Ethyl Esters of Coumarin-4-Acetic Acids

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A one step method for the preparation of five coumarin-4-acetic esters from phenols and diethyl acetone dicarboxylate by the condensing action of trifluoroacetic acid is described. The ultraviolet absorption maxima are given for the esters. Hydrolysis of the esters gave the free coumarin-4-acetic acids in four instances, and their melting points and fluorescence behavior are characterized.

IN A RECENT publication (*3*) we have reported a new one-step method of preparing substituted coumarins in which phenols were condensed with various β-keto esters under the influence of trifluoroacetic acid. Since the method was efficient, it appeared that the procedure could be expanded to prepare the ethyl esters of coumarin-4-acetic acids if diethyl acetone dicarboxylate is the β-ketonic ester component. Dey (*1*), whose work is the standard, describes the usual method of preparing the coumarin-4-acetic acids and many of the difficulties encountered in their preparation.

CHART I

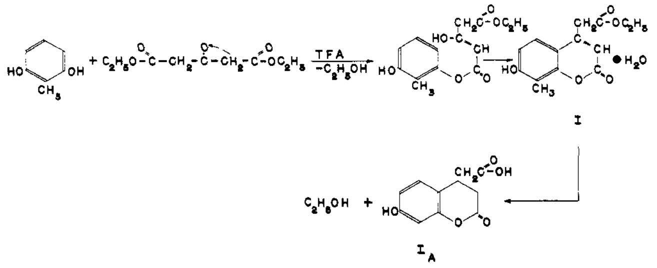

Figure 1. Formation of the coumarin-4-acetic esters

RESULTS AND DISCUSSION

The fact that coumarin-4-acetic acids are subject to easy dehydration to an internal ester makes the ester a more satisfactory compound for consistent syntheses. Further, since the free acid is a malonic acid vinylog (*2*), methods of isolation and purification often cause considerable decarboxylation. Figure 1 illustrates the course of the reaction for the formation of the coumarin-4-acetic esters. Table I lists the esters which were prepared as members of the I$_{A-E}$ series, and Table II gives their ultraviolet absorption maxima obtained on a Bausch and Lomb Spectronic-505 spectrograde methanol. Hydrolysis of these esters gave the II$_{B-E}$ series described in Table III. Compound I$_A$ could

Table I. Ethyl Esters of Coumarin-4-Acetic Acids

Compound[a]	Phenol	Reaction Time, Hr.	Yield, %	M.P. ° C.	Empirical Formula	Analysis Carbon	 Hydrogen	 Other
I$_A$	2-Methyl-resorcinol	4	93	253–255	$C_{14}H_{14}O_5$	64.11(calcd) 64.40(found)	5.38(calcd.) 5.17(found)	
I$_B$	Orcinol	4	69	227–228.5[b]	$C_{14}H_{14}O_5$	64.11(calcd.) 63.92(found)	5.38(calcd.) 5.31(found)	
I$_C$	4-Chloro-resorcinol	4	24	199.5–200.5	$C_{13}H_{11}ClO_5$	55.23(calcd.) 55.20(found)	3.92(calcd.) 3.85(found)	12.54(calcd.)Cl 12.69(found)
I$_D$	3-Hydroxy-diphenylamine	5	71	138–139.5	$C_{19}H_{17}NO_4$	70.56(calcd.) 70.73(found)	5.29(calcd.) 5.32(found)	4.33(calcd.)N 4.37(found)
I$_E$	Phloroglucinol	1	62	204–205	$C_{13}H_{12}O_6 \cdot 2H_2O$	52.00(calcd.) 52.33(found)	5.37(calcd.) 4.93(found)	

[a] I$_A$ - Ethyl-7-hydroxy-8-methylcoumarin-4-acetate
I$_B$ - Ethyl-5-methyl-7-hydroxycoumarin-4-acetate
I$_C$ - Ethyl-6-chloro-7-hydroxycoumarin-4-acetate
I$_D$ - Ethyl-7-phenylaminocoumarin-4-acetate
I$_E$ - Ethyl-5,7-dihydroxycoumarin-4-acetate
[b] Literature value (*1*), 219° C. (poor analysis).

