RING TRANSFORMATION OF URACILS TO 2-PYRIDONES. HYDROLYSIS OF 6-(2-DIMETHYLAMINOVINYL)URACILS

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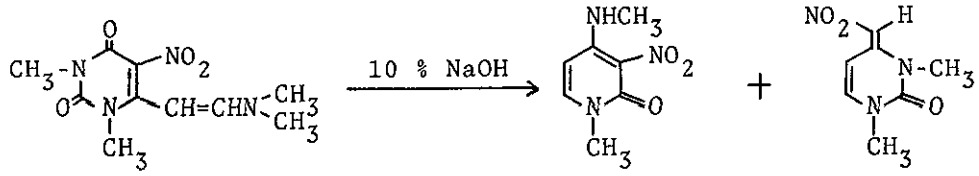
Hydrolysis of 1,3-disubstituted 6-(2-dimethylaminovinyl)uracil derivatives (I) in aqueous sodium hydroxide caused a novel ring transformation giving 2-pyridone(II) along with 4-methylenepyrimidine(III) or the degradation product (IV or V).

It has been already known[1] that uracils undergo ring contractions upon treatment with some kinds of nucleophiles. For example, hydrazinolysis of uracil and thymine affords 3-pyrazolone and 4-methyl-3-pyrazolone, respectively.[2] In our previous paper[3] we also reported that 5-bromo-6-methyluracils underwent ring contraction into hydantoins upon treatment with alkylamines. In this communication we describe a new type of ring transformation giving 2-pyridones by hydrolysis of 6-(2-di-

methylaminovinyl)uracils. This is a novel and facile synthesis of 3-substituted 4-alkyl(or aryl)amino-2-pyridones.

A suspension of 1,3-dimethyl-6-(2-dimethylaminovinyl)-5-nitrouracil (Ia)[4] in 10 % aqueous sodium hydroxide was heated to 90° until Ia was completely dissolved and then the heating was continued for further 10 min. Upon cooling to room temperature the resulting precipitates were filtered off and washed with water to give 1,2-dihydro-1-methyl-4-methylamino-3-nitro-2-pyridone (IIa) in 62 % yield. The mother liquor was acidified with acetic acid to yield an additional product, 1,2,3,4-tetrahydro-1,3-dimethyl-4-nitromethylene-2-pyrimidone (III)[5], mp 259-260°, in 14 % yield.



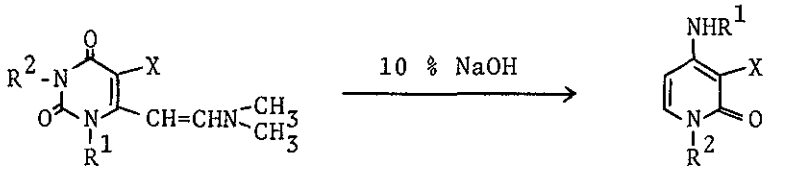
Ia IIa III

Scheme 1

Structural elucidation of IIa and III was fully achieved on the basis of their elemental analyses and the following spectral data; IIa: NMR($CDCl_3$) 2.99 (3H, d, NH-$\underline{CH_3}$, J=5.5Hz, collapsing with D_2O to singlet), 3.37 (3H, s, N-CH_3). 6.04 (1H, d, C5-H, J=8.0Hz), 7.78 (1H, d, C6-H, J=8.0Hz), 8.82 (1H, br, NH,

vanishing with D_2O), UV λ_{max}^{EtOH} 242 nm(log ε 4.1), 340(3.9), IR (KBr) 3280 cm^{-1} (NH), 1640(C=O); III: NMR($CDCl_3$) 3.36 and 3.44 (each 3H, each s, each N-CH_3), 6.87 (1H, d, =$CHNO_2$, J= 1.0Hz), 7.00 (1H, dd, C5-H, J=8.5 and 1.0Hz), 7.75 (1H, d, C6-H, J=8.5Hz), UV λ_{max}^{EtOH} 257 nm (log ε 3.6), 285(3.5), 384(4.5).

Hydrolysis of various 1,3-disubstituted 6-(2-dimethylamino-vinyl)uracil derivatives (Ib-g)[4,6] with 10 % aqueous sodium hydroxide at 90° for one hr caused the ring transformation giving predominantly 1,2-dihydro-2-pyridone derivatives (IIb-g). Open-chain compounds such as IVb and Vd,f[7] were obtained as by-prosucts and a ring transformation product corresponding to III was not isolated. The products thus obtained are shown in the Table.



