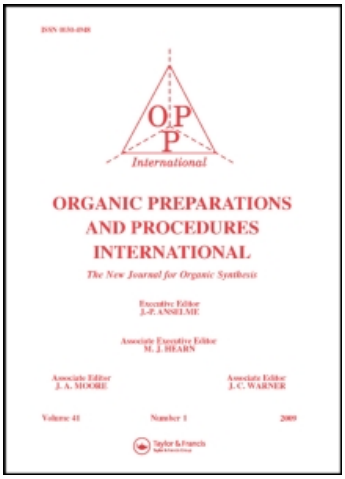

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SYNTHESIS OF URACIL, 6-METHYLURACIL AND SOME DIHYDROURACILS

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SYNTHESIS OF URACIL, 6-METHYLURACIL AND SOME DIHYDROURACILS†

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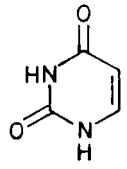
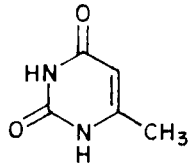
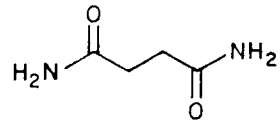
Uracil (4a),one of the components of nucleic acids, is of great importance in biological chemistry.[1] 6-Methyluracil (4b) is an intermediate for the synthesis of biologically important compounds such as orotic acid,[2] sparsomycin[3] and mepirizole.[4] The synthesis of uracil (4a) from the condensation of urea with malic acid in the presence of oleum though known for a long time,[5] proceeds in poor yields. Uracil (4a) has also been obtained by the condensation of urea with maleic acid in PPA,[6] with fumaric acid in PPA[6] and with propiolic acid;[7] 4a can also be synthesized by the palladium (II) salt-induced oxidative cyclization of acryloylurea and by other methods.[8] Recently it has been reported that the reaction of succinamide (1a) with lead tetraacetate furnishes dihydrouracil (2a) in high yields.[9]



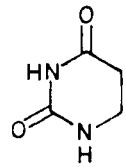
4a



4b



1a



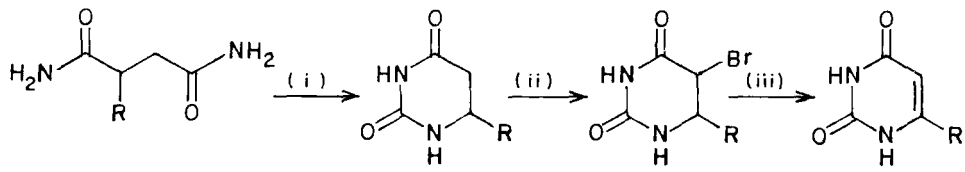
2a

This result coupled with the earlier report[10] that dihydrouracil can be converted to uracil via bromination and dehydrobromination encouraged us to carry out a systematic study of

lead tetraacetate oxidation of some substituted succinamides.

Lead tetraacetate oxidation of methylsuccinamide (1b) is regioselective and furnishes 6-methyldihydrouracil (2b) in 90% yield, suggesting that the amide nearer to C-CH_3 reacts selectively with the oxidising agent. Bromination of 2b furnishes the bromocompound (3b)[10] which gives 6-methyluracil (4b) on heating with a mixture of NaOAc, acetic acid and acetic anhydride. The bromocompound (3a)[10] also gives good yields of uracil (4a) on heating with NaOAc, acetic acid and acetic anhydride. The yields in these transformations are high and this sequence constitutes a convenient route for the

Scheme I



1 2 3 4

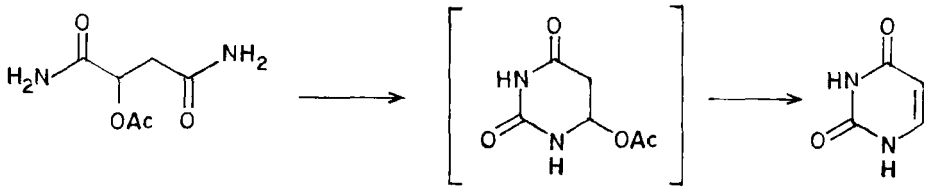
a) R = H; (b) R = CH_3

Reagents : (i) $Pb(OAc)_4$; (ii) Br_2, AcOH; (iii) NaOAc, AcOH, Ac_2O

synthesis of 6-methyluracil (4b) and uracil (4a).

