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A NOVEL SYNTHESIS OF PYRIDO[2,3-d]PYRIMIDINES BY REACTION OF URACILS WITH 6-AMINOURACILS VIA PYRIMIDINE-TO-PYRIDINE TRANSFORMATION.

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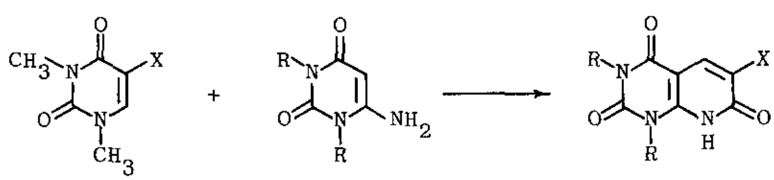
Abstract —— Reaction of 1,3-dimethyluracils with 1,3-dialkyl-6-aminouracils in basic media caused the pyrimidine-to-pyridine transformation to afford new pyrido[2,3-d]pyrimidine derivatives. A plausible mechanism for the ring transformation is offered.

Recently we have reported novel ring transformation reactions of "pyrimidine to pyrimidine"[1] and "pyrimidine to pyridine"[2] involving exchange of N_1-C_2-N_3 of pyrimidines for N-C-N and N-C-C fragments, respectively, of an attacking nucleophile. This paper describes a new synthesis of pyrido[2,3-d]pyrimidine derivatives (3) by the reaction of 5-substituted 1,3-dimethyluracils (1) and 1,3-dialkyl-6-aminouracils (2) via pyrimidine-to-pyridine transformation.

Reaction of 1,3-dimethyluracil (1a) with 6-amino-1,3-dimethyluracil (2a) in the presence of sodium ethoxide in refluxing ethanol for 95 hr, followed by neutralization of the reaction mixture with conc HCl, afforded 1,3-dimethylpyrido[2,3-d]-pyrimidine-2,4,7(1H,3H,8H)-trione (3a) and 1,3-dimethylurea. The structure of (3a) was confirmed by comparison with an authentic sample prepared according to the method by Broom et al.[3] Similar treatment of 1,3-dimethyluracils (1b-c) with



(1a): X=H
(1b): X=CN
(1c): X=NO_2
(1d): X=$COCH_3$

(2a): R=CH_3
(2b): R=C_2H_5
(2c): R=C_3H_7

(3a-f)

Scheme I

1,3-dialkyl-6-aminouracils (2a-c) gave the corresponding pyrido[2,3-d]pyrimidines (3b-e)[4] as summarized in Table.

The treatment of 6-amino-1,3-diethyl(or dipropyl)uracil (2b or 2c) with (1b) gave the 1,3-diethyl(or dipropyl)pyrido[2,3-d]pyrimidine (3c or 3d), respectively. It indicates that the 1,3-dialkyl groups of the product (3) obtained in these conversions are derived from those of 6-aminouracils (2).

Table Formation of Pyrido[2,3-d]pyrimidines (3)

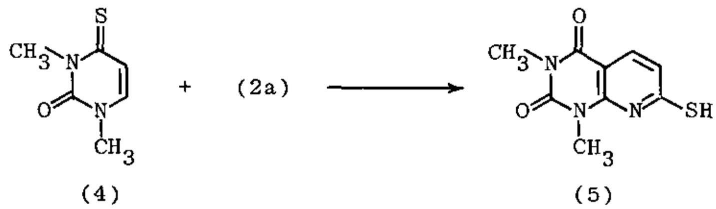
starting material	reaction* time (h)	product	X	R	mp. (°C)	yield (%)*
(1a) + (2a)	95	(3a)	H	CH_3	288-289	33
(1b) + (2a)	5 (4)	(3b)	CN	CH_3	>300	52 (63)
(1b) + (2b)	1	(3c)	CN	C_2H_5	294-295	65
(1b) + (2c)	2	(3d)	CN	C_3H_7	264-265	63
(1c) + (2a)	3 (3)	(3e)	NO_2	CH_3	239-240	34 (50)
(1d) + (2a)	(9)	(3f)	$COCH_3$	CH_3	242-243	(65)

* When potassium hydroxide instead of sodium ethoxide was used as a base, the reaction time and yield given in parentheses were applied and resulted, respectively.

