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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 us to obtain various acyclic and heteroaromatic systems. These substances demonstrate a wide range of biological activity. Meanwhile, it is known that depending on the 1,3-oxazine cycle number in the molecule, pharmacological activity may vary. Therefore, the purpose of our work was to study the reaction of benzene-1,4-dicarboxamide with methylmalonyl dichloride, as a rational way to obtain new compounds of a given structure. This interaction can potentially lead to both mono- and bis(1,3-oxazine-6-one) derivatives. The reaction between terephthalamide and methylmalonyl dichloride was conducted at an equimolar ratio, with a twofold excess of the latter. Syntheses were carried out in two media—absolute benzene and 1,2-dichloroethane. The reaction of equimolar amounts of reagents resulted in obtaining only one product—4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide (**1**). In twofold excess of methylmalonyl dichloride, only product **1** was obtained after 24 h of refluxing; after 58 h, only 2,2′-(benzene-1,4-diyl)bis(4-hydroxy-5-methyl-6H-1,3-oxazine-6-one) (**2**) was formed. The determination of the partial negative charge on the nitrogen atoms of the amido groups of terephthalamide and compound **1** allowed us to confirm the sequential formation firstly of the mono- (**1**) and then the bis(1,3-oxazine-6-one) derivative (**2**) in the reaction mass. The structure of the obtained compounds was proven using NMR spectroscopy on ^{1}H and ^{13}C nuclei. When studying solvent influence on the 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

According to research data [1–3], compounds of the 1,3-oxazine-6-one family are promising starting reagents that make it possible to obtain aromatic systems containing various heteroatoms and also systems with acyclic structures [4]. These substances also demonstrate a wide range of biological activity, e.g., antimicrobial, antifungal, or antioxidant [5]. 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 its pharmacological activity [6]. 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 this goal, it is necessary to solve the following problems:

1. Carrying 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 reagents, i.e., 1:1 and 1:2, respectively.
2. Giving a comparative assessment of the use of benzene and 1,2-dichloroethane as the medium of this reaction, calculating the yields, and setting the time required for the formation of products.
3. Proving the structure of the synthesized products in the reactions of benzene-1,4-dicarboxamide: methylmalonyl dichloride at 1:1 and 1:2 using modern physicochemical methods of analysis, namely NMR spectroscopy and 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 at (1:1) (**1.1**) and (1:2) (**1.2**) (Figure 1). The yield of 4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide (**1**) in reaction **1.1** in benzene and 1,2-dichloroethane was 70% and 67%, respectively. The synthesis was carried out 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.

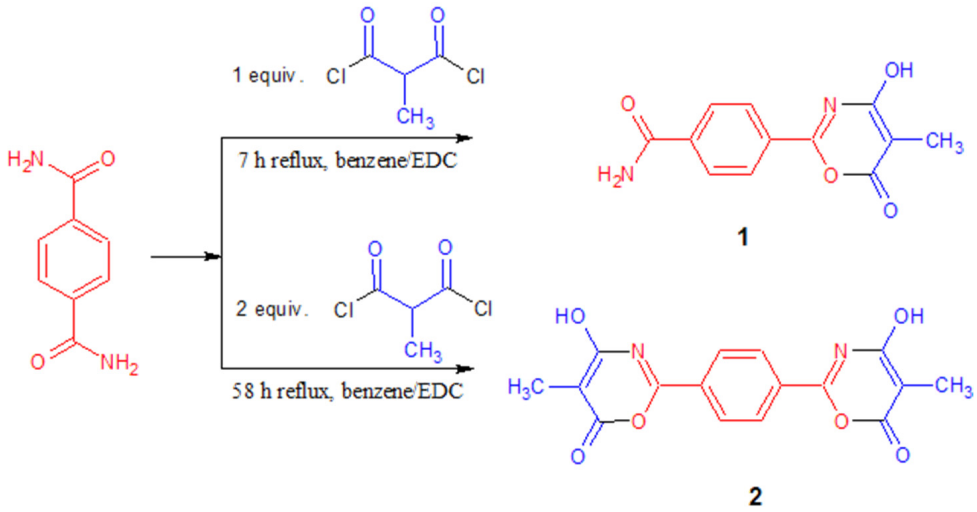


Figure 1. Interaction of benzene-1,4-dicarboxamide with methylmalonyl dichloride.

