

# A Synthesis of Alloxazine 5-Oxides by the Reaction of 6-Anilinouracils with Nitric Acid and 4-Phenylurazole

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The treatment of 6-anilinouracils with a mixture of nitric acid and 4-phenylurazole (which is virtually a mixture of nitrous acid and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)) in dioxane gave the corresponding alloxazine 5-oxides exclusively. This reaction involves the nitrosative cyclization of 6-anilinouracils by nitrous acid, followed by the dehydrogenation of the hydroxylamine intermediates with PTAD. 6-Anilinouracils react with PTAD to give the corresponding Michael-type adducts, 6-anilino-5-(4-phenylurazol-1-yl)uracils.

Nitric acid quickly oxidizes 4-phenylurazole (I) to 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) (II),<sup>2)</sup> while nitric acid itself should be reduced to nitrous acid. Therefore, the mixture of nitric acid and 4-phenylurazole (which is virtually the mixture of nitrous acid and PTAD) must have oxidizing as well as nitrosating power. From these considerations, we have examined the utility of this mixture for the synthesis of alloxazine 5-oxides by the oxidative cyclization of 6-anilinouracils.

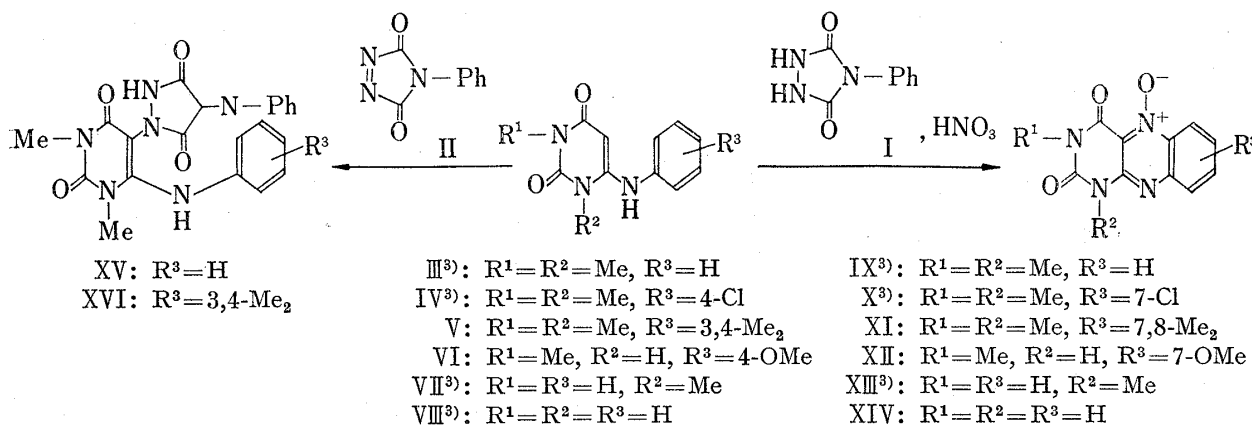


Chart 1

Thus I was added portion by portion to a suspension of a 6-anilinouracil in dioxane including nitric acid under stirring and the mixture was warmed at about 40° for a while to give the corresponding alloxazine 5-oxide exclusively. The structures of these alloxazine 5-oxides thus obtained were determined by satisfactory analytical and spectral data and furthermore some of them were identified with the authentic samples prepared by alternative synthesis.<sup>3)</sup>

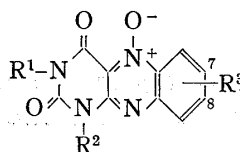
This reaction is initiated without doubt by the nitrosative cyclization of 6-anilinouracils, followed by the dehydrogenation of the hydroxylamine intermediates with PTAD generated *in situ*, on the basis of following facts. (1) The initial reaction mixture included PTAD, which was rapidly consumed for the oxidation and eventually decomposed to unknown substances

1) Location: Oe-honmanchi, Kumamoto 862, Japan.

2) W. Ried and S.H. Lim, *Ann.*, **1973**, 129.

3) H. Goldner, G. Dietz, and E. Carstens, *Ann.*, **694**, 142 (1966).

