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Acid-catalyzed Cyclization of Chalcones derived from Various Nitrogenous Heteroaromatic Compounds[1)]

KATSUHIDE MATOBA,*,[a] KENICHI ITOH,[a] KAKUYA KONDO,[a] TAKAO YAMAZAKI,[a] and MASANORI NAGATA[b]

Faculty of Pharmaceutical Sciences[a] and Faculty of Medical Sciences,[b] Toyama Medical and Pharmaceutical University, Sugitani, Toyama, 930-01, Japan

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2-(2-Furfurylidene)acetylquinoxaline (Ia) and its 3-methyl analog (Ib) were cyclized to pyrrolo[1,2-*a*]quinoxaline ring systems (IIa and IIb) by hydrochloric acid treatment. 2-(4-Methoxybenzylidene)acetylpyridine could be cyclized directly to the 2,3-dihydroindolizine ring system (V) by treatment with perchloric acid. 2-Arylideneacetyl-3-methylquinoxalines (IX) also were cyclized to the corresponding pyrrolo[1,2-*a*]quinoxaline systems by hydrochloric acid or perchloric acid. The cyclization of 2-(2-furfurylidene)-acetylquinoline (XI) was performed by using acetic anhydride in the presence of a catalytic amount of trifluoroacetic acid. 2-(2-Furfurylidene)acetylpyrazine (XIII) was cyclized easily by hydrochloric acid treatment.

The structures of the adducts of these cyclic products with dimethyl acetylenedicarboxylate are discussed.

Keywords——acid-catalyzed cyclization; acid-catalyzed isomerization; pyrrolo-[1,2-*a*]quinoxaline; pyrrolo[1,2-*a*]quinoline; pyrrolo[1,2-*a*]pyrazine; indolizine; dimethyl acetylenedicarboxylate; Diels–Alder reaction

In our laboratory, a number of diazasteroid systems have been synthesized and their biological activities examined.[2)] To synthesize the 6,9-diazasteroid system, 2-(2-furfurylidene)acetylquinoxaline (Ia) was chosen as a starting material. Robinson[3)] reported the synthesis of a steroid skeleton starting with 2-(2-furfurylidene)acetyl-6-methoxynaphthalene, and Popp *et al.*[4)] also tried to synthesize azasteroid skeletons in a similar manner, but unsuccessfully.

First, we carried out the reaction of Ia with hydrochloric acid in ethanol. The mixture was refluxed to give a yellow precipitate (IIa), the structure of which was identified as 1-(2-furanyl)-3-hydroxypyrrolo[1,2-*a*]quinoxaline on the basis of the following data. The ferric chloride test was positive but weak. In the nuclear magnetic resonance (NMR) spectrum, signals were observed only at lower field than δ 6 ppm, and no signal was seen in the aliphatic region. Thus the acid treatment of Ia did not give any product corresponding to those reported by Robinson[3)] or Popp *et al.*[4)] The infrared (IR) spectrum of IIa showed absorption at 1630—1600 cm^{-1}. IIa could be derived to an enol methyl ether, 1-(2-furanyl)-3-methoxy pyrrolol[1,2-*a*]quinoxaline (IIIa), and enol acetate, 3-acetoxy-1-(2-furanyl) pyrrolo[1,2-*a*]-quinoxaline (IVa), by treatment with diazomethane and acetic anhydride, respectively. In the NMR spectra of two derivatives, only ten protons appeared in the aromatic region under δ 6 ppm, and the pattern of signals was similar to that of IIa except for the imine proton (C_4-proton). (In the NMR spectrum of IIa measured in trifluoroacetic acid (TFA), the imine proton appeared as a doublet (J=6 Hz) at δ 8.67 ppm. On the other hand, the imine proton of IIIa or IVa appeared as a singlet. This phenomenon in IIa was ascribed to the coupling of C_4-proton with iminium proton.) Therefore it was suggested that the skeletal change did not occur during the treatment with diazomethane or acetic anhydride and that one vinylic or aromatic proton was lost upon the reaction of Ia with hydrochloric acid.

IIa was confirmed to be stable under the reported conditions (refluxing with concentrated hydrochloric acid in acetic acid[4)]). Thus the furan ring in the substrate (Ia) is quite

