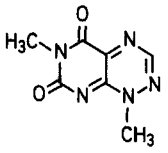
A New Synthetic Method of Toxoflavin Derivatives

Fumio YONEDA and Tomohisa NAGAMATSU

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

Toxoflavin (**1**)[1] is an interesting antibiotic having a pyrimido-[5,4-*e*]-*as*-triazine ring system. Previously, we reported a synthesis of toxoflavin and its analogs by the nitrosative cyclization of the aldehyde hydrazones of 3-methyl-6-(1′-methylhydrazino)-uracil[2]. This communication describes another convenient synthesis of toxoflavin derivatives, which



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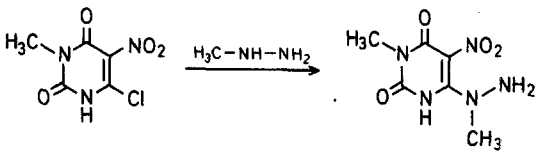
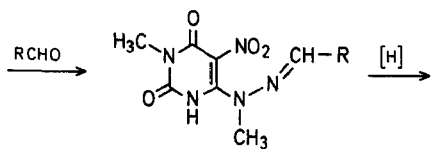


2 **3**



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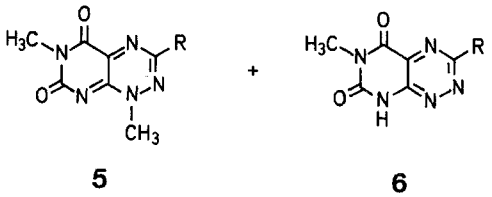

5 **6**

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Table 1. Preparation of 6-(Benzylidene-1′-methylhydrazino)-3-methyl-5-nitrouracil (**4**)

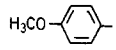
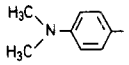
R	m.p.	Yield (%)	Elemental Analyses				
	225–226°	85	$C_{13}H_{13}N_5O_4$ (303.3)	calc.	C 51.48	H 4.32	N 23.09
				found	51.32	4.30	23.29
	244–246°	87	$C_{13}H_{12}ClN_5O_4$ (337.7)	calc.	C 46.23	H 3.58	N 20.74
				found	46.21	3.48	20.63
	224–226°	85	$C_{14}H_{15}N_5O_5$ (330.3)	calc.	C 50.45	H 4.54	N 21.01
				found	50.32	4.49	20.89
	241–243°	98	$C_{14}H_{13}N_5O_5$ (347.3)	calc.	C 48.42	H 3.77	N 20.17
				found	48.22	3.73	20.02
	> 300° (sublim.)	84	$C_{15}H_{18}N_6O_4$ (346.3)	calc.	C 52.02	H 5.24	N 24.27
				found	52.30	5.26	24.04

Table 2. Preparation of 3-Substituted Toxoflavins (**5**)

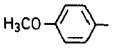
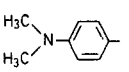
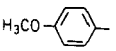
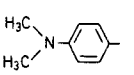
R	m.p.	Yield (%)	Elemental Analyses				
	228° (dec.)[2]	42	$C_{13}H_{11}N_5O_2$ (269.3)	calc.	C 57.98	H 4.12	N 26.01
				found	58.06	4.07	26.20
	205–207°	54	$C_{13}H_{10}N_5O_2Cl$ (319.7)	calc.	C 51.41	H 3.32	N 23.06
				found	51.30	3.29	23.11
	243–244° (dec.)	38	$C_{14}H_{13}N_5O_2$ (299.3)	calc.	C 56.18	H 4.38	N 23.40
				found	56.33	4.37	23.22
	262–264° (dec.)	61	$C_{14}H_{11}N_5O_2$ (313.3)	calc.	C 53.67	H 3.54	N 22.36
				found	53.72	3.58	22.31
	270° (dec.)	52	$C_{15}H_{16}N_6O_2$ (312.3)	calc.	C 57.68	H 5.16	N 26.91
				found	57.51	4.81	26.65

Table 3. Preparation of 3-Substituted 1-Demethyltoxoflavins (**6**)

R	m.p.	Yield (%)	Elemental Analyses				
	> 300°[4]	12	$C_{12}H_9N_5O_2$ (255.3)	calc.	C 56.47	H 3.55	N 27.44
				found	56.23	3.62	27.31
	> 300°[4]	18	$C_{12}H_8ClN_5O_2$ (289.7)	calc.	C 49.75	H 2.78	N 24.18
				found	49.69	2.77	24.02
	> 300°	15	$C_{13}H_{11}N_5O_3$ (285.3)	calc.	C 54.73	H 3.89	N 24.55
				found	54.49	3.73	24.24
	> 300°	10	$C_{13}H_9N_5O_4$ (299.2)	calc.	C 52.18	H 3.03	N 23.41
				found	52.36	3.29	23.26
	> 300°	13	$C_{14}H_{14}N_6O_2$ (298.3)	calc.	C 56.37	H 4.73	N 28.18
				found	56.22	4.65	28.23

consists of the catalytic reduction of 6-(benzylidene-1′-methylhydrazino)-3-methyl-5-nitrouracils.

Stirring of 6-chloro-3-methyl-5-nitrouracil (**2**)[3] in ethanol with an equimolar amount of methylhydrazine at room temperature for a few minutes gave 3-methyl-6-(1′-methylhydrazino)-5-nitrouracil (**3**), m.p. 199–200°, in almost quantitative yield. The above reaction solution was usually treated *in situ* with various aryl aldehydes for about 30 minutes to give the corresponding hydrazones (**4**) (Table 1).

The hydrazones thus obtained were hydrogenated in ethanol over palladium/carbon. After the consumption of hydrogen stopped, the reaction solution was filtered and the filtrate was concentrated to give a mixture of the corresponding toxoflavins (**5**) and 1-demethyltoxoflavins (**6**), which were separated by fractional recrystallization from ethanol (Tables 2 and 3). These products were identical in all respects with authentic samples prepared by alternative routes[2,4].

6-(Benzylidene-1′-methylhydrazino)-3-methyl-5-nitrouracil; General Procedure:

To a stirred solution of 6-chloro-3-methyl-5-nitrouracil (0.01 mol) in ethanol (100 ml) was added methylhydrazine (0.01 mol) at room temperature and stirred for a few minutes. An aryl aldehyde (0.01 mol) was then added to the above reaction solution. After stirring was continued for 1 h, the product which separated was filtered, dried, and recrystallized from ethanol.

3-Substituted Toxoflavins and 3-Substituted 1-Demethyltoxoflavins; General Procedure:

A suspension of a 6-(benzylidene-1′-methylhydrazino)-3-methyl-5-nitrouracil (0.01 mol) in ethanol (300 ml) containing 5% palladium/carbon (0.3 g) was hydrogenated at room temperature and at atomospheric pressure. After the consumption of hydrogen stopped, the reaction solution was filtered and the filtrate was concentrated to a small volume and allowed to stand overnight in the refrigerator to precipitate a mixture of toxoflavins and

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1-demethyltoxoflavins. Fractional recrystallization from ethanol gave the corresponding toxoflavins. 1-Demethyltoxoflavins, which were less soluble in ethanol, were recrystallized from dimethylformamide.

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[2] F. Yoneda, K. Shinomura, S. Nishigaki, *Tetrahedron Lett.* **1971,** 851.
[3] T. K. Liao, F. Baiocchi, C. C. Cheng, *J. Org. Chem.* **31,** 900 (1966).
[4] F. Yoneda, T. Nagamatsu, *Tetrahedron Lett.* **1973,** 1577.

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