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Synthesis in the Diazasteroid Group. XVIII. Syntheses of the 9,17-Diazasteroid System[1]

Katsuhide Matoba,* Akiko Fukushima, Hiroki Takahata, Yoshiro Hirai, and Takao Yamazaki

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani, Toyama, 930-01, Japan

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A 9,17-diazasteroid system, I, was synthesized from an aminoester, III, and cyclohexanone. Unfortunately the yield was poor. Another 9,17-diazasteroid system, II, was prepared from the condensation product, XVa, of quinoline *N*-oxide with an active methine compound, IV. Thus, XVa was hydrolyzed, followed by decarboxylation, reduction and cyclization. The yield in each step to II was moderate.

Keywords——azasteroid; diazasteroid; quinoline *N*-oxide; cyclization; Pictet-Spengler reaction; active methylene compound; pyrrolopyridine; quinolylpyrrolidine

Syntheses of various diazasteroid systems are of interest in view of their possible biological activities. We have succeeded in synthesizing the 9,17-diazasteroid system (I and II) *via* two different routes, A and B. For the route A, ethyl 4,5,6,7-tetrahydro[1*H*]pyrrolo[3,2-*c*]-pyridine-4-acetate (IIIa) or its 1-methyl derivative (IIIb) and cyclohexanone were chosen as the starting materials. For the route B, quinoline and ethyl 3-carbethoxy-2-carbethoxymethylidene-1-methylpyrrolidine (IV) were chosen. We are not aware of any previous report on the 9,17-diazasteroid system.

First, the former method will be described. In attempts to obtain IIIa or IIIb as a possible synthetic intermediate, the reaction[2] of 4-chloro-2,3,6-trimethyl[1*H*]pyrrolo-[3,2-*c*]pyridine (Vc) and ethyl acetoacetate and the reaction[3] of 2,3,6-trimethyl[1*H*]pyrrolo-[3,2-*c*]pyridine (Vd) and acetic anhydride were tried, but without success. This result indicated that nucleophilic substitution at the C_2-position of the pyrrolo[3,2-*c*]pyridine system was difficult under these conditions. IIIa and IIIb could be synthesized moderately effectively by the following method. [1*H*]pyrrole or 1-methyl[1*H*]pyrrole was derived to 2-(2-aminoethyl)[1*H*]pyrrole (VIa) or its 1-methyl derivative (VIb) by the method reported by Herz *et al.*[4] The amide (VII) obtained from VIa and ethyl malonate was subjected to the Bischler–Napieralski reaction under various conditions to give a product, 4-carbethoxymethylidene-4,5,6,7-tetrahydro[1*H*]pyrrolo[3,2-*c*]pyridine (VIII), though in poor yield. VIII exhibited triplet signals at δ 7.17 ppm in the nuclear magnetic resonance (NMR) spectrum due to the vinylic proton in the vinylogous urethane moiety. To obtain a better result, the Pictet–Spengler reaction was examined; VIa was treated with ethyl 3,3-diethoxy propionate (IX) in hydrochloric acid to give IIIa as a viscous oil in satisfactory yield. In a similar fashion, the *N*-methyl analog (IIIb) could be synthesized in 20.9% yield. The condensation reaction of IIIa and cyclohexanone was examined using a Dean–Stark water separator under an Ar atmosphere. When toluene was used as a solvent, 9,17-diazagona-5(10), 13,15-trien-6-one (Ia) was obtained in 2.1% yield. Ia exhibited absorption signals at 1610 and 1530 cm^{-1} due to the vinylogous amide group in the infrared (IR) spectrum, and absorption maxima at 332 and 226 nm in the ultraviolet (UV) spectrum. The yield of Ia was improved a little by using xylene as a solvent. In this case, 2-[2-(*N*-cyclohexylidene)aminoethyl]-3-carbethoxymethylidenemethyl[1*H*]pyrrole (X), an intermediate, was also obtained. However, the formation of Ia could not be detected when trifluoroacetic acid (TFA) or *p*-toluenesulfonic acid was used as an acid catalyst in the condensation reaction.[2] In a similar manner, the *N*-methyl analog

