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Synthesis of Macrocyclic Pyrimidine Derivatives

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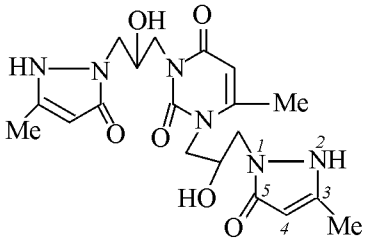
Abstract—A reaction was studied of previously unknown 1,3-bis(2-hydroxy-3-chloropropyl)uracil, 1,3-bis(2-hydroxy-3-chloropropyl)-6-methyluracil, and 1,3-bis(2-hydroxy-3-chloropropyl)-5-fluorouracil with 1,3-bis[3-(3-methyl-2*H*-5-pyrazolon-1-yl)-2-hydroxypropyl]-6-methyluracil.

Pyrimidine derivative found recently wide application as biologically active compounds and pharmaceuticals [1]. Pyrimidine derivatives are characterized by antiphlogistic activity [2, 3]. Among them should be mentioned mebron (or mepyrizol), 3-methyl-5-methoxy-1-(6-methyl-4-methoxy-2-pyrimidyl)pyrazole, applied as antiphlogistic drug [4].

We showed formerly that pyrimidine derivatives possessed immunotropic, antiphlogistic, and membrane-stabilizing activity [5–9]. One of them (hydroxymethyluracil) got permission to be used as a medicine.



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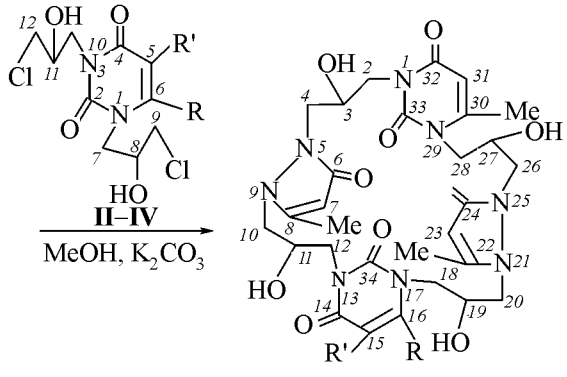

II–IV

MeOH, K_2CO_3

V–VII

R = R' = H (**II, V**); R = CH_3, R' = H (**III, VI**); R = H, R' = F (**IV, VII**).

We developed a synthetic pattern for the synthesis of macrocyclic pyrimidine derivatives aiming at preparation of new biologically active compounds.

Along this procedure were obtained macrocyclic pyrimidine derivatives: 3,11,19,27-tetrahydroxy-8,22,30-trimethyl-1,5,9,13,17,21,25,29-octaazapentacyclo[27.3.1.1^{13,17}.0^{5,9}.0^{21,25}]tetratriaconta-7,15,22,30-tetraene-6,14,24,32,33,34-hexaone (**V**), 3,11,19,27-tetrahydroxy-8,16,22,30-tetramethyl-1,5,9,13,17,21,25,29-octaazapentacyclo[27.3.1.1^{13,17}.O^{5,9}.0^{21,25}]tetratriaconta-7,15,22,30-tetraene-6,14,24,32,33,34-hexaone (**VI**), 3,11,19,27-tetrahydroxy-8,22,30-trimethyl-15-fluoro-1,5,9,13,17,21,25,29-octaazapentacyclo[27.3.1.1^{13,17}.0^{5,9}.0^{21,25}]tetratriaconta-7,15,22,30-tetraene-6,14,24,32,33,34-hexaone (**VII**) by reaction in methanol solution of 1,3-bis[3-(3-methyl-2*H*-5-pyrazolon-1-yl)-2-hydroxypropyl]-6-methyluracil (**I**) [10] with 1,3-bis(2-hydroxy-3-chloropropyl)uracil (**II**), 1,3-bis(2-hydroxy-3-chloropropyl)-6-methyluracil (**III**), and 1,3-bis(2-hydroxy-3-chloropropyl)-5-fluorouracil (**IV**). Dichloro compounds **II–IV** were obtained by reaction of uracil, 6-methyluracil, and 5-fluorouracil with epichlorohydrin.

