solution stirred directly into a solution of 3,4-dichlorophenyl isocyanate [38.2 g. (0.15 mole)] in 50 ml. of ether. The product was filtered and recrystallized from ethanol as small white rosettes, m.p. 119.1–119.6°, wt. 31.0 g. (66.2%).

Anal. Calcd. for $C_9H_9Cl_2BrN_2O$: Cl, 22.75; Br, 25.60; N, 8.95. Found: Cl, 22.80; Br, 25.35; N, 8.80.

1-(3,4-Dichlorophenyl)-2-imidazolidone (XII).—A solution of 1-(2-bromoethyl)-3-(3,4-dichlorophenyl)urea 15.6 g. (0.05 mole) in 80 ml. of acetone and a slight excess of 10% aqueous sodium hydroxide was refluxed 3 hr. The acetone layer was separated and evaporated to *ca.* 25 ml. from which the product separated. Recrystallization from acetone gave small glistening plates, m.p. 184.1–185.0°, wt. 10.1 g. (88.0%).

Anal. Calcd. for $C_9H_8Cl_2N_2O$: Cl, 30.70; N, 12.10. Found: Cl, 30.60; N, 11.97.

3-(3,4-Dichlorophenyl)tetrahydro-1,3-oxazine-2-one (XIV).—A solution of 1-(3-bromopropyl)-3,4-dichlorocarbanilate 25.0 g. (0.076 mole) in 250 ml. of 5% sodium hydroxide was refluxed for 1 hr. An oil separated and solidified on cooling. Recrystallization of the solid from 95% ethanol gave small white granules, m.p. 136.2–137.0 (63.8%).

Anal. Calcd. for $C_{10}H_9Cl_2NO_2$: Cl, 28.82; N, 5.69. Found: Cl, 28.87; N, 5.55.

3-(3,4-Dichlorophenyl)-1,3-oxazolidine-2-one (XV).—The same procedure using 1-(2-chloroethyl)-3,4-dichlorocarbanilate 42.0 g. (0.146 mole) gave fine, colorless needles on recrystallization from ethanol; m.p. 126.3–127.0°, wt. 26.0 g. (73.0%).

Anal. Calcd. for $C_9H_7Cl_2NO_2$: Cl, 30.60; N, 6.03. Found: Cl, 30.68; N, 6.10.

1-(3,4-Dichlorophenyl)-3-(2-propynyl)urea (XVI).—Maximum yields were obtained by dissolving propargylamine hydrochloride 27.5 g. (0.3 mole) in 100 ml. of water, made strongly alkaline with 20% sodium hydroxide at 0–5°, and immediately extracted with three 100-ml. portions of ether. The ether was filtered through calcium chloride and added to a solution of 3,4-dichlorophenyl isocyanate 38.0 g. (0.2 mole) in 100 ml. of ether. After evaporation to 75 ml. the product precipitated. Two recrystallizations from ethyl acetate gave small white plates, m.p. 178.7–179.3°, wt. 35.0 g. (72.1%, based on isocyanate).

Anal. Calcd. for $C_{10}H_8Cl_2N_2O$: Cl, 29.22; N, 11.52. Found: Cl, 29.40; N, 11.35.

New Syntheses in the Coumarin Series

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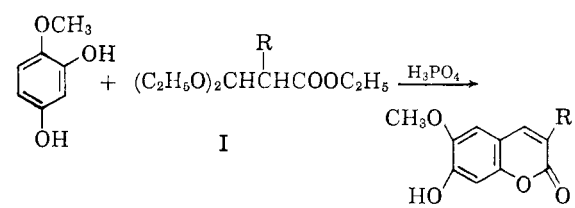
Reaction of the appropriate substituted phenols with ethyl 3,3-diethoxypropionate (I) in the presence of mineral acid provided good yields of the coumarins scopoletin, isoscopoletin, and scoparone. Substitution of ethyl 3,3-diethoxy-2-methylpropionate gave the corresponding 3-methylcoumarins. Two moles of 3,4-methylenedioxyphenol reacted with I to form a 3,4-dihydro-4-substituted coumarin which decomposed to ayapin upon heating. The coumarins, including ayapin, also could be obtained by the replacement of the diethoxy ester with 3-ethoxyacrylyl chloride.

