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SEARCH FOR A SIMPLER SYNTHETIC MODEL SYSTEM FOR INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITION TO THE 5,6-DOUBLE BOND OF A PYRIMIDINE NUCLEOSIDE

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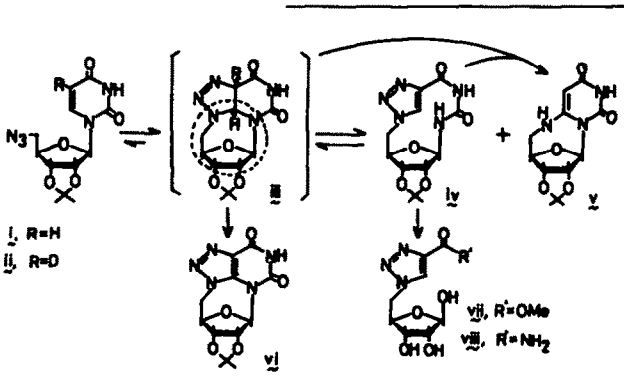
Abstract—In search for a simpler model system for the study of intramolecular thermal reactions between the base and 5'-functionalized sugar moiety in nucleosides, 1-(3-azidopropyl)uracil (2), 1-(4-azidobutyl) pyrimidines (12 and 13) and 1-(5-azidopentyl)-uracil (14) was synthesized through the corresponding ω-benzoyloxy-(6, 7 and 8) and ω-hydroxyalkyl-pyrimidines (9, 10 and 11). Heating 2 gave 1,N⁶-trimethylene-6-aminouracil (4), while heating 12 and 13 gave N¹-C₆ cleaved addition products, 15 and 16, respectively. 15 was regiospecifically transformed to 1,2,3-triazole derivatives, 17, 18 and 19. Heating 1-(4-azidobutyl)-5-bromouracil (20) yielded 3,9-tetramethylene-8-azaxanthine (22). 9 with NBA gave 1,0⁶-tetramethylene-5-bromo-6-hydroxy-5,6-dihydrouracil (24) and the 5-brominated analog of 9 (25). The 4-functionalized butyl side chain proved to serve as a substitute for the 5'-functionalized sugar moiety in pyrimidine ribonucleosides.

Recent reports[1,2] from this laboratory have described the unique chemical behavior of the derivatives (i and ii, Scheme 1) of 5'-deoxy-5'-azidouridine in a thermally induced cycloaddition reaction. The most intriguing aspect in this reaction was the facile bond cleavage and recombination between N¹ and C₆ in the pyrimidine part of the transient intermediate (iii): the adduct iii led to N¹,5'-anhydro-N³-(2',3'-O-isopropylidene-β-D-ribofuranosyl)-4-allophanoyl-1,2,3-triazole (iv) and a 6,5'-imino cyclonucleoside (v), while in the presence of 2,3-dichloro-s,6-dicyano-1,4-benzoquinone (DDQ) it gave an aromatized cyclonucleoside, vi. Compound iv was regio- and stereospecifically transformed to triazole reversed nucleosides, vii and viii.

simpler synthetic substitute could serve as a basis for expanding the variety of 1,3-dipolar species to apply to the natural nucleosides. Direct derivatization of nucleosides to a variety of 1,3-dipoles seems to be a hard task at present. This paper describes the results of a synthetic study directed toward the determination of the necessary length of a simple alkyl chain introduced at the N¹-position of uracil for causing the N¹-C₆ cleavage, utilizing an azido function as one of the most easily accessible 1,3-dipoles.

Prolonged heating of 1-(3-azidopropyl)uracil (2) (Scheme 2) obtainable from 1-(3-bromopropyl)uracil (1)[3a] in toluene at 110° gave 1,N⁶-trimethylene-6-aminouracil (4) in 92% yield. During the reaction tlc

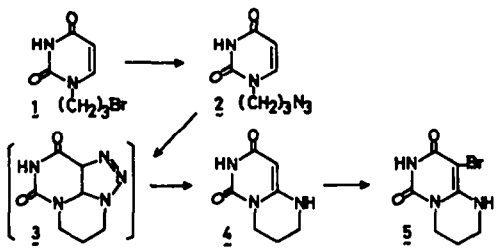


Scheme 1.

Our attention was directed next to a more simpler model system which can meet the steric requirement stemming from the unique 2,5-diaza-10-oxa-bicyclo[5.2.1]-decane system in the intermediate iii (dotted circle in Scheme 1), since it was expected that such a

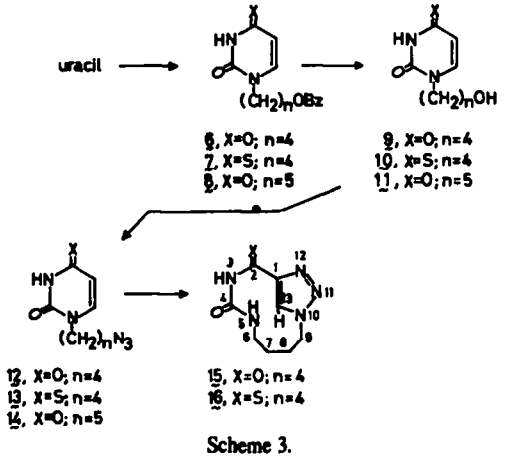
indicated the appearance of a tiny amount of another polar product, the quantity of which did not seem to increase however. This product was hence supposed to be the initial adduct, 3, which must have rapidly decomposed to 4. Compound 4 was very sparingly soluble in

organic solvents and accordingly brominated to 1,N^6-trimethylene-6-amino-5-bromouracil (5) for NMR measurement.



