Monatshefte für Chemie 132, 633–638 (2001)

Monatshefte für Chemie
Chemical Monthly

Studies on Pyrimidines: Synthesis of Pyrimidine-Annelated Heterocycles from 5-Amino-6-cyclohex-2-enyl-1,3-dimethyl-uracil

Krishna C. Majumdar* and **Nirmal K. Jana**

Department of Chemistry, University of Kalyani, Kalyani-741235, India

Summary. Treatment of 5-amino-6-cyclohex-2-enyl-1,3-dimethyl-uracil with pyridinium hydrotribromide or hexamethylenetetrammonium hydrotribromide furnished the corresponding linear heterocyclic 6-bromo-1,3-dimethylhexahydroindolo[3,2-*d*]pyrimidine-2,4-diones in 90% yield. Reaction of the same educt with molecular bromine in chloroform afforded the bicyclic 9-bromo-1,3-dimethylhexahydrobicyclo[3.3.1]indolo[3,2-*d*]pyrimidine-2,4-diones in 85% yield. Upon treatment of the above substrate with cold concentrated sulfuric acid, a mixture of 1,3-dimethylhexahydroindolo[3,2-*d*]pyrimidine-2,4-dione (28%) and 1,3-dimethylhexahydrobicyclo[3.3.1]indolo[3,2-*d*]pyrimidine-2,4-dione (60%) was obtained.

Keywords. Amino-*Claisen* rearrangement; Cyclization; Cyclohexene; Heterocycles; Pyridine hydrotribromide.

Introduction

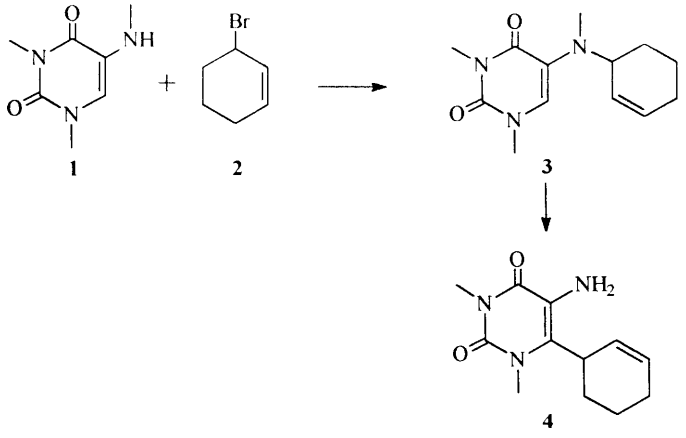
Recently there has been considerable activity in the synthesis of pyrimidine derivatives due to their biological activity and medicinal utility [1]. We have reported the synthesis of a number of pyrimidine-annelated heterocycles fused at positions 5 and 6 of uracil [2]. In continuation of this work, we tackled the problem of the regioselective synthesis of a number of hitherto unreported pyrimidine-annelated heterocycles from 5-amino-6-cyclohex-2-enyl-1,3-dimethyluracil (**4**). The results of this investigation is reported here.

Results and Discussion

The starting material for this study, **4**, was obtained in 38% yield by the amino-*Claisen* rearrangement of 5-(N-(cyclohex-2-enyl)-N-methyl)-1,3-dimethyluracil (**3**) in refluxing EtOH/HCl for 10 h. In turn, **3** was prepared in 80% yield by the reaction of 1,3-dimethyl-5-N-methylamino-uracil (**1**) with 3-bromocyclohexene (**2**) in refluxing acetone in the presence of anhydrous potassium carbonate (Scheme 1).

