	A	47	"	46	"	"	"	"	71.53	5.51	15.25
4-CH ₃	A	94	"	72	"	"	"	"	70.57	5.14	15.04
2-C ₂ H ₅	A	47~48	"	38	C ₁₂ H ₁₂ N ₂ O	71.98	6.04	13.99	71.61	6.13	13.95
2- <i>n</i> -C ₃ H ₇	A	58~61	"	23	C ₁₃ H ₁₄ N ₂ O	72.87	6.59	13.07	72.24	6.53	12.54
2- <i>i</i> -C ₃ H ₇	A	96.5~98	"	58	"	"	"	"	72.86	6.52	12.90
2- <i>n</i> -C ₄ H ₉	A	127~136(0.4mm)	—	49	C ₁₄ H ₁₆ N ₂ O	73.66	7.06	12.27	73.68	7.01	12.44
2- <i>sec</i> -C ₄ H ₉	A	53	Ligroin	38	"	"	"	"	73.59	7.15	12.47
2- <i>t</i> -C ₄ H ₉	A	78~79	"	72	"	"	"	"	73.49	7.03	12.17
4- <i>t</i> -C ₄ H ₉	A	121~123	"	25	"	"	"	"	72.60	7.12	11.86
2- <i>n</i> -C ₇ H ₁₅	A	165~174(0.4mm)	—	48	C ₁₇ H ₂₁ N ₂ O	75.80	7.86	10.40	75.30	8.41	9.74
2, 3-di-CH ₃	A	88~95	Ligroin	24	C ₁₂ H ₁₂ N ₂ O	71.98	6.04	13.99	69.98	5.94	13.48
2, 4-di-CH ₃	A	66~68	"	51	"	"	"	"	72.11	5.82	13.65
2, 5-di-CH ₃	A	77~79	"	48	"	"	"	"	71.41	6.04	14.60
2, 6-di-CH ₃	A	94~95	"	19	"	"	"	"	72.98	6.11	13.96
3, 4-di-CH ₃	A	88~91	"	95	"	"	"	"	71.41	6.15	14.26
2-CH ₃ -5- <i>i</i> -C ₃ H ₇	A	142~150(0.07mm)	—	39	C ₁₄ H ₁₆ N ₂ O	73.66	7.06	12.27	73.92	7.11	12.06
3-CH ₃ -4- <i>i</i> -C ₃ H ₇	A	135~143(0.04mm)	—	43	"	"	"	"	73.94	7.48	12.12
2- <i>i</i> -C ₃ H ₇ -5-CH ₃	A	79~80	Ligroin	49	"	"	"	"	73.51	7.25	12.38
2- <i>sec</i> -C ₄ H ₉ -5-CH ₃	A	57~58	"	45	C ₁₅ H ₁₈ N ₂ O	74.35	7.49	11.56	74.25	7.51	11.44
3-CH ₃ -4- <i>sec</i> -C ₄ H ₉	A	155~165(0.05mm)	—	46	"	"	"	"	74.60	7.52	11.51
2, 3, 5-tri-CH ₃	A	132~135	Ligroin	71	C ₁₃ H ₁₄ N ₂ O	72.87	6.59	12.07	72.78	6.47	12.78
2-C ₆ H ₅	B	122~123	Ligroin-EtOH	24	C ₁₆ H ₁₂ N ₂ O	77.40	4.87	11.28	77.38	4.95	11.28
2-Cl	A	108~109	"	99	C ₁₀ H ₇ ClN ₂ O	58.13	3.41	13.56	57.61	3.51	13.51
3-Cl	A	90.5	Ligroin	60	"	"	"	"	58.44	3.44	13.64
	B		"	18							
4-Cl	A	106	"	42	"	"	"	"	58.33	3.34	14.50
	B			8							
2, 4-di-Cl	A	98	Ligroin	70	C ₁₀ H ₆ Cl ₂ N ₂ O	49.82	2.51	11.62	49.57	2.65	11.43
	B			8							
2, 6-di-Cl	A	87~88	Ligroin	59	"	"	"	"	50.00	2.67	10.98
	B			3							
2, 4, 5-tri-Cl	A	132~133	Ligroin	56	C ₁₀ H ₅ Cl ₃ N ₂ O	43.59	1.83	10.17	43.98	1.94	10.10
2, 4, 6-tri-Cl	A	153	"	72	"	"	"	"	43.96	1.87	10.26
2-CH ₃ -4-Cl	A	98~99	"	53	C ₁₁ H ₉ ClN ₂ O	59.87	4.11	12.70	59.01	4.11	12.50
2-CH ₃ -6-Cl	A	89	"	70	"	"	"	"	60.90	4.23	12.56
3-CH ₃ -4-Cl	A	86	"	77	"	"	"	"	59.97	4.32	12.58
	B			40							
2-Cl-4-C ₆ H ₅	A	93~95	Ligroin	50	C ₁₆ H ₁₁ ClN ₂ O	67.97	3.92	9.91	66.65	3.93	9.75
2, 4-di-Cl-6-CH ₃	A	126	"	55	C ₁₁ H ₈ Cl ₂ N ₂ O	51.79	3.16	10.98	51.82	3.32	10.87
3-NO ₂	B	86	EtOH-H ₂ O	37	C ₁₀ H ₇ N ₃ O ₃	55.30	3.25	19.35	55.22	3.41	19.07
4-NO ₂	B	151	Ligroin	4	"	"	"	"	55.08	3.30	19.18
4-CH ₃ O	B	88.5	"	30	C ₁₁ H ₁₀ N ₂ O ₂	65.34	4.98	13.85	65.06	4.95	13.78

