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Syntheses of Nitrogen-containing Heterocyclic Compounds. XXIX.[1] An Improved Method for the Preparation of 10*H*-Pyrido[3,2-*b*]-[1,4]benzoxazine (1-Azaphenoxazine)[2]

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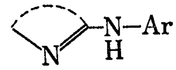
Syntheses of 10*H*-pyrido[3,2-*b*][1,4] and 5*H*-pyrido[3,4-*b*][1,4]benzoxazine (**1** and **3**) were carried out by the cyclization reaction of 2- and 4-(2′-hydroxyanilino)-3-nitropyridines (**7** and **9**) in dimethylformamide in the presence of sodium hydroxide. This method is an improvement over the past reports that this kind of anilino compounds are difficult to undergo intramolecular cyclization because they have an intramolecular hydrogen bonding properties. 3-Substituted (methyl, chloro, bromo, nitro), 7-nitro, and 8-methyl derivatives of 10*H*-pyrido[3,2-*b*][1,4]benzoxazine (**1a**—**1f**) were synthesized in a high yield by the application of this method. The anilino compound was obtained by the selective condensation of 2-chloro-3-nitro-5-substituted pyridine and *o*-aminophenol in ethanol in the presence of copper and sodium hydroxide. However, 5*H*-pyrido[2,3-*b*][1,4]benzoxazine (**4**) was not obtained from 3-(2′-nitroanilino)-2-pyridone (**10**) in this sodium hydroxide-dimethylformamide system, while 5*H*-pyrido[2,3-*b*][1,4] and 10*H*-pyrido[4,3-*b*][1,4]benzoxazine (**4** and **2**) were synthesized by the cyclization of 2- and 4-(2′-bromophenoxy)-3-(N-formylamino)pyridines (**13** and **17**), respectively, in xylene in the presence of copper and potassium carbonate.

Keywords——10*H*-pyrido[3,2-*b*][1,4]benzoxazine deriv.; improved synthetic method; base-catalyzed intramolecular cyclization; 2-(2′-hydroxyanilino)-3-nitropyridine deriv.; Ullmann reaction

We have been studying the chemical nature of compounds possessing an anilino group in the α-position of the nitrogen-containing heterocycle, already reported on those in pyridine and quinoline series.[4] In order to develop the observation gained to date, we examined synthesis and reactivity of 1-azaphenoxazines having  as a functional group in its partial structure, and the present report is concerned with an improved method for the synthesis of 1-azaphenoxazine and its related compounds.

Four isomers are possible for monoazaphenoxazine but, with the exception of 5*H*-pyrido-[3,4-*b*][1,4]benzoxazine (3-azaphenoxazine),[5] the parent ring of 1-, 2-, and 4-azaphenoxazines has not been synthesized as yet. Of these, 1-azaphenoxazine (**1**) was synthesized by the method (route 1) indicated in Chart 1, with reference to the literature of Takahashi and Yoneda,[6] and of Clarke.[5] Its yield was *ca.* 15% through 6 steps. This synthetic method requires N-benzyl-*o*-aminophenol as an intermediate, and its condensation product (**5**) with 2-chloro-3-nitropyridine and the cyclization product (**6**) could not be obtained in a high yield.

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1) Part XXVIII: Y. Hamada, K. Morishita, and M. Hirota, *Chem. Pharm. Bull.* (Tokyo), **26**, 350 (1978).

2) A part of this work was reported at the Tokai Local meeting of the Pharmaceutical Society of Japan, Shizuoka, February, 1974.

3) Location: *15-Yagoto-Urayama, Tenpaku-ku, Nagoya 468, Japan.*

4) *a*) T. Takahashi, Y. Hamada, and Y. Ito, *Chem. Pharm. Bull.* (Tokyo), **17**, 2250 (1969); Y. Hamada, Y. Ito, and M. Hirota, *ibid.*, **18**, 2095 (1970); T. Mizuno, M. Hirota, Y. Hamada, and Y. Ito, *Tetrahedron*, **27**, 6011 (1971); *b*) Y. Ito, Y. Hamada, and M. Hirota, *Chem. Pharm. Bull.* (Tokyo), **20**, 2678 (1972); *c*) Y. Takahashi, S. Otsuka, M. Hirota, Y. Ito, and Y. Hamada, *Bull. Chem. Soc. Jpn.*, **49**, 2770 (1976).

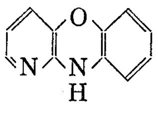
5) F.H. Clarke, U.S. Patent, 3118884 (1964) [*C.A.*, **60**, 10696 (1964)].

6) T. Takahashi and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **6**, 378 (1958).

In order to improve the yield of the objective products, condensation of N-methyl-*o*-aminophenol and 2-chloro-3-nitropyridine was carried out demethylation of 10-methyl-1-azaphenoxazine was found to be difficult.[6)]

An attempt was therefore made to find a more simple method of synthesis because of a necessity to obtain a large amount of 1-azaphenoxazines as a material for examination of their reactivity. The first attempt was made to obtain **1** directly by the cyclization of 2-(2′-hydroxyanilino)-3-nitropyridine (**7**) but there is already a report[7)] that intramolecular cyclization of 2-(2′-hydroxyanilino)-3,5-dinitropyridine is stereochemically difficult with potassium hydroxide in ethanol because it has an intramolecular hydrogen bonding properties.

