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Fused 1,3-Oxazine Derivatives. Synthesis of 2*H*-1,3-Oxazino[5,6-*b*]-quinoxaline-2,4(3*H*)-diones (1-Oxaalloxazines), 2*H*-1,3-Oxazino-[6,5-*b*]quinoline-2,4(3*H*)-diones (5-Deaza-1-oxaalloxazines), and 2*H*-Pyrido[3,2-*e*]-1,3-oxazine-2,4(3*H*)-diones

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Reactions of 6-anilino-3-methyl-2*H*-1,3-oxazine-2,4(3*H*)-diones (**1**) with triethyl orthoformate, *N*,*N*-dimethylformamide dimethyl acetal, diethyl azodicarboxylate, and dimethyl acetylenedicarboxylate were carried out with the aim of synthesizing fused-ring 1,3-oxazine derivatives 3-Methyl-2*H*-1,3-oxazino[6,5-*b*]quinoline-2,4(3*H*)-dione (3-methyl-5-deaza-1-oxaalloxazine) (**2**) and 3-methyl-2*H*-1,3-oxazino[5,6-*b*]quinoxaline-2,4(3*H*)-dione (3-methyl-1-oxaalloxazine) (**8**) were obtained by the reactions of the 6-anilinooxazine (**1a**) with triethyl orthoformate and diethyl azodicarboxylate, respectively. Treatment of **1a** with dimethyl acetylenedicarboxylate gave methyl 3-methyl-2,4,7-trioxo-8-phenyl-3,4,7,8-tetrahydro-2*H*-pyrido[3,2-*e*]-1,3-oxazine-5-carboxylate (**9a**) as well as methyl 1-methyl-2,5-dioxo-1,2,5,10-tetrahydrobenzo[*b*][1,8]naphthyridine-4-carboxylate (**10**) as a ring transformation product. The 6-(*p*-anisidino)- (**1b**) and the 6-(3,4-xylidino)-oxazine (**1c**) also gave the corresponding pyrido[3,2-*e*]-1,3-oxazines (**9b**) and (**9c**).

Keywords——2*H*-1,3-oxazino[5,6-*b*]quinoxaline; 2*H*-1,3-oxazino[6,5-*b*]quinoline; 2*H*-pyrido[3,2-*e*]-1,3-oxazine; benzo[*b*][1,8]naphthyridine; *N*,*N*-dimethylformamide dimethyl acetal; diethyl azodicarboxylate; dimethyl acetylenedicarboxylate; ring transformation

A number of fused pyrimidines are known in nature, and they play very interesting and important roles in biological systems. Many investigators[1] have directed their efforts toward the synthesis of fused pyrimidines, because of their biological importance. On the other hand, the structure of 2*H*-1,3-oxazine-2,4(3*H*)-dione is formally derived by a replacement of the nitrogen atom at the 1-position of the uracil ring with an oxygen atom. In the course of our studies on the synthesis and reactions of 2*H*-1,3-oxazine-2,4(3*H*)-dione derivatives,[2] we have been interested in the synthesis of fused 1,3-oxazine-2,4-dione derivatives, which are regarded as isosteres of fused uracil derivatives, from the viewpoint of biological activities.

In this paper we wish to report the reactions of 6-anilino-3-methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione (**1a**)[2a] with one-carbon reagents such as triethyl orthoformate and *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA), one-nitrogen reagents such as nitrous acid and diethyl azodicarboxylate (DAD), and dimethyl acetylenedicarboxylate (DMAD) to afford 2*H*-1,3-oxazino[6,5-*b*]quinoline-2,4(3*H*)-dione (5-deaza-1-oxaalloxazine) and 2*H*-1,3-oxazino[5,6-*b*]quinoxaline-2,4(3*H*)-dione (1-oxaalloxazine) derivatives as well as 2*H*-pyrido[3,2-*e*]-1,3-oxazine-2,4(3*H*)-dione derivatives.

Refluxing of **1a** with ethyl orthoformate in chlorobenzene gave the desired 3-methyl-2*H*-1,3-oxazino[6,5-*b*]quinoline-2,4(3*H*)-dione (3-methyl-5-deaza-1-oxaalloxazine) (**2**) and *N*,3-dimethyl-2,4-dioxo-8-phenyl-7-phenylimino-3,4,7,8-tetrahydro-2*H*-pyrido[3,2-*e*]-1,3-oxazine-6-carboxamide (**3**) in 15 and 71% yields, respectively. The characterization of **3** was based on the following evidence. The analytical and mass spectral (MS) data established the molecular

