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Synthetic Studies on Pyrroloquinolines. I.[1] Syntheses of 2,3-Dihydro-1H-pyrrolo[2,3-*b*]quinoline Derivatives

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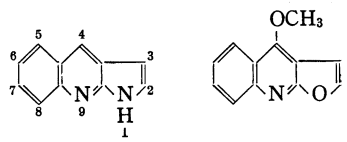
2,3-Dihydro-4-hydroxy-1H-pyrrolo[2,3-*b*]quinolines (III) were prepared by reactions of 4-chloro-2,3-dihydrofuro[3,2-*c*]quinolines (1) with ammonia or primary amines. 4-Chloro-2,3-dihydro-1H-pyrrolo[2,3-*b*]quinolines (VIII) were also prepared by the same amination of 2,4-dichloro-3-(β-chloroethyl)-quinolines (II) accompanied with various minor products.

The structures of these compounds were mainly confirmed by chemical methods.

Little attention has been paid to the synthesis and properties of pyrrolo[2,3-*b*]quinolines, depicted as a combination of 7-azaindole and quinoline skeleton.[3] This system with a methoxyl substituent on the 4-position is also regarded as an aza-analogue of "Furoquinoline alkaloids" *e.g.*, dictamnine.[4] The present investigation was undertaken to find out some definite methods for synthesizing the pyrroloquinoline and its derivatives.

As the starting materials, 4-chloro-2,3-dihydrofuro-[3,2-*c*]quinoline (1a) and 2,4-dichloro-3-(β-chloroethyl)-quinoline (IIa), both of which were obtainable by the chlorination of 2,3,4,5-tetrahydro-4-oxofuro[3,2-*c*]quinoline with phosphorus oxychloride subsequent chromatographic separation, were choosen.[5]



It was found that, on heating Ia with ethanolic ammonia in xylene in a sealed tube at 160—180° for 10 hours, fission of the dihydrofuran ring in Ia took place accompanied with recyclization giving 2,3-dihydro-4-hydroxy-1H-pyrrolo[2,3-*b*]quinoline (IIIa) in good yield. The structure assignment of III, was accomplished from the consideration of the elementary microanalysis and the presence of an acidic hydrogen which was characterized by the solubility in aqueous alkali hydroxide. This novel reaction was observed to occur in a series of compounds having a chloro or a methoxy substituent on the benzene ring of I. Primary amines such as methyl amine and benzyl amine including ethanolamine were also successfully used to afford the 1-substituents of III. In one instance where rather mild conditions were used, Ic gave 4-benzylamino-7-chloro-2,3-dihydrofuro[3,2-*c*]quinoline (IV) in addition to the expec-

1) A part of the work was presented at the 90th Annual Meeting of Pharmaceutical Soceity of Japan, Sapporo, July 1970.

2) Location: *2-2-50, Kawagishi, Toda, Saitama.*

3) *a*) W.H. Perkin and R. Robinson, *J. Chem. Soc.*, **103**, 1973 (1913); *b*) Farbenfabriken Bayer Akt. Ges., Brit. Patent 804514 (1958) [*C.A.*, **53**, 11416^c (1959)]; *c*) A.N. Shkrob, Yu. I. Krylova, V.K. Antonov and M.M. Shemiakin, *J. Gen. Chem.*, **38**, 1987 (1968); *d*) H. Zimmer, D.C. Armbruster, S.P. Kharidia and D.C. Lakin, *Tetrahedron Letters*, **1969**, 4053; *e*) Von A. Vogel, F. Troxler and A. Lindemann, *Helv. Chim. Acta*, **52**, 1929 (1969).

4) H.T. Openshaw, "The Alkaloids: Chemistry and Physiology," Vol. VII, ed. by R.H.F. Manske, Academic Press Inc., New York, N.Y., 1960, Chapter 12.

5) *a*) M.F. Grundon, N.J. McCorkindale and M.N. Rodger, *J. Chem. Soc.*, **1955**, 4234; *b*) T. Sato and M. Ohta, *Bull. Chem. Soc. Japan*, **31**, 161 (1958).

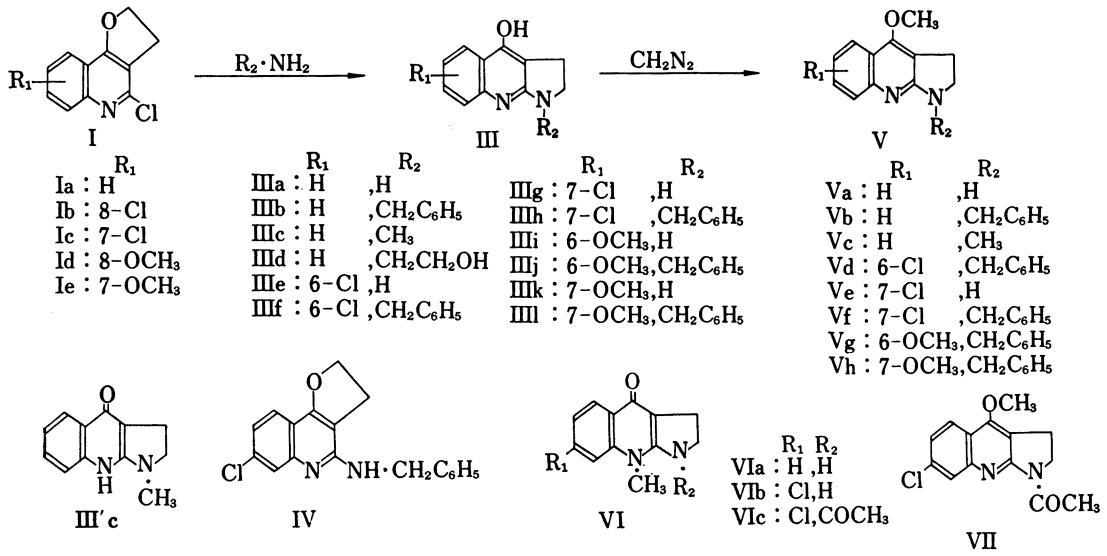
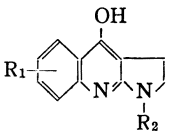


