TABLE I

COUMARINS FROM 2-HYDROXYARYL ACIDS

Compd.[a]	Acid used	% yield	M.p., °C.	Formula	Calcd., % C	H	N	Halogen	Found, % C	H	N	Halogen
I	Salicylic	61	162.5–163	$C_{10}H_6O_5$	58.26	2.93			58.58	3.21		
II	5-Chlorosalicylic	70	172.5–173.5	$C_{10}H_5ClO_5$	49.91	2.09		14.73	49.45	2.36		14.39
III	5-Bromosalicylic	80	179.5–180.5	$C_{10}H_5BrO_5$	42.13	1.76		28.03	41.76	2.19		27.71
IV	5-Nitrosalicylic	39	268–269	$C_{10}H_5NO_7$	47.78	2.00	5.57		47.57	2.19	5.74	
V	3-Nitrosalicylic	40	142–143	$C_{10}H_5NO_7$	47.78	2.00	5.57		47.59	2.14	5.40	
VI	2,4-Dihydroxybenzoic	36	232–233	$C_{10}H_6O_6$	54.06	2.72			53.49	3.00		

[a] I, 4-hydroxycoumarin-3-carboxylic acid; II, 6-chloro-4-hydroxycoumarin-3-carboxylic acid; III, 6-bromo-4-hydroxycoumarin-3-carboxylic acid; IV, 4-hydroxy-6-nitrocoumarin-3-carboxylic acid; V, 4-hydroxy-8-nitrocoumarin-3-carboxylic acid; and VI, 4,7-dihydroxycoumarin-3-carboxylic acid.

TABLE II

SPECTRAL ABSORBANCE CHARACTERISTICS AND *p*-BROMOPHENACYL DERIVATIVES OF THE I–VI SERIES

Compd. used	Infrared absorption bands 1800–1500 cm.$^{-1}$[a]	Ultraviolet absorption bands, mμ (log ε)[b]	Phenacyl ester Formula	M.p., °C.	Calcd. % C	H	Br	Found, % C	H	Br
I	1661, 1613	241 (3.56), 310.5 (3.51)	$C_{18}H_{11}BrO_6$	145–146	53.62	2.75	19.81	53.39	2.88	19.64
II	1667, 1608, 1575	237.5 (3.74), 321 (3.53)	$C_{18}H_{10}BrClO_6$	163.5–164	49.39	2.30		49.10	2.52	
III	1667, 1605	236 (3.93), 315 (3.80)	$C_{18}H_{10}Br_2O_6$	167–168	44.84	2.09	33.15	44.59	2.22	33.37
IV	1667, 1623, 1575	232 (3.95), 321 (4.00)	$C_{18}H_{10}BrNO_8$	149.5–150	48.23	2.24	17.82	48.04	2.11	17.97
V	1686, 1600	238.5 (3.65), 316 (3.50)	$C_{18}H_{10}BrNO_8$	186–186.5	48.23	2.24	17.82	47.95	2.37	18.07
VI	1667, 1626	226 (4.04), 259 (4.10), 298 (3.98)	$C_{18}H_{11}BrO_7$	196–197	51.57	2.64	19.06	50.92	2.91	19.22

[a] Spectra were determined on Beckman IR-5 using KBr pellets. [b] Spectra were determined on Bausch and Lomb Spectronic 505 in Spectrograde methanol.

for the carboxyl radical in their infrared spectra, and, in general, give expected ultraviolet absorption patterns. Compound VI, however, differs in that it gives three absorption maxima in the range of 200–350 mμ which was indeed the spectral range examined for all of the six compounds reported here.

The reaction of compound I with resorcinol in the presence of trifluoroacetic acid provides an easy—if somewhat time consuming—method to prepare hydroxyaryl ketones of the coumarin acids.

Experimental Section[6]

Preparation of 4-Hydroxy-3-coumarin Acids.—A mixture consisting of 0.1 mole of the 2-hydroxyaryl acid, 0.1 mole of malonic acid, and 30 ml. of trifluoroacetic acid was heated in an all-glass reflux assembly immersed in a Fisher Hitemp oil bath set so that the temperature remained between 95 and 100° and was never permitted to exceed 100°.

The mixture was heated for 20 hr., diluted with 100–150 ml. of water, chilled, and filtered, and the precipitates were dried in air.

The analytical samples were obtained by recrystallizing the compounds twice from heptane or by taking the compounds up in the smallest amount of tetrahydrofuran possible and precipitating them with heptane. The latter process was repeated for a second precipitation.

