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Studies on Heterocyclic Compounds. XVI.[1] Synthesis of Furo[2,3-*d*]pyridazine Derivatives. (5). Synthesis of 4,7-Dichlorofuro[2,3-*d*]pyridazine-2-carboxaldehyde and some of Its Derivatives[2]

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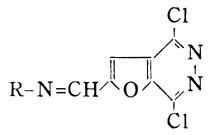
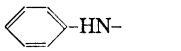
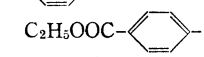
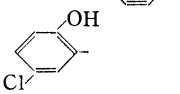
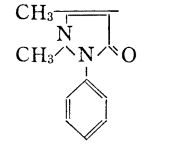
A number of derivatives of furo[2,3-*b*]pyridine,[4] furo[2,3-*b*]quinoline,[5] furo[2,3-*d*]pyrimidine[6] and furo[2,3-*d*]pyridazine[7] have been known. However, derivatives possessing an aldehyde group on the furan ring of these heteroaromatics have not yet been reported.

In a continuation of our studies of furo[2,3-*d*]pyridazine[1,8] as a source of compounds of potential biological interest, 4,7-dichlorofuro[2,3-*d*]pyridazine-2-carboxaldehyde (Ia) and

TABLE I



R	mp (°C)	Yield (%)	Appearance	Formula	Analysis(%) Calcd. C	H	N	Found C	H	N
H_2NCOHN–	233 (decomp.)	93	colorless needles	$C_8H_5O_2N_5Cl_2$	35.06	1.84	25.55	35.28	1.53	25.28
	236.5—237.5	96	yellow needles	$C_{13}H_8ON_3Cl_2$	53.27	2.75	14.33	53.20	2.54	14.46
	239 (decomp.)	81	yellow needles	$C_{16}H_{11}O_3N_3Cl_2$	52.77	3.04	11.54	52.61	3.39	11.67
	198 (decomp.)	80	yellow needles	$C_{13}H_6O_2N_3Cl_3$	45.58	1.77	12.27	45.36	1.63	12.48
	245 (decomp.)	99	yellow needles	$C_{18}H_{13}O_2N_5Cl_2$	53.75	3.26	17.41	53.52	3.68	17.35

1) Part XV: S. Yoshina and I. Maeba, *Chem. Pharm. Bull.* (Tokyo), **19**, 1465 (1971).
2) Presented at the 91th Annual Meeting of Pharmaceutical Society of Japan, Fukuoka, April, 1971.
3) Location: *Tenpaku-cho, Showa-ku, Nagoya.*
4) H.R. Snyder and F.F. Ebetino, *J. Heterocyclic Chem.*, 3, 202 (1966); J. Reisch, *Arch. Pharm.*, **297**, 754 (1964).
5) M.F. Grundon, N.J. McCorkindale and M.N. Rodger, *J. Chem. Soc.*, **1955**, 4285; H. Fujimura, T. Tanaka, I. Iijima, M. Miyazaki and M. Masaki, Ger. Patent, 1944914 (1968) [*C.A.*, **72**, 10067c (1970)].
6) H. Saikachi, T. Matsuo and T. Matsuda, *Yakugaku Zasshi*, **89**, 1434 (1969); J.P. Marquet, E. Bisagni and J. Andre-Louisfert, *Bull. Soc. Chim. France*, **1969**, 4344.
7) M. Robba and M.C. Zaluski, *Compt. Rend.*, **266**, 31 (1968); J.P. Marquet, E. Bisagni and J. Andre-Louisfert, *Chim. Ther.*, 3, 348 (1968).
8) *a*) S. Yoshina, I. Maeba and K. Hirano, *Chem. Pharm. Bull.* (Tokyo), **17**, 2158 (1969); *b*) S. Yoshina and I. Maeba, *ibid.*, **18**, 379 (1970); *c*) *Idem, ibid.*, **18**, 842 (1970).

its derivatives were prepared. For the synthesis of Ia, 2-bromomethyl-4,7-dichlorofuro-[2,3-*d*]pyridazine (II)[1] served as the starting material. The Sommelet method was unsuccessful for the conversion of II to the aldehyde (Ia). Although the yield of hexamethylenetetramine salt (III) was nearly quantitative, attempts to hydrolyze it in 50% acetic acid solution were unsuccessful. Treatment of II with sodium 2-propanenitronate according to the procedure of Bambury,[9] who successfully converted the 5-bromomethyl-2-trifluoromethylfuran to its aldehyde derivatives, led to resinification.

