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## Synthesis of alkyl derivatives of 3,7,10-trioxo-2,4,6,8,9,11-hexaaza[3.3.3]propellane and evaluation of their biological activity

Today 3,7,10-trioxo-2,4,6,8,9,11-hexaaza[3.3.3]propellane (THAP) has not yet received widespread research attention due to the complexity of the synthesis. This work is devoted to the development of a method for the THAP derivatives synthesis, as well as to the study of their biological activity in comparison with alkyl-substituted glycolurils (subject of comparison). THAP was *N*-alkylated to furnish novel hexaalkyl derivatives of THAP with methyl, ethyl and propyl substituents. The conditions for obtaining the maximum yield of the target product were optimized on the base of methyl derivative. The reaction proceeded in DMSO/KOH at 75–80 °C for 13 hours in a moderate yield of 56 %. The ethyl and propyl derivatives of THAP were synthesized under the same conditions. The biological activity of the obtained THAP alkyl derivatives and glycoluril alkyl derivatives was evaluated against *Sporosarcina ureae*, *Bacillus pumilus*, *Salmonella typhimurium* and *Staphylococcus aureus* bacteria and influenza A virus. All the samples were found to exhibit antibacterial activity against *Staphylococcus aureus*. It was shown that 2,4,6,8,9,11-hexapropyl-THAP, di-*tert*-butyl-diphenyl-, di-*tert*-butyl-dibenzyl-, di-*tert*-butyl-dimethyl- and di-isopropyl-dibenzylglycoluril, have exhibited also toxicity to living cells besides antiviral activity.

**Keywords:** propellane, azapropellane, THAP, glycoluril, *N*-alkylation, biological activity, influenza virus, *Sporosarcina ureae*, *Bacillus pumilus*, *Salmonella typhimurium*, *Staphylococcus aureus*

### Introduction

Propellanes are molecules with a central single (ethane) bond and three bridged rings (carbon or heteroatomic) [1]. They are found in natural resources [2–3] and are widely applied in polymeric materials, medicines, pesticides and so on [4–6]. Zalkow et al. [7] were the first to isolate sesquiterpene modephene from the poisonous plant *Isocoma Wrightii* in 1978. It was the first compound with a [3.3.3]propellane skeleton discovered in natural products [3.3.3]. Due to their structure, modephene and its derivatives exhibit a variety of biological activity [8, 9] and its toxicity can passivate certain biological enzymes and selectively inhibit anti-proliferation of some cancer cells. Thus, propellanes have been in focus of many chemists and biologists over a few last decades.

Among propellanes, heterocyclic compounds, especially those with nitrogen atoms (azapropellanes), are of considerable interest, since they can be easily be functionalized.

Research on the synthesis of azapropellanes was carried out by Ashkenazi et al. [10]. Shin and co-workers managed to have synthesized propellane bearing five nitrogen atoms through the glycoluril derivative in three stages in 2014 [11].

Lee, Zhang and co-workers developed a synthetic method for 3,7,10-trioxo-2,4,6,8,9,11-hexaaza[3.3.3]propellane (Fig. 1) [12–13].

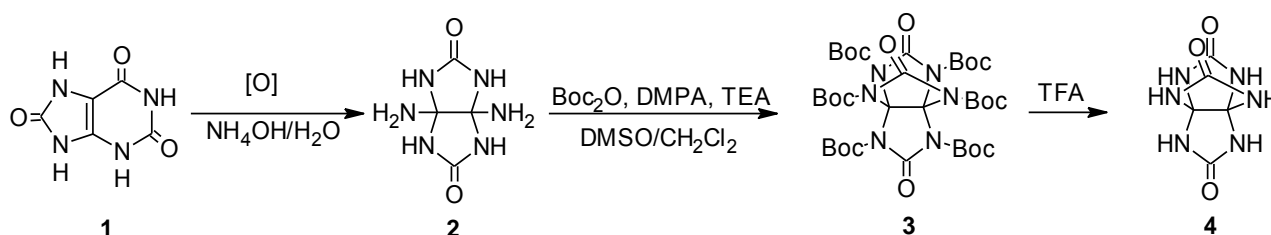


Figure 1. A synthetic protocol for 3,7,10-trioxo-2,4,6,8,9,11-hexaaza[3.3.3]propellane



