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A NOVEL SYNTHESIS OF AZOLOPYRIMIDINES[1)]

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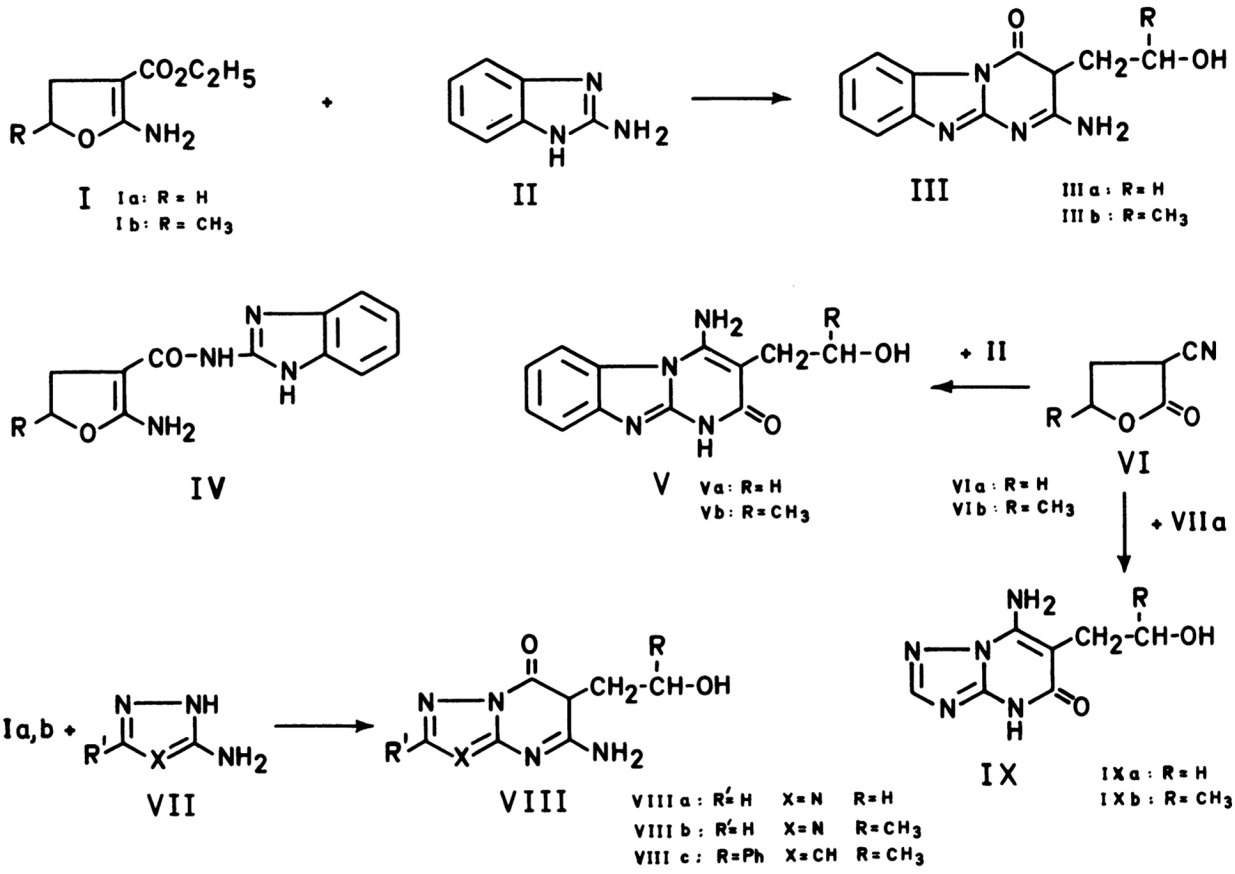
A novel synthesis of several azolopyrimidine derivatives is reported via reaction of heterocyclic ß-enamino esters with 2-amino heterocycles.

