[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Pyridine Derivatives. II. Some Halogen Substituted 2-Pyridoxyacetic Acids[1]

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A number of halogenated 2-pyridoxyacetic acids have been prepared, *via* their ethyl esters, by the reaction of ethyl diazoacetate with the appropriate halogenated 2-pyridones.

A number of halo derivatives of phenoxyacetic acid have attracted considerable interest, both theoretical and practical, because of the marked hormonal activity which they exhibit in higher plants.[2] The study reported here was undertaken with the object of synthesizing some pyridine analogs of these halo acids for plant physiological testing purposes.

The reaction of 2-pyridone with ethyl diazoacetate has been reported to give a mixture of *N*- and *O*-alkylation products; the latter, ethyl 2-pyridoxyacetate, was converted by hydrolysis to 2-pyridoxyacetic acid.[3] This sequence of reactions has been extended to a number of halogenated 2-pyridones. The initially produced pyridoxyacetic esters were, in some cases, purified and analyzed. In other cases, the crude esters were hydrolyzed directly to the crystalline oxyacetic acids. In two cases (V and XI) the esters were converted also to the corresponding amides. The results of these experiments are summarized in Table I.

Of the substituted 2-pyridones employed as starting materials, only 3-methyl-5-chloro-2-pyridone and 3,5-dichloro-6-methyl-2-pyridone have not been described previously. They were obtained by direct chlorination of 3-methyl-2-pyridone and 6-methyl-2-pyridone, respectively, as described further in the experimental section.

The direct chlorination of 2-pyridone itself to 3,5-dichloro-2-pyridone deserves comment. The only recorded observation of this reaction[4] mentions the use of chloroform as solvent: no further details or yields are given. It has been found now, after investigating this chlorination under a variety of conditions, that it proceeds best at room temperature in 20% sulfuric acid, 3,5-dichloro-2-pyridone being obtained in 63% yield. It was found necessary, however, to remove the dichloro derivative by filtration several times during the course of the chlorination, since it is converted slowly by excess chlorine to water soluble decomposition products.

The most interesting of the pyridoxyacetic acids prepared are 3,5-dichloro-2-pyridoxyacetic acid (X) and 3,5,6-trichloro-2-pyridoxyacetic acid (XVI), which are direct pyridine analogs of the well-known herbicides[2] 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid. The plant physiology of these and other compounds described here is under investigation by Dr. R. L. Weintraub[5] and will be described elsewhere.

EXPERIMENTAL[6]

Pyridones. The following pyridines were prepared following methods in the literature: 3-chloro-2-pyridone,[7] 4-chloro-2-pyridone,[8] 5-chloro-2-pyridone,[9] 6-chloro-2-pyridone,[7] 5-bromo-2-pyridone,[10] 3,5-dibromo-2-pyridone,[10] 3,5,6-trichloro-2-pyridone.[11]

3,5-Dichloro-2-pyridone. The more readily prepared sodium 2-pyridoxide[12] gave results identical to those obtained using 2-pyridone itself: A stream of chlorine was passed through a stirred solution of sodium 2-pyridoxide dihydrate (8.0 g.) in a mixture of water (25 ml.) and sulfuric acid (5 ml.) at room temperature. After 6 min. white solid appeared and the solution soon set to a paste of crystals. These were filtered and washed with a little cold water. The combined filtrate and washings were treated with chlorine as before, and additional crystals were removed in three further crops. The combined 3,5-dichloro-2-pyridone, m.p. 170–173°, weighed 6.5 g. (63%). Recrystallization from benzene raised the melting point to 179–181° (reported[13] 178–179°).

3-Methyl-5-chloro-2-pyridone. Gaseous chlorine was passed through a solution of 3-methyl-2-pyridone[14] (12.0 g.) in chloroform (175 ml.) until the odor of chlorine persisted after introduction of the gas was stopped. The resulting paste of pyridone hydrochloride was filtered, washed with chloroform, and suspended in fresh chloroform (200 ml.). The suspension was refluxed gently, when hydrogen chloride

(1) Supported by a contract with the U. S. Army Chemical Corps., Fort Detrick, Frederick, Md.

