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SYNTHESIS OF NEW HETEROCYCLIC COMPOUNDS FROM A NUMBER OF SUBSTITUTED TETRAHYDROPYRANONES

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Abstract. By the modified Morgan condensation of acetone and formaldehyde 3,5-bis(hydroxymethyl)tetrahydro-4H-pyran-4-one was synthesized (yield 67.4%). Structure of synthesized compound was confirmed by IR and NMR spectroscopy. Bicyclo[3.3.1]nonan-9-one, oxime and Schiff base were synthesized from the obtained product. The physical properties of the new heterocyclic compounds were studied and the structures identified.

Keywords: *tetrahydropyranone, acetone, formaldehyde, synthesis, condensation, heterocyclic compounds, bicyclo[3.3.1]nonan-9-one, oximes.*

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1. Introduction

The isomeric tetrahydropyranones and their derivatives are among the most simple, most widely studied and used in medicine (Wang *et al.*, 2012, Makarov *et al.*, 2012, Nottelet *et al.*, 2012, Kandhare *et al.*, 2012) classes of heterocyclic compounds.

We carried out the synthesis of 3,5-bis(hydroxymethyl)tetrahydro-4H-pyran-4-one and its derivatives in order to further study their pharmacological properties.

Among the variety of derivatives of heterocycles a number of compounds potentially possessing pharmaceutical activity can be distinguished. For instance, members of the heterocyclic bicyclo[3.3.1]nonan-9-one-like compounds are potent κ-opioid receptor specific agonists. It was shown (Benyhe *et al.*, 2003) by molecular modelling that heterocyclic bicyclo[3.3.1]nonan-9-ones fit very well with the structure of ketazocine, a prototypic κ-selective benzomorphan compound.

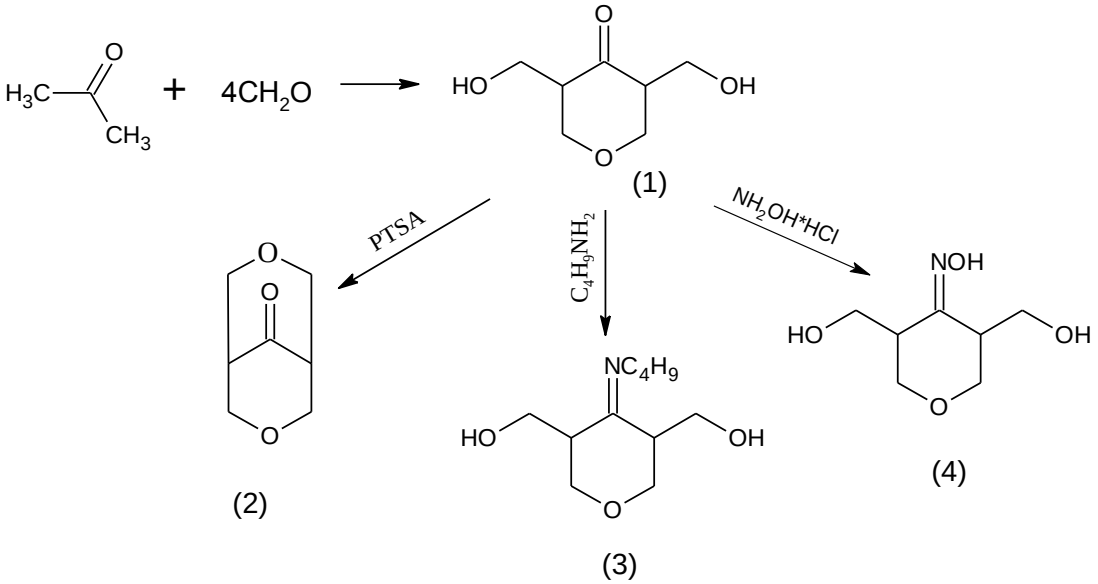
Oximes and Schiff bases, synthesized on the basis of tetrahydropyranone, are very important in medicinal and pharmaceutical fields because of their wide spectrum of biological activities. Schiff bases are versatile ligands which are synthesized from the condensation of primary amines with carbonyl groups. Most of them show biological activities such as antibacterial, antifungal as well as antitumor activity (Al Zoubi, 2013).

