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THE FACILE SYNTHESIS OF 6-AZAPURINES BY TRANSFORMATION OF TOXOFLAVINS (7-AZAPTERIDINES)

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Abstract – This paper describes a reliable and facile synthesis of 6-azapurines (1,5-dimethyl-1*H*-imidazo[4,5-*e*][1,2,4]triazin-6(5*H*)-ones) by treatment of toxoflavins (7-azapteridines) with 10% aqueous sodium hydroxide at 5–25 °C along with a benzilic acid type rearrangement, followed by decarboxylation and oxidation by air. Furthermore, heating the **6**-azapurines in 10% ethanolic sodium hydroxides afforded the corresponding 1,2,4-triazine-5,6(1*H*,4*H*)-diones to be caused by ring fission of the imidazole of 6-azapurines.

As the 7-azapteridine (pyrimido[5,4-*e*][1,2,4]triazines) antibiotics isolated from natural sources, toxoflavin (**1**), fervenulin (**2**) and reumycin (**3**) are known.[1] We have developed several convenient synthetic procedures for the preparation of toxoflavin (**1**) and its 3- and/or 6-substituted derivatives,[2–7] and evaluated their potential anti-viral[7] and antitumor activities[8] and their ability as herbicides.[9] However, we encountered difficulties when attempting to prepare the derivatives possessing a substituent of some kind at the 1-position of the toxoflavin skeleton (**1**). Because, we have previously reported that toxoflavin and its 3-substituted derivatives (**1**) readily undergo demethylation at the 1-position upon heating with some nucleophiles, *e.g.* DMF and dimethylacetamide, to give the corresponding 1-demethyltoxoflavin (reumycins **3**) derivatives, while the nucleophiles themselves were methylated by the methyl group eliminated, and during the reactions novel radical species were observed (Scheme 1).[10,11] On the other hand, the methylation of reumycin and its 3-substituted derivatives (**3**) under alkaline conditions with dimethyl sulfate or methyl iodide in DMF provided not toxoflavins (**1**) but fervenulins (**2**), whose methyl

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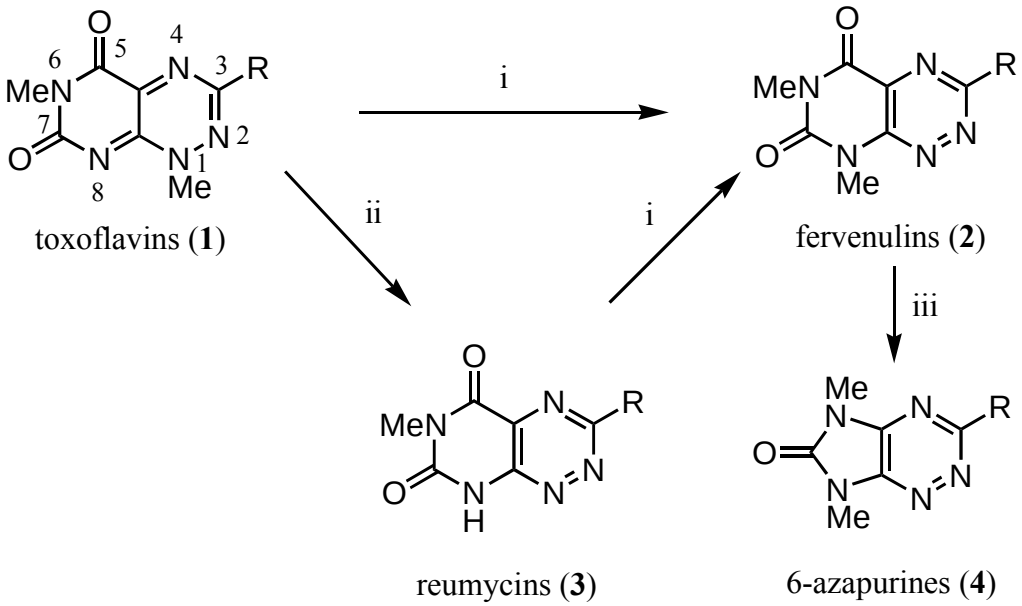
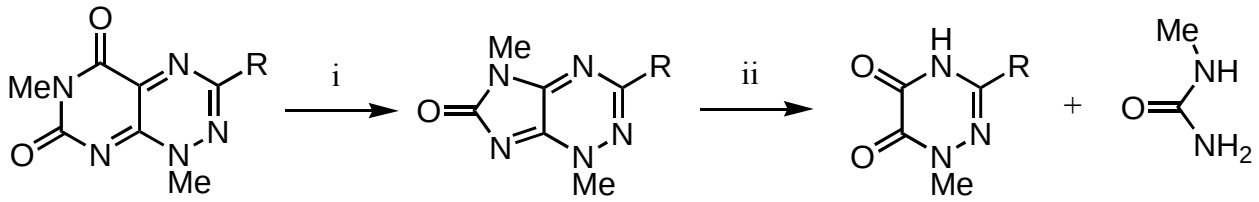
This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.



