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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF AN AZOMETHINE DERIVATIVE OF PHENOTHIAZINE WITH ACETAMIDE BENZALDEHYDE

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Abstract: *This paper presents the synthesis of an amino derivative of phenothiazine with acetamide benzaldehyde. The method of preparation is described in detail. The newly synthesized compound was proved by IR spectroscopy. Some of its most important physicochemical properties have been established. Its antimicrobial activity was investigated.*

Keywords: *phenothiazine, azomethine, antimicrobial activity, synthesis*

INTRODUCTION

Interest in phenothiazine derivatives has been increasing in recent years due to their newly discovered properties and actions. Recent studies have shown that these compounds possess antimicrobial, antiprion, insecticidal and anthelmintic activities (Pluta, K.,Morak-Młodawska, B., & Jele ´n, M., 2011). Phenothiazine derivatives can be used as anticonvulsants (Mia, L. L., Ralph, R. R., et al, 1988), antitumor(Andreani, A., et al, 1991), antimalarial (Artha, K., Nectarios, K., Leann, T., Leslie, W. D., 2002), antituberculosis (Aaron B. B., et al, 2007), antiemetic (Manish, S., Norman, B. D., Mellar, P. D., Marie, L., Ruth, L., 2003), antihistamine (Oliver, H. W., Alexander, S., Frank, L. H., Wolfram H., Stephan, G., 2006) and antipsychotic (Bateman, D. N., 2003) agents.

Schiff bases are organic compounds used as pigment in dyes, cosmetic industry and are easily synthesized. They have excellent properties such as high thermal stability, biological activity, form metal complexes applicable in many fields (Dhar, D. N. & Taploo, C., 1982; Bringmann, G., et al, 2004; Zabulica, A., Balan, M., Belei, D., Sava, M., Simionescu, B. C., & Marin, L., 2013; Tanak, H., Ağar, A. A., & Büyükgüngör, O., 2014). They can be used as anticorrosive agents (Nikolova, I., Kostova, I., Haralanova, T., Borisov, G., Marinov, M., & Stoyanov, N., 2023).

Increasing resistance of microorganisms to already known drugs necessitates the search for new treatment options. Therefore, we focused our attention on the synthesis and investigation of phenothiazine derivatives containing azomethine bases.

EXPERIMENTAL PART

Schiff base of 6-phenothiazinyl-1,8-naphthalene anhydride synthesis

0.005mol 2-amino-6-(10*H*-phenothiazin-10-yl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (2.05g) was dissolved in 40mL CH_3OH and 0.005mol aldehyde was added. It was heated in a water bath for 1h (~100°C). It was cooled, crystallized and was filtered under vacuum. It was washed with CH_3OH. A pure product was obtained.

Analysis of antimicrobial activity

To determine the antimicrobial activity of the substances, the method of diffusion in agar was used with the following test microorganisms: Gram-positive bacteria *Staphylococcus aureus ATCC 6538*, *Bacillus subtilis ATCC 6633*, Gram-negative bacteria *Escherichia coli ATCC 8739*, *Pseudomonasa aeruginosa ATCC 9027* and *Salmonella abony NTCC 6017*, the yeasts *Candida albicans ATCC 10231*, *Saccharomyces cerevisiae ATCC 2601* and the molds *Aspergillus brasiliensis ATCC 16404* and *Fusarium moniliforme*.

A 1% solution of the test substance in dimethyl sulfoxide (DMSO) solvent was prepared.

The experiments were carried out on Soy-Casein Agar medium (Himedia) for bacteria and Sabouraud Dextrose Agar (Himedia) for yeasts and moulds. The agar media were melted in a Koch apparatus. They were cooled to a temperature of 50-48°C, inoculated with 1% of the previously prepared suspensions of the test microorganisms and mixed well. 20mL of the inoculated media was poured into sterile petri dishes (∅= 90mm). The agar was allowed to solidify. Using a stopper punch, wells (∅= 8mm) were made in the agar. Into the wells, 50µL of the previously prepared solutions were dropped and after 30 min of prediffusion at room temperature, the petri dishes were incubated at 37°C for 24h for bacteria, 28°C for 24h for yeasts and for 7h for fungi.

