Pyrimidine Derivatives and Related Compounds. XVII.¹
Hydrolysis of 5-Cyanouracil Derivatives²

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When 1-substituted 5-cyanouracils, 3-substituted 5-cyanouracils or 1,3-disubstituted 5-cyanouracils (substituents: phenyl, cyclohexyl, methyl) were heated to reflux in conc. HBr, the cyano group in the 5-position was removed and 1-substituted, 3-substituted or 1,3-disubstituted uracils were obtained, respectively. When warmed with conc. H₂SO₄, they gave 5-carbamoyluracil derivatives. Refluxing of the 5-carbamoyluracil derivatives with conc. HCl in AcOH, produced 5-carboxyuracil derivatives. Detailed consideration was made on mechanism of hydrolysis and decarboxylation of 5-cyanouracil derivatives under acidic conditions. Furthermore, hydrolysis of 5-cyanouracils under alkaline conditions was investigated.

The present study has been carried out in order to provide a method for a rational synthesis of 5-carboxyuracil derivatives by hydrolysis of the corresponding 5-cyanouracil derivatives. Hydrolysis in an acidic solution of 5-cyanouracil derivatives [substituents: 1-C₆H₅, 3-H (1); 1-cyclohexyl, 3-H (2); 1-H, 3-C₆H₅ (3); 1-H, 3-cyclohexyl (4); 1-C₆H₅, 3-CH₃ (5); 1-cyclohexyl, 3-CH₃ (6); 1-CH₃, 3-C₆H₅ (7); 1-CH₃, 3-cyclohexyl (8)] prepared in the preceding report¹ was at first investigated. Thus, the 5-cyanouracil derivatives (1—8) were heated to reflux in 10% HCl but only the starting 5-cyanouracils were recovered due to their very low solubilities. They were then heated to reflux in a large volume of conc. HCl, but due to their low solubilities in hot conc. HCl, the desired reaction scarcely proceeded and gave the desired 5-carboxyuracil derivative in only very low yields such as 2 to 3%.

Refluxing in conc. HBr was then attempted. However, the desired 5-carboxyuracils were not obtained but uracils lacking a nitrile group in the 5-position were produced in comparatively high yields such as 50—79% (Method A in Table I).

When 1—8 were warmed in conc. H₂SO₄ at 45—55°, 5-carbamoyluracils (17—24) were obtained in comparatively high yields (61—99%) (Method D in Table II). Since we found that refluxing of 7 in an equi-volume mixture of acetic acid and conc. HCl gave 5-carboxy-1-methyl-3-phenyluracil (31) in 17% yield, we applied this reaction condition to the hydrolysis of 5-carbamoyluracils (17—24) and succeeded in producing the desired 5-carboxyuracils (25—32) in comparatively high yields (Method E in Table III).

From the above experimental results, the best route to synthesize 5-carboxyuracils from 5-cyanouracils is to change the nitrile group in the 5-position of the 5-cyanouracil compounds to carbamoyl using conc. H₂SO₄ and then hydrolyzing in AcOH—H₂SO₄ to convert to carboxyl.

The afore-mentioned reaction in which uracils without a 5-nitrile group were produced by heating 5-cyanouracils in conc. HBr was further investigated. The hydrolytic removal of the nitrile group is presumed to proceed in the following manner: CN—CONH₂—COOH, and the resulting carboxyl group was decarboxylated. In order to confirm the process, 5-carbamoyluracils (17—24) and 5-carboxyuracils (25—28) were heated to reflux in conc.

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³ Location: Mitakura, Gifu.
HBr and the corresponding uracils (9–16) were found to be produced easily (Method B and Method C in Table I). When the gas generated by heating 5-cyanouracils in conc. HBr was bubbled through an aqueous solution of Ba(OH)_2, a white precipitate of BaCO_3 was produced. Accordingly, the following experiments were carried out in order to examine the decarboxylation mechanism of the 5-carboxyuracils.