The replacement of chlorine in compounds **II–IV** by the secondary nitrogen from compound **I** occurs readily at boiling in methanol in the presence of potassium carbonate. The structure of compounds obtained was confirmed by ^{1}H, ^{13}C, and IR spectra, their composition by elemental analysis, their homogeneity by TLC. In the IR spectra of all compounds appear absorption bands in the region 1620–1720 cm^{-1}, the characteristic bands of pyrimidine fragment vibrations [ν(C=O, =N–C=O)]. The absorption bands in the region 1060–1240 cm^{-1} are usually observed in the spectra of compounds containing tertiary nitrogen atoms (–N=), the absorption bands in the 3300–3400 cm^{-1} region belong to the

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stretching vibrations of the OH bonds. In the spectra of all compounds a band is observed at 3400 cm^{-1} corresponding to hydroxy group attached to atoms $C^{3,11}$ and involved into a hydrogen bond.

In the ^{13}C NMR spectra of all compounds the carbons from uracil moiety appear as usual at 164.4; 162.53 ($C^{32,34}$); 157.0 ($C^{8,16,22,30}$); 153.0 ($C^{33,34}$); 98.53 ppm ($C^{15,31}$). Also are observed signals at 12.97 ($CH_3C^{8,22}$); 14.62 ppm ($CH_3C^{16,30}$).

In the molecules of compounds obtained was found a strong hydrogen bond between hydroxy groups of the substituents and oxo groups; the bond is not destroyed in solutions. This hydrogen bond results in strong difference in the chemical shifts in the ^{13}C NMR spectrum of peaks corresponding to carbons in substituents at N^1 and N^3 of pyrimidine moiety; also the signals from atoms C^{15} and C^{31} are shifted upfield from their initial locations characteristic of unsubstituted uracils and 6-methyluracil. In the spectra of compounds **V–VII**) the signals from atoms $C^{6,24}$ appear in the 168 ppm region, and signals of carbon atoms of the double bond from the pyrazole fragment are observed in 100 ppm region.

In the ^1H NMR spectra of compounds **II, V** the proton signals in positions $C^{15,16}$ and $C^{30,31}$ of uracil are observed as doublets with *J* 6–7.5 Hz. The probable formation of two diastereomers at centers C^3, C^{11}, C^{19}, C^{27} was not observed. In the ^{13}C NMR spectra no double sets of signals was found, although signals from C^3, C^{11}, C^{19}, C^{27} were broadened apparently due to dynamic process of hydrogen bonds formation between hydroxy groups at C^3, C^{11}, C^{19}, C^{27} and carbonyl groups at C^{14}, C^{32}, C^{33}, C^{34}.

EXPERIMENTAL

^1H and ^{13}C NMR spectra were registered on spectrometer Bruker AM-300 at operating frequencies 300 and 75.7 MHz respectively from solutions in $CDCl_3$ or D_2O of concentrations 1% or 10–20% respectively. Chemical shifts of carbons are given in δ scale (ppm) with respect to TMS. IR spectra were recorded on spectrophotometer UR-20 (Carl Zeiss Jena) with NaCl and LiF prisms from thin liquid films or mulls in mineral oil. Melting points were measured on Boetius heating block. Elemental analyses were performed on C-H-N Analyzer M-185B. The reaction progress was monitored and homogeneity of compounds was checked by TLC on Silufol UV-254 plates, eluent ethanol-aqueous ammonia, 4:1, development under UV irradiation (λ 254 nm) or in iodine vapor.