a) A: Catalytic hydrogenation of 3-phenoxy-6-chloropyridazines.

B: Reaction of 3-chloropyridazine (IV) with phenols in the presence of base.

b) Lit.⁴⁾ mp 74°C.

certain phenoxy pyridazines, especially those containing nitro groups on their benzene rings. Owing to the heat-instability of IV, however, yields were generally poor as compared with those in the hydrogenation procedure mentioned above. For example, III was obtained in an 8% yield by the fusion of IV with phenol in the presence of anhydrous potassium carbonate for 15 min at 120°C, and only 0.5% by the treatment of IV with sodium phenoxide in boiling benzene for several hrs. On the other hand, catalytic dehalogenation of I over 5% palladium on carbon in ammoniacal methanol at ordinary pressure and room temperature afforded III in a 90% yield. Various 3-phenoxy pyridazines prepared by the both methods are listed in Table I.

In the preceding papers,^{5,6)} 3-phenoxy-6-chloropyridazines, which are also required in the present study as the starting materials, were synthesized by treating various phenols with 3,6-dichloropyridazine (V) in the presence of metallic sodium in boiling benzene or toluene. To obtain mono-ethers by this method, however, so large excess of phenols should be used respectively, that formation of undersirable bis-ethers often ensued. Especially *o*-halophenols, such as *o*-chloro, *o*-bromo- and 2-chloro-4-phenylphenols did not give corresponding mono-ethers, but afforded bis-ethers in low yields irrespective of amounts of phenols employed. In order to avoid these difficulties, reaction conditions were examined for the preparation of 3-(2-methylphenoxy)-6-chloropyridazine (VI) from *o*-cresol (VII) and V according to various procedures, and yields were accurately measured with gas chromatography, since 3-(2-methylphenoxy) pyridazine (VIII) derived from VI seemed promising as a practical herbicide. The results are shown in Table II. When V, VII and anhydrous potassium carbonate in an equimolar ratio were heated at 160°C without any solvent

TABLE II. REACTION OF *o*-CRESOL AND 3,6-DICHLOROPYRIDAZINE TO PRODUCE 3-(2-METHYLPHENOXY)-6-CHLOROPHYRIDAZINE (VI) IN VARIOUS CONDITIONS

Base (equiv)	<i>o</i> -Cresol, equiv	Solvent	Time, hr	Temp., °C	Yield, %
Na(1)	Excess	—	2	180	5.3 ^{a)}
"	4	Toluene	2	Reflux	73.4
Na(2)	4	"	2	"	18.0 ^{a)}
NaOH(1)	1	Water	4	80	26.4
"	4	"	4	80	60.7
K ₂ CO ₃ (1)	1	—	0.5	160	85.1

a) Large quantity of bis-ether, 3,6-di (2-methylphenoxy)pyridazine was produced.

for 30 min, VI was obtained in the best yield (85.1%). Treatment of V, VII and metallic sodium according to the previous method¹⁾ in the molar ratio of 1:4:1 in boiling toluene gave VI in a yield of 73.4%. Increase of the ratio of VII or metallic sodium to V significantly reduced the yield of VI. Furthermore, the reaction carried out in aqueous sodium hydroxide solution showed a poorer yield. Thus, all the 3-phenoxy-6-chloropyridazines mentioned here were prepared by the fusion of V with phenols in the presence of potassium carbonate. By this procedure *o*-chlorophenol and 2-chloro-4-phenylphenol afforded respectively the anticipated mono-ethers, which could not be obtained previously, in fairly good yields, still 2-methyl-6-*t*-butylphenol and 2,6-di-*t*-butylphenol did not react with V probably due to the bulky substituent on the *ortho*-position. In Table III, only new 3-phenoxy-6-chloropyridazines are illustrated.