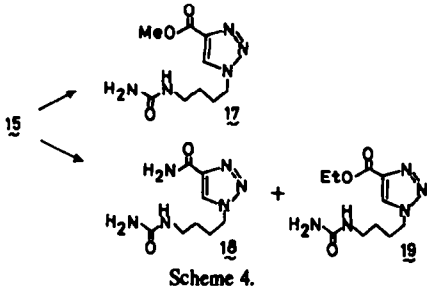
Scheme 2.

We next investigated the effect of chain elongation by one or two carbon units (Scheme 3). Although the synthesis of 1-(4-bromobutyl)- and 1-(5-bromopentyl)uracil is described,[3b] we chose to start from 1-(ω-benzoyloxyalkyl)uracils (6–8), since we wanted at the same time to establish the synthesis of 1-(ω-hydroxyalkyl)-uracils (9–11) to use for another unrelated purpose. These compounds could also lead to their ω-azidoalkyl analogs (12–14) easily.



Scheme 3.

Alkylation of uracil with 4-chlorobutyl benzoate[4] was examined under a variety of conditions and the most favorable one is described in the Experimental. In all the tried reactions, bis-alkylation at N^1 and N^3 was inevitable but the use of excess uracil allowed the formation of 1-(4-benzoyloxybutyl)uracil (6) in 54% yield. 1 - (5 - Benzoyloxypentyl)uracil (8) was similarly prepared using 5-chloropentyl benzoate.[5] 1 - (4 - Benzoyloxybutyl) - 4 - thiouracil (7) was also synthesized from 6 by the standard method to observe the influence of the 4-thioxo group in the cycloaddition reaction. Compound 6, 7 and 8 were converted to 1 - (4 - hydroxybutyl)uracil (9), 1 - (4 - hydroxybutyl) - 4 - thiouracil (10) and 1 - (5 - hydroxypentyl)uracil (11), respectively, in excellent yields by simple alkaline hydrolysis. Successive tosylation and azidation on 9–11 afforded the required 1 - (4 - azidobutyl)uracil (12), 1 - (4 - azidobutyl) - 4 - thiouracil (13) and 1 - (5 - azidopentyl)uracil (14) in moderate yields. Heating 12 in toluene for totally 206 hr (compare with the 55 hr's heating needed to convert i to iv and v) gave 2,4 - dioxo - 3,5,10,11,12 - pentaaza - bicyclo[8,2,1] - trideca - 1,11 - diene (15) as single product in over 80% yield. Compound 15 does not absorb above 210 nm and exhibits NMR signals for two NH groups and an olefinic proton. These spectral properties coincide with the data reported for compound iv.[1,2] Similarly, compound 13 afforded 2 - thioxo - 4 - oxo - 3,5,10,11,12 - pentaaza - bicyclo[0,2,1] - trideca - 1,11 - diene (16) in 74% yield in a shorter reaction time. The UV-absorptions of 16 at 230 and 287 nm are distinctly blue-shifted as compared with those of the starting material (247 and 332 nm) and comparable with the absorptions of 1 - β - D - ribofuranosyl - 1,2,3 - triazole - 4 - thiocarboxamide in a neutral medium (239 and 299 nm).[6] The differences of about 10 nm between the corresponding peaks of both compounds could be ascribed to the limited co-planarity of the triazole ring and side chain in 16 as suggested by a molecular model. NMR-Measurement for this compound was abandoned owing to its limited solubility. Interestingly, compound 13 in solid state became a mixture of two components after standing at room temperature for one week. The minor, slightly slower-running (silica gel, chloroform/methanol, 9:1) substance was supposed to be the initial cycloadduct (triazoline) which was also observed when heated as judged by tlc. The unexpected facile cycloaddition of 13 is especially interesting in relation to further transformations involving amination of the thioxo group, since we have not succeeded in characterizing the products in the thermal reactions of some derivatives of 5' -deoxy - 5' - azido - cytidine.[7] On the other hand heating 14 caused no reaction, the starting material being recovered unaffected. Thus, it became clear that the fusion of a seven-membered ring to the dihydro - 8 - azaxanthine system (Scheme 5, 23) can trigger the N^1-C_6 decyclization.



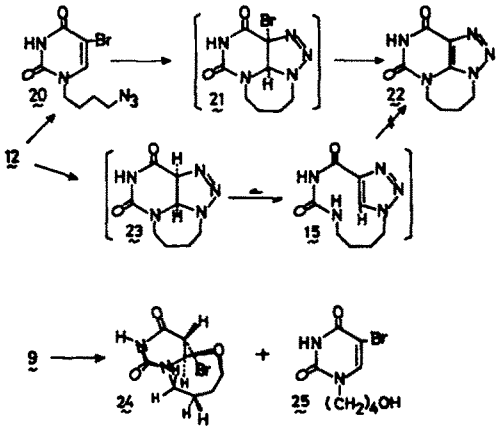
Scheme 4.

