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Synthesis in the Diazasteroid Group. XVII.[1] Syntheses of the 4,11-Diazasteroid System

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5-(2-Oxocyclopentanecarboxamido)quinoline (IVb) was prepared from 5-aminoquinoline (IVa) and 2-carbethoxycyclopentanone (III) and isolated as a crystalline compound. IVb was treated with polyphosphoric acid-xylene to give 4,11-diazagona-1,3,5(10),6,8,13-hexaen-12-one (I). Two isomers, 4,11-diazagona-5,7,9,13-tetraen-12-one (II) and 1,2,3,4,7,8,9,10,11-nonahydro-4,11-diazacyclopenta[*b*]phenanthren-7-one (VI), were synthesized by the reaction of 1,2,3,4-tetrahydro-5-aminoquinoline (Va) and III in the presence of trifluoroacetic acid. 5-(2-Oxocyclopentanecarboxamido)-2-methoxyquinoline (X) could not be cyclized to the expected diazasteroid system under various conditions tested.

Keywords——diazasteroid; diazaphenanthrene; cyclopentaphenanthrene; photochemistry; aminoquinoline

We have succeeded in synthesizing the 4,11-diazasteroid system (I and II) starting with 5-aminoquinoline derivatives and 2-carbethoxycyclopentanone (III) as the steroidal segments of the A, B rings and the D ring, respectively. Many examples can be found in the literature[2] of syntheses of diazasteroids from aminoquinoline or aminoisoquinoline derivatives. One of these synthesized diazasteroids exhibited slight antileukemic activity.

First, we carried out the reaction of 5-aminoquinoline (IVa) and III to examine the experimental results obtained by Popp *et al.*[2b] IVa was prepared by catalytic reduction of 5-nitroquinoline using Adams' catalyst under ordinary pressure, and it was added to III heated at 150°. The reaction mixture was separated into methanol-soluble and -insoluble fractions. From the latter, a green resinous material was obtained. The structure could not be determined from the physical data, such as mass, infrared (IR), and nuclear magnetic resonance (NMR) spectra. Upon fractionation of the former through a silica gel column, a viscous oil was eluted with ethanol–chloroform. From the physical data, it appeared to be the expected product, 5-(2-oxocyclopentanecarboxamido)quinoline (IVb), which exhibited absorption signals at 1675 and 1742 cm^{-1} due to the carbonyl streching vibration in the IR spectrum. The NMR spectrum showed that IVb existed as about 50% enol form in chloroform solution. Although Popp *et al.*[2b] reported that IVb was an oily compound, it was easily crystallized from ether and could be recrystallized from benzene. The elemental analysis of IVb supported this structure. The semicarbazone of IVb melted at 222—224°, which was considerably higher than the melting point (204.5—206°) reported by Popp *et al.*[2b] The cyclization of IVb was carried out by treating it with polyposphoric acid (PPA) in xylene[3] to give a product accompanied by a large amount of hydrolysis product, IVa. The product exhibited the parent peak at *m/e* 236 in the mass spectrum, an absorption maximum at 1635 cm^{-1} in the IR spectrum and absorption maxima at 212, 240, 263, 324, and 350 nm in the ultraviolet (UV) spectrum. On the basis of these physical data, the product appeared to be 4,11-diazagona-1,3,5(10),6,8,13-hexaen-12-one (I). However, the yield of I from IVb was not satisfactory.

Next, we tried to synthesize the 4,11-diazasteroid system from 1,2,3,4-tetrahydro-5-aminoquinoline (Va), which was prepared from 5-nitroquinoline by catalytic reduction under medium pressure using Adams' catalyst (70.5% yield). Va was added to the heated III to

