Studies on Uracil Derivatives and Analogues. Part 8. A Non-catalytic Method for the Conversion of Uracil Derivatives into Dihydrouracil Derivatives[1,2]

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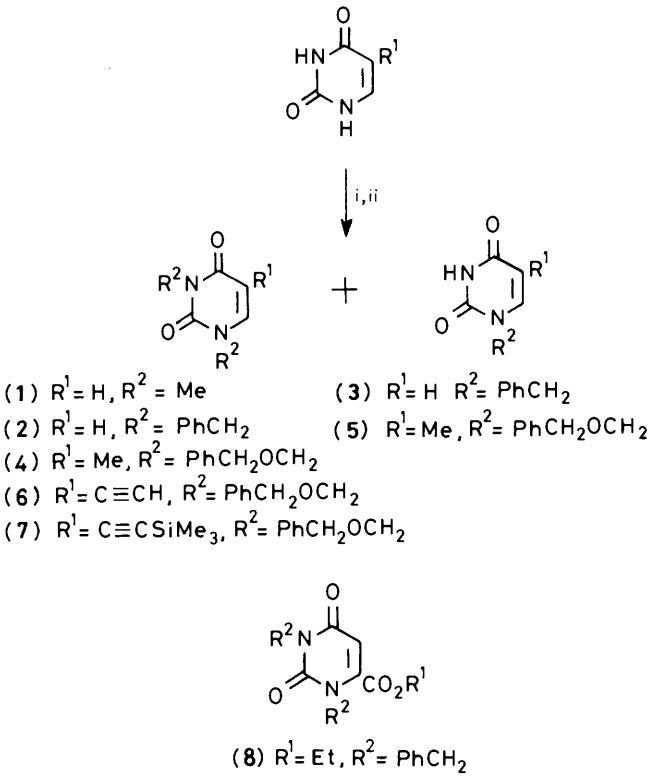
A mild and highly efficient method for the reduction of the 5,6-double bond of *N*-alkylated uracils with lithium tri-s-butylborohydride gives the corresponding 5,6-dihydro derivatives. The method can also be used for alkylation of the 5-position of *N*-alkyluracils to give 5-alkyl-5,6-dihydrouracil derivatives.

5,6-Dihydrouracils are of considerable biological importance, 5,6-dihydrouracil itself being an intermediate in the catabolism of uracil,[3] 5,6-dihydrothymine an intermediate in the catabolism of thymine,[4] and 5-fluorouracil, an anticancer drug, being catabolised to α-fluoro-β-alanine *via* 5-fluoro-5,6-dihydrouracil.[5] The role of 5,6-dihydro-orotic acid (6-carboxy-5,6-dihydrouracil) as an intermediate in pyrimidine biosynthesis is also well established.[6] We have an interest in 5,6-dihydrouracil and 5,6-dihydro-orotic acid derivatives as possible anticancer agents, their ability to act as inhibitors of enzymes involved in pyrimidine biosynthesis making them attractive candidates for this purpose. Specifically, 5-ethynyl-5,6-dihydrouracils are potential k_{cat} inhibitors.[7] In spite of their importance, there are few methods for the synthesis of these compounds, catalytic hydrogenation of uracil or orotic acid derivatives[8] often leading to elimination of sensitive functional groups.[9] Thus, catalytic hydrogenation of 5-fluorouracil with a Pd–C catalyst yielded 80% of uracil and with Rh only 6.5% of 5-fluorodihydrouracil.[10] Alternative methods[11] for the synthesis of dihydrouracils give low yields and are of limited applicability where sensitive functional groups are to be retained at the 5- or 6-positions. The paucity of methods for dihydrouracil synthesis, and their limitations, have led us to seek alternative methods. Since many 5- or 6-substituted uracils are known or have been synthesized,[12] we felt it would be more appropriate to prepare the corresponding dihydrouracils.

Lithium tri-s-butylborohydride (LTB) has been found to be a versatile reagent for the stereoselective reduction of cyclic ketones,[13] and Ganem and co-workers[14] have shown that it can reduce double bonds conjugated with a carbonyl or ester group. We have now used it for the reduction of the 5,6-double bond of various uracils.



Scheme 1. *Reagents:* i, anhydrous K_2CO_3; ii, R^2X.

Results and Discussion

N-Alkylation of Uracil and its Derivatives.—One of the conditions necessary for reduction of uracils with LTB is that they should be soluble in an appropriate solvent; thus, the insolubility of uracil in tetrahydrofuran (THF), dimethylformamide (DMF) or liquid ammonia made its reduction impossible. *N*-Alkylation of uracils however provided twin benefits in that (i) the products were soluble in THF and (ii) they were locked in the 'ene-one' form required for the reduction of the 5,6-double bond by LTB.