On the other hand, we have already found that the anilino group in α-position of pyridine has an electron-donating properties against a hetero-ring in weakly acidic solvent.[4b)] If the report of Musso[8)] for the synthesis of 3-nitrophenoxazine from 2,4-dinitro-2′-hydroxydiphenylamine were utilized, intramolecular cyclization of **7** with a strong base in a polar aprotic solvent would become advantageous. After various examinations, **7** was cyclized with sodium hydroxide in dimethylformamide, and an improved method (route 2) for the synthesis of **1** was established (Chart 1). Further, this method provides a new selective and satisfactory preparation of **7** undescdribed in the past literature and its related compounds, from *o*-aminophenols and 2-chloro-3-nitropyridines.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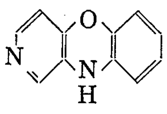
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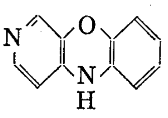
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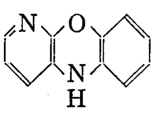
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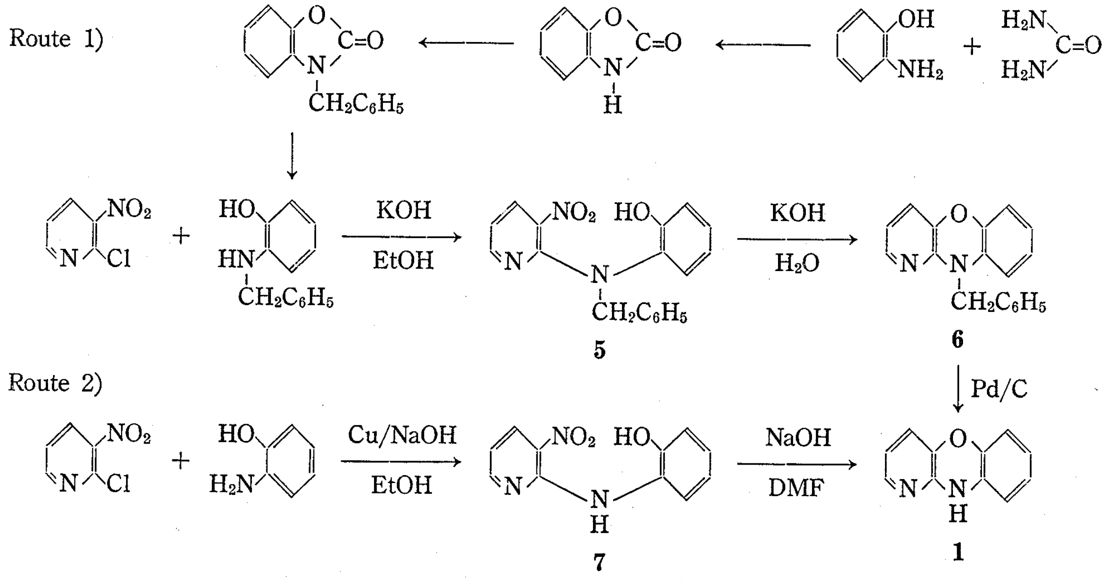


Chart 1

Synthesis of 2-(2′-Hydroxyanilino)-3-nitropyridine (7) and Its Derivatives

Refluxing of 2-chloro-3-nitropyridine and *o*-aminophenol in ethanol in the presence of potassium hydroxide gave the objective **7** together with dipyridino compound (**8**) (Table I). Infrared (IR) spectrum of **7** has no absorption band for a primary amine and aryl ether, as shown in comparison with that of other compounds in Table III, supporting the anilino structure.

[7)] *a*) T. Takahashi and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **6**, 46 (1958); *b*) G.S. Turpin, *J. Chem. Soc.*, **59**, 722 (1891); O.L. Brady and C. Waller, *ibid.*, 1218 (1930).

[8)] H. Musso, *Chem. Ber.*, **96**, 1927 (1963).

Table I. Reactions of 2-Chloro-3-nitropyridine (I) and *o*-Aminophenol (II) with Various Reagents

I/II (Equivalent)	Reagent	EtOH (Volume)	Yield (%) of product		
			7	**8**	Recovery (I)
1:1.2	KOH	1	50	20	10
1:1.2	Cu/Na_2CO_3	1	35	Trace	48
1:2	Cu/KOH	2	70	5	Trace
1:2	Cu/NaOH	2	82	—	Trace

8:

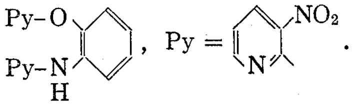
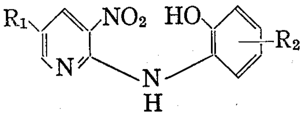


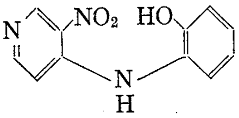
Table II. Anilino Derivatives (**7**) from 5-Substituted 2-Chloro-3-nitropyridine and *o*-Aminophenols with Copper and Sodium Hydroxide in EtOH



Compd. No.	R_1	R_2	Yield (%)	mp (°C)	Formula	Analysis (%)					
						Calcd.			Found		
						C	H	N	C	H	N
7	H	H	82	131—132	$C_{11}H_9N_3O_3$	57.14	3.92	18.18	57.41	4.15	17.89
7a	CH_3	H	60	162—163	$C_{12}H_{11}N_3O_3$	58.77	4.52	17.14	58.46	4.27	16.91
7b	Cl	H	73	188—191	$C_{11}H_8ClN_3O_3$	49.73	3.04	15.82	49.45	3.37	16.11
7c	Br	H	75	193—195	$C_{11}H_8BrN_3O_3$	42.60	2.60	13.55	42.35	2.51	13.81
7d	NO_2	H	74	240—241[a]	$C_{11}H_8N_4O_5$	47.83	2.92	20.29	48.05	3.13	19.98
7e	H	4'-NO_2	63	229—231	$C_{11}H_8N_4O_5$	47.83	2.92	20.29	47.69	2.79	20.04
7f	H	5'-CH_3	79	136—138	$C_{12}H_{11}N_3O_3$	58.77	4.52	17.14	58.91	4.64	17.51

[a] Lit.[7a] mp 230—232° (dec.).

