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A New Synthesis of 5,6-Dihydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxaline-5-ones[1]

Hirotaka Otomasu, Shigeru Ohmiya, Hiroshi Takahashi, Kei Yoshida, and Shiro Sato

Hoshi College of Pharmacy[2]

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Reduction of N-(2,6-dinitrophenyl)-α-amino acids afforded 5-amino-1,2,3,4-tetrahydroquinoxaline-2-ones (IIIa, b), which on heating with carboxylic acids, ring-closure reaction occurred to form 5,6-dihydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxaline-2-ones (VIa—g). By the reaction of IIIa,b with urea, 1,2,5,6-tetrahydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxaline-2,5-diones (VIIa,b) were obtained.

We have been reporting the synthesis of condensed quinoxalines for their pharmacological evaluation.[1] In the extension of this series, we attempted the synthesis of a nitrogen-bridgehead compound, imidazo[1,5,4-*d*,*e*]quinoxaline.

There are two reports[3] sofar known on the synthesis of the title compounds. Both of them involve the same synthetic route: N-(2-hydroxyethyl)- or N-(2-chloroethyl)-2,6-dinitroaniline is reduced and subsequently condensed with formic acid to 3-substituted 4-aminobenzimidazole, which was further derived into final compound by cyclization. We are to report in this paper a new synthesis of 5,6-dihydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxaline-5-one by way of the ring-closure of 5-amino-1,2,3,4-tetrahydroquinoxaline-2-one with carboxylic acid.

2,6-Dinitrochlorobenzene derivatives were reacted with amino acids, such as glycine and alanine, in 80% aqueous methanol to give N-(2,6-dinitrophenyl)-α-amino acids, (Ia—d) in

Table I. N-(2,6-Dinitrophenyl)-α-amino Acids (Ia—d) and Their Ethyl Esters (IIa—d)

Compound	R_1	R_2	Yield (%)	mp (°C)	Appearance (from MeOH)	Formula	Analysis (%) Calcd. / Found C	H	N	IR cm^{-1} (Nujol) C=O
Ia	H	H	87	173	yellow needles	$C_8H_7O_6N_3$	39.84 40.01	2.93 2.81	17.43 17.80	1710
Ib	CH_3	H	80	136	yellow needles	$C_9H_9O_6N_3$	42.36 42.22	3.56 3.56	16.47 16.25	1710
Ic	H	Cl	88	188	yellow plates	$C_8H_6O_6N_3Cl$	34.85 35.25	2.18 2.25	15.25 15.37	1720
Id	CH_3	Cl	90	154	yellow prisms	$C_9H_8O_6N_3Cl$	37.24 37.78	2.76 3.13	14.50 13.84	1720
IIa	H	H	97	86	yellow needles	$C_{10}H_{11}O_6N_3$	44.61 44.51	4.12 3.98	15.61 15.83	1740
IIb	CH_3	H	89	—	yellow oil	$C_{11}H_{13}O_6N_3$	—	—	—	1740
IIc	H	Cl	94	93	yellow plates	$C_{10}H_{10}O_6N_3Cl$	39.54 39.78	3.29 3.29	13.84 13.72	1735
IId	CH_3	Cl	95	55	yellow prisms	$C_{11}H_{12}O_6N_3Cl$	41.32 41.67	3.79 3.89	13.24 13.08	1740

1) This paper consists Part IV of "Synthesis of Condensed Quinoxalines." Part III: H. Otomasu, K. Yoshida, and H. Takahashi, *Yakugaku Zasshi*, **90**, 1391 (1970).
2) Location: *Ebara 2-4-41, Shinagawa-ku, Tokyo.*
3) I. Molner, *Chimia* (Switz), **14**, 364 (1960); *idem*, *Pharm. Acta Helv.*, **39**, 288 (1964) [*C.A.*, **62**, 1662*d*, (1965)]; W. Knoblock and G. Lietz, *J. Praky. Chem.*, **36**, 113 (1967) [*C.A.*, **68**, 2847*j* (1968)].

high yields. They were each led to their ethyl esters (IIa—d) by usal method. These compounds (I and II) are listed in Table I.