Scheme 1. *Reagents and conditions:* i, MeI, K_2CO_3, DMF, reflux; ii, DMF, reflux; iii, 10% NaOH in EtOH, 60 °C or reflux.

at the 8-position was stable.[12–15] Heating **2** with alcoholic sodium hydroxide afforded the corresponding 6-azapurines (5,7-dimethyl-5*H*-imidazo[4,5-*e*][1,2,4]triazin-6(7*H*)-ones) (**4**) along with the benzilic acid type rearrangement.[16] We have been thinking that it is impossible to produce such 6-azapurines from toxoflavins (**1**) by the rearrangement up-to-date due to tendency to eliminate the methyl or alkyl by acid, nucleophilic solvent or heating. However, we found now that the methyl group at the 1-position of toxoflavins (**1**) is appreciably stable in alkali solution, not in acid solution, and the toxoflavins (**1**) transformed gradually to the 6-azapurines (1,5-dimethyl-1*H*-imidazo[4,5-*e*][1,2,4]triazin-6(5*H*)-ones) without demethylation. Recent years have seen dramatic development in the synthesis of modified purine derivatives and azapurines as therapeutic agents[17–21] and antiviral agents.[22–25] Herein, we wish to report a further unique synthetic approach to be 6-azapurines (**5**) by the transformation of toxoflavins (7-azapteridines) (**1**) along with a benzilic acid type rearrangement (Scheme 2).

The desired 3-substituted toxoflavins (**1a–l**) were prepared by nitrosative cyclization of the appropriate 6-(2-alkylidene- or 2-benzylidene-1-methylhydrazino)-3-methyluracils according to our previous reports.[1-6,15] Treatment of the 3-substituted toxoflavins (**1a–l**) (2.5 mmol) with 10% aqueous sodium hydroxide (10 mL) under the conditions described in Table 1, followed by neutralization with 10% aqueous hydrochloric acid, and the solution was concentrated to dryness *in vacuo*. The solid thus obtained was recrystallized from a mixture of ethanol and water to afford the corresponding 6-azapurines (1,5-dimethyl-1*H*-imidazo[4,5-*e*][1,2,4]triazin-6(5*H*)-ones) (**5a–l**) as colorless needles in 40–90% yields. Furthermore, treatment of the 6-azapurines (**5e**, **i**, **j**, and **k**) (1.2 mmol) with 10% ethanolic sodium hydroxide (10 mL) under reflux for 6 h, followed by neutralization with glacial acetic acid to deposit the



toxoflavins (**1a–l**) 6-azapurines (**5a–l**) 1,2,4-triazines (**6a–d**)

a: R = H
b: R = Me
c: R = Et
d: R = Pr
e: R = Ph
f: R = 4-F-C_6H_4
g: R = 4-Cl-C_6H_4
h: R = 4-HO-C_6H_4
i: R = 4-Me-C_6H_4
j: R = 4-MeO-C_6H_4
k: R = 3,4,5-$(MeO)_3$-C_6H_2
l: R = 4-Me_2N-C_6H_4

a: R = Ph
b: R = 4-Me-C_6H_4
c: R = 4-MeO-C_6H_4
d: R = 3,4,5-$(MeO)_3$-C_6H_2

Scheme 2. *Reagents and conditions:* i, 10% aq NaOH, 5–25 °C, 1–3 d for R = H and alkyl, 60–70 °C, 10–45 min for R = aryl; ii, 10% NaOH in EtOH, reflux, 6 h.

