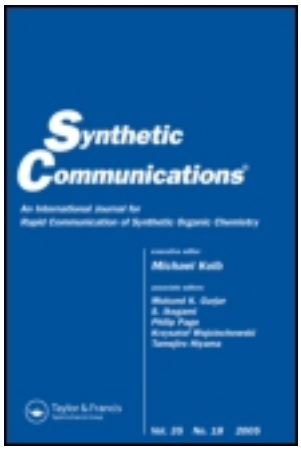

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

SYNTHESIS OF SOME NEW S-DABO AND HEPT ANALOGUES WITH EXPECTED BIOLOGICAL ACTIVITY AGAINST HBV

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Version of record first published: 17 Aug 2006.

To cite this article: Mohammed Taha Abdel Aal (2002): SYNTHESIS OF SOME NEW S-DABO AND HEPT ANALOGUES WITH EXPECTED BIOLOGICAL ACTIVITY AGAINST HBV, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:9, 1365-1377

To link to this article: http://dx.doi.org/10.1081/SCC-120003633

SYNTHETIC COMMUNICATIONS, 32(9), 1365–1377 (2002)

SYNTHESIS OF SOME NEW *S*-DABO AND HEPT ANALOGUES WITH EXPECTED BIOLOGICAL ACTIVITY AGAINST HBV

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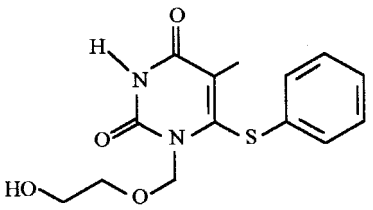
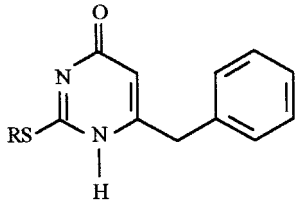
ABSTRACT

Ethyl4-(3,4-dimethoxyphenyl)-2-methyl-3-oxobutanoate (**1**) is synthesized in a high yield from 3,4-dimethoxybenzylcyanide and 2-bromopropionate. Condensation of (**1**) with thiourea in EtOH/NaOEt afforded the thiopyrimidine (**2**). Alkylation of (**2**) with halo compounds gave new thio-analogues of DABO's (**3–7**), whereas desulfurization of (**2**) by chloroacetic acid afforded the uracil (**3**). Reaction of (**3**) with chloromethyl ethers yielded new analogues of HEPT (**10a**,**b**).

The virally coded enzyme, reverse transcriptase (RT), is an attractive target in the search for new antiviral agents against human immunodeficiency virus type-1 (HIV-1). This enzyme is a pivot in the retro viral cycle of HIV as it with viral RNA as template synthesizes viral DNA for integration in the host genome.[1] Several specific inhibitors of HIV-1 RT have been reported.[2,3] Some of these are 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) derivatives and 3,4-dihydro-2-alkoxy-6-benzyl-4-oxopyrimidines (DABO) derivatives. Since HEPT[4] was recognized as a non-nucleoside inhibitor of HIV-1, there has been a wide interest for



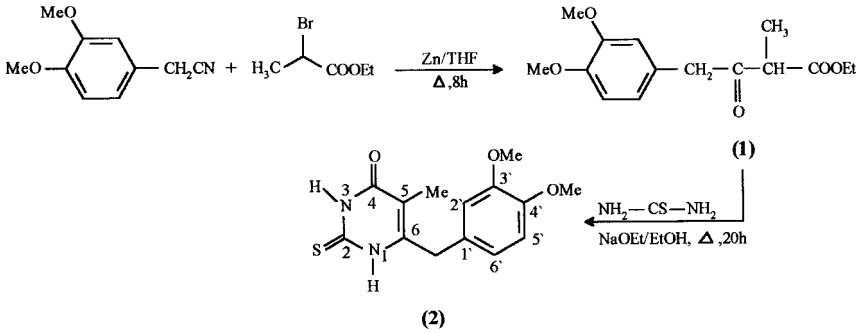
HEPT



S-DABO$_S$

development within this group of compounds that specifically inhibit the HIV-1 enzyme reverse transcriptase (RT) of HIV type 1. Many reviews[5-8] have been made about NNRTIs but the focus has mainly been on the development and pharmacological aspects.