Finally, we succeeded in the preparation of desired aldehyde (Ia) by the method of Kröhnke and Börner.[10] The reaction of II with pyridine gave the pyridinium salt (IVa), which was subsequently treated with *p*-nitroso-N,N-dimethylaniline and alkali to produce the nitrone (Va) in 93% yield. Hydrolysis of Va with 5N sulfuric acid solution gave 4,7-dichlorofuro-[2,3-*d*]pyridazine-2-carboxaldehyde (Ia) of mp 170—171° in a yield of 94%.

In the mass spectrum of Ia, besides M^+ ion (*m/e* 216), the following ions are remarkable, *m/e* 146, 133, 131, 127, 125 and 97 (base peak). The infrared spectrum of Ia showed the absorption band at 1715 cm^{-1} attributed to a carbonyl group. In addition, the nuclear magnetic resonance (NMR) spectrum (ppm in DMSO-d_6) of Ia showed the following signals;

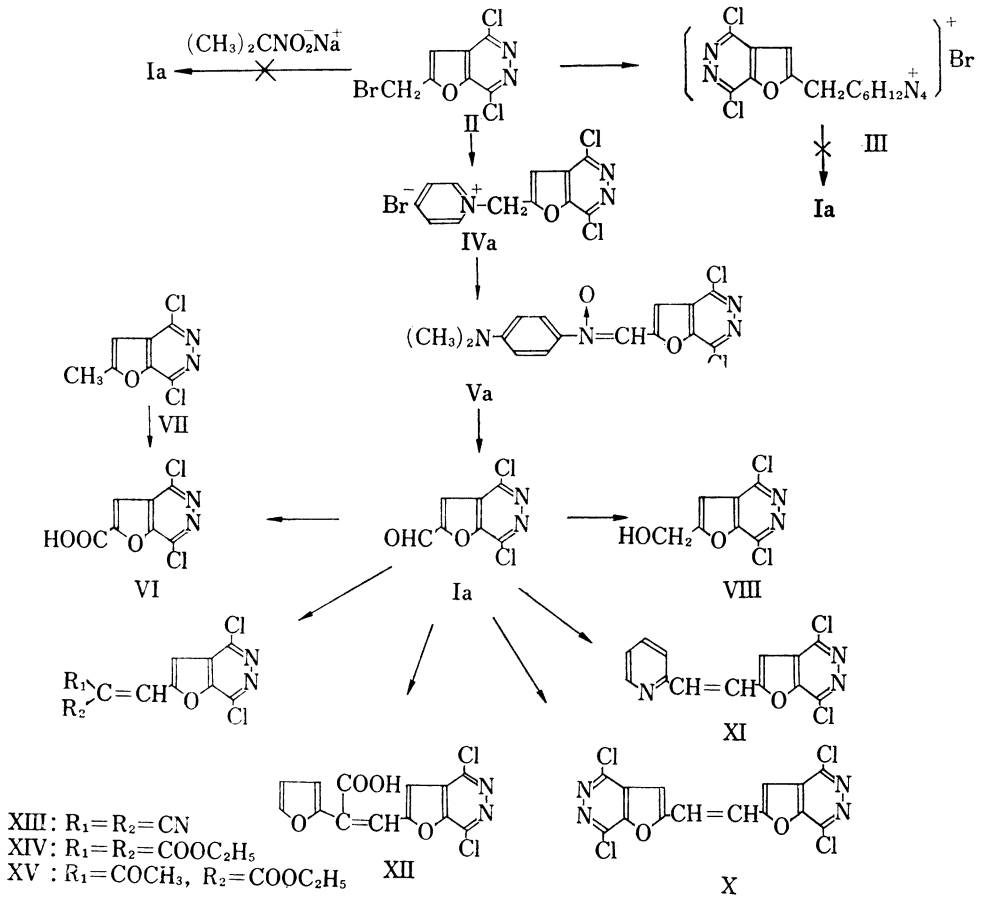


Chart 1

9) R.E. Bambury, H.K. Yakine and K.K. Wyckoff, *J. Heterocyclic Chem.*, **5**, 95 (1968).
10) F. Kröhnke and Börner, *Chem. Ber.*, **69**, 2006 (1936).