Coumarins are becoming recognized as common minor constituents of plants. Among the naturally occurring compounds, those with oxygen attached at the 6- and 7-positions appear to be of special interest; scopoletin (6-methoxy-7-hydroxycoumarin), in particular, has been widely implicated in plant functions.

The glycoside esculin (6-β-D-glucosyloxy-7-hydroxycoumarin) has been the most usual starting point for synthetic work in this series. For instance, it may be methylated and then hydrolyzed to isoscopoletin (6-hydroxy-7-methoxycoumarin),[2] hydrolyzed directly to provide esculetin (6,7-dihydroxycoumarin),[3] or carried through a series of reactions to give scopoletin.[4] Esculetin has served as precursor for scoparone (6,7-dimethoxycoumarin)[5] and ayapin (6,7-methylenedioxycoumarin)[6]; it has been prepared synthetically in low yield from 1,2,4-triacetoxybenzene,[7] but the synthesis of its derivatives such as scopoletin has been much more elaborate. The Pechmann synthesis and related methods are unsatisfactory in these instances.

We have found that reaction of the appropriate phenol with ethyl 3,3-diethoxypropionate (I. R = H) in the presence of mineral acid provides good yields of these substituted coumarins. For example:



The reaction was conducted at steam bath temperatures in the presence of an excess of acid condensing agent which also acted as solvent. Although concentrated sulfuric acid, polyphosphoric acid, and, in some cases, even aqueous hydrochloric acid were effective, optimum results were obtained with 85% sirupy phosphoric acid. Organic acids and acidic ion exchange resins were unsatisfactory. The coumarins were formed rapidly, and heating periods longer than one or two hours did not afford increased yields.

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(2) F. S. H. Head and A. Robertson, *J. Chem. Soc.*, 1241 (1931); R. Seka and P. Kallir, *Ber.*, **64B**, 622 (1931).

(3) E. Zwenger, *Ann.*, **90**, 68 (1854).

(4) H. D. Braymer, M. R. Shetlar, and S. H. Wender, *Biochem. Biophys. Acta*, **44**, 163 (1960).

(5) F. Tiemann and W. Will, *Ber.*, **15**, 2072 (1882).

(6) E. Späth, P. K. Bose, and J. Schläger, *ibid.*, **70**, 702 (1937).

(7) G. Amiard and A. Allais, *Bull. soc. chim. France*, 512 (1947).

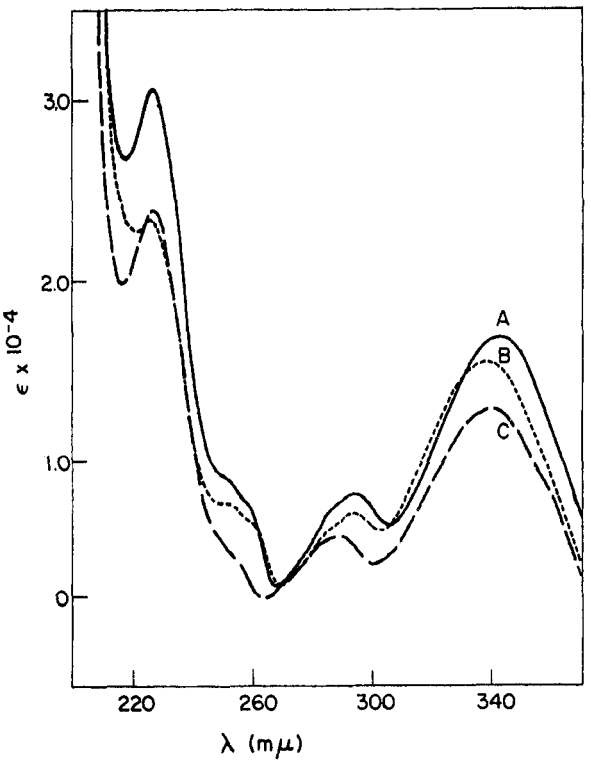

Fig. 1.—Ultraviolet spectra of coumarins. A. Scoparone. B. 3-Methylscoparone. C. 4-Methylscoparone.

