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The Dimroth Rearrangement of 6-Aminouracil Derivatives[1]

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The reaction of 6-amino-5-formyl (or acetyl) uracils (4) possessing a phenyl group at the 1-position with caustic alkali resulted in Dimroth rearrangement to give 6-anilino-5-formyl (or acetyl) uracils (5). This is the first example of Dimroth rearrangement observed in the uracil ring system. The presence of both the N_1-phenyl group and the 5-formyl (or acetyl) group on the uracil ring is requisite for the occurrence of the rearrangement.

Keywords Dimroth rearrangement; molecular rearrangement; alkaline hydrolysis; 6-aminouracil; 6-anilinouracil

In a previous paper,[2] we reported the intramolecular rearrangement of 5-cyanouracils to 6-aminouracils by reaction with amines and hydroxide ion. For example, the reaction of 5-cyano-3-methyl-1-phenyluracil (**1**) with caustic alkali smoothly gives 6-amino-5-formyl-3-methyl-1-phenyluracil (**3**: X=O) *via* an acyclic intermediate (**2**: X=O) through ring fission and reclosure as depicted in Chart 1. In the course of our study on the reaction of **1** with carbanions as a nucleophile, we have found that the rearranged product (**3**: X=O) further undergoes the Dimroth rearrangement to give a 6-anilinouracil derivative.

The well-known Dimroth rearrangement[3] can be regarded as an isomerization proceeding by ring fission and subsequent ring closure, whereby an *N*-substituted ring nitrogen exchanges places with an exo-imino (or potential exo-imino) nitrogen which is located in the α-position (for a typical Dimroth rearrangement, see Chart 1). No example of Dimroth rearrangement in uracil derivatives, however, has appeared in the literature.[3,4] In this paper we describe the Dimroth rearrangement of 6-amino-5-formyl (or acetyl)-1-phenyluracils (**4**) into the corresponding 6-anilinouracils (**5**) in the context of the previous observation in **3** (X=O).

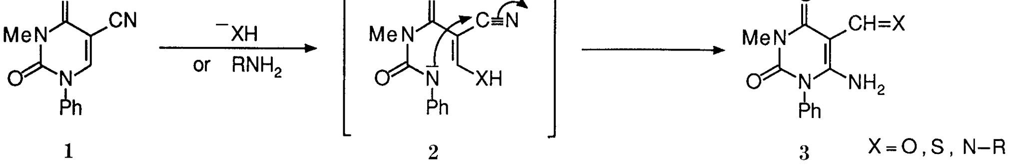
Treatment of 6-amino-5-formyl-3-methyl-1-phenyluracil (**4a**)[2] with potassium hydroxide in refluxing ethanol for 20 h afforded 6-anilino-5-formyl-3-methyluracil (**5a**) in 51% yield. The structure of **5a** was confirmed by direct comparison with an authentic sample prepared by Vilsmeier–Haack reaction of 6-anilino-3-methyluracil (**6**). Analogous reactions of other 5-formyluracil derivatives (**4b**) and (**4c**) in ethanolic alkaline solution gave the corresponding rearranged products (**5b**) and (**5c**),[5] respectively.

When 5-acetyl-6-amino-3-methyl-1-phenyluracil (**4d**) was allowed to react in a similar manner, the rearranged product (**5d**) was isolated in 32% yield together with an unexpected product, 2-anilino-3-cyano-*N*-methylcrotonamide (**7**), in 29% yield. The 5-acetyl-6-anilinouracil (**5d**) was alternatively synthesized by acetylation of **6** with acetyl chloride. The structure of **7** was confirmed by direct comparison with an authentic sample which had been independently prepared by alkaline hydrolysis of 5-cyano-3,6-dimethyl-1-phenyluracil (**8**).[6]

In the case of 5-acetyl-3-methyl-6-methylamino-1-phenyluracil (**4e**), however, the Dimroth rearrangement proceeded smoothly to give the corresponding 6-anilinouracil (**5e**) in 81% yield. No formation of the crotonamide derivative was observed.[7]

On the other hand, similar alkaline treatment of 6-amino-5-formyl-1,3-dimethyluracil (**9**)[8] and 6-amino-3-methyl-1-phenyluracil (**10**)[2] did not induce the Dimroth rearrangement but resulted in recovery of the starting materials. These facts indicate that both the N_1-phenyl group and the 5-acyl group on the uracil ring are requisite for the occurrence of the rearrangement.

