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A NEW RING TRANSFORMATION OF PYRAZOLO[4,3-d]PYRIMIDINES TO PYRIMIDO[5,4-d]PYRIMIDINES

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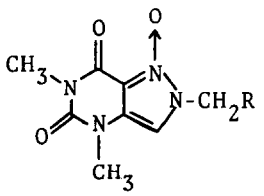
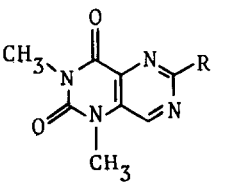
In our studies of the reaction of uracil derivatives with nucleophiles we have recently found a novel and facile synthesis of pyrazolo[4,3-d]pyrimidines and their 1-oxides using 6-bromomethyl-1,3-dimethyl-5-nitrouracil and amines.[1] This communication describes a new type of ring transformation[2] of these 1-oxides (I) into the pyrimido[5,4-d]pyrimidines (II).[3]

2-Benzyl-4,6-dimethyl-2H-pyrazolo[4,3-d]pyrimidine-5,7(4H,6H)-dione 1-oxide (Ia) was refluxed with sodium ethoxide in absolute ethanol to give a ring expansion product, 1,3-dimethyl-6-phenylpyrimido[5,4-d]pyrimidine-2,4(1H,3H)-dione (IIa) in 71 % yield. The structure of IIa was confirmed by its elemental and spectroscopic analyses. The NMR spectrum of IIa shows a characteristic signal (1H, s, C8-H) at 9.55 ppm with disappearance of the benzylic protons of Ia. Similar treatment of the pyrazolopyrimidine 1-oxides (Ib: R=p-methoxyphenyl and Ic: R=2-furyl) gave the corresponding pyrimido[5,4-d]pyrimidines (IIb



Ia-d

a: R=C_6H_5
b: R=p-$CH_3OC_6H_4$
c: R= 
d: R=$CO_2C_2H_5$

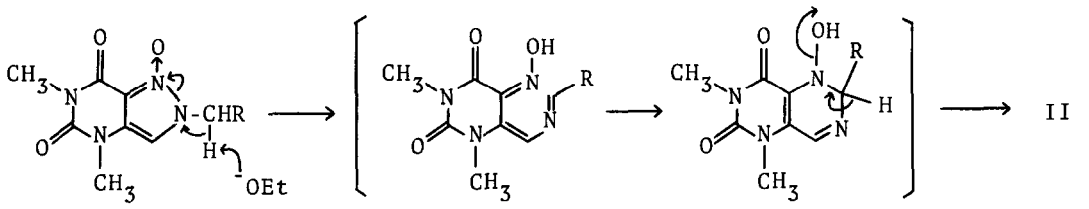


IIa-d

IIa: mp 263-264°
IIb: mp 259-260°
IIc: mp 298-299°
IId: mp 202-203°

and IIc) in 61 and 50 % yields, respectively. When the 1-oxide (Id: R=$CO_2C_2H_5$) was treated under the same conditions, the ring transformation product (IId) was not obtained. However, heating of Id in diglyme with sodium hydride afforded the expected product (IId) in 34 % yield. On the other hand, the 2-alkyl(or aryl)-pyrazolopyrimidine 1-oxides having no active methylene group at the 2-position did not cause the ring transformation under various conditions.

A reasonable mechanism for the transformation of I to II is shown in Scheme. Proton abstraction from the N-2 active methylene by an ethoxyl anion followed by cleavage of the N1-N2 bond would give an open-chain azahexatriene (A), which undergoes the intramolecular cycloaddition[4] yielding a dihydro intermediate (B). Finally, the aromatization of (B) by dehydration would lead to the product (II).



I (A) (B)

References and Footnotes

1) S. Senda, K. Hirota, T. Asao, and Y. Yamada, J.C.S. Chem. Comm., 556 (1977).

2) H.C. van der Plas, "Ring Transformations of Heterocycles" Vol. 1, Academic Press, London, 1973, p 271.

3) The synthesis of pyrimido[5,4-d]pyrimidine ring system has established in conjunction with the study of coronary vasodilative activity,[3a] but the principal synthetic method is performed only by condensation of 5-amino-4-carboxypyrimidines with C-N (C-N-C) fragment reagents[3b]; 3a) V.R. Kadatz, Arzneimittel-Forsch., 9, 39 (1959); 3b) F.G. Fischer and J. Roch, Ann., 572 217 (1951).

4) It is known that azahexatrienes thermochemically undergo the intramolecular cycloaddition to six membered heterocycles; F. Yoneda, M. Higuchi, and T. Nagamatsu, J. Am. Chem. Soc., 96, 5607 (1974); F. Yoneda and M. Higuchi, J.C.S. Perkin I, 1336 (1977).