Synthesis of Dimethoxypyrimidines and Uracils with Novel C-5 Substituents[1,2]

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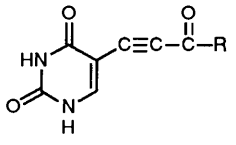
5-Iodo-2,4-dimethoxypyrimidine **1** on treatment with copper(I) 3-tetrahydropyran-2-yloxyprop-1-ynide was converted into 2,4-dimethoxy-5-(3-tetrahydropyran-2-yloxyprop-1-ynyl)pyrimidine **2** which on treatment with toluene-*p*-sulphonic acid in methanol led to 5-(3-hydroxyprop-1-ynyl)-2,4-dimethoxypyrimidine **3**. This was oxidised with Swern reagent to 5-(formylethynyl)-2,4-dimethoxypyrimidine **4**. Compound **4** on treatment with a number of Grignard reagents gave 5-[(3-alkyl or aryl-3-hydroxy)prop-1-ynyl]-2,4-dimethoxypyrimidines **6–12**. These were oxidised to 5-(acylethynyl)-2,4-dimethoxypyrimidines **13–19**. On treatment with 6 mol dm^{-3} hydrochloric acid, 5-(acylethynyl)-2,4-dimethoxypyrimidines were converted into 5-(2-acyl-1-chlorovinyl)uracils **20–23**. Compounds **20–22** were dehydrohalogenated with sodium hydroxide in 95% ethanol to 5-(acylethynyl)uracils **24–26**.

Uracils with suitable C-5 substituents (*e.g.* 5-FU, FUdR, F_3TdR and BVdU) have been important in the chemotherapy of cancer[3] and viral diseases.[4] Recently, a 5-substituted uracil, *e.g.* 3′-azido-3′-deoxythymidine (AZT), has been found to be a potent inhibitor of the human immunodeficiency virus (HIV) and is being used amongst AIDS patients.[5] Other 3′-azido analogues of pyrimidine deoxyribonucleosides have been developed as potent inhibitors of human immunodeficiency virus.[6]

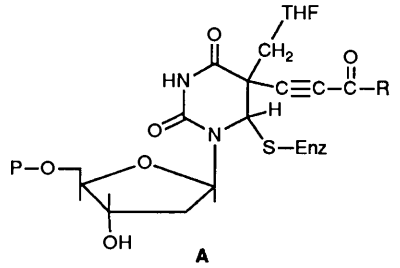


I (R = alkyl or aryl group)

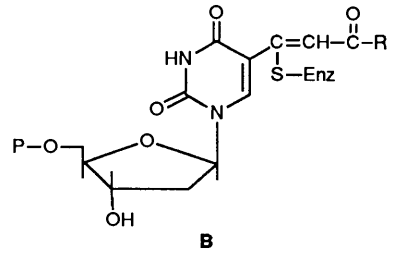
Our interest in uracil derivatives stemmed from the possibility of these compounds acting as inhibitors of thymidylate synthase (TS), a critical enzyme required for the cellular multiplication processes.[7] With that objective we designed a series of novel uracil derivatives of structure **I** which are characterized by the presence of an acyl conjugated ethynyl side chain in the C-5 position of the uracil ring.

We felt such molecules, after being converted into the corresponding 2′-deoxyribonucleotides, could act as potent inhibitors of TS because (i) the attack of the cysteine group of TS at the C-6 position of the nucleotides of **I** will be facilitated by the presence of the acyl conjugated ethynyl group at the C-5 position of the uracil ring (Structure **A**); (ii) the attack of the thiol group of cysteine could also take place at the ethynyl side chain (Structure **B**); (iii) a very tight enzyme–inhibitor complex could result from further interaction with another basic (or nucleophilic) group on the enzyme (Structure **C**); (iv) furthermore, the complex **D** between the 2′-deoxyribonucleotide of **I** (where R is an aromatic group) and TS mimics the TS-dUMP-methylene tetrahydrofolic acid complex **E**.

Recently we have reported the synthesis of a few compounds of structure **I** and also their biological and biochemical properties.[8] These compounds were found to be active against Ehrlich ascites carcinoma (EAC) cells *in vivo* and also against CCRF-CEM and L1210/0 cell lines *in vitro* testing. In view of the promising biological properties of these compounds and lack of methods for the synthesis of uracil derivatives with highly functionalised C-5 substituents, it became necessary to develop alternative methods for the synthesis of uracil derivatives with an activated ethynyl substituent. Here we report an extremely convenient and general procedure for the synthesis of dimethoxypyrimidines and uracils with highly functionalised C-5 substituents.



A

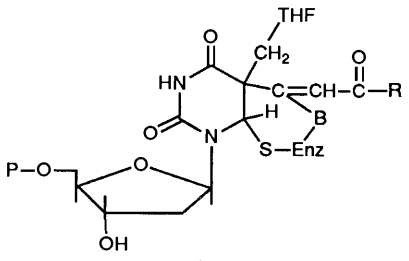


B

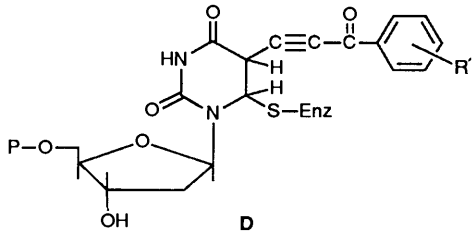
The following abbreviations refer to structures **A**–**E**: P = PO_3^{2-}, R = alkyl or aryl group, Enz = TS enzyme, THF = tetrahydrofolate, B = another basic or nucleophilic group on TS enzyme, R′ = a substituent on the aromatic ring, and Glu = glutamate moiety

