REACTIONS OF 2-ACETYL-3-METHYLQUINOXALINE 1,4-DIOXIDE AND ITS DERIVATIVES[1]

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Abstract —— 2-Cinnamoyl-3-methylquinoxaline 1,4-dioxide(2) was inert to hydrochloric acid in refluxing ethanol. When a xylene solution of 2-acetyl-3-methylquinoxaline 1,4-dioxide(1-dioxide) was refluxed overnight, the dioxide was reduced mainly to 1-4-oxide and the oxidative products from xylene were also obtained. 2-Cinnamoyl-3-methylquinoxaline 4-oxide(4a) and 3-methyl-4-oxido-2-quinoxalyl 4-phenyl-1,3-butadienyl ketone(4b) were quantitatively cyclized into 4-methyl-3-oxo-1-phenyl- and 4-methyl-3-oxo-1-styryl-3H-pyrrolo[1,2-a]quinoxalin-10-ium chloride(6a and 6b), respectively, when the ethanolic solution were refluxed in the presence of hydrochloric acid.

In our previous papers[2], we described an interesting isomerization or cyclization reaction of chalcones and vinylogous chalcones derived from 2-acetyl-3-methylquinoxaline(1). In this paper, we wish to report the results observed in the reactions of 2-acetyl-3-methylquinoxaline 1,4-dioxide(1-dioxide) and the chalcones derived from the dioxide, which was prepared from benzofuroxan and acetylacetone by the known method[3]. 2-Cinnamoyl-3-methylquinoxaline 1,4-dioxide(2) was synthesized in 43.7% yield by treatment of 1-dioxide with benzaldehyde in ethanol using a catalytic amount of sodium hydroxide under ice-cooling. When an ethanolic solution of 2 was refluxed in the presence of hydrochloric acid to obtain [1,2]oxazino[2,3-a]quinoxaline(3), the starting material was wholly recovered.

To achieve a thermal cyclization of 2 to 3, a solution of 2 in xylene was refluxed

overnight. Unexpectedly, compound 2 was reduced mainly to a monoxide, which was afterward revealed to be 2-cinnamoyl-3-methylquinoxaline 4-oxide(4a), and xylene used as a solvent was oxidized to the corresponding aldehyde or alcohol. The interesting and unknown intermolecular redox reaction was examined in detail using 1-dioxide and o-xylene as a dioxide and solvent, respectively. The products obtained after refluxing for about 18 h were o-methylbenzaldehyde, o-methylbenzyl-alcohol, 1, 1-4-oxide, and 1-1-oxide in the yields of 36, 60, 2.3, 55.5, and 19.8%, respectively, based on the consumed 1-dioxide. These products were isolated by using a medium pressure liquid chromatography. Compound 1-4-oxide was also obtained by treatment of 1 with hydrogen peroxide in acetic acid catalyzed by sodium tungstate in 52.6% yield. The physical data for 1-4-oxide and 1-1-oxide explain well these structures. Especially, the comparison of the carbonyl bands in the ir spectra of 1-1-oxide and 1-4-oxide showed the conjugation between the carbonyl and N-oxide groups in 1-1-oxide.