TABLE I. Alloxazine 5-Oxides



Compd. No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	mp (°C)	Yield (%)	Formula	Analysis (%)		
							Calcd. (Found)	C	H N
IX <sup>3)</sup>	Me	Me	H	237	82	C <sub>12</sub> H <sub>10</sub> O <sub>3</sub> N <sub>4</sub>	55.81 (56.03)	3.90 (3.76)	21.70 (21.58)
X <sup>3)</sup>	Me	Me	7-Cl	232	78	C <sub>12</sub> H <sub>9</sub> O <sub>3</sub> N <sub>4</sub> Cl	49.26 (48.96)	3.08 (3.31)	19.14 (19.05)
XI	Me	Me	7,8-Me <sub>2</sub>	242	79	C <sub>14</sub> H <sub>14</sub> O <sub>3</sub> N <sub>4</sub>	58.73 (58.68)	4.93 (5.01)	19.57 (19.39)
XII	Me	H	7-OMe	>320	80	C <sub>12</sub> H <sub>10</sub> O <sub>4</sub> N <sub>4</sub>	52.55 (52.38)	3.68 (3.82)	20.43 (20.51)
XIII <sup>3)</sup>	H	Me	H	>320	84	C <sub>11</sub> H <sub>8</sub> O <sub>3</sub> N <sub>4</sub>	54.10 (54.01)	3.30 (3.35)	22.94 (22.82)
XIV	H	H	H	>320	92	C <sub>10</sub> H <sub>6</sub> O <sub>3</sub> N <sub>4</sub>	52.18 (52.24)	2.63 (2.62)	24.34 (24.29)

(probably polymers). (2) When 6-anilinouracils were treated with nitric acid in dioxane in the absence of I, the reaction did not proceed even on heating and the starting material was recovered. (3) 6-Anilinouracils react with PTAD in dioxane upon heating to give the corresponding Michael-type adducts, 6-anilino-5-(4-phenylurazol-1-yl)uracils, which did not change however to the alloxazine 5-oxides by treatment with both nitric acid and nitrous acid generated from sodium nitrite in acid.

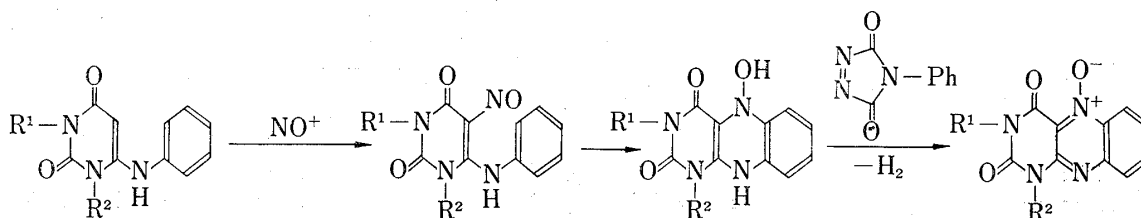


Chart 2

The reaction mechanism is further supported by following facts. Stirring 6-anilinouracil (VIII) in acetic acid with sodium nitrite and PTAD at room temperature gave alloxazine 5-oxide (XIV) as expected. On the other hand, it is known that the usual nitrosation of VIII leads to the exclusive formation of alloxazine.<sup>3)</sup>

Diethyl hydrazodicarboxylate instead of I is also effective for the formation of alloxazine 5-oxides. For example, a mixture of 6-anilino-1,3-dimethyluracil (III), diethyl hydrazodicarboxylate and nitric acid in dioxane was heated at 80° for 1 hr to give 1,3-dimethylalloxazine 5-oxide (IX), although in less satisfactory yield.

#### Experimental<sup>4)</sup>

**1,3-Dimethyl-6-(3,4-xylylidino)uracil (V) and 6-(4-Methoxyphenyl)-3-methyluracil (VI)**—V and VI were prepared by the known procedure.<sup>3)</sup> V: mp 235°. *Anal.* Calcd. for C<sub>14</sub>H<sub>17</sub>O<sub>2</sub>N<sub>3</sub>: C, 64.84; H, 6.61; N, 16.21. Found: C, 64.64; H, 6.27; N, 16.36. VI: mp 272°. *Anal.* Calcd. for C<sub>12</sub>H<sub>13</sub>O<sub>3</sub>N<sub>3</sub>: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.20; H, 5.28; N, 16.82.

4) Melting points were determined on a Yanagimoto micro-melting point apparatus and uncorrected.

**Alloxazine 5-Oxides**—General Procedure: 4-Phenylurazole (I) (0.015 mole) was added portion by portion to a stirred suspension of 6-anilino-uracil (0.01 mole) in dioxane (20 ml) including nitric acid ( $d=1.38$ , 1 ml) at room temperature and the mixture was warmed at 40° for 30 min and then cooled with ice-water. The crystals thus separated were collected by filtration, dried and recrystallized from acetone or DMF to give the corresponding alloxazine 5-oxides as yellow needles.

