Notes

[Chem. Pharm. Bull. 22(7)1652—1655(1974)] UDC 547.854.81.04

Nitrosative and Nitrative Cyclizations of 6-Benzylamino-1,3-dimethyl-4-N-phenylcytosine

Fumio Yoneda and Shigeru Matsumoto

Faculty of Pharmaceutical Sciences, Kumamoto University[1]

(Received June 19, 1973)

Nitrosative cyclization of 6-alkylaminouracils or 6-anilinouracils gives generally xanthines or alloxazines together with the respective N-oxides.[2,3] Nitrative cyclization, on the other hand, leads to the exclusive formation of the N-oxides.[4] These facts stimulated us to examine what kinds of products can be obtained from 6-benzylamino-1,3-dimethyl-4-N-phenylcytosine (I), which has at least two reactive sites on electrophiles, by the nitrosative and nitrative cyclizations; the intramolecular condensation of the presumable intermediate III by path a would give a theophylline derivative, while the condensation by path b would give an alloxazine derivative. This paper describes the results of the nitrosation and nitration of I.

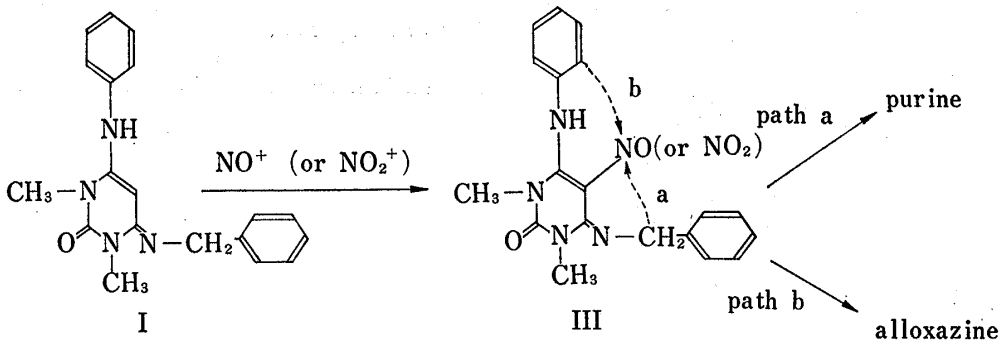

Chart 1

The key intermediate I was prepared by treatment of N-benzyl-6-chloro-1,3-dimethylcytosine (II)[5] with aniline in ethanol. The compound (I) thus obtained was unexpectedly resistant to nitrosation under usual conditions (for example, treatment of I with sodium nitrite in dilute hydrochloric acid or acetic acid at 0° through 80° for 2 hr), with the starting material being recovered. However, refluxing I with excess sodium nitrite in acetic acid at 120° for 2 hr gave a product having an empirical formula of $C_{19}H_{16}O_3N_6$ (mol. wt. 376). The infrared (IR) spectrum of the product showed the absorptions attributed to a nitro group at 1548 and 1328 cm^{-1}, as well as a secondary amino absorption band at 3300 cm^{-1}, a carbonyl band at 1679 cm^{-1} and an imino absorptions at 1626 cm^{-1}. In the nuclear magnetic resonance (NMR) spectrum (CF_3COOH) there were A_2B_2 quartet (δ 7.76 and 8.52; J_{AB}=9 Hz) suggesting that a nitro group was introduced into the *para*-position of one of phenyl groups, besides identical two N-methyl protons (δ 6.03) and another phenyl protons (δ 7.53—7.92). These data appeared to be consistent with 1,3-dimethyl-6-*p*-nitroanilino-8-phenyl-6-deoxytheophylline (IV) rather than an alloxazine derivative. Compound (IV) was alternatively prepared by the following

1) Location: *Oe-honmachi, Kumamoto.*
2) H. Goldner, G. Dietz and E. Carstens, *Ann.*, **691**, 142 (1966).
3) H. Goldner, G. Dietz and E. Carstens, *Ann.*, **694**, 142 (1966).
4) F. Yoneda and Y. Sakuma, *Chem. Pham. Bull.* (Tokyo), **21**, 448 (1973).
5) K. Senga, F. Yoneda and S. Nishigaki, *J. Org. Chem.*, **36**, 1829 (1971).