(i) Hydrolysis and decarboxylation of 5-ethoxycarbonyl-3-phenylcytosines [1-H (33); 1-CH_3 (34)] (Chart 2): When 33 and 34 were heated to reflux in conc. HBr, the ester group in the 5-position was easily hydrolyzed giving 5-carboxy-3-phenylcytosines (35, 36) but no further decarboxylation took place. From this fact, it is believed that the carbonyl group in the 4-position played some part in the decarboxylation of the 5-carboxyuracils.

(ii) Intramolecular hydrogen bond of 5-carboxy-3-methyl-1-phenyluracil (29) (Chart 2): According to determination by infrared (IR) spectra, an absorption of 29 due to OH was
observed in the wide range of 2640—2740 cm\(^{-1}\). Since its methyl ester 37 was free of any intramolecular hydrogen bond, the absorption of 4-CO existed at 1663 cm\(^{-1}\) while that of 29 existed at 1638 cm\(^{-1}\), a 25 cm\(^{-1}\) lower wave number. An OH absorption of 5-carboxy-1-cyclohexyl-3-methyluracil (38) which did not have an intramolecular hydrogen bond occurred at 3100 cm\(^{-1}\) while that of 29 was shifted down 360 cm\(^{-1}\). These facts showed that, unlike 37 and 38, 29 had an intramolecular hydrogen bond between the 4-carbonyl and 5-carboxyl moieties.

(iii) Additional experiments: Besides the afore-mentioned decarboxylation in conc. HBr, refluxing of 5-carbamoyl-3-cyclohexyluracil (20) in conc. HCl-AcOH was carried out and a small amount of 3-cyclohexyluracil (12) was isolated. The yield was 8%. Heating of 5-carboxy-1-cyclohexyluracil (24) in quinoline for 2 hours at 240°, however, did not cause decarboxylation and only the starting material was recovered.

From the results of the above experiments (i), (ii) and (iii), the authors have presumed the decarboxylation mechanism to be as follows (Chart 3).

\[
\begin{align*}
\text{A} & \quad \xrightarrow{\text{H}^+} \quad \text{a} \\
\text{b} & \quad \xrightarrow{\text{H}^+} \quad \text{B}
\end{align*}
\]

Thus the 5-carboxyuracil forms a six-membered structure (A) having an intramolecular hydrogen bond and, when it is treated with a strong acid such as HBr, a cationic structure shown at (a) first contributes\(^4\) by protonation and then decarboxylation proceeds by electron transfer as shown at (b). After the decarboxylation, a cationic structure (d) results via c. When d is diluted or neutralized, a proton is removed and a uracil (B) is formed.

Hydrolysis of 5-cyanouracils in an alkaline solution was then studied. When 5-cyanouracils were hydrolyzed with 5—10% aqueous NaOH solution, the uracil ring was usually opened and a favorable result was not obtained. However, if 5-cyano-1-cyclohexyluracil (2) was hydrolyzed with 10% aqueous NaOH solution, 1-cyclohexyl-5-carboxyuracil (26) was obtained in 50% yield.

When 1,3-disubstituted 5-cyanouracil (C) is kept in aqueous alkali solution, it is believed that OH\(^-\) attacks a carbon atom of 4-carbonyl in the uracil ring forming a ketal structure (e) which is ring-opened to form f in most cases. Therefore, if there is no alkyl substituent at the nitrogen atom in 3-position (R\(_3\)=H), then 2 is comparatively stable even in alkali solution in order to inhibit the attack of OH\(^-\) to a carbonyl carbon in 4-position by a contribution of g or an \(\alpha\)-effect due to a negative charge of a nitrogen at 3-position (Chart 4).

3-H (40); 1-C₆H₅, 3-CH₃ (41); 1-cyclohexyl, 3-CH₃ (42)] were similarly hydrolyzed by 98% H₂SO₄ or conc. HBr but no hydrolysis took place and only the starting materials were recovered. Hydrolysis of these with an aqueous 10% NaOH solution also did not proceed, resulting only in an opening of the uracil ring.

Then 1-cyclohexyl-5-ethoxycarbonyl-6-methyluracils [substituents: 3-H (43); 3-CH₃ (44)] were hydrolyzed with a 5% aqueous NaOH solution to give 5-carboxy-1-cyclohexyl-6-methyluracils (45, 46). The yield of 46 was very low due to low solubility of 44 in alkali.

