lated: 0.31 g. of VIII (63%); 0.19 g. of II (35%); 0.20 g. of salicylic acid and traces of carbomethoxysalicylic acid. One gram of the ester under the same conditions yielded 0.18 g. of VIII after refluxing for five minutes.

3,3′-Methylenebis-(4-hydroxycoumarin) dibenzoate (1.12 g.) in 12 ml. of absolute ethanol was refluxed with 2 moles of sodium ethoxide for fifteen hours. Two moles of 1 *N* hydrochloric acid was added and the combined precipitate of II and VIII was filtered off and II separated from VIII by means of its solubility in dilute NaOH. VIII (0.13 g.) m. p. 318–320° and II (0.56 g.) m. p. 290° were obtained. One mole of $NaHCO_3$ was added to the filtrate and after concentration to dryness *in vacuo*, the residue was acidified and extracted with ether. The acid fraction yielded 0.12 g. of benzoic acid, m. p. 118–120°, and the neutral solution yielded 0.02 g. of ethyl benzoate, b. p. 206–207°.

3,3′-Methylenebis-(4-hydroxycoumarin) Disalicylate.—The di-(*o*-benzyloxybenzoate) of I (3.9 g.) in 200 ml. of dioxane was hydrogenated at 1900 pounds pressure and 100° for three hours over Raney nickel. The catalyst was filtered off and the filtrate concentrated to dryness *in vacuo*. The residue was taken up in a small volume of hot dioxane and the insoluble residue of II was filtered from the hot solution. This process was repeated three times. After a final recrystallization from acetic acid the disalicylate of II melted at 223–225°, yield 0.7 g.

Anal. Calcd. for $C_{33}H_{20}O_{10}$: C, 68.75; H, 3.47. Found: C, 68.62; H, 3.68.

3-Phenyl-4-hydroxycoumarin Salicylate.—3-Phenyl-4-hydroxycoumarin *o*-benzyloxybenzoate (1.5 g.) was dissolved in 200 ml. of acetic acid–ethyl acetate (1:1) and hydrogenated at 1 atmosphere over palladium on charcoal. In thirty minutes one mole of hydrogen had reacted. The catalyst was filtered off and the filtrate concentrated to dryness *in vacuo*. The residue was recrystallized twice from ethyl acetate and once from benzene, m. p. 185–187°, yield 0.9 g.

Anal. Calcd. for $C_{22}H_{14}O_6$: C, 73.74; H, 3.63. Found: C, 73.72; H, 4.09.

Acknowledgment.—The authors are indebted to Dr. Ivan Wolff for carrying out the high pressure hydrogenation experiments and to Mr. Miyoshi Ikawa for some of the C and H determinations.

Summary

1. A series of diesters of some 3,3′-alkylidenebis-(4-hydroxycoumarin)s and of monoesters of 3-phenyl-4-hydroxycoumarin have been prepared.

2. The *o*-benzyloxybenzoic acid esters have been converted to the corresponding salicylic acid esters by hydrogenolysis.

3. The 3,3′ - alkylidenebis - (4 - hydroxycoumarin)s yield 3,3′ - alkylidene - 4,4′ - epoxydicoumarins upon treatment with sodium ethoxide.

MADISON, WIS. RECEIVED DECEMBER 14, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, THE UNIVERSITY OF WISCONSIN]

Studies on 4-Hydroxycoumarins. V. The Condensation of α,β-Unsaturated Ketones with 4-Hydroxycoumarin[1]

BY MIYOSHI IKAWA, MARK ARNOLD STAHMANN AND KARL PAUL LINK

It has been observed by Sullivan, *et al.*,[2] that when salicylaldehyde is condensed with 4-hydroxycoumarin (I), an α,β-unsaturated ketone is formed, which reacts with another molecule of I by a Michael type addition. Accordingly a study of the condensation of other α,β-unsaturated ketones with 4-hydroxycoumarin was undertaken. The Michael type condensation is usually carried out in an alcoholic medium in the presence of an acid[3] or base catalyst. According to Conner and McClellan[4] secondary amines (*e. g.*, piperidine) are the most suitable catalysts in that they seldom cause other than the normal condensation, but they are not as effective as the metallic alkoxides.

