[Chem. Pharm. Bull.]
34(5) 2018—2023(1986)

Condensed Heteroaromatic Ring Systems. V.¹⁾ Formal Synthesis of Matrine and Related Compounds Using Palladium-Catalyzed Carbon–Carbon Bond Formations as Key Reactions

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(Received October 15, 1985)

The iodination and subsequent dehydroxychlorination of 1,6-naphthyridin-5(6*H*)-one gave 5-chloro-8-iodo-1,6-naphthyridine, which was converted to the 5-methoxy derivative. Starting from this compound, didehydromatrine was synthesized by using palladium-catalyzed cross-coupling reactions with ethyl acrylate and 3-butyn-1-ol, as key reactions. Similarly, nordehydro- α -matrinidine was synthesized through four steps from 8-bromo-1,6-naphthyridine, obtained by the bromination of unsubstituted 1,6-naphthyridine.

Keywords—synthesis; matrine; didehydromatrine; nordehydro- α -matrinidine; palladium-catalyzed reaction; 1,6-naphthyridine; ethyl acrylate; 3-butyn-1-ol

As a part of our investigations on the synthesis of condensed heteroaromatic ring systems, we developed^{1,2)} two methods for the general synthesis of various naphthyridinones from halopyridines using palladium-catalyzed reactions. In order to utilize these methods in the field of natural product syntheses, extensive studies have been carried out. The present paper deals with a synthesis of didehydromatrine (**15**), which has already been transformed to matrine (**16**).³⁾

Chart 1

Firstly, 1,6-naphthyridine derivatives, having favorable substituents for the synthesis of didehydromatrine (**15**) were prepared in the following manner. The reaction of 1,6-naphthyridin-5(6*H*)-one (**1**)²⁾ with iodine under alkaline conditions gave 8-iodo-1,6-

naphthyridin-5(6*H*)-one (2), which was converted to 5-chloro-8-iodo-1,6-naphthyridine (3) by the conventional phosphoryl chloride treatment. Although 3 reacted with ethyl acrylate in the presence of palladium acetate in triethylamine to give the desired ethyl 5-chloro-1,6-naphthyridine-8-acrylate (4) selectively, further condensation of 4 with 3-butyn-1-ol in the presence of dichlorobis(triphenylphosphine)palladium in triethylamine failed to give the desired ethyl 5-(4-hydroxybut-1-yn-1-yl)-1,6-naphthyridine-8-acrylate (5). It is likely that the chloro substituent at the 5-position of 4 is removed during the transformation of the unsaturated side-chain of 4 to a saturated one by catalytic hydrogenation.

Thus, in order to protect the 5-position from catalytic hydrogenation, 3 was converted to 8-iodo-5-methoxy-1,6-naphthyridine (6) by treatment with sodium methoxide, palladium-catalyzed reaction of which with ethyl acrylate gave ethyl 5-methoxy-1,6-naphthyridine-8-acrylate (7) in 88% yield. The structure of the 1,6-naphthyridine-8-acrylates (4 and 7), including the *trans* side-chain geometry, was supported by the spectral data.

Chart 2

Then, the skeleton of 15 was constructed by intramolecular amide formation. The catalytic hydrogenation of 7 over platinum dioxide gave selectively ethyl 5-methoxy-1,2,3,4-tetrahydro-1,6-naphthyridine-8-propionate (8). On treatment with sodium methoxide, 8 underwent cyclization to give the desired tricyclic lactam (9) in good yield. Demethylation of 9 with hydroiodic acid yielded the tricyclic α -pyridone (10). When 10 was heated with phosphoryl bromide, dehydroxybromination accompanied with oxidation resulted in the formation of the bromonaphthyridinone (11), whose spectral data clearly demonstrated the presence of an olefinic linkage.

Subsequently, another side-chain with four carbon atoms was introduced into 11 by the palladium-catalyzed reaction of 11 with 3-butyn-1-ol, and the butynyl compound (12) was obtained in 70% yield, as expected. The butynyl compound (12) was hydrogenated to the butanol (13) by catalytic hydrogenation over palladium carbon under atmospheric pressure. The catalytic hydrogenation of 13 with Raney nickel under moderate hydrogen pressure (6 atm), yielded the dihydropyridonebutanol (14). Compound 12 was directly hydrogenated to 14 with Raney nickel under the same hydrogen pressure (6 atm) in 79% yield. Finally, the carbonyl group of 14 was removed by reduction with sodium bis(2-methoxyethoxy)aluminum hydride (Vitrider®) in toluene at 100°C. The didehydromatrine (15) thus obtained has already been derived to matrine (16) in three steps by Okuda *et al.*³⁾

In addition to the investigation described above, the synthesis of nordehydro- α -matrinidine (22), the skeleton of didehydromatrine (15), was accomplished in a similar

Chart 3

manner.

