A Novel Ring Transformation of 5-Carbamoyluracils into Barbituric Acids

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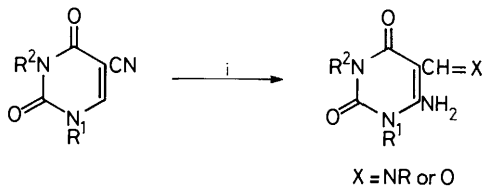
Heating of 5-thiocarbamoyl- (**3**) and 5-carbamoyl-3-methyl-1-phenyluracil derivatives (**5**) in ethanolic sodium ethoxide causes a novel ring transformation to give 5-anilinomethylene-4-thiobarbituric acid (**2**) and 5-anilinomethylenebarbituric acids (**6**), respectively.

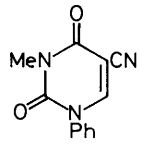
Uracil derivatives on treatment with various nucleophiles undergo ring transformation reactions.[1] Our previous studies have demonstrated[2] that the reaction of 1,3-disubstituted 5-cyanouracil derivatives with nucleophiles such as amines and sodium hydroxide (NaOH) causes a pyrimidine-to-pyrimidine ring transformation leading to 6-amino-5-iminomethyluracils and 6-amino-5-formyluracils, respectively (see Scheme 1). When sodium hydrosulphide (NaSH) was employed as a nucleophile instead of NaOH in the above reaction to obtain a 6-amino-5-thioformyluracil derivative, we unexpectedly encountered a novel ring transformation of the 5-cyanouracil (**1**) into the 4-thiobarbituric acid (**2**) *via* the 5-thiocarbamoyluracil (**3**). Consideration of the mechanism for this reaction led to the successful extension of the ring transformation of 5-carbamoyluracils (**5**) into barbituric acids (**6**). This type of reaction has never been reported in the ring transformation of uracil derivatives.

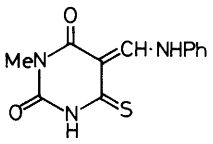


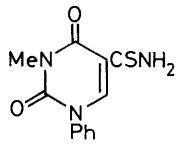
Scheme 1. *Reagents:* i, RNH_2 or NaOH

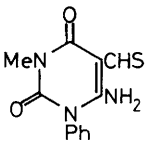
Treatment of 5-cyano-3-methyl-1-phenyluracil (**1**) with an excess of NaSH in refluxing ethanol for 12 h gave 5-anilinomethylene-1-methyl-4-thiobarbituric acid (**2**) (78%). T.l.c. analysis of the reaction mixture failed to detect the presence of the expected 6-amino-3-methyl-1-phenyl-5-thioformyluracil (**4**).* The structure of (**2**) was determined on the basis of microanalytical results and spectral data. The ^{1}H n.m.r. spectrum † of (**2**) at room temperature shows the presence of (*E*)- and (*Z*)-isomers.

Formation of another product was observed by t.l.c. at the early stage of the reaction. Thus, when the reaction time was shortened to 30 min, the 5-thiocarbamoyluracil (**3**) was isolated (24%) together with the barbituric acid (**2**). Further treatment of (**3**) with NaSH gave the 4-thiobarbituric acid (**2**) (64%). Use of sodium ethoxide (NaOEt) instead of NaSH improved the yield of (**2**) (92%). These results clearly indicate that the ring transformation of the 5-cyanouracil (**1**) into the 4-thiobarbituric acid (**2**) proceeds *via* the 5-thiocarbamoyluracil (**3**) as an intermediate.

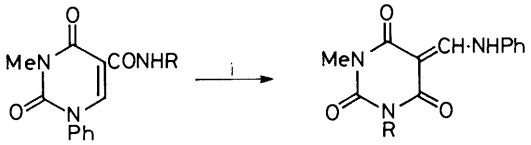

(**1**)


(**2**)


(**3**)


(**4**)

The reaction described above was extended to the ring transformation of 5-carbamoyluracils (**5**) into barbituric acids (**6**). Thus, treatment of 5-carbamoyl-3-methyl-1-phenyluracil


(**5**) (**6**)

Scheme 2. *Reagent:* i, NaOEt

(**5a**) with NaOEt afforded 5-anilinomethylene-1-methylbarbituric acid (**6a**), which was alternatively synthesized by the reaction of 5-formyl-1-methylbarbituric acid with aniline in the presence of triethylamine.[4]

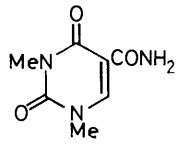
Analogous reaction of 5-(*N*-substituted carbamoyl)uracil derivatives (**5b**—**d**) with NaOEt also gave the corresponding barbituric acids (**6b**—**d**) as shown in the Table.

