[Chem. Pharm. Bull. 18(10)2065—2069(1970)]

UDC 547.863.1.04 : 547.759.07

Synthesis of Condensed Quinoxalines. II.[1] A New Synthesis of Pyrrolo-[2,3-*b*]quinoxalines

Hirotaka Otomasu, Shigeru Ohmiya, Toshie Sekiguchi and Hiroshi Takahashi

Hoshi College of Pharmacy[2]

(Received April 13, 1970)

The reaction of ethyl 2-(3-chloro-2-quinoxalinyl)-2-cyanoacetate (I) with various amines: ammonia, methylamine, ethanolamine, γ-dimethylaminopropylamine, benzylamine, and *p*-phenetidine, gave the corresponding 1-substituted ethyl 2-aminopyrrolo[2,3-*b*]quinoxaline-3-carboxylates (IIIa—f) at about 80—90% yield.

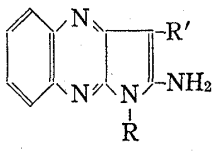
The similar reaction of α-(3-chloro-2-quinoxalinyl)-malondinitrile (II) with various primary amines was carried out to give the corresponding 1-substituted 2-aminopyrrolo-[2,3-*b*]quinoxaline-3-carbonitriles (VIIa—d) at 86—94% yield (Table I).

In Part I[1] of this series, the synthese and the reactions of indeno[1,2-*b*]quinoxalines have been studied for evaluation of their pharmacological activity. In the present work, we attempted to synthesize the condensed ring taking advantage of the reactivity of the substituents at 2- and 3-positions of quinoxaline.

Pratt, *et al.*[3] reported that 2,3-dichloroquinoxaline reacted with active methylene compounds such as ethyl cyanoacetate and malondinitrile in the presence of potassium *t*-butoxide to give ethyl 2-(3-chloro-2-quinoxalinyl)-2-cyanoacetate (I) and α-(3-chloro-2-quinoxalinyl)-malondinitrile (II), respectively, in good yields. And the present authors successfully synthesized pyrrolo[2,3-*b*]quinoxalines by replacing the chloro group at I and II with various primary amines and the subsequent intramolecular cyclization.

The mono-chloroquinoxaline compounds (I and II) were allowed to react for 1—2 hr with about two molar equivalent of various primary amines in the mixture of benzene and

Table I.

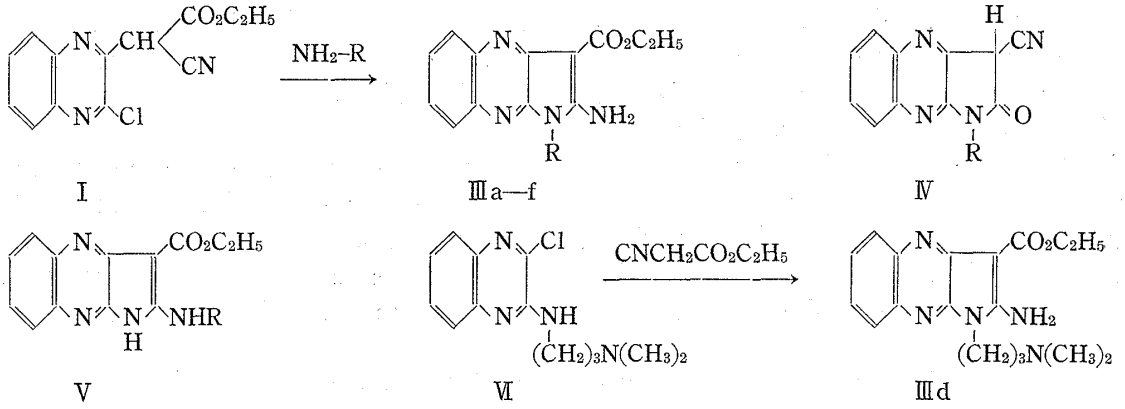


Product	R′	R	Yield (%)	mp° (decomp.)	Appearance
IIIa	$CO_2C_2H_5$	H	43	360	yellow
IIIb	$CO_2C_2H_5$	CH_3	87	237—238	yellow
IIIc	$CO_2C_2H_5$	CH_2CH_2OH	84	239—240	pale yellow
IIId	$CO_2C_2H_5$	$(CH_2)_3N(CH_3)_2$	92	164	colorless
IIIe	$CO_2C_2H_5$	$CH_2C_6H_5$	87	248	colorless
IIIf	$CO_2C_2H_5$	$C_6H_4OC_2H_5(p)$	90	242	colorless
VIIa	CN	CH_3	86	236—237	pale yellow
VIIb	CN	CH_2CH_2OH	90	268	yellow
VIIc	CN	$CH_2C_6H_5$	94	328	yellow
VIId	CN	$C_6H_4OC_2H_5(p)$	80	278	pale yellow