The bromination of 1,6-naphthyridine (17) in carbon tetrachloride was reported⁴⁾ to give a mixture of 8-bromo- (18) (23%), 3-bromo- (18%), and 3,8-dibromo-1,6-naphthyridine (11%). When 17 was brominated with bromine in acetic acid, however, 18 was obtained as the main product.

Chart 4

The palladium-catalyzed cross-coupling reaction of 18 with ethyl acrylate smoothly proceeded to give ethyl 1,6-naphthyridine-8-acrylate (19). When 19 was hydrogenated over palladium carbon under atmospheric pressure, the tetrahydro intermediate (20), in contrast to the case of the similar compound (8), cyclized to the tricyclic lactam (21) during the hydrogenation. Although 21 was resistant to lithium aluminum hydride reduction, the amide group was successfully removed by treatment with Vitride[®] to give the desired product (22).

The hydrobromide of **22** was identical with an authentic specimen of nordehydro- α -matrinidine hydrobromide.

The present results demonstrate that the palladium-catalyzed carbon-carbon bond formation is efficient for the construction of hetero-polycyclic ring systems.

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. Proton nuclear magnetic resonance (^1H -NMR) spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer, and chemical shifts are expressed in δ (ppm) values relative to Me_4Si and sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal standards. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=double doublet, and br=broad.

8-Iodo-1,6-naphthyridin-5(6H)-one (2)—A mixture of 1,6-naphthyridin-5(6H)-one (**1**)² (1.46 g, 10 mmol), **I**₂ (2.52 g, 10 mmol), and 0.4 N NaOH (50 ml) was heated at 80 °C for 3 h. The mixture was diluted with H_2O , then the precipitate was collected and recrystallized from MeOH to give pale yellow needles, mp 274–277 °C. Yield 1.90 g (70%). IR (KBr) cm^{-1} : 3160, 1660. ^1H -NMR ($\text{DMSO}-d_6$): 7.62 (1H, dd, $J=4.0, 8.0$ Hz), 7.95 (1H, s), 8.55 (1H, dd, $J=2.0, 8.0$ Hz), 9.05 (1H, dd, $J=2.0, 4.0$ Hz), 11.7–12.0 (1H, br s). Anal. Calcd for $\text{C}_8\text{H}_5\text{IN}_2\text{O}$: C, 35.32; H, 1.85; N, 10.30. Found: C, 35.33; H, 1.63; N, 9.89.

5-Chloro-8-iodo-1,6-naphthyridine (3)—A mixture of **2** (1.76 g, 6.5 mmol) and POCl_3 (30 ml) was refluxed for 1.5 h. After evaporation of the excess POCl_3 , the residue was poured into ice-water. The resulting mixture was made alkaline with K_2CO_3 and extracted with CHCl_3 . The crude product obtained from the CHCl_3 extract, was recrystallized from cyclohexane to give colorless needles, mp 127–129 °C. Yield 1.20 g (64%). ^1H -NMR (CDCl_3): 7.68 (1H, dd, $J=4.0, 8.0$ Hz), 8.58 (1H, dd, $J=2.0, 8.0$ Hz), 8.96 (1H, s), 9.20 (1H, dd, $J=2.0, 4.0$ Hz). Anal. Calcd for $\text{C}_8\text{H}_4\text{ClIN}_2$: C, 33.08; H, 1.39; N, 9.64. Found: C, 33.09; H, 1.24; N, 9.26.