(2) *E.g.* see: *Plant Regulators in Agriculture*, edited by H. B. Tukey, John Wiley and Sons, Inc., New York, 1954.

(3) G. B. R. deGraaff, J. Maas, and H. J. den Hertog, *Rec. trav. chim.*, **74**, 175 (1955).

(4) M. Dohrn and R. Dirksen, U. S. Patent **1,706,775**; *Chem. Abstr.*, **23**, 2189 (1929).

(5) U. S. Army Biological Warfare Laboratories, Fort Detrick, Md.

(6) Analyses carried out by Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected.

(7) M. P. Cava and N. K. Bhattacharyya, *J. Org. Chem.*, **23**, 1287 (1958).

(8) R. Graf, *Ber.*, **64**, 21 (1931).

(9) A. E. Chichibabin and A. F. Egorov, *J. Russ. Phys.-Chem Soc.*, **60**, 683 (1928).

(10) A. E. Chichibabin and V. S. Tyazhelova, *J. Russ. Phys.-Chem. Soc.*, **50**, 483 (1920).

(11) H. J. den Hertog and J. de Bruyn, *Rec. trav. chim.*, **70**, 182 (1951).

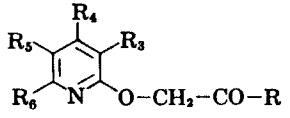
(12) W. T. Caldwell, F. T. Tyson, and L. Lauer, *J. Am. Chem. Soc.*, **66**, 1479 (1944).

(13) W. J. Sell, *J. Chem. Soc.*, **93**, 2001 (1908).

(14) O. A. Seide, *Ber.*, **57**, 1802 (1924).

TABLE I

SUBSTITUTED 2-PYRIDOXYACETIC ACIDS AND DERIVATIVES



Cpd.[a]	R	R_3	R_4	R_5	R_6	Yield, %	B.p. °C.	B.p. Mm.	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found
I	OH	Cl	H	H	H	85[c]	—	—	141–142	$C_7H_6ClNO_3$	44.80	44.83	3.20	3.11	7.46	7.36	18.93	18.85
II	OH	H	Cl	H	H	85[c]	—	—	134–135	$C_7H_6ClNO_3$	44.80	45.08	3.20	2.86	7.46	7.31	18.93	18.98
III	OH	H	H	Cl	H	86[c]	—	—	130–131	$C_7H_6ClNO_3$	44.80	44.96	3.20	3.21	7.46	7.41	18.93	18.89
IV	OH	H	H	H	Cl	87[c]	—	—	126–127	$C_7H_6ClNO_3$	44.80	45.28	3.20	3.19	7.46	7.53	18.93	18.93
V	OEt	H	H	Cl	H	76[b]	107–115	2	32–33	$C_9H_{10}ClNO_3$	50.11	50.03	4.64	4.41	6.50	6.42	16.47	16.49
VI	NH_2	H	H	Cl	H	81[c]	—	—	126–128	$C_7H_7ClN_2O_2$	45.10	45.23	3.75	3.85	15.06	14.95	19.05	19.00
VII	OEt	Cl	H	H	H	36[b]	115–116	2	—	$C_9H_{10}ClNO_3$	50.11	50.14	4.64	4.54	6.50	6.46	16.47	16.31
VIII	OEt	H	Cl	H	H	68[b]	110–112	3	38–39	$C_9H_{10}ClNO_3$	50.11	50.17	4.64	4.66	6.50	6.43	16.47	16.38
IX	OH	H	H	Br	H	71[b]	—	—	134–135	$C_7H_6BrNO_3$	36.20	36.19	2.58	2.69	6.04	5.88	34.50	34.47
X	OH	Cl	H	Cl	H	93[c]	—	—	170–171	$C_7H_5Cl_2NO_3$	37.83	37.62	2.25	2.65	6.30	6.10	31.98	31.55
XI	OEt	Cl	H	Cl	H	74[b]	115–117	2	40–41	$C_9H_9Cl_2NO_3$	43.20	43.73	3.60	3.80	5.06	5.43	28.41	27.62
XII	NH_2	Cl	H	Cl	H	83[c]	—	—	167–168	$C_7H_6Cl_2N_2O_2$	38.00	37.89	2.72	2.48	12.67	12.50	32.12	31.78
XIII	OH	Br	H	Br	H	82[c]	—	—	166–167	$C_7H_5Br_2NO_3$	27.00	27.13	1.61	1.69	4.51	4.55	51.50	51.29
XIV	OEt	Br	H	Br	H	80[b]	122–124	2	134–135	$C_9H_9Br_2NO_3$	31.90	32.19	2.66	2.73	4.14	4.13	47.20	47.02
XV	OH	CH_3	H	Cl	H	65[b]	—	—	131–132	$C_8H_8ClNO_3$	47.90	48.07	3.98	4.15	6.98	7.09	17.65	17.39
XVI	OH	Cl	H	Cl	Cl	17[b]	—	—	149–150	$C_7H_4Cl_3NO_3$	32.70	32.63	1.56	1.51	5.45	5.61	41.50	41.24
XVII	OH	Cl	H	Cl	CH_3	46[b]	—	—	144–145	$C_8H_7Cl_2NO_3$	40.60	40.76	2.97	3.20	5.94	6.03	30.50	30.23

