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Synthesis of α,ω-Bis(3-methyl- or 3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)alkanes

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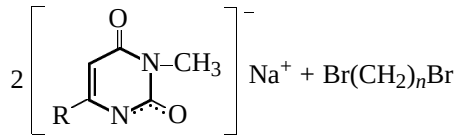
Abstract — The reactions of stoichiometric amounts of sodium salts of 2-hydroxy-3-methyl-4-oxo-3,4-dihydropyrimidine or 2-hydroxy-3,6-dimethyl-4-oxo-3,4-dihydropyrimidine and dibromoalkanes in dimethylformamide were used to synthesize α,ω-bis(3-methyl- or 3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyirimidinyl)alkanes with 1 and 3–5 methylene units in the hydrocarbon brigde.

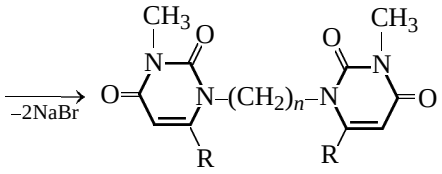
Derivatives of 2,4-dioxo-1,2,3,4-tetrahydropyrimidine (uracil), linked with each other by a hydrocarbon bridge, offer interest as model compounds for studying interactions between pyrimidine bases in nucleic acids [1], as potential ionophores [2], and as starting compounds for synthesis of pyrimidinophanes [3]. Such derivatives have been synthesized by reactions of 1-(bromoalkyl)uracils with uracils [1, 4] or 1-acetyluracils [5] in the presence of K_2CO_3 in DMSO or with *O*,*O*-bis(trimethylsilyl)uracils [6], as well as by reactions of 1,3-oxazines with $Br(CH_2)_nBr$ [2] or of 1,3-dioxins with diisocyanatoalkanes [7] with subsequent conversion of the reaction products under the action of amines and aminoalcohols into pyrimidine derivatives. Noteworthy are also interesting methods of synthesis of bis(1-propargyl-2,4-dioxo-1,2,3,4-tetrahydro-3-pyrimidinyl)methane by reaction of 1-propargyluracil and CH_2Cl_2 in the presence of 1,8-diazabicyclo[5.4.0]undecene [8] and of α,ω-bis(2-hydroxy-6-methyl-4-oxo-3,4-dihydro-3-pyrimidinyl)alkanes by hydrolysis of the corresponding bis-(6-methyl-2-methylthio-4-oxo-3,4-dihydro-3-pyrimidinyl)alkanes or 3-[ω-(6-methyl-2-methylthio-4-oxo-3,4-dihydro-3-pyrimidinyl)]alkyl-6-methyluracils [9].

Reznik and co-workers have studied reactions of sodium salts of uracils with α,ω-dibromoalkanes in DMF at the reagent ratios 1 : 1, 1 : 2, 1 : 3, etc. [10–12]. They showed that the bromoalkylation mostly involves the nitrogen atoms of the uracil ring. It was noted that the reactions give, along with *N*-bromoalkylation products, oligomeric products of intermolecular interalkylation. We used these results for the synthesis of α,ω-bis(2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)]-alkanes.

We found that 3-methyluracil and 3,6-dimethyluracil sodium salts (**I**, **II**) react with $Br(CH_2)_nBr$ (n = 1, 3–5) at a 2 : 1 reagent ratio to give α,ω-[1,1'-bis-(3-methyl- or 3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)]alkanes (**III**–**X**).



I, II



III–**X**

I, II, R = H (I), CH_3 (**II**); **III**–**X**, R = H, n = 1 (**III**), 3 (**IV**), 4 (**V**), 5 (**VI**); R = CH_3, n = 1 (**VII**), 3 (**VIII**), 4 (**IX**), 5 (**X**).

The purity of the reaction products was checked by TLC. The IR spectra of compounds **III**–**X** lack absorption bands in the range 3100–3600 cm^{-1}, which is characteristic of 1,3-disubstituted uracils, and contain absorption bands at 3060–3100 [uracil ν(CH)], 1640–1690 and 1700–1715 [ν(C=O)], 1615, and 760 cm^{-1} (uracil ring). The composition of compounds **III**–**X** was confirmed by elemental analysis (Table 1), and their structure, by ^1H NMR spectroscopy (Table 2).

