Reaction of 6-Ethylamino-3-methyluracil with Nitrobenzenes

Takashi Harayama, Hideto Jinno, Yasuhiro Tezuka and Fumio Yoneda*

Faculty of Pharmaceutical Sciences, Kyoto University,
Sakyo-ku, Kyoto 606, Japan

Received July 29, 1985

Reaction of 6-ethylamino-3-methyluracil (**1**) with nitrobenzenes in hexamethylphosphoric triamide gave isoalloxazines in 3.8-18 percent yield. In the presence of potassium carbonate, reaction of **1** with *o*-fluoronitrobenzene afforded 5-substituted uracil **3** in moderate yield.

J. Heterocyclic Chem., **23**, 1507 (1986).

Isoalloxazines have been used for studies of flavin-catalyzed redox reactions [1-3] and various synthetic methods of the isoalloxazine ring system have been developed [4-7]. In 1976, one of the authors (Yoneda) reported a new synthetic method of isoalloxazines *via* an intermediate **A** in Scheme 1 [5]. From this mechanism, we envisioned that if an intermediate **B** was prepared by substitution reaction of *o*-halogenonitrobenzene with 6-aminouracil (**1**), a similar cyclization would proceed to produce isoalloxazines. Then, reaction of 6-ethylamino-3-methyluracil (**1**) with *o*-fluoronitrobenzene in several solvents was examined. The reaction afforded isoalloxazine **2** only in very poor yield as summarized in Table 1 [8]. Interestingly, in the presence of potassium carbonate (entries 2 and 4), 5-substituted uracil **3** was obtained as the major product, the structure of which was assigned on the basis of its spectral and analytical properties. Its ^{1}H-nmr spectrum showed the presence of ethylamino group at δ 6.38 (t, J = 6.1 Hz, 1H; disappeared by adding deuterium oxide), 3.20 (dq, J = 6.1, 7.1 Hz, 2H; changed to q, J = 7.1 Hz by adding deuterium oxide), and 1.00 (t, J = 7.1 Hz, 3H), but no olefinic proton. Therefore, the product can be represented by formula **3**. In the reaction of **1** with *o*-fluoronitrobenzene in hexamethylphosphoric triamide (HMPA) (entry 3), came out an insoluble compound **6**, which was also obtained by heating **1** in HMPA. The structure of **6** was elucidated on the basis of elemental analyses ($C_{15}H_{22}N_6O_4$), mass spectrum (M^+, 350), and other spectroscopic evidences. Thus, the ^{1}H-nmr spectrum of **6** showed the signal due to methylene at δ 3.53 (s) besides the signals due to *N*-ethyl and *N*-methyl groups, but no signal due to olefinic proton. Although mechanism of the formation of **6** leaves ambiguous, the source of methylene group in **6** would come from HMPA.

Scheme 1

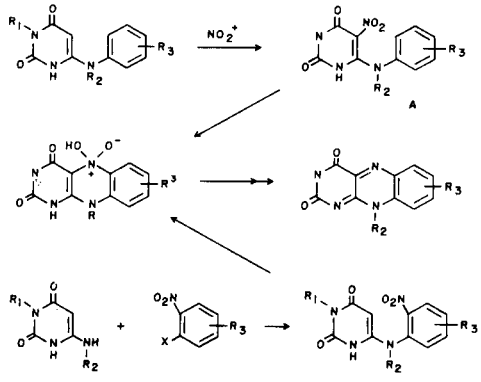


Table 1

Reaction of 6-Ethylamino-3-methyluracil (**1**) with *o*-Fluoronitrobenzene

Entry	Reaction Condition	**2**	**3**	**4a**	**5**	**6**
1	DMF, 48 hours, 160°	0.5%	---	2.7%	22%	---
2	DMF, potassium carbonate (2 eq) 40 hours, 160°	---	59%	0.6%	2.1%	---
3	HMPA, 3 hours, 160°	3.8%	---	---	86%	14%
4	HMPA, potassium carbonate (2 eq) 3 hours, 160°	---	52%	---	---	---
5	sulfolane, 72 hours, 160° [a]	0.9%	---	29%	---	---
6	*N*-methylpyrrolidone, 30 hours, 160° [b]	3.5%	---	16%	---	---

[a] *o*-Methylaminonitrobenzene (**4b**) was obtained in 0.5% yield. [b] The compound **4b** was obtained in 9.8% yield.

