SYNTHESIS OF CURCUMIN DERIVATIVES

MAGDA GABRIELA BRATU

"Valahia" University of Targoviste, Romania, bratugabriela@xnet.ro

Abstract: In this paper the synthesis of curcumin and curcumin derivatives is realised, based on the condensation of benzaldehydes substituted by acetyl acetone. The synthesis way is described and the obtained products are characterised in terms of substituted benzaldehydes, colour, melting point and elemental composition.

Keywords: curcumin, curcumin derivatives, chemical synthesis

INTRODUCTION

The first synthesis of curcumin started from the chloride of the carbometoxy-feruloic acid. This synthesis method is also extremely difficult as it presupposes going through several stages until the curcumin is obtained (Paban, 1937).

The second synthesis consists on the condensation of carbometoxy-feruloilchloride with vinyl acetate in the presence of anhydrous aluminum chloride in a carbon sulfide environment. Using water treatment of the complex aluminum salt carbon dioxide is given off and curcumin is obtained.

The method originates in the biosynthesis of curcumin in plant cells as the blocking of the medial carbonyl group can be performed under the influence of the adenozitriphosphoric acid through estherification with the phosphoric acid of the enolic form of the acetyl acetone (Tabarasu et al., 1997).

Starting from the idea of simplifying these methods, Jan Van Alphen and Hendrik Jacob Paban synthesized the curcumin in 1959, based on acetyl acetone and vanillin, through the blocking of the medial methylene group of the acetyl acetone with boric anhydride. Although they do not explain the mechanism of the reactions within this synthesis process, it can be noticed that the blocking of the central methylene group is based on the acetyl acetone's capacity to enolize by means of the said methylene group.

The enolic form is stabilized by boric anhydride- mediated estherification. Following the condensation of the two lateral methylenes with two vanillin molecules, the esther is hydrolyzed in acid catalysis, therefore obtaining free curcumin.

The reaction medium used is an esther, usually the ethyl acetate. The product of the condensation of the acetyl acetone and of the boric anhydride is practically insoluble in the ethyl acetate (Perrati, 1975).
The condensation reaction occurs, in this case, within a homogenous environment. In order that this reaction to take place under best conditions, it is necessary to use a slightly alkaline medium, which is obtained by adding into the system of a small quantity of a primary amine with low volatility. To this purpose, one of the following amines: buthylamine, pentylamine or hexylamine can be used.
Starting from this synthesis process, a series of curcumin derivatives were obtained by using vanillin for the synthesis of the sample and of the substituted benzaldehydes such as: 4-metoxy-benzaldehyd, 4-N, N'-dimetiyamino-benzaldehyd, 4-hydroxi-benzaldehyd and 4-nytro-benzaldehyd for the synthesis of the curcumin derivatives.
This paper refers to the synthesis of the curcumin derivatives starting from the condensation of benzaldehydes substituted by acetyl acetone. Within this condensation process, the substituted benzaldehydes react as carbonyl components, whereas the acetyl acetone reacts as a methyl component by means of its two lateral methyl groups. The problem that arises is the fact that the acetyl acetone also contains a medial methyl group whose reactivity is higher than that of the lateral groups. Due to this, it is necessary to block the methyl group, throughout the synthesis process, such group being released at the end of the said process (Bratu, 2004).