Though syntheses of certain 4-phenoxy-3,6-dichloropyridazines were reported in the previous paper,⁶⁾ 4-phenoxy pyridazines without any substituent on their heterocyclic rings have not been hitherto reported. Then, 3,4,5-trichloropyridazine (IX) was heated with phenol or *p*-methoxyphenol in the presence of anhydrous potassium carbonate to give the corresponding 5-phenoxy-3,4-dichloro-2-pyridazine (Xa or Xb), which was subsequently dehalogenated catalytically to 4-phenoxy pyridazine (XIa or XIb). XIa was also

5) S. Tamura and T. Jojima, *Agr. Biol. Chem.*, **27**, 653 (1963).

6) T. Jojima and S. Tamura, *ibid.*, **29**, 151 (1965).

TABLE III. 3-PHENOXY-6-CHLOROPYRIDAZINES

R	mp or bp, °C	Solvent for crystn	Yield, %	Molecular formula	Calcd, %			Found, %		
					C	H	N	C	H	N
2, 4-di-Cl-6-CH ₃	147	Ligroin-EtOH	41	C ₁₁ H ₇ Cl ₃ N ₂ O	45.63	2.44	9.68	46.30	2.43	9.90
2-C ₂ H ₅	130~142(0.04mm)	—	46	C ₁₂ H ₁₁ N ₂ ClO	61.42	4.72	11.94	61.50	4.70	11.99
2- <i>n</i> -C ₃ H ₇	82~83	Ligroin	56	C ₁₃ H ₁₃ ClN ₂ O	62.78	5.27	11.26	62.75	5.36	11.26
2- <i>n</i> -C ₄ H ₉	156~165(0.18mm)	—	47	C ₁₄ H ₁₅ ClN ₂ O	64.00	5.75	10.66	63.62	5.74	10.57
2- <i>sec</i> -C ₄ H ₉	92~94	Ligroin	37	"	"	"	"	63.91	5.70	10.70
2- <i>t</i> -C ₄ H ₉	109~110	"	92	"	"	"	"	64.09	5.79	10.72
4- <i>t</i> -C ₄ H ₉	112~114	"	95	"	"	"	"	63.84	5.71	10.44
2- <i>n</i> -C ₇ H ₁₅	178~187(0.25mm)	—	45	C ₁₇ H ₂₁ ClN ₂ O	66.98	6.94	9.19	66.32	6.93	9.10
2, 3-di-CH ₃	95~96	Ligroin	90	C ₁₂ H ₁₁ N ₂ ClO	61.42	4.72	11.94	61.59	4.83	12.00
2, 4-di-CH ₃	67	"	91	"	"	"	"	61.20	4.87	11.86
2, 5-di-CH ₃	77~79	"	87	"	"	"	"	61.24	4.89	12.17
2, 6-di-CH ₃	94~95	"	93	"	"	"	"	61.30	4.79	12.16
2-CH ₃ -5- <i>i</i> -C ₃ H ₇	145~149(0.12mm)	—	58	C ₁₄ H ₁₅ ClN ₂ O	64.00	5.75	10.66	63.20	5.81	10.30
3-CH ₃ -4- <i>i</i> -C ₃ H ₇	84	Ligroin	81	"	"	"	"	63.74	5.77	10.63
2- <i>i</i> -C ₃ H ₇ -5-CH ₃	85~87	"	52	"	"	"	"	63.20	5.81	10.30
2- <i>sec</i> -C ₄ H ₉ -5-CH ₃	72	"	42	C ₁₅ H ₁₇ ClN ₂ O	65.09	6.19	10.12	65.01	6.21	10.15
3-CH ₃ -4- <i>sec</i> -C ₄ H ₉	165~175(0.4mm)	—	45	"	"	"	"	67.63	6.58	9.47
2, 3, 5-tri-CH ₃	130~131	Ligroin	61	C ₁₃ H ₁₃ ClN ₂ O	62.78	5.27	11.26	62.67	5.29	11.36
2-Cl	68~69	Ligroin-pet.-ether	94	C ₁₀ H ₆ Cl ₂ N ₂ O	49.82	2.51	11.62	49.92	2.62	11.51
2, 4, 6-tri-Cl	167~168	Acetone-EtOH	53	C ₁₀ H ₄ Cl ₄ N ₂ O	38.75	1.30	9.04	38.75	1.43	9.11
2-CH ₃ -4-Cl	92~94	Ligroin	100	C ₁₁ H ₈ Cl ₂ N ₂ O	51.79	3.16	10.98	51.47	3.30	11.19
2-CH ₃ -6-Cl	101~102	"	80	"	"	"	"	51.57	3.10	11.21
2-Cl-4-C ₆ H ₅	102~106	"	47	C ₁₆ H ₁₀ Cl ₂ N ₂ O	60.59	3.18	8.83	60.13	3.30	9.02