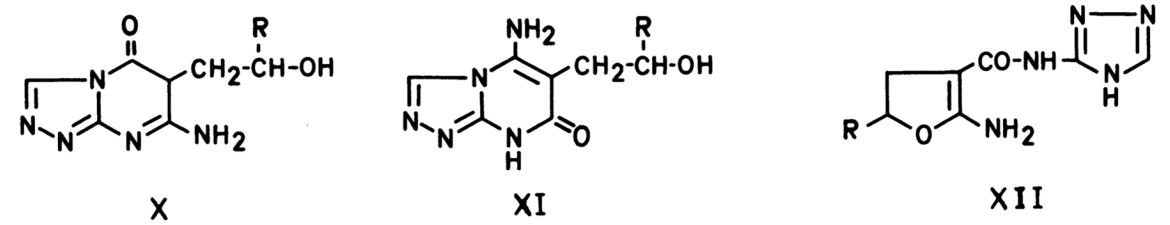
Heterocyclic ß-enamino esters are versatile synthons and their chemistry has recently received considerable attention.[3)] We report here a novel synthesis of azolopyrimidines with bridgehead nitrogens, employing heterocyclic ß-enamino esters as starting materials. The compounds obtained possess latent functional substituents and appear promising for further chemical transformations.[4)] Moreover, they are of interest for biological studies.

Thus, in a typical procedure, equimolar amounts (20 mmoles) of the 2-amino-3-ethoxycarbonyl-4,5-dihydrofurans (Ia,b) and 2-aminobenzimidazole (II) are refluxed in pyridine (30 ml) for 3 - 12 hrs (TLC control). Removal of pyridine, washing with petroleum ether, and trituration with ethanol affords products of molecular formulae corresponding to condensation of Ia,b with II via elimination of ethanol.

We took three alternative theoretically possible structures into consideration (cf. structures III - V, and Table 1). III (and alternate tautomeric structures respectively) proved to be the reaction product based on ^{1}H-NMR which revealed 6-H at lower field than 7-H, 8-H, or 9-H. This downfield shift can only be rationalized in terms of a deshielding by the anisotropy of the adjacent carbonyl group as in III. Reaction products with structures IV or V would be difficult to account for this downfield shift. In turn, the isomeric compound V was obtained independently by the reaction of II with α-cyano-γ-valerolactone (VIb).

Analogously, condensation products are formed from Ia,b and 5-amino-1H-1,2,4-triazole (VIIa), and from Ib and 5-amino-3-phenylpyrazole (VIIb)with elimination of ethanol. Five isomeric structures for the product of reaction Ia,b with VIIa, and three structures for the product of reaction of Ia,b with VIIb can be discussed (cf. structures VIII - XII). The enamino-amide XII could be excluded


I Ia: R = H
Ib: R = CH3
II
III
IIIa: R = H
IIIb: R = CH3
IV
V
Va: R = H
Vb: R = CH3
+ II
VI
VIa: R = H
VIb: R = CH3
+ VIIa
IX
IXa: R = H
IXb: R = CH3
Ia,b +
VII
VIII
VIIIa: R' = H X = N R = H
VIIIb: R' = H X = N R = CH3
VIIIc: R = Ph X = CH R = CH3


X
XI
XII

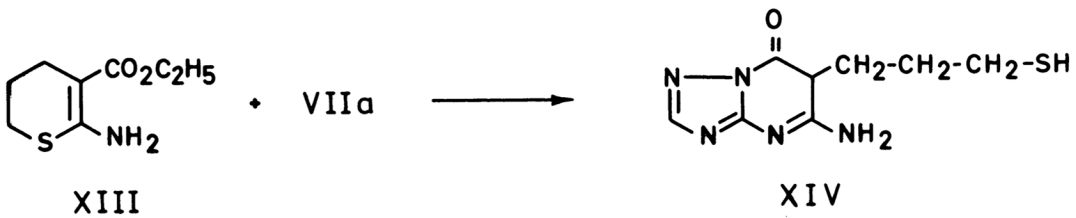

XIII
+ VIIa
XIV

Table I. Azolopyrimidine Derivatives IIIa,b, Vb, VIIIa-c, IXa,b, XIV

Compound	Cryst. Solvent	M.p. [°C]	Yield [%]	Mol. Formulae (M.W.)	M^+ m/e
IIIa	Pyridine	286	76	$C_{12}H_{12}N_4O_2$ (244.3)	244
IIIb	Pyridine	261	82	$C_{13}H_{14}N_4O_2$ (258.3)	258
Vb	Ethanol	262	41	$C_{13}H_{14}N_4O_2$ (258.3)	258
VIIIa	Water	274-276	51	$C_7H_9N_5O_2$ (195.2)	195
VIIIb	Water	246-247	71	$C_8H_{11}N_5O_2$ (209.1)	209
VIIIc	Pyridine	285	71	$C_{15}H_{16}N_4O_2$ (284.3)	284
IXa	Water	279-281	71	$C_7H_9N_5O_2$ (195.2)	195
IXb	Water	225	35	$C_8H_{11}N_5O_2$ (209.1)	209
XIV	Ethanol	286	65	$C_8H_{11}N_5OS$ (225.3)	