**6-Anilino-1,3-dimethyl-5-(4-phenylurazol-1-yl)uracil (XV)**—To a suspension of 6-anilino-1,3-dimethyluracil (III) (0.2 g, 0.0009 mole) in dioxane (5 ml) was added PTAD (0.2 g, 0.0011 mole) and the mixture was heated at 90° for 10 min. After the solution was evaporated *in vacuo* to dryness and the residue was recrystallized from EtOH to give 0.27 g (75%) of colorless crystals, mp 235—236°. Mass Spectrum  $m/e$ : 406 ( $M^+$ ). IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 3310 (NH), 1776, 1715, 1696 (CO). Anal. Calcd. for  $\text{C}_{20}\text{H}_{18}\text{O}_4\text{N}_6$ : C, 59.10; H, 4.46; N, 20.68. Found: C, 59.23; H, 4.40; N, 20.37.

**1,3-Dimethyl-5-(4-phenylurazol-1-yl)-6-(3,4-xylylidino)uracil (XVI)**—To a stirred suspension of 1,3-dimethyl-6-(3,4-xylylidino)uracil (V) (0.6 g, 0.0023 mole) was added PTAD (0.6 g, 0.0034 mole) in dioxane (15 ml) and the mixture was heated at 90° for 10 min. The solution was evaporated to dryness and the residue was recrystallized from EtOH to give 0.7 g (70%) of colorless powder, mp 242°. Mass Spectrum  $m/e$ : 434 ( $M^+$ ). IR  $\nu_{\text{max}}^{\text{Nujol}}$   $\text{cm}^{-1}$ : 3340 (NH), 1780, 1700 (CO). Anal. Calcd. for  $\text{C}_{22}\text{H}_{22}\text{O}_4\text{N}_6$ : C, 60.82; H, 5.10; N, 19.35. Found: C, 60.79; H, 5.13; N, 19.13.

**Nitrosative Cyclization of 6-Anilino-uracil (VIII) in the Presence of PTAD**—To a stirred solution of VIII (0.2 g, 0.001 mole) in AcOH (10 ml) was added saturated aqueous solution of  $\text{NaNO}_2$  (0.1 g, 0.0015 mole) and PTAD (0.2 g, 0.0011 mole) under cooling at 5°. The mixture was stirred at room temperature for 30 min, during which time the reaction mixture changed its colour from red to yellow. The reaction mixture was diluted with  $\text{H}_2\text{O}$  and allowed to stand overnight at room temperature. The crystals thus separated were collected by filtration, washed with  $\text{H}_2\text{O}$  and recrystallized from DMF to give 1.8 g (80%) of alloxazine 5-oxide (XIV).

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## Synthèse de Pyrimidines et de Pyrazoles à partir d'Acyl-3 halogéno-5 benzofurannes

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En partant des chloro-5 ou bromo-5 salicylaldéhydes, nous avons synthétisé quatre acyl-3 halogéno-5 benzofurannes: acétyl-3 chloro-5-(1), benzoyl-3 chloro-5-(2), acétyl-3 bromo-5-(3) et benzoyl-3 bromo-5-(4) éthyl-2 benzofurannes. Ces acyl-3 benzofurannes halogénés peuvent être transformés en (halogéno-5 hydroxy-2 phényl)-5 pyrimidines, par la guanidine, la thiourée, l'acétamidine et la cyanoguanidine, mais pas par l'urée. On peut classer les aptitudes des réactifs diamminés à donner des pyrimidines avec les acyl-3 halogéno-5 benzofurannes dans le même ordre que celui que nous avons déjà relevé pour les benzofurannes non-halogénés: guanidine > thiourée > acétamidine > urée.

Dans plusieurs mémoires antérieurs, nous avons reporté<sup>2)</sup> que des réactifs nucléophiles tels que la guanidine et ses quelques dérivés, l'acétamidine, la thiourée et l'urée peuvent, dans diverses conditions, attaquer l'hétérocycle des benzofurannes substitués en position

1) Adresse: 5-9-1, Shirokane, Minato-ku, Tokyo.

2) a) K. Takagi, M. Hubert-Habart et R. Royer, *Compt. Rend.*, **260**, 5302 (1965); b) M. Hubert-Habart, K. Takagi, A. Cheutin et R. Royer, *Bull. Soc. Chim. France*, **1966**, 1587; c) M. Hubert-Habart, K. Takagi et R. Royer, *Bull. Soc. Chim. France*, **1967**, 356; d) M. Hubert-Habart, K. Takagi, G. Menichi, A. Cheutin, M.-L. Devoye et R. Royer, *Chim. Thérap.* (Paris), **1968**, 280; e) K. Takagi et M. Hubert-Habart, *Chim. Thérap.* (Paris), **1970**, 264; f) K. Takagi et T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **20**, 2053 (1972); g) M. Hubert-Habart, C. Pène, G. Bastian et R. Royer, *Chim. Thérap.* (Paris), **1973**, 314.