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RING CONTRACTION OF URACILS TO HYDANTOINS

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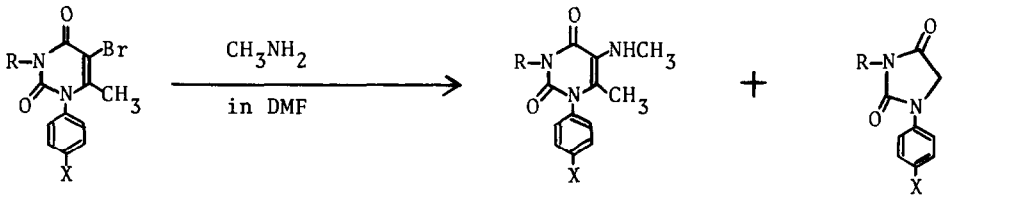
In the course of our studies on the nucleophilic substitution of 5-bromo-6-methyluracil derivatives with a variety of amines[1], we found that the reaction of 5-bromouracils(I) with monoalkylamines causes ring contraction to give hydantoin derivatives(III). To our knowledge, such a ring transformation of a uracil ring to a hydantoin ring has not been previously reported[2].

5-Bromo-3,6-dimethyl-1-phenyluracil(Ia) in dimethylformamide was heated with 30% aqueous solution of methylamine in a sealed tube at 100° for 18 hours to give a normal substitution product, 3,6-dimethyl-5-methylamino-1-phenyluracil (IIa)(mp 128°, 21%) and an abnormal product(mp 192-194°, 30%), whose structure was confirmed as 3-methyl-1-phenylhydantoin(IIIa) by direct comparison with an authentic specimen[3].

Similar treatment of 5-bromo-6-methyluracil derivatives(Ib-e) bearing a phenyl group at 1-position with methylamine gave the corresponding hydantoin



Ia-e

a: R=CH_3, X=H
b: R=CH_3, X=OCH_3
c: R=CH_3, X=NO_2
d: R=C_2H_5, X=H
e: R=$CH_2CH{=}CH_2$, X=H

IIa,b

a: mp 128°
b: mp 164°

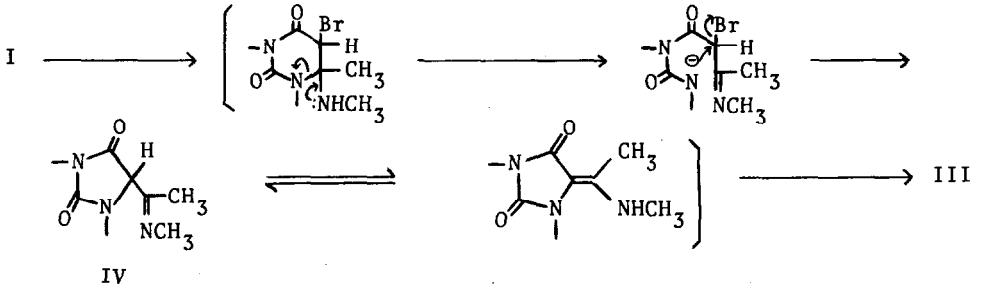
IIIa-e

a: mp 192-194°
b: mp 198°
c: mp 158°
d: mp 149°
e: mp 124°

Scheme 1

derivatives(IIIb-e) in 5-34% yields together with IIb[4]. Their structures were established by elemental analyses and spectroscopic data (ir, uv, and pmr spectra). The ring contraction of Ia using ethylamine instead of methylamine under the same conditions proceeded to yield the hydantoin(Ia), but the reaction of Ia with tertiary amines such as triethylamine resulted in the recovery of the starting material. On treatment of Ia with dialkylamines and aromatic amines, no ring contraction occurred but alternative reactions proceeded to give 5-dialkylaminouracils[1a] and 6-arylaminomethyluracils[1b] respectively as reported previously.

From the above results, a reasonable reaction mechanism for the ring contraction can be considered to involve the following steps: the first step is addition of methylamine to the 5,6-double bond and subsequent ring opening by a cleavage of the 1,6-bond. The second step is ring closure caused by an intramolecular nucleophilic substitution, affording the hydantoin intermediate(IV), which on tautomerism is hydrolyzed to give the final product(III).



Scheme 2

References and Footnotes

1) a) S. Senda, K. Hirota, and K. Banno, J. Med. Chem., 15, 471(1972).
b) S. Senda and K. Hirota, J. Chem. Soc. Chem. Commun., 1974, in press.

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

3) H. Biltz and K. Slotta, J. Pract. Chem., 113, 233(1926).

4) 5-Methylaminouracils(IIc-e) were confirmed in a mixture by uv and pmr spectra but could not be isolated and purified.