Ethyl 5-Chloro-1,6-naphthyridine-8-acrylate (4)—A mixture of **3** (1.26 g, 4.3 mmol), ethyl acrylate (0.60 g, 6.0 mmol), $\text{Pd}(\text{OAc})_2$ (30 mg), and Et_3N (2 ml) was heated in a sealed tube at 100 °C for 14 h. After dilution with H_2O , the mixture was extracted with CHCl_3 . The CHCl_3 extract was purified by SiO_2 column chromatography using C_6H_6 as an eluent. The C_6H_6 eluate gave colorless needles, which were recrystallized from cyclohexane, mp 129.5–131 °C. Yield 0.53 g (47%). IR (CHCl_3) cm^{-1} : 1720. ^1H -NMR (CDCl_3): 1.38 (3H, t, $J=7.0$ Hz), 4.37 (2H, q, $J=7.0$ Hz), 7.06 (1H, d, $J=16.0$ Hz), 7.69 (1H, dd, $J=4.0, 8.0$ Hz), 8.55 (1H, d, $J=16.0$ Hz), 8.65 (1H, dd, $J=2.0, 8.0$ Hz), 8.73 (1H, s), 9.22 (1H, dd, $J=2.0, 4.0$ Hz). Anal. Calcd for $\text{C}_{13}\text{H}_{11}\text{ClN}_2\text{O}_2$: C, 59.44; H, 4.22; N, 10.66. Found: C, 59.28; H, 3.97; N, 10.33.

8-Iodo-5-methoxy-1,6-naphthyridine (6)—A solution of **3** (2.90 g, 10 mmol) in MeONa – MeOH , prepared from Na (0.25 g, 10 mmol) and dry MeOH (20 ml), was refluxed for 1 h. After removal of the MeOH, the residue was diluted with H_2O , and the mixture was extracted with CHCl_3 . The crude product, obtained from the CHCl_3 extract, was recrystallized from CH_2Cl_2 –hexane to give pale yellow needles, mp 120–121 °C. Yield 2.80 g (98%). ^1H -NMR (CDCl_3): 4.13 (3H, s), 7.51 (1H, dd, $J=4.0, 8.0$ Hz), 8.50 (1H, dd, $J=2.0, 8.0$ Hz), 8.65 (1H, s), 9.12 (1H, dd, $J=2.0, 4.0$ Hz). Anal. Calcd for $\text{C}_9\text{H}_7\text{IN}_2\text{O}$: C, 37.78; H, 2.46; N, 9.79. Found: C, 37.70; H, 2.19; N, 9.62.

Ethyl 5-Methoxy-1,6-naphthyridine-8-acrylate (7)—A mixture of **6** (4.20 g, 15 mmol), ethyl acrylate (2.50 g, 25 mmol), $\text{Pd}(\text{OAc})_2$ (50 mg), Et_3N (2.50 g, 25 mmol), and MeCN (50 ml) was heated at 85 °C in a sealed tube for 24 h. After dilution with H_2O , the mixture was extracted with CHCl_3 . The crude product, obtained from the CHCl_3 extract, was purified by SiO_2 column chromatography using CHCl_3 as an eluent. The CHCl_3 eluate gave colorless needles, which were recrystallized from hexane, mp 101–104 °C. Yield 3.33 g (88%). IR (CHCl_3) cm^{-1} : 1710. ^1H -NMR (CDCl_3): 1.37 (3H, t, $J=7.0$ Hz), 4.17 (3H, s), 4.33 (2H, q, $J=7.0$ Hz), 7.13 (1H, d, $J=16.0$ Hz), 7.50 (1H, dd, $J=4.0, 8.0$ Hz), 8.40 (1H, d, $J=16.0$ Hz), 8.47 (1H, s), 8.57 (1H, dd, $J=2.0, 8.0$ Hz), 9.12 (1H, dd, $J=2.0, 4.0$ Hz). Anal. Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.09; H, 5.22; N, 10.60.

Ethyl 5-Methoxy-1,2,3,4-tetrahydro-1,6-naphthyridine-8-propionate (8)—A solution of **7** (3.00 g, 12 mmol) in MeOH (200 ml) was hydrogenated over PtO_2 (200 mg) under atmospheric pressure at room temperature. The reaction was stopped after 3 eq of H_2 had been absorbed, and the reaction mixture was filtered. After removal of the MeOH, the residue was distilled under reduced pressure to give a colorless liquid, bp 150 °C (3 mmHg). Yield 2.56 g (83%). IR (CHCl_3) cm^{-1} : 3460, 1725. ^1H -NMR (CDCl_3): 1.25 (3H, t, $J=7.0$ Hz), 1.6–2.3 (2H, m), 2.4–2.9 (6H, m), 3.0–3.6 (2H, m), 3.90 (3H, s), 4.16 (2H, q, $J=7.0$ Hz), 4.54 (1H, br s), 7.57 (1H, s). Monopicrate: yellow needles (CH_2Cl_2 –hexane), mp 130–134 °C (dec.). Anal. Calcd for $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_3$ (monopicrate): C, 48.68; H, 4.70; N, 14.19. Found: C, 48.72; H, 4.60; N, 13.90.