Table III. Infrared Spectral Data



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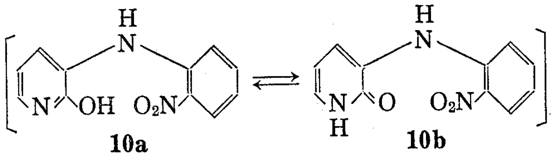
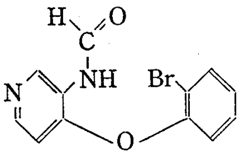


10a **10b**



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Compound No.	KBr ν_{max} cm^{-1}			
	OH	NH	Amido C=O	C–O–C
7	3460	3290	—	—
9	3400	3320	—	—
10	3420	3320	1650	—
13[a]	—	3400	1690	1240
17[a]	—	3400	1695	1230

[a] $CHCl_3$.

The mass spectrum of **8** indicates *m/e* 353 (M^+), and reaction of **8** with piperidine resulted in its decomposition into an oily substance and reddish brown crystals of mp 131—132°. The oily product was identified with the product of a reaction of 2-chloro-3-nitropyridine and piperidine, and the reddish brown crystals with **7**, from the agreement of their IR spectra.

However, separation of **8** from the objective substance was not easy and, since the relative amount of **8** increased with larger amount of the reactants, this reaction was improved in the following way. The Ullmann reaction often gives a good result in the synthesis of anilino compounds[9] and, therefore, this reaction was carried out under various conditions indicated in Table I. It was thereby found that the use of activated copper[10] in a catalytic amount and sodium hydroxide gave a result in hardly any formation of **8**. The reaction with this copper-sodium hydroxide system did not produce aryloxy compound and the other substituted anilino compound was obtained in a high yield even when a halogen is present in 5-position of the pyridine ring, this position being not substituted with the anilino group (Table II). This reaction was also found to be applicable for the synthesis in a large quantity. The active copper in this reaction is considered to protect the hydroxyl group in *o*-aminophenol, and to work effectively for nucleophilic attack of the amino group in 2-position of the pyridine ring and for liberation of chlorine.

Synthesis of 1-Azaphenoxazine (1) and Its Derivatives

For the cyclization reaction of **7**, a use of anhydrous dimethylformamide and sodium hydroxide pellets under nitrogen atmosphere seemed to be essential as shown in Table IV. Even in the substituted derivatives of **7**, this reaction gave the objective compound (**1a**—**1f**) in a high yield (Table V).

The chemical composition of **1** corresponded to $C_{11}H_8N_2O$. Its IR spectrum showed disappearance of absorption bands at 3460 cm^{-1} for a hydroxyl and at 1360 cm^{-1} for the stretching vibration of the NO_2 group, and a new appearance of an absorption band (1280 cm^{-1}) due to C–O–C bond. In the nuclear magnetic resonance (NMR) spectrum of **1**, the signal of C(3)–H on the pyridine ring appeared as double doublets (J=5 and 8 Hz) at δ 6.55 ppm. Since these spectral data agreed with those of the authentic sample synthesized by another route (route 1), **1** was determined as 1-azaphenoxazine. Compounds **1a** to **1f** were identified by comparison of maximum absorption wavelength and absorbance in their ultraviolet (UV) spectra with those of **1** as shown in Table VI.

TABLE IV. Syntheses of X-Azaphenoxazine (X=1, 2, 3, and 4)

Substrate	Base	Solvent	Yield (%) of product				
			1	2	3	4	Recovery
7	K-Salt	DMSO	10	—	—	—	90
7	NaH	DMF	5	—	—	—	95
7	NaH	Diglyme	Nil	—	—	—	100
7	NaOH	DMF	82	—	—	—	—
9	NaOH	DMF	—	—	82	—	—
10	KOH	DMSO	—	—	—	Nil	100
13	Cu/K_2CO_3	Xylene	—	—	—	29[a]	—
17	Cu/K_2CO_3	Xylene	—	66	—	—	—

a) Total yield of two steps (see Chart 2).

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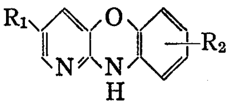
9) R.M. Acheson, "Heterocyclic Compounds," Vol. 9, John Wiley and Sons, Inc., New York, 1973, pp. 161—164.

10) R.Q. Brewster and T. Groening, "Organic Syntheses," Coll. Vol. II, ed. by A.H. Blatt, John Wiley, and Sons, Inc., New York, 1943, p. 446.

Table V. 10*H*-Pyrido[3,2-*b*][1,4]benzoxazine (1-Azaphenoxazine (**1**)) Derivatives



Compd. No.	R_1	R_2	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	H	H	82	209—210	$C_{11}H_8N_2O$	71.72	4.38	15.21	71.63	4.26	15.13
1a	CH_3	H	69	230—234	$C_{12}H_{10}N_2O$	72.71	5.09	14.13	72.58	4.92	14.01
1b	Cl	H	70	238—241	$C_{11}H_7ClN_2O$	60.43	3.23	12.81	60.15	3.01	12.63
1c	Br	H	75	239—242	$C_{11}H_7BrN_2O$	50.22	2.68	10.65	49.98	2.39	10.91
1d	NO_2	H	89	275—276	$C_{11}H_7N_3O_3$	57.64	3.08	18.34	58.02	3.22	18.51
1e	H	7-NO_2	60	>300	$C_{11}H_7N_3O_3$	57.64	3.08	18.34	57.29	3.16	18.09
1f	H	8-CH_3	75	223—225	$C_{12}H_{10}N_2O$	72.71	5.09	14.13	72.96	5.19	13.85