1) Part I: H. Otomasu and S. Ohmiya, *Yakugaku Zasshi*, **89**, 607 (1969).
2) Location: *2-4-41, Ebara, Shinagawa-ku, Tokyo.*
3) E.F. Pratt and J.C. Keresztesy, *J. Org. Chem.*, **32**, 49 (1967).

ethanol (1:1). The corresponding reaction products were obtained at 84—94% yield. They were all single product from the evidence of thin layer chromatography. The primary amines used in this reaction were methylamine, ethanolamine, γ-dimethylaminopropylamine, benzylamine, and p-phenetidine. The reaction of ammonia in place of primary amines on the compound (I) produced ethyl 2-amino-1H-pyrrolo[2,3-b]quinoxaline-3-carboxylate at 43% yield. The properties of the products thus obtained are summarized in Table I.

Regarding the structure of the products obtained from the reaction of ethyl 2-(3-chloro-2-quinoxalinyl)-2-cyanoacetate (I) with primary amines, we expected, at first, the formula IV which could possibly be produced through an intermediary carboxamide and the subsequent cyclization to the pyrrolidone ring. However, the infrared (IR) spectra of all these products showed the typical absorptions of amino group and α,β-unsaturated ethyl carboxylate at 3250—3500 cm^{-1} and 1660—1695 cm^{-1}, respectively, in KBr Tab. and exhibited lack of sharp absorption peak characteristic of cyano group. The nuclear magnetic resonance (NMR) spectra of these products in deuterodimethylsulfoxide showed the signal that could be attributed to the carboethoxyl group at 1.35—1.40 ppm (triplet, three proton) at 4.3—4.5 ppm (quartet, two proton), and showed the broad signal (singlet, two proton) at 7.5—9.0 ppm, which was shifted very much by addition of little water and attributable to amino group. Their analytical values were also identical with those of aminopyrrolo compounds (III and V).



I IIIa—f IV

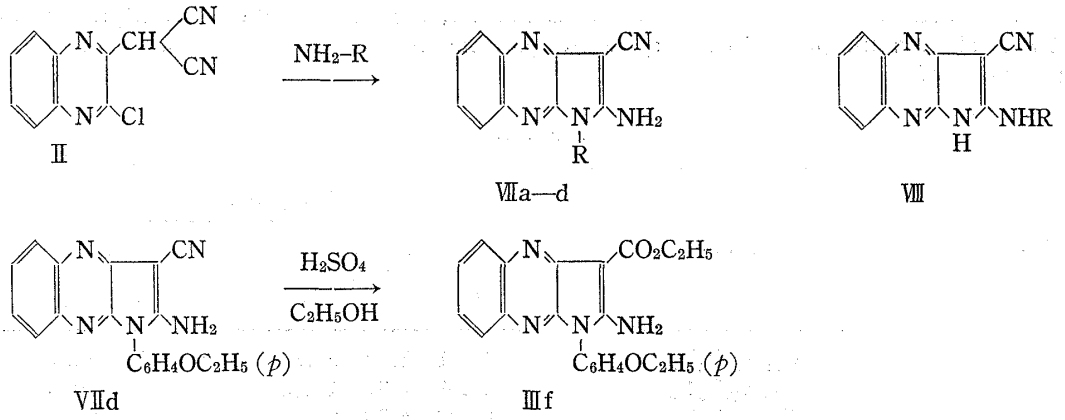
V VI IIId

Chart 1

From the above results, the structural formula (IV) was denied, and either III or V was presumed. With the purpose of confirming the structure of either type III or V, the synthesis of alternative compound and some experiments for the circumstantical evidence were attempted. 2-Chloro-3-dimethylaminopropylaminoquinoxaline (VI), prepared by mono amination of 2,3-dichloroquinoxaline,[4] was refluxed with ethyl cyanoacetate in the presence of potassium t-butoxide in t-butyl alcohol and the product, mp 164° was obtained in 39% yield. This was identical with the foregoing condensation product of I with γ-dimethylaminopropylamine. Therefore, the structure of pyrrolo[2,3-b]quinoxaline was certainly determined as III.