Methanolysis of 15 smoothly proceeded to give 1 - (4 - ureidobutyl) - 4 - methoxycarbonyl - 1,2,3 - triazole (17) in 95% isolated yield (Scheme 4). The structure of 17 was evident on the basis of its uv[8] and NMR spectra (*see* Experimental). Treatment of 15 with ethanolic ammonia gave 1 - (4 - ureidobutyl) - 4 - carboxamido - 1,2,3 - triazole (18) and 1 - (4 - ureidobutyl) - 4 - ethoxycarbonyl - 1,2,3 - triazole (19) in 71 and 8% yields, respectively. In the NMR spectrum of 18 the signal of the carboxamido group appeared as a pair of one proton singlets. These and other resonance features are in agreement with the data for the ammonolysis product obtained from iv.[1,2] The NMR measurement for 19 was not conducted owing to the material paucity, but the proposed structure of 19 would be correct in view of the high regiospecificity of the methanolysis reaction to yield 17. Thus, the resulting macrocyclic compounds, 15 and 16, can also serve as a good model for iv, which also undergoes regiospecific nucleophilic scission.[1,2]

We then examined the chemical behavior of this system in an addition-elimination reaction often observed in the nucleoside area[9] when a leaving group is present at the 5-position. For this purpose, 1 - (4 - azidobutyl) - 5 - bromouracil (20) was synthesized from 12 and submitted to a similar thermal reaction, when, as expected, 3,9 -

tetramethylene - 8 - azaxanthine (22) formed by cis elimination of hydrogen bromide from the intermediate 21 (Scheme 5). The nucleosidic analog vi (Scheme 1) was initially synthesized by a similar method.[9f] In contrast with the formation of vi through iv and iii (Scheme 1), 22 was not obtained by heating 15 with DDQ. This suggests that recyclization of 15 to 23 is much more difficult as compared with that of iv to iii. This minor discrepancy of chemical behavior is also reflected in the thermal reactions of 12 and 13, because no other sideproducts such as 4 formed by triazoline decomposition was isolated.

It was further shown that this simple model system carrying a tetramethylene side chain can replace a pyrimidine nucleoside also in the case of an intramolecular nucleophilic reaction which usually occurs at C_6: 9 reacted with N-bromoacetamide (NBA) to give first two main products in comparable amounts. These were tightly running in terms of tlc. On leaving a solution of the mixture at room temperature for one week, the slower moving substance disappeared and a new very polar substance formed. Separation at this stage gave 1,O^6 - tetramethylene - 5 - bromo - 6 - hydroxy - 5,6 - dihydrouracil (24) and more polar 1 - (4 - hydroxybutyl) - 5 - bromouracil (25) as stable products. Comparable reactions to form 5',6-O-cyclo pyrimidine nucleosides are well documented.[10] The structure of 24 is evident on the basis of its spectral data. In the NMR spectrum, a very small H_5–H_6 coupling constant (J = 2.25 Hz) was observed. This suggests a dihedral angle of approximately 110–120° that is also supported by a model study. In another experiment we separated the unstable, slower moving main product as crystals, the UV spectrum of which showed a week absorption at 276 nm, indicating the partial conversion of this compound into 25: in fact, this compound smoothly transformed into 25 on slight warming in methanol. Moreover, this unstable product in solid state completely transformed into 24 after two months at room temperature and, accordingly, was concluded to be a steric isomer of 24. Compound 24 also tended to decyclize, but more slowly, to 25 in protic solvents as judged by a similar absorption at 276 nm.



Scheme 5.

In conclusion, uracil derivatives with ω-functionalized butyl chain at N^1 can serve as simple synthetic models for the study of intramolecular interaction between the base and 5'-functionalized sugar moiety in the pyrimidine nucleosides in spite of the slight discrepancy from the steric requirement pertinent to the latter. Notably, the thermal reactions of 2, 12 and 13 were generally quite sluggish as compared with the nucleosides, i and ii. This should be attributed, at least in part, to the linear structures of these models which are in contrast with the favorable geometry in nucleoside derivatives carrying the 5'-terminus on the same side with the base.

EXPERIMENTAL

All the mps are uncorrected. The UV spectra were measured on a Hitachi Model 200-10 spectrophotometer. The ^{1}HNMR spectra were determined using a JNM C-60 HL spectrometer and TMS as an internal standard. Elemental analyses were conducted by Miss Y. Kawai using a Perkin-Elmer 240 elemental analyzer in this laboratory. Mallinckrodt silicic acid (100 mesh) was used for column chromatography. All evaporations were carried out *in vacuo* at or below 40°.

1-(3-*Azidopropyl*)*uracil* (2). A mixture of 1[3] (300 mg, 1.3 mmol), tetraethylammonium chloride (640 mg, 3.9 mmol) and sodium azide (251 mg, 3.9 mmol) in DMF (6 ml) was stirred at room temp for 3 hr and then evaporated. The residue was partitioned between EtOAc (150 ml) and water (20 ml). The separated organic layer was evaporated to a gum, which crystallized on digesting with a small volume of EtOH. Recrystallization from EtOH gave 230 mg (92%) of 2 of mp 88–90°: IR (KBr)νN_3 2080 cm^{-1}; UV (MeOH) 264 nm (ε 9800); ^{1}HNMR ($CDCl_3$) δ 1.97 (2H, m, J = 7 Hz, 2-CH_2), 3.41 (2H, t, J = 7 Hz, 3-CH_2), 3.83 (2H, t, J = 7 Hz, 1-CH_2), 5.70 (1H, d, $J_{5,6}$ = 8 Hz, H_5), 7.20 (1H, d, $J_{5,6}$ = 8 Hz, H_6) and 10.08 (1H, br s, NH, D_2O-exchangeable). (Found: C, 43.10; H, 4.84; N, 35.73. Calc. for $C_7H_9N_5O_2$: C, 43.08; H, 4.65; N, 35.88%).