On the basis of the above results, the reaction sequence for the formation of **5** and **7** is outlined in Chart 3. The formation of **7** can be explained in terms of a reverse-type reaction of the molecular rearrangement[2] shown in Chart 1 and subsequent hydrolysis and decarboxylation of the resulting 5-cyanouracil (**8**) at the 2-position: the 5-acetyl-6-aminouracil (**5d**) corresponding to the 5-formyluracil (**3**) is transformed into the 5-cyano-6-methyluracil (**8**) corresponding to the 5-cyanouracil (**1**) *via* N_1–C_6 bond cleavage of an imino-tautomer (**11**) and subsequent recyclization.



typical Dimroth rearrangement process

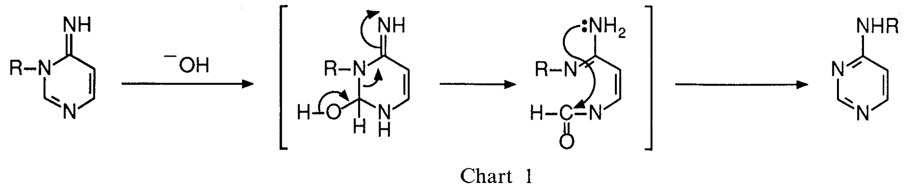
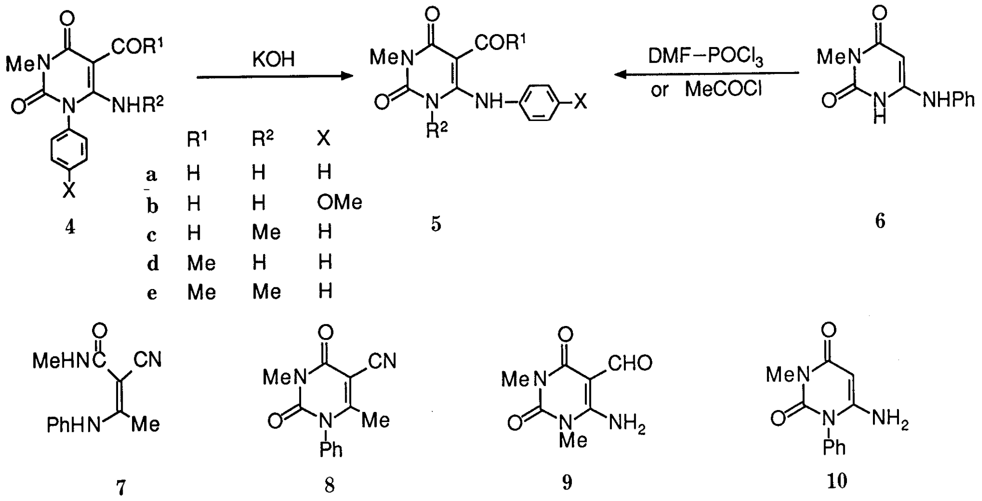


Chart 1



	R^1	R^2	X
a	H	H	H
b	H	H	OMe
c	H	Me	H
d	Me	H	H
e	Me	Me	H

Chart 2

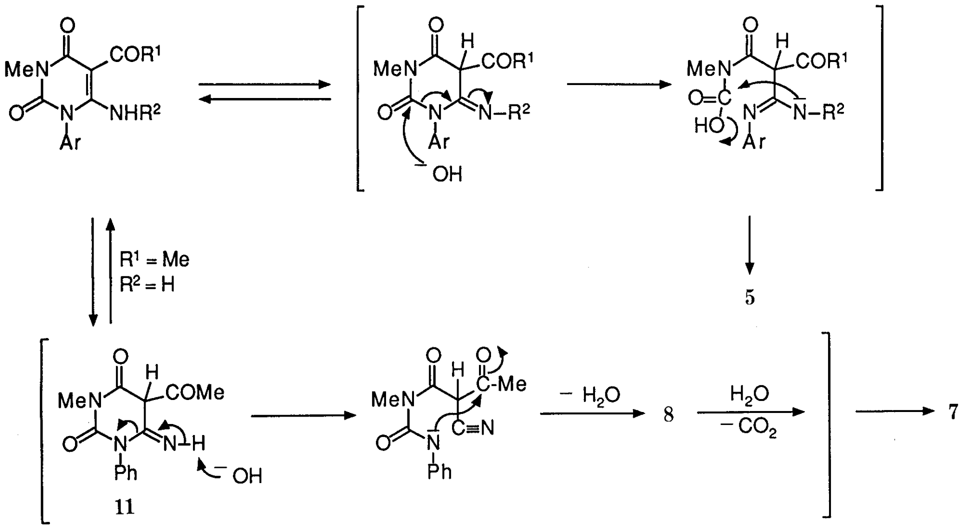


Chart 3

Uracil derivatives possessing an electron-withdrawing group at the 5-position are remarkably sensitive to nucleophilic attack on the 6-position[9] and frequently undergo various types of ring transformations.[10] Although 6-aminouracil derivatives are generally inactive toward nucleophiles, introduction of a phenyl group at the 1-position facilitates the cleavage of the N$_1$–C$_2$ bond by attack of hydroxide ion on the 2-position and consequently induces the Dimroth rearrangement. Such an N$_1$-substitution effect of the phenyl group has been observed in the ring transformation of uracil derivatives.[11]