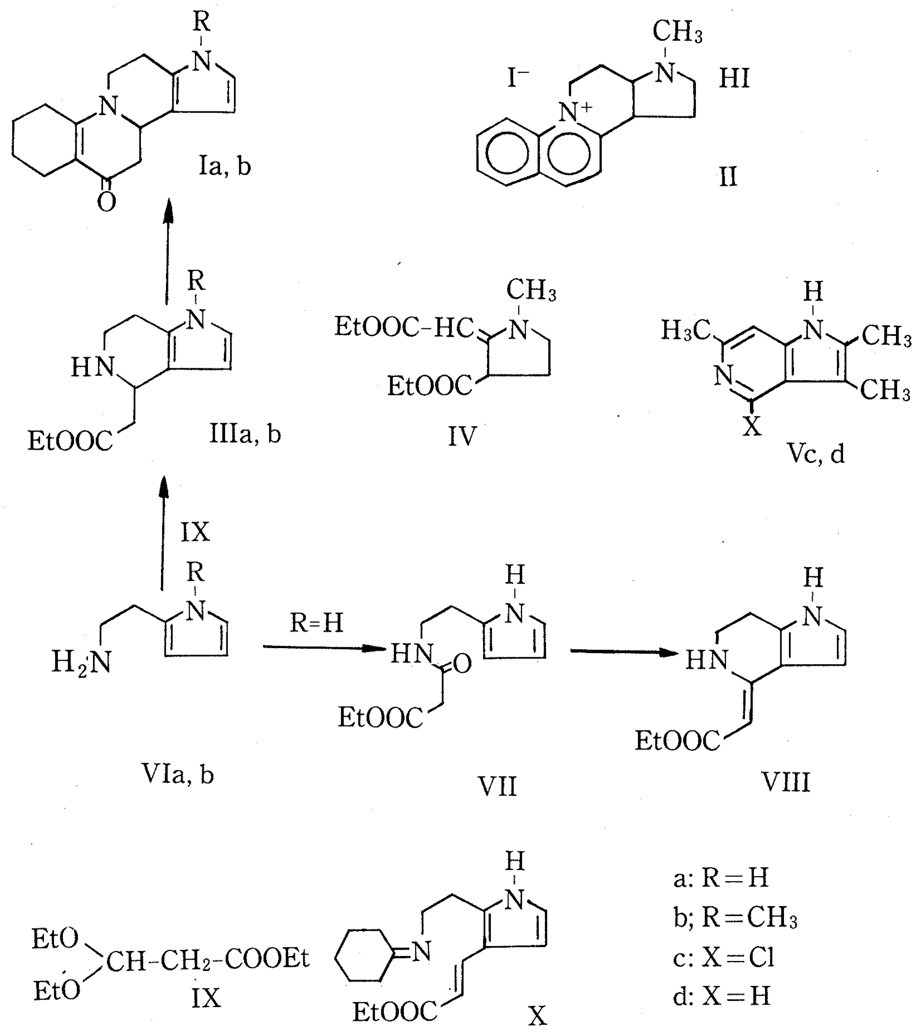

Chart 1

(IIIb) was treated with cyclohexanone in xylene to give the corresponding diazasteroid (Ib) in 4.2% yield. In the NMR spectrum of Ib, two doublet signals at δ 5.95 and 6.54 ppm due to the protons at C_{15} and C_{16} were observed. The invariable formation of a resinous product suggested that decomposition of the pyrrole ring moiety of III was preferred to the condensation between III and cyclohexanone. Therefore, the 9,17-diazasteroid system had to be constructed without using a pyrrole ring as the steroidal segment of the D ring. For this purpose, the reaction between quinoline *N*-oxide and pyrrolidine derivatives containing an active methine group at the C_3-position was examined (route B). Quinoline N-oxide was treated in the presence of acetic anhydride[5] with 3-carbethoxy-1-methyl-2-pyrrolidone (XI) to give the expected product, 3-carbethoxy-1-methyl-3-(2-quinolyl)-2-pyrrolidone (XIIa), in 55% yield. XIIa exhibited absorption signals at 1720 and 1670 cm^{-1} in the IR spectrum and a singlet peak at δ 2.9 ppm in the NMR spectrum due to the protons of the *N*-methyl group. XIIa was hydrolyzed and decarboxylated by heating it on a water bath for 30 min with sodium hydroxide in aqueous methanol to give 1-methyl-3-(2-quinolyl)-2-pyrrolidone (XIIb). XIIb was a solid which melted at 52—54°C, and the IR spectrum showed an absorption signal at 1665 cm^{-1}. To apply the sulfide contraction sequence,[6] XIIb was treated with phosphorus pentasulfide in pyridine or carbon disulfide to give only a purple pigment in a low yield. The structure of the pigment was deduced to be 2-mercapto-1-methyl-3-(2-quinolyl)[1*H*]pyrrole (XIII) from the mass and NMR spectra. The NMR spectrum showed a pair of doublets at δ 7.86 and 8.95 ppm due to the protons attached at C$_4$ and C$_5$ of the pyrrole ring. As the above attempt was unsuccessful, the synthesis of IV and its condensation with quinoline N-oxide were examined. First, 1-methyl pyrrolidone was derived to thiolactam with phosphorus pentasulfide followed by the sulfide contraction sequence with ethyl bromoacetate to give 2-carbethoxymethylidene-1-methylpyrrolidine (XIV), which exhibited absorption bands at 1670 and 1590 cm^{-1} in the IR spectrum due to the vinylogous urethane moiety, and exhibited a singlet singnal at δ 4.35 ppm due to the vinylic proton in the NMR spectrum. However, XIV could not be derived to IV by the reaction with ethyl carbonate in the presence of sodium hydride in benzene.7) Therefore, XI was treated with phosphorus pentasulfide followed by ethyl bromoacetate to give IV. In this case, ethyl iodoacetate was used instead of ethyl bromoacetate, and the yield improved dramatically. IV exhibited two singlet signals at δ 2.80 and 4.45 ppm due to the protons of the *N*-methyl group and vinylic proton, respectively, in the NMR spectrum. IV was condensed with quinoline *N*-oxide in the presence of