Hydrolysis of 43 with AcOH and conc. HCl did not yield 45 but gave 1-cyclohexyl-6-methyluracil (47) which was a decarboxylation product of 45. The reason why 45 is easily decarboxylated may be that a cationic structure (h) is more stable due to a hyperconjugation of a methyl group in the 6-position or the uracil ring becomes more susceptible to be subjected to protonation by the I-effect of the methyl group. Nevertheless, even if 5-cyano-6-methyluracils (39–42) could be hydrolyzed by heating in acid, the resulting 5-carboxy-6-methyluracils may be easily
decarboxylated and, therefore, this method is not suitable for the synthesis of 5-carboxy-6-methyluracils (Chart 5).

When 1-substituted (or 3-substituted) 5-carbamoyluracils (17–20) and 5-carboxyuracils (25–28) obtained in the above hydrolysis were methyalted with dimethyl sulfate in 10% NaOH, 1,3-disubstituted 5-carbamoyluracils (21–24) (Method F in Table II) and 1,3-disubstituted 5-carboxyuracils (29–32) (Method G in Table III), respectively, were obtained in comparatively high yields. In the latter methylation reaction, two moles each of NaOH and dimethyl sulfate were used for each mole of substituted uracil starting material and, in general, N-methylation took precedence over esterification of the carboxyl group in the 5-position. In case of methylation of 5-carboxy-1-phenyluracil (25), however, 5-methoxy-carbonyl-3-methyl-1-phenyluracil (37) and 29 were obtained.

Experimental

1,3-Substituted Uracils (9–16) (Table I)—Method A: To 25–35 ml of 48% HBr was added 5 g of a 5-cyanouracil (1, 2, 5, 7 or 8) and the mixture was refluxed for 2 hr. After the reaction, the mixture was poured over ice water or the reaction solution was evaporated in vacuo, H$_2$O was added to the residue, and the solution was neutralized with Na$_2$CO$_3$. The precipitated product was filtered off and washed with H$_2$O.

Method B: To 25–40 ml of 48% HBr was added 5 g of a 5-carbamoyluracil (17–24), the mixture was heated to reflux for 2 hr and treated the same as in Method A.

Method C: To 10–15 ml of 48% HBr was added 0.5 g of a 5-carboxyuracil (25–28), the mixture was heated to reflux for 2 hr, and treated the same as in Method A.

\[ 
\begin{align*}
\text{TABLE I. 1,3-Substituted Uracils} \\
\begin{array}{|c|c|c|c|c|c|c|}
\hline
\text{Compd. No.} & R_1 & R_2 & mp (\degree\text{C}) & \text{Appearance}^{(a)} & \text{Yield}^{(b)} & \text{Analysis (C)} \\
 & & & & \text{(Recryst.} & \text{Formula} & \text{A} & \text{B} & \text{N} \\
 & & & & \text{solv.}) & \text{ (%)} & \text{ (%)} & \text{ (%)} \\
\hline
9 & C_4H_5 & H & 251 & needles (MeOH) & 51 & 71 & 98 & C_{10}H_{16}O_2N_2 & 63.82 & 4.29 & 14.89 \\
10 & H & 220 & prisms (MeOH) & 75 & 79 & 80 & C_{10}H_{16}O_2N_2 & 61.83 & 7.27 & 14.42 \\
11 & C_4H_5 & C_5H_11 & 253 & needles (MeOH) & 54 & 50 & C_{19}H_{24}O_2N_2 & 65.71 & 4.39 & 14.93 \\
12 & H & 270 & prisms (EtOH) & 36 & 95 & C_{19}H_{16}O_2N_2 & 61.83 & 7.27 & 14.42 \\
13 & C_4H_5 & CH_3 & 138 & needles (H$_2$O) & 50 & 71 & C_{11}H_{16}O_2N_2 & 65.33 & 4.98 & 13.86 \\
14 & CH_3 & 103 & prisms (ligroin) & 42 & C_{11}H_{16}O_2N_2 & 65.49 & 4.93 & 13.86 \\
15 & CH_3 & 134 & prisms (AcOEt) & 79 & 90 & C_{12}H_{16}O_2N_2 & 65.33 & 4.98 & 13.86 \\
16 & CH_3 & 127 & prisms (ligroin) & 70 & 54 & C_{12}H_{16}O_2N_2 & 65.47 & 7.72 & 13.71 \\
\hline
\end{array}
\end{align*}
\]

\textit{a)} All compounds are colorless crystals. \textit{b)} A: method A, B: method B, C: method C.