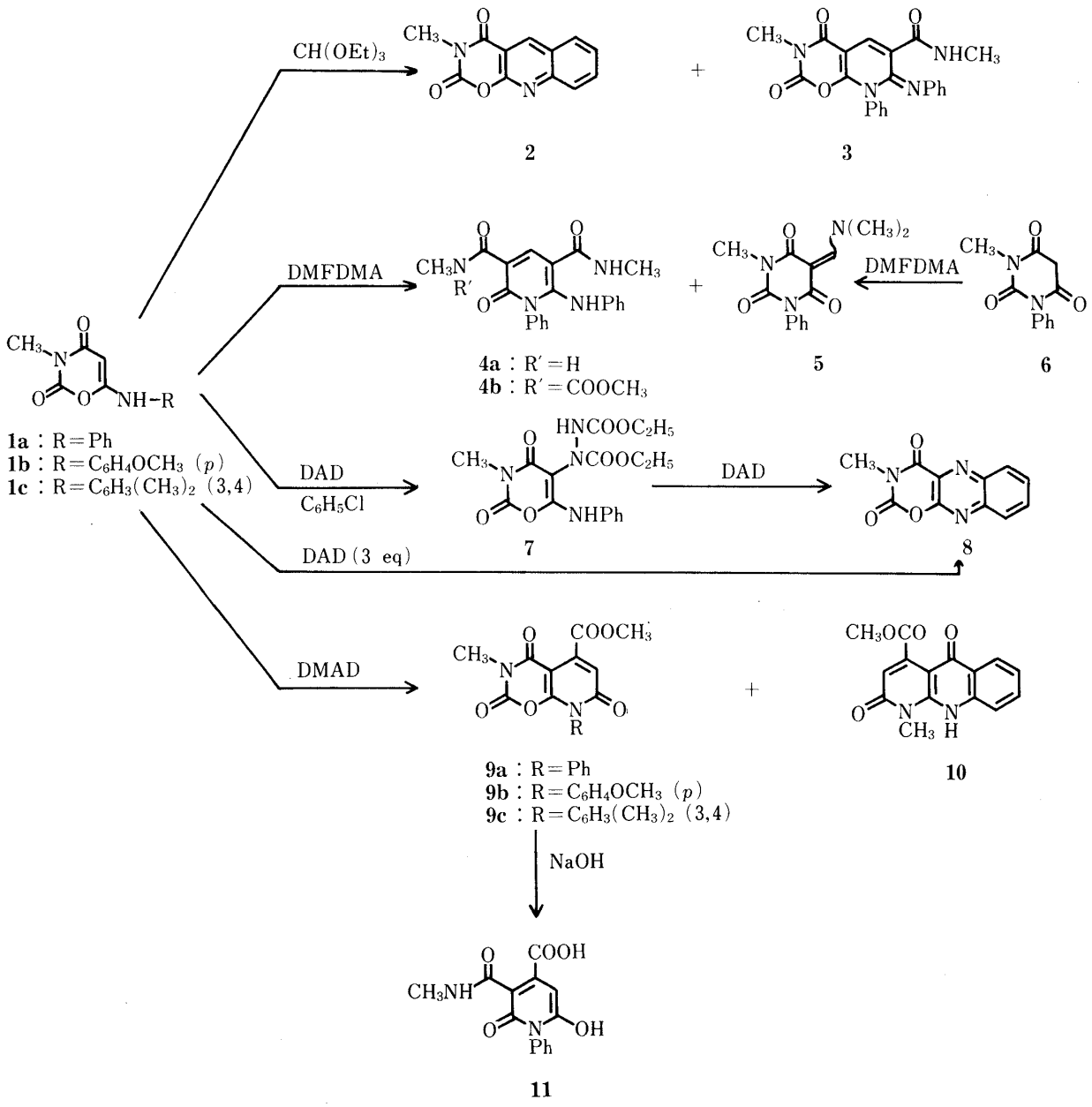

Chart 1

formula as $C_{22}H_{18}N_4O_4$. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum showed a 1H singlet signal at δ 8.66 due to the β proton of the enone system, a 10H multiplet signal at δ 7.22—6.21 due to two phenyl groups, and two methyl signals at δ 3.34 and 2.84, the latter of which was coupled with an NH proton (J=5 Hz) and changed to a singlet signal on addition of D_2O, as well as an NH proton signal at δ 9.56. Compound **3** was obtained as a precipitate on cooling the reaction mixture, and was purified by recrystallization from benzene. However, purification of the reaction mixture by centrifugal thin-layer chromatography (CTLC) using silica gel with chloroform as an eluent did not afford the pyrido[3,2-*e*]-1,3-oxazine (**3**). Unexpectedly, cleavage of the oxazine ring in **3** occurred and 6-anilino-*N*,*N'*-dimethyl-2-oxo-1-phenyl-1,2-dihydropyridine-3,5-dicarboxamide (**4a**) was obtained, though **2** was isolated unchanged. Upon being subjected to CTLC, compound **3** was hydrolyzed and decarboxylated to give **4a** in 96% yield. The ^{1}H-NMR spectrum of **4a** showed a 1H singlet signal at δ 9.02 due to C_4–H, a 10H multiplet signal at δ 7.06—6.50 due to two phenyl groups,

and two methyl signals at δ 2.88 and 2.83 which were coupled with an NH proton ($J=6$ Hz) and changed to singlet signals, respectively, on addition of D_2O, as well as three NH proton signals at δ 11.58, 9.24, and 7.68. Furthermore, the ultraviolet (UV) spectrum of **4a** showed a similar absorption pattern to that of 6-amino-1-methylpyridin-2(1*H*)-one.[3] These spectral results apparently support the structure of **4a**, hence that of **3**. On the other hand, heating of **1a** with 2 mol eq of DMFDMA at 90—95 °C afforded not the desired product but two other products, methyl *N*-(6-anilino-5-methylcarbamoyl-2-oxo-1-phenyl-1,2-dihydronicotinoyl)-*N*-methylcarbamate (**4b**) and 5-(*N*,*N*-dimethylaminomethylene)-1-methyl-3-phenylbarbituric acid (**5**), in 30 and 49% yields, respectively. The structure of **4b** was fully supported by its analytical and spectral data. In particular, the UV absorption pattern of **4b** is quite similar to that of **4a**. The structure of **5** was assumed from its analytical and spectral data, and confirmed by comparison of **5** with an authentic sample prepared by the reaction of 1-methyl-3-phenylbarbituric acid (**6**)[4] with DMFDMA.