On the products obtained from the reaction of α-(3-chloro-2-quinoxalinyl)-malondinitrile (II) with primary amines, two types of structure VII and VIII were considered by analogy of the afore mentioned reaction of ethyl 2-(3-chloro-2-quinoxalinyl)-2-cyanoacetate (I). The IR spectra of the products showed the typical absorption amino group and cyano group at 3150—3350 cm^{-1} and 2205—2215 cm^{-1}, respectively, in KBr Tab. The NMR spectra in deuterodimethylsulfoxide exhibited the broad signal (singlet, two proton) characteristic of amino group at 8.0—9.0 ppm. One of the reaction product from II with primary amine, VIId was converted into IIIf in which the cyano group was hydrolyzed and esterified by refluxing with sulfuric acid in ethanolic solution. These facts indicated that the structure of the products from the reaction of II with primary amines was expressed as VII.

4) R.D. Haworth and S. Robinson, *J. Chem. Soc.*, **1948**, 777.

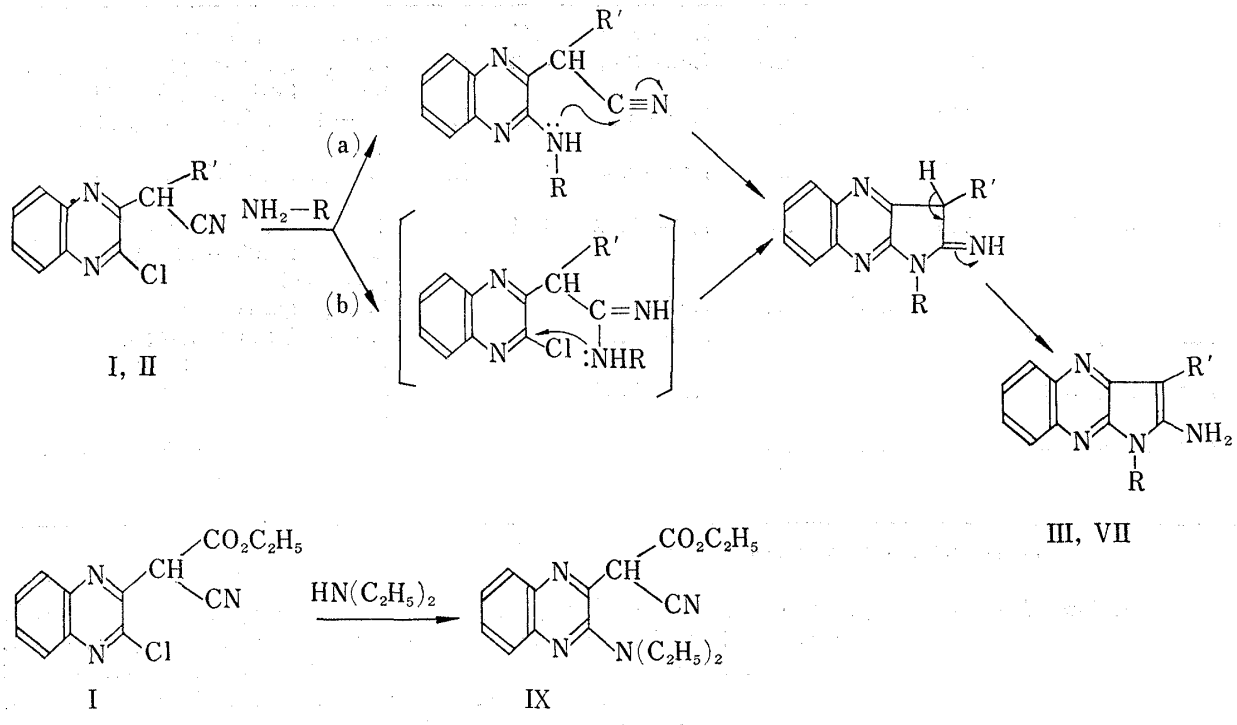


II VIIa—d VIII VIId IIIf

Chart 2

From the results so far described, it can be concluded that the reaction products obtained from the reaction of I or II with primary amines are represented by the structure of 1-substituted 2-aminopyrrolo[2,3-*b*]quinoxalines (III or VII).

Furthermore, the reaction of I with diethylamine in place of primary amine was attempted. The obtained product (IX), yellow needles of mp 132—133°, showed a sharp absorption peak characteristic of cyano group at 2215 cm^{-1} in IR spectra and agreed with ethyl 2-(3-diethylamino-2-quinoxalinyl)-2-cyanoacetate from elementary analysis. This fact confirmed that the reaction of amine with I or II proceeded through the route of "cause a" in Chart 3 to form 2-aminopyrrolo[2,3-*b*]quinoxalines (III or VII).



