A TRANSFORMATION OF 7-AZAPTERIDINES INTO 6-AZAPURINES (IMIDAZO[4,5-e]-as-TRIAZINES)

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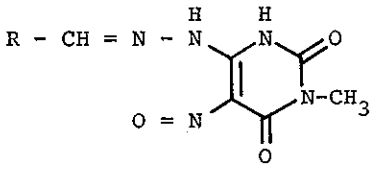
Treatment of 6-substituted 3-methyl-7-azalumazines and 6-substituted 1,3-dimethyl-7-azalumazines (fervenulins) with alcoholic sodium hydroxide caused a benzylic acid type rearrangement followed by decarboxylation and oxidation by air to give the respective 5-methyl- and 5,7-dimethyl-5H-imidazo[4,5-e]-as-triazine-6(7H)-ones.

The reaction of 7-azapteridine 5-oxides with acetic anhydride or alcoholic sodium hydroxide caused a ring contraction to give the corresponding 6-azapurines (imidazo[4,5-e]-as-triazines)[1] which are interesting from the chemical and potentially biological point of view. We now wish to report a further new synthetic approach to 6-azapurines which involves a benzylic acid type rearrangement of 7-azapteridines.

The key intermediates, 7-azapteridine derivatives were prepared by the following methods. It is known that the treatment of 6-benzylidenehydrazino-3-methyluracil in acetic acid with saturated aqueous sodium nitrite gives 6-benzylidenehydrazino-3-methyl-5-nitrosouracil (Ia).[2] By this method, 6-(4-chlorobenzylidenehydrazino)- (Ib) (mp 224°, 89%), 6-(3,4-dichlorobenzylidenehydrazino)- (Ic) (mp 230°, 83%), 6-(4-methoxybenzylidenehydrazino)- (Id) (mp 245°, 75%), 6-(3,4-methylenedioxybenzylidenehydrazino)- (Ie) (mp 233°, 75%), and 6-(4-dimethylaminobenzylidenehydrazino)-3-methyl-5-nitrosouracil (If) (mp 220°, 68%) were obtained from the corresponding 6-benzylidenehydrazino-3-methyluracils.[3] Refluxing of



(I) a; R = C_6H_5 d; R = 4-CH_3O-C_6H_4

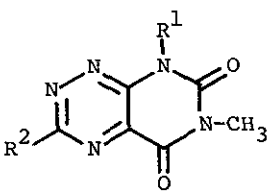
b; R = 4-Cl-C_6H_4 e; R = 3,4-CH_2O_2-C_6H_3

c; R = 3,4-Cl_2-C_6H_3 f; R = 4-$(CH_3)_2N$-C_6H_4

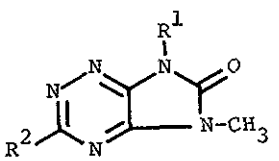
these 5-nitroso derivatives (Ia-f) in acetic anhydride for 1 hr caused dehydrative cyclization to give the respective 6-substituted 3-methyl-7-azalumazines (IIa-f) in 40-60% yields, which were identical with authentic samples[4] prepared by the demethylation of toxoflavins. 6-Substituted 1,3-dimethyl-7-azalumazines (fervenulins) (IIg-l) were obtained by the condensation of 6-amino-1,3-dimethyl-5-nitrosouracil with aldehyde hydrazones according to the procedure

described previously.[5]

Treatment of the 3-methyl- (IIa-f) and 1,3-dimethyl-7-azaluma-zines (IIg-l) thus obtained with 10% alcoholic sodium hydroxide under the conditions described in Table, followed by acidification[6] with acetic acid, precipitated the respective 3-substituted 5-methyl- (IIIa-f) and 3-substituted 5,7-dimethyl-5H-imidazo[4,5-e]-as-



(II)



(III)

a; R^1 = H, R^2 = C_6H_5

b; R^1 = H, R^2 = 4-Cl-C_6H_4

c; R^1 = H, R^2 = 3,4-Cl_2-C_6H_3

d; R^1 = H, R^2 = 3-CH_3O-C_6H_4

e; R^1 = H, R^2 = 3,4-CH_2O_2-C_6H_3

f; R^1 = H, R^2 = 4-$(CH_3)_2N$-C_6H_4

g; R^1 = CH_3, R^2 = C_6H_5

h; R^1 = CH_3, R^2 = 4-Cl-C_6H_4

i; R^1 = CH_3, R^2 = 3,4-Cl_2-C_6H_3

j; R^1 = CH_3, R^2 = 4-CH_3O-C_6H_4

k; R^1 = CH_3, R^2 = 3,4-CH_2O_2-C_6H_3

l; R^1 = CH_3, R^2 = 4-$(CH_3)_2N$-C_6H_4

triazine-6(7H)-ones (IIIg-l)[1] (see Table). The structures of compounds (IIIa-l) were derived on the basis of elemental analysis,