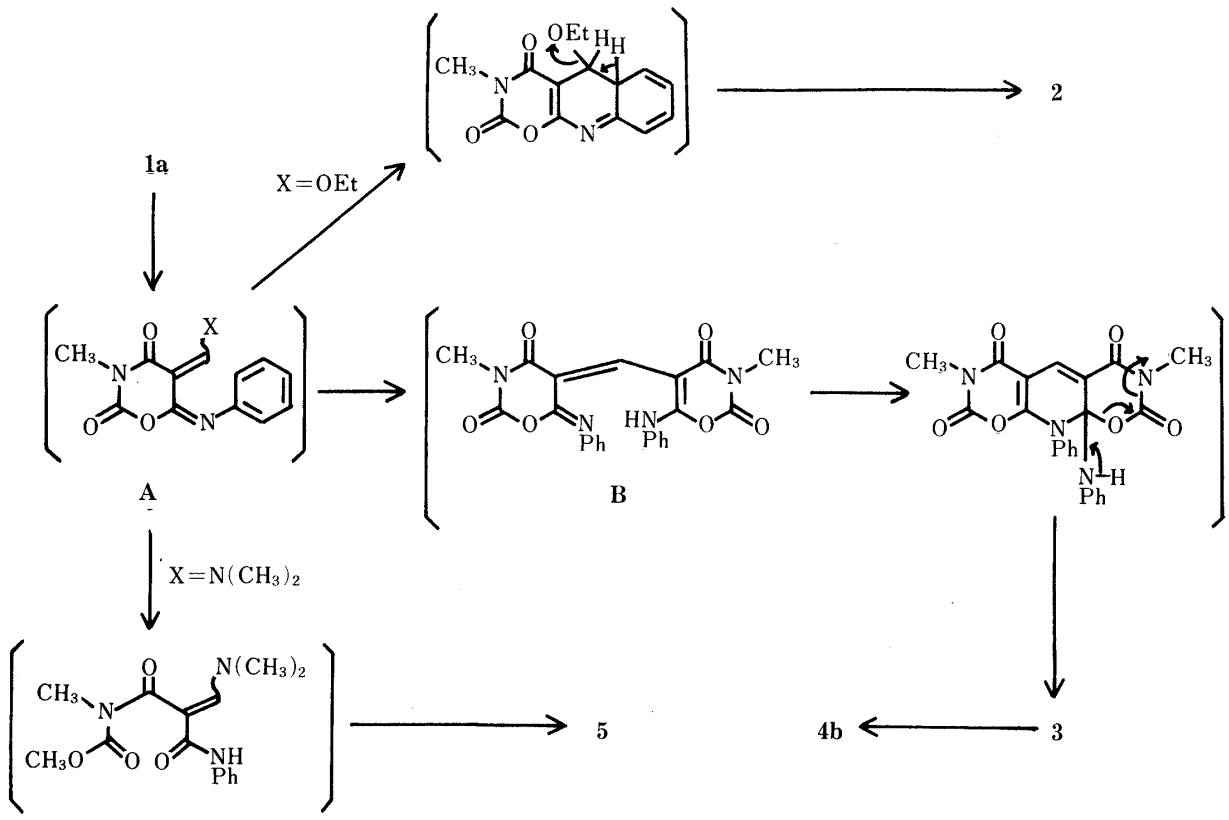

Chart 2

A plausible mechanism for the formation of compounds **2**, **3**, **4b**, and **5** is shown in Chart 2. An initial step is the formation of an intermediate (**A**) in both cases, by a process closely related to the mechanism[5] of 5-deazaalloxazine synthesis by the reaction of 6-anilinouracils with ethyl orthoformate or DMFDMA. The formation of **2** proceeds by an intramolecular cyclization of the intermediate (**A**; X=OEt). On the other hand, the intermediate (**A**) reacts intermolecularly with an additional molecule of **1a** to afford an azahexatriene intermediate (**B**), which cyclizes and is decarboxylated to **3**. In the reaction of **1a** with DMFDMA, however, the oxazine ring of **3** is cleaved by methoxide anion, which is derived from methanol formed as a by-product in the formation of the intermediate (**A**) under basic conditions, to afford the carbamate (**4b**). In fact, heating of **3** with DMFDMA and methanol gave **4b**. The reaction of the intermediate (**A**; X=NMe_2) with methanol gives the barbituric acid (**5**).

The reaction of **1a** with one-nitrogen reagents was also examined in the expectation of obtaining 3-methyl-2*H*-1,3-oxazino[5,6-*b*]quinoxaline-2,4(3*H*)-dione (3-methyl-1-oxaalloxazine) (**8**). The reaction of **1a** with sodium nitrite in acetic acid afforded a complicated mixture, presumably owing to cleavage of the oxazine ring. No oxazine derivative was detected in the reaction mixture. Then, the reactions of **1a** with DAD[6] were examined. Treatment of **1a** with 1.2 mol eq of DAD in chlorobenzene afforded the ene-adduct 6-anilino-5-(1,2-bisethoxycarbonylhydrazino)-3-methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione (**7**) in 75% yield. Oxidation of **7** with lead tetraacetate in dioxane gave a complicated mixture. However, heating of **7** with DAD at 180—185 °C gave the desired 3-methyl-1-oxaalloxazine (**8**) though the yield was low (10%). On the other hand, the reaction of **1a** with 3 mol eq of DAD also afforded **8** in 9% yield. Thus, the anilinooxazine (**1a**) was found to react with electrophilic DAD giving the Michael-type adduct (**7**). Then, examination of the reaction of **1a** with an electrophile, DMAD, was carried out.