The oximes obtained on the basis of heterocyclic compounds, which include 3,5-substituted tetrahydropyranone, possess biological activity (Abele *et al.*, 2007; 2010). Gopalakrishnan and co-authors (Gopalakrishnan *et al.*, 2009) synthesized some 2,6-diarylpiperidin/tetrahydrothiopyran/tetrahydropyran-4-one oximes and evaluated for

their *in vitro* antibacterial activity against clinically isolated bacterial strains i.e. *S.aureus*, *b-H.Streptococcus*, *E.coli*, *P.aeruginosa*, *S.typhii* and *in vitro* antifungal activities against fungal strains i.e. *C.albicans*, *Rhizopus*, *A.niger* and *A.flavus*.

2. Results and discussions

We studied the reactions of obtaining 3,5-bis(hydroxymethyl)tetrahydro-4H-pyran-4-one and its derivatives according to the scheme below:



Formaldehyde condensation with acetone or its homologues an alkaline medium proceeds according to a complex scheme studied by Holmes and Morgan. The nature of the final products depends on the ratio of components taken for the reaction. In his paper (Morgan & Holmes, 1932), Morgan suggested 2 products of condensation of one mole of acetone and four moles of formaldehyde: 3,5-bis(hydroxymethyl)tetrahydro-4H-pyran-4-one and 5-(β-oxipropionyl)-1,3-dixane.

We carried out the modified condensation of acetone and formaldehyde at a ratio of 1:4 in an alkaline medium described in the paper (Bazhykova *et al.,* 2018). The reaction mixture was stirred at a temperature of 30-35 ^{0}C for 7 days.

As a result, 21.5 g of 3,5-bis(hydroxymethyl)tetrahydro-4H-pyran-4-one were obtained in the form of a light yellow powder. The physicochemical properties of the compound were studied and elemental analysis was performed. Results of elemental analysis of 3,5-bis(hydroxymethyl)tetrahydro-4H-pyran-4-one are given in table 1.

Table 1. The percentage by mass of the elements included in the 3,5-bis(hydroxymethyl)tetrahydro-4H-pyran-4-one (Gross formula $C_7H_{12}O_4$)

Element	Detected, %	Estimated, %
C	52,41	52,50
H	7,93	7,55
O	39,65	39,94

Functional composition and structural elements were identified using IR spectroscopy. To confirm that the compound corresponds to the structure of 3,5-bis(hydroxymethyl)tetrahydro-4H-pyran-4-one, ^{1}H and ^{13}C NMR spectra were obtained. Spectrum analysis shows that the structure of the obtained product is consistent with the structure of 3,5-bis(hydroxymethyl)tetrahydro-4H-pyran-4-one.

For the 3,7-dioxabicyclo[3.3.1]nonan-9-one (2) synthesis, the method described in the paper (Khrustalev, 2008) was applied. Para-toluenesulfonic acid was used as a catalyst.

In a round-bottomed flask with a capacity of 250 ml 0.5 g (0.003 mole) of 3,5-bis(hydroxymethyl)tetrahydro-4H-pyran-4-one were placed and dissolved in ethyl alcohol (90%). To completely dissolve the ketone, the flask was slightly warmed. After dissolving the ketone, 0.17 g (0.001 mole) of para-toluenesulfonic acid were added.

The mixture was boiled with a Dean-Stark trap for 7 hours. The reaction mixture was washed with water, then with sodium bicarbonate solution. After that it was dried with anhydrous sodium sulfate. After distilling off the solvent, 0.23 g of the product was obtained in the form of a dark yellow oil (yield 52%).

For [4-(butylimino)tetrahydro-2H-pyran-3,5-diyl]dimethanol (3) synthesis, 1.5 g (0.009 mole) of 3,5-bis(hydroxymethyl)tetrahydro-4H-pyran-4-one was applied on 20 g of alumina and mixed by shaking for equitable adsorption. Similarly, 0.89 g (0.01 mole) of butanolamine was applied to an equal portion (20 g) of alumina. Both portions of the adsorbent were thoroughly mixed and left in a sealed flask for 7 days under argon, stirring occasionally with shaking. Then, 50 ml of benzene was added to the mixture and filtered on a fritted funnel. After distilling off the solvent in a water jet vacuum pump, 1.94 g of product was obtained.

