DOUBLE RING-TRANSFORMATION OF URACILS TO PYRAZOLONES VIA HYDANTOIN RING SYSTEM

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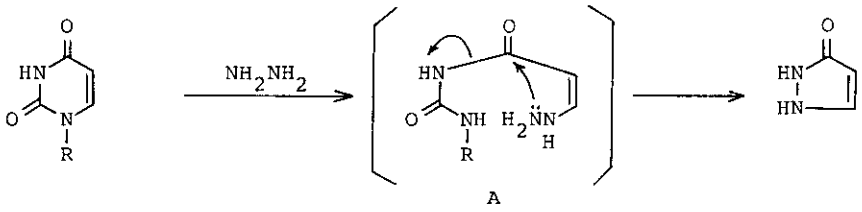
Abstract —— Hydrazinolysis of 3-alkyl-1-aryl-5-bromo-6-methyluracil derivatives (1) causes a novel double ring-transformation to pyrazolones (2) via hydantoin ring system.

The ring-transformation of uracils to pyrazolones by hydrazinolysis is well documented.[1] This type of the facile transformation, which proceeds via an open-chain intermediate (A), has been employed extensively for the chemical modification of nucleic acids.[2]



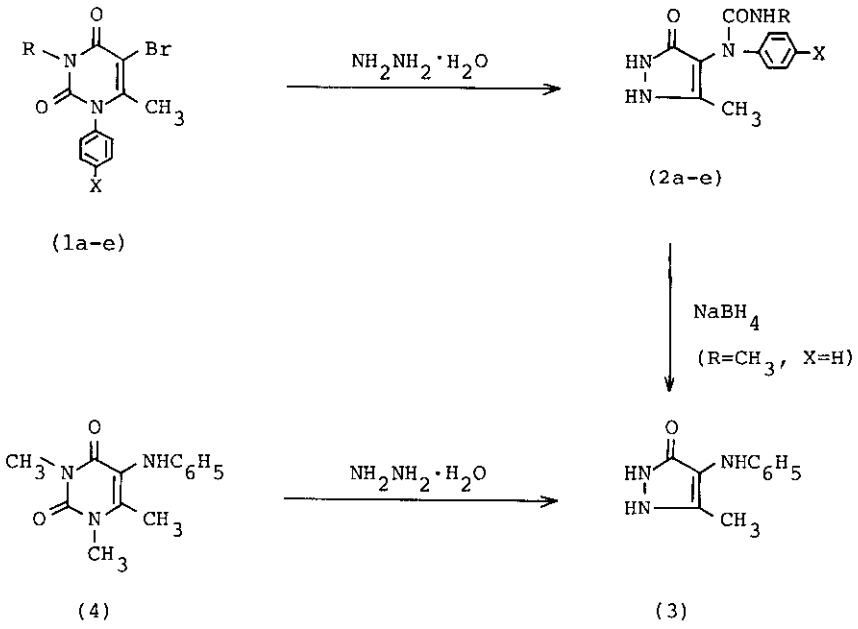
A

Scheme I

In the course of studies on the reactivity of 5-bromouracil derivatives towards nucleophiles,[3,4] we found that 1-aryl-5-bromo-6-methyluracils (1) undergo a novel double ring-transformation into pyrazolones (2) via an intermediacy of hydantoin by the reaction with hydrazine hydrate.[5] The present reaction proceeds in a different manner from the well-known uracil-to-pyrazolone transformation[1] in respect of the reaction mechanism.

When 5-bromo-3,6-dimethyl-1-phenyluracil (1a) and excess hydrazine hydrate were heated in refluxing 2-propanol for 24 hr, 4-(3-methyl-1-phenyl)ureido-5-methyl-

pyrazol-3(2H)-one (2a) was formed in 89% yield. The structure of (2a) was pressumed by its elemental analysis and the following spectroscopic data; ^{1}Hnmr (DMSO-d_6) δ 2.00(s, 5-Me), 2.61(d, J=4.5 Hz, NHMe, collapsed to a sharp singlet by deuterium exchange), 5.98(br, J=4.5 Hz, NH), 7.00-7.40(m, C_6H_5); uv(EtOH) λmax nm(log ε) 242(3.91). The ultimate proof of the structure was provided by the reduction of (2a) to 4-amino-5-methylpyrazol-3(2H)-one (3). N,N,N'-Trisubstituted ureas are easily reduced to formamides and amines with sodium borohydride in pyridine.[6] In agreement with the previous result, the reduction of (2a) with sodium borohydride allowed isolation of an amine (3)[7] (69% yield), which was



