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Synthesis of Pyrimidine Annelated Heterocycles [1]. Regioselective Heterocyclization of 6-Cyclopent-2-enyl-5-hydroxy-1,3-dimethylpyrimidine-2,4(*1H*,*3H*)-dione and 5-Cyclopent-2-enyl-6-hydroxy-1,3-dimethylpyrimidine-2,4(*1H*,*3H*)-dione

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Summary. Two hitherto unreported pyrimidine annelated heterocycles were synthesized from 6-cyclopent-2-enyl-5-hydroxy-1,3-dimethylpyrimidine-2,4(*1H*,*3H*)-dione and 5-cyclopent-2-enyl-6-hydroxy-1,3-dimethylpyrimidine-2,4(*1H*,*3H*)-dione by reaction with pyridine hydrotribromide or hexamethylenetetramine hydrotribromide. The first one was also obtained by reaction with concentrated sulfuric acid.

Keywords. Pyridine hydrotribromide; Heterocycles; Cyclization; Hexamethylenetetramine hydrotribromide; 6-*endo* Cyclization.

Introduction

Pyrimidine derivatives are important due to their proven biological activity and medicinal utility [2–9]. We have recently reported the synthesis of a number of pyrimidine annelated heterocycles [10–12]. Here we report a simple and regioselective synthesis of a number of hitherto unknown pyrimidine annelated heterocycles.

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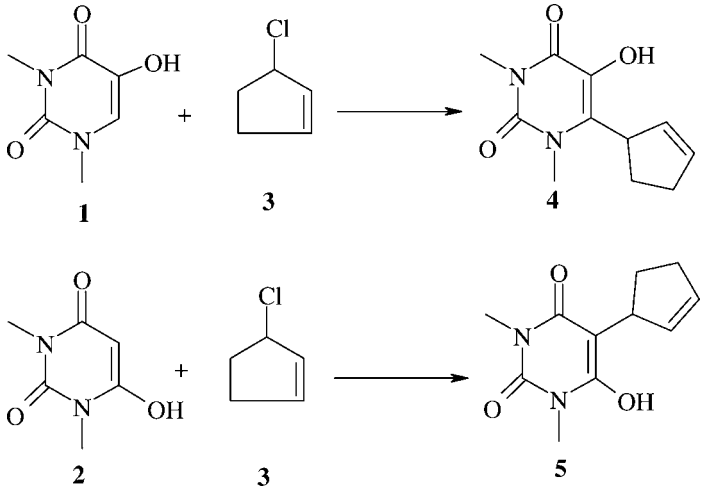
Results and Discussion

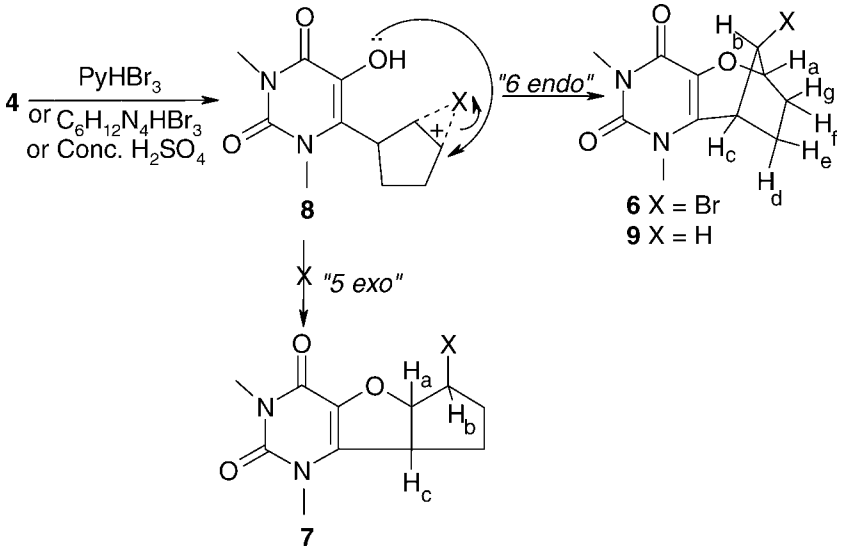
The starting materials **4** and **5** for this study were easily obtained from the reaction of 1,3-dimethyl-5-hydroxyuracil (**1**) and 1,3-dimethyl-6-hydroxyuracil (**2**) with 3-chloro-cyclopentene (**3**) in refluxing acetone in the presence of anhydrous potassium carbonate for 20 and 8 h (Scheme 1).

