

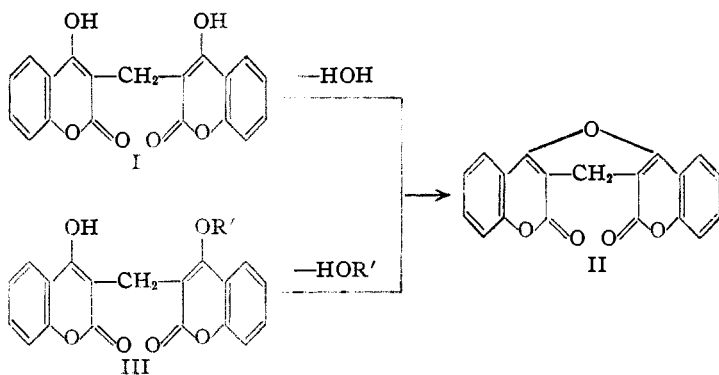
[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF WISCONSIN]

Studies on 4-Hydroxycoumarin. III. Dehydration of the Aldehyde Condensation Products¹

BY CHARLES F. HUEBNER, WILLIAM R. SULLIVAN, MARK A. STAHMANN AND KARL PAUL LINK

In the study of the condensation of 4-hydroxycoumarin with aldehydes, it was found that generally two molecules of 4-hydroxycoumarin react with one of the aldehyde to form compounds of the type $C_9H_6O_3-\overset{H}{\underset{R}{C}}-C_9H_6O_3$.² In an attempt to form diacetates of the enol forms of these substances by the pyridine-acetic anhydride technique, the method by which the diacetate of the anticoagulant 3,3'-methylenebis-(4-hydroxycoumarin) (I) from spoiled sweet clover hay was prepared,³ high melting compounds were obtained which by analysis proved to be dehydration products of the parent substances (II). These products are substituted 1,4-pyrans.

It is well known that 1,5-dienols may be dehydrated to form pyrans. Methylenebis-(β -naphthol) is dehydrated to dibenzoxanthene by phosphorus oxychloride.⁴ Dehydration of the aldehyde condensation products of dihydroresorcinol is brought about by such reagents as acetic anhydride or sulfuric acid to form substituted 1,8-diketoöctahydroxanthenes.^{5,6,7} 1,4-Pyran derivatives are obtained from methylenebis-(α -tetronic acid)⁸ and benzylidenebis-(acetoacetic ester)⁹ by dehydration.



Besides forming these compounds by the intra-

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

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

(4) Wolf, *Ber.*, **26**, 84 (1893).

(5) Vorländer and Kalkow, *Ann.*, **309**, 365 (1899).

(6) Klein and Leuser, *Mikrochem., Pregel. Festr.*, 204 (1929).

(7) Sonn and Schrieber, *J. prakt. Chem.*, **156**, 65 (1940).

(8) Feofilkatov, *C. A.*, **24**, 832 (1930).

(9) Hantzsch, *Ber.*, **18**, 2584 (1885).

molecular removal of water with dehydrating agents, they have been realized by the intramolecular removal of the molecule HOR' either with basic reagents or by heating. R' may be $-CH_3$, $-COC_6H_5$, or $-PO(OCH_3)_2$ (III) and indeed dehydration may in some cases proceed via the second route.

Thus in the dehydration by pyridine and acetic anhydride, a monoacetate is probably the intermediate and in the basic medium acetic acid is intramolecularly removed. Credence for this belief is furnished by the fact that the diacetates of certain of the aldehyde condensation products are stable in pyridine and acetic anhydride under conditions which would form the dehydration product from the parent substances.

Differences in the conditions required to effect this type of ring closure in the aldehyde condensation products of 4-hydroxycoumarin exist. The larger the R group becomes, the greater becomes the tendency of the compound to lose water. Thus in 3,3'-methylenebis-(4-hydroxycoumarin) (I), the simplest member of the series (R is H), ring closure could not be realized with acetic anhydride-pyridine, a method by which all the higher members of the series were dehydrated. More drastic methods, such as melting with fused potassium acid sulfate or heating in a sealed tube with red phosphorus and iodine, had to be used, the yield in both cases being low. However, it was found that diphenylphosphoric acid chloride effects the removal of water from I readily. These latter methods can of course also be used to dehydrate higher members of the series.