After cultivating, the diameters of the zones of growth inhibition were recorded with a digital caliper, in mm, with: up to 15mm, the microbial culture was weakly sensitive, from 15 to 25mm – sensitive, and above 25 mm- highly sensitive.

The experiments were carried out in parallel with solvent control, and its effect was accounted for.

Antimicrobial activity data were averaged from three measurements.

RESULTS AND DISCUSSION

The synthesis of the Schiff base went through several steps, the starting compound we used being 1,8-naphthalene anhydride. From this we have obtained 4-bromo-1,8-naphthalene anhydride. The interaction proceeds according to the scheme presented in Figure 1:

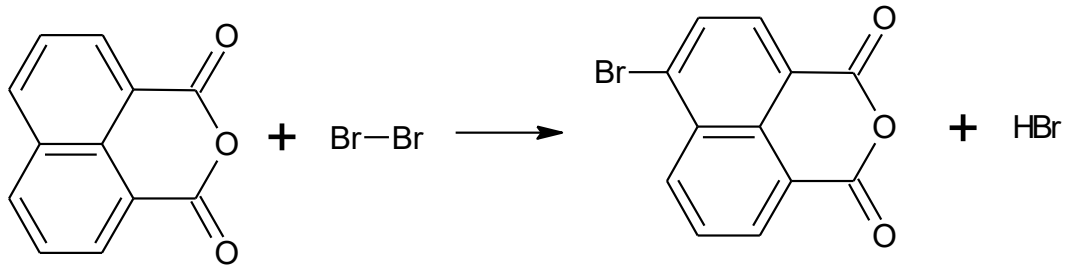

Fig. 1. Synthesis of 4-bromo-1,8-naphthalene anhydride

The 4-phenothiazinyl-1,8-naphthalene anhydride itself was obtained by the interaction of 4-bromo-1,8-naphthalene anhydride with phenothiazine in the presence of DMFA and boiling for 5h (Fig. 2):

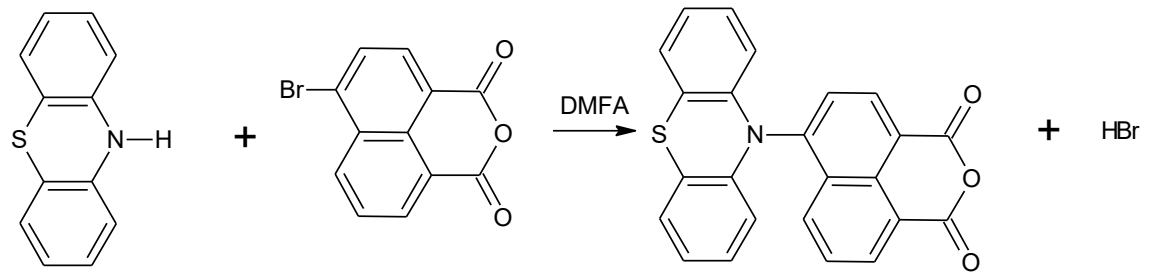

Fig. 2. Preparation of 4-phenothiazinyl-1,8-naphthalene anhydride

The obtained 4-substituted-1,8-naphthalene anhydride appears to be an efficient luminophore, which is sensitive to the action of alkaline reagents in the presence of which the anhydride ring opens, and the formed salts of the substituted naphthalene acid luminesce in low quantum yield (Kostova I., Nikolova I., & Marinov M., 2020).