*Evaluation of biological activity*

To determine the antibacterial activity, two-fold dilution of experimental preparations (volume 100  $\mu$ l) was made in the cells of a 96-well culture plate with a U-shaped bottom on MPB medium (mesopotamia broth). 100  $\mu$ l of an overnight culture diluted to a concentration of 10<sup>6</sup> cells/ml was added to each well. Incubation took place at 37 °C for 40 hours. Determination of optical density in relation to control (growth of bacterial culture without preparation) was performed.

To examine the antiviral activity *in vitro*, two methods were used:

- 1) the inhibition of the virus-induced cytopathic effect was determined visually under a microscope [17];
- 2) by changing the absorption of the vital dye by cells — neutral red [17, 18].

For this purpose, a 96-well plate was seeded with a MDCK (dog, kidney, cell monolayer) cell line, with a seed dose of  $2 \times 10^4$  cell per well. After 90 % of the monolayer was formed (20-h incubation at 37 °C under 5 % CO<sub>2</sub>), the influenza A/California/ 07/09 (H1N1pdm09) virus strain was inserted at a dose of 100 TCID<sub>50</sub> per well. This dose is equivalent to the multiplicity of infection at 0.001 of infection particles per cell. 30 minutes after infection, the test sample contained in the culture medium was placed in the wells and incubated at 37 °C under 5 % CO<sub>2</sub> for 72 h. After that, neutral red (0.34 % final concentration) was added into each well, the cells were washed in 1.5 h, and a solution (0.1 M NH<sub>4</sub>H<sub>2</sub>PO<sub>4</sub> and 96 % ethanol in equal volumes) was added for the stain extraction, and the optical density of the liberated stain was measured at a wavelength of 490 nm. The antiviral activity of the compound was estimated as a dose (concentration) of the test drug, which 50 % inhibits the viral reproduction or IC<sub>50</sub>. Although IC<sub>50</sub> was estimated by the two methods (determination of virus-induced cytopathic effect and incubation with neutral red), here we presented data obtained only with neutral red as more objective.

To assess the toxicity of the compounds, the 96-well plate was seeded with a MDCK cell culture with a seed dose of  $2 \times 10^4$  cells per well. After a 20-hour incubation at 37 °C in an atmosphere of 5 % CO<sub>2</sub>, the compounds dissolved in a MEM medium (Gibco) containing 5 % fetal bovine serum were introduced. Three days after incubation, the inhibition percentage of cell proliferation was evaluated using neutral red, as described above. The toxicity of the compounds was estimated as a dose (concentration) of the test drug at which 50 % cells are died (CD<sub>50</sub>).

The therapeutic index or index of selectivity (IS) was determined as the ratio of CD<sub>50</sub> to IC<sub>50</sub>.

*Results and Discussion**Synthesis of alkyl derivatives of 3,7,10-trioxo-2,4,6,8,9,11-hexaaza[3.3.3]propellane*

It would be logical to apply the glycoluril alkylation methods to THAP since it molecule is characterized by the presence of three imidazolidinone rings and has a structure similar to glycoluril. We have earlier developed a synthetic method for tetrasubstituted glycolurils with mono- and heterofunctional substituents in an acetonitrile/KOH medium [14, 15]. The method incorporates the alkyl groups into the partially substituted glycoluril and uses a low-boiling solvent to simplify the isolation of reaction products.

The alkylation reaction of 3,7,10-trioxo-2,4,6,8,9,11-hexaaza[3.3.3]propellane was carried out under conditions similar to the alkylation of glycoluril. In this case, the yield of hexaaryl derivatives of THAP was found low and reached only 6–8 % in acetonitrile medium.