Results and Discussion

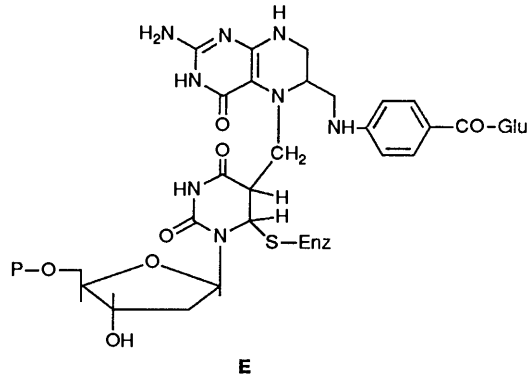
Although many 5-substituted uracils have been synthesized by various specific methods,[9–16] general methods[17–21] for the synthesis of pyrimidines and uracils with highly functionalised C-5 substituents are limited in number. Recently we have reported a versatile method for the synthesis of 5-(acylethynyl)-2,4-dimethoxypyrimidines and 5-(acylethynyl)uracils starting from 2,4-dimethoxy-5-(trimethylsilylethynyl)pyrimidine.[8,22] This method, however, suffers from the disadvantage that the starting material is not commercially available and is synthesized[11,23] starting from diketene and urethane which are possible carcinogens. In order to obviate these difficulties,



C



D

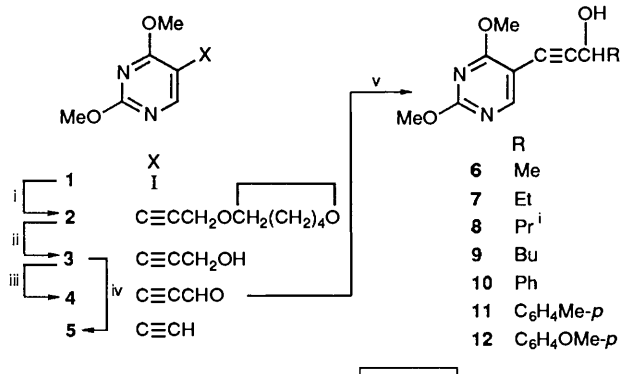


E

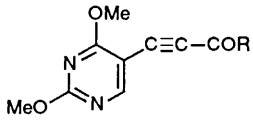
we developed a simpler and safer method for the synthesis of 5-(acylethynyl)-2,4-dimethoxypyrimidines and 5-(acylethynyl)-uracils.

The starting material in this new strategy is 5-iodo-2,4-dimethoxypyrimidine **1** which could be obtained by the procedure of Prystas and Sörm.[24] An alternative and less hazardous method for the synthesis of **1** has also been reported by us.[25] Copper(I) 3-tetrahydropyran-2-yloxyprop-1-ynide has been a useful reagent for the synthesis of aromatic and heterocyclic ethynyl substituted compounds.[26] The reaction of this unique reagent with 5-iodo-2,4-dimethoxypyrimidine **1** in pyridine for 2.5 h under reflux yielded 2,4-dimethoxy-5-(3-tetrahydropyran-2-yloxyprop-1-ynyl)pyrimidine **2** in excellent yield (Scheme 1). The yield of the reaction was dependent on the purity of the copper(I) reagent. Its conversion into the bivalent copper state will lower the yield of compound **2**. Compound **2** was identified by its ^{1}H NMR spectrum where signals due to the methoxy groups (δ 3.86 and 3.90) and the 6-H (δ 8.05) on the pyrimidine ring were present together with the signals due to the methylene of the side chain (δ 4.37) and the other hydrogens of the tetrahydropyran ring. The tetrahydropyranyl protecting group on compound **2** was removed by refluxing it with toluene-*p*-sulphonic acid in methanol when 5-(3-hydroxyprop-1-ynyl)-2,4-dimethoxypyrimidine **3** was obtained as a crystalline solid. This on oxidation with Swern reagent[28] yielded 5-(formylethynyl)-2,4-dimethoxypyrimidine **4**. Alternatively, oxidation of **3** with manganese dioxide in dichloromethane converted it smoothly into compound **4** in comparable yield. However, when **3** was treated with manganese dioxide in the presence of potassium hydroxide, concurrent oxidation and deformylation took place leading to 5-ethynyl-2,4-dimethoxypyrimidine[23] **5**.

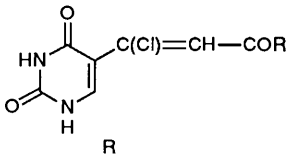
5-(Formylethynyl)-2,4-dimethoxypyrimidine **4** was found to be a crucial compound in our synthetic strategy. On reaction of compound **4** with various Grignard reagents, a number of 5-(3-hydroxyalk-1-ynyl)-2,4-dimethoxypyrimidines **6**–**12** were obtained. The Grignard reaction was carried out either in ether (Method A) in the case of alkyl halides or in tetrahydrofuran with subsequent addition of benzene (Method B) in the case of aryl halides. The yields of desired products were mostly excellent to fair (90–70%) in most of the cases except in the case of products derived from isopropyl (20%), and butyl (46%) halides. The lower yields could be attributed to some extent to the formation of secondary products like 5-(3-hydroxyprop-1-ynyl)-2,4-dimethoxypyrimidine **3**. The 5-(3-hydroxyalk-1-ynyl)-2,4-dimethoxypyrimidines were mostly crystalline solids except compounds **8** and **10**, which were gums. They were well-characterised by their IR, UV and NMR spectra.