Chart 1

ted product IIIh. Both were readily separable on treating with dilute sodium hydroxide solution.

The compounds (III) were further led to the 4-methoxy-2,3-dihydro-1H-pyrrolo[2,3-*b*]-quinolines (V) in the expected fasion by the agency of ethereal diazomethane. Some physical data of III and V series are summarized in Table I and II, respectively.

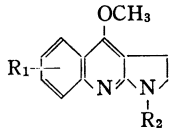
TABLE I. 2,3-Bihydro-4-hydroxy-1H-pyrrolo[2,3-*b*]quinolines (III)



Compound	Yield (%)	HCl salt mp (°C) (decomp.)[a]	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIIa	54.1	236—238	$C_{11}H_{10}ON_2 \cdot HCl \cdot H_2O$	54.89	5.44	11.64	55.76	5.64	11.78
IIIb	60.7	251—255	$C_{18}H_{16}ON_2 \cdot HCl$	69.11	5.47	8.95	69.01	5.78	8.62
IIIc	46.0	272—273	$C_{12}H_{12}ON_2 \cdot HCl \cdot 1/2H_2O$	58.65	5.74	11.40	58.91	5.72	11.01
IIId	55.3	220—225	$C_{13}H_{14}O_2N_2 \cdot HCl$	58.54	5.67	10.50	58.42	5.82	10.38
IIIe	54.4	277—278	$C_{11}H_9ON_2Cl \cdot HCl \cdot H_2O$	48.02	4.03	10.18	48.22	4.45	9.84
IIIf	59.2	275—278	$C_{18}H_{15}ON_2Cl \cdot HCl$	62.26	4.64	8.07	62.12	4.71	8.14
IIIg	66.0	263—265	$C_{11}H_9ON_2Cl \cdot HCl$	48.94	4.71	10.19	48.34	4.67	9.89
IIIh	75.0	262—264	$C_{18}H_{15}ON_2Cl \cdot HCl$	62.12	4.64	8.07	62.49	4.43	7.85
IIIi	77.1	254—256	$C_{12}H_{12}O_2N_2Cl \cdot I/2H_2O$	55.07	5.39	10.70	55.29	5.37	10.30
IIIj	60.4	251—253	$C_{19}H_{18}O_2N_2 \cdot HCl$	66.57	5.59	8.17	66.20	5.54	8.36
IIIk	47.4	268	$C_{12}H_{12}O_2N_2 \cdot HCl \cdot 1/2H_2O$	55.07	5.39	10.70	54.83	5.91	10.20
IIIl	64.5	242	$C_{19}H_{18}O_2N_2 \cdot HCl$	66.57	5.59	8.17	66.07	5.28	8.17

a) Generally, the free bases have indistinct melting points near 300°.

TABLE II. 4-Methoxy-2,3-dihydro-1H-pyrrolo[2,3-*b*]quinolines (V)



Compound	Yield (%)	HCl salt mp (°C) (decomp.)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Va	45.0	212—213	$C_{12}H_{12}ON_2 \cdot HCl$	60.88	5.54	11.84	60.69	5.39	11.87
Vb	68.3	199—200	$C_{19}H_{18}ON_2 \cdot HCl$	69.82	5.85	8.57	69.50	5.46	8.22
Vc	56.1	227	$C_{13}H_{14}ON_2 \cdot HCl$	62.27	6.03	11.17	62.32	6.15	11.46
Vd	63.8	193—195	$C_{19}H_{17}ON_2Cl \cdot HCl$	63.17	5.03	7.76	63.42	5.42	7.52
Ve	71.6	202—203	$C_{12}H_{11}ON_2Cl \cdot HCl$	53.16	4.46	10.34	53.50	4.33	10.28
Vf	76.0	203—205	$C_{19}H_{17}ON_2Cl \cdot HCl$	63.17	5.03	7.76	63.52	4.97	7.64
Vg	74.8	195—196	$C_{20}H_{20}O_2N_2 \cdot HCl$	67.32	5.93	7.85	67.80	6.09	8.14
Vh	61.8	188—189	$C_{20}H_{20}O_2N_2 \cdot HCl$	67.32	5.93	7.85	67.02	5.85	7.86

With respect to the structures of III and V, the tautometric forms analogous to the relationship between 4-hydroxy- and 4-oxo-[6] and 2-amino- and 2-imino-[7] forms in quinolines would be capable of drawing. Practically, the ultraviolet (UV) spectrum of the 1-methyl compound (IIIc), measured in methanol solution, differed from that of Vc, possessing an unambiguous electronic structure, and was closely similar to that of the 9-methyl compound (VIa).[1c] This evidence discloses that IIIc exists in the 4-oxo form (III'c) in methanol.