1.1 Synthesis of 4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide (1). In total, 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 from the start of the reaction, it was noted that product **1** began to form 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). A total of 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 using NMR spectroscopy on 1H 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.

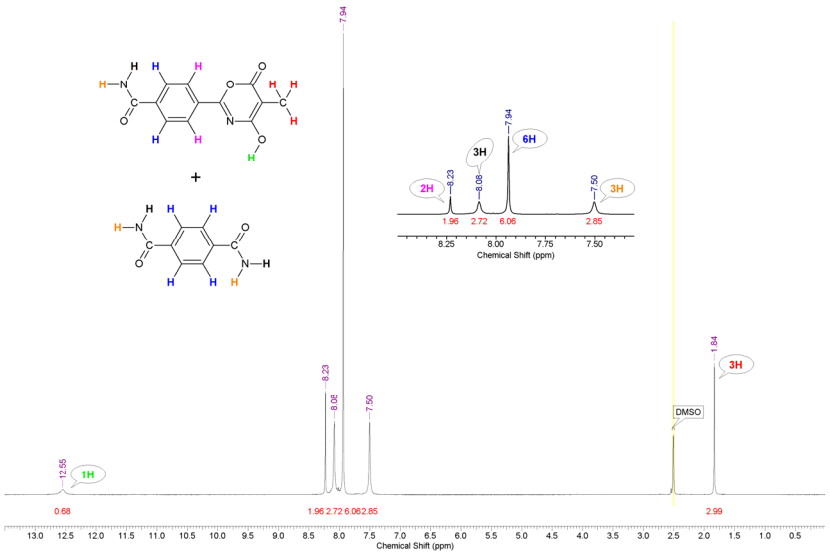


Figure 2. ^{1}H NMR spectrum of 4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide (after 7 h of refluxing) in DMSO-d6.

After carrying out reactions **1.1** and **1.2**, the following results were obtained. 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 product **1**.

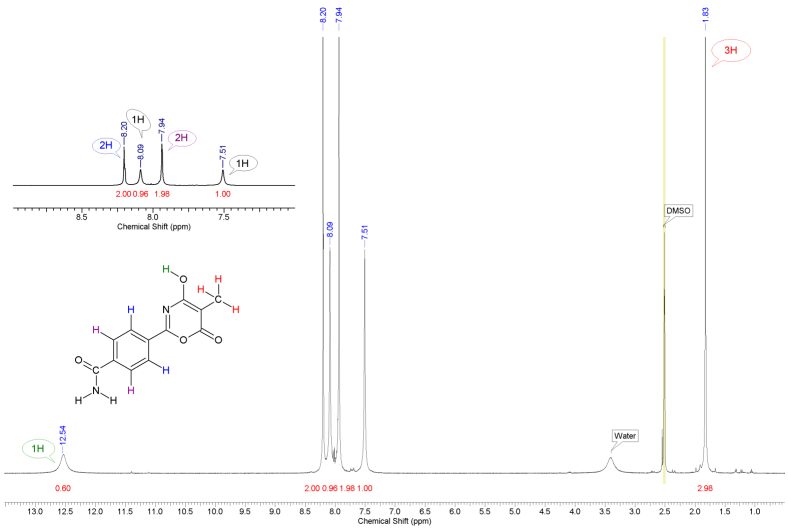


Figure 3. ^{1}H NMR spectrum of 4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide in DMSO-d6.

When the amount of methylmalonyl dichloride was doubled, after 24 h of reacting, only the mono-1,3-oxazine-6-one derivative (1) was obtained; 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).