Recently, we have reported the use of pyridine hydrotribromide [13–19] and hexamethylenetetramine hydrotribromide [20] for this type of heterocyclization. Thus, **4** was treated with one equivalent of pyridine hydrotribromide or hexamethylenetetramine hydrotribromide in chloroform at 0–5°C for 30 min. to give the bridged tricyclic bromo compound **6** (80%). The product was characterized by its elemental analysis and spectral data. The IR spectrum of **6** showed $\bar{\nu}_{max} = 1700\,cm^{-1}$ due to a carbonyl group. Two structures, **6** and **7**, may be considered for the product. The ^1H NMR spectrum showed three nonequivalent protons, a one proton triplet at $\delta = 3.91$ ppm ($J = 8$ Hz) assignable to H_c, a one proton broad singlet at $\delta = 4.57$ ppm assignable to H_a, and a one proton doublet at $\delta = 5.37$ ppm ($J = 8$ Hz) assignable to H_b. From the splitting pattern and the coupling constant values it is clear that H_b and H_c are vicinal protons. This clearly shows that the product has the bridged tricyclic structure **6** instead of the linearly fused structure **7** where H_b and H_c are not at adjacent carbons.

Final confirmation for the structure of **6** came from its ^{13}C NMR, DEPT, COSY, and HETCOR experiments. The COSY spectrum of compound **6** shows that proton H_a at $\delta = 4.57$ ppm correlates with protons H_f and H_g at $\delta = 2.91$–2.24 ppm, proton H_b at $\delta = 5.37$ ppm correlates with proton H_c at $\delta = 3.91$ ppm, and H_c correlates with a proton resonance at $\delta = 2.48$–2.59 ppm (H_d/H_e). H_d, H_e, H_f, and H_g are correlated with each other. The ^{13}C chemical shifts of compound **6** were assigned by DEPT and HETCOR experiments. Multiplicity was established by DEPT experiment. DEPT showed seven protonated carbons, two $-CH_3$, three $>CH-$, and two $-CH_2-$. Protonated carbon resonances were established by direct correlation with proton resonances by a HETCOR experiment (normal one bond C–H