Table 1. Formation of 6-azapurines (**5a–l**) and 1,2,4-triazines (**6a–d**) by reaction of toxoflavins (7-azapteridines) (**1a–l**) with 10% NaOH aqueous solution or ethanolic solution.

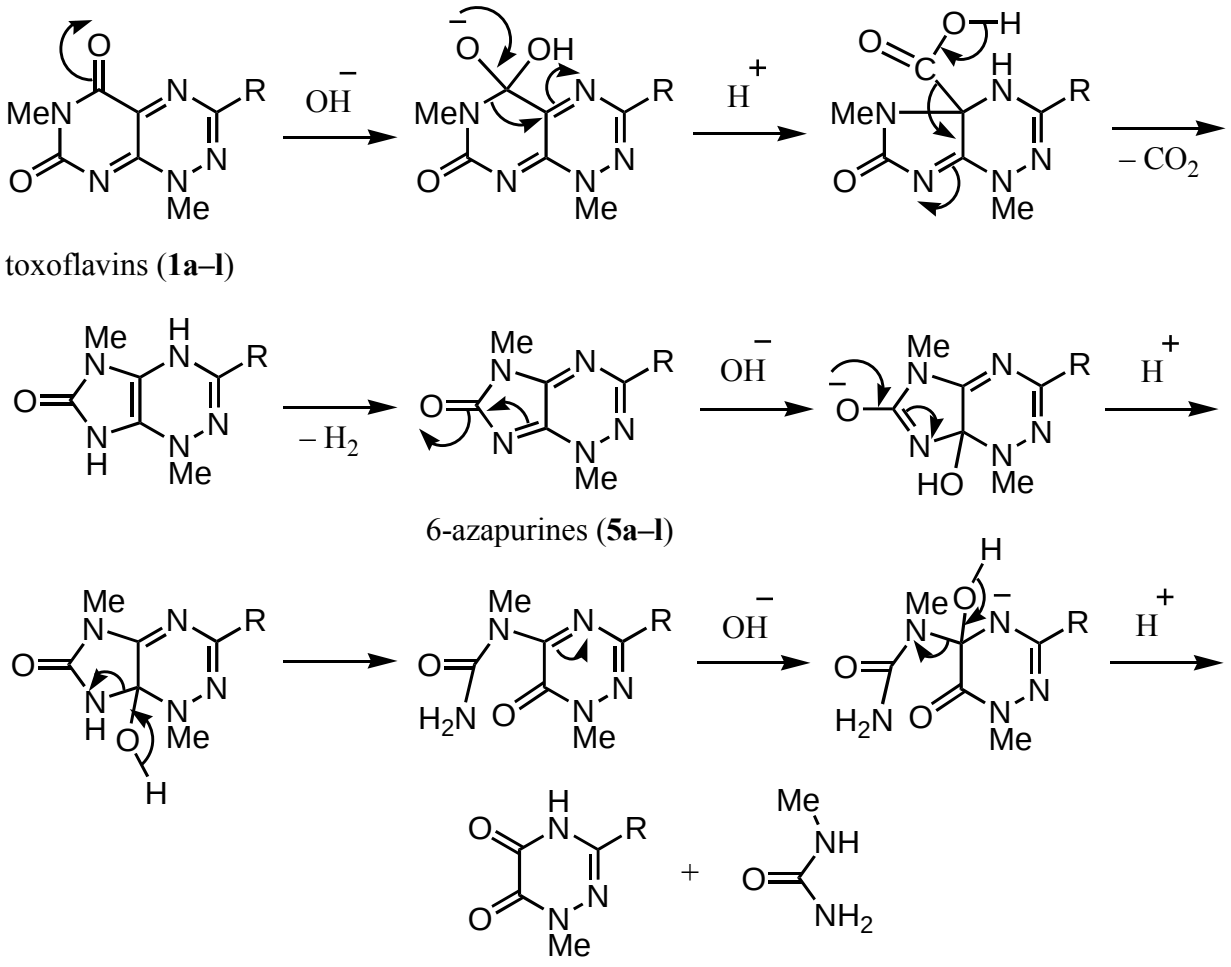
Starting material	R	Reaction conditions[a]	Product	Mp (°C)[b]	Yield (%)
1a	H	5–10 °C, 3 d	**5a**	192–194	89
1b	Me	5–10 °C, 3 d	**5b**	211–213	68
1c	Et	5–10 °C, 3 d	**5c**	215–217	42
1d	Pr	20–25 °C, 1 d	**5d**	218–220	46
1e	Ph	60–70 °C, 15 min	**5e**	211–213	80
1f	4-F-C_6H_4	60–70 °C, 10 min	**5f**	253–255	63
1g	4-Cl-C_6H_4	60–70 °C, 15 min	**5g**	262–264	40
1h	4-HO-C_6H_4	60–70 °C, 20 min	**5h**	> 300	50
1i	4-Me-C_6H_4	60–70 °C, 20 min	**5i**	233–235	61
1j	4-MeO-C_6H_4	60–70 °C, 15 min	**5j**	235-237	76
1k	3,4,5-$(MeO)_3$-C_6H_2	60–70 °C, 25 min	**5k**	202–204	82
1l	4-Me_2N-C_6H_4	60–70 °C, 45 min	**5l**	193–195	47
5e	Ph	reflux, 6 h	**6a**	243–245	84
5i	4-Me-C_6H_4	reflux, 6 h	**6b**	246–248	87
5j	4-MeO-C_6H_4	reflux, 6 h	**6c**	256–258	83
5k	3,4,5-$(MeO)_3$-C_6H_2	reflux, 6 h	**6d**	279–281	89

