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# Synthesis and Conformation of 4,5-Disubstituted 5,6-Dihydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxalines[1]

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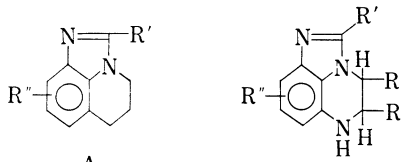
Catalytic hydrogenations of 5-acylamido-2,3-disubstituted quinoxalines (IIa—e) with palladized carbon in carboxylic acid afforded 4,5-disubstituted 5,6-dihydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxalines (IIIa—e) . Conformations of the substituents at 4- and 5-position of the products were also investigated.

In previous paper,[1] we reported a new synthetic method of 5,6-dihydro-4*H*-imidazo-[1,5,4-*d*,*e*]quinoxalin-5-one by the ring-closure of 5-amino-1,2,3,4-tetrahydroquinoxalin-2-one with carboxylic acid. As a continuation in this series, we have investigated another synthetic route for this ring system compound.

Among various synthetic methods for 5,6-dihydro-4*H*-imidazo[4,5,1-*i*,*j*]quinoline (A), which is structurally related to the above compound, there is a report by Werbel, *et al.*[3] who obtained the same compound by catalytic hydrogenation of 8-acylamidoquinoline.



A B

Chart 1

In view of the fact that 1,2-dihydro- or 1,2,3,4-tetrahydroquinoxalines are not suitable as the synthetic intermediate for their instability to air oxidation, the above method is undoubtedly a convenient one for the synthesis of the title compounds. In this paper, we describe the synthesis of 5,6-dihydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxaline compounds (B) by the catalytic hydrogenation of 5-acylamidoquinoxaline, and also discuss the conformation of the products.

First of all, we prepared some requisite 5-aminoquinoxalines. 5-Amino-2,3-dimethyl (Ia)[4] and 5-amino-2,3-diphenylquinoxaline (Ib) were obtained by the condensation of 1,2,3-triaminobenzene with diacetyl and benzil, respectively. 5-Amino-6-methoxy-(Ic) and 5-amino-8-methoxy-2,3-dimethylquinoxaline (Id) were prepared according to the method previously reported by us.[5]

2,3-Dinitro-*p*-anisidine was reduced catalytically and, without isolation of 2,3,4-triamino-anisole, was allowed to react with diacetyl, and the reaction mixture was purified by chromatography on alumina. The products were separated into two crystalline compounds, yellow needles, mp 134° (Ic) and orange prisms, mp 171° (Id), in the ratio of 8:2. Both of them indicated the same empirical formula by elemental analysis. On the other hand, 2,3-dinitro-*p*-acetamidoanisole was subjected to reduction, and followed by condensation with diacetyl to give 5-acetamido-8-methoxy-2,3-dimethylquinoxaline (IId) in good yield. This

1) This paper consists Part V of "Synthesis of Condensed Quinoxalines," Preceding paper, Part IV: H. Otomasu, S. Ohmiya, H. Takahashi, K. Yoshida, and S. Sato, *Chem. Pharm. Bull.* (Tokyo), **21**, 353 (1973).
2) Location: *Ebara 2-4-41, Shinagawa-ku, Tokyo.*
3) L.M. Werbel, J. Battaglia, and M.L. Zamora, *J. Heterocyclic Chem.*, **5**, 371 (1963).
4) P. Vetesnik, *Collection Czech. Chem. Commun.*, **33**, 556 (1963) [*C.A.*, **68**, 68323*s* (1968)].
5) H. Otomasu and S. Nakajima, *Chem. Pharm. Bull.* (Tokyo), **6**, 566 (1958).

