REACTION OF PYRIDAZINE N-OXIDES WITH PYRIDYNES: FORMATION OF THE FIRST EXAMPLES OF PYRIDO-OXEPINS

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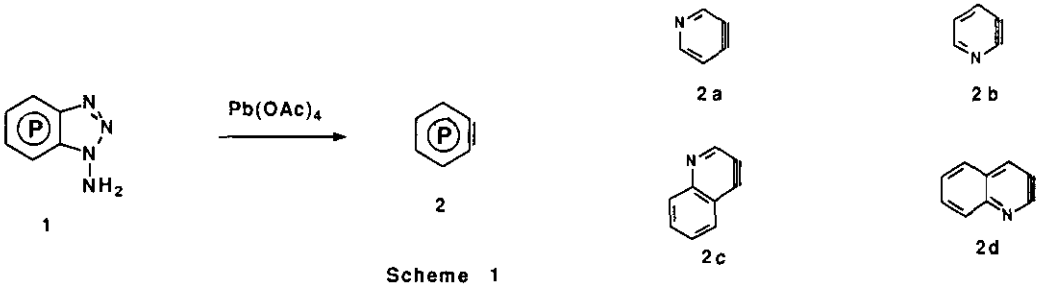
Abstract —— Reaction of pyridazine N-oxides (3) with pyridynes and quinolynes (2) gave the corresponding novel fully unsaturated pyrido-oxepins (4-6) and quino-oxepins (13-15) via the cycloadducts (11).

1-Benzoxepins have been prepared by several methods,[1,2] However, fused 1-oxepins condensed with aromatic heterocyclic rings are unknown,[3] although the synthesis of new seven-membered heterocyclic ring systems has recently been the object of extensive study.[3,4] We report here the formation of the first examples of fully unsaturated pyrido-oxepins and quino-oxepins.[5]

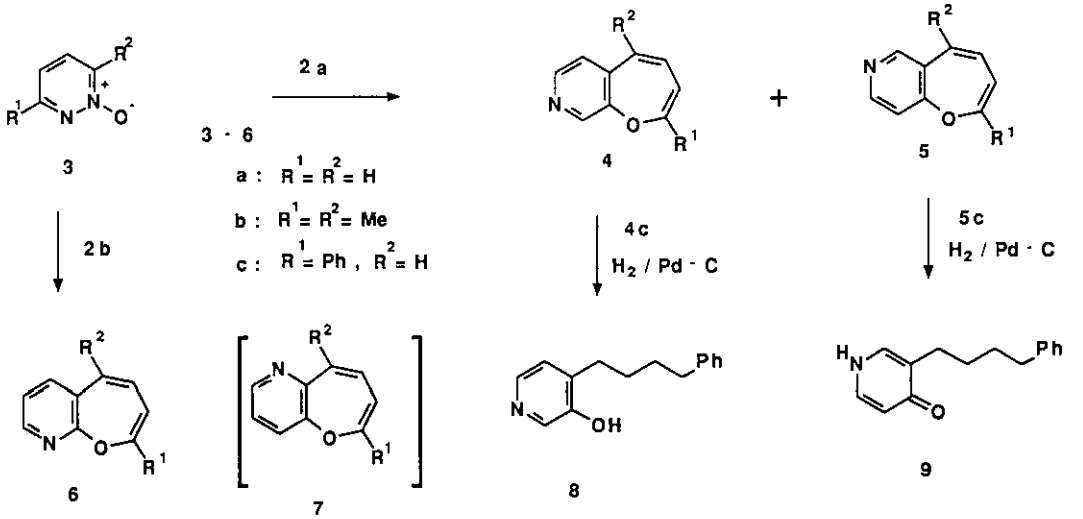
In the course of the studies on 1,3-dipolar cycloaddition of azine N-imides and N-oxides, we have found that the reaction of pyridazine N-imides with benzyne gave the stable cycloadducts, whereas that of pyridazine N-oxides resulted in the formation of 1-benzoxepins via the initially formed unisolable cycloadducts.[2] This result prompted us to examine the reaction of pyridazine N-oxides with pyridynes (didehydropyridines) and quinolynes (didehydroquinolines).