The most common laboratory method for the synthesis of oximes is the reaction of aldehydes and ketones with hydroxylamine. For [4-(hydroxyimino)tetrahydro-2H-pyran-3,5-diyl]dimethanol (4) synthesis, in a round-bottomed flask with a capacity of 150 ml 0.94 g (0.006 mole) of 3,5-bis(hydroxymethyl)tetrahydro-4H-pyran-4-one, 1.2 g (0.017 mole) of hydroxylamine hydrochloride and 2 g of sodium hydroxide dissolved in 10 ml of water were added and boiled for 40 minutes under reflux condenser. Then 60 ml of cold water was added and unreacted 3,4-dimethylenoxytetrahydropyran-4-one was filtered. The resulting oxime was filtered and dried at a temperature of 70-80 ^{0}C. The product was recrystallized in ethyl alcohol. As the result, 0.61 g of product was obtained.

The courses of the reactions were monitored by TLC in the butanol-ice acetic acid-water system (40:12.5:29). Some analytical data of the obtained synthesis products are given in table 2.

Table 2. The yield, melting point and R_f of the products

Compound	Yield, %	T_m, ^{0}C	R_f
1	67.4	138-140	0.24
2	52.0	-	0.22
3	68.8	-	0.93
4	60.0	128	0.54

Functional composition and structural elements of obtained compounds were identified using IR spectroscopy.

3. Experimental part. General remarks

Melting points were measured on an Zhukov's apparatus. The $^{1}H/^{13}C$ NMR spectra were recorded on a JNN-ECA Jeol 400 spectrometer at a frequency of 399.78 MHz and 100.53 MHz respectively with a solvent $CDCl_3$. To monitor the progress of reactions thin-layer chromatography (TLC) on commercial aluminum-backed plates of silica gel was used.

Experimental procedure

3,5-bis(hydroxymethyl)tetrahydro-4H-pyran-4-one (1) was obtained from 11.2 g of acetone (0.2 mol), 24 g (0.8 mole) of formaldehyde at a temperature of 30-35 ^{0}C and stirring for 7 days. Yield 21.5 g (67.4%), light yellow crystals. T_m=138-140 °C. IR spectrum, ν, cm^{-1}: 3432 (OH), 2933.2872 (CH_2), 1703 (C=O), 1657.1452 (C-C), 1101 (C-O-C). NMR ^{1}H (DMSO), δ, ppm: 3.61 (dd, 4H, CH_2), 2.19 (tp, 2H, CH), 3.53 (tp, 4H, CH_2), 5.15 (tp, 1H, OH). NMR ^{13}C (DMSO), δ, ppm: 66.18 (CH_2), 50.39 (CH), 62.02 (CH_2), 215.19 (C).

3,7-dioxabicyclo[3.3.1]nonan-9-one (2) was obtained from 0.5 g of 3,5-bis(hydroxymethyl)tetrahydro-4H-pyran-4-one (0.003 mole), 0.17 g (0.001 mole) of para-toluenesulfonic acid as a catalyst. Yield 0.23 g (52%), dark yellow oil. IR spectrum, ν, cm^{-1}: 2935.06 (CH_2), 1707.10 (C=O), 1660.17 (C-C), 1107.27 (C-O-C), 1045.91 (C-O-C).

[4-(butylimino)tetrahydro-2H-pyran-3,5-diyl]dimethanol (3) was obtained from 1.5 g of 3,5-bis(hydroxymethyl)tetrahydro-4H-pyran-4-one (0.009 mole), 0.89 g of butanolamine (0.01 mole). Yield 1.94 g (68.8%), brown oil. IR spectrum, ν, cm^{-1}: 3414.94 (OH), 3150.25 (OH), 2925.77 (CH_2), 1662.64 (C=N), 1658.19 (C-C), 1107.16 (C-O-C), 935.57 (N-O).

[4-(hydroxyimino)tetrahydro-2H-pyran-3,5-diyl]dimethanol (4) was obtained from 0.94 g of 3,5-bis(hydroxymethyl)tetrahydro-4H-pyran-4-one (0.006 mole), 1.2 g of hydroxylamine hydrochloride (0.017 mole). Yield 0.61 g (60%), yellow crystals, T_m=128^{0}C. IR spectrum, ν, cm^{-1}: 3436.94 (OH), 2923.84 (CH_2), 2854.49 (CH_2), 1657.1452 (C-C), 1642.49 (C=N), 1101.61 (C-O-C), 957.80 (N-O).

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