The condensation of benzalacetone with 4-hydroxycoumarin under the usual conditions in ethanol with either sodium ethylate, hydrochloric acid, or piperidine as catalyst gives a mixture of products. The mixture contains the normal condensation product and the cyclic ketal formed by reaction with ethanol. However, by carrying out the reaction in pyridine alone, satisfactory yields of the Michael condensation products can be obtained. The condensation of benzalacetone with 4-hydroxycoumarin can also be brought about by refluxing the two components with water without the addition of a catalyst.

The α,β-unsaturated ketones II–VIII which were condensed with 4-hydroxycoumarin (I) are indicated below along with the structures of the resulting condensation products (IX–XV). On treatment of the condensation products (IX–XV) with 4% hydrogen chloride in absolute methanol cyclic ketals (XVI–XXII) are formed. This reaction is rationalized on the basis that the Michael type condensation products are δ-hydroxy ketones and can therefore undergo ring closure to the corresponding cyclic hemi-ketals which are then methylated. An analogous example is the reversible ketal formation of 4-salicyl-butan-2-one.[5] Evidence for the cyclic ketal structure of the benzalacetone product XVIII resides in the following transformations. When XI was methylated with diazomethane, the methyl ether XXIII was obtained, which differed from the isomeric cyclic ketal XVIII. By refluxing XVIII with aqueous methanolic HCl the

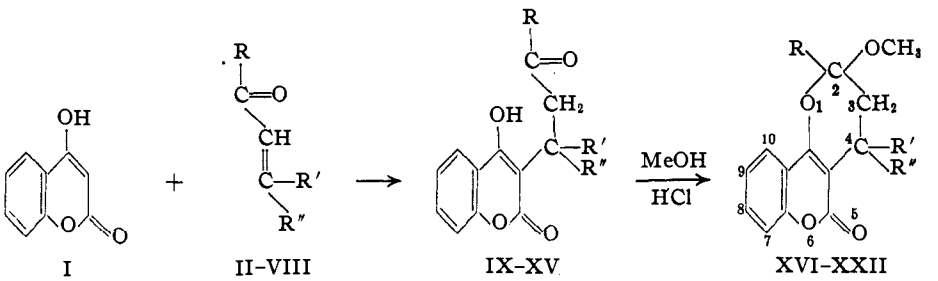
(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Supported through special grants from the Graduate School Research Committee, and the Wisconsin Alumni Research Foundation.

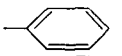
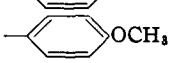
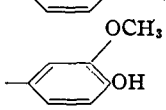
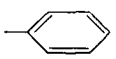
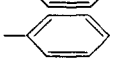
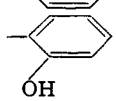
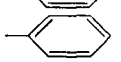
(2) Sullivan, Huebner, Stahmann and Link, THIS JOURNAL, **65**, 2288 (1943).

(3) Breslow and Hauser, *ibid.*, **62**, 2385 (1940).

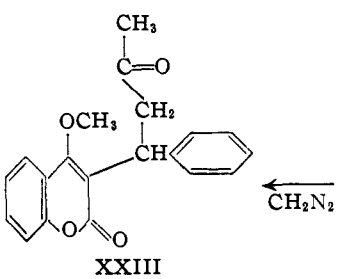
(4) Conner and McClellan, *J. Org. Chem.*, **3**, 570 (1939).

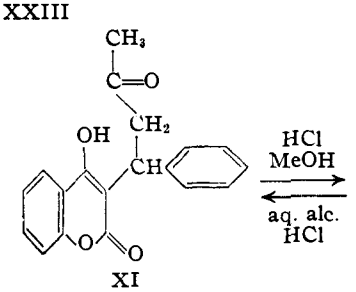
(5) Baker and Walker, *J. Chem. Soc.*, 646 (1935).