Scheme 2

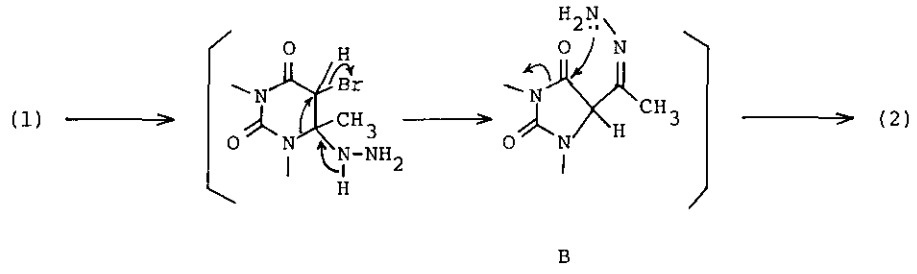
Table 4-(3-Alkyl-1-aryl)ureido-5-methylpyrazol-3(2H)-ones (2)

No.	R	X	Recryst. solvent	mp(°C)	Yield(%)
(2a)	CH_3	H	EtOH-ether	254	89
(2b)	C_2H_5	H	2-PrOH	245-246	75
(2c)	$CH_2CH=CH_2$	H	2-PrOH	238-239	59
(2d)	C_4H_9	H	2-PrOH	228-229	73
(2e)	CH_3	OCH_3	2-PrOH	256-257	57

identical with a sample prepared conventionally by hydrazinolysis of 5-anilino-1,3-dimethyluracil (4).[8]

Analogously, treatment of 5-bromo-6-methyluracil derivatives (1b-e) possessing a phenyl group at the 1-position with hydrazine hydrate led to the formation of the corresponding pyrazolones (2b-e) as shown in Table.

On the other hand, the 5-bromo-6-methyluracils having an alkyl group at the 1-position did not undergo the ring-transformation despite of many trials under various conditions. Above experimental observations may be explained in terms of that a phenyl substituent at the 1-position plays a role for the facile cleavage of the N_1-C_6 bond on the uracil ring. Thus, a reasonable mechanism for the transformation of (1) to (2) is outlined as shown in Scheme 3. An initial nucleophilic addition of hydrazine hydrate to the 5,6-double bond followed by cleavage of the N_1-C_6 bond could give a hydantoin intermediate (B). The intermediate (B) subsequently undergoes an intramolecular nucleophilic attack of the terminal amino group on the 4-carbonyl group to give the pyrazolones(2).



Scheme 3

Involvement of a hydantoin intermediate in the present ring-transformation accommodates that (1) undergoes ring contraction to hydantoin upon treatment with a primary alkylamine in the place of hydrazine.[4]

REFERENCES AND NOTES

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2) N.K. Kochetkov and E.I. Budwsky, Progr. Nucleic Acid Res. Mol. Biol., 1969, 9, 403; H. Töler, "Procedures in Nucleic Acid Research",Vol. 2, G.L. Cantoni and D.R. Davies, Eds., Happer and Row, New York, 1971, pp. 680-699.

3) S. Senda, K. Hirota, and K. Banno, J. Med. Chem., 1972, 15, 471; S. Senda, K. Hirota, and T. Asao, J. Org. Chem., 1975, 40, 353; K. Hirota, Y.Yamada, Y. Kitade, and S. Senda, J. Chem. Soc. Perkin I, 1981, 2943.

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5) For an excellent review of ring-transformations of pyrimidines, see H.C. van der Plas, "Ring Transformation of Heterocycles", Vol. 2, Academic Press, London, 1973, pp. 116-146.

6) Y. Kikugawa, S. Yamada, H. Nagashima, and K. Kaji, Tetrahedron Lett., 1969, 699.

7) For (3): ^{1}Hnmr(DMSO-d_6) δ 1.98(s, Me), 6.38-7.14(m, C_6H_5); uv(EtOH) λmax nm(log ε) 247(4.22).

8) 5-Anilino-1,3,6-trimethyluracil (4) was prepared by methylation of 5-anilino-6-methyluracil[8a] with dimethyl sulfate; 8a) F.R. Gerns, A. Perrotta, and G.H. Hitchings, J. Med. Chem., 1966, 9, 108.

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