The *N*-alkylation of uracils has been the subject of a number of reports:[15] our method is shown in Scheme 1 where the potassium salts of uracil were treated with various alkylating agents, to give excellent yields of the products. The potassium salts were prepared by stirring uracil with anhydrous potassium carbonate in DMF. The process, which was relatively slow, gave the potassium salts as a thick gel. The reaction of this gel with alkylating agents yielded either a mixture of mono- and di-alkyl products or, predominantly, the dialkyl products, depending on the amount of alkylating agent used. In most cases, the total yields of the alkylated products were relatively high. For dihydrouracil and dihydrothymine, use of sodium hydride rather than potassium carbonate gave better yields of the alkylated species.

Alkylation with conventional alkylating agents (methyl iodide, benzyl halides) led to alkylated species which could subsequently be reduced with LTB. Since subsequent removal of the alkyl groups, however, proved difficult, we investigated the use of other NH protecting groups. In particular, we found that benzyloxymethyl chloride,[16] which has been used as an acid protecting group,[17] was very useful for this purpose, leading to good yields of the *N*-alkylated species. The removal of *N*-benzyloxymethyl groups from such situations has already been described.[18]

Table 1. ^{1}H N.m.r. spectra (δ values) of *N*-alkylated products of uracils

Compd.	N^1CH_2	N^3CH_2	OCH_2Ph	5-H	6-H	Other H
(**2**)	4.9 (s)	5.12 (s)		5.7 (d) ($J_{5,6}$ 7 Hz)	7.05 (d)	7.3 (m, ArH)
(**3**)	4.88 (s)			5.5 (d) ($J_{5,6}$ 7 Hz)	7.12 (d)	7.3 (s, ArH)
(**4**)	5.12 (s)	5.48 (s)	4.58 (s) 4.7 (s)		7.0 (s)	1.88 (s, C_5-Me) 7.3 (s, ArH)
(**5**)	5.17 (s)		4.57 (s)		7.07 (s)	1.9 (s, C_5-Me) 7.3 (s, ArH)
(**6**)	5.18 (s)	5.45 (s)	4.6 (s) 4.68 (s)		7.5 (s)	3.17 (s, acetylene) 7.32 (s, ArH)
(**7**)	5.18 (s)	5.48 (s)	4.58 4.69		7.5 (s)	0.28 (s, $Si(Me)_3$) 7.32 (s, ArH)
(**8**)	5.13 (s)	5.3 (s)		6.15 (s)		1.1 (t, CMe) 4.12 (q, OCH_2) 7.28 (m, ArH)

Table 2. ^{1}H N.m.r. spectra (δ values) of *N*-alkylated products of 5,6-dihydrouracils

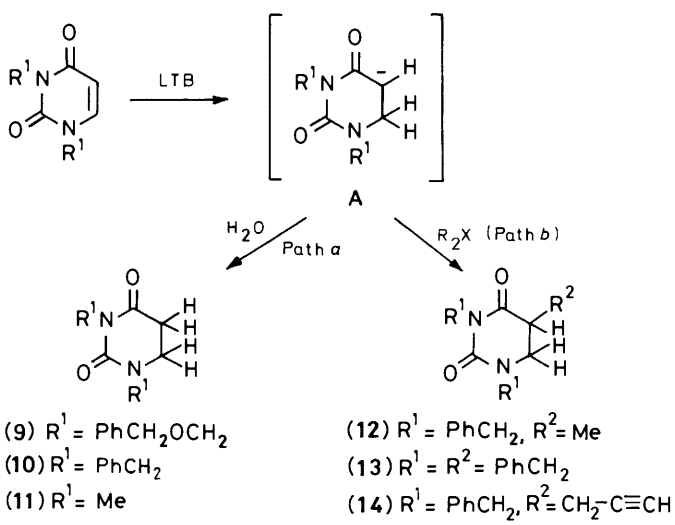
Compd.	N_1CH_2	N_3CH_2	OCH_2Ph	5-H	6-H	ArH	Other H
(**9**)	4.9 (s)	5.35	4.52 (s) 4.7 (s)	2.45 (t) ($J_{5,6}$ 7 Hz)	3.2 (t)	7.35 (s)	
(**10**)	4.58 (s)	5.0 (s)		2.54 (t) ($J_{5,6}$ 7 Hz)	3.18 (t)	7.3 (s)	
(**12**)	4.58 (s)	4.98 (s)		2.7 (m)	3.15 (m)	7.28 (s, br)	1.1 (d, C_5-Me) (J 7 Hz)
(**13**)	4.42 (s) 4.55 (s)	5.0 (s)		2.3—3.3 (m, 5-H, 6-H and CCH_2Ph)		7.2 (s)	
(**14**)	4.58 (s)	4.95 (s)		2.15—3.3 (m) and 2.85 (m)		7.2 (s)	1.9 (d, -C≡CH) (J 2 Hz)
(**15**)	4.88 (s) 4.92 (s)	5.3 (s)	4.5 (s) 4.62 (s)	2.48 (m)	2.88 (m) 3.29 (q) (J_{gem} 12 Hz; $J_{5,6}$ 7 Hz)	7.35 (s)	1.1 (d, C_5-Me) (J 7 Hz)
(**16**)	4.95 (s)	5.12 (s) 5.32(s)		2.88 (d) (J 6 Hz)	3.95 (m)	7.3 (s)	1.05 (t, OCMe) (J 7 Hz)
(**17**)	4.6 (s)	5.0 (s)			3.5 (m) ($J_{F,6}$ 12.5 Hz)	7.28 (s)	