Among the compounds yielding the dehydration product by the loss of HOR', a quantitative yield was obtained from 3,3'-methylenebis-(4-hydroxycoumarin) mono-(dimethylphosphate) (IV) by refluxing its sodium salt in methanol for several minutes. The same conversion in poorer yields was brought about by decomposition of the salt in water at 25° or by heating the phosphate ester just above its melting point. The phosphoric acid ester itself was prepared by decomposing in methanol the crude mixture of compounds realized from the action of phosphorus pentachloride on I. Its structure was established by preparing the identical 3,3'-methylenebis-(4-hydroxycoumarin) mono-(dimethylphosphate) monomethyl ether from IV with diazomethane and from 3,3'-methylenebis-(4-hydroxycoumarin) monomethyl

ether (V) by the action of phosphorus oxychloride and methanol. Acid hydrolysis of IV with three per cent. hydrochloric acid in methanol yields I.

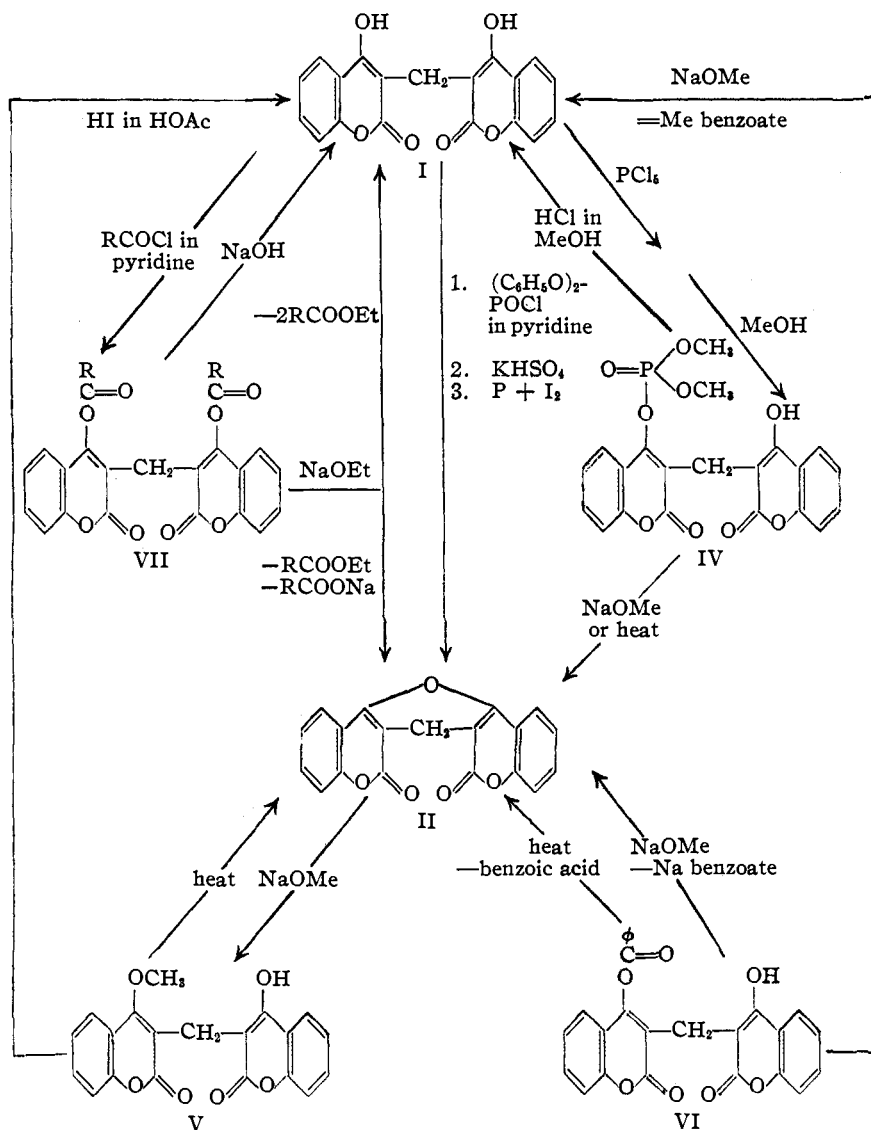
The reaction of 3,3'-methylenebis-(4-hydroxycoumarin) monobenzoate (VI) in hot methanol with one equivalent of sodium methoxide apparently goes in two directions simultaneously: first, the formation of the dehydration product with the loss of sodium benzoate and, second, alcoholysis to the monosodium salt of I and methyl benzoate. If the reaction, however, be carried out at room temperature, none of the dehydration product can be isolated and some V is formed.