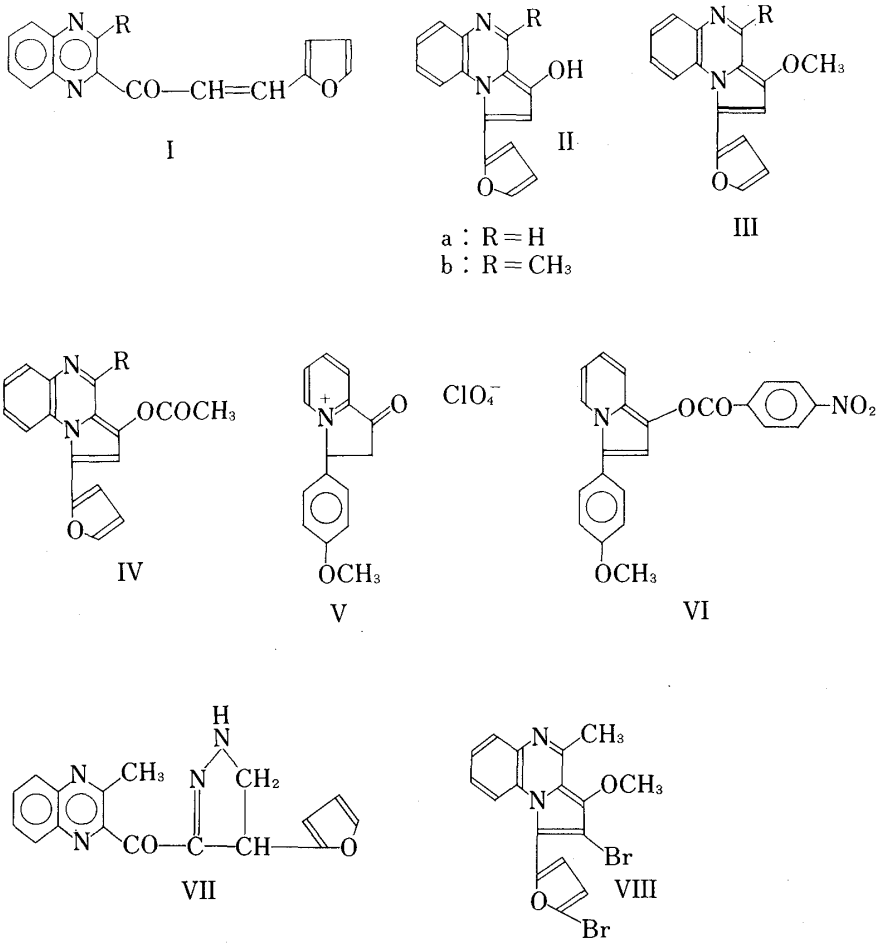


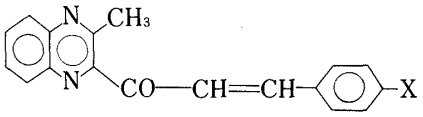
Chart 1

stable under these acidic conditions. Kröhnke and Kröck obtained the cyclized product (V) from 2-acetylpyridine and *p*-anisaldehyde.[5] We could also obtain V directly from 2-(4-methoxybenzylidene)acetylpyridine by treatment with perchloric acid in ethanol. In this case, hydrochloric acid gave no fruitful result. The cyclized product could be isolated as its perchlorate, which could not be converted to the free base by treatment with sodium bicarbonate solution. The perchlorate existed as the keto pyridinium salt, 3-(4-methoxyphenyl)-1-oxo-2,3-dihydroindolizinium perchlorate (V) as judged from the NMR spectrum, while V could be derived to the *p*-nitrobenzoate (VI) by the Schotten–Baumann method.

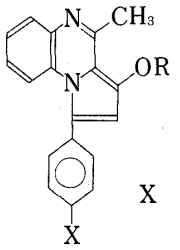
Similarly, 1-(2-furanyl)-3-hydroxy-4-methylpyrrolo[1,2-*a*]quinoxaline (IIb) was obtained from 2-(2-furfurylidene)acetyl-3-methylquinoxaline (Ib) in good yield. IIb could be led to the methyl ether, 1-(2-furanyl)-3-methoxy-4-methylpyrrolo[1,2-*a*]quinoxaline (IIIb), and enol acetate, 3-acetoxy-1-(2-furanyl)-4-methylpyrrolo[1,2-*a*]quinoxaline (IVb), in better yields than those of IIIa and IVa from IIa. On the other hand, Ib gave the dihydropyrazole derivative (VII) on treatment with diazomethane. In the NMR spectrum of IIIb, three singlet-like peaks, each of which corresponds to one proton, were observed between δ 6.5—6.8 ppm due to two β-protons of the furan ring and the C_2-proton, and one triplet signal was observed at δ 7.68 ppm due to the α-proton of the furan ring. In the IR spectrum of IVb, an absorption maximum due to the enol acetate was observed at 1760 cm^{-1}. IIb was treated with bromine in carbon tetrachloride to give the dibromide, whose methyl ether lacked signals due to the α-proton of the furan ring and C_2-proton and exhibited a pair of doublets (J=2 Hz) due to two β-protons of the furan ring in the NMR spectrum. Therefore, the structure of the dibromide

TABLE I. Time-dependent Conversion of Chalcones (IX) to the Cyclized Products (X) at 32.5°C (Ratios were determined from the integrations of vinylic methyl protons in the NMR spectra)

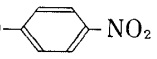
IX	Time	Ratio	
		IX	X
IXa	0 h	1	0
(in $CDCl_3$–TFA(4 drops))	1.5	1	1
	4.5	1	8
	6.0	1	16.5
	24	0	1
IXb			
(in $CDCl_3$–TFA(4 drops))	0 h	1	0
	2	2	1
	3	1	1
	6	1	2.5
	8	crystallized	
IXc			
(in TFA)	0 d	1	0
	1	3.3	1
	2	1	1.1
	3	1	2.5
	4	1	4.5
	7	1	18.7
	8	1	23.9
	10	0	1

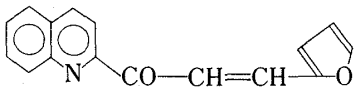


IX a : X=H
b : X=OCH_3
c : X=NO_2

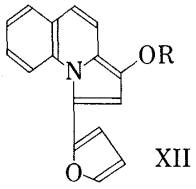


X

a : X=H, R=CH_3
a′ : X=H, R=$COCH_3$
b : X=OCH_3, R=CH_3
c : X=NO_2, R=H
d : X=NO_2, R=—CO— 

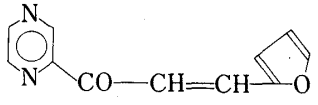


XI

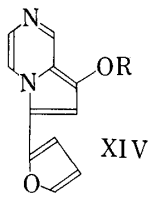


XII

a : R=H
b : R=$COCH_3$



XIII



XIV

a : R=H
b : R=C_2H_5
c : R=CH_3

Chart 2

methyl ether was suggested to be 2-bromo-1-(5-bromo-2-furanyl)-4-methyl-3-methoxypyrrolo-[1,2-*a*]quinoxaline (VIII).

Next we examined the acid-catalyzed cyclization of 2-arylideneacetyl-3-methylquinoxalines (IX). The unsubstituted compound (IXa) was converted to 3-methoxy-4-methyl-1-phenylpyrrolo[1,2-*a*]quinoxaline (Xa) and 3-acetoxy-4-methyl-1-phenyl pyrrolo[1,2-*a*]quinoxaline (Xa′) by cyclization with hydrochloric acid followed by methylation and acetylation, respectively. In a similar manner, the 2-(4-methoxybenzylidene)acetyl derivative (IXb) gave the 1-(4-methoxyphenyl) derivative (Xb). On the other hand, the 2-(4-nitrobenzylidene)-acetyl derivative (IXc) gave no cyclized products on treatment with hydrochloric acid but the cyclization could be caused by perchloric acid. It was revealed from the NMR spectrum that the perchlorate of the 1-(4-nitrophenyl) derivative (Xc) existed as the enol quinoxalinium salt. The salt of Xc could not be neutralized by aqueous sodium bicarbonate solution. These properties of Xc are interesting compared with those of V. Xc resisted methylation with diazomethan and it was derived to the *p*-nitrobenzoate (Xd). The time-dependent change of IX to X was examined in NMR tube using deuteriochloroform-TFA as solvent systems. The results are shown in Table I.

It is clear from this table that IXc was difficult to cyclize in comparison with IXa and IXb, possibly owing to electron deficiency at the carbon to be cyclized.

Popp *et al.* reported that 2-(2-furfurylidene)acetylquinoline (XI) gave only a decomposition product, quinaldic acid, on treatment with hydrochloric acid in ethanol.[4] To obtain the corresponding cyclized product, 1-(2-furanyl)-3-hydroxypyrrolo[1,2-*a*]quinoline (XIIa), XI was treated with hydrochloric acid or perchloric acid in ethanol, but the only product isolated was 2-quinaldic acid, which was identified as its methyl ester. However XI was treated with acetic anhydride in the presence of a catalytic amount of TFA to give 3-acetoxy-1-(2-furanyl)pyrrolo[1,2-*a*]quinoline (XIIb) in a yield of 47.3%.