Heating of **1a** with 2 mol eq of DMAD in chlorobenzene for 18 h afforded methyl 3-methyl-2,4,7-trioxo-3,4,7,8-tetrahydro-2*H*-pyrido[3,2-*e*]-1,3-oxazine-5-carboxylate (**9a**) and methyl 1-methyl-2,5-dioxo-1,2,5,10-tetrahydrobenzo[*b*][1,8]naphthyridine-4-carboxylate (**10**) in 26 and 17% yields, respectively. The structure of **9a** was readily established from the following evidence. Previously, Ogura *et al.*[7] obtained methyl 1,3-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-5-carboxylate and its 2,4,5-trioxo isomer by the reaction of 6-anilino-1,3-dimethyluracil with DMAD, and showed that the ^{1}H-NMR signal of C_6–H of the 7-oxopyrido[2,3-*d*]pyrimidine appears at δ 6.34, in contrast to δ 7.42 for the 5-oxo isomer. Approximation of the chemical shift of C_6–H of **9a** (δ 6.57) to that of C_6–H of the above-stated 7-oxopyrido[2,3-*d*]pyrimidine suggested the possibility of **9a** having the 7-oxo structure. On the other hand, it is well known that 4(1*H*)-pyridinone[8] and 4(1*H*)-quinolinone[9] derivatives generally show a carbonyl carbon signal at lower magnetic field than δ 170 in their carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra. The ^{13}C-NMR spectrum of **9a** showed no signal at lower field than δ 170 and the lowest signal appeared at δ 165.5. This fact also suggested that compound **9a** is not the 5-oxopyrido[3,2-*e*]-1,3-oxazine having the 4(1*H*)-pyridinone ring but rather the 7-oxopyrido[3,2-*e*]-1,3-oxazine having the 2(1*H*)-pyridinone ring. Furthermore, treatment of **9a** with sodium hydroxide gave 6-hydroxy-3-methylcarbamoyl-2-oxo-1-phenyl-1,2-dihydroisonicotinic acid (**11**) whose structure was confirmed on the basis of the analytical and spectral data. In particular, in the MS of **11**, an ion peak at *m/z* 270, which is formed by loss of H_2O from the molecular ion, appeared as the base peak whereas the molecular ion peak at *m/z* 288 appeared as a very weak peak. This MS datum apparently supported the structure of **11**, hence that of **9a**. The characterization of **10** was based on the following evidence. The analytical and MS data established the molecular formula as $C_{15}H_{12}N_2O_4$. In the aromatic proton region in the ^{1}H-NMR spectrum of **10**, four proton signals at δ 8.18 (1H) and 7.74—7.23 (3H) were observed. The lower signal at δ 8.18 was characteristic of a proton deshielded by a carbonyl group at its *peri*-position. The sharp signal at δ 6.73 was assignable to the α proton of the enone system and other signals at δ 3.95 and 3.33 were assigned to an ester methyl and an *N*-methyl group, respectively. Furthermore, compound **10** was allowed to react with phosphorus oxychloride to give methyl 5-chloro-1-methyl-2-oxo-1,2-dihydrobenzo[*b*][1,8]naphthyridine-4-carboxylate (**12**) and methyl 5-chloro-3-hydroxy-1-methyl-2-oxo-1,2,3,4-tetrahydrobenzo[*b*][1,8]naphthyridine-4-carboxylate (**13**). The latter compound (**13**) can be formed by addition of water to **12**, presumably during work-up of the reaction mixture with water. On the other hand, **10** was converted to 5-chloro-1-methylbenzo[*b*][1,8]naphthyridin-2(1*H*)-one (**14**) by hydrolysis, decarboxylation, and chlorination. Compound **14** showed AB-type quartet signals at δ 8.22 and 6.84, characteristic of α and β protons of the enone system, in its ^{1}H-NMR spectrum.

The 6-anilinooxazine (**1a**) apparently involves an enaminone system. Thus, an initial step