1,N^6-*Trimethylene*-6-*aminouracil* (4). Compound 2 (500 mg, 2.56 mmol) in dry toluene (50 ml) was stirred at 110° for 50 hr and evaporated after cooling. The residue was digested with a small volume of acetone to give practically homogeneous crystals of 4 (205 mg) which was far slower moving on tlc ($CHCl_3$/MeOH, 9:1) than the starting material. The filtrate was evaporated and the residue again heated in toluene (20 ml) at 110° for additional 36 hr to give 80 mg of the same product. The same treatment of the residual starting material in toluene (20 ml) for 47 hr gave further 105 mg of crystals (Total 390 mg, 91.1%). Analysis sample was recrystallized from MeOH, mp above 300°: UV (MeOH) 271 nm (ε 26200). (Found: C, 50.28; H, 5.52; N, 25.06. Calc. for $C_7H_9N_3O_2$: C, 50.29; H, 5.43; N, 25.14%).

1,N^6 - *Trimethylene* - 6 - *amino* - 5 - *bromouracil* (5). A mixture of 4 (100 mg, 0.6 mmol) and NBA (100 mg, 1.2 mmol) in DMF (10 ml) was stirred at room temp for 1.5 hr. The resulting soln was evaporated to dryness and the solid residue collected by filtration with water (5 ml). Recrystallization from a mixture of MeOH and EtOH gave 126 mg (86%) of pale yellow powder (5), mp above 300°: UV (MeOH) 279 nm (ε 19800); ^{1}HNMR (DMSO-d_6) δ 1.6-2.2 (2H, m, 2-CH_2), 3.1-3.55 (2H, m, 3-CH_2), 3.6-3.9 (2H, m, 1-CH_2), 7.30 (1H, br s, 6-NH, D_2O-exchangeable) and 10.69 (1H, s, lactam NH, D_2O-exchangeable). (Found: C, 34.20; H, 3.38; N, 16.17. Calc. for $C_7H_8N_3O_2Br \cdot 1/3$ MeOH: C, 34.31; H, 3.66; N, 16.37%).

1-(4-*Benzoyloxybutyl*)*uracil* (6). A mixture of uracil (1.12 g, 10 mmol) and 50% oil-immersed sodium hydride (340 mg, 7 mmol) in DMF (50 ml) was stirred at 70–80° for 1 hr and cooled to room temp. 4-Chlorobutyl benzoate[4] (1.3 g, 6 mmol) was added and the mixture stirred at 90° for 12 hr. Tlc (silica gel, $CHCl_3$/MeOH, 9:1) showed two main products and the starting material. The mixture was neutralized with AcOH, evaporated and the residue partitioned between $CHCl_3$ (80 ml) and water (30 ml). The sparingly soluble uracil was recovered by filtration (490 mg). The separated organic layer was dried, evaporated and applied on a silica gel column (3 × 15 cm). Elution with $CHCl_3$ gave from the first main fraction 860 mg (31%) of 1,3 - bis - (4 - benzoyloxybutyl)uracil as colorless paste: ^{1}HNMR ($CDCl_3$) δ 1.6–2.2 (8H, m, 2-CH_2 × 2 and 3-CH_2 × 2), 3.6–4.1 (4H, m, 1-CH_2 × 2), 4.2–4.6 (4H, m, 4-CH_2 × 2), 5.69 (1H, d, $J_{5,6}$ = 8 Hz, H_5), 7.19 (1H, $J_{5,6}$ = 8 Hz, H_6), 7.2–7.7 (6H, m, aryl) and 7.9–8.2 (4H, aryl).

The next main fraction was eluted with 10% EtOAc in $CHCl_3$ and then with 5% MeOH in $CHCl_3$. Recrystallization of the obtained solid from EtOH gave 956 mg (54.3% on the basis of the

used haloester) of crystals (6), m.p. 143–145°: UV (MeOH) 226 (ε 14000) and 264 nm (ε 10800); ^{1}HNMR ($CDCl_3$) δ 1.6–2.2 (4H, m, 2- and 3-CH_2), 3.6–4.1 (2H, m, 1-CH_2), 4.2–4.6 (2H, m, 4-CH_2), 5.69 (1H, d, $J_{5,6}$ = 8 Hz, H_5), 7.19 (1H, d, $J_{5,6}$ = 8 Hz, H_6), 7.2–7.7 (3H, m, aryl), 7.9–8.2 (2H, m, aryl) and 9.95 (1H, br, s, NH, D_2O-exchangeable). (Found: C, 62.41; H, 5.64; N, 9.42. Calc. for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72%).

1 - (4 - *Benzoyloxybutyl*) - 4 - *thiouracil* (7). A mixture of 6 (500 mg, 1.74 mmol) and sulfur pentasulfide (413 mg, 3.48 mmol) in pyridine (5 ml) was stirred at 110° for 40 min. Further sulfur pentasulfide (413 mg) was added and heating continued at the same temp for additional 4 hr. After evaporation, the residue was partitioned between $CHCl_3$ (40 ml) and water (7 ml). The separated organic layer was dried over Na_2SO_4 and evaporated to give a solid residue, which was collected with a small volume of EtOH and recrystallized from MeOH to afford 360 mg (68%) of 7, mp 146–147°: UV (MeOH) 228 (ε 14800), 251 (ε 5700, sh) and 332 nm (ε 19400); ^{1}HNMR ($CDCl_3$) δ 1.6–2.2 (4H, m, 2- and 3-CH_2), 3.6–4.0 (2H, m, 1-CH_2), 4.2–4.5 (2H, m, 4-CH_2), 6.35 (1H, d, $J_{5,6}$ = 8 Hz, H_5), 6.98 (1H, d, $J_{5,6}$ = 8 Hz, H_6), 7.1–7.7 (3H, m, aryl), 7.85–8.20 (2H, m, aryl) and 10.12 (1H, br s, D_2O-exchangeable). (Found: C, 59.07; H, 5.42; N, 9.00. Calc. for $C_{15}H_{16}N_2O_3S$: C, 59.20; H, 5.30; N, 9.21%).

