## Communications to the Editor

Chem. Pharm. Bull. 21(2) 448—450 (1973)

UDC 547.7'546.21.057

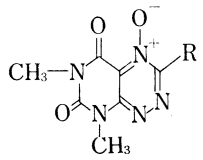
# Heterocycle N-Oxide Synthesis by the Nitrative Cyclization. New Syntheses of Fervenulin N-Oxide, Alloxazine N-Oxide, Isoalloxazine N-Oxide and Purine N-Oxide

It is well-known that the nitro group undergoes intramolecular dehydrative cyclization with a substituent in the molecule possessing active hydrogen to form an aromatic N-oxide. A similar intermolecular cyclization of nitro compounds into phenazine N-oxides is known as the Wohl-Aue reaction. A number of this type of reactions were briefly reviewed in a book of Ochiai.[1] Recently such a nitro functionality was applied to the synthesis of pyrimido-[5,4-*g*]pteridine 10-oxides.[2]

We describe here convenient new syntheses of several heterocycle N-oxides including fervenulin N-oxide, alloxazine N-oxide, isoalloxazine N-oxide and purine N-oxide by means of the nitration-cyclization.

A mixture of an aldehyde hydrazone of 1,3-dimethyl-6-hydrazinouracil (I)[3] (1 mole) and potassium nitrate (1 mole) in acetic acid including a few drops of sulfuric acid was stirred at 50° for about 1 hr, during which time the reaction mixture changed its colour from pale yellow to brown. After removal of the solvent under reduced pressure, the residue was neutralized with aqueous sodium bicarbonate to separate yellow to orange crystals, which were collected by filtration, washed with water, dried and purified by recrystallization to give the respective 6-substituted 1,3-dimethyl-7-azalumazine 5-oxides (3-substituted fervenulin 4-oxides) (III) in good yields.

Table I. Preparation of Fervenulin 4-Oxides[a]



| 3-Substituent (R) | mp (°C) | Yields (%) |
|---|---|---|
| Phenyl | 233 | 73 |
| 3,4-Dichlorophenyl | 165 | 70 |
| 3-Pyridyl | 178 | 85 |

*a*) All compounds were recrystallized from MeOH.

The process may involve the key intermediates 1,3-dimethyl-6-hydrazino-5-nitrouracil aldehyde hydrazones (II), which were protonated with sulfuric acid and then cyclized by intramolecular dehydration to give the corresponding N-oxides. It is interesting to note that the intermediates (II) gave pyrazole[3,4-*d*]pyrimidines by the elimination of the nitro group when they were treated under neutral conditions.[4]

1) E. Ochiai, "Aromatic Amine Oxides," Elsvier, 1967, pp. 59—65.
2) Y. Maki, M. Sako, and E.C. Taylor, *Tetrahedron Letters*, **1971**, 4271.
3) W. Pfleiderer and G. Blankenhorn, *Tetraheron Letters*, **1969**, 4699.
4) Y. Maki, K. Izuta, and M. Suzuki, *Chem. Commun.*, **1971**, 1442.

The structures of these N-oxides were ascertained by satisfactory elemental analyses, the presence of the parent ions and strong M-16 ions in their mass spectra[5] and the formation of the corresponding fervenulines (IV)[6] by their reduction using sodium dithionite in water.

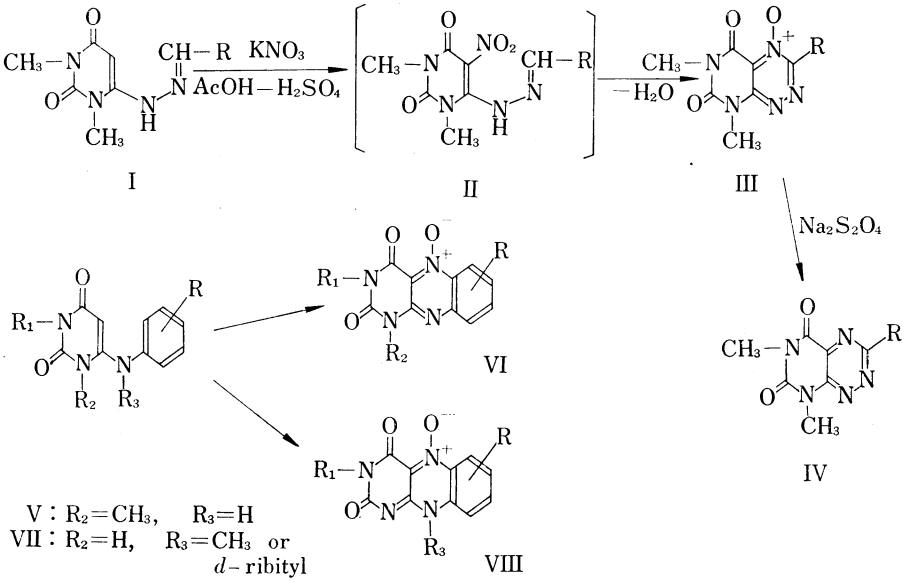
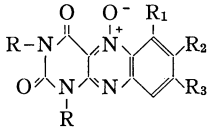