unequivocal synthesis. Heating of 1,3-dimethyl-8-phenyltheophylline with excess phosphorus oxychloride in the presence of *p*-nitroaniline gave IV in excellent yield. The latter procedure is an application of the known 6-deoxytheophylline synthesis[6]

In the above reaction, 1,3-dimethyl-7-nitroalloxazine-5-oxide (*vide infra*) and 1,3-dimethylalloxazine-5-oxide were detected by gas chromatography as the by-products. Nitrosation of the preformed 6-anilino-8-phenyl-6-deoxytheophylline (V)[6] with excess sodium nitrite in acetic acid under the same conditions gave also IV in high yield. This suggests that the nitrosative cyclization of I to IV involves the initial formation of V, followed by the *para*-nitration to the 6-anilino group of V. The formation of this nitro compound may be caused by nitrous acid oxidation[7] of the corresponding *p*-nitrosoanilino compound, which may be derived from N-nitrosoanilino derivative by Fischer–Hepp rearrangement.

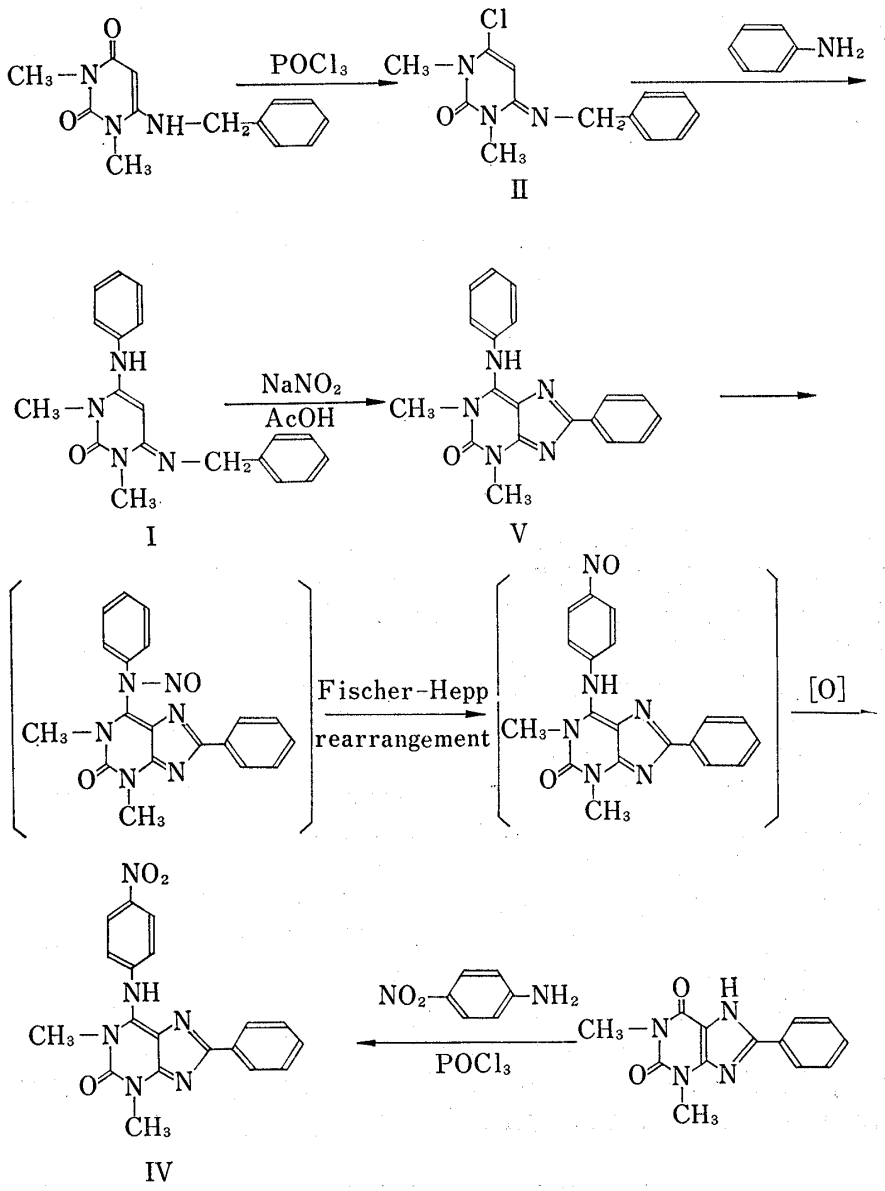

Chart 2

6) K. Senga, S. Nishigaki, M. Higuchi and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **20**, 1473 (1972).
7) It is known that the oxidation of nitroso compounds to nitro compounds can be effected with sodium nitrite in acid; S. Nishigaki, K. Ogiwara and F. Yoneda, *Chem. Pharm. Bull.* (Tokyo), **19**, 418 (1971); F. Yoneda, M. Higuchi, K. Senga, M. Kanahori and S. Nishigaki, *Chem. Pharm. Bull.* (Tokyo), **21**, 473 (1973).