EXPERIMENTAL

The IR spectra were measured on a Specord IR-75

1070-3632/01/7107-1088 $25.00

Table 1. Yields, melting points, and elemental analyses of compounds **III**–**X**

Comp. no.	Yield, %	mp, °C (solvent for crystallization)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
III	68	253–254 (water)	50.08	4.60	21.30	$C_{11}H_{12}N_4O_4$	50.00	4.54	21.21
IV	60	171–173	53.35	5.54	19.02	$C_{13}H_{16}N_4O_4$	53.42	5.48	19.18
V	65	214–215 (2-propanol–water, 10:1)	54.98	5.82	18.12	$C_{14}H_{18}N_4O_4$	54.90	5.88	18.30
VI	78	91–92	56.30	6.40	17.38	$C_{15}H_{20}N_4O_4$	56.25	6.25	17.50
VII	43	259–260 (water)	53.19	5.44	19.34	$C_{13}H_{16}N_4O_4$	53.42	5.48	19.18
VIII	45	193–195 (2-propanol)	56.18	6.15	17.79	$C_{15}H_{20}N_4O_4$	56.25	6.25	17.50
IX	44	239–241	57.29	6.55	16.60	$C_{16}H_{22}N_4O_4$	57.49	6.59	16.77
X	61	184–185 (2-propanol)	58.56	6.85	16.14	$C_{17}H_{24}N_4O_4$	58.62	6.90	16.09

Table 2. ^{1}H NMR spectra of compounds **III**–**X** in $CDCl_3$

Comp. no.	δ, ppm (*J*, Hz)
III	3.47 s (6H, $2NCH_3$), 5.85 s (2H, CH_2), 6.13 d (2H, $2C^5H$, $^3J_{HH}$ 8), 8.05 d (2H, $2C^6H$, $^3J_{HH}$ 8)
IV	2.00–2.30 m (2H, CCH_2C), 3.35 s (6H, $2NCH_3$), 3.85 t (4H, $2NCH_2$, $^3J_{HH}$ 6), 5.80 d (2H, $2C^5H$, $^3J_{HH}$ 8), 7.25 d (2H, $2C^6H$, $^3J_{HH}$ 8)
V	1.55–1.95 m (4H, $2CCH_2C$), 3.35 s (6H, $2NCH_3$), 3.80 t (4H, $2NCH_2$, $^3J_{HH}$ 6), 5.75 d (2H, $2C^5H$, $^3J_{HH}$ 8), 7.15 d (2H, $2C^6H$, $^3J_{HH}$ 8)
VI	1.35–1.95 m (6H, $3CCH_2C$), 3.35 s (6H, $2NCH_3$), 3.80 t (4H, $2NCH_2$, $^3J_{HH}$ 6), 5.80 d (2H, $2C^5H$, $^3J_{HH}$ 8), 7.22 d (2H, $2C^6H$, $^3J_{HH}$ 8)
VII	2.50 s (6H, $2CCH_3$), 3.23 s (6H, $2NCH_3$), 5.53 s (2H, CH_2), 5.63 s (2H, $2C^5H$)
VIII	2.06 m (2H, CCH_2C), 2.30 s (6H, $2CCH_3$), 3.26 s (6H, $2NCH_3$), 3.87 t (4H, $2NCH_2$), 5.60 s (2H, $2C^5H$)
IX	1.75–1.95 m (4H, $2CCH_2C$), 2.30 s (6H, $2CCH_3$), 3.33 s (6H, $2NCH_3$), 3.87 t (4H, $2NCH_2$), 5.65 s (2H, $2C^5H$)
X	1.30–1.90 m (6H, $3CCH_2C$), 2.25 s (6H, $2CCH_3$), 3.30 s (6H, $2NCH_3$), 3.82 t (4H, $2NCH_2$), 5.60 s (2H, $2C^5H$)

instrument in Vaseline oil. The ^{1}H NMR spectra were obtained on a Varian T-60 instrument (60 MHz) in $CDCl_3$, internal reference TMS.

