[CONTRIBUTION FROM THE WM. H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

SOME NEW COUMARINS AND CHROMONES AND THEIR ULTRAVIOLET ABSORPTION SPECTRA

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During the course of an investigation of phenolic compounds in this laboratory a series of thirteen new coumarins and four new chromones has been prepared and their ultraviolet absorption spectra have been recorded. The formulas for these compounds are given in Tables I and II and other pertinent data are assembled in Table III.

These compounds have been prepared by standard methods and in most cases from known intermediates. The 6-alkyl-7-hydroxy-4-methylcoumarins (I and II) were obtained from resorcinol through the intermediate 4-alkylresorcinols which condensed with ethyl acetoacetate in 82% sulfuric acid to yield the coumarins. In the same way the 6-alkyl-7,8-dihydroxy-4-methylcoumarins (VI and VII) were prepared from pyrogallol through the intermediate 4-alkylpyrogallols.

The methoxyl derivatives (III, IV, V, VIII, IX) were obtained by the action of diazomethane on the corresponding hydroxycoumarins. However, the use of methyl iodide for metholation of 7,8-dihydroxycoumarins was found to give better yields and purer products.

Pyrogallol was the starting material for the preparation of X and XI. Following the procedure of Gardner, Wenis, and Lee (1) 2,6-dibenzyloxy-1,4-dimethoxybenzene was prepared and was converted into 2,4-dihydroxy-3,6-dimethoxyacetophenone by the method of Sastri and Seshadri (2). Clemmenson reduction followed by condensation of the resulting alkylresorcinol with ethyl acetoacetate gave X. This was converted to XI by treatment with methyl iodide.

The esters of 6-ethyl-7-hydroxycoumarin-3-carboxylic acid, (XII and XIII), were prepared by condensation of 6-ethyl-β-resorcylaldehyde with the corresponding malonic ester after the method of Knoevenagel (3).

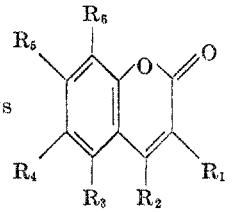
Ethyl 7-benzyloxychromone-2-carboxylate (XIV), was synthesized by benzylation of resacetophenone (4), condensation of the resulting 4-benzyloxy-2-hydroxyacetophenone with diethyl oxalate in the presence of sodium ethoxide to form ethyl 4-benzyloxy-2-hydroxybenzoylpyruvate and ring closure to give XIV. The conversion of XIV to butyl 7-hydroxychromone-2-carboxylate (XVI), was accomplished by simultaneous debenzylation and ester hydrolysis of XIV with a mixture of glacial acetic acid and 48% hydrobromic acid followed by esterification of the 7-hydroxychromone-2-carboxylic acid. In this synthesis it was necessary to benzylate resacetophenone in order to achieve condensation with diethyl oxalate. Attempted condensation of resacetophenone with diethyl oxalate failed due probably to the deactivating influence of the phenolic groups.

By the same series of reactions 5-ethylresacetophenone (5) was converted into ethyl 7-benzyloxy-6-ethylchromone-2-carboxylate (XV), which in turn was transformed into butyl 6-ethyl-7-hydroxychromone-2-carboxylate (XVII).

The ultraviolet absorption maxima of these coumarins and chromones are given in Table IV. The spectra may be roughly divided into four series, an absorption curve of a typical example of each series being shown in Figure 1. The absorption curves of the other compounds in each series were found to be

TABLE I

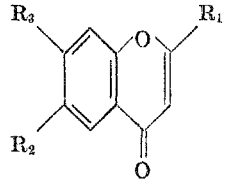
COUMARINS



COMPOUND	R_1	R_2	R_3	R_4	R_5	R_6
I	H	CH_3	H	n-C_4H_9	OH	H
II	H	CH_3	H	iso-C_4H_9	OH	H
III	H	CH_3	H	n-C_3H_7	OCH_3	H
IV	H	CH_3	H	n-C_4H_9	OCH_3	H
V	H	CH_3	H	n-C_6H_{13}	OCH_3	H
VI	H	CH_3	H	n-C_4H_9	OH	OH
VII	H	CH_3	H	n-C_6H_{13}	OH	OH
VIII	H	CH_3	H	C_2H_5	OCH_3	OCH_3
IX	H	CH_3	H	n-C_6H_{13}	OCH_3	OCH_3
X	H	CH_3	OCH_3	C_2H_5	OH	OCH_3
XI	H	CH_3	OCH_3	C_2H_5	OCH_3	OCH_3
XII	$CO_2C_2H_5$	H	H	C_2H_5	OH	H
XIII	$CO_2C_4H_9$	H	H	C_2H_5	OH	H