1-Methoxy-6-oxo-4,5,9,10-tetrahydro-6H,8H-pyrido[3,2,1-ij][1,6]naphthyridine (9)—A solution of **8** (2.56 g, 9.7 mmol) in MeONa – MeOH , prepared from Na (0.27 g, 12 mmol) and dry MeOH (70 ml), was refluxed for 0.5 h. After removal of the MeOH, the residue was diluted with H_2O , and extracted with CHCl_3 . The crude product, obtained from the CHCl_3 extract, was recrystallized from hexane to give colorless needles, mp 102–103 °C. Yield 2.00 g (95%). IR (CHCl_3) cm^{-1} : 1675. ^1H -NMR (CDCl_3): 1.7–2.2 (2H, m), 2.4–3.2 (6H, m), 3.7–4.1 (2H, m), 3.92

(3H, s), 7.70 (1H, s). *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.29; H, 6.50; N, 12.94.

1,6-Dioxo-1,2,4,5,9,10-hexahydro-6H,8H-pyrido[3,2,1-ij][1,6]naphthyridine (10)—A solution of **9** (2.44 g, 11 mmol) in 57% HI (30 ml) was heated at 80 °C for 4.5 h. The mixture was poured into ice-water, made alkaline with K_2CO_3 , and extracted with $CHCl_3$. The crude product, obtained from the $CHCl_3$ extract, was recrystallized from MeOH–AcOEt to give colorless needles, mp 265–270 °C (dec.). Yield 1.93 g (85%). IR ($CHCl_3$) cm^{-1} : 1640. 1H -NMR ($CDCl_3$): 1.6–2.3 (2H, m), 2.4–3.0 (6H, m), 3.7–4.1 (2H, m), 7.14 (1H, s), 12.7–13.5 (1H, br s). *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.42; H, 5.95; N, 13.57.

1-Bromo-6-oxo-9,10-dihydro-6H,8H-pyrido[3,2,1-ij][1,6]naphthyridine (11)—A mixture of **10** (3.00 g, 15 mmol) and $POBr_3$ (30 g) was heated at 120 °C for 5 h. The mixture was poured into ice-water, made alkaline with K_2CO_3 , and extracted with $CHCl_3$. The crude product, obtained from the $CHCl_3$ extract, was purified by SiO_2 column chromatography using C_6H_6 –AcOEt (3:1) and AcOEt as eluents. The AcOEt eluate gave colorless needles, mp 215–218 °C, which were recrystallized from CH_2Cl_2 –hexane. Yield 2.49 g (64%). IR ($CHCl_3$) cm^{-1} : 1660. 1H -NMR ($CDCl_3$): 1.8–2.6 (2H, m), 2.8–3.3 (2H, m), 4.0–4.4 (2H, m), 6.75 (1H, d, $J=10.0$ Hz), 7.72 (1H, d, $J=10.0$ Hz), 8.43 (1H, s). *Anal.* Calcd for $C_{11}H_9BrN_2O_2$: C, 49.83; H, 3.42; N, 10.56. Found: C, 49.84; H, 3.21; N, 10.41.

4-(6-Oxo-9,10-dihydro-6H,8H-pyrido[3,2,1-ij][1,6]naphthyridin-1-yl)-3-butyn-1-ol (12)—A mixture of **11** (1.50 g, 5.7 mmol), 3-butyn-1-ol (0.60 g, 8.6 mmol), $Pd(PPh_3)_2Cl_2$ (200 mg), CuI (100 mg), Et_3N (1.00 g, 10 mmol), and dimethylformamide (DMF) (20 ml) was heated at 65 °C for 5 h. After removal of the DMF under reduced pressure, the residue was diluted with H_2O , made alkaline with K_2CO_3 , and extracted with $CHCl_3$. The crude product, obtained from the $CHCl_3$ extract, was purified by SiO_2 column chromatography using $CHCl_3$ – Et_3N (9:1) as an eluent. The $CHCl_3$ – Et_3N (9:1) eluate gave colorless needles, mp 189–191 °C, which were recrystallized from C_6H_6 . Yield 1.01 g (70%). IR ($CHCl_3$) cm^{-1} : 3300, 2240, 1660. 1H -NMR ($CDCl_3$): 1.8–2.6 (2H, m), 2.7–3.4 (4H, m), 3.5–4.5 (5H, m), 6.72 (1H, d, $J=10.0$ Hz), 7.68 (1H, d, $J=10.0$ Hz), 8.56 (1H, s). *Anal.* Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.54; N, 11.01. Found: C, 70.53; H, 5.48; N, 10.73.