The structures of the alkylated species follow from their elemental analyses and their spectroscopic data. N.m.r. results indicated that monoalkylation had occurred at N^1 and that the N^1-CH_2 groups have higher field chemical shifts than the N^3-CH_2 groups (see Table 1). The latter observation provides an independent method for the identification of N^1- and N^3-alkyluracils and is in agreement with earlier observations for *N*-alkylated 5-fluorouracils.[19]

The u.v. spectra were characteristic of *N*-alkylated derivatives, those of the mono-alkylated derivatives showing no shift in absorption in the presence of acid or alkali. I.r. absorptions characteristic of the carbonyl function (1 730—1 700 cm^{-1}) and the ureido function (1 690—1 630 cm^{-1}) (see Experimental section) were observed.

The mass spectra of the benzyloxymethyluracils are also in agreement with their assigned structures; although no molecular ion peaks were seen, all the dialkylated derivatives showed loss of a fragment of mass 106 (PhCHO) and mass 136 ($PhCH_2 - O - CH_2 - N - H$). The presence of strong base peaks at mass 91 ($C_7H_7^+$) and fragments mass 65 ($C_5H_5^+$) and mass 51 ($C_4H_3^+$) confirmed the structures of these compounds.

Reduction with Lithium Tri-s-butylborohydride (LTB).—LTB reduction of alkylated uracils was carried out at −78 °C under argon with rigorous exclusion of moisture and oxygen. The reduction, which was fast and complete within 5—10 min, proceeded *via* the carbanion (**A**) (Scheme 2). The latter, on

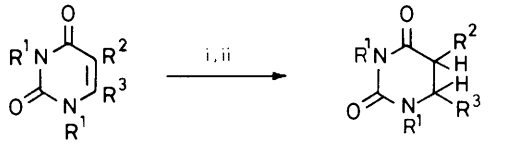


Scheme 2.

treatment with saturated aqueous ammonium chloride (path *a*) gave the *N*-substituted dihydrouracils (**9**)—(**11**). Alternatively, the carbanion could be alkylated (path *b*) *in situ* to give the 5-substituted 5,6-dihydrouracils (**12**)—(**14**) (Scheme 2). The use of potassium tri-s-butylborohydride in place of the lithium compound led to lower yields of the products. Dihydrouracils obtained by alkyl borohydride reduction were always contaminated with alkylboranes, and extensive column chromatography (on silica gel) or p.l.c. was needed for purification. Alkaline oxidative work-up was avoided in order to protect both sensitive functional groups and the dihydrouracil entity itself.

The yields of unsubstituted dihydro compounds were in the range 80—90% and for those with a 5- or 6-substituent 47—70%.

N^1,N^3-Dimethyl-5-fluoro-5,6-dihydrouracil[19] was obtained in 99% yield and the N^1,N^3-dibenzyl compound (**17**) in 47% yield (Scheme 3). By contrast, 5-fluoro-5,6-dihydrouracil was



(**15**) R^1 = $PhCH_2OCH_2$
R^2 = Me
R^3 = H

(**16**) R^1 = $PhCH_2$
R^2 = H
R^3 = $EtCO_2$

(**17**) R^1 = $PhCH_2$
R^2 = F
R^3 = H

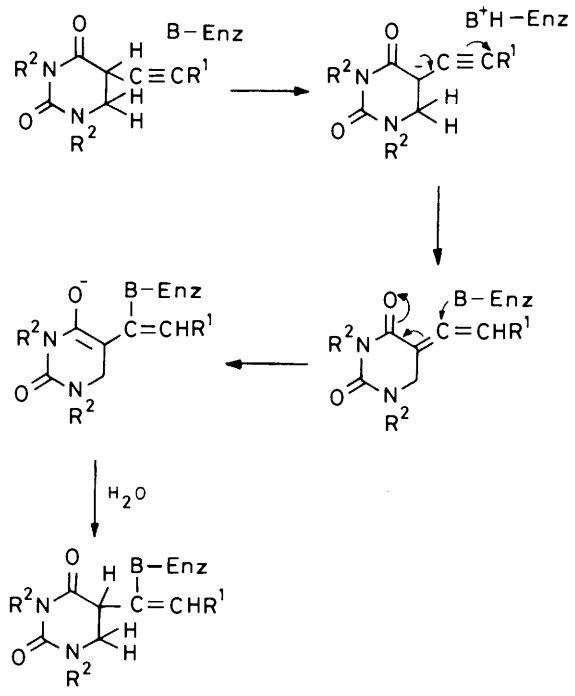
Scheme 3. *Reagents:* i, LTB; ii, aqueous ammonium chloride

obtained in only 6.5% yield.[10] Since 5-fluorouracil and its 2-deoxyribonucleoside are important chemotherapeutic agents,[20] *N*-alkylated 5-fluoro-5,6-dihydrouracils have a similar potential.

