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A SYNTHESIS OF CURCUMIN AND RELATED COMPOUNDS

BY

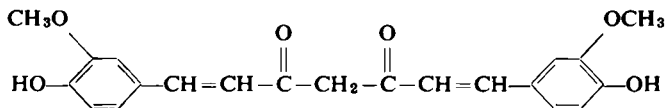
H. J. J. PABON

(Unilever Research Laboratory, Vlaardingen, The Netherlands)

Curcumin has been prepared in 80% yield from vanillin and acetyl-acetone/B₂O₃ in the presence of tri-*sec.* butyl borate and butylamine. The reaction was carried out in ethyl acetate at room temperature. Eight compounds related to curcumin have also been synthesized.

I. Introduction

For many centuries the dried and ground roots of *Curcuma Longa Kunir*, known as curcuma or turmeric, have been used as a dye for foods and spices (curry) in the far East ¹. The colouring substance (1.5-2% of the dried root) curcumin, an orange-red compound, was isolated in 1870, but it was not until 1910 that *Lampe et al.*² elucidated the structure as shown:



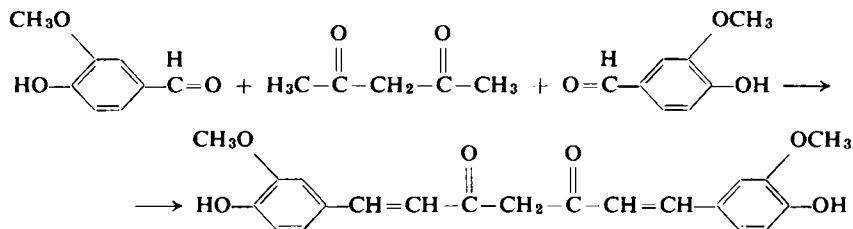
which was later confirmed by synthesis. This synthesis ³, starting from vanillin builds up curcumin in eight steps and has little practical value.

¹ Ullmans Encyklopädie der technischen Chemie, Urban and Schwarzenberg, München-Berlin 1956, Vol. 7, p. 104.

² J. Milobedzka, St. v. Kostanecki and V. Lampe, Ber. **43**, 2163 (1910).

³ V. Lampe, Ber. **51**, 1347 (1918). For a review see: E. H. Rodd "Chemistry of Carbon Compounds" Elsevier Publishing Company, Amsterdam-London-New York, Princeton 1956, Vol. III B, p. 1181.

Pavolini et al.^{4, 5} prepared curcumin by heating vanillin, acetylacetone and boric anhydride (2 : 1 : 2) over a free flame for 30 minutes and claimed a yield of 10% in this one step procedure:



This method proved to be unsatisfactory in our hands and gave us yields of about 1.5% only.

We observed, however, that condensation of vanillin and acetylacetone in the presence of boric anhydride took place at 150°, if minor amounts of butanol and piperidine were also present (yield = 10%). This led us to the idea that boric esters^{6, 7} and bases like piperidine might be used with success for this type of condensation. An experiment with tributyl borate, piperidine and the reaction product of acetylacetone and boric anhydride (yield 25%), prompted us to study all factors involved more systematically*.

II. Results

Of the bases tested (pyridine, morpholine, mono-, di- and tri-alkylamines and alkanolamines) only the mono-alkylamines and especially *n*-butylamine had a strong catalytic effect. This effect was increased by adding the amine in small portions during the reaction. When butylamine only was used, a yield of 10% could be obtained. This yield rose to 45% when 0.27 mole of tributyl borate/mole of vanillin was used. A further increase in this ratio resulted in no higher yield. The best temperature range for the condensation was 85-110°.

Higher yields could be obtained by using a solvent. Of the solvents tested ethyl acetate gave the best results. In this case the amount of tributyl borate had to be raised to 1.5-2 moles per mole of vanillin. Finally, tri-isopropyl borate and tri-*sec.* butyl borate proved to give the best yields (80%: see Table I).

* Patents have been applied for in various countries. See, for example, Brit. Pat. 914,047 (1962) by *J. van Alphen* and *H. J. J. Pabon*, assignors to Unilever Ltd.

⁴ *T. Pavolini*, Riv. Ital. Essenze **19**, 167 (1937).

⁵ *T. Pavolini, F. Gambarin* and *A. M. Grinzato*, Ann. Chim. Roma **40**, 280 (1950).

⁶ *H. Steinberg* and *D. L. Hunter*, Ind. Eng. Chem. **49**, 174 (1957).

