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Studies on Ketene and Its Derivatives. LXXV.*,[1] Reaction of Diketene with N-Benzylacetimidate and Lactim Ethers to give 1,6-Naphthyridine Derivatives

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Reaction of diketene with ethyl N-benzylacetimidate (Ia) in acetic acid gave 3-acetyl-1,6-dibenzyl-4,7-dimethyl-1*H*,6*H*-1,6-naphthyridine-2,5-dione (IIa) in 51% yield. Similarly lactim ethers such as 2-methoxy-1-pyrroline (Ib), 2-methoxy-3,4,5,6-tetrahydropyridine (Ic), and 2-methoxy-3,4,5,6-tetrahydro-7*H*-azepine (Id) gave the corresponding 5-acetyl-6-methyl-4,7-dioxo-1,2,10,11-tetrahydro-4*H*,7*H*,9*H*-dipyrrolo[1,2-*g*: 3′,2′, 1′-*ij*]-1,6-naphthyridine (IIb) (35%), 6-acetyl-7-methyl-5,8-dioxo-2,3,10,11,12,13-hexahydro-1*H*,5*H*,8*H*-quinolizino[1,9-*ab*]quinolizine (IIc) (66%), and 7-acetyl-8-methyl-6,9-dioxo-1,2,3,4,12,13,14,15-octahydro-6*H*,9*H*,11*H*-bisazepino[1,2-*g*: 3′,2′,1′-*ij*]-1,6-naphthyridine (IId) (40%).

Treatment of IIa—d with KOH in EtOH resulted in the formation of the deacetylated derivatives IIIa—d.

In the preceding papers of this series,[3] we have reported that diketene reacts with alkyl imidates to give 1,3-oxazine or pyridone derivatives. For instance, ethyl acetimidate reacts with diketene in ether or benzene to give 2-ethoxy-2,6-dimethyl-2*H*,3*H*-1,3-oxazin-4-one in fairly good yield. However, reaction of diketene with ethyl 2-ethoxycarbonylacetimidate and ethyl 2-cyanoacetimidate under the same condition affords ethyl 2-ethoxy-4-hydroxy-6-methylpyridine-3-carboxylate and 2-ethoxy-4-methyl-6-oxo-1,6-dihydropyridine-3-carbonitrile, respectively.

In the present paper we wish to report the reaction of diketene with some N-substituted imidates in acetic acid, in which condition 1,6-naphthyridine derivatives are obtained in moderate yields.

When ethyl N-benzylacetimidate (Ia) was allowed to react with diketene in glacial acetic acid, colorless needles of mp 117°, $C_{26}H_{24}O_3N_2$ (IIa), were obtained in 51% yield. Elemental analysis showed that IIa was a condensation product of 2 moles of Ia and 2 moles of diketene by the elimination of 2 moles of ethanol and one mole of H_2O. The infrared (IR) spectrum indicated the absence of OH and NH absorptions and the presence of carbonyl groups at 1700 and 1635 cm^{-1}. The nuclear magnetic resonance (NMR) spectrum showed three singlet signals due to methyl protons (2.24, 2.54, and 2.65 ppm), a signal owing to an olefinic proton (6.02 ppm), and signals due to benzyl methylene protons (5.24 and 5.48 ppm). These data suggested the structure being the 1,6-naphthyridine derivative (IIa).

Treatment of IIa with potassium hydroxide in ethanol afforded the deacetylated compound (IIIa). Hydrogenolysis of IIIa with H_2 in the presence of Pd-C gave rise to the monobenzyl derivative (IV), which on treatment with phosphoryl chloride was transformed into the monochloro derivative (V). Catalytic reduction of V with Pd-C afforded the 1,6-naph-

* Dedicated to the memory of Prof. Eiji Ochiai.

1) Part LXXIV: T. Kato and T. Chiba, *Chem. Pharm. Bull.* (Tokyo), **23**, 2263 (1975).