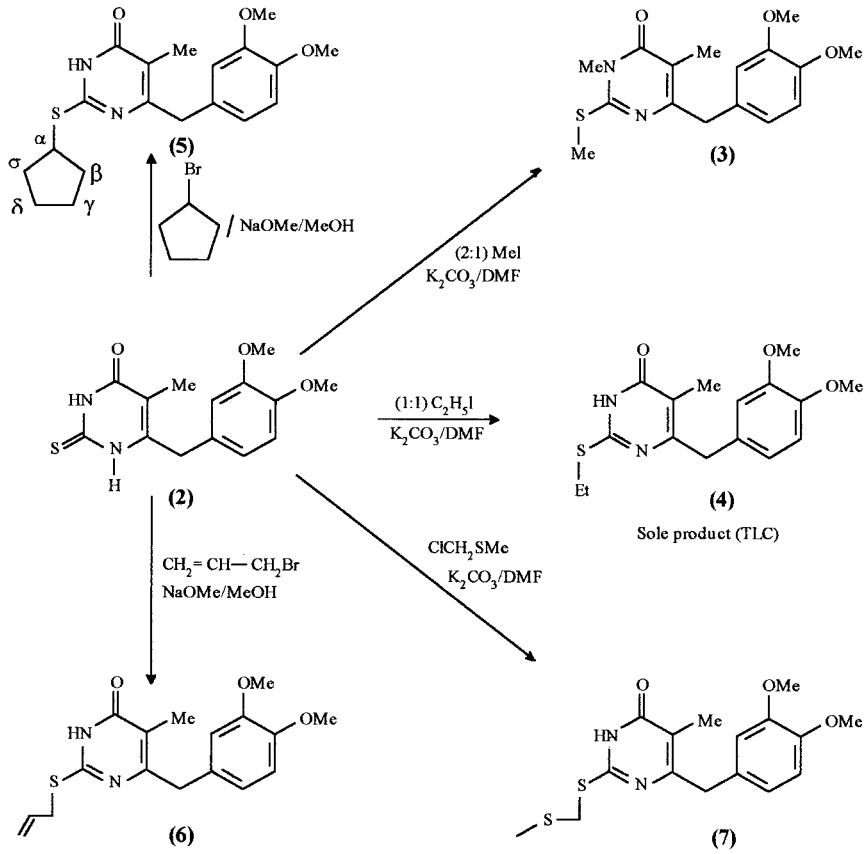
S-DABOs derivatives which are 2-alkylthio analogues of dihydroalkoxypyrimidines (DABO) and their activity against HIV-1 were also reported.[9] The 3-oxo ester (**1**) was prepared according to the method of Pedersen et al.,[10] by reaction of 3,4-dimethoxybenzylcyanide with ethyl-2-bromopropionate in the presence of activated zinc in refluxing THF for 8 h. The so formed 3-oxo ester (**1**) was converted into the 2-thiouracil (**2**) by its reaction with thiourea and sodium in boiling ethanol for 20 h. (Scheme 1).



Scheme 1.

The promising biological activity of various thio analogues of dihydroalkoxybenzyloxopyrimidines (DABOs) prompted us to synthesize the new derivatives (**3–7**) to investigate their biological activities against HBV. The reaction of (**2**) with different types of halo compounds as alkyl halides, halo

esters, and halo alkyl sulfides in a mixture of DMF/K_2CO_3 or NaOMe/MeOH by stirring at room temperature for 18–24 h afforded the desired 2-(alkylthio)-6-(3′,4′-dimethoxyphenylmethyl)-pyrimidine-4(1H) ones (**3–7**) in a fair yield (Scheme 2).

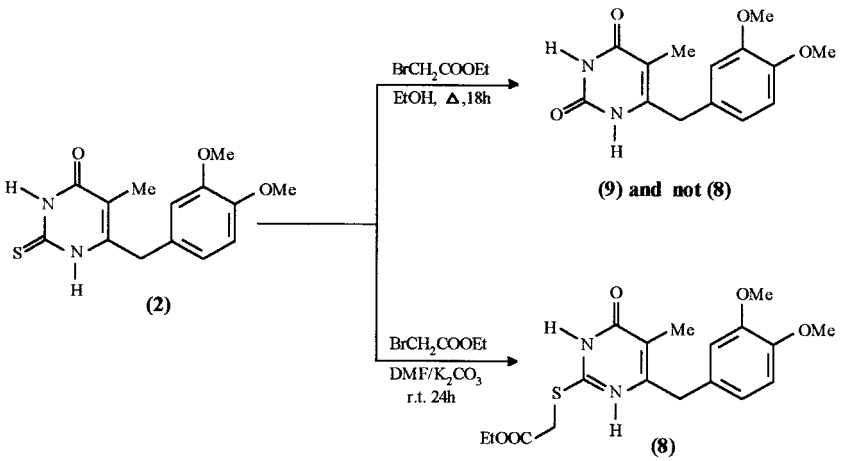


Scheme 2.

Mai et al.[11] have reported that alkylation of 6-(2′,6′-difluro-phenylmethyl)-3,4-dihydro-5-methyl-2-thiopyrimidine-4(3H)-one with iodo-methane in DMF at room temperature in the molar ratio 1 : 2 gave the corresponding *S*-alkylated product. In our hands, treatment of (**2**) with iodomethane in DMF and K_2CO_3 in molar ratio 1 : 1 or in excess afforded