The reaction is highly dependent on the 5-substituent of 1,3-dimethyluracils. Thus, when the uracils (1b-d) bearing an electron-withdrawing group such as CN, NO_2 and $COCH_3$ at C_5 were allowed to react with (2), the conversion was completed in a short time giving the product in better yield as compared with the reaction of (1a) with (2a). On the other hand, the presence of methyl group at C_5 suppressed the reaction. Thus, 1,3-dimethylthymine did not give the corresponding pyrido[2,3-d]pyrimidine.

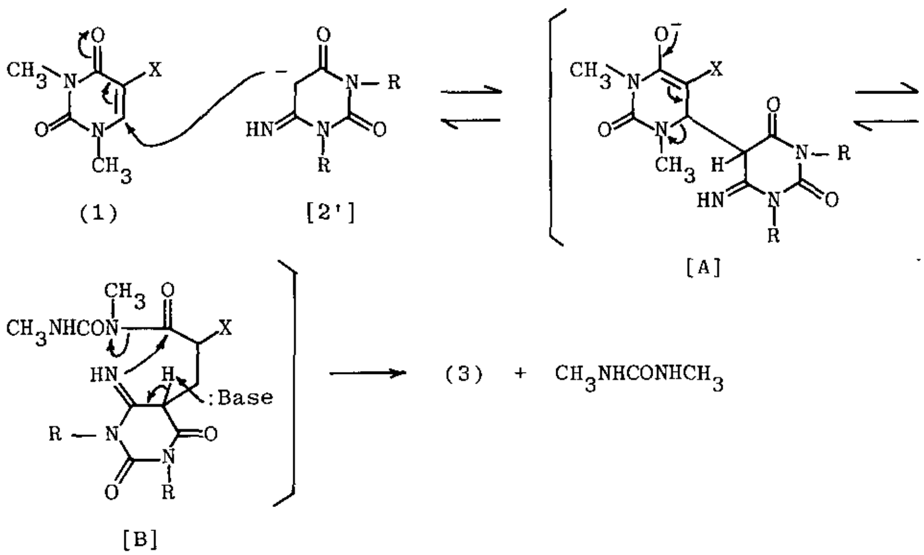
The reaction of 5-acetyl-1,3-dimethyluracil (1d) with (2a) under the same conditions did not give the expected transformation product (3f), while the use of potassium hydroxide instead of sodium ethoxide gave it in 65% yield. Such a use of potassium hydroxide in the reaction of (1b) or (1c) with (2a) caused a little improvement in the yield as shown in Table.

Reaction of 1,3-dimethyl-4-thiouracil (4) with (2a) in ethanolic sodium ethoxide was also carried out and the reaction was found to proceed smoothly giving the corresponding 7-mercaptopyrido[2,3-d]pyrimidine (5), mp 191-193°, in 78% yield.



Scheme II

On the basis of the isolation of 1,3-dimethylurea from the reaction mixture and the fact that the reaction product is a 7-oxopyrido[2,3-d]pyrimidine[5], a plausible mechanism for the conversion of (1) into (3) was formulated as shown in Scheme III. *The initial step would be attack by the carbanion* [2'][6] at C_6 of (1) to give rise to Michael adduct [A] followed by scission of the N_1-C_6 bond to the open-chain intermediate [B]. Subsequent cyclization of [B] would afford (3) and 1,3-dimethylurea.



Scheme III

In this conversion by the reaction of uracils (1) with 6-aminouracils (2), (1) acts as a sourse of three carbon unit to form a pyridine ring system. Thus, (1) may be regarded as a formylacetate masked with 1,3-dialkylurea, so (1) is a useful synthone for the synthesis of heterocycles.[1,2,7]

REFERENCES AND NOTES

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2) K. Hirota, Y. Kitade, S. Senda, M. J. Halat, K. A. Watanabe, and J. J. Fox, J. Am. Chem. Soc., 1979, 101, 4423.

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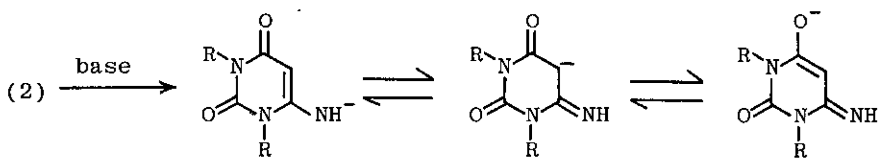
4) New compounds reported herein gave satisfactory elemental analyses and spectral data.

5) No 5-oxopyrido[2,3-d]pyrimidine compound was detected from the reaction mixture.

6) The carbanion [2'] is one of tautomeric forms in basic media as described below and would act as a 1,3-ambient nucleophile in this conversion.



[2']

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