Preparation of *p*-Bromophenacyl Derivatives of the Compounds of the I–VI Series.—Two grams of the compound, 1 g. of sodium bicarbonate and 2 g. of the 2,4′-dibromoacetophenone were refluxed in 100 ml. of absolute ethanol for 3 hr. The solutions were filtered while boiling hot. The filtrate was chilled and the precipitates thus obtained were recrystallized twice from absolute ethanol.

Preparation of 3-(2,4-Dihydroxybenzoyl)-4-hydroxycoumarin.—A mixture of 0.01 mole of compound I, 0.01 mole of resorcinol, and 10 ml. of trifluoroacetic acid was refluxed for 8 hr., poured into water, chilled, and filtered. The precipitate was dried in air and recrystallized once from boiling heptane: m.p. 162.5–163°.

Anal. Calcd. for $C_{16}H_{10}O_6$: C, 62.34; H, 3.27. Found: C, 62.10; H, 3.44.

(6) All analyses were performed by Dr. Carl Tiedcke, Teaneck, N. J. All melting points were taken on Fisher-Johns melting point blocks.

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Synthetic Furocoumarins. VII. Oxazolocoumarins from 6-Hydroxy-4-methylcoumarin

KURT D. KAUFMAN, DAVID W. MCBRIDE, AND DAVID C. EATON

Kalamazoo College, Kalamazoo, Michigan

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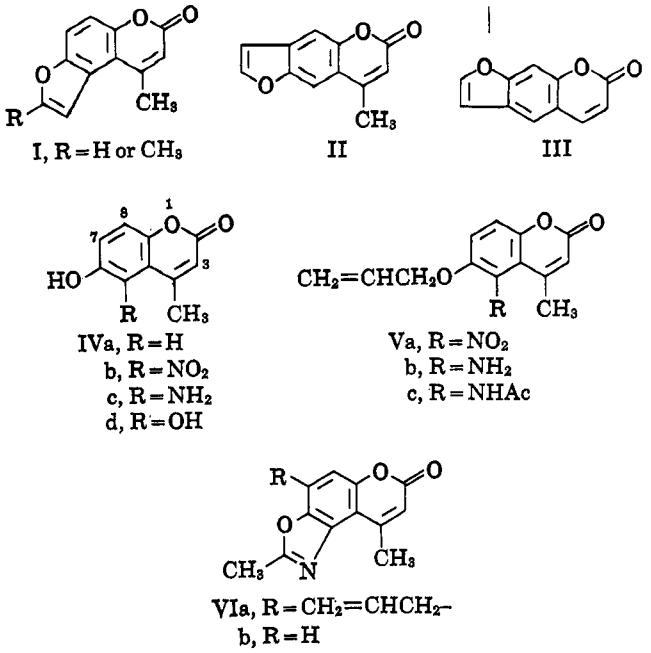
The preceding paper[1] in this series describes the conversion of 6-hydroxy-4-methylcoumarin (IVa) to two angular furocoumarins (I). Owing to the reactivity of the 5-position, 6-hydroxy-4-methylcoumarin cannot be converted directly to a linear furocoumarin (II). The linear compound is of greater interest because of its structural similarity to psoralene (III, see Chart I), which possesses unique biological photosensitizing activity.[2] A similar problem in the synthesis of psoralenes was overcome by blocking the reactive 8-position of a 7-hydroxycoumarin with an acetamido group, which was removed after formation of the furan ring fused to the 6- and 7-positions.[3] The present paper describes an attempt to utilize the same sequence of reactions for the conversion of 6-hydroxy-4-methylcoumarin (IVa) to a linear furocoumarin by blocking the reactive 5-position with an acetamido group.

(1) K. D. Kaufman, J. F. W. Keana, R. C. Kelly, D. W. McBride, and G. Slomp, *J. Org. Chem.*, **27**, 2567 (1962).

(2) M. A. Pathak, J. H. Fellman, and K. D. Kaufman, *J. Invest. Dermatol.*, **35**, 165 (1960).

(3) K. D. Kaufman, W. E. Russey, and L. R. Worden, *J. Org. Chem.*, **27**, 875 (1962).

