Synthesis of new 6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione derivatives containing the substituted aliphatic ring

R. F. Papoyan,[a] L. A. Khachatryan,[a] G. A. Panosyan,[b] and V. T. Kochikyan[c]*

[a] *Yerevan State University,*
1 A. Manukyan str., 0025 Yerevan, Armenia
[b] *Molecular Structure Research Center of Scientific-Technological Center of Organic and Pharmaceutical Chemistry,*
National Academy of Sciences of the Republic of Armenia,
26 Azatutyan aven., 0014 Yerevan, Armenia
[c] *Scientific and Production Center Armbiotechnology, National Academy of Sciences of the Republic of Armenia,*
14 Gyurdzhyan str., 0056 Yerevan, Armenia.
E-mail: ruxanpapoyan@yahoo.com

The bromination of 6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (**1**) resulted in the substitution in the aliphatic ring. The reaction of this product with different N-nucleophiles gives new derivatives of the starting compound. The direction of the substitution in the alicycle was established by studying further transformations of some of these compounds by means of NMR spectroscopy.

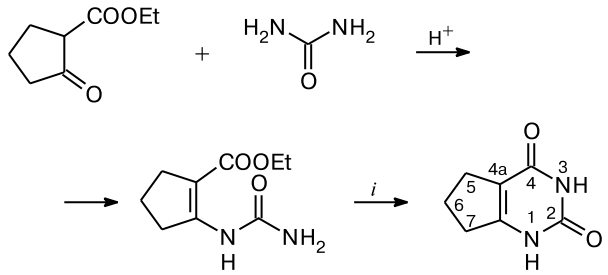
Key words: pyrimidine-2,4(1*H*,3*H*)-diones; uracils; piperidine, methylpiperazine, morpholine, pyrrolidine, azepane, hydrazine.

Derivatives of pyrimidine-2,4(1*H*,3*H*)-dione (uracil) possess unique properties due to their low toxicity and a wide range of biological activity, such as immune-stimulating, anti-inflammatory, antitumor, antiviral, and so on.[1] Uracil derivatives containing halogen atoms are widely used as antitumor agents (fluorouracil, dopan). Compounds containing cyclic amines, for instance, morpholine, piperazine, piperidine, and so on, in the substituent are used as antihypertensive agents (urapidil, ketanserin).[2] Compounds containing piperidine or morpholine rings exhibit high psychotropic activity.[3]

In spite of the fact that alicycle-fused uracils also possess a wide range of biological activity,[4,5] these systems are poorly known, which is apparently because they are difficulty accessible. Hence, the search of new efficient compounds in this series is an important problem.

The target systems were synthesized starting from cyclopentane-fused uracil **1**, which was prepared by the reaction of 1-ethoxycarbonylcyclopentan-2-one with urea in two steps[6] (Scheme 1).

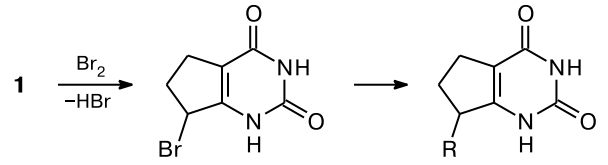
Scheme 1



1

i. Anion-exchange resin A-550.

Scheme 2



2 **3a—f**

R = $N(CH_2)_5$ (**a**), $N(CH_2CH_2)_2NCH_3$ (**b**), $N(CH_2CH_2)_2O$ (**c**), $N(CH_2)_4$ (**d**), $N(CH_2)_6$ (**e**), $NHNH_2$ (**f**)

The bromination of **1** in glacial acetic acid at 5—10 °C was accompanied by the substitution in the aliphatic ring to form compound **2** (Scheme 2). The position of the bromine atom was determined by analyzing the NMR spectra of the products of further transformations of **2**.

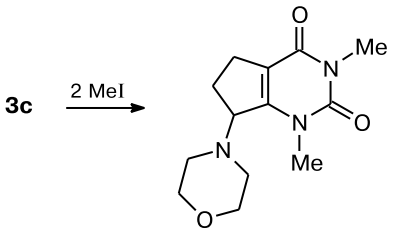
The reactions of **2** with different N-nucleophiles, such as piperidine, methylpiperazine, morpholine, pyrrolidine, azepane, and hydrazine, were performed in ethanol in the presence of an excess of the corresponding amine (see Scheme 2).

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1639—1641, August, 2012.