Experimental

Melting points were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded at 270 MHz on a JEOL JNX-270 spectrometer in CDCl$_3$ or (CD$_3$)$_2$SO (DMSO-d_6). Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad, brs = broad singlet). Mass spectra (MS) were measured at 70 eV with a JEOL JMS-D300 spectrometer. Infrared (IR) spectra were obtained with Perkin-Elmer 1600 FT-IR instrument for KBr pellets. Column chromatography was carried out on silica gel (Wako gel C-300).

6-Amino-5-formyl-1-(4-methoxyphenyl)-3-methyluracil (4b) 6-Amino-1-(4-methoxyphenyl)-3-methyluracil[12] (1.235 g, 5 mmol) was added to a mixture of phosphorus oxychloride (1.32 g) in dry dimethylformamide (DMF) (20 ml). The mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure. Water was added to the residue and the solution was allowed to stand overnight to give a crude product (1.276 g, 93%) as a precipitate. Recrystallization from MeOH gave analytically pure 6-amino-5-formyl-1-(4-methoxyphenyl)-3-methyluracil, mp 250—251 °C. MS *m/z*: 275 (M$^+$, 69%), 247 (M$^+$ − CO, 93%), 190 (247 − MeNCO, 91%), 149 (MeOC$_6$H$_4$NCO$^+$, 100%). ^{1}H-NMR (DMSO-d_6) δ: 3.16 (3H, s, N-Me), 3.83 (3H, s, O-Me), 7.12, 7.35 (each 2H, each d, J = 8.8, 7.8 Hz, respectively, aromatic H), 7.28, 9.81 (each 1H, each brs, NH$_2$), 9.79 (1H, s, CHO). *Anal.* Calcd for C$_{13}$H$_{13}$N$_3$O$_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.75; H, 4.78; N, 15.34.

5-Formyl-3-methyl-6-methylamino-1-phenyluracil (4c) A mixture of 6-chloro-3-methyl-1-phenyluracil[13] (2.36 g, 0.01 mol) and a 40% aqueous solution of methylamine (7.75 ml, 0.1 mol) in DMF (40 ml) was heated at 70 °C for 3 h. The solution was evaporated under reduced pressure and the residue was triturated with water to give a crude product (2.31 g, 62%). Recrystallization from ethyl acetate gave 3-methyl-6-methylamino-1-phenyluracil, mp 215—217 °C. MS *m/z*: 231 (M$^+$, 100%). ^{1}H-NMR (DMSO-d_6) δ: 2.63 (3H, d, 3 Hz, NH$\underline{\text{Me}}$), 3.18 (3H, s, NMe), 4.77 (1H, s, C$_5$-H), 5.64 (1H, br, NH), 7.40—7.59 (5H, m, C$_6$H$_5$). *Anal.* Calcd for C$_{12}$H$_{13}$N$_3$O$_2$: C, 62.32; H, 5.67; N, 18.17. Found: C, 62.34; H, 5.72; N, 18.03.

The obtained 6-methylaminouracil (462 mg, 2 mmol) was added to a mixture of POCl$_3$ (368 mg, 2.4 mmol) and dry DMF (10 ml). The mixture was stirred at room temperature for 2 h and then poured into ice-water (30 ml). The solution was allowed to stand overnight in a refrigerator. The resulting precipitate was recrystallized from MeOH to give **4c** in 65% yield, mp 231—232 °C. MS *m/z*: 259 (M$^+$, 42%), 231 (M$^+$ − CO, 33%), 230 (M$^+$ − CHO, 26%), 201 (33%), 91 (100%). ^{1}H-NMR (DMSO-d_6) δ: 2.23 (3H, d, J = 5.4 Hz, NH$\underline{\text{Me}}$), 3.26 (3H, s, N-Me), 7.62 (5H, s, C$_6$H$_5$), 9.89 (1H, s, CHO), 11.06 (1H, brs, NH). *Anal.* Calcd for

$C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.03; H, 5.03; N, 16.18.