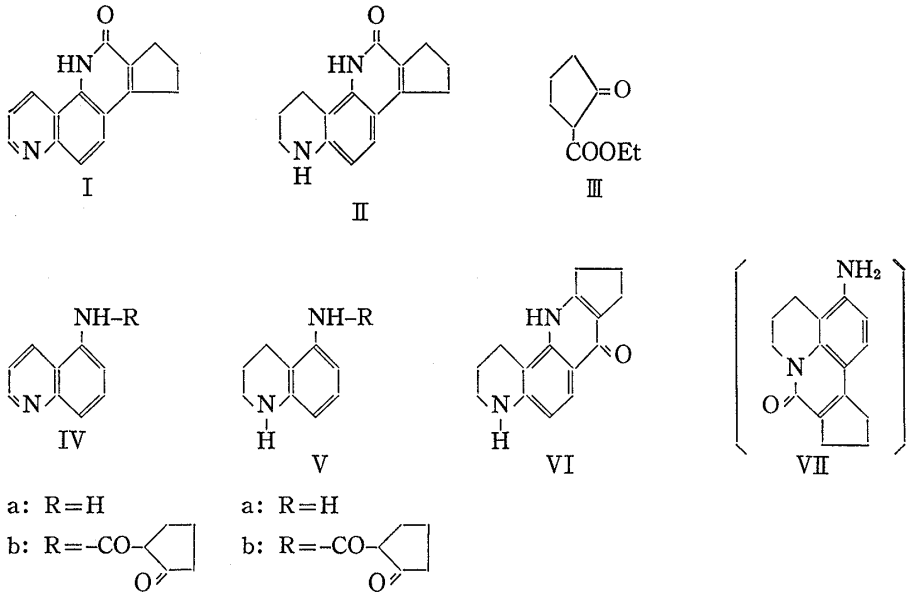

Chart 1

give the corresponding amide, 5-(2-oxocyclopentanecarboxamido)-1,2,3,4-tetrahydroquinoline (Vb), in 68.8% yield. The composition of Vb was confirmed by elemental analysis. It was positive in the ferric chloride test and was cyclized in PPA to give a diazasteroid system, 4,11-diazagona-5,7,9,13-tetraen-12-one(II) accompanied by a hydrolysis compound (Va) in yields of 14.2% and 70.0%, respectively. The cyclization with PPA-phosphorus pentoxide (P_2O_5) gave II and Vb in yields of 8.6% and 83.6%, respectively. The condensation reaction of Va and III using trifluoroacetic acid (TFA) was examined by heating in xylene.[4] From the cooled reaction mixture, II was precipitated, and fractionation of the filtrate on a silica gel column gave an isomer of II, 1,2,3,4,7,8,9,10,11-nonahydro-4,11-diazacyclopenta[*b*]-phenanthren-7-one (VI). The yields of II and VI were 24.7% and 21.9%, respectively. Their melting points were sharp and slightly different from each other. Hinsberg's test showed that they were not primary amines but secondary amines. Thus, a structure such as VII was ruled out. The weak absorption at 1720 cm^{-1} in their IR spectra (measured as paste) showed that both of them existed in lactam form, at least in the solid state. In the NMR spectrum of II measured in TFA, two doublet signals appeared at δ 8.05 and 7.70 ppm due to the protons at C_6 and C_7, respectively. On the other hand, in the NMR spectrum of VI measured in TFA, two doublet signals at δ 8.13 and 7.90 ppm due to the protons at C_5 and C_6 were observed. The results can be explained in terms of the anisotropy effect of the carbonyl group on the proton at C_6 in VI. In their UV spectra, II exhibited absorption maxima at 227, 270, 280, 302, and 359 nm, while VI exhibited absorption maxima at 230, 270, 300, and 348 nm. However no marked difference was found in their mass spectra.

Finally we tried to synthesize the 3-methoxy analog (VIII) of I in view of its expected biological activities.[5] The starting material, 5-amino-2-methoxyquinoline (IX), was prepared as shown in Chart 2.