Upon catalytic reduction using palladized carbon in acetone, the compounds which have no substituents on benzene ring, *i.e.*, IIa and IIb, absorbed required amount of hydrogen smoothly, and afforded 5-amino-1,2,3,4-tetrahydroquinoxaline-2-one (IIIa and IIIb), as the result of intramolecular cyclization between the reduced amino and carboxyl groups. However IIIa and IIIb thus produced were both found to be unstable to air, and were not obtained in a pure state when they were tried to recrystallized in a usual manner. In the case of IIIb, the formation of 5-amino-3-methyl-2(1*H*)-quinoxalinone (IIIb′) was disclosed by nuclear magnetic resonance (NMR) data. It is well known that 1,2-dihydroquinoxalines are readily oxidized to quinoxalines merely by distillation or by boiling in alcohol with charcoal.[4] Therefore, a reduction treatment was necessary to prevent air oxidation before succesively carring out the next procedure.

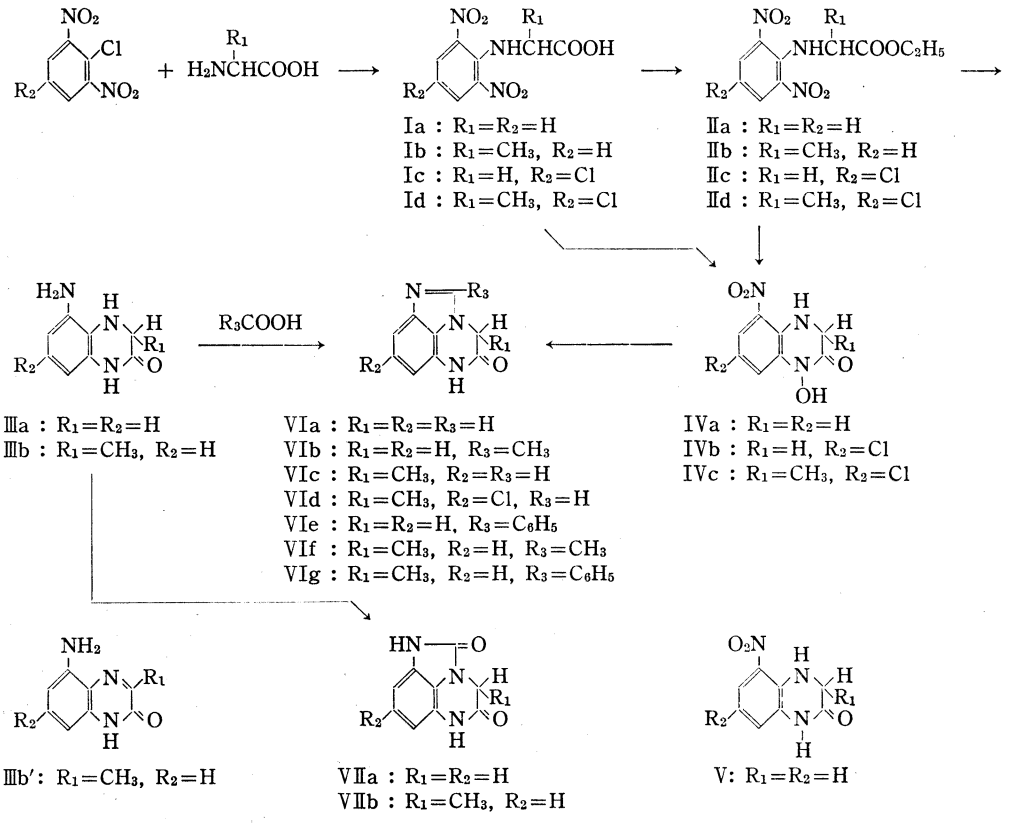

Chart 1

Subsequently, the catalytic reduction of the compounds IIc and IId where the benzene ring was attached with chlorine atom at 4-position was carried out. In this case the reaction mixture separated out orange crystals when one molar equivalent of hydrogen was absorbed, after which hydrogen uptake slowed down and ceased at the point of five molar equivalent was consumed. The colored products here obtained were stable to air and the structures were determined as 1-hydroxy-5-nitro-1,2,3,4-tetrahydroquinoxaline-2-ones (IVa—c) from

4) J.G.E. Simpson, "The Chemistry of Heterocyclic Compounds," (Condensed Pyridazine and Pyrazine Rings), Interscience Publishers, Inc., 1953, p. 324.

their infrared (IR) and analytical data. These compounds, so-called cyclic hydroxamic acids, are known to be highly intramolecularly hydrogen-bonded between the N-hydroxy and 2-oxo group and their N–O bond is very resistant to reduction.[5] To avoid producing these hydroxamic acids upon reduction, attempts were made by use of various catalysts and solvents, and it was found in the end that hydroxamic acids themselves in formic or acetic acid with palladized carbon could be reduced finally to objective compounds. A convenient method for the preparation of nitrohydroxamic acid (IV) was found to reduce compound I by use of stannous chloride in the presence of hydrochloric acid.