The structures of **3** and **4** were assigned from their elemental analyses and spectroscopic data. Thus, the IR spectrum of **3** showed the absence of an N–H

* Corresponding author



Scheme 1

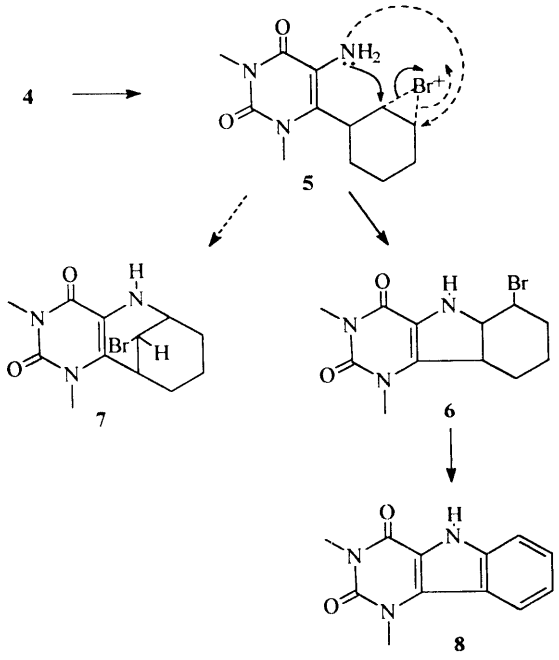
absorption band; its ^{1}H NMR spectrum consisted of three N–CH_3 singlets and a two multiplets of ethylenic protons, together with the singlet of the C_6–H of the uracil moiety. The IR spectrum of **4** exhibited an N–H absorption band, and its ^{1}H NMR spectrum exhibited two N–CH_3 singlets, two ethylenic multiplets and one multiplet accounting for eight aliphatic protons. The molecular ion peak in the mass spectrum of **4** appeared at $m/z = 235$ (M^+).

Two approaches were considered for the cyclization of **4**. The first one involved brominating agents like pyridinium hydrotribromide [3] (*Py*HBr_3), hexa-methylenetetrammonium hydrotribromide [4] ($C_6H_{12}N_4HBr_3$), and bromine. When **4** was treated with *Py*HBr_3 in dichloromethane at 0–5°C for 30 minutes, the novel linearly fused bromocompound **6** was obtained in 90% yield. The same product in the same yield resulted also from the reaction of $C_6H_{12}N_4HBr_3$ in dichloromethane at 0–5°C for 15 minutes. However, treatment of **4** with bromine in chloroform at 0–5°C for 6 h afforded the novel bicyclic bromocompound **7** in 85% yield.

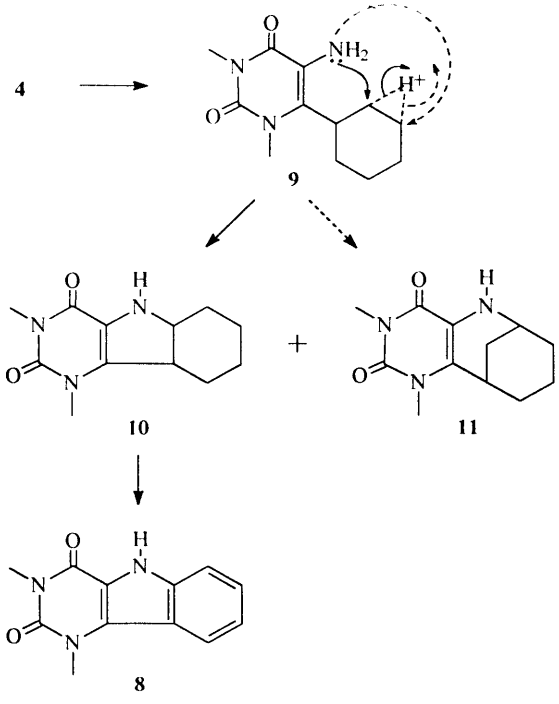
The formation of the cyclic products **6** and **7** from **4** may be easily explained *via* an intermediate cyclic bromonium ion (**5**). This may be opened by the nucleophilic attack of NH_2 group to give products **6** and **7** instead of the dibromide. Compound **6** was dehydrogenated with 10% palladized charcoal in refluxing diphenyl ether for 30 minutes to give **8** in 91% yield. When compound **7** was treated similarly, only unchanged starting material was recovered (Scheme 2).

The structures of compounds **6**, **7**, and **8** were established from their elemental analyses and spectroscopic data. The IR spectra of all compounds showed broad N–H absorption bands at 3320 cm^{-1}, their ^{1}H NMR spectra were in accordance with the proposed structures. The mass spectra of both **6** and **7** gave the same molecular ion peak at $m/z = 315$, 313 (M^+); the molecular ion peak of **8** was observed at m/z 229 (M^+).