2) Location: *Aobayama, Sendai, 980, Japan.*

3) T. Kato, Y. Yamamoto, and M. Kondo, *Yakugaku Zasshi*, **92**, 886 (1972); T. Kato, *Accounts of Chemical Research*, **7**, 265 (1974).

thyridine derivative (VI). Elemental analysis and spectral data are well consistent with these structures.

Attempt was made to confirm the structure of VI by the comparison of an authentic sample of N-benzyl-1,6-naphthyridine derivative. Namely, 1,6-naphthyridine was allowed to react with benzyl chloride followed by treatment with potassium ferricyanide to give 6-benzyl-1,6-naphthyridin-5(6H)-one (VII). It is a well documented fact that the alkylation of 1,6-naphthridine with alkyl halide, gives rise to 6-alkyl quaternary ammonium salt,[4] therefore, the structure of 1-benzyl isomer (VII') is considered to be unlikely. The ultraviolet (UV) spectrum of VII is also identical with that of VI.

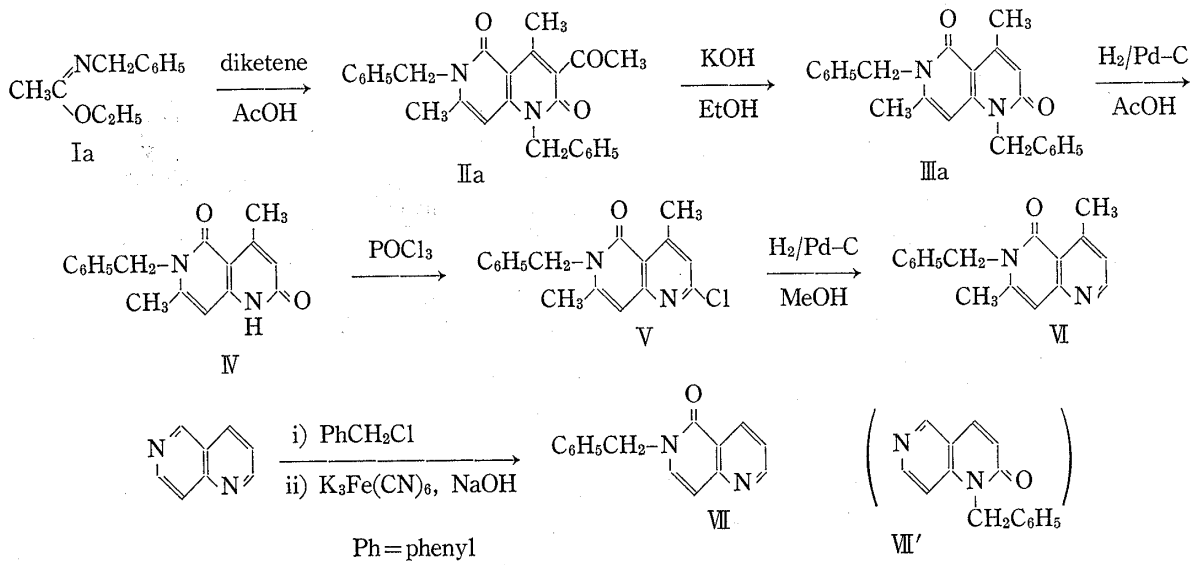


Chart 1

Similarly, cyclic imidates or lactim ethers such as 2-methoxy-1-pyrroline (Ib), 2-methoxy-3,4,5,6-tetrahydropyridine (Ic), and 2-methoxy-3,4,5,6-tetrahydro-7*H*-azepine (Id) were allowed to react with diketene to give the 1,6-naphthyridine derivatives (IIb—d), which on treatment with potassium hydroxide in ethanol were transformed into the deacetylated derivatives (IIIb—d).