Subsequently, reaction of **1** with *o*-chloronitrobenzene in HMPA was examined. The reaction gave a mixture of isoalloxazine **2** and 6-chloroisoalloxazine **7** [9] in a few percent yield along with **5** (41%) and **6** (27%). This result indicates that the intermediate **C** (R = Cl) was initially formed and subsequent oxidative cyclization afforded two products **2** and **7** as shown in Scheme 2. Therefore, we considered that reaction of **1** with nitrobenzene itself might yield **2**. The reaction was examined and the results are summarized in Table 2. The reactions in HMPA (entries 4 and 5) gave the expected isoalloxazine **2** though in

Scheme 2

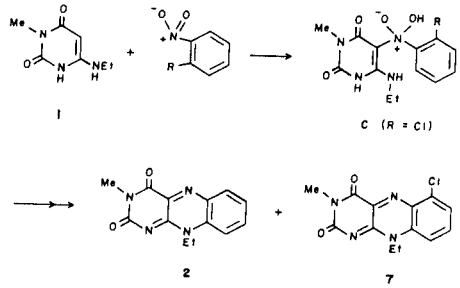


Table 2

Reaction of 6-Ethylamino-3-methyluracil (**1**) with Nitrobenzene

Entry	Reaction Condition	**2**	**6**
1	no solvent, 7 hours, 160°	---	---
2	DMF, 86 hours, 160°	---	---
3	*N*-methylpyrrolidone, 2 hours, 160°	---	---
4	HMPA, 8 hours, 160° [a]	8.5%	67%
5	HMPA, 62 hours, 160°	13%	66%

[a] Addition of hexamethylphosphorous triamide or tributylphosphite to a reaction mixture afforded no isoalloxazine **2**.

about ten percent yield. The results suggest that the reaction of two equivalents of **1** with one equivalent of dinitrobenzene would give benzodipteridine (s), e.g. $\mathbf{D_1}$ and/or $\mathbf{D_2}$, as shown in Scheme 3. However, *p*-dinitrobenzene gave *p*-dimethylaminonitrobenzene (**8**) and **6** in 51% and 47% yields, respectively, while *m*-dinitrobenzene gave 7-nitroisoalloxazine (**9**) and **6** in 18% and 48% yields, respectively.

Scheme 3

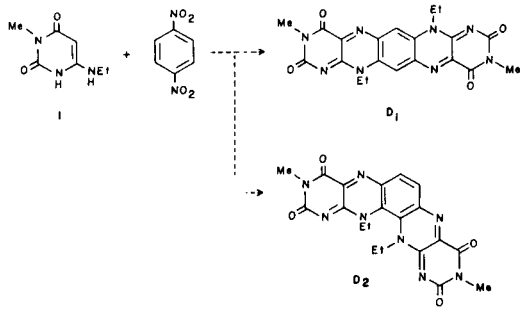
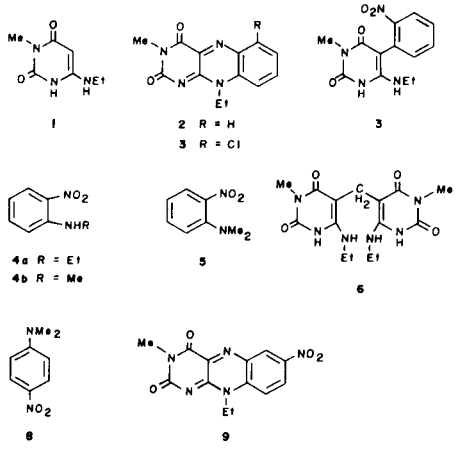


Chart 1



EXPERIMENTAL

Melting points were determined on an electrically heated block and are uncorrected. The ^{1}H-nmr spectra were recorded on a JEOL FX-200 spectrometer in deuteriochloroform solution unless otherwise stated. The ir spectra were recorded on a Shimazu IR 400 spectrometer in chloroform solution unless otherwise stated. Mass spectra were taken with a JEOL JMS-01SG-2 spectrometer using a heated direct inlet system. Column chromatography was performed using 70-230 mesh (Merck) silica gel and preparative tlc on silica gel (Merck GF 254).