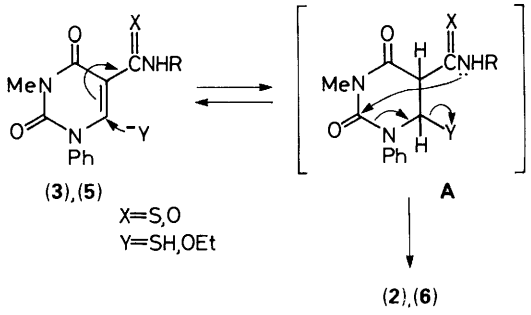
5-Carbamoyl-1,3-dimethyluracil (**7**), which has no phenyl group at the 1-position, on treatment with NaOEt under similar conditions gave only recovery of the starting material. This fact suggests that the presence of the 1-phenyl group significantly facilitates the cleavage of the N(1)–C(2) bond by attack of the 5-carbamoyl group on the 2-position in the C(6)-addition intermediate as shown in Scheme 3. Taking the above facts into consideration, a plausible reaction sequence for the present reaction is outlined in Scheme 3. An initial nucleophilic attack at the 6-position of the 5-carbamoyluracil (**3**) or (**5**) by a hydrosulphide ion or an ethoxide ion could give rise to an adduct **A** (Michael addition). The conversion of sp^2-carbon into sp^3-carbon at the 5-position allows an intramolecular nucleophilic attack of the 5-carbamoyl group on the 2-carbonyl group followed by cleavage of the N(1)–C(2) bond to give the barbituric acid (**2**) or (**6**).

Table 1. Formation of barbituric acids (**6**)

Compd.	R	Reaction time (h)	Yield (%)	^{1}H N.m.r. (δ)[a] C(5)=CH[b]	^{1}H N.m.r. (δ)[a] NHPh[c]
(**6a**)	H	3	61	8.54 (br)	11.84
(**6b**)	Me	4	71	8.64 (d, *J* 13.5 Hz)	12.17
(**6c**)	Pr	5	39	8.68 (d, *J* 14.0 Hz)	12.05
(**6d**)	CH_2Ph	2	68	8.68 (d, *J* 14.0 Hz)	12.03

[a] Measured in $CDCl_3$ except (**6a**) [in $(CD_3)_2SO$]. [b] Collapsed to singlet by deuterium exchange. [c] Deuterium exchangeable.


(**7**)


(**3**),(**5**) X=S,O Y=SH,OEt A (**2**),(**6**)

Scheme 3.

The thermal ring transformation of uracils involving the cleavage of the N(1)–C(2) bond has been unprecedented except for the uracil-to-pyridine ring transformation reported recently.[5] Thus, the present reaction is most intriguing with respect to involvement of the rare N(1)–C(2) bond-cleavage.

* The 5-thioformyluracil (**4**) was prepared from 6-amino-1-methyl-3-phenyluracil according to Raid's method.[3] The ^{1}H n.m.r. spectrum of (**4**) shows a singlet at δ [$(CD_3)_2SO$] 10.74 due to the 5-thioformyl group.
† δ_H[$(CD_3)_2SO$] 3.17 (s, NMe), 7.31—7.53 (m, Ph), 8.91 and 9.17 [each d, *J* 15.0 Hz, collapsed to singlet by deuterium exchange, C(5)=CH], 12.18 and 12.23 [each br s, deuterium exchangeable, N(3)–H], 12.42 and 14.56 (each br d, *J* 15.0 Hz, deuterium exchangeable, N*H*Ph). Each pair of peaks of the isomers merges at 100 °C.

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