Several 6,7-dioxygenated coumarins were easily prepared by this method and were identified by comparison of their ultraviolet spectra, chromatographic characteristics, and melting points with those of authentic specimens prepared by established methods (Table I).

TABLE I
SYNTHESIS OF COUMARINS

Substituent	Name	M.p., °C. (corr.)	R_f[a] A	R_f[a] B	Yield,[b] %
6-Hydroxy-7-methoxy-	Isoscopoletin	184	0.38	0.62	51
6-Methoxy-7-hydroxy-	Scopoletin	204–205	0.52	0.55	73 (65)[c]
6,7-Dimethoxy-	Scoparone	138	0.40	0.67	45
6,7-Methylenedioxy-	Ayapin	223–224	0.52	0.72	60[c]

[a] Ascending chromatograms on Whatman No. 3 paper. Solvent A: water. Solvent B: 10% aqueous acetic acid. [b] From ethyl 3,3-diethoxypropionate. [c] From 3-ethoxyacrylyl chloride.

Repeated attempts to obtain 7-hydroxycoumarin and 5,7-dihydroxycoumarin from resorcinol and phloroglucinol, respectively, by reaction with ethyl diethoxypropionate were unsuccessful, and, unlike the synthesis of ethyl scopoletin-4-carboxylate,[8] esters of the phenols also failed to react. This and further extension of the method are under investigation.

(8) D. G. Crosby, *J. Org. Chem.*, **26**, 1215 (1961).

Replacement of ethyl diethoxypropionate with ethyl 3,3-diethoxy-2-methylpropionate (I. R = CH_3) resulted in good yields of the corresponding 3-methyl-6,7-disubstituted coumarins (Table II).

TABLE II
3-METHYLCOUMARINS

Substituent	Yield, %	M.p., °C. (corr.)	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
6-Hydroxy-7-methoxy-	34	202–203.5	64.1	64.2	4.9	4.8
6-Methoxy-7-hydroxy-	56	151–152	64.1	64.3	4.9	5.0
6,7-Dimethoxy-	37	129–130	65.1	65.4	5.5	5.5

The ultraviolet absorption spectra of these derivatives were compared with those of their unsubstituted relatives and the corresponding 4-methylcoumarins prepared by condensation of the phenols with ethyl acetoacetate in phosphoric acid.[8] Although members of each of the three groups showed very close spectral similarity, distinct differences were noted between groups (Fig. 1). The use of these differences as an aid in characterization of natural coumarins will be discussed in a future communication.

Repeated attempts to obtain ayapin (IV) directly from 3,4-methylenedioxyphenol were unsuccessful. Reaction of the phenol and ethyl diethoxypropionate under a variety of conditions resulted in the rapid formation of a white crystalline product (II). Analysis, spectral examination, and formation of a monoacetyl derivative of the expected composition (III) indicated that II resulted from the condensation of two moles of the phenol with one of ester (Chart I). This compound appeared to be the sole product even at high ester-phenol ratios.

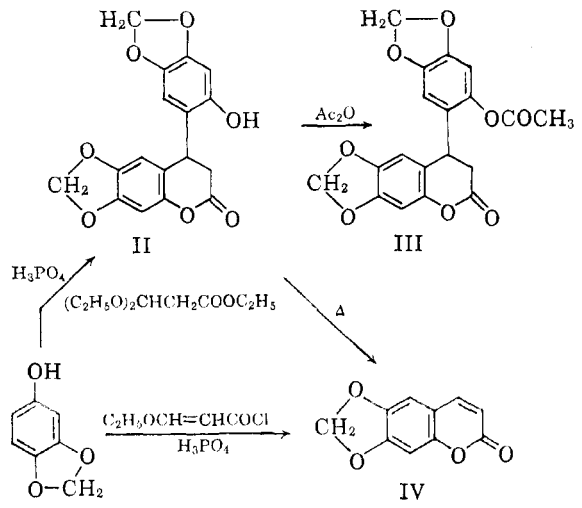

Chart I

When heated *in vacuo* above its melting point, II was converted slowly to ayapin. Since II may be regarded as the Michael addition product of the phenol with the coumarin, it is possible that other appropriate 4-substituted coumarins might be cracked similarly to provide the unsubstituted compounds.