It is known that a cross-linkage reaction between the ring nitrogen and the amino group at 8-position occurrs to give 5,6-dihydro-4*H*-imidazo[4,5,1-*i*,*j*]quinolines[6] when 8-amino-1,2,3,4-tetrahydroquinoline is reacted with carboxylic acids. Therefore, a reaction of the same type was expected to take place at the structurally related 5-amino-1,2,3,4-tetrahydroquinoxalines. Thus the compounds IIIa and IIIb were successfully cyclized either with formic, acetic or benzoic acid to give 5,6-dihydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxaline-5-one compounds (VIa—g).

Table II. 5,6-Dihydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxaline-5-ones (VI)

Compound (VI)	R_1	R_2	R_3	Yield (%)	mp (°C)	Formula	Analyses (%) Calcd. / Found C	H	N	IR cm^{-1} (Nujol) C=O	C=N
a	H	H	H	83	288	$C_9H_7ON_3$	62.42 62.49	4.07 4.03	24.27 24.53	1680	1650
b	H	H	CH_3	41	255	$C_{10}H_9ON_3$	64.16 64.34	4.85 4.63	22.45 22.85	1685	1655
c	CH_3	H	H	69	300	$C_{10}H_9ON_3$	64.16 64.44	4.85 4.83	22.45 22.77	1685	1655
d	CH_3	Cl	H	84	323	$C_{10}H_8ON_3Cl$	54.05 53.74	3.63 3.76	18.46 19.24	1696	1660
e	H	H	C_6H_5	51	277	$C_{15}H_{11}ON_3$	72.72 72.49	4.45 4.02	16.86 16.95	1685	1665
f	CH_3	H	CH_3	49	228	$C_{11}H_{11}ON_3$	65.69 65.68	5.51 5.30	20.88 20.54	1690	1668
g	CH_3	H	C_6H_5	16	216	$C_{16}H_{13}ON_3$	72.98 72.69	6.08 5.86	15.96 16.29	1683	1660

The convenient method for the preparation of the compounds (VIa, VIc, and VId), where there were no substituents at 2-position (R_3=H) was to reduce compound (I or IV) catalytically over palladized carbon in formic acid, followed by heating of the reaction mixture to reflux temperature. But, as an exceptional case, the reduction of IVb did not give the corresponding product but an unexpected product VIa which had lost the chlorine atom during the reaction. For the preparation of the compounds (VIb, VIe, VIf, and VIg) having substituents (R_3) at their 2-positions, such as methyl or phenyl, a cross-linkage reaction was carried out with acetic or benzoic acid using ethyl polyphosphate as solvent. The products obtained were stable to air, and their structural formulae were confirmed by IR spectra and by analytical values. These were listed in Table II.

Finally, the ring-closure reaction of compounds IIIa and IIIb were worked up by heating with urea in place of carboxylic acid, and 1,2,5,6-tetrahydro-4*H*-imidazo[1,5,4-*d*,*e*]quino-

5) A.R. Katritzky and J.M. Lagowski, "Chemistry of the Heterocyclic N-oxides," Academic Press, 1971, pp. 191—192.
6) R. Elderfield and F. Kreysa, *J. Am. Chem. Soc.*, **70**, 44 (1948); A. Richardson and E.D. Amstutz, *J. Org. Chem.*, **25**, 1138 (1960).

xaline-2,5-dione (VIIa) and its 4-methyl derivative (VIIb) were obtained at the yields of 80% and 65%, respectively. The IR spectra of the compound VII showed intense carbonyl absorption in the wide range of 1700 and 1650 cm^{-1}, which could be assigned to the two carbonyl groups at 2- and 5-positions.

Experimental

All melting points are uncorrected. IR spectra were measured with JASCO DS-302 spectrophotometer. NMR spectra were recorded on Hitachi-Perkin-Elmer Model R-20 spectrometer using TMS as the internal standard. Mass spectra were recorded on Hitachi Model RMS-4 spectrometer.