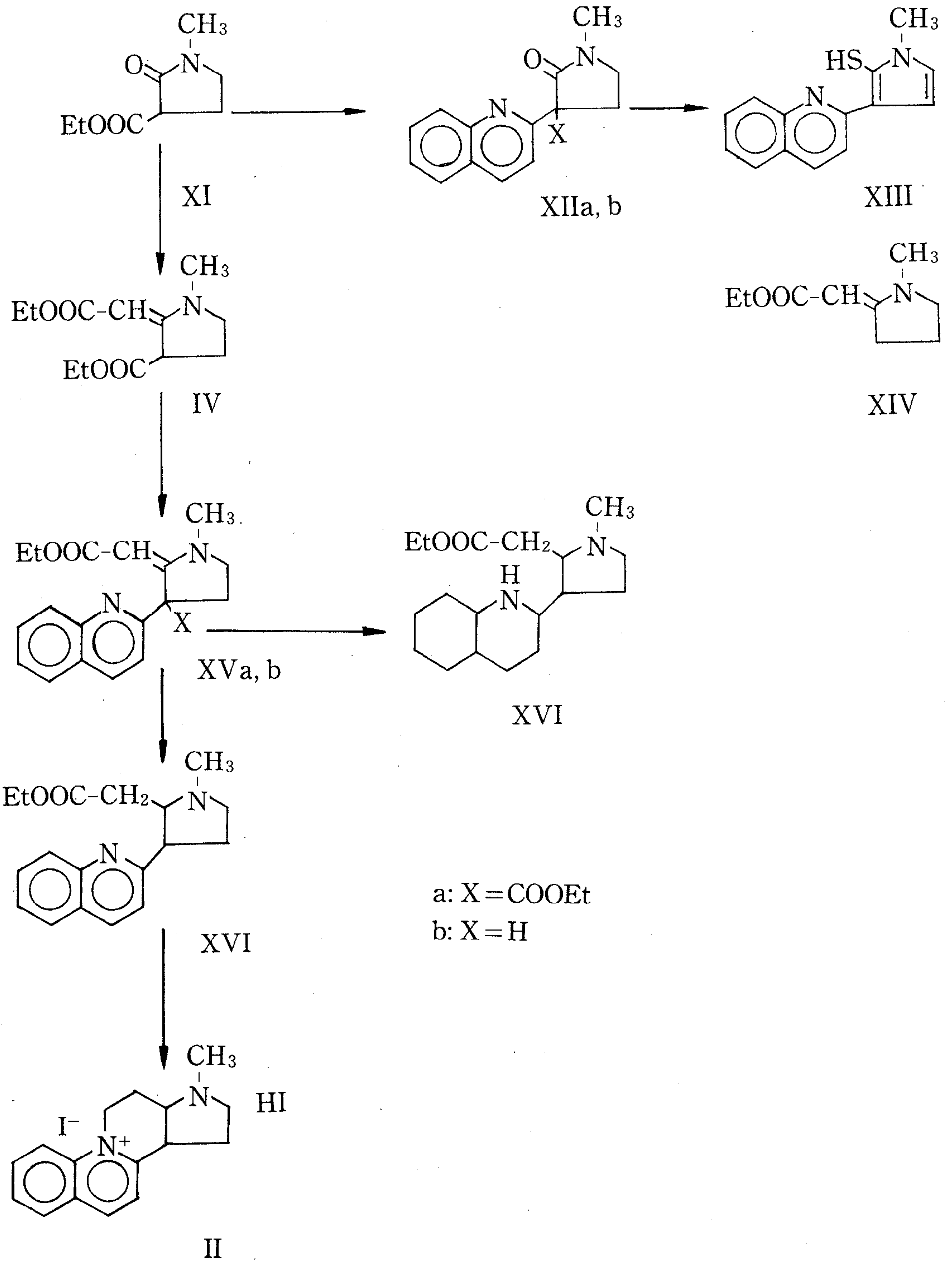

Chart 2

acetic anhydride at 70°C to give 3-carbethoxy-2-carbethoxymethylidene-1-methyl-3-(2-quinolyl)pyrrolidine (XVa), which melted at 101—102°C and exhibited absorption maxima at 1730, 1670 and 1580 cm^{-1} in the IR spectrum. The hydrolysis and decarboxylation of XVa were performed by treatment with aqueous sodium hydroxide in methanol on a water bath. 2-Carbethoxymethylidene-1-methyl-3-(2-quinolyl)pyrrolidine (XVb) prepared in such a way melted at 77—78°C and exhibited absorption bands at 1660 and 1580 cm^{-1} in the IR spectrum and exhibited signals at δ 5.3 and 4.5 ppm due to the C$_3$-proton and vinylic proton, respectively, in the NMR spectrum. Next, the double bond and the ester group in the vinylogous urethane moiety of XVb had to be reduced to construct the C-ring of the diazasteroid skeleton. First, XVb was reduced in acetic acid in the presence of Adams' catalyst to give 2-carbethoxymethyl-1-methyl-3-(2-perhydroquinolyl)pyrrolidine (XVI) in a yield of 88.5%. When ethanol was used as a solvent in the catalytic reduction, the starting material was entirely recovered. Finally XVb was reduced with sodium cyanoborohydride in methanolic hydrochloric acid8) to give 2-carbethoxymethyl-1-methyl-3-(2-quinolyl)pyrrolidine (XVII) as a viscous oily material in a moderate yield. The IR spectrum of XVII showed an absorption band at 1730 cm^{-1} due to the ester group, and the NMR spectrum showed the absence of a vinylic proton. XVII was treated with lithium aluminum hydride in tetrahydrofuran followed by *p*-toluenesulfonyl chloride in pyridine.9) The product obtained in each step was not purified, and the crude tosylate in hydrochloric acid was derived to the iodide, II, the structure of which was elucidated by consideration of the mass spectrum and the elemental analysis data. In view of the sharp melting point, II was supposed to be a single isomer in terms of the C/D ring junction. A study of Dreiding stereomodels suggested that the trans isomer may be prefered to the cis isomer. As the purity of XVII could not be confirmed, the stereochemistry was not studied. II was moderately soluble in water and adequate for biological assay.