Reaction of 3-ethoxyacrylyl chloride, prepared from vinyl ethyl ether and phosgene,[9] with phenols provided the expected esters; these glassy substances could not be induced to crystallize and decomposed upon attempts at distillation *in vacuo*. However, treatment of the crude intermediates with hot phosphoric acid produced the desired coumarins as indicated in Chart I. Simultaneous Fries rearrangement and condensation of these intermediate esters to the corresponding substituted chromones is under investigation.

Experimental[10]

Ethyl 3,3-Diethoxypropionate.—A mixture of 395 g. (2.67 moles) of triethyl orthoformate and 20 ml. of 47% boron trifluoride etherate was cooled to 0° with vigorous stirring, 78 g. (1.85 moles) of gaseous ketene was fed in from a generator over a period of 2 hr. at 5–10°, the dark solution was allowed to stand for 30 min., 30 g. of sodium bicarbonate was stirred in, and the solids were removed by filtration. Distillation of the filtrate through an efficient column provided 190 g. (54%) of the desired ester, b.p. 91–98° (15 mm.), $n^{20}D$ 1.4117.

3-Ethoxyacrylyl Chloride.[11]—Vinyl ethyl ether (134 g., 1.86 moles) was weighed into a pressure bottle and cooled to about −70° in Dry Ice. Liquid phosgene (190 g., 1.93 moles) was then added and the vessel was purged with dry nitrogen and capped. As it warmed spontaneously, the container was vented several times and finally was allowed to stand at room temperature for 46 hr. in a protective shield.

The mixture then was chilled to low temperature again, transferred to a distillation flask, and unchanged phosgene was allowed to evaporate (vigorous gas evolution upon warming). The remaining liquid was distilled under reduced pressure to provide 133 g. (53% yield) of straw-colored oil, b.p. 88–91° (19 mm.).

2,5-Dihydroxyanisole,[12] **3,4-dimethoxyphenol,**[13] **and 3,4-methylenedioxyphenol**[14] were prepared by oxidation of vanillin, veratraldehyde, and piperonal, respectively, with peracetic acid in ethyl acetate in the manner used for synthesis of **2,4-dihydroxyanisole.**[8]

Scopoletin. Method A.—2,4-Dihydroxyanisole (10.0 g., 0.072 mole) and ethyl 3,3-diethoxypropionate (8.0 g., 0.042 mole) were dissolved in 20 ml. of 85% sirupy phosphoric acid in a small flask or beaker and heated on the steam bath for 2 hr. The mixture was poured over 250 g. of crushed ice, the tacky solid which precipitated was allowed to stand until it became completely hard, and after removal by filtration and thorough washing with water, it was air-dried. The crude yield of scopoletin was 10.0 g. (73%), m.p. 199°, and a single recrystallization from glacial acetic acid provided glistening yellow plates, m.p. 202°. Spectral and chromatographic characteristics were identical with those of an authentic specimen.

In the same way, isoscopoletin was prepared from 2,5-dihydroxyanisole and scoparone from 3,4-dimethoxyphenol.

Method B.—2,4-Dihydroxyanisole (14.0 g., 0.10 mole) was dissolved in a mixture of 17 g. of pyridine and 120 ml. of benzene and a solution of 3-ethoxyacrylyl chloride (13.5 g., 0.10 mole) in 25 ml. of benzene was added dropwise with stirring over a period of 30 min. The solution was boiled under reflux for 2 hr., chilled, and shaken with 500 ml. of water. The organic layer was washed with water, dried over anhydrous sodium sulfate, and solvent was removed *in vacuo*. Attempts either to crystallize the glassy residue or to distill it under high vacuum were unsuccessful.