Scheme 1

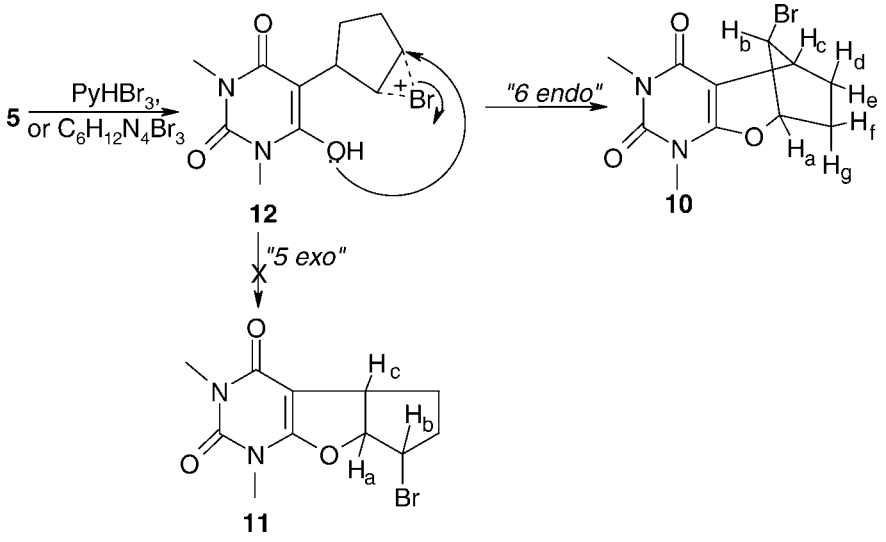


Scheme 2

coupling). Methyl protons (NMe) resonance at $\delta = 3.34$ ppm is related to a carbon resonance at $\delta = 28.68$ ppm and the other methyl protons signal at $\delta = 3.38$ ppm (NMe) is related to a carbon resonance at $\delta = 32.87$ ppm. Methine proton resonance at $\delta = 4.57$ ppm (H_a) is related to a carbon resonance at $\delta = 53.37$ ppm (C_8) and two methine protons resonances at $\delta = 5.37$ (H_b) and 3.91 ppm (H_c) are related to carbon resonances at $\delta = 93.51$ (C_{12}) and 45.63 ppm (C_{11}). Methylene protons resonance at $\delta = 2.48$–2.59 ppm (H_f, H_g) is related to the carbon resonance at $\delta = 33.47$ ppm (C_9), another two methylene protons resonances at $\delta = 2.19$–2.24 and 1.87–1.97 ppm (H_d, H_e) are related with a carbon resonance at $\delta = 29.51$ ppm (C_{10}).

The mass spectrum of **6** showed molecular ion peaks at $m/z = 300$, 302. Final confirmation for the structure **6** was gained from the observation that **6** remained unchanged upon treatment with alcoholic KOH at reflux for 2 h or on heating with palladised charcoal in diphenyl ether at 260°C for 2 h (Scheme 2). Therefore, the alternating structure **7** was ruled out on the basis of chemical and spectroscopic evidence.

Cold conc. H_2SO_4 has been widely used for the cyclization of *ortho*-allyl phenols [21–23] and other related substrates [24, 25]. Thus, **4** was treated with conc. H_2SO_4 at 0–5°C to give a white solid. This was characterized as the bridged tricyclic product **9** by its elemental analysis and spectral data. The IR spectrum of **9** showed $\bar{\nu}_{max} = 1700\,cm^{-1}$ due to the carbonyl group. The ^1H NMR spectrum of **9** revealed a one proton broad singlet at $\delta = 3.29$ ppm due to the proton H_c and a one proton broad singlet at $\delta = 4.91$ ppm due to the proton H_a. The mass spectrum of **9** showed a molecular ion peak at $m/z = 222$. ^{13}C NMR showed eleven carbon atoms and DEPT experiment showed seven protonated carbon atoms, two $-CH_3$, three $>CH_2$, and two $>CH-$. Confirmation for structure **9** came from the observation that the product **9** remained unchanged when heated with palladised charcoal in diphenyl ether at 260°C for 2 h. (Scheme 2).



Scheme 3

The substrate **5** was similarly treated with one equivalent of pyridine hydrotribromide or hexamethylenetetramine hydrotribromide to afford a gummy mass. This was characterized as the bridged tricyclic bromo compound **10** by its elemental analysis and spectral data. The IR spectrum of **10** showed $\bar{\nu}_{max} = 1690\,\mathrm{cm}^{-1}$ due to a carbonyl group. Two structures **10** and **11** may be considered for the product. The ^{1}H NMR spectrum showed three lone protons, one a triplet at $\delta = 3.99$ ppm ($J = 8$ Hz) assignable to H_c, a broad singlet at $\delta = 4.47$ ppm assignable to H_a, and a doublet at $\delta = 5.49$ ppm ($J = 8$ Hz) assignable to H_b. ^{13}C NMR showed eleven carbon atoms and DEPT experiment showed seven protonated carbon atoms, two $-CH_3$, two $>CH_2$, and three $>CH-$. Arguments presented for assignment of structure **6** were extended to this product and bridged tricyclic structure **10** was assigned to it instead of the linearly fused structure **11** (Scheme 3). As proton H_a appears as a broad singlet in compounds **6** and **10** it is not easily possible to specify the particular diastereoisomer for the product. However, the chemical shift of proton H_b (a doublet) being at relatively down field ($\delta = 5.37$ (**6**) and 5.49 ppm (**10**)) indicate that the proton is in the deshielding cone of the $>C=O$. Thus, the products may be assigned as diastereoisomers with *exo*-Br (**6** and **10**). The mass spectrum of **10** showed molecular ion peaks at $m/z = 300$, 302. Final confirmation for structure **10** could be reached when it was found that **10** remained unchanged on treatment with alcoholic KOH at reflux for 2 h and on heating with palladised charcoal in diphenyl ether at 260°C for 2 h.

The formation of products **6**, **9**, and **10** from **4** and **5** may be explained *via* the formation of the ionic intermediates **8a**, **8b**, and **12**, which may then undergo a "6-*endo*" cyclization to give the products **6**, **9**, and **10** [26].

