NEW SYNTHESIS OF 2-ARYL-1,2,4-TRIAZINE-3,5(2H,4H)-DIONES (1-ARYL-6-AZAURACILS)

Fumio Yoneda* and Masatsugu Higuchi
Faculty of Pharmaceutical Sciences, Kumamoto University,
Oe-honmachi, Kumamoto 862, Japan
Yoshihiro Nitta
Shizuoka College of Pharmacy, Oshika, Shizuoka 422, Japan

Treatment of 6-amino-5-arylazo-1,3-dimethyluracils with urea gave the respective 6-aryl-1,3-dimethyl-6,7-dihydro-6-azalumazine-7(6H)-ones, which were hydrolyzed with alkali to afford 2-aryl-1,2,4-triazine-3,5(2H,4H)-dione-6-carboxylic acids (1-aryl-6-azauracil-5-carboxylic acids). Thermal decarboxylation of these carboxylic acids gave the corresponding 2-aryl-1,2,4-triazine-3,5(2H,4H)-diones (1-aryl-6-azauracils).

1,2,4-Triazine-3,5(2H,4H)-dione (6-Azauracil) and its derivatives[1] are biologically interesting compounds, because of their demonstrated antitumor activity.[2] However, the 6-azauracils possessing aryl substituents at the 1-position have not been widely investigated. The only known synthetic method for the preparation of the 1-aryl-6-azauracils has involved the cyclization of aryl-hydrazones of N-acetylurethan derivatives.[3,4] Here we

report a new synthetic approach to 1-aryl-6-azauracils which consists of the hydrolysis of 6-azalumazine-7(6H)-one derivatives followed by decarboxylation.

The key intermediates, 6-aryl-1,3-dimethyl-6,7-dihydro-6-azalumazine-7(6H)-ones (IIa-e)[5] were prepared by the reaction of the appropriate 6-amino-5-arylazo-1,3-dimethyluracils (Ia-e)[6] with excess urea at 200-220° for 1.5 hr (Table 1).

TABLE 1. 6-Aryl-1,3-dimethyl-6,7-dihydro-6-azalumazine-7(6H)-ones

Starting material	Substituent (R)	Product	Mp (°C)[a]	Yield (%)
Ia	C_6H_5	IIa[b]	219	70
Ib	$3\text{-}CH_3\text{-}C_6H_4$	IIb[b]	227	61
Ic	$4\text{-}CH_3\text{-}C_6H_4$	IIc	195	62
Id	$3\text{-}Cl\text{-}C_6H_4$	IId	199	49
Ie	$3,4\text{-}(CH_3)_2\text{-}C_6H_3$	IIe	220	55

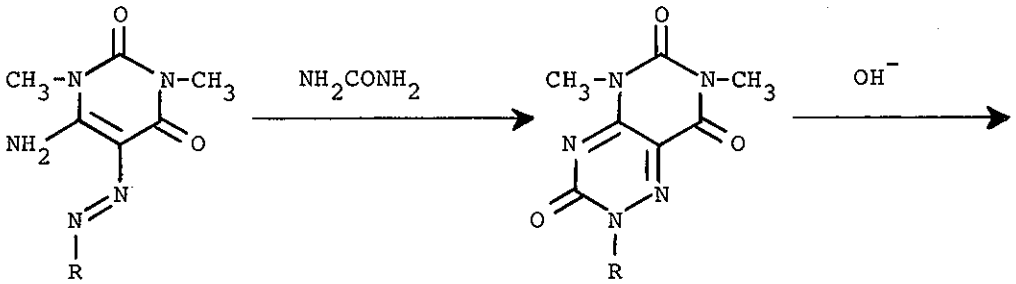
a) All compounds were recrystallized from ethanol to yield yellow crystals.

b) see reference 7.

