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Diels-Alder Reactions of Bicyclic 1,2,4-Triazines: The Conversion of Pyrimido[4,5-e]-1,2,4-triazines to Pyrido[2,3-d]pyrimidines (5-Deazapteridines)[1,2]

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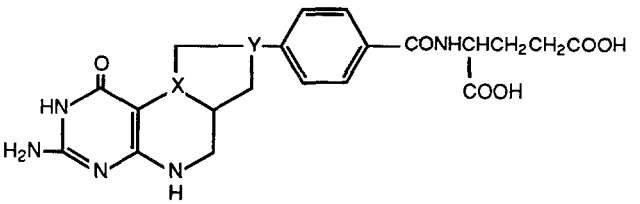
Summary: Inverse electron-demand cycloaddition of aldehyde enamines with 6-azapterins and 6-azalumazines (pyrimido[4,5-e]-1,2,4-triazines) leads regiospecifically to 6-substituted 5-deazapterins and 5-deazalumazines (pyrido[2,3-d]pyrimidines) respectively. 5,6-Fused cyclopenteno and cyclohexeno derivatives are formed with enamines derived from cyclopentanone and cyclohexanone respectively.

5,10-Methylene-5,6,7,8-tetrahydrofolic acid (1) is the natural cofactor for thymidylate synthase (dTMP synthase, TS), an enzyme which catalyzes the conversion of deoxyuridylate to thymidylate. It has long been recognized that inhibition of TS should result in significant inhibition of cell division;[3] indeed, 9-propargyl-5,8-dideazafolic acid (CB 3717), which is a potent TS inhibitor, is currently undergoing extensive clinical trials as an antitumor agent.[4,5] In an attempt to prepare surrogates of 1 which would, however, be incapable of accomplishing the one-carbon transfer reactions characteristic of the natural cofactor, we have been engaged in a program aimed at the synthesis of its 5-deaza (2), 10-deaza (3) and 5,10-dideaza (4) analogs. We report in this paper our preliminary results on an extremely promising, novel synthetic strategy for construction of the tricyclic skeleton characteristic of 2.



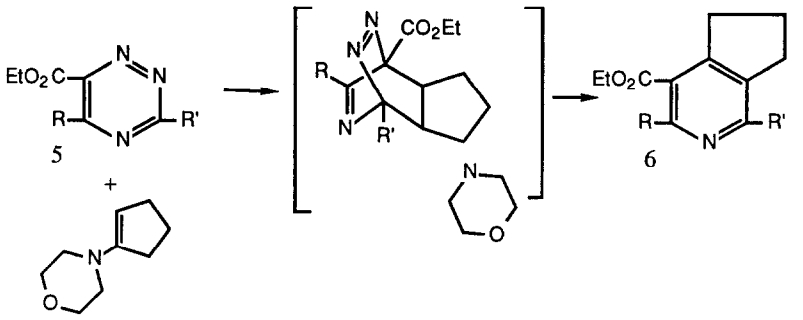
1, X = Y = N
2, X = CH, Y = N
3, X = N, Y = CH
4, X = Y = CH

Our preliminary work in this area was aimed at the preparation of 4,5-cyclopenteno-2-amino-3-carboalkoxypyridines (6), to which the requisite pyrimidine ring was to have been annulated by

cyclization with guanidine. We have prepared these supposed key intermediates by a number of different routes; one which is relevant to the methodology to be discussed herein is the cycloaddition of 1-morpholinocyclopentene with 2-amino- and 2-ethoxy-3-ethoxycarbonyl-1,2,4-triazines (5). However, although the Diels-Alder reaction proceeded smoothly (Scheme 1), we have thus far been totally frustrated in attempts to annulate the requisite 2-amino-4(3H)-pyrimidinone ring, either by intermolecular or by intramolecular strategies.[6] An unprecedented potential solution to this problem appeared to be first to fuse the pyrimidine ring to the 1,2,4-triazine ring, and then to carry out the Diels-Alder reaction on the resulting pyrimido[4,5-e]-1,2,4-triazine (6-azapterin). We describe in this paper the successful implementation of this alternative strategy.

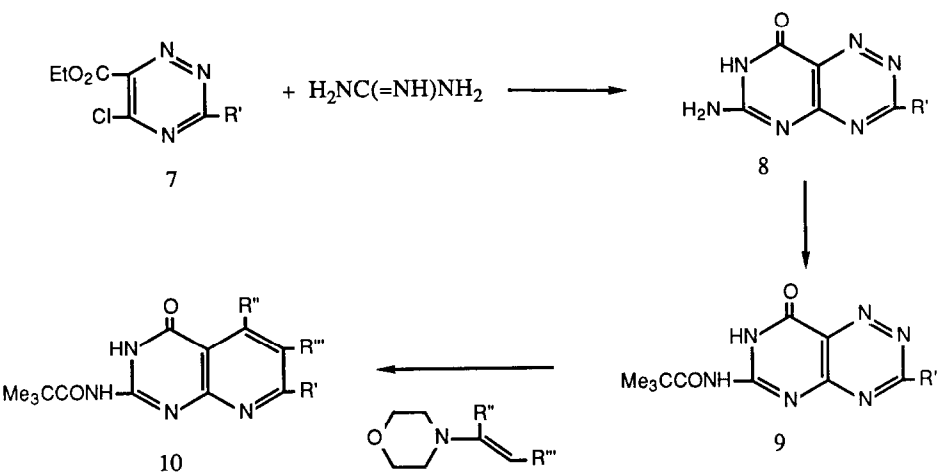
The requisite 6-azapterins (8) were prepared by cyclization of 6-carboethoxy-5-chloro-3-methylthio-1,2,4-triazine (7a) and the 3-(p-tolyl) analog (7d) with guanidine.[7] Although neither 8a nor 8d was sufficiently soluble to undergo reaction with 1-morpholinocyclopentene, the 2-pivaloyl derivatives 9a and 9d (prepared by reaction with pivalic anhydride at 165° C. in the presence of pyridine) proved to be readily soluble in a variety of organic solvents, and reacted smoothly with enamines to give the 5-deazapterin derivatives 10a-f (Scheme 2). A consistent byproduct with enamines less reactive than 1-morpholinocyclopentene (when R' = methylthio) was the 7-morpholino derivative of the starting pyrimidotriazine (e.g., 9, R' = morpholino). Morpholine is released in the final aromatization step of the initial Diels-Alder cycloadduct, and its presence in the reaction mixture is thus unavoidable; presumably because of increased electron density due to the morpholino substituent, these byproducts failed to react with remaining enamine. It is noteworthy that cycloaddition with 1-morpholino-1-butene led regiospecifically to the 2-pivaloyl derivatives of 7-methylthio- (10c) and 7-(p-tolyl)-6-ethyl-5-deazapterin (10f); none of the 5-ethyl isomers could be detected in the reaction mixture.