Reaction of 6-Ethylamino-3-methyluracil (**1**) with *o*-Fluoronitrobenzene.

A mixture of **1** (1 mmole) and *o*-fluoronitrobenzene (1 mmole) in the solvent (2 ml) was stirred under the reaction conditions indicated in Table 1. The reaction mixture was diluted with hexane except entry 3 in Table 1 and chromatographed on silica gel. In entry 3, the reaction mixture was diluted with ether and an insoluble compound **6** was filtered off. The filtrate was concentrated to dryness *in vacuo* and the residue in hexane was chromatographed on silica gel. Elution with hexane gave the products **4a**, **4b** and/or **5**. These products were separated by preparative tlc using a hexane-ether (95:5) solvent system. Elution with chloroform afforded **2** and with 5% methanol-chloroform **3**.

10-Ethyl-3-methylisoalloxazine (**2**).

This compound had mp 293-295° and was identified with an authentic sample [5].

6-Ethylamino-3-methyl-5-(2-nitrophenyl)uracil (**3**).

This compound had mp 259-260° (orange prisms from chloroform-methanol); ^{1}H-nmr: δ 1.00 (t, 3H, J = 7.1 Hz), 3.06 (s, 3H), 3.20 (dq, 2H, J = 6.1, 7.1 Hz, changed to q, J = 7.1 Hz by adding deuterium oxide), 6.38 (t, 1H, J = 6.1 Hz, exchangeable with deuterium oxide), 7.39 (dd, 1H, J = 1.4, 7.5 Hz), 7.52 (ddd, 1H, J = 1.4, 7.3, 8.1 Hz), 7.68 (ddd, 1H, J = 1.2, 7.3, 7.5 Hz), 7.96 (dd, 1H, J = 1.2, 8.1 Hz), 10.71 (s, 1H, exchangeable with deuterium oxide); ir (Nujol): 3350, 3150, 1690, 1610 and 1585 cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.49; H, 4.83; N, 19.13.

o-Ethylaminonitrobenzene (**4a**).

This compound had ^{1}H-nmr: δ 1.38 (t, 3H, J = 7.2 Hz), 3.36 (dq, 2H, J = 5.1, 7.2 Hz), 6.63 (ddd, 1H, J = 1.2, 6.8, 8.5 Hz), 6.85 (dd, 1H, J = 1.2, 8.4 Hz), 7.43 (ddd, 1H, J = 1.6, 6.8, 8.4 Hz), 8.17 (dd, 1H, J = 1.6, 8.5 Hz); ir: 3400, 1620, 1575, 1515 and 1355 cm^{-1}; ms: 166 (M$^+$), and was identified with an authentic sample [10].

o-Methylaminonitrobenzene (**4b**).

This compound had mp 37-38° (lit mp 36-37°) [10]; ^{1}H-nmr: δ 3.03 (d, 3H, J = 5.1 Hz), 6.65 (ddd, 1H, J = 1.2, 7.0, 8.6 Hz), 6.84 (dd, 1H, J = 1.2, 8.1 Hz), 7.47 (ddd, 1H, J = 1.6, 7.0, 8.1 Hz), 8.18 (dd, 1H, J = 1.6, 8.6 Hz); ir: 3450, 1620, 1575, 1515 and 1355 cm^{-1}; ms: 152 (M$^+$), and was identified with an authentic sample [10].

o-Dimethylaminonitrobenzen (**5**).

This compound had ^{1}H-nmr: δ 2.89 (s, 6H), 6.81 (ddd, 1H, J = 1.2, 7.1, 8.3 Hz), 7.02 (dd, 1H, J = 1.2, 8.5 Hz), 7.40 (ddd, 1H, J = 1.7, 7.1, 8.5 Hz), 7.76 (dd, 1H, J = 1.7, 8.3 Hz); ir: 1610, 1540, 1525 and 1350 cm^{-1}; ms: 166 (M$^+$), and was identified with an authentic sample [11].