Treatment of the 6-azalumazine-7(6H)-ones (IIa-e) (0.001 mol) with 10% potassium hydroxide in ethanol and water (3:1) (50 ml) at 90° for 1 hr, followed by acidification with hot hydrochloric acid caused the separation of colorless crystals which were filtered off and recrystallized from hot water to give the monohydrates of the corresponding 2-aryl-1,2,4-triazine-3,5(2H,4H)-dione-6-carboxylic acids (1-aryl-6-azauracil-5-carboxylic acids) (IIIa-e) (Table 2).

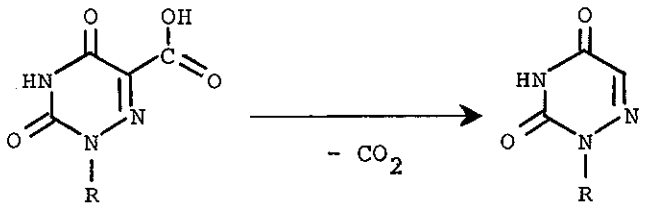
Heating of these carboxylic acids (IIIa-d) in diphenyl ether at 200-220° for 1.5 hr, followed by dilution of the reaction

mixture with ethyl ether, caused the separation of crystals, which were purified by sublimation or by recrystallization from ethanol to give the respective 2-aryl-1,2,4-triazine-3,5(2H,4H)-diones (1-aryl-6-azauracils) (IVa-d) as colorless crystals (Table 2).



I a; R = C_6H_5
b; R = 3-CH_3-C_6H_4
c; R = 4-CH_3-C_6H_4
d; R = 3-Cl-C_6H_4
e; R = 3,4-$(CH_3)_2$-C_6H_3

II a; R = C_6H_5
b; R = 3-CH_3-C_6H_4
c; R = 4-CH_3-C_6H_4
d; R = 3-Cl-C_6H_4
e; R = 3,4-$(CH_3)_2$-C_6H_3



III a; R = C_6H_5
b; R = 3-CH_3-C_6H_4
c; R = 4-CH_3-C_6H_4
d; R = 3-Cl-C_6H_4
e; R = 3,4-$(CH_3)_2$-C_6H_3

IV a; R = C_6H_5
b; R = 4-CH_3-C_6H_4
c; R = 3-Cl-C_6H_4
d; R = 3,4-$(CH_3)_2$-C_6H_3

The structures of compounds IVa-d were characterized by the presence of C^6-H [for example, sharp singlet at 7.80 ppm (in CF_3COOH) for IVa] in NMR.

TABLE 2. 1-Aryl-6-azauracil Derivatives

Compound No.	Substituent (R)	Mp (°C)	Yield (%)
IIIa	C_6H_5	205	72
IIIb	$3\text{-}CH_3\text{-}C_6H_4$	206	48
IIIc	$4\text{-}CH_3\text{-}C_6H_4$	200	49
IIId	$3\text{-}Cl\text{-}C_6H_4$	181	73
IIIe	$3,4\text{-}(CH_3)_2\text{-}C_6H_3$	222	76
IVa	C_6H_5	215	61
IVb	$4\text{-}CH_3\text{-}C_6H_4$	212	59
IVc	$3\text{-}Cl\text{-}C_6H_4$	222	60
IVd	$3,4\text{-}(CH_3)_2\text{-}C_6H_3$	153	57

REFERENCES

1 For example, J. Gut, "Advances in Heterocyclic Chemistry," Vol. 1, ed. A. R. Katritzky, Academic Press, New York, 1963, p. 203.

2 For example, C. A. Pasternak and R. E. Handschumacher, J. Biol. Chem., 1959, 234, 2992.

3 M. A. Whitely and D. Yapp, J. Chem. Soc., 1927, 521.

4 J. Slouka, Monats. Chem., 1969, 100, 342.

5 Satisfactory analytical and spectral data were obtained for all compounds.

6 a) M. Ishidate, M. Sekiya, Y. Osaki, and Y. Harada, Yakugaku Zasshi, 1956, 76, 1107; b) F. Yoneda and M. Higuchi, Heterocycles, 1977, 6, 1901.

7 F. Yoneda and M. Higuchi, Chem. Pharm. Bull. (Tokyo), 1977, 25, 2794.

Received, 1st July, 1978