That is why we investigated the effects of different solvents (DMSO, DMF, ethanol, 1,4-dioxane and methylene chloride), reaction temperature and bases on the target product yield by an example of the **5c** synthesis (Table 1).

Table 1

**Selection of synthesis conditions for 2,4,6,8,9,11-hexamethyl-2,4,6,8,9,11-hexaaza[3.3.3]propellane 5c**

Exp.	Solvent	Base	Reaction temperature, °C	Yield, %	Exp.	Solvent	Base	Reaction temperature, °C	Yield, %
1	DMSO	KOH	80	24	6	DMSO	K <sub>2</sub> CO <sub>3</sub>	80	–
2	DMF	KOH	80	11	7	DMF	K <sub>2</sub> CO <sub>3</sub>	80	–
3	Ethanol	KOH	70	–	8	Ethanol	K <sub>2</sub> CO <sub>3</sub>	70	–
4	1,4-Dioxane	KOH	80	–	9	1,4-Dioxane	K <sub>2</sub> CO <sub>3</sub>	80	–
5	Methylene chloride	KOH	40	–	10	Methylene chloride	K <sub>2</sub> CO <sub>3</sub>	40	–

Note. «→» THAP was quantitatively isolated back; no reaction has occurred.

As can be seen from Table 1, the N-alkylation reaction took place only at 80 °C and only in the two solvents such as DMSO and DMF. It is also evident that the yield of the target product **5c** in DMSO is almost 2 times more than that in DMF. The superbasic medium DMSO / KOH was selected for further research based on these preliminary results (Table 1). The results of the THAP alkylation with methyl iodide in the superbasic medium as a function of the reaction temperature and time are given in Figure 3.

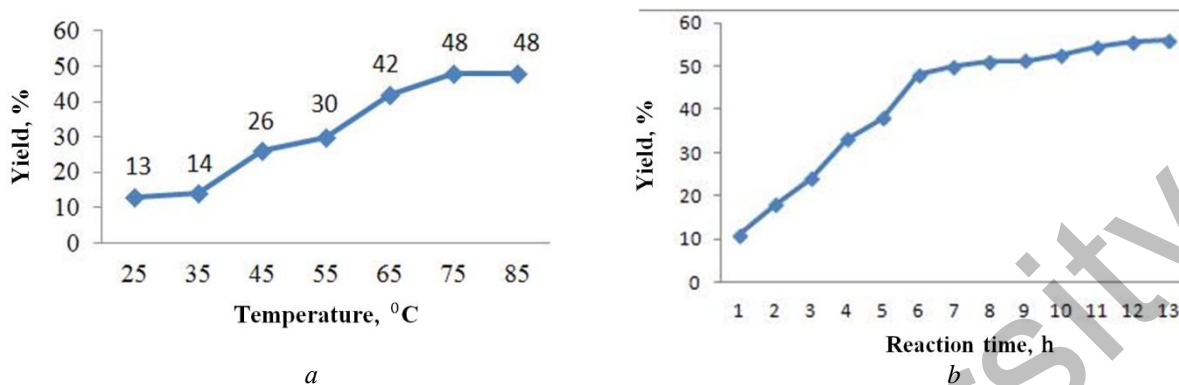


Figure 3. Dependence of the **5c** yield: (a) on the reaction temperature (reaction time 6 hours) and (b) on the reaction time (temperature 75 °C)

Figure 3a shows that an increase in the reaction temperature from 25 °C to 85 °C led to a smooth raising in the content of product **5c** from 12 % to 48 %. An increase of the alkylation time from 6 to 8 hours (3b) showed a slight growing in the yield of product **5c** to 51 %. When the reaction time was extended to 13 h, the yield of product **5c** got higher insignificantly and was 56 %. The slowdown in the formation of reaction product **5c** in 13 hours can be explained by the emerging of competing reactions due to the prolonged residence of the reagents in the superbasic medium at high temperature.

