CONVERSION OF 3-(N,N-DIMETHYLAMINOCARBONYL)*FURO[2,3-b]QUINOXALINE* TO NOVEL PYRIDAZINO[3,4-b]QUINOXALINES

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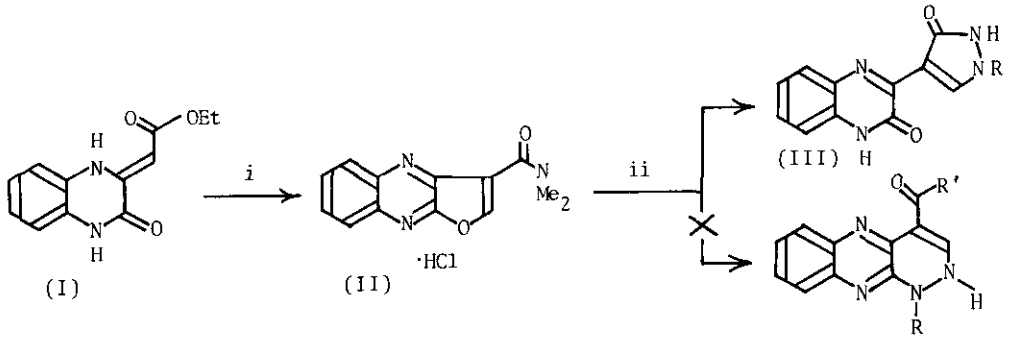
Abstract — *3-(N,N-Dimethylaminocarbonyl)furo[2,3-b]quinoxaline* was converted to 4-substituted 1,2-dihydropyridazino[3,4-b]quinoxalines via 3-(quinoxaline-2'-yl)-2H-pyrido[1,2-a]pyrimidine-2-ones.

In the previous paper,[1] we reported that 3-(N,N-dimethylaminocarbonyl)furo[2,3-b]quinoxaline hydrochloride (II) was synthesized from 3-ethoxycarbonylmethylene-2-oxo-1,2,3,4-tetrahydroquinoxaline (I), which was obtained by the reaction of o-phenylenediamine with diethyl acetylenedicarboxylate,[2] and that the reaction of II with hydrazines gave 4-(3'-oxo-3',4'-dihydroquinoxaline-2'-yl)pyrazolones (III), but not pyridazino[3,4-b]quinoxalines, as shown in Chart 1. We now report a conversion of II to pyridazino[3,4-b]quinoxalines.

Refluxing of II (18.0 mmol) with 2-aminopyridine (90 mmol) in BuOH (400 ml) at 150-160° for 4 hr gave 3-(3'-oxo-3',4'-dihydroquinoxaline-2'-yl)-2H-pyrido[1,2-a]pyrimidine-2-one (V), mp 306-309°, yellow needles (EtOH) (60%). The structure assignment of V was based on IR and NMR spectra.[3]