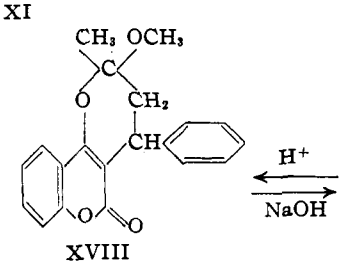


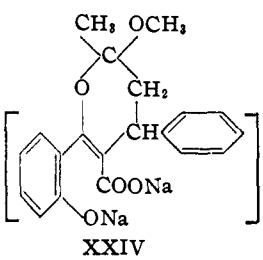
Ketones	Products		Substituent groups R	R′	R″
Ethylideneacetone (II)	IX	XVI	—CH₃	—CH₃	—H
Mesityl oxide (III)	X	XVII	—CH₃	—CH₃	—CH₃
Benzalacetone (IV)	XI	XVIII	—CH₃		—H
Anisalacetone (V)	XII	XIX	—CH₃		—H
Vanillylalacetone (VI)	XIII	XX	—CH₃		—H
Benzalacetophenone (VII)	XIV	XXI			—H
Benzal-*o*-hydroxyacetophenone (VIII)	XV	XXII			—H

original material XI was recovered. On treatment of XVIII with aqueous methanolic NaOH an alkali soluble product was obtained, which on acidification gave XVIII with no trace of XI. The sodium hydroxide had evidently opened up









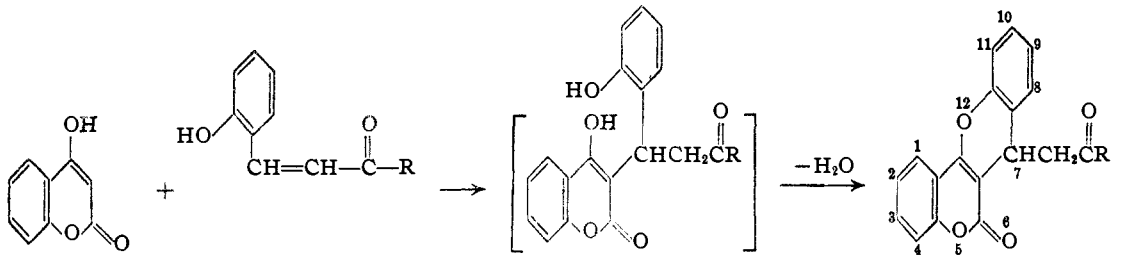
the lactone ring (product XXIV), which closed on acidification, without affecting the ketal system.

When α,β-unsaturated ketones derived from salicylaldehyde (XXV–XXVII) are condensed with 4-hydroxycoumarin, the Michael condensation products undergo spontaneous dehydration to give products with high melting points, which are alkali insoluble and have low solubility in ethanol (XXVIII–XXX).

A similar dehydration has been observed by Sullivan, *et al.*,[2] in the condensation of salicylaldehyde with 4-hydroxycoumarin.

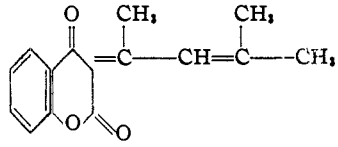
Mesityl oxide (III) when condensed with 4-hydroxycoumarin gives rise to two compounds. In addition to the normal condensation product (X) there is obtained an alkali insoluble product. It can easily be separated from X by its solubility in hexane. The properties and elementary analysis indicate XXXI to be the structure for this compound.

The compound XV resulting from the condensation of benzal-*o*-hydroxyacetophenone (VIII) with 4-hydroxycoumarin has also been prepared by degrading 3,3′-benzylidenebis-(4-hydroxycou-



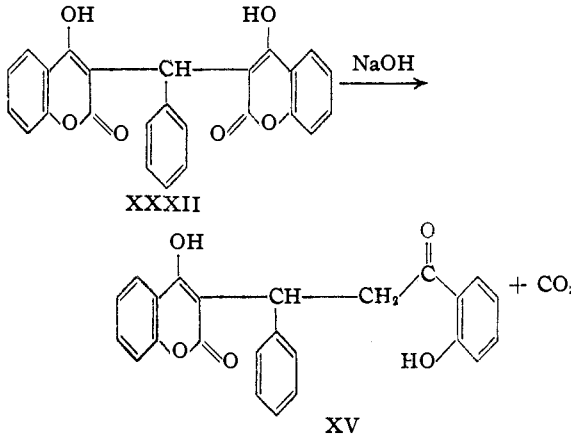
I XXV R = —CH₃
XXVI R =
XXVII R =

XXVIII R = —CH₃
XXIX R =
XXX R =



XXXI

marin) (XXXII) with sodium hydroxide.[6] The synthesis of XV by these two different methods establishes its structure.