The pyridynes (2a,b) and quinolynes (2c,d) used were generated from the corresponding 1-aminotriazolopyridines (1) by oxidation with lead tetra-acetate,[6] Scheme 1.



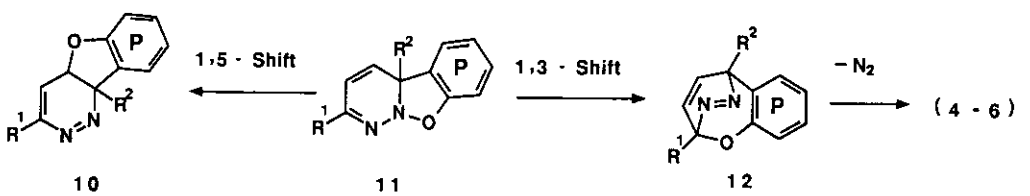
Scheme 1

Treatment of the pyridazine N-oxides (3a-c) with 3,4-pyridyne (2a)[7] gave pyrido-[3,4-b]oxepins (4a-c) and pyrido[4,3-b]oxepins (5a-c) in 10-15% and 15-20% yields. Similarly, the reaction of the N-oxides (3) with 2,3-pyridyne (2b) afforded pyrido[2,3-b]oxepins (6a-c) in 20-30% yields, but no [3,2-b]-isomers (7).[8] These pyrido-oxepins obtained were characterized by elemental and spectroscopic analyses and the results of some chemical studies. For example, in the ^{1}H-nmr spectra of unsubstituted compounds (4a, 5a, and 6a), the signals due to 3-H appeared at around δ 5.5 and those due to other three oxepin ring protons lay in the olefinic range (δ 6.0-6.5). Catalytic hydrogenation of the 2-phenyl compounds (4c) and (5c) resulted in ring opening to give the 3-hydroxypyridine derivative (8) and 4-pyridone derivative (9), respectively, Scheme 2.



Scheme 2

In the case of the reaction of 3,6-dimethylpyridazine 1-oxide (3b) with 2,3-pyridyne (2b), the rearrangement product (10b) was also obtained in ca. 10% yield. We also observed that the reaction of 3-methyl- and 3-methoxypyridazine 1-oxides

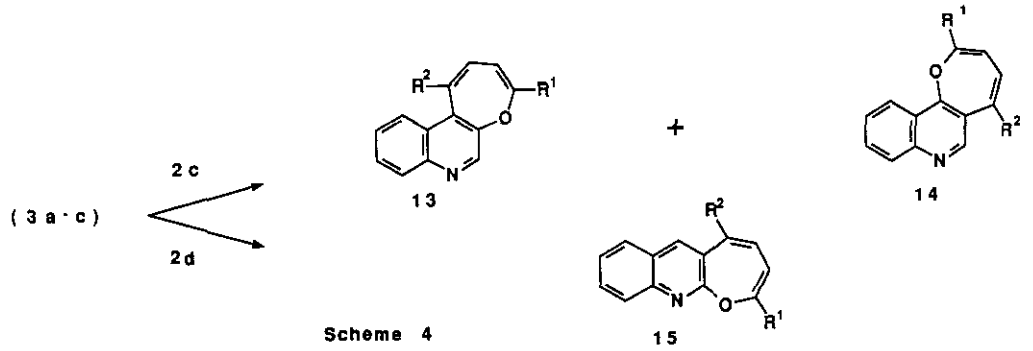


Scheme 3

with benzyne gave the corresponding similar rearrangement products together with 1-benzoxepins. Therefore, the previously proposed mechanism for the reaction of pyridazine N-oxides with benzyne, involving diazo-keto intermediates derived from the initially formed cycloadducts by N-O bond fisson,[2] seems unlikely. Based on the above additional results, a possible mechanism for the reaction is shown in Scheme 3. The cycloadducts (11) initially formed may undergo N-O bond fission followed by competing 1,3- and 1,5-shift. The former shift predominates to give the pyrido-oxepins (4-6) as major products probably via the intermediates (12), and the latter affords the rearrangement products (10). The electron-donating methyl or methoxyl group may promote the 1,5-shift.