Experimental

All melting points are uncorrected. IR spectra were determined by using a Hitachi 215 grating spectrophotometer or JASCO IRA-1 diffraction grating spectrophotometer; absorption data are given in cm^{-1}. NMR spectra were recorded on a JEOL C-60H spectrometer, JEOL PMX-60 spectrometer, or Varian EM-390 spectrometer with TMS as an internal standard. The chemical shifts and coupling constants(J) are given in δ and Hz, respectively. Mass spectra were measured with a JEOL TMS-01SG (70 eV, direct inlet system) spectrometer. UV spectra were obtained in ethanol with a Hitachi 200-10 spectrophotometer, and absorption maxima are given in nm. All solvents were removed by evaporation under reduced pressure.

Reaction of Vc and Sodio Ethyl Acetoacetate2)——A suspension of Vc (1.0 g, 5.2 mmol), sodio ethyl acetoacetate (1.2 g, 7.8 mmol), and ethyl acetoacetate (0.1 g) in xylene was refluxed with stirring for 20 h. After being cooled, the mixture was poured into ice-water to give a precipitate which was recrystallized from aq. EtOH and identified as Vc. The recovery yield was 0.75 g (75%).

2,3,6-Trimethyl [1*H*]Pyrrolo[3,2-*c*]pyridine (Vd)——A methanolic solution of Vc (0.4 g, 2.0 mmol) was shaken with fused AcOK (1.4 g, 14.3 mmol) and 10% Pd-C (0.2 g) under moderate pressure10) (3—4 atm) of H$_2$ for 5.5 h. The filtrate was concentrated and the residue was washed (as its CHCl$_3$ solution) with aq. Na$_2$CO$_3$ solution and brine. The dried organic layer was concentrated to give a crystalline compound, which was recrystallized from aq. EtOH. mp 201—203°C. The yield of Vd was 128 mg (38.8%). IR (Nujol): $\nu_{C=C}$ 1620, 1583, 1560. NMR (CDCl$_3$): 2.15, 2.30 (each 3H, s, 2×-CH$_3$), 2.59 (3H, s, C$_6$-CH$_3$), 7.20 (1H, s, C$_7$-H), 8.25 (1H, d, J=6, C$_4$-H). MS *m/e*: 160 (M$^+$, base peak).

Reaction with Vd and Acetic Anhydride3)——A mixture of Vd (0.35 g, 2.2 mmol) and acetic anhydride (3 ml) was refluxed for 2 d. The reaction mixture was poured into ice-water and extracted with CHCl$_3$. The organic layer was washed with 10% NaOH solution and brine. The residue obtained after the removal of CHCl$_3$ by evaporation was deduced from the data mentioned below to be 1-acetyl-2,3,6-trimethylpyrrolo[3,2-*c*]pyridine. The yield was 0.17 g (38.5%). IR (Nujol): $\nu_{C=O}$ 1675, $\nu_{C=C}$ 1605, 1560. NMR (CDCl$_3$): 2.15 (3H, s, -COCH$_3$), 2.46, 2.63, 2.65 (each 3H, s, 3×-CH$_3$), 7.65 (1H, s, C$_7$-H), 8.60 (1H, s, C$_4$-H).

1-Carbethoxy-*N*-[2-(2-pyrrolylethyl)]acetamide (VII)——A mixture of 2-pyrrolylethylamine (VI)4) (1.7 g, 15.4 mmol) and diethyl malonate (24.6 g, 15.4 mmol) was heated overnight at 110—120°C under an Ar atmosphere. The mixture was cooled and diethyl malonate was distilled off, bp 54°C (6 mmHg). The residue was purified by passage through an Al$_2$O$_3$ column and VII was eluted with CHCl$_3$. The yield was 1.6 g (44.8%). It was a viscous oily compound. IR (film): $\nu_{C=O}$ 1740, 1655, δ_{NH} 1560. NMR (CDCl$_3$): 1.25

(3H, t, $J=7$, $-CH_2-\underline{CH_3}$), 2.65—3.67 (6H, m, $3\times>CH_2$), 4.14 (2H, q, $J=7$, $-\underline{CH_2}-CH_3$), 5.88—6.07 (2H, m β-H of pyrrole), 6.59 (1H, m, α-H of pyrrole). MS *m/e* (%): 224 (M^+, 100), 179 (M-OEt, 38.7).

