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.

MADISON, WIS. RECEIVED DECEMBER 14, 1943

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

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

BY CHARLES F. HUEBNER, SULO A. KARJALA, WILLIAM R. SULLIVAN AND KARL PAUL LINK

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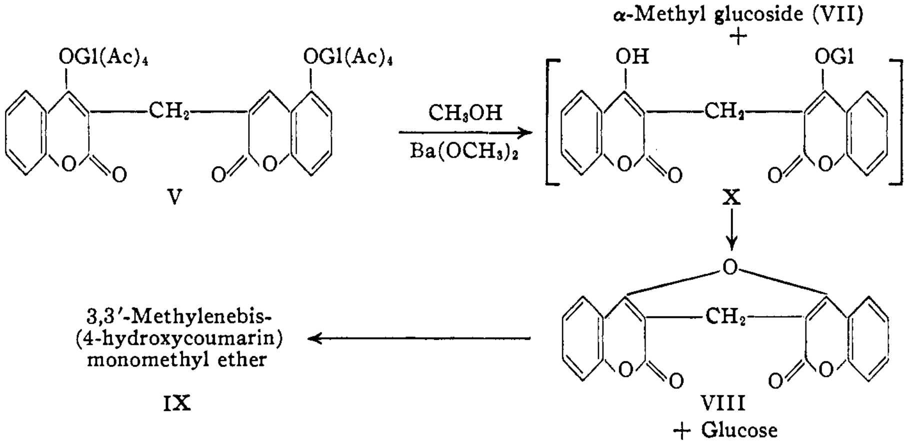
[2] Stahmann, Huebner and Link, *J. Biol. Chem.*, **138**, 513 (1941).

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

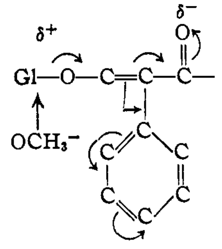
[4] Fisher, Hawkins and Hibbert, THIS JOURNAL, **63**, 3031 (1941).

converted to 3-phenyl-4-hydroxycoumarin and α-methyl glucoside (VII).

Isbell[5] has recently pointed out that the cleavage of the sugar-oxygen bond in enol glycosides is favored over fission at the aglucone-oxygen bond. The methanolysis of III furnishes experimental proof for this suggestion. The formation of 3-phenyl-4-hydroxycoumarin rather than 3-phenyl-4-methoxycoumarin and the Walden inversion accompanying the production of VII indicate the point of fission. Conversely, methanolysis of sugar esters usually occurs at the aglycone-oxygen bond with no inversion and formation of the methyl ester of the acid involved in the sugar ester. The presence of the phenyl and carbonyl groups in III favors the indicated electronic shift. The glucosidic carbon is the positive center of this polarized molecule and it is attacked by the methoxyl anion with cleavage of the sugar-oxygen bond.



Gl(Ac)$_4$ = The 2,3,4,6-tetraacetylglucopyranose residue



III

When the catalytic deacetylation of V was attempted, 3,3′-methylene-4,4′-epoxydicoumarin (VIII) and some 3,3′-methylenebis-(4-hydroxycoumarin) monomethyl ether (IX) were obtained instead of the glucoside.[6] Recognizing that III yields 3-phenyl-4-hydroxycoumarin and VII under these conditions, the formation of VIII and IX can be attributed to the following reactions. One glucose residue is liberated initially by alcoholysis yielding VII and 3,3′-methylenebis-(4-hydroxycoumarin) monoglucoside (X). A ring closure of the type noted in mono esters of 3,3′-methylenebis-(4-hydroxycoumarin)[6] then produces VIII and glucose. Part of VIII is then converted to IX by the alkoxide as indicated previously.[6] The production of IX in this manner is preferred over formation by methanolysis of X because the latter reaction would be expected to yield as the methylated component, VII rather than IX.