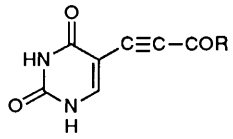
Scheme 1. Reagents i, Cu^I–C≡CCH$_2$OCH(CH$_2$)$_4$O; ii, *p*-TSA, MeOH; iii, oxalyl chloride, DMSO, Et_3N or MnO_2 in CH_2Cl_2; iv, MnO_2, KOH in CH_2Cl_2 (**5** was obtained from **3** presumably *via* **4** as an intermediate); v, RMgX in ether or THF



R
13 Me
14 Et
15 Pr^i
16 Bu
17 Ph
18 C$_6$H$_4$Me-*p*
19 C$_6$H$_4$OMe-*p*



R
20 Ph
21 C$_6$H$_4$Me-*p*
22 C$_6$H$_4$OMe-*p*
23 Me



R
24 Ph
25 C$_6$H$_4$Me-*p*
26 C$_6$H$_4$OMe-*p*

The acetylenic alcohols **6–12** were oxidised with chromium trioxide in the presence of pyridine in dichloromethane (Collins's reagent)[29] or with neutral manganese dioxide in dichloromethane to the corresponding 5-(acylethynyl)-2,4-dimethoxypyrimidines **13–19**. The acetylenic ketones were characterised on the basis of their IR spectra [2200–2190 (C≡C) and 1660 cm^{-1} (conjugated carbonyl)], their UV absorption at *ca.* 300 nm and their characteristic ^1H NMR spectra (see Experimental section).

We have previously described the use of iodotrimethylsilane or chlorotrimethylsilane and sodium iodide mixture for the *O*-demethylation of 5-(acylethynyl)-2,4-dimethoxypyrimidines.[8,27] We have observed that successful demethylation took place with concurrent addition of hydrogen iodide to the triple bond leading to 5-(2-acyl-1-iodovinyl)uracils. These compounds were, however, found to be unstable and difficult to characterise. The 5-(acylethynyl)-2,4-dimethoxypyrimidines could also be demethylated by heating with 6M hydrochloric acid, when 5-(2-acyl-1-chlorovinyl)uracils **20–23** were formed. These compounds were found to be more stable and easier to handle than the corresponding 1-iodo analogues.

Of 5-(2-acyl-1-chlorovinyl)uracils, compounds **20–22** with aromatic groups in the acyl moiety, could be dehydrohalogenated to the corresponding 5-(acylethynyl)uracils **24–26** respectively on treatment with sodium hydroxide in 95% ethanol or with potassium hydroxide in dioxane. The aliphatic analogue, *e.g.* 5-(1-chloro-3-oxobut-1-enyl)uracil **23**, however, did not yield the corresponding acetylenic compound under the above conditions. The 5-(acylethynyl)uracils **24–26**, were found to be active against CCRF-CEM human lymphoblastoid cells and L1210/0 mouse leukemia cells in culture. They were also active against Ehrlich ascites carcinoma cells in Swiss Albino mice.[8]

Experimental

M.p.s were determined on a Reichert (285980) (Austria) melting point bath and are uncorrected. The UV spectra recorded on a Hitachi 200-20 spectrometer in spectrophotometric grade ethanol (Baker). The IR spectra were taken on a Perkin-Elmer 298 instrument on KBr plates. ^1H NMR spectra (reported in δ) were recorded on a Varian XL-200 spectrometer and a 100 MHz FX-100 spectrometer in solvents as indicated with tetramethylsilane as internal reference; *J* values in Hz. Silica gel TLC was performed on 60F-254 precoated sheets (E. Merck) and column chromatography was done on silica gel (60–120 mesh). Elemental analyses were performed on Perkin-Elmer Elemental Analyser 240C.

2,4-*Dimethoxy*-5-(3-*tetrahydropyran*-2-*yloxyprop*-1-*ynyl*)-*pyrimidine* **2**.—A suspension of 5-iodo-2,4-dimethoxypyrimidine **1** (7 g, 26 mmol) and copper(I) 3-tetrahydropyran-2-yloxyprop-1-ynide (7 g, 34 mmol) in dry pyridine (90 ml) was stirred and refluxed under a nitrogen atmosphere for 2.5 h. From the reaction mixture, pyridine was removed under reduced pressure and the resultant dark residue was poured into ice–water (500 ml). The mixture was then extracted with chloroform (3 × 100 ml). The combined chloroform extracts were washed with cold hydrochloric acid (1 mol dm^{-3}; 3 × 50 ml), water (2 × 50 ml), saturated aqueous sodium carbonate (2 × 50 ml) and then with water again. The chloroform layer was dried (Na_2SO_4) and evaporated to yield a greenish mobile syrup. This was then chromatographed (SiO_2, 60–120 mesh) when 2,4-dimethoxy-5-(3-tetrahydropyran-2-yloxyprop-1-ynyl)pyrimidine **2** was obtained as a yellow gum [eluent, 10% ethyl acetate in light petroleum (b.p. 60–80 °C), v/v] (6.33 g, 22.77 mmol, 86.6%) (Found: C, 60.05; H, 6.7; N, 10.3. Calc. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07%); ν_{max}/cm^{-1} 2230w (C≡C), 1600s; λ_{max}(EtOH)/nm 282 (ε 10 286) and 248 (17 653); δ($CDCl_3$, 200 MHz) 1.54–1.80 (m, 6 H, 3-CH_2 of tetrahydropyran ring), 3.48 (t, 2 H, *J* 4, OCH_2 of tetrahydropyran ring), 3.86 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 4.37 (d, 2 H, *J* 4, C≡CCH_2O), 4.74 (br, 1 H, OCHO) and 8.05 (s, 1 H, 6-H).