[a] For the acids (R = OH): benzene; for the esters (R = OEt): petroleum ether; for the amides (R = NH_2): ethanol. [b] Based on the pyridone used. [c] Based on the corresponding oxyester.

was evolved gradually and most of the solid dissolved. The filtered solution was concentrated and 30–60° petroleum ether was added to yield the methylchloropyridone as a white solid, m.p. 160–162° (9.0 g.). From the mother liquor was obtained a further 2.5 g. (total yield 11.5 g., 73%). Recrystallization from benzene gave long white needles, m.p. 162–163°.

Anal. Calcd. for C_6H_6ClNO: C, 50.02; H, 4.18; N, 9.77; Cl, 24.42. Found: C, 50.23; H, 4.13; N, 9.83; Cl, 24.37.

3,5-Dichloro-6-methyl-2-pyridone. Gaseous chlorine was passed through a cooled solution of 6-methyl-2-pyridone[15] (18.0 g.) in 2*N* sodium hydroxide (90 ml.). The precipitated solid was filtered, and the mother liquor chlorinated once more to obtain a second crop. The combined solids were dissolved in benzene, the solution dried (sodium sulfate), concentrated, and cooled. The crystalline precipitate (11.5 g., 40%: m.p. 215–218°) was filtered and dried. Recrystallization from benzene raised the melting point to 219–220°.

Anal. Calcd. for $C_6H_5Cl_2NO$: C, 40.50; H, 2.81; N, 7.86; Cl, 39.30. Found: C, 40.93; H, 2.87; N, 8.08; Cl, 38.99.

2-Pyridoxyacetic acids and derivatives. The procedures employed are exemplified by the following preparations in the 3,5-dichloro series: *Ethyl 3,5-dichloro-2-pyridoxyacetate* (XI). A 150 ml. 3-necked flask fitted with a reflux condenser, mechanical stirrer, and dropping funnel, and containing 3,5-dichloro-2-pyridone (8.0 g.), was heated in an oil bath (bath temperature 160–165°). Ethyl diazoacetate (10.0 ml.) was added dropwise to the stirred pyridone over a period of 3 hr. (bath temperature 155–165°). Heating was continued for 1 additional hr. and the hot dark sirup transferred to a Claisen flask. Distillation at 2 mm. yielded the desired ester XI (b.p. 110–120°; 9.0 g., 74%). On redistillation most of the ester boiled at 115–117° (2 mm.), and solidified on cooling. Crystallized from 30–60° petroleum ether, it formed needles, m.p. 40–41°. For analysis see Table I.