TABLE II

CHROMONES



COMPOUND	R_1	R_2	R_3
XIV	$CO_2C_2H_5$	H	OCH_2-Φ
XV	$CO_2C_2H_5$	C_2H_5	OCH_2-Φ
XVI	$CO_2C_4H_9$	H	OH
XVII	$CO_2C_4H_9$	C_2H_5	OH

very similar. The 7-hydroxy- and 7-methoxy-coumarins (I to V) comprise one group of compounds all of which show two maxima at about 223 mμ and 330 mμ, variation of the 6-alkyl group having little effect on the spectrum. Another series of coumarins having similar spectra consists of the 7,8-dihydroxycoumarins (VI and VII). The 7-hydroxy-5,8-dimethoxycoumarins (VIII and IX) and the

7-hydroxycoumarin-3-carboxylates (XII and XIII) have only one absorption peak, the former at 300 mμ and the latter at about 365 mμ.

The change in the absorption spectrum of coumarin brought about by substitution of one or more hydroxyl groups on the benzene ring has already been reported by Taski (6). It was found that coumarin has maxima at 320 mμ and 360 mμ while the hydroxycoumarins have only one maximum in this region at some intermediate wave length. This result is substantiated here. Neither addition of the 4-methyl group nor of the 6-alkyl groups has significant effect on the spectrum.

TABLE III

PHYSICAL PROPERTIES AND ANALYSES

COMPOUND	YIELD, %	M.P., °C.	RECRYST. SOLVENT	ANALYSIS			
				Calc'd		Found	
				C	H	C	H
I	75	159.8–160.2	95% Ethanol	72.4	6.9	72.0	6.8
II	66	200.0–200.5	95% Ethanol	72.4	6.9	72.6	6.9
III	77	172.4–172.8	95% Ethanol	72.4	6.9	72.5	6.9
IV	80	172.0–172.5	95% Ethanol	73.2	7.4	73.4	7.3
V	63	162.6–163.2	95% Ethanol	74.4	8.1	74.7	8.1
VI	77	181.0–181.4	50% Ethanol	67.7	6.5	67.9	6.6
VII	72	174.6–175.2	50% Ethanol	69.5	7.3	69.5	7.3
VIII	67	106.6–107.0	40% Ethanol	67.7	6.5	67.7	6.5
IX	11	66.0–66.5	55% Ethanol	71.0	8.0	71.1	8.2
X	39	244.0–245.0	60% Ethanol	63.6	6.1	63.6	6.3
XI	9	113.2–114.2	20% Ethanol	64.7	6.5	64.5	6.5
XII	25	192.0–193.0	95% Ethanol	64.1	5.4	64.3	5.4
XIII	23	158.0–158.5	50% Ethanol	66.3	6.2	66.1	6.1
XIV	84	172.5–173.5	Acetic acid	70.4	5.0	70.3	5.1
XV	92	109.0–110.0	Ethanol-water	71.6	5.7	71.7	5.7
XVI	41	135–137	80% Ethanol	64.1	5.4	63.9	5.8
XVII	61	177–178	80% Ethanol	66.2	6.3	66.0	6.1

The chromones (XIV, XV, XVI) form another series the spectra of which have three like maxima in the region of 210 mμ, 240 mμ, and 315 mμ. The spectrum of tetrahydrofurfuryl chromone-2-carboxylate has been reported (7) to show maxima at 238 mμ and 310 mμ. The addition of the 7-hydroxyl group in XIV, XV, and XVI produces a slight bathochromic shift in these maxima as might be expected.

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EXPERIMENTAL[1]

Hydroxycoumarins. The following procedure for the preparation of 6-*n*-butyl-7-hydroxy-4-methylcoumarin (I), exemplifies the general method for the preparation of the 6-alkyl-7-hydroxy (and 7,8-dihydroxy) -4-methylcoumarins listed in Table I.

[1] All melting-points were taken with Anschutz thermometers.