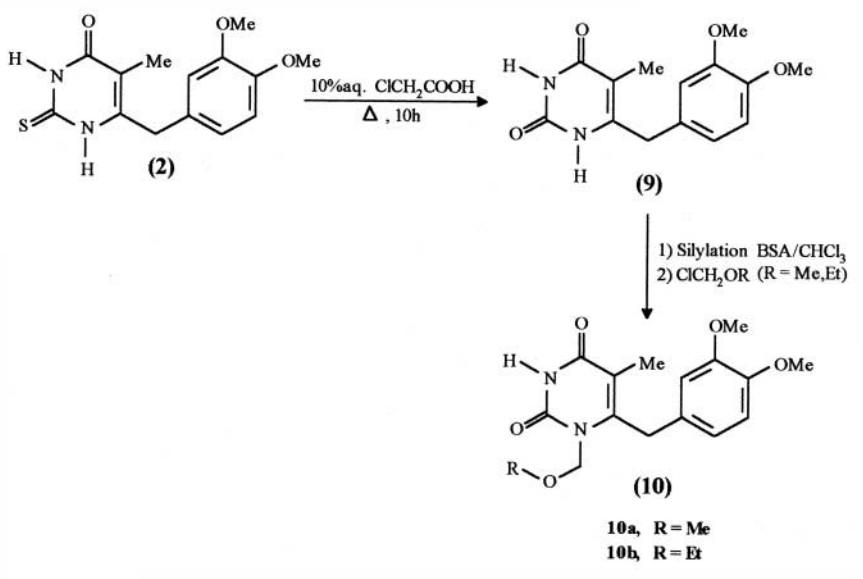
the *bis* *N*-and *S*-alkylated product (**3**) as the sole product. However, the reaction of (**2**) with iodoethane 1 : 1 in DMF and K_2CO_3 at room temperature gave only the mono *S*-alkylated product (**4**).

It is worthy to mention that the reaction of (**2**) with ethylbromoacetate in refluxing ethanol for 18 h afforded unexpectedly the corresponding oxo analogue (**9**) as the sole product (TLC) through hydrolysis process, while the reaction of (**2**) with the bromoester in DMF/K_2CO_3 at room temperature for 24 h gave the normal 2-alkylthio derivative (**8**) (Scheme 3).



Scheme 3.

The synthesis of HET analogues could also be achieved by the desulfurization of (**2**) using 10% aqueous chloroacetic acid at the refluxing temperature for 20 h in 65% yield. The pyrimidine (**9**) was silylated by its treatment with *N*,*O*-*bis*(trimethylsilyl)acetamide (BSA) in anhydrous chloroform for 3 h at room temperature under N_2. The silylated product was treated with chloromethyl methyl ether and/or chloromethyl ethyl ether to afford the corresponding uracil derivatives (**10a**,**b**), respectively (Scheme 4). The elucidation of the structures of all new compounds was confirmed by IR, ^{1}H NMR, ^{13}C NMR and MS. The compounds were purified by chromatography on silica gel column. The IR spectra display absorption bands in the regions 3436–3423 and 1689–1627 cm^{-1} corresponded to NH and C=O, respectively.



Scheme 4.

The ^{1}H NMR spectra of the products exhibited the CH_3 signals as a singlet (3H) in the range 1.90–2.20 ppm, OCH_3 signals as a singlet (3H) at 3.70–3.87 ppm, while the NH appeared as a singlet (1H) in the range 8.67–12.34 ppm. In the ^{13}C NMR spectra, the CH_3 signals appeared in the range 9.72–14.96 ppm, the OCH_3 carbons at 55.19–56.88 and the C=O at 158.10–163.32 ppm.

Viral screening against HBV was tested at the National Liver Institute, El-Menofeia University, Egypt.

Maintenance media were added to the cell culture (Hep G2 2.2.15) together with the tested compounds (final concentration = 10 μM). The supernatant liquid was collected after one, two and/or three weeks. The DNA replication was estimated by the PCR (polymerase chain reaction) technique. The percentage inhibition could be calculated by the relation between the blanc experiment (containing maintenance media without the tested compounds) and the results obtained after the above mentioned periods.

The percentage cytotoxicity could be estimated by the relation between the number of the living and dead cells after three weeks counted by the Haemocytometer. Compounds **3**, **4**, **5**, **8** and **10a**, **b** showed high viral replication inhibition and low cytotoxicity. Compounds **6** and **7** showed moderate inhibition with moderate cytotoxicity.

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were obtained using Perkin Elmer 1720 Infrared Fourier Transform Spectrometer. NMR spectra were recorded on a Varian Gemini 2000 NMR spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C or on a Brucker AC-250 FT spectrometer at 250 MHz for ^{1}H and at 62.9 MHz ^{13}C with TMS as an internal standard. EI mass spectra were recorded on a Finnigan Mat SSQ 710. The progress of the reaction was monitored by TLC analytical silica gel plates 60 F_{254}. Merk silica gel (0.040–0.063) was used for column chromatography. Tetrahydrofuran (THF) was distilled from sodium/bezophenone prior to use. All the newly prepared compounds gave satisfactory C, H, N.