In conclusion the heterocyclization of **4** and **5** was found to be regioselective with pyridine hydrotribromide, hexamethylenetetramine hydrotribromide, and cold conc. H_2SO_4 to give the bridged tricyclic heterocycles **6**, **9**, and **10**.

Experimental

Melting points were measured in a sulfuric acid bath and are uncorrected. UV absorption spectra were recorded in EtOH on a Hitachi 200–20 spectrophotometer. IR spectra were run on KBr disks on a Perkin-Elmer 1330 apparatus. ^{1}H NMR Spectra were determined for solutions in $CDCl_3$ with *TMS* as internal standard on a 200 MHz spectrometer (Bruker). ^{13}C NMR Spectra were measured of 75 MHz. Elemental analyses results agreed favorably with the calculated values and recording of mass spectra was carried out by RSIC (CDRI) Lucknow on a JEOL D-300 (El) instrument. Silica gel (60–120 mesh), Spectrochem, India, was used for chromatographic separations. Petroleum ether refers to the fraction boiling between 60 and 80°C.

6-Cyclopent-2-enyl-5-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**4**, $C_{11}H_{14}N_2O_3$)

A mixture of 1.56 g of **1** (10 mmol), 1.02 g of **3** (10 mmol), and 3 g of anhydrous K_2CO_3 in 100 cm^3 of dry acetone was refluxed on a water bath for 20 h. The reaction mixture was cooled, filtered, and the solvent was removed. The residue was extracted with 3×25 cm^3 of $CHCl_3$, the organic layer was separated, washed with 2×25 cm^3 of H_2O, dried (Na_2SO_4), and the solvent was evaporated. Purification of the crude product by column chromatography (ethylacetate:benzene = 1:9) over silica gel gave **4**. Yield: 65%; white solid; mp 144°C; ^{1}H NMR: $\delta = 1.7$–2.7 (m, 4H), 3.42 (s, N–CH_3), 3.43 (s, N–CH_3), 4.40–4.47 (m, 1H), 5.71–5.79 (m, 1H), 5.91–5.97 (m, 1H) ppm; IR (KBr): $\bar{\nu} = 1070, 1600, 1690, 2900, 3300$ cm^{-1}; UV-Vis (EtOH): $\lambda_{max} = 215, 291$ nm; MS: $m/z = 222$ (M^+).

5-Cyclopent-2-enyl-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**5**, $C_{11}H_{14}N_2O_3$)

A mixture of 1.56 g of 1,3-dimethylbarbituric acid (10 mmol), 1.02 g of 3-chlorocyclopentene (10 mmol), and 3 g of anhydrous K_2CO_3 in 100 cm^3 of dry acetone was refluxed for 8 h. The reaction mixture was cooled, filtered, and the solvent was removed. The residue was extracted with 3×25 cm^3 of $CHCl_3$, the organic layer was separated, washed with 2×25 cm^3 of water, dried (Na_2SO_4), and the solvent was evaporated. Purification of the crude product by column chromatography (benzene:petroleum-ether = 3:1) over silica gel gave **5**. Yield: 55%; gummy mass; ^{1}H NMR: $\delta = 1.97$–2.36 (m, 4H), 3.26 (s, N–CH_3), 3.30 (s, N–CH_3), 3.48–3.54 (m, 1H), 5.56–5.59 (m, 1H), 5.89–5.92 (m, 1H) ppm; IR (neat): $\bar{\nu} = 1120, 1700, 2980, 3420$ cm^{-1}; UV-Vis (EtOH): $\lambda_{max} = 214$, 260 nm; MS: $m/z = 222$ (M^+).

(10-anti)-10-Bromo-6,7,8,9-tetrahydro-1,3-dimethyl-6,9-methanooxepano[2,3-e]-pyrimidine-2,4(1H,3H)-dione (**6**, $C_{11}H_{13}BrN_2O_3$)

