Pyrimidine Derivatives and Related Compounds. Part 48.[1] Uracil Ring Transformation: Conversion of 5-Nitrouracils into 5-Carbamoyluracils[2]

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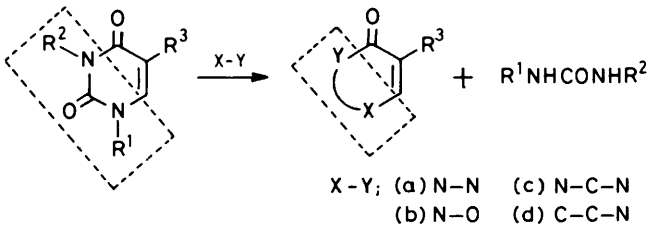
1,3-Disubstituted 5-nitrouracils (**1**) react with malonamide in ethanolic sodium ethoxide to afford 1-substituted 5-carbamoyluracils (**3**) *via* rearrangement of the N(3)–C(4)–C(5) portion of the uracil. This ring transformation has been applied to the preparation of 2',3',5'-tri-*O*-acetyl-5-carbamoyluridine (**8**).

Uracils can be converted into pyrazolone (a) and isoxazolone (b) by the reaction with hydrazine and hydroxylamine, respectively.[3] These reactions involve the direct displacement of the N(1)–C(2)–N(3) portion of the uracil by the N–N or N–O portion of 1,2-ambident nucleophiles. We have already reported the conversion of 1,3-disubstituted uracil derivatives into other pyrimidines (c)[4] and into pyridines (d)[5] involving the displacement of the N(1)–C(2)–N(3) portion of the uracils by the N–C–N and C–C–N portion of 1,3-ambident nucleophiles, respectively.



Scheme 1.

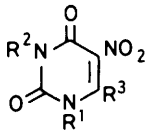
We now describe a new type of ring transformation in which 1,3-disubstituted 5-nitrouracils (**1**) give 1-substituted 5-carbamoyluracils (**3**) *via* a retro-Michael reaction.[6] This is the first example of a uracil ring transformation *via* the direct displacement of the N(3)–C(4)–C(5) fragment of the uracils (**1**) by the N–C–C fragment of a 1,3-ambident nucleophile (*i.e.* malonamide).

Results and Discussion

The pyrimidine-to-pyridine ring transformation described above[5] was attempted for the reaction of 5-nitrouracils (**1**) with a C–C–N type of 1,3-ambident nucleophile. Thus, treatment of 1,3-dimethyl-5-nitrouracil (**1a**)[7] with 4 mol equiv. each of malonamide and sodium ethoxide in ethanol at room temperature for 24 h, followed by neutralization of the reaction mixture, failed to give the expected ring transformation product, 3-carbamoyl-2,6-dihydroxy-5-nitropyridine (**2**), 5-carbamoyl-1-methyluracil (**3a**) being obtained instead (63% yield). Assignment of structure (**3a**) to the product was supported by microanalytical and spectral results and ultimately confirmed by comparison with an authentic sample prepared by hydrolysis of 5-cyano-1-methyluracil (**4**)[8] with concentrated sulphuric acid.

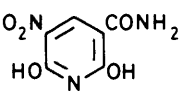
When the reaction was carried out under reflux for 1 h, the 5-carbamoyluracil (**2a**) was obtained in 84% yield, along with *N*-methyl-2-nitroacetamide (**5**). Compound (**5**) was identified by comparison of its spectral data with those of an authentic sample.[9] Analogous treatment of 1-cyclohexyl-3-methyl-5-nitrouracil (**1b**) and 3-cyclohexyl-1-methyl-5-nitrouracil (**1c**) with malonamide afforded the corresponding 1-substituted 5-carbamoyluracils (**3b**)[10] and (**3a**) in 89% and 86% yields, respectively. However, the reaction of 1-methyl-5-nitrouracil (**1d**) and 5-nitrouracil (**1e**) with malonamide failed to give the expected 5-carbamoyluracils. This is because both the 5-nitrouracils (**1d**) and (**1e**) contain dissociable protons and, in the presence of base, are in the anionic form which inhibits their reaction with nucleophiles. Substitution at C-6 of the 5-nitrouracil (**1a**) suppressed the reaction; 1,3,6-trimethyl-5-nitrouracil (**1f**) was recovered almost quantitatively in an attempted reaction with malonamide. Under the same conditions, the reaction of the 5-nitrouracil (**1a**) with cyanoacetamide, acetoacetamide, and phenylacetamide, instead of malonamide, gave none of the corresponding ring transformation products. This ring transformation is, therefore, limited to the reaction of 1,3-disubstituted 5-nitrouracils and malonamide.