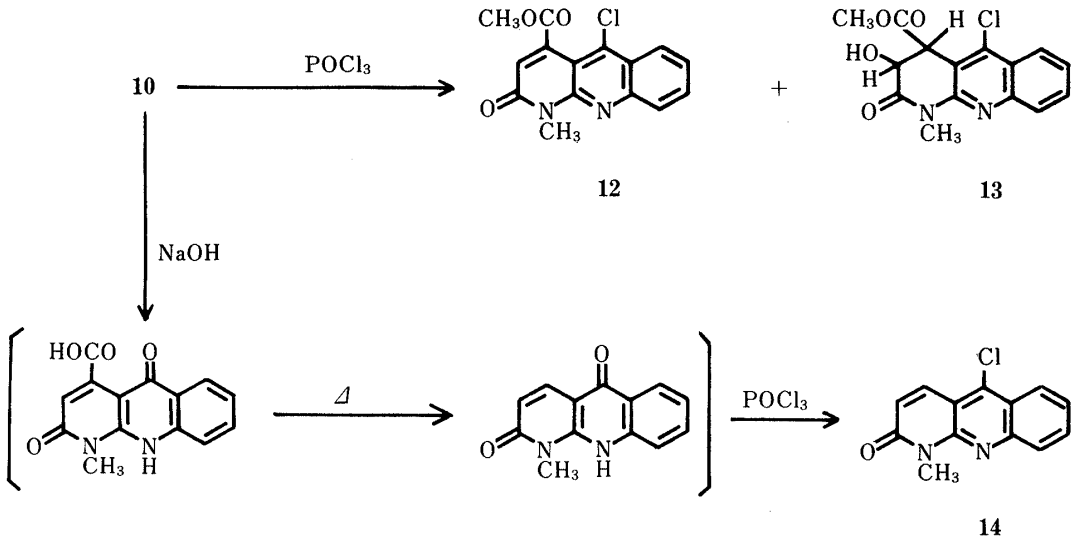

Chart 3

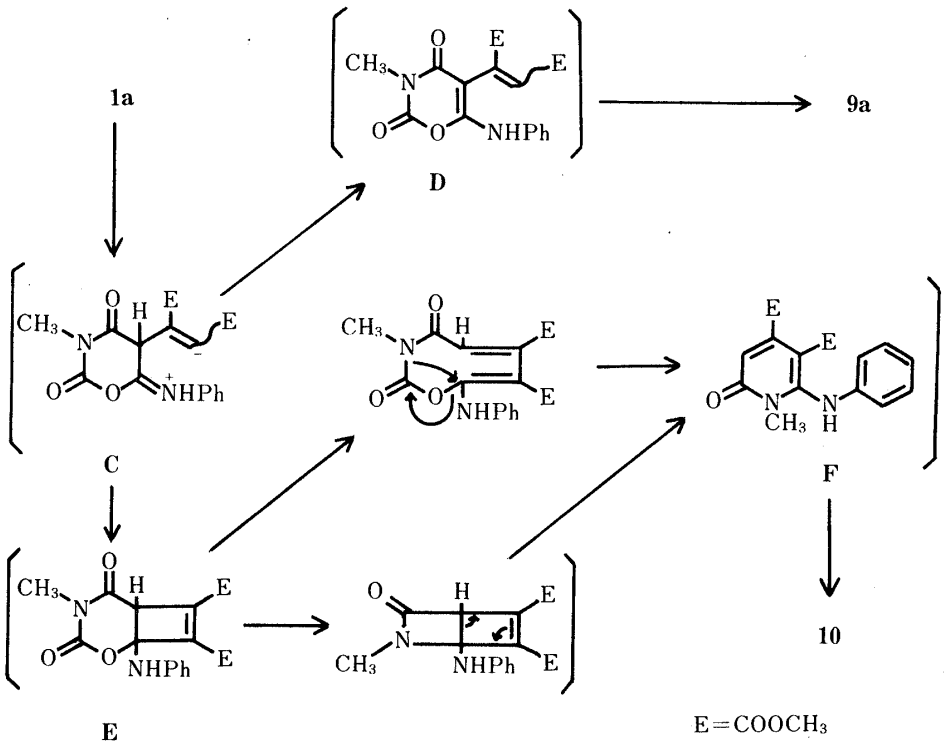

Chart 4

for the conversion of **1a** into **9a** and **10** is the formation of the zwitterion (**C**) which is converted to a Michael adduct-type intermediate (**D**). The intermediate (**D**) further cyclizes to give the pyrido[3,2-*e*]-1,3-oxazine (**9a**). An cyclobutene intermediate (**E**) is formed *via* a non-concerted process from **1a** *via* the zwitterion (**C**), and is converted into the anilinopyridine (**F**) *via* either ring expansion followed by decarboxylation or decarboxylation followed by ring expansion as depicted in Chart 4. Cyclization of the anilinopyridine (**F**) affords the benzo[*b*][1,8]naphthyridine (**10**). The mechanisms for the formation of intermediates (**D**) and (**E**) are similar to those described by Ogura *et al.*[7] and Acheson *et al.*[10] Similar reaction of the 6-(*p*-anisidino)- (**1b**) and the 6-(3,4-xylidino)-oxazine (**1c**) with DMAD gave the corresponding pyrido-1,3-oxazines (**9b** and **9c**). However, the corresponding benzonaphthyridines were

not isolated.

Of the new compounds obtained above, 3-methyl-5-deaza-1-oxaalloxazine (**2**) showed *in vitro* antimicrobial activities against *Shigella flexneri*, *Proteus vulgaris*, and *Yersinia enterocolitica*, though the activities were relatively low. Details of the microbial activities will be reported elsewhere.

Experimental

All melting points are uncorrected. Column chromatography was run on silica gel (Wakogel C-200) and CTLC was carried out on a Harrison centrifugal thin-layer chromatotron (Model 7924) with Kieselgel 60 GF_{254} (Merck) of 2 mm layer thickness. The flow rate was 4 ml/min. Preparative thin-layer chromatography (PLC) was performed on glass plates precoated with Kieselgel 60 F_{254} (Merck). MS were recorded on a Hitachi M-52 spectrometer and high resolution MS on a JEOL JMS-D-300 spectrometer. Infrared (IR) spectra were obtained on a JASCO IRA-1 spectrophotometer and UV spectra on a JASCO UVIDEC-1 double-beam spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-PS-100 NMR spectrometer or a JEOL JNM-FX-100 Fourier transform spectrometer and ^{13}C-NMR spectra on a JEOL JNM-FX-100 Fourier transform spectrometer operating at 25.00 MHz, with tetramethylsilane as an internal standard. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, dd = doublet-of-doublets, ddd = doublet-of-doublets-of-doublets, t = triplet, q = quartet, br = broad).

6-(*p*-Anisidino)-3-methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione (1b) and 1-(*p*-Methoxyphenyl)-3-[*N*-(*p*-methoxyphenyl)malonamoyl]-3-methylurea——A solution of *p*-anisidine (2640 mg, 21.5 mmol) in tetrahydrofuran (THF) (10 ml) was added to a stirred solution of 6-chloro-3-methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione (1620 mg, 10 mmol) in THF (10 ml) at room temperature, and stirring was continued for 24 h. The resulting precipitate (**1b**) was filtered off and washed with water. The filtrate was evaporated *in vacuo* and the residue was subjected to column chromatography with hexane–ethyl acetate (1 : 1, v/v). The earlier fractions yielded further crops of **1b**. The combined **1b** was recrystallized from acetone to give colorless plates (1540 mg, 62%), mp 188—189 °C (dec.). *Anal.* Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.01; H, 4.91; N, 11.12. MS *m/z*: 248 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.16 and 6.92 (each 2H, each d, each J = 9 Hz, C_6H_4), 6.53 (1H, br, NH), 4.98 (1H, s, C_5–H), 3.83 (3H, s, OCH_3), 3.30 (3H, s, NCH_3).

The methylurea was isolated from the later fractions with the same solvent and recrystallized from methanol to afford colorless needles (600 mg, 16%), mp 167—168 °C. *Anal.* Calcd for $C_{19}H_{21}N_3O_5$: C, 61.44; H, 5.70; N, 11.32. Found: C, 61.52; H, 5.73; N, 11.29. MS *m/z*: 371 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 10.95 and 8.65 (each 1H, each br, NH × 2), 7.45 and 7.42 (each 2H, each d, each J = 9 Hz, C_6H_4), 6.87 (4H, d, J = 9 Hz, C_6H_4), 3.79 (6H, s, OCH_3 × 2), 3.74 (2H, s, CH_2), 3.44 (3H, s, NCH_3).

3-Methyl-6-(3,4-xylidino)-2*H*-1,3-oxazine-2,4(3*H*)-dione (1c) and 1-(3,4-Dimethylphenyl)-3-[*N*-(3,4-dimethylphenyl)malonamoyl]-3-methylurea——A solution of 3,4-xylidine (2600 mg, 21.5 mmol) in THF (10 ml) was added to a stirred solution of 6-chloro-3-methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione (1620 mg, 10 mmol) in THF (10 ml) at room temperature, and stirring was continued for 24 h. The solvent was evaporated off, and the residue was washed with water, dried, and subjected to column chromatography with hexane–ethyl acetate (2 : 1, v/v). The earlier fractions yielded **1c**, which was recrystallized from acetone to give colorless prisms (1490 mg, 61%), mp 187—189 °C (dec.). *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.82; H, 5.68; N, 11.55. MS *m/z*: 246 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.18—6.88 (3H, m, C_6H_3), 6.48 (1H, br, NH), 5.13 (1H, s, C_5–H), 3.30 (3H, s, NCH_3), 2.26 (6H, s, CH_3 × 2).

The methylurea was obtained from the later fractions with the same solvent and recrystallized from methanol to afford colorless needles (490 mg, 13%), mp 171—172 °C. *Anal.* Calcd for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44. Found: C, 68.69; H, 6.96; N, 11.28. MS *m/z*: 367 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 10.98 and 8.62 (each 1H, each br, NH × 2), 7.31—7.02 (6H, m, C_6H_3 × 2), 3.71 (2H, s, CH_2), 3.41 (3H, s, NCH_3), 2.25 and 2.22 (each 6H, each s, CH_3 × 4).

