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Study of the Interaction of Benzene-1,4-dicarboxamide with Methylmalonyl Dichloride †

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Abstract: Studies show that compounds such as 1,3-oxazine-6-ones are promising starting reagents that allow to obtain various acyclic and heteroaromatic systems. These substances demonstrate a wide range of biological activity. Meanwhile, it is known that depending on 1,3-oxazine cycles number in molecule, pharmacological activity may vary. Therefore, purpose of our work was to study reaction of benzene-1,4-dicarboxamide with methylmalonyl dichloride as the most rational way to obtain new compounds of given structure. This interaction can potentially lead to both mono- and bis(1,3-oxazine-6-one) derivatives. Reaction between terephthalamide and methylmalonyl dichloride was conducted at their equimolar ratio and with twofold excess of the latter. Syntheses were carried out in two media: absolute benzene and 1,2-dichloroethane. Reaction of equimolar amounts of reagents resulted in obtaining the only product 4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide (**1**). In twofold excess of methylmalonyl dichloride, just product **1** was obtained after 24 h of refluxing and after 58 h only 2,2′-(benzene-1,4-diyl)bis(4-hydroxy-5-methyl-6H-1,3-oxazine-6-one) (**2**) formed. Determination of partial negative charge on nitrogen atoms of amido groups of terephthalamide and compound **1** allowed us to confirm sequential formation firstly of mono- (**1**) and then bis(1,3-oxazine-6-one) derivative (**2**) in reaction mass. Structure of obtained compounds was proved by NMR spectroscopy on ^{1}H and ^{13}C nuclei. When studying solvent influence on synthesis rate, no significant differences were noted between benzene and 1,2-dichloroethane. However, the yield of 2,2′-(benzene-1,4-diyl)bis(4-hydroxy-5-methyl-6H-1,3-oxazine-6-one) during synthesis in 1,2-dichloroethane was lower—77% compared with 85% in benzene.

Keywords: benzene-1,4-dicarboxamide; methylmalonyl dichloride; condensation; 1,3-oxazine-6-ones; bis(1,3-oxazine-6-ones)

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1. Introduction

It is known [1–3,6–11] that compounds of the 1,3-oxazine-6-one family, according to research data, are promising starting reagents which make it possible to obtain both aromatic systems containing various heteroatoms and systems of acyclic structure [3]. These substances also demonstrate a wide range of biological activity, for example, antimicrobial, antifungal, antioxidant [4]. Meanwhile, the structure of the key molecule, specifically, the number of 1,3-oxazine cycles included in its composition, has an important effect on the severity of pharmacological activity [5]. Therefore, the aim of our work was to study the reaction of benzene-1,4-dicarboxamide with methylmalonyl dichloride which can lead

to both mono- and bis(1,3-oxazine-6-one) derivatives. To achieve the goal it is necessary to solve the following main problems:

1. To carry out the reaction of benzene-1,4-dicarboxamide with methylmalonyl dichloride in two media—benzene and 1,2-dichloroethane—and at two ratios of starting reagets 1:1 and 1:2, respectively;
2. To give a comparative assessment of the use of benzene and 1,2-dichloroethane as the medium of this reaction, calculate the yields and set the time required for the formation of products;
3. To prove the structure of the synthesized products in the reactions of benzene-1,4-dicarboxamide: methylmalonyl dichloride 1:1 and 1:2 using modern physico-chemical methods of analysis: NMR spectroscopy, elemental analysis.

2. Materials and Methods

The reaction of benzene-1,4-dicarboxamide with methylmalonyl dichloride was carried out in two media (absolute benzene and 1,2-dichloroethane (EDC)) and at two ratios of starting reagents benzene-1,4-dicarboxamide: methymalonyl dichloride (1:1) (**1.1**) and (1:2) (**1.2**) (Figure 1). The yield of the compound 4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide (**1**) in the reaction **1.1** in benzene and 1,2-dichloroethane was 70% and 67%, respectively. The synthesis was conducted for 24 h. The compound 2,2′-(benzene-1,4-diyl)bis(4-hydroxy-5-methyl-6H-1,3-oxazine-6-one) (**2**) was obtained in the reaction **1.2** with a yield of 85% (in benzene) and 77% (in EDC). The final compound **2** was isolated after 58 h of refluxing.