Additional support for the above mechanism was obtained from a study of the glucose content of the resulting reaction mixture. One half of the theoretical amount was present as free glucose based on the exhibited reducing power. The second half of the reducing power could be liberated by acid hydrolysis, indicating the presence of a methyl glucoside in the reaction mixture. The tetraacetate (IV) of the intermediate (X) was synthesized and it showed the predicted properties. It gave VIII and IX on catalytic deacetylation, and the amount of IX increased as larger amounts of catalyst were used. This further substantiates the mechanism of formation of IX, since in the conversion of VIII to IX the amount of IX produced parallels mole for mole the amount of metal alkoxide used. IV can also be converted to VIII by simply dissolving it in pyridine.

Experimental

Preparation of the Silver Salts of the 3-Substituted-4-Hydroxycoumarins.—The following method was used for the silver salts, with a slight modification in the case of 4-hydroxycoumarin. The 3-substituted-4-hydroxycoumarin was dissolved in one equivalent of 1.5 *N* aqueous sodium hydroxide and one equivalent of silver nitrate plus 2% excess, dissolved in a small amount of water, was added with vigorous stirring. The gelatinous, white silver salt precipitated immediately. It was filtered and resuspended in water, washed thoroughly with water, pressed dry on the funnel and washed once with ethanol. Precautions were taken to work in a feeble light. Since the silver salt of 4-hydroxycoumarin is appreciably soluble in water it was not washed but recrystallized from the minimum volume of water. The salts were dried over calcium chloride *in vacuo*, finely pulverized and dried again at 45° under 0.05 mm. pressure over phosphorus pentoxide.

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[5] Isbell, *Ann. Rev. Biochem.*, **XII**, 215 (1943).

[6] Huebner, Sullivan, Stahmann and Link, THIS JOURNAL, **65**, 2292 (1943).

TABLE I

MONOGLUCOSIDES OF 4-HYDROXYCOUMARINS

Hydrogen, % Compound	Recrystallized from	M. p., °C.	Yield, %	$[\alpha]^{25}D$	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
4-Hydroxycoumarin glucoside tetraacetate (I)	Methanol	178–179	40	−63.2° (*C*, 2; $CHCl_3$)	$C_{23}H_{24}O_{12}$	56.09	56.17	4.88	4.97
4-Hydroxycoumarin glucoside	Methanol	201–202	90	−106° (*C*, 16; CH_3OH)	$C_{15}H_{16}O_8$	55.55	55.72	4.94	4.94
4-Hydroxy-6-methylcoumarin glucoside tetraacetate (II)	Ethanol	168–170	36	−24.9° (*C*, 2; C_6H_6)	$C_{24}H_{26}O_{12}$	56.91	57.11	5.14	5.35
4-Hydroxy-6-methylcoumarin glucoside	Pyridine water	223–224	90	−86° (*C*, 0.75) pyridine	$C_{16}H_{18}O_8$	56.80	56.98	5.32	5.32
3-Phenyl-4-hydroxycoumarin glucoside tetraacetate (III)	Ethanol	156–158	47	−58.4° (*C*, 3.2; C_6H_6)	$C_{29}H_{28}O_{12}$	61.35	61.74	4.94	5.12
3,3′-Methylenebis-(4-hydroxycoumarin) monoglucoside tetraacetate (IV)	Dry benzene	Sinters 185[a]	25	+14.0° (*C*, 2.5; C_6H_6)	$C_{33}H_{30}O_{15}$	59.45	59.53	4.50	4.67

[a] At 185° the monoglucoside is converted to 3,3′-methylene-4,4′-epoxydicoumarin which then melts at 290°. This behavior is characteristic of monosubstituted 3,3′-methylenebis-(4-hydroxycoumarin)s.[6]

yields 80–90%. The monosilver salt of 3,3′-methylenebis-(4-hydroxycoumarin) was prepared as directed by Huebner, *et al.*[6]

Condensation of the Silver Salts with Acetobromoglucose.—The condensations of all the silver salts were carried out similarly until the resulting sirupy glucoside acetates were crystallized. Five grams of the silver salt was shaken with 0.9 equivalent of acetobromoglucose and 1.0 g. of Drierite in 50 ml. of dry benzene contained in a black bottle. Upon completion of the reaction (two to four days), the silver salts were centrifuged off and washed with hot benzene. The benzene solution was concentrated *in vacuo* yielding a sirup. These sirups were crystallized from a suitable solvent as indicated in Table I. Deacetylation of I and II was accomplished by the method of Brauns[7] (Table I).