On the basis of the above results, a reaction sequence for the present ring transformation is proposed (see Scheme 2). An initial nucleophilic attack at C-6 of the uracil (**1a**) by a carbanion would give rise to an adduct A (a Michael reaction). Abstraction of the exocyclic α-proton from the latter by an ethoxide anion accompanied by scission of the C(5)–C(6) bond would give an open-chain intermediate B (a retro-Michael reaction[6]), which would then cyclize to afford the 5-carbamoyluracil (**3a**) and *N*-methyl-2-nitroacetamide (**5**).

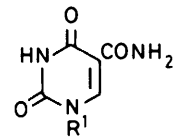


(**1**)

a; $R^1 = R^2 = Me$, $R^3 = H$
b; $R^1 = c\text{-}C_6H_{11}$, $R^2 = Me$, $R^3 = H$
c; $R^1 = Me$, $R^2 = c\text{-}C_6H_{11}$, $R^3 = H$
d; $R^1 = Me$, $R^2 = R^3 = H$
e; $R^1 = R^2 = R^3 = H$
f; $R^1 = R^2 = R^3 = Me$

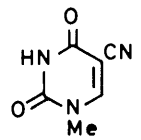


(**2**)

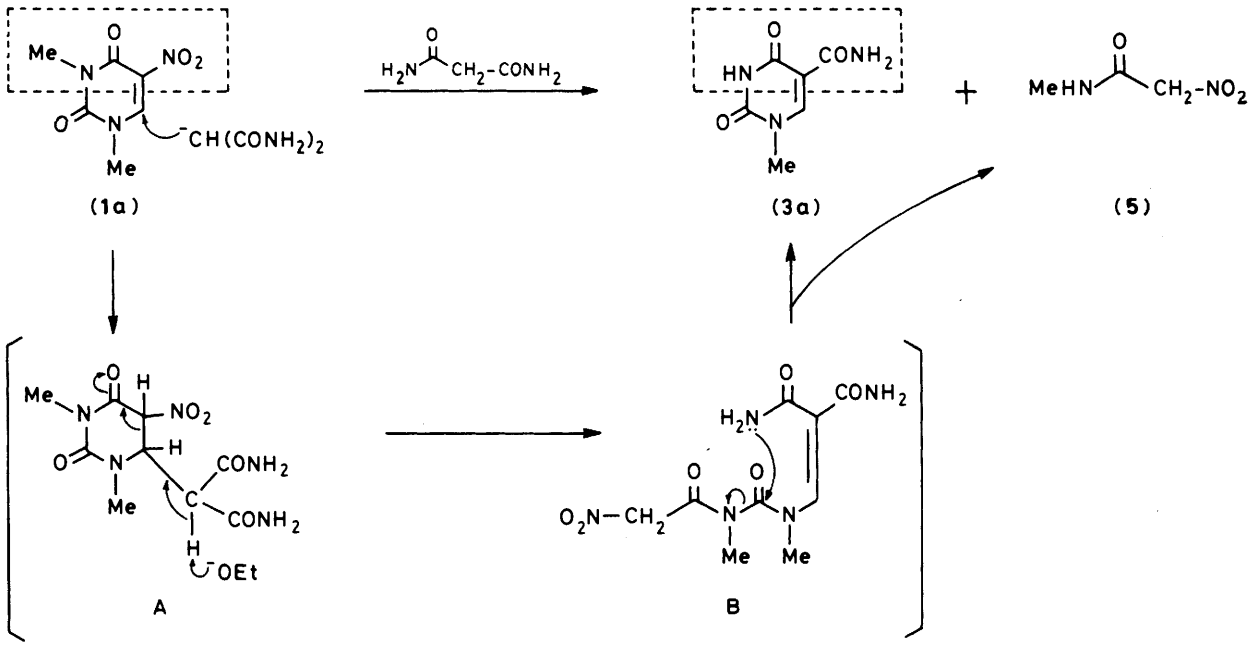


(**3**)

a; $R^1 = Me$
b; $R^1 = c\text{-}C_6H_{11}$

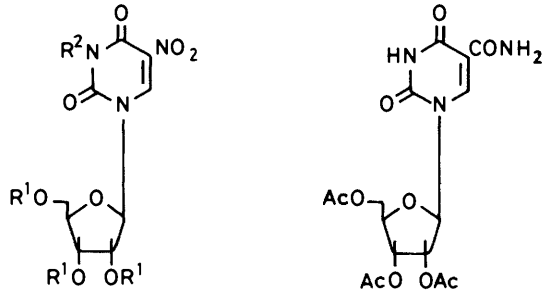


(**4**)



Scheme 2.

This ring transformation was applied to the preparation of the unknown 5-carbamoyluridine derivative (**8**). Thus 2′,3′,5′-tri-*O*-benzoyl-3-methyl-5-nitrouridine (**7**) [prepared by reaction of 2′,3′,5′-tri-*O*-benzoyl-5-nitrouridine (**6**)[11] with dimethylformamide dimethyl acetal in dimethylformamide] was treated with