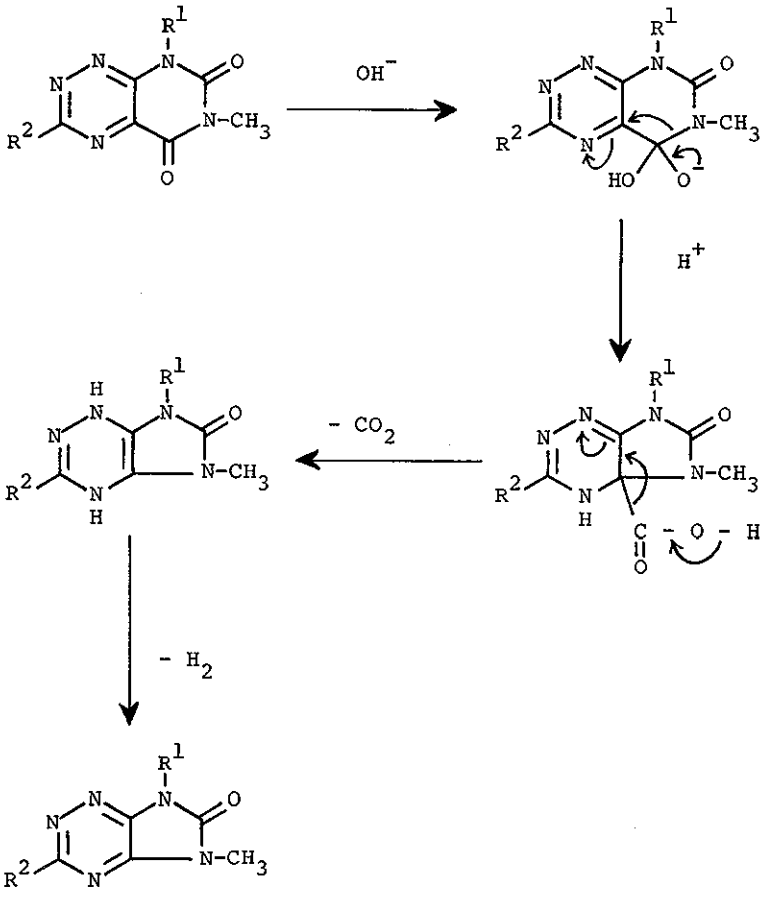
molecular weight determination and fragmentation study by mass spectrometry, ir (the presence of a carbonyl band at 1760 cm^{-1}) and nmr data, and by consideration of its probable mode of formation (Scheme). Furthermore, compounds (IIIa-f) were converted into the 5,7-dimethyl derivatives (IIIg-l) by methylation with methyl iodide and potassium carbonate in dimethylformamide for identification purpose.

Table 6-Azapurines Formation by Reaction of 7-Azapteridines with Alcoholic Sodium Hydroxide

Starting material	Reaction condition	Product	Mp(°C)[a]	Yield(%)
IIa	reflux, 1 hr	IIIa	283	61
IIb	reflux, 1 hr	IIIb	266	49
IIc	reflux, 1 hr	IIIc	284	52
IId	reflux, 1 hr	IIId	292	37
IIe	reflux, 2 hr	IIIe	324	35
IIf	reflux, 2 hr	IIIf	281	50
IIg	60°, 10 min	IIIg	203	71
IIh	60°, 10 min	IIIh	251	65
IIi	60°, 10 min	IIIi	247	55
IIj	60°, 30 min	IIIj	255	58
IIk	60°, 30 min	IIIk	330	51
IIl	60°, 30 min	IIIl	290	87

a) These compounds were recrystallized from ethanol.

We suggest that these 6-azapurines are formed from 7-azapteridines by a benzylic acid type rearrangement, followed by decarboxylation[6] and oxidation by air, as depicted in the following Scheme.



Scheme

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1. F. Yoneda, T. Nagamura, and M. Kawamura, J. Chem. Soc. Chem. Comm., in press (Com. 642).
2. F. Yoneda and T. Nagamatsu, Chem. Pharm. Bull. (Tokyo), 1975, 23, 1885
3. F. Yoneda and T. Nagamatsu, Bull. Chem. Soc. Japan, 1975, 48, 1484.
4. F. Yoneda and T. Nagamatsu, Chem. Pharm. Bull. (Tokyo), 1975, 23, 2001.
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6. Evolution of carbon dioxide was observed here.

Received, 15th July, 1976