A solution of 4-butylresorcinol (11.3 g., 0.068 mole) in ethyl acetoacetate (8.9 g., 0.068 mole) was added during 40 minutes to vigorously stirred 82% sulfuric acid (300 g., 183 ml.) cooled to −10°, not allowing the temperature to rise above 5°. After standing for 20 hours at room temperature the reaction mixture was poured over 1000 g. of crushed ice, and a

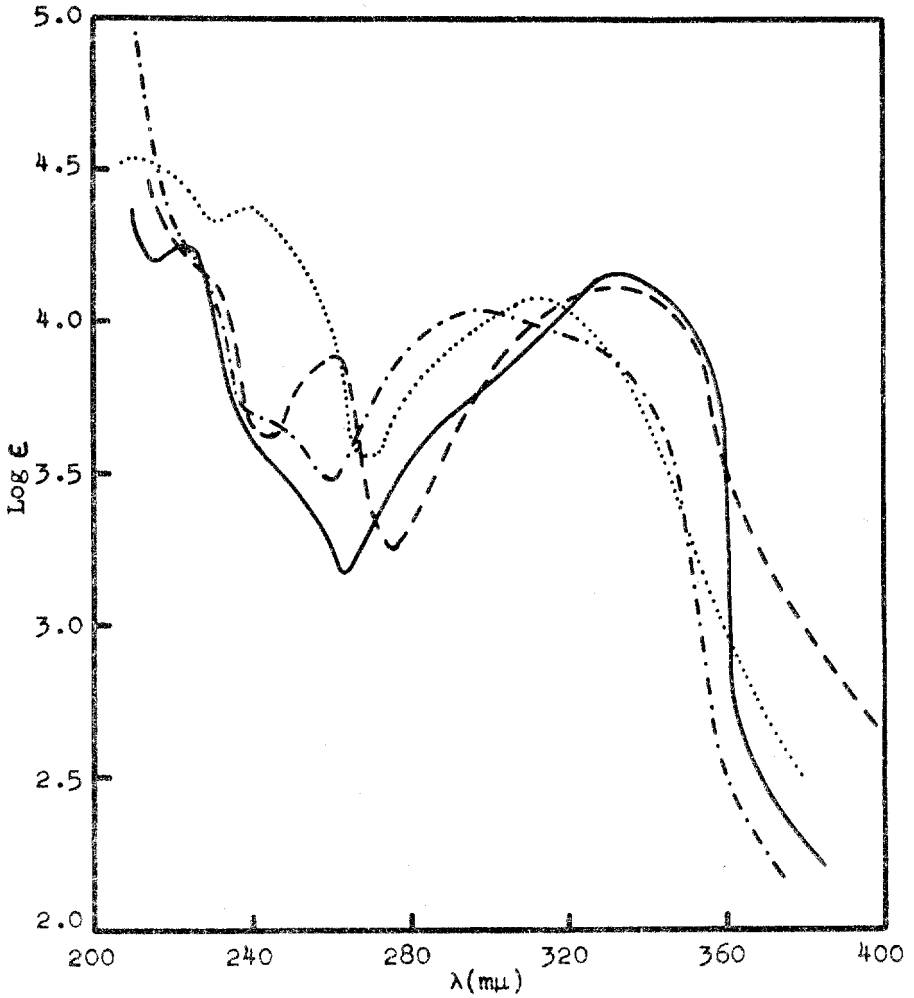

FIG. 1. TYPICAL ULTRAVIOLET ABSORPTION CURVES FOR THE FOUR SERIES OF COUMARINS AND CHROMONES. ——— 6-Isobutyl-7-hydroxy-4-methylcoumarin (II). ——— 6-*n*-Butyl-7,8-dihydroxy-4-methylcoumarin (VI). -•-•-• 6-Ethyl-7,8-dimethoxy-4-methylcoumarin (VIII). ••••••• Ethyl 7-benzyloxychromone-2-carboxylate (XIV)

gummy brown mass, which slowly solidified, separated out. The crude product was filtered off, washed with cold water, and recrystallized from 95% ethanol. Yield: 11.9 g., (75.4%), m.p. 155–157°. Two more recrystallizations gave m.p. 159.8–160.2°.

Methoxycoumarins. The examples given here illustrate the methods used for the preparation of the methoxycoumarins (Table I) through use of diazomethane (Method A) and methyl iodide (Method B).