1-(5-*Benzoyloxypentyl*)*uracil* (8). Uracil (3.36 g, 30 mmol) and 50% oil-immersed sodium hydride (1.02 g, 30 × 0.7 mmol) in DMF (200 ml) was stirred at 70° for 1 hr and then cooled to room temp. 5-Chloropentyl benzoate[5] (4.21 g, 30 × 0.6 mmol) was added and the mixture stirred at room temp for 2 hr, and then at 90° for 6 hr. After evaporation, ice-water (50 ml) was added to the residue and the mixture neutralized with AcOH under swirling. The resulting ppt of unconsumed uracil was collected by suction and washed with $CHCl_3$ (1.27 g, 11.3 mmol). The filtrate was extracted with $CHCl_3$ (70 ml) and the separated $CHCl_3$ soln evaporated after drying. The obtained gum was applied on a silica gel column (2 × 18 cm) and eluted with $CHCl_3$. The faster-running oily fraction (716 mg, 8% on the basis of the used haloester) proved to be 1,3 - bis - (5 - benzoyloxypentyl)uracil: ^{1}HNMR ($CDCl_3$) δ 1.2–2.2 (12H, m, 2-, 3- and 4-CH_2, ×2), 3.76 (4H, t, J = 7 Hz, 1-CH_2 × 2), 4.32 (4H, t, J = 6 Hz, 5-CH_2 × 2), 5.66 (1H, d, $J_{5,6}$ = 8 Hz, H_5), 7.06 (1H, d, $J_{5,6}$ = 8 Hz, H_6), 7.1–7.65 (6H, m, aryl) and 7.85–8.2 (4H, m, aryl). This product was discarded. The second main fraction gave 1.92 g (34% on the basis of the used haloester) of 8 as crystals of mp 113–116° after recrystallization from EtOH: UV (MeOH) 225 (ε 27200) and 264 nm (ε 20700); ^{1}HNMR ($CDCl_3$) δ 1.2–2.2 (6H, m, 2-, 3- and 4-CH_2), 3.76 (2H, t, J = 7 Hz, 4-CH_2), 4.32 (2H, t, J = 6 Hz, 5-CH_2), 5.66 (1H, d, J = 8 Hz, H_5), 7.14 (1H, d, J = 8 Hz, H_6), 7.1–7.65 (3H, m, aryl), 7.85–8.2 (2H, m, aryl) and 9.80 (1H, br s, NH, D_2O-exchangeable). (Found: C, 63.50; H, 6.03; N, 9.08. Calc. for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27%).

1-(4-*Hydroxybutyl*)*uracil* (9). Compound 6 (2.31 g, 8.0 mmol) in a mixture of MeOH (100 ml) and conc ammonia (100 ml) was stirred at room temp for 43 hr and the resulting soln evaporated. The residue was co-evaporated with EtOH a couple of times and digested with a small volume of EtOH to give crystals. Recrystallization from EtOH containing a small amount of MeOH gave 1.46 g (98.9%) of 9 as homogeneous crystals, m.p. 125–128°: UV (MeOH) 264 nm (ε 9800). (Found: C, 52.45; H, 6.41; N, 15.08. Calc. for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.57; N, 15.21%).

1 - (4 - *Hydroxybutyl*) - 4 - *thiouracil* (10). A mixture of 7 (361 mg, 1.19 mmol) and NaOMe (260 mg, 4.81 mmol) in MeOH (30 ml) was heated to reflux for 1 hr. After cooling, the mixture was neutralized with AcOH, evaporated and the residue extracted with hot acetone (3 × 20 ml). The combined acetone soln was evaporated to a gum, which was digested with a small volume of a mixture of EtOH and ether to give 211 mg (89%) of practically homogeneous crystals (10). A part was recrystallized from a mixture of EtOAc and acetone for analysis, m.p. 122–123°: UV (MeOH) 247 (ε 5000) and 332 nm (ε 20000). (Found: C, 47.85; H, 5.99; N, 13.75. Calc. for $C_8H_{12}N_2O_2S$: C, 47.99; H, 6.04; N, 13.99%).

1-(5-*Hydroxypentyl*)*uracil* (11). Compound 8 (1.52 g, 5 mmol) in a 1:1 mixture (150 ml) of MeOH and conc ammonia was stirred at room temp for 1 hr and the resulting soln left at room temp for 90 hr. After evaporation, the residue was partitioned between EtOAc (30 ml) and water (20 ml). The separated aqueous layer was evaporated and the residue recrystallized from EtOAc to give 826 mg (83%) of 11, mp 81–84°: UV (MeOH) 264 nm (ε 10000); ^{1}HNMR ($CDCl_3$/DMSO-d_6, 3:1) δ 1.1-2.0 (6H, m, 2-, 3- and 4-CH_2), 3.2–3.9 (4H, m, 1- and 5-CH_2), 4.13 (1H, t, J = 5 Hz, OH, D_2O-exchangeable), 5.55 (1H, d, $J_{5,6}$ = 8 Hz, H_5), 7.36 (1H, d, $J_{5,6}$ = 8 Hz, H_6) and 9.98 (1H, br s, NH, D_2O-exchangeable). (Found: C, 54.80; H, 6.85; N, 13.90. Calc. for $C_8H_{14}N_2O_3$: C, 54.53; H, 7.12; N, 14.13%).