5-(3-*hydroxyprop*-1-*ynyl*)-2,4-*dimethoxypyrimidine* **3**.—A mixture of 2,4-dimethoxy-5-(3-tetrahydropyran-2-yloxyprop-1-ynyl)pyrimidine **2** (1.08 g, 3.8 mmol) and toluene-*p*-sulphonic acid monohydrate (64 mg, 0.34 mmol) in methanol (16 ml) was refluxed for 1.25 h. The reaction mixture was cooled to room temperature, stirred with anhydrous potassium carbonate (25 mg, 1.81 mmol) for 5 min and filtered. The filtrate was concentrated to dryness and the residue was dissolved in chloroform (100 ml). The chloroform layer was washed with water (3 × 20 ml), dried (Na_2SO_4) and evaporated to yield 5-(3-hydroxyprop-1-ynyl)-2,4-dimethoxypyrimidine **3** (610 mg, 3.14 mmol, 81%), crystallised from benzene, m.p. 120–122 °C (Found: C, 55.45; H, 5.15; N, 14.55. Calc. for $C_9H_{10}N_2O_3$: C, 55.66; H, 5.19; N, 14.43%); ν_{max}/cm^{-1} 3250s, 3010w, 2940w, 2840s, 2230vs and 1595s; λ_{max}(EtOH)/nm 282 (ε 6715) and 248 (12 610); δ($CDCl_3$, 200 MHz) 3.40 (br s, 1 H, OH), 4.02 (s, 3 H, OCH_3), 4.08 (s, 3 H, OCH_3), 4.56 (br s, 2 H, CH_2O) and 8.42 (s, 1 H, 6-H).

5-(*Formylethynyl*)-2,4-*dimethoxypyrimidine* **4**.—*Method A: oxidation with Swern reagent.* A dichloromethane solution of dimethyl sulphoxide (6 ml, 6.6 g, 84.6 mmol) was added dropwise with stirring to a cooled (−78 °C) solution of oxalyl chloride (3.7 ml, 5.36 g, 42.20 mmol) in dichloromethane (24 ml) under a nitrogen atmosphere. After being stirred for 10 min, the solution was slowly treated with a solution of 5-(3-hydroxyprop-1-ynyl)-2,4-dimethoxypyrimidine **3** (6 g, 30.9 mmol) in a mixture of dichloromethane (120 ml) and dimethyl sulphoxide (7.5 ml) and stirring continued for 0.5 h at −78 °C. Triethylamine (30 ml) was added to the mixture which was then allowed to warm to room temperature. The reaction mixture was then diluted with dichloromethane (240 ml) and washed consecutively with water (3 × 50 ml), saturated brine (3 × 40 ml) and water (3 × 50 ml). The dichloromethane solution was dried (Na_2SO_4), and evaporated and the residue was crystallized from a small amount of benzene to afford a light yellow solid, m.p. 128–130 °C (4.5 g, 23.4 mmol, 76%) (Found: C, 56.65; H, 4.15; N, 14.5. Calc. for $C_9H_8N_2O_3$: C, 56.25; H, 4.20; N, 14.58%); ν_{max}/cm^{-1} 2190s, 1645s and 1600s; λ_{max}(EtOH)/nm 285 (ε 9466) and 247 (13 978); δ($CDCl_3$, 200 MHz) 3.98 (s, 3 H, OCH_3), 4.02 (s, 3, H, OCH_3), 8.47 (s, 1 H, 6-H) and 9.40 (s, 1 H, CHO).

Method B: oxidation with manganese dioxide. A mixture of 5-(3-hydroxyprop-1-ynyl)-2,4-dimethoxypyrimidine **3** (100 mg, 0.52 mmol) and finely powdered manganese dioxide (850 mg, 9.8 mmol) in dry dichloromethane (10 ml) was stirred vigorously at room temperature (28–30 °C) for 20 h. The mixture was then filtered and the residue was washed with dichloromethane (30 ml). The combined organic layers were evaporated when a solid was obtained which was purified by column chromatography on neutral alumina (chloroform as eluent) to yield 5-(formylethynyl)-2,4-dimethoxypyrimidine **4** as light yellow solid (70 mg, 0.36 mmol, 71%), m.p. 130 °C, identical with the sample made by Method A.

Conversion of 5-(3-*Hydroxyprop*-1-*ynyl*)-2,4-*dimethoxypyrimidine* **3** *into* 5-*Ethynyl*-2,4-*dimethoxypyrimidine* **5**.—To a solution of 5-(3-hydroxyprop-1-ynyl)-2,4-dimethoxypyrimidine **3** (100 mg, 0.52 mmol) in dry dichloromethane (8 ml), potassium hydroxide powder (150 mg, 2.68 mmol) and finely powdered active manganese dioxide (850 mg, 9.77 mmol) were added. The mixture was stirred at room temperature (28 °C) for 10 h,

filtered and the residue was washed with dichloromethane (3 × 10 ml). The combined organic solvents were evaporated to dryness to yield a solid which was purified by column chromatography on neutral alumina (chloroform as eluent) (70 mg, 0.43 mmol, 83%), crystallized from chloroform–light petroleum (b.p. 60–80 °C) as a white solid, m.p. 82–84 °C, identical with an authentic sample of 5-ethynyl-2,4-dimethoxypyrimidine from IR and ^{1}H NMR spectroscopic comparisons.