IX was treated with keto ester, III, according to the method described above to give an amide compound, 5-(2-oxocyclopentanecarboxamido)-2-methoxyquinoline (X), and 5-(2-ethoxycarbonylcyclopentenyl)amino-2-methoxyquinoline (XI) in yields of 32.5% and 15.3%, respectively. Their structures were supported by their NMR and mass spectra. A mixture of XI and phenyl ether was refluxed to give quantitatively 7,8,9,10,11-pentahydro-3-methoxy-4,11-diazacyclopenta[*b*]phenanthren-7-one (XII), which exhibited absorption maxima at 248, 283, 338, and 353 nm in the UV spectrum. Attempts to cyclize the seco steroid system, X, to a steroid system, VIII, were carried out. First, X was treated in PPA at 100—115° to

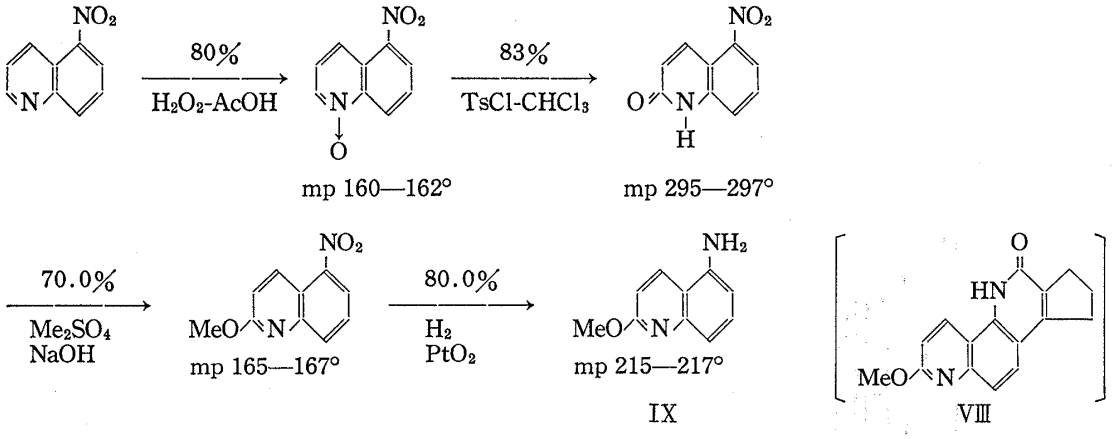

Chart 2

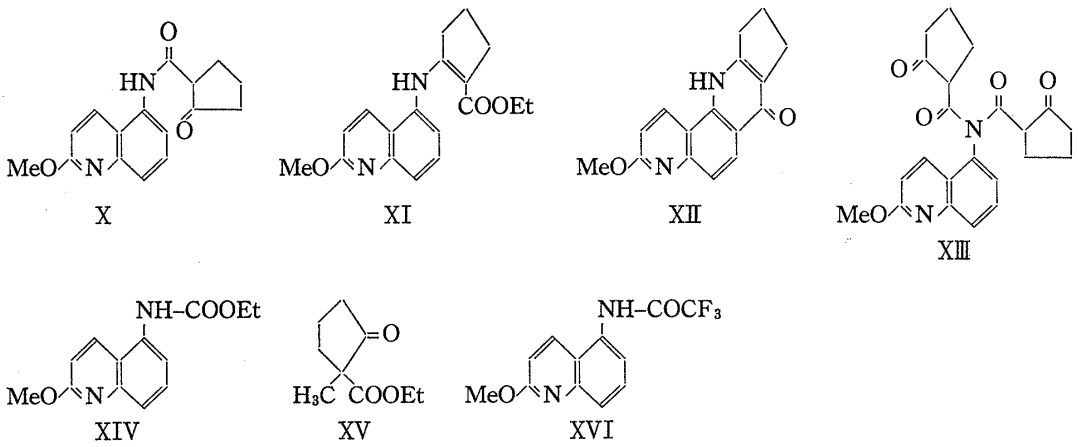

Chart 3

give 2-methoxy-5-[N,N-bis(2-oxocyclopentylcarbonyl)amino]quinoline (XIII) and IX in yields of 10.3% and 78.5%, respectively. In PPA–P_2O_5, XIII and IX were obtained in lower yields. Next, a xylenic mixture of X was refluxed in the presence of TFA for 5 hr to give XII and IX in yields of 17.3% and 54.4%, respectively. It appeared that XII was produced *via* hydrolysis of X followed by enamine formation and cyclization. Since the carbonyl group existed at least partially in the enol form (positive ferric chloride test for X), photochemical cyclization was also examined.[6] Irradiation of the seco steroid, X, in 95% ethanol with a high-pressure mercury lamp gave 5-ethoxycarbonylamino-2-methoxyquinoline (XIV), but unfortunately the expected cyclized product was not detected.