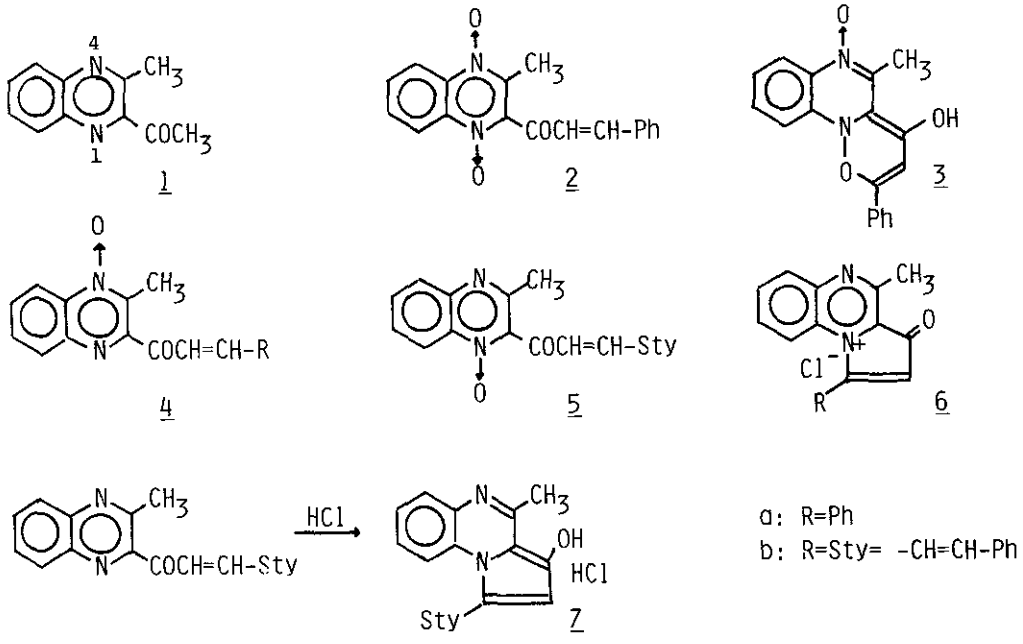

Chart 1

Then the 1-1-oxide and 1-4-oxide were derived to the corresponding vinylogous chalcones, 3-methyl-1-oxido- and 3-methyl-4-oxido-2-quinoxalyl 4-phenyl-1,3-butadienyl ketone(5 and 4b), respectively, by treating with cinnamaldehyde in the

presence of base. Their physical data[6] could also explain well their structures. An ethanolic solution of 5 was refluxed in the presence of hydrochloric acid on a water bath for 2 h to give only a tary compound accompanied with a recovered starting material. On the other hand, compound 4h gave quantitatively a crystalline compound, 4-methyl-3-oxo-1-styryl-3H-pyrrolo[1,2-a]quinoxalin-10-ium chloride (6b). There are remarkable differences between the physical data[7] of 6b and 3-hydroxy-4-methyl-1-styrylpyrrolo[1,2-a]quinoxaline hydrochloride(7), which was obtained by acid-catalyzed cyclization of 3-methyl-2-quinoxalyl 4-phenyl-1,3-butadienyl ketone. Under the similar conditions 4a was quantitatively cyclized to 4-methyl-3-oxo-1-phenyl-3H-pyrrolo[1,2-a]quinoxalin-10-ium chloride(6a). The mechanism to form 6 from 4 was proposed in Chart 2.

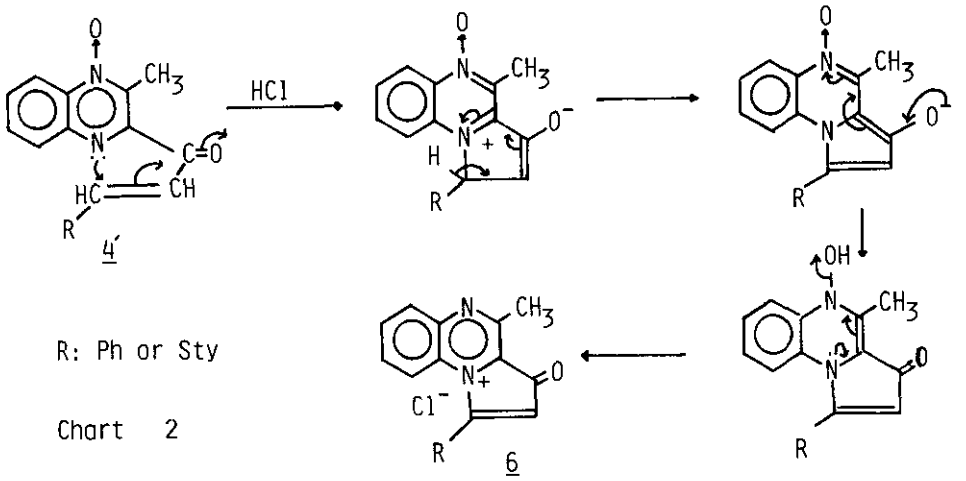

Chart 2

Thus the fact that 4 gave 6 and 5 did not cyclize under the similar conditions provided the evidence for the position of oxide in the compounds obtained reductively from 1-dioxide. It is interesting that 1-dioxide was reduced mainly to 1-4-oxide and chalcone derived from it was cyclized into 6.

REFERENCES AND NOTES

1) A part of this work was presented at the 106th Annual Meeting of the Pharmaceutical Society of Japan, April 1986, Chiba.

2) a) K. Matoba, K. Itoh, K. Kondo, T. Yamazaki, and M. Nagata, Chem. Pharm. Bull., 1981, 29, 2442; b) K. Matoba, Y. Miyata, and T. Yamazaki, ibid., 1983, 31, 476.

3) a) C. H. Issidorides and M. J. Haddadin, J. Org. Chem., 1966, 31, 4067;
b) M. Hasegawa and T. Takabatake, Synthesis, 1985, 938.