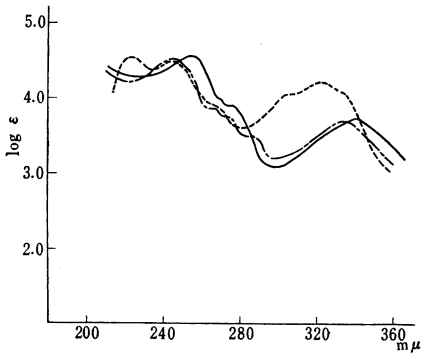


Fig. 1.
———: Vc
———: Va
--------: III'c
in MeOH

Methylation of the 7-chloro compound (IIIg) using methyl *p*-toluenesulphonate and sodium hydroxide gave rise to two kinds of methyl derivatives, of which one was found to be identical with the 4-methoxy compound (Ve). Nuclear magnetic resonance (NMR) spectral comparison of the methyl signal of the other product (6.15τ) with that of the 7-dechloro-1-methyl compound (IIIc) (6.73 τ) revealed distinct difference of the chemical shift between them.[8,9] Therefore, the structure was ascribed to 7-chloro-2,3,4,9-tetrahydro-9-methyl-4-oxo-1H-pyrrolo[2,3-*b*] quinoline (VIb). Moreover, the signal of the C_5 proton (1.68τ, d, J=9Hz) of its 1-acetyl derivative (VIc)[10] showed expected down field shift of 0.54 ppm when compared with that of the 1-acetyl drivative[10] (VII) (2.22 τ, d, J=9Hz) obtained from Ve because of the anisotropic deshielding due to the 4-oxo group in VIc.[11] These spectroscopic data also indicate that III possess the linear pyrrolo[2,3-*b*]quinoline framework, but not the angular furo[3,2-*c*]quinoline structure.

6) G.W. Ewing and E.A. Steck, *J. Am. Chem. Soc.*, **68**, 2181 (1946).
7) E.A. Steck, F.C. Nachod, G.W. Ewing and N.H. Gorman, *J. Am. Chem. Soc.*, **70**, 3406 (1948).
8) Their NMR spectra were measured in trifluoroacetic acid.
9) The methyl signal of VIa appears at 6.02 τ. Private communication from Dr. A.N. Shkrob.
10) They were prepared in order to increase the solubility in chloroform.
11) E.A. Clarke and M.F. Grundon, *J. Chem. Soc.*, **1964**, 4190.

On the other hand, reactions of the trichloroquinoline (IIa—f) with ammonia or primary amines gave various products depending upon the molar ratio of the amines used and reaction conditions. For instance, when IIc was heated in xylene with 3 molar equivalents of benzyl amine in a sealed tube at 140—150° for 15 hours, 1-benzyl-4,7-dichloro-2,3-dihydro-1H-pyrrolo[2,3-*b*] quinoline (VIIIe) was obtained as a single product in 37% yield with recovery of about 30% of the starting material.

While, heating of IIc in excess benzyl amine at 180—190° for 9 hours in an atmospheric pressure gave three products. One of which, obtained in 20% yield, was identical with VIIIe described above and the other two, obtained in 28.6% and 13.6% were determined to 1-benzyl-4-benzylamino-7-chloro-2,3-dihydro-1H-pyrrolo[2,3-*b*]quinoline (X) and 1-benzyl-4-benzylamino-7-chloro-2,3-dihydro-1H-pyrrolo[3,2-*c*]quinoline (XI) respectively. The structures of these compounds were confirmed by the following chemical evidence shown in Chart 2.

