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NOVEL REACTION OF 5-NITRO(OR CARBAMOYL)URACIL DERIVATIVES WITH AMINES. THERMAL EXCHANGE REACTION OF N_1-PORTION OF THE URACILS FOR AMINES VIA RING-OPENING AND RING-CLOSURE PROCESSES[1]

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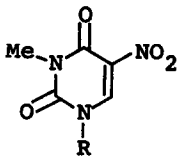
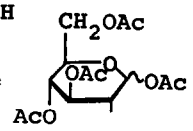
Summary: The reaction of 1,3-disubstituted uracils possessing an electron withdrawing group at the 5-position with amines induced exchange of N_1-portion of the uracil ring for amines. This reaction was accelerated by substitution of phenyl groups at the N_1-position.

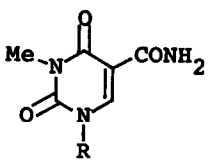
Saito et al. previously documented[2] that irradiation of N_1-substituted thymines and primary amines with 254 nm light at ambient temperature induced the photo-exchange of N_1-portion of the uracil ring for amines. For example, thymidine was converted into 1-butylthymine upon irradiation with butylamine. This reaction involves an initial nucleophilic-attack of the employed amines on the 2-position of the photo-excited thymine.[2a] On the other hand, little work has appeared[3] on the thermal reaction of uracil derivatives other than 5-bromouracils[4,5] with amines. We have investigated the reaction of uracil derivatives containing an electron withdrawing group at the 5-position with amines.[3b] In this paper, a novel reaction of 5-nitro(or carbamoyl)uracils involving the displacement of N_1-portion of the uracil by amines is described.

Treatment of 1,3-dimethyl-5-nitrouracil (1a) with an excess of buthylamine in absolute ethanol under reflux and argon atmosphere for 20 h led to the formation of 1-butyl-3-methyl-5-nitrouracil (1c) in 71% yield along with the recovered (1a) in 18% yield. The presence of water in the reaction solution drastically inhibited this reaction.[6] The structure of (1c) was confirmed by direct comparison with an authentic sample prepared by butylation of 3-methyl-5-nitrouracil with dimethylformamide dibutylacetal. Analogous reaction of (1a) with propylamine and cyclohexylamine gave the corresponding uracils (1b) and (1d) incorporating the employed amines at the N_1-position. The use of bulky amines such as cyclohexylamine reduced the yield of the products (1d) (see Table 1). When the reaction of 1-butyl-3-methyl-5-nitrouracil (1c), possessing different substituents at the N_1- and N_3-positions, with propylamine was carried out, 3-methyl-5-nitro-1-propyluracil (1b) was obtained in high yield. This result clearly shows that the N_1-portion of the uracil is exchanged directly for the employed amine.



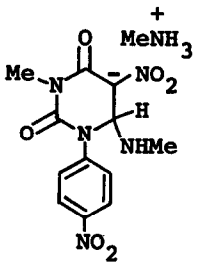
(1)

a; R=Me
b; R=Pr
c; R=Bu
d; R=cyclohexyl
e; R=p-$NO_2C_6H_4$
f; R=H
g; R= 
h; R=Et



(2)

a; R=Ph
b; R=Me
c; R=Pr
d; R=Bu



(3)

Table 1 Reaction of 1,3-disubstituted uracil derivatives with amines

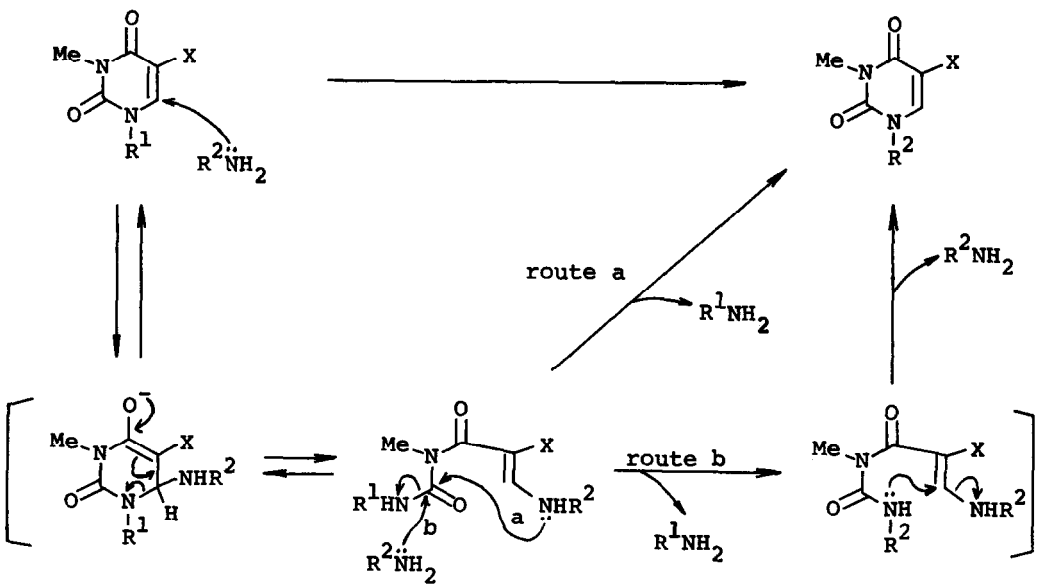
Starting compound	Amine	Reaction conditions	Product	Yield(%)
(1a)	$PrNH_2$	80°C, 60h	(1b)	75[a]
	$BuNH_2$	80°C, 20h	(1c)	87[a]
	cyclohexylamine	80°C, 30h	(1d)	18
(1c)	$PrNH_2$	80°C, 20h	(1b)	86
(1e)	NH_3	r.t., 4h	(1f)	93
	$MeNH_2$	r.t., 0.5h	(1a)	95
	cyclohexylamine	80°C, 3h	(1d)	77
	glucosamine	60°C, 24h	(1g)	67
(2a)	$MeNH_2$	60°C, 24h	(2b)	85
	$PrNH_2$	120°C, 48h	(2c)	77
	$BuNH_2$	120°C, 48h	(2d)	97