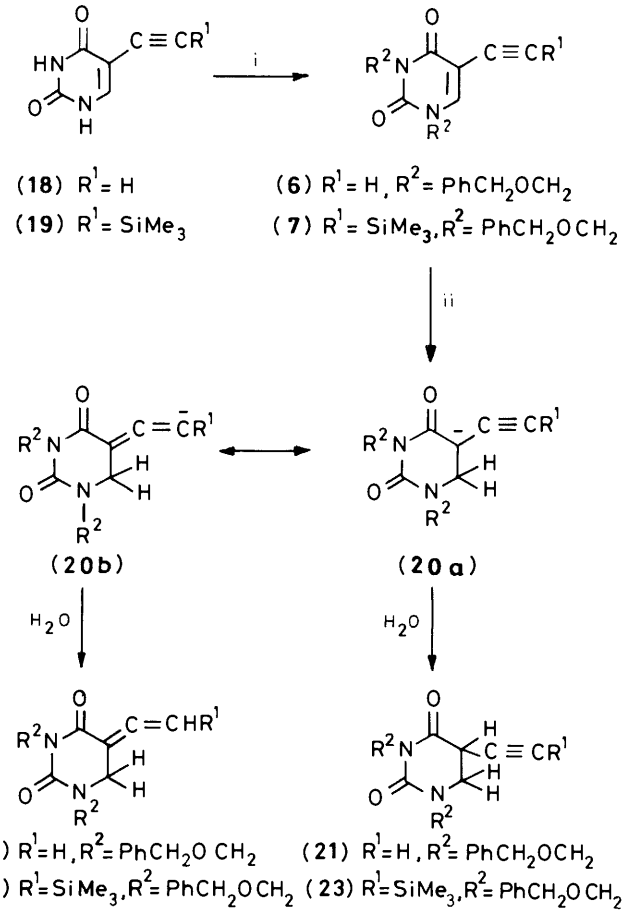
5-Ethynyluracils[21] (**18**) which are important antiviral and anticancer agents,[22] were of interest to us since *N*-alkylated 5-ethynyl-5,6-dihydrouracils, we believed, could act as k_{cat} inhibitors (see Scheme 4). Treatment with benzyl chloromethyl ether of the potassium salt of 5-ethynyluracil (**18**) gave the N^1,N^3-dibenzyloxymethyl derivative (**6**) and this with LTB yielded a 1:1 mixture of the 5-ethynyl-5,6-dihydrouracil (**21**) and the corresponding allenic isomer (**22**) (see Scheme 5). The trimethylsilyl derivative (**7**) could be obtained from (**19**) in a similar fashion or, by trimethylsilylation of (**6**) with t-butyllithium and chlorotrimethylsilane. On reduction it gave a mixture of the 5,6-dihydroacetylene (**23**) and the corresponding allenic isomer (**24**).

The spectral results for the dihydrouracils were characterized by the absence of u.v. absorption (no C=C) and i.r. absorption for CO and N·CO·N.[23] The n.m.r. spectra (Table 1) showed an upfield shift of the 5- and 6-H resonances, compared with those for the corresponding unsaturated precursors. In the unsubstituted N^1,N^3-dialkyl derivatives, the 5- and 6-H signals were seen as twin triplets, the 5-H having the higher chemical shift.

The mass spectra of the *N*-alkylated (alkyl Me or $PhCH_2$) derivatives of 5,6-dihydrouracil were characterized by having



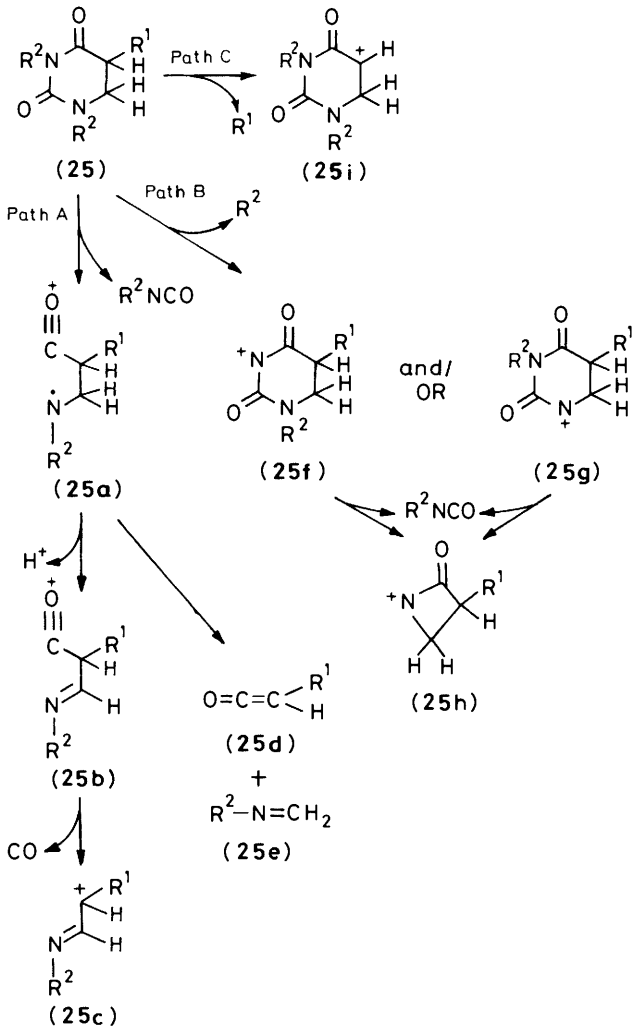
Scheme 4.