3-Methyl-2*H*-1,3-oxazino[6,5-*b*]quinoline-2,4(3*H*)-dione (3-Methyl-5-deaza-1-oxaalloxazine) (2) and *N*,3-Dimethyl-2,4-dioxo-8-phenyl-7-phenylimino-3,4,7,8-tetrahydro-2*H*-pyrido[3,2-*e*]-1,3-oxazine-6-carboxamide (3)——A mixture of **1a** (870 mg, 4 mmol), ethyl orthoformate (20 ml), and chlorobenzene (30 ml) was refluxed for 3 h, then cooled. The precipitate was filtered off and recrystallized from benzene to give pale yellow needles (**3**) (570 mg, 71%), mp 249—251 °C (dec.). *Anal.* Calcd for $C_{22}H_{18}N_4O_4$: C, 65.66; H, 4.51; N, 13.92. Found: C, 65.53; H, 4.63; N, 14.08. MS *m/z*: 402 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 9.56 (1H, br, NH), 8.66 (1H, s, C_5–H), 7.22—6.21 (10H, m, C_6H_5 × 2), 3.34 (3H, s, NCH_3), 2.84 (3H, d, J = 5 Hz, $NHCH_3$).

The filtrate was evaporated *in vacuo*, and the residue was washed with ether and recrystallized from benzene to give colorless needles (**2**) (140 mg, 15%), mp 245—247 °C (dec.). *Anal.* Calcd for $C_{12}H_8N_2O_3$: C, 63.16; H, 3.53; N, 12.28. Found: C, 63.13; H, 3.38; N, 12.24. MS *m/z*: 228 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 9.03 (1H, s, C_5–H), 8.41—7.52 (4H, m, C_6–, C_7–, C_8–, and C_9–H), 3.52 (3H, s, NCH_3).

6-Anilino-*N*,*N'*-dimethyl-2-oxo-1-phenyl-1,2-dihydropyridine-3,5-dicarboxamide (4a)——The pyrido[3,2-*e*]-1,3-oxazine (**3**) (100 mg, 0.25 mmol) was subjected to CTLC. Elution with chloroform followed by recrystallization from methanol gave colorless needles (**4a**) (90 mg, 96%), mp 315—317 °C (dec.). *Anal.* Calcd for $C_{21}H_{20}N_4O_3$: C, 67.01; H, 5.36; N, 14.89. Found: C, 67.22; H, 5.27; N, 14.89. MS *m/z*: 376 (M^+). UV λ_{max}^{MeOH} nm (log ε): 209 (4.42), 291 (4.04), 361 (4.36). ^{1}H-NMR ($CDCl_3$) δ: 11.58 (1H, br s, NH), 9.24 (1H, br, NH), 9.02 (1H, s, C_4–H), 7.68 (1H, br, NH), 7.06—6.50 (10H, m, $C_6H_5 \times 2$), 2.88 and 2.83 (each 3H, each d, each $J=6$ Hz, $NHCH_3 \times 2$).

Methyl *N*-(6-Anilino-5-methylcarbamoyl-2-oxo-1-phenyl-1,2-dihydronicotinoyl)-*N*-methylcarbamate (4b) and 5-(*N*,*N*-Dimethylaminomethylene)-1-methyl-3-phenylbarbituric Acid (5)——A mixture of **1a** (440 mg, 2 mmol) and DMFDMA (480 mg, 4 mmol) was heated at 90—95 °C on a water-bath for 80 min. The reaction mixture was subjected to CTLC with ethyl acetate as an eluent. The earlier fractions yielded **4b**, which was recrystallized from acetone to give colorless needles (130 mg, 30%), mp 210—212 °C (dec.). *Anal.* Calcd for $C_{23}H_{22}N_4O_5$: C, 63.58; H, 5.10; N, 12.90. Found: C, 63.30; H, 5.03; N, 12.74. MS *m/z*: 434 (M^+). UV λ_{max}^{MeOH} nm (log ε): 210 (4.47), 297 (4.05), 367 (4.31). ^{1}H-NMR ($CDCl_3$) δ: 11.30 (1H, br s, NH), 8.08 (1H, s, C_4–H), 7.04—6.44 (10H, m, $C_6H_5 \times 2$), 6.42 (1H, br, NH), 3.60 (3H, s, OCH_3), 3.23 (3H, s, NCH_3), 2.86 (3H, d, $J=5$ Hz, $NHCH_3$).

Compound **5** was isolated from the later fractions with the same solvent and recrystallized from ethanol to give colorless needles (270 mg, 49%), mp 157—159 °C. *Anal.* Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.74; H, 5.38; N, 15.34. MS *m/z*: 273 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1700, 1640, 1620 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 8.10 (1H, s, –CH=), 7.56—7.08 (5H, m, C_6H_5), 3.38, 3.35, and 3.33 (each 3H, each s, $CH_3 \times 3$). Refluxing of the compound (**5**) in chlorobenzene for 24 h followed by evaporation of the solvent and recrystallization of the residue from ethanol gave **5** as a polymorphic compound, mp 186—187 °C. IR and ^{1}H-NMR spectral data of the polymorphic compound are in complete agreement with those of compound **5** in $CHCl_3$ or $CDCl_3$, although the IR spectrum taken in a KBr pellet shows a different absorption pattern from that of **5**, especially in the fingerprint region.

Heating of the Pyrido[3,2-*e*]-1,3-oxazine (3) with DMFDMA and Methanol——A mixture of **3** (100 mg, 0.25 mmol), DMFDMA (200 mg, 0.25 mmol), and methanol (20 mg, 0.54 mmol) was heated at 90—95 °C on a water-bath for 80 min. The reaction mixture was subjected to CTLC with ethyl acetate as an eluent to give **4b** (150 mg, 47%).

Preparation of 5 by the Reaction of 1-Methyl-3-phenylbarbituric Acid (6) with DMFDMA——DMFDMA (90 mg, 0.76 mmol) was added to a solution of **6** (110 mg, 0.51 mmol) in chlorobenzene (5 ml) and the mixture was refluxed for 30 min. After evaporation of the solvent *in vacuo*, ether was added to the residue, and the precipitate was collected and recrystallized from ethanol to give **5** (110 mg, 79%), mp 184—185 °C, which was identical with the polymorphic **5** prepared by the method described above.

