

New Perspectives in Therapy of Intoxications by Organophosphoric Compounds

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Abstract

Little references actually exist on neutralization therapy which could constitute the missing ring from an efficient treatment. As structural model capable to interact with organophosphoric substances, at the level of phosphor (P) atom, the common chemical element of the hole class of substances, was proposed those of benzimidazole. Different quantities of benzimidazole were put in contact with a fix quantity of trichlorphon in acid conditions and formation of a new compound was evidenced by infrared spectrometry. Similar experiments were made utilizing benzimidazole derivatives (2 methyl or 2 benzyl benzimidazole) and different temperatures: 35°C and 40°C. By increasing massic rate: benzimidazole/trichlorfon as well an increased reaction temperature, have favourably influenced trichlorphon capture. The obtained results justified an continuation of researches in the direction of new compounds with a structure similar with that of benzimidazole for funding an efficient neutralization therapy for organophosphoric substances.

Introduction

The accidental or voluntary intoxications by organophosphoric compounds (OPC) are continuously representing an important medical problem due to their high frequency along with the mortality and morbidity involved [1].

This undesirable situation often arises although antidote therapies are known and properly applied (atropine, cholinesterase activators, diazepam) while for other types of intoxications the available therapies are rather few.

There are still summary information on the possibilities of neutralizing the organophosphoric compounds within the digestive tract of the intoxicated patients, hence till their systemic absorption. The absorption stoppage of organophosphoric compounds could be the additional therapeutic element conferring a better control for the patients intoxicated by the above mentioned substances.

The benzimidazole structure [2] was proposed as a structural model able to interact with the organophosphoric substances at the level of the chemical

element common to all of them, the phosphorus.

By taking the two unshared p electrons of the sp³ nitrogen atom into account, in the benzimidazole derivatives, their reaction with the organophosphoric compounds was supposed to be possible and the trichlorphon [3] chosen as a representative. The literature mentions the synthesis of such products and highlights in the most cases their biological activity [4,5]. The present paper is aimed to estimate the reaction possibility of trichlorphon with several benzimidazole derivatives as well as the influence of different parameters on the reaction efficiency in the purpose of substantiate an efficient therapy of neutralizing the organophosphoric substances.

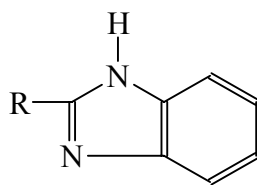
Experimental

Materials

Benzimidazole, methyl-benzimidazole, benzyl-benzimidazole-synthesized in the laboratory of Organic Chemistry "Al. I. Cuza" University of Iasi (analytical grade).

Their structure is given below,

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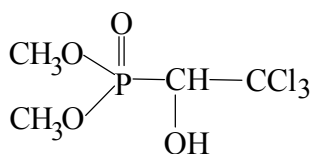
II-IV

where: **II**: R= -H

III: R= -CH₃

IV: R= -CH₂-C₆H₅

Trichlorphon – white powder, stable for more than 40 days in aqueous solutions of pH = 1-5 and temperatures between 30-40°C, of the following structure:



I

Method

Various amounts of benzimidazole (0.0295 g, 0.0591 g, 0.118 g, 0.1772 g and 0.2363 g, respectively, to correspond to the different values of the molar ratio benzimidazole/trichlorphone) were suspended into 100 ml of 0.1 N hydrogen chloride solution, under stirring, on a water bath at 30°C. The trichlorphon

was then added in equal amounts (0.2575 g, 0.001 mole) to the five samples and the stirring at 30°C continued. After 2 hours the solution was transferred into a beaker where the product **V** precipitated by cooling at room temperature. It was then filtered under vacuum, dried for 3 hours in an oven at 60°C, finally weighted and the yield estimated. The experiments were repeated at the temperatures of 35°C and 40°C, with the same amounts of reagents.

The compounds **VI** and **VII** were prepared similarly to the compound **V** by using 0.0330 g, 0.0661 g, 0.1321 g, 0.1982 g and 0.2643 g 2-methyl-benzimidazole, and 0.0520 g, 0.1040g, 0.2080 g 0.3120 g and 0.4160 g 2-benzyl-benzimidazole, respectively.

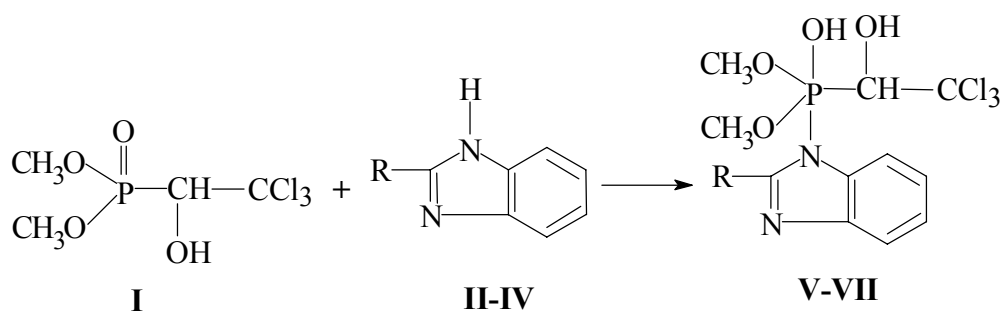
The reaction between the benzimidazole derivatives and trichlorphon was proved by submitting the products to IR spectral measurements.

Results and Discussions

The trichlorphon corresponds to the conditions required for the study, namely:

- pH value similar to the gastric pH;
- working temperature: 30, 35, 40°C.

When treated with benzimidazole derivatives (**II-IV**) the trichlorphone is inactivated by a nucleophilic addition mechanism, being included into compounds of larger molecules (**V-VII**).