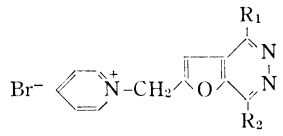
10.06 (1H, s, —CHO) and 8.30 (1H, s, ring proton 3 pos.). The elemental analysis of Ia supported a molecular formula $C_7H_2O_2N_2Cl_2$. Further, Ia was characterized as its semicarbazone, phenylhydrazone and other Schiff's bases (Table I).

The aldehyde (Ia) was readily oxidized with silver oxide to 4,7-dichlorofuro[2,3-*d*]pyridazine-2-carboxylic acid (VI) of mp 193° (decomp.). The acid (VI) was identical with the product which was obtained by the oxidation of 2-methyl-4,7-dichlorofuro[2,3-*d*]pyridazine (VII) with sodium dichromate. The aldehyde (Ia) was readily reduced with sodium borohydride to 2-hydroxymethyl-4,7-dichlorofuro[2,3-*d*]pyridazine (VIII) of mp 121—122°.

Reaction of Ia with 2-(4,7-dichlorofuro[2,3-*d*]pyridazinylmethyl)triphenylphosphonium bromide (IX)[1] by means of sodium carbonate solution gave 1,2-bis[2-(4,7-dichlorofuro[2,3-*d*]-pyridazinyl)]ethylene (X) in good yield. Condensation of Ia with α-picoline in acetic anhydride gave *trans*-2-[2-(2-pyridyl)vinyl]-4,7-dichlorofuro[2,3-*d*]pyridazine (XI), which was proved to be identical with the product obtained by the Wittig reaction[1] of 2-pyridylaldehyde with IX. Treatment of Ia with potassium furylacetate in acetic anhydride gave 2-furyl-3-[2-(4,7-dichlorofuro[2,3-*d*]pyridazinyl)]acrylic acid (XII) in 38% yield.

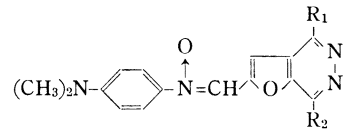
Condensation of Ia with malononitrile, diethyl malonate and ethyl acetoacetate produced XIII, XVI and XV in 98, 44 and 40% yields, respectively. From these results, Ia was shown to behave as a typical and reactive aromatic aldehyde, and it seems promising as a versatile intermediate for synthesis of a variety of derivatives.

TABLE II



Compound No.	R_1	R_2	mp (°C)	Yield (%)	Appearance	Formula	Analysis(%) Calcd. C	H	N	Found C	H	N
IVa	Cl	Cl	219	98	colorless needles	$C_{12}H_8ON_3BrCl_2$	39.92	2.23	11.64	40.13	1.97	11.36
IVb	OCH_3	Cl	192 (decomp.)	95	colorless needles	$C_{13}H_{11}O_2N_3BrCl$	43.79	3.11	11.78	43.62	3.18	11.53
IVc	Cl	OCH_3	181—182	97	colorless needles	$C_{13}H_{11}O_2N_3BrCl$	43.79	3.11	11.78	43.56	2.91	11.85
IVd	OH	Cl	252 (decomp.)	91	colorless needles	$C_{12}H_9O_2N_3BrCl$	42.07	2.65	12.27	42.21	2.54	12.33