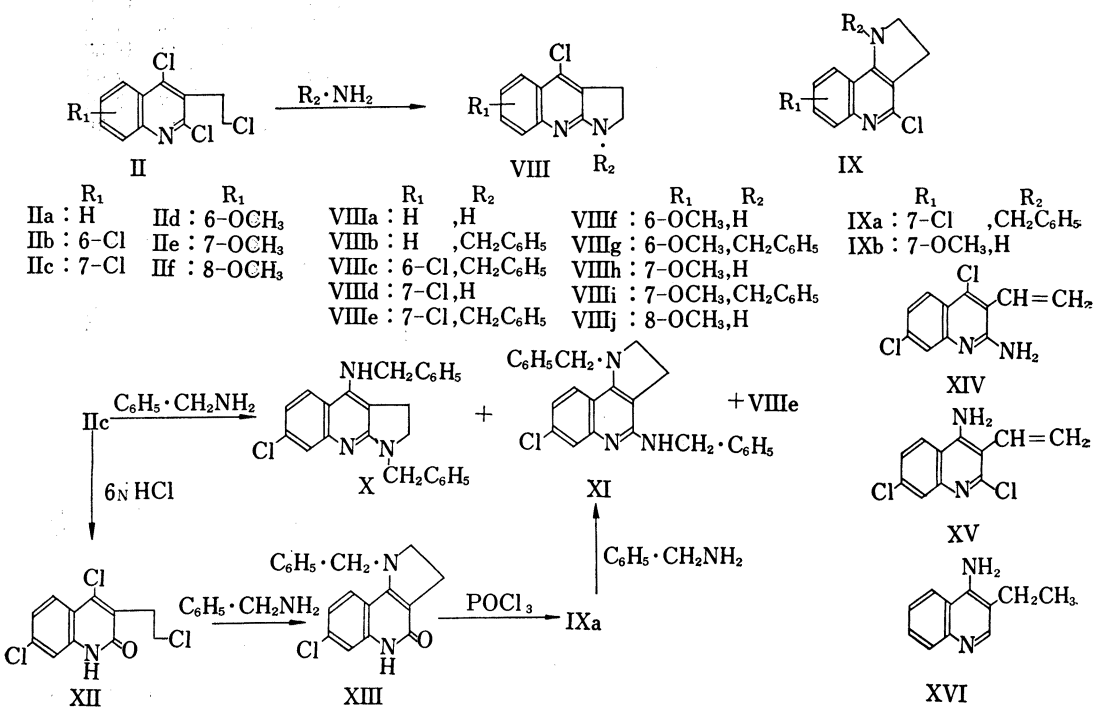


Chart 2

Acidic hydrolysis of IIc caused selective removal of the chlorine atom at the 2-position furnishing 4,7-dichloro-3-(β-chloroethyl)-2-quinolone (XII) almost quantitatively.[12a] This was submitted to condensation reaction with excess benzyl amine to give 1-benzyl-7-chloro-2,3,4,5-tetrahydro-4-oxo-1H-pyrrolo[3,2-*c*] quinoline (XIII). In conformity with their structures, XII and XIII showed a strong infrared (IR) band at 1645 and 1630 cm^{-1}, respectively, due to the 2-quinolone moiety.[12a,b] The compound (XIII) was chlorinated with phosphorus oxychloride to yield 1-benzyl-4,7-dichloro-2,3-dihydro-1H-pyrrolo[3,2-*c*]quinoline (IXa), a structural isomer of VIIIe. Then, IXa was again benzylaminated to give XI, which was identical with the compound obtained from IIc directly in 13.6% yield.

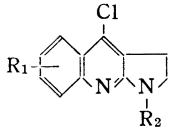
Reaction of IIe with ethanolic ammonia in a sealed tube at 110—120° for 9 hours brought about formation of two products which showed the same composition, $C_{11}H_{11}ON_2Cl$. One was

12) *a*) M.F. Grundon and N.J. McCorkindale, *J. Chem. Soc.*, **1957**, 2177; *b*) N.J. McCorkindale, *Tetrahedron*, **14**, 223 (1961).

identified by comparing its IR spectrum with that of an authentic sample of VIIIh derived from IIIk by chlorination with phosphorus oxychloride. Accordingly, the structure of the other compound was attributed to 4-chloro-2,3-dihydro-7-methoxy-1H-pyrrolo[3,2-*c*]quinoline (IXb).

Reaction of IIc with ammonia using the same reaction conditions as with IIe yielded three products. The major product, isolated in 55% yield, wae further benzylated with benzyl chloride and sodium hydride to afford VIIIe, thus establishing the former structure VIIId. The minor two products were estimated to be 2-amino-4,7-dichloro-3-vinylquinoline (XIV) and its isomeric 4-amino-2,7-dichloro-3-vinylquinoline (XV) on the basis of the analytical and spectroscopic data. They were discriminated by converting XV to 4-amino-3-ethylquinoline (XVI), which was characterized by the appearance of a proton due to the 2-position in quinolines at 1.55τ, by means of catalytic hydrogenation.

TABLE III. 4-Chloro-2,3-dihydro-1H-pyrrolo[2,3-*b*]quinolines (VIII)



Compound	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
VIIIa	52.0	212—214[a]	$C_{11}H_9N_2Cl$	64.55	4.43	13.69	64.52	4.48	13.85
VIIIb	58.5	138—139	$C_{18}H_{15}N_2Cl \cdot HCl$[b]	65.46	4.87	8.46	65.07	5.00	8.91
VIIIc	40.0	130—133	$C_{18}H_{14}N_2Cl_2$	65.66	4.29	8.51	65.32	4.38	8.49
VIIId	59.4	228—232[a]	$C_{11}H_8N_2Cl_2$	55.25	3.37	11.66	55.44	3.41	11.88
VIIIe	53.0	116—117	$C_{11}H_{14}N_2Cl_2HCl$[b]	59.12	4.13	7.65	58.91	3.48	7.38
VIIIf	40.5	243—245	$C_{12}H_{11}ON_2Cl \cdot HCl$[b]	53.15	4.46	10.34	53.37	4.26	10.30
VIIIg	43.2	146—147	$C_{19}H_{17}ON_2Cl \cdot HCl \cdot 1/2H_2O$[b]	61.63	5.17	7.75	61.75	4.90	7.93
VIIIh	35.0	211—213[a]	$C_{12}H_{11}ON_2Cl$	61.41	4.72	11.93	60.99	4.40	11.94
VIIIi	40.3	112—113	$C_{19}H_{17}ON_2Cl$	70.26	5.28	8.63	69.97	5.18	8.68
VIIIj	62.0	218—220[a]	$C_{12}H_{11}ON_2Cl \cdot HCl \cdot 1/2H_2O$[b]	51.44	4.68	10.00	51.67	4.83	10.07

a) decomposition *b*) analyzed as the hydrochloride

Experimental[13]

