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A NEW RING TRANSFORMATION OF ISOXAZOLO[3,4-d]PYRIMIDINES INTO PYRIMIDO[4,5-d]PYRIMIDINES

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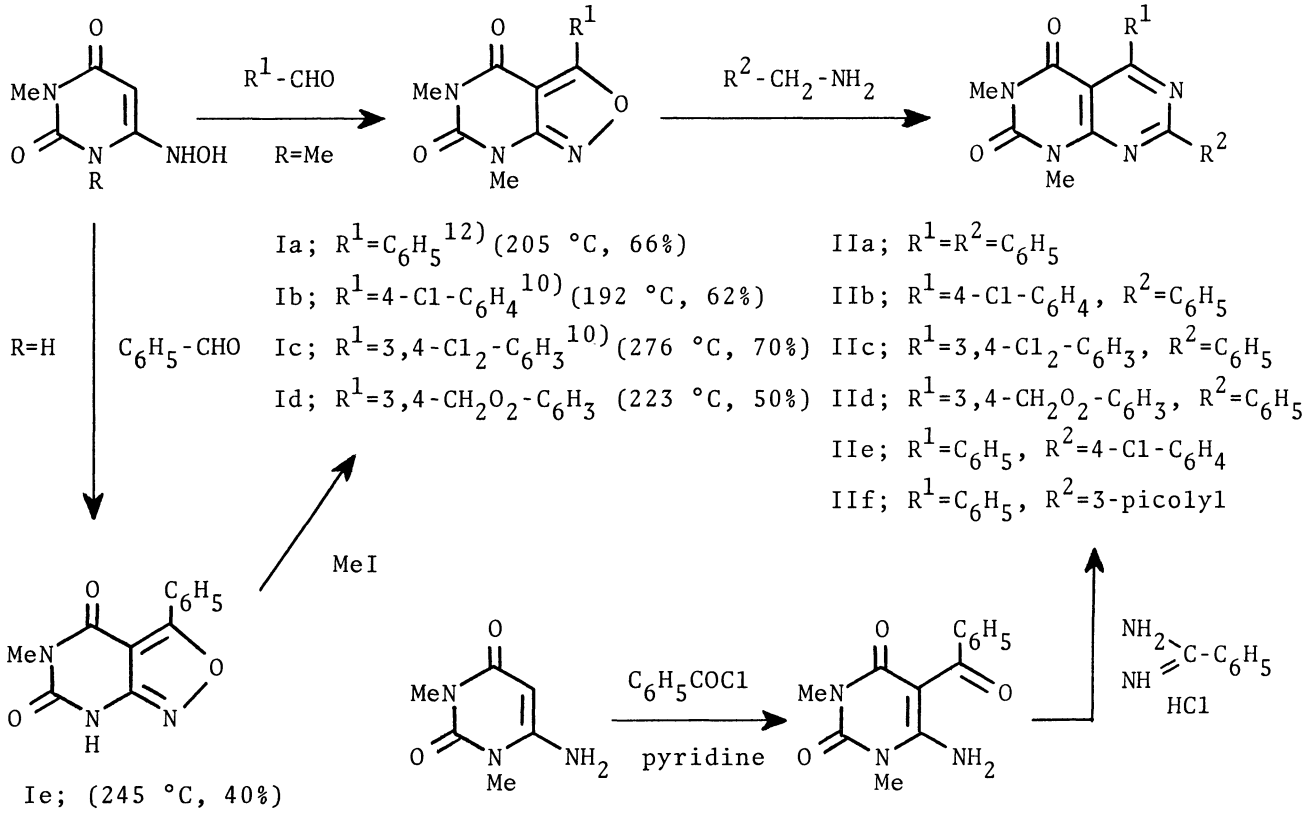
The treatment of isoxazolo[3,4-d]pyrimidines with benzylamines and 4-picolylamine caused ring expansion to the respective pyrimido-[4,5-d]pyrimidines by intramolecular cycloaddition of 1,5-diazahexa-triene intermediates. Reaction mechanism of this ring transformation will be discussed.