(**18**) R^1 = H
(**19**) R^1 = $SiMe_3$
(**6**) R^1 = H, R^2 = $PhCH_2OCH_2$
(**7**) R^1 = $SiMe_3$, R^2 = $PhCH_2OCH_2$
(**20b**)
(**20a**)
(**22**) R^1 = H, R^2 = $PhCH_2OCH_2$
(**21**) R^1 = H, R^2 = $PhCH_2OCH_2$
(**24**) R^1 = $SiMe_3$, R^2 = $PhCH_2OCH_2$
(**23**) R^1 = $SiMe_3$, R^2 = $PhCH_2OCH_2$

Scheme 5. *Reagents:* i, Benzyl chloromethyl ether; ii, LTB

strong molecular ion peaks in agreement with previous observations.[24] For the *N*-benzyloxymethyl derivatives (**23**) and (**24**) however, extensive fragmentation resulted in the presence of only a weak molecular ion and compounds (**21**) and (**22**) showed no molecular ion peak. The fragmentation patterns of the dihydrouracil derivatives follow three major paths (A, B, and C, Scheme 6).



Scheme 6.

In the case of 5-alkyl-5,6-dihydrouracils, loss of the 5-alkyl group (path C) was found to be quite significant. Similarly, a C-6 substituent (CO_2Et) was easily lost from ethyl N^1,N^3-dibenzyl-5,6-dihydro-orotate (**16**).

Experimental

^{1}H N.m.r. spectra were recorded on a Varian EM-360 90 MHz spectrometer in solvents as indicated. Mass spectra were taken on a Hewlett-Packard Model 5985 spectrophotometer. U.v. spectra were taken in 100% ethanol in a Beckman DU-2 u.v. spectrophotometer. I.r. spectra were taken as KBr plates on Acculab 4 (Beckman Instruments Co). Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, Tennessee or Spang Microanalytical Laboratory, Ann Arbor, Michigan, USA.

General Method for the Synthesis of N-*Alkylated Uracils.*—A mixture of uracil or its 5- or 6-substituted derivatives (0.05 mol) and anhydrous potassium carbonate (0.1 mol) in DMF (500 ml) was stirred for 1—2 days to give a thick suspension of the potassium salts of uracil. The alkyl halide (0.12 mol) was added and the mixture was stirred at room temperature for a further 4—5 days. DMF was removed under reduced pressure and the residue was treated with chloroform (500 ml) and water. The chloroform layer was separated and the aqueous layer was further extracted with chloroform (2 × 100 ml). The combined chloroform layers were washed with water, dried ($MgSO_4$) and evaporated to yield an oil which was purified by chromatography on silica-gel (60—120 mesh). After a preliminary wash with light petroleum (b.p. 35—60 °C, 1 l), the N^1,N^3-dialkylated derivative was eluted with dichloromethane–ethyl acetate (15:1). The monoalkyl derivative was eluted with dichloromethane–methanol (10:1). On t.l.c. in the solvents chloroform or chloroform–methanol (10:1), the dialkyl derivatives were much faster moving than the monoalkyl derivatives.

N^1,N^3-*Dimethyluracil* (**1**). White needles (100%) from 95% ethanol, m.p. 121—123 °C (lit.,[25] 121—122 °C).

N^1,N^3-*Dibenzyluracil* (**2**) *and* N^1-*benzyluracil* (**3**). A suspension of uracil (10 g, 89 mmol) in distilled DMF (350 ml) was treated with anhydrous potassium carbonate (24.6 g, 178 mmol). The mixture was stirred overnight at room temperature to give a thick gel of the potassium salts. This was treated with benzyl bromide (16.5 ml, 139 mmol) and again stirred at room temperature for 2 days. The reaction mixture was filtered off, and DMF was removed under reduced pressure. The residue was treated with water (150 ml) and extracted with chloroform (3 × 100 ml). The chloroform layer was dried (Na_2SO_4) and evaporated to yield a semisolid mass (17 g). This was crystallised from ethanol to yield a solid (6.9 g), m.p. 168—170 °C. The mother liquor, after evaporation was then chromatographed (SiO_2, 60—120 mesh); N^1,N^3-dibenzyluracil (**2**) (7.94 g, 27.2 mmol, 31%) was eluted with chloroform as a thick oil, m.p. 61—62 °C (from alcohol), (lit.,[25] m.p. 61—63 °C), $\nu_{max.}$(KBr) 1 705 and 1 665 cm^{-1}; $\lambda_{max.}$(EtOH) 265 (ε 9 559). N^1-Monobenzyluracil (**3**) was eluted with chloroform–methanol (10:1) (total yield combined with previous solid was 8.6 g, 42.6 mmol, 48%) which crystallized from ethanol as white needles, m.p. 169—170 °C (lit.,[26] m.p. 177—179 °C); $\nu_{max.}$(KBr) 1 700 and 1 665 cm^{-1}; $\lambda_{max.}$(EtOH) 265nm (ε 11 370). When uracil (9.46 mmol) was treated with potassium carbonate (19.53 mmol) and benzyl bromide (25.22 mmol) under the above conditions, dibenzyl-(8.08 mmol, 80%) and monobenzyl-uracil (1.8 mmol, 18%) were isolated.

