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

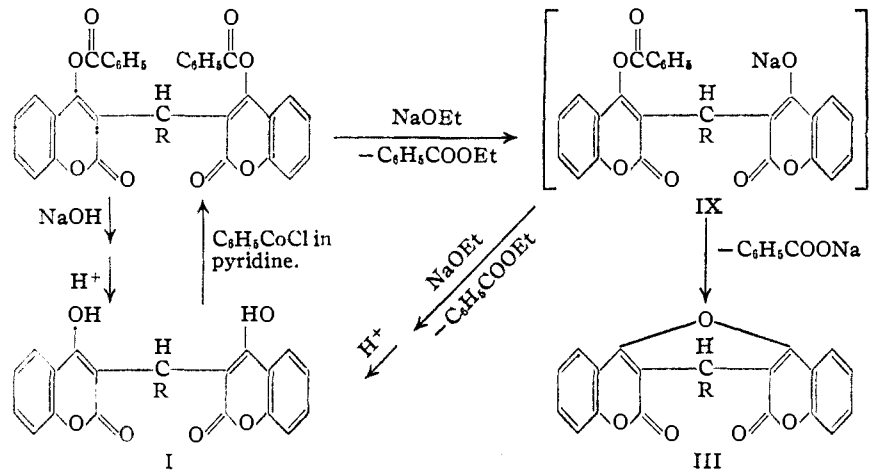
Studies on 4-Hydroxycoumarins. IV. Esters of the 4-Hydroxycoumarins[1]

BY MARK A. STAHMANN, LLOYD H. GRAF, CHARLES F. HUEBNER, SAUL ROSEMAN AND KARL PAUL LINK

The 3,3′-alkylidenebis- and -arylidenebis-(4-hydroxycoumarin)s (I) aldehyde condensation products of 4-hydroxycoumarin, may exist in an enol or keto form. In the enol form they may react with acid halides or acid anhydrides to esterify both enolic hydroxyl groups. This paper discusses the synthesis of some of these diesters, principally those of 3,3′-methylenebis-(4-hydroxycoumarin) (II). Since certain experiments of Link, *et al.*,[2] indicate that the 4-hydroxycoumarins may exert their anticoagulant action after degradation in the body to salicylic acid, salicylic acid esters are included. These compounds were prepared as part of the study dealing with the relation of structure in the 4-hydroxycoumarin group to anticoagulant activity.

II was readily converted to its acetate by treatment with acetic anhydride in pyridine.[3] In this study other diesters of II were prepared by a similar method.

When the methylene carbon atom of I carries a substituent other than hydrogen, treatment with acetic anhydride or acetyl chloride in pyridine does not give the esters. Dehydration occurs between the enolic hydroxyls with the formation 3,3′-alkylidene- or -arylidene-4,4′-epoxydicoumarins (III).[4] IV and V appear to be the most easily dehydrated bis-4-hydroxycoumarins. Both are dehydrated by refluxing with acetic anhydride, the former also being dehydrated by treatment with benzoyl chloride in pyridine. In contrast, VI and VII form stable diacetates when refluxed in acetic anhydride, and stable dibenzoates when treated with benzoyl chloride in pyridine. When a diester of I is treated with one equivalent of sodium ethoxide, a partial conversion to the unesterified parent substance and to the anhydride, III results. Studies with the dibenzoate of II revealed that the acyl residue is removed as sodium benzoate and ethyl benzoate. Since it has been shown that treatment of the monobenzoate and mono-(dimethylphosphate) of II with one mole of sodium ethoxide transforms them to the anhydro compound, 3,3′-methylene-4,4′-epoxydicoumarin (VIII), the conversion of the diesters of II to VIII (and in general the conversion of a diester of I to III) probably proceeds over a mono ester (IX) as an intermediate. This mono ester then loses one mole of acid (as the sodium salt) intramolecularly to form the dehydration product. These reactions can be illustrated by the following transformations of the dibenzoate of I