MATERIALS AND METHODS

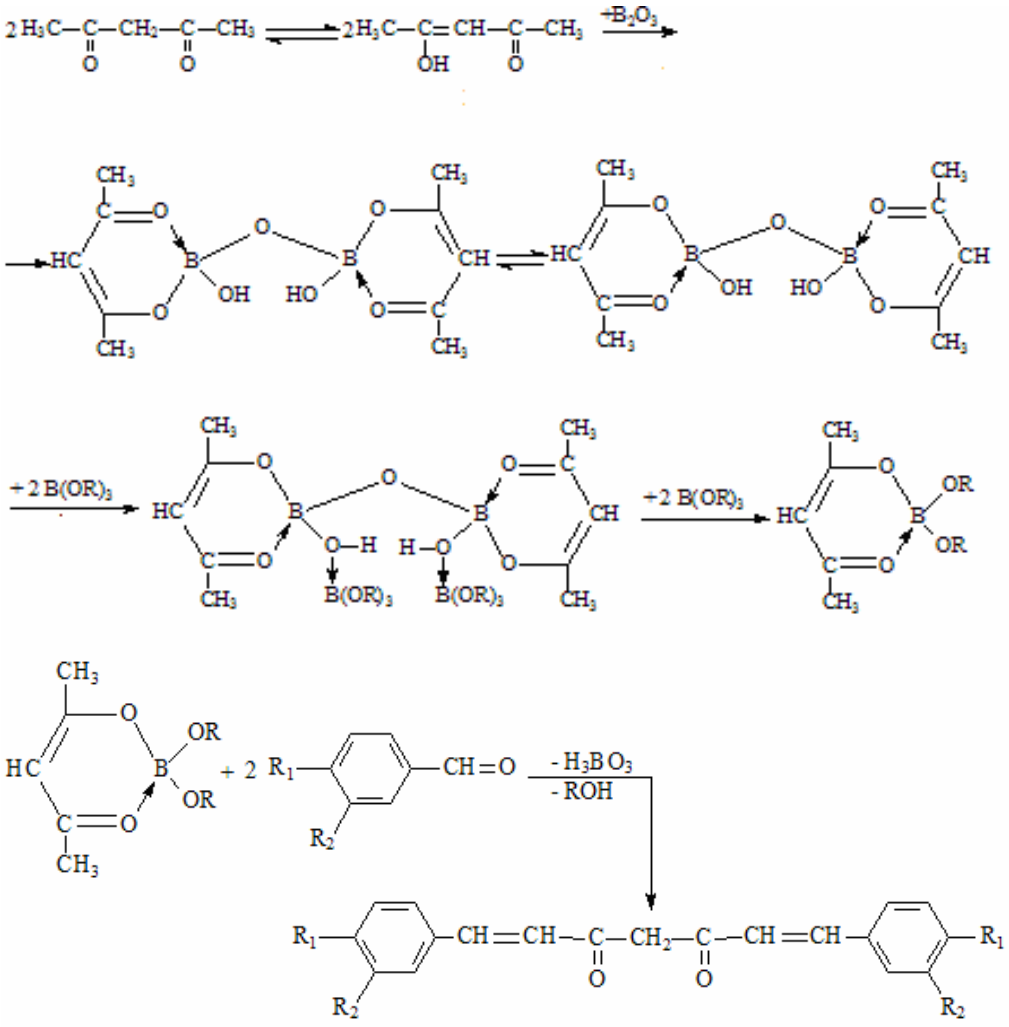
Stages of the synthesis process followed the procedure presented in (Paban, 1937). In all cases, the synthesis alternative chosen supposed the stages indicated in Figure 1 (***, 1995).

A. Estherification of the acetyl acetone with boron trioxide

This process was performed in a grinding mortar, by mixing in- excess acetyl acetone with the solid boron anhydride powder, in a cold environment. While homogenizing the mixture, a clear solution is obtained which, upon the completion of the estherification process, turns into a solid mass of an acetyl acetone boron esther (the enolic form). Having been ground, such esther was then used in the synthesis process.