N-Alkylated uracil derivatives also have great practical value and are widely used in the clinical practice (aminometradine, amisometradine, urapidil). These heterocyclic derivatives often have similar therapeutic properties but lower toxicity compared to unsubstituted analogs.[7] Hence, the alkylation of the synthesized compounds is a promising method for the synthesis of new biologically active compounds. At the same time, the spectra of N-alkylated derivatives of uracil are more informative and provide evidence for the direction of the substitution in product **2**.

Based on the foregoing, we performed the methylation of **3c**. Due to the presence of several active centers in the uracil ring, the alkylation usually affords a mixture of products. However, after the heating with a twofold molar excess of methyl iodide in a KOH aqueous solution under reflux, only N(1),N(3)-dialkylated derivative **4** of the starting compound was isolated as the reaction product (Scheme 3).

Scheme 3



4

An analysis of the chemical shifts of methyl groups in the ^{1}H and ^{13}C NMR spectra of compound **4** shows that the methylation occurs at both nitrogen atoms. The presence of the NOE signal between the protons H(7) and N(1)Me in the 2D NOESY spectrum indicates that the morpholine group is bound to C(7). For the N(3)Me group, no NOE signals are observed because this group is far remote from the other protons. Hence, the bromination of uracil **1** also occurs at the C(7) atom.

The structures of the synthesized compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopy. The assignment of the signals in the NMR spectra was made using the HMQC and DEPT methods.

Experimental

The NMR spectra were measured on a Varian Mercury-300Vx spectrometer (300.08 and 75.46 MHz for ^{1}H and ^{13}C, respectively) in a 1 : 3 DMSO-d_6—CCl_4 solution at 30 °C. The chemical shifts are given with respect to $SiMe_4$ as the internal standard. The individuality and purity of the synthesized compounds were confirmed by TLC on Silufol UV-254 plates; the spots were visualized with iodine vapor. Elemental analyses of solid samples were carried out on a EuroVector EA 3000-Single analyzer.

7-Bromo-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4-(3*H*,5*H*)-dione (2). A solution of bromine (30 mL) in glacial acetic acid (50 mL) was added to a suspension of uracil **1** (9 g, 0.06 mol) in glacial acetic acid (25 mL) with cooling to 5—10 °C. The reaction mixture was stirred at room temperature for 2 h. The precipitate that formed was filtered off and successively washed on a filter with acetic acid and diethyl ether. White crystals were obtained in a yield of 11 g (73%); the crystals decompose at 220 °C. Found (%): C, 36.72; H, 3.27; N, 12.51. $C_7H_7BrN_2O_2$. Calculated (%): C, 36.39; H, 3.05; N, 12.12. R_f 0.7 (CH_3COOH—EtOH (3 : 0.5)). ^{1}H NMR, δ: 2.34 and 2.48—2.69 (both m, 1 H, 3 H, H(5), H(6)); 5.12 (dd, 1 H, H(7), J = 6.0 Hz, J = 2.2 Hz); 10.71 and 11.07 (both br.s, 1 H each, NH). ^{13}C NMR, δ: 24.6, 33.8 (C(5), C(6)); 49.3 (C(7)); 112.1 (C(4a)); 151.6, 153.0, 161.2 (NC).

Synthesis of compounds 3a—f (general procedure). The corresponding nucleophile (0.04 mol) was added to a suspension of compound **2** (0.02 mol) in ethanol (100 mL). The reaction mixture was stirred at room temperature for 4—6 h (monitoring by TLC). The crystals that precipitated were filtered off and successively washed on a filter with ethanol and diethyl ethanol.

7-(Piperidin-1-yl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (3a). The reaction mixture was stirred for 5 h. Yield 3.8 g (81%), m.p. 248—250 °C (sublim.). Found (%): C, 61.31; H, 7.24; N, 17.81. $C_{12}H_{17}N_3O_2$. Calculated (%): C, 61.26; H, 7.28; N, 17.86. ^{1}H NMR, δ: 1.41 and 1.47—1.59 (both m, 2 H, 4 H, β,β′,γ-CH_2, piperidine); 1.87 and 2.02 (both m, 1 H each, H(6)); 2.30—2.46 (m, 6 H, H(5), α,α′-CH_2, piperidine); 4.03 (dd, 1 H, H(7), J = 8.7 Hz, J = 4.3 Hz); 10.65 (br.s, 2 H, NH). ^{13}C NMR, δ: 20.5, 24.0, 25.0 (C(5), C(6), γ-CH_2, piperidine); 25.6 (β,β′-CH_2, piperidine); 49.0 (α,α′-CH_2, piperidine); 68.1 (C(7)); 110.9 (C(4a)); 152.2, 153.7, 161.9 (NC).