At the beginning of the reaction a small amount of the anhydro compound does crystallize from the methanol solution but because of the much longer time needed for the decomposition of the sodium salt of the monobenzoate at room temperature than at 65°, a competing reaction, the formation of V from the anhydro compound, occurs in the basic solution. As a result the small amounts of the anhydro compound forming are isolated after twenty-four hours as the monomethyl ether. This route of formation of V is probable, since when the anhydro compound is allowed to react with one equivalent of sodium methoxide in methanol at 25°, after twelve hours complete conversion to V has taken place. Formation of the dehydration product also resulted by heating the monobenzoate above its melting point, with the benzoic acid subliming out of the melt. The monobenzoate was realized by the action of benzoyl chloride on an excess of the mono silver salt of I.

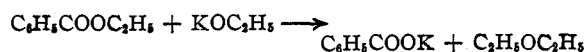
It was noted that treatment of certain diesters of the alkylidenebis-(4-hydroxycoumarin)s (VII) with one equivalent of sodium ethoxide gave both the dehydration product of the parent substance and the unesterified bis-4-hydroxycoumarin. In

view of the behavior of VI in alkaline solution, this transformation probably proceeds in like manner over the monoester.

Because of the stability of the monoesters in neutral solvents in contrast to the behavior of the weakly alkaline solutions of their salts, a saponification type reaction might be expected to account for this formation of anhydro compounds. This type of reaction is analogous to the saponification of an ester by the action of potassium



ethoxide in absolute alcohol resulting in the formation of an ether.¹⁰



In the monosodium salts of the 3,3'-methylenebis-(4-hydroxycoumarin) monoesters both the ester grouping and alkoxide grouping are in the same molecule so an intramolecular reaction would

(10) Magnani and McElvain, *THIS JOURNAL*, 60, 813 (1938).

TABLE I
DEHYDRATION PRODUCTS FROM 3,3'-ALKYLIDENE-4,4'-EPOXYDICOUMARIN(S) AND 3,3'-ARYLIDENE-4,4'-EPOXYDICOUMARIN(S)

Compound	M. p., °C., uncor.	Recrystallized from	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
3,3'-Methylene-4,4'-epoxydicoumarin	321-323 d.	Cyclohexanone	C ₁₉ H ₁₀ O ₅	71.70	71.67	3.14	3.38
3,3'-Ethylidene-4,4'-epoxydicoumarin	322-323 d.	Benzene	C ₂₀ H ₁₂ O ₅	72.29	72.24	3.61	3.50
3,3'- <i>n</i> -Propylidene-4,4'-epoxydicoumarin	292-294 d.	Dioxane	C ₂₁ H ₁₄ O ₅	72.83	72.99	4.05	4.06
3,3'- <i>n</i> -Butylidene-4,4'-epoxydicoumarin	246 d.	Acetic acid	C ₂₂ H ₁₆ O ₅	73.33	72.99	4.44	4.51
3,3'-Isobutylidene-4,4'-epoxydicoumarin	303	Acetic acid	C ₂₂ H ₁₆ O ₅	73.33	73.39	4.44	4.42
3,3'- <i>n</i> -Pentylidene-4,4'-epoxydicoumarin	231	Ethanol-Acetone (3:1)	C ₂₃ H ₁₈ O ₅	73.80	73.91	4.81	5.00
3,3'-Isopentylidene-4,4'-epoxydicoumarin	290	Dioxane	C ₂₃ H ₁₈ O ₅	73.80	73.89	4.81	4.92
3,3'- <i>n</i> -Hexylidene-4,4'-epoxydicoumarin	182	Acetic acid	C ₂₄ H ₂₀ O ₅	74.22	73.85	5.15	5.13
3,3'-Benzylidene-4,4'-epoxydicoumarin	393-395	Cyclohexanone	C ₂₅ H ₁₄ O ₅	76.14	76.10	3.55	3.65
3,3'-Phenylethylidene-4,4'-epoxydicoumarin	385 d.	Cyclohexanone	C ₂₅ H ₁₆ O ₅	76.47	76.47	3.92	3.85
3,3'-Phenylpropylidene-4,4'-epoxydicoumarin	243-245	Acetic acid	C ₂₇ H ₁₈ O ₅	76.78	76.77	4.26	4.41
3,3'-(<i>p</i> -Methoxybenzylidene)-4,4'-epoxydicoumarin ^a	345 d.	Cyclohexanone	C ₂₆ H ₁₆ O ₆	73.58	73.50	3.77	4.00
3,3'-(<i>m</i> -Methoxy- <i>p</i> -acetoxymethylidene)-4,4'-epoxydicoumarin ^b	288-289	Dioxane	C ₂₈ H ₁₈ O ₈	69.71	69.88	3.73	3.94
3,3'-(<i>m,p</i> -Methylenedioxybenzylidene)-4,4'-epoxydicoumarin	355-356	Cyclohexanone	C ₂₆ H ₁₄ O ₇	71.23	71.06	3.20	3.38