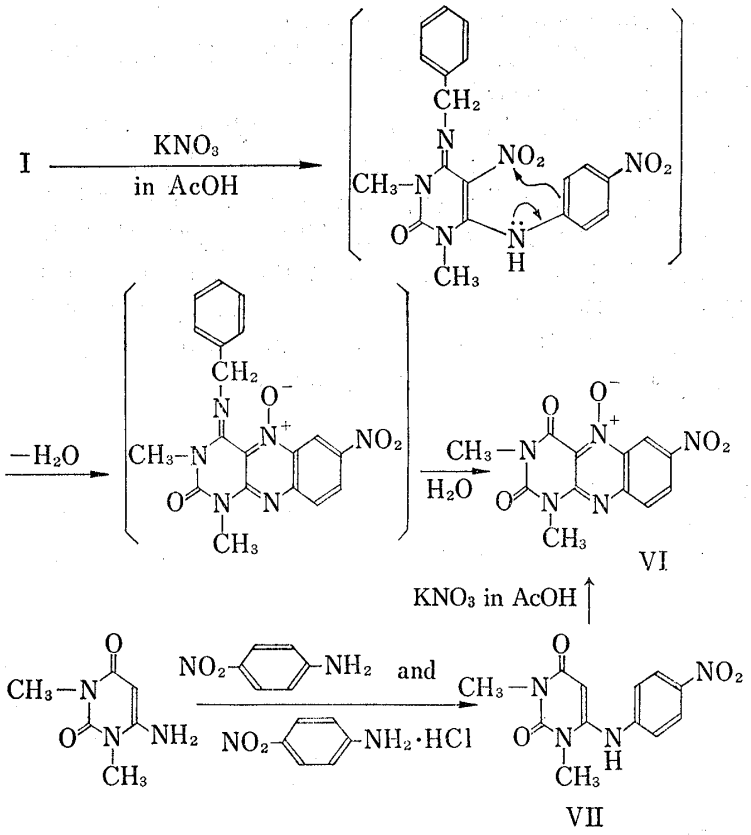

Chart 3

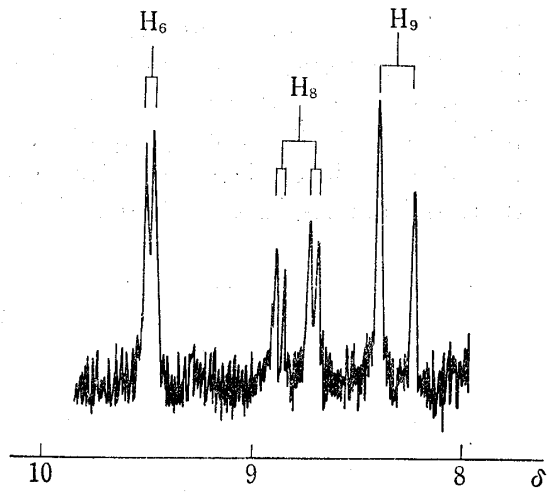

Fig. 1. NMR Spectra of VI

Next, the nitrative cyclization of I was undertaken. Heating I in acetic acid with excess potassium nitrate at 90°[8] for 1 hr, followed by evaporation of the solvent and dilution with water caused separation of a *ca.* 4:1 mixture of 1,3-dimethyl-7-nitroalloxazine-5-oxide (VI) and 1,3-dimethylalloxazine-5-oxide along with a trace of IV, which was barely detected by gas chromatography. The structure of VI was assigned on the basis of the following evidence. Compound (VI) showed the absorptions attributed to a nitro group at 1340 and 1542 cm^{-1} as well as two carbonyl bands at 1720 and 1674 cm^{-1}, but no secondary amino absorption band. The NMR spectrum (CF_3COOH) of VI showed two singlets of N-methyl protons (δ 3.68 and δ 4.02), two aryl protons of 8-position (δ 8.33; q, J=2.4 and 9.6 Hz) and 9-position (δ 8.80; d, J=9.6 Hz), and an aryl proton of 6-position (δ 9.5; d, J=2.4 Hz) (Fig. 1). The mass spectrometry reveals a parent ion (*m/e* 303) and a strong M-16 peak (*m/e* 287) which indicated the presence of a labile oxygen, probably an N-oxide.[9] The structure of VI was finally established by the nitrative cyclization[4] of 1,3-dimethyl-6-*p*-nitroanilinouracil (VII) to 1,3-dimethyl-7-nitroalloxazine-5-oxide (VI). The nitrative cyclization of 6-anilino-1,3-dimethyluracil to 1,3-dimethylalloxazine does not undergo the introduction of nitro group to the benzene ring. Therefore, the nitration to the *para*-position of the anilino group *prior* the cyclization would be presumed and after the cyclization the hydrolysis of benzylimino group could occur.

From the above observations, it is concluded that path a is favored in the nitrosative cyclization, while path b is rather predominant in the nitrative cyclization under the conditions employed.

8) Reactions at higher temperature led to the partial decomposition of the product.
9) For recent review on the mass spectrum of heterocycle N-oxide, see Q.N. Porter and J. Baldas, "Mass Spectrometry of Heterocyclic Compounds," Wiley-Interscience, 1971, for example p. 384.