5-Acetyl-6-amino-3-methyl-1-phenyluracil (4d) A mixture of 6-amino-3-methyl-1-phenyluracil[2] (4.88 g, 22.5 mmol) and acetic anhydride (50 ml) in acetic acid (100 ml) was heated at 120 °C for 40 min. The reaction mixture was evaporated to dryness under reduced pressure and the residue was recrystallized from MeOH to give 4.4 g (75%) of **4d**, mp 272—273 °C. MS *m/z*: 259 (M^+, 73%), 258 (M^+-1, 100%), 244 (M^+-Me, 80%), 119 (53%). ^{1}H-NMR (DMSO-d_6) δ: 2.56 (3H, s, COMe), 3.20 (3H, s, N-Me), 7.45, 10.90 (each 1H, each s, NH_2), 7.45—7.62 (5H, m, C_6H_5). *Anal.* Calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.01; H, 5.16; N, 16.06.

5-Acetyl-3-methyl-6-methylamino-1-phenyluracil (4e) 3-Methyl-6-methylamino-1-phenyluracil, an intermediate for the preparation of **4c**, was employed as a starting compound. A mixture of the 6-methylaminouracil (463 mg, 2 mmol) and acetyl chloride (314 mg, 4 mmol) in dry pyridine (15 ml) was heated at 80 °C for 3 h. The reaction solution was evaporated under reduced pressure and a small amount of water was added to the residue. The solution was extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give **4e** (361 mg, 66%), which was recrystallized from EtOH, mp 158—159 °C. MS *m/z*: 273 (M^+, 93%), 258 (M^+-Me, 100%). ^{1}H-NMR (DMSO-d_6) δ: 2.11 (3H, d, J=4.9 Hz, $NH\underline{Me}$), 2.52 (3H, s, COMe), 3.16 (3H, s, N-Me), 7.49 (5H, s, C_6H_5), 12.08 (1H, br, NH). *Anal.* Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.55; H, 5.58; N, 15.33.

6-Anilino-5-formyl-3-methyluracil (5a) a) A mixture of **4a**[2] (375 mg, 3 mmol) and KOH (336 mg, 6 mmol) in EtOH (30 ml) was refluxed for 22 h. The solvent was removed under reduced pressure and the residue was dissolved in water (20 ml). Insoluble matter was removed by filtration and the filtrate was acidified with acetic acid to give **5a** in 51% yield, mp 280—281 °C (EtOH). MS *m/z*: 245 (M^+, 25%), 244 (M^+-1, 100%), 216 (M^+-CHO, 50%). ^{1}H-NMR (DMSO-d_6) δ: 3.22 (3H, s, N-Me), 7.42—7.58 (5H, m, C_6H_5), 9.86 (1H, s, CHO), 11.55 (1H, br, NH), 11.86 (1H, br s, NH). *Anal.* Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.14. Found: C, 58.50; H, 4.49; N, 17.00.

b) Phosphorus oxychloride (520 mg, 3.4 mmol) was dissolved in dry DMF (10 ml) below 5 °C and 6-anilino-1-methyluracil[14] (488 mg, 2.25 mmol) was added thereto. The mixture was stirred at room temperature for 4 h. The reaction solution was poured into cold water. The resulting precipitate was collected by filtration to give **5a** (491 mg, 89%), which was identical with the sample prepared above.

5-Formyl-6-(4-methoxyanilino)-3-methyluracil (5b) A mixture of **4b** (963 mg, 3.5 mmol) and KOH (392 mg, 7 mmol) in EtOH (20 ml) was refluxed for 20 h. The precipitate was filtered off and dissolved in a small amount of water. The solution was acidified with acetic acid. The resulting precipitate was filtered off and recrystallized from EtOH to give **5b** (216 mg, 52%), mp 215—216 °C. MS *m/z*: 275 (M^+, 49%), 274 (M^+-1, 100%), 246 (M^+-CHO, 48%). ^{1}H-NMR (DMSO-d_6) δ: 3.10 (3H, s, N-Me), 3.78 (3H, s, O-Me), 7.00, 7.28 (each 2H, each d, J=8.7, 8.3 Hz, respectively, aromatic H), 9.78 (1H, s, CHO), 11.30 (1H, br s, NH), 11.61 (1H, s, NH). *Anal.* Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27. Found: C, 56.58; H, 4.74; N, 15.03.