^a Anal. Calcd. for C₂₆H₁₈O₆(OCH₃): OCH₃, 7.32. Found: OCH₃, 7.20. ^b Prepared from the vanillin condensation product of 4-hydroxycoumarin. The hydroxyl group of the vanillin residue was acetylated with acetic anhydride. Anal. Calcd. for C₂₈H₁₈O₈(OCH₃)(COCH₃): OCH₃, 6.43; COCH₃, 8.92. Found: OCH₃, 6.50; COCH₃, 8.91.

yield a cyclic ether of the type 3,3'-methylene-4,4'-epoxydicoumarin (II).

These dehydration products may be conveniently considered as 3,3'-alkylidene-4,4'-epoxydicoumarins and 3,3'-arylidene-4,4'-epoxydicoumarins (Table I). Chemically these products are relatively inert. The anhydride ring is stable toward aqueous alkali, acid and boiling aniline. On fusion with potassium hydroxide, small yields of salicylic acid are obtained. However, opening of the pyran ring can be achieved by treating the anhydro product with sodium methoxide to form monomethyl ethers of the parent substances (V). The parent substances themselves may then be prepared by demethylation with hydriodic acid in acetic acid. On heating the monomethyl ether above its melting point, the original anhydride is regenerated. These anhydro compounds gave negative ferric chloride tests and dissolved in cold concentrated sulfuric acid to produce light yellow to orange colored solutions. None of the dehydration products showed the anticoagulant action of the parent substances.

Experimental

Preparation of 3,3'-Alkylidene-4,4'-epoxydicoumarins and 3,3'-Arylidene-4,4'-epoxydicoumarins.—The *bis*-4-hydroxycoumarins were prepared by condensing the aldehydes with 4-hydroxycoumarin as described by Sullivan, *et al.*² 4-Hydroxycoumarin was prepared by the method of Stahmann, *et al.*¹¹ With the exception of 3,3'-methylenebis-(4-hydroxycoumarin) (I) all the *bis*-4-hydroxycoumarins were dehydrated by treatment with acetic anhydride in pyridine.

a. Dehydration by Acetic Anhydride-Pyridine.—The parent substance (1 to 1.5 g.) was dissolved or suspended in pyridine (5 ml.) and an equal volume of acetic anhydride added. The mixture was allowed to stand about twelve

hours, during which time the dehydration product usually crystallized out. In some cases the addition of a small amount of water to the reaction mixture was necessary to initiate the crystallization. The products were recrystallized using the solvents listed in Table I. The yield was above 90% in most cases.

b. Dehydration by Hydriodic Acid.—Five grams of 3,3'-benzylidenebis-(4-hydroxycoumarin) was refluxed in 200 ml. of acetic acid and 50 ml. of 58% hydriodic acid solution for thirty minutes. The mixture was cooled and filtered. The unchanged starting substance was extracted with 5% sodium hydroxide leaving 3.1 g. of the crude dehydration product, m. p. 350°. After recrystallization from cyclohexanone, pure 3,3'-benzylidene-4,4'-epoxydicoumarin, m. p. 393-395°, was obtained.