1,3-Substituted 5-Carboxamoyluracils (17–24) (Table II)—Method D: To 0.1 mole of a 5-cyanouracil (1–8) was added 1.8 ml of H$_2$O$_2$, the uracil was dissolved by adding 125–150 ml of conc. H$_2$SO$_4$ thereto and the mixture was warmed at 45–55\degree for 3 hr. After the reaction, the mixture was poured over ice and the precipitated product was filtered off and washed with H$_2$O.

Method F: To 0.1 mole of 5-carbamoyluracils (17–20) was added 80 ml of 5% aq. solution of NaOH and the resulting suspension was made to react for 2–3 hr under dropwise addition of 12.8 g (0.1 mole) of di-
methyl sulfate with stirring. After the reaction, the precipitated product was filtered off and washed with H$_2$O.

**Table II. 1,3-Substituted 5-Carbamoyluracils**

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>mp ($^\circ$C)</th>
<th>Appearance$^a$</th>
<th>Yield (%)$^b$</th>
<th>Analysis (%)</th>
<th>C</th>
<th>H</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>$C_4H_9$</td>
<td>H</td>
<td>$&gt;300$</td>
<td>needles (AcOH)</td>
<td>99 — $C_{11}H_{15}O_2N_3$</td>
<td>Caled. 57.14</td>
<td>3.92</td>
<td>18.18</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>$C_4H_9$</td>
<td>H</td>
<td>306</td>
<td>prisms (MeOH)</td>
<td>95 — $C_{11}H_{15}O_2N_3$</td>
<td>Found 57.14</td>
<td>4.06</td>
<td>17.89</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>H</td>
<td>$C_4H_9$</td>
<td>308</td>
<td>needles (MeOH)</td>
<td>99 — $C_{11}H_{15}O_2N_3$</td>
<td>Caled. 57.14</td>
<td>3.92</td>
<td>18.18</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>H</td>
<td>$C_4H_9$</td>
<td>302</td>
<td>needles (MeOH-H$_2$O)</td>
<td>96 — $C_{11}H_{15}O_2N_3$</td>
<td>Caled. 57.14</td>
<td>3.92</td>
<td>18.18</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>$C_4H_9$</td>
<td>CH$_3$</td>
<td>256</td>
<td>needles (acetone)</td>
<td>65 81 $C_{12}H_{17}O_3N_3$</td>
<td>Caled. 58.77</td>
<td>4.52</td>
<td>17.14</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>$C_4H_9$</td>
<td>CH$_3$</td>
<td>242</td>
<td>needles (MeOH)</td>
<td>61 84 $C_{12}H_{17}O_3N_3$</td>
<td>Caled. 57.35</td>
<td>6.82</td>
<td>16.79</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>CH$_3$</td>
<td>$C_4H_9$</td>
<td>$&gt;315$</td>
<td>needles (dioxane)</td>
<td>65 71 $C_{12}H_{17}O_3N_3$</td>
<td>Caled. 58.77</td>
<td>4.52</td>
<td>17.14</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>CH$_3$</td>
<td>CH$_3$</td>
<td>306</td>
<td>prisms (AcOH-H$_2$O)</td>
<td>95 84 $C_{12}H_{17}O_3N_3$</td>
<td>Caled. 57.35</td>
<td>6.82</td>
<td>16.72</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ All compounds are colorless crystals.  
$^b$ D: Method D, F: Method F.