Extrapolation of this ring transformation concept to the synthesis of 5-deazalumazines was also successful (Scheme 3). The 1,3-dimethyl-6-azalumazines 11a, 11d and 11g were prepared by known methods.[8] Treatment with acyclic and cyclic enamines led smoothly to the 1,3-dimethyl-5-deazalumazines 12a-e. The cycloaddition reaction in this system also proved to be regiospecific; only the 6-ethyl-5-deaza-1,3-dimethyllumazines 12c, 12f and 12i were formed upon reaction of the respective 6-azalumazines with 1-morpholino-1-butene.



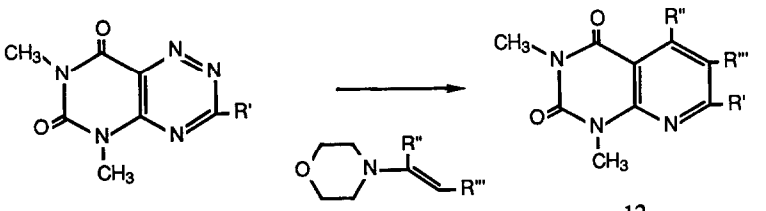
	R	R'	Yield,%
a)	NH_2	SCH_3	48
b)	OEt	SCH_3	59
c)	NH_2	p-tolyl	40
d)	OEt	p-tolyl	81

Scheme 1



	R'	R''	R'''	Yield (%) of 10
a)	SCH_3	$-CH_2CH_2CH_2-$		44
b)	SCH_3	$-CH_2CH_2CH_2CH_2-$		15
c)	SCH_3	H	CH_2CH_3	18
d)	p-tolyl	$-CH_2CH_2CH_2-$		57
e)	p-tolyl	$-CH_2CH_2CH_2CH_2-$		3
f)	p-tolyl	H	CH_2CH_3	22

Scheme 2



11 12

	R'	R"	R"'	Yield,%
a)	SCH_3	$-CH_2CH_2CH_2-$		61
b)	SCH_3	$-CH_2CH_2CH_2CH_2-$		12
c)	SCH_3	H	CH_2CH_3	41
d)	p-tolyl	$-CH_2CH_2CH_2-$		60
e)	p-tolyl	$-CH_2CH_2CH_2CH_2-$		26
f)	p-tolyl	H	CH_2CH_3	41
g)	H	$-CH_2CH_2CH_2-$		74
h)	H	$-CH_2CH_2CH_2CH_2-$		61
i)	H	H	CH_2CH_3	66

Scheme 3

In conclusion, it appears that cycloaddition of condensed 1,2,4-triazines with electron-rich dienophiles should prove to be generally useful for the synthesis of fused pyridine systems. Subsequent papers from our laboratory will report on extensions of this cycloaddition chemistry to the preparation of 5-deazapterins of considerable biological significance (e.g. 2).

References

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2. For previous papers in this series, and leading references, see Taylor, E. C.; French, L. G. Tet. Lett., **1986**, 27, 1967 and references cited therein.

3. Danenberg, P.V. Biochim. Biophys. Acta, **1977**, 473, 73.

4. (a) Jones, T.R.; Calvert, A.H.; Jackman, A.L.; Brown, S.J.; Jones, M.; Harrap, K.R. Europ. J. Cancer, **1981**, 17, 11: (b) Calvert, A.H.; Alison, D.L.; Harland, S.J.; Jackman, A.L.; Mooney, C.J.; Smith, J. E.; Harrap, K. R. Brit. J. Cancer, **1983**, 48, 116: (c) Alison, D.L.; Newell, D.R.; Calvert, A.H. Brit. J. Cancer, **1983**, 48, 126.

5. Drugs of the Future, **1984**, 9, 893 and references cited therein.

6. Taylor, E.C.; Fletcher, S.R. unpublished results.

7. Huang, J. J. Org. Chem., **1964**, 50, 2293.

8. (a) Heinisch, L.; Ozegowski, W.; Muhlstadt, M. Chem. Ber., **1964**, 97, 5: (b) Taylor, E. C.; Sowinski, F. J. Org. Chem., **1975**, 40, 2329.

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