Synthesis of Ethyl-2-methyl-4-(3,4-dimethoxyphenyl)-3-oxobutyrate (1)

Activated zinc dust (zinc dust washed sequentially with 3 M aq. HCl, distilled H_2O, EtOH, Et_2O, and then dried in vacuo); (38 g, 580 mmol) was suspended in refluxing THF (280 ml) under nitrogen. A few drops of ethyl 2-bromopropionate were added to initiate the reaction. When the mixture turned green (approx. 3 h), 3,4-dimethoxybenzylcyanide (14 g, 79 mmol) was added in one portion, followed by slow addition (6 h) of ethyl-2-bromopropionate (36.7 g, 203 mmol). The mixture was refluxed for 30 min. After cooling and dilution with 700 ml THF, the reaction mixture was stirred with 130 ml 50% K_2CO_3 for 6 h. The THF fraction was decanted and the water fraction was washed with THF (3×100 ml). The combined THF fractions were stirred with 10% aq. HCl (120 ml) at room temperature for 45 min. The solvent was evaporated and the residue was redissolved in 400 ml CH_2Cl_2, washed with sat. $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to furnish after column chromatography on silica gel using ether/ligoin (1 : 1 v/v) the oxo-ester (**1**) as colorless oil, yield 92.7%.

IR (KBr): 1718 (C=O) cm^{-1}.

^{1}H NMR (DMSO-d_6/TMS): $\delta = 1.48$ (d, 3H, CH_3), 1.16 (t, 3H, CH_3, $j = 7.08$), 3.67 (s, 2H, CH_2), 3.7 (s, 6H, $2 \times OCH_3$), 4.07 (q, 2H, CH_2-CH_3, $j = 6.96$), 4.09 (m, 1H, CH), 6.66–6.88 (aromatic H).

^{13}C NMR (DMSO-d_6/TMS): $\delta = 12.55$ ($\underline{C}H_3$), 13.76 ($\underline{C}H_3$-CH_2), 47.24 ($\underline{C}H_2$-ph), 51.12 ($\underline{C}H$), 55.35 ($O\underline{C}H_3$), 55.42 ($O\underline{C}H_3$), 60.73 ($\underline{C}H_2$-O), 111.83, 113.55, 121.87, 126.46, 147.87, 148.69 (aromatic carbons), 170.30 ($\underline{C}$=O), 204.23 ($\underline{C}$=O).

$C_{15}H_{20}O_5$ (280.32), Calc.: C 64.37, H 7.19. Found: C 63.97, H 7.20.

Reaction of Ethyl-2-methyl-4-(3,4-dimethoxyphenyl)-3-oxobutyrate (1) with Thiourea Formation of 5-Methyl-6-(3,4-dimethoxybenzyl)-2-thio-4-1(H) Pyrimidine (2)

Compound **1** (1.68 g, 5.99 mmol) was added to a mixture of sodium (3.0 g, 130 mmol) and thiourea (6.95 g, 91.3 mmol) in abs. ethanol (70 ml). The mixture was refluxed for 18 h (TLC). After cooling, the solvent was removed in vacuo and the residue was dissolved in water (50 ml) and neutralized with HCl (25 ml). The precipitate was collected, washed with water and recrystallized from EtOH to give (**2**) as white crystals, yield 9.3 g 53.14%; m.p. 191–192°C.

IR (KBr): 3436 (NH), 3154 (NH), 1684 (C=O) cm^{-1}.

^{1}H NMR (DMSO-d_6/TMS): $\delta = 1.83$ (s, 3H, CH_3), 3.69 (s, 2H, CH_2,), 3.74 (s, 6H, $2 \times OCH_3$), 6.75 (d, 1H, aromatic), 6.89 (d, 2H, aromatic), 12.34 (sbr., 2H, $2 \times$ NH).

^{13}C NMR (DMSO-d_6/TMS): $\delta = 9.87$ ($H_3\underline{C}$-C=), 34.40 ($\underline{C}H_2$), 55.44 ($2 \times O\underline{C}H_3$), 110.91 (<u>C</u>-5), 111.99, 112.44, 119.98, 128.54 (aromatic carbons), 149.91 (<u>C</u>-6), 161.91 (C-4), 173.95 (<u>C</u>-2).

$C_{14}H_{16}N_2O_3S$(292.35), Calc.: C 57.52, H 5.52, N 9.58. Found: C 57.48, H 5.20, N 9.43.

General Procedure for the Preparation of Compounds 3–7

A mixture of (**2**) (292 mg, 1 mmol), the appropriate halo compounds (1 mmol) and anhydrous potassium carbonate (138 mg, 1 mmol) in anhydrous *N*,*N*-dimethyformamide (3 ml) or NaOMe/MeOH (1.1 mmol) was stirred overnight at room temperature. After treatment with water (60 ml), the solution was extracted with ethylacetate (3×50 ml). The organic layers were collected, washed with brine (3×50 ml), dried over anhydrous Na_2SO_4 and evaporated till dryness under vacuo to furnish the corresponding crude 2-alkylthio derivatives (**3–7**).

6-(3′,4′-Dimethoxyphenylmethyl)-3,5-dimethyl-2-(methylthio)pyrimidin-4(3H)-one (3): Yield (0.24 g, 47.0%), m.p. 89–90°C, purified on silica gel column using ethyl acetate/ligroin 1 : 1 (v/v).