Although the mechanism of this reaction is still obscure at present, a likely pathway is shown in Chart 3. For instance, lactim ether (Ic) has an enamine character (Ic'), nucleophilic attack of which to another molecule of Ic would give rise to IX *via* a dimerized intermediate (VIII). Nucleophilic attack of IX to the carbonyl carbon of diketene gives rise to the aceto-acetylated intermediate (X), which cyclizes to the pyridonaphthyridine derivative (XI). Addition of the second molecule of diketene to XI affords an intermediate (XII), which transforms to 6-acetyl-7-methyl-2,3,10,11,12,13-hexahydro-1*H*,5*H*,8*H*-quinolizino-[1,9-*ab*]quinolizine-5,8-dione (IIc).

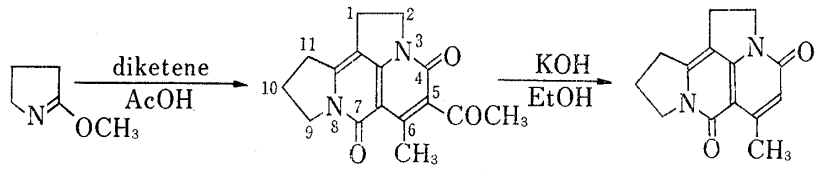
Since IIc has a modified structure of matridine, an alkaloid of *Sophora alopecuroides* L., further investigation to obtain allomatridine is now in progress.

Experimental[5]

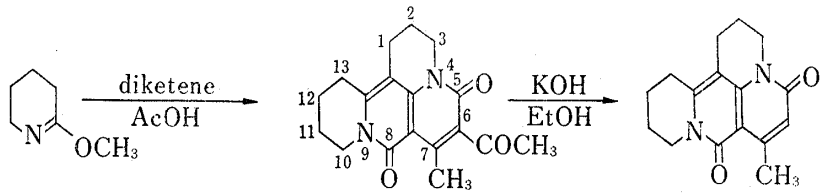
3-Acetyl-1,6-dibenzyl-4,7-dimethyl-1*H*,6*H*-1,6-naphthyridine-2,5-dione (IIa)——To a solution of ethyl N-benzylacetimidate (Ia) (11 g) in AcOH (30 ml), was added diketene (11 g) dropwise. After allowing

4) W.W. Paudler and T.J. Kress, *J. Heterocyclic Chem.*, **5**, 561 (1968).

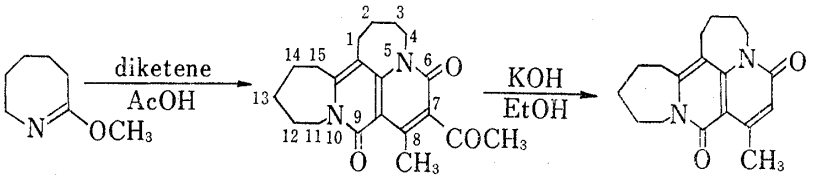
5) All melting points are uncorrected. The IR spectra were determined on a Jasco IR-S Spectrophotometer. The NMR spectra were obtained on a Hitachi-Perkin-Elmer R-20 NMR spectrometer with tetramethylsilane as an internal standard. The UV spectra were measured on a Beckman DB-G UV spectrophotometer. Abbreviation: s, singlet; d, doublet; dd, double doublet, m, multiplet.



