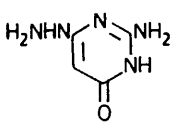
6-Azapurines (Imidazo[4,5-*e*]-*as*-triazines)

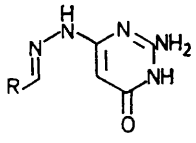
By FUMIO YONEDA,* TETSUYA NAGAMURA, and MITSUKO KAWAMURA
(*Faculty of Pharmaceutical Sciences, Kumamoto University, Oe-honmachi, Kumamoto* 862, *Japan*)

Summary Treatment of 3-substituted 7-amino-5-hydroxypyrimido[5,4-e]-*as*-triazine 4-oxides (IIIa—d) with acetic anhydride or alcoholic sodium hydroxide caused a benzylic acid-type rearrangement followed by decarboxylation and dehydration to give the corresponding 6-acetylaminoimidazo[4,5-*e*]-*as*-triazines (IVa—d) or 3-aminoimidazo[4,5-*e*]-*as*-triazines (Va—c); similarly, 3-substituted toxoflavin 4-oxides (VIa—c) gave the respective 1,5-dimethyl-1*H*-imidazo[4,5-*e*]-*as*-triazin-6-(5*H*)-ones (VIIa—c), and 3-substituted fervenulin 4-oxides (VIIIa—c) gave the respective 5,7-dimethyl-5*H*-imidazo[4,5-*e*]-*as*-triazin-6(7*H*)-ones (IXa—c).

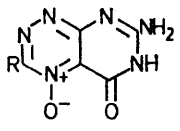
THE 6-azapurine (imidazo[4,5-*e*]-*as*-triazine) ring system is of interest from a chemical as well as from a potential biological point of view. Because this type of substance has apparently not been described previously, we report here a novel synthesis of 6-azapurines from pyrimido[5,4-*e*]-



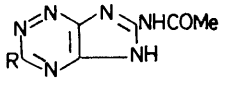
(I)



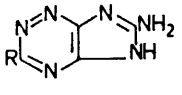
(II)



(III)



(IV)



(V)

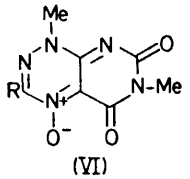
a; R = Ph
b; R = *p*-ClC$_6$H$_4$
c; R = 3,4-Cl$_2$C$_6$H$_3$
d; R = *p*-MeOC$_6$H$_4$

as-triazine 4-oxides, *via* oxidative nitrosation of the pyrimidine-6-ylhydrazones of aromatic aldehydes. The readily available pyrimido[5,4-*e*]-*as*-triazine 4-oxides undergo ring contraction on reaction with acetic anhydride or alcoholic sodium hydroxide to yield the corresponding 6-azapurines.

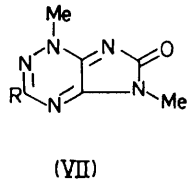
Heating 2-amino-6-chloropyrimidin-4-ol with excess of hydrazine hydrate in n-butanol afforded the hydrazine derivative (I), m.p. 297 °C, in 86% yield. Refluxing (I) with an equimolar amount of benzaldehyde in methyl cellosolve for 3 h followed by cooling caused separation of the hydrazone (IIa) (m.p. 285 °C; 84%). The hydrazones (IIb) (m.p. 290 C; 88%), (IIc) (m.p. 301 °C; 96%), and (IId) (m.p. 276 °C, 79%) were obtained similarly.

Treatment of the hydrazones (IIa—d) with an excess of saturated aqueous sodium nitrite and diethyl azodicarboxylate in acetic acid at 5 °C for *ca.* 1 h, followed by dilution with water, gave the *N*-oxides (IIIa) (m.p. 295 °C; 98%), (IIIb) (m p. 262 °C; 95%), (IIIc) (m.p. 292 °C; 93%), and (IIId) (m p. 265 °C; 92%), respectively.

Treatment of (IIIa) with excess of acetic anhydride under reflux for 3 h, removal of the solvent, and dilution with ethanol gave the 6-azapurine (IVa) in moderate yield. The

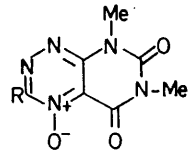


(VI)

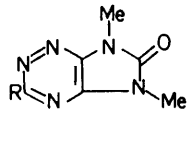


(VII)

a; R = Ph
b; R = 3,4-Cl$_2$C$_6$H$_3$
c; R = *p*-MeOC$_6$H$_4$



(VIII)



(IX)

a; R = Ph
b; R = *p*-ClC$_6$H$_4$
c; R = *p*-MeOC$_6$H$_4$

structure of (IVa) was derived on the basis of elemental analysis, molecular weight and fragmentation pattern by mass spectrometry, i.r. and n.m.r. spectral data, and by consideration of its probable mode of formation. Compounds (IIIb—d) under similar conditions yielded the corresponding 6-azapurines (IVb—d) (Table).

TABLE

Compound	M.p./°C	Yield/%
(IV)[a]	360 (decomp.)	47
(IVb)[a]	360 (decomp.)	33
(IVc)[a]	349 (decomp.)	39
(IVd)[a]	353 (decomp.)	42
(Va)[a]	365	72
(Vb)[a]	>360	69
(Vc)[a]	>360	70
(VIIa)[b]	225	42
(VIIb)[b]	245	45
(VIIc)[b]	220	38
(IXa)[b]	198	52
(IXb)[b]	251	58
(IXc)[b]	249	48

[a] Recrystallized from dimethylformamide. [b] Recrystallized from ethanol.

Compounds (IIIa—c) were treated with alcoholic sodium hydroxide under reflux for 2 h. Neutralization with acetic acid precipitated the respective 6-amino-compounds (Va—c) (Table). Refluxing (Va—c) in acetic anhydride for 1 h gave compounds (IVa—c), which were identical with the products described above.

In analogy with the above results, the toxoflavin 4-oxides (VIa—c)[1] yielded the imidazo-*as*-triazinones (VIIa—

c) on reaction with alcoholic sodium hydroxide. The fervenulin 4-oxides (VIIIa—c)[1,2] likewise gave the imidazo-*as*-triazinones (IXa—c) (Table).

We suggest that these 6-azapurines are formed from 7-azapteridine 5-oxides by a benzylic acid-type rearrangement. An important feature of this rearrangement is that concerted decarboxylation and dehydration lead to aromatization of the *as*-triazine ring. An analogous ring contraction was reported in the reaction of 1,3,7,9-tetramethylpyrimido[5,4-*g*]pteridine-2,4,6,8(1*H*,3*H*,7*H*,9*H*)-tetrone 5-oxide with aqueous sodium hydroxide giving 1,3-dimethyl-5-methylaminocarbonyl-6-methylamino-1*H*-imidazo[4,5-*b*]pyrazin-2(3*H*)-one.[3]

(*Received*, 4*th June* 1976; *Com.* 642.)

[1] F. Yoneda and T. Nagamatsu, *Chem. Pharm. Bull.* (*Japan*), 1975, **23**, 1885; F. Yoneda, T. Nagamatsu, and K. Shinomura, *J.C.S. Perkin I*, 1976, 713.
[2] Y. Sakuma, S. Matsumoto, T. Nagamatsu, and F. Yoneda, *Chem. Pharm. Bull.* (*Japan*), 1976, **24**, 339.
[3] E. C. Taylor, Y. Maki, and A. McKillop, *J. Org. Chem.*, 1972, **37**, 1601.