IR (KBr): 1656 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 1.58$ (s, 3H, CH_3), 2.13 (s, 3H, S-CH_3), 2.52 (s, 2H, CH_2), 3.49 (s, 3H, N-CH_3), 3.857 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.79 (d, 1H, H-5′), 6.85 (s, 1H, H-6′), 7.27 (s, 1H, H-2′).

^{13}C NMR ($CDCl_3$/TMS): $\delta = 11.52$ ($\underline{C}H_3$-C=), 14.80 (S-$\underline{C}H_3$), 30.48 ($\underline{C}H_2$), 40.46 (N-$\underline{C}H_3$), 55.19 ($O\underline{C}H_3$), 55.43 ($O\underline{C}H_3$), 111.76 (<u>C</u>-2′), 112.81 (<u>C</u>-5), 113.54 (<u>C</u>-5′), 120.60 (<u>C</u>-6′), 130.43 (<u>C</u>-1′), 158.63 (<u>C</u>=O), 162.09 (<u>C</u>-2).

Mass spectrum (m/z) = 320 (M^+, 100), 305 (M^+-CH_3, 31), 291 (M^+-NCH_3, 2.5), 290 (M^+-3 CH_3, 12.5), 182 (M^+-3,4-dimethoxyphenyl, 12.5), 152 ($^+CH_2$–3,4-dimethoxyphenyl, 4), 138 (3,4-dimethoxyphenyl$^+$, 23.8), 91 ($^+CH_2Ph$, 4).

$C_{16}H_{20}N_2O_3S$ (320.40), Calc.: C 59.98, H 6.29, N 8.74, S 9.99. Found: C 60.07, H 6.22, N 8.77, S 10.03.

6-(3′,4′-Dimethoxyphenylmethyl)-3,4-dihydro-5-methyl-2-(ethylthio)pyrimidin-4(3H)-one (4): Yield (56%), m.p. 161–162°C.

IR (KBr): 3434 (NH), 1656 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 1.34 (t, 3H, CH_3-CH_2), 2.13 (s, 3H, CH_3), 3.14 (q, 2H, CH_2-CH_3), 3.87 (s, 6H, 2 OCH_3), 6.80 (d, 1H, H-5′), 6.84 (s, 1H, H-6′), 7.30 (s, 1H, H-2′).

^{13}C NMR ($CDCl_3$/TMS): δ = 11.09 ($\underline{C}H_3$-CH_2), 14.96 ($\underline{C}H_3$-C=), 25.48 ($\underline{C}H_2$), 41.07 ($\underline{C}H_2$-S), 56.29 (OCH_3), 56.34 (OCH_3), 111.58 ($\underline{C}$-5), 112.72 ($\underline{C}$-2′), 116.39 ($\underline{C}$-5′), 121.34 ($\underline{C}$-6′), 130.95 ($\underline{C}$-1′), 148.11 ($\underline{C}$-3′), 149.24 ($\underline{C}$-4′), 156.85 (C-2), 162.87 (C=O), 165.93 (C-2).

Mass spectrum (m/z) = 320 (M^+, 100), 305 (M^+-CH_3, 52.8), 291 (M^+-C_2H_5, 17.5), 287 (M^+-SH, 28.4), 259 (M^+-SEt, 6.5), 182 (M^+-3,4-dimethoxyphenyl, 2.2), 152 ($^+CH_2$-3,4-dimethoxyphenyl, 3.7), 138 (3,4-dimethoxyphenyl$^+$, 22.5), 91 ($^+CH_2Ph$, 13.4).

$C_{16}H_{20}N_2O_3S$ (320.40), Calc.: C 59.98, H 6.29, N 8.74. Found: C 60.03, H 6.34, N 9.01.

6-(3′,4′-Dimethoxyphenylmethyl)-3,4-dihydro-5-methyl-2-(cyclopentylthio)pyrimidin-4(3H)-one (5): Yield (58%); m.p. 145–146°C.

IR (KBr): 3436 (NH), 1651 (C=O) cm^{-1}.

^{1}H NMR (DMSO-d_6/TMS): δ = 1.54 (m, 4H, 2 × 2 CH_2), 1.96 (s, 3H, CH_3), 2.05 (m, 4H, 2 × CH_2), 3.33 (s, 2H, CH_2), 3.705 (s, 3H, OCH_3), 3.714 (s, 3H, OCH_3), 3.76 (m, 1H, H-S), 6.76 (d, 1H, H-5′), 6.84 (s, 1H, H-6′); 6.87 (s, 1H, H-2′), 12.47 (bs, 1H, NH).

^{13}C NMR (DMSO-d_6/TMS): δ = 10.28 ($\underline{C}H_3$), 24.22 ($\underline{C}_\gamma$-$\underline{C}_\delta$), 32.61 ($\underline{C}_\beta$-C_σ), 42.93 ($\underline{C}_\alpha$), 55.29 (OCH_3), 55.34 (OCH_3), 111.74 ($\underline{C}$-2′), 112.87 ($\underline{C}$-5), 114.60 ($\underline{C}$-5′), 120.71 ($\underline{C}$-6′), 130.57 ($\underline{C}$-1′), 147.28 ($\underline{C}$-4′), 148.44 ($\underline{C}$-3′), 154.80 ($\underline{C}$-6), 158.10 (C=O), 162.10 (C-2).