4-Carbethoxymethylidene-4,5,6,7-tetrahydro[1*H*]pyrrolo[3,2-*c*]pyridine (VIII)——A toluene solution (50 ml) of $POCl_3$ (1.1 g, 6.7 mmol) was added dropwise to a toluene solution (180 ml) of VII (1.5 g, 6.7 mmol) over 20 min at room temperature, then the mixture was refluxed for 4 h to give a red solution with a deep-red precipitate. The residue obtained after removal of the solvent was extracted with $CHCl_3$. From the organic layer, VII (0.3 g) was obtained. The mother solution was basified with conc. KOH and extracted with Et_2O. The residue obtained from the organic layer was recrystallized from benzene. mp 128—129°C. The yield was 32 mg (2.3%). IR (Nujol): $\nu_{C=O}$ 1635, $\nu_{C=C}$ 1592, 1550. NMR ($CDCl_3$): 1.20 (3H, t, $J=7$, $-CH_2-\underline{CH_3}$), 2.62 and 3.28 (each 2H, t like, $J=6.5$, $>CH_2$), 4.00 (2H, q, $J=7$, $-\underline{CH_2}-CH_3$), 4.77 (1H, s, $>NH$), 6.13, 6.44, and 7.17 (each 1H, d, $J=3$, vinylic H), 8.07 (1H, br s, $>NH$ of pyrrole). *Anal.* Calcd for $C_{11}H_{14}N_2O_2$: C, 64.08; H, 6.80; N, 13.59. Found: C, 63.88; H, 6.87; N, 13.30.

4-Carbethoxymethyl-4,5,6,7-tetrahydro[1*H*]pyrrolo[3,2-*c*]pyridine (IIIa)——Ethyl 3,3-diethoxypropionate (IX) (8.17 g, 43 mmol)$^{11)}$ was added to an aq. solution (120 ml) of VI (4.5 g, 41 mmol) adjusted to pH 4.0 with conc. HCl, and the mixture was heated at 75°C with stirring for 24 h under an Ar atmosphere. After being basified with 10% NaOH solution, the mixture was extracted with $CHCl_3$. The organic solution was washed with brine and dried over $MgSO_4$. A deep-red oil obtained after the removal of $CHCl_3$ was fractionated through an Al_2O_3 column and IXa was obtained from the fraction eluted with benzene. The yield was 3.2 g (37.8%). IR (film): $\nu_{C=O}$ 1705. UV, λ_{max}: 327, 312. NMR ($CDCl_3$): 1.27 (3H, t, $J=8$, $-CH_2-\underline{CH_3}$), 2.30—3.31 (7H, m, $3\times>CH_2+>NH$), 4.20 (2H, q, $J=8$, $-\underline{CH_2}-CH_3$), 4.36 (1H, t, $J=6$, $-CH<$), 5.98 (1H, t, $J=4$, β-H of pyrrole), 6.63 (1H, t, $J=4$, α-H of pyrrole), 8.73 (1H, br s, $>NH$ of pyrrole).

4-Carbethoxymethyl-1-methyl-4,5,6,7-tetrahydro[1*H*]pyrrolo[3,2-*c*]pyridine (IIIb)——In a manner similar to that used in the preparation of IIIa, IIIb was obtained from VI (2.0 g, 16 mmol) and IX (3.1 g, 16 mmol). In this case, IIIb was eluted with $CHCl_3$–benzene (1:9) in Al_2O_3 column chromatography. The yield was 750 mg (20.9%). NMR ($CDCl_3$): 1.27 (3H, t, $J=7$, $-CH_2-\underline{CH_3}$), 2.11—3.50 (7H, m, $3\times>CH_2+>CH-$), 3.49 (3H, s, $>N-CH_3$), 4.20 (2H, q, $J=7$, $-\underline{CH_2}-CH_3$), 5.90 (1H, d, $J=3$, β-H of pyrrole), 6.50 (1H, d, $J=3$, α-H of pyrrole).

9,17-Diazagona-5(10),13,15-trien-6-one (Ia)——A mixture of IIIa (0.53 g, 2.5 mmol) and cyclohexanone (0.5 g, 5 mmol) in toluene (20 ml) was refluxed using an apparatus equipped with a Dean-Stark water separator for 100 h. The residue obtained after removal of the solvent was purified through an Al_2O_3 column. Ia was eluted with benzene–$CHCl_3$ (1:1) and recrystallized from EtOH. mp>300°C. The yield was 12.8 mg (2.1%). IR (Nujol): ν_{NH} 3220, $\nu_{C=O}$ 1610, $\nu_{C=C}$ 1530. NMR ($CDCl_3$): 1.23—1.63 and 2.10 (10H, br s, $5\times>CH_2$), 2.54 and 3.10 (each 2H, symmetrical t, $J=6$, C_{11}- and C_{12}-H), 4.16 (1H, m, C_8-H), 6.05 and 6.63 (each 1H, t, $J=3$, C_{15}- and C_{16}-H), 8.00 (1H, br s, C_{17}-H). UV, λ_{max} (ε): 332 (29000), 226 (16000). *Anal.* Calcd for $C_{15}H_{18}N_2O$: C, 74.38; H, 7.44; N, 11.57. Found: C, 74.21; H, 7.61; N, 11.76. When xylene was used as a solvent, the reaction mixture was refluxed for 70 h and molecular sieves (3A: 4A=1: 1) were packed into the water separator. The yield of Ia was 6.7%. In Al_2O_3 column chromatography, 2-[2-(*N*-cyclohexylidene)-aminoethyl]-3-carbethoxymethylidenemethyl[1*H*]pyrrole (X) was eluted in the benzene fraction. The yield of X was 1.8%. mp 156—158°C (recrystallized from EtOH). IR (Nujol): $\nu_{C=O}$ 1675, 1607. NMR ($CDCl_3$): 1.32 (3H, t, $J=7$, $-CH_2-\underline{CH_3}$), 1.70—1.87 (10H, $5\times>CH_2$), 2.88 and 3.09 (each 2H, d, $J=4$, $>N-CH_2-CH_2-$), 4.28 (2H, q, $J=7$, $-\underline{CH_2}-CH_3$), 6.03 and 7.70 (each 1H, $J=16$, AB type, vinylic H), 6.41 and 6.73 (each 1H, d, $J=3$, β- and α-H of pyrrole). *Anal.* Calcd for $C_{17}H_{24}N_2O_2$: C, 70.83; H, 8.34; N, 9.72. Found: C, 70.87; H, 8.59; N, 9.85.