The amide (5) which can be prepared from malic acid furnishes uracil (4a) in 70% yield on oxidation with lead tetraacetate.

Scheme II

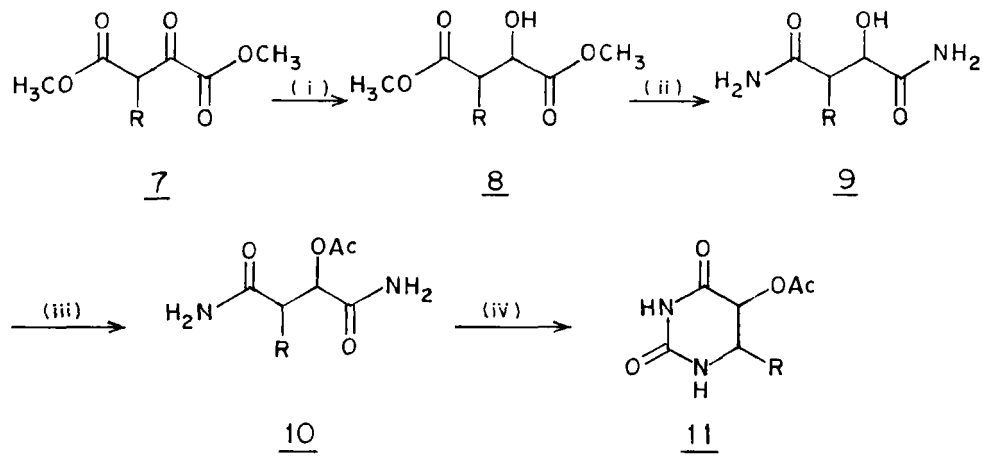


5 6 4a

The facile elimination of acetic acid from the dihydrouracil (6), presumably generated by the action of lead tetraacetate on 5, suggested the possibility of preparing uracils from amides 10a, 10b and 10c in a similar fashion; however, the dihydrouracils 11a, 11b and 11c (obtained regioselectively by the action of lead tetraacetate on 10a, 10b and 10c respectively) were considerably less reactive than acetate 6 and are thermally stable even at 200° since the acetate is located at C_5 and not at C_6.

Sodium borohydride reduction of keto ester 7a furnished hydroxy ester 8a (as a 6:1 mixture of erythro and threo isomers),[11] which on treatment with methanolic ammonia afforded hydroxy amide 9a; acylation of 9a yielded acetoxy amide 10a (as a 6:1 mixture of erythro and threo isomers). Similarly acetoxy amides 10b and 10c were prepared from keto esters 7b and 7c.

Scheme III



7 8 9

10 11

(a) R = CH_3 ; (b) R = C_2H_5; (c) R = C_6H_5;

Reagents: (i) $NaBH_4$; (ii) NH_3, CH_3OH; (iii) NaOAc, AcOH, Ac_2O; (iv) $Pb(OAc)_4$

EXPERIMENTAL SECTION

The ^1H NMR spectra were obtained on a Varian T-60 or WH-90 FT spectrometer. Chemical shift values are expressed in parts per million (δ) downfield from internal TMS. The IR spectra were measured using a Perkin-Elmer Infracord Spectrometer-model 137B spectrometer. All melting points are uncorrected.

6-Methyl-5,6-dihydrouracil (2b).- A mixture of methylsuccinamide (1b) (0.55 g, 4.2 mmol), DMF (10 ml) and $Pb(OAc)_4$ (3 g, 6.7 mmol) was stirred at 50-60° for 40 min. DMF was removed under reduced pressure and the residue was heated with 10 ml of water at 100° for 10 min, cooled and the solid (2b, 0.49 g, 90%, mp. 215-216°) was collected. A sample recrystallized from ethanol showed mp. 216-218°, lit.[10] 217-218°. IR(mull): 3280, 3155, 1740, 1700 cm^{-1}; PMR ($DMSOd_6$) : δ 1.16 (d, J = 7 Hz, 3H, CH-CH_3), 2.36 (m, 2H, -CO-CH_2-), 3.63 (m, 1H, CH-CH_3), 7.60 (br s, exchanged with D_2O, 1H, NH), 10.06 (br s, exchanged with D_2O, 1H, NH).