2-(2-Furfurylidene)acetylpyrazine (XIII) gave 1-(2-furanyl)-3-hydroxypyrrolo[1,2-*a*]-pyrazine (XIVa) and its 3-ethoxy analog (XIVb). The yield of XIVb was 13.6%. XIVa was methylated with diazomethane to provide the 3-methoxy derivative (XIVc). The yield of XIVc from XIII was 25.5%.

Finally we wish to describe the reaction of dimethyl acetylenedicarboxylate (DMAD) with the cyclized products mentioned above. IIIb and IVb were treated with DMAD in benzene to give amorphous 1:2 adducts, which unfortunately could not be crystallized. The amorphous compounds were identified by mass spectroscopy and elemental analyses. However Xa and XIVc gave the corresponding the 1:2 adducts as fine crystalline compounds in yields of 21.7 and 59.4%, respectively. On the other hand, XIIb reacted with DMAD to give a crystalline 1:1 adduct as the major product, and an amorphous 1:2 adduct as the minor product. As the cyclized products (except XIIb) included vinylogous imino ether moieties, the reactions of the compounds containing the similar functional group with DMAD were examined. The model compound chosen was 7-ethoxy-2,3,4,4a,5,6-hexahydroquinoline hydroiodide (XV) prepared from 2,3,4,4a,5,6-hexahydroquinolin-7[1H]one (XVI).[6] XV reacted with only one molar equivalent of DMAD in benzene to give the N-substituted product(XVII). On the other hand, the starting material, XVI, gave an amide compound (XVIII). Acheson *et al.* reported that 1,2-dimethyl benzimidazole gave the corresponding 1:2 adduct with DMAD in various solvents.[7] The 1:2 adduct from Xa melted at 210—212°C and exhibited a singlet peak at δ 1.69 ppm due to aliphatic methyl protons. The peak due to the corresponding methyl protons in Xa was observed at δ 2.66 ppm. A hypochromic shift was observed with the change from Xa to the 1:2 adduct in the ultraviolet (UV) spectra. Therefore, the 1:2 adduct formed from Xa was suggested to be an adduct (XIX), in which the C_4–N_5 part of Xa was condensed with 2 molar equivalents of DMAD. The structure of the 1:2 adduct from XIVc was deduced to be XX. In the UV spectra, the hypochromic shift from XIVc to XX was smaller than that from Xa to XIX. In the adduct formed from XIVc,

isomerization to XX was possible because the C_4 position was unsubstituted. On the other hand, Acheson *et al.* reported the chemical shift of C_4-proton in 4H-quinolizine-1,2,3,4-tetracarboxylate (XXI) to be δ 6.56—6.01 ppm.[8] In XX, the corresponding proton signal appeared at δ 6.01 ppm. The 1:1 adduct formed from XIIb was suggested to be a phenolic product, XXII. In the NMR spectrum of XXII, the phenolic proton was observed at δ 12.0 ppm. The ferric chloride test was positive but weak. The enol acetate, 3-acetoxy-1-[4-acetoxy-2,3-di(ethoxycarbonyl)phenyl]pyrrolo[1,2-*a*]quinoline (XXIII) could be obtained by acetylation with acetic anhydride in pyridine. The proposed mechanism for the reaction of XIIb giving XXII is shown in Chart 3. As the other adducts of cyclized products with DMAD could not be purified, their structures have not yet been determined.

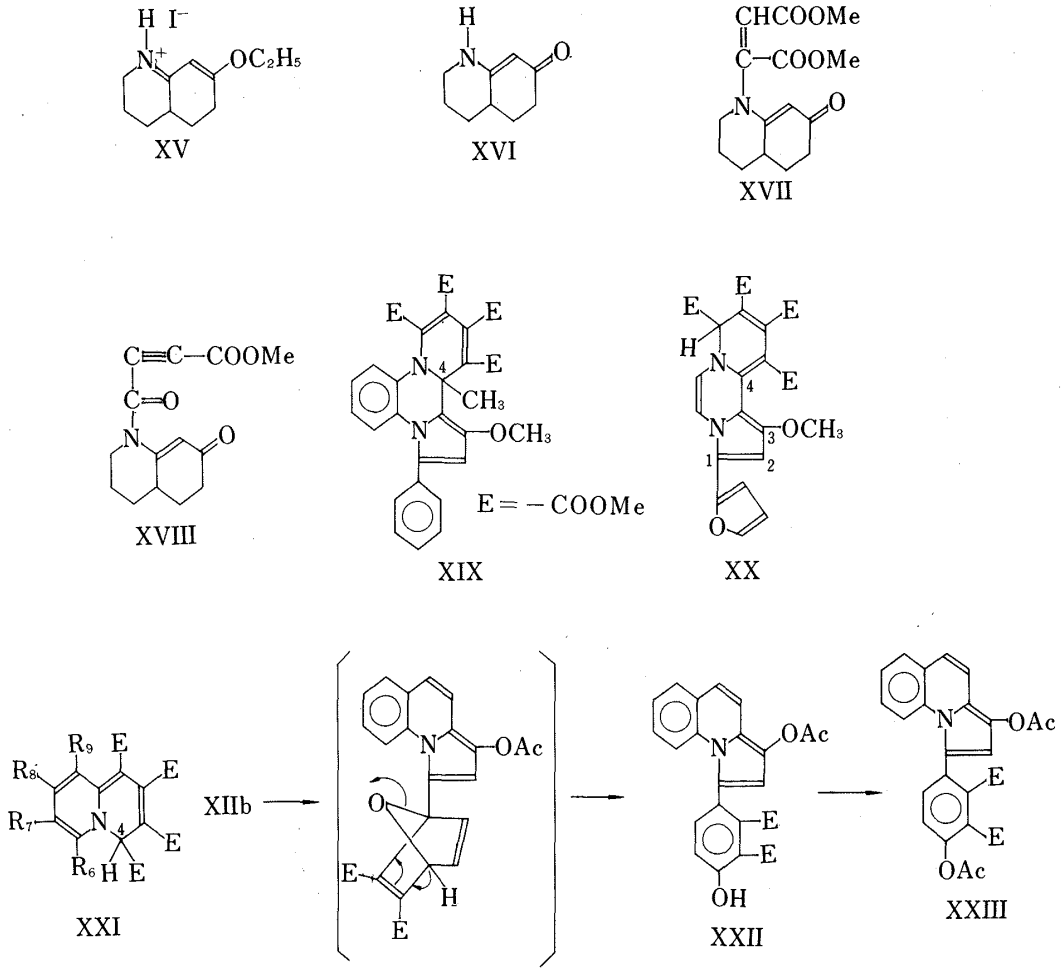


Chart 3

Experimental

All melting points are uncorrected. IR spectra were determined by using a Hitachi 215 grating spectrometer and a JASCO IRA-1 diffraction 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.