17-Methyl-9,17-diazagona-5(10),13,15-trien-6-one (Ib)——A xylenic solution of IIIb (0.5 g, 2.3 mmol) and cyclohexanone (0.44 g, 4.5 mmol) was refluxed for 40 h. The residue obtained after removal of the solvent by evaporation was purified through an Al_2O_3 column. Ib was eluted with benzene and recrystallized from $CHCl_3$–Et_2O. mp 149—151°C. The yield of Ib was 24 mg (4.2%). IR (Nujol): ν 1600, 1535. UV, λ_{max} (ε): 333 (12400). NMR ($CDCl_3$): 1.27—2.80 (14H, m, $7\times>CH_2$), 3.53 (3H, s, $>N-CH_3$), 4.20 (1H, m, C_8-H), 5.95 and 6.54 (each 1H, d, $J=3$, C_{15}- and C_{16}-H). MS *m/e*: 256 (M^+, base peak). *Anal.* Calcd for $C_{16}H_{20}N_2O$: C, 75.00; H, 7.81; N, 10.94. Found: C, 74.91; H, 7.87; N, 10.72.

3-Carbethoxy-1-methyl-3-(2-quinolyl)-2-pyrrolidone (XIIa)——A mixture of quinoline *N*-oxide (3 g, 20.7 mmol), 3-carbethoxy-1-methyl-2-pyrrolidone$^{7)}$ (4.6 g, 26.9 mmol), and Ac_2O (2.8 g, 27.5 mmol) was heated at 70°C for 20 h. The mixture was poured into a mixture of pyridine (1 ml) and water (20 ml). The solution was extracted with $CHCl_3$. The organic layer was washed with sat. $NaHCO_3$ and brine. After removal of the solvent, the residue was purified through an Al_2O_3 column. XIIa was eluted with benzene and recrystallized from hexane–Et_2O. mp 99—101°C. The yield was 55.0%. IR (Nujol): $\nu_{C=O}$ 1720, 1670. NMR (CCl_4): 1.20 (3H, t, $J=8$, $-CH_2-\underline{CH_3}$), 2.80 (3H, s, $>N-CH_3$), 3.2—3.9 (4H, m, $2\times>CH_2$), 4.20 (2H, q, $J=8$, $-\underline{CH_2}-CH_3$), 7.2—8.3 (6H, m, aromatic H). *Anal.* Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.52; H, 6.12; N, 9.30.

1-Methyl-3-(2-quinolyl)-2-pyrrolidone (XIIb)——A mixture of XIIa (1.5 g, 5.0 mmol) in MeOH (9 ml) and NaOH (0.8 g, 20 mmol) in water (10 ml) was warmed on a water bath at 60°C for 30 min. The cooled reaction mixture was diluted with water and extracted with $CHCl_3$. After the removal of the solvent by evaporation, the residue was crystallized and recrystallized from Et_2O. mp 52—54°C. The yield was

84.1%. IR (Nujol): $\nu_{C=O}$ 1665. NMR ($CDCl_3$): 2.4—3.2 and 3.3—3.8 (each 2H, m, $>CH_2$), 2.95 (3H, s, $>N-CH_3$), 4.00 (1H, t m, $J=8$, $>CH-$), 7.2—8.4 (6H, m, aromatic H). *Anal.* Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.11; H, 6.26; N, 12.09.

2-Mercapto-1-methyl-3-(2-quinolyl)[1*H*]pyrrole (XIII)——A mixture of XIIb (1.0 g, 4.4 mmol) and P_2S_5 (0.5 g, 2.3 mmol) in CS_2 was refluxed for 18 h. The cooled reaction mixture was poured into water and the solution was extracted with $CHCl_3$. The purple residue obtained after removal of the solvent was purified on an SiO_2 column. XIII was obtained from the benzene fraction and recrystallized from benzene. mp 138—139°C (purple prisms). IR (Nujol): ν 1600. NMR ($CDCl_3$–TFA): 3.37 (3H, s, $>N-CH_3$), 7.86 and 8.95 (each 1H, pair of d, $J=8$, vinylic H). MS *m/e* (%): 240 (M^+, base peak), 239 (M-1, 44). *Anal.* Calcd for $C_{14}H_{12}N_2S+H_2O$: C, 65.09; H, 5.46; N, 10.84. Found: C, 65.25; H, 5.55; N, 10.78.