Experimental[10]

N-Benzyl-6-chloro-1,3-dimethylcytosine (II)[5]——A mixture of 19.6 g (0.08 mole) of 6-benzylamino-1,3-dimethyluracil and 100 ml of $POCl_3$ was violently refluxed at 240° (oil bath) for 3 hr. After the excess of $POCl_3$ was evaporated under reduced pressure, the residue was diluted with 100 ml of H_2O and the solution was made alkaline with 5% aqueous NH_3. The crystals thus separated were collected by filtration, washed with H_2O, dried and recrystallized from aqueous EtOH to give 17.9 g (58%) of colorless needles, mp 81°. *Anal.* Calcd. for $C_{13}H_{14}ON_3Cl$: C, 59.21; H, 5.35; N, 15.93. Found: C, 59.09; H, 5.36; N, 16.02.

6-Benzylamino-1,3-dimethyl-4-N-phenylcytosine (I)——To a solution of 2.6 g (0.01 mole) of II in 100 ml of EtOH was added 1.9 g (0.02 mole) of aniline and the mixture was refluxed for 2 hr. After evaporation of the solvent, 50 ml of H_2O was added to the resulting residue. The crystals which separated were collected by filtration, washed with H_2O, and dried. Recrystallization from EtOH gave 2.8 g (88%) of colorless needles, mp 260°. Mass Spectrum: *m/e* 320 (M^+). *Anal.* Calcd. for $C_{19}H_{20}ON_4$: C, 71.22; H, 6.29; N, 17.49. Found: C, 71.30; H, 6.28; N, 17.29.

Nitrosative Cyclization of I. Formation of 1,3-Dimethyl-6-*p*-nitroanilino-8-phenyl-6-deoxytheophylline (IV)——A mixture of 0.64 g (0.002 mole) of I and 0.69 g (0.01 mole) of $NaNO_2$ in 20 ml of AcOH was refluxed at 120° for 2 hr. After AcOH was removed, 100 ml of H_2O was added to the residue. The yellow crystals were collected by filtration and dissolved in 20 ml of EtOH and then chromatographed on alumina using chloroform as the eluate to separate 0.4 g (53%) of IV. Recrystallization from EtOH gave yellow needles, mp 285°, which were in all respects identical with an authentic sample prepared by the alternative synthesis described below. Mass Spectrum: *m/e* 376 (M^+). *Anal.* Calcd. for $C_{19}H_{16}O_3N_6$: C, 60.63; H, 4.29; N, 22.33. Found: C, 60.49; H, 4.23; N, 22.30.