2-(2-Furfurylidene)acetylquinoxaline (Ia)——A solution of 2% alcoholic KOH (9 ml) was added dropwise to an alcoholic mixture of 2-acetylquinoxaline[8] (3 g) and freshly distilled furfural (1.7 g) with ice-cooling. The whole was stirred for 10 h at room temperature to give a precipitate which was collected on a filter and recrystallized from a large amount of EtOH to give yellow needles of Ia. Yield, 3 g (57.3%). mp 200—202°C.

IR (Nujol): $\nu_{C=O}$ 1670, $\nu_{C=C}$ 1600. NMR ($CDCl_3$): 6.48 (1H, q, $J=2$, 1, β-H of furan ring), 6.65 (1H, d, $J=2$, β-H of furan ring), 7.45 (1H, d, $J=1$, α-H of furan ring), 7.6—8.3 (6H, m), 9.45 (1H, s, –N=CH–). MS, *m/e* (%): 250 (M^+, 88.7), 222 (M–CO, 54.2), 221 (M–CHO, 84.0), 121 (100). *Anal.* Calcd for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.20. Found: C, 71.84; H, 4.08; N, 11.22.

1-(2-Furanyl)-3-hydroxypyrrolo[1,2-*a*]quinoxaline (IIa)——A mixture of Ia (0.9 g) in EtOH (18 ml) and conc. HCl (4.5 ml) was refluxed for 20 h, then concentrated. The resulting dark oily compound was basified with 10% Na_2CO_3 to give a yellow-brown compound, which was recrystallized from EtOH. 0.6 g (67%). mp 254—262°C. IR (Nujol): $\nu_{C=O}$ 1620. NMR (TFA): 6.76 (1H, s, C_2–H), 6.6—7.1 (2H, m, β-H of furan ring), 7.4—7.9 (5H, m), 8.67 (1H, d, $J=6$, C_4–H). MS, *m/e* (%): 251 (M+1, 32.7), 250 (M^+, 100), 222 (M–CO, 29.5).

1-(2-Furanyl)-3-methoxypyrrolo[1,2-*a*]quinoxaline (IIIa)——CH_2N_2-etherate was added to a suspension of IIa (0.6 g) in MeOH, and the mixture was allowed to stand overnight. The residue obtained after removal of the solvent was fractionated through an SiO_2 column. A yellow crystalline compound obtained from the benzene–Et_2O (9: 1) eluate was recrystallized from CCl_4 to give yellow needles. 0.4 g (63.5%). mp 141—142°C. IR ($CHCl_3$): $\nu_{C=O}$ 1620. NMR ($CDCl_3$): 3.83 (3H, s, $-OCH_3$), 6.40 (1H, s, C_2–H), 6.50 (2H, s, like, β-H of furan ring), 6.8—7.9 (5H, m), 8.67 (1H, s, C_4–H). MS, *m/e* (%): 264 (M^+, 18.0), 263 (M–1, 95.8), 249 (M–CH_2, 65.7), 130 (quinoxaline, 100). *Anal.* Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.69; H, 4.87; N, 10.33.

3-Acetoxy-1-(2-furanyl)pyrrolo[1,2-*a*]quinoxaline (IVa)——A mixture of IIa (0.5 g) and Ac_2O (5 ml) in pyridine was heated on a water bath for 2 h, then excess Ac_2O was destroyed by the addition of water. A dark oil obtained after concentration was dissolved in $CHCl_3$ and the organic layer was washed with aq. Na_2CO_3 and sat. NaCl solution. The crude compound obtained from the dried organic layer was fractionated through an SiO_2 column. The crystalline product obtained from the benzene–Et_2O (1: 1) eluate was recrystallized from benzene to give yellow-brown needles. 0.3 g (51.2%). mp 152—154°C. IR (Nujol): $\nu_{C=O}$ 1750. NMR ($CDCl_3$): 2.40 (3H, s, –Ac), 6.62 (2H, s. like, β-H of furan ring), 6.94 (1H, s, C_2–H), 8.75 (1H, s, C_4–H). *Anal.* Calcd for $C_{17}H_{12}N_2O_3$: C, 69.85; H, 4.14; N, 9.59. Found: C, 69.81; H, 4.07; N, 9.44.

Further Treatment of Ia under Acidic Conditions——A mixture of Ia (0.2 g), conc. HCl (2.3 ml), g-AcOH (2.3 ml), and H_2O (5 ml) was refluxed for 3 h, then basified with aq. Na_2CO_3 solution to give Ia (quantitative recovery of the starting material).

2-(2-Furfurylidene)acetyl-3-methylquinoxaline (Ib)——In a similar to that used for the synthesis of Ia, Ib was obtained as pale yellow needles from 2-acetyl-3-methylquinoxaline[10] (0.7 g). The yield was quantitative. IR (Nujol): $\nu_{C=O}$ 1670, $\nu_{C=C}$ 1600. UV, λ_{max} nm (ε): 234 (16500), 251 (18100), 307 (12800), 357 (21300). NMR ($CDCl_3$): 3.02 (3H, s, $-CH_3$), 6.57 (1H, m, β-H of furan ring), 6.80 (1H, d, $J=2.5$, β-H of furan ring), 7.4—8.3 (7H, m). *Anal.* Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.98; H, 4.35; N, 10.87.

1-(2-Furanyl)-3-hydroxy-4-methylpyrrolo[1,2-*a*]quinoxaline (IIb)——A mixture of Ib (1.1 g) and conc. HCl (5.6 ml) in EtOH (24 ml) was refluxed for 5 min to precipitate a yellow-green crystalline compound, which did not change upon further refluxing. The precipitated compound was recrystallized from EtOH. mp 285—287°C. The Beilstein test was positive. The compound obtained by neutralization was recrystallized from EtOH to give brown needles. mp 225—227°C. The yield was quantitative. IR (Nujol): $\nu_{C=O}$ 1620. UV, λ_{max} nm (ε): 229 (25000), 277 (11100), 363 (6800). NMR (TFA): 3.13 (3H, s, $-CH_3$), 6.86 (2H, s. like, β-H of furan ring and C_2–H), 7.04 (1H, d, $J=3.5$, β-H of furan ring), 7.2—8.0 (5H, m). MS, *m/e* (%): 264 (M^+, 71.7), 235 (M–CHO, 57.0), 144 (methylquinoxalyl, 100). *Anal.* Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.49; H, 4.50; N, 10.85.