Finally, IX was treated with III in xylene in the presence of TFA to give XI and XII in yields of 10.7% and 26.1%, respectively. Under similar conditions, attempts to condense IX and 2-ethoxycarbonyl-2-methylcyclopentanone (XV) led only to the isolation of 2-methoxy-5-trifluoroacetamidoquinoline (XVI).

The biological activities of II, VI, and XII will be examined.

Experimental

All melting points are uncorrected. IR spectra were determined by using a Hitachi 215 grating spectrophotometer; absorption data are given in cm^{-1}. NMR spectra were recorded on a JEOL C-60H 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.

5-(2-Oxocyclopentanecarboxamido)quinoline (IVb)——5-Aminoquinoline (IVa), which was prepared from 5-nitroquinoline (1.5 g) by catalytic reduction in the presence of PtO_2 (0.5 g) under ordinary pressure, was added to heated (150°) 2-ethoxycarbonylcyclopentanone (III, 1 g) over a period of 5 min. When the addition was complete, the temperature was increased to 170—180° for 4 min. The mixture was cooled and MeOH was added. From the MeOH-insoluble part, a green resin was obtained (*ca.* 0.5 g). Silica gel column chromatography of the MeOH-soluble part with $CHCl_3$–EtOH (9: 1) provided IVb as a viscous oil, which was crystallized from Et_2O and recrystallized from benzene. mp 147—149°. The yield was 0.3 g (18.9%). IR (Nujol): $\nu_{C=O}$ 1742 (weak), 1675, ν 1600. NMR ($CDCl_3$): 9.5 (0.5 H, br.s, enolic OH), 8.98 (1H, d.d, $J=6$, 2, C_2–H), 8.6—7.3 (5H, m, aromatic H), 3.5 (1H, br.s, >NH), 3.5—1.3 (m, aliphatic H). MS *m/e*: 254 (M^+, 100%), 171 (40%), 144 (IVa, 100%). *Anal.* Calcd for $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 71.05; H, 5.50; N, 11.03. IVb-semicarbazone: mp 222—224° (recrystallized from EtOH, lit.[2b] mp 204.5—206°). *Anal.* Calcd for $C_{16}H_{17}N_5O_2+1/3H_2O$: C, 60.56; H, 5.61; N, 22.07. Found: C, 60.58; H, 5.38; N, 21.98.

4,11-Diazagona-1,3,5(10),6,8,13-hexaen-12-one (I)——IVb (265 mg) was added to PPA (*ca.* 10 g) at 100—115° during 15 min. The reaction took place with foaming. The mixture was kept at 100—115° for 1 hr with stirring and then poured onto crushed ice. This mixture was basified with NH_3 water, and extracted with $CHCl_3$. The residue obtained after concentration of the dried organic solution was fractionated on a silica gel column. Elution with $CHCl_3$ and $CHCl_3$–EtOH (9: 1) provided 5-aminoquinoline (116 mg, 77.5%) and I (4.1%), respectively. I: mp>300°. IR (Nujol): $\nu_{C=O}$ 1730 (weak), 1633. UV, λ_{max}: 350 (sh.), 324, 263, 240, 212. MS *m/e*: 236 ($C_{15}H_{12}N_2O$, base peak), 235 (M−1, 75.6%).

5-(2-Oxocyclopentanecarboxamido)-1,2,3,4-tetrahydroquinoline (Vb)——In a manner similar to that used for the synthesis of IVb, Vb was synthesized from III (1 g) and 5-amino-1,2,3,4-tetrahydroquinoline (Va, 1 g) [prepared by the catalytic reduction of 5-nitroquinoline (1.6 g) in the presence of PtO_2 (0.5 g) under moderate pressure (3—4 atm)]. The yield was 1.2 g (68.8%). mp 158—160° (recrystallized from MeOH). The $FeCl_3$ test was positive (blue). IR (Nujol): $\nu_{C=O}$ 1738 (weak), 1655, ν 1603, 1580. NMR ($CDCl_3$): 8.6 (0.8H, br.s, enolic OH), 7.5—6.2 (3H, m, aromatic H), 3.9 (1H, br.s, >NH), 3.5—1.6 (m, aliphatic H+>NH). MS *m/e*: 258 (M^+, base peak), 174 (74%), 148 (Va, 100%). *Anal.* Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.48; H, 6.96; N, 10.71.