i Vilsmeier reagent
ii NH_2NHR

Chart 1

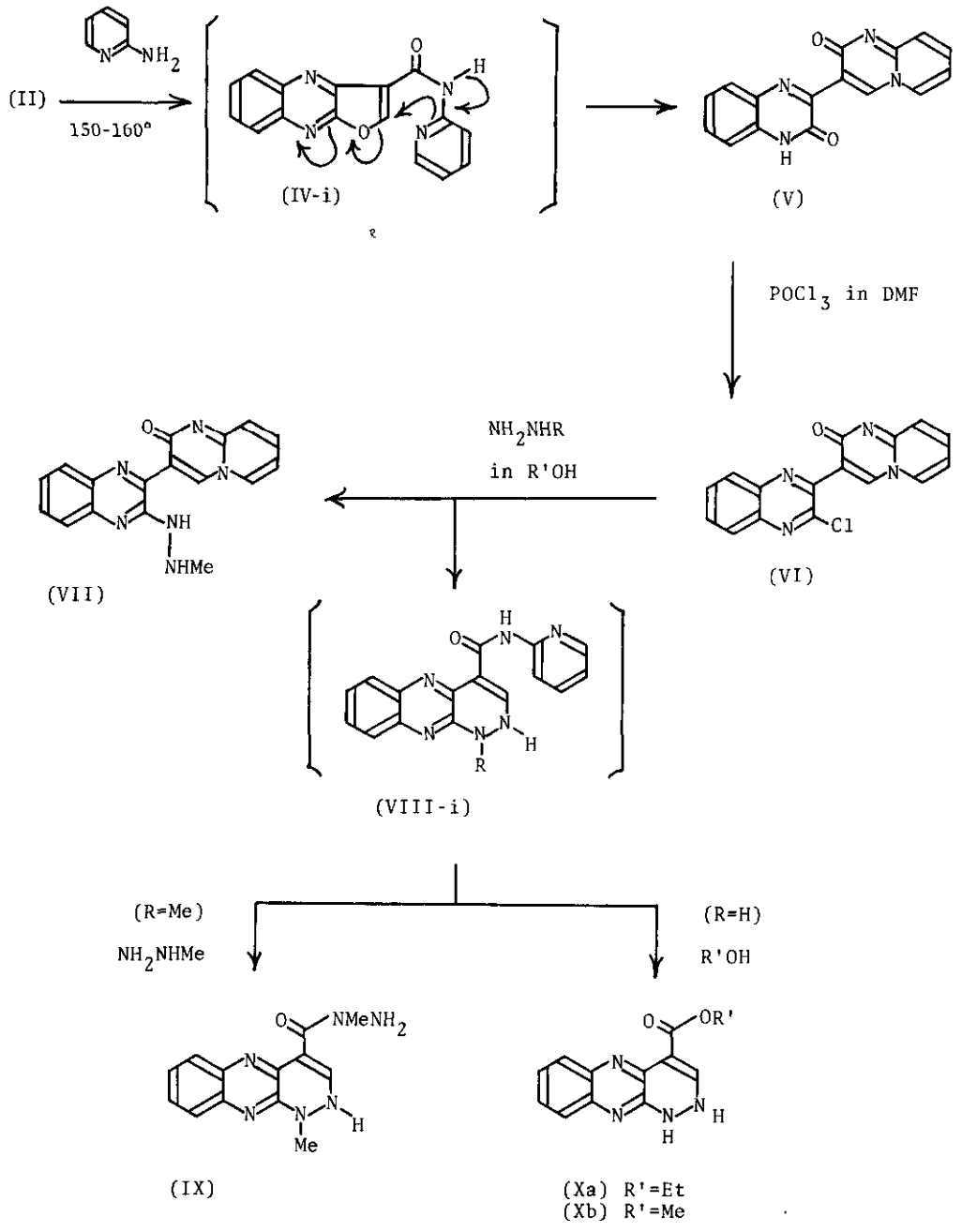


Chart 2 *

* Satisfactory mass spectral and elemental analytical data were obtained for all new samples.

Since 2-aminopyridine is known to give 2-acylaminopyridine by means of carboxylic ester,[4,5] the formation of V may be rationalized by the course involving (IV-i) as an intermediate as shown in Chart 2. Chlorination of V (1.72 mmol) with $POCl_3$ (50 ml) in DMF (20 ml) produced the 3'-chloro compound (VI),[6] mp 229-231°, pale yellow needles (EtOH) (87%).

The reaction of VI (1.62 mmol) with methylhydrazine (4.05 mmol) in EtOH-$CHCl_3$ (50 ml, 20 ml) afforded 2-(2'H-pyrido[1',2'-a]pyrimidine-2'-one-3'-yl)-3-(2'-methylhydrazino)quinoxaline (VII),[7] mp 316-319°, red needles (EtOH-$CHCl_3$) (4%) and 4-(1'-methylhydrazinocarbonyl)-1-methyl-1,2-dihydropyridazino[3,4-b]quinoxaline (IX),[8] mp 195-196°, yellow needles (EtOH-$CHCl_3$) (78%). Product VII was found not to be an intermediate to IX by the thin-layer chromatographic examination of the reaction mixture, which was obtained by refluxing of VII (0.0629 mmol) with methylhydrazine (2.5 mmol) in EtOH-$CHCl_3$ (20 ml,10 ml); The chromatogram showed two spots (Rf=0.071, 0.414), but not the spot (Rf=0.556) due to IX.

On the other hand, the reaction of VI (1.62 mmol) with hydrazine hydrate (16.2 mmol) in EtOH-$CHCl_3$ (50 ml, 20 ml) provided 4-ethoxycarbonyl-1,2-dihydropyridazino[3,4-b]quinoxaline (Xa),[9] mp 255-257°, yellow needles (EtOH-$CHCl_3$) (90%). When MeOH-$CHCl_3$ (50 ml, 20 ml) was employed as a solvent system in the reaction of VI (1.62 mmol) with hydrazine hydrate (16.2 mmol), 4-methoxycarbonyl-1,2-dihydropyridazino[3,4-b]quinoxaline (Xb),[9] mp 252-254°, yellow powder (MeOH-$CHCl_3$) (77%) was obtained.

From the above results, the conversion of VI to IX, Xa, and Xb may be formulated as shown in Chart 2. While the 2-aminopyridinyl group of an intermediate (VIII-i) can be replaced with methylhydrazine to give IX, this replacement does not occur with hydrazine because its nucleophilicity is weaker as compared with methylhydrazine, but instead alcoholysis takes place to produce Xa and Xb.