XXXII

XV

The α,β-unsaturated esters, ethyl cinnamate and ethyl benzalmalonate, as well as phorone, dibenzalacetone, and furfuralacetone, when refluxed in pyridine with 4-hydroxycoumarin failed to yield the Michael products.

The condensation products obtained from 4-hydroxycoumarin and α,β-unsaturated ketones as well as the corresponding cyclic ketals have relatively high anticoagulant properties when compared with 3,3′-methylenebis-(4-hydroxycoumarin). A report on their physiological activity will appear elsewhere.

Experimental

The α,β-Unsaturated Ketones and Esters.—The mesityl oxide (III), benzalacetone (IV), anisalacetone (V), *o*-hydroxybenzalacetophenone (XXVI), furfuralacetone, dibenzalacetone, ethyl cinnamate and phorone were obtained from the Eastman Kodak Company. Ethylideneacetone[7] (II), vanillylalacetone[8] (VI), benzalacetophenone[9] (VII), benzal-*o*-hydroxyacetophenone[10] (VIII), salicylalacetone[11] (XXV), and ethyl benzalmalonate[9] were prepared according to the references cited.

2,2′-Dihydroxybenzalacetophenone (XXVII).—Ten grams of salicylaldehyde and 10 g. of *o*-hydroxyacetophenone were dissolved in 300 cc. of water containing 10 g. of sodium hydroxide and kept at 85° for ten to fifteen hours. Upon acidification of the reaction mixture an oil was obtained which crystallized partially on standing. The product was filtered off and recrystallized from ethanol, m. p. 160° dec., yield 2.4 g. (14%).

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 75.0; H, 5.0. Found: C, 75.0; H, 5.2.

The **dibenzoate** was prepared by heating XXVII with benzoyl chloride in pyridine and was recrystallized from ethanol, m. p. 114°.

Anal. Calcd. for $C_{29}H_{20}O_5$: C, 77.7; H, 4.5. Found: C, 77.5; H, 4.8.

The Condensation of 4-Hydroxycoumarin with α,β-Unsaturated Ketones and Esters.—The condensations were made by refluxing the reactants in 2 to 3 times their weight of pyridine. Equimolar amounts of the reactants were used (except for mesityl oxide). The reaction mixture was poured into a large volume of water and acidified with hydrochloric acid. An oil separated out in all cases which, if condensation took place, solidified. The products IX–XV were purified by recrystallization from ethanol and XXVIII–XXX by recrystallization from dioxane. IX–XV were soluble in dilute sodium hydroxide whereas XXVIII–XXX were not. Other details are given in Table I.

Condensation of 4-Hydroxycoumarin with Mesityl Oxide.—Sixteen and two-tenths grams (0.1 mole) of 4-hydroxycoumarin and 19.6 g. (0.2 mole) of mesityl oxide were refluxed in 50 cc. of pyridine for 2 days. The reaction mixture was poured into 1.5 l. of water. An oil was obtained which solidified. It could be separated into 2 fractions with boiling hexane. The hexane insoluble material (X) was recrystallized from ethanol and melted at 212° (3.3 g.). The hexane solution on concentration yielded large crystals of XXXI which, when recrystallized from hexane, melted at 93° (8.3 g.). Other details are included in Table I.

The Condensation of 4-Hydroxycoumarin with Benzalacetone in Water.—Thirty grams (0.18 mole) of 4-hydroxycoumarin and 27 g. (0.18 mole) of benzalacetone were refluxed in 500 cc. of water for twelve hours. The mixture

(6) Unpublished work of this Laboratory.

(7) Grignard and Fluchaire, *Ann. chim.*, **9**, 10 (1928).

(8) Francesconi and Cusmano, *Gass. chim. ital.*, **38**, II, 75 (1908).

