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SYNTHESIS OF 3-METHYLBENZYL-4-HYDROXYCOUMARINS, AND THEIR HYDROLYSIS

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A number of 3-methylbenzyl derivatives of 4-hydroxycoumarin are synthesized by thermal condensation of monosubstituted malonic esters with phenols. Alkaline hydrolysis and simultaneous decarboxylation of the latter gives o-hydroxy-β-tolylpropiophenones.

4-Hydroxycoumarin and its derivatives are widely distributed in nature, and of great interest, as many of them have physiological activity [1]. One of the most convenient methods of synthesizing 3-substituted 4-hydroxycoumarins is thermal condensation of monosubstituted malonic esters with phenols [2].

We have used this reaction to synthesize a number of 3-methylbenzyl derivatives of 4-hydroxycoumarin:

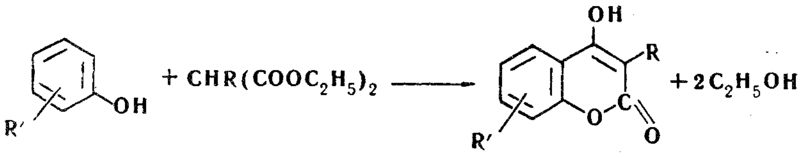

Table 1 gives the reaction conditions and physical constants of the compounds.

Table 1

Properties of Compounds Prepared

Compound No.	R	R′	Mp, °C	Condensation temperature, °C	Condensation time, hr[*]	Found, %[**]		Yield, %
						C	H	
I	o-$CH_3C_6H_4CH_2$	H	217—217.5	293—297	7.0(2,5)	76.90	5.32	77.2
II	m-$CH_3C_6H_4CH_2$	H	201—202	293—297	8.0(2,5)	76.79	5.37	82.2
III	p-$CH_3C_6H_4CH_2$	H	183.5—184	293—296	7.5(2,0)	76.90	5.29	86.2
IV	p-$CH_3C_6H_4CH_2$	8-CH_3	202—203.5	291—295	8.0(2,0)	77.12	5.75	84.0
V	p-$CH_3C_6H_4CH_2$	6-CH_3	191.5—192.5	290—293	7.5(1,5)	77.14	5.80	75.5

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[*] In brackets, time of heating from 250° to the reaction temperature.

[**] For compounds I-III; $C_{17}H_{14}O_3$. Calculated: C 76.68; H 5.30%; for IV-V: $C_{18}H_{16}O_3$. Calculated: C 77.12; H 5.75%.

Compounds I-III were submitted to alkaline hydrolysis and simultaneous decarboxylation (Table 2):

Experimental

m- and p-Methylbenzylchlorides were prepared chlorinating m- and p-xylenes: m-methylbenzylchloride, bp 47-53° (3 mm), yield 70%; p-methylbenzylchloride, bp 85-90° (13 mm), yield 60%. o-Methylbenzylbromide was obtained by brominating o-xylene [3], bp 70-75° (4 mm), yield 66%. o-Methylbenzyl-, m-methylbenzyl-, and p-methylbenzylmalonic esters (Table 3) were prepared by alkylating sodiomalonic ester with the alkyl halides [4].

Table 2

o-Hydroxy-β-tolylpropiophenone

R	Mp, °C	Bp, °C (pressure mm)	Found, %		Yield, %
			C	H	
o-$CH_3C_6H_4CH_2$	51.2—51.8	165—166 (2)	80.05	6.73	83.6
m-$CH_3C_6H_4CH_2$	41.2—41.6	159—161 (2.5)	80.19	6.74	94.0
p-$CH_3C_6H_4CH_2$	45—45.7	160—161 (2)	80.07	6.76	84.3

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* $C_{16}H_{16}O_2$. Calculated: C 79.97; H 6.71%.

Table 3

o-, m-, and p-Methylbenzylmalonic Esters

Compound	Bp, °C (pressure mm)	Yield, %
o-Methylbenzylmalonic ester	129—130 (2)	60
p-Methylbenzylmalonic ester	160—161 (7)	48
m-Methylbenzylmalonic ester	138 (3)	58

The thermal condensation was effected in the apparatus previously described [5]. 0.05 mole methylbenzylmalonic ester and 0.1 mole phenol were placed in a small flask holding 100 ml. The mixture was heated at 100-120°, left overnight then immersed in an oil bath at about 250°, and the temperature gradually raised till condensation began. The course of the reaction was followed by the amount of alcohol which distilled over. When condensation was finished, the melt was poured into a beaker of toluene. The crystals of coumarin which came down were filtered off under suction, and recrystallized from glacial AcOH. Using an ester: phenol ratio of 1:1, the coumarin yield was considerably less.

o-Hydroxy-β-tolylpropiophenone was prepared by refluxing a solution of 20 g coumarin in 600 ml 12% KOH for 19–22 hr. When reaction had finished, the solution was cooled and saturated with CO_2. The hydroxyketone which separated was extracted with ether, the extract dried over $MgSO_4$, the ether distilled off, and the residue distilled under reduced pressure.

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