Preparation of 3,3′-Methylenebis-(4-hydroxycoumarin) Diglucoside Octaacetate (V).—A solution of 25 g. of acetobromoglucose in 150 ml. of dry benzene was shaken with 10 g. of 3,3′-methylenebis-(4-hydroxycoumarin), 8 g. of silver oxide, 10 g. of Drierite and 4 drops of quinoline for four days. The silver salts and unreacted 3,3′-methylenebis-(4-hydroxycoumarin) were centrifuged off and washed with cold benzene. The combined benzene fraction was concentrated to half its volume, and cooled. The small amount of 3,3′-methylenebis-(4-hydroxycoumarin) that crystallized was filtered off. The benzene solution was extracted with cold 1% sodium hydroxide, then with cold 1% hydrochloric acid solution, and finally with ice water. It was dried over sodium sulfate and concentrated to a sirup. The sirup was dissolved in a minimum of ethanol, filtered from some 3,3′-methylenebis-(4-hydroxycoumarin) which had crystallized out, and stored at 0°. After seven months, partial crystallization had taken place. These crystals were dissolved in the minimum of hot ethanol, the solution filtered while hot and, on cooling, 1 g. of hair-like crystals, m. p. 160–165°, was deposited. After eight crystallizations from ethanol the rotation and m. p. remained constant, m. p. 167–168°; $(\alpha)^{30}D$ + 58.0° (*C*, 2.5; benzene). *Anal.* Calcd. for $C_{47}H_{48}O_{24}$: C, 56.62; H, 4.84. Found: C, 56.97; H, 4.50.

Preparation of 3-[6-Oxo(1)benzopyrano(4,3-b)(1)benzopyran-7-yl]-4-hydroxycoumarin Glucoside Tetraacetate (VI).—A mixture of 4 g. of 3-[6-oxo(1)benzopyran(4,3-b)(1)benzopyran-7-yl]-4-hydroxycoumarin, 12 g. of acetobromoglucose, 5 g. of silver oxide, 5 g. of Drierite, and 5 drops of quinoline was shaken for twenty-four hours. The procedure for working up the reaction mixture was the same as that given for V. The sirup obtained after concentration was rubbed with a small amount of hot ethanol and crystallization occurred. This crop was recrystallized from pyridine diluted with water; yield 3.0 g., m. p. 234–235°: $(\alpha)^{25}D$ −9.0° (*C*, 8; pyridine), *Anal.* Calcd. for $C_{39}H_{32}O_{16}$: C, 63.24; H, 4.32. Found: C, 63.27; H, 4.38.

Alcoholysis of 3-Phenyl-4-hydroxycoumarin Glucoside Tetraacetate (III).—To 10 g. of III dissolved in 300 ml. of methanol was added 10 ml. of 0.2 *N* barium methoxide. Mutarotation stopped after two weeks. The small amount of 3-phenyl-4-hydroxycoumarin which had crystallized out during the reaction was filtered off. The barium was removed with 0.1 *N* sulfuric acid. An equal volume of water was added, the solution concentrated to 50 ml. and the aglucone that crystallized during the concentration was filtered off; 3.4 g. of 3-phenyl-4-hydroxycoumarin was obtained, (81%), m. p. 233–236°. The filtrate was concentrated to a sirup and dissolved in a minimum of hot ethanol. On cooling 1.2 g. of α-methylglucoside (VII) crystallized, m. p. 165–167°; $(\alpha)^{30}D$ +159° (*C*, 1.2; water).