The second approach proceeded *via* an acid catalyzed cyclization [5] of **4**. Thus, **4** was treated with concentrated sulfuric acid at 0–5°C for 2 h to furnish **10** and **11**. Refluxing compound **10** in diphenyl ether with 10% palladized charcoal gave **8** as verified by TLC and mixed melting point determinations with an authentic sample. When **11** was treated similarly, only unchanged starting material was recovered (Scheme 3).



Scheme 2



Scheme 3

Compounds **10** and **11** were characterized by their elemental analyses and spectroscopic data. The ^{1}H NMR spectrum of **10** showed a multiplet for eight cyclohehexenyl protons and two ring juncture protons. The ^{1}H NMR spectrum of **11** exhibited similar but shifted peaks. The mass spectra of **10** and **11** gave the same molecular ion peak at $m/z = 235$ (M^+).

In conclusion, **4** was regioselectively cyclized under simple and mild reaction conditions to give different pyrimidine-annelated heterocycles in excellent yields, the cyclization with molecular bromine being especially noteworthy.

Experimental

Melting points are uncorrected. UV/Vis spectra were recorded on a Hitachi 200-20 spectrophotometer (absolute ethanol). IR spectra were run as KBr discs on a Perkin-Elmer 1330 apparatus. ^{1}H NMR spectra were recorded in $CDCl_3$ with *TMS* as internal standard on a 300 MHz spectrometer (Bruker). Elemental analyses (data in accordance with the calculated values) and mass spectra were obtained from RSIC (CDRI), Lucknow. Silica gel (60–120) was purchased from Spectrochem. Extracts were dried over anhydrous Na_2SO_4.

5-(N-(Cyclohex-2-enyl)-N-methyl)-1,3-dimethylamino-uracil (**3**; $C_{13}H_{19}N_3O_2$)

A mixture of 16.9 g **1** (0.1 mol), 16.1 g **2** (0.1 mol), and 3 g anhydrous K_2CO_3 was refluxed in 200 cm^3 dry acetone on a water bath for 10 h. The reaction mixture was then cooled and filtered. The solvent was removed, and the residue was extracted with 3×50 cm^3 $CHCl_3$, washed with H_2O, and dried over Na_2SO_4. Removal of the solvent gave a crude mass which was chromatographed over silica eluting with ethyl acetate-benzene (1:3) to give **3**.

Yield: 80%; viscous liquid; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 6.59 (s, 1H), 5.61–5.87 (m, 2H), 4.23 (m, 1H), 3.38 (s, 3H), 3.36 (s, 3H), 2.55 (s, 3H), 1.53–2.03 (m, 6H) ppm; IR (neat): $\nu = 2950$, 1680, 1630, 1450 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 217$ (10657), 309 (4058) nm; MS: $m/z = 249$ (M^+).

5-Amino-6-(cyclohex-2-enyl)-1,3-dimethyluracil (**4**; $C_{12}H_{17}N_3O_2$)

A mixture of 10 g **3** (0.04 mol), 60 cm^3 EtOH, and 3 cm^3 concentrated HCl was refluxed on a water bath for 10 h. The reaction mixture was evaporated to dryness, cooled, neutralized with $NaHCO_3$ solution, and extracted with ether. The organic layer was washed with H_2O and dried over Na_2SO_4. Ether was distilled off, and the product was obtained by column chromatography over silica (ethyl acetate:benzene = 1:9).

Yield: 38%; m.p.: 170–172°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 5.59–5.89 (m, 2H), 4.07–4.10 (m, 1H), 3.42 (s, 3H), 3.38 (s, 3H), 1.65–2.10 (m, 8H) ppm; IR (KBr): $\nu = 3280$, 2900, 1680, 1605 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 213$ (4958), 289 (5663) nm; MS: $m/z = 235$ (M^+).