1,3-Dimethyl-6-*p*-nitroanilino-8-phenyl-6-deoxytheophylline (IV)——Method A: A mixture of 0.51 g (0.002 mole) of 8-phenyltheophylline, 5 ml of $POCl_3$, 2 ml of sulfolane[11] and 0.83 g (0.006 mole) of *p*-nitroaniline was refluxed for 3 hr at 250—260°. After excess $POCl_3$ was removed under reduced pressure, the resulting syrupy residue was diluted with 30 ml of 5% aqueous NH_3. After standing for 1 hr, the insoluble materials were collected by filtration, washed with H_2O and dried to give 0.68 g (90%) of yellow powder. Recrystallization of EtOH gave yellow needles, mp 283°.

Method B: A mixture of 0.33 g (0.001 mole) of 6-anilino-8-phenyltheophylline (V) and 0.35 g (0.005 mole) of $NaNO_2$ in 10 ml of AcOH was refluxed at 120° for 2 hr. After AcOH was removed, 50 ml of H_2O was added to the residue. The yellow crystals which separated were collected by filtration and recrystallized from EtOH to give yellow needles, mp 283°, in almost quantitative yield.

Nitrative Cyclization of I. Formation of 1,3-Dimethyl-7-nitro-alloxazine-5-oxide (VI)——To a solution of 0.32 g (0.001 mole) of I in 10 ml of AcOH was added 0.3 g (0.003 mole) of KNO_3 and heated at 90° for 1 hr. After AcOH was removed, 30 ml of H_2O was added to the residue. The crystals thus separated were collected by filtration, washed with H_2O and dried to give yellow crystals (a *ca.* 4: 1 mixture of 1,3-dimethyl-7-nitro-alloxazine-5-oxide (VI) and 1,3-dimethylalloxazine-5-oxide contaminated by a trace of IV by gas chromatography). Recrystallization from aqueous AcOH caused separation of 0.2 g (67%) of VI, mp 248°, which was in all respects identical with an authentic sample prepared by the alternative route described below. Mass Spectrum: *m/e* 303 (M^+). *Anal.* Calcd. for $C_{12}H_{19}O_5N_5$: C, 47.53; H, 2.99; N, 23.10. Found: C, 47.29; H, 2.98; N, 23.38.

1,3-Dimethyl-6-*p*-nitroanilinouracil (VII)——To a mixture of 2.8 g (0.02 mole) of *p*-nitroaniline and 2.8 g (0.016 mole) of *p*-nitroaniline hydrochloride was added 3.1 g (0.02 mole) of 6-amino-1,3-dimethyluracil and thoroughly mixed and then the mixture was fused at 160° for 6 hr. After cooling, the reaction mixture was crushed in H_2O, collected by filtration, and washed with H_2O. The crushed mass was recrystallized from DMF to give 1.4 g (25%) of dark yellow needles, mp 260°. *Anal.* Calcd. for $C_{12}H_{12}O_4N_4$: C, 52.12; H, 4.38; N, 20.28. Found: C, 51.93; H, 4.40; N, 20.07.

1,3-Dimethyl-7-nitroalloxazine-5-oxide (VI)——A mixture of 0.55 g (0.002 mole) of VII and 0.51 g (0.005 mole) of KNO_3 in 15 ml of AcOH and 2 ml of H_2SO_4 was heated at 90° for 1 hr. The reaction mixture was evaporated *in vacuo* and the resulting residue was diluted with 30 ml of H_2O. The crystals which separated were collected by filtration and recrystallized from DMF to give 0.55 g (90%) of yellow crystals, mp 248°.

10) All melting points are corrected and were determined on a Mettler FP-1 apparatus. NMR spectra were determined at 60 MHz using tetramethylsilane as the internal standard. Chemical shifts were expressed in δ value.

11) Sulfolane was used as an inert, high boiling solvent.