5-(3-*Hydroxybut*-1-*ynyl*)-2,4-*dimethoxypyrimidine* **6**.—*Method A*. To a cooled (10 °C) and well-stirred solution of methylmagnesium iodide [made from magnesium turnings (100 mg, 4.16 mmol) and methyl iodide (560 mg, 3.94 mmol) in dry ether (10 ml)], 5-(formylethynyl)-2,4-dimethoxypyrimidine **4** (400 mg, 2.08 mmol) in benzene (20 ml) was added dropwise. After the addition was complete, the mixture was refluxed for 1 h, cooled in ice–water bath, decomposed with aqueous ammonium chloride (saturated; 10 ml) and then extracted with ether (3 × 15 ml). The combined ethereal layers were washed with aqueous sodium thiosulphate (10%; 3 × 5 ml) and saturated brine (3 × 5 ml), dried (Na_2SO_4) and evaporated. The residue was crystallised from ether–light petroleum (40–60 °C) to give colourless crystals (390 mg, 1.88 mmol, 90%), m.p. 110 °C; R_f(chloroform–ethyl acetate, 9:1) 0.42 (Found: C, 57.95; H, 5.7; N, 13.5. Calc. for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.46%); ν_{max}/cm^{-1} 3310s and 1600s; λ_{max}/nm 282 (9120), 250 (17 280); δ($CDCl_3$, 100 MHz) 1.54 (d, 3 H, *J* 6, CH_3), 2.26 (br s, 1 H, OH), 3.98 (s, 3 H, OCH_3), 4.02 (s, 3 H, OCH_3), 4.78 (q, 1 H, *J* 6 Hz, CH) and 8.30 (s, 1 H, 6-H).

5-(3-*Hydroxypent*-1-*ynyl*)-2,4-*dimethoxypyrimidine* **7**.—Compound **7** was synthesized by following the same procedure as for compound **6** [from magnesium turnings (150 mg, 6.25 mmol), ethyl iodide (750 mg, 4.81 mmol) in ether (10 ml) and 5-(formylethynyl)-2,4-dimethoxypyrimidine **4** (500 mg, 2.60 mmol) in dry benzene (20 ml)]. It crystallised from ether–light petroleum (b.p. 60–80 °C) as a colourless solid (83%), m.p. 75 °C; R_f(chloroform–ethyl acetate, 9:1) 0.38 (Found: C, 59.4; H, 6.35; N, 12.85. Calc. for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60%); ν_{max} 3330s and 1605s; λ_{max}/nm 282 (7126), 249 (13 575); δ($CDCl_3$, 100 MHz) 1.06 (t, 3 H, *J* 8, CH_3), 1.82 (m, 2 H, CH_2), 2.34 (br, 1 H, OH), 3.98 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 4.58 (t, 1 H, *J* 8, CH) and 8.30 (s, 1 H, 6-H).

5-(3-*Hydroxy*-4-*methylpent*-1-*ynyl*-2,4-*dimethoxypyrimidine* **8**.—The compound was synthesized by following method A from an appropriate Grignard reagent [made from magnesium turnings (150 mg, 6.25 mmol) isopropyl bromide (750 mg, 6.09 mmol) in ether (10 ml)] and 5-(formylethynyl)-2,4-dimethoxypyrimidine **4** (300 mg, 1.56 mmol) in dry benzene (15 ml). After work-up, thin layer chromatography indicated the presence of two compounds which were separated by column chromatography on neutral alumina (chloroform–ethyl acetate, 10:1 as eluent). The first fractions afforded the product **8** as a gum (75 mg, 0.32 mmol, 20%); R_f(chloroform–ethyl acetate, 9:1) 0.37. This was followed by a further product, m.p. 120–122 °C (170 mg, 34%) identified as 5-(3-hydroxyprop-1-ynyl)-2,4-dimethoxypyrimidine **3**. Compound **8** (Found: C, 61.4; H, 7.15; N, 12.1. Calc. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86%); ν_{max}/cm^{-1} 3600–3200br, 2190w and 1600s; λ_{max}/nm 283 (ε 7039) and 249 (13 503); δ($CDCl_3$, 200 MHz), 1.08 [d, 6 H, *J* 4, $C(CH_3)_2$], 2.0 (m, 1 H, CH), 4.04 (s, 3 H, OCH_3), 4.06 (s, 3 H, OCH_3), 4.46 [d, 1 H, *J* 4, C*H*(OH)] and 8.38 (s, 1 H, 6-H).

5-(3-*Hydroxyhept*-1-*ynyl*)-2,4-*dimethoxypyrimidine* **9**.—This compound was synthesized according to Method A from the Grignard reagent [made from magnesium turnings (100 mg, 4.16 mmol) and butyl bromide (300 mg, 2.18 mmol) in dry ether (10 ml)] and 5-(formylethynyl)-2,4-dimethoxypyrimidine **4** (200 mg, 1.04 mmol) in dry benzene (15 ml). The crude residue obtained as a gum (300 mg) was purified by chromatography on neutral alumina (chloroform–ethyl acetate, 9:1 as eluent). The first fractions afforded the desired product **9** (120 mg, 0.48 mmol, 46%); R_f(chloroform–ethyl acetate, 9:1) 0.55, followed by second product, compound **3** (60 mg). The desired product **9** crystallised from ether–light petroleum (b.p. 40–60 °C) as a white granular solid, m.p. 66 °C. For compound **9** (Found: C, 62.45; H, 7.35; N, 11.55. Calc. for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19%); ν_{max}/cm^{-1} 3300s and 1605s; λ_{max}/nm 282 (9430) and 250 (15 190); δ($CDCl_3$, 200 MHz) 0.94 (t, 3 H, *J* 6, CH_3), 1.42 (m, 4 H, CH_2CH_2), 1.80 [m, 2 H, C(OH)CH_2], 4.02 (s, 3 H, OCH_3), 4.06 (s, 3 H, OCH_3), 4.64 (t, 1 H, *J* 6, CH) and 8.36 (s, 1 H, 6-H).