1,3-Substituted 5-Carboxyuracils (25–32) (Table III) —— a) Method E: 5-Carbamoyluracils (17–24) were added to a mixture of 250 ml of AcOH and 250 ml of conc. HCl and the mixture was heated to reflux for 5–7 hr. After the reaction, the mixture was concentrated in vacuo and H$_2$O was added to the residue whereupon a crude product separated out.

b) 5-Carboxy-1-methyl-3-phenyluracil (31): To a mixture of 30 ml of AcOH and 30 ml of conc. HCl was added 3.0 g of 5-cyano-1-methyl-3-phenyluracil (7) and the mixture was heated to reflux for 8 hr. After the reaction, the reaction solution was concentrated in vacuo, and the mixture was heated to reflux for 1 hr. The crude product was filtered off. It was dissolved in saturated aq. solution of NaHCO$_3$, the solution was filtered, and the precipitated product was filtered off. The crude product was dried to obtain a yield of 0.8 g (17%). Recrystallization from AcOEt gave colorless needles of mp 208°. It was confirmed to be identical with the compound 31 obtained in Method E by IR comparison.

c) 1-Cyclohexyl-5-carboxyuracil (26): To 50 ml of 10% aq. solution of NaOH was added 4.6 g (0.02 mole) of 5-cyano-1-cyclohexyluracil (2) and the mixture was heated to reflux for 10 hr. The crude product was filtered off, and the precipitated product was washed with H$_2$O to give a yield of 4.5 g (50%) of crude product, mp 303–305°. Recrystallization from dioxane gave colorless needles of mp 316°. It was confirmed by IR comparison to be identical with the compound 26 obtained by Method E.

d) Method G: In 8 ml of 10% aq. solution of NaOH were dissolved 0.01 mole of a 5-carboxyuracil (26–28), the mixture was stirred for 1–2 hr with 0.02 mole of dimethyl sulfate, the reaction solution was filtered, and the precipitated product was washed with HCl, and the precipitated product (30–32) was filtered off and washed with H$_2$O.

**Methylation of 5-Carboxy-1-phenyluracil (25)** —— In 8 ml of 10% aq. solution of NaOH, 2.4 g (0.01 mole) of compound 25, 2.6 g (0.02 mole) of dimethyl sulfate was added dropwise thereto., and the mixture was stirred for 2 hr. After the reaction, the separated product was filtered off and washed with H$_2$O to give 1.4 g (50%) of crude 5-methoxycarbonyl-3-methyl-1-phenyluracil (37), mp 185–200°. It was dissolved in AcOEt, and the solution was purified by column chromatography using activated alumina and recrystallized from AcOEt to give colorless needles of mp 221°. It was confirmed by IR comparison to be identical with compound 37 obtained by esterification of 29. The filtrate in the above procedure was acidified with HCl to give 1.2 g (49%) of 5-carboxy-3-methyl-1-phenyluracil (29).
Table III. 1,3-Substituted 5-Carboxyuracils

<table>
<thead>
<tr>
<th>Compd. No.</th>
<th>R₁</th>
<th>R₂</th>
<th>mp (°C)</th>
<th>Appearance¹)</th>
<th>Yield (%)b)</th>
<th>Formula</th>
<th>Analysis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Recryst. solv.)</td>
<td>E</td>
<td>G</td>
<td>C</td>
</tr>
<tr>
<td>25</td>
<td>C₆H₅</td>
<td>H</td>
<td>278</td>
<td>prisms (AcOEt)</td>
<td>80</td>
<td>—</td>
<td>C₁₁H₁₄O₄N₄</td>
</tr>
<tr>
<td>26</td>
<td>H</td>
<td>H</td>
<td>316</td>
<td>needles (dioxane)</td>
<td>50</td>
<td>—</td>
<td>C₁₁H₁₄O₄N₄</td>
</tr>
<tr>
<td>27</td>
<td>H</td>
<td>C₆H₅</td>
<td>267</td>
<td>powder (dioxane)</td>
<td>66</td>
<td>—</td>
<td>C₁₁H₁₄O₄N₄</td>
</tr>
<tr>
<td>28</td>
<td>H</td>
<td>H</td>
<td>235</td>
<td>needles (dioxane)</td>
<td>30</td>
<td>—</td>
<td>C₁₁H₁₄O₄N₄</td>
</tr>
<tr>
<td>29</td>
<td>C₆H₅</td>
<td>CH₃</td>
<td>208</td>
<td>prisms (AcOEt)</td>
<td>70</td>
<td>40c)</td>
<td>C₁₁H₁₄O₄N₄</td>
</tr>
<tr>
<td>30</td>
<td>CH₃</td>
<td>CH₃</td>
<td>208</td>
<td>needles (AcOEt)</td>
<td>64</td>
<td>96</td>
<td>C₁₁H₁₄O₄N₄</td>
</tr>
<tr>
<td>31</td>
<td>CH₃</td>
<td>CH₃</td>
<td>199</td>
<td>plates (AcOEt)</td>
<td>70</td>
<td>84</td>
<td>C₁₁H₁₄O₄N₄</td>
</tr>
<tr>
<td>32</td>
<td>CH₃</td>
<td>CH₃</td>
<td>233</td>
<td>needles (AcOEt)</td>
<td>70</td>
<td>71</td>
<td>C₁₁H₁₄O₄N₄</td>
</tr>
</tbody>
</table>