a) Based on the consumed (1a).

These N_1-exchange reactions seem to involve a cleavage of the 1-2 or 1-6 bond of the uracil ring as a key step. We previously demonstrated[5] that the substitution of a phenyl group at the N_1-position of 5-bromouracil derivatives facilitates the cleavage of the 1-6 bond by attack of nucleophiles. Therefore, 3-methyl-5-nitro-1-(p-nitrophenyl)uracil (1e)[7] was employed for the conversion. When the compound (1e) was treated with methylamine in ethanol with stirring at room temperature for a few minutes, the formation of precipi-

tate was observed. The precipitate was gradually dissolved in solution and further stirring for 30 min gave 1,3-dimethyl-5-nitrouracil (1a) as a precipitate in high yield. In the above reaction the first precipitate was isolated as a reaction intermediate and its structure was determined as an adduct, 5,6-dihydro-3-methyl-6-methylamino-1-(p-nitrophenyl)uracil methylammonium salt (3) on the basis of its spectral data and the following experimental results. The adduct (3) in ethanol was stable at room temperature, but was easily converted into the product (1a) upon heating at 80°C or upon treatment with triethylamine at room temperature. On the other hand, the adduct (3) reverted to the starting material (1e) on addition of a catalytic amount of hydrochloric acid. When (3) was treated with an excess of ethylamine in ethanol at room temperature, 1-ethyl-3-methyl-5-nitrouracil (1h) was obtained in 71% yield together with (1a) in 27% yield.

Two plausible mechanisms (routes a and b) to explain the above results may be formulated as shown in Scheme 1 for the N_1-exchange reaction. Interestingly the both mechanisms involving an initial attack of the amine on the 6-position of uracil ring are different from that of the photo-induced N_1-exchange reaction.[2a]



Scheme 1

The reaction of (1e) even with a less nucleophillic base, e.g., ammonia and with bulky amines, e.g., cyclohexylamine and glucosamine under mild conditions led to the formation of the corresponding N_1-exchange products (1f),(1d), and (1g)[8], respectively, in good yields (see Table 1).

5-Carbamoyl-3-methy-1-phenyluracil (2a) also underwent with ease the N_1-exchange reaction to be converted into the corresponding 5-carbamoyluracil

derivatives (2b-d), which were confirmed by an alternative synthesis.[9] However treatment of 5-carbamoyl-1,3-dimethyluracil (2b) with butylamine under various conditions resulted in the recovery of the starting material. These results also indicate that an introduction of phenyl groups at the N_1-position accelerates the present reaction.

References and Notes

1 This paper is dedicated to Professor Morio Ikehara for the occasion of his retirement from Osaka University on March, 1986.

2 a) I.Saito, H. Sugiyama, N. Furukawa, and T. Matsuura, Tetrahedron Lett., 1981, **22**, 3265; I. Saito, H. Sugiyama, S. Ito, N. Furukawa, and T. Matsuura, J. Am. Chem. Soc., 1981, **103**, 1598; I. Saito, H. Sugiyama, and T. Matsuura, ibid., 1983, **105**, 956.

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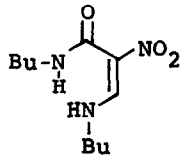
4 For examples; A. P. Phillips, J. Am. Chem. Soc., 1951, **73**, 1061; S. Senda, K. Hirota, and K. Banno, J. Med. Chem., 1972, **15**, 471.

5 S. Senda, K. Hirota, and K. Banno, Tetrahedron Lett., 1974, 3087; K. Hirota, Y. Yamada, J. Haruta, and S. Senda, Heterocycles, 1982, **19**, 2309; K. Hirota, K. Banno, Y. Yamada, and S. Senda, J. Chem. Soc., Perkin Trans. 1, 1985, 1137.

6 The starting material (1a) was recovered under such conditions. When the reaction was carried out in the presence of water under more drastic conditions, an open-chain product (4) was formed.



(4)

7 The nitration of 3-methyl-1-phenyluracil for preparing 3-methyl-5-nitro-1-phenyluracil gave the dinitro compound (1e).

8 This product was isolated as a tetraacetyl-derivative by the acetylation with acetic anhydride.

9 S. Senda, K. Hirota, and J. Notani, Chem. Pharm. Bull., 1972, **20**, 1389; S. Senda , K. Hirota, and T. Asao, ibid., 1978, **26**, 3208.

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