6-Anilino-5-(1,2-bisethoxycarbonylhydrazino)-3-methyl-2*H*-1,3-oxazine-2,4(3*H*)-dione (7)——A mixture of **1a** (1.1 g, 5 mmol), DAD (1.1 g, 6 mmol), and chlorobenzene (10 ml) was refluxed for 5 h. After cooling and addition of ether to the reaction mixture, the precipitate (**7**) was filtered off. The filtrate was evaporated *in vacuo* and the residue was column-chromatographed. Elution with hexane–ethyl acetate (2 : 1, v/v) gave a further crop of **7**. The combined **7** was recrystallized from ethanol to give colorless flakes (1.5 g, 75%), mp 181—183 °C. *Anal.* Calcd for $C_{17}H_{20}N_4O_7$: C, 52.04; H, 5.14; N, 14.28. Found: C, 52.00; H, 4.99; N, 14.21. MS *m/z*: 392 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 10.32 and 9.96 (each 1H, each br, NH × 2), 7.60—7.12 (5H, m, C_6H_5), 4.19 and 4.11 (each 2H, each q, each $J=7$ Hz, $CH_2 \times 2$), 3.16 (3H, s, NCH_3), 1.23 and 1.14 (each 3H, each t, each $J=7$ Hz, $CH_3 \times 2$).

3-Methyl-2*H*-1,3-oxazino[5,6-*b*]quinoxaline-2,4(3*H*)-dione (3-Methyl-1-oxaalloxazine) (8)——a) A mixture of the hydrazinooxazine (**7**) (1.2 g, 3.0 mmol) and DAD (0.8 g, 4.6 mmol) was heated at 180—185 °C for 2 h. After cooling and addition of ether to the reaction mixture, the precipitate was filtered off and recrystallized from benzene to give colorless needles (**8**) (70 mg, 10%), mp 256—258 °C (dec.). *Anal.* Calcd for $C_{11}H_7N_3O_3$: C, 57.64; H, 3.08; N, 18.34. Found: C, 57.84; H, 3.03; N, 18.12. MS *m/z*: 229 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 8.40—7.80 (4H, m, C_6–, C_7–, C_8–, and C_9–H), 3.36 (3H, s, NCH_3).

b) A mixture of **1a** (1.1 g, 5 mmol) and DAD (2.6 g, 15 mmol) was heated at 180—190 °C for 6 h, and treatment of the reaction mixture as described above gave **8** (100 mg, 9%).

Methyl 3-Methyl-2,4,7-trioxo-8-phenyl-3,4,7,8-tetrahydro-2*H*-pyrido[3,2-*e*]-1,3-oxazine-5-carboxylate (9a) and Methyl 1-Methyl-2,5-dioxo-1,2,5,10-tetrahydrobenzo[*b*][1,8]naphthyridine-4-carboxylate (10)——A mixture of **1a** (870 mg, 4 mmol), DMAD (1140 mg, 8 mmol), and chlorobenzene (20 ml) was refluxed for 18 h, then cooled. The precipitate was filtered off and recrystallized from ethyl acetate to give colorless prisms (**9a**) (340 mg, 26%), mp 289—290 °C (dec.). *Anal.* Calcd for $C_{16}H_{12}N_2O_6$: C, 58.54; H, 3.68; N, 8.53. Found: C, 58.29; H, 3.45; N, 8.44. MS *m/z*: 328 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 7.70—7.33 (5H, m, C_6H_5), 6.57 (1H, s, C_6–H), 3.85 (3H, s, OCH_3), 3.16 (3H, s, NCH_3). ^{13}C-NMR (DMSO-d_6) δ: 165.5 (s), 159.9 (s), 157.8 (s), 154.8 (s), 145.0 (s), 142.0 (s), 132.7 (s), 129.5 (d), 129.3 (d), 128.1 (d), 113.4 (d), 89.8 (s), 52.8 (q), 28.4 (q).

The filtrate was evaporated *in vacuo*, and the residue was washed with ethyl acetate and recrystallized from benzene to give yellow needles (**10**) (190 mg, 17%), mp 224—225 °C (dec.). *Anal.* Calcd for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.26; N, 9.86. Found: C, 63.60; H, 4.14; N, 9.85. MS *m/z*: 284 (M^+), 252 ($M^+ - CH_3OH$), 223, 197, 169. ^{1}H-NMR ($CDCl_3$) δ: 8.18 (1H, d, $J=8$ Hz, C_6–H), 7.74—7.23 (3H, m, C_7–, C_8–, and C_9–H), 6.73 (1H, s, C_3–H), 3.95 (3H, s, OCH_3), 3.33 (3H, s, NCH_3). ^{13}C-NMR ($CDCl_3$) δ: 171.2 (s), 167.1 (s), 160.6 (s), 157.8 (s), 149.2 (s), 136.5 (s), 132.5

(d), 127.4 (d), 125.0 (d), 124.4 (d), 120.6 (s), 114. 8 (d), 98.1 (s), 53.8 (q), 26.0 (q).

Methyl 8-(*p*-Methoxyphenyl)-3-methyl-2,4,7-trioxo-3,4,7,8-tetrahydro-2*H*-pyrido[3,2-*e*]-1,3-oxazine-5-carboxylate (9b)——A mixture of **1b** (500 mg, 2 mmol), DMAD (570 mg, 4 mmol), and chlorobenzene (10 ml) was refluxed for 24 h, then cooled. The precipitate was filtered off and recrystallized from chlorobenzene to give colorless sticks (260 mg, 36%), mp 297—299 °C (dec.). *Anal.* Calcd for $C_{17}H_{14}N_2O_7$: C, 56.98; H, 3.94; N, 7.82. Found: C, 57.12; H, 3.86; N, 7.37. MS *m/z*: 358 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.36 and 7.11 (each 2H, each d, each $J=9$ Hz, C_6H_4), 6.49 (1H, s, C_6–H), 3.99 and 3.87 (each 3H, each s, $OCH_3\times2$), 3.37 (3H, s, NCH_3).