Alcoholysis of 3,3′-Methylenebis-(4-hydroxycoumarin) Monoglucoside Tetraacetate (IV).—In 10 ml. of dry methanol to which had been added 0.2 ml. of 0.5 *N* sodium methoxide solution, 87.8 mg. of IV was refluxed for one half hour; needles of the anhydride VIII crystallized out in the first minute. VIII, which is practically insoluble in methanol, was filtered on a sintered glass funnel, the yield being 23.2 mg. (55%). The methanol filtrate was poured into two volumes of water and a flocculent precipitate of IX was thrown out of solution. After recrystallizing from methanol, the product melted at 171–172°, yield 24 mg. A reducing sugar determination[8] on an aliquot of the water-methanol solution showed that 20.2 mg. of glucose was produced in the reaction. After hydrolysis at 95° in 1 *N* sulfuric acid, 22.0 mg. of glucose (93%) was shown to be present. The reducing sugar in an aliquot of the solution was identified by the osazone method.[9] If one half of the indicated quantity of $NaOCH_3$ was used the yield of VIII was increased to 86%.

Alcoholysis of 3,3′-Methylenebis-(4-hydroxycoumarin) Diglucoside Octaacetate (V).—In 4 ml. of dry methanol to which had been added 0.1 ml. of 0.2 *N* barium methoxide. 67.8 mg. of V was refluxed for one half hour. The technique of separation was the same as above; 12.7 mg. (59%) of VIII was formed. Before the acid hydrolysis, 13.0 mg. of reducing sugar (as glucose) was present (theoretical for one mole of glucose from V is 12.2 mg.). After acid hydrolysis 24.0 mg. of glucose was present (theoretical for two moles of glucose is 24.4 mg.).

Summary

1. A series of glucosides of the 4-hydroxy-

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[7] Brauns, THIS JOURNAL, **48**, 2776 (1926).

[8] Shaffer and Somogyi, *J. Biol. Chem.*, **100**, 695 (1933).

[9] Hassid and McCready, *Ind. Eng. Chem., Anal. Ed.*, **14**, 683 (1942).

coumarins has been prepared. The glucoside acetates of 4-hydroxycoumarin, 4-hydroxy-6-methylcoumarin, 3-phenyl-4-hydroxycoumarin and the monoglucoside acetate of 3,3′-methylenebis-(4-hydroxycoumarin) were prepared by treating the enol silver salts with acetobromoglucose.

2. The diglucoside octaacetate of 3,3′-methylenebis-(4-hydroxycoumarin) and of 3-[6-oxo(1)-benzopyrano(4,3-b)(1)benzopyran-7-yl]-4-hydroxycoumarin glucoside tetraacetate were prepared by coupling the aglucone with acetobromoglucose in the presence of catalytic amounts of quinoline and an excess of silver oxide.

3. The two 4-hydroxycoumarin glucoside tetraacetates unsubstituted on position 3 were successfully deacetylated by the catalytic barium methoxide procedure.

4. The 3-substituted-4-hydroxycoumarin glucoside acetates underwent alcoholysis with the removal of the glucose residue involving a Walden inversion. A course of reaction in which both glucoside residues were removed from 3,3′-methylenebis-(4-hydroxycoumarin) diglucoside octaacetate with the formation of 3,3′-methylene-4,4′-epoxydicoumarin, and 3,3′-methylenebis-(4-hydroxycoumarin) monomethyl ether is proposed

MADISON, WISCONSIN RECEIVED DECEMBER 14, 1943

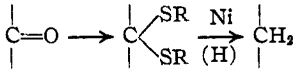
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Carbonyl Reduction by Thioacetal Hydrogenolysis