5-(3-*Hydroxy*-3-*phenylprop*-1-*ynyl*)-2,4-*dimethoxypyrimidine* **10**.—*Method B*. To an ice-cooled solution of Grignard reagent [made from magnesium turnings (150 mg, 6.25 mmol) and bromobenzene (800 mg, 5.09 mmol) in tetrahydrofuran (10 ml)], 5-(formylethynyl)-2,4-dimethoxypyrimidine (500 mg, 2.6 mmol) in dry tetrahydrofuran (20 ml) was added dropwise under a nitrogen atmosphere. After the addition was complete, the mixture was refluxed for 1 h and then tetrahydrofuran was distilled off (30 ml) with continuous addition of benzene (20 ml). The reaction mixture was then cooled and the Grignard complex was decomposed with saturated aqueous ammonium chloride (10 ml); the mixture was then extracted with ether (3 × 20 ml). The combined organic layers were washed with saturated brine (3 × 10 ml), dried (Na_2SO_4) and evaporated to yield a gum (800 mg). This was purified by column chromatography on neutral alumina (chloroform–ethyl acetate, 9:1 as eluent). The first fractions afforded the desired product **10** as a gum (520 mg, 192 mmol, 74%); R_f(chloroform–ethyl acetate, 9:1) 0.48 (Found: C, 66.9; H, 5.25; N, 10.25. Calc. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37%); ν_{max}/cm^{-1} 1595s; λ_{max}/nm 280 (ε 9782) and 252 (15 135); δ($CDCl_3$, 200 MHz) 4.00 (s, 3 H, OCH_3), 4.04 (s, 3 H, OCH_3), 5.76 (s, 1 H, CH), 7.44 (d, 3 H, *J* 8, $ArH_{m,p}$), 7.66 (d, 2 H, *J* 8, ArH_o) and 8.38 (s, 1 H, 6-H).

5-(3-*Hydroxy*-3-p-*tolylprop*-1-*ynyl*)-2,4-*dimethoxypyrimidine* **11**.—This compound was synthesized according to Method B [from magnesium turnings (150 mg, 6.25 mmol), *p*-bromotoluene (850 mg, 4.97 mmol) and 5-(formylethynyl)-2,4-dimethoxypyrimidine (500 mg, 2.60 mmol)]. Purification by column chromatography on neutral alumina gave, compound **11** as a solid (520 mg, 1.84 mmol, 70%) which crystallized from ether–light petroleum (b.p. 40–60 °C) as a colourless crystalline solid, m.p. 110 °C; R_f(chloroform–ethyl acetate, 9:1) 0.27 (Found: C, 67.65; H, 5.65; N, 9.55. Calc. for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85%); ν_{max}/cm^{-1} 3260s and 1600s; λ_{max}/nm 281 (9514) and 251 (18 419); δ($CDCl_3$, 100 MHz) 2.34 (s, 3 H, $ArCH_3$), 2.64 (d, 1 H, *J* 6, OH), 3.96 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 5.66 (d, 1 H, *J* 6, CH), 7.18 (d, 2 H, *J* 8, ArH_m), 7.48 (d 2, H, *J* 8, ArH_o) and 8.32 (s, 1 H, 6-H).

5-(3-*Hydroxy*-3-p-*methoxyphenyl*)*prop*-1-*ynyl*)-2,4-*dimethoxypyrimidine* **12**.—Compound **12** was synthesized according to Method B [from magnesium turnings (150 mg, 6.25 mmol), *p*-bromoanisole (1 g, 5.35 mmol) and 5-(formylethynyl)-2,4-dimethoxypyrimidine **4** (500 mg, 2.60 mmol)]. Column chromatography on neutral alumina (eluent, chloroform–ethyl acetate, 9:1) gave the pure product (630 mg, 2.10 mmol, 80%) which crystallized from ether–light petroleum (b.p. 40–60 °C) as colourless crystals, m.p. 116–117 °C (Found: C, 64.3; H, 5.1; N, 9.3. Calc. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33%); ν_{max}/cm^{-1} 3600–3200br, 2200w and 1590s; λ_{max}(EtOH)/

nm 283 (ε 11 668) and 233 (16 610); δ($CDCl_3$, 100 MHz) 3.80 (s, 3 H, OCH_3), 4.00 (s, 3 H, OCH_3), 4.04 (s, 3 H, OMe), 5.68 (s, 1 H, CH), 6.32 (d, 2 H, *J* 8, ArH_o), 7.56 (d, 2 H, *J* 8, ArH_m) and 8.34 (s, 1 H, 6-H).