Table II. Ultraviolet Absorption Maxima Compounds I_{A-E} Series Range 200–350 Mμ

Compound[a]	Absorption Maxima, Mμ	
I_A	259	327
I_B	301 single maximum	
I_C	276	331
I_D	203	277
I_E	271.5	327.5

[a] See Table I.

Table IV. Fluorescence of Coumarin-4-Acetic Acids of II_{B-E} Series

Compound[a]	Concn., Grams/Ml., × 10^8	Dial Reading	QRU[b]
II_B	20	18	0.47
II_C	0.16	11	36.1
II_D	8	78	5.1
II_E	20	18	0.47
Quinine sulfate	20	38	

[a] See Table I.

[b] QRU (quinine reference unit) = (concn. quinine, grams/ml.) (dial reading, for substance)/(concn. substance, grams/ml.) (dial reading for quinine).

Table III. Coumarin-4-Acetic Acids

Compound[a]	Coumarin Produced	M.P., ° C.	Empirical Formula	Analysis		
				Carbon	Hydrogen	Other
II_B	5-Methyl-7-hydroxycoumarin-4-acetic acid	250[b]	$C_{12}H_{10}O_5$	61.53(calcd.) 61.61(found)	4.30(calcd.) 4.33(found)	
II_C	6-Chloro-7-hydroxycoumarin-4-acetic acid	286–287	$C_{11}H_7ClO_5$	51.48(calcd.) 51.59(found)	2.77(calcd.) 2.97(found)	13.92(calcd.)Cl 14.07(found)
II_D	7-Phenylaminocoumarin-4-acetic acid	Dec. above 160	$C_{17}H_{13}NO_4$			4.74(calcd.)N 4.50(found)
II_E	5,7-Dihydroxycoumarin-4-acetic acid	Darkens above 243, does not melt below 300[c]	$C_{11}H_8O_6$	55.93(calcd.) 55.92(found)	3.41(calcd.) 3.60(found)	

[a] See Table I. [b] Literature value (*1*), 260°–265° C. [c] Literature value (*1*), 204°–205° C.

not be hydrolyzed by pure water or by various mixtures with hydrochloric acid without considerable decarboxylation so that a reasonable analysis was never obtained.

Although, Dey (*1*) calls the coumarin-4-acetic acid from orcinol 5-hydroxy-7-methyl-coumarin-4-acetic acid, such a designation presumes that the acetone dicarboxylic acid had attacked the orcinol in position 2 between the two hydroxyls. This seems unlikely because we have shown (*3*) that β-keto esters attack the phenol in a position *ortho* to one of the powerful nucleophilic groups and *para* to the other—never between the two. We feel confident, therefore, that the compound which has been named 5-hydroxy-7-methyl-coumarin-4-acetic acid is actually compound II_B.

Since all of the acetic acids prepared were fluorescent—some of them powerfully so—a comparison of this fluorescence with that of quinine sulfate was made. In the absence of standard units, a unit called quinine reference unit, QRU, has been created. These fluoroescence data are given in Table IV. All measurements were made on a Turner Model 110 fluorophotometer in distilled water using a mercury vapor lamp as the source of monochromatic light, using a 465 mu. filter.

EXPERIMENTAL

All analyses were performed by Galbraith Laboratories, Knoxville 21, Tenn. and all melting points were taken on a Fisher-Johns melting point assembly.

Preparation of Compounds of I_{A-E} Series. A mixture consisting of 0.1 mole each of the phenol and diethyl acetone dicarboxylate was treated with 20 ml. of trifluoroacetic acid. The material was then refluxed for various periods of time as indicated in Table I. Following the reflux period, 150 ml. of water was added to the reaction mixture, and the solution was chilled. The resulting precipitate was filtered and dried in air.

The analytical sample was obtained by extracting a small amount of the powdered compound with heptane to remove any unreacted diethyl acetone dicarboxylate. The residue was then extracted with ethyl acetate, and the solvent solution was treated with three to four volumes of heptane to precipitate the ester. If the melting point of the compound had a range of 3° C. or more, this process was repeated.

Preparation of Compounds of II_{B-E} Series. A powdered 2-gram sample of the ester was refluxed 24 hours in 50 ml. of distilled water. The solution was filtered while boiling hot and then chilled. The coumarin-4-acetic acid was recovered as a tan or yellow powder which after drying in air was dissolved in ethyl acetate and precipitated with heptane.

LITERATURE CITED

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