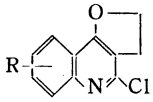
4-Chloro-2,3-dihydrofuro[3,2-*c*]quinolines (1) and 2,4-Dichloro-3-(*β*-chloroethyl)quinolines (11)——Although these compounds were prepared according to the general procedure reported by Grundon and by Sato[5] substancially, some improvements were made: While 1 were obtained mainly (20—40% yields) by treating 2,3,4,5-tetrahydro-4-oxofuro[3,2-*c*]quinolines with refluxing $POCl_3$ for a short period (30 min), prolonged heating (3—6 hr) caused formation of 11 predominantly (50—60% yields). Of those compounds 1 and 11, new substances are listed in Table IV.

General Procedure for the Preparation of 2,3-Dihydro-4-hydroxy-1H-pyrrolo[2,3-*b*]quinolines (III)——A mixture of 40 ml of 30% ethanolic ammonia, 0.06 mole of 1, and 30 ml of xylene was heated in an autoclave at 160—180° for 8—12 hr. The reaction mixture was treated with 50 ml of warm 10% NaOH solution. The alkali layer was separated and neutralized with glacial AcOH and precipitated solids were collected. Thus obtained crude free base was converted to the hydrochloride by use of 10% HCl–MeOH, and recrystallized from MeOH–ether to give colorless well crystalline solid. The compounds (III) generally contain 1—1/2 mole of water of crystallization.

General Procedure for the Preparation of 1-Substituted 2,3-Dihydro-4-hydroxy-1H-pyrrolo[2,3-*b*]quinolines (III)——A mixture of 0.5 mole of appropriate primary amine, 0.1 mole of 1, 100 ml of xylene, and

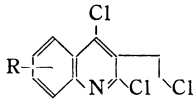
13) All melting points were not corrected. The NMR spectra were measured with a Japan Electron Optics Co., JNM-C-60 (60 Mc) spectrometer with tetramethyl silane as internal reference. UV spectra were recorded on a Hitachi EPS-2U spectrometer. IR spectra were obtained on a IASCO 1R-E spectrometer.

Table IV. 4-Chloro-2,3-dihydrofuro[3,2-*c*]quinolines (I)



Compound	R	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
Ib	8-Cl	197—198	$C_{11}H_7ONCl$	55.03	2.94	5.83	29.53	54.92	3.18	5.95	29.84
Ic	7-Cl	138	$C_{11}H_7ONCl$	55.35	2.94	5.83	29.53	54.92	2.74	6.01	29.35
Id	8-OCH_3	152—153	$C_{12}H_{10}O_2NCl$	61.16	4.28	5.94	15.04	60.90	3.99	5.95	15.22
Ie	7-OCH_3	132—133	$C_{12}H_{10}O_2NCl$	61.16	4.28	5.94	15.04	61.40	4.41	5.78	15.31

3-(β-Chloroethyl)-2,4-dichloroquinolines (II)



Compound	R	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
IIb	6-Cl	115—117	$C_{11}H_7NCl_4$	44.78	2.39	4.74		44.70	2.48	4.90	
IIc	7-Cl	99—100	$C_{11}H_7NCl_4$	44.78	2.39	4.74		44.81	2.23	4.85	

3 ml of H_2O was heated in a sealed tube at 160—180° for 8—12 hr. The reaction mixture was extracted with 150 ml of 10% NaOH solution, and the alkali layer was separated, neutralized with glacial AcOH. The precipitated solid was collected and converted to the hydrochloride by the same manner described above.

Reaction of 1c with Benzyl Amine in an Atmospheric Pressure——A mixture consisting 3.0 g of 1c, 6.0 g of benzyl amine, and 0.4 ml of H_2O, and 15 ml of xylene was heated for 45 hr at reflux temperature. After evaporation of the solvents *in vacuo*, the residue was treated with warm 10% NaOH solution. Alkali insoluble solid was collected, washed with H_2O, and dried. This was converted to the hydrochloride by the usual manner to give 1.1 g (23.5%) of 4-benzylamino-7-chloro-2,3-dihydrofuro[3,2-*c*]quinoline (IV) HCl salt as colorless rhombs, mp 185—189° (decomp.). *Anal.* Calcd. for $C_{18}H_{16}ON_2Cl_2 \cdot 1/2H_2O$: C, 60.68; H, 4.81; N, 7.87. Found: C, 60.39; H, 4.75; N, 7.85. IR ν_{max}^{Nujol} cm^{-1}: 3310, 3120, 1650, 1605. Alkali soluble part was neutralized with glacial acetic acid and the resulted solid was collected. This was converted to the hydrochloride to give 2.2 g (53.0%) of IIIh. HCl salt as colorless sandy crystals, mp 271—273° (decomp.). IR ν_{max}^{Nujol} cm^{-1}: 2700—2800, 1655.