Table VI. Infrared and Ultraviolet Spectral Data

Compd. No.	IR ν_{max}^{KBr} cm^{-1} NH	C–O–C	UV λ_{max}^{MeOH} nm (log ε)	
1	3200	1280	230(4.29)	339(3.69)
1a	3200	1290	230(4.53)	343(3.98)
1b	3200	1270	232(4.66)	350(4.05)
1c	3200	1270	232(4.71)	349(4.10)
1d[a]	3180	1280	—	—
1e[a]	3180	1290	—	—
1f	3200	1250	231(4.45)	338(3.91)
2[b]	3220	1300	238(4.57)	312(3.88)
3[b]	3220	1260	241(4.54)	319(3.70)
4[b]	3240	1295	230(4.41)	323(3.92)

a) The NMR spectral data are shown in experimental section.
b) These spectra were measured in EtOH solution.

As shown in Table IV, when the phenoxide of **7** prepared beforehand was heated in dimethyl sulfoxide or when **7** was added to a mixture of dimethylformamide and sodium hydride and heated, a crystalline salt precipitated out and the starting material was almost wholly recovered from its neutral solution. Thus, the yield of the objective was very low when the alkali concentration was high from the beginning of the reaction. The compound **7** and its related compounds tend easily to form a crystalline alkali salt in a highly polar and alkaline solvent. This may be the reason why a cyclization product is difficult to obtain.

In the past, intramolecular hydrogen bonding was given as the reason for the difficulty in the cyclization of this kind of anilino compounds. In order to examine this reason, we are currently studying the structure and stability of the salt formed, and the formation mechanism of the cyclized product.

Syntheses of X-Azaphenoxazine (X=2(2), 3(3), and 4(4))

3-Azaphenoxazine (**3**) has already been synthesized by route 1 by Clarke[5] but we synthesized it by the improved method employed for that of **1**. In this case, 4-chloro-3-nitropyridine and *o*-aminophenol were condensed in ethanol in the presence of sodium acetate, and the product was cyclized with sodium hydroxide in dimethylformamide. Structure of the anilino compound (**9**) was proved from its mass spectrum and by comparison of its IR spectral data with those of the other compounds as shown in Table III.

The cyclized compound (3) gave elemental analytical values corresponding to $C_{11}H_8N_2O$. Its structure was confirmed from its IR spectrum (a new appearance of absorption band of C–O–C at 1260 cm^{-1}), an appearance of C(3)–H signal on the pyridine ring as a doublet ($J=$ 5 Hz) at δ 7.58 ppm in its NMR spectrum, and agreement of those spectral data with those of the authentic sample synthesized by another route (route 1).[5]

5*H*-Pyrido[2,3-*b*][1,4]benzoxazine (4-azaphenoxazine (**4**)) was not obtained from the anilino compound (**10**) prepared from the reaction of 3-amino-2-hydroxypyridine and *o*-nitrochlorobenzene due to the failure to undergo cyclization with potassium hydroxide in dimethyl sulfoxide and the starting material was recovered. In this case, as shown in Table III, contribution of the pyridone isomer (**10b**) may be considerable. Takahashi and Yoneda[7a] have obtained 3-chloro-6,8-dinitro-5*H*-pyrido[2,3-*b*][1,4]benzoxazine (2-chloro-7,8-dinitro-4-azaphenoxazine) in a high yield by refluxing 5-chloro-3-nitro-2-pyridone and *s*-trinitroanisole in methanol in the presence of potassium hydroxide. Therefore, it seems that the failure of **10** to undergo cyclization is due more to the weakly intramolecular nucleophilic property of **10**, when compared to the intermediate of 5-chloro-3-(2′,4′,6′-trinitroanilino)-2-pyridone described above.

4-Azaphenoxazine (**4**) was synthesized by the reaction shown in Chart 2, following the method for synthesis of phenoxazine by Olmsted, *et al.*[11] In this case, 2-chloro-3-nitropyridine and *o*-bromophenol reacted in ethanol in the presence of potassium hydroxide, to give the 2′-bromophenoxy compound (**11**). The compound (**11**) was reduced with activated iron in acetic acid to give the amino compound (**12**), which was heated formic acid to yield the formamide compound (**13**). As shown in Table III, the structure of **13** was supported from its IR spectrum. The compound (**13**) was then heated with active copper and anhyd. potassium carbonate in xylene to form the cyclized product (**14**) which was deformylated in dil.