A solution of 0.33 g of **4** (1.5 mmol) in 100 cm^3 of $CHCl_3$ was stirred with 0.45 g of pyridine hydrotribromide (1.5 mmol) or 0.58 g hexamethylenetetramine hydrotribromide (1.5 mmol) at 0–5°C for 1 h. The $CHCl_3$ solution was washed with 2×25 cm^3 of 5% Na_2CO_3 solution, then with 2×25 cm^3 of H_2O, and dried (Na_2SO_4). Evaporation of $CHCl_3$ left a gummy residue. This was purified by column chromatography over silica gel. Compound **6** was obtained when the column was eluted with ethylacetate:benzene = 1:3. Yield: 80%; white solid; mp 168°C; ^{1}H NMR: $\delta = 1.89$–1.97 (m, 1H), 2.19–2.24 (m, 2H), 2.48–2.59 (m, 1H), 3.34 (s, N–CH_3), 3.38 (s, N–CH_3), 3.91 (t, $J = 8$ Hz, H_c), 4.57 (brs, H_a), 5.37 (d, $J = 8$ Hz, H_b) ppm; ^{13}C NMR: $\delta = 28.68, 29.51, 32.87, 33.47, 45.63, 53.37, 93.51, 132.15, 136.37, 151.72$ (>C=O), 155.12 (>C=O); IR (KBr): $\bar{\nu} = 1110, 1700, 2970$ cm^{-1}; UV-Vis (EtOH): $\lambda_{max} = 218$, 299 nm; MS: $m/z = 300$, 302 (M^+).

6,7,8,9-Tetrahydro-1,3-dimethyl-6,9-methanooxepano[2,3-e]-pyrimidine-2,4(1H,3H)-dione (**9**, $C_{11}H_{14}N_2O_3$)

To 2 cm^3 of concentrated H_2SO_4 0.22 g of **4** (1 mmol) were added in portions at 0–5°C and the mixture was stirred for 2 h at this temperature. The solution was then poured into crushed ice and extracted with 3×25 cm^3 of $CHCl_3$. The $CHCl_3$ layer was washed with 3×10 cm^3 of 5% Na_2CO_3 solution, then with 3×20 cm^3 of H_2O, and dried (Na_2SO_4). Evaporation of $CHCl_3$ gave a gummy mass. This was purified by column chromatography over silica gel. Elution of the column with benzene:ethylacetate = 3:1 gave **9**. Yield: 75%; white solid; mp 128°C; ^{1}H NMR: $\delta = 1.56$–2.3 (m, 6H), 3.29 (brs, H_c), 3.42 (s, N–CH_3), 3.48 (s, N–CH_3), 4.91 (brs, H_a) ppm; ^{13}C NMR: $\delta = 27.89$, 30.11, 31.93, 31.95, 32.16, 33.64, 33.69, 126.79, 135.90, 150.12 (>C=O), 158.18 (>C=O); IR (KBr): $\bar{\nu} = 1140$, 1700, 2970 cm^{-1}; UV-Vis (EtOH): $\lambda_{max} = 216$, 296 nm; MS: $m/z = 222$ (M^+).

(10-anti)-10-Bromo-5,6,7,8-tetrahydro-1,3-dimethyl-5,8-methanooxepano[3,2-e]-pyrimidine-2,4(1H,3H)-dione (**10**, $C_{11}H_{13}BrN_2O_3$)

A solution of 0.33 g of **5** (1.5 mmol) in 100 cm^3 of $CHCl_3$ was stirred with 0.45 g of pyridine hydrotribromide (1.5 mmol) or 0.58 g of hexamethylenetetramine hydrotribromide (1.5 mmol) at 0–5°C for 1 h. The $CHCl_3$ solution was washed with 2×25 cm^3 of 5% Na_2CO_3 solution, then with 2×25 cm^3 of H_2O, and dried (Na_2SO_4). Evaporation of $CHCl_3$ left a gummy residue. This was purified by column chromatography over silica gel. Compound **10** was obtained when the column was eluted with benzene:petroleum ether = 1:1. Yield: 70%; gummy mass; ^{1}H NMR: $\delta = 2.04$–2.57 (m, 4H), 3.30 (s, 6H, N–CH_3), 3.99, (t, $J = 8$ Hz, H_c), 4.47 (brs, H_a), 5.49 (d, $J = 8$ Hz, H_b) ppm; ^{13}C NMR: $\delta = 28.90$, 29.73, 33.09, 33.68, 45.83, 53.57, 93.71, 131.32, 135.59, 151.97 (>C=O), 156.32 (>C=O); IR (neat): $\bar{\nu} = 1110, 1690, 2970$ cm^{-1}; UV-Vis (EtOH): $\lambda_{max} = 216$, 299 nm; MS: $m/z = 300$, 302 (M^+).

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