5-Bromo-6-methyl-5,6-dihydrouracil (3b).- Bromination of 2b[10] furnished 3b in 85% yield. A sample recrystallized from ethanol showed mp. 312-315°(dec), lit.[10] 313-15°(dec); IR (mull): 3330, 3110, 1700 cm^{-1}; PMR ($DMSOd_6$) : δ 1.30 (d, J = 7 Hz, 3H, CH-CH_3), 3.73 (m, 1H, CH-CH_3), 4.53 (d, J = 4 Hz, 1H, CH-Br), 7.91 (br s, exchanged with D_2O, 1H, NH), 10.38 (br s, exchanged with D_2O, 1H, NH).

6-Methyluracil (4b).- A mixture of 3b (2 g, 9.7 mmol), sodium acetate (1 g), acetic acid (15 ml) and acetic anhydride (8 ml) was heated under reflux for 5 hrs. Acetic acid and acetic anhydride removed under reduced pressure. The residue was heated with 10 ml of water at 100° for 5 min and cooled. The solid (4b, 1.06 g, 87%, mp. 315-318°) was collected. An

analytical sample was obtained by sublimation at 190°/1 mm, mp. 320°, lit.[8] 320°; IR and NMR spectra were identical with the authentic sample.

Anal. Calcd. for $C_5H_6N_2O_2$: C, 47.62; H, 4.76.
Found : C, 47.81; H, 4.60.

5,6-Dihydrouracil (2a).- Using succinamide (1a) as starting material, 2a was prepared in 94% yield, by the action of $Pb(OAc)_4$ in DMF mp. 276-277°, lit.[10] 276-278°.
IR(mull) : 3345, 3195, 1770, 1710 cm^{-1}.

5-Bromo-5,6-dihydrouracil (3a).- It was prepared according to literature method by the bromination of 2a using bromine in acetic acid, yield 84%; mp. 206-208°, lit.[10] 207-208°.
IR(mull) : 3340, 3125, 1700 cm^{-1}.

O-Acetylmalamide (5).- A mixture of dl-malamide (6.6 g, 50 mmol), acetic anhydride (40 ml) and anhydrous sodium acetate (0.2 g) was heated under reflux for 30 min. Acetic anhydride was removed under reduced pressure, the residue was triturated with 20 ml of chloroform and the solid [5, 8.3 g, 95%, mp. 168-170 (dec)] was collected.
IR (mull) : 3395, 3300, 1740, 1670, 1625 cm^{-1}.
Anal. Calcd. for $C_6H_{10}N_2O_4$: C, 41.39; H, 5.79.
Found : C, 41.70; H, 6.00

Uracil (4a). Method A - A mixture of 3a (1 g, 5.2 mmol), acetic acid (8 ml), acetic anhydride (6 ml) and sodium acetate (0.6 g) was heated under reflux for 6 hrs and worked up (as in the case of 4b) to furnish 4a (0.42 g), yield 72%, identified by the direct comparison of IR spectrum and m.mp. with an authentic sample.

Method B - To a suspension of 5 (2 g, 11.5 mmol) in 20 ml of DMF, $Pb(OAc)_4$ (6.5 g, 15 mmol) was added and the mixture was stirred at 50-60° for 1 hr. DMF was removed under reduced pressure. The residue was heated with 10 ml of water at 100° for 15 min and cooled. The solid (4a, 0.91 g, 71%) was collected. Analytical sample was obtained by sublimation at 185°/1 mm.

Anal. calcd. for $C_4H_4N_2O_2$: C, 42.86; H, 3.57.

Found : C, 42.68; H, 3.68.

Dimethyl α-hydroxy-β-methyl-succinate (8a).- To a stirred solution of methyl methoxalylpropionate[12] (7a, 8.8 g, 50 mmol) in methanol (30 ml), maintained at 5-10°, $NaBH_4$ (1g, 26 mmol) was added in portions. After complete addition of $NaBH_4$, reaction mixture was stirred at room temperature for 1 hr, diluted with water, saturated with sodium chloride and extracted with ether. Ether extract was washed with water, dried concentrated and the residue was distilled under vacuum to furnish 8a (8.5 g, as a 6:1 mixture of erythro and threo isomers).[11]

IR (mull) : 3610 (OH), 1748 (C = O).