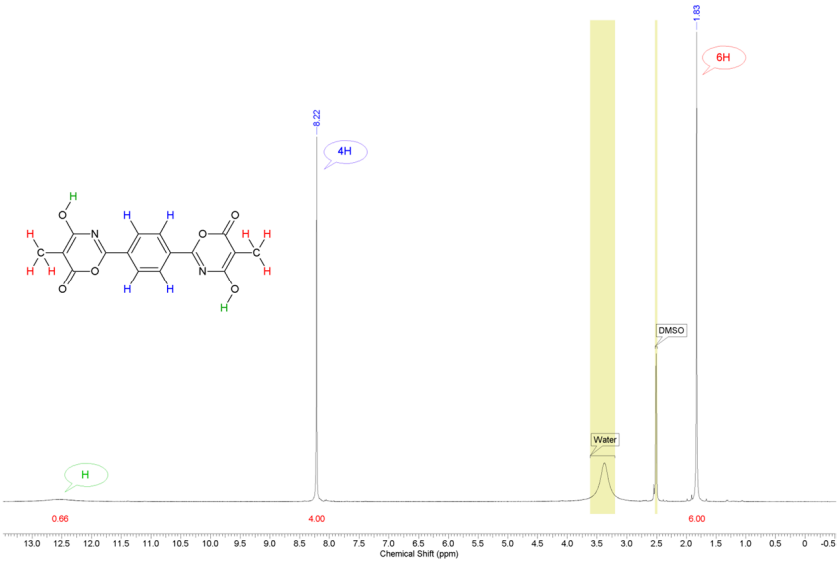


Figure 4. ^{1}H NMR spectrum of 2,2′-(benzene-1,4-diyl)bis(4-hydroxy-5-methyl-6H-1,3-oxazine-6-one) in DMSO-d6.

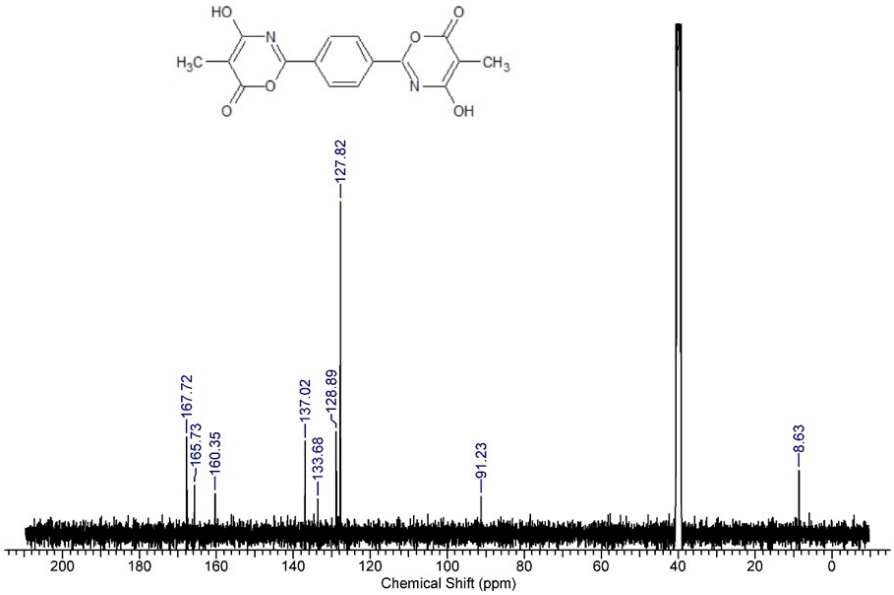


Figure 5. ^{13}C NMR spectrum of 2,2′-(benzene-1,4-diyl)bis(4-hydroxy-5-methyl-6H-1,3-oxazine-6-one) in DMSO-d6.

The structure of the obtained compounds was proven using NMR spectroscopy on ^{1}H and ^{13}C nuclei, which was subsequently confirmed using 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 belonging to the carbon of the amido group. A number of signals corresponding to the 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 the carbon atoms of the 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 a signal at 91.23 ppm belonging to the sp^2 hybrid carbon atoms C_5 of the 1,3-oxazine cycles. A number of signals corresponding to the 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 in the formation of the target compound—85% compared to 77% in EDC.