6-Oxo-9,10-dihydro-6H,8H-pyrido[3,2,1-ij][1,6]naphthyridine-1-butanol (13)—A solution of **12** (0.50 g, 20 mmol) in MeOH (30 ml) was hydrogenated over 10% Pd–C (150 mg) under atmospheric pressure at room temperature. The reaction was stopped after 2 eq of H_2 had been absorbed, and the reaction mixture was filtered. After removal of the MeOH, the residue was recrystallized from C_6H_6 –hexane to give colorless needles, mp 135–137 °C. Yield 0.47 g (93%). IR ($CHCl_3$) cm^{-1} : 3640, 1660. 1H -NMR ($CDCl_3$): 1.3–2.6 (6H, m), 2.7–3.2 (4H, m), 3.13 (1H, s), 3.6–4.0 (2H, m), 4.0–4.3 (2H, m), 6.68 (1H, d, $J=10.0$ Hz), 7.38 (1H, d, $J=10.0$ Hz), 8.59 (1H, s). *Anal.* Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.80; H, 7.03; N, 10.58.

6-Oxo-4,5,9,10-tetrahydro-6H,8H-pyrido[3,2,1-ij][1,6]naphthyridine-1-butanol (14)—i) A solution of **13** (0.60 g, 2.3 mmol) in MeOH (30 ml) was hydrogenated over Raney Ni, prepared from Ni–Al alloy (3.0 g), under a pressure of 6 atm at room temperature. The reaction was stopped after 1 eq of H_2 had been absorbed, and the reaction mixture was filtered. After removal of the MeOH, the residue was recrystallized from CH_2Cl_2 –hexane to give colorless needles, mp 136.5–137 °C. Yield 0.51 g (83%). IR ($CHCl_3$) cm^{-1} : 3640, 1680. 1H -NMR ($CDCl_3$): 1.2–2.3 (6H, m), 2.3–3.1 (8H, m), 3.1–4.0 (5H, m), 8.10 (1H, s). *Anal.* Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 68.95; H, 7.92; N, 10.51.

ii) A solution of **12** (1.32 g, 5.2 mmol) in MeOH (40 ml) was hydrogenated over Raney Ni, prepared from Ni–Al alloy (6.0 g), under a pressure of 6 atm at room temperature. The reaction was stopped after 3 eq of H_2 had been absorbed, and the reaction mixture was filtered. After removal of the MeOH, the residue was recrystallized from CH_2Cl_2 –hexane to give **14**. Yield 1.07 g (79%).

Didehydromatrine (15)—Vitride® (70% in toluene) (3 ml, 10 mmol) was added to a solution of **14** (0.69 g, 2.7 mmol) in dry toluene (15 ml), and the mixture was heated at 100 °C for 1 h. The mixture was poured into ice-water and extracted with $CHCl_3$. The crude product, obtained from the $CHCl_3$ extract, was recrystallized from CH_2Cl_2 –hexane to give colorless prisms, mp 101–103 °C (lit.⁵⁾ mp 105–106 °C). Yield 0.48 g (74%). IR ($CHCl_3$) cm^{-1} : 3640. 1H -NMR ($CDCl_3$): 1.3–2.3 (8H, m), 2.3–3.0 (6H, m), 3.0–3.5 (4H, m), 3.5–3.9 (2H, m), 4.66 (1H, br s), 7.70 (1H, s).