Similarly hydroxy esters 8b (as a 7:4 mixture of erythro and threo isomers) and 8c (as a 3:7 mixture of erythro and threo isomers) were prepared by $NaBH_4$ reduction of keto esters 7b and 7c respectively and the results are presented in Table 1.

α-Hydroxy-β-methyl succinamide (9a).- A solution of 8a (5 g, 28 mmol) in methanol (25 ml) was saturated with ammonia at 0°-5° and kept at the same temperature for 30 hr.Methanol

TABLE 1 Hydroxy esters 8a, 8b and 8c

Compd.	Yield	bp°(bath temp)	^{1}H-NMR (CCl_4)
8a	95	140-145/12 mm	1.23 (d, J = 8 Hz, CH-C<u>H</u>$_3$), 2.93 (m, 1H, C<u>H</u>-CH$_3$), 3.40 (br s, exchanged with D_2O, 1H, O<u>H</u>), 3.66 (s, 3H, -COOC<u>H</u>$_3$), 3.80 (s, 3H, -COOC<u>H</u>$_3$), 4.23 (m, 1H, C<u>H</u>-OH).
8b	94	140-148/6 mm	0.98 (m, 3H, -CH$_2$-C<u>H</u>$_3$), 1.71(m,2H, -C<u>H</u>$_2$-CH$_3$), 2.63 (m, 1H, C<u>H</u>$_2$-C$_2$H$_5$), 3.30 (br s, exchanged with D_2O, 1H, O<u>H</u>), 3.60 (s, 3H, -COOC<u>H</u>$_3$), 3.73 (s, 3H, -COOC<u>H</u>$_3$), 4.20 (m, 1H, C<u>H</u>-OH).
8c	92	150-155/0.2 mm	3.33 (s, 6H, -COOC<u>H</u>$_3$), 3.70 (d, J = 6 Hz, 1H, C<u>H</u>-Ph), 4.13 (d, J = 6 Hz, 1H, C<u>H</u>-OH), 6.73 (s, 5H, aromatic)

was removed under reduced pressure, the residue was triturated with chloroform (15 ml) and solid (9a, 3.3 g, 77.5%, mp. 154-156°) was collected. A sample recrystallized from methanol showed mp. 156-158°, lit.[13] 159-160°.

Similarly hydroxy esters 8b and 8c were transformed to hydroxy amides 9b (mp. 168-170°) and 9c (mp. 160-162°) in 81 and 63% yield respectively.

α-Acetoxy-β-methyl succinamide (10a).- A mixture of 9a (2 g, 14 mmol), acetic anhydride (10 ml), acetic acid (5 ml) and

sodium acetate (0.1 g) was stirred at 100° for 30 min. Acetic anhydride and acetic acid were removed under reduced pressure and the residue was triturated with 1:1 mixture of pet.ether and acetone (20 ml). The solid (10a, as a 6:1 mixture of erythro and threo isomers, 2.35 g, 91%, mp. 180-181°) was collected. A sample recrystallized from water-acetone (1:5) showed mp. 182-183°.

IR (mull) : 3300, 3247, 1757, 1681, 1653, 1232 cm^{-1}.

Similarly acetoxy amides 10b (as a 7:4 mixture of erythro and threo isomers, mp. 200-202°) and 10c (as the threo isomer, mp. 180-181°) were prepared from hydroxy amides 9b and 9c in 95 and 66% yield respectively and the results are presented in the Table 2.

5-Acetoxy-6-methyl-dihydrouracil (11a).- To a suspension of 10a (1.8 g, 9.5 mmol) in DMF (25 ml), $Pb(OAc)_4$ (7.00 g, 15 mmol) was added and the reaction mixture was stirred at 60° for 40 min. DMF was removed under reduced pressure. The residue was heated at 100° with 10 ml of water for 5 min and cooled. The solid [11a, as a 11:1 mixture of cis and trans isomers, 1.35 g, 76%, mp. 255-258°(dec)] was collected. Analytical sample was obtained by sublimation at 190°/1 mm, mp. 258-260 (dec).

IR (mull) : 3322, 3125, 1757, 1724, 1667, 1227 cm^{-1}.

Similarly dihydrouracils 11b [as a 5:2 mixture of cis and trans isomers, m.p. 282-285°(dec)] and 11c [as the trans isomer, mp. 272 (dec)] were prepared in 85 and 70% yield starting from 10b and 10c respectively and the results are presented in the Table 2.