TABLE IV. 4-PHENOXYPYRIDAZINES

R	X	Y	Z	Method ^{a)}	mp, °C ^{b)}	Yield, %	Molecular formula	Calcd, %			Found, %		
								C	H	N	C	H	N
C ₆ H ₅	Cl	H	Cl	A	87~88	21	C ₁₀ H ₈ Cl ₂ N ₂ O	49.82	2.51	11.62	49.82	2.60	11.68
C ₆ H ₅	Cl	Cl	H	A	68~69	68	"	"	"	"	49.99	2.58	11.54
4-CH ₃ O-C ₆ H ₄	Cl	Cl	H	A	60~64	53	C ₁₁ H ₈ Cl ₂ N ₂ O ₂	48.74	2.98	10.33	48.93	3.07	10.30
C ₆ H ₅	H	H	H	B	70~71	55 ^{c)} 34 ^{d)}	C ₁₀ H ₈ N ₂ O	69.76	4.68	16.27	69.63	4.76	16.05
4-CH ₃ O-C ₆ H ₄	H	H	H	B	81~84	27	C ₁₁ H ₁₀ N ₂ O ₂	65.34	4.98	13.85	65.08	5.52	13.88

a) A: From trichloropyridazine, phenol and anhyd. K₂CO₃.

B: Catalytic hydrogenation of dichlorophenoxy pyridazines.

b) All samples are recrystallized from ligroin.

c) From 3, 6-dichloro-4-phenoxy pyridazine.

d) From 3, 4-dichloro-5-phenoxy pyridazine.

obtained through the reaction of 3, 4, 6-trichloropyridazine (XII) with phenol, followed by hydrogenation of resulting 4-phenoxy-3, 6-dichloropyridazine (XIII). Physical properties of these 4-phenoxy pyridazines are shown in Table IV. Herbicidal activities of these pyridazine derivatives will be disclosed in the succeeding paper.

EXPERIMENTAL

Preparation of 3-phenoxy-6-chloropyridazines.

In general, an equimolar mixture of phenol, 3, 6-dichloropyridazine (V) and anhydrous potassium carbonate was heated at 160~180°C for 30~60 min. After cooling, dilute aqueous sodium hydroxide solution was added to the reaction mixture, from which crude 3-phenoxy-6-chloropyridazine was usually separated as crystals. Then the product was filtered and recrystallized from an appropriate solvent. On the other hand, when the product was a liquid as in the case of the reaction between *o*-*n*-butylphenol and V, the alkaline solution was repeatedly extracted with ether. After evaporation of the solvent, the residue was distilled under reduced pressure to give a pure product. Synthesis of 3-(2-methylphenoxy)-6-chloropyridazine (VI) is illustrated below as a typical run.

An equimolar mixture (0.134 mole each) of 14.5 g of *o*-cresol, 20.0 g of V and 18.5 g of anhydrous potassium carbonate was heated at 160°C in an oil bath for 30 min. After cooling, the reaction mixture was treated with 2N sodium hydroxide solution and

the resulting crude crystalline solid (28.8 g) was filtered and washed with water. Recrystallization from ligroin gave VI as colorless rods, mp 85~86°C.

In order to measure exactly the yields of VI, which was prepared in the various ways including the above procedure, an F & M Model 402 gas chromatograph was used under the following conditions: stainless steel tubing, 1 m by 3.2 mm, packed with 1% XE-60 on 80/100 mesh Chromosorb; column temperature, 260°C; hydrogen flow, 40 ml/min. The results are shown in Table II.