⁷ *J. Kollonitsch* and *J. Vita*, Nature **178**, 1307 (1956).

Table I

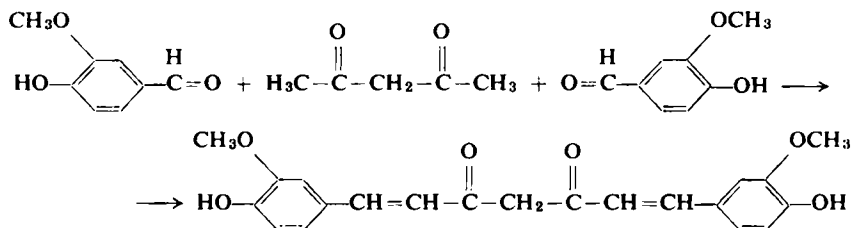
Influence of the nature of the trialkyl borate on condensation at room temperature of 0.4 mole of vanillin with the reaction product from 0.2 mole of acetylacetone and 0.14 mole of boric anhydride in 200 ml of ethyl acetate, adding 0.8 mole trialkyl borate and 4 ml butylamine.

Trialkyl borate	Yield on curcumin (%)
Trimethyl borate	63
Triethyl borate	71
Tripropyl borate	72
Tri-isopropyl borate	80
Tri- <i>n</i> -butyl borate	73
Tri(2-butyl) borate	78
Tri-isobutyl borate	69
Tri- <i>tert</i> .butyl borate	58
Tripentyl borate	59
Tri(2-methylbutyl) borate	66
Trioctyl borate	57
Trioctadecyl borate	± 5

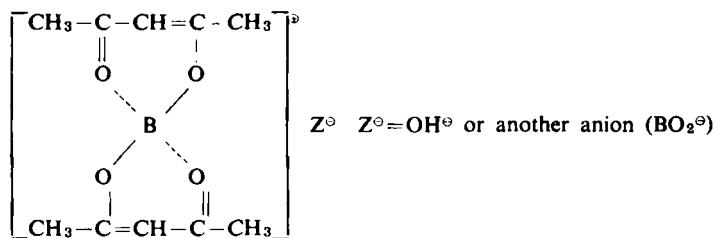
Using the procedure developed for the synthesis of curcumin, several other aldehydes were condensed with acetylacetone/B₂O₃. Only aromatic and heterocyclic aldehydes gave well defined products, whereas saturated aliphatic aldehydes failed to couple at all. In some cases reactions had to be carried out at elevated temperature since at room temperature the condensation product of 1 molecule of aldehyde and 1 molecule of acetylacetone was formed as the main product.

III. Discussion

*Pavolini et al.*⁴ prepared curcumin in low yield by heating a mixture of vanillin, acetylacetone and boric anhydride for 30 minutes over a free flame. The low yield is not unexpected in view of the high reaction temperature. On the other hand, under these conditions a high temperature is necessary to get any reaction at all. In this synthesis vanillin condenses with the less reactive methyl groups of acetylacetone thus:

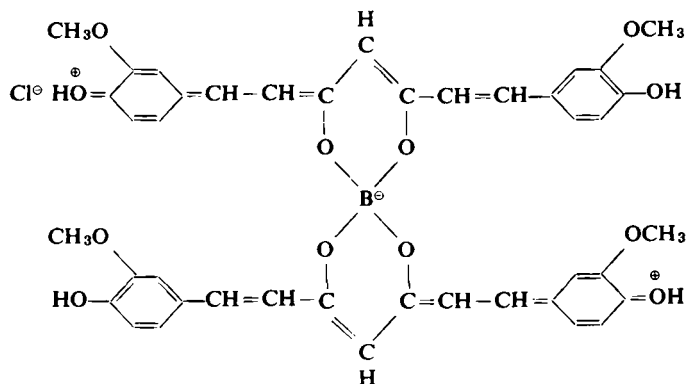


In our opinion this behaviour must be ascribed to the properties of the acetylacetone/boric anhydride complex. This compound, which is not mentioned by *Pavolini*, probably has the structure ^{8, 9}:



Its formation would explain several facts:

1. An "active" methylene group is absent. Reactions appear to occur with its methyl groups.
2. If acetylacetone/boric anhydride is actually the condensing species then it follows from the equation:
 $6 \text{C}_4\text{H}_9\text{OH} + \text{acetylacetone/B}_2\text{O}_3 \rightleftharpoons 2(\text{C}_4\text{H}_9)_3\text{BO}_3 + \text{acetylacetone}$
 that any alcohols in excess will suppress the formation of the acetylacetone/boric anhydride complex whereas trialkyl borate will further it. This has been confirmed by experiments.
3. Curcumin is not obtained in the free state in this procedure but as a complex containing boron. This complex, metallic green when formed, brick red in acid medium and deep purple in alkaline medium, has properties identical with rosocyanin for which *Spicer* and *Strickland* ¹⁰ propose the structure:



⁸ W. Dilthey, Ann. **344**, 300 (1906).