Ib IIb IIIb

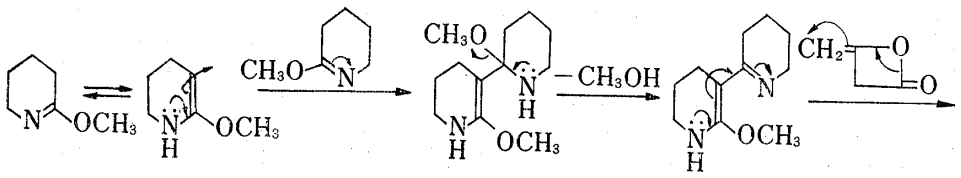


Ic IIc IIIc

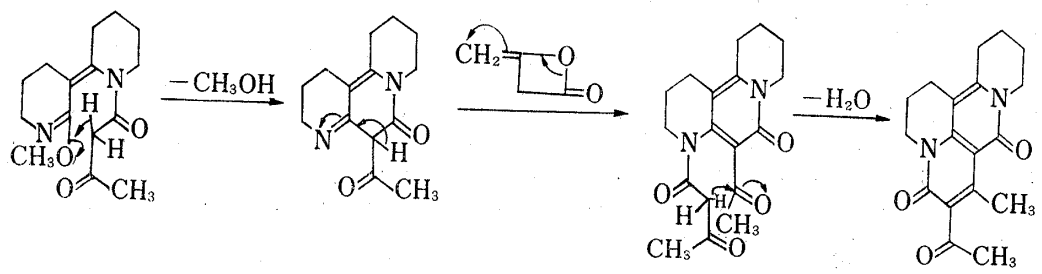


Id IId IIId

Chart 2



Ic Ic′ VIII IX



X XI XII IIc

Chart 3

to stand at room temperature overnight, the reaction mixture was condensed *in vacuo*. The residue was purified by alumina chromatography using ether as an eluant to give a crystalline substance. Recrystallization from EtOH gave colorless needles of mp 117°. Yield, 6.5 g (51%). *Anal.* Calcd. for $C_{26}H_{24}O_3N_2$ (IIa): C, 75.70; H, 5.87; N, 6.79. Found: C, 75.49; H, 5.94; N, 6.84. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1635. NMR ($CDCl_3$, ppm): 2.24 (3H, s, CH_3), 2.54 (3H, s, CH_3), 2.65 (3H, s, CH_3), 5.24 (2H, s, $-NCH_2-$), 5.48 (2H, s, $-NCH_2-$), 6.02 (1H, s, $-CH=C\langle$), 7.0—7.4 (10H, m). UV λ_{max}^{EtOH} nm (log ε): 228 (4.50), 263 (3.99), 346 (4.14).

1,6-Dibenzyl-4,7-dimethyl-1*H*,6*H*-1,6-naphthyridine-2,5-dione (IIIa)——A suspension of IIa (2 g) in a mixture of 50% KOH (20 ml) and EtOH (30 ml) was refluxed for 7 hr, and condensed under reduced pressure to give an oily residue, to which H_2O was added. The mixture was washed with benzene. The benzene washing was dried over K_2CO_3, and the solvent was removed. The residue was purified by alumina column chromatography using ether as an eluant to give a crystalline substance. Recrystallization from $CHCl_3$–cyclohexane gave colorless needles of mp 143—145°. Yield, 1.7 g (95%). *Anal.* Calcd. for $C_{24}H_{22}O_2N_2$ (IIIa): C, 77.81; H, 5.99; N, 7.56. Found: C, 78.10; H, 5.98; N, 7.73. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650. NMR ($CDCl_3$, ppm): 2.18 (3H, s, CH_3), 2.66 (3H, s, CH_3), 5.14 (2H, s, $-NCH_2-$), 5.26 (2H, s, $-NCH_2-$), 5.86 (1H, s, $-CH=C\langle$), 6.26 (1H, s, $-CH=C\langle$), 6.9—7.3 (10H, m). UV λ_{max}^{EtOH} nm (log ε): 228 (4.48), 260 (4.10), 270 (3.98), 333 (4.08).

6-Benzyl-4,7-dimethyl-1*H*,6*H*-1,6-naphthyridine-2,5-dione (IV)——A suspension of IIIa (0.74 g) and 20% Pd-C (1 g) in AcOH (20 ml) was shaken in H_2 stream at 80° until the absorption of H_2 had been ceased. After removal of the catalyst by suction, the filtrate was condensed *in vacuo*. The residual solid was recrystallized from MeOH to colorless needles of mp 283—285° (decomp.). Yield, 0.28 g (50%). *Anal.* Calcd. for $C_{17}H_{16}O_2N_2$ (IV): C, 72.84; H, 5.75; N, 9.99. Found: C, 73.03; H, 5.95; N, 9.61. IR ν_{max}^{KBr} cm^{-1}: 3400—3440, 1655. NMR (CF_3CO_2H, ppm): 2.62 (3H, s, CH_3), 3.02 (3H, s, CH_3), 5.56 (2H, s, $-NCH_2-$), 6.80 (1H, s, $-CH=C\langle$), 6.98 (1H, s, $-CH=C\langle$), 7.0—7.4 (5H, m). UV λ_{max}^{EtOH} nm (log ε): 244 (4.33), 325 (4.17).

