A NEW SYNTHESIS OF FURO[2,3-b]QUINOXALINE AND ITS RING CONVERSIONS

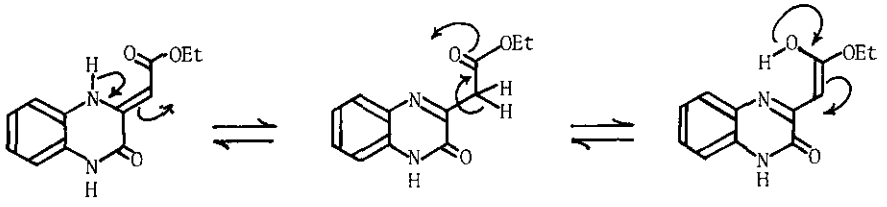
Yoshihisa Kurasawa* and Atsushi Takada

School of Pharmaceutical Sciences

Kitasato University, Shirokane, Minato-ku, Tokyo 108, Japan

Abstract —— A new synthesis of 3-(N,N-dimethylaminocarbonyl)furo[2,3-b]quinoxaline was described. This compound was converted to 2-ethoxycarbonylmethylene-3-oxo-1,2,3,4-tetrahydroquinoxaline, 2-methyl-3-oxo-3,4-dihydroquinoxaline, 4-(3'-oxo-3',4'-dihydroquinoxalin-2'-yl)pyrazolones, and pyrazolo[3,4-c]pyridazino[3,4-b]quinoxalines.

2-Ethoxycarbonylmethylene-3-oxo-1,2,3,4-tetrahydroquinoxaline (I) has been reported to have tautomeric structures such as (Ia-c),[1] and I was postulated to react with electrophilic reagents at the methylenic carbon atom. Among the electrophilic reagents, the Vilsmeyer reagent [DMF(N,N-dimethylformamide)-$POCl_3$] was used to insert formyl group, which easily reacted with various bases. However, its reaction with the Vilsmeyer reagent did not give a formylated compound (II) as an end product. During the reaction, a further intramolecular cyclization was caused to form furo[2,3-b]quinoxaline. We now report a novel synthesis of furo[2,3-b]quinoxaline[2] and its ring conversions.



(Ia) (Ib) (Ic)

Chart 1

Compound I (43 mmol) was allowed to react with the Vilsmeyer reagent [DMF-$POCl_3$ (100-100 ml)], heating on a water bath for 2 hr, to give 3-(N,N-dimethylaminocarbonyl)furo[2,3-b]quinoxaline hydrochloride (III) (83%). The free base (IV) was obtained by treatment of III with pyridine in EtOH.

The structure of IV was established on the basis of its IR, NMR, mass spectral, and elemental analytical data.[3]