a) All reactions were carried out in the atmosphere.
b) Products (**5a–l**) were recrystallized from aqueous EtOH and **6a–d** were recrystallized from DMF.

products as solid, which were recrystallized from DMF to afford the corresponding 3-substituted 1-methyl-1,2,4-triazine-5,6(1*H*,4*H*)-diones (**6a–d**) as colorless powdery crystals in 80–90% yields. The

structures of compounds (**5** and **6**) were confirmed on the basis of elemental analysis, ir and ^{1}H-NMR[26] spectra.

We suggest that these 6-azapurines (**5**) are formed from toxoflavins (7-azapteridines) (**1**) by a benzilic acid type rearrangement in alkali solution, followed by decarboxylation and oxidation by air, as depicted in the following Scheme 3. Moreover, heating the 6-azapurines (**5**) in alkali solution gave 1,2,4-triazines (**6**) and methylurea to be caused by ring fission of the imidazole of **5**.



Scheme 3. Plausible mechanism for formation of 1,2,4-triazines via 6-azapurines produced by transformation of toxoflavins (7-azapteridines).

Thus, the reliable and facile synthetic method for 6-azapurines is noteworthy owing to expectation of biological activities. Further synthetic and mechanistic investigations and biological activities for 6-azapurine nucleosides produced by the benzilic acid type rearrangement from 7-azapteridine nucleosides are in progress, and will be reported in detail shortly.