Synthesis of 5-(*Acylethynyl*)-2,4-*dimethoxypyrimidines*

Method A: Oxidation with Collins's Reagent.—A typical procedure to prepare 5-(*benzoylethynyl*)-2,4-*dimethoxypyrimidine* **17**. To a magnetically stirred solution of pyridine (1.6 ml, 19.8 mmol) in dichloromethane (50 ml), chromium trioxide (1.02 g, 10.20 mmol) was added and the mixture was stirred at room temperature (28–30 °C) for 30 min. A solution of 5-(3-hydroxy-3-phenylprop-1-ynyl)-2,4-dimethoxypyrimidine **10** (450 mg, 1.66 mmol) in dichloromethane (5 ml) was added to the above mixture in one portion when a tarry black residue separated immediately. After being stirred for an additional 40 min at room temperature (28–30 °C), the solution was decanted from the residue which was washed with dichloromethane (60 ml). The combined organic layers were washed with 2% aqueous sodium hydroxide (3 × 10 ml) and saturated brine (3 × 20 ml), dried (Na_2SO_4), and evaporated to afford a residue (400 mg) which was chromatographed on neutral alumina (chloroform as eluent) to yield a solid (240 mg, 0.89 mmol, 54%) which was crystallised from chloroform–light petroleum (b.p. 40–60 °C), m.p. 124–125 °C (lit.,[8] m.p. 122–125 °C).

2,4-*Dimethoxy*-5-(3-*oxobut*-1-*ynyl*)*pyrimidine* **13**. This was prepared in 60% yield, m.p. 96 °C (lit.,[27] m.p. 94–96 °C).

2,4-*Dimethoxy*-5-(3-*oxopent*-1-*ynyl*)*pyrimidine* **14**. This was prepared in 64% yield, m.p. 76 °C (lit.,[27] m.p. 78–80 °C).

2,4-*Dimethoxy*-5-(4-*methyl*-3-*oxopent*-1-*ynyl*)*pyrimidine* **15**. This was synthesized in 50% yield; crystallised from chloroform–light petroleum (b.p. 60–80 °C), m.p. 92 °C; R_f(chloroform–ethyl acetate, 9:1), 0.63 (Found: C, 61.45; H, 6.35; N, 11.75. Calc. for $C_{12}H_{14}N_2O_3$: C, 61.52; H, 6.02; N, 11.96%); ν_{max}/cm^{-1} 2190, 1660 and 1600; λ_{max}(EtOH)/nm 296 (ε 9520) and 271 (7254); δ($CDCl_3$, 200 MHz), 1.25 (d, 6 H, *J* 2, CMe_2), 2.71–2.88 (m, 1 H, CH), 4.07 (s, 3 H, OMe), 4.10 (s 3, H, OMe) and 8.50 (s, 1 H, 6-H).

2,4-*Dimethoxy*-5-(3-*oxohept*-1-*ynyl*)*pyrimidine* **16**. This was a gum (70%); R_f(chloroform–ethyl acetate, 9:1) 0.72 (Found: C, 62.75; H, 6.7; N, 10.9. Calc. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28%); ν_{max}/cm^{-1} 2200, 1670 and 1595; λ_{max}(EtOH)/nm 297 (ε 12 751); δ($CDCl_3$, 200 MHz) 0.95 (t, 3 H, *J* 7.5, CH_3), 1.32–1.82 (m, 4 H, CH_2CH_2), 2.67 (t, 2 H, *J* 7.5, $COCH_2$), 4.11 (s, 3 H, OCH_3), 4.13 (s, 3 H, OCH_3) and 8.47 (s, 1 H, 6-H).

2,4-*Dimethoxy*-5-(p-*toluoylethynyl*)*pyrimidine* **18**. This was obtained in 90% yield, m.p. 140–141 °C (lit.,[8] m.p. 140–141 °C).

2,4-*Dimethoxy*-5-(p-*methoxybenzoylethynyl*)*pyrimidine* **19**. This was obtained in 50% yield; it crystallised from chloroform–light petroleum (b.p. 60–80 °C) as white crystalline solid, m.p. 136 °C (lit.,[8] m.p. 124–126 °C).

Method B: Oxidation with Manganese Dioxide.—A typical procedure to prepare 2,4-*dimethoxy*-5-(3-*oxobut*-1-*ynyl*)*pyrimidine* **13**. 5-(3-Hydroxybut-1-ynyl)-2,4-dimethoxypyrimidine **6** (90 mg, 0.43 mmol) was added to a vigorously stirred suspension of finely powdered manganese dioxide (800 mg, 9.19 mmol) in dichloromethane (15 ml). The mixture was stirred at room temperature (30 °C) for 10 h, filtered and the residue was washed with dichloromethane (30 ml). The combined organic layers were evaporated to dryness to yield a residue which was chromatographed on neutral alumina (chloroform as eluent) to afford the title compound **13** (67%), m.p. 96 °C, identical from spectroscopic comparison with an authentic sample of compound **13** made by Method A.

Yields of the other compounds obtained by oxidation by Method B are: **14** (70%), **15** (58%), **17** (62%), **18** (80%) and **19** (71%).

Demethylation of 5-(*acylethynyl*)-2,4-*dimethoxypyrimidines.—A typical procedure: synthesis of* 5-(2-*benzoyl*-1-*chlorovinyl*)-*uracil* **20**. A mixture of 5-(benzoylethynyl)-2,4-dimethoxypyrimidine **17** (150 mg, 0.56 mmol) and 6M HCl (1.5 ml) was stirred and heated at 90 °C for 4 h. The mixture was cooled and filtered. The residue was washed with a little water, dried and crystallised from methanol to afford a white crystalline solid **20** (130 mg, 0.47 mmol, 84%), m.p. 258–260 °C (Found: C, 56.3; H, 3.25; N, 10.0. Calc. for $C_{13}H_9ClN_2O_3$: C, 56.42; H, 3.25; N, 10.13); ν_{max}/cm^{-1} 1715, 1670 and 1600; λ_{max}(EtOH)/nm 322 (ε 18 620); δ([$^2H_6$]DMSO, 200 MHz) 7.56–7.76 (m, 3 H, *J* 8.0, $ArH_{m,p}$), 7.98 (d, 2 H, *J* 8.0, ArH_o), 8.08 (br s, 1 H, vinylic-H), 8.44 (s, 6-H), 11.64 (s, 1 H, NH) and 11.82 (s, 1 H, NH).