The crude intermediate was heated for 10 min. on the steam bath with 50 ml. of 85% sirupy phosphoric acid, poured over 150 g. of ice, and the solid product was removed by filtration, washed well with water, and air-dried to provide 12.5 g. (65% yield) of scopoletin. Recrystallization from acetic acid gave a product, m.p. 204–205°, identical with an authentic specimen.

3-Methylscopoletin.—2,4-Dihydroxyanisole (4.9 g., 0.035 mole), ethyl 3,3-diethoxy-2-methylpropionate (Aldrich Chemical Co.) (5.1 g., 0.025 mole), and 25 ml. of 85% sirupy phosphoric acid were heated together on the steam bath for 1 hr., poured over 100 g. of crushed ice, and the tan precipitate was recovered by filtration and washed with cold water. Recrystallization from toluene provided 2.4 g. (56% yield) of yellow solid, m.p. 151–152°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.1; H, 4.9. Found: C, 64.3; H, 5.0.

3,4-Dihydro-4-(3′,4′-methylenedioxy-6′-hydroxyphenyl)-6,7-methylenedioxycoumarin (II).—3,4-Methylenedioxyphenol (10.0 g., 0.072 mole) was mixed with 85% sirupy phosphoric acid and ethyl 3,3-diethoxypropionate (8.0 g., 0.042 mole) was added dropwise to the stirred mixture at room temperature. Addition was accompanied and followed by foaming; after this had subsided, the solution was heated on the steam bath with occasional stirring for about 1 hr., poured over 250 g. of crushed ice, and the fine white precipitate was collected by filtration, washed with water, air-dried, and recrystallized from glacial acetic acid. The yield of white crystals, m.p. 249°, was 10.7 g. (65%).

Anal. Calcd. for $C_{17}H_{12}O_7$: C, 62.2; H, 3.7. Found: C, 62.2; H, 3.7.

II Acetate (III).—The phenol II was acetylated with acetic anhydride and the product was recrystallized from ethanol to provide white crystals, m.p. 206–207°.

Anal. Calcd. for $C_{19}H_{14}O_8$: C, 61.6; H, 3.8. Found: C, 61.4; H, 3.8.

Ayapin. Method A.—The phenol II was heated slowly to 350° under 0.1 mm. pressure for about 15 min. After cooling, the dark residue was recrystallized from methanol (Darco) to provide about a 10% yield of ayapin, m.p. 223°, whose spectral and chromatographic characteristics were identical with those of an authentic specimen prepared by reaction of esculetin with methylene iodide.

Method B.—3,4-Methylenedioxyphenol (11 g., 0.08 mole) and 15 g. (0.11 mole) of 3-ethoxyacrylyl chloride were mixed and stirred until homogeneous. Stirring was accompanied by the evolution of heat and gaseous hydrogen chloride. After the reaction had subsided, 85% sirupy phosphoric acid (50 ml.) was added, the mixture was heated on the steam bath for about 1 hr., poured onto 200 g. of ice, and stirred for 1 hr. The pale yellow solid was removed by filtration, washed with water, and recrystallized from methanol (Darco). The yield of ayapin, m.p. 223–224°, was 9 g. (60%).

Acknowledgment.—The authors are indebted to Mr. Roy Spencer, Jr., for capable technical assistance and to Mr. Quentin Quick and his group for microanalyses.

(9) R. E. Paul and S. Tchelitcheff, U.S. Patent 2,768,174 [*Chem. Abstr.*, **51**, 5818 (1957)].

(10) All melting points were measured in a Vanderkamp block and are corrected.

(11) Prepared by W. J. Skraba and associates.

(12) H. D. Dakin, *Am. Chem. J.*, **42**, 474 (1909).

(13) R. I. Meltzer and J. Doczi, *J. Am. Chem. Soc.*, **72**, 4986 (1950).

(14) J. Boeseken, W. D. Cohen, and C. J. Kip, *Rec. trav. chim.*, **55**, 815 (1936).