6-Benzyl-2-chloro-4,7-dimethyl-6*H*-1,6-naphthyridin-5-one (V)——A mixture of IV (1.4 g) and $POCl_3$ (10 ml) was heated on a steam bath for 3 hr. The reaction mixture was poured into ice water, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The extract was dried over K_2CO_3, and the solvent was evaporated. The residue was purified by recrystallization from ether to colorless needles of mp 126—127°. Yield, 1.25 g (84%). *Anal.* Calcd. for $C_{17}H_{15}ON_2Cl$ (V): C, 68.34; H, 5.03; N, 9.38; Cl, 11.89. Found: C, 68.55; H, 5.27; N, 9.11; Cl, 11.61. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1635. NMR ($CDCl_3$, ppm): 2.35 (3H, s, CH_3), 2.84 (3H, s, CH_3), 5.28 (2H, s, $-NCH_2-$), 6.46 (1H, s, $-CH=C\langle$), 7.02 (1H, s, $-CH=C\langle$), 7.1—7.4 (5H, m). UV λ_{max}^{EtOH} nm (log ε): 250 (3.95), 304 (4.05).

6-Benzyl-4,7-dimethyl-6*H*-1,6-naphthyridin-5-one (VI)——A mixture of V (0.6 g) and 5% Pd-C (0.1 g) in MeOH (50 ml) was shaken in H_2 stream until the absorption of H_2 had been ceased. After removal of the catalyst by suction, the filtrate was evaporated. The residue was recrystallized from ether–petroleum ether to colorless needles of mp 111—112°. Yield, 0.4 g (75%). *Anal.* Calcd. for $C_{17}H_{16}ON_2$ (VI): C, 77.25; H, 6.10; N, 10.60. Found: C, 76.83; H, 6.28; N, 10.68. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1655. NMR ($CDCl_3$, ppm): 2.34 (3H, s, CH_3), 2.88 (3H, s, CH_3), 5.28 (2H, s, $-NCH_2-$), 6.50 (1H, s, $-CH=C\langle$), 7.1—7.3 (5H, m), 7.98 (1H, d, J=4.5 Hz, $-CH=CH-$), 8.52 (1H, d, J=4.5 Hz, $-CH=CH-$), UV λ_{max}^{EtOH} nm (log ε): 299 (4.03).

6-Benzyl-6*H*-1,6-naphthyridin-5-one (VII)——A mixture of 1,6-naphthyridine[6] (1.3 g, 0.01 mole) and benzyl chloride (1.2 g, 0.01 mole) was heated on a steam bath for 1 hr. After cooling, the mixture was diluted with H_2O (30 ml) and washed with ether. To the H_2O fraction, was added a solution of potassium ferricyanide (6.6 g) in H_2O (20 ml). The mixture was made alkaline with 8% NaOH (20 ml, 0.04 mole), and stirred at room temperature for 3 hr. The reaction mixture was extracted with $CHCl_3$, and the solvent was evaporated. The resulting residue was purified by alumina chromatography, using $CHCl_3$ as an eluant to afford colorless crystals, which were recrystallized from ether to colorless needles of mp 122—123.5°. Yield, 1.3 g (55%). *Anal.* Calcd. for $C_{15}H_{12}ON_2$ (VII): C, 76.25; H, 5.12; N, 11.86. Found: C, 76.04; H, 5.36; N, 11.81. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1650. NMR ($CDCl_3$, ppm): 5.22 (2H, s, $-NCH_2-$), 6.75 (1H, d, J=7.5 Hz), 7.3—7.7 (7H, m), 8.70 (1H, dd, J=8.0, 2.0 Hz), 8.88 (1H, dd, J=4.5, 1.5 Hz). UV λ_{max}^{EtOH} nm (log ε): 244 (4.00), 295 (4.00).