Recently we have reported the novel synthetic method for preparation of heterocycles such as purines,[1,2,5] pteridines,[2,3] pyrazolo[3,4-d]pyrimidines,[1,4] and 6-azapteridines[5] by intramolecular cycloaddition of aza analogs of hexatriene. The usefulness of this methodology has been further demonstrated in the synthesis of pyrimido[4,5-d]quinolines (5-deazaalloxazines)[6] and pyrimido[4,5-c]pyridazines (4-deazafervenulins)[7,8] and in the ring transformation of pyrazolo[4,3-d]pyrimidine 1-oxides to pyrimido[5,4-d]pyrimidines.[9] This communication describes a new type of ring transformation of 5,7-dimethylisoxazolo[3,4-d]pyrimidine-4,6(5H,7H)-diones into 1,3-dimethylpyrimido[4,5-d]pyrimidine-2,4(1H,3H)-diones which involves an intramolecular cycloaddition of 1,5-diazahexatriene intermediates.

As found independently by Senga et al.,[10] 1,3-dimethyl-6-hydroxylaminouracil[11] readily condensed with aryl aldehydes by refluxing in ethanol to form the corresponding 5,7-dimethylisoxazolo[3,4-d]pyrimidine-4,6(5H,7H)-diones (Ia-d)[12] (Melting points and yields are indicated below the formulae. Senga et al. used dimethylformamide as solvent in this condensation. Use of ethanol as solvent instead of dimethylformamide caused much improvement in the yields.) Furthermore 3-methyl-6-

hydroxylaminouracil[12,13] gave the corresponding 5-methylisoxazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (Ie) by the condensation with benzaldehyde, whose structure was confirmed by the conversion to the 5,7-dimethyl derivative (Ia) by the conventional methylation with methyl iodide in the presence of potassium carbonate in dimethylformamide.