B. Condensation of the boron esther with the substitute benzaldehydes

All reactions used ethyl acetate as solvent. The process was experimented by dissolving the aldehyde in ethyl acetate, possibly by heating, cooling at 200°C, followed by the addition of tributhylborate and of acetaldehyde boron esther , at room temperature.



where: $\mathbf{R_1}$=CH_3O, NO_2, $(CH_3)_2N$, OH, $\mathbf{R_2}$=H, OH

Figure 1. Obtaining of the curcumin derivatives

C. Reaction Mass Processing

The reaction mass is acidified at 50°C with diluted acid in order to obtaining a total hydrolysis of the estheric compound. Following the addition of the aqueous hydrochloric acid solution, two layers separate. The more hydrophobic curcumin derivative appears in the organic phase. Such derivative is extracted with ethyl acetate, in portions.
The curcumin compound is isolated from the ethyl acetate- based solution by adding methanol, in a cold environment, for 3-4 hours. The resulting precipitate is washed in cold methanol until the filtrate is almost colourless.

D. Re-crystallization

The re-crystallization of curcumin and of the curcumin analogues was performed based on a solution containing ethyl acetate: a 3:2 methanol ratio (volume), with a 7:1 solvent: curcumin ratio (mass).
The compounds obtained in this way underwent physical- chemical measurements in order to determine their structures and purities.
The analyses were performed by means of an automated analyzer provided by a gas chromatograph.

RESULTS AND DISCUSSIONS

Table 1 presents the synthesis data.

Table 1. Experimental data on the curcumin synthesis and of analogous derivatives

Curcumin **d**erivative			**Substituted benzaldehydes**		**Colour**	**Melting point, °C**
	R_1	R_2	g	mol		
1a	OH	OCH_3	15	0.1	Orange-yellow	176 – 178, brut 183, pure
1b	CH_3O	H	14	0.1	Red	161
1c	NO_2	H	15	0.1	Straw -yellow	142
1d	$(CH_3)_2$ N	H	15	0.1	Straw -yellow	150
1e	OH	H	12	0.1	Dark red	177

The curcumin derivatives quantities listed in Table 1 are obtained from 0.1 vanillin moles or 0.1 substituted benzaldehydes

The synthesized compounds were characterized by means of an elemental analysis, the resulting data being presented in Table 2.

Table 2. Experimental data on the elemental analysis of the synthesized curcumin derivatives

Comp. no.	**Gross formula**	**Elemental Analysis**					
		% C		**% H**		**%N**	
		Calc.	Found	Calc.	Found	Calc.	Found
1a	$C_{21}H_{20}O_6$	68.47	68.00	5.47	5.42	-	-
1b	$C_{21}H_{20}O_4$	74.98	74.88	5.99	6.08		
1c	$C_{19}H_{14}N_2O_6$	62.30	62.42	3.85	3.60	7.65	7.50
1d	$C_{23}H_{26}N_2O_2$	72.48	72.31	7.23	7.29	7.73	7.60
1e	$C_{19}H_{16}O_4$	74.01	73.90	5.23	5.34		

As indicated in Table 2, the values of the theoretical and actual carbon and hydrogen percentage in the synthesized compounds are quite close, an argument in favour of the structure attributed to such compounds.

The use of such derivatives as food colours shall only be possible after analysing their toxicity by means of standard biological determinations.

CONCLUSIONS

Curcumin as well as a number of 4 analogous curcumin derivatives, not previously mentioned in the specialized literature, were obtained in this research as a result of the experiments.
The resulted products were characterized by means of an elemental analysis. The analyses having been performed attest the above mentioned structures of the synthesized compounds.

REFERENCES

1. ***, *Curcumin derivatives synthesis*, Research grant, Universitatea Politehnica Bucuresti, 1995, Identification number 45-95-03
2. Bratu M., *Coloranti alimentari polifunctionali* - Teza de doctorat (parte experimentala), 2004
3. Paban, H. J. J., Curcumin synthesis, *Rec. Trav. Chim. Pays Bas*, 1937, 83, 167-172
4. Peratti, G., 1975, *Ind. Aliment.* 14, 66, cf. Chem. Abstr. 1975, 83, R3244a.
5. Tarabasanu, C., Gorduza, V., Radu, F., Mazgareanu, M., *Coloranti organici de interes alimentar, cosmetic si farmaceutic*, 1997, Ed. Uni-Pres, Bucuresti