8-Bromo-1,6-naphthyridine (18)—Bromine (14.0 g, 85 mmol) was added to a solution of 1,6-naphthyridine (**17**) (10.0 g, 77 mmol) in AcOH (100 ml), and the mixture was heated at 80 °C for 12 h. After removal of the AcOH under reduced pressure, the residue was poured into ice-water, made alkaline with K_2CO_3 , and extracted with $CHCl_3$. The crude product, obtained from the $CHCl_3$ extract, was purified by SiO_2 column chromatography using $CHCl_3$ as an eluent. The $CHCl_3$ eluate gave colorless needles, mp 82–84 °C (lit.⁴⁾ mp 84–86 °C), which were recrystallized from cyclohexane. Yield 8.80 g (55%). 1H -NMR ($CDCl_3$): 7.63 (1H, dd, $J=4.0, 8.0$ Hz), 8.31 (1H, dd, $J=2.0, 8.0$ Hz), 9.00 (1H, s), 9.18 (1H, s), 9.1–9.4 (1H, m).

Ethyl 1,6-Naphthyridine-8-acrylate (19)—A mixture of **18** (0.80 g, 3.9 mmol), ethyl acrylate (0.80 g, 7.8 mmol), $Pd(OAc)_2$ (20 mg), PPh_3 (40 mg), Et_3N (0.50 g, 4.7 mmol), and MeCN (4 ml) was heated at 120 °C in a sealed tube for 24 h. After dilution with H_2O , the mixture was extracted with $CHCl_3$, and the $CHCl_3$ layer was extracted with 3N HCl. The 3N HCl layer was made alkaline with K_2CO_3 and extracted with ether. The crude product, obtained from the ethereal extract, was recrystallized from ether–hexane to give pale yellow needles, mp 90–92 °C. Yield 0.60 g

(69%). IR (CHCl₃) cm⁻¹: 1720. ¹H-NMR (CDCl₃): 1.38 (3H, t, *J*=7.0 Hz), 4.35 (2H, q, *J*=7.0 Hz), 7.14 (1H, d, *J*=16.0 Hz), 7.62 (1H, dd, *J*=4.0, 8.0 Hz), 8.37 (1H, dd, *J*=2.0, 8.0 Hz), 8.62 (1H, d, *J*=16.0 Hz), 9.00 (1H, s), 9.20 (1H, dd, *J*=2.0, 4.0 Hz), 9.30 (1H, s). *Anal.* Calcd for C₁₃H₁₂N₂O₂: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.18; H, 5.44; N, 12.00.

6-Oxo-4,5,9,10-tetrahydro-6*H*,8*H*-pyrido[3,2-*ij*][1,6]naphthyridine (21)—A solution of 19 (4.15 g, 18 mmol) in EtOH (100 ml) was hydrogenated over 10% Pd-C (1.0 g) under atmospheric pressure at room temperature. The reaction was stopped after 3 eq of H₂ had been absorbed, and the reaction mixture was filtered. After removal of the EtOH, the residue was purified by SiO₂ column chromatography using CHCl₃ as an eluent. The CHCl₃ eluate gave colorless needles, mp 109.5–111.5 °C, which were recrystallized from cyclohexane. Yield 2.62 g (76%). IR (CHCl₃) cm⁻¹: 1660. ¹H-NMR (CDCl₃): 1.7–2.2 (2H, m), 2.3–3.1 (6H, m), 3.7–4.1 (2H, m), 8.25 (2H, s). *Anal.* Calcd for C₁₁H₁₂N₂O: C, 70.18; H, 6.43; N, 14.88. Found: C, 70.07; H, 6.35; N, 14.80.

Nordehydro- α -matrinidine (22)—Vitride® (70% in toluene) (9 ml, 30 mmol) was added to a solution of 21 (2.00 g, 11 mmol) in dry toluene (30 ml), and the mixture was refluxed for 48 h. The mixture was poured into ice-water and extracted with CHCl₃. The crude product, obtained from the CHCl₃ extract, was distilled under reduced pressure to give a pale yellow solid, bp 145 °C (3 mmHg). Yield 1.20 g (64%). ¹H-NMR (CDCl₃): 1.7–2.2 (4H, m), 2.4–2.9 (4H, m), 3.0–3.4 (4H, m), 7.79 (2H, s). Hydrobromide: colorless needles (MeOH-AcOEt), mp 272 °C (lit.⁶) mp 275 °C).

Acknowledgement The authors are grateful to Professor Shigenobu Okuda, Institute of Applied Microbiology, University of Tokyo, for providing an authentic specimen of nordehydro- α -matrinidine hydrobromide.

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