a mixture of malonamide (4 equiv.) and sodium ethoxide (10 equiv.) in ethanol under reflux for 1 h. Acetylation of the product then afforded 2′,3′,5′-tri-*O*-acetyl-5-carbamoyluridine (**8**) (64% yield).



(**6**) R^1 = Bz, R^2 = H
(**7**) R^1 = Bz, R^2 = Me

(**8**)

Experimental

M.p.s were determined on a Yanagimoto melting-point apparatus and are uncorrected. I.r. spectra were recorded with a Hitachi Model 215 spectrometer, using KBr pellets; ^{1}H n.m.r. spectra were determined with a Hitachi Perkin-Elmer R-20B 60-MHz instrument, using tetramethylsilane as internal standard; mass spectra were taken on a JEOL JMS-D300 machine operating at 70 eV. Elemental analyses were carried out at the Microanalytical Laboratory of our University.

1-*Cyclohexyl*-3-*methyl*-5-*nitrouracil* (**1b**).—To a mixture of concentrated HNO_3 (1.5 ml) and concentrated H_2SO_4 (1.5 ml) was added 1-cyclohexyl-3-methyluracil[10] (3.0 g, 14.4 mmol). The mixture was heated at 80 °C for 3 h and then poured over ice. The precipitate was filtered off. Recrystallization from ethanol gave analytically pure 1-*cyclohexyl*-3-*methyl*-5-*nitrouracil* (**1b**) (2.90 g, 80%), m.p. 174—175 °C (Found: C, 51.9; H, 5.95; N, 16.45. $C_{11}H_{15}N_3O_4$ requires C, 52.15; H, 5.95; N, 16.6%); δ[$(CD_3)_2SO$] 1.10—2.30 (10 H, br), 3.40 (3 H, s), 4.58 (1 H, br), and 8.73 (1 H, s).