General Procedure for the Preparation of N-(2,6-Dinitrophenyl)-α-amino Acids (Ia—d)——In a typical experiment, a solution of glycine (8.3 g, 0.12 mole) and $NaHCO_3$ (18.5 g) in H_2O (60 ml) was added to a solution of 2,6-dinitrochlorobenzene (20 g, 0.1 mole) in MeOH (200 ml) and refluxed for 1.5 hr. The reaction mixture was concentrated to dryness in a rotary evaporator. The residue was dissolved in H_2O (*ca.* 300 ml), purified with 'Norit A,' and was acidified with 10% HCl to give yellow solid precipitate of Ia.

Ib was prepared by the reaction of 2,6-dinitrochlorobenzene with *dl*-α-alanine in the same procedure described for Ia.

Ic and Id were obtained similarly by reacting 1,4-dichloro-2,6-dinitrobenzene with glycine and *dl*-alanine, respectively. Yield, mp and data of analyses were listed in Table I.

General Procedure for the Preparation of Ethyl Esters (IIa—d)——A mixture of the compound I (0.05 mole), conc. H_2SO_4 (3.5 ml) and absolute EtOH (300 ml) was refluxed for 4 hr. The reaction mixture was concentrated to a thick syrup, and, to this, was added H_2O (*ca.* 150 ml) to give the product (IIa, IIc, and IId) as yellow solid precipitate. IIb was not obtained as a crystalline substance by this procedure. Compounds (II) are listed on Table I.

Catalytic Reduction of IIa——A mixture of IIa (10 g) and Pd-C (10%, 0.3 g) in acetone (300 ml) was shaken with H_2 at atmospheric pressure and room temperature. When the absorption of H_2 ceased, the reaction mixture was filtered to remove the catalyst and the filtrate was concentrated to dryness under N_2. The residue was recrystallized twice from benzene–MeOH to give 4.3 g of pale yellow prisms of mp 162—163°, which did not show a good agreement on analysis. IR ν_{max}^{Nujol} cm^{-1}: 1695 (C=O). NMR [$(CD_3)_2SO$] ppm: 3.65 (2H, singlet, CH_2); 4.8 (3H, broad signal, NH, NH_2); 6.0—6.6 (3H, multiplet, aromatic proton); 9.98 (1H, broad signal, CONH). The reduction product was used without isolation from the reaction mixture under N_2.

Catalytic Reduction of IIb——By a similar treatment as described above, a pale yellow product was obtained from IIb. NMR [$(CD_3)_2SO$] ppm: 2.35 (3H, singlet, CH_3); 5.72 (2H, broad signal, NH_2); 6.25—7.25 (3H, multiplet, aromatic proton); 11.89 (1H, broad signal, CONH). This product was assumed to be 5-amino-3-methyl-2(1*H*)-quinoxalinone (IIIb'). Therefore, the reduction product was used without isolation from the reaction mixture under N_2.

Catalytic Reduction of IIc: Formation of 7-Chloro-1-hydroxy-5-nitro-1,2,3,4-tetrahydroquinoxaline-2-one (IVb)——A mxiture of IIc (5 g) and Pd-C (10%, 0.2 g) in acetone (80 ml) was shaken with hydrogen at atmospheric pressure and room temperature. When one molar equivalent of H_2 (*ca.* 400 ml) was consumed, the reaction mixture deposited an orange solid. This product was collected together with catalyst, dissolved in MeOH and filtered to remove catalyst. After concentration of the solution, 0.9 g of orange crystals were obtained. From the acetone solution, another 1.5 g of the same solid was obtained. Total yield, 2.4 g or 60%. Orange needles, mp 218° (MeOH). *Anal.* Calcd. for $C_8H_6O_4N_3Cl$: C, 39.34; H, 2.46; N, 17.21. Found: C, 39.47; H, 2.58; N, 17.11. IR ν_{max}^{Nujol} cm^{-1}: 3380 (NH); 1685, 1645 (C–O); 1520, 1300 (NO_2).

Even if the reduction was continued, not more than 5 molar equivalent of H_2 was absorbed.

The same product was also obtained from the reduction of Ic by use of $SnCl_2$ and HCl.

Reduction of Compound I with $SnCl_2$: 1-Hydroxy-5-nitro-1,2,3,4-tetrahydroquinoxaline-2-one (IVa) and Its Dehydroxygenated Product (V)——To a solution of Ia (1 g) in MeOH (4 ml) and conc. HCl (2 ml), a solution of $SnCl_2 \cdot 2H_2O$ (2 g) in conc. HCl (2 ml) was added in a single portion at 60° under stirring. The reaction mixture turned red immediately and separated out an orange red solid. Recrystallization from MeOH gave 0.6 g of IVa as orange red needles, mp 188°. *Anal.* Calcd. for $C_8H_7O_4N_3$: C, 45.95; H, 3.37; N, 20.09. Found: C, 46.14; H, 3.35; N, 20.05. M^+: 209. IR ν_{max}^{Nujol} cm^{-1}: 3350 (NH); 1685, 1645 (C=O); 1520, 1285 (NO_2).