7-(4-Methylpiperazin-1-yl)-6,7-dihydro-1*H*-cyclopenta[*d*]-pyrimidine-2,4(3*H*,5*H*)-dione (3b). The reaction mixture was stirred for 6 h. Yield 3.8 g (76%), m.p. 248—250 °C (sublim.). Found (%): C, 57.62; H, 7.29; N, 22.31. $C_{12}H_{18}N_4O_2$. Calculated (%): C, 57.58; H, 7.25; N, 22.38. ^{1}H NMR, δ: 1.90 and 2.02 (both m, 1 H each, H(6)); 2.17 (s, 3 H, NMe); 2.27—2.48 (m, 10 H, H(5), NCH_2); 4.06 (dd, 1 H, H(7), J = 8.5 Hz, J = 4.0 Hz); 10.60 (br.s, 1 H, NH); 10.70 (br.s, 1 H, NH). ^{13}C NMR, δ: 20.8, 25.0 (C(5), C(6)); 45.6 (NMe); 47.4, 54.6 (NCH_2); 67.2 (C(7)); 111.1 (C(4a)); 152.2, 153.2, 161.9 (NC).

7-Morpholino-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4-(3*H*,5*H*)-dione (3c). The reaction mixture was stirred for 5 h. Yield 3.7 g (78%), m.p. 250 °C (sublim.). Found (%): C, 55.73; H, 6.25; N, 17.75. $C_{11}H_{15}N_3O_3$. Calculated (%): C, 55.69; H, 6.37; N, 17.71. ^{1}H NMR, δ: 1.94 and 2.06 (both m, 1 H each, H(6)); 2.36—2.52 (m, 6 H, H(5), NCH_2); 3.59 (m, 4 H, OCH_2); 4.03 (dd, 1 H, H(7), J = 8.5 Hz, J = 4.3 Hz); 10.54 (br.s, 1 H, NH); 10.62 (br.s, 1 H, NH). ^{13}C NMR, δ: 20.9, 24.9 (C(5), C(6)); 48.2 (NCH_2); 66.1 (OCH_2); 67.6 (C(7)); 111.2 (C(4a)); 152.1, 152.5, 161.5 (NC).

7-(Pyrrolidin-1-yl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (3d). The reaction mixture was stirred for 3 h. Yield 3.6 g (81%), m.p. 260 °C (sublim.). Found (%): C, 59.66; H, 6.83; N, 19.06. $C_{11}H_{15}N_3O_2$. Calculated (%): C, 59.71; H, 6.83; N, 18.99. ^{1}H NMR, δ: 1.72 (m, 4 H, β,β′-CH_2, pyrrolidine); 1.93—2.01 (m, 2 H, H(6)); 2.36—2.51 (m, 2 H, H(5)); 2.55 (m, 4 H, α,α′-CH_2, pyrrolidine); 4.16 (br.s, 1 H, H(7)); 10.57 (br.s, 2 H, NH). ^{13}C NMR, δ: 22.5, 24.9 (C(5), C(6)); 23.0

(β,β′-CH_2, pyrrolidine); 47.9 (α,α′-CH_2, pyrrolidine); 63.2 (C(7)); 110.5 (C(4a)); 152.1, 153.7, 161.8 (NC).

7-(Azepan-1-yl)-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4(3*H*,5*H*)-dione (3e). The reaction mixture was stirred for 4 h. Yield 3.9 g (78%), m.p. 248—251 °C (sublim.). Found (%): C, 62.60; H, 7.73; N, 16.83. $C_{13}H_{19}N_3O_2$. Calculated (%): C, 62.63; H, 7.68; N, 16.85. ^{1}H NMR, δ: 1.49—1.72 (m, 8 H, β,β′,γ,γ′-CH_2, $C_6H_{12}N$); 1.87 and 2.04 (both m, 1 H each, H(6)); 2.32—2.48 (m, 2 H, H(5)); 2.56 (m, 4 H, α,α′-CH_2, $C_6H_{12}N$); 4.13 (m, 1 H, H(7)); 10.45 (br.s, 2 H, NH). ^{13}C NMR, δ: 21.9, 24.4 (C(5), C(6)); 26.3, 28.9 (β,β′,γ,γ′-CH_2, $C_6H_{12}N$); 50.7 (α,α′-CH_2, $C_6H_{12}N$); 68.9 (C(7)); 110.3 (C(4a)); 152.1, 154.2, 161.7 (NC).