Bis(6-ethylamino-3-methyluracil-5-yl)methane (**6**).

This compound had mp >290°; ^{1}H-nmr (DMSO-d$_6$): δ 1.38 (t, 6H, J = 7.2 Hz), 3.42 (q, 4H, J = 7.2 Hz), 3.43 (s, 6H), 3.53 (s, 2H); ir (Nujol): 3150, 1700, 1650, 1600 and 1585 cm^{-1}; ms: 350 (M$^+$).

Anal. Calcd. for $C_{15}H_{22}N_6O_4$: C, 51.42; H, 6.33; N, 23.99; O, 18.27. Found: C, 51.23; H, 6.35; N, 24.14; O, 18.23.

Reaction of **1** with *o*-Chloronitrobenzene in HMPA.

A mixture of **1** (169.2 mg, 1.0 mmole) and *o*-chloronitrobenzene (175.8 mg, 1.1 mmoles) in HMPA (1 ml) was stirred for 2 hours at 160° under an argon atmosphere. The reaction mixture was diluted with ether and the crystalline compound was filtered off. This crystalline compound was washed with chloroform-methanol to be identified with **6** (47 mg, 27%).

The filtrate was concentrated *in vacuo* and chromatographed on silica gel. Elution with chloroform gave **5** (73.4 mg, 41%) and further elution with the same solvent provided a mixture (8.1 mg) of **2** and 6-chloroisoalloxazine (**7**).

6-Chloro-3-methylisoalloxazine (**7**).

To a solution of *o*-chloronitrobenzene (1.554 g, 9.87 mmoles) and ammonium chloride (1.238 g, 23.4 mmoles) in water-methanol (4:1, 40 ml) was added zinc dust (1.538 g, 23.52 mmoles) over 10 minutes under stirring. After the reaction mixture was stirred for another 10 minutes, the precipitate was filtered off. The filtrate was diluted with water and extracted with ether. The extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The residue in dry ether (10 ml) was added to a solution of diethyl azodicarbonate (1.557 g, 8.95 mmoles) in dry ether (10 ml). The reaction mixture was stirred for 10 minutes. The precipitate was filtered off and the filtrate was concentrated *in vacuo* to give a crude *o*-chloronitrosobenzene. A solution of **2** (2.682 g, 15.9 mmoles) and the crude *o*-chloronitrosobenzene [12] obtained above in dimethyl formamide (2 ml) was refluxed for 2 hours under an argon atmosphere. The reaction mixture was concentrated *in vacuo*. The residue was triturated with ether and the resulting crystalline solid was collected. The solid in chloroform was chromatographed on silica gel. Elution with chloroform gave **2** (15.9 mg, 0.6%), mp 294-296° (from ethanol). Successive elution with chloroform gave a mixture (413 mg) of **2** and 6-chloro-3-methylisoalloxazine (**7**). Further elution with the same solvent gave **7** (355.2 mg, 12%), mp >290° (from chloroform-methanol), orange needles: ^{1}H-nmr: δ 1.51 (t, 3H, J = 7.1 Hz), 3.53 (s, 3H), 4.78 (q, 2H, J = 7.1 Hz), 7.56 (dd, 1H, J = 1.5, 8.1 Hz), 7.70 (dd, 1H, J = 1.5, 8.1 Hz), 7.81 (dd, 1H, J = 8.1, 8.1 Hz); ir: 1715, 1665, 1605, 1585 and 1565 cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}ClN_4O_2$: C, 53.71; H, 3.81; N, 19.27. Found: C, 53.74; H, 3.71; N, 19.21.

Reaction of **1** with Nitrobenzene.

A mixture of **1** (1 mmole) and nitrobenzene (1 mmole) in solvent (1 ml) was stirred under reaction condition indicated in Table 2. After removal of solvent *in vacuo*, the residue was diluted with chloroform-methanol and the precipitate **6** was filtered off. The filtrate was concentrated to dryness and the residue in chloroform was chromatographed on silica gel. Elution with chloroform provided **2**, which was identified with an authentic sample [5].