From 4-phenothiazinyl-1,8-naphthalene anhydride with hydrazine hydrate we obtained an amine derivative, which on reaction with 4-acetamidobenzaldehyde leads forming of the corresponding Schiff base. The interaction is presented in Fig. 3

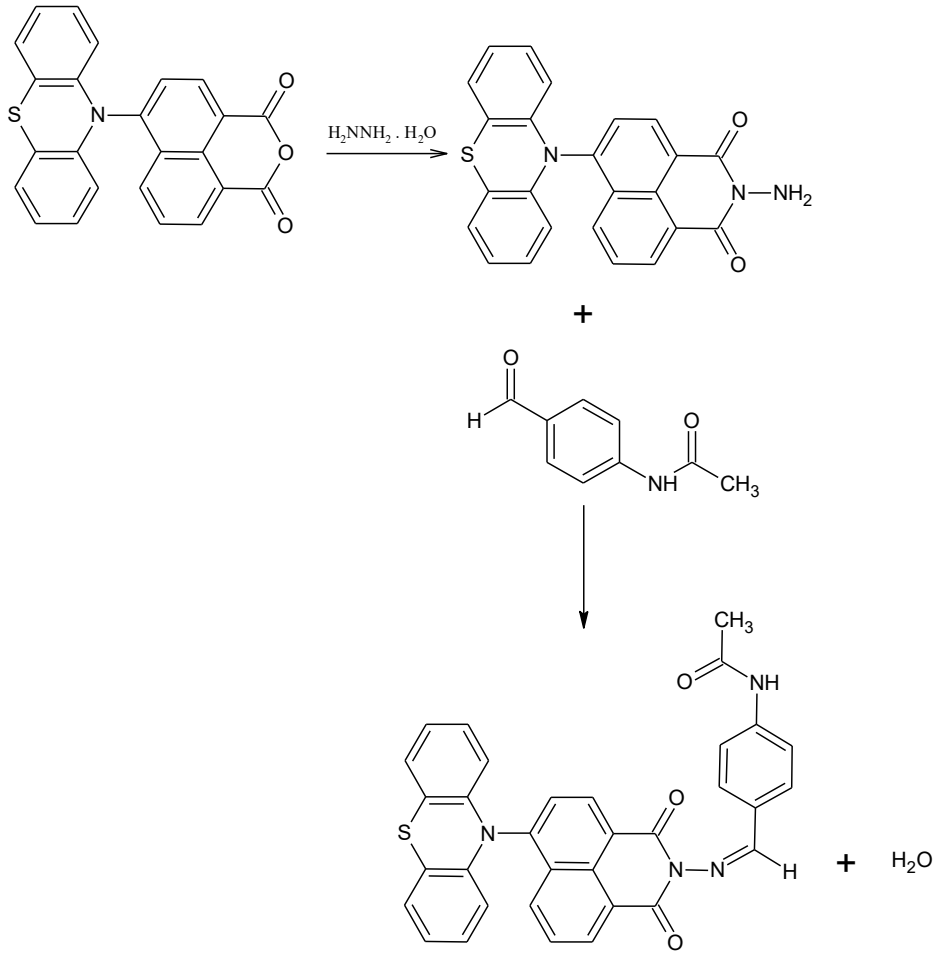

Fig. 3. Synthesis of Schiff base

The newly obtained Schiff base has a m.p. of 186-187°C. The practical yield of the newly obtained compound is 30%.

Table 1 lists the values of the wavelengths that prove the production of a new compound:

Table 1 IR-spectral data for the newly obtained Schiff base

$\nu_{C=O}$	$\nu_{C=N}$	ν_{C-N}	$\nu_{Arom.}$	ν_{NH}
1699 1663	1606	1324	3096	3371

The results of the performed antimicrobial activity analyses showed no clear zone near the wells. From this it can be concluded that the compound does not exhibit activity towards the test microorganisms used.

CONCLUSION

A new azomethine derivative of phenothiazine has been synthesized and its physicochemical properties have been determined. The compound was proven by IR spectroscopy. Its antimicrobial activity was investigated.

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