(9) Gilman and Blatt, "Organic Synthesis," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 78.

(10) Feurstein and v. Kostanecki, *Ber.*, **31**, 715 (1898).

(11) Harries, *ibid.*, **24**, 3180 (1891).

TABLE I

PRODUCTS FROM THE CONDENSATION OF α,β-UNSATURATED KETONES WITH 4-HYDROXYCOUMARIN

No.	Compound	Reflux time, hours	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
	(a) R = 4-hydroxycoumarin								
IX	3-(α-Methyl-β-acetylethyl)-R	24	44	141	$C_{14}H_{14}O_4$	68.3	68.0	5.7	5.5
	3-(α-Methyl-β-acetylethyl)-R methyl ether[a]			liq.	$C_{15}H_{16}O_4$				
X	3-(α,α-Dimethyl-β-acetylethyl)-R	48	13	212	$C_{15}H_{16}O_4$	69.2	69.2	6.2	6.3
XI	3-(α-Phenyl-β-acetylethyl)-R	4–8	40	161	$C_{19}H_{16}O_4$	74.0	74.2	5.2	5.4
	3-(α-Phenyl-β-acetylethyl)-R methyl ether[b]			127	$C_{20}H_{18}O_4$	74.5	74.3	5.6	5.7
XII	3-(α-Anisyl-β-acetylethyl)-R	4–12	45	160	$C_{20}H_{18}O_5$	71.0	70.9	5.3	5.2
	3-(α-Anisyl-β-acetylethyl)-R methyl ether[c]			Sirup	$C_{21}H_{20}O_5$				
XIII	3-[α-(p-Hydroxy-m-methoxyphenyl)-β-acetylethyl]-R	6–24	18	181	$C_{20}H_{18}O_6$	67.8	68.0	5.1	5.2
XIV	3-(α-Phenyl-β-benzoylethyl)-R	4	37	160	$C_{24}H_{18}O_4$	77.8	77.7	4.9	5.0
	3-(α-Phenyl-β-benzoylethyl)-R methyl ether[d]			91	$C_{25}H_{20}O_4$	78.1	78.0	5.2	5.3
XV	3-(α-Phenyl-β-salicylylethyl)-R	12	34	194	$C_{24}H_{18}O_5$	74.6	74.8	4.7	4.6
	(b) R = (1)benzopyrano-(4,3-b)(1)benzopyran								
XXVIII	6-Oxo-7-acetonyl-R	1	69	263d	$C_{19}H_{14}O_4$	74.5	74.4	4.6	4.6
XXIX	6-Oxo-7-benzoylmethyl-R	12	76	240d	$C_{24}H_{16}O_4$	78.25	78.25	4.4	4.4
XXX	6-Oxo-7-salicylylmethyl-R	12	75	241d	$C_{24}H_{16}O_5$	75.0	74.7	4.2	4.3
XXXI	3-(2-Methyl-Δ^2-penten-4-ylidene)-2,4-diketochroman	48	34	93	$C_{15}H_{14}O_3$	74.4	74.1	5.8	6.0

[a] Distilled at 0.5 mm. at a bath temperature of 170°. *Anal.* Calcd. OCH_3, 11.9; found, 11.4. [b] *Anal.* Calcd. OCH_3, 9.6; found, 9.4. [c] Distilled at 0.5 mm. at a bath temperature of 240°. *Anal.* Calcd. OCH_3, 17.6; found 16.1. [d] *Anal.* Calcd. OCH_3, 8.1; found, 8.3.