1-(2-Furanyl)-3-methoxy-4-methylpyrrolo[1,2-*a*]quinoxaline (IIIb)——In a manner similar to that used in the preparation of IIIa from IIa, IIb was methylated with CH_2N_2 to give IIIb. mp 160—162°C (recrystallized from EtOH). Yield, 83.5%. IR (Nujol): $\nu_{C=O}$ 1620. UV, λ_{max} nm (ε): 222 (34500), 227 (34800), 275 (16800), 363 (9300). NMR ($CDCl_3$): 2.87 (3H, s, C–CH_3), 3.96 (3H, s, O–CH_3), 6.5—6.8 (3H, $3\times$s, $2\times\beta$-H of furan ring and C_2–H), 7.68 (1H, t, $J=1$, α-H of furan ring), 6.8—8.0 (4H, m). *Anal.* Calcd for $C_{17}H_{14}N_2O_2$: C, 73.36; H, 5.07; N, 10.07. Found: C, 73.20; H, 4.98; N, 10.30.

3-Acetoxy-1-(2-furanyl)-4-methylpyrrolo[1,2-*a*]quinoxaline (IVb)——In a manner similar to that used in the preparation of IVa, IVb was obtained in quantitative yield. mp 174—176°C (recrystallized from benzene). IR ($CHCl_3$): $\nu_{C=O}$ 1760. NMR ($CDCl_3$): 2.37 (3H, s, –Ac), 2.77 (3H, s, C–CH_3), 6.4—8.0 (8H, m). *Anal.* Calcd for $C_{18}H_{14}N_2O_3$: C, 70.59; H, 4.58; N, 9.15. Found: C, 70.45; H, 4.58; N, 9.19.

3-(4-Methoxyphenyl)-1-oxo-2,3-dihydroindolizinium Perchlorate (V) and Its *p*-Nitrobenzoate (VI)——In a manner similar to that used in the preparation of Ia, 2-(4-methoxybenzylidene)acetylpyridine (a chalcone) was synthesized in quantitative yield. mp 82—83°C IR (Nujol): $\nu_{C=O}$ 1685, $\nu_{C=C}$ 1590. NMR ($CDCl_3$): 3.83 (3H, s, $-OCH_3$), 6.93 and 7.70 (each 2H, d, $J=9$, anisyl), 7.3—8.5 (5H, m), 8.78 (1H, d.d, $J=5$, 1, –CH=N–). Perchlorate: mp 159—162°C (red prisms from EtOH). *Anal.* Calcd for $C_{15}H_{14}ClNO_6$: C, 53.02; H, 4.12; N, 4.12. Found: C, 52.84; H, 4.12; N, 4.40. The chalcone (2 g) was treated with conc. HCl (2 ml) in EtOH (10 ml) at room temperature. No identifiable compound could be isolated from the green-purple colored solution. A red ethanolic solution of the chalcone perchlorate was refluxed for 30 min on a water bath to give a green-colored solution. The residue obtained from the solution was recrystallized from

MeOH. 80.0%. V: mp 203—205°C (orange-yellow prisms, lit.[5] mp 203—205°C). IR (Nujol): $\nu_{C=O}$ 1755 (strong). UV, λ_{max} nm: 332. NMR (TFA): 3.2—4.5 (2H, m, $>CH_2$), 4.06 (3H, s, $-OCH_3$), 6.60 (1H, t, $J=6.5$, >CH–), 7.25 and 7.57 (each 2H, d, $J=9$, anisyl), 8.2—9.1 (4H, m). The addition of CH_2N_2-etherate to a methanolic solution of V gave a complex mixture. On the other hand, addition of sat. $NaHCO_3$ aq. solution to a suspension of V in Et_2O gave a purple pigment, the structure of which could not be determined. In a manner similar to that reported,[5] V was derived to the *p*-nitrobenzoate. mp 167°C (lit.[5] double mp 161—163°C and 178—179°C) (recrystallized from MeOH–DMSO). IR (Nujol): $\nu_{C=O}$ 1733, $\nu_{N=O}$ 1535, 1345. NMR ($CDCl_3$): 3.88 (3H, s, $-OCH_3$), 6.97 (1H, s, C_2–H), 7.06 and 7.52 (each 2H, d, $J=9$, anisyl H), 6.3—6.9 (2H, m), 7.3 (1H, s. like), 8.0—8.3 (1H, m), 8.44 (4H, s, nitrobenzene).

2-(3-Methylquinoxalyl) 3-[4-(2-Furanyl)-4,5-dihydropyrazolyl] ketone (VII)——Ib was treated with CH_2N_2 in Et_2O to give VII in 80—90% yield. mp 182—184°C (recrystallized from EtOH). IR (Nujol): ν_{NH} 3330, $\nu_{C=O}$ 1615. NMR ($CDCl_3$): 2.65 (3H, s, C–CH_3), 3.8—4.3 (2H, m, >N–CH_2–), 4.83 (1H, q, $J=9$, 12, >CH–), 6.33 (2H, s. like, β-H of furan ring), 7.38 (1H, br. s, α-H of furan ring), 7.5—8.3 (4H, m). MS, *m/e* (%): 306 (M^+, 100), 143 (80.8). *Anal.* Calcd for $C_{17}H_{14}N_4O_2$: C, 66.65; H, 4.61; N, 18.29. Found: C, 66.38; H, 4.67; N, 18.52.

2-Bromo-1-(5-bromo-2-furanyl)-3-methoxy-4-methylpyrrolo[1,2-*a*]quinoxaline (VIII)——An excess of bromine was added to a solution of IIb (0.5 g) in CCl_4 until no more bromine was consumed. The CCl_4 solvent was replaced with MeOH, CH_2N_2-etherate was added and the mixture was allowed to stand overnight. The crude compound obtained after removal of the solvent was recrystallized from MeOH. The overall yield was 0.6 g (72.7%). IR (Nujol): $\nu_{C=C}$ 1590, 1610. NMR (CCl_4): 2.83 (3H, s, C–CH_3), 4.04 (3H, s, $-OCH_3$), 6.57 and 6.70 (each 1H, d, $J=1.2$, β-H of furan ring), 6.8—7.9 (4H, symmetrical m). MS, *m/e* (%): 438 (M+4, 53.3), 436 (M+2, 100), 434 (M, 53.3), 357 (M+2–Br, 80.0), 355 (M–Br, 80.0), 329 (*m/e* 357–CO, 56.4), 327 (*m/e* 355–CO, 56.4). *Anal.* Calcd for $C_{17}H_{12}Br_2N_2O_2$: C, 46.82; H, 2.77; N, 6.42. Found: C, 46.75; H, 2.70; N, 6.16.