a) All compounds are colorless crystals. b) E: Method E, G: Method G. c) By-product:

5-Methoxycarbonyl-1-methyl-3-phenylcytosine (34)—In 100 ml of MeOH was dissolved 7.5 g (0.025 mole) of 5-methoxycarbonyl-3-phenylcytosine (33),5 5.5 g (0.05 mole) of Na₂CO₃ was added thereto, 3.3 g (0.025 mole) of dimethyl sulfate was added with stirring, and the mixture was further stirred for 4 hr. Insoluble residue was filtered off, 200 ml of H₂O were added to the filtrate, and the mixture upon standing gave 7.6 g (92%) of crystalline product, mp 145—148°. Recrystallization from MeOH—H₂O gave colorless needles of mp 150—152°. Anal. Calcd. for C₁₅H₁₄O₄N₅: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.50; H, 5.56; N, 15.32.

5-Carboxy-3-phenylcytosine (35)—To 30 ml of conc. HBr was added 5.2 g (0.02 mole) of 5-carboxy-3-phenylcytosine (33), the mixture was heated to reflux for 20 min, the precipitated product was filtered off, and washed with H₂O to give 4.0 g (93%) of crude product, mp 275—276°. Recrystallization from a mixture of DMF and H₂O gave colorless needles of mp 284—286°. Anal. Calcd. for C₁₅H₁₄O₄N₅: C, 56.90; H, 3.47; N, 18.17. Found: C, 56.81; H, 3.86; N, 18.46.

5-Carboxy-1-methyl-3-phenylcytosine (36)—To 20 ml of conc. HBr was added 2.0 g of 5-carboxy-1-methyl-3-phenylcytosine (34) and the mixture was heated to reflux for 2 hr. After the reaction, conc. HBr was evaporated in vacuo, H₂O was added to the residue, the resulting crude product was filtered off, and washed with H₂O to give 1.0 g of crude product, mp 275—278°. Recrystallization from MeOH gave colorless needles of mp 275—280° (decomp.). Anal. Calcd. for C₁₅H₁₄O₄N₅: C, 58.77; H, 4.52; N, 17.14. Found: C, 58.50; H, 4.80; N, 17.01.

5-Methoxycarbonyl-3-methyl-1-phenyluracil (37)—Into 100 ml of MeOH were dissolved 2 g of 5-methoxycarbonyl-3-methyl-1-phenyluracil (29), HCl gas was bubbled thereinto for 30 min, and the mixture was heated to reflux for 4 hr. After the reaction, the MeOH was evaporated off, the residue was washed with H₂O and then with an aq. solution of NaHCO₃, and recrystallized from AcOEt to give 1.2 g of colorless needles, mp 221°. Anal. Calcd. for C₁₅H₁₄O₄N₅: C, 59.99; H, 4.65; N, 10.77. Found: C, 60.03; H, 4.71; N, 10.54.