The mother liquor upon recrystallization of IVa gave 0.1 g of dehydroxygenated product V as red needles of mp 222° (acetone). *Anal.* Calcd. for $C_8H_7O_3N_3$: C, 49.74; H, 3.65; N, 21.76. Found: C, 49.72; H, 3.54; N, 22.02. M^+: 193. IR ν_{max}^{Nujol} cm^{-1}: 3360 (NH); 1670 (C=O); 1520, 1300 (NO_2).

7-Chloro-1-hydroxy-3-methyl-1,2,3,4-tetrahydroquinoxaline-2-one (IVc)——This compound was obtained from Id by a similar procedure as described for IVa. Yield, 94%. Orange needles, mp 174° (MeOH). *Anal.* Calcd. for $C_9H_8O_4N_3Cl$: C, 41.86; H, 3.10 N, 16.28. Found: C, 41.64; H, 3.36; N, 16.50. IR ν_{max}^{Nujol} cm^{-1}: 3360 (NH); 1680, 1645 (C=O); 1520, 1285 (NO_2). Dehydroxygenated product of IVc was not obtained.

General Procedure for the Preparation of 5,6-Dihydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxaline-5-ones (R_3=H VIa, VIc, and VId)——In a typical experiment, a mixture of Ia (4 g) and Pd-C (10%, 1 g) and formic acid (99%, 80 ml) was shaken with H_2 at atmospheric pressure and room temperature. After the absorption of H_2 was completed, the reaction mixture was refluxed for 4 hr under N_2. The reaction mixture was filtered to remove the catalyst and washed with water. The combined filtrate and washings were concentrated to dryness under reduced pressure, and the residue was mixed with water (*ca.* 30 ml) and then neutralized with NaOH to give a white solid of VIa. This conpound was also obtained from the same reaction of IVa.

Compounds VIc and VId were obtained from Ib and IVc, respectively, by the same procedure as described for VIa. In the case of the reaction of IVb, unexpected product VIa which lost the chlorine atom was obtained. These compounds were listed in Table II.

General Procedure for the Preparation of 2-Substituted 5,6-Dihydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxaline-5-ones (R_3=CH_3, R_3=C_5H_5 VIb, VIe, VIf, and VIg)——In a typical experiment, a solution of ester IIb (2 g) in acetone (100 ml) was catalytically reduced over Pd-C. After the absorption of H_2 was completed, the reaction mixture was filtered, and the filtrate was concentrated to dryness under N_2. The residue was heated with acetic acid (1.2 g) and ethyl polyphosphate (50 ml) at 100° for 30 min under N_2 with stirring. After cooling, the reaction mixture was poured in to cold water (*ca.* 200 ml) and neutralized with aqueous NaOH to give a white solid of VIb.

Compounds VIe, VIf, and VIg were also obtained by the same procedure as described for VIb. These compounds were listed in Table II.

1,2,5,6-Tetrahydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxaline-2,5-dione (VIIa)——A solution of IIa (1.6 g) in acetone (100 ml) was reduced catalytically over Pd-C in a similar treatment as described for VIb. The resulting product was heated with urea (0.55 g) in an oil bath to 160° under N_2. The solid melted with gass evolution, and gradually solidified. The solid mass was pulverized, washed with water, and recrystallized from MeOH to give 0.8 g or 80% of colorless needles, mp 250°. *Anal.* Calcd. for $C_9H_7O_2N_3$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.35; H, 3.50; N, 22.67. IR ν_{max}^{Nujol} cm^{-1}: 3200 (NH); 1700—1650 (C=O).

4-Methyl-1,2,5,6-tetrahydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxaline-2,5-dione (VIIb)——This compound was obtained by the reaction between the reduction product of IIb and urea in a similar treatment as described for VIIa. Yield, 65%. Pale yellow needles, mp 270—272°. *Anal.* Calcd. for $C_{10}H_9O_2N_3$: C, 59.10; H, 4.46; N, 20.68. Found: C, 58.78; H, 4.16; N, 21.06. IR ν_{max}^{Nujol} cm^{-1}: 3220 (NH); 1695—1660 (C=O).