In conclusion, we found the new conversion of 3-(*N*,*N*-dimethylaminocarbonyl)furo[2,3-b]quinoxaline to 4-substituted 1,2-dihydropyridazino[3,4-b]quinoxalines via 3-(quinoxaline-2'-yl)-2H-pyrido-[1,2-a]pyrimidine-2-ones.

References and Footnotes

1. Y. Kurasawa and A. Takada, Heterocycles, 1980, 14, 281.

2. Y. Iwanami, Y. Kenjo, K. Nishibe, M. Kajiura, and S. Isoyama, Bull. Chem. Soc. Japan, 1964, 37, 1740; Y. Iwanami, S. Isoyama, and Y. Kenjo, ibid., 1964, 37, 1945.

3. V: ν(KBr) 1725(3'-C=O), 1660(2-C=O), δ(DMSO-d_6) 12.50(1H, br.s, 4'-NH), 9.08(1H, d, J=6 Hz, 5-H), 8.60(1H, s, 4-H), 8.33-7.00(7H, m, aromatic). δ(DMSO-d_6-CF_3COOH) 10.00(1H, s, 4-H), 9.48(1H, d, J=7 Hz, 5-H), 8.83-7.00(7H, m, aromatic). 4'-NH proton was not observed in this solvent system.

4. M. Shur and S. S. Israelstam, J. Org. Chem., 1968, 33, 3015.

5. A. S. Tomcufcik and L. N. Starker, "Heterocyclic Compounds, Pyridine and derivatives: Part III," ed. by E. Klingsberg, Interscience Publishers, A Division of John Wiley and Sons, New York, London, Sydney, 1962, p. 19.

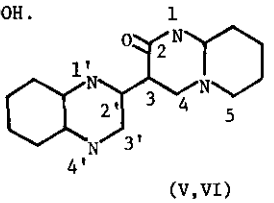
6. VI: ν(KBr) 1690(2-C=O), δ(DMSO-d_6) 9.11(1H, d, J=6 Hz, 5-H), 8.67(1H, s, 4-H), 8.30-7.03(7H, m, aromatic). δ(DMSO-d_6-CF_3COOH) 9.53(1H, d, J=7 Hz, 5-H), 8.83(1H, s, 4-H), 8.80-7.67(7H, m, aromatic).

7. VII: ν(KBr) 1650(2-C=O), δ(DMSO-d_6-CF_3COOH) 12.01(1H, br.s, 3-NHNHMe), 9.93(1H, s, 4'-H), 7.73(1H, d, J=7 Hz, 5'-H), 7.47-6.67(7H, m, aromatic), 4.33(1H, br.s, 3-NHNHMe), 3.70(3H, s, 3-NHNHMe). Proton of 3-NHNHMe was observed in a lower magnetic field, which should be due to the hydrogen bonding.

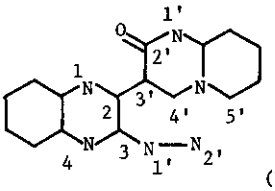
8. IX: ν(KBr) 3280, 3160(NH), 1630, 1610(C=O), δ($CDCl_3$) 10.24(1H, br.s, 2-NH), 7.27(1H, s, 3-H), 7.00-6.17(4H, m, aromatic), 4.00(2H, br.s, CONMeNH_2), 3.28(3H, s, NMe), 3.23(3H, s, NMe). δ(DMSO-d_6) 10.33(1H, br.s, 2-NH), 7.23(1H, s, 3-H), 7.00-6.47(4H, m, aromatic), 4.83(2H, br.s, CONMeNH_2), 3.13(3H, s, NMe), 3.08(3H, s, NMe). δ(DMSO-d_6-CF_3COOH) 10.47 1H, br.s, 2-NH), 7.77(1H, s, 3-H), 7.00-6.67(4H, m, aromatic), 3.68(3H, s, NMe), 3.33 3H, s, NMe). Protons of CONMeNH_2 were not observed in this solvent system.

9. Xa: ν(KBr) 1660, 1650(C=O), δ(DMSO-d_6-CF_3COOH) 10.33(1H, br.s, 2-NH), 8.28(1H, s, 3-H), 7.27-6.47(4H, m, aromatic), 4.33(2H, q, J=7 Hz, CH_2), 1.35(3H, t, J=7 Hz, Me).
Xb: (KBr) 1665, 1650(C=O), δ(DMSO-d_6-CF_3COOH) 10.30(1H, br.s, 2-NH), 8.28(1H, s, 3-H), 7.23-6.43(4H, m, aromatic), 3.87(3H, s, Me). 1-NH proton of Xa and Xb was not observed.

Since VII, Xa, and Xb were hardly soluble in DMSO-d_6, their NMR spectra were measured by dissolving in DMSO-d_6-CF_3COOH.



(V,VI)



(VII)

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