2-Benzylideneacetyl-3-methylquinoxaline (IXa)——An aq. ethanolic solution of KOH (0.1 g) was added to a mixture of 2-acetyl-3-methyl quinoxaline (0.7 g) and benzaldehyde (0.4 g) with ice-cooling and stirring. After the mixture had been stirred for 15 min at room temperature, the crude product was obtained and recrystallized from EtOH to give white needles. mp 150—151°C. Yield, 0.65 g (63.1%). NMR ($CDCl_3$): 3.00 (3H, s, $-CH_3$), 7.2—8.4 (11H, m). *Anal.* Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 79.00; H, 5.29; N, 10.27.

3-Methoxy-4-methyl-1-phenylpyrrolo[1,2-*a*]quinoxaline (Xa) and Its 3-Acetoxy Analog (Xa′)——Conc. HCl (2 ml) was added to an ethanolic solution of IXa (0.45 g) with stirring. The mixture was warmed for 10 min on a water bath to give a precipitate (mp *ca.* 265°C), which was treated with CH_2N_2-etherate (at room temperature in MeOH–Et_2O) and with acetic anhydride (for 2 h on a water bath) to give Xa and Xa′, respectively. Xa: mp 124—126°C (yellow needles from Et_2O–*n*-hexane). Yield, 35.6%. IR (KBr): $\nu_{C=C}$ 1585, 1601. UV, λ_{max} nm: 366, 282, 246, 233, 215. NMR ($CDCl_3$–CD_3OD): 2.66 (3H, s, C–CH_3), 3.79 (3H, s, $-OCH_3$), 6.20 (1H, s, C_2–H). *Anal.* Calcd for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.37; H, 5.66; N, 9.55. Xa′: mp 135—137°C (needles from EtOH). Yield, 73.5%. IR (Nujol): $\nu_{C=O}$ 1752. NMR ($CDCl_3$): 2.41 (3H, s, –Ac), 2.80 (3H, s, C–CH_3), 6.76 (1H, s, C_2–H), 7.52 (5H, s, benzene H), 6.9—8.0 (4H, m). *Anal.* Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.53; H, 5.05; N, 8.58. Calcd for $C_{20}H_{16}N_2O_2+1/10H_2O$: C, 75.51; H, 5.13; N, 8.80.

2-(4-Methoxybenzylidene)acetyl-3-methylquinoxaline (IXb)——In a manner similar to that used in the preparation of IXa, IXb was prepared. Yield, 78.0%. mp 147—149°C (yellow needles from EtOH). NMR ($CDCl_3$): 2.97 (3H, s, C–CH_3), 3.81 (3H, s, $-OCH_3$), 6.90 and 7.63 (each 2H, d, $J=9$, benzene H), 7.5—8.4 (6H, m). *Anal.* Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.59; H, 5.17; N, 9.34.

3-Methoxy-1-(4-methoxyphenyl)-4-methylpyrrolo[1,2-*a*]quinoxaline (Xb)——CH_2N_2-etherate was added to a suspension of the cyclized product, prepared in the usual manner from IXb. The residue obtained after removal of the solvent was purified through an SiO_2 column. The yellow compound eluted with $CHCl_3$ was recrystallized from aq. MeOH. mp 139—141°C. Yield, 31%. NMR ($CDCl_3$): 2.76 (3H, s, C–CH_3), 3.84 and 3.90 (each 3H, s, $2\times OCH_3$), 6.30 (1H, s, C_2–H), 6.94 and 7.36 (each 2H, d, $J=9$, benzene H). *Anal.* Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.14; H, 5.57; N, 8.98.

3-Methyl-2-(4-nitrobenzylidene)acetylquinoxaline (IXc)——In a manner similar to that used in the preparation of IXa, IXb was obtained in a yield of 60.9%. mp 208—210°C (orange prisms from Me_2CO). NMR ($CDCl_3$–5 drops of TFA): 3.38 (3H, s, C–CH_3), 7.8—8.7 (10H, m). NMR (TFA): 3.50 (3H, s, C–CH_3), 7.8—8.9 (10H, m). MS, *m/e* (%): 319 (M^+, 100), 290 (44), 244 (20).

4-Methyl-3-(4-nitrobenzoyloxy)-1-(4-nitrophenyl)pyrrolo[1,2-*a*]quinoxaline (Xd)——A suspension of IXc (0.29 g) in EtOH was treated with 60% $HClO_4$ solution (5 ml). After being refluxed overnight, the mixture was concentrated to give a cyclized product as a yellow sand. mp 220—222°C (recrystallized from EtOH). Yield, 63.5%. NMR (TFA): 3.17 (3H, s, C–CH_3), 6.78 (1H, s, C_2–H), 7.87 and 8.40 (each 2H, d, $J=9.5$, benzene H), 6.9—7.9 (4H, m). 5% aq. NaOH solution (5 ml) was added to a mixture of this cyclized product (0.51 g), *p*-nitrobenzoyl chloride (0.4 g), H_2O (2 ml), and $CHCl_3$ with vigorous stirring. The crystalline compound was recrystallized from DMSO. mp 268—270°C (yellow sand). Yield, 38.9%. NMR ($CDCl_3$–5 drops of TFA): 3.25 (3H, s, C–CH_3), 7.2—8.2 (6H, m), 7.60 (1H, s, C_2–H), 8.3—8.7 (2H, m), 8.50

(4H, s). MS, *m/e* (%): 468 (M^+, 77), 318 (M–nitrobenzoyl, 100), 143 (methylquinoxalyl, 100). *Anal.* Calcd for $C_{25}H_{16}N_4O_6+1/3H_2O$: C, 63.29; H, 3.51; N, 11.80. Found: C, 63.25; H, 3.80; N, 11.83.

2-(2-Furfurylidene)acetylquinoline (XI)——An aq. solution of KOH (0.3 g) was added to an ethanolic solution of 2-acetylquinoline[11] (0.9 g) and furfural (0.5 g) with ice-cooling under an Ar atmosphere. The mixture was stirred for 1.5 h at room temperature to give a white crystalline compound, which was collected on a filter and recrystallized from EtOH. mp 117—119°C (lit.[4] 110—112°C) (white needles). Yield, 0.92 g (71.2%). IR (Nujol): $\nu_{C=O}$ 1670, $\nu_{C=C}$ 1600. NMR (CCl_4–$CDCl_3$=1:1): 6.55 (1H, m, C_4–H of furan ring), 6.80 (1H, d, J=3, C_3–H of furan ring), 7.4—8.1 (6H, m), 8.25 (3H, s. like).