Method A. 6-n-Butyl-7-methoxy-4-methylcoumarin (IV). An ether solution of diazomethane (approx. 2.6 g., 0.06 mole) [prepared by the method of Arndt (8)] was distilled directly into an ether suspension of 6-*n*-butyl-7-hydroxy-4-methylcoumarin (6.0 g., 0.026 mole) with cooling in a salt ice-bath. During several hours slow warming to room temperature a vigorous evolution of gas occurred and the reaction mixture was allowed to stand overnight. After decomposing the excess diazomethane with acetic acid, the ether was evaporated and the residual yellow solid was ground under 100 ml. of 5% sodium hydroxide. The undissolved solid was filtered off, washed with water, and recrystallized twice from 95% ethanol yielding 5.1 g. of pale yellow needles, m.p. 170.5–172.0°. Two more recrystallizations gave product that melted at 172.0–172.5°.

Method B. 7,8-Dimethoxy-6-ethyl-4-methylcoumarin (VIII). A mixture of 7,8-dihydroxy-6-ethyl-4-methylcoumarin (11.0 g., 0.05 mole), methyl iodide (35.5 g., 0.25 mole), and one-half of a solution of sodium methoxide (6.0 g., 0.11 mole) in 300 ml. of absolute methanol was refluxed for one hour. The rest of the sodium methoxide solution and more methyl

TABLE IV

ULTRAVIOLET ABSORPTION MAXIMA

COMPOUND	WAVELENGTH (mμ) OF MAXIMA (log ε)		
I	223 (4.25)		330 (4.18)
II	223 (4.26)		332 (4.16)
III	223 (4.35)		330 (4.18)
IV	223 (4.33)		328 (4.15)
V	223 (4.35)		328 (4.17)
VI		260 (3.89)	330 (4.12)
VII		261 (3.86)	330 (4.11)
VIII			300 (4.04)
IX			300 (4.03)
X		260 (3.86)	325 (4.14)
XI	Spectrum not measured		
XII			363 (4.26)
XIII			365 (4.22)
XIV	210 (4.60)	240 (4.38)	312 (4.10)
XV	214 (4.60)	238 (4.35)	320 (4.03)
XVI	211 (4.43)	242 (4.20)	315 (3.91)
XVII	Spectrum not measured		

iodide (35.5 g., 0.25 mole) were added and reflux was continued for six hours, the originally dark red solution becoming yellow. Addition of more sodium methoxide (0.5 g., 0.01 mole) in 10 ml. of methanol caused the solution to become dark red again and the reflux was continued for four hours. Concentration of the solution *in vacuo* left an orange solid that was ground under 100 ml. of 5% sodium hydroxide solution, washed with water, and filtered. Two recrystallizations from 40% ethanol gave 8.3 g. (67%) of long colorless needles. m.p. 106.2–107.0°. Another recrystallization gave m.p. 106.6–107.0°.

Ethyl 6-ethyl-7-hydroxycoumarin-3-carboxylate (XII). A mixture of 6-ethyl-β-resorcylaldehyde (5.0 g., 0.03 mole), diethyl malonate (6.4 g., 0.04 mole), 10 ml. of absolute ethanol, and 0.5 ml. of piperidine was refluxed for six hours and allowed to stand overnight. The crystals which had formed upon standing were filtered off and were recrystallized from 95% ethanol. Yield: 2.0 g., m.p. 192.0–193.0°.

Butyl 6-ethyl-7-hydroxycoumarin-3-carboxylate (XIII) was prepared by the above method for the ethyl ester using dibutyl malonate.

Ethyl 4-benzyloxy-2-hydroxybenzoylpyruvate. A solution of 4-benzyloxy-2-hydroxyaceto-

phenone (4) (5.0 g., 0.02 mole) in 15 ml. of diethyl oxalate was added to a solution of sodium ethoxide prepared by dissolving sodium (1.8 g., 0.08 mole) in 10 ml. of 95% ethanol. The mixture was stirred into a thin paste and heated on the steam-bath for five minutes. The resulting yellow solid was filtered off, washed with ether, dried, and stirred into 50 ml. of 6% acetic acid. The free pyruvate thus obtained was recrystallized from 95% ethanol giving colorless crystals. Yield: 5.0 g., m.p. 117.5–118.0°.

Anal. Calc'd for $C_{19}H_{18}O_6$: C, 66.7; H, 5.6.
Found: C, 66.7; H, 5.5.