from the ^{13}C-NMR data, as a furan C-5 could not be detected and, instead, there was found a resonance for the terminal $-\overset{|}{\underset{|}{C}}-OH$[5,6] as required by the azolopyrimidine structures VIII - XI. By ^{1}H-NMR the 1,2,4-triazolo[3,4-a]pyrimidines X and XI could also be excluded as reaction products of VIIa and Ia,b. Accordingly, we found the triazole proton signal (3-H) at higher field (δ = 8.15 ppm) than as we expected for the 1,2,4-triazolo[3,4-a]pyrimidines X or XI (δ ~ 8.7-9.0 ppm).[7] Spectroscopic methods however, are only of little help for distinguishing between structures VIII and IX. Thus, samples of IX were prepared independently via reaction of VIa,b with VIIa. And in fact, these compounds (IXa,b) are proved to be completely different from VIIIa-c obtained from Ia,b and VIIa,b. Consequently, the latter product was assigned the structure VIII (and the alternate tautomeric structures respectively).

Furthermore, 2-amino-3-ethoxycarbonyl-4,5-dihydrothiophenes have been found unable to condense with 2-amino heterocycles under conditions similar to those chosen above. However, 2-amino-3-ethoxycarbonyl-5,6-dihydro-4H-thiopyrane (XIII) reacted with VIIa in refluxing pyridine to give the 1,2,4-triazolo[1,5-a]-pyrimidine derivative XIV. The structure of this product was deduced from spectroscopic data. At present, reactions of 2-aminothiazoles and further 2-aminoazolines with heterocyclic ß-enamino esters, as well as an extension to corresponding ß-enamino nitriles are investigated.[4]

Most likely, the reaction of I with the 2-amino heterocycles proceeds via a *Michael*-type addition of the primary amino group to the activated double bond in I followed by ring cleavage and recyclization into the final products.[8] Evidence for this is our observation that other heterocyclic ß-enamino esters with aromatic nature are not capable of condensing with amino heterocycles under similar and stronger conditions.

Since the ring nitrogens are nucleophilic centers as well, it may be considered that the products formed can result from the addition of ring nitrogens to the enamino moiety in I and XIII. It seems, however, that due to steric factors such an addition will be less favoured and thus, products resulting from initial attack by the primary amino group are only formed.

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REFERENCES AND NOTES

1) Heterocyclic ß-Enamino Esters, 26; Part 25: G. SZILÁGYI and H. WAMHOFF, Synthesis, 1980, 698; also part 11 of the series "Reactions with Heterocyclic Amidines", part 10: M.H. ELNAGDI, M.R.H. ELMAGHAYER, and E.A. HAFEZ, J. Heterocycl. Chem., in press.

2) Alexander von Humboldt fellow 1979/80.

3) H. WAMHOFF in R.N. CASTLE and S.W. SCHNELLER (eds.), "Lectures in Heterocyclic Chemistry", Vol. V, p. S-61, Heterocorporation, Orem/Utah 1980.

4) The chemistry of the synthesized azolopyrimidines as well as full experimental details will be reported later; M.H. ELNAGDI and H. WAMHOFF, J. Heterocycl. Chem., in preparation.

5) G. HAFFMANNS, Diplomarbeit, Universität Bonn 1978.

6) E. BREITMAIER and W. VOELTER, ^{13}C-NMR Spectroscopy, Verlag Chemie, Weinheim, 2nd ed. 1978, p. 153 and table 4.23.

7) H. REIMLINGER, R. JACQUIER, and J. DAUNIS, Chem.Ber. 104, 2702 (1971).

8) In an analogous procedure ethylenediamine and o-phenylenediamine afford products resulting from initial *Michael* addition to the activated double bond; cf. H. WAMHOFF and C. MATERNE, Chem.Ber. 107, 1794 (1977); further evidence: M.H. ELNAGDI and H. WAMHOFF, J. Heterocycl. Chem., in preparation.

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