Mass spectrum (m/z) = 360 (M^+, 84.5), 345 (M^+-CH_3, 4.5), 329 (M^+-OCH_3, 7.3), 327 (M^+-SH, 100), 291 (M^+-cyclopentyl, 35.7), 259 (M^+-S-cyclopentyl, 101), 152 ($^+CH_2$-3,4-dimethoxyphenyl, 12.2), 138 (3,4-dimethoxyphenyl$^+$, 31.3), 101 (S^+-cyclopentyl, 3.7), 91 ($^+CH_2Ph$, 10.2).

$C_{19}H_{24}N_2O_3S$ (360.37), Calc.: C 63.33, H 6.71, N 7.77. Found: C 62.92, H 6.53, N 7.72.

6-(3′,4′-Dimethoxyphenylmethyl)-3,4-dihydro-5-methyl-2-(allylthio)pyrimidin-4(3H)-one (6): Yield (51%), m.p. 155–156°C.

IR (KBr): 3435 (NH), 1659 (C=O) cm^{-1}.

^{1}H NMR (DMSO-d_6/TMS): $\delta = 1.96$ (s, 3H, CH_3), 3.34 (s, 2H, CH_2), 3.62 (d, 2H, CH_2-CH=), 3.74 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 5.14 (dd, 2H, CH_2), 5.85 (m, 1H, CH=CH_2), 6.75 (d, 1H, H-5′), 6.84 (s, 1H, H-6′), 6.88 (s, 1H, H-2′).

^{13}C NMR (DMSO-d_6/TMS): $\delta = 10.33$ ($\underline{C}H_3$), 32.12 ($\underline{C}H_2$), 39.59 (S-$\underline{C}H_2$), 55.29 (OCH_3), 55.44 (OCH_3), 111.81 ($\underline{C}$-2′), 112.79 ($\underline{C}$-5), 117.96 ($\underline{C}H_2$=CH), 120.59 ($\underline{C}$-6′), 126.50 ($\underline{C}H$=CH_2), 133.49 ($\underline{C}$-1′), 147.30 (C-4′), 148.47 ($\underline{C}$-3′), 157.50 ($\underline{C}$-6), 158.50 (C=O), 167.32 (C-2).

Mass spectrum (m/z) = 332 (M^+, 100), 317 (M^+-CH_3, 5.11), 299 (M^+-SH, 38.60), 291 (M^+-CH_2=CH-CH_2, 12.87), 259 (M^+-S-CH_2-CH=CH_2, 3.50), 152 ($^+CH_2$-3,4-dimethoxyphenyl, 3.51), 138 (3,4-dimethoxyphenyl$^+$, 12.87), 91 ($^+CH_2$Ph 5.85).

$C_{17}H_{20}N_2O_3S$ (332.42), Calc.: C 61.42, H 6.06, N 8.43. Found: C 61.29, H 6.18, N 8.39.

6-(3′,4′-Dimethoxyphenylmethyl)-5-methyl-2-[(methylthiomethyl)thio] pyrimidin-4(3H)-one (7): Yield (53%), m.p. 153–155°C; crystallized from ethylacetate/legroin 1 : 1 (v/v).

IR (KBr): 3435 (NH), 1659 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 2.11$ (s, 3H, CH_3), 2.17 (s, 3H, S-CH_3), 3.78 (s, 2H, CH_2), 3.85 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.31 (s, 2H, S-CH_2), 12.55 (s, 1H, NH).

^{13}C NMR ($CDCl_3$): $\delta = 10.70$ ($\underline{C}H_3$-C=), 15.55 (S-$\underline{C}H_3$), 3.67 ($\underline{C}H_2$), 40.62 (S-$\underline{C}H_2$), 55.91 (OCH_3), 111.91 ($\underline{C}$-2′), 112.31 ($\underline{C}$-5), 116.61 ($\underline{C}$-5′), 120.97 ($\underline{C}$-6′), 130.27 ($\underline{C}$-1′), 147.75 (C-4′), 148.90 ($\underline{C}$-3), 155.30 ($\underline{C}$-6), 162.31 (C=O), 165.32 (C-2).

Mass spectrum (m/z) = 352 (20.0), 305 (M^+-S-CH_3, 100), 291 (M^+-CH_2-S-CH_3, 6.3), 259 (M^+-SCH_2S-CH_3, 7.00), 152 ($^+CH_2$-3,4-dimethoxyphenyl, 2.5), 138 (3,4-dimethoxyphenyl$^+$, 6.3), 91 ($^+CH_2$Ph 3.7).

$C_{16}H_{20}N_2O_3S$ (352.45), Calc.: C 54.53, H 5.72, S 18.19. Found: C 54.38, H 5.71, S 18.03.