II, V: R= -H; **III, VI**: R= -CH₃; **IV, VII**: R= -CH₂-C₆H₅

The coupling is influenced by several factors, namely: reagent nature, benzimidazole derivative/trichlorphone molar ratio and temperature. Their influence on the reaction was studied. The temperatures chosen were of values as close as possible to the human organism temperature in order to simulate its specific conditions.

The IR spectra of the coupling products (**V-VII**) show the absorption bands characteristic of benzi-

midazole, as well as a wide band at 940-1000 cm⁻¹ attributable to the vibration of the P-OH band. The absence of the intense band at 1250-1300 cm⁻¹ characteristic of the P=O group is noticed which confirms the reaction development. Besides, the absorption bands at 700-750 ν_{C-Cl} and 1030-1050 cm⁻¹, ν_{CH₃-O-P}, are to be found.

The physical characteristics of the products (solubility, melting point) correspond with those already

mentioned in the specific literature [4-6].

The content of the trichlorphon chemically bound by the benzimidazole derivatives was found to increase with increasing benzimidazole derivative/trichlorphon molar ratio at a constant temperature.

The temperature increase had a favourable influence on the reaction causing an increased percentage of the coupled trichlorphon. The conjugated influence of the two parameters under study is depicted in Figures 1-3.

In every case the trichlorphon was found to couple at the nitrogen atom in the benzimidazole derivative by means of the phosphorus atom, the coupling product percentage being influenced by the parameters under study: benzimidazole derivative/trichlorphon mass ratio, temperature.

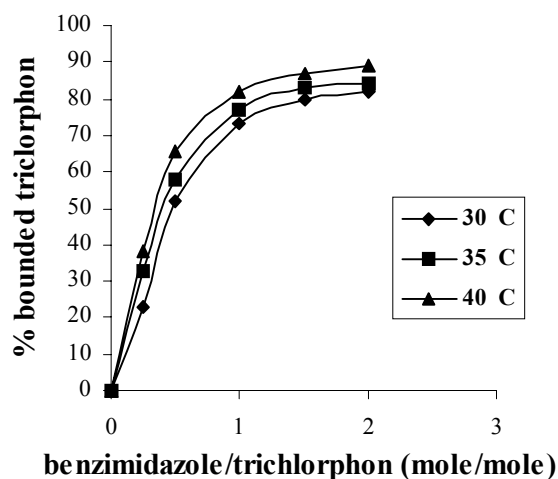


Fig. 1. Variation of the coupling product amount in function of the benzimidazole/trichlorphon molar ratio, at different temperatures

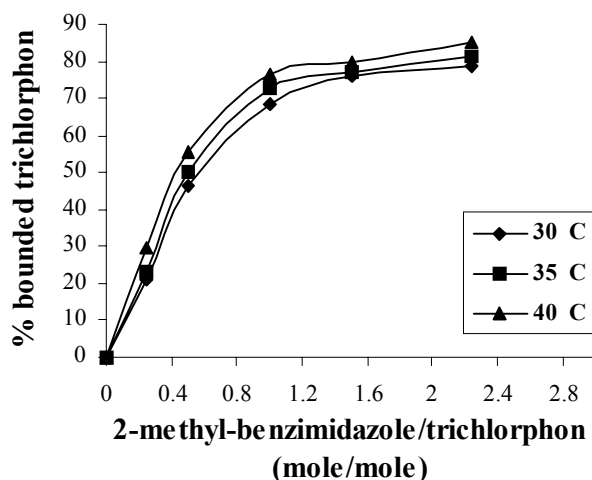


Fig. 2. Variation of the coupling product amount in function of 2-methyl-benzimidazole/trichlorphon molar ratio, at different temperatures

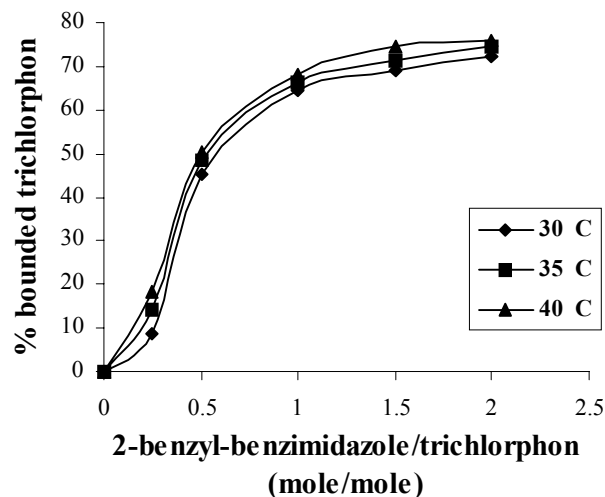


Fig. 3. Variation of the coupling product amount in function of 2-benzyl-benzimidazole/trichlorphon molar ratio, at different temperatures

The obtained results would justify the carrying on the studies on other compounds of structures of the benzimidazole type in order to substantiate an efficient therapy for neutralizing the organophosphoric substances.

Conclusions

The benzimidazole derivatives can bind the trichlorphon at the phosphorus atom, the chemical element which is common to all organophosphoric compounds. Consequently, these derivatives would be supposed to become useful in the treatment of the intoxications with organophosphoric compounds.

The reaction yields were higher when the trichlorphon was coupled with benzimidazole than with monosubstituted benzimidazole where the bulky substituents determine the steric hindrance.

The amount of the coupling product was found to increase with increasing benzimidazole derivative/trichlorphon molar ratio, exceeding 80% with benzimidazole.

The coupling is favourably influenced by the temperature.

References

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