BY M. L. WOLFROM AND J. V. KARABINOS

In connection with another problem being pursued in this Laboratory, we were interested in convenient methods of synthesis for 1- and 2-desoxy sugar alcohols. The present methods are laborious and are not always of general applicability. The reduction of the 2-desoxyaldoses, synthesized through the glycals, constitutes the only present synthesis for the 2-desoxy sugar alcohols.[1] More numerous are the procedures for the preparation of the 1-desoxy sugar alcohols. These may be prepared through the reduction of a terminal halide in a sugar alcohol and special methods exist for obtaining these halides by utilizing the preferential reactivity of the primary alcohol function.[2] The 1-desoxy sugar alcohols are also preparable by reduction of the ω-desoxy-aldoses, either naturally occurring or synthesized[3] from the aldoses by reduction therein of a terminal halide group. In the acyclic sugar derivatives, a diisopropylidene-*aldehydo*-pentose has reacted with methyl Grignard reagent to produce, after hydrolysis of the isopropylidene groups, a 1-desoxy-hexitol.[4] Reduction of the first carbon of the diazomethyl ketones[5] of the acyclic sugar acetates or the reaction of diazomethane with *aldehydo*-sugar esters,[6] led to the synthesis of 1-desoxy-*keto*-sugar acetates which on reduction with subsequent deacetylation, led to the synthesis of a mixture of two 1-desoxy sugar alcohols.[7]

The remarkable discovery of the simultaneous desulfurizing and reducing action of Raney nickel[8] by Bougault, Cattelain and Chabrier[9] and its subsequent extension by Mozingo and co-workers,[10] offered the promise of establishing a simple and direct route to the 1- and 2-desoxy sugar alcohols. The French workers had demonstrated this reaction with the thiocarbonyl compounds, thiols, disulfides and heterocyclic sulfur (thiophene); the latter group had extended the reaction to sulfides, sulfoxides and sulfones; and Richtmyer, Carr and Hudson[11] had ememployed reductive hydrolysis with Raney nickel in their synthesis of polygalitol (1,5-anhydro-(*levo*)-sorbitol) tetraacetate from the acetates of glucothiopyranose and its disulfide. We have now found that this reaction is applicable to thioacetals, leading to easy reduction to the hydrocarbon stage.



$$\overset{|}{\underset{|}{C}}{=}O \longrightarrow \overset{|}{\underset{|}{C}}\!\left\langle\begin{matrix}SR\\SR\end{matrix}\right. \xrightarrow[(H)]{Ni} \overset{|}{\underset{|}{C}}H_2$$

The other products of the reaction are presumably sulfide sulfur (verified in the present work) and the hydrocarbon RH. Following the directions of Mozingo and co-workers, we employed dilute ethanol as the solvent. Under these conditions we have noted that acetaldehyde is formed. This is to be expected from the dehydrogenating action of Raney nickel in the liquid phase,[12] but it may play some part in the reaction by furnishing a source of active hydrogen.

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[1] M. Bergmann, H. Schotte and W. Leschinsky, *Ber.*, **56**, 1052 (1923); E. Fischer, *ibid.*, **47**, 196 (1914).

[2] *Cf.* R. M. Hann, A. T. Ness and C. S. Hudson, THIS JOURNAL, **66**, 73 (1944).

[3] *Cf.* E. Fischer and K. Zach, *Ber.*, **45**, 3761 (1912).

[4] K. Gätzi and T. Reichstein, *Helv. Chim. Acta*, **21**, 914 (1938).

[5] M. L. Wolfrom and R. L. Brown, THIS JOURNAL, **65**, 1516 (1943).

[6] P. Brigl, H. Mühlschlegel and R. Schinle, *Ber.*, **64**, 2921 (1931); M. L. Wolfrom, D. I. Weisblat, W. H. Zophy and S. W. Waisbrot, THIS JOURNAL, **63**, 201 (1941).

[7] Unpublished work of Dr. B. W. Lew of this Laboratory.

[8] M. Raney, U. S. Patent 1,628,190 (1927).

[9] J. Bougault, E. Cattelain and P. Chabrier, *Bull. soc. chim.*, [5] **5**, 1699 (1938); *ibid.*, [5] **7**, 780, 781 (1940).

[10] R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, THIS JOURNAL, **65**, 1013 (1943); V. du Vigneaud, D. B. Melville, K. Folkers, D. E. Wolf, R. Mozingo, J. C. Keresztesy and S. A. Harris, *J. Biol. Chem.*, **146**, 475 (1942).

[11] N. K. Richtmyer, C. J. Carr and C. S. Hudson, THIS JOURNAL, **65**, 1477 (1943).

[12] W. Reeves and H. Adkins, *ibid.*, **62**, 2874 (1940).