⁹ L. J. Bellamy, G. S. Spicer and J. D. H. Strickland, J. Chem. Soc. **1952**, 4653.

¹⁰ G. S. Spicer and J. D. H. Strickland, *ibid.* **1952**, 4644.

It is decomposed by dilute acids and by bases. We preferred decomposition with dilute acids because curcumin itself is unstable towards alkali.

IV. Experimental *

All temperatures are uncorrected. Melting points were determined with a "Büchi" apparatus. Commercially available chemicals were purified and dried by standard methods.

IV. 1 Synthesis of curcumin at elevated temperature

Vanillin (60.8 g, 0.4 mole) and tributyl borate (25.5 g; 0.11 mole) were heated to 100°. Subsequently the reaction product ** from 20 g of acetylacetone (0.2 mole) and 10 g of boric anhydride (0.14 mole) was added and the mixture heated for 30 min, while stirring, in order to get a homogeneous mixture.

After cooling to 85°, 1 ml of butylamine was added every 5 min (total 4 ml). The colour of the mixture immediately changed to dark green with a metallic lustre. Finally, after having been kept for 30 min at 100°, while stirring, the mixture turned brown.

After cooling to 50°, 300 ml of 0.4 *N* hydrochloric acid (60°) were added; the mixture was then stirred for another 30 min, after which 400 ml of ethyl acetate were added. The layers were separated, and the aqueous layer was extracted once with 100 ml of ethyl acetate. The combined ethyl acetate layers were washed acid-free, dried over sodium sulfate and evaporated. The residue was dissolved in 100 ml of methanol and subsequently cooled, after which the crystals were sucked off. Yield 33 g (45%) orange-red crystals, m.p. 177-178° (lit. ⁴: 183°).

Found : C 68.2 ; H 5.4 ; OCH₃ 16.1

Calc. for C₂₁H₂₀O₆ (368.37): „ 68.48; „ 5.44; „ 16.86.

IV. 2 Synthesis of curcumin at room temperature in ethyl acetate

Vanillin (60 g, 0.4 mole) and 210 ml (184 g) of tributyl borate (0.8 mole) were dissolved in 200 ml of dry ethyl acetate. The compound formed from 20 g of acetylacetone (0.2 mole) and 10 g of boric anhydride (0.14 mole) was added and the mixture stirred for 5 min. While stirring, 1 ml of butylamine was added drop by drop every 10 min (total 4 ml). Stirring was continued for 4 h, after which the mixture was allowed to stand overnight.

The next day 300 ml of 0.4 *N* hydrochloric acid (60°) were added and the mixture was stirred for 60 min. The layers were separated, and the aqueous layer was extracted three times with 100 ml of ethyl acetate. The combined ethyl acetate layers were washed acid-free and evaporated to about 150 ml. Then 100 ml of methanol were added and, after 3 h in the refrigerator, curcumin was filtered off, washed with cold methanol until the wash liquid was yellow and dried. Yield 50 g (68%) orange-red crystals, m.p. 176-178°. From the mother liquor and the washing 3 g of curcumin (m.p. 176-178°) could be obtained. Total yield 53 g (73%).