5-Acetyl-6-methyl-4,7-dioxo-1,2,10,11-tetrahydro-4*H*,7*H*,9*H*-dipyrrolo[1,2-*g*: 3′,2′,1′-*ij*]-1,6-naphthyridine (IIb)——To a solution of Ib (5 g) in AcOH (20 ml), was added dropwise diketene (8.4 g) with stirring. After allowing to stand overnight, the reaction mixture was condensed *in vacuo*, the crystals separated were collected by suction, washed with small amount of acetone, and recrystallized from EtOH to pale yellow needles (IIb) of mp 255—257° (decomp.). Yield, 1.2 g. The filtrate was condensed *in vacuo*, and the resulting residue was purified by alumina column chromatography using ether as an eluant giving additional 1.3 g of IIb. Total yield, 2.5 g (35%). *Anal.* Calcd. for $C_{16}H_{16}O_3N_2$ (IIb): C, 67.59; H, 5.67; N, 9.81. Found: C, 67.64; H, 5.75; N, 9.85. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1695 (shoulder), 1680, 1640. NMR ($CDCl_3$, ppm): 1.9—2.4 (2H, m), 2.50 (3H, s, CH_3), 2.60 (3H, s, CH_3), 2.8—3.3 (4H, m), 3.9—4.5 (4H, m). UV λ_{max}^{EtOH} nm (log ε): 228 (4.37), 251 (4.27), 267 (3.98), 338 (4.07).

6-Methyl-4,7-dioxo-1,2,10,11-tetrahydro-4*H*,7*H*,9*H*-dipyrrolo[1,2-*g*: 3′,2′,1′-*ij*]-1,6-naphthyridine (IIIb)——A suspension of IIb (0.57 g) in a mixture of 50% KOH (10 ml) and EtOH (20 ml) was refluxed for 6 hr. After removal of EtOH by vacuum distillation, the residue was extracted with $CHCl_3$. The extract was dried over K_2CO_3, and condensed. The residue was purified by alumina column chromatography, using MeOH as an eluant to afford a crystalline substance. Recrystallization from acetone gave colorless needles of mp 250—252° (decomp.). Yield, 0.28 g (56%). *Anal.* Calcd. for $C_{14}H_{14}O_2N_2$ (IIIb): C, 69.40; H, 5.83; N, 11.56. Found: C, 69.13; H, 5.82; N, 11.42. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670. NMR ($CDCl_3$, ppm): 2.0—2.5 (2H, m), 2.64 (3H, s, CH_3), 2.8—3.3 (4H, m), 3.9—4.5 (4H, m), 6.12 (1H, s, $-CH=C\langle$). UV λ_{max}^{EtOH} nm (log ε): 228 (4.37), 248 (4.30), 262 (4.08), 272 (3.95), 320 (4.02).

6-Acetyl-7-methyl-5,8-dioxo-2,3,10,11,12,13-hexahydro-1*H*,5*H*,8*H*-quinolizino[1,9-*ab*]quinolizine(IIc)——Diketene (8.4 g) was added dropwise to a solution of Ic (5.6 g) in AcOH (20 ml) with stirring. After allow-

ing to stand overnight at room temperature, the reaction mixture was condensed *in vacuo* to give crystalline substance, which was purified by recrystallization from EtOH to colorless needles of mp 241°. Yield, 5.1 g (66%). *Anal.* Calcd. for $C_{18}H_{20}O_3N_2$ (IIc): C, 69.21; H, 6.45; N, 8.97. Found: C, 68.82; H, 6.56; N, 9.14. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1630. NMR ($CDCl_3$, ppm): 1.7—2.2 (6H, m), 2.48 (3H, s, CH_3), 2.60 (3H, s, CH_3), 2.40—3.0 (4H, m), 3.8—4.2 (4H, m). UV λ_{max}^{EtOH} nm (log ε): 231 (4.42), 250 (4.26), 270 (3.92), 352 (4.17).