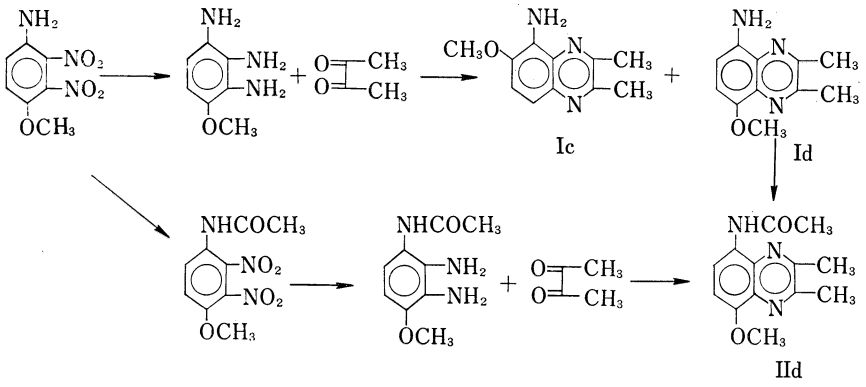


Chart 2

product was identical with the acetylation product of the compound, mp 171° (Id). The other compound having mp 134° (Ic) is therefore certain to be 5-amino-6-methoxy-2,3-dimethylquinoxaline. The 5-aminoquinoxalines thus obtained were allowed to react with formic acid and acetic anhydride to yield corresponding 5-acylamidoquinoxalines. In this case, the acetylation of 5-aminoquinoxaline with acetic anhydride had to be carried out under a mild condition to avoid the formation of diacetate.

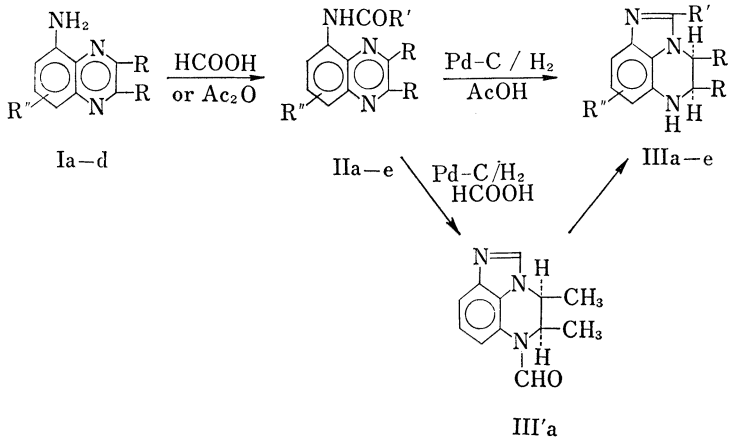
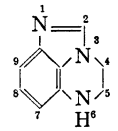


Chart 3

TABLE I

| Product | R | R′ | R″ | Yield (%) | mp (°C) | Formula | Analysis (%) Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IIa | $CH_3$ | H | H | 95 | 157 | $C_{11}H_{11}ON_3$ | 65.67 | 5.51 | 20.88 | 65.75 | 5.27 | 21.03 |
| IIb | $CH_3$ | $CH_3$ | H | 94 | 195 | $C_{12}H_{13}ON_3$ | 66.95 | 6.09 | 19.52 | 66.75 | 6.33 | 19.02 |
| IIc | $CH_3$ | $CH_3$ | 6-$OCH_3$ | 90 | 184 | $C_{13}H_{15}O_2N_3$ | 63.66 | 6.16 | 17.13 | 63.85 | 6.22 | 17.28 |
| IId | $CH_3$ | $CH_3$ | 8-$OCH_3$ | 78 | 227 | $C_{13}H_{15}O_2N_3$ | 63.66 | 6.16 | 17.13 | 63.65 | 6.03 | 16.77 |
| IIe | $C_6H_5$ | $CH_3$ | H | 80 | 226 | $C_{22}H_{17}ON_3$ | 77.85 | 5.05 | 12.38 | 77.52 | 4.72 | 12.33 |
| IIIa | $CH_3$ | H | H | 93 | 150 | $C_{11}H_{13}N_3$ | 70.56 | 7.00 | 22.44 | 70.77 | 7.02 | 21.99 |
| IIIb | $CH_3$ | $CH_3$ | H | 70 | 178 | $C_{12}H_{15}N_3$ | 71.61 | 7.51 | 20.88 | 71.58 | 7.45 | 20.67 |
| IIIc | $CH_3$ | $CH_3$ | 9-$OCH_3$ | 72 | 138 | $C_{13}H_{17}ON_3$ | 67.50 | 7.41 | 18.17 | 67.71 | 7.41 | 18.00 |
| IIId | $CH_3$ | $CH_3$ | 7-$OCH_3$ | 75 | 165 | $C_{13}H_{17}ON_3$ | 67.50 | 7.41 | 18.17 | 67.71 | 7.39 | 17.85 |
| IIIe | $C_6H_5$ | $CH_3$ | H | 62 | 195 | $C_{22}H_{19}N_3$ | 81.20 | 5.89 | 12.91 | 80.96 | 6.07 | 12.85 |