4. Discussion

For the nitrogen atoms of the 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 using the semi-empirical PM6 method (taking into account the solvent benzene); 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 the mono- (1) and then the 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 a greater nucleophilicity in the reaction with methylmalonyl dichloride compared to 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 the mono-1,3-oxazine-6-one derivative (1). At the second stage of the reaction, the amido groups of the 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.

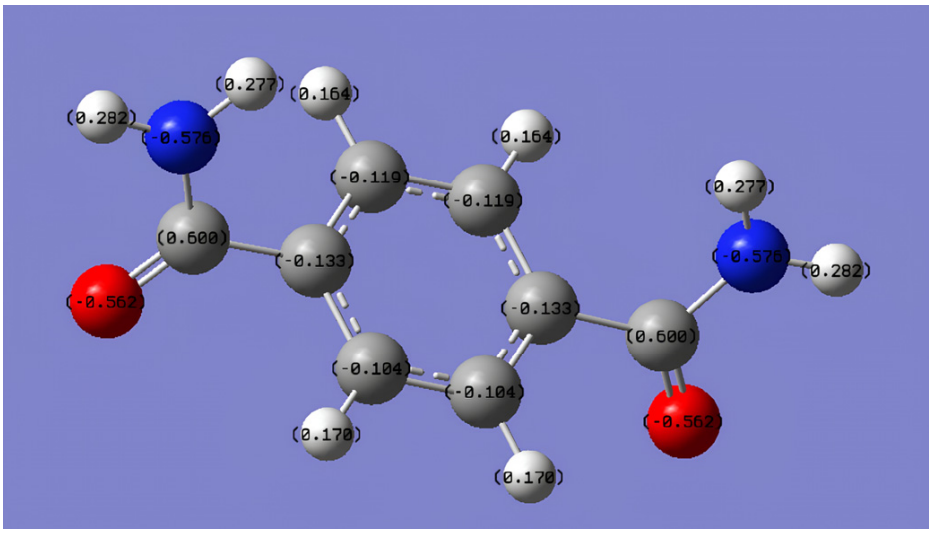


Figure 6. Charges on atoms in benzene-1,4-dicarboxamide molecule.

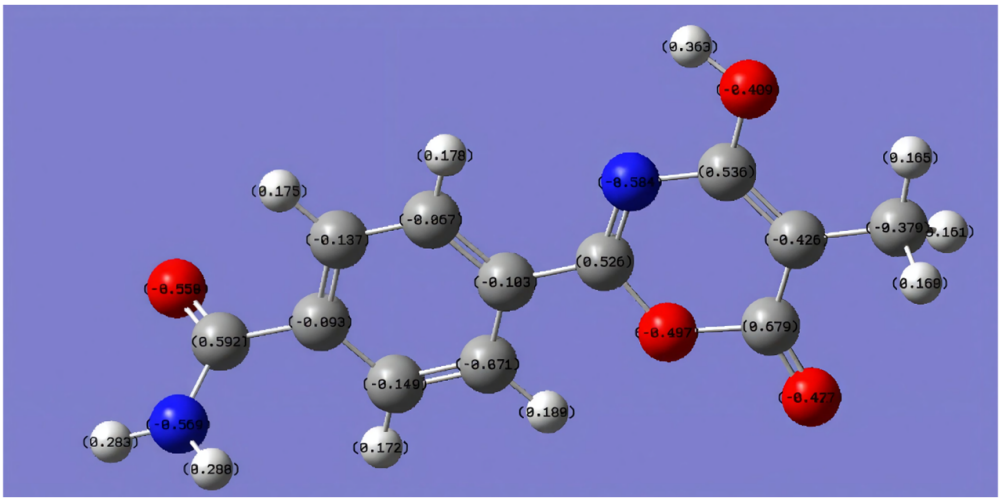


Figure 7. Charges on atoms in 4-(4-hydroxy-5-methyl-6-oxo-6H-1,3-oxazine-2-yl)benzamide molecule.

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; 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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Conflicts of Interest: The authors declare no conflicts of interest.

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