4,11-Diazagona-5,7,9,13-tetraen-12-one (II)——a) In a manner similar to that used for the synthesis of I, the mixture of Vb (0.95 g) and PPA (*ca.* 10 g) was heated and worked up. Elution with $CHCl_3$–EtOH (9: 1) from a silica gel column provided Va and II in yields of 70.0% and 14.2%, respectively. II: mp>300° (recrystallized from EtOH). IR (Nujol): ν_{NH} 3300, $\nu_{C=O}$ 1720, ν 1650—1570. UV, λ_{max} (log ε): 227 (4.64), 270 (sh., 3.99), 280 (4.02), 302 (3.82), 359 (4.27). NMR (TFA): 8.05 (1H, d, $J=8$, C_6–H), 7.70 (1H, d, $J=8$, C_7–H), 4.2—3.8 (2H, m), 3.8—2.9 (6H, m), 2.9—2.0 (4H, m). MS *m/e*: 240 (M^+, base peak), 239 (M−1, 60%), 225 (M−15, 37%). *Anal.* Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.58; H, 6.62; N, 11.51. *cf.* Calcd for $C_{15}H_{16}N_2O+1/9H_2O$: C, 74.36; H, 6.75; N, 11.56.

b) In the manner described in a), a mixture of Vb (250 mg) and PPA (*ca.* 10 g) –P_2O_5 (*ca.* 2 g) was heated and the material extracted from the basic solution was fractionated. Va and II were obtained in yields of 83.6% and 8.6%, respectively.

1,2,3,4,7,8,9,10,11-Nonahydro-4,11-diazacyclopenta[*b*]phenanthren-7-one (VI)——A solution of Va (1 g), III (1 g), and TFA (0.78 g) in xylene was refluxed for 6 hr under an Ar atmosphere. The reaction mixture was cooled to precipitate II. The yield was 0.4 g (24.7%). The filtrate was fractionated on a SiO_2 column. Elution with $CHCl_3$–EtOH (49: 1) provided VI, which was recrystallized from EtOH. The yield was 0.36 g (21.9%). VI: mp 287—292°. IR (Nujol): ν_{NH} 3310, $\nu_{C=O}$ 1720 (weak), 1650—1620, ν 1580. UV, λ_{max} (log ε): 230 (4.60), 270 (3.97), 300 (3.71), 348 (4.16). NMR (TFA): 8.13 and 7.90 (each 1H, d, $J=8$, aromatic H), 5.0—4.5 (2H, m), 4.2—3.8 (1H, m), 3.8—3.0 (5H, m), 3.0—2.0 (4H, m). MS *m/e*: 240 (M^+, base peak), 239 (M−1, 64%), 225 (M−15, 44%). *Anal.* Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.28; H, 6.79; N, 11.85.

5-Amino-2-methoxyquinoline (IX)——Me_2SO_4 (45.4 g) was added dropwise to a stirred mixture of 5-nitro-2[1H]quinolinone[7] (23 g) in 10% aq. NaOH solution (50 ml) at room temperature. The mixture was heated at about 60° for 1 hr, while the pH of the solution was held at 8.0 by the addition of small portions of 10% aq. NaOH solution. After the mixture had cooled, the precipitate was collected on a filter, washed with water and recrystallized from EtOH to give pure 2-methoxy-5-nitroquinoline. The yield was 17.4 g (70.1%). *Anal.* Calcd for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 59.05; H, 4.12; N, 13.92.

An ethanolic solution of the nitro compound (5 g) was shaken under 3 to 4 atm of H_2 in the presence of PtO_2 (1 g). When the uptake of H_2 had ceased, the mixture was filtered and the solvent was evaporated off to give a crystalline compound, which was recrystallized from EtOH. The yield of IX was 3.6 g (80%). mp 215—217°. *Anal.* Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.77; H, 5.50; N, 16.11.