The catalytic hydrogenations of 5-acylamidoquinoxalines (IIa—e) were carried out in an autoclave, in the presence of palladized carbon, at 100°, with an initial pressure of 50 atm in formic or acetic acid as solvent, and the corresponding reaction products were obtained with fairly good yields. In the case of the hydrogenation of 5-formamido-2,3-dimethylquinoxaline (IIa) in formic acid, the product obtained was 6-formyl compound (IIIa'), which was readily hydrolyzed with 10% hydrochloric acid to give 4,5-dimethyl-5,6-dihydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxaline (IIIa). Their analytical values agreed with those of 4,5-disubstituted 5,6-dihydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxaline, and their structural formulae were confirmed by nuclear magnetic resonance (NMR) spectra.

TABLE II 

| Product | NH (1H, s) | 2-H (1H, s) | 4-H D | 5-H C | 2-$CH_3$ (3H, s) | 5-$CH_3$ (3H, d, $J$=7Hz) B | 4-$CH_3$ (3H, d, $J$=7Hz) A |
|---|---|---|---|---|---|---|---|
| IIIa | 5.98 | 8.08 | 4.53[a] | 3.59[a] | — | 1.23 | 1.18 |
| IIIa' | — | 8.30 | 4.98[a] | 4.48[a] | — | 1.64 | 0.86 |
| IIIb | 5.86 | — | 4.50[a] | 3.51[a] | 2.45 | 1.26 | 1.08 |
| IIIc | 5.49 | — | 4.42[a] | 3.45[a] | 2.42 | 1.20 | 1.06 |
| IIId | 5.23 | — | 4.48[a] | 3.45[a] | 2.42 | 1.28 | 1.09 |
| IIIe | 6.49 | — | 5.77[b] | 4.99[b] | 2.21 | — | — |

*a*) doublet ($J$=3 Hz) of quartet ($J$=7 Hz) *b*) doublet ($J$=4 Hz)

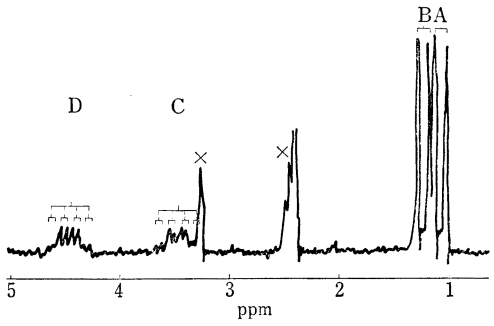



Fig. 1. NMR Spectrum of IIIb in $d_6$-DMSO

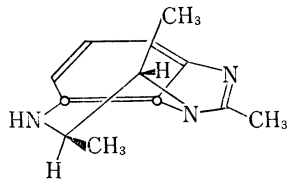


Fig. 2. Structure of IIIb

There are some reports[6] on the reduction of quinoxalines, and it is known that the catalytic reduction of 2,3-disubstituted quinoxalines is stereospecific, giving the *cis* form of 1,2,3,4-tetrahydroquinoxalines. Accordingly the compounds we obtained were postulated to be the *cis* form since we applied the catalytic reduction. Therefore, we attempted to confirm the conformation of the substituent groups at C-4 and C-5 of the compound III by means of NMR spectra.

The respective chemical shifts of two methyl groups and two ring protons at C-4 and C-5 in the compound III were observed as four signals. They were summerized in Table II and were expediently designated as A, B, C, and D toward lower field. As an example

6) C.S. Gibson, *J. Chem. Soc.*, **1927**, 342; R.C. DeSelmsand and H.S. Mosher, *J. Am. Chem. Soc.*, **82**, 3762 (1960).

of typical pattern, NMR spectra of the compound IIIb was presented in Fig. 1. Investigation of these signals of the compound III clarified the following evidences.