1,3-Bis(2-hydroxy-3-chloropropyl)-5-fluorouracil (IV) was prepared in 80% yield similarly to 1,3-bis(2-hydroxy-3-chloropropyl)uracil [10] from 13.0 g (0.1 mol) of 5-fluorouracil, 100 ml DMF, 4.5 g (0.03 mol) of K_2CO_3, and 25 ml [29.5 g (0.32 mol) of epichlorohydrin (1-chloro-2,3-epoxypropane). Thick yellow fluid, well soluble in water, sparingly soluble in chloroform, acetone. IR spectrum, cm^{-1}: 560, 616, 690 [ν(CCl)], 1000 [ν(CF)], 1248, 1288 [ω CH_2Cl)]; 1624, 1650, 1710 [ν(C=O, =N-CO)], 3450 (OH). ^{13}C NMR spectrum (D_2O), δ, ppm: 161 (C^4≡O, J_{C-F} 20 Hz); 151 (C^3=O), 139 (C^5, J_{C-F} 251 Hz); 129 (C^6, J_{C-F} 20 Hz); 71.1 ($C^{8,11}$); 51.2 (C^7); 44.8 (C^{10}). Found, %: C 38.60; H 4.60; Cl 22.0; F 5.85; N 8.90. $C_{10}H_{13}Cl_2FN_2O_4$. Calculated, %: C 38.11; H 4.16; Cl 22.50; F 6.03; N 8.89.

3,11,19,27-Tetrahydroxy-8,22,30-trimethyl-1,5,9,13,17,21,25,29-octaazapentacyclo-[27.3.1.1^{13,17}.0^{5,9}.0^{21,25}]tetratriaconta-7,15,22,30-tetraene-6,14,24,32,33,34-h”x`°n (V). To a mixture of 5.1 g (0.0088 mol) of 1,3-bis[2-hydroxy-3-(3-methyl-2*H*-5-pyrazolon-1-yl)propyl]-6-methyluracil (**I**), 7.0 g (0.051 mol) of K_2CO_3, 1 g of catalyst (tetrabutylammonium bromide) was added at room temperature within 20 min 2.6 g (0.0088 mol) of 1,3-bis(2-hydroxy-3-chloropropyl)uracil(II) in 50 ml of methanol. The stirring at this temperature continued for 1 h, and the reaction mixture was left overnight. On the next day the reaction mixture was stirred at reflux for 4 h, cooled, and salts (4.1 g) were filtered off. From the filtrate was evaporated methanol to obtain 7.7 g of potassium salt as thick dark fluid. Found, %: C 41.86; H 5.63; K 14.50; N 13.40. $C_{29}H_{38}K_3N_8O_{10}$–$3H_2O$. Calculated, %: C 42.12; H 5.00; K 14.18; N 13.55. The salt obtained was dissolved in 100 ml of methanol, the solution was diluted with 150 ml of acetone, pH of the solution was adjusted to neutral with concn. HCl. The solution turned light-yellow, the separated crystals and insoluble initial compound were filtered off, from the filtrate the solvent was distilled off to furnish 4.7 g (75%) of compound **V**, insoluble in hexane. The product obtained was again dissolved in methanol and passed through a glass column charged with silica gel. The column was additionally washed with methanol, the combined eluates were evaporated to afford 3.1 g (50%) of thick yellow fluid, R_f 0.54 (ethanol–aqueous ammonia, 4:1). IR spectrum, cm^{-1}: 1060–1250 (–N=), 1380 (δS CH_3), 1630, 1660, 1710 [ν(C=O, =NC=O)], 3490 [ν(OH)]. ^1H NMR spectrum (D_2O), δ, ppm: 2.1 s, 2.12 s, 2.15 s (9H, CH_3, $C^{8,22,30}$); 2.4–2.7 m (4H, $C^{2,12}H_2$); 3.3–3.9 m