The Reactions of IX and III——a) IX (2.4 g) and III (2.4 g) were allowed to react in the usual manner to give a crystalline compound, which was fractionated on a SiO_2 column. From the fractions eluted with $CHCl_3$ and $CHCl_3$–EtOH (9: 1), 5-(2-ethoxycarbonylcyclopentenyl)amino-2-methoxyquinoline (XI) and 5-(2-oxocyclopentanecarboxamido)-2-methoxyquinoline (X) were obtained in yields of 0.65 g (15.3%) and 1.55 g (32.5%), respectively. X: mp 172—174° (recrystallized from H_2O). The ferric chloride test was

positive (blue-black). IR (Nujol): $\nu_{C=O}$ 1735 (weak), 1690 (weak), ν 1625, 1575. NMR (TFA): 9.73 (1H, br.s, >NH), 9.00 (1H, d, $J=10$, C_4–H), 8.4—7.9 (3H, m, aromatic H), 7.73 (1H, d, $J=10$, C_3–H), 4.37 (3H, s, $-OCH_3$), 3.8 (1H, m, –CO–CH<), 3.1—1.8 (6H, m, aliphatic H). NMR ($CDCl_3$): 9.3 (1H, br.s, >NH), 7.90 (1H, d, $J=9$, C_4–H), 7.77—7.0 (3H, m, aromatic H), 6.73 (1H, d, $J=9$, C_3–H), 3.67 (3H, s, $-OCH_3$), 3.36 (1H, t, $J=8$, –CO–CH<), 2.8—1.6 (6H, m, aliphatic H). *Anal.* Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.45; H, 5.56; N, 10.05.

XI: mp 147—150° (recrystallized from aq. EtOH). IR (Nujol): ν 1650, 1590. NMR ($CDCl_3$): 10.0 (1H, br.s, >NH), 8.10 (1H, d, $J=10$, C_4–H), 7.9—6.9 (3H, m, aromatic H), 6.80 (1H, d, $J=10$, C_3–H), 4.30 (2H, q, $J=7.5$, $-\underline{CH_2}-CH_3$), 3.76 (3H, s, $-OCH_3$), 1.36 (3H, t, $J=7.5$, $-CH_2-\underline{CH_3}$). *Anal.* Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.04; H, 6.45; N, 8.82.

b) A solution of IX (1 g), III (0.9 g), and TFA (0.66 g) in xylene was refluxed for 4 hr under an Ar atmosphere. The cooled solution was filtered to obtain the precipitate, which was washed with benzene and recrystallized from water to give 7,8,9,10,11-pentahydro-3-methoxy-4,11-diazacyclopenta[*b*]phenanthren-7-one (XII) in a yield of 0.4 g (26.1%). On the other hand, the residue obtained after removal of the solvent from the filtrate was purified on a SiO_2 column to give XI in a yield of 0.2 g (10.7%).

XII: mp>300°. IR (Nujol): ν_{NH} 3250, $\nu_{C=O}$ 1653, ν 1615, 1595, 1580. UV, λ_{max} (log ε): 248 (4.72), 283 (4.50), 338 (4.09), 353 (4.06). NMR (TFA): 9.26 (1H, d, $J=10$, C_1–H), 9.00 (1H, d, $J=11$, C_6–H), 8.30 (1H, d, $J=10$, C_2–H), 7.63 (1H, d, $J=11$, C_5–H), 4.37 (3H, s, $-OCH_3$). MS *m/e*: 266 (M^+, base peak), 237 (M−29, 27%). *Anal.* Calcd for $C_{16}H_{14}N_2O_2+3/4H_2O$: C, 68.68; H, 5.58; N, 10.01. Found: C, 68.74; H, 5.70; N, 9.85.

From XI to XII——A mixture of XI (0.13 g) and phenyl ether (10 ml) was refluxed for 10 min. The cooled solution was filtered and the brown residue thus obtained was well washed with benzene. Recrystallized from EtOH gave XII in quantitative yield.