7-Hydrazino-6,7-dihydro-1*H*-cyclopenta[*d*]pyrimidine-2,4-(3*H*,5*H*)-dione (3f). The reaction mixture was stirred for 4 h. Yield 2.9 g (80%), m.p. 250 °C (sublim.). Found (%): C, 46.19; H, 5.50; N, 30.69. $C_7H_{10}N_4O_2$. Calculated (%): C, 46.15; H, 5.53; N, 30.75. ^{1}H NMR, δ: 1.91 and 2.09 (both m, 1 H each, H(6)); 2.29 and 2.44 (both m, 1 H each, H(5)); 4.07 (m, 1 H, H(7)); 5.50 (br.s, 3 H, $NHNH_2$); 10.75 (br.s, 2 H, NH).

1,3-Dimethyl-7-morpholino-6,7-dihydro-1*H*-cyclopenta[*d*]-pyrimidine-2,4(3*H*,5*H*)-dione (4). Compound **3c** (2.4 g, 0.01 mol) was added to a solution of potassium hydroxide (1.1 g, 0.02 mol) in water (50 mL). The reaction mixture was stirred for 1 h, and then methyl iodide (4 g, 0.028 mol) was added. The mixture was stirred at room temperature for 3 h and then refluxed for 4 h until pH reached 7. The solution was extracted with diethyl ether and concentrated. The crystals that precipitated were washed with chloroform and dried. The yield of the crystals was 1.6 g (61%), m.p. 173 °C. Found (%): C, 58.91; H, 7.18; N, 15.88. $C_{13}H_{19}N_3O_3$. Calculated (%): C, 58.85; H, 7.22; N, 15.84. ^{1}H NMR, δ: 1.85 and 2.21 (both m, 1 H each, H(6)); 2.45 (m, 4 H, NCH_2); 2.49—2.65 (m, 2 H, H(5)); 3.20 (s, 3 H, N(3)Me); 3.46 (s, 3 H, N(1)Me); 3.52—3.63 (m, 4 H, OCH_2); 4.29 (dt, 1 H, H(7), J = 8.8 Hz, J = 2.2 Hz). ^{13}C NMR, δ: 18.8 (C(6)); 26.4 (C(5)); 27.1 (N(3)Me); 31.0 (N(1)Me); 47.6 (NCH_2); 66.2 (OCH_2); 68.0 (C(7)); 112.4 (C(4a)); 150.4, 152.1, 159.7 (NC).

References

1. M. Debi, *Indian J. Exp. Biol.*, 1997, **35**, 1208; G. P. Connoly, J. A. Duley, *Trends Pharm. Sci.*, 1999, **20**, 218; M. S. Novikov, A. A. Ozerov, O. G. Sim, R. W. Buckheit, *Khim. Geterotsikl. Soedin.*, 2004, **42** [*Chem. Heterocycl. Compd.*, 2004, **40**, 37 (*Engl. Transl.*)]; M. S. Novikov, A. A. Ozerov, Yu. A. Orlova, R. W. Buckheit, *Khim. Geterotsikl. Soedin.*, 2005, 726 [*Chem. Heterocycl. Compd.*, 2005, **41**, 625 (*Engl. Transl.*)]; N. N. Karkishchenko, Zh. K. Aslanyants, *Farmakologiya i toksikologiya* [*Pharmacology and Toxicology*], 1989, **52**, 100 (in Russian); M. D. Mashkovskii, *Lekarstvennye sredstva* [*Drugs*], Novaya Volna, Moscow, 2010, 1216 pp. (in Russian).
2. H. Wamhoff, J. Dzenis, K. Hirota, *Adv. Heter. Chem*, 1992, **55**, 132.
3. G. Beaton, *J. Med. Chem.*, 1988, **44**, 6419.
4. US Pat.7,638,520 B2 (2009).
5. US Pat. 0212937 (2011).
6. R. F. Papoyan, *Uchenye zapiski EGU* [*Scientific Proceedings of the Yerevan State University*], 2010, 38 (in Armenian).
7. E. P. Studentsov, *Izv. Sankt-Peterb. gos. tekhn. un-ta [Bull. St. Petersburg State Tech. Univ.*], 2009, 3 (in Russian).

Received November 17, 2011;
in revised form March 14, 2012