3-*Cyclohexyl*-1-*methyl*-5-*nitrouracil* (**1c**).—To a mixture of concentrated HNO_3 (0.5 ml) and concentrated H_2SO_4 (0.5 ml) was added 3-cyclohexyl-1-methyluracil[10] (0.624 g, 3 mmol). The mixture was heated at 70 °C for 1 h and then poured over ice. The precipitate was filtered off and recrystallized from ethanol to give analytically pure 3-*cyclohexyl*-1-*methyl*-5-*nitrouracil* (**1c**) (0.730 g, 96%), m.p. 214 °C (Found: C, 52.35; H, 6.1; N, 16.45. $C_{11}H_{15}N_3O_4$ requires C, 52.15; H, 5.95; N, 16.6%); δ[$(CD_3)_2SO$] 1.00—2.10 (10 H, br), 3.48 (3 H, s), 4.73 (1 H, br), and 9.26 (1 H, s) (in this case, the ^{1}H n.m.r. spectrum was measured using sodium 2,2-dimethyl-2-silapentane-5-sulphonate as internal standard).

5-*Carbamoyl*-1-*methyluracil* (**3a**).—(*a*) A mixture of the 5-nitrouracil (**1a**)[7] (0.555 g, 3 mmol) and malonamide (1.2 g, 12 mmol) in ethanolic sodium ethoxide [prepared from Na (0.276 g, 12 mg-atom) in dry ethanol (40 ml)] was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was treated with water (20 ml). The solution was neutralized with concentrated HCl and the precipitate was filtered off and recrystallized from water to give analytically pure 5-*carbamoyl*-1-*methyluracil* (**3a**) (0.319 g, 63%), m.p. > 300 °C (Found: C, 42.5; H, 4.2; N, 24.7. $C_6H_7N_3O_3$ requires C, 42.6; H, 4.15; N, 24.85%); δ[$(CD_3)_2SO$] 3.37 (3 H, s), 7.41 (1 H, br), 8.11 (1 H, br), 8.48 (1 H, s), and 11.73 (1 H, br). The product was identical with a sample prepared by hydrolysis of the 5-cyanouracil (**4**) with concentrated H_2SO_4.

(*b*) A mixture of the 5-cyanouracil (**4**)[8] (1.51 g, 10 mmol) and concentrated H_2SO_4 (3 ml) was heated at 60 °C for 3 h. The mixture was poured over ice and the precipitate was filtered off and washed with water. Recrystallization from water gave the 5-carbamoyluracil (**3a**) (1.428 g, 84%), m.p. > 300 °C. The product was identical with the sample prepared above.

(*c*) 5-*Carbamoyluracil* (**3a**) *and* N-*Methyl*-2-*nitroacetamide* (**5**). A mixture of the 5-nitrouracil (**1a**) (0.555 g, 3 mmol) and malonamide (1.2 g, 12 mmol) in ethanolic sodium ethoxide [prepared from Na (0.276 g, 0.012 g-atom) in dry ethanol (40 ml)] was refluxed for 1 h. The solvent was removed under reduced pressure and the residue was treated with water (20 ml). The solution was neutralized with concentrated HCl and the precipitate was filtered off and recrystallized from water to give the 5-carbamoyluracil (**3a**) (0.425 g, 84%), m.p. >300 °C. The product was identical with the sample prepared by procedure (*b*).

The remaining aqueous solution was evaporated to dryness and the residue was washed with chloroform. The solvent was removed under reduced pressure and the residue was recrystallized from ether to give *N*-methyl-2-nitroacetamide (**5**) (0.02 g), m.p. 67—69 °C (lit.,[9] 75—76 °C); $\nu_{max.}$ 3 300, 1 670, 1 570, and 1 340 cm $^{-1}$; δ($CDCl_3$) 2.93 (3 H, d, *J* 5 Hz) and 5.09 (2 H, s); the signal due to the amide group could not be observed.

(*d*) A mixture of the 5-nitrouracil (**1c**) (0.253 g, 1 mmol) and malonamide (0.4 g, 4 mmol) in ethanolic sodium ethoxide [prepared from Na (0.092 g, 4 mg-atom) in dry ethanol (10 ml)] was refluxed for 2 h. The solvent was removed under reduced pressure and the residue was neutralized with concentrated HCl. The precipitate was filtered off to afford the 5-carbamoyluracil (**3a**) (0.15 g, 89%), m.p. >300 °C, which was identical with the sample prepared by procedure (*b*).