Attempts to Cyclize X——a) X (0.28 g) was added to heated (100°) PPA during 10 min and then the mixture was further heated at 120° for 2 hr. The mixture was allowed to cool, then poured onto crushed ice. The precipitate was filtered off and recrystallized from EtOH to give pure 2-methoxy-5-[N,N-bis(2-oxocyclopentylcarbonyl)amino]quinoline (XIII) in a yield of 0.04 g (10.3%). Extraction with $CHCl_3$ of the basified filtrate followed by purification on a SiO_2 column (eluent: $CHCl_3$–EtOH=9: 1) gave IX in a yield of 0.135 g (78.5%).

XIII: mp 259—260° (dec.). IR (Nujol): $\nu_{C=O}$ 1705, 1660, 1645, ν 1577. UV, λ_{max}: 293, 233, 216. NMR (TFA): 8.80 (1H, d, $J=9$, C_4–H), 8.4—7.8 (3H, m, aromatic H), 7.67 (1H, d, $J=9$, C_3–H), 4.38 (3H, s, $-OCH_3$), 3.4—1.9 (12H, m, aliphatic H). MS *m/e*: 394 (M^+, 56%), 216 (50%), 175 (IX+1, 75%), 174 (IX, base peak), 110 (52%). *Anal.* Calcd for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; H, 7.10. Found: C, 66.95; H, 5.63; N, 7.22. Instead of PPA, PPA-P_2O_5 was used as described for the cyclization of Vb; the yields of XIII and IX were 1.9% and 28.4%, respectively.

b) A xylenic solution of X (0.3 g) and TFA (0.1 g) was heated for 5 hr. The residue obtained by filtration of the hot solution was recrystallized from EtOH. The compound was identified as XII by means of IR, UV, and NMR spectra. The yield of XII was 0.05 g (17.3%). From the residue obtained by filtration of the cooled filtrate, IX was obtained in the yield of 0.1 g (54.4%). Compounds IX and X were detected by TLC in the final filtrate.

c) A solution of X (0.52 g) in 95% EtOH (100 ml) was irradiated with a 200W mercury lamp for 5 hr at 10°. The residue obtained after removal of the solvent was fractionated on a SiO_2 column. The compound obtained from the fraction eluted with $CHCl_3$ was recrystallized from aq. EtOH to give pure 5-ethoxycarbonylamino-2-methoxyquinoline (XIV) in a yield of 0.1 g (22.2%). mp 159—162°. IR (Nujol): $\nu_{C=O}$ 1728, 1655, ν 1585. NMR ($CDCl_3$): 8.1—6.6 (5H, m, aromatic H), 4.30 (2H, q, $J=8$, $-\underline{CH_2}-CH_3$), 3.76 (3H, s, $-OCH_3$), 3.40 (1H, s, >NH), 1.30 (3H, t, $J=8$, $-CH_2-\underline{CH_3}$). MS *m/e*: 246 (M^+, base peak), 174 (IX, 56%).

2-Methoxy-5-trifluoroacetamidoquinoline (XVI)——A xylenic solution of IX (0.2 g), 2-ethoxycarbonyl-2-methylcyclopentanone (V, 0.2 g),[8] and TFA (0.1 g) was refluxed for 48 hr. From the fractions eluted from a SiO_2 column with benzene, $CHCl_3$, and $CHCl_3$–EtOH (9: 1), V, IX (0.15 g), and XVI (0.05 g) were obtained.

XVI: mp 218—220° (recrystallized from EtOH). NMR ($CDCl_3$): 9.2 (1H, br.s, >NH), 7.80 (1H, d, $J=10$, C_3–H), 7.7—7.2 (3H, m, aromatic H), 6.75 (1H, d, $J=10$, C_4–H), 3.75 (3H, s, $-OCH_3$). IR (Nujol): $\nu_{C=O}$ 1727, 1660, ν 1595. MS *m/e*: 270 (M^+, base peak), 200 (65.9%), 173 (IX−1, 49.5%), 145 (67.6%). *Anal.* Calcd for $C_{12}H_9F_3N_2O_2$: C, 53.33; H, 3.33; N, 10.37. Found: C, 53.04; H, 3.20; N, 10.44.

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