N^1,N^3-*Dibenzyloxymethyl-* (**4**) *and* N^1-*benzyloxymethylthymine* (**5**). Compound (**4**) was obtained as a thick *oil* (19%) (Found: C, 68.85; H, 5.95; N, 7.7. Calc. for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65%); $\nu_{max.}$(KBr) 1 695 (CO), 1 650 (N·CO·N). Compound (**5**) was obtained as a white crystalline *solid* (34%) from carbon tetrachloride, m.p. 114—116 °C (Found: C, 63.15; H, 5.75; N, 11.35. Calc. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38%); $\nu_{max.}$(KBr) 3 160 (NH), 1 690 and 1 650 (CO); $\lambda_{max.}$(EtOH) 264 (ε 9 200).

N^1,N^3-*Dibenzyloxymethyl-5-ethynyluracil* (**6**).—5-Ethynyluracil[21] was converted into compound (**6**) which was obtained as a light cream coloured *solid* (60%), from ethyl acetate–light petroleum (b.p. 30—75 °C), m.p. 93—94 °C (Found: C, 70.2; H, 5.25; N, 7.2. Calc. for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44%); $\nu_{max.}$ 3 230 (C≡CH), 2 110 (weak C≡C), 1 715, 1 660, and 1 630; $\lambda_{max.}$(EtOH) 290 (ε 13 480); *m/z* 270 (*M* − 106, 23), 240 (*M* − 136, 9%), 91 ($C_7H_7^+$ 100), and 65 ($C_5H_5^+$).

N^1,N^3-*Dibenzyloxymethyl* 5-(2-*trimethylsilylethynyl*)*uracil* (**7**). 5-(2-Trimethylsilylethynyl)uracil (**19**), synthesized accord-

ing to Kundu and Schmitz,[27] was alkylated with benzyl chloromethyl ether according to the general procedure. The product (40%) crystallized from ethyl acetate–light petroleum (b.p. 30—75 °C) as fine white needles, m.p. 76—77 °C (Found: C, 67.2; H, 5.25; N, 6.55; Si, 6.6. Calc. for $C_{25}H_{28}N_2SiO_4$: C, 67.54; H, 5.41; N, 6.31; Si, 6.31%); $\nu_{max.}$ 2 160 (C≡C), 1 725, 1 678, 1 652, 1 630; $\lambda_{max.}$(EtOH) 295 (ε 13 110) and 232 (13 170); *m/z* 448 (0.1 M^+), 342 (M − 106, 23), 312 (M − 136), 91 (100), and 65 (13). Compound (**6**) was also obtained (25%) in the above reaction.

In an alternative synthesis of compound (**7**), a solution of compound (**6**) (2.2 g, 5.85 mmol) in THF (120 ml) was cooled in a solid CO_2–acetone bath for 10 min and then injected with a solution of t-butyl-lithium (Aldrich Chem. Co.) (2M; 3.6 ml). The cold mixture was stirred for 30 min after which chlorotrimethylsilane (1.2 ml) was added to it. The mixture was further stirred for 2 h in the cold after which it was warmed to room temperature. Glacial acetic acid (5 ml) was added, the mixture evaporated to dryness, and the residue treated with water (30 ml), and extracted with dichloromethane. The dichloromethane layer was washed with water, dried (Na_2SO_4), and evaporated to yield an oil (2.03 g, 4.5 mmol, 77%) which was chromatographed over silica gel (60—120 mesh). After a preliminary wash with light petroleum (b.p. 30—75 °C), the desired product was eluted with chloroform–ethyl acetate (15:1), identical in all respects with the sample obtained by the direct alkylation of 5-(2-trimethylsilylethynyl)uracil.

Ethyl N^1,N^3-*Dibenzylorotate* (**8**).—Ethyl orotate was alkylated with benzyl bromide by the general procedure (yield 92%). The product crystallized from ethyl acetate–light petroleum (b.p. 30—75 °C) as white *granules*, m.p. 75—76 °C (Found: C, 69.3; H, 5.45; N, 7.75. Calc. for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69%); $\nu_{max.}$ 1 720, 1 710, 1 660, and 1 600; $\lambda_{max.}$(EtOH) 280 (ε 7 964).

