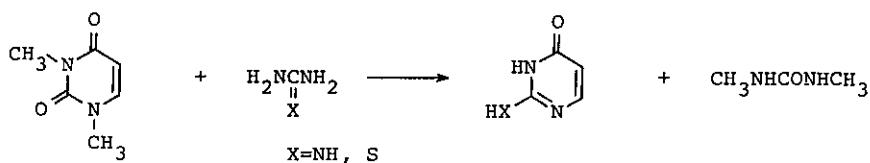


**NOVEL SYNTHESIS OF 2-THIOCYTOSINE DERIVATIVES VIA PYRIMIDINE-TO-PYRIMIDINE RING TRANSFORMATION**

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**Abstract** — The reaction of 1,3-disubstituted 5-cyanouracils (1) with thioureas (2) and sodium hydroxide causes novel pyrimidine-to-pyrimidine ring transformation to give 2-thiocytosines (3) and 6-amino-5-formyluracils (4), respectively.

Our previous works have demonstrated<sup>1</sup> that the reaction of uracil derivatives with various 1,3-ambident nucleophiles causes an intermolecular ring-fragmentation reaction<sup>2</sup> involving the apparent displacement of an appropriate fragment of the uracil ring by the nucleophiles. For example, when 1,3-dimethyluracil is allowed to react with guanidine and thiourea, the corresponding 2-amino- and 2-mercaptopyrimidines are obtained, respectively. These ring transformations resulted in the displacement of the N(1)-C(2)-N(3) fragment of the uracil by the N-C-N fragment of the nucleophiles (Scheme 1).<sup>1a</sup> During our investigation on the reaction of 5-cyanouracils<sup>3</sup> with thioureas, we have found novel pyrimidine-to-pyrimidine ring transformation leading to 2-thiocytosines (3) and 6-amino-5-formyluracils (4).

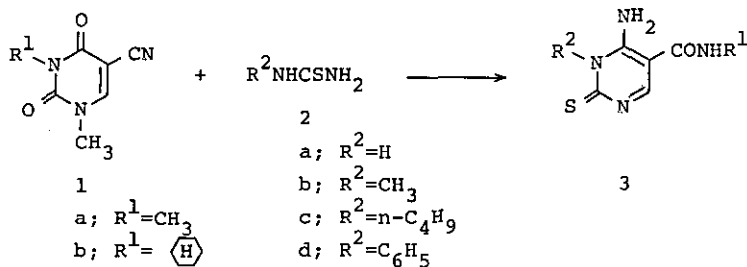


Scheme 1

Treatment of 5-cyano-1,3-dimethyluracil (1a) with 3 molar equivalents each of thiourea (2a) and sodium hydroxide in ethanol under reflux for 10 min led to the

formation of 5-N-methylcarbamoyl-2-thiocytosine (**3a**)<sup>4,5</sup> in 75% yield along with a trace amount of 6-amino-5-formyl-1,3-dimethyluracil (**4a**).<sup>6</sup> The structure of **3a** was supported by the spectral and microanalytical data,<sup>7</sup> and confirmed by the direct comparison with an authentic sample prepared by the reaction of 5-ethoxycarbonyl-2-thiocytosine<sup>8</sup> with methylamine. Analogous treatment of **1a** with methyl-, butyl-, and phenylthioureas (**2b-d**) gave the corresponding 3-substituted 2-thiocytosines (**3b-d**), respectively, in good yield.

In order to determine a source of the 5-carbamoyl group, the reaction of 5-cyano-3-cyclohexyl-1-methyluracil (**1b**), possessing different substituent at N(1)- and N(3)-positions, with thioureas (**2a** and **2b**) was carried out. Both reactions afforded the corresponding 5-(N-cyclohexylcarbamoyl)-2-thiocytosines (**3e** and **3f**), respectively. This result clearly shows that the N-substituent of 5-carbamoyl group of **3** originates from N(3)-substituent of the parent uracils (**1**). The UV spectra of the 3-substituted 2-thiocytosines (**3b-d** and **f**) (see Table) are superimposable on that of 5-ethoxycarbonyl-3-methyl-2-thiocytosine [221 ( $\epsilon$  10500), 292 ( $\epsilon$  12300), and 351 nm ( $\epsilon$  21200)].<sup>8</sup>