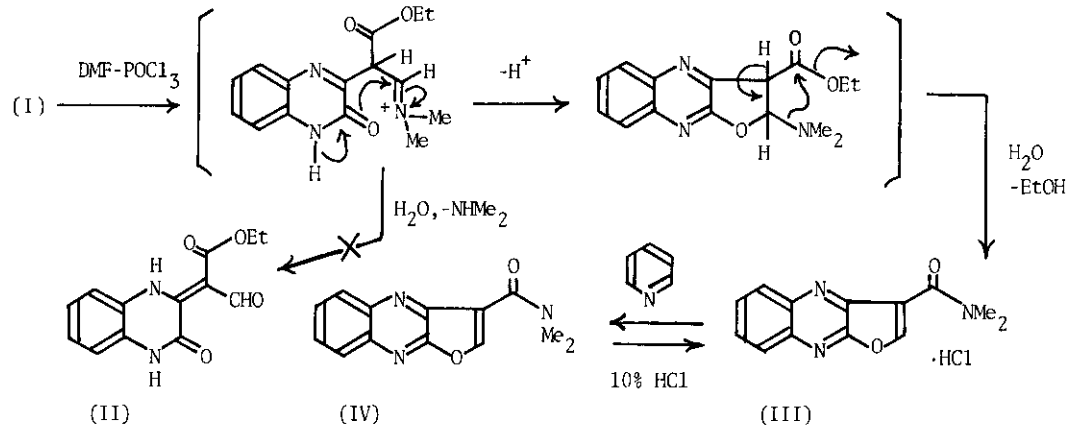


Chart 2*

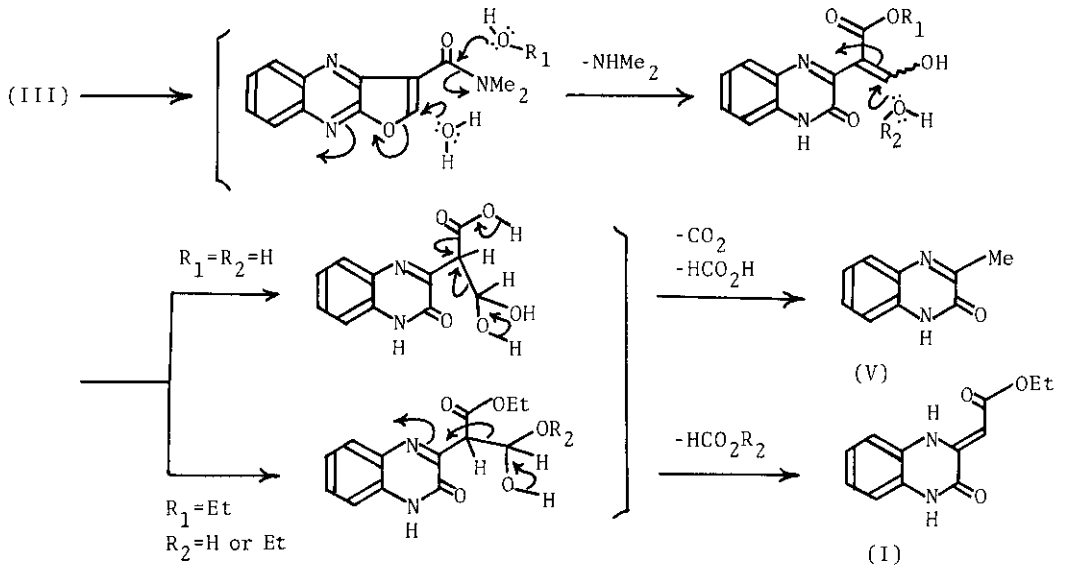


Chart 3

Table I

Reaction Medium	Product (Yield %)
10% NaOH	V (95)
10% HCl	V (60)
H_2O-AcOH	V (17)
EtO^-/EtOH	I (96)
H_2O-EtOH	I (80)

An attempt was made to convert III to the 3-carboethoxyl and 3-carboxyl derivatives. However, the reaction of III (3.6 mmol) in 10% NaOH-EtOH (30-30 ml) afforded 2-methyl-3-oxo-3,4-dihydroquinoxaline (V)[4] (95%), while the reaction of III (3.6 mmol) in EtO^-/EtOH (50 ml) brought about I (95%). The reaction of III in 10% HCl, H_2O-AcOH, and H_2O-EtOH also gave V, V, and I, respectively. These results are shown in Chart 3 and Table I, and suggest that 2-C of III is electron-deficient due to 3-C=O group so that its furan ring is reactive for acid and bases.

In relation to the above results, the reaction of III with hydrazines was examined. Refluxing of III (0.72 mmol) with 1,1-dimethylhydrazine (1.5 mmol) in EtOH (30 ml) afforded 3-(N,N-dimethylhydrazinocarbonyl)furo[2,3-b]quinoxaline (VI)[5] (92%), while a similar reaction of III (0.72 mmol) with hydrazine hydrate, methylhydrazine, and phenylhydrazine (1.5 mmol) in EtOH (30 ml) effected the cleavage of furan ring to produce 4-(3'-oxo-3',4'-dihydroquinoxaline-2'-yl)pyrazolones (VIIa-c)[6] (85-90%). Since a singlet signal was observed for 3-H of pyrazolone ring in VIIb and VIIc,[7] the methyl and phenyl groups were assumed to exist in the 2-position. Therefore, the reaction may be formulated, as shown in Chart 4. The reaction of VIIb (3.3 mmol) with $POCl_3$ (200 ml) in DMF (50 ml)