General Procedure for the Preparation of 2,3-Dihydro-4-methoxy-1H-pyrrolo[2,3-*b*]quinolines (V)——To a suspension of 0.05 mole of III ln 40 ml of MeOH was added an excess ethereal diazo methane and the mixture was allowed to stand at room temperature overnight. After evaporation of the solvents *in vacuo*, the residue was treated with 10% NaOH solution in order to dissolve any unreacted starting material. Alkali-insoluble solid was collected, washed with H_2O, and dried. This was led to the monohydrochloride by the usual manner using MeOH–HCl.

7-Chloro-2,3,4,9-tetrahydro-9-methyl-4-oxo-1H-pyrrolo[2,3-*b*]quinoline (VIb)——To a solution of 2.20 g (0.01 mole) of III g in 50 ml of 3% NaOH and 50 ml of MeOH was added, while stirring, 3.72 g (0.02 mole) of *p*-TsOMe at room temperature and the mixture was allowed to stand for 3 days. After evaporating the solvents to a half volume under diminished pressure, separated solid was collected, washed with H_2O, and recrystallized from MeOH to give 0.42 g (17.9%) of VIb as colorless needles, mp>270°. *Anal.* Calcd. for $C_{12}H_{11}ON_2Cl \cdot H_2O$: C, 57.03; H, 5.18; N, 11.09; Cl, 14.03. Found: C, 56.87; H, 5.04; N, 10.97; Cl, 14.62. IR ν_{max}^{Nujol} cm^{-1}: 1610, 1580. NMR ($CDCl_3$) τ: 6.70 (2H, t, J=9 Hz), 6.25 (3H, s), 5.96 (2H, t, J=9 Hz), 2.40—2.60 (2H, m), 1.87 (1H, d, J=9 Hz). Mass Spectrum *m/e*: 234 (M^+). From the alkaline filtrate, 0.8 g (35.4%) of Ve was obtained which was identical with an authentic specimen by their IR spectral comparison.

1-Acetyl Derivative (VIc) of VIb——A solution of 0.08 g of VIb in 1 ml of Ac_2O was refluxed for 15 min. After cooling, 15 ml of ether was added to the solution and the separated colorless needles were filtered and washed with 10 ml of ether to give 0.08 g (85.1%) of VIc, mp 238—241° (decomp.). *Anal.* Calcd. for $C_{14}H_{13}O_2N_2Cl \cdot H_2O$: C, 57.05; H, 5.13; N, 9.50; Cl, 12.03. Found: C, 56.99; H, 5.14; N, 9.79; Cl, 12.27. IR ν_{max}^{Nujol} cm^{-1}: 1655. 1615, 1575. NMR ($CDCl_3$) τ: 7.68 (3H, s), 6.98 (2H, t, J=8 Hz), 6.42 (3H, s), 5.30 (2H, t, J=8 Hz), 2.70 (1H, q, J=9, 2.5 Hz), 2.52 (1H, d, J=2.5 Hz), 1.68 (1H, d, J=9 Hz). Mass Spectrum m/e: 276 (M^+).

1-Acetyl Derivative (VII) of Ve——A solution of 0.35 g of Ve in 4 ml of Ac_2O was refluxed for 30 min. After cooling, separated solid was collected and recrystallized from benzen to give 0.36 g (86.7%) of VII as colorless needles, mp 176—177°. *Anal.* Calcd. for $C_{14}H_{13}O_2N_2Cl$: C, 60.76; H, 4.73; N, 10.21; Cl, 12.81. Found: C, 61.07; H, 4.76; N, 10.07; Cl, 12.76. IR ν_{max}^{Nujol} cm^{-1}: 1650, 1620, 1570. NMR ($CDCl_3$) τ: 7.25 (3H, s), 6.73 (2H, t, J=8 Hz), 5.98 (2H, t, J=8 Hz), 5.88 (3H, s), 2.86 (1H, q, J=9, 2.5 Hz), 2.40 (1H, d, J=2.5 Hz), 2.20 (1H, d, J=9 Hz).

General Procedure for the Preparation of 4-Chloro-2,3-dihydro-1H-pyrrolo[2,3-*b*]quinolines——To a mixture of 70 ml of 28% NH_4OH and 70 ml of EtOH ammonia gas was saturated at 5—8°. To the resulting solution, 0.05 mole of II was suspended and the whole was heated at 110—130° for 10—12 hr in an autoclave. After cooling, separated solid was collected, washed with H_2O thoroughly, and recrystallized from MeOH or MeOH·$CHCl_3$. The free bases (VIII) having no substituent in the 1-position showed very high melting points and were difficult to purify. They were characterized by forming the mono-hydrochlorides.

General Procedure for the Preparation of 1-Benzyl-4-chloro-2,3-dihydro-1H-pyrrolo[2,3-*b*]quinolines (VIII) A solution of 8.0 g of benzyl amine, 0.0177 mole of II, 15 ml of xylene, and trace of H_2O was heated in a sealed tube at 160—180°. After heating for 8—12 hr. The reaction mixture was evaporated *in vacuo* and 50 ml of H_2O was added to the residue. The mixture was extracted with $CHCl_3$ several times and the whole $CHCl_3$ layer was washed with H_2O, dried over anhyd. Na_2SO_4, then evaporated. The residue was purified by means of column chromatography using alumina or silica gel.