Product	Substituent R
II	H
IV	C_6H_5
V	CH_3
VI	C_2H_5
VII	C_3H_7

Product	Substituent R
VIII	H
X	C_3H_7

o-Hydroxy substituted salicylates of II were prepared by condensation with the appropriate acid chloride in pyridine. The di-(carbomethoxysalicylate) of II was used in an attempt to prepare the disalicylate, but all efforts to remove the carbomethoxy group (acidic and basic hydrolysis and ammonolysis) resulted in further hydrolysis and loss of the salicylate group. The remarkable lability of the salicylate linkage is illustrated by the conversion of the di-(carbomethoxysalicylate) of II to VIII by as weak a base as sodium acetate. In this reaction some carbomethoxysalicylic acid is formed. This indicates that the salicylate linkage is as labile as the readily hydrolyzed carbomethoxy group. The disalicylate of II was successfully prepared by hydrogenolysis of the di-(*o*-benzyloxybenzoate)

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(2) Link, Overman, Sullivan, Huebner and Scheel, *J. Biol. Chem.*, **147**, 463 (1943).

(3) Stahmann, Huebner and Link, *ibid.*, **138**, 513 (1941).

(4) Huebner, Sullivan, Stahmann and Link, THIS JOURNAL, **65**, 2292 (1943).

TABLE I

ESTERS OF 3,3′-ALKYLIDENEBIS-(4-HYDROXYCOUMARIN)S AND 3-PHENYL-4-HYDROXYCOUMARIN

Derivative	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
(a) Esters of 3,3′-methylenebis-4-hydroxycoumarin							
Dipropionate	77	247–248[d]	$C_{25}H_{20}O_8$	66.96	67.03	4.46	4.57
Di-*n*-butyrate	69	227–228	$C_{27}H_{24}O_8$	68.07	68.52	5.04	5.26
Di*iso*butyrate	82	233–234	$C_{27}H_{24}O_8$	68.07	67.78	5.04	5.15
Di-*n*-valerate	48	224–225	$C_{29}H_{28}O_8$	69.05	68.87	5.55	5.60
Di*iso*valerate	63	220–221	$C_{29}H_{28}O_8$	69.05	69.01	5.55	5.55
Dicaproate	62	225–226	$C_{31}H_{32}O_8$	69.93	69.93	6.02	6.22
Diheptanoate	50	215–216	$C_{33}H_{36}O_8$	70.72	70.86	6.43	6.03
Dibenzoate	81	263–264	$C_{33}H_{20}O_8$	72.97	73.22	3.68	3.80
Di-(trimethylacetate)	27	210–211	$C_{29}H_{28}O_8$	69.06	69.37	5.55	5.76
Di-(benzylcarbonate)[a]	60	188–189	$C_{35}H_{24}O_{10}$	69.55	69.32	3.97	4.03
Di-(acetylsalicylate)[b]	62	253–256	$C_{37}H_{24}O_{12}$	67.27	66.85	3.64	3.38
Di-(carbomethoxysalicylate)[c]	63	213–216	$C_{37}H_{24}O_{14}$	64.16	63.89	3.47	3.77
Di-(*o*-benzyloxybenzoate)[b]	67	212–213	$C_{47}H_{32}O_{10}$	74.60	74.21	4.23	4.39
Di-(*o*-chlorobenzoate)[d]	31	250–252	$C_{33}H_{18}O_8Cl_2$	64.60	64.76	2.94	3.45
Di-(*p*-chlorobenzoate)[d]	71	288–291	$C_{33}H_{18}O_8Cl_2$	64.60	64.27	2.94	3.38
Difuroate[d]	29	298–300[d]	$C_{29}H_{16}O_{10}$	66.41	66.11	3.06	3.52
(b) Further esters, R = 4-hydroxycoumarin							
3,3′-Ethylidenebis-(R) dibenzoate	76	209–210	$C_{34}H_{22}O_8$	73.12	73.09	3.94	4.23
3,3′-Propylidenebis-(R) diacetate	54	202–203	$C_{25}H_{20}O_8$	66.98	66.97	4.46	4.71
3,3′-Propylidenebis-(R) dibenzoate	84	203–204	$C_{35}H_{24}O_9$	73.42	73.47	4.20	4.31
3,3′-Butylidenebis-(R) diacetate	69	210–211	$C_{26}H_{22}O_8$	67.53	67.28	4.76	5.25
3,3′-Butylidenebis-(R) dibenzoate	85	226–227	$C_{36}H_{20}O_8$	73.72	73.91	4.44	4.72
3-Phenyl-R acetylsalicylate[a]	60	183–185	$C_{24}H_{16}O_6$	72.00	71.63	4.00	4.40
3-Phenyl-R *o*-benzyloxybenzoate[e]	65	173–175	$C_{29}H_{20}O_5$	77.67	77.67	4.46	4.53