General Method for the LTB *Reduction of* N-*Alkylated Uracils.*—A solution of the *N*-alkyluracil (1 mmol) in THF (5 ml) was cooled in a solid CO_2–acetone bath under argon. LTB (1M solution in THF; 1.1 ml) was injected into the well-stirred solution *via* a syringe and the mixture was stirred at −78 °C for 10 min. The alkylating agent was injected in and the whole stirred for 10—30 min; subsequently, a saturated aqueous ammonium chloride solution (5 ml) was added. (Addition of the alkylating agent should be omitted where alkylation of the 5-position is unwanted.) The mixture was then warmed to room temperature (30 min) and the THF removed under reduced pressure; the mixture was then extracted with chloroform (3 × 50 ml). The combined chloroform extracts were washed with brine, dried ($MgSO_4$), and evaporated to yield the reduced material as an oil. The latter was usually accompanied by alkylboron compounds which were removed by column chromatography (SiO_2). After a preliminary wash with light petroleum (b.p. 40—60 °C) and chloroform–light petroleum, the pure reduced material was eluted with chloroform and chloroform–ethyl acetate (15:1). Purification was also possible by preparative t.l.c. on silica-gel plates. The reduced material has almost the same R_f as the starting material.

N^1,N^3-*Dibenzyloxymethyl*-5,6-*dihydrouracil* (**9**). This compound was obtained as a thick oil (80%) by LTB reduction of N^1,N^3-dibenzyloxymethyluracil.[1] It was identical (n.m.r., i.r. and u.v.) with a sample obtained by direct alkylation of 5,6-dihydrouracil.

N^1,N^3-*Dibenzyl*-5,6-*dihydrouracil* (**10**). This compound, obtained by reduction of N^1,N^3-dibenzyluracil (**2**), formed white crystals (94%), m.p. 78—79 °C (Found: C, 73.35; H, 6.1; N, 9.4. Calc. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52%); $\nu_{max.}$(KBr) 1 710 (CO) and 1 660 (N·CO·N); *m/z* 294 (M^+), 203 (M^+ − C_7H_7), 160 (M^+ − $PhCH_2NCO$, $-H^+$), 132 [(**25c**; R^1 = H, R^2 = $PhCH_2$], 118 [(**25b**), R^1 = H, R^2 = $PhCH_2$–$COCH_2$], 91 ($C_7H_7^+$), 70 ($COCH_2CH_2N)^+$, and 65 ($C_5H_5^+$), and 42 (CH_2=CO).

N^1,N^3-*Dimethyl*-5,6-*dihydrouracil* (**11**). The reduction of N^1,N^3-dimethyluracil (**1**) led to N^1,N^3-dimethyl 5,6-dihydrouracil (**11**) (82%), m.p. 53—55 °C (lit.,[28] 54—56 °C); *m/z* 142 (M^+), 127 (M^+ − CH_3), 113 (M^+ − $2CH_3$ + H), 84 (M^+ − CH_3NCO, −H), 70 ($COCH_2CH_2N$), 56 [(**25c**; R^1 = H, R^2 = Me)], 43 ($MeNCH_2$), and 42 (CH_2CO).

N^1,N^3-*Dibenzyl*-5,6-*dihydrothymine* (**12**).—The LTB of N^1,N^3-dibenzyluracil (**2**) and *in situ* alkylation (30 min) with methyl iodide led to (**12**) as a thick oil (88%) (Found: C, 73.6; H, 6.95; N, 8.5. Calc. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08%); ν_{max} (neat) 1 712 (CO) 1 670 (N·CO·N); *m/z* 308 (M^+), 293 (M^+ − Me), 217 (M^+ − C_7H_7), 175 (M^+ − $PhCH_2NCO$), 174 (M^+ − $PhCH_2NCO$, −H), 160 (M^+ − Me, −$PhCH_2$-NCO), 146 [(**25b**; R^1 = Me, R^2 = $PhCH_2$) −CO], 132 ($PhCH_2NCHCH_2$), 118 ($PhCH_2N$=CH), 91 ($C_7H_7^+$), 84 [COC(Me)CH_2N], 65 ($C_5H_5^+$), 56 ($C_3H_4O^+$), and 42 ($C_3H_6^+$).

N^1,N^3-5-*Tribenzyl*-5,6-*dihydrouracil* (**13**).—This compound was obtained as a thick gum (79%) by reduction of (**2**) and *in situ* benzylation (10 min) (Found: C, 77.95; H, 6.35; N, 7.35. Calc. for $C_{25}H_{24}N_2O_2$: C, 78.10; H, 6.29; N, 7.29%); $\nu_{max.}$(neat) 1 700 (CO), 1 660 (N·CO·N), *m/z* 384 (M^+), 293 (M^+ − C_7H_7), 265 [(**25i**; R^2 = $PhCH_2$) − CO], 251 (M^+ − $PhCH_2NCO$), 132 ($PhCH_2CHCO$), 118 ($PhCH$=CH_2), 91 ($C_7H_7^+$), and 65 ($C_5H_5^+$).