TABLE 2. Acetoxy amides 10a-c and dihydrouracils 11a-c

Compd.	Elemental analysis Calcd. (Found) C	H	^{1}H-NMR[a] (DMSOd_6)
10a	44.68 (44.98)	6.43 (6.53)	1.05 (d, J = 7 Hz, 3H, CH-C$\underline{H}_3$), 2.02 (s, 2.60H, OCOC$\underline{H}_3$), 2.08 (s, 0.40H, OCOCH_3), 2.73 (m, 1H, C$\underline{H}$-CH_3), 4.89 (d, J = 10 Hz, 0.86H, C$\underline{H}$-OAc), 5.23 (d, J = 6 Hz, 0.14 H C$\underline{H}$-OAc), 6.80-7.56 (m, 4H, exchanged with D_2O, -N$\underline{H}_2$)
10b	47.52 (47.22)	6.98 (6.94)	0.84 (t, J = 6 Hz, -CH_2-C$\underline{H}_3$), 1.48 m, 2H, -C$\underline{H}_2$-CH_3), 2.02 (s, 1.90H, OCOC$\underline{H}_3$), 2.08 (s, 1.10H, OCOCH_3), 2.61 (m, 1H, C$\underline{H}$-C_2H_5), 4.88 (d, J = 10 Hz, 0.64H, C$\underline{H}$-OAc), 5.15 (d, J = 6 Hz, 0.36 H, C$\underline{H}$-OAc)
10c	57.59 (57.47)	5.64 (5.72)	1.93 (s, 3H, OCOC$\underline{H}_3$), 4.00 (d, J = 8 Hz, 1H, CH-Ph), 5.50 (d, J = 8 Hz, 1H, C$\underline{H}$-OAc), 7.25 (s, 5H, aromatic)
11a	45.16 (45.24)	5.41 (5.52)	1.03 (d, J = 7 Hz, 3H, CH-C$\underline{H}_3$), 2.08 (s, 3H, OCOC$\underline{H}_3$), 3.55 (m, 1H, CH_3-C$\underline{H}$), 4.88 (d, J = 10 Hz, 0.08H, C$\underline{H}$-OAc), 5.25 (d, J = 6 Hz, 0.92H, C$\underline{H}$-OAc), 7.68 (br s, 1H, N$\underline{H}$), 10.15 (br s, 1H, N$\underline{H}$)
11b	47.99 (48.31)	6.04 (6.03)	1.00 (t, J = 7 Hz, 3H, CH_2-C$\underline{H}_3$), 1.53 (m, 2H, C$\underline{H}_2$-CH_3), 2.20 (s, 3H, OCOC$\underline{H}_3$), 3.57 (m, 1H, C$\underline{H}$-C_2H_5), 5.27 (d, J = 10 Hz, 0.28 H, C$\underline{H}$-OAc), 5.57 (d, J = 6 Hz, 0.72H, C$\underline{H}$-OAc), 7.95 (br s, 1H, N$\underline{H}$), 10.25 (br s, 1H, N$\underline{H}$)
11c	58.06 (58.38)	4.87 (5.01)	2.00 (s, 3H, OCOC$\underline{H}_3$), 4.76 (d, J = 10 Hz, 1H, CH-Ph), 5.40 (d, J = 10 Hz, 1H, C$\underline{H}$-OAc), 7.33 (s, 5H,Ar-H)

a. Duplication of some signals is due to stereoisomers.

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† NCL Communication No. 3224.

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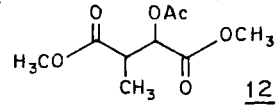
11. The PMR spectrum of 8a is not helpful in determining the erythro-threo ratio of stereoisomers, since the signals due to CH-OH of erythro and threo isomers overlap. However signals due to CH-OAc in PMR spectrum of 12 (derived from



12

8a) are useful for determining the ratio for stereoisomers; PMR spectrum of 12 showed two doublets (6:1) at δ 5.10 (J = 6 Hz) and 5.36 (J = 4 Hz). Doublet at δ 5.10 with coupling constant 6 Hz is assigned to erythro isomer. Similar method was used to give the ratios of erythro and threo

isomers in 8b and 8c.

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