Cyclization of **4** with brominating agents

Solid pyridinum hydrotribromide (0.9 g, 3 mmol) was added slowly to 20 cm^3 of a well-stirred solution of 0.705 g (3 mmol) **4** in CH_2Cl_2 at 0–5°C, and stirring was continued for 30 min. The reaction mixture was washed with H_2O and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography over silica (ethyl acetate:benzene = 1:1). When **4** was treated similarly with hexamethylenetetrammonium hydrotribromide in a CH_2Cl_2 solution at 0–5°C for 15 minutes, also **6** was formed. When, however, 3 cm^3 Br_2 in 30 cm^3 $CHCl_3$ were added to 0.705 g **4** (3 mmol) in 30 cm^3 $CHCl_3$ at 0–5°C, **7** was obtained. Stirring was continued for 6 h, and

after usual workup the residue was subjected to column chromatography (silica, ethyl acetate: benzene = 1:3). The product was recrystallised from ethanol.

6-Bromo-1,3-dimethylhexahydroindolo[3,2-d]pyrimidine-2,4-dione (**6**; $C_{12}H_{16}BrN_3O_2$; mixture of diastereomers)

Yield: 90%; gummy mass; ^{1}H NMR ($CDCl_3, \delta, 300$ MHz): 4.86 (m, 1H), 3.59 (s, 3H), 3.41 (s, 3H), 2.79–2.89 (m, 1H), 2.63–2.73 (m, 1H), 2.09–2.10 (m, 1H), 1.39–2.06 (m, 6H) ppm; IR (neat): $\nu = 2940$, 1700, 1650, 1440 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 218$ (2215), 300 (1874) nm; MS: $m/z = 315$, 313 (M^+).

9-Bromo-1,3-dimethylhexahydrobicyclo[3.3.1]indolo[3,2-d]pyrimidine-2,4-dione (**7**; $C_{12}H_{16}BrN_3O_2$; mixture of diastereomers)

Yield: 85%; m.p.: 150°C; ^{1}H NMR ($CDCl_3, \delta, 300$ MHz): 4.71–4.75 (m, 2H), 3.38 (s, 3H), 3.36 (s, 3H), 3.28–3.32 (m, 1H), 2.06–2.15 (m, 3H), 1.68–1.83 (m, 1H), 1.55–1.67 (m, 2H), 1.21–1.32 (m, 1H) ppm; IR (KBr): $\nu = 2940$, 1700, 1650, 1440 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 218$ (2235), 300 (1954) nm; MS: $m/z = 315$, 313 (M^+).

Attempted dehydrogenation of **6** and **7**

Compound **6** (0.314 g, 1 mmol) was refluxed with 0.1 g 10% Pd/C in 2 cm^3 diphenyl ether for 30 min. It was then subjected to column chromatography over silica. Diphenyl ether was eluted with petrol ether, and **8** was obtained when the column was eluted with ethyl acetate: benzene = 1:9. The product was recrystallized from EtOH. Similarly, **7** was refluxed with 10% Pd/C in diphenyl ether for 1 h. However, only unchanged starting material was recovered in this case.

1,3-Dimethyl-indolo[3,2-d]pyrimidine-2,4-dione (**8**; $C_{12}H_{11}N_3O_2$)

Yield: 91%; m.p.: 225°C; ^{1}H NMR ($CDCl_3, \delta, 300$ MHz): 7.94–7.96 (m, 1H), 7.60–7.68 (m, 2H), 7.39–7.44 (m, 1H), 3.92 (s, 3H), 3.51 (s, 3H) ppm; IR (KBr): $\nu = 2940$, 1700, 1640, 1440 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 220$ (19007), 294 (12252) nm; MS: $m/z = 229$ (M^+).

Cyclization of **4** in concentrated sulfuric acid

Compound **4** (0.705, 3 mmol) was added to 4 cm^3 of well-stirred concentrated sulfuric acid at 0–5°C, and stirring was continued for 2 h at this temperature. The reaction mixture was poured onto crushed ice and extracted with 3×20 cm^3 $CHCl_3$. The $CHCl_3$ extract was washed with 2×25 cm^3 5% $NaHCO_3$ solution, 2×25 cm^3 H_2O, and dried over Na_2SO_4. Removal of the solvent gave a crude mass which was subjected to column chromatography over silica. **10** and **11** were obtained as white solids using ethyl acetate:benzene = 1:3 as the eluent.