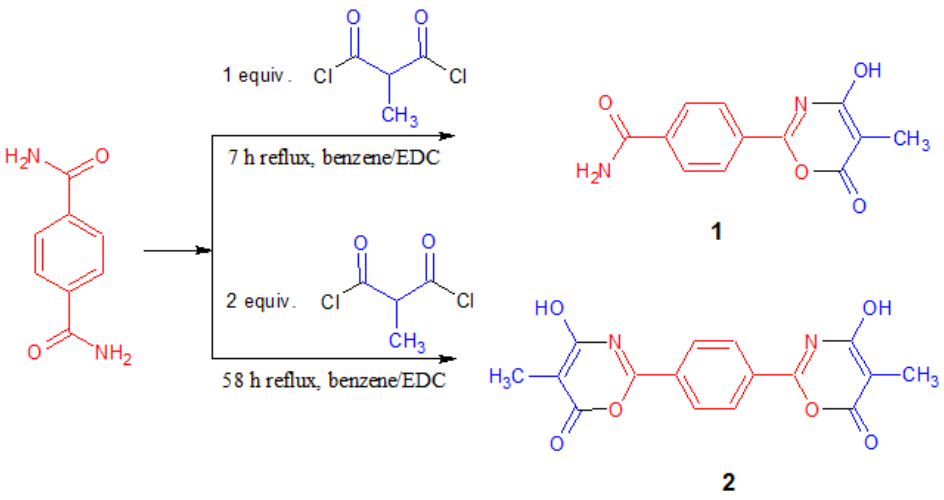

Figure 1. Interaction of benzene-1,4-dicarboxamide with methylmalonyl dichloride.

1.1 Synthesis of 4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide (1). 6.96 g (0.0424 mol) of benzene-1,4-carboxamide was suspended in benzene (EDC), then 4.75 mL (0.0424 mol) of methylmalonyl dichloride was added and refluxed for 24 h. The completeness of the reaction was monitored using thin-layer chromatography on TLC Silica gel 60 F254 plates in the methanol: dichloromethane: dimethyl sulfoxide (1:9:0.5) system. After 7 h since the start of the reaction, it was noted the beginning of formation of product **1** in the reaction mass. At the end of the synthesis, the resulting 4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide was filtered under vacuum. The precipitate was recrystallized from glacial acetic acid.

1.2 Synthesis of 2,2′-(benzene-1,4-diyl)bis(4-hydroxy-5-methyl-6H-1,3-oxazine-6-one) (2). 3.48 g (0.0212 mol) of benzene-1,4-carboxamide was suspended in benzene (EDC), then 4.75 mL (0.0424 mol) of methylmalonyl dichloride was added and refluxed for 58 h. The completeness of the reaction was monitored using thin-layer chromatography on TLC Silica gel 60 F254 plates in the methanol: dichloromethane: dimethyl

sulfoxide (1:9:0.5) system. At the end of the synthesis, the resulting 2,2′-(benzene-1,4-diyl)bis(4-hydroxy-5-methyl-6H-1,3-oxazine-6-one) was filtered under vacuum. The precipitate was recrystallized from glacial acetic acid.

3. Results

After 7 h of refluxing, the reaction mass (**1.1**) was analyzed and its composition was determined by NMR spectroscopy on ^{1}H nuclei (Figure 2). It was established that the end product **1** formed in the reaction mass and the initial compound benzene-1,4-dicarboxamide still remained.