(12H, $C^{4,10,18,20,26,28}H_2$); 3.9–4.0 m (4H, $C^{3,11,19,27}H$); 5.27 s (2H, $C^{7,23}H$); 5.68 s (2H, $C^{15,31}H$); 6.31 s (4H, 4CHOH), 8.0 d (1H, C^{16}, *J* 7.3 Hz). ^{13}C NMR spectrum (D_2O), δ, ppm: 166.52 ($C^{6,24}$); 163.20 ($C^{14,32}$); 157.06 ($C^{8,22,30}$); 153.47 ($C^{33,34}$); 147.17 (C^{16}); 102.55 (C^{15}); 101.6 ($C^{7,23}$); 99.90 (C^{31}); 70.48 ($C^{11,19}$); 67.00 (C^{27}); 64.31 (C^{3}); 56.44 (C^{10}); 56.37 (C^{20}); 50.0 (C^{18}); 46.90 ($C^{2,12}$); 45.20 (C^{28}); 36.0 (C^{4}); 35.70 (C^{26}); 14.00 (CH_3–C^{30}); 12.90 (CH_3–$C^{8,22}$). Found, %: C 48.9; H 7.7; N 15.32. $C_{29}H_{38}N_8O_{10}$–$3H_2O$. Calculated, %: C 48.88; H 6.22; N 15.72.

3,11,19,27-Tetrahydroxy-8,16,22,30-tetramethyl-1,5,9,13,17,21,25,29-octaazapentacyclo[27.3.1.1^{13,17}.O^{5,9}.0^{21,25}]tetratriaconta-7,15,22,30-tetraene-6,14,24,32,33,34-hexaone (VI). To a mixture of 14.5 g (0.025 mol of compound **I**, 20.0 g (0.145 mol) of K_2CO_3, 3 g of catalyst (tetrabutylammonium bromide) was added 8.2 g (0.025 mol) of 1,3-bis(2-hydroxy-3-chloropropyl)-6-methyluracil (**III**) in 100 ml of methanol. The stirring at room temperature continued for 2 h, then the mixture was brought to boiling and stirred at reflux for 4 h On cooling the salts (14.4 g) were filtered off, and methanol was distilled off to furnish residue of 23.4 g. It was dissolved in a mixture of 50 ml of acetone and 50 ml of DMF, the separated crystals (9.2 g of KCl) were filtered off, and on distilling off the solvent from the filtrate we obtained 17.2 g (77%) of compound well soluble in water, DMF, and acetone. R_f 0.79. Found, %: C 44.50; H 6.40; K 4.50; N 13.63; Cl 1.48. $C_{30}H_{40}KN_8O_{10}$–$5H_2O$. Calculated, %: C 44.94; H 6.28; K 4.88; N 13.97.

The salt obtained was dissolved in 150 ml of methanol, the solution was diluted with 150 ml of acetone, pH of the solution was adjusted to neutral with concn. HCl (2 ml). Therewith the solution from bright-red turned orange. On cooling the solution was passed through a column charged with silica gel and activated carbon. From the transparent solution the solvent was evaporated in a vacuum of a water-jet pump, and we obtained 10.4 g (55%) of compound **VI** as thick light-brown fluid, R_f 0.60. IR spectrum, cm^{-1}: 1060–1250 (–N=), 1380 (δ_S CH_3), 1630, 1660, 1710 [ν(C=O, =NC=O)], 3490 [ν(OH)]. ^1H NMR spectrum (D_2O), δ, ppm: 2.1 s, 2.13 s (12H, $CH_3C^{8,16,22,30}$); 2.7–2.9 m (4H, $C^{2,12}H_2$); 3.3–3.9 m (12H, $C^{4,10,18,20,26,28}H_2$); 3.9–4.0 m (4H, $C^{3,11,19,27}H$); 5.27 s (2H, $C^{7,23}H$); 5.68 s (2H, $C^{15,31}H$); 6.31 s (4H, 4OH). ^{13}C NMR spectrum (D_2O), δ, ppm: 168.9 ($C^{6,24}$); 162.4 ($C^{14,32}$); 157.86 ($C^{14,30}$); 157.06 ($C^{8,22}$); 153.47 ($C^{33,34}$); 99.02 ($C^{7,23}$); 98.53 ($C^{15,31}$); 69.03 (C^{19}); 67.28 (C^{11}); 66.73 (C^{27}); 64.98 (C^{3}); 56.44 (C^{10}); 56.37 (C^{20}); 48.7 (C^{28}); 47.80 (C^{18}); 46.90 (C^{2}); 45.90 (C^{12}); 35.88 (C^{4}); 35.50 (C^{26}); 14.60 ($CH_3C^{16,30}$); 12.90 ($CH_3C^{8,22}$). Found, %: C 47.3; H 7.4; N 14.35. $C_{30}H_{40}N_8O_{10}$–$5H_2O$. Calculated, %: C 47.24; H 6.61; N 14.69.