1-(4-*Azidobutyl*)*uracil* (12). A mixture of 9 (645 mg, 3.5 mmol) and tosyl chloride (800 mg, 10.5 mmol) in pyridine (14 ml) was stirred at room temp for 5 hr and treated with water (2 ml) for 1 hr. After evaporation, the mixture was partitioned between EtOAc (150 ml) and water (50 ml). The separated organic layer was dried over Na_2SO_4 and evaporated to a light-yellow paste. This was combined with sodium azide (683 mg, 10.5 mmol) and tetraethylammonium chloride (1.74 g, 10.5 mmol) in DMF (24 ml), and the mixture stirred at room temp overnight. The insoluble material was filtered off and the filtrate evaporated. The residue was partitioned between EtOAc (50 ml) and water (30 ml). The separated aqueous layer was again extracted with EtOAc (40 + 30 ml) and the combined EtOAc soln evaporated after drying to a gum, which gave 480 mg (66%) of 12 from MeOH, m.p. 107–109°: UV (MeOH) 265 nm (ε 10300); IR (KBr) ν N_3 2100 cm^{-1}; ^{1}HNMR ($CDCl_3$) δ 1.71 (4H, br t, 2- and 3-CH_2), 3.36 (2H, t, J = 6.6 Hz, 4-CH_2), 3.78 (2H, t, J = 6.6 Hz, 1-CH_2), 5.73 (1H, d, $J_{5,6}$ = 8 Hz, H_5), 7.21 (1H, d, $J_{5,6}$ = 8 Hz, H_6) and 10.08 (1H, br s, NH, D_2O-exchangeable). (Found: C, 46.08; H, 5.36; N, 33.28. Calc. for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48%).

1 - (4 - *Azidobutyl*) - 4 - *thiouracil* (13). A mixture of 10 (783 mg, 3.74 mmol) and tosyl chloride (970 mg, 5.1 mmol) in pyridine (15 ml) was stirred at room temp for 9 hr and then left at 0° overnight. The mixture was treated with a small volume of water, evaporated and the residue partitioned between EtOAc (50 ml) and water (10 ml). The organic layer was worked up as usual to afford a gum, which was applied on a silica gel column (3 × 17 cm) and eluted with $CHCl_3$/EtOAc (3:1) to give 884 mg (2.5 mmol, 55%) of 1 - (4 - tosyloxybutyl) - 4 - thiouracil as a gum. The total was combined with sodium azide (487 mg, 7.5 mmol) and tetra-ethylammonium chloride (1.24 g, 7.5 mmol) in DMF (6 ml). The mixture was stirred at room temp for 3 days and evaporated. The residue was partitioned between EtOAc (40 ml) and water (8 ml). The separated organic layer was worked up as usual and the finally obtained paste was submitted to silica gel column chromatography (2 × 18 cm, $CHCl_3$/EtOAc, 3:1) to give 420 mg (1.86 mmol, 74.5%) of 13 as crystals of m.p. 88–90° after recrystallization from a mixture of MeOH and EtOH: UV (MeOH) 247 (ε 5900) and 332 nm (ε 19000); ^{1}HNMR ($CDCl_3$) δ 1.4–2.1 (4H, m, 2- and 3-CH_2), 3.2–3.55 (2H, m, 4-CH_2), 3.65–3.95 (2H, m, 1-CH_2), 6.35 (1H, d, $J_{5,6}$ = 8 Hz, H_5), 6.98 (1H, d, $J_{5,6}$ = 8 Hz, H_6). No distinct signal for NH group appeared. (Found: C, 42.41; H, 4.97; N, 31.32. Calc. for $C_8H_{11}N_5OS$: C, 42.66; H, 4.92; N, 31.10%).

1-(5-*Azidopentyl*)*uracil* (14). A mixture of 11 (583 mg, 3.0 mmol) and tosyl chloride (813 mg, 3.53 mmol) in pyridine (15 ml) was left at room temp overnight. The usual work-up involving EtOAc extraction gave a paste, which was combined with sodium azide (573 mg, 8.8 mmol) and tetraethylammonium chloride (1.77 g, 8.8 mmol) in DMF (25 ml) and the mixture stirred at 65° for 3 hr. After evaporation, the residue was partitioned between $CHCl_3$ (30 ml) and water (7 ml). The organic layer was dried and evaporated to give 372 mg (57%) of practically pure 14 as a pale yellow syrup. A portion was purified by tlc [silica gel, $CHCl_3$/EtOAc (1:1)] for analysis. IR (neat) ν N_3 2090 cm^{-1}; UV (MeOH) 263 nm (ε 10900); ^{1}HNMR ($CDCl_3$) δ 1.1–2.1 (6H, m, 2-, 3- and 4-CH_2), 3.29 (2H, t, J = 5 Hz, 5-CH_2), 3.76 (2H, t, J = 7 Hz, 1-CH_2), 5.71 (1H, d, $J_{5,6}$ = 8 Hz, H_5), 7.19 (1H, d, $J_{5,6}$ = 8 Hz, H_6) and 10.1 (1H, br s, NH, D_2O-exchangeable). (Found: C, 48.65; H, 5.98; N, 31.20. Calc. for $C_9H_{13}N_5O_2$: C, 48.42; H, 5.87; N, 31.38%).