N^1,N^3-*Dibenzyl*-5-*prop*-2-*ynyl*-5,6-*dihydrouracil* (**14**).—This compound was obtained as a thick oil (89%) by reduction of (**2**) and *in situ* alkylation with prop-2-ynyl bromide (10 min) (Found: C, 75.8; H, 6.15; N, 8.35. Calc. for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43%); $\nu_{max.}$(neat) 3 280 (≡CH), 2 120 (C≡C), 1 702 (CO), 1 660 (N·CO·N); *m/z* 332 (M^+), 293 (M^+ − CH_2C≡CH), 265 [(**25i**; R^2 = $PhCH_2$)], 241 (M^+ − C_7H_7), 198 (M^+ − $PhCH_2NCO$, −H), 170 [(**25c**; R^2 = $PhCH_2$, R^1 = C_3H_3)−CO], 91 ($C_7H_7^+$), and 65 ($C_5H_5^+$).

N^1,N^3-*Dibenzyloxymethyl*-5,6-*dihydrothymine* (**15**).—The reduction of (**4**) yielded (**15**) as a very light yellow oil (60%) (Found: C, 68.75; H, 6.7; N, 7.5. Calc. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60%); $\nu_{max.}$(neat) 1 710 and 1 670 cm^{-1}

Ethyl N^1,N^3-*Dibenzyl*-5,6-*dihydro-orotate* (**16**).—This compound was obtained by the reduction of compound (**8**); it was purified by chromatography on silica gel, and eluted with 6% ethyl acetate in chloroform; it crystallized from ethyl acetate–light petroleum (b.p. 40—60 °C) as colourless stout *plates*, m.p. 82—83 °C (Found: C, 68.9; H, 6.1; N, 7.55. Calc. $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65%); $\nu_{max.}$(KBr) 1 735 (OCO), 1 710 (CO) 1 650 (N·CO·N); *m/z* 366 (M^+), 293 (M^+ − CO_2Et), 91 ($C_7H_7^+$), and 65 ($C_5H_5^+$).

N^1,N^3-*Dibenzyl*-5-*fluoro*-5,6-*dihydrouracil* (**17**).—N^1,N^3-Dibenzyl-5-fluorouracil[19] (0.14 g, 0.45 mmol) was reduced with LTB by following the general procedure. Work-up gave a yellow glassy material which was purified by preparative t.l.c. on silica gel. The product, which has the same R_f as that of the starting material, was obtained as a yellow glass (66 mg, 0.21 mmol, 47%) (Found: C, 69.1; H, 5.6; N, 8.75; F, 5.9. Calc. for $C_{18}H_{17}FN_2O_2$: C, 69.23; H, 5.45; N, 8.99; F, 6.09%); $\nu_{max.}$ 1 725 (CO), 1 690 (N·CO·N); *m/z* 312 (M^+), 221 (M^+ − C_7H_7), 178 (M^+ − $PhCH_2NCO$, −H), 150 [(**25b**, R^2 = $PhCH_2$, R^1 = F) −CO], 91 (C_7H_7), 88 (COCHFCH_2N), and 65 ($C_5H_5^+$).

N^1,N^3-*Dibenzyloxymethyl*-5-*ethynyl*-5,6-*dihydrouracil* (**21**) *and its allenic isomer* (**22**). The reduction of N^1,N^3-dibenzyloxy-

methyl-5-ethynyluracil (**6**) led to a 1:1 mixture (65%) of (**21**) and (**22**), purified by preparative t.l.c. on silica gel developed with chloroform–ethyl acetate (15:1): (**21**) δ 2.85 (d, *J* 6 Hz, C≡CH), 3.12 (m, 6-H); (**22**) δ 3.8 (m, 6-H), 4.5 (s, OCH_2Ph), 4.7 (s, OCH_2Ph), 4.88 and 4.92 (2 s, N^1CH_2O), and 5.3 and 5.4 (2 s, N^3CH_2O and allenic H's); $\nu_{max.}$ 2 180 (C≡C), 1 940 (allene), 1 712 (CO), 1 665 (N·CO·N); *m/z* 138 ($C_6H_6N_2O_2^+$), 91 ($C_7H_7^+$), and 65 ($C_5H_5^+$).

N^1,N^3-Dibenzyloxymethyl-5-(2-trimethylsilylethynyl)-5,6-dihydrouracil (**23**) *and its allenic isomer* (**24**). The mixture of (**23**) and (**24**) (70%) was obtained by the reduction of (**7**) and subsequent purification by preparative t.l.c. on silica gel developed with chloroform–ethyl acetate (15:1); (**23**) δ($CDCl_3$) 0.1 (s, $SiMe_3$), 3.38 (m, 6-H); (**24**) δ 3.78 (m, 6-H); 4.5 and 4.6 (OCH_2Ph), 4.9 and 5.4 (NCH_2O), and 7.3 (ArH); $\nu_{max.}$ 2 160 (C≡C), 1 975 (allene), 1 715 (CO), 1 670 cm^{-1} (N·CO·N); *m/z* 446 (M^+, v weak), 91 ($C_7H_7^+$), and 65 ($C_5H_5^+$).

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