We sequentially have obtained THAP hexa-derivatives with methyl (**5c**), ethyl (**5d**) and propyl (**5e**) substituents (Fig. 4).

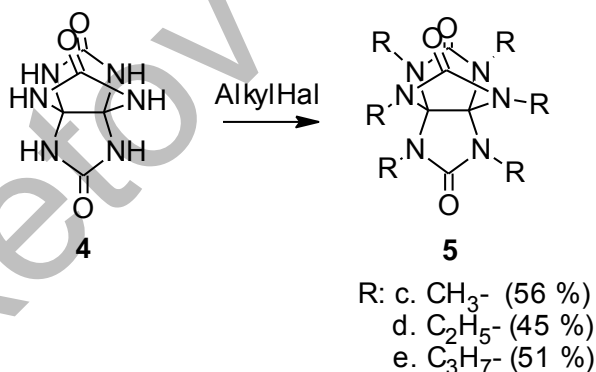


Figure 4. Synthesis of alkyl derivatives of 3,7,10-trioxo-2,4,6,8,9,11-hexaaza[3.3.3]propellane

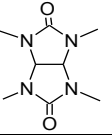
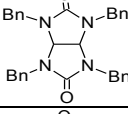
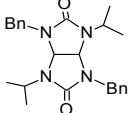
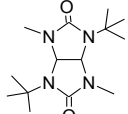
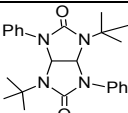
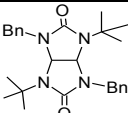
An attempted of isopropyl and *tert*-butyl groups incorporation into THAP did not lead to the expected result. This is probably due to the steric factor of the radicals.

#### Biological activity

The tetrasubstituted glycolurils synthesized previously [14, 15] and the new THAP derivatives were evaluated *in vitro* against some bacteria (*Sporosarcina ureae*, *Bacillus pumilus*, *Salmonella typhimurium* and *Staphylococcus aureus*) and influenza A virus. Tables 2 and 3 summarize the biological activity evaluation results.

Table 2

## Evaluation of antibacterial activity of the THAP hexaaza- derivatives and tetrasubstituted glycolurils

Compound	<i>Sporosarcina ureae</i>	<i>Bacillus pumilus</i>	<i>Salmonella typhimurium</i>	<i>Staphylococcus aureus</i>
<b>5c</b>	$1,3 \cdot 10^{-2}$	$2,6 \cdot 10^{-2}$	$1,3 \cdot 10^{-2}$	$1,3 \cdot 10^{-2}$
<b>5d</b>	$4,2 \cdot 10^{-3}$	$8,4 \cdot 10^{-3}$	$4,2 \cdot 10^{-3}$	$4,2 \cdot 10^{-3}$
<b>5e</b>	$5,9 \cdot 10^{-3}$	no	no	$2,9 \cdot 10^{-3}$
<b>6a</b>	 $4,6 \cdot 10^{-2}$	$9,2 \cdot 10^{-2}$	$9,2 \cdot 10^{-2}$	$4,6 \cdot 10^{-2}$
<b>6b</b>	 $2,0 \cdot 10^{-3}$	no	no	$8,0 \cdot 10^{-3}$
<b>6c</b>	 $1,2 \cdot 10^{-3}$	no	$9,8 \cdot 10^{-3}$	$4,6 \cdot 10^{-3}$
<b>6d</b>	 $1,8 \cdot 10^{-2}$	$1,8 \cdot 10^{-2}$	$1,8 \cdot 10^{-2}$	$8,8 \cdot 10^{-3}$
<b>6e</b>	 $4,2 \cdot 10^{-3}$	no	no	$4,2 \cdot 10^{-3}$
<b>6f</b>	 no	no	no	$7,0 \cdot 10^{-3}$

*Sporosarcina ureae* are spore-forming bacteria and ammonifying microorganisms that decompose urea. They are used in agriculture for nitrogen enrichment of the soil. *Bacillus pumilus* are phytopathogenic bacteria affecting agricultural crops (flax, pumpkin, corn, beet, oranges, apricots, marrow-type pumpkin, etc.) and thus cause significant economic damage to agricultural and processing companies. *Salmonella typhimurium* is a salmonellosis causal agent. *Staphylococcus aureus* (opportunistic pathogenic bacterium) initiates skin diseases (furuncles), respiratory diseases (angina, pneumonia), nervous system and sensory organ diseases (otitis media, conjunctivitis, cerebral fever), digestive system diseases (stomatitis, acute food poisoning) and etc.