CHART I



Surprisingly, the results were not the same as in the 7-hydroxycoumarin series. A linear furocoumarin was not obtained owing to the formation of an oxazolocoumarin (VIa) during an intermediate Claisen rearrangement step. Oxazolocoumarins of both the linear[4] and angular type, including the compounds prepared in this study, have been shown to possess no photosensitizing activity.[2]

In order to introduce the blocking acetamido group in the 5-position, 6-hydroxy-4-methylcoumarin (IVa) was nitrated with 1 equiv. of nitric acid in concentrated sulfuric acid. Borsche[5] considered the product of this reaction to be the 7-nitro derivative, but Fries and Lindemann[6] obtained evidence that the 5-nitro isomer IVb is a product, although the yield was not stated. Mewada and Shah[7] also obtained a mononitro product from this reaction and they assumed it to be the 5-nitro isomer, because of Fries and Lindemann's work. Unfortunately, the 5-nitro compound obtained by Fries and Lindemann was not sufficiently characterized to enable comparison with our sample, and it was necessary to secure additional evidence to establish its identity. Paper chromatography showed that our crude reaction product was a mixture of unreacted 6-hydroxy-4-methylcoumarin, a mononitrio derivative, and the 5,7-dinitro derivative.[5,7] The use of three different solvent systems failed to disclose the presence of more than one mononitro product. Pure 6-hydroxy-4-methyl-5-nitrocoumarin (IVb) was isolated by fractional precipitation during the gradual acidification of an aqueous sodium carbonate solution of the crude nitration product. Its structure was confirmed by reduction to 5-amino-6-hydroxy-4-methylcoumarin (IVc) which gave 5,6-dihydroxy-4-methylcoumarin (IVd) upon treatment with ferric chloride in 10% aqueous hydrochloric acid. Both the dihydroxy compound and its diacetate were shown to be identical with authentic samples[1] by comparison of infrared spectra and by the method of mixture melting point. The ferric chloride reaction is noteworthy since it represents the conversion of an *o*-aminophenol to an *o*-dihydroxy compound in one step. Oxidation of *o*-aminophenols with ferric chloride usually produces *o*-quinones, which may be reduced to *o*-dihydroxy compounds in a separate step.[8] Presumably, in this case, ferrous ion reduces the *o*-quinone as it is formed.

6-Hydroxy-4-methyl-5-nitrocoumarin was converted to its allyl ether Va by treatment with allyl bromide and potassium carbonate in acetone. Reduction with stannous chloride gave the 5-amino derivative Vb, which was acetylated to obtain 5-acetamido-6-allyloxy-4-methylcoumarin (Vc). Several attempts to cause the Claisen rearrangement by heating the ether Vc in either diethylaniline or dimethylaniline at temperatures ranging from 160 to 216° led to an oxazolocoumarin (VIa) instead of the expected *o*-allylhydroxycoumarin, which was to be converted to a linear furocoumarin. Structure VIa for the oxazolocoumarin was assigned on the basis of its elemental analysis, its infrared spectrum, and the similarity of its ultraviolet spectrum to that of the oxazolocoumarin VIb prepared from the acetate of 6-hydroxy-4-methyl-5-nitrocoumarin.

Attempts to prepare an intermediate, suitable for conversion to a linear furocoumarin, by Claisen rearrangement of the ethers Va or Vb were unsuccessful owing to uncontrollable decomposition of either compound at the high temperatures required. Linear furocoumarins of type II have been prepared by an alternative route.[1]

Experimental Section[9]

6-Hydroxy-4-methyl-5-nitrocoumarin (IVb).—A solution of 70% nitric acid (5.08 g., 0.057 mole) in 12 ml. of concentrated sulfuric acid was added over a period of 45 min. to a stirred solution of 6-hydroxy-4-methylcoumarin[10] (10.0 g., 0.057 mole) in 80 ml. of concentrated sulfuric acid, kept at a temperature between 2 and 4°. Ninety minutes after the addition was complete, the cold reaction mixture was poured over crushed ice (*ca.* 1 kg.), and the crude nitration product (11.91 g.), m.p. 208–215° dec., was collected by filtration. A chromatogram of the crude product on Whatman No. 2 paper, using descending *t*-butyl alcohol saturated with water, showed the presence of three compounds. The starting material (R_f 0.73) appeared as a bright yellow spot under ultraviolet light[11] after treatment with alcoholic potassium hydroxide. After development with ammonium hydroxide, 6-hydroxy-4-methyl-5-nitrocoumarin (R_f 0.98) appeared as a bright yellow spot which turned brown on contact with alcoholic potassium hydroxide. Before development, 5,7-dinitro-6-hydroxy-4-methylcoumarin[5,7] (R_f 0.58) appeared as an orange spot which turned violet on contact with alcoholic potassium hydroxide. Chromatograms were also prepared using mixtures of petroleum ether (b.p. 30–60°), benzene, and 95% ethanol (5:4:2) or acetic acid, benzene, and water (1:1:2).