3,11,19,27-Tetrahydroxy-8,22,30-trimethyl-15-fluoro-1,5,9,13,17,21,25,29-octaazapentacyclo-[27.3.1.1^{13,17}. 0^{5,9}.0^{21,25}]tetratriaconta-7,15,22,30-tetraene-6,14,24,32,33,34-hexaone (VII). To a mixture of 5.3 g (0.0091 mol) of 1,3-bis[2-hydroxy-3-(3-methyl-2*H*-5-pyrazolon-1-yl)propyl]-6-methyluracil (**I**), 7.28 g (0.053 mol) of K_2CO_3, 1 g of catalyst (tetrabutylammonium bromide) was added 2.9 g (0.0091 mol) of 1,3-bis(2-hydroxy-3-chloropropyl)-5-fluorouracil (**IV**) in 50 ml of methanol. The stirring at this temperature continued for 1 h, and the reaction mixture was left overnight. On the next day the reaction mixture was stirred at reflux for 4 h and left overnight. The salts (6.1 g of KCl) were filtered off. From the filtrate the solvent was evaporated to obtain 7.3 g of the reaction product. Found, %: C 42.8; H 7.2; F 2.0; K 9.32; N 13.43. $C_{29}H_{37}FKN_8O_{10}$–$3H_2O$. Calculated, %: C 43.06; H 5.36; F 2.34; K 9.67; N 13.85.

The salt obtained was dissolved in 100 ml of acetone–methanol mixture (1:1), and the solution was neutralized with concn. HCl (2 ml); therewith the solution changed color from red to yellow. The precipitated salts were filtered off, and the filtrate was subjected to column chromatography on silica gel, eluent acetone–methanol, 1:1. Yield of compound **VII** 50%, thick yellow-brown fluid, R_f 0.52 (ethanol–aqueous ammonia, 4:1). IR spectrum, cm^{-1}: 980, 1010–1400 (ν CF), 1030–1250 (–N=), 1380 (δ_S CH_3), 1630, 1660, 1710 [ν(C=O, =NC=O)], 3490 [ν(OH)]. ^1H NMR spectrum (D_2O), δ, ppm: 2.02 s (6H, CH_3, $C^{8,22}$); 2.05 s (3H, CH_3, C^{30}); 2.7–2.9 m (4H, $C^{2,12}H_2$); 3.5–3.9 m (12H, $C^{4,10,18,20,26,28}H_2$); 3.9 m (4H, $C^{3,11,19,27}H$); 5.27 s (2H, $C^{7,23}H$); 5.68 s (1H, $C^{31}H$); 6.31 s (4H, 4OH), 7.48 s (1H, C^{16}). ^{13}C NMR spectrum (D_2O), δ, ppm: 168.9 ($C^{6,24}$); 162.4 (C^{32}); 162.3 d ($C^{14,}$ J_{C-F} 19 Hz); 157.90 ($C^{22,30}$); 153.20 ($C^{33,34}$); 139.0 (C^{15} J_{C-F} 249 Hz); 130.9 ($C^{16,}$ J_{C-F} 19 Hz); 99.0 ($C^{7,23}$); 98.80 (C^{31}); 67.88 ($C^{11,}44^{19,27}$); 64.90 (C^{3}); 56.04 (C^{10}); 55.45 (C^{20}); 50.36 (C^{28}); 47.80 (C^{18}); 46.90 (C^{2}); 46.30 (C^{12}); 35.80 ($S^{4,26}$); 14.60 (SH_3C^{30}); 12.90

($CH_3C^{8,22}$). Found, %: S 45.00; N 6.7; F 2.0; N 14.3. $C_{29}H_{37}FN_8O_{10}$–$5H_2O$. Calculated, %: C 45.44; H 6.21; F 2.48; N 13.65.

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