All the test samples were found to inhibit the growth of *Staphylococcus aureus* at low concentrations. In contrast, suppression of the reproduction of *Sporosarcina ureae* is an undesirable effect as they are used in agriculture.

Table 3

## Evaluation of antiviral activity of the THAP hexaaza derivatives and tetrasubstituted glycolurils

Sample	CD <sub>50</sub> toxicity (the lowest dilution at which 50 % cells survive)	IC <sub>50</sub> antiviral activity (the highest dilution which protects 50 % cells from virus)	Therapeutic index IS (ratio of toxic dose to the efficient)
<b>5c</b>	$6.6 \cdot 10^{-3}$	no	no
<b>5d</b>	$2.1 \cdot 10^{-3}$	no	no
<b>5e</b>	$3.7 \cdot 10^{-4}$	$2.9 \cdot 10^{-4}$	1.28
<b>6a</b>	$5.7 \cdot 10^{-3}$	no	no
<b>6b</b>	$5.0 \cdot 10^{-4}$	no	no
<b>6c</b>	$5.8 \cdot 10^{-4}$	$4.6 \cdot 10^{-4}$	1.26
<b>6d</b>	$4.4 \cdot 10^{-3}$	$2.8 \cdot 10^{-3}$	1.57
<b>6e</b>	$2.1 \cdot 10^{-3}$	$1.7 \cdot 10^{-3}$	1.24
<b>6f</b>	$3.5 \cdot 10^{-3}$	$2.8 \cdot 10^{-3}$	1.25

As can be seen from Table 3, only **5e** propyl derivative of THAP exhibited an antiviral activity, while the methyl and ethyl derivatives did not. It was found that compound **5e** at a concentration of  $2.9 \cdot 10^{-4}$  g/ml is able to protect 50 % of cells from influenza virus. Tetrasubstituted glycolurils **6c-e** were also active at low concentrations. Further studies of the antiviral activity of these compounds were unreasonable because they had a high toxicity and a low therapeutic index. Samples **6a** and **6b** did not exert the antiviral activity. Note that sample **6a** has found its application as a day-time sedative and is marketed as Mebicar [16]. Therefore, the biological activity of the resultant hexaalkyl derivatives of THAP should be further examined.

### Conclusions

New hexaalkyl derivatives of THAP with methyl, ethyl and propyl substituents were synthesized. The conditions for the maximum product yield were selected using the example of a methyl derivative: the reaction proceeded in DMSO/KOH at 85 °C for 13 hours with a 56 % yield. The biological activity of the obtained compounds and of earlier synthesized model compounds (tetrasubstituted glycolurils) against influenza A virus was evaluated. The biological activity against the *Staphylococcus aureus* bacterium was exhibited by all of the test compounds, while the antiviral activity was exhibited by 2,4,6,8,9,11-hexapropyl-THAP, di-*tert*-butyl-dibenzyl-, di-*tert*-butyl-diphenyl-, di-*tert*-butyl-dimethyl- and di-isopropyl-dibenzylglycoluril. However, these compounds proved to be toxic to living cells.