4) J. Młochowski, K. Kloc, and J. Piatkowska, Heterocycles, 1982, 19, 1889.

5) 1-4-Oxide: $C_{11}H_{10}N_2O_2$, yellow needles, mp 95-97°C(ether-hexane), ir(nujol): 1700 cm^{-1}(C=O), uv(MeOH),λmax nm(ε), 322(8100), 251(29800), nmr($CDCl_3$), δ 2.88 (6H, s), 7.8-8.1(2H, m), 8.1-8.5 and 8.6-8.9(each 1H, m), ms, m/z(%), 202(M^+, 95), 185(M^+-OH, 94), 144(23), 143(100), 102(34), 43(Ac^+, 94).

1-1-Oxide: $C_{11}H_{10}N_2O_2$, colorless needles, mp 102-104°C(ether-hexane), ir(nujol), 1695 cm^{-1}(C=O), uv(MeOH), λmax nm(ε), 344(sh, 5600), 317(6700), 242(29900), nmr ($CDCl_3$),δ2.60 and 2.71(each 3H, s), 7.5-8.1(3H, m), 8.3-8.6(1H, m), ms, m/z(%), 202(M^+,31), 185(M^+-OH, 24), 144(59), 143(100), 102(39), 43(Ac^+, 19).

6) 4b: $C_{20}H_{16}N_2O_2$, mp 163-165°C(EtOH), ir(nujol), cm^{-1}, 1660(C=O), 1580(C=C), uv(MeOH), λmax nm(ε), 350(32100), 335(32300), 236(31000), 205(18600), nmr($CDCl_3$), δ2.84(3H, s, CH_3), 7.0-7.2(2H, m), 7.2-7.8(7H, m), 7.8-8.0(2H, m), 8.1-8.3 and 8.6-8.8(each 1H, m), ms, m/z(%), 316(M^+, 29), 299(M^+-OH, 26), 271(21), 194(24), 160(2-methylquinoxaline 1-oxide, 100), 143(63), 128(96).

5: $C_{20}H_{16}N_2O_2$, mp 201-202°C(EtOH), ir(nujol), cm^{-1}, 1640(C=O), 1610(C=C), uv(MeOH), λmax nm(ε), 348(38200), 339(sh., 37500), 238(37500), nmr($CDCl_3$), δ2.65(3H, s, CH_3), 6.72(1H, d, J=15, CO-CH=C), 6.9-7.1(2H, m), 7.2-7.6(6H, m), 7.76(1H, t, J=7, C_7-H), 7.88(1H, t, J=7, C_6-H), 8.10 and 8.56(each 1H, d, J=7, C_5- and C_8-H, respectively), ms, m/z(%), 316(M^+, 6), 300(M^+-O, 11), 259(54), 195(25), 171(49), 144(2-methylquinoxaline, 83), 143(99), 102(styrene, 100).

7) 6b: $C_{20}H_{15}N_2O^+Cl^- H_2O$, mp 210-214°C(dec., EtOH), ir(nujol), cm^{-1}, 1610, 1570, 1535, uv(MeOH), λmax nm(ε), 415(11600), 322(17200), 269(11700), 237(sh., 19000), 225(sh., 20000), 207(24500), nmr($CDCl_3$-3 drops TFA),δ3.10(3H, s, CH_3), 6.41(1H, s, C_2-H), 6.90 and 7.21(each 1H, d, J=14, styryl), 7.30(1H, t, J=8, C_6-H), 7.42(5H, s, Ph), 7.56, 7.75, and 8.15(each 1H, t, J=8, C_7-, C_5-, and C_8-H, respectively), ms, m/z(%), 300(M^++1, 78), 299(M^+, 37), 223(M^++1-Ph, 100), 144 (2-methylquinoxaline, 20), 143(49). 7: $C_{20}H_{16}N_2O \cdot HCl$, mp 244-247°C(dec., EtOH), ir(nujol) cm^{-1}, 1625, 1610, 1585, 1555, 1530, uv(MeOH), λmax nm(ε), 397(9300), 318(13500), 295(sh., 11000), 260(13500), 226(23100), 205(22700), nmr($CDCl_3$-3 drops TFA),δ2.96(3H, s, CH_3), 6.69(1H, s, C_2-H), 7.26 and 7.35(each 1H, d, J=15, styryl), 7.4-7.7(7H, m), 7.6-7.8 and 7.9-8.1(each 1H, m), ms, m/z(%), 300(M^+, 84), 299(M^+-1, 32), 223(M^+-Ph, 100), 144(2-methylquinoxaline, 20), 143(41).

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