1) A and D are assigned to each signal of methyl group and ring proton which are attached to the one carbon atom, because A was decoupled by the iradiation of D. Similarly, B and C are assigned to a set of methyl and ring proton at another carbon atom.

2) In the compound IIIa' possessing a formyl group at 6-position, the shifts of B and C toward lower field are more remarkable than those of A and D, as compared with those signals of compound IIIa. This noteworthy fact can be interpreted that a set of methyl group and ring proton (B and C) are affected more sensitively under the influence of the formyl group. Therefore, B and C can be assigned to the signal of methyl and ring proton at C-5 which is adjasent to the formyl group. Accordingly, A and D can be assigned to the methyl and ring proton belonging to C-4 which is far from the formyl group.

3) A and C were observed at higher field than B and D, respectively. This fact suggested that C-4 methyl group and C-5 proton are nearly parallel to benzimidazole ring (pseudo equatorially oriented) while C-5 methyl group and C-4 proton are almost perpendicular to the same ring (pseudo axially oriented), possibly due to the influence of the magnetic anisotropy of aromatic benzimidazole ring.

4) Both C and D were observed as double-quartet signal due to the coupling with the methyl ($J$=7 Hz) and with vicinal proton ($J$=3 Hz). In the compound IIIe (4,5-diphenyl compound), the coupling constant of vicinal proton showed 4 Hz with doublet. The magnitude of the coupling constant of vicinal proton is 3—4 Hz, which indicated that the diheadral angle was approximately 60° by Karplus' equation.

In view of the above data of the NMR spectra and considering the fact that all of the compounds were obtained by the catalytic reduction of 2,3-disubstituted quinoxalines, it is likely that the compounds IIIa-e possess the *cis* conformation and their stereostructures are as represented in Fig. 2.

## Experimental

All melting points are uncorrected. Infrared spectra were recorded on JASCO DS-301 spectrophotometer. NMR spectra were recorded on Hitachi-Perkin-Elmer Model R-20 spectrometer using TMS as the internal standard. Mass spectra were registered on Hitachi Model RMS-4 spectrometer.

**5-Amino-2,3-dimethylquinoxaline (Ia)**——This compound was briefly described by Vetesnik.[4] It was obtained by the following method. A mixture of 2,6-dinitroaniline (6.0 g) and Pd-C (10%, 1.0 g) in MeOH (200 ml) was shaken with hydrogen at room temperature. When the absorption of hydrogen ended, the reaction mixture was added with diacetyl (2.9 g) along with few drops of AcOH, and refluxed for 30 min under nitrogen. The catalyst was removed, the solution was evaporated under reduced pressure and the residue (5.0 g) was recrystallized from MeOH to give orange needles, mp 162—163,° which coincided with Vetesnik's description.

**5-Amino-2,3-diphenylquinoxaline (Ib)**——This compound was prepared from 2,6-dinitroaniline and benzil according to the similar procedure as described above. Yellow needles, mp 149° (MeOH). *Anal.* Calcd. for $C_{20}H_{15}N_3$: C, 80.78; H, 5.09; H, 14.13. Found: C, 81.21; H, 4.62; N, 14.16.

**Condensation of 2,3,4-Triaminoanisole and Diacetyl: Formation of 5-Amino-6-methoxy- (Ic) and 5-Amino-8-methoxy-2,3-dimethylquinoxaline (Id)**——A mixture of 2,3-dinitro-*p*-anisidine (9.0 g) and Pd-C (10%, 1.2 g) in MeOH (400 ml) was shaken with hydrogen. After the absorption of hydrogen was completed diacetyl (3.5 g) and few drops of AcOH was added to the reaction mixture, and refluxed for 30 min under nitrogen. The reaction mixture was filtered to remove the catalyst and the solution was evaporated to dryness. The residue was dissolved in HCl (10%, 150 ml), purified with 'Norit A' and the solution was basified with $NH_4OH$ to give a yellow solid. This was dissolved in benzene and run through a column of $Al_2O_3$. The first effluent gave 4.8 g of yellow needles, mp 134° (ligroin). *Anal.* Calcd. for $C_{11}H_{13}ON_3$ (Ic): C, 65.00; H, 6.45; N, 20.68. Found: C, 65.21; H, 6.25; N, 19.91.