Reaction of (2) with Ethylbromoacetate: Formation of 6-(3′,4′-Dimethoxyphenylmethyl)-5-methyl-2-[(carboethoxymethyl)thio]pyrimidin-4(3H)-one (8)

To 0.29 g (1 mmol) of (**2**) in 2 ml anhydrous DMF, 0.138 g (1 mmol) of K_2CO_3 and 0.11 ml (1 mmol) of bromoester were added. The reaction mixture was stirred at room temperature for 29 h. TLC (ethylacetate/ligroin 1 : 1 v/v) revealed disappearance of the starting material and appearance of one spot. The reaction mixture was worked up by adding (50 ml) water and extraction with ethylacetate. The aqueous phase was extracted three times

(3×10 ml) with ethylacetate. The combined extractions were washed with saturated NaCl (2×50 ml), dried over $MgSO_4$, filtered and concentrated in vacuo to furnish the title compound (**8**). Yield (59%), m.p. 170–171°C.

IR (KBr): 3435 (NH), 1659 (C=O) cm^{-1}.

^1H NMR ($CDCl_3$): $\delta = 1.22$ (t, 3H, CH_3-CH_2), 2.09 (s, 3H, CH_3-C=), 3.84 (s, 2H, CH_2), 3.87 (s, 2H, SCH_2), 3.88 (s, 6H, OCH_3), 4.13 (q, 2H, CH_2), 6.77 (d, 1H, H-5′), 6.8 (s, 1H, H-6′), 7.26 (s, 1H, H-2′), 12.48 (sb, 1H, NH).

^{13}C NMR ($CDCl_3$): $\delta = 10.55$ ($\underline{C}H_3$-CH_2), 13.99 ($\underline{C}H_3$-C=), 15.55 (S-$\underline{C}H_3$), 32.78 ($\underline{C}H_2$), 40.49 ($\underline{C}H_2$-C=O), 55.85 ($2 \times \underline{C}H_3$), 61.85 ($O\underline{C}H_2$), 111.23 (C-2′), 112.24 (C-5), 116.72 (C-5′), 120.84 (C-6′), 130.35 (C-1′), 147.85 (C-4′), 149.03 (C-3′), 154.97 (C-6), 162.32 (C=O), 165.33 (C-2), 168.52 (O-C=O).

Mass spectrum (m/z) = 378 (M^+, 100), 363 (M^+-CH_3, 5.0), 347 (M^+-OCH_3, 2.0), 333 (m -OEt, 21.3, 305 (M^+ -COOEt, 66.2), 291 (M^+-CH_2-COOEt, 32.5), 259 (M^+ -SCH_2COOEt, 6.5), 152 ($^+CH_2$-3,4-dimethoxyphenyl, 3.1), 138 (3,4-dimethoxyphenyl$^+$, 24.5), 119 ($^+SCH_2COOEt$, 3.5) 91 ($^+CH_2Ph$ 5.0).

$C_{18}H_{22}N_2O_5S$ (378.44), Calc.: C 57.13, H 5.85, N 7.40. Found: C 56. 93, H 5.79, N 7.38.

Reaction of (2) with Ethylbromoacetate: Formation of 6-(3′,4′-Dimethoxyphenylmethyl)-5-methyluracil (9)

A mixture of (**2**) (292 mg, 1 mmol) and ethylbromoacetate (167 g, 1 mmol) was refluxed in enthanol (10 ml) for 18 h (TLC). The solvent was evaporated till dryness under vacuo and the residual solid was crystallized from methanol to afford (**9**) as a colorless crystal. Yield (55%); m.p. 220–222°C.

Reaction of (2) with Chloracetic Acid: Formation of 6-(3′,4′-Dimethoxyphenylmethyl)-5-methyluracil (9)

A mixture of (**2**) (6 g, 20 mmol) and 600 ml (10%) aqueous chloroacetic acid was refluxed for 20 h (TLC). The mixture was cooled to room temperature. The precipitated solid was filtered off and washed with ethanol (15 ml) followed by ether (15 ml) to give (**9**) as a colorless crystals, yield (3.8 g, 67.0%); m.p. 220–222°C.

IR (KBr): 3432 (NH), 3167 (NH), 1707 (C=O), 1664 (C=O) cm^{-1}.

^{1}H NMR (DMSO-d_6/TMS): $\delta = 1.80$ (s, 3H, CH_3), 3.66 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 6.79–6.93 (aromatic H), 10.75 (s, 1H, NH), 11.01 (s, 1H, NH).

^{13}C NMR (DMSO-d_6/TMS): $\delta = 9.72$ ($\underline{C}H_3$-C=), 34.94 ($\underline{C}H_2$), 55.44 ($2 \times OCH_3$), 104.75 (C-5), 111.98, 112.43, 120.04, 128.76 (aromatic carbons), 147.62 (C-6).

$C_{14}H_{16}N_2O_4$ (276.29), Calc.: C 60.86, H 5.84. Found: C 60.81, H 5.83.