A solution of the crude nitration product (3.20 g.) in 10% aqueous sodium carbonate was acidified with concentrated hydrochloric acid to a pH of 6.5, and the precipitate was recrystallized from water to obtain yellow prisms (2.40 g.): instantaneous m.p. 220–222° dec. (lit.[5,7] m.p. 210°); λ_{max}^{MeOH} 272 mμ (log ε 4.34) and 345 mμ (log ε 4.00); λ_{min} 243 mμ (log ε 3.96) and 303 mμ (log ε 3.48). Only one spot was observed on a paper chromatogram of this sample.

(4) R. B. Moffett, *J. Med. Pharm. Chem.*, **5**, 335 (1962).
(5) W. Borsche, *Ber.*, **40**, 2731 (1907).
(6) K. Fries and H. Lindemann, *Ann.*, **404**, 47 (1914).
(7) G. S. Mewada and N. M. Shah, *Ber.*, **89**, 2209 (1956).
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(11) Blak-Ray BLB 15, Ultra-Violet Products, Inc., South Pasadena, Calif.

The **acetate**, m.p. 122.5–123° (lit.[7] m.p. 121°), was obtained in 92% yield with boiling acetic anhydride containing a few drops of concentrated sulfuric acid.

5-Amino-6-hydroxy-4-methylcoumarin (IVc).—A cold solution of sodium hydrosulfite (150 g.) in 600 ml. of water was added rapidly to an ice-cold solution of 6-hydroxy-4-methyl-5-nitrocoumarin (9.70 g., 0.044 mole) in 120 ml. of concentrated ammonium hydroxide. The orange solution was stirred for 90 min. while a yellow crystalline precipitate (7.0 g., 84% yield) of m.p. 253–255.5° dec. formed. Recrystallization from 95% ethanol gave yellow prisms, m.p. 257–259° dec.

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.74; H, 5.02; N, 7.46.

5,6-Dihydroxy-4-methylcoumarin (IVd).—A 10% aqueous solution of ferric chloride (75 ml., 0.028 mole) was added to a stirred solution of 5-amino-6-hydroxy-4-methylcoumarin (5.00 g., 0.026 mole) in 60 ml. of 10% hydrochloric acid. A black precipitate formed almost immediately, and from it light yellow prisms (1.50 g., 30% yield), instantaneous m.p. 247–249° (lit.[1] m.p. 251–252°), were obtained by vacuum sublimation at 0.1 mm.

The **diacetate**, m.p. 174–175° (lit.[1] m.p. 173–175°), was obtained in 63% yield using acetic anhydride and pyridine.

6-Allyloxy-4-methyl-5-nitrocoumarin (Va).—A mixture of crude 6-hydroxy-4-methyl-5-nitrocoumarin (100 g., 0.452 mole) of m.p. 208–215° dec., allyl bromide (190 ml.), anhydrous potassium carbonate (150 g.), and acetone (3 l.) was refluxed for 12 hr. The reaction mixture was concentrated under reduced pressure on the steam bath and water was added to the dry residue. A solution of the water-insoluble product in benzene was filtered through a short column of acid-washed alumina and concentrated to a solid which crystallized from 95% ethanol as yellow needles (80 g., 68% yield), m.p. 155–156°.

Anal. Calcd. for $C_{13}H_{11}NO_5$: C, 59.77; H, 4.24; N, 5.36. Found: C, 59.94; H, 4.24; N, 5.39.

6-Allyloxy-5-amino-4-methylcoumarin (Vb).—A suspension of 6-allyloxy-4-methyl-5-nitrocoumarin (10.0 g., 0.038 mole) and stannous chloride dihydrate (40.0 g., 0.18 mole) in 95% ethanol (40 ml.) and concentrated hydrochloric acid (120 ml.) was boiled for 5 min. to form a clear solution. Upon being cooled in the refrigerator, the solution deposited crystals which were washed with 5% aqueous sodium bicarbonate and recrystallized from carbon tetrachloride to obtain yellow needles (6.2 g., 71% yield), m.p. 117–118°.