Reaction of IIC with Excess Benzyl Amine——A mixture of 10 g (0.038 mole) of IIC and 45 ml (0.41 mole) of $C_6H_5CH_2NH_2$ was heated at 180—190° for 9 hr. After cooling, 5% HCl was added to the reaction mixture and the resultant solution was extracted with 50 ml of $CHCl_3$ for three times. The hydrochlorides of the reaction products were soluble in $CHCl_3$ and excess $C_6H_5CH_2NH_2$ passed into the water layer. The $CHCl_3$ layer was then washed with 10% NaOH, with H_2O, and dried. The solvent was distilled *in vacuo* and the residue was triturated with warm isopropyl ether. The insoluble solid was filtered off. From the filtrate, 2.4 g (20%) of VIIIe was obtained as colorless rhombs, mp 116—117° (C_6H_6–*n*-hexane). IR ν_{max}^{Nujol} cm^{-1}: 1635, 1608, 1564. NMR ($CDCl_3$) τ: 6.88 (2H, t, J=8 Hz), 6.40 (2H, t, J=8 Hz), 5.22 (2H, s), 2.73 (1H, q, J=9, 2.5 Hz), 2.25 (1H, d, J=2.5 Hz), 2.15 (1H, d, J=9 Hz). The insoluble solid in isopropyl ether was treated with 10% HCl–MeOH, and the resulting mixture of hydrochlorides was purified by fractional recrystallization from EtOH several times to yield 4.5 g (28.6%) of 1-benzyl-4-benzylamino-7-chloro-2,3-dihydro-1H-pyrrolo[2,3-*b*]quinoline (X) hydrochloride as colorless fine needles, mp 220° (decomp.). *Anal.* Calcd. for $C_{25}H_{22}N_3Cl \cdot HCl$: C, 68.80; H, 5.31; N, 9.62; Cl, 16.24. Found: C, 68.65; H, 5.28; N, 9.53; Cl, 16.06. From the ethanol mother liquor, 2.05 g (13%) of 1-benzyl-4-benzylamino-7-chloro-2,3-dihydro-1H-pyrrolo[3,2-*c*]quinoline (XI) hydrochloride was obtained as colorless prisms, mp 254—256°. *Anal.* Calcd. for $C_{25}H_{22}N_3Cl \cdot HCl$: C, 68.81; H, 5.32; N, 9.63; Cl, 16.26. Found: C, 69.07; H, 5.36; N, 9.54; Cl, 16.30.

4,7-Dichloro-3-(β-chloroethyl)-carbostyril (XII)——A solution of 5.9 g of IIc, 160 ml of 6 N HCl, and 130 ml of dioxane was refluxed for 70 min. The reaction mixture was kept at room temperature for 16 hr and the separated crystals were collected, washed with H_2O and dried to give 4.97 g (90%) of colorless needles, mp 217—218° (dioxane). *Anal.* Calcd. for $C_{11}H_8ONCl_3$: C, 47.77; H, 2.92; N, 5.07; Cl, 38.46. Found: C, 47.92; H, 2.98; N, 4.89; Cl, 38.54. IR ν_{max}^{Nujol} cm^{-1}: 1655.

1-Benzyl-7-chloro-2,3,4,5-tetrahydro-4-oxo-1H-pyrrolo[3,2-*c*]quinoline (XIII)——A mixture of 1.00 g of XII and 2.86 g of $C_6H_5CH_2NH_2$ was heated at 180° for 17 hr. After cooling, 50 ml of ether was added to the reaction mixture and the separated solid was filtered, washed with H_2O and dried. This was crystallized from dimethyl formamide (DMF) to give 0.63 g. (58.0%) of colorless fine needles, mp 258—260°. *Anal.* Calcd. for$C_{18}H_{15}ON_2Cl$: C, 69.56; H, 4.87; N, 9.01; Cl, 11.41. Found: C, 69.48; H, 4.49; N, 8.86; Cl, 11.23. IR ν_{max}^{Nujol} cm^{-1}: 1630.

1-Benzyl-4,7-dichloro-2,3-dihydro-1H-pyrrolo[3,2-*c*]quinoline (IXa)——A mixture of 0.156 g of XIII and 3 ml of $POCl_3$ was refluxed for 3 hr, and excess $POCl_3$ was distilled *in vacuo*. The residue was decomposed with ice–water and the resulting solution was made alkaline with 1% NaOH, extracted with $CHCl_3$, washed with H_2O, and dried. After evaporating the solvent, the residue was purified by column chromatography on alumina using $CHCl_3$. The whole eluent was collected and crystallized from MeOH·$CHCl_3$ to give 0.065 g (40%) of colorless needles, mp 164—165°. *Anal.* Calcd. for $C_{18}H_{14}N_2Cl_2$: C, 65.66; H, 4.29; N, 8.51; Cl, 21.54. Found: C, 65.82; H, 4.34; N, 8.57; Cl, 22.59.

Benzylamination of IXa——A mixture of 5.60 g (0.017 mole) of IXa and 5.60 g (0.523 mole) of $C_6H_5CH_2NH_2$ was heated at 190—200° for 20 hr. After cooling, 300 ml of $CHCl_3$ was added to the mixture and the whole was extracted with 10% HCl to remove excess $C_6H_5CH_2NH_2$. The $CHCl_3$ layer was separated, shaken with 10% NaOH, washed with H_2O, and dried. The solvent was removed and MeOH·HCl was added

to the residue. The resultant hydrochloride was purified by recrystallization to give 7.12 g (96.5%) of XI as colorless fine needles, mp 258—260° (MeOH–ether).