1,3-Dimethylhexahydroindolo[3,2-d]pyrimidine-2,4-dione (**10**; $C_{12}H_{17}N_3O_2$; mixture of diastereomers)

Yield: 28%; m.p.: 124°C; ^{1}H NMR ($CDCl_3, \delta, 500$ MHz): 4.57–4.56 (m, 1H), 3.41 (s, 3H), 3.38 (s, 3H), 2.98–3.00 (m, 1H), 2.35–2.38 (m, 1H), 1.55–2.05 (m, 6H), 1.24–1.32 (m, 2H) ppm; IR (KBr): $\nu = 2940$, 1700, 1650, 1440 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 217$ (5617), 300 (5006) nm; MS: $m/z = 235$ (M^+).

1,3-Dimethylhexahydrobicyclo[3.3.1]indolo[3,2-d]pyrimidine-2,4-dione (**11**; $C_{12}H_{17}N_3O_2$; mixture of diastereomers)

Yield: 60%; m.p.: 84°C; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 4.60 (s, 1H), 3.40 (s, 3H), 3.36 (s, 3H), 3.06 (s, 1H), 2.17–2.20 (m, 1H), 1.82–1.96 (m, 4H), 1.48–1.68 (m, 4H) ppm; IR (KBr): $\nu = 2940$, 1690, 1630, 1430 cm^{-1}; UV/Vis (EtOH): $\lambda_{max}(\varepsilon) = 216$ (9235), 293 (8201) nm; MS: $m/z = 235$ (M^+).

Attempted dehydrogenation of **10** and **11**

Compound **10** (0.05 g, 0.2 mmol) was refluxed with 0.01 g Pd/C (10%) in 2 cm^3 diphenyl ether for 2 h. The formation of **8** was monitored by TLC and confirmed by a mixed melting point with an authentic sample. Compound **11** was treated similarly, but no change was observed and the starting material was recovered.

Acknowledgements

We are grateful to CSIR (New Delhi) for financial assistance. *N. K. Jana* is grateful to CSIR (New Delhi) for a fellowship.

References

[1] a) Griengl H, Bodenteich M, Hayden W, Wanek E, Streicher W, Stutz P, Bachmayer H, Ghazzouli I, Rosenwirth B (1985) J Med Chem **28**: 1679; b) Macilwain C (1993) Nature **365**: 378; c) Chu CK, Schinagi RF, Ahn MK, Ulas GV, Gu ZP (1989) J Med Chem **32**: 612; d) Miyasaka T, Tanaka H, Baba M, Hayakawa H, Walker RT, Balzarini J, de Clercq E (1989) J Med Chem **32**: 2507; e) de Clercq E (1993) Medicinal Res Rev **13**: 229

[2] a) Majumdar KC, Das U (1997) J Chem Res (S), 309; (M), 2062; b) Majumdar KC, Das U (1997) Synth Commun **27**: 4013; c) Majumdar KC, Das U, Jana NK (1998) J Org Chem **63**: 3550; d) Majumdar KC, Das U (1998) J Org Chem **63**: 9997

[3] a) Majumdar KC, Choudhury PK, Nethaji M (1994) Tetrahedron Lett **35**: 5927; b) Majumdar KC, Kundu AK (1993) Indian J Chem **32B**: 605; c) Majumdar KC, Kundu AK (1995) Can J Chem **73**: 1727; d) Majumdar KC, Kundu AK, Chatterjee P (1996) Synth Commun **26**: 893; e) Majumdar KC, Das U, Kundu AK (1998) Synth Commun **28**: 1593

[4] Majumdar KC, Kundu AK, Chatterjee P (1996) Synth Commun **26**: 4023

[5] Majumdar KC, Khan AT, Gupta AK, Kundu AK, Choudhury PK (1992) Indian J Chem **31B**: 667

Received August 4, 2000. Accepted (revised) November 15, 2000