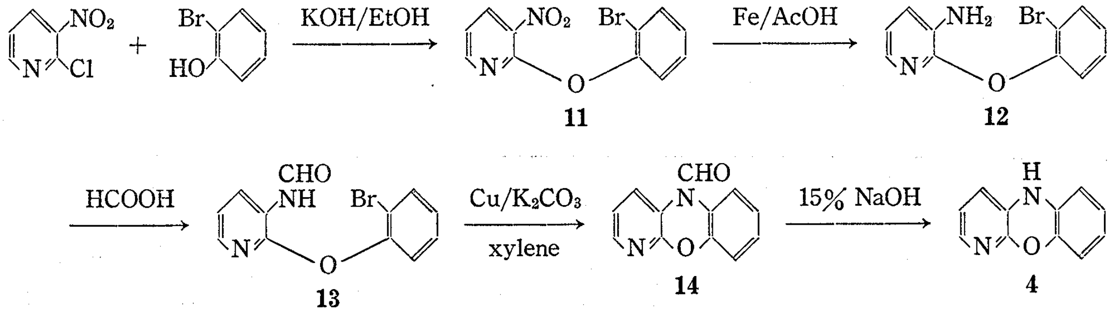


Chart 2

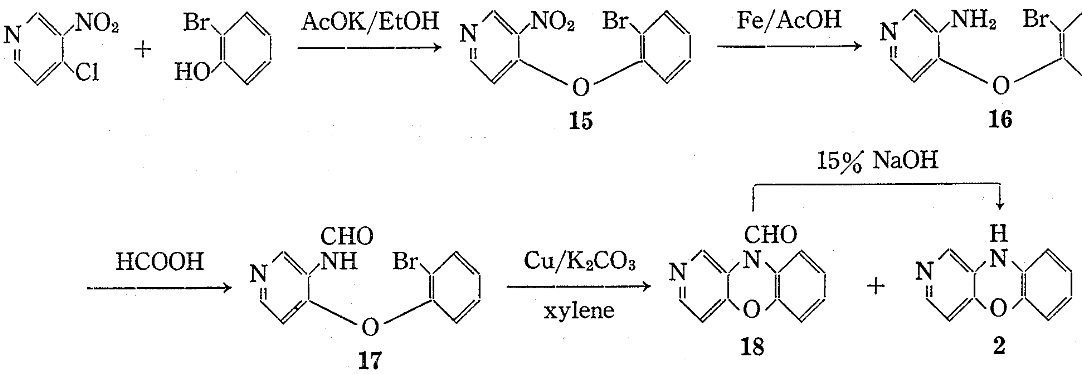


Chart 3

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[11] M.P. Olmsted, P.N. Craig, and J.J. Lafferty, *J. Org. Chem.*, **26**, 1901 (1961).

sodium hydroxide solution to yield the objective 4-azaphenoxazine (**4**). Structure of **4** was confirmed from its UV spectrum and by comparison with other compounds as shown in Table VI. 10*H*-Pyrido[4,3-*b*][1,4]benzoxazine (2-azaphenoxazine (**2**)) was synthesized by the same method as for **4**, using 4-chloro-3-nitropyridine as shown in Chart 3.

These experimental results show that, among the four isomers of monoazaphenoxazine, 1- and 3-azaphenoxazine can be synthesized by the greatly improved reaction procedure and with a satisfactory yield. It is believed that this method offers a useful synthetic route for azaphenoxazine derivatives from anilinopyridine derivatives with intramolecular hydrogen bonding properties.

Experimental

All melting points were measured on a Yanagimoto Melting Point Apparatus and are uncorrected. Unless otherwise stated, IR spectra were measured with discs in potassium bromide, using a JASCO Model IR-S spectrophotometer. NMR spectra were measured in deuteriodimethyl sulfoxide solutions on a Varian A-60 Spectrometer with tetramethylsilane as an internal standard. Mass spectra were taken on a Hitachi Mass Spectrometer Model RMU-6D. UV spectra were determined with a Shimadzu Model UV-200 Spectrophotometer.

2-(N-Benzyl-2′-hydroxyanilino)-3-nitropyridine (5)——To a solution of N-benzyl-*o*-aminophenol[5] (1.4 g) and KOH (0.4 g) in 20 ml of EtOH was added 2-chloro-3-nitropyridine (1.1 g) and the mixture was refluxed for 30 min. When cooled, the crude reddish crystals which had formed were collected by filtration and recrystallized from EtOH to **5** (1.1 g, 52%) as reddish yellow needles, mp 115—116°. IR $\nu_{\max}$ cm^{-1}: 3400 (OH), 1330 (NO_2). MS *m/e*: 321 (M^+), 274, 183. *Anal.* Calcd. for $C_{18}H_{10}N_3O_3$: C, 68.35; H, 3.19; N, 13.28. Found: C, 68.10; H, 3.08; N, 13.13.

10-Benzyl-10*H*-pyrido[3,2-*b*][1,4]benzoxazine (6)——A solution of **5** (0.5 g) in 10 ml of 10% KOH was heated on a steam bath for 1 hr and worked up as above. Recrystallization from EtOH afforded **6** (0.25 g, 58.5%) as colorless needles, mp 116—117°. IR $\nu_{\max}$ cm^{-1}: 1230 (C–O–C). MS *m/e*: 274 (M^+), 180 ($M-PhCH_2$). *Anal.* Calcd. for $C_{18}H_9N_2O$: C, 80.29; H, 3.37; N, 10.40. Found: C, 80.15; H, 3.57; N, 10.63.

10*H*-Pyrido[3,2-*b*][1,4]benzoxazine (1)——Method A: A solution of **6** (0.3 g) and conc. HCl (2 drops) in 50 ml of EtOH was hydrogenated over 5% Pd/C (0.15 g) at room temperature and atmospheric pressure. Absorption of H_2 (70 ml) was completed in 1 hr. After removal of the catalyst by filtration, the filtrate was concentrated to dryness *in vacuo*, and the residue was chromatographed over silica gel with $CHCl_3$ to give **1** (0.16 g, 80%) as colorless needles, mp 209—210°. IR $\nu_{\max}$ cm^{-1}: 3200 (NH), 1280 (C–O–C). NMR δ: 6.55 (H, double doublets, $J=8.0$ Hz and $J=5.0$ Hz, C_3–H), 6.6—6.8 (4H, multiplet, benzene ring protons), 6.92 (H, double doublets, $J=8.0$ Hz and $J=2.0$ Hz, C_4–H), 7.58 (H, double doublets, $J=5.0$ Hz and $J=2.0$ Hz, C_2–H), 8.95 (H, broad, NH). MS *m/e*: 184 (M^+). *Anal.* Calcd. for $C_{11}H_8N_2O$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.58; H, 4.19; N, 15.09.