TABLE II

PRODUCTS FROM THE METHANOLIC HYDROGEN CHLORIDE TREATMENT OF THE MICHAEL CONDENSATION PRODUCTS

No.	Derivatives of -5-oxo-dihydropyrano(3,2-c) (1)benzopyran	Reflux time, hours	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Methoxyl Calcd.	Methoxyl Found
XVI	2,4-Dimethyl-2-methoxy-	1	29	124	$C_{15}H_{16}O_4$	69.2	69.4	6.2	6.0	11.9	11.6
XVII	2,4,4-Trimethyl-2-methoxy-	24	80	102	$C_{16}H_{18}O_4$	70.1	70.1	6.6	6.4	11.3	10.1
XVIII	2-Methyl-2-methoxy-4-phenyl-	1/4	83	166	$C_{20}H_{18}O_4$	74.5	74.5	5.6	5.9	9.6	9.5
XIX	2-Methyl-2-methoxy-4-anisyl-	4	75	163	$C_{21}H_{20}O_5$	71.6	71.5	5.7	5.8	17.6	16.7
XX	2-Methyl-2-methoxy-4-(p-hydroxy-m-methoxyphenyl)-	1	82	187	$C_{21}H_{20}O_6$	68.5	68.6	5.5	5.6	16.8	16.5
XXI	2,4-Diphenyl-2-methoxy-	20	13	205	$C_{25}H_{20}O_4$	78.1	77.9	5.2	5.4	8.1	8.4
XXII	2-Salicyl-2-methoxy-4-phenyl-[a]	1	50	194d	$C_{25}H_{20}O_5$	75.0	74.9	5.0	5.1	7.7	7.6

[a] Recrystallized from 4% hydrochloric acid in methanol. Should be thoroughly dried before taking a melting point. Gave a melting point depression when mixed with XV.

was cooled to 0° for twelve hours, whereupon a heavy gum separated out. The aqueous phase was decanted off and the gum recrystallized from an acetone–water mixture. The yield of XI was 27.5 g. (48%).

Treatment of the Michael Condensation Products with Methanolic Hydrogen Chloride.—One gram of the condensation products was refluxed with 10 g. of 4% hydrochloric acid in absolute methanol for the times indicated in Table II. The products were obtained either directly from the reaction mixture on cooling or by the addition of water, and were recrystallized from ethanol. Further details are given in Table II.

2-Methyl-2-ethoxy-4-phenyl-5-oxo-dihydropyrano(3,2-C)(1)benzopyran.—Two grams of XI was refluxed with 25 cc. of 3% hydrochloric acid in ethanol for twenty-two hours. Crystals were obtained on cooling (m. p. 135–152°). After two recrystallizations from ethanol 70 mg. of the desired product was obtained melting at 177°. It was also obtained in poor yield when 4-hydroxycoumarin and benzalacetone were refluxed in ethanol + sodium ethylate for two days.

Anal. Calcd. for $C_{21}H_{20}O_4$: C, 75.0; H, 6.0. Found: C, 75.0; H, 6.2.

Methylation of the Michael Condensation Products with Diazomethane.—The methyl ethers of IX, XI, XII, XIV were prepared by distilling an excess of ethereal diazomethane into an ether suspension of the compounds and allowing to stand for several hours. On methylation the solids went into solution. The excess diazomethane was decomposed by adding glacial acetic acid. The ether solutions were concentrated and the products, when solid, recrystallized from ethanol. The ethers of XII and IX could not be crystallized and were therefore distilled under low pressure. Further details are included in Table I.

Treatment of XVIII with Aqueous Methanolic Hydrochloric Acid.—One-half gram of XVIII was refluxed with 50 cc. of 10% hydrochloric acid (in 50% methyl alcohol) for six hours. The methanol was distilled off. The reaction mixture was made alkaline with sodium hydroxide, thoroughly triturated and filtered. The filtrate was acidified with hydrochloric acid and the precipitate obtained recrystallized from ethanol: 170 mg. of a product was obtained which melted at 159–161° and showed no m. p. depression when mixed with XI.

Treatment of XVIII with Aqueous Methanolic Sodium Hydroxide.—One-half gram of XVIII was refluxed with 50

cc. of 10% sodium hydroxide (in 50% methyl alcohol) for six hours. The methyl alcohol was distilled off. An oil was obtained which on the addition of water dissolved completely. Upon acidification of the aqueous solution with hydrochloric acid an oil separated which solidified. This acidic solution including the solid was again made alkaline with sodium hydroxide, thoroughly triturated and filtered. This time some insoluble material remained. The filtrate was acidified with hydrochloric acid and 97 mg. of an oily precipitate was obtained from which no XI could be isolated. From the sodium hydroxide insoluble solid the starting material XVIII was isolated.