The regioselectivity for the initial 1,3-dipolar cycloaddition of the N-oxides with the pyridynes is analogous to that observed in the reaction of pyridynes with ammonia;[9] 3,4-pyridyne gives both 3- and 4-aminopyridine, whereas only 2-aminopyridine is formed from 2,3-pyridyne.

Similarly, upon treatment with pyridazine N-oxides (3a-c), 3,4-quinolyne (2c) gave quino[3,4-b]oxepins (13a-c) and quino[4,3-b]oxepins (14a-c) in 20-25% and 8-12% yields, respectively, and 2,3-quinolyne (2d) afforded only quino[2,3-b]-oxepins (15a-c) in 20-30% yields,[10] Scheme 4.



Scheme 4

Further application of the present results to other hetarynes such as didehydrodiazines and didehydroazoles is under investigation.

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2. H. Igeta, H. Arai, H. Hasegawa, and T. Tsuchiya, Chem. Pharm. Bull., 1975, 23, 2791.

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5. Although these compounds are usually named as oxepinopyridines and oxepinoquinolines, we used in the present paper the pyrido-oxepin name in connection with benzoxepins in order to emphasize the new seven-membered ring systems.

6. G. W. J. Fleet and I. Fleming, J. Chem. Soc. (C), 1969, 1758.

7. A solution of $Pb(OAc)_4$ (1.1 mol eq.) in CH_2Cl_2 was added dropwise over a 10-15 min period to a suspension of 3 (3-4 mol eq.), 2, (0.5-1.0 g), and CaO (large excess) in CH_2Cl_2 with stirring at 0 °C. The isolated yields of the oxepins were calculated from the starting tetrazolopyridines (1).

8. Satisfactory elemental analyses and spectral data were obtained for all new pyrido-oxepins reported; 4a: viscous oil; ^{1}H-nmr ($CDCl_3$) δ : 5.49 (1H, dd, J= 6 and 6 Hz, 3-H), 6.20 (1H, dd, J=6 and 11 Hz, 4-H), 6.25 (1H, d, J=6 Hz, 2-H), 6.55 (1H, d, J=11 Hz, 5-H), 6.95 (1H, d, J=5 Hz, 6-H), 8.19 (1H, s, 9-H), 8.29 (1H, d, J=7 Hz, 7-H); 4b: viscous oil; 4c: mp 94-96 °C; 5a: viscous oil; ^{1}H-nmr δ : 5.42 (1H, dd, J=6 and 6 Hz, 3-H), 6.03 (1H, dd, J=6 and 11 Hz, 4-H), 6.07 (1H, d, J=6 Hz, 2-H), 6.54 (1H, d, J=11 Hz, 5-H), 6.75 (1H, d, J=5.5 Hz, 9-H), 8.27 (1H, s, 6-H), 8.43 (1H, d, J=5.5 Hz, 8-H); 5b: viscous oil; 5c: mp 54-55 °C; 6a: viscous oil; ^{1}H-nmr δ : 5.55 (1H, dd, J=5.5 and 5.5 Hz, 3-H), 6.08 (1H, dd, J=5.5 and 11 Hz, 4-H), 6.29 (1H, d, J=5.5 Hz, 2-H), 6.51 (1H, d, J=11 Hz, 5-H), 7.07 (1H, dd, J=4.5 and 7.5 Hz, 7-H), 7.46 (1H, dd, J=2 and 7.5 Hz, 6-H), 8.19 (1H, dd, J=2 and 4.5 Hz, 8-H); 6b: mp 50-51 °C; 6c: mp ca. 20 °C.

9. W. Adams, A. Grimison, and R. Hoffmann, J. Am. Chem. Soc., 1969, 91, 2590; M. G. Reinecke, Tetrahedron, 1982, 38, 427.

10. 13a: mp 77-78 °C; 13b: mp 63-65 °C; 13c: mp 121-122 °C; 14a: mp 101-102 °C; 14b: mp 82-83 °C; 14c: mp 135-136 °C; 15a: mp 83-84 °C; 15b: mp 96-97 °C; 15c: mp 146-147 °C.

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