Ethyl 7-benzyloxychromone-2-carboxylate (XIV). A solution of ethyl 4-benzyloxy-2-hydroxybenzoylpyruvate (5.0 g., 0.015 mole) in 10 ml. of glacial acetic acid containing two dops of concentrated hydrochloric acid was heated on a steam-bath for 30 minutes. The white crystals which separated were filtered off, washed with 95% ethanol, and dried, yielding 4 g. of ethyl 7-benzyloxychromone-2-carboxylate, m.p. 172.5–173.5°.

Butyl 7-hydroxychromone-2-carboxylate (XVI). A mixture of ethyl 7-benzyloxychromone-2-carboxylate (6.0 g., 0.02 mole), 25 ml. of glacial acetic acid, and 15 ml. of 48% hydrobromic acid was refluxed for three hours. The starting material quickly went into the solution which slowly deposited small crystals of 7-hydroxychromone-2-carboxylic acid. A 3 g. (70%) yield of the crude acid was obtained, m.p. 330° (dec.).

Without further purification the acid was dissolved in 25 ml. of butyl alcohol containing one drop of concentrated sulfuric acid and the solution was refluxed for three hours. Concentration of the solution *in vacuo* followed by recrystallization of the solid residue from benzene gave 3 g. of pale yellow crystals. Recrystallization from 80% ethanol gave 2 g. of white needles, m.p. 135–137°.

4-Benzyloxy-5-ethyl-2-hydroxyacetophenone. [This procedure was adopted from that of Gulati (4)]. A mixture of ethylresacetopheone (9) (37 g., 0.2 mole), benzyl chloride (98 g., 0.77 mole), anhydrous potassium carbonate (58 g.), and 200 ml. of acetone was refluxed for eight hours and allowed to stand overnight. The resulting brown solution was filtered and evaporated at reduced pressure on a water-bath. The residue was recrystallized from 300 ml. of 95% ethanol yielding 30 g. (50%) of white needles melting at 105.0–105.5°.

Anal. Calc'd for $C_{17}H_{18}O_3$: C, 75.5; H, 6.7.
Found: C, 75.4; H, 6.8.

Ethyl 4-benzyloxy-5-ethyl-2-hydroxybenzoylpyruvate. A solution of 4-benzyloxy-5-ethyl-2-hydroxyacetophenone (10 g., 0.027 mole) in 30 ml. of warm ethyl oxalate was added to a solution of sodium ethoxide prepared by dissolving sodium (3.5 g., 0.15 mole) in 15 ml. of absolute ethanol. After 30 minutes heating on a steam-bath no precipitate of the disodio pyruvate was obtained. Neither did a precipitate form upon cooling and dilution with an equal volume of ether. A dilute solution (1:10) of hydrochloric acid (100 ml.) was added and the mixture was shaken. The ether layer was separated and evaporated on a steam-bath to an oily solid. Recrystallization from an ethanol-water mixture gave 9 g. (70%) of product melting at 102–107°. Another recrystallization from ethanol gave crystals of m.p. 112–113°.

Anal. Calc'd for $C_{21}H_{22}O_6$: C, 68.1; H, 6.0.
Found: C, 67.8; H, 6.1.

Ethyl 7-benzyloxy-6-ethylchromone-2-carboxylate (XV). This compound was prepared by a procedure identical with that used for the preparation of ethyl 7-benzyloxychromone-2-carboxylate (XIV).

6-Ethyl-7-hydroxychromone-2-carboxylic acid was prepared by the same procedure used for the preparation of 7-hydroxychromone-2-carboxylic acid (see under preparation of XVI). A 65% yield was obtained. Recrystallization from acetic acid gave colorless crystals that melted with decomposition above 300°.

Anal. Calc'd for $C_{12}H_{10}O_5$: C, 61.5; H, 4.3.
Found: C, 61.3; H, 4.5.

Butyl 6-ethyl-7-hydroxychromone-2-carboxylate (XVII). Esterification of the above crude acid by the method employed for the preparation of butyl 7-hydroxychromone-2-carboxylate (XVI) gave colorless needles.

Ultraviolet absorption spectra. All data were obtained on a Beckman Model DU quartz spectrophotometer using 95% ethanolic solutions at a concentration of 10 milligrams per liter.

SUMMARY

A series of thirteen new coumarins and four new chromones has been prepared and their ultraviolet absorption spectra have been recorded.

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