6-Anilino-5-formyl-1,3-dimethyluracil (5c) A mixture of **4c** (519 mg, 2 mmol) and KOH (225 mg, 4 mmol) in EtOH (20 ml) was refluxed for 1 h. The reaction solution was evaporated under reduced pressure and the residue was dissolved in water (10 ml). The solution was acidified with acetic acid to give **5c** (419 mg, 81%), which was recrystallized from ethyl acetate and shown to be identical with an authentic sample.[5]

5-Acetyl-6-anilino-3-methyluracil (5d) and 2-Anilino-3-cyano-*N*-methylcrotonamide (7) A mixture of **4d** (518 mg, 2 mmol) and KOH (224 mg, 4 mmol) in EtOH (20 ml) was refluxed for 16 h. The solvent was removed under reduced pressure and water (20 ml) was added to the residue. Insoluble material was collected by filtration and recrystallized from ligroin to give **7** (98 mg, 29%), mp 140—141 °C. IR (KBr): 2190 (C≡N) cm^{-1}. MS *m/z*: 215 (M^+, 87%), 184 (M^+-MeNH_2, 73%), 157 ($M^+-MeNHCO$, 51%), 118 (100%). ^{1}H-NMR ($CDCl_3$) δ: 2.23 (3H, s, C-Me), 2.89 (3H, d, J=4.4 Hz, N-Me), 5.95 (1H, br, $MeN\underline{H}$), 7.12 (2H, d, J=7.8 Hz, *ortho*-H of phenyl group), 7.30 (1H, t, J=7.8 Hz, *para*-H of phenyl group), 7.39 (2H, t, J=7.8 Hz, *meta*-H of phenyl group), 12.42 (1H, br s, $PhN\underline{H}$). *Anal.* Calcd for $C_{12}H_{13}N_3O$: C, 66.95; H, 6.09; N, 19.52. Found: C, 67.04; H, 6.09; N, 19.48.

The filtrate was acidified with acetic acid to give a crude product. Recrystallization from MeOH gave **5d** in 32% yield, mp 260—261 °C. MS *m/z*: 259 (M^+, 22%), 244 (M^+-Me, 10%), 168 (100%). ^{1}H-NMR ($CDCl_3$) δ: 2.70 (3H, s, COMe), 3.28 (3H, s, N-Me), 7.23—7.55 (5H, m, C_6H_5), 7.70 (1H, br s, $PhN\underline{H}$), 13.10 (1H, br s, CONH). *Anal.* Calcd for $C_{13}H_{13}N_3O_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.38; H, 5.08; N, 16.23.

Alternative Preparation of 5d A mixture of 6-anilino-3-methyluracil[14] (326 mg, 1.5 mmol) and acetyl chloride (236 mg, 3 mmol) in dry pyridine (10 ml) was heated at 80 °C for 2.5 h. The solvent was removed under reduced pressure and the residue was triturated with a small amount of water to give **5d** (296 mg, 91%), which was identical with the product obtained by the Dimroth rearrangement of **4d**.

Alternative Preparation of 7 A mixture of 5-cyano-3,6-dimethyl-1-phenyluracil (**8**)[6] (241 mg, 1 mmol) and KOH (112 mg, 2 mmol) in 90% EtOH was refluxed for 1 h. The solvent was removed under reduced pressure and a small amount of water was added to the residue. The insoluble product (191 mg, 89%) was filtered off and recrystallized from ether to give pure **7**, which was identical with the compound obtained by the reaction of **4d** with KOH.

5-Acetyl-6-anilino-1,3-dimethyluracil (5e) a) A mixture of **4e** (135 mg, 0.5 mmol) and KOH (56 mg, 1 mmol) in EtOH (5 ml) was refluxed for 5 h. The solvent was removed under reduced pressure and the residue was dissolved in a small amount of water and acidified with acetic acid. The resulting precipitate was filtered off and recrystallized from ligroin to give **5e** (82 mg, 61%), mp 154—155 °C. MS *m/z*: 273 (M^+, 16%), 182 (100%). ^{1}H-NMR (DMSO-d_6) δ: 2.63 (3H, s, COMe), 2.95, 3.28 (each 3H, each s, N-Me × 2), 7.32—7.52 (5H, m, C_6H_5), 13.07 (1H, s, NH). *Anal.* Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.76; H, 5.55; N, 15.35.

b) A mixture of 6-anilino-1,3-dimethyluracil[14] (462 mg, 2 mmol) and acetyl chloride (314 mg, 4 mmol) in dry pyridine was heated at 80 °C for 4 h. The solvent was removed under reduced pressure. The residue was triturated with water to give crude 5-acetyl-6-anilino-1,3-dimethyluracil (241 mg, 44%), which was identical with the product obtained by the Dimroth rearrangement of **4e**.

References and Notes

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