2-Carbethoxymethylidene-1-methylpyrrolidine (XIV)—A mixture of 1-methyl-2-thiopyrrolidone (25 g, 217 mmol) and ethyl bromoacetate (36.3 g, 217 mmol) in CH_3CN (40 ml) was stirred for 16 h at room temperature. The crude salt (28.2 g) precipitated from the cooled mixture. Ph_3P (26.2 g, 0.1 mol) was dissolved in a solution of the crude salt (28.2 g, *ca.* 0.1 mol) in CH_3CN (100 ml), and then Et_3N (10.2 g, 0.1 mol) was added dropwise to the solution over 15 min (exothermic reaction). The mixture was stirred for 4 h, then filtered. The filtrate was diluted with benzene and the benzene solution was washed with brine. After removal of the solvents, the residue was purified through an SiO_2 column and XIV was eluted after Ph_3PS with benzene. bp 140—142°C (5 mmHg). The overall yield from thiolactam was 5.2 g (14.2%). XIV: IR (film): $\nu_{C=O}$ 1670, $\nu_{C=C}$ 1590. NMR (CCl_4): 1.20 (3H, t, $J=8$, $-CH_2-\underline{CH_3}$), 2.76 (3H, s, $>N-CH_3$), 3.97 (2H, q, $J=8$, $-\underline{CH_2}-CH_3$), 4.35 (1H, s, vinylic H). To a benzene solution of XIV (11 g, 70 mmol) and ethyl carbonate (32.5 g, 0.28 mol), NaH (5.5 g of 60% dispersed in oil, 0.14 mol) was added in one portion.[7] The mixture was refluxed overnight but the salt of the expected product could not be obtained. Excess NaH was destroyed with EtOH, then the benzene solution was washed with water and dried. The residue obtained after removal of solvent was distilled. bp 152—154°C (10 mmHg). The physical data were identical with those of XIV. The recovery yield was 5.8 g (52.7%).

3-Carbethoxy-2-carbethoxymethylidene-1-methylpyrrolidine (IV)——A solution of XI (13 g, 76 mmol) in CS_2 (50 ml) was added to a solution of P_2S_5 (8.6 g, 38 mmol) in CS_2 (100 ml) at room temperature with stirring. The reaction mixture was refluxed for 8 h. Benzene and water were added to the residue obtained after removal of the solvent. The benzene layer was washed with brine and dried. After removal of the solvent, the residue was purified through an SiO_2 column and distilled to give 3-carbethoxy-1-methyl-2-thiopyrrolidone. bp 165°C (3 mmHg). The yield of thiolactam was 58.8%. A mixture of the thiolactam (7 g, 37.4 mmol) and ethyl bromoacetate (6.5 g, 38.9 mmol) in CH_3CN (200 ml) was refluxed for 4 h. Ph_3P (9.8 g, 37.4 mmol) and Et_3N (3.7 g, 36.3 mmol) were added to the cooled reaction mixture, and the solution was stirred for 4 h at room temperature. The filtrate was concentrated and the residue was extracted with hexane. The residue obtained after removal of the solvent was purified through an SiO_2 column and distilled to give IV. bp 140°C (0.4 mmHg). The yield was 26.1%. The purity of this compound was checked by GLC [Shimadzu GC-6AM; column SE-30; column temperature 250°C; t_R 4.5 min (cf thiolactam, t_R 3.9 min)]. NMR (CCl_4): 1.26 and 1.30 (each 3H, t, $J=7$, $-CH_2-\underline{CH_3}$), 2.80 (3H, s, $>N-CH_3$), 4.02 and 4.10 (each 2H, q, $J=7$, $-\underline{CH_2}-CH_3$), 4.45 (1H, s, vinylic H). When ethyl iodoacetate (1 mol eq to thiolactam) was used instead of ethyl bromoacetate in the above experiment, the yield was improved to 81.3%.

3-Carbethoxy-2-carbethoxymethylidene-1-methyl-3-(2-quinolyl)pyrrolidine (XVa)——A mixture of IV (5.4 g, 24.2 mmol), quinoline *N*-oxide (2.7 g, 18.6 mmol) and acetic anhydride (2.5 g, 24.5 mmol) was warmed at 70°C for 10 h then at 100°C for 1 h. The reaction mixture was poured into ice-water. The acidified aq. solution was washed with benzene and basified with NH_4OH. The basic solution was extracted with benzene and the benzene layer was dried and concentrated. The residue was purified through an SiO_2 column. XVa and IV were eluted successively with benzene. The yields of XVa and IV were 27.5 and 31.3%, respectively. XVa: mp 101—102°C (white-orange prisms from EtOH). IR (Nujol): $\nu_{C=O}$ 1730, 1670, $\nu_{C=C}$ 1580. NMR ($CDCl_3$): 1.16 and 1.22 (each 3H, t, $J=7$, $-CH_2-\underline{CH_3}$), 2.84 (3H, s, $>N-CH_3$), 4.01 and 4.13 (each 2H, q, $J=7$, $-\underline{CH_2}-CH_3$), 4.47 (1H, s, vinylic H), 7.2—8.5 (6H, m, aromatic H). *Anal.* Calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.56; H, 6.57; N, 7.33.