*This work was performed using instruments provided by the Biysk Regional Center for Shared Use of Scientific Equipment of the SB RAS (IPCET SB RAS, Biysk). The reported study was funded by RFBR, project number 19-33-90060.*

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### 3,7,10-триоксо-2,4,6,8,9,11-гексааза[3.3.3]пропелланның алкил туындыларын синтездеу және олардың биологиялық белсенділігін зерттеу

Жұмыс 3,7,10-триоксо-2,4,6,8,9,11-гексааза[3.3.3]пропелланның алкил туындыларын синтездеу әдісін жасауға және алынған заттардың алкилалмасқан гликолурилдермен (зерттеу объектісі) салыстырғанда биологиялық белсенділігін зерттеуге арналған. Бұл бағыт синтездің күрделілігі себебінен зерттеушілердің назарынан тыс қалған. ТНАР-ты N-алкилдеу әдісі арқылы гексаалкил-туындыларының метилді, этилді және пропилді гексаалкил туындыларымен жаңа қосылыстары синтезделді. Метил туындысы мысалында негізгі өнімнің максималды шығымы болатындай тиімді жағдайлары жасалды. Реакция ДМСО/КОН ортасында 75–80 °С температурада 13 сағат бойы жүреді, реакция шығымы 56 %. ТНАР этилді және пропилді туындылары тура осындай жағдайда синтезделген. ТНАР-тың және гликолурилдың алынған алкилтуындыларының *Sporosarcina ureae*, *Bacillus pumilus*, *Salmonella typhimurium* u *Staphylococcus aureus* бактерияларына және А тұмауының вирусына қатысты биологиялық белсенділігі зерттелген. Барлық үлгілер *Staphylococcus aureus* қарсы бактериалды белсенділік көрсететіні анықталған. 2,4,6,8,9,11-гексапропил-ТНАР, ди-*трет*-бутил-дифенил-, ди-*трет*-бутил-добензил-, ди-*трет*-бутил-диметил-, ди-изопропил-добензилгликолурил қосылыстарының вирусқа қарсы белсенділіктен басқа тірі жасушалар үшін уытты болатыны байқалған.

*Кілт сөздер:* пропеллан, азапропеллан, ТНАР, гликолурил, N-алкилдеу, биологиялық белсенділік, тұмау вирусы, *Sporosarcina ureae*, *Bacillus pumilus*, *Salmonella typhimurium*, *Staphylococcus aureus*.

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### Синтез алкилпроизводных 3,7,10-триоксо-2,4,6,8,9,11-гексааза[3.3.3]пропеллана и изучение их биологической активности

Работа посвящена разработке метода синтеза производных 3,7,10-триоксо-2,4,6,8,9,11-гексааза[3.3.3]пропеллана (ТНАР), который ещё не получил широкого внимания исследователей ввиду сложности синтеза, а также изучению биологической активности синтезированных соединений в сравнении с алкилзамещенными гликолурилами (объектом сравнения). Методом N-алкилирования ТНАР были синтезированы новые гексаалкилпроизводные ТНАР с метильными, этильными и пропиловыми заместителями. На примере метильного производного были оптимизированы условия получения максимального выхода целевого продукта. Реакция протекает в среде ДМСО/КОН при температуре 75–80 °С в течение 13 ч с умеренным выходом 56 %. Этильные и пропиловые производные ТНАР синтезированы в аналогичных условиях. Изучена биологическая активность полученных алкилпроизводных ТНАР и алкилпроизводных гликолурила в отношении бактерий *Sporosarcina ureae*, *Bacillus pumilus*, *Salmonella typhimurium* и *Staphylococcus aureus*, а также вируса гриппа А. Установлено, что все образцы проявляют антибактериальную активность против *Staphylococcus aureus*. Было показано, что, наряду с проявленной противовирусной активностью, у соединений 2,4,6,8,9,11-гексапропил-ТНАР, ди-*трет*-бутил-дифенил-, ди-*трет*-бутил-добензил-, ди-*трет*-бутил-диметил-, ди-изопропил-добензилгликолурил также обнаружена токсичность для живых клеток.

*Ключевые слова:* пропеллан, азапропеллан, ТНАР, гликолурил, N-алкилирование, биологическая активность, вирус гриппа, *Sporosarcina ureae*, *Bacillus pumilus*, *Salmonella typhimurium*, *Staphylococcus aureus*.

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