

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

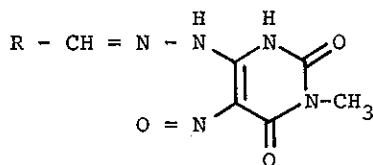
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Treatment of 6-substituted 3-methyl-7-azalumazines and 6-substituted 1,3-dimethyl-7-azalumazines (fervenulins) with alcoholic sodium hydroxide caused a benzylic acid type rearrangement followed by decarboxylation and oxidation by air to give the respective 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

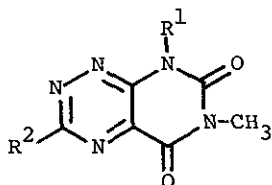


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|---|--|
| (I) a; R = C ₆ H ₅ | d; R = 4-CH ₃ O-C ₆ H ₄ |
| b; R = 4-Cl-C ₆ H ₄ | e; R = 3,4-CH ₂ O ₂ -C ₆ H ₃ |
| c; R = 3,4-Cl ₂ -C ₆ H ₃ | f; R = 4-(CH ₃) ₂ N-C ₆ H ₄ |

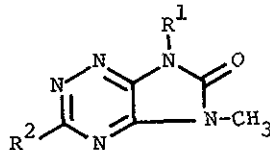
these 5-nitroso derivatives (Ia-f) in acetic anhydride for 1 hr caused dehydrative cyclization to give the respective 6-substituted 3-methyl-7-azalumazines (IIa-f) in 40-60% yields, which were identical with authentic samples⁴ prepared by the demethylation of toxo-flavins. 6-Substituted 1,3-dimethyl-7-azalumazines (fervenulins) (IIg-1) 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 acidification⁶
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,

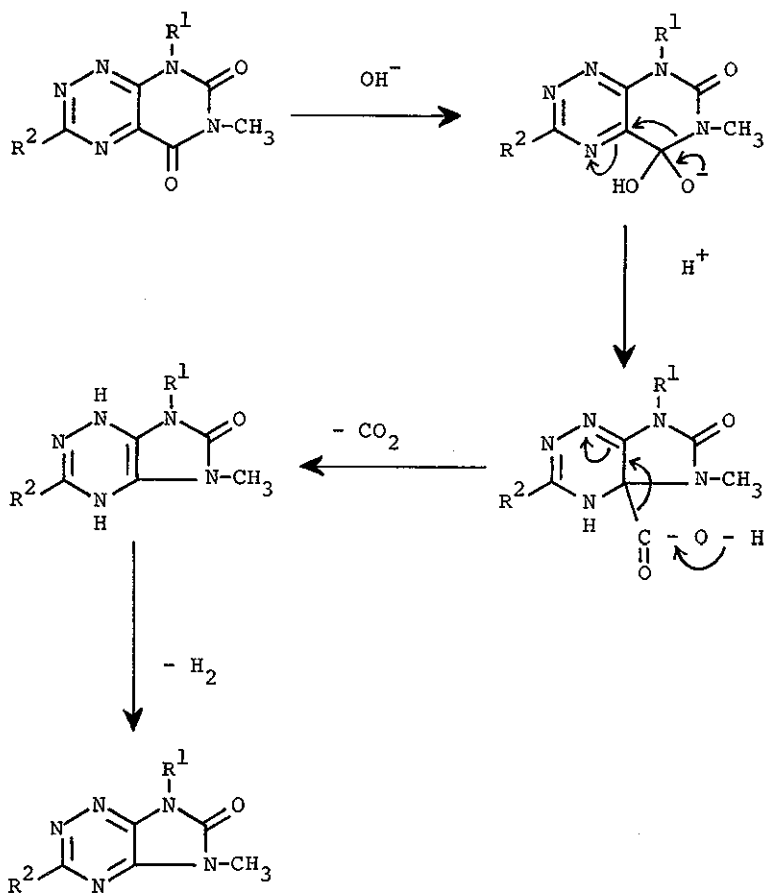
molecular weight determination and fragmentation study by mass spectrometry, ir (the presence of a carbonyl band at 1760 cm^{-1}) and nmr data, and by consideration of its probable mode of formation (Scheme). Furthermore, compounds (IIIa-f) were converted into the 5,7-dimethyl derivatives (IIIg-l) by 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-azappteridines by a benzylic acid type rearrangement, followed by decarboxylation⁶ and oxidation by air, as depicted in the following Scheme.



Scheme

REFERENCES AND NOTES

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6. Evolution of carbon dioxide was observed here.

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