Preparation of 3,3'-Methylene-4,4'-epoxydicoumarin (II).—This compound was prepared from I by the following procedures:

a. Dehydration by Potassium Acid Sulfate.—A mixture of 30 g. of freshly fused potassium acid sulfate and 10 g. of I was heated to 270° and maintained at that temperature with stirring for thirty minutes. The melt was cooled and triturated with hot water. The remaining brown solid was ground and extracted five times with 5% sodium hydroxide in a centrifuge tube. The alkali insoluble material (5.5 g.) was collected. This was suspended in 200 ml. of boiling cyclohexanone and filtered while hot. On cooling, 2.7 g. of II, m. p. 320-323°, separated.

b. Dehydration by Red Phosphorus and Iodine.—A mixture of 1 g. of I, 1 g. of iodine, 3 g. of red phosphorus, 2 ml. of water and 70 ml. of glacial acetic acid was heated in a sealed tube at 155-165° for seven hours. The contents were then filtered through an asbestos pad, poured into water, and the solid material which separated was collected. From three trials 2.5 g. of solids was obtained. This was shaken with 150 ml. of 0.1 *N* sodium hydroxide for three hours, filtered and washed; yield 0.5 g. of II. After recrystallization from cyclohexanone the melting point was 320-323°.

c. Dehydration by Diphenylphosphoric Acid Chloride.—Compound I (10 g.) was dissolved in 200 ml. of dry pyridine and 6.5 ml. of diphenylphosphoric acid chloride was added. The mixture was allowed to stand three days then poured into ice water, filtered and washed. After

(11) Stahmann, *et al.*, THIS JOURNAL, 65, 2285 (1943).

recrystallization from cyclohexanone the yield was 6.2 g., m. p. 320–323°.

d. Loss of the Phosphate Residue from 3,3'-Methylenebis-(4-hydroxycoumarin) Mono-(dimethylphosphate) (IV).—IV was converted to II by dissolving 1.99 g. in 500 ml. of hot methanol and slowly adding 13.4 ml. of 0.33 *N* sodium methoxide. It was necessary that this addition be made very slowly and that an excess be avoided, to prevent cleavage of the pyran ring. After cooling, 1.39 g. (97%) of II, m. p. 320–323°, was collected. The phosphate residue in the mother liquor was not characterized. It gave no precipitate with molybdate reagent.

The anhydro compound was formed when 0.7 ml. of 0.68 *N* potassium hydroxide in 20 ml. of water was allowed to act on the monophosphate ester (200 mg.) at 25° for ten hours. After the ester was dissolved as the sodium salt the solution became turbid immediately, and then the long characteristic needles of II formed. The yield was 135 mg. (94%).

The anhydro compound was also formed when 100 mg. of the monophosphate ester was heated at 200° for fifteen minutes. After suspension in ethanol and filtration, the precipitate was resuspended in 0.1 *N* sodium hydroxide and the insoluble material collected. This was dissolved in hot cyclohexanone. On cooling, 45 mg. of II, m. p. 320–323°, separated.

e. Removal of the Benzoate Residue from 3,3'-Methylenebis-(4-hydroxycoumarin) Monobenzoate (VI).—The monobenzoate was converted to II in the following manner. The monobenzoate (2.021 g.) was suspended in 200 ml. of absolute methanol and one equivalent of 0.504 *N* sodium methoxide was added drop by drop, precautions being taken to keep conditions anhydrous. Because of the formation of some I, the solution was not alkaline to phenolphthalein, so one third more of an equivalent of base was added. The reaction mixture was then allowed to cool. The anhydride II (0.504 g.) separated out. The filtrate was acidified with hydrochloric acid and 1.0 g. of I crystallized out. This was filtered and the methanol carefully removed by distillation leaving a solid residue which was extracted with ether. From the ether extract, the crude acidic fraction (165 mg.) yielded 85 mg. of benzoic acid, m. p. 119°, on sublimation. The neutral fraction consisted of 20 mg. of methyl benzoate which gave benzoic acid on hydrolysis. The amide of benzoic acid was prepared, m. p. 128°. Some unchanged VI (40 mg.) was recovered from the residue left after ether extraction.