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26. *^{1}H-NMR spectral data in (DMSO-d_6).* For **5a**: δ 3.23 (3H, s, 5-Me), 3.91 (3H, s, 1-Me), 8.33 (1H, s, 3-H). For **5b**: δ 2.45 (3H, s, 3-Me), 3.25 (3H, s, 5-Me), 3.87 (3H, s, 1-Me). For **5c**: δ 1.16 (3H, t, *J* = 6.9 Hz, 3-CH_2*Me*), 2.90 (2H, q, *J* = 6.9 Hz, 3-*CH_2*Me), 3.30 (3H, s, 5-Me), 3.99 (3H, s, 1-Me). For **5d**: δ 0.90 (3H, t, *J* = 6.9 Hz, 3-CH_2CH_2*Me*), 1.77 (2H, m, 3-CH_2*CH_2*Me), 2.94 (2H, t, *J* = 6.9 Hz, 3-*CH_2*CH_2Me), 3.33 (3H, s, 5-Me), 4.00 (3H, s, 1-Me). For **5e**: δ 3.25 (3H, s, 5-Me), 4.00 (3H, s, 1-Me), 7.52-7.58 (3H, m, Ph-*m,p*H), 8.19-8.28 (2H, m, Ph-*o*H). For **5f**: δ 3.35 (3H, s, 5-Me), 3.99 (3H, s, 1-Me), 7.39 (2H, dd, $J_{H,H}$ = 8.4, $J_{H,F}$ = 8.7 Hz, Ar-*m*H), 8.27 (2H, dd, $J_{H,H}$ = 8.4, $J_{H,F}$ = 5.8 Hz, Ar-*o*H). For **5g**: δ 3.39 (3H, s, 5-Me), 3.98 (3H, s, 1-Me), 7.86 (2H, d, *J* = 8.7 Hz, Ar-*m*H), 8.22 (2H, d, *J* = 8.7 Hz, Ar-*o*H). For **5h**: δ 3.33 (3H, s, 5-Me), 3.96 (3H, s, 1-Me), 6.90 (2H, d, *J* = 8.7 Hz, Ar-*m*H), 8.07 (2H, d, *J* = 8.7 Hz, Ar-*o*H), 10.02 (1H, s, exchangeable with D_2O, Ar-OH). For **5i**: δ 2.38 (3H, s, Ar-Me), 3.36 (3H, s, 5-Me), 4.19 (3H, s, 1-Me), 7.32 (2H, d, *J* = 8.1 Hz, Ar-*m*H), 7.96 (2H, d, *J* = 8.1 Hz, Ar-*o*H). For **5j**: δ 3.33 (3H, s, 5-Me), 3.83 (3H, s, Ar-O*Me*), 3.96 (3H, s, 1-Me), 7.08 (2H, d, *J* = 8.7 Hz, Ar-*m*H), 8.16 (2H, d, *J* = 8.7 Hz, Ar-*o*H). For **5k**: δ 3.33 (3H, s, 5-Me), 3.76 (3H, s, 4'-OMe), 3.89 (6H, s, 3'- and 5'-OMe), 4.00 (3H, s, 1-Me), 7.54 (2H, s, 2'- and 6'-H). For **5l**: δ 3.01 (6H, s, Ar-N*Me_2*), 3.32 (3H, s, 5-Me), 3.94 (3H, s, 1-Me), 6.79 (2H, d, *J* = 9.0 Hz, Ar-*m*H), 8.04 (2H, d, *J* = 9.0 Hz, Ar-*o*H). For **6a**: δ 3.48 (3H, s, 1-Me), 7.44–7.50 (3H, m, Ph-*m,p*H), 7.79–7.85 (2H, m, Ph-*o*H), 12.56 (1H, br s, exchangeable with D_2O, 4-NH). For **6b**: δ 2.33 (3H, s, Ar-*Me*), 3.47 (3H, s, 1-Me), 7.27 (2H, d, *J* = 8.4 Hz, Ar-*m*H), 7.71 (2H, d, *J* = 8.4 Hz, Ph-*o*H), 12.42 (1H, br s, exchangeable with D_2O, 4-NH). For **6c**: δ 3.47 (3H, s, 1-Me), 3.79 (3H, s, Ar-*OMe*), 7.01 (2H, d, *J* = 8.7 Hz, Ar-*m*H), 7.77 (2H, d, *J* = 8.7 Hz, Ar-*o*H), 12.47 (1H, br s, exchangeable with D_2O, 4-NH). For **6d**: δ 3.53 (3H, s, 1-Me), 3.72 (3H, s, 4'-OMe), 3.86 (6H, s, 3'-OMe and 5'-OMe 7.19 (2H, s, 2'- and 6'-H), 12.61 (1H, br s, exchangeable with D_2O, 4-NH).