A NOVEL CONVERSION OF 7-AZAPTERIDINES TO PURINES

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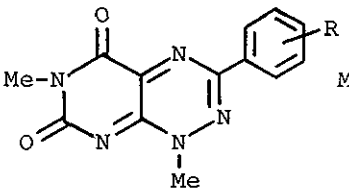
Treatment of 7-azalumazines such as toxoflavins and fervenulins with formamide led to the formation of the corresponding xanthine derivatives.

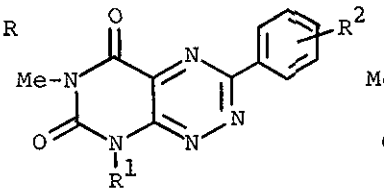
The reactions of 7-azapteridines with sodium dithionite in acetic or formic acid and with formic acid alone lead to the formation of 9-aminopurine derivatives.[1-3] 6-Azapteridines also give purines by the reaction with sodium dithionite in formic acid.[4] All these reactions involve the reductive cleavage of the as-triazine moiety followed by recyclization to give the corresponding purine derivatives.

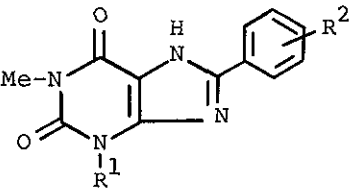
We now wish to report a novel type of conversion of 7-azapteridines to purines, in which formamide is a good choice of reagents and the reaction proceeds without reduction.

The heating of 1 part of 3-phenyltoxoflavin (Ia)[5] in 6 parts of formamide at 190° for 3 hr, followed by dilution with ethanol, caused the separation of 1-methyl-8-phenylxanthine (IIa) in a moderate yield. This conversion involves the initial demethy-

lation of Ia to 3-phenyl-1-demethyltoxoflavin (3-phenyl-8-demethylfervenulin) (IIIa),[5] because the early reaction solution includes only IIIa. Furthermore, treatment of an isolated 1-demethyltoxoflavin with formamide at 190° for 1 hr gave also the corresponding 1-methylxanthine in a better yield. Some examples of this conversion are summarized in Table.







(Ia) R=H	(IIIa) R^1=R^2=H	(IIa) R^1=R^2=H
(Ib) R=4-Cl	(IIIb) R^1=H, R^2=4-Cl	(IIb) R^1=H, R^2=4-Cl
(Ic) R=3,4-Cl_2	(IIIc) R^1=H, R^2=3,4-Cl_2	(IIc) R^1=H, R^2=3,4-Cl_2
	(IVa) R^1=Me, R^2=H	(Va) R^1=Me, R^2=H
	(IVb) R^1=Me, R^2=4-Cl	(Vb) R^1=Me, R^2=4-Cl
	(IVc) R^1=Me, R^2=3,4-Cl_2	(Vc) R^1=Me, R^2=3,4-Cl_2

Similarly, the reaction of 3-phenylfervenulin (IVa)[6] with formamide at 190° for 6 hr gave 8-phenyltheophylline (Va).[7] Other fervenulin derivatives gave likewise the corresponding theophyllines (see Table).

This novel ring conversion is best rationalized by assuming the initial nucleophilic attack of formamide on position 8a (which is the most electron-deficient position in the as-triazine moiety)[8] of 7-azalumazine, followed by the ring cleavage accompaning the elimination of nitrogen molecule to give 5-benzylidene-

amino-6-formylaminouracil. Subsequent hydrolysis to 6-amino-5-benzylideneaminouracil with water generated during the reaction and then cyclization and dehydrogenation could give the final xanthine derivative.

The scope and limitation of this conversion are currently under investigation.

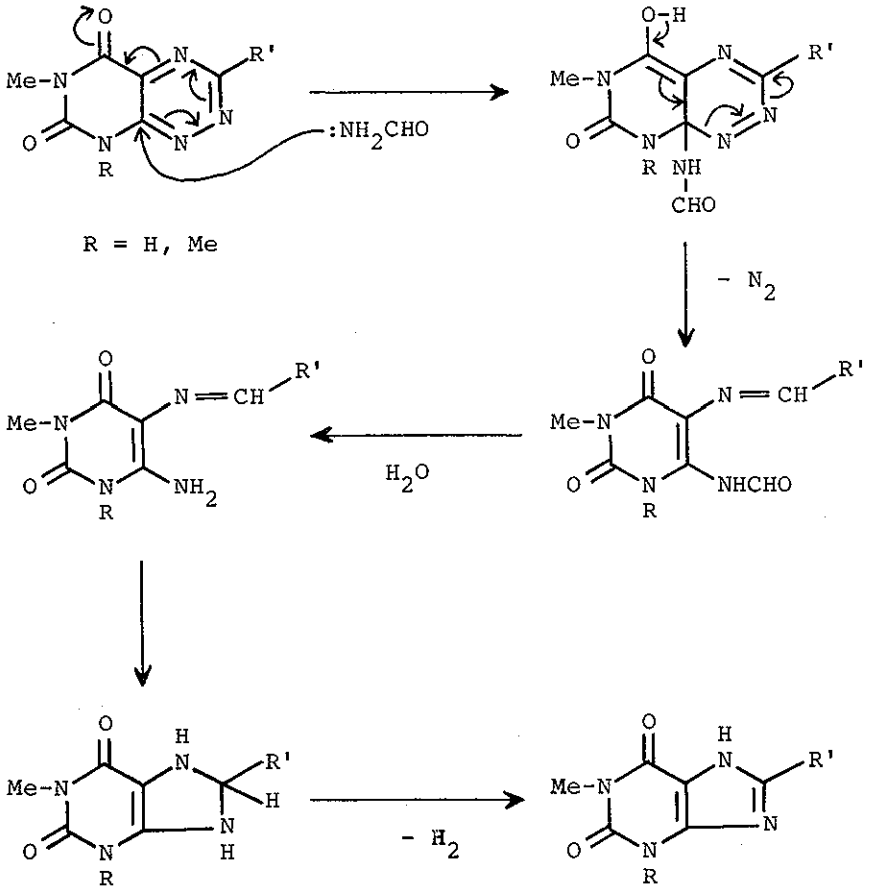


Table Xanthine Formation by Reaction of 7-Azalumazine with Formamide at 190°

Starting material	Time/hr	Product	Yield/%
(Ia)	3	(IIa)	40
(Ib)	3	(IIb)	42
(Ic)	3	(IIc)	43
(IIIa)	1	(IIa)	45
(IIIb)	1	(IIb)	50
(IIIc)	1	(IIc)	56
(IVa)	6	(Va)	52
(IVb)	6	(Vb)	59
(IVc)	6	(Vc)	62

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