Method B: To a solution of **7** (2.0 g) in 40 ml of DMF (anhydrous) was added NaOH pellets (0.9 g) at 100° under nitrogen atmosphere and the temperature was raised to 120°. The mixture was heated for 2 hr and condensed under reduced pressure to give a residue, which was poured into ice water. The aqueous solution was neutralized with dil. HCl, the liberated solid was collected by filtration, washed with H_2O, and dried. Recrystallization from C_6H_6 gave **1** (1.3 g, 82%) as pale yellow needles, mp 209—210°.

This product was identified by mixed melting test and comparison of IR spectrum with an authentic sample obtained by method A.

2-(2′-Hydroxyanilino)-3-nitropyridine (7)——Method 1: To a solution of *o*-aminophenol (1.32 g) and KOH (1.32 g) in 20 ml of EtOH was added 2-chloro-3-nitropyridine (3.0 g) and the mixture was refluxed for 1 hr and cooled. After addition of 20 ml of H_2O, the precipitated solid was collected by filtration and dried, and separated by chromatography over silica gel with $CHCl_3$. The first eluted product **8** (0.7 g, 10%), yellowish brown needles, mp 153—154°, was found to be 2-[2′-(3″-nitro-2″-pyridoxy)anilino]-3-nitropyridine, which was identified by the reaction of **8** with piperidine. IR $\nu_{\max}$ cm^{-1}: 3290 (NH), 1345 (NO_2), 1230 (C–O–C). MS *m/e*: 353 (M^+), 214 ($M-O_2NC_5H_3O$), 168 ($214-NO_2$).

The second product was recrystallized from benzene to give **7** (3.3 g, 76%) as reddish needles, mp 131—132°. IR $\nu_{\max}$ cm^{-1}: 3460 (OH), 3280 (NH), 1360 (NO_2). MS *m/e*: 231 (M^+), 214 ($M-OH$), 168 ($214-NO_2$).

Method 2: A mixture of 2-chloro-3-nitropyridine (10 g), *o*-aminophenol (14 g), Cu powder (0.5 g), and NaOH (5 g) in 500 ml of EtOH was refluxed for 2 hr, and condensed under reduced pressure to give an oily residue, to which H_2O was added. The aqueous solution was acidified (*ca.* pH 5) with dil. HCl, the separated solid was collected by filtration, washed with H_2O, and dried. The crude product (**7**) was dissolved in a mixture of C_6H_6 and C_6H_{12} (6: 4) to give a crystalline substance, which was purified by passing through silica gel in C_6H_6, affording **7** (12 g, 82%) as reddish needles, mp 131—132°. This product was identified by mixed melting test and comparison of IR spectrum with an authentic sample obtained by the method 1.

Reaction of 8 with Piperidine——A mixture of **8** (0.3 g) and piperidine (0.2 g) was heated on a steam bath for 1 hr, cooled, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$, and evaporated to give a reddish residue (oil). The residue was dissolved in $CHCl_3$ and chromatographed over silica gel with $CHCl_3$. The first eluted product (0.17 g, 95%) as a reddish oil, was found to be 3-nitro-2-piperidinopyridine, which was identified by IR spectra with an authentic sample obtained by the reaction of 2-chloro-3-nitropyridine and piperidine with KOH and EtOH. IR $\nu_{\max}^{\text{neat}}$ cm^{-1}: 2920, 2860 (CH_2), 1330 (NO_2). MS *m/e*: 207 (M^+).

The second product was recrystallized from benzene to give **7** (0.19 g, 95%), mp 131—132°, which was identified by IR spectra with an authentic 2-(2′-hydroxyanilino)-3-nitropyridine.

Syntheses of 2-(2′-Hydroxyanilino)-3-nitro-5-substituted (methyl, chloro, bromo, and nitro) pyridine (7a—7d), 2-(2′-Hydroxy-4′-nitroanilino)-3-nitropyridine (7e) and 2-(2′-Hydroxy-5′-methylanilino)-3-nitropyridine (7f)——From 2-chloro-3-nitropyridine or 2-chloro-3-nitro-5-substituted pyridine (1.0 equivalent), *o*-aminophenols (2.0 equivalents), Cu powder and NaOH in EtOH, compound (**7a**—**7f**) were obtained according to the procedure (method 2) as described for **7**.

The results are shown in Table II.

4-(2′-Hydroxyanilino)-3-nitropyridine (9)——4-Chloro-3-nitropyridine (1.0 g), *o*-aminophenol (0.83 g), and AcONa (1.25 g) were dissolved in 20 ml of EtOH under ice chilling. The mixture was heated on a steam bath for 30 min and cooled to room temperature. After addition of 20 ml of H_2O, the precipitate was collected by filtration, washed with H_2O, and dried. Recrystallization from EtOH gave **9** (1.29 g, 82%) as yellowish orange needles, mp 243—244°. IR $\nu_{\max}$ cm^{-1}: 3400 (OH), 3320 (NH), 1340 (NO_2). MS *m/e*: 231 (M^+), 214 (M−OH), 168 (214−NO_2). *Anal.* Calcd. for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.18. Found: C, 56.93; H, 4.05; N, 18.41.

5*H*-Pyrido[3,4-*b*][1,4]benzoxazine (3)——To a solution of **9** (2.0 g) in 40 ml of DMF (anhydrous) was added NaOH pellets (0.9 g) at 100° under nitrogen atmosphere and the temperature was raised to 120°. The mixture was heated for 3 hr and treated as described for **1** by method B. Yield of 1.3 g (82%) of **3** as colorless needles, mp 245—246°. IR $\nu_{\max}$ cm^{-1}: 3220 (NH), 1260 (C–O–C). NMR δ: 6.45 (H, doublet, J=5.0 Hz, C_4–H), 6.5—6.7 (4H, multiplet, benzene ring protons), 7.57 (H, singlet, C_1–H), 7.58 (H, doublet, J=5.0 Hz, C_3–H), 8.78 (H, broad, NH). MS *m/e*: 184 (M^+). *Anal.* Calcd. for $C_{11}H_8N_2O$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.56; H, 4.21; N, 15.03.