Hydrolysis of XI——Conc. HCl (1 ml) was added to an ethanolic solution of XI (210 mg). The mixture was refluxed for 10 h. The residue obtained after removal of the solvent was dissolved in a mixture of g. AcOH (25 ml), conc. HCl (25 ml) and H_2O. The solution was refluxed for 3 h then concentrated. The residue was extracted with AcOEt. The dried organic layer was concentrated and the residue was methylated with CH_2N_2-etherate in MeOH–Et_2O. The methyl ester was purified through an SiO_2 column. From the fraction eluted with $CHCl_3$, methyl 2-quinaldate was obtained (*ca.* 20 mg). NMR (CCl_4): 4.06 (3H, s, $-OCH_3$), 7.5—8.0 (3H, m), 8.1—8.4 (3H, m).

3-Acetoxy-1-(2-furanyl)pyrrolo[1,2-*a*]quinoline (XIIb)——A mixture of XI (125 mg), Ac_2O (10 ml) and TFA (8 drops) was allowed to stand overnight at room temperature under an Ar atmosphere. The colour changed from orange to red and then deep green. The mixture was poured onto ice and extracted three times with Et_2O. The Et_2O layer was washed with sat. NaCl solution and dried over $MgSO_4$. The crude product obtained upon removal of the solvent was purified through an SiO_2 column. XIIb was eluted with benzene. XI (25 mg) was eluted successively with the same solvent. XIIb was recrystallized from *n*-hexane. XIIb: mp 107—110°C. Yield, 55 mg (conversion yield, 47.3%). IR (Nujol): $\nu_{C=O}$ 1753. NMR (CCl_4): 2.31 (3H, s, $-COCH_3$), 6.60 (2H, s. like), 6.90 (1H, s, C_2–H), 6.9—7.8 (7H, m). MS, *m/e* (%): 291 (M^+, 28), 249 (M–CH_2CO, 100), 128 (quinolyl, 48). *Anal.* Calcd for $C_{18}H_{13}NO_3$: C, 74.21; H, 4.50; N, 4.81. Found: C, 74.47; H, 4.55; N, 4.63.

2-(2-Furfurylidene)acetylpyrazine (XIII)——To an ethanolic solution of acetylpyrazine (0.43 g)[12] and freshly distilled furfural (0.34 g), 2% ethanolic solution (0.98 ml) of KOH was added. The mixture was stirred for 10 min to give a precipitate, which was recrystallized from EtOH. mp 117—119°C. Yield, 0.33 g (46.8%). IR (Nujol): $\nu_{C=O}$ 1660, $\nu_{C=C}$ 1600. NMR ($CDCl_3$): 6.60, 6.90 and 7.65 (each 1H, m, furan H), 7.86 and 8.07 (each 1H, d, J=5, vinylic H), 8.88 (2H, s. like), 9.47 (1H, s. like). *Anal.* Calcd for $C_{11}H_8N_2O_2$: C, 65.99; H, 4.03; N, 13.99. Found: C, 65.80; H, 3.93; N, 13.72.

Acid Treatment of XIII——An ethanolic solution of XIII (2.2 g) and conc. HCl (10 ml) was refluxed overnight. The residue obtained upon removal of the solvent was washed with benzene. From the benzene-insoluble and the benzene-soluble parts, 1-(2-furanyl)-3-hydroxy-4-methylpyrrolo[1,2-*a*]pyrazine (XIVa) and 3-ethoxy-1-(2-furanyl)-4-methylpyrrolo[1,2-*a*]pyrazine (XIVb) were obtained respectively. XIVa was difficult to recrystallize. mp *ca.* 217—219°C. The yield was about 1.7 g. The product was soluble in 5% HCl, 10% NaOH aq. solution, and insoluble in sat. $NaHCO_3$ solution. IR (Nujol): ν: 1655, 1610, 1595, 1565. MS, *m/e* (%): 200 (M^+, 100), 171 (M–HCO, 98). XIVb: mp 77—79°C (recrystallized from *n*-hexane). Yield, 0.34 g (13.6%). IR (Nujol): ν: 1622, 1558. NMR ($CDCl_3$): 1.48 (3H, t, J=7, $-CH_3$), 4.22 (2H, q, J=7, $>CH_2$), 6.59 (1H, s, C_2–H), 6.61 and 6.68 (each 1H, s. like, β-H of furan ring), 7.3—7.8 (2H, m), 8.15 (1H, d.d, J=5.5, 1), 8.86 (1H, br.s). MS, *m/e* (%): 228 (M^+, 63), 199 (M–C_2H_5, 100), 79 (pyridazinyl, 86). *Anal.* Calcd for $C_{13}H_{12}N_2O_2$: C, 68.42; H, 5.26; N, 12.28. Found: C, 68.50; H, 5.37; N, 12.22. CH_2N_2-etherate was added to a solution MeOH–Et_2O, and the solution was allowed to stand overnight at room temperature. The residue obtained upon removal of the solvent was crystallized from *n*-hexane. XIVc: mp 96—98°. Yield, 0.6 g (25.5%). IR (Nujol): ν: 1555, 1602, 1619. UV, λ_{max} nm (ε): 354 (9800), 338 (10800), 325 (7900), 283 (23500), 222 (17300). NMR ($CDCl_3$): 4.02 (3H, s, $-OCH_3$), 6.62 (2H, s. like), 6.73 (1H, s. like), 7.3—7.7 (2H, m, including α-H of furan ring), 8.17 (1H, d.d, J=5, 1), 8.87 (1H, d, J=1). *Anal.* Calcd for $C_{12}H_{10}N_2O_2$: C, 67.29; H, 4.67; N, 13.08. Found: C, 67.10; H, 4.59; N, 13.02.