On heating VI above its melting point, benzoic acid sublimed out and 3,3'-methylene-4,4'-epoxydicoumarin was isolated from the molten residue.

f. Removal of the Methyl Residue from 3,3'-Methylenebis-(4-hydroxycoumarin) Monomethyl Ether (V).—To convert the monomethyl ether to the dehydration product, 36 mg. of V was heated at 180° for thirty minutes. Part of the melt had then solidified. The mixture was then suspended in ethanol and filtered. II (8 mg.) m. p. 320–323°, was collected. Unchanged monomethyl ether was recovered from the filtrate.

Preparation of 3,3'-Methylenebis-(4-hydroxycoumarin) Mono-(dimethylphosphate) (IV).—I (20 g.) and phosphorus pentachloride (30 g.) were mixed under dry benzene and the mixture refluxed with 500 ml. of dry benzene for eight hours. The solution was cooled and filtered. The solid product was suspended in 2 l. of hot methanol and filtered. On cooling, 18 g. of IV separated, m. p. 186–187°.

Anal. Calcd. for $C_{19}H_{11}O_5P(OCH_3)_2$: C, 56.75; H, 3.83; P, 6.98; OCH_3 , 13.97; neutralization equivalent, 444. Found: C, 56.74; H, 3.88; P, 6.90; OCH_3 , 13.84; neutralization equivalent, 448.

IV (185 mg.) was hydrolyzed to I by refluxing for one hour in 20 ml. of methyl alcohol containing 3% hydrogen chloride. The mixture was cooled, and 106 mg. of I was obtained.

Preparation of 3,3'-Methylenebis-(4-hydroxycoumarin) Mono-(dimethylphosphate) Monomethyl Ether.—An excess of an ethereal solution of diazomethane was distilled

into a suspension of 100 mg. of IV in 25 ml. of dry ethyl ether. The mixture was allowed to stand twelve hours, and the excess diazomethane and ether removed by distillation. The residue was recrystallized from methanol. The yield was 70 mg., m. p. 140–141°.

Anal. Calcd. for $C_{19}H_{11}O_5P(OCH_3)_2$: OCH_3 , 20.31. Found: OCH_3 , 20.38.

3,3'-Methylenebis-(4-hydroxycoumarin) monomethyl ether (V) was converted to 3,3'-methylenebis-(4-hydroxycoumarin) mono-(dimethylphosphate) monomethyl ether by dissolving 600 mg. of V in 30 ml. of dry pyridine, cooling to 0°, and adding 0.3 ml. of phosphorus oxychloride. After standing for one hour at 0°, 10 ml. of methyl alcohol was added, the mixture poured into ice water and filtered. The solids were extracted with 0.5% sodium hydroxide solution and dissolved in hot methanol. On cooling 169 mg. of 3,3'-methylenebis-(4-hydroxycoumarin) mono-(dimethylphosphate) monomethyl ether separated, m. p. 140–141°.

Preparation of 3,3'-Methylenebis-(4-hydroxycoumarin) Monobenzoate (VI).—The monosodium salt of I was prepared by refluxing 5 g. of the parent substance in one equivalent of 0.05 *N* aqueous sodium hydroxide for fifteen minutes and filtering hot to separate it from any undissolved substance. On cooling the fine hair-like crystals of the monosodium salt were deposited. It was recrystallized from ethanol. The yield was 3.6 g. The parent substance not isolated as the sodium salt could be recovered.

Anal. Calcd. for $C_{19}H_{11}O_5(Na)$: Na, 6.42. Found: Na, 6.32.

The monosilver salt was prepared by adding one equivalent of silver nitrate dissolved in a small amount of water to a hot ethanolic solution of the sodium salt. An immediate precipitate of the silver salt appeared. The salt was filtered and washed copiously with water, then alcohol and ether and finally dried *in vacuo* over phosphoric anhydride. The salt was ground to a fine powder and again dried over phosphoric anhydride at 50° under 0.05 mm. pressure. Two grams was obtained from 2 g. of the sodium salt.