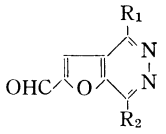
TABLE III



Compound No.	R_1	R_2	mp (°C)	Yield (%)	Appearance	Formula	Analysis(%) Calcd. C	H	N	Found C	H	N
Va	Cl	Cl	240	93	orange yellow needles	$C_{15}H_{12}O_2N_4Cl_2$	51.30	3.44	15.95	51.11	3.27	16.03
Vb	OCH_3	Cl	212 (decomp.)	90	orange yellow needles	$C_{16}H_{15}O_3N_4Cl$	55.42	4.36	16.16	55.28	4.30	15.86
Vc	Cl	OCH_3	232 (decomp.)	95	orange yellow needles	$C_{16}H_{15}O_3N_4Cl$	55.42	4.36	16.16	55.32	4.16	16.24
Vd	OH	Cl	262 (decomp.)	87	orange yellow needles	$C_{15}H_{13}O_3N_4Cl$	54.15	3.94	16.84	53.95	4.13	16.57

7-Chloro-4-methoxyfuro[2,3-*d*]pyridazine-2-carboxaldehyde (Ib), 4-chloro-7-methoxyfuro-[2,3-*d*]pyridazine-2-carboxaldehyde (Ic) and 4-hydroxy-7-chlorofuro[2,3-*d*]pyridazine-2-carboxaldehyde (Id) were also prepared in good yields by the Kröhnke and Börner method.

TABLE IV



Compound No.	R_1	R_2	mp (°C)	Yield (%)	Appearance	Formula	Analysis(%) Clacd. C	H	N	Found C	H	N
Ia	Cl	Cl	170—171	94	colorless prisms	$C_7H_2O_2N_2Cl_2$	38.74	0.93	12.91	38.51	1.07	12.73
Ib	OCH_3	Cl	196—197	86	colorless prisms	$C_8H_5O_3N_2Cl$	45.20	2.37	13.18	45.34	2.21	12.96
Ic	Cl	OCH_3	174—175	90	colorless needles	$C_8H_5O_3N_2Cl$	45.20	2.37	13.18	45.18	2.50	13.08
Id	OH	Cl	224—225	85	colorless prisms	$C_7H_3O_3N_2Cl$	42.34	1.52	14.11	42.25	1.31	13.94

Experimental[11]

2-(4,7-Dichlorofuro[2,3-*d*]pyridazinylmethyl)hexamethylenetetramine Bromide (III)——A mixture of 0.01 mole of II, 0.01 mole of hexamethylenetetramine and 30 ml of dry $CHCl_3$ was refluxed for 2 hr. The reaction mixture was kept at 5° overnight and the white salt was collected and washed twice with 10 ml portions of cold $CHCl_3$ to give 4.1 g of III. An analytical sample was recrystallized twice from MeOH to yield colorless needles, mp >300°. *Anal.* Calcd. for $C_{13}H_{15}ON_6BrCl_2$: C, 36.99; H, 3.58; N, 19.91. Found: C, 37.24; H, 3.41; N, 20.08.

General Procedure for the Preparation of 2-(4,7-Disubstitutedfuro[2,3-*d*]pyridazinylmethyl)pyridinium Bromides (IVa—d)——A mixture of 0.01 mole of 2-bromomethyl-4,7-disubstitutedfuro[2,3-*d*]pyridazine[1] and 10 ml of anhydrous pyridine in a flask equipped with a $CaCl_2$ tube was heated on a water bath for 20 minutes. After cooling, the crystals were collected and washed with AcOEt. Recrystallization from absolute EtOH does not change the melting point (Table II).

General Procedure for the Preparation of 2-(4,7-Disubstitutedfuro[2,3-*d*]pyridazinyl)-N-(*p*-dimethylaminophenyl)nitrones (Va—d)——To a stirred solution of 0.01 mole of IVa—d in 30 ml of EtOH and 0.015 mole of *p*-nitrosodimethylaniline in 30 ml of EtOH, saturated Na_2CO_3 solution was added over a period of 15 minutes. Stirring was continued for an additional 1 hr.

The orange yellow nitrone was filtered off, washed with a cold mixture of EtOH and water (1:3) and recrystallized from ethyleneglycol monomethyl ether (Table III).