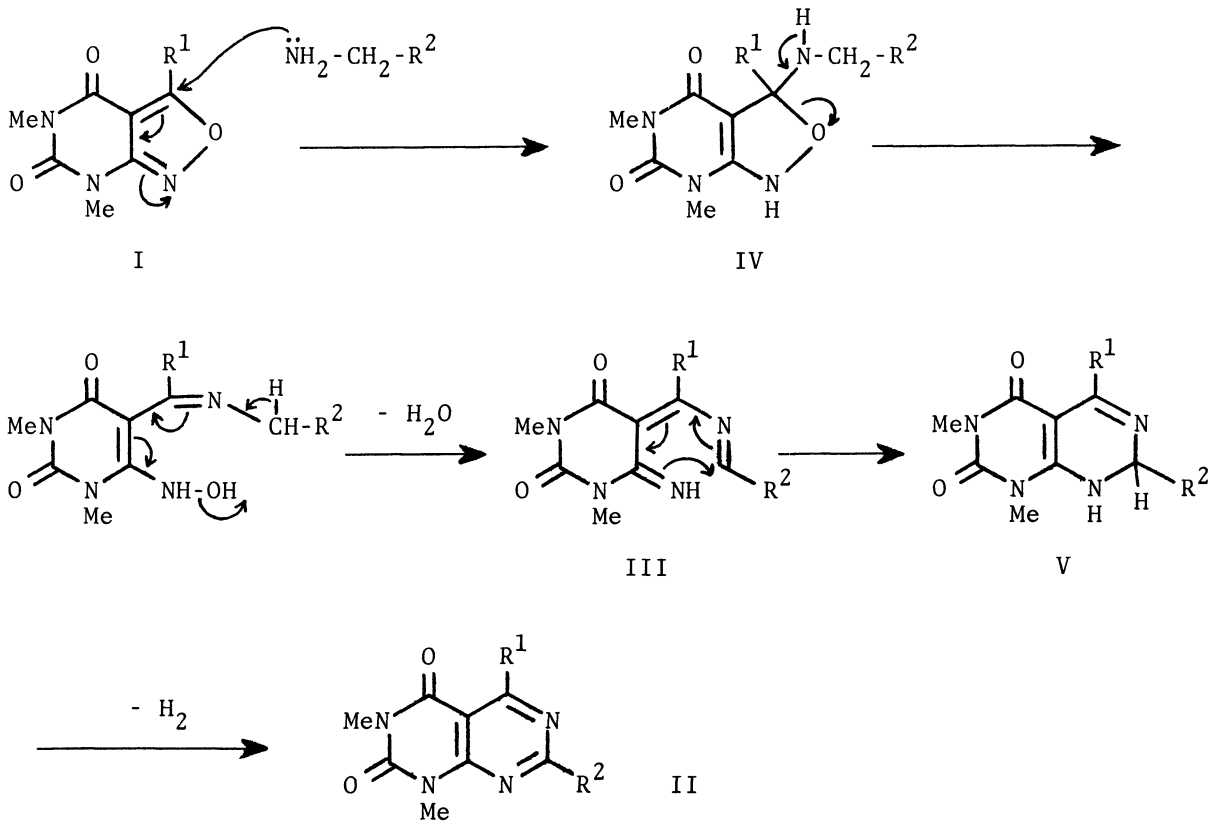
Heating of 5,7-dimethyl-3-phenylisoxazolo[3,4-d]pyrimidine-4,6(5H,7H)-dione (Ia) with benzylamine at 200 °C for 2 h gave a ring expansion product, 1,3-dimethyl-5,7-diphenylpyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione (IIa). Its structure was established by comparison with an authentic sample prepared unequivocally as follows. Heating of 6-amino-1,3-dimethyluracil with benzoyl chloride in pyridine at 90 °C for 1 h afforded 6-amino-5-benzoyl-1,3-dimethyluracil, mp 254 °C, in 95% yield. This was fused with benzamidine hydrochloride at 270 °C for 20 min to give compound IIa in 70% yield, which was identical in all respects with the foregoing product. Similarly, treatment of compounds Ia-d with benzylamines and 3-picolylamine under the conditions indicated in Table yielded the corresponding pyrimido[4,5-d]pyrimidines (IIb-f).

Fusion of Ia with benzylamine at 200 °C for a few min gave the 1,5-diazahexatriene intermediate (III), mp 235 °C (decomp.). Refluxing of III in ethanol for 2 h caused ring closure followed by dehydrogenation to give IIa. The structure of III was assigned by its elemental analysis and spectral data. The nuclear magnetic resonance spectrum (CF_3COOH) revealed three singlets at δ 3.56 (N-Me), 3.68 (N-Me) and 10.35 (N=CH), and the presence of aromatic protons of two phenyl groups at δ 7.5-8.5. The infrared spectrum (Nujol) showed a sharp NH= absorption at 3342 cm^{-1}.

TABLE Formation of Pyrimidopyrimidines by Reaction of Isoxazolopyrimidines with Amines

Starting material	Amine	Reaction condition Temp (°C)	Time (h)	Product	Mp(°C)[a]	Yield(%)
Ia	Benzylamine	200	2	IIa	230	44
Ib	Benzylamine	200	3	IIb	256	55
Ic	Benzylamine	280	3	IIc	258	54
Id	Benzylamine	200	2	IId	272	48
Ia	4-Chlorobenzylamine	250	3	IIe	245	53
Ia	3-Picolylamine	280	2	IIf	233	50

a) These compounds were recrystallized from acetic acid.



Therefore, we rationalize this new transformation in terms of initial nucleophilic attack of the benzylamine on the 3-position of I giving the 3-benzyl adduct (IV). Prototropic rearrangement followed by dehydration would give the 1,5-diazahexatriene intermediate (III), which is ideally disposed for intramolecular cycloaddition to dihydropyrimidopyrimidine (V). Subsequent dehydrogenation by air would lead to the final product (II).

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