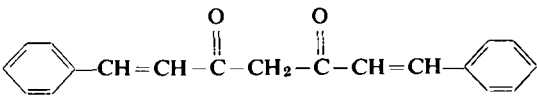
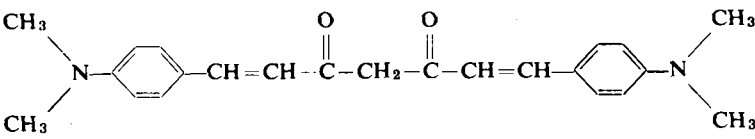
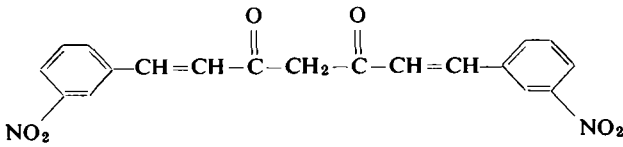
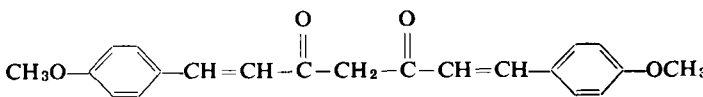
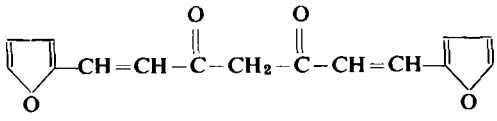
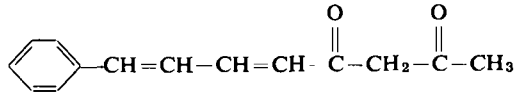
IV. 3 Synthesis of related compounds

Aldehyde (0.2 mole), tributyl borate (0.4 mole) and the reaction product of acetylacetone (0.1 mole) and boric anhydride (0.07 mole) were dissolved in 100 ml of dry

* The elementary analyses were carried out by Messrs. P. J. Hubers, H. Pieters and W. J. Buis, Laboratory of Organic Chemistry, University of Amsterdam.

** When stirring 20 g of acetylacetone (0.2 mole) with 10 g of boric anhydride (0.14 mole) the temperature rises to about 75° and a thick paste is formed.

Table
Synthesis of compounds

No.	Formula	Yield
1	 <chem>O=C1C=CC(=O)C=Cc2ccccc2</chem>	23%
2	 <chem>CN(C)c1ccc(cc1)/C=C/C(=O)CC(=O)/C=C/c2ccc(cc2)N(C)C</chem>	36%
3	 <chem>O=C1C=CC(=O)C=Cc2ccc(cc2)[N+](=O)[O-]</chem>	25% ^b
4	 <chem>COC1=CC=C(C=C1)/C=C/C(=O)CC(=O)/C=C/c2ccc(cc2)OC</chem>	57% ^b
5	 <chem>O=C1C=CC(=O)C=Cc2ccoc2</chem>	8%
6	 <chem>CC(=O)C=CC=Cc1ccccc1</chem>	20% ^d

^a After acidification, filtered and crystallized from dimethylformamide.

^b Condensed at 50°.

^c Crystallized from dioxan.

^d 1 mole aldehyde/mole acetylacetone.

lated to curcumin

Melting point	Colour	Formula	Molecular weight	C		H		O	
				Found	Calc.	Found	Calc.	Found	Calc.
140.5°	Greenish-yellow	$C_{19}H_{18}O_2$	276.32	82.3	82.58	5.7	5.84	12.2	11.58
206-207° ^a	Purple-red	$C_{23}H_{26}O_2N_2$	362.46	75.8	76.21	7.2	7.23	9.0	8.83
221-223° ^c	Canary-yellow	$C_{19}H_{14}O_6N_2$	366.32	62.5	62.29	4.0	3.85	26.2	26.21
164-165°	Orange	$C_{21}H_{20}O_4$	336.37	74.4	74.98	6.0	5.99	19.0	19.03
129-130°	Straw yellow	$C_{15}H_{12}O_4$	256.25	70.2	70.30	4.9	4.72	25.1	24.98
214-215°	Brown yellow	$C_{14}H_{14}O_2$	214.25	78.5	78.48	6.5	6.58	15.0	14.94

ethyl acetate. Butylamine was added (0.5 ml every 10 min; total 2 ml) while stirring. Stirring was continued for 4 h. After standing overnight the mixture was worked up. Six new compounds were synthesized in this way (see Table II).

Cinnamic aldehyde gave 1,11-diphenyl-1,3,8,10-undecatetraene-5,7-dione (29%; reaction temperature 50°), m.p. 184-185° (lit. ⁵: yield 11%; m.p. 189-190°) and piperonal gave 1,7-dipiperonyl-1,6-heptadiene-3,5-dione (59%; reaction temperature 40°), m.p. 198-199° (lit. ⁵: yield 8%; m.p. 190-195°).

Acknowledgement

The author thanks Dr. *J. van Alphen* for helpful suggestions and Miss *L. E. Scheurer*, Mr. *D. E. N. Kandou* and Mr. *L. van der Wolf* for valuable assistance.

(Received December 3rd. 1963).