Syntheses of 3-Substituted (methyl, chloro, bromo, and nitro)-10*H*-pyrido[3,2-*b*][1,4]benzoxazine (1a—1d), 7-Nitro-10*H*-pyrido[3,2-*b*][1,4]benzoxazine (1e), and 8-Methyl-10*H*-pyrido[3,2-*b*][1,4]benzoxazine (1f)——From **7a**—**7f** (2.0 g) and NaOH (0.9 g) in DMF, compounds (**1a**—**1f**) were obtained according to the procedure (method B) as described for **1**.

The results are shown in Table V.

1d; NMR δ: 6.65—6.8 (4H, multiplet, benzene ring protons), 7.4 (H, doublet, J=2.0 Hz, C_4–H), 8.4 (H, doublet, J=2.0 Hz, C_2–H).

1e; NMR (DMSO-d_6) δ: 6.3 (H, doublet, J=9.0 Hz, C_9–H), 6.6 (H, double doublets, J=8.0 Hz and J=5.0 Hz, C_3–H), 6.8 (H, double doublets, J=8.0 Hz and J=1.5 Hz, C_4–H), 7.36 (H, doublet, J=2.0 Hz, C_6–H), 7.5 (H, double doublets, J=9.0 Hz and J=2.0 Hz, C_8–H), 7.6 (H, double doublets, J=5.0 Hz and J=1.5 Hz, C_2–H).[12]

2-Hydroxy-3-(2′-nitroanilino)pyridine (10)——A mixture of 3-amino-2-hydroxypyridine (1.3 g), *o*-chloronitrobenzene (1.9 g), KOH (0.6 g), Cu powder (0.1 g), and pyridine (10 drops) was heated at 120° for 3 hr. When cooled, the reaction mixture was extracted with $CHCl_3$, the extract was evaporated under reduced pressure, and the residue was separated by chromatography over silica gel. The product which was eluted with $CHCl_3$–acetone (8: 2) was recrystallized from EtOH to give **10** (1.6 g, 68%) as reddish orange needles, mp 260—262°. IR $\nu_{\max}$ cm^{-1}: 3420 (OH), 3320 (NH), 1650 (C=O), 1340 (NO_2). MS *m/e*: 231 (M^+), 185 (M−NO_2). *Anal.* Calcd. for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.18. Found: C, 57.36; H, 4.18; N, 18.32.

2-(2′-Bromophenoxy)-3-nitropyridine (11)——To a solution of *o*-bromophenol (1.4 g) and KOH (0.5 g) in 10 ml of EtOH was added 2-chloro-3-nitropyridine (1.0 g) with heating on a steam bath and the mixture was refluxing for 1 hr. When cooled, the mixture was diluted with 10 ml of H_2O. The crystals formed were collected by filtration, washed with H_2O, and dried. Recrystallization from C_6H_{12} gave **11** (1.6 g, 86%) as colorless needles, mp 69—70°. IR $\nu_{\max}$ cm^{-1}: 1345 (NO_2), 1230 (C–O–C). MS *m/e*: 296 (M+2), 294 (M^+), 215 (M−Br), 169 (215−NO_2). *Anal.* Calcd. for $C_{11}H_9N_3O_3$: C, 57.14; H, 3.92; N, 18.18. Found: C, 57.36; H, 4.18; N, 18.32.

3-Amino-2-(2′-bromophenoxy)pyridine (12)——A mixture of **11** (2.0 g), H_2O (16 ml), and Fe powder (3.0 g) was heated at reflux, and glacial AcOH (6.4 g) was added over a period of 3 hr. The reaction mixture was refluxed for 1 hr and cooled in an ice bath. The precipitated solid was by filtration and the filtrate was concentrated to dryness on a steam bath. The precipitated solid and the residue were combined and refluxed with benzene. After removal of the catalyst by filtration, the filtrate was evaporated to dryness *in vacuo* and the crude crystals were recrystallized from C_6H_{12} to afford **12** (1.6 g, 90%) as colorless needles, mp 97—

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[12] This spectrum was obtained using a JNM-PS-100 (100 Hz) spectrometer.

98°. IR ν_{max} cm^{-1}: 3410, 3300 (NH_2), 1220 (C–O–C). MS *m/e*: 266 (M+2), 264 (M^+), 185 (M−Br). *Anal.* Calcd. for $C_{11}H_9BrN_2O$: C, 49.84; H, 3.42; N, 10.57. Found: C, 50.12; H, 3.71; N, 10.29.

2-(2′-Bromophenoxy)-3-(N-formylamino)pyridine (13)——A solution of **12** (1.0 g) in 5 ml of 98% formic acid was heated gradually in an oil bath for 1 hr. The temperature was raised to 120°. Water was distilled off and removed by the water separator attached to the reflux condenser. The last trace of water and formic acid were removed under reduced pressure. The resulting oil was dissolved in $CHCl_3$, the solution was washed with H_2O, dried over $MgSO_4$, and evaporated to give a violet residue (oil). Recrystallization from C_6H_{12} afforded **13** (0.9 g, 82%) as colorless needles, mp 93—95°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1690 (C=O), 1240 (C–O–C). MS *m/e*: 294 (M+2), 292 (M^+), 213 (M−Br). *Anal.* Calcd. for $C_{12}H_9BrN_2O_2$: C, 49.17; H, 3.95; N, 9.56. Found: C, 49.01; H, 3.82; N, 9.46.