Acknowledgment.—We are indebted to Mr. Lloyd Graf for some of the C and H determinations and to Dr. Charles F. Huebner for the many valuable suggestions that he contributed to this work.

Summary

1. 4-Hydroxycoumarin has been condensed with the following α,β-unsaturated ketones by the Michael type addition: ethylideneacetone, mesityl oxide, benzalacetone, anisalacetone, vanillylalacetone, benzalacetophenone, benzal-*o*-hydroxyacetophenone, salicylalacetone, salicylalacetophenone, and 2,2′-dihydroxybenzalacetophenone. The condensations were carried out by refluxing in pyridine.

2. The condensation products from salicylalacetone, salicylalacetophenone, and 2,2′-dihydroxybenzalacetophenone undergo spontaneous dehydration to 7-substituted 6-oxo-(1)benzopyrano(4,3-b)(1)-benzopyrans.

3. The other condensation products (not included above) were converted to the corresponding cyclic methyl ketals by refluxing in methanolic hydrogen chloride.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN]

Studies on 4-Hydroxycoumarins. VI. Glucosides of 4-Hydroxycoumarins[1]

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Glucosides of the anticoagulant, 3,3′-methylenebis-(4-hydroxycoumarin)[2] and of related 4-hydroxycoumarins were desired for use in the study of the relationship between chemical structure and hypoprothrombinemia inducing capacity. Glucosides of the keto-enol 4-hydroxycoumarins have heretofore not been prepared. Certain chemical properties of these glucosides are worthy of note. They are readily hydrolyzed by alkali and some of them undergo cleavage to the aglucone when their acetates are subjected to catalytic deacetylation in methanol by metal alkoxides. Because of the uniqueness of this behavior, the deacetylation reaction was studied in detail.

When stable silver salts of the enol aglucones were realizable they were treated with acetobromoglucose to form the acetylated glucosides. A modification of Robertson's method for phenol β-glycosides[3] was applied to the cases in which the silver salts of the enol aglucones were unstable. No reaction occurs between these enols and acetobromoglucose in the presence of silver oxide unless a catalytic quantity of quinoline is included. In all probability quinoline hydrobromide is the first product of the coupling and the excess of silver oxide regenerates the catalyst. If more than a trace of quinoline is used, the reaction proceeds with decomposition and the production of uncrystallizable sirups.

4-Hydroxycoumarin glucoside tetraacetate (I), 4-hydroxy-6-methylcoumarin glucoside tetraacetate (II), 3-phenyl-4-hydroxycoumarin glucoside tetraacetate (III), and 3,3′-methylenebis-(4-hydroxycoumarin) monoglucoside tetraacetate (IV) were prepared by the silver salt method. The modified Robertson method was used in the preparation of 3,3′-methylenebis-(4-hydroxycoumarin) diglucoside octaacetate (V) and 3-[6-oxo(1)benzopyrano(4,3-b)(1)benzopyran-7-yl]-4-hydroxycoumarin glucoside tetraacetate (VI).

Because of the method of preparation and the substantial negative rotation of all except two of these glucosides (IV and V), the β-configuration can be assigned with some confidence.

All the glucosides and glucoside acetates involving the 4-hydroxycoumarins reduce boiling Fehling solution within two minutes. The acidic nature of 4-hydroxycoumarin ($K_a = 2.3 \times 10^{-6}$) probably accounts for this alkaline hydrolysis. Hibbert[4] and co-workers have shown that the rate of alkaline hydrolysis of phenol glycosides increases with the order of acidity of the parent phenol.

The deacetylation of I and II was accomplished by the catalytic barium methoxide procedure. No method was found for effecting simple deacetylation of the glucoside acetates in which there are substituents on position 3 of the coumarin residue. When III was catalytically deacetylated, the rate of mutarotation gradually fell and the rotation became constant after two weeks. At least 80% of the starting compound had been

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(2) Stahmann, Huebner and Link, *J. Biol. Chem.*, **138**, 513 (1941).

(3) Robertson and Waters, *J. Chem. Soc.*, 2729 (1930).

(4) Fisher, Hawkins and Hibbert, THIS JOURNAL, **63**, 3031 (1941).