I II

IV V

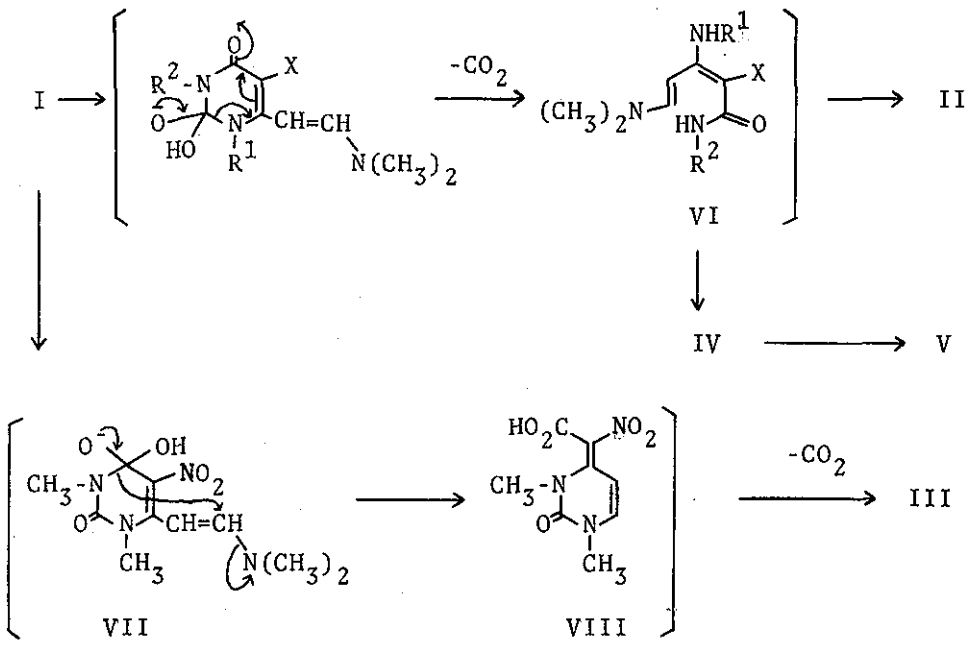
Scheme 2

Table Formation of 2-pyridones (II)

Starting Material	X	R^1	R^2	Product II Yield (%)	Product II mp (°C)	By-product (%)
Ia	NO_2	CH_3	CH_3	62	168-169	III(14)
Ib	NO_2	CH_3	C_6H_{11}	26	177-178	IV(10)
Ic	NO_2	CH_3	p-$NO_2C_6H_4$	21	274-275	
Id	CN	CH_3	CH_3	70	243-244	V(20)
Ie	CN	C_6H_5	CH_3	85	173-174	
If	CN	$CH_2C_6H_5$	CH_3	35	209-210	V(20)
Ig	H	C_6H_5	CH_3	56	239-240	

We suggest the mechanism for the hydrolysis of I as outlined in the Scheme 3. Thus, conversion of I into II, IV, and V would involve the initial addition of hydroxide ion to the C-2 position, followed by fission of the N1-C2 bond and decarboxylation giving the open-chain product VI.[8] Recyclization of VI accompanied by elimination of dimethylamine leads to the formation of II. On the other hand, further hydrolysis of VI affords IV and V.

As to the mechanism for the formation of III, the first step is an addition of hydroxide ion to the C-4 position rather than to the C-2. The resulting intermediate VII undergoes recyclization to VIII with fission of the N3-C4 bond and elimina-



Scheme 3

tion of dimethylamine. Compound III is obtained by decarboxylation of VIII.

References and Footnotes

*Satisfactory analytical data have been obtained for all crystalline compounds described in this communication.

1. For a review of ring transformations of pyrimidines, see H.C. van der Plas, "Ring Transformations of Heterocycles"

Vol. 2, Academic Press, London, 1973, pp 116; K. Hirota, K.A. Watanabe, and J.J. Fox, J. Heterocycl. Chem., 14, 537 (1977).

2. D.H. Hayes and F. Hayes-Baron, J. Chem. Soc. (C), 1528 (1967).
3. S. Senda, K. Hirota, and K. Banno, Tetrahedron Lett., 3087 (1974).
4. Compounds I were prepared by reaction of the corresponding 6-methyluracils with DMF-dimethylacetal in dry DMF; S. Sneda and K. Hirota, Chem. Pharm. Bull. (Tokyo), 22, 2593 (1974).
5. The geometry of III has not been determined.
6. The geometry of the vinyl moiety was assigned as a trans form by the coupling constant (J=13Hz) in the NMR spectrum.
7. The structure of IV and V was confirmed by the following data; IVb: mp 193°C NMR($CDCl_3$)δ 1.05-2.20 (10H, m, cyclohexyl), 2.47 (3H, s, C-CH_3), 3.12 and 8.65 (each 1H, each br, each NH) 3.22 (3H, d, $NHCH_3$, J=5.5Hz), 3.55-4.05 (1H, m, N-CH<); IR(KBr) 1630 cm^{-1}(C=O), 3290 (NH); Vd: mp 100°C NMR($CDCl_3$)δ 2.29 (3H, s, C-CH_3), 2.91 (3H, d, $NHCH_3$, J=5.5 Hz), 6.30 and 16.15 (each 1H, each br, NH and OH); IR(KBr) 1600 cm^{-1}(C=O), 2205 (CN), 3350 (NH).
8. Compound VId was actually isolated when Id was heated in 10 % aqueous sodium hydroxide at 90° for 10 min. Treatment of VId under the ring transformation conditions yielded IId in a quantitative yield.

Received, 1st March, 1978