5-Formyl-5*H*-pyrido[2,3-*b*][1,4]benzoxazine (14)——A mixture of **13** (0.3 g), anhyd. K_2CO_3 (0.5 g), active Cu powder (0.05 g), and 5 ml of xylene was heated at 150—155° for 12 hr. When cooled, xylene was evaporated under reduced pressure. The resulting mixture was extracted with $CHCl_3$ and the extract was evaporated to dryness *in vacuo*. The residue was purified by passing through silica gel with $CHCl_3$ affording **14** (0.2 g, 95%) as colorless needles, mp 162—163°. IR ν_{max} cm^{-1}: 1685 (C=O), 1250 (C–O–C). MS *m/e*: 212 (M^+), 183 (M–CHO). *Anal.* Calcd. for $C_{11}H_8N_2O$: C, 67.92; H, 3.80; N, 13.20. Found: C, 68.00; H, 3.44; N, 12.79.

5*H*-Pyrido[2,3-*b*][1,4]benzoxazine (4)——A mixture of **14** (0.2 g) and 5 ml of 15% NaOH was heated on a steam bath for 1 hr and diluted with H_2O. The precipitate was collected by filtration, washed H_2O, and dried. Recrystallization from benzene gave **4** (0.05 g, 30%) as colorless platelets, mp 219—221°. IR ν_{max} cm^{-1}: 3240 (NH), 1295 (C–O–C). MS *m/e*: 184 (M^+). *Anal.* Calcd. for $C_{11}H_8N_2O$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.58; H, 4.15; N, 14.97.

4-(2′-Bromophenoxy)-3-nitropyridine (15)——To a solution of 4-chloro-3-nitropyridine (2.0 g) and *o*-bromophenol (2.6 g) in 15 ml of EtOH was added anhyd. AcOK (1.5 g) under ice chilling. The mixture was heated gradually on a steam bath, refluxed for 5 hr, and cooled to room temperature. After addition of 10 ml of cold EtOH, the precipitate was collected by filtration and washed with cold EtOH. The filtrate was concentrated to remove excess EtOH and the concentrated solution was worked up as described for **11** to give **15** (2.5 g, 70%) as colorless prisms (from C_6H_{12}), mp 102—104°. IR ν_{max} cm^{-1}: 1365 (NO_2), 1205 (C–O–C). MS *m/e* 296 (M+2), 294 (M^+), 215 (M−Br), 169 (215−NO_2). *Anal.* Calcd. for $C_{11}H_7BrN_2O_2$: C, 47.34; H, 2.53; N, 10.04. Found: C, 47.25; H, 2.39; N, 10.17.

3-Amino-4-(2′-bromophenoxy)pyridine (16)——A mixture of **15** (2.0 g), Fe powder (3.0 g), and 30 ml of 50% EtOH was heated at reflux, and glacial AcOH (5.0 g) in 5 ml of 50% EtOH was added over a period of 3 hr. The reaction mixture was worked up as described for **12** to give **16** (1.2 g, 67%) as colorless prisms (from C_6H_{12}), mp 68—70°. IR ν_{max} cm^{-1}: 3550, 3300 (NH_2), 1225 (C–O–C). MS *m/e*: 266 (M+2), 264 (M^+), 185 (M−Br). *Anal.* Calcd. for $C_{11}H_9BrN_2O$: C, 49.84; H, 3.42; N, 10.57. Found: C, 49.65; H, 3.18; N, 10.41.

4-(2′-Bromophenoxy)-3-(N-formylamino)pyridine (17)——A mixture of **16** (0.5 g) and 3 ml of 98% formic acid was worked up in a similar manner as described for **13**. Recrystallization from C_6H_{12} afforded **17** (0.4 g, 80%) as colorless prisms, mp 132—134°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1695 (C=O), 1230 (C–O–C). MS *m/e*: 294 (M+2), 292 (M^+), 213 (M−Br). *Anal.* Calcd. for $C_{12}H_9BrN_2O_2$: C, 49.17; H, 3.95; N, 9.56. Found: C, 49.25; H, 4.07; N, 9.68.

10-Formyl-10*H*-pyrido[4,3-*b*][1,4]benzoxazine (18) and 10*H*-Pyrido[4,3-*b*][1,4]benzoxazine (2)——A mixture of **17** (0.5 g), anhyd. K_2CO_3 (1.0 g), active Cu powder (1.0 g), and 10 ml of xylene was heated at 150—155° for 6 hr. The reaction mixture was worked up in a similar manner as described for **14**. The residue was separated by chromatography over silica gel with $CHCl_3$–acetone (9:1). The first eluted product was recrystallized from C_6H_{12} to give **18** (0.1 g, 27%) as colorless needles, mp 188—189°. IR ν_{max} cm^{-1}: 1690 (C=O), 1230 (C–O–C). MS *m/e*: 212 (M^+), 184 (M−CO), 183 (M−CHO). *Anal.* Calcd. for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 68.00; H, 3.53; N, 13.00.

The second product was recrystallized from benzene to give an unknown substance (10 mg) as reddish brown crystals, mp 260—264°. IR ν_{max} cm^{-1}: 1500, 1300. MS *m/e*: 366 (M^+), 183 (M−183).

The third product was recrystallized from benzene to give **2** (0.2 g, 66%) as colorless platelets, mp 200—202°. IR ν_{max} cm^{-1}: 3220 (NH), 1300 (C–O–C). MS *m/e*: 184 (M^+). *Anal.* Calcd. for $C_{11}H_8N_2O$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.64; H, 4.25; N, 14.99.

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