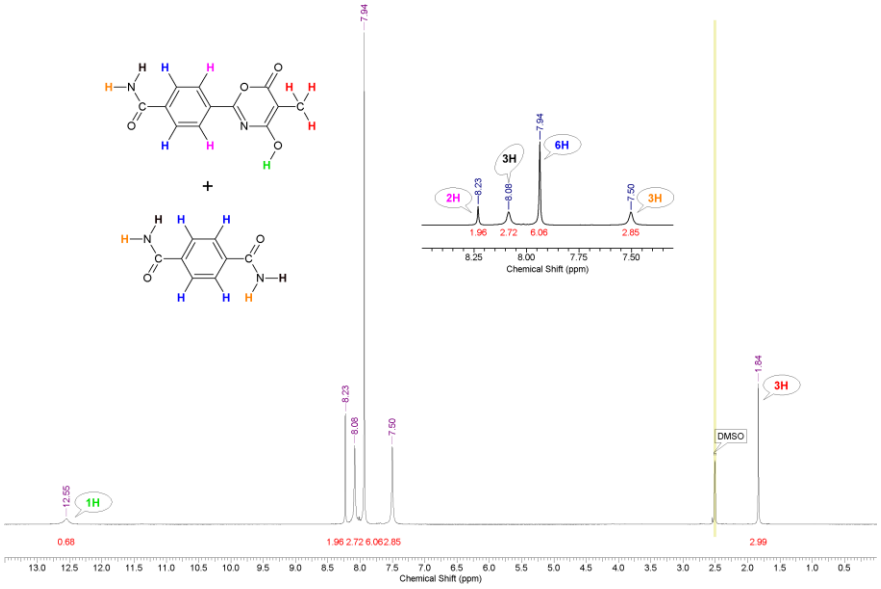

Figure 2. ^{1}H NMR spectrum of 4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide (after 7 h of refluxing) in DMSO-d6.

After carrying out the reactions **1.1** and **1.2**, the following results were received. The interaction of equimolar amounts of reagents led to the formation of the only product—4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide after 24 h of refluxing with a yield of 70% (in benzene) and 67% in (EDC) (Figure 3). The solvents (benzene and EDC) used as a synthesis medium did not have a significant effect on the yield of the product **1**.

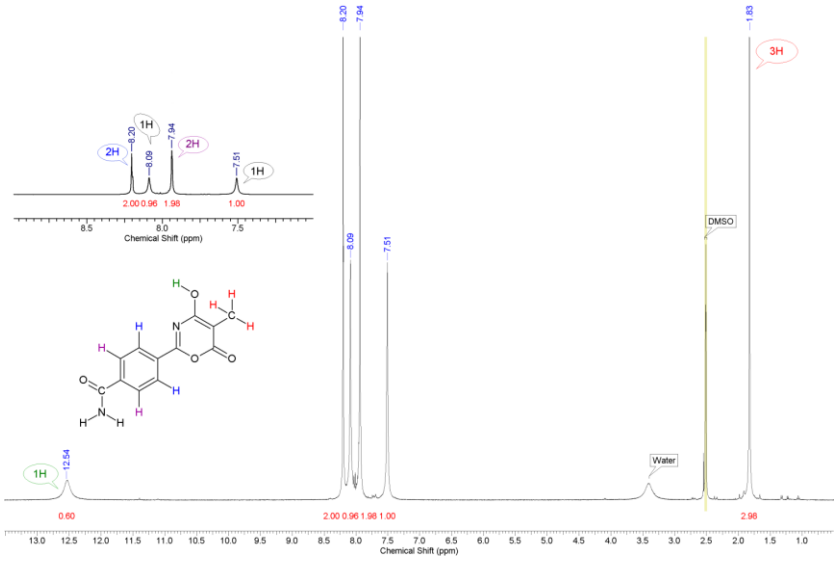

Figure 3. ^{1}H NMR spectrum of 4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide in DMSO-d6.

When the amount of methylmalonyl dichloride was doubled, after 24 h of reaction, only mono- 1,3-oxazine-6-one derivative (**1**) was obtained, and after 58 h only 2,2′-(benzene-1,4-diyl)bis(4-hydroxy-5-methyl-6H-1,3-oxazine-6-one) formed in the reaction mass with a yield of 85% in benzene and 77% in 1,2-dichloroethane (Figures 4 and 5).