Catalytic dehalogenation of 3-phenoxy-6-chloropyridazines to 3-phenoxy pyridazines. The reactions were conducted in a glass hydrogenating apparatus over 5% Pd-C in ammoniacal methanol at room temperature and ordinary pressure. Sometimes, the apparatus was externally warmed to 50~60°C to promote hydrogenation. In a preparative scale, the reduction was conducted in a stainless steel autoclave. Typical runs are given below.

Twenty g (0.91 mole) of 3-(2-methylphenoxy)-6-chloropyridazine (VI) dissolved in a mixture of 100 ml of ethanol and 8 ml of concentrated aqueous ammonia was hydrogenated over 1.6 g of 5% Pd-C in 1-l glass hydrogenating apparatus at 50°C and ordinary pressure. One equivalent of hydrogen was absorbed within 40 min. The reaction mixture was filtered to remove the catalyst, and the filtrate was evaporated under reduced pressure. A small amount of water was added to the residue, which was then extracted with ether. After removal of the solvent, there remained 15 g of 3-(2-methylphenoxy) pyri-

dazine (VIII) as colorless needles, mp 78~80°C.

For the large scale preparation of VIII, 2 kg of VI, 10 liters of methanol, 80 ml of water, 700 ml of concentrated aqueous ammonia and 80 g of 5% Pd-C were charged in a 20-l autoclave. Hydrogenation was conducted at 50~70°C, initial hydrogen pressure being 10 kg/cm². Then, the reaction mixture was treated as described above to give 1.65 kg of crude crystalline VIII melting at 76°C.

Preparation of 3-phenoxy pyridazines from 3-chloropyridazine (IV) and phenols. As typical runs, syntheses of 3-phenoxy pyridazine (III) from 3-chloropyridazine (IV) and phenol in the presence of anhydrous potassium carbonate and metallic sodium are described below.

An equimolar mixture (0.017 mole each) of 2 g of IV, 1.69 g of phenol and 2.4 g of anhydrous potassium carbonate was heated at 120°C for 15 min. During the reaction vigorous decomposition of IV was observed. After cooling, the reaction mixture was treated with 100 ml of 2N sodium hydroxide and stood overnight. The resulting crystals were filtered to give 0.4 g of 3-phenoxy pyridazine (III), as colorless crystals, mp 71°C, lit.⁴⁾ 74°C.

Alternatively, 2.0 g (0.017 mole) of IV, 3 g (0.032 mole) of phenol, 0.39 g (0.017 mole) of metallic sodium and 20 ml of benzene were treated according to the procedure described previously⁵⁾ to give 15 mg of III.

Preparation of 4-phenoxy pyridazines. As typical runs, syntheses of 4-phenoxy pyridazine (XIa) are shown below.

a) From 3,4,5-trichloropyridazine (IX). An equimolar mixture (0.038 mole each) of 7 g of IX,

3.6 g of phenol and 5.3 g of anhydrous potassium carbonate was heated at 160°C for 15 min. The reaction mixture was treated with 2N sodium hydroxide and repeatedly extracted with ether. The combined extracts were evaporated and the residue was fractionally distilled under reduced pressure. A fraction boiling in the range of 130~150°C/0.27 mmHg gave 6.1 g of semi-solid crystals, a part of which was recrystallized for analysis from ligroin to yield colorless crystals of 3,4-dichloro-5-phenoxy pyridazine (Xa), mp 68~69°C. Hydrogenation of 4 g of crude Xa afforded 1.2 g of solid product. Recrystallization from ligroin gave 1.0 g of 4-phenoxy pyridazine (XIa) as colorless crystals, mp 70~71°C.

b) From 3,4,6-trichloropyridazine (XII). An equimolar mixture (0.043 mole each) of 8 g of XII, 4.1 g of phenol and 5.96 g of anhydrous potassium carbonate was treated as described above. A fraction boiling in the range of 136~179°C/0.5 mmHg was collected and stood overnight to become solid. Recrystallization from ligroin gave 2.1 g of 3,6-dichloro-4-phenoxy pyridazine (XIII), mp 87~88°C. Hydrogenation of 1.5 g of XIII in the usual manner afforded 0.59 g of the crude product. Recrystallization from ligroin-petroleum ether gave colorless leaflets, mp 71~72°C, which was identified as XIa by the mixture melting point as well as by the comparison of infrared and NMR spectra.

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