Reaction of (9) with Chloromethyl Methyl Ether and/or Chloromethyl Ethyl Ether: Formation of 6-(3′,4′-Dimethoxyphenylmethyl)-1-methoxymethyl-5-methyluracil (10a) and 6-(3′,4′-Dimethoxyphenylmethyl)-1-ethoxymethyl-5-methyluracil (10b)

Compound (**9**) (0.276 g, 1 mmol) was suspended in anhydrous chloroform (20 ml), *N*,*O*-*bis*tri-methylsilyl acetamide (0.60 g, 2.5 mmol) was added while stirring under nitrogen atmosphere at room temperature for 2 h until the solution became clear. The appropriate chloroether (0.15 mmol) was added dropwise and stirring was continued for 8–10 h until the starting material was consumed (TLC). Saturated sod. bicarbonate solution (7 ml) and ethanol (20 ml) were added to the reaction mixture while stirring. The organic layer was separated, washed with water and dried over anhydrous sod. Sulphate to afford (**10a**) and/or (**10b**).

6-(3′,4′-Dimethoxyphenylmethyl)-1-methoxymethyl-5-methyluracil (10a): Yield (55%); m.p. 110–111°C, crystallized from ethylacetate/ligroin 1 : 1 (v/v).

IR (KBr): 3435 (NH), 1659 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 2.20$ (s, 3H, CH_3), 3.50 (s, 3H, O-CH_3), 3.80 (s, 6H, $2 \times OCH_3$), 4.28 (s, 2H, CH_2), 5.10 (s, 2H, OCH_2-N), 6.50–6.80 (m, 3H, aryl-H), 9.8 (s, 1H, NH).

^{13}C NMR ($CDCl_3$): $\delta = 10.75$ ($\underline{C}H_3$-C=), 33.35 ($\underline{C}H_2$), 55.86 ($2 \times O\underline{C}H_3$), 56.88 ($O\underline{C}H_3$), 74.10 ($O\underline{C}H_2$-N), 110.72 (C-5), 111.75 (C-2′), 114.16 (C-5′), 119.1 (C-6′), 126.95 (C-1′), 147.50 (C-4′), 147.80 (C-3′), 149.67 (C-6), 152.11 (C=O), 164.21 (C-2).

Mass spectrum (m/z) = 320 (M^+, 31.9), 289 (M^+-OCH_3, 11.1), 288 (M^+-O_2, 29.6), 275 (M^+-CH_2O-CH_3, 3.7), 138 (3,4-dimethoxyphenyl$^+$, 5.18), 91 ($^+CH_2Ph$, 6.66).

$C_{16}H_{20}N_2O_5$ (320.34), Calc.: C 59.99, H 6.29, N 8.74. Found: C 60.11, H 5.95, N 8.62.

6-(3′,4′-Dimethoxyphenylmethyl)-1-ethoxymethyl-5-methyluracil (10b): Yield (43%); m.p. 130–131°C, crystallized from ethylacetate/ligroin 1 : 1 (v/v).

IR (KBr): 3423 (NH), 1689 (C=O), 1627 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): $\delta = 1.20$ (t, 3H, CH_3), 2.03 (s, 3H, CH_3-C=), 3.62 (q, 2H, CH_2-CH_3), 3.85 (3, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 5.16 (s, 2H, OCH_2-N), 6.63 (d, 1H, H-5′), 6.79 (s, 1H, H-2′), 6.80 (d, 1H, H-6′), 8.67 (s, 1H, NH).

^{13}C NMR ($CDCl_3$): $\delta = 10.96$ ($\underline{C}H_3$-CH_2), 15.07 ($\underline{C}H_3$-C=), 33.52 ($\underline{C}H_2$-CH_3), 55.95 ($2 \times OCH_3$), 56.95 ($\underline{C}H_2$), 72.076 (OCH_2), 74.10 (OCH_2-N), 110.72 (C-5), 111.75 (C-2′), 114.16 (C-5′), 119.2 (C-6′), 148.38 (C-1′), 149.62 (C-4′), 149.92 (C-3′), 155.50 (C-6), 159.21 (C=O), 163.66 (C-2).

Mass Spectrum (m/z) = 334 (M^+, 25.9), 303 (M^+-OCH_3, 3.7), 288 (M^+-EtOH, 45.88), 275 (M^+-CH_2O-C_2H_5, 4.4), 186 ($^+CH_2$-3,4-dimethoxyphenyl, 7.4), 138 (3,4-dimethoxyphenyl$^+$, 14.1), 107 ($^+$PhOMe, 8.14), 91 ($^+CH_2Ph$, 2.96), 77. ($^+$Ph, 8.14), 59 ($CH_3CH_2OCH_2^+$, 21.46).

$C_{17}H_{22}N_2O_5$ (334.37), Calc.: N 8.38. Found: N 7.94.

ACKNOWLEDGMENT

I'm really indebted to Prof. Dr. E. B. Pedersen for much kind advice and fruitful discussions as well as for giving me the chance to carry out this research work at his laboratory in Chemistry Department, Odense University, Denmark.

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Received in the USA May 10, 2001