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.24; H, 5.87; N, 5.64.

5-Acetamido-6-allyloxy-4-methylcoumarin (Vc).—Treatment of 6-allyloxy-5-amino-4-methylcoumarin with acetic anhydride in boiling acetic acid gave the amide, which crystallized from ethanol as colorless plates, m.p. 149° (87% yield).

Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.02; H, 5.37; N, 4.90.

7-Allyl-β,2-dimethyl-5-hydroxy-4-benzoxazoleacrylic Acid δ-Lactone (VIa).—A solution of 5-acetamido-6-allyloxy-4-methylcoumarin (2.00 g., 0.0073 mole) in 5 ml. of diethylaniline was refluxed for 1 hr. Dilution of the cooled reaction mixture with 5% aqueous hydrochloric acid gave a tan solid (1.85 g., 99% yield), m.p. 177–178°. Recrystallization from carbon tetrachloride gave an analytical sample, m.p. 179°. Its infrared spectrum showed absorption at 1720 (C=O) and 1680 $cm.^{-1}$ (C=N), and its ultraviolet spectrum in ethanol showed a peak at 298 mμ (log ε 4.27) and inflections at 240 mμ (log ε 3.55), 324 (3.96), and 340 (3.58).

Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.47; H, 5.06; N, 5.31.

β,2-Dimethyl-5-hydroxy-4-benzoxazoleacrylic Acid δ-Lactone (VIb).—Powdered iron (3.00 g.) was added to a solution of 6-hydroxy-4-methyl-5-nitrocoumarin acetate (3.00 g., 0.0114 mole), sodium acetate (2.00 g.), acetic anhydride (6.0 ml.), and acetic acid (50 ml.) while the solution was being stirred and heated on a steam bath. After 2 hr., the reaction mixture was diluted with water and filtered to obtain a solid which crystallized from chloroform as colorless needles (0.45 g., 18% yield), m.p. 246°. Its ultraviolet spectrum in ethanol showed a peak at 292 mμ (log ε 4.26) and inflections at 244 mμ (log ε 3.57) and 336 (3.41).

Anal. Calcd. for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51. Found: C, 67.50; H, 4.46; N, 6.40.

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The Nuclear Magnetic Resonance Analysis of the Disaccharide in Flavonoid Rhamnoglucosides

HEINZ RÖSLER, T. J. MABRY, M. F. CRANMER, AND JACQUES KAGAN

Botany Department and Cell Research Institute, University of Texas, Austin, Texas

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Rutinose and neohesperidose, 6- and 2-O-α-L-rhamnopyranosyl-β-D-glucopyranose, respectively, are the only two disaccharides containing glucose and rhamnose which have been reported in naturally occurring flavonoid glycosides.[1] The presence of the individual sugars, rhamnose and glucose, obtained after hydrolysis of the diglycoside, is readily established by paper chromatography or, after trimethylsilylation, by gas chromatography.[2] On the other hand, the structure of the disaccharide is often determined with difficulty. The hydrolysis of the flavonoid–disaccharide linkage without breaking the bond between the two sugars is sometimes possible for flavonoid 3-rhamnoglucosides[3] but usually fails for 7-diglycosides unless specific enzymes are used.[4] An alternate procedure has been the ozonolysis of the diglycoside which yields the disaccharide but destroys the flavonoid portion of the molecule.[5]

We now report that the two known types of flavonoid rhamnoglucosides, rutinosides and neohesperidosides, are distinguished by the n.m.r. analysis of their acetates and of their trimethylsilyl ethers. Furthermore, the original glycosides can be recovered nearly quantitatively from these derivatives.

The structures of the disaccharide in rutin, hesperidin, neohesperidin, and naringin (Chart I) are well established and were recently reviewed by Horowitz.[6] In order to study the influence of the oxidation level of the aglycone on the sugar part of the n.m.r. spectra, representative examples of flavonol and flavone rutinosides and neohesperidosides have been prepared (Chart I).

The flavonols tamarixetin 7-rutinoside (**7**), tamarixetin 7-neohesperidoside (**8**), and kaempferol 7-neohesperidoside (**9**) were obtained in good yield from **1**, **3**, and **2**, respectively, by the elegant method of Pacheco, *et al.*[7] The flavone rhamnoglucosides diosmin (**4**) and

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(7) M. H. Pacheco and A. Grouiller, *Compt. rend.*, **255**, 3432 (1962); **256**, 4927 (1963).