7-Methyl-5,8-dioxo-2,3,10,11,12,13-hexahydro-1*H*,5*H*,8*H*-quinolizino[1,9-*ab*]quinolizine (IIIc)——A suspension of IIc (0.63 g) in a mixture of 50% KOH (10 ml) and EtOH (20 ml) was refluxed for 6 hr. After removal of the organic solvent, the reaction mixture was diluted with H_2O, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over K_2CO_3, filtered, and condensed. The resulting residue was purified by recrystallization from EtOH to pale yellow needles of mp 238—240° (decomp.). Yield, 0.45 g (84%). *Anal.* Calcd. for $C_{16}H_{18}O_2N_2$ (IIIc): C, 71.09; H, 6.71; N, 10.36. Found: C, 71.37; H, 7.04; N, 10.61. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1640. NMR ($CDCl_3$, ppm): 1.7—2.2 (6H, m), 2.4—2.9 (4H, m), 2.66 (3H, s, CH_3), 3.8—4.2 (4H, m), 6.22 (1H, s, –CH=C⟨). UV λ_{max}^{EtOH} nm (log ε): 230 (4.32), 250 (4.20), 268 (3.87), 340 (4.00).

7-Acetyl-8-methyl-6,9-dioxo-1,2,3,4,12,13,14,15-octahydro-6*H*,9*H*,11*H*-bisazepino[1.2-*g*: 3′,2′,1′-*ij*]-1,6-naphthyridine (IId)——Diketene (8.4 g) was added dropwise to a solution of Id (6.4 g) in AcOH with stirring. After allowing to stand overnight at room temperature, the reaction mixture was condensed *in vacuo*. Ether was added to the residue, and the mixture was allowed to stand at room temperature to give a crystalline substance, which was purified by recrystallization from benzene–$CHCl_3$ to give colorless prisms of mp 203—204°. Yield, 3.4 g (40%). *Anal.* Calcd. for $C_{20}H_{24}O_3N_2$ (IId): C, 70.56; H, 7.11; N, 8.23. Found: C, 70.70; H, 7.26; N, 8.31. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1630. NMR ($CDCl_3$, ppm): 1.6—2.2 (10H, m), 2.50 (3H, s, CH_3), 2.60 (3H, s, CH_3), 2.5—3.1 (4H, m), 4.1—4.5 (4H, m). UV λ_{max}^{EtOH} nm (log ε): 232 (4.41), 252 (4.22), 274 (3.96), 358 (4.13).

8-Methyl-6,9-dioxo-1,2,3,4,12,13,14,15-octahydro-6*H*,9*H*,11*H*-bisazepino[1,2-*g*: 3′,2′,1′-*ij*]-1,6-naphthyridine (IIId)——A suspension of IId (0.68 g) in a mixture of 50% KOH (10 ml) and EtOH (20 ml) was refluxed for 6 hr. After removal of EtOH by vacuum distillation, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ solution was dried, and condensed. The resulting residue was purified by alumina chromatography using $CHCl_3$ as an eluant to give a crystalline substance. Recrystallization from acetone gave colorless needles of mp 185—186°. Yield, 0.32 g (54%). *Anal.* Calcd. for $C_{18}H_{22}O_2N_2$ (IIId): C, 72.45; H, 7.43; N, 9.37. Found: C, 72.50; H, 7.56; N, 9.59. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1654. NMR ($CDCl_3$, ppm): 1.6—2.3 (10H, m), 2.65 (3H, s, CH_3), 2.6—3.1 (4H, m), 4.1—4.5 (4H, m), 6.25 (1H, s, –CH=C⟨). UV λ_{max}^{EtOH} nm (log ε): 232 (4.35), 252 (4.20), 270 (3.97), 345 (4.02).

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