2-Carbethoxymethylidene-1-methyl-3-(2-quinolyl)pyrrolidine (XVb)——A mixture of XVa (0.11 g, 0.3 mmol) and NaOH (0.1 g, 2.5 mmol) in MeOH (7 ml) was refluxed on a water bath for 5 min. After removal of the solvent, the residue was extracted with Et_2O. An oily material obtained from the Et_2O layer was crystallized from Et_2O. mp 77—78°C (orange prisms). The yield was quantitative. IR (Nujol): $\nu_{C=O}$ 1660, $\nu_{C=C}$ 1580. NMR ($CDCl_3$): 1.17 (3H, t, $J=7$, $-CH_2-\underline{CH_3}$), 3.00 (3H, s, $>N-CH_3$), 3.98 (2H, q, $J=7$, $-\underline{CH_2}-CH_3$), 4.40 (1H, s, vinylic H), 5.0—5.5 (1H, m, C_3–H), 7.2—8.4 (6H, m, aromatic H). *Anal.* Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.16; H, 6.88; N, 9.43.

Reduction of XVb——1) XVb (0.24 g, 0.8 mmol) in AcOH (30 ml) was catalytically reduced in the presence of PtO_2 (0.3 g) under ordinary pressure for 3 h. The filtrate was concentrated and the residue was dissolved in benzene. The benzene layer was washed with sat. $NaHCO_3$ solution and brine, then dried. The oily material obtained after removal of the solvent was purified through an SiO_2 column. From the benzene eluate, 2-carbethoxymethyl-1-methyl-3-(2-perhydroquinolyl)pyrrolidine (XVI) was obtained. The yield was 88.5%. IR (film): $\nu_{C=O}$ 1720. NMR (CCl_4): 1.26 (3H, t, $J=7.5$, $-CH_2-\underline{CH_3}$), 2.16 (3H, s, $>N-CH_3$), 4.09 (2H, q, $J=7.5$, $-\underline{CH}_2-CH_3$). MS *m/e*: 308 (M^+, base peak).

2) XVb (390 mg, 1.3 mmol) in EtOH was catalytically reduced in the presence of PtO_2 (0.3 g) under ordinary pressure for 4 h. The oily material obtained after work-up similar to that used in the preparation of XVI was XVb (365 mg, recovery yield: 93.6%) as judged from the NMR and IR spectra.

3)[8] To a methanolic solution of XVb (580 mg, 2 mmol) was added a pinch of bromocresol green, followed by $NaBH_3CN$ (126 mg, 2 mmol). A 1 M methanolic HCl solution was added dropwise over 3 min until the mixture maintained a yellow color. The mixture was stirred at room temperature for 2 h, then poured into 20 ml of 0.1 N aq. NaOH, and extracted with CH_2Cl_2. The extracts were washed with brine and dried. The residue obtained after removal of the solvent was purified through an SiO_2 column. From the benzene eluate, 2-carbethoxymethyl-1-methyl-3-(2-quinolyl)pyrrolidine (XVII) was obtained. The yield was 53.0%. IR (Nujol): $\nu_{C=O}$ 1730, $\nu_{C=N}$ 1600. NMR (CCl_4): 0.89 (3H, t, $J=7$, $-CH_2-\underline{CH}_3$), 2.30 (3H, s, $>N-CH_3$), 3.81 (2H, q, $J=7$, $-\underline{CH}_2-CH_3$), 7.2—8.2 (6H, m, aromatic H).

17-Methyl-9,17-diazagona-1,3,5(10),6,8-pentaene Hydroiodide (II)——$LiAlH_4$ (0.15 g, 3.9 mmol) was added at room temperature to a solution of XVII (0.2 g, 0.7 mmol) in THF (10 ml). After the mixture had been stirred for 1 h and refluxed for 1 h, NH_4Cl (1 g, 18.7 mmol) and water were added to the cooled reaction mixture to destroy excess reagent. The filtrate was concentrated to give a viscous oily material, 2-(2-hydroxyethyl)-1-methyl-3-(2-quinolyl)pyrrolidine. The crude yield was 55.0%. IR (Nujol): ν_{OH} 3340, $\nu_{C=N}$ 1600. NMR ($CDCl_3$): 2.39 (3H, s, $>N-CH_3$), 4.90 (1H, br s, -OH), 7.3—8.2 (6H, m, aromatic H). To a solution of the crude alcohol (110 mg, 0.43 mmol), *p*-TsCl (110 mg, 0.58 mmol) was added with ice-cooling and stirring. The precipitate obtained after stirring for 2 d was dissolved in 10% HCl (1 ml) and sat. NaI solution (1 ml) was added to give a crystalline compound, which was recrystallized from water. mp 250—252°C. The overall yield from the alcohol was 26.3%. IR (Nujol): $\nu_{C=N}$ 1606. NMR ($CDCl_3$): 2.50 (3H, s, $>N^+(H)\underline{CH}_3$), 4.34 (1H, br s, $>N^+(\underline{H})CH_3$), 7.2—8.3 (6H, m, aromatic H). MS *m/e* (%): 239 (M^+, base peak), 128 (HI, 100). *Anal.* Calcd for $C_{16}H_{20}I_2N_2$: C, 38.89; H, 4.08; N, 5.67. Found: C, 38.85; H, 4.31; N, 5.38.

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References and Notes

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