The second effluent gave 1.2 g of orange prisms, mp 171° (benzene). *Anal.* Calcd. for $C_{11}H_{13}ON_3$ (Id): C, 65.00; H, 6.45; N, 20.68. Found: C, 65.21; H, 6.45; N, 20.82.

**5-Acetamido-8-methoxy-2,3-dimethylquinoxaline (IId)**——i) Acetylation of Id: A mixture of Id (0.9 g), AcOH (4 ml) and $Ac_2O$ (4 ml) was refluxed for 15 min and concentrated to dryness under reduced pressure. The residue was recrystallized from benzene to give pale yellow prisms of mp 227°. This was identical with the sample prepared by the following method.

ii) Condensation of 2,3-Diamino-*p*-acetamidoanisole and Diacetyl: By a similar procedure described for Ia, from the reduction product of 2,3-dinitro-*p*-acetamidoanisole (4 g) and diacetyl (1.35 g) was obtained 3.2 g of Id of mp 227°. The yield was nearly theoretical.

**5-Formamido-2,3-dimethylquinoxaline (IIa)**——A solution of Ia (5 g) in formic acid (99%, 40 ml) was refluxed for 2 hr. The excess of formic acid was removed and water was added to give a white solid. Recrystallization from MeOH provided an analytical sample (Table I).

**5-Acetamido-2,3-disubstituted Quinoxalines (IIb—e)**——The amino compound (Ia—d) was heated with a mixture of each five fold of AcOH and $Ac_2O$ under a mild condition at 100° for 30 min. The excess of AcOH and $Ac_2O$ was removed under reduced pressure and water was added to give the corresponding acetamides. The compounds were listed in Table I. All of the acetamides obtained showed strong absorption at 1680—1690 $cm^{-1}$ in IR spectrum.

**5-Diacetylamino-6-methoxy-2,3-dimethylquinoxaline**——The acetylation was carried out with more drastic condition, that is, by refluxing with $Ac_2O$ and AcONa for 1 hr, diacetate of Ic was isolated as white needles, mp 164° (MeOH). *Anal.* Calcd. for $C_{13}H_{15}O_2N_3$: C, 62.70; H, 5.86; N, 14.63. Found: C, 62.75; H, 5.93; N, 14.66. M+: 233. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1720, 1695 (C=O).

**4,5-Dimethyl-6-formyl-5,6-dihydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxaline (IIIa′)**——A mixture of IIa (2.6 g), Pd-C (10%, 0.4 g) and formic acid (99%, 50 ml) was shaken under 50 atm of hydrogen pressure in an autoclave at 100° for 2 hr. The reaction mixture was filtered to remove the catalyst, the filtrate was concentrated, water was added and purified with 'Norit A'. The solution was basified with $NH_4OH$ and extracted with $CHCl_3$. Removal of the solvent gave white needles, mp 175° (benzene). Yield, 75%. *Anal.* Calcd. for $C_{12}H_{13}ON_3$: C, 66.95; H, 6.09; N, 19.52. Found: C, 67.31; H, 5.89; N, 20.20. M+: 215. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: 1670 (C=O).

**4,5-Dimethyl-5,6-dihydro-4*H*-imidazo[1,5,4-*d*,*e*]quinoxaline (IIIa)**——A solution of IIIa′ (0.3 g) in HCl (10%, 25 ml) was heated on a water bath for 40 min. The solution was basified with $NH_4OH$ and extracted with $CHCl_3$. Removal of the solvent gave white needles (benzene) (Table I and II).

**General Procedure for the Preparation of 4,5-Disubstituted 2-methyl-5,6-dihydro-4*H*-imidazo[1,5,4-*d*,*e*]-quinoxaline (IIIb—e)**——Compound II (3 g) was hydrogenated in AcOH (60 ml) at an initial pressure of 50 atm and 100° in the presence of Pd-C for 2 hr. By a similar treatment of the reaction mixture as described for IIIa′, the products obtained were purified by chromatography on $Al_2O_3$. Recrystallization from benzene did not change the melting point. Analysis and NMR data were listed in Table I and II.