Distillation of the pot residue from the diazoacetic ester reaction gave a small amount of viscous liquid (b.p. 160–200° at 2 mm.), solidifying on standing to a semisolid mass. After several crystallizations from chloroform–petroleum ether, the pure *ethyl 3,5-dichloropyridone N-acetate* formed gleaming white flakes, m.p. 105–106°.

Anal. Calcd. for $C_9H_9Cl_2NO_3$: C, 43.20; H, 3.60; N, 5.06; Cl, 28.41. Found: C, 43.36; H, 3.62; N, 5.22; Cl, 28.20.

3,5-Dichloro-2-pyridoxyacetic acid (X). To a solution of the ethyl ester XI (3.0 g.) in ethanol (20 ml.) was added 1.023*N* sodium hydroxide (25 ml.), and the mixture was refluxed for 5.5 hr. The solvent was removed under vacuum and the residue dissolved in the minimal amount of water and neutralized by the addition of the theoretical quantity (22 ml.) of 1.162*N* sulfuric acid. The precipitated oxyacetic acid (2.45 g., 93%) was filtered, washed with a little cold water, and dried. Recrystallization from benzene gave small hard prisms, m.p. 170–171°. For analysis see Table I.

3,5-Dichloro-2-pyridoxyacetamide (XII). A solution of the ethyl ester XI (3.0 g.) in absolute ethanol (65 ml.) was cooled and saturated with gaseous ammonia. After several days in a refrigerator, the amide separated as long colorless needles, m.p. 167–168°, which were filtered and washed with cold ethanol. Concentration of the mother liquor yielded a second crop; the total yield was 2.2 g. (83%). The first crop of amide was directly analytically pure. For analysis see Table I.

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Pyridine Derivatives. III. The Rearrangement of Some Simple 3-Halopyridine-*N*-oxides[1]

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3-Chloropyridine, 3-bromopyridine, and 3-fluoropyridine were oxidized to the corresponding *N*-oxides, which were converted by hot acetic anhydride to haloacetoxypyridines. Hydrolysis of the latter yielded in all three cases the 3-halo-2-pyridones rather than the 5-halo isomers.

When pyridine-*N*-oxide is heated with acetic anhydride rearrangement of the oxygen function into the α-position of the ring occurs with the production of 2-acetoxypyridine.[2] The only simple β-substituted pyridine-*N*-oxide which has been subjected to this rearrangement is the 3-methyl derivative, which gives 3-methyl-2-acetoxypyridine, hydrolyzed by aqueous acid to 3-methyl-2-pyridone.[3] The object of the work reported here was to determine whether 3-halopyridine-*N*-oxides would rearrange in a similar manner to 3-halo-2-acetoxypyridines, or whether the rearrangement would occur para to the halogen atoms to give 5-halo-2-acetoxypyridines.

3-Fluoropyridine (I), 3-chloropyridine (II), and 3-bromopyridine (III) were converted to the corresponding *N*-oxides (IV, V, and VI) by oxidation with peracetic acid. Each *N*-oxide was rearranged by boiling acetic anhydride, and the substituted 2-acetoxypyridines (VII, VIII, and IX) which were formed were hydrolyzed to the corresponding 2-pyridones. In all cases only a single 2-pyridone was obtained, and this proved to be the 3-halo-derivative (X, XI, and XII). 3-Chloro-2-pyridone has been reported previously,[4] but 3-bromo-2-pyridone and 3-fluoro-2-pyridone are new compounds. However, 5-bromo-2-pyridone[5] and 5-

(1) Supported by a contract with the U. S. Army Chemical Corps, Fort Detrick, Frederick, Md.

(2) For a review of pyridine-*N*-oxide reactions, see: A. R. Katritzsky, *Quart. Revs.*, **10**, 395 (1956).

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