Thin-layer chromatography was performed on Silufol-254 plates, development in UV light.

All the reagents and solvents were thoroughly dried.

3-Methyluracil was prepared by alkylation of 1-acetyluracil with methyl iodide in the presence of K_2CO_3 [13]. 3,6-Dimethyluracil was obtained by condensation of acetoacetic ester with tiourea, followed by dimethylation with dimethyl sulfate and hydrolysis with the *N*,*S*-dimethyl derivative, mp 263–265°C [14].

Sodium salts **I** and **II** were prepared as described in [10].

Bis(3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)methane (III). A solution of 1.04 g of dibromomethane in 10 ml of DMF was added dropwise with stirring over the course of 15 min to a suspesion of 1.74 g of salt **I** in 60 ml of DMF. The mixture was stirred at 55–65°C to pH 7–8 (~7 h), after which it was evaporated in a vacuum, and the residue was treated with 50 ml of boiling CH_2Cl_2 to extract the reaction products. The precipitate that formed was filtered off, washed with CH_2Cl_2, and the solvent was removed. The residue was recrystallized from 15 ml of H_2O to obtain 1.04 g of compound **III**, R_f 0.57 (eluent chloroform–methanol, 9:1).

1,3-Bis(3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)propane (IV) was obtained like compound **III** from 1.15 g of salt **I** and 0.8 g of 1,3-dibromopropane. Boiling of the extraction products in 15 ml of 2-propanol for 15 min gave 0.7 g of compound **IV**, R_f 0.43 (eluent chloroform–methanol, 11 : 1.5).

1,4-Bis(3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)butane (V) was obtained like compound **III** from 3 g of sodium salt **I** and 2.16 g of 1,4-

dibromobutane. Yield 2 g, R_f 0.55 (eluent chloroform–methanol, 11.5 : 1.5).

1,5-Bis(3-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)pentane (VI) was obtained in a similar way from 2.4 g of salt **I** and 1.84 g of 1,5-dibromopentane. The oily residue obtained after removal of CH_2Cl_2 crystallized after addition of diethyl ether (20 ml). The precipitate was filtered off, treated with 20 ml of benzene, the undissolved residue was filtered off, and the benzene was removed in a vacuum to obtain 2 g of compound **VI**, R_f 0.34 (eluent dichloromethane–methanol, 17 : 1).

Bis(3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)methane (VII). A solution of 2.6 g dibromomethane in 25 ml of DMF was added dropwise with stirring over the course of 20 min to a suspension of 4.8 g of salt **II** in 120 ml of DMF. The mixture was stirred at 55–65°C to pH 7–8 (12.5 h), evaporated in a vacuum, and the residue was boiled for 10 min in 100 ml of $CHCl_3$. The precipitate was filtered off, washed with $CHCl_3$, and the solvent was removed. The residue was recrystallized from 50 ml of H_2O to obtain 1.45 g of compound **VII**. Removal of water from the mother liquor, followed by recrystallization of the residue from methanol gave an additional 0.45 g of compound **VII**, R_f 0.42 (eluent dichloromethane–methanol, 12.5 : 1).

1,3-Bis(3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)propane (VIII) was obtained like compound **VII** from 1.8 g of salt **II** and 1.2 g of dibromopropane. Yield 0.8 g, R_f 0.56 (eluent methanol).

1,4-Bis(3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)butane (IX) was obtained in a similar way from 8.1 g of salt **II** and 5.4 g of 1,4-dibromobutane. The residue after removal of $CHCl_3$ was boiled for 15 min first in 100 ml of H_2O and then in 20 ml of 2-propanol. Yield 3.7 g, R_f 0.60 (eluent dichloromethane–methanol, 12.5 : 2).

1,5-Bis(3,6-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)pentane (X) was obtained like compound **VII** from 2.5 g of salt **II** and 1.8 g of 1,5-dibromopentane. Yield 1.5 g, R_f 0.67 (eluent methanol).

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