General Procedure for the Preparation of 4,7-Disubstitutedfuro[2,3-*d*]pyridazine-2-carboxaldehydes (Ia—d)——To a suspension of the powdered nitrone (0.01 mole) in 10 ml of water in a separatory funnel, 50 ml of 5N H_2SO_4 and 50 ml of benzene were added. This mixture was throughly shaken until the nitrone dissolved. The water layer was extracted six times with benzene and the combined benzene extracts were washed twice with 5N H_2SO_4, and then with water. They were filtered and evaporated under reduced pressure. The crystalline residue was recrystallized from AcOEt (Table III). Schiff's bases of the aldehyde (Ia) were prepared by standard procedures (Table I).

Ib: NMR $\delta_{ppm}^{CDCl_3}$: 7.62 (1H, s, ring proton 3 pos.), 10.02 (1H, s, -CHO), 4.30 (3H, s, $-OCH_3$). *m/e* 212 (M^+).

Ic: NMR $\delta_{ppm}^{CDCl_3}$: 10.04 (1H, s, -CHO), 7.58 (1H, s, ring proton 3 pos.), 4.31 (3H, s, $-OCH_3$). *m/e* 212 (M^+).

Id: NMR $\delta_{ppm}^{DMSO\text{-}d_6}$: 13.30 (1H, b, -OH), 9.92 (1H, s, -CHO), 8.16 (1H, s, ring proton 3). *m/e* 198 (M^+).

4,7-Dichlorofuro[2,3-*d*]pyridazine-2-carboxylic Acid (VI)——a) From Ia: A solution of 4.24 g (0.025 mole) of $AgNO_3$ in 10 ml of water was added with efficient stirring to a solution of 2 g (0.05 mole) of NaOH in 10 ml of water. To this brown semisolid silver oxide mixture was added 2.2 g (0.01 mole) of Ia in small portions with stirring and cooling. After the addition, the mixture was stirred for 0.5 hr at room temperature

11) All melting points were not corrected. The NMR spectra were taken on a Varian A-60-A spectrometer with tetramethylsilane as an internal standard.

and the black silver suspension was separated by aspirator filtration and washed with water. The alkaline filtrate was acidified with 6N HCl and the white precipitates were collected and recrystallized from 80% MeOH to yield 2 g (90%) of VI as colorless needles, mp 193—194°. *Anal.* Calcd. for $C_7H_2O_3N_2Cl_2$: C, 36.08; H, 0.87; N, 12.02. Found: C, 36.32; H, 1.03; N, 12.29. NMR $\delta_{ppm}^{DMSO\text{-}d_6}$: 7.99 (1H, s, ring proton 3 pos.). *m/e* 232 (M^+).

b) From VII: To an ice-cooled conc. H_2SO_4 (35 ml) was added dropwise a solution of $Na_2Cr_2O_7$ (6.6 g) in H_2O (10 ml) with stirring. Compound (VII) 4 g in conc. H_2SO_4 (10 ml) was added to the mixture with stirring at 5—10°. The mixture was stirred for 3 hr at room temperature and then it was poured slowly with stirring onto 150 g of chipped ice. The precipitate was filtered off and washed with cold water. The crude product was dissolved in Na_2CO_3 solution and filtered off. The filtrate was acidified to Congo red with HCl. The precipitate was filtered off and recrystallized from 80% MeOH to yield 3 g (65%) of VI, mp 193—194°.

Identity was confirmed by comparing infrared (IR) spectra and mixed melting point.

2-Hydroxymethyl-4,7-dichlorofuro[2,3-*d*]pyridazine (VIII)——To 1 g (0.0045 mole) of Ia dissolved in 5 ml of MeOH was added dropwise a solution of 0.09 g of $NaBH_4$ in 1 ml of 0.2N NaOH solution. The reaction mixture was cooled to maintain a reaction temperature of 20—25°. After the addition, the mixture was boiled on the water bath to remove the MeOH and then 20 ml of water was added. The basic solution was extracted with two 30 ml portions of ether and the combined organic phase was dried with anhydrous $MgSO_4$. Removal of the ether and recrystallization of the residue from MeOH gave 0.4 g (40%) of a colorless needles, mp 121—122°. *Anal.* Calcd. for $C_7H_4O_2N_2Cl_2$: C, 38.39; H, 1.84; N, 12.79. Found: C, 38.35; H, 1.66; N, 12.53. *m/e* 218 (M^+).