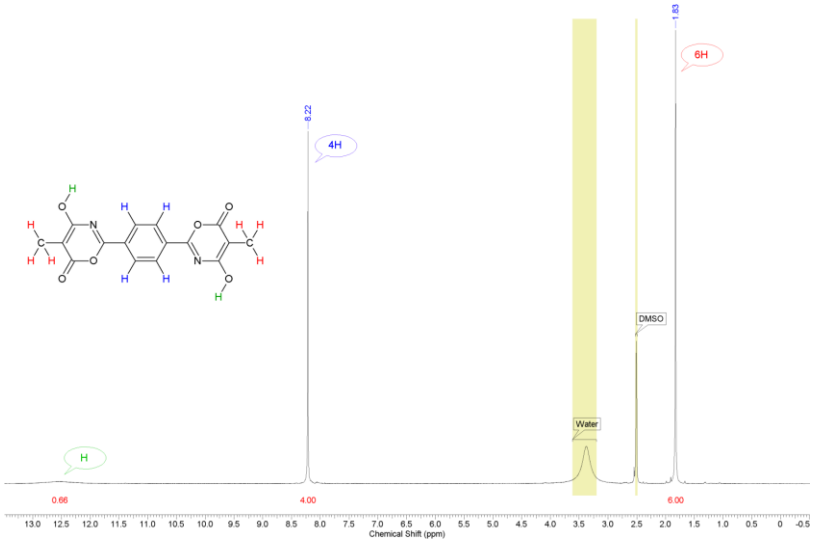

Figure 4. ^{1}H NMR spectrum of 2,2′-(benzene-1,4-diyl)bis(4-hydroxy-5-methyl-6H-1,3-oxazine-6-one) in DMSO-d6.

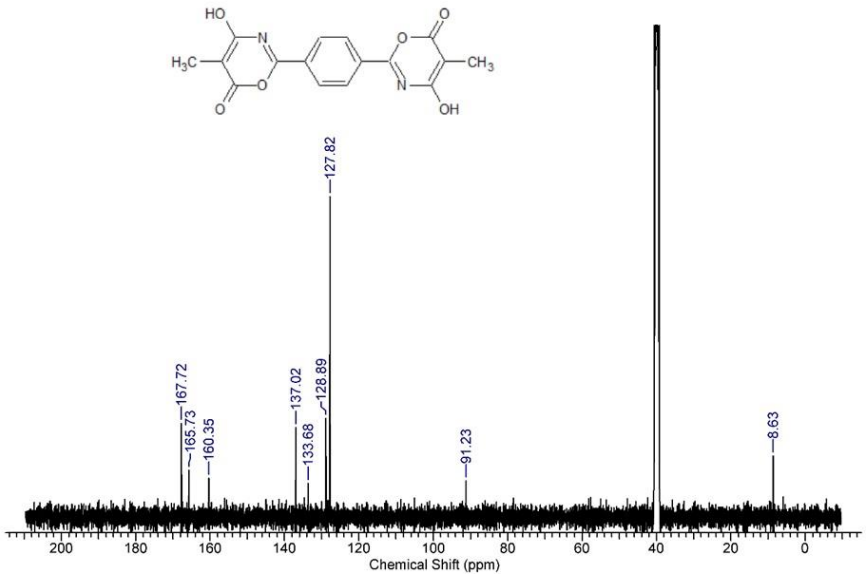

Figure 5. ^{13}C NMR spectrum of 2,2′-(benzene-1,4-diyl)bis(4-hydroxy-5-methyl-6H-1,3-oxazine-6-one) in DMSO-d6.

The structure of the obtained compounds was proved by NMR spectroscopy on ^{1}H and ^{13}C nuclei and confirmed by elemental analysis. The ^{1}H and ^{13}C NMR spectra were obtained using a Bruker AM-500 spectrometer from solutions in DMSO-d6.

4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide. ^{1}H NMR (DMSO-d6): δ 1.83 (s, 3H, CH_3); δ 7.51 (s, 1H, NH_2); δ 7.94 (s, 2H, C_6H_6); δ 8.09 (s, 1H, NH_2); δ 8.20 (s, 2H, C_6H_6); δ 12.54 (s, 1H, OH). ^{13}C NMR spectrum contains a characteristic signal corresponding to a carbon atom of the CH_3-group (9.50 ppm), 91.25 ppm signal belonging to

the sp^2-hybrid carbon atom C_5 of the 1,3-oxazine cycle and a signal 168.12 ppm of carbon of amido group. A number of signals corresponding to C_4, C_2 and C_6 atoms of the 1,3-oxazine cycle are also observed (160.36, 165.75, 167.74 ppm). The signals of carbon atoms of benzene ring are in the range of 128.31-130.70 ppm.

Molecular formula: $C_{12}H_{10}N_2O_4$. Found %: C—58,25; H—3,92; N—11,34; O—25,36. Calculated %: C—58,54; H—4,09; N—11,38; O—25,99.

2,2′-(benzene-1,4-diyl)bis(4-hydroxy-5-methyl-6H-1,3-oxazine-6-one). ^{1}H NMR (DMSO-d6): δ 1.83 (s, 6H, CH_3); δ 8.22 (s, 4H, C_6H_6); δ 12.54 (s, 2H, OH). ^{13}C NMR spectrum contains a characteristic signal corresponding to carbon atoms of the CH_3-groups (8.63 ppm) and 91.23 ppm signal belonging to the sp^2-hybrid carbon atoms C_5 of the 1,3-oxazine cycles. A number of signals corresponding to C_4, C_2 and C_6 atoms of the 1,3-oxazine cycle are also observed (160.35–167.72 ppm).