Chart 1

Next, this nitrative cyclization was extended to the syntheses of alloxazine 5-oxides and isoalloxazine 5-oxides. Thus, heating of 6-anilinouracils (V) with equimolar potassium nitrate in acetic acid in the presence of a few drops of sulfuric acid at 90° for 30 min followed by removal of the solvent by evaporation and dilution with water gave exclusively the respective alloxazine 5-oxides (VI) in high yields. This procedure offers a convenient synthetic method of alloxazine 5-oxides, because nitrosation of 6-anilinouracil leads in general

Table II. Preparation of Alloxazine 5-Oxides[a]

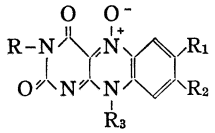


| R | $R_1$ | $R_2$ | $R_3$ | mp (°C) | Yields (%) |
|---|---|---|---|---|---|
| H | H | H | H | >320[7] | 90 |
| H | H | $CH_3$ | $CH_3$ | >320 | 85 |
| $CH_3$ | H | H | H | 237[7] | 92 |
| $CH_3$ | H | $CH_3$ | H | 242[7] | 90 |
| $CH_3$ | Cl | H | Cl | >320 | 82 |
| $CH_3$ | H | $NO_2$ | H | >320 | 93 |

a) All compounds were recrystallized from EtOH.

5) For recent review on the mass spectrum of heterocycle N-oxide, see Q.N. Porter and J. Baldas, "Mass Spectrometry of Hetrocyclic Compounds," Wiley-Interscience, 1971, p. 384 and others.
6) F. Yoneda, M. Kanabori, K. Ogiwara, and S. Nishigaki, *J. Heterocyclic Chem.*, **7**, 1443 (1970).
7) H. Goldner, G. Dietz, and E. Carstens, *Ann.*, **694**, 142 (1966).

TABLE III. Preparation of Isolalloxazine 5-Oxides[a]



| R | $R_1$ | $R_2$ | $R_3$ | mp (°C) | Yield (%) |
|---|---|---|---|---|---|
| H | $CH_3$ | $CH_3$ | $CH_3$ | >300[8] | 78 |
| $CH_3$ | H | H | $CH_3$ | 301[8] | 86 |
| $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | 259[8] | 90 |
| H | $CH_3$ | $CH_3$ | *d*-ribityl | >300[8] | 85 |

*a*) All compounds were recrystzllized from EtOH.

to a mixture of alloxazine and alloxazine 5-oxide.[7] Similarly, nitration of several 6-(N-methylanilino)uracils (VII) under the same conditions gave the corresponding isoalloxazine 5-oxides (VIII).[8] Nitration of 6-(N-*d*-ribityl-3,4-xylidine)uracil gave riboflavin 5-oxide[8] in good yield.

Nitration of 6-benzylamino-1,3-dimethyluracil (IX) with potassium nitrate in acetic acid in the presence of a few drops of sulfuric acid at 70° for 1 hr followed by dilution with water gave 65% of 8-phenyltheophylline 7-oxide (X),[9] which was converted into 8-phenyltheophylline (XI) by treatment with dimethylformamide.[9a]

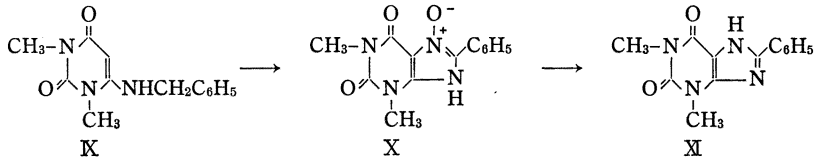


Chart 2

Application of this procedure to the preparation of other heterocycle N-oxides are in progress.

*Faculty of Pharmaceutical Sciences,*
*Kumamoto University*
*Oe-honmachi, Kumamoto*

FUMIO YONEDA
YOSHIHARU SAKUMA

Received July 6, 1972

8) F. Yoneda, Y. Sakuma, M. Ichiba, and K. Shinomura, *Chem. Pharm. Bull.* (Tokyo), **20**, 1832 (1972).
9) *a*) E.C. Taylor and E.E. Garcia, *J. Am. Chem. Soc.*, **86**, 4721 (1964); *b*) H. Goldner, G. Dietz, and E. Carstens, *Ann.*, **691**, 142 (1966).