Methyl 8-(3,4-Dimethylphenyl)-3-methyl-2,4,7-trioxo-3,4,7,8-tetrahydro-2*H*-pyrido[3,2-*e*]-1,3-oxazine-5-carboxylate (9c)——A mixture of **1c** (490 mg, 2 mmol), DMAD (570 mg, 4 mmol), and chlorobenzene (10 ml) was treated as described for the preparation of **9b** and the precipitate was recrystallized from acetone to give colorless prisms (280 mg, 39%), mp >300 °C. *Anal.* Calcd for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.79; H, 4.48; N, 7.68. MS *m/z*: 356 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 7.34—6.90 (3H, m, C_6H_3), 6.48 (1H, s, C_6–H), 3.98 (3H, s, $COOCH_3$), 3.37 (3H, s, NCH_3), 2.32 (6H, s, $CH_3\times2$).

6-Hydroxy-3-methylcarbamoyl-2-oxo-1-phenyl-1,2-dihydroisonicotinic Acid (11)——A mixture of **9a** (980 mg, 3 mmol), sodium hydroxide (600 mg, 15 mmol), water (8 ml), and ethanol (8 ml) was refluxed for 10 min. Ethanol was evaporated off *in vacuo* and the remaining aqueous solution was acidified with dil. hydrochloric acid. The resulting precipitate was filtered off, washed with water, dried, and recrystallized from acetone to give yellow prisms (**11**) (670 mg, 78%), mp 260 °C (dec.). *Anal.* Calcd for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.46; H, 4.14; N, 9.64. MS *m/z*: 288 (M^+), 270 (M^+-H_2O). ^{1}H-NMR (DMSO-d_6) δ: 7.78 (3H, br, NH+OH×2), 7.60—7.17 (5H, m, C_6H_5), 5.67 (1H, s, C_5–H), 2.71 (3H, s, CH_3).

Methyl 5-Chloro-1-methyl-2-oxo-1,2-dihydrobenzo[*b*][1,8]naphthyridine-4-carboxylate (12) and Methyl 5-Chloro-3-hydroxy-1-methyl-2-oxo-1,2,3,4-tetrahydrobenzo[*b*][1,8]naphthyridine-4-carboxylate (13)——A mixture of **10** (150 mg, 0.53 mmol) and phosphorus oxychloride (6 ml) was refluxed for 3 h. The reaction mixture was poured into ice-water and extracted with chloroform. The chloroform solution was washed successively with water, an aqueous solution of sodium hydrogencarbonate, and water, then dried over magnesium sulfate. After concentration, the residue was subjected to CTLC using chloroform as an eluent. The earlier fractions yielded **12**, which was recrystallized from acetone to give pale yellow needles (50 mg, 31%), mp 183—185 °C. *Anal.* Calcd for $C_{15}H_{11}ClN_2O_3$: C, 59.51; H, 3.66; N, 9.25. Found: C, 59.38; H, 3.72; N, 9.33. MS *m/z*: 304 (M^++2), 302 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 8.16—7.32 (4H, m, C_6–, C_7–, C_8–, and C_9–H), 7.46 (1H, s, C_3–H), 3.95 (3H, s, OCH_3), 3.34 (3H, s, NCH_3).

Compound **13** was isolated from the later fractions with the same solvent and recrystallized from acetone to give colorless needles (40 mg, 24%), mp 250 °C (dec.). *Anal.* Calcd for $C_{15}H_{13}ClN_2O_4$: C, 56.17; H, 4.09; N, 8.73. Found: C, 56.11; H, 4.28; N, 8.69. MS *m/z*: 322 (M^++2), 320 (M^+), 304 (M^+-16), 302 (M^+-18). ^{1}H-NMR ($CDCl_3$) δ: 8.19—7.38 (4H, m, C_6–, C_7–, C_8–, and C_9–H), 5.25 (1H, dd, $J=2$ and 4 Hz, changed to d in D_2O, $J=2$ Hz, C_3–H), 4.25 (1H, d, $J=2$ Hz, C_4–H), 3.97 (3H, s, OCH_3), 3.36 (3H, s, NCH_3), 3.20 (1H, d, $J=4$ Hz, C_3–OH).

5-Chloro-1-methylbenzo[*b*][1,8]naphthyridin-2(1*H*)-one (14)——A mixture of **10** (370 mg, 1.3 mmol) and a 20% aqueous solution of sodium hydroxide (35 ml) was refluxed for 4 h, and neutralized with dil. hydrochloric acid to give a crude product (220 mg, 63%), mp >300 °C. This crude product was heated with copper powder (30 mg) on a salt-bath at 380—400 °C for 10 min. The reaction mixture was extracted with hot *N*,*N*-dimethylformamide (DMF). After evaporation of DMF, the residue was refluxed with phosphorus oxychloride (5 ml) for 3 h. The reaction mixture was poured into ice-water and extracted with chloroform. The chloroform solution was washed successively with water, aqueous solution of sodium hydrogencarbonate, and water, then dried over magnesium sulfate. After concentration, the residue was subjected to PLC using chloroform as a developer, giving **14** (3 mg, 1%), which was recrystallized from acetone to give pale yellow needles, mp 188—190 °C. MS *m/z*: Calcd for $C_{13}H_9{}^{37}ClN_2O$ (M^++2): 246.0373. Found: 246.0388; Calcd for $C_{13}H_9{}^{35}ClN_2O$ (M^+): 244.0403. Found: 244.0394. ^{1}H-NMR ($CDCl_3$) δ: 8.28 (1H, dd, $J=8.3$ and 1.5 Hz, C_6–H or C_9–H), 8.22 (1H, d, $J=10.0$ Hz, C_4–H), 8.05 (1H, dd, $J=8.3$ and 1.5 Hz, C_9–H or C_6–H), 7.80 (1H, ddd, $J=8.3$, 6.6, and 1.5 Hz, C_7–H or C_8–H), 7.58 (1H, ddd, $J=8.3$, 6.6, and 1.5 Hz, C_8–H or C_7–H), 6.84 (1H, d, $J=10.0$ Hz, C_3–H), 3.92 (3H, s, NCH_3).

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