I, II III, VII I IX

Chart 3

Experimental[5]

General Procedure for Syntheses of 2-Aminopyrrolo[2,3-*b*]quinoxalines (IIIb—f, VIIa—d)——To a solution of I or II (*ca.* 2.0 g) in benzene–EtOH mixture (1:1) (*ca.* 100 ml), two molar equivalent of primary amine

5) All melting points are uncorrected. The IR spectra were taken with JASCO Model DS-301 spectrophotometer, and the NMR spectra were measured with Hitachi–Parkin–Elmer Model R-20 spectrometer.

was added and refluxed for 1—2 hr. After cooled the mixture, or concentrated the solvent, the solid product separated was collected and purified by recrystallization from EtOH to give fine needles. These data were shown in Table I and II.

Table II-1

Product	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIIb	$C_{14}H_{14}O_2N_4$	62.21	5.22	20.73	62.45	5.14	20.81
IIIc	$C_{15}H_{16}O_3N_4$	59.99	5.37	18.66	60.14	5.23	19.06
IIId	$C_{18}H_{23}O_2N_5$	63.32	6.79	20.52	61.02	6.83	20.56
IIIe	$C_{20}H_{18}O_2N_4$	69.35	5.24	16.18	69.13	5.33	15.80
IIIf	$C_{21}H_{20}O_3N_4$	67.01	5.36	14.89	66.85	5.48	15.00
VIIa	$C_{12}H_9N_5$	64.56	4.06	31.38	64.55	4.07	31.62
VIIb	$C_{13}H_{11}ON_5$	61.65	4.38	27.66	61.56	4.38	27.56
VIIc	$C_{18}H_{13}N_5$	72.22	4.38	23.40	72.51	4.06	23.01
VIId	$C_{19}H_{15}ON_5$	69.28	4.59	21.27	69.03	4.69	21.11

Table II-2

Product	IR (cm^{-1} in KBr) ν_{N-H}	$\nu_{C=O}$	$\nu_{C\equiv N}$	NMR (ppm in $(CD_3)_2SO$) NH_2 (2H,s)	Aromatic (4H,m)	$-OCH_2-$ (2H,q)	$-CH_3$ (3H,t)	Appendices
IIIb	3370, 3470	1690		8.38	7.54—8.26	4.41	1.37	3.68 (3H, s, NC_3H)
IIIc	3270—3480	1695		8.20	7.42—8.03	4.40	1.38	3.86 (2H, t, CH_2–); 4.28 (2H, m, OCH_2–); 5.12 (1H, t, OH)
IIId	3360, 3420	1670		8.45	7.33—8.0	4.38	1.37	1.8—4.4 (6H, m, $-CH_2$–); 2.22 (6H,s,NCH_3)
IIIe	3360, 3470	1675		8.33	7.40—8.05	4.38	1.36	5.56 (2H,s, $-CH_2$–); 7.23 (5H, s, C_6H_5)
IIIf	3350, 3460	1665		7.85	7.03—8.02	4.41	1.37	1.40 (3H, t, $-CH_3$); 4.17 (2H, q, OCH_2–); 7.03—8.02 (4H, aromatic)
VIIa	3160, 3310		2205	8.56	7.47—8.03			3.59 (3H,s, NCH_3)
VIIb	3210, 3350		2215	8.46	7.41—8.10			3.80 (2H, b, OCH_2–); 4.33 (2H, t, NCH_2–); 5.05 (1H,b, OH)
VIIc	3150, 3340		2205	8.59	7.43—8.02			5.51 (2H,s, $-CH_2$–); 7.26 (5H,s, C_6H_5)
VIId	3190, 3320		2210	8.19	7.0 —8.10			1.40(3H,t, $-CH_3$); 4.16 (2H, q, OCH_2–); 7.0—8.10 (4H, aromatic)