5-Carboxymethyl-1-cyclohexyl-3-methyluracil (38)—i) 5-(1-Cyclohexyl-3-methyl-2,4-dioxo[1H,3H]-pyrimidyl)-acetoimidomorphone: To 10 g (0.04 mole) of 5-acetyl-1-cyclohexyl-3-methyluracil8 were added 1.6 g (0.05 mole) of sulfur and 20 ml of morpholine and the mixture was heated to reflux for 8 hr. After the reaction, 20 ml of EtOH and activated carbon were added to the reaction solution and the mixture was filtered. The filtrate was evaporated and ether was added to the residue to give 8.0 g (57%) of crude product, mp 133—136°. Recrystallization from acetone—H₂O gave yellow needles, mp 145°. Anal. Calcd. for C₁₉H₁₄O₄N₅S: C, 58.10; H, 7.17; N, 11.96. Found: C, 58.30; H, 6.94; N, 11.74.

ii) 5-Carboxymethyl-1-cyclohexyl-3-methyluracil (38): To a mixture of 30 ml of AcOH and 30 ml of conc. HCl were added 3.5 g (0.01 mole) of 5-(1-cyclohexyl-3-methyl-2,4-dioxo[1H,3H]pyrimidyl)-acetothio-
morpholide and the mixture was heated to reflux for 5—6 hr. After the reaction, the mixture was concent-
rated in vacuo, H₂O was added to the residue, and the precipitated product was filtered off and washed with
H₂O to give 80% of crude product. mp 195—200°. Recrystallization from AcOEt gave colorless needles

Hydrolysis of 5-Carbamoyl-3-cyclohexy luracil (20) with conc. HCl—AcOH——A mixture of compound
20 (15 g), AcOH (100 ml) and conc. HCl (100 ml) was refluxed for 5 hr. After the reaction, the mixture was
concentrated in vacuo, H₂O was added to the residue, the precipitated product was filtered off and washed with
H₂O. The resulting crude product was added to a saturated aq. solution of NaHCO₃, the mixture was
filtered, the insoluble residue was dissolved in acetone, and the solution was chromatographed on activated
alumina to give 1.0 g (8%) of crude product, mp 267—268°. Recrystallization from acetone–H₂O gave
colorless needles of mp 272°. It was confirmed by IR comparison to be identical with 3-cyclohexyluracil (12).
The mother liquor (NaHCO₃ solution) was then acidified with HCl and the precipitated crystals were
filtered off and washed with H₂O to give 5.0 g (30%) of crude 5-carboxy-3-cyclohexyluracil (28), mp 238—
241°. Recrystallization from dioxane–H₂O gave colorless needles, which were found to be identical by a
mixed melting point with the compound 28 previously synthesized.

Hydrolysis of 1-Cyclohexyl-5-ethoxycarbonyl-6-methyluracil₃ (43, 44)——a): To 20 ml of 5% aqueous
solution of NaOH was added compound 43 (10 g) and the mixture was heated to reflux for 1 hr. After
the reaction, the mixture was acidified with HCl with cooling to give 7.9 g (90%) of crude 5-carboxy-1-cyclo-
hexyl-6-methyluracil (45), mp 208—215°. Recrystallization from benzene gave colorless needles of mp 219°.
Anal. Calcd. for C₃₃H₅₆O₂N₂: C, 57.13; H, 6.39; N, 11.11. Found: C, 57.64; H, 6.43; N, 11.16.

b): A mixture of compound 44 (3 g), 30 ml of dioxane and 30 ml of 5% NaOH solution was heated to
reflux for 1 hr. After the reaction the mixture was concentrated in vacuo, 30 ml of H₂O was added to the
residue, the mixture was filtered, and the mother liquor was acidified with HCl to give 0.3 g (10%) of crude
5-carboxy-1-cyclohexyl-3,6-dimethyluracil (46), mp 151—160°. Recrystallization from benzene gave color-
less needles of mp 192—193°. Anal. Calcd. for C₃₅H₅₄O₂N₂: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.88;
H, 6.74; N, 10.42.

c): To a mixture of 20 ml of AcOH and 20 ml of 10% HCl were added 2.5 g of 43 and the mixture was
heated to reflux for 2 hr. After the reaction the mixture was concentrated in vacuo, H₂O was added to the
residue, the precipitated product was filtered off and washed with H₂O to give 1.75 g (99%) of crude
1-cyclohexyl-6-methyluracil (47), mp 212—222°. Recrystallization from AcOEt gave colorless needles of
mp 236°. It was confirmed by IR to be identical with an authentic sample of compound 47.₃