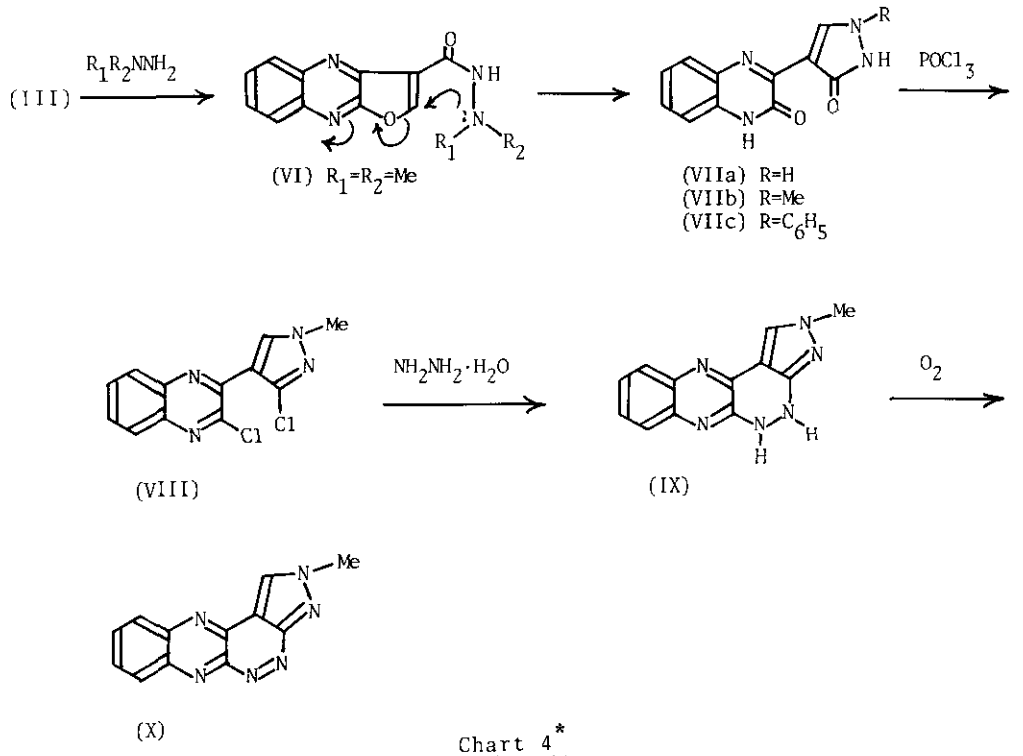


Chart 4*

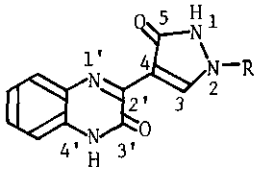
* Satisfactory mass spectral and elemental analytical data were obtained for all new samples.

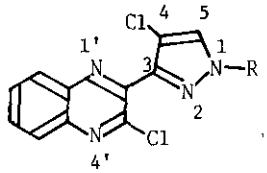
gave dichloride (VIII)[8] (90%). The yield for the dichlorination of VIIa and VIIc was low. Refluxing of VIII (1.34 mmol) in excess of hydrazine hydrate (20ml) at 150-160°C produced a tetracyclic quinoxaline derivative, pyrazolo[3,4-c]pyridazino[3,4-b]quinoxaline (IX) (80%), wherein the ring transformation of quinoxaline to benzimidazole scarecely took place.[9] Compound IX (0.2 mmol) was easily oxidized with O_2 (by aeration) to compound (X)[10] (80%), and hence the compound IX was checked by a mass analysis (M^+=238).

In conclusion, it may be said that the above novel furo[2,3-b]quinoxaline III is a useful intermediate to synthesize the various quinoxaline derivatives.

References and Footnotes

1. Mondelli and L. Merlini, Tetrahedron, 1966, 22, 2356.
2. C. Iijima and E. Hayashi, Yakugaku Zasshi, 1972, 92, 729; Idem, ibid., 736.
3. $\nu_{C=O}$(KBr) 1755; δ(DMSO-d_6) 7.93-7.43(4H, m, aromatic), 7.90(1H, s, 2-H), 4.02(3H, s, NMe), 3.50(3H, s, NMe).
4. C. L. Lees and H. N. Rydon, J. Chem. Soc., 1955, 303.
5. $\nu_{C=O}$(KBr) 1735; δ(DMSO-d_6) 12.20(1H, br.s, CONHNMe$_2$), 9.50(1H, s, 2-H), 7.73-7.00(4H, m, aromatic), 3.00(6H, s, CONHNMe$_2$).
6. $\nu_{C=O}$(KBr) 1675 and 1620 (VIIa and VIIc), 1683 and 1620 (VIIb); δ(DMSO-d_6) 12.35(1H, br.s, 2-NH), 8.30(1H, br.s, 3-H), 7.67-7.00(4H, m, aromatic) (VIIa); 8.07(1H, s, 3-H), 7.67-7.00(4H, m, aromatic), 3.40(3H, s, 2-Me) (VIIb); 8.43(1H, s, 3-H), 8.23-7.00(9H, m, aromatic) (VIIc). Protons of CONH were not observed, presumably due to moisture in the solvent.
7. 3-H of VIIb and VIIc was observed as a sharp singlet, but that of VIIa as a broad singlet.
8. δ(CF_3COOH) 8.68(1H, s, 5-H), 8.83-7.33(4H, m, aromatic), 4.33(3H, s, NMe) (VIIIb).
9. E. C. Taylor and A. McKillop, J. Org. Chem., 1965, 30, 2858; G. W. H. Cheeseman and M. Rfig, J. Chem. Soc.(C), 1971, 452.
10. δ(CF_3COOD) 9.43(1H, s, 1-H), 9.00-7.57(4H, m, aromatic), 4.80(3H, s, 2-Me) (Xb).





Received, 19th December, 1979