2,4 - *Dioxo* - 3,5,10,11,12 - *pentaaza* - *bicyclo*(8,2,1) - *trideca* - 1,11 - *diene* (15). Compound 12 (420 mg, 2 mmol) in toluene (40 ml) was heated to reflux for 60 hr. Repeated tlc analysis [silica

gel, $CHCl_3$/MeOH (85:15)] during the reaction invariably showed the presence of only one, more polar product and the starting material. The mixture was evaporated and the residue triturated with a small volume of $CHCl_3$ to give 165 mg of homogeneous powder. The filtrate was evaporated and the residue again heated in toluene (20 ml) to reflux for 72 hr to give further 150 mg of the product. Another similar treatment with the residual starting material (toluene, 10 ml, 74 hr) afforded an additional crop (50 mg) (total 340 mg, 81%). A portion was recrystallized from acetone to colorless prisms (**15**), which gradually melted between 240 and 300° with decomposition; UV (MeOH) transparent above 210 nm; ^{1}HNMR (DMSO-d_6) δ 0.9–2.0 (4H, m, $-CH_2CH_2-$), 2.90–3.25 (2H, m, 6-CH_2), 4.2–4.6 (2H, m, 9-CH_2), 6.38 (1H, br t, 5-NH, D_2O-exchangeable), 8.51 (1H, s, =CH-) and 9.77 (1H, s, 3-NH, D_2O-exchangeable). (Found: C, 46.12; H, 5.18; N, 33.19. Calc. for $C_8H_{11}N_5O_2$: C, 45.93; H, 5.30; N, 33.48%).

2 - *Thioxo* - 4 - *oxo* - 3,5[10],11,12 - *pentaaza* - *bicyclo*[8.2.1] - *trideca* - 1,11 - *diene* (**16**). Compound **13** (115 mg, 0.5 mmol) in toluene (12 ml) was heated to reflux for 49 hr. After evaporation, the residue was triturated with a small volume of acetone and the solid collected by filtration (48 mg). The filtrate was evaporated and the residue again heated in toluene (6 ml) at 110° for additional 50 hr to give an additional crop (40 mg) (total 88 mg, 74%, tlc-pure). Recrystallization from MeOH gave pale yellow crystals of mp 210–212°: UV (MeOH) 230 (ϵ 7600) and 287 nm (ϵ 14300). (Found: C, 42.72: H, 5.08; N, 30.88. Calc. for $C_8H_{11}N_5OS$: C, 42.66; H, 4.92; N, 31.10%).

1 - (4 - *Ureidobutyl*) - 4 - *methoxycarbonyl* - 1,2,3 - *triazole* (**17**). Compound **15** (50 mg, 0.24 mmol) in MeOH (10 ml) was heated to reflux for 4 hr. Tlc (silica gel, 20% ethanol in benzene) indicated that the reaction was complete and only one polar product formed. After evaporation, the residual solid was recrystallized from EtOH to give 55 mg (95.4%) of colorless powder (**17**), mp 181–183°; UV (MeOH) 213 nm (ϵ 11700); ^{1}HNMR (DMSO-d_6) δ 1.0–2.2 (4H, m, 2- and 3-CH_2), 2.8–3.2 (2H, m, 4-CH_2), 3.83 (3H, s, methoxyl), 4.43 (2H, br t, J = 7.5 Hz, 1-CH_2), 5.38 (2H, s, NH_2, D_2O-exchangeable), 5.96 (1H, br t, J = 7 Hz, NH, D_2O-exchangeable) and 8.80 (1H, s, H_5). (Found: C, 44.59; H, 6.17; N, 28.92. Calc. for $C_9H_{15}N_5O_3$: C, 44.80; H, 6.27; N, 29.03%).

1 - (4 - *Ureidobutyl*) - 4 - *carboxamido* - 1,2,3 - *triazole* (**18**) *and* 1 - (4 - *Ureidobutyl*) - 4 - *ethoxycarbonyl* - 1,2,3 - *triazole* (**19**). Compound **15** (130 mg, 0.62 mmol) and saturated ethanolic ammonia (20 ml) was combined in a pressure tube and the mixture stirred at room temp for 3 hr. After evaporation, the residual solid was digested with a small volume of warm MeOH and cooled to give tlc-homogeneous crystals (**18**) (90 mg). The filtrate was evaporated and the residue digested with a small volume of acetone to give another crop of **18**. The combined solid was recrystallized from MeOH to give 100 mg (71.2%) of **18** as colorless crystals, m.p. 226–228°: UV (MeOH) 211 nm (ϵ 11600); ^{1}HNMR (DMSO-d_6) δ 1.1–2.1 (4H, m, 2- and 3-CH_2), 2.75–3.2 (2H, m, J = 6.2 Hz, 4-CH_2), 4.41 (2H, t, J = 6.3 Hz, 1-CH_2), 5.36 (2H, s, ureido NH_2, D_2O-exchangeable), 5.94 (1H, t, J = 6.2 Hz, NH, D_2O-exchangeable), 7.44, 7.79 (each 1H, br s, carboxamide NH_2, D_2O-exchangeable) and 8.49 (1H, s, triazole H_5). (Found: C, 42.44; H, 6.22; N, 35.28. Calc. for $C_8H_{14}N_6O_2 \cdot 1/3$ MeOH: C, 42.29; H, 6.46; N, 35.49%).

The acetone solution separated from **18** gave a faster-moving product, which was recrystallized from acetone to afford 13 mg (8.2%) of **19** as colorless crystals, m.p. 164–165°: UV (MeOH) 212 nm (ϵ 12300). (Found: C, 47.74; H, 6.50; N, 26.95. Calc. for $C_{10}H_{17}N_3O_3 \cdot 1/10\ CH_3COCH_3$: C, 47.54; H, 6.77; N, 26.92%).