[a] Recrystallized from acetic acid. [b] Recrystallized from amyl alcohol. [c] Recrystallized from dioxane. [d] Recrystallized from β,β′-dichloroethyl ether. [e] Recrystallized from ethyl acetate.

at high pressure over Raney nickel. The crude product is separated from the small quantity of II which is produced in the reaction by repeated recrystallizations from dioxane. The *o*-benzyloxybenzoate of 3-phenyl-4-hydroxycoumarin is converted to 3-phenyl-4-hydroxycoumarin salicylate by hydrogenolysis at atmospheric pressure over palladium. Under these conditions the di-(*o*-benzyloxybenzoate) of II is unchanged. Table I lists the esters prepared.

The anticoagulant activity of the ester is lower than that of the parent 3,3′-alkylidenebis-(4-hydroxycoumarin). It appears that they act as anticoagulants after hydrolysis *in vivo*. A report on their activity will appear elsewhere.

Experimental

Esterification of 3,3′-Methylenebis-(4-Hydroxycoumarin) (I).[5]—All the diesters of II were prepared by slowly adding with vigorous stirring, 4 equivalents (100% excess) of the corresponding acid chloride to an 8% solution of the parent substance (usually about 2 g.) in dry pyridine (25 ml.) at 0°. After a few minutes the diesters usually crystallized from the reaction mixture. The mixture was allowed to stand for six hours at 25°, filtered, and washed with ethanol. In most cases, the crude product was recrystallized from cyclohexanone. The exceptions are noted in Table I.

(5) The 3,3′-alkylidenebis-(4-hydroxycoumarin)s were prepared by condensing 4-hydroxycoumarin with the corresponding aldehyde by the method of Sullivan, *et al.*, THIS JOURNAL, **65**, 2288 (1943). 4-Hydroxycoumarin was prepared by the method of Stahmann, *et al.*, *ibid.*, **65**, 2285 (1943).

Acetylation of I was accomplished by refluxing the parent substance (usually about 2 g.) with 12.5 parts of acetic anhydride (25 g.) for six hours. In some cases the diacetate crystallized out when the reaction mixture was cooled. When this did not take place the excess anhydride was decomposed by pouring the reaction mixture into six volumes of ice-water. The acetates then separated as crystalline products. IV and V were converted to the anhydrides by this procedure.

Benzoylation of 3,3′-Alkylidenebis-(4-hydroxycoumarin)s.—Benzoates were prepared by adding benzoyl chloride to a pyridine solution of the 3,3′-alkylidenebis-(4-hydroxycoumarin). 3,3′-Benzylidenebis-(4-hydroxycoumarin) underwent dehydration under these conditions, but all the other compounds which were studied formed stable dibenzoates which were recrystallized from cyclohexanone.

Action of Bases on Esters of I.—A mixture of 5 g. of **3,3′-methylenebis-(4-hydroxycoumarin) dipropionate,** and 0.76 g. of sodium ethoxide was suspended in 100 ml. of absolute ethanol and refluxed for twelve hours. The mixture was then filtered while hot, yielding 1.85 g. (49%) of VIII m. p. 317–321°. After recrystallization from cyclohexanone the melting point was 320–323°. II (1.55 g.) was recovered from the filtrate by acidification. Treatment of **3,3′-methylenebis-(4-hydroxycoumarin) diacetate** with sodium ethoxide under these conditions gave a lower yield of the dehydration product. Saponification of the esters of I with aqueous sodium hydroxide gave the unesterified parent substances.

Treatment of **3,3′-butylidenebis-(4-hydroxycoumarin) diacetate** with one equivalent of sodium ethoxide in boiling ethanol for twelve hours gave a 40% yield of **X**, m. p. 246°.

3,3′-Methylenebis-(4-hydroxycoumarin) di-(carbomethoxysalicylate) (1.0 g.) was dissolved in 45 ml. of boiling dioxane. A solution of 4.70 g. of hydrated sodium acetate in 25 ml. of water was added and the mixture was refluxed for ten hours. The following products were iso-

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.

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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.

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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

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(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).