5-*Carbamoyl*-1-*cyclohexyluracil* (**3b**).—A mixture of the 5-nitrouracil (**1b**) (0.759 g, 3 mmol) and malonamide (1.2 g, 12 mmol) in ethanolic sodium ethoxide [prepared from Na (0.276 g, 12 mg-atom) in dry ethanol (40 ml)] was refluxed for 1 h. The solvent was removed under reduced pressure and the residue was dissolved with water (20 ml). The solution was neutralized with concentrated HCl and the precipitate was filtered off and recrystallized from methanol to give analytically pure 5-carbamoyluracil (**3b**) (0.685 mg, 86%), m.p. >300 °C (lit.,[10] >300 °C) (Found: C, 55.75; H, 6.3; N, 17.75. Calc. for $C_{11}H_{15}N_3O_3$: C, 55.7; H, 6.35; N, 17.7%); δ[$(CD_3)_2SO$] 1.05—2.30 (10 H, br), 4.30 (1 H, br), 7.55 (1 H, br), 8.18 (1 H, br), 8.35 (1 H, s), and 11.78 (1 H, br).

2′,3′,5′-*Tri*-O-*benzoyl*-3-*methyl*-5-*nitrouridine* (**7**).—A mixture of the 5-nitrouridine (**6**)[11] (3.0 g, 5 mmol) and dimethylformamide dimethyl acetal (1.78 g, 15 mmol) in dimethylformamide (7 ml) was stirred at room temperature for 30 min. The solvent was removed under reduced pressure and the residue was subjected to column chromatography (silica gel, chloroform) to afford 2′,3′,5′-*tri*-O-*benzoyl*-3-*methyl*-5-*nitrouridine* (**7**) (2.55 g, 83%). Recrystallization from ethanol gave an analytically pure sample, m.p. 97—99 °C (Found: C, 60.1; H, 4.0; N, 6.8. $C_{31}H_{25}N_3O_{11}$ requires C, 60.5: H, 4.1; N, 6.8%); δ($CDCl_3$) 3.32 (3 H, s), 4.80 (3 H, br), 5.91 (2 H, m), 6.25 (1 H, d, *J* 4 Hz), 7.20—7.70 (9 H, m), 7.80—8.25 (6 H, m), and 8.90 (1 H, s).

2′,3′,5′-*Tri*-O-*acetyl*-5-*carbamoyluridine* (**8**).—A mixture of the 5-nitrouridine (**7**) (1.845 g, 3 mmol) and malonamide (1.2 g, 12 mmol) in ethanolic sodium ethoxide [prepared from Na (0.6 g) in dry ethanol (40 ml)] was refluxed for 1 h. The precipitate was filtered off and dissolved in acetic anhydride (30 ml). The mixture was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in water (30 ml). The solution was extracted with chloroform and the extract was dried with $MgSO_4$. The solvent was removed under reduced pressure and the residue was subjected to column chromatography [silica gel, chloroform–methanol (50:1)] to give analytically pure 2′,3′,5′-*tri*-O-*acetyl*-5-*carbamoyluridine* (**8**) (0.805 g, 64%), m.p. 112—116 °C (Found: C, 45.8; H, 4.8; N, 9.8. $C_{16}H_{19}N_3O_{10}\cdot 0.5H_2O$ requires C, 45.5: H, 4.75; N, 9.95%); *m/z* 413 (M^+); δ($CDCl_3$) 2.08 (3 H, s), 2.13 (3 H, s), 2.23 (3 H, s), 4.38 (3 H, s), 5.45 (2 H, br), 6.09 (1 H, d, *J* 4 Hz), 6.47 (1 H, br), 8.42 (1 H, br), 8.65 (1 H, s), and 10.49 (1 H, br).

Acknowledgements

This work was supported, in part, by the Grant-in-Aid for Scientific Research from the Ministry of Education, which is gratefully acknowledged.

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Received 24*th October*, 1983; *Paper* 3/1874