Reaction of **1** with *p*-Dinitrobenzene.

A mixture of **1** (169.4 mg, 1.0 mmole) and *p*-dinitrobenzene (91.8 mg, 0.55 mmole) in HMPA (1 ml) was stirred at 160° for 8 hours under an argon atmosphere. The reaction mixture was diluted with chloroform-methanol and the insoluble compound **6** (82.5 mg, 47%) was filtered off. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica gel. Elution with chloroform gave *p*-dimethylaminonitrobenzene (**8**) (45.9 mg, 51%), mp 171-172° (yellow needles from ethanol) (lit mp 163-166°) [13]; ^{1}H-nmr: δ 3.11 (s, 6H), 6.58 (dd, 2H, J = 2.2, 7.3 Hz), 8.09 (dd, 2H, J = 2.2, 7.3 Hz); ir: 1595, 1520, 1490 and 1320 cm^{-1}; ms: 166 (M^+).

Reaction of **1** with *m*-Dinitrobenzene.

A mixture of **1** (381 mg, 1.5 mmoles) and *m*-dinitrobenzene (126 mg, 0.75 mmole) in HMPA (2 ml) was stirred at 160° for 6 hours. After evaporation of solvent, the residue was diluted with chloroform-methanol and the precipitate **6** (190.8 mg, 48%) was filtered off. The filtrate was concentrated *in vacuo* and was chromatographed on silica gel. Elution with chloroform gave 7-nitro-3-methylisoalloxazine **9** (39.2 mg, 18%), mp >279°, (from chloroform-methanol), yellow prisms; ^{1}H-nmr: δ 1.54 (t, 3H, J = 7.2 Hz), 3.55 (s, 3H), 4.80 (q, 2H, J = 7.2 Hz), 7.77 (d, 1H, J = 9.4 Hz), 8.68 (dd, 1H, J = 2.7,9.4 Hz), 9.20 (d, 1H, J = 2.7 Hz); ir: 1715, 1665, 1570, 1530 and 1345 cm^{-1}.

Anal. Calcd. for $C_{13}H_{11}N_5O_4$: C, 51.83; H, 3.68; N, 23.25. Found: C, 51.83; H, 3.56; N, 23.08.

REFERENCES AND NOTES

[1] C. Walsh, *Acc. Chem. Res.*, **13**, 148 (1980).

[2] T. C. Bruice, *Acc. Chem. Res.*, **13**, 256 (1980).

[3] T. C. Bruice, in "Progress in Bioorganic Chemistry", Vol **4**, E. T. Kaiser and F. T. Kezdy, ed, John Wiley & Sons, Inc., New York, NY, 1976, p 1.

[4] F. Yoneda, K. Shinozuka, K. Tsukuda and A. Koshiro, *J. Heterocyclic Chem.*, **16**, 1365 (1979).

[5] F. Yoneda, Y. Sakuma, M. Ichiba and K. Shinomura, *J. Am. Chem. Soc.*, **98**, 830 (1976).

[6] M. Sako, Y. Kozima, K. Hirota and Y. Maki, *J. Chem. Soc., Chem. Commun.*, 1691 (1984).

[7] J. P. Lambooy, in "Heterocyclic Compounds", Vol 9, R. C. Elderfield, ed, John Wiley & Sons, Inc., New York, NY, 1957, p 118.

[8] Ethylamino and methylamino groups in **4a** and **4b** would come from **1** and/or solvent.

[9] An authentic sample of **7** was prepared from **1** and *o*-chloronitrosobenzene [12] as described in Experimental.

[10] R. Weidenhagen and G. Train, *Chem. Ber.*, **75**, 1936 (1942).

[11] H. H. Hodgson and A. Kershaw, *J. Chem. Soc.*, 277 (1930).

[12] E. C. Taylor and F. Yoneda, *J. Chem. Soc., Chem. Commun.*, 199 (1967).

[13] A. E. Senear, M. M. Rapport, J. F. Mead, J. T. Maynard and J. B. Koepfli, *J. Org. Chem.*, **11**, 378 (1946).