1 - (4 - *Azidobutyl*) - 5 - *bromouracil* (**20**). A mixture of **12** (300 mg, 1.4 mmol) and NBA (218 mg, 1.54 mmol) in THF (10 ml) was stirred at room temp for 45 min. After evaporation, the residue was partitioned between EtOAc (30 ml) and water (7 ml). The organic layer was dried and evaporated to give a solid residue which was recrystallized from MeOH to afford 300 mg (73%) of **20** as colorless crystals, m.p. 137–139°: UV (MeOH) 281 nm (ϵ 9200); ^{1}HNMR ($CDCl_3$/DMSO-d_6, 5:1) δ 1.5–2.0 (4H, m, 2- and 3-CH_2), 3.36 (2H, t, J = 6 Hz, 4-CH_2), 3.78 (2H, t, J = 7 Hz, 1-CH_2), 7.67 (1H, s, H_6) and 11.57 (1H, br s, NH, D_2O-exchangeable). (Found: C, 33.73; H, 3.58; N, 23.54. Calc. for $C_8H_{10}N_5O_2Br \cdot \frac{1}{2}CH_3OH$: C, 33.45; H, 3.74; N, 23.65%).

3,9-*Tetramethylene*-8-*azaxanthine* (**22**). Compound **20** (210 mg, 0.73 mmol) in toluene (20 ml) was heated to reflux. After *ca* 18 hr precipitation of a solid was observed. After totally 55 hr, the mixture was cooled and the solid collected. The filtrate was evaporated and the residue again heated in DMF (10 ml) at 110° for 92 hr. After evaporation, the residue was triturated with acetone and the sparingly soluble solid collected. Recrystallization of the combined solid from a large volume of acetonitrile gave 75 mg (49%) of **22**, m.p. above 300°: UV (MeOH) 238 (ϵ 7300) and 255 nm (ϵ 8600); ^{1}HNMR (DMSO-d_6) δ 1.8–2.4 (4H, 2- and 3-CH_2), 3.9–4.3 (2H, m, $\rangle$N-CH_2), 4.4–4.8 (2H, m, $\rangle$N-CH_2) and 10.36 (1H, br s, NH, D_2O-exchangeable). (Found: C, 46.23; H, 4.53; N, 33.78. Calc. for $C_8H_9N_5O_2$: C, 46.37; H, 4.38; N, 33.80%).

1,6[6] - *Tetramethylene* - 5 - *bromo* - 6 - *hydroxy* - 5,6 - *dihydrouracil* (**24**) *and* 1 - (4 - *hydroxybutyl*) - 5 - *bromouracil* (**25**)

(A). A mixture of **9** (223 mg, 1.21 mmol) and NBA (200 mg, 1.45 mmol) in THF (5 ml) was stirred at room temp for 1 hr and evaporated. The residue was partitioned between EtOAc (30 ml) and water (7 ml). The separated organic layer was left at room temp for 1 week, and then worked up appropriately. The obtained product mixture was applied on a silica gel column (2 × 15 cm) and eluted with $CHCl_3$/EtOAc (3:1) to give **24** (90 mg, 28%) as colorless crystals of m.p. 144–146° after recrystallization from MeOH at room temp. UV ($CHCl_3$) 238 nm (ϵ 15200); ^{1}HNMR ($CDCl_3$) δ 1.5–2.2 (4H, m, $-CH_2CH_2-$), 2.7–3.3 (1H, m, $\rangle$N-CH-), 3.82 (2H, m, -O-CH_2-), 4.15–4.65 (1H, m, $\rangle$N-CH-), 4.33 (1H, dd, $J_{5,6}$ = 2.25 Hz, $J_{5,NH}$ = 1.6 Hz, H_5), 4.83 (1H, d, $J_{5,6}$ = 2.25 Hz, H_6) and 8.75 (1H, br m-like s). (Found: C, 36.45; H, 4.13; N, 10.65. Calc. for $C_8H_{11}N_2O_3Br$: C, 36.52; H, 4.21; N, 10.65%).

The column was then thoroughly eluted with EtOAc to give an impure solid, which was repeatedly recrystallized from acetone to give 70 mg (27%) of **25**, m.p. 159–160°: UV (MeOH) 281 nm (ϵ 9500); ^{1}HNMR ($CDCl_3$/DMSO-d_6, 5:1) δ 1.2–2.0 (4H, m, 2- and 3-CH_2), 3.3–4.0 (4H, m, 1- and 4-CH_2), 4.22 (1H, t, J = 5.3 Hz, OH, D_2O-exchangeable), 7.74 (1H, s, H_6) and 11.51 (1H, very shallow s, NH, D_2O-exchangeable). (Found: C, 36.30; H, 4.18; N, 10.74. Calc. for $C_8H_{11}N_2O_3Br$: C, 36.52; H, 4.21; N, 10.65%).

(B) A mixture of **9** (252 mg, 1.37 mmol) and NBA (227 mg, 1.64 mmol) in THF (6 ml) was stirred at room temp for 40 min. The mixture was evaporated and taken into EtOAc (30 ml). The soln was quickly washed with water (5 ml) and dried over Na_2SO_4. The solvent was removed and the residue applied on a silica gel column (2 × 17 cm). Elution with $CHCl_3$/EtOAc (3:1) gave 113 mg (31.4%) of **24**, identical with the product in method A in all respects. The column was then eluted with $CHCl_3$/EtOAc (2:1) to give the other main product as a tlc-homogeneous solid (85 mg, 23.4%). Recrystallization from MeOH at room temp gave crystals which gradually melted between 130 and 155°. UV ($CHCl_3$) 249 (ϵ 6100) and 276 nm (ϵ 1800, sh). (Found: C, 36.28; H, 4.12; N, 10.73. Calc. for $C_8H_{11}N_2O_3Br$: C, 36.53; H, 4.21; N, 10.65%).

This crystalline sample as such completely transformed into **24** after two months at room temp as judged by tlc and IR-spectroscopy.

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