5-(1-*Chloro*-2-p-*toluoylvinyl*)*uracil* **21**. This was obtained from 2,4-dimethoxy-5-(*p*-toluoylethynyl)pyrimidine **18** (by demethylation with 6 mol dm^{-3} HCl in a yield of 87%; it crystallised from methanol as a white crystalline compound, m.p. 262–264 °C (Found: C, 58.25; H, 3.85; N, 9.75. Calc. for $C_{14}H_{11}ClN_2O_3$: C, 57.83; H, 3.79; N, 9.64%); ν_{max}/cm^{-1} 1710, 1670br, 1630 and 1608; λ_{max}(EtOH)/nm 320 nm (ε 17 780), δ([$^2H_6$]DMSO, 100 MHz), 2.32 (s, 3 H, $ArCH_3$), 7.32 (d, 2 H, *J* 8.0, ArH_m), 7.76 (d, 2 H, *J* 8.0, ArH_o), 7.96 (s, 1 H, vinylic-H), 8.28 (s, 1 H, 6-H) and 11.56 (br s, 2 H, NH).

5-(2-p-*Anisoyl*-1-*chlorovinyl*)*uracil* **22**. This was obtained in 85% yield from 5-(*p*-anisoylethynyl)-2,4-dimethoxypyrimidine **19** (by demethylation with 6 mol dm^{-3} HCl; it crystallised from methanol as a white crystalline solid, m.p. 242–244 °C (Found: C, 54.35; H, 3.65; N, 8.9. Calc. for $C_{14}H_{11}ClN_2O_4$: C, 54.81; H, 3.59; N, 9.14%); ν_{max}/cm^{-1} 1710, 1670 and 1600; λ_{max}(EtOH)/nm 306 (ε 16 980); δ([$^2H_6$]DMSO, 200 MHz), 3.84 (s, 3 H, OMe), 7.10 (d, 2 H, *J* 8, ArH_m), 7.94 (d, 2 H, *J* 8.0, ArH_o), 8.00 and 8.04 (two s, 1 H, vinylic-H), 8.34 (s, 1 H, 6-H), 11.65 (s, 1 H, NH) and 11.78 (br s, 1 H, NH).

5-(1-*Chloro*-3-*oxobut*-1-*enyl*)*uracil* **23**. This was synthesized in 67% yield from 2,4-dimethoxy-5-(3-oxobut-1-ynyl)pyrimidine **13** (50 mg, 0.24 mmol) by demethylation with 1% HCl (50 ml), m.p. 236 °C (Found: C, 45.25; H, 3.05; N, 12.8. Calc. for $C_9H_7ClN_2O_3$: C, 44.76; H, 3.26; N, 13.05%); ν_{max}/cm^{-1} 1740, 1680 and 1620; λ_{max} (EtOH)/nm 320 (ε 9512); δ([$^2H_6$]DMSO, 200 MHz), 2.12 (s, 3 H, COMe), 6.86 (s, 1 H, vinylic-H), 8.22 (s, 1 H, 6-H), 11.48 (s, 1 H, NH) and 11.92 (s, 1 H, NH).

Synthesis of 5-(*Acylethynyl*)*uracils.—A typical procedure to prepare* 5-(*benzoylethynyl*)*uracil* **24**. A mixture of 5-(2-benzoyl-1-chlorovinyl)uracil **20** (140 mg, 0.51 mmol) and NaOH (200 mg, 5 mmol) in 95% ethanol (4 ml) was stirred at room temperature under a nitrogen atmosphere for 20 min. Hydrochloric acid (6M) was then added to neutralise the base and the mixture evaporated under reduced pressure to afford the solid uracil. This was treated with cold water (1 ml), filtered off, washed with a little cold water and dried to yield a solid (100 mg, 0.42 mmol, 82%); it was crystallised from methanol–water to yield a white powder, m.p. >290 °C, identical with an authentic sample[8] of 5-(benzoylethynyl)uracil **24** from spectroscopic comparisons.

Alternative procedure. To a suspension of compound **20** (50 mg, 0.18 mmol) in dioxane (2 ml), aqueous potassium hydroxide (2 mol dm^{-3}, 0.7 ml) was added to give a clear solution. This was stirred at room temperature for 9 h and then heated at 80 °C for 15 min. It was then cooled and neutralised with hydrochloric acid (1 mol dm^{-3}) to pH 6–7 to give a white solid. This was filtered off and crystallised from methanol–water (30 mg, 0.13 mmol, 69%); it had m.p. >290 °C, identical with the above sample of 5-(benzoylethynyl)uracil.

5-p-*Toluoylethynyl*)*uracil* **25** and 5-(p-*anisoylethynyl*)*uracil* **26**. These were obtained from the corresponding chlorovinyl-

uracils by following the above methods in 83 and 85% yields respectively. They were identical with the corresponding authentic samples.[8]

Acknowledgements

L. N. C. thanks the UGC, Government of India, for a UGC fellowship. Thanks are also due to Mr. B. Das for helping with the *O*-demethylation experiments.

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Paper 0/05347C
Received 27*th November* 1990
Accepted 26*th February* 1991