s, singlet; t, triplet; q, quirtet; m, multiplet; b, broad signal

Preparation of IIIa——I (1 g) was suspended in EtOH (7 ml) saturated with NH_3, this was heated in an autoclave at 70° for 3 hr. After evaporation of EtOH, the residue was washed with CH_2Cl_2 and water. The product was treated with HCl in ethanolic solution and yellow needles (EtOH) was obtained as ethyl 2-amino-1H-pyrrolo[2,3-*b*]quinoxaline-3-carboxylate hydrochloride. Yield 0.4 g, mp 226° (decomp.). *Anal.* Calcd. for $C_{13}H_{13}O_2N_4Cl\cdot H_2O$: C, 50.24; H, 4.83; N, 18.04. Found: C, 50.55; H, 4.74; N, 17.99. Its free base (IIIa) was obtained by treatment with 10% NaOH solution, yellow neeedles mp 360° (EtOH), IR ν_{max}^{KBr} cm^{-1}: 3260, 3520 (N–H), 1680 (C=O). NMR (in $(CD_3)_2SO$) ppm: 1.36 (3H, triplet, J=7 Hz, $-CH_3$), 4.35 (2H, quartet, J=7 Hz, $-OCH_2$–), 7.2—8.0 (6H, multiplet).

2-Chloro-3-dimethylaminopropylaminoquinoxaline (VI)——This was prepared by the following modification of literature procedure.[4] γ-Dimethylaminopropylamine (4.1 g) was added to 2,3-dichloroquinoxaline (4.0 g) in small portion with good agitation at 0°. After kept 1.5 hr at 0°, and allowed to stand for 4 hr at 15°, the reaction mixture was dissolved in dil. HCl solution, purified with charcoal, and basified with NaOH solution. The free base was extracted with ether, the extract was evaporated and purified by chromatography on Al_2O_3 to give yellow oil (3.0 g). NMR (in $CDCl_3$) ppm: 1.80 (2H, quintet, $-CH_2$–), 2.29

(6H, singlet, NCH_3), 2.50 (2H, triplet, CH_2N<), 3.62 (2H, quartet, $-NHCH_2-$), 7.15—8.10 (5H, multiplet). The product was treated with HCl in ethanolic solution to yield 2-chloro-3-dimethylaminopropylamino-quinoxaline hydrochloride as yellow needles, mp 140—142°. *Anal.* Calcd. for $C_{13}H_{19}N_4Cl_3$: C, 46.24; H, 5.67; N, 16.59. Found: C, 46.45; H, 5.56; N, 16.96.

Reaction of VI with Ethyl Cyanoacetate, Formation of IIId——To a stirred solution of potassium (0.33 g) in *t*-butanol (15 ml), kept the temperature at 70—80°, ethyl cyanoacetate (1.18 g) was added to form a homogenous suspension. VI (1 g) was added to the suspension and refluxed for 6 hr with stirring. After *t*-butanol was removed *in vacuo*, the residue was extracted with CH_2Cl_2 and dried over Na_2SO_4. The CH_2Cl_2 solution was purified by chromatography on Al_2O_3 and 0.5 g of yellow product was obtained. This was found to be identical with IIId by mixed fusion and by the comparison of IR spectra.

Conversion of VIId to IIIf——To a suspension of VIId (1 g) in absolute EtOH (70 ml), conc. H_2SO_4 (15 ml) was added and refluxed for 6 hr. After addition of water (*ca.* 50 ml), the reaction mixture was neutrlized with 10% NaOH and evaporated *in vacuo*. The product was purified by chromatography on Al_2O_3 to give colorless needles (0.5 g). This was identical with IIIf, which was prepared from I with *p*-phenetidine, by mixed fusion and by the comparison of IR spectra.

Reaction of I with Diethylamine——To a solution of I (0.5 g) in EtOH (20 ml), diethylamine (0.3 g) was added and refluxed for 1.5 hr. After evaporation of the solvent, the residue was purified by chromatography on Al_2O_3 and ethyl 2-(3-diethylamino-2-quinoxalinyl)-2-cyanoacetate (IX) as yellow needles (EtOH), mp 132—133°, was obtained. Yield 0.35 g. *Anal.* Calcd. for $C_{17}H_{20}O_2N_4$: C, 65.36; H, 6.45; N, 17.94. Found: C, 65.23; H, 6.11; N, 17.91. IR ν_{max}^{KBr} cm^{-1}: 2215 (C≡N), 1650 (C=O). NMR (in $(CD_3)_2SO$) ppm: 1.05 (6H, triplet, $NCH_2C\underline{H}_3$), 1.29 (3H, triplet, $OCH_2C\underline{H}_3$), 3.42 (4H, quartet, $NC\underline{H}_2CH_3$), 4.28 (2H, quartet, $OC\underline{H}_2CH_3$), 7.32—7.87 (4H, multiplet), 13.62 (1H, singlet, $-CH$<).