Amination of IIe——To a solution of 60 ml of 28% NH_4OH and 60 ml of EtOH gaseous ammonia was saturated at 5—7°. To this solution 14 g of IIe was added and the mixture was heated in an autoclave at 110—120° for 9 hr. After cooling, H_2O was added to the mixture and extracted with $CHCl_3$, washed with H_2O, and dried. The solvent was distilled off and the residue was washed with ether several times to give white solid which was recrystallized from $CHCl_3$ to give 3.9 g (35%) of VIIIh as colorless needles, mp 212—213° (decomp.). *Anal.* Calcd. for $C_{12}H_{11}ON_2Cl$: C, 61.41; H, 4.72; N, 11.93; Cl, 15.11. Found: C, 61.21; H, 4.90; N, 11.94; Cl, 15.20. IR ν_{max}^{Nujol} cm^{-1}: 1640, 1610, 1590. UV λ_{max}^{MeOH} mμ(ε): 356 (12000), 340 (12100), 248 (36600), 223 (50400). NMR ($CDCl_3$–TFA) τ: 6.78 (2H, t, J=7 Hz), 6.15 (3H, s), 5.96 (2H, t, J=7Hz), 3.12 (1H, d, J=9 Hz), 3.05 (1H, q, J=9, 3Hz), 2.23 (1H, d, J=3 Hz). The ether washings were collected and the solvent was removed. The residue was recrystallized from C_6H_6 to give 0.4 g of 4-chloro-2,3-dihydro-7-methoxy-1H-pyrrolo [3,2-*c*]quinoline (IXb) as colorless prisms, mp 180° (decomp.). *Anal.* Calcd. for $C_{12}H_{11}ON_2Cl$: C, 61.41; H, 4.72; N, 11.93; Cl, 15.11. Found: C, 60.97; H, 4.48; N, 12.28; Cl, 15.08. IR ν_{max}^{Nujol} cm^{-1}: 1620, 1590 (sh), 1570. UV λ_{max}^{MeOH} mμ(ε): 340 (11200), 267 (28400), 230 (44000). NMR ($CDCl_3$–TFA) τ: 6.76 (2H, t, J=9 Hz), 6.13 (3H, s), 5.88 (2H, t, J=9 Hz), 3.07 (1H, d, J=3 Hz), 2.96 (1H, q, J=9, 3Hz), 2.30 (1H, d, J=9Hz).

Amination of IIc——A solution consisting of 45 ml of EtOH, and 45 ml of 28 % NH_4OH was saturated with ammonia gas at 5—7°. To this mixture, 20.4 g of IIc was added and the suspension was heated in an autoclave at 110—120° for 11 hr. After cooling, separated crystals were collected and washed with H_2O, with EtOH, then crystallized from $CHCl_3$ to give 5.5 g of VIIId as slightly yellow solid, mp 237—240°, the hydrochloride mp 262° (decomp.) (EtOH). The $CHCl_3$ mother liquor was purified by column chromatography on alumina using $CHCl_3$. From the first portion of the eluent, further 1.18 g (total 40.5%) of VIIId was obtained. The second portion afforded 2.3 g (15.2%) of 4-amino-2,7-dichloro-3-vinylquinoline (XV), as colorless needles, mp 219—220° ($CHCl_3$). *Anal.* Calcd. for $C_{11}H_8N_2Cl_2$: C, 55.25; H, 3.37; N, 11.72; Cl, 29.66. Found: C, 55.42; H, 3.48; N, 11.46; Cl, 29.68. The last portion gave 0.7 g of 2-amino-4,7-dichloro-3-vinylquinoline (XIV) as colorless needles, mp 166—167° ($CHCl_3$). *Anal.* Calcd. for $C_{11}H_8N_2Cl_2$: C, 55.25; H, 3.37; N, 11.72; Cl, 29.66. Found: C, 55.17; H, 3.33; N, 11.81; Cl, 29.43.

Hydrogenation of XV——A solution of 0.36 g of XV in 20 ml of monoglyme and 20 ml of MeOH was hydrogenated in an atmospheric pressure using 0.10 g of 10% Pd-carbon catalyst. After 4 hr, absorption of H_2 was stopped and the catalyst was removed. The filtrate was distilled *in vacuo* and 1% NaOH was added to the residue. Then, the mixture was extracted with $CHCl_3$ and the whole $CHCl_3$ layer was dried over anhyd. Na_2SO_4. The residue, after removal of the solvent, was purified by column chromatography on alumina using $CHCl_3$ as eluate. From the first portion of the eluent, 0.09 g of 4-amino-3-ethylquinoline (XVI) was obtained as colorless plates, mp 113—115° (diisopropyl ether). *Anal.* Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.49; H, 7.13; N, 16.40. NMR ($CDCl_3$) τ: 8.70 (3H, t, J=8 Hz), 7.31 (2H, q, J=8 Hz), 5.20 (2H, broad s), 1.95—2.70 (4H, m), 1.55 (1H, s).

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