

REACTIONS OF 2-ACETYL-3-METHYLQUINOXALINE 1,4-DIOXIDE AND ITS
DERIVATIVES¹

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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 papers² 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 method³. 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.

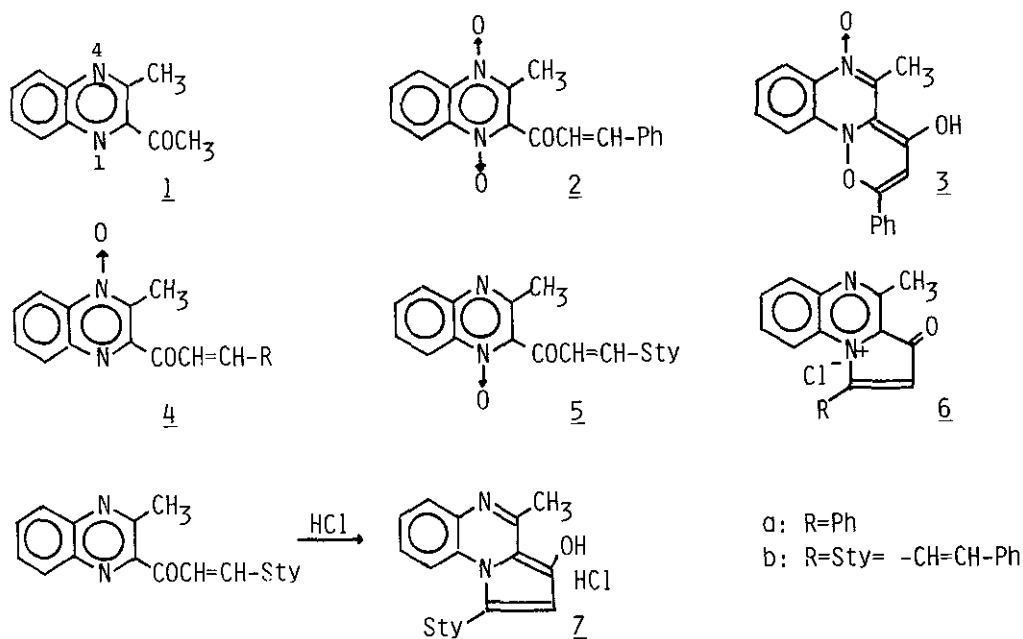
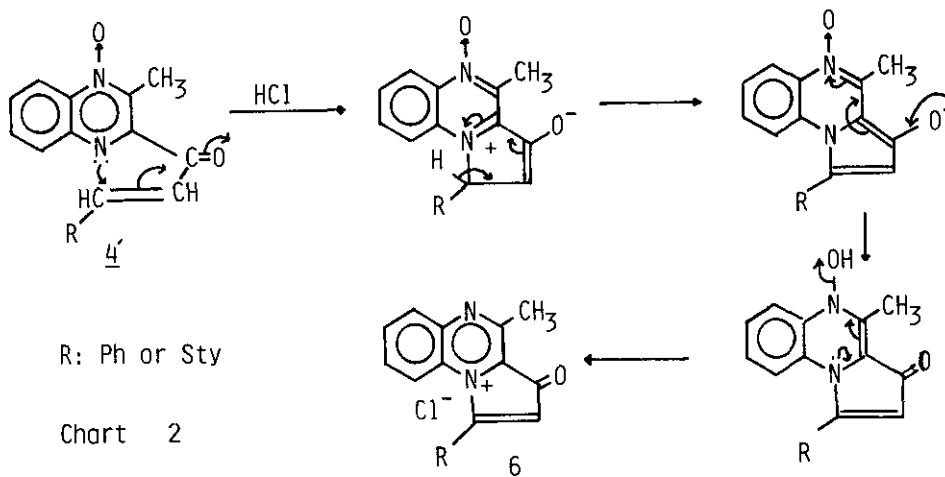


Chart 1

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 data⁶ 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 data⁷ 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.



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), λ_{max} 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), λ_{max} nm(ϵ), 344(sh, 5600), 317(6700), 242(29900), nmr($CDCl_3$), δ 2.60 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), λ_{max} nm(ϵ), 350(32100), 335(32300), 236(31000), 205(18600), nmr($CDCl_3$), δ 2.84(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), λ_{max} nm(ϵ), 348(38200), 339(sh., 37500), 238(37500), nmr($CDCl_3$), δ 2.65(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: $C_{20}H_{15}N_2O^+Cl^- \cdot H_2O$, mp 210-214°C(dec., EtOH), ir(nujol), cm^{-1} , 1610, 1570, 1535, uv(MeOH), λ_{max} nm(ϵ), 415(11600), 322(17200), 269(11700), 237(sh., 19000), 225(sh., 20000), 207(24500), nmr($CDCl_3$ -3 drops TFA), δ 3.10(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), λ_{max} nm(ϵ), 397(9300), 318(13500), 295(sh., 11000), 260(13500), 226(23100), 205(22700), nmr($CDCl_3$ -3 drops TFA), δ 2.96(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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