Molecular formula: $C_{16}H_{12}N_2O_6$. Found %: C—58,25; H—3,53; N—8,5; O—28,53. Calculated %: C—58,54; H—3,68; N—8,53; O—29,24.

It was found that the solvents used in the synthesis (benzene and 1,2-dichloroethane) do not have a significant effect on the synthesis time, however, the calculation of the yield of the end product bis(1,3-oxazine-6-one) derivative (**2**) determined that the use of benzene as a reaction medium is more profitable due to an increase of the formation of the target compound—85% compared to 77% in EDC.

4. Discussion

For nitrogen atoms of amido groups of the initial compound benzene-1,4-dicarboxamide and 4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide partial negative charges were calculated by the semi–empirical PM6 method (taking into account the solvent benzene) and they amounted to −0,576 and −0,569, respectively (Figures 6 and 7). The results obtained make it possible to confirm and justify the sequential formation firstly of mono- (**1**) and then bis(1,3-oxazine-6-one) derivative (**2**) in the reaction mass. Due to the higher electron density, the nitrogen of the amido group of benzene-1,4-dicarboxamide exhibits greater nucleophilicity in reaction with methylmalonyl dichloride compared with 4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide, therefore the first stage of the reaction ends with the formation of mono- 1,3-oxazine-6-one derivative (**1**). At the second stage of the reaction the amido groups of 4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide molecules are attacked, and 2,2′-(benzene-1,4-diyl)bis(4-hydroxy-5-methyl-6H-1,3-oxazine-6-one) forms.

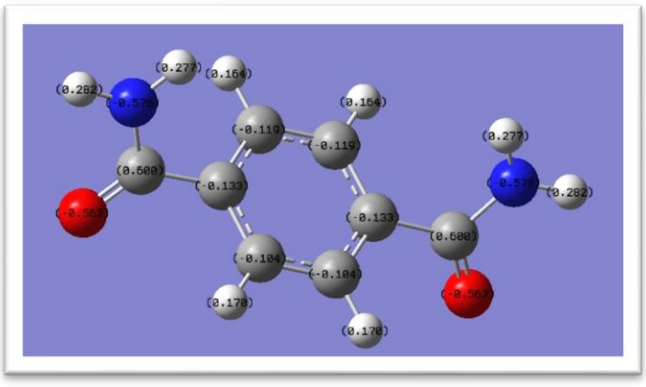

Figure 6. Charges on atoms in benzene-1,4-dicarboxamide molecule.

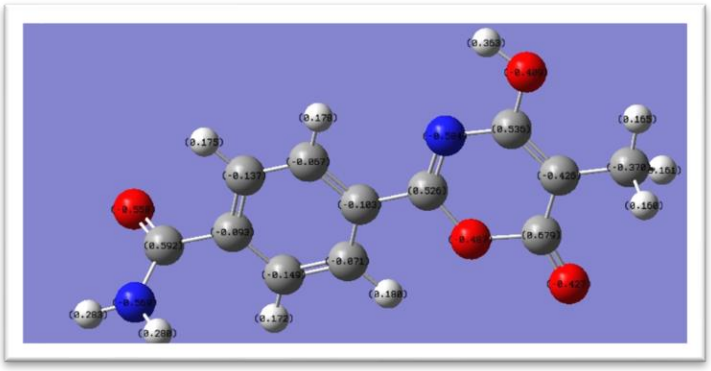

Figure 7. Charges on atoms in 4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide molecule.

5. Conclusions

This paper presents the results of studying of the reaction between benzene-1,4-dicarboxamide and methylmalonyl dichloride. It was shown that in the interaction of equimolar amounts of reagents, the only product was 4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide (**1**). In a twofold excess of methylmalonyl dichloride, only product **1** was obtained after 24 h of refluxing and after 58 h only 2,2′-(benzene-1,4-diyl)bis(4-hydroxy-5-methyl-6H-1,3-oxazine-6-one) (**2**) formed. It was found that the choice of solvent affects the yield of product **2** (in benzene—85%, in EDC—77%).

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