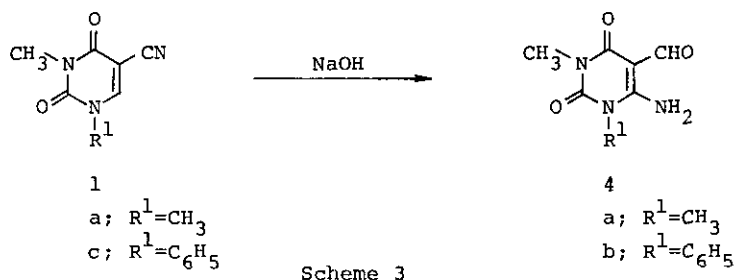


Scheme 2

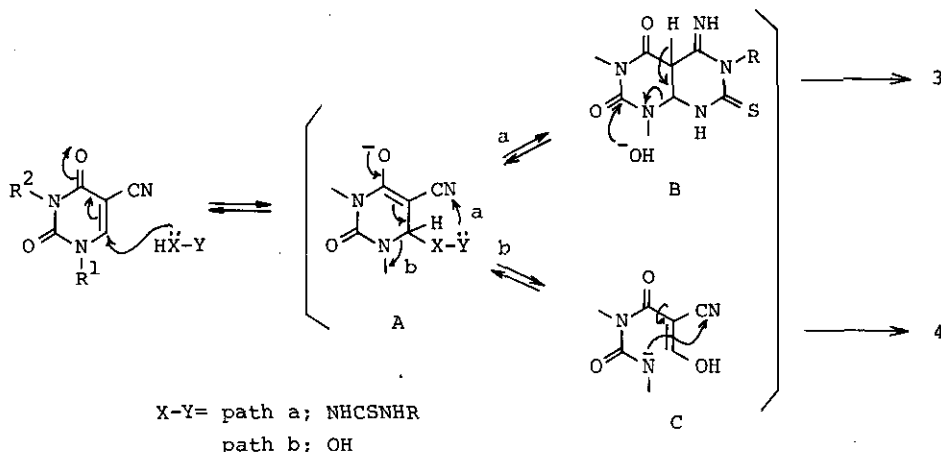
Table 5-Carbamoyl-2-thiocytosine derivatives (**3**)

No.	R <sup>1</sup>	R <sup>2</sup>	Mp °C	Yield %	UV spectra ( $\lambda_{\text{max}}^{\text{EtOH}}$ , nm, $\epsilon$ )
3a	CH <sub>3</sub>	H	276.5-277.5	75	241 (14700), 299 (23600)
3b	CH <sub>3</sub>	CH <sub>3</sub>	264.5-265	88	224 (11200), 291 (13000), 355 (17500)
3c	CH <sub>3</sub>	n-C <sub>4</sub> H <sub>9</sub>	224-225	41	226 (11100), 293 (13100), 358 (17100)
3d	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	227-228	75	225 (15900), 293 (13500), 363 (14800)
3e		H	>300	81	241 (15800), 299 (26000)
3f		CH <sub>3</sub>	256-258	59	227 (9600), 291 (13400), 355 (18300)

In the above reaction, the formation of a trace amount of the 6-amino-5-formyluracil (4a) was observed and its molecule does not contain the fragment arising from thioureas. This fact prompts us to examine the reaction in the absence of thioureas. The reaction of 1a with sodium hydroxide in ethanol under reflux for 7 h gave in accord with expectations the 6-amino-5-formyluracil (4a) as the sole product in 58% yield. Analogous reaction of 5-cyano-3-methyl-1-phenyluracil (1c) with sodium hydroxide gave the corresponding 6-amino-5-formyluracil (4b)<sup>6</sup> in 82% yield even upon heating for a short time (10 min). The introduction of phenyl group at the 1-position facilitates cleavage of the 1,6-bond in the uracil ring.<sup>9</sup> Therefore, this result suggests that the 1,6-bond cleavage is a key step for this ring transformation.



Plausible mechanisms for the present ring transformations are outlined in Scheme 4. An initial attack of the nucleophile on the 6-position affords an adduct A. In the case of the thiourea, cyclization between the terminal amino group of the thiourea and the 5-cyano group preferentially occurs and produces an intermediate B, which subsequently undergoes hydrolysis, decarboxylation, and deamina-



tion leading to 3 (path a). The formation of 4 can be explained in terms of an intramolecular rearrangement involving the 1,6-bond cleavage of A and subsequent recyclization of an open-chain intermediate C (path b). The latter ring transformation is mechanistically similar to the ring transformation reported by Su and Watanabe.<sup>10</sup>

#### REFERENCES AND NOTES

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- 2 This terminology represents most adequately the nature of our ring transformation in order to distinguish it from intramolecular rearrangements, such as the Dimroth rearrangement or photochemical transposition reaction; see the reference 1c.
- 3 Starting 5-cyanouracils were prepared according to the previously reported procedure; S. Senda, K. Hirota, and J. Notani, Chem. Pharm. Bull., 1972, **20**, 1380.
- 4 All new compounds gave satisfactory microanalytical results and spectral data consistent with their proposed structures.
- 5 For convenient drawings, 3-unsubstituted 2-thiocytosines (3a and 3e) were represented as their 3H form at the N(3)-position, respectively.
- 6 Compounds 4a<sup>6a)</sup> and 4b were alternatively prepared by the Vilsmeier reaction of the corresponding 6-aminouracils; 6a) H. Bredereck, G. Simchen, R. Wahl, and F. Effenberger, Chem. Ber., 1968, **101**, 512.
- 7 3a: <sup>1</sup>H-NMR (60 MHz, in DMSO-d<sub>6</sub>) 2.68 (3H, d, CH<sub>3</sub>, collapsing with D<sub>2</sub>O to singlet), 7.98 (1H, s, C<sub>6</sub>-H), 8.45 (2H, br, NH<sub>2</sub>), and 12.41 (1H, br, NH).
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