1,2-Bis[2-(4,7-dichlorofuro[2,3-*d*]pyridazinyl)ethylene (X)——Saturated Na_2CO_3 solution (2 ml) was added in a small portions to a solution of 2.1 g (0.004 mole) of phosphonium salt (IX)[1] and 0.8 g (0.004 mole) of Ia in MeOH with stirring at room temperature. The resulting crystalline substance was collected by filtration. Recrystallization from dimethylformamide gave 1.3 g (94%) of a white powder, mp >300°. *Anal.* Calcd. for $C_{14}H_4O_2N_4Cl_4$: C, 41.83; H, 1.00; N, 13.94. Found: C, 41.85; H, 1.06; N, 13.87.

***trans*-2-[2-(2-Pyridyl)vinyl]-4,7-dichlorofuro[2,3-*d*]pyridazine (XI)**——A mixture of 0.22 g (0.001 mole) of Ia, 0.1 g (0.001 mole) of α-picoline and 30 ml of Ac_2O was refluxed for 5 hr. After cooling, the reaction mixture was poured into ice water. The product was filtered off, and recrystallized from AcOEt to give 0.1 g (35%) of colorless needles, mp 216—217°.

2-Furyl-3-[2-(4,7-dichlorofuro[2,3-*d*]pyridazinyl)]acrylic Acid (XII)——A mixture of 2.2 g (0.01 mole) of Ia, 1.7 g (0.01 mole) of potassium furylacetate and 30 ml of Ac_2O was refluxed in an oil-bath at 150—160° for 2 hr, using an air condenser. The contents of the flask were cooled and poured with stirring into ice water. The precipitate was filtered off and washed with water. Recrystallization from AcOEt gave 1.2 g (38%) of a yellow needles, mp 200°. *Anal.* Calcd. for $C_{13}H_6O_4N_2Cl_2$: C, 48.03; H, 1.86; N, 8.62. Found: C, 48.41; H, 2.03; N, 8.54. *m/e* 324 (M^+).

α-Cyano-β-[2-(4,7-dichlorofuro[2,3-*d*]pyridazinyl)]acrylonitrile (XIII)——A mixture of 2.2 g (0.01 mole) of Ia, 0.66 g (0.01 mole) of malononitrile and 50 ml of dry benzene was refluxed for 2 hr. The solvent was removed under reduced pressure and the oily residue was treated with ether. The precipitate was filtered off and recrystallized from benzene to give 2.6 g (98%) of colorless needles, mp 195°. *Anal.* Calcd. for $C_{10}H_2ON_4Cl_2$: C, 45.31; H, 0.76; N, 21.14. Found: C, 45.58; H, 0.91; N, 20.93. *m/e* 264 (M^+).

Ethyl 2-(4,7-Dichlorofuro[2,3-*d*]pyridazinal)malonate (XIV)——A mixture of 2.2 g (0.01 mole) of Ia, 1.6 g (0.01 mole) of diethyl malonate, one drop of piperidine and 20 ml of dry benzene was refluxed for 4 hr. The solvent was removed under reduced pressure and the oily residue was treated with ether. The precipitate was filtered off and recrystallized from MeOH to give 1.6 g (44%) of pale yellow needles, mp 136°. *Anal.* Calcd. for $C_{14}H_{12}O_5N_2Cl_2$: C, 46.82; H, 3.37; N, 7.80. Found: C, 46.73; H, 2.84; N, 8.22. *m/e* 358 (M^+).

Ethyl α-Acetyl-β-[2-(4,7-dichlorofuro[2,3-*d*]pyridazinyl)]acrylate (XV)——This compound was prepared from 2.2 g (0.01 mole) of Ia, 1.3 g (0.01 mole) of ethyl acetoacetate, one drop of piperidine and 20 ml of dry benzene as described for XIV above. The yield of XV, mp 165—167°, was 1.3 g (40%). *Anal.* Calcd. for $C_{13}H_{10}O_4N_2Cl_2$: C, 47.44; H, 3.06; N, 8.51. Found: C, 47.56; H, 2.74; N, 8.47. *m/e* 328 (M^+).