General Method to prepare Adducts of Cyclized Products with Dimethyl Acetylenedicarboxylate (DMAD)——A benzene solution of a cyclized product and DMAD (5 eq. mol) was treated under the conditions mentioned below until no more starting material was detected in TLC (SiO_2). After removal of the solvent, the residue was purified through an SiO_2 column.

a) From IIIb: A benzene solution of IIIb and DMAD was refluxed for 5 h, and applied to an SiO_2 column. The product was eluted with Et_2O. It was an amorphous compound. Yield, 70%. IR (Nujol): $\nu_{C=O}$ 1740, 1700. MS, *m/e* (%): 562 (M^+, 42), 547 (M–CH_3, 90), 476 (100). *Anal.* Calcd for $C_{29}H_{26}N_2O_{10}$: C, 61.92; H, 4.66; N, 4.98. Found: C, 61.70; H, 4.83; N, 4.70.

b) From IVb: In a manner similar to that described for IIIb, the adduct of IVb was obtained in 65% yield (eluted with $CHCl_3$–EtOH (9:1)). Amorphous compound, mp *ca.* 238—240°C. IR (Nujol): $\nu_{C=O}$ 1772, 1750, 1737, 1700. MS, *m/e* (%): 590 (M^+, 15), 504 (24), 462 (53), 430 (100). *Anal.* Calcd for $C_{30}H_{26}N_2O_{11}$: C, 61.02; H, 4.44; N, 4.74. Found: C, 60.77; H, 4.16; N, 4.52.

c) From Xa: A benzene solution of Xa and DMAD was refluxed for 3 h. The adduct XIX was eluted from an SiO_2 column with benzene–Et_2O (9:1) and recrystallized from MeOH. mp 210—212°C (yellow prisms). Yield, 59.4%. IR (KBr): $\nu_{C=O}$ 1750, 1710. UV, λ_{max} nm (ε): 256 (28200). NMR ($CDCl_3$):

1.69 (3H, s, C–CH_3), 3.76, 3.78, 3.78, 3.82 and 3.88 (each 3H, s, OCH_3), 6.63 (1H, t, $J=6$), 6.84 (1H, d, $J=6$), 7.04 (1H, t, $J=8$), 6.22 (1H, s, C_2–H), 7.3—7.6 (6H, m). *Anal.* Calcd for $C_{31}H_{28}N_2O_9$: C, 65.03; H, 4.93; N, 4.89. Found: C, 64.95; H, 4.99; N, 4.87.

d) From XIVc: XIVc was treated with DMAD at room temperature. The reaction took place immediately. The product, XX, was eluted with Et_2O from an SiO_2 column and recrystallized from Et_2O. mp 182—184°C. IR (Nujol): $\nu_{C=O}$ 1740, 1715, 1700. UV, λ_{max} (ε): 303 (22900), 244 (18700). NMR ($CDCl_3$): 3.68, 3.72, 3.73, 3.90 and 3.93 (each 3H, s, –OCH_3), 6.01 (1H, s, E–CH<), 6.30 (1H, s, C_2–H), 6.44 (1H, d, $J=1$, C_5–H of furan ring). 6.50 (1H, d.d, $J=2$, 1, C_4–H of furan ring), 5.98 and 7.27 (each 1H, d, $J=4$, >N–CH=CH–N<), 7.47 (1H, d, $J=1$, C_5–H of furan ring). MS, *m/e* (%): 498 (M^+, *ca.* 20), 439 (M–COOMe, 100). *Anal.* Calcd for $C_{24}H_{22}N_2O_{10}$: C, 57.83; H, 4.42; N, 5.62. Found: C, 57.58; H, 4.48; N, 5.71.

e) From XIIb: A benzene solution of XIIb and DMAD was refluxed for 3 d. 3-Acetoxy-1-(2,3-dicarbomethoxy-4-hydroxyphenyl)pyrrolo[1,2-*a*]quinoline (XXII) and the 1:2 molar adduct were eluted successively with benzene. XXII was recrystallized from Et_2O. XXII: mp 159—162.5°C. Yield, 46.4%. IR (Nujol): $\nu_{C=O}$1760, 1680. NMR ($CDCl_3$): 2.35 (3H, s, –$COCH_3$), 3.57 and 3.96 (each 3H, s, –OCH_3), 6.66 (1H, s, C_2–H), 6.9—7.7 (8H, m), 12.0 (1H, s, phenolic OH). *Anal.* Calcd for $C_{24}H_{19}NO_7$: C, 66.51; H, 4.42; N, 3.23. Found: C, 66.31; H, 4.39; N, 3.34. The 1:2 molar adduct: Amorphous compound. Yield, 5.8%. NMR ($CDCl_3$): 2.36 (3H, s, –$COCH_3$), 3.4—4.1 (12H, m, –OCH_3), 7.0—7.8 (10H, m). MS, *m/e* (%): 575 (M^+, 30), 533 (M–$COCH_3$, 54), 128 (quinoxalyl, 100).

XXII was acetylated with Ac_2O in pyridine in a usual manner to give 3-acetoxy-1-(4-acetoxy-2,3-dicarbomethoxyphenyl)pyrrolo[1,2-*a*]quinoline (XXIII). mp 145—148°C (yellow needles from Et_2O). NMR ($CDCl_3$): 2.33 (6H, s, $2\times COCH_3$), 3.50 and 3.90 (each 3H, s, $2\times OCH_3$), 6.70 (1H, s, C_2–H), 6.8—7.8 (8H, m).

f) From 7-Ethoxy-2,3,4,4a,5,6-hexahydroquinoline Hydroiodide (XV): A mixture of XV and DMAD was allowed to stand overnight at room temperature in benzene. The N-substituted product (XVII) was eluted with $CHCl_3$–EtOH (49:1) from an SiO_2 column. XVII: mp 93—94°C (recrystallized from Et_2O). Yield, 26.3%. IR (Nujol): $\nu_{C=O}$ 1743 (weak), 1720 (strong), 1640 (sharp), $\nu_{C=C}$ 1573 (sharp). NMR (CCl_4): 1.1—3.0 (9H, m), 3.50 (2H, t, $J=5$, >N–CH_2–), 3.72 and 3.78 (each 3H, s, $2\times OCH_3$), 5.39 (1H, d, $J=1.5$, C_8–H), 5.50 (1H, s, vinylic H). *Anal.* Calcd for $C_{15}H_{19}NO_5$: C, 61.43; H, 6.48; N, 4.78. Found: C, 61.15; H, 6.46; N, 5.00.

g) From 2,3,4,4a,5,6-Hexahydroquinolin-7[1H]one (XVI): A benzene solution of XVI and DMAD was refluxed for 2 h. An amide compound (XVIII) was obtained from the fraction eluted from an SiO_2 column with $CHCl_3$. mp 154—155°C (recrystallized from EtOH). Yield, 28.6%. IR (Nujol): $\nu_{C=O}$ 1728 (sharp), 1660 (broad). NMR (CCl_4–$CDCl_3$=1:1): 1.0—3.3 (8H, m), 3.92 (3H, s), 3.5—4.3 (3H, m), 6.43 (1H, s, vinylic H). *Anal.* Calcd for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79; N, 5.36. Found: C, 64.36; H, 5.79; N, 5.52.

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