Seven grams of the monosilver salt was shaken with 300 ml. of dry benzene and drierite (2 g.) for one hour. Then 1.8 ml. of benzoyl chloride, carefully freed from hydrogen chloride, in 50 ml. of benzene was added and the mixture shaken for six hours. The solid residue was centrifuged off and the benzene removed *in vacuo*. The residue was recrystallized from acetic acid. After two recrystallizations the product melted at 225–229°, the yield being 2.5 g. Moisture had to be excluded rigorously during the reaction or I resulted.

Anal. Calcd. for $C_{19}H_{11}O_5(OCOC_6H_5)$: C, 70.90; H, 3.64. Found: C, 70.95; H, 3.92.

Preparation of 3,3'-Methylenebis-(4-hydroxycoumarin) Monomethyl Ether (V).—II (400 mg.) was refluxed with 20 ml. of 0.5 *N* sodium methylate in methanol for thirty minutes. The solution was then poured into water and acidified. The crude product was collected by filtration and recrystallized from a methanol-water mixture. The yield was 300 mg., m. p. 171–172°. The same compound was produced by refluxing the parent substance with 1 *N* potassium hydroxide in methanol.

Anal. Calcd. for $C_{19}H_{11}O_5(OCH_3)$: C, 68.57; H, 4.00; OCH_3 , 8.88. Found: C, 68.52; H, 4.22; OCH_3 , 8.86.

The monomethyl ether was converted to the dimethyl ether by treatment with diazomethane. One hundred mg. yielded 65 mg. of the dimethyl ether, m. p. 153–155°, after crystallization from methanol. On demethylation with hydriodic acid in acetic acid, 100 mg. of the monomethyl ether gave 80 mg. of I, m. p. 287–289°.

Preparation of 3,3'-Methylenebis-(4-hydroxycoumarin) Monomethyl Ether Monoacetate.—3,3'-Methylenebis-(4-hydroxycoumarin) monomethyl ether was acetylated in pyridine and acetic anhydride, 0.9 g. yielding 0.8 g. of the acetate. After recrystallization from benzene the m. p. was 198–200°.

Anal. Calcd. for $C_{21}H_{18}O_6(OCH_3)$: OCH_3 , 7.91. Found: OCH_3 , 7.58.

Preparation of 3,3'-Methylenebis-(4-hydroxycoumarin) Monoethyl Ether.—The monoethyl ether was prepared by a method similar to the one described for the monomethyl ether. From the action of a hot sodium ethoxide solution on 1.3 g. of the dehydration product, 0.9 g. of the monoethyl ether, m. p. 163–166°, was obtained after two recrystallizations from ethanol.

Anal. Calcd. for $C_{21}H_{18}O_6$: C, 69.25; H, 4.40. Found: C, 69.10; H, 4.68.

Preparation of 3,3'-Ethyldenebis-(4-hydroxycoumarin) Monomethyl Ether.—Three grams of the ethylidene dehydration product was refluxed in 40 ml. of 1 *N* potassium hydroxide in methanol. The methanol insoluble salt separated out after five minutes. It was filtered off, dissolved in water, acidified and finally recrystallized twice from methanol. One gram of needles resulted, m. p. 154–155°.

Anal. Calcd. for $C_{20}H_{18}O_6(OCH_3)$: OCH_3 , 8.52. Found: OCH_3 , 8.46.

Acknowledgment.—We are indebted to our colleague, Mr. Lloyd Graf, for many of the C and H analyses reported in this paper, and to Dr. Ivan Wolff for carrying out the experiment on the dehydration with hydriodic acid and phosphorus.

Summary

1. The aldehyde condensation products of 4-hydroxycoumarin have been dehydrated to form substituted 1,4-pyran derivatives, the 3,3'-alkylidene-4,4'-epoxydicoumarins and 3,3'-arylidene-4,4'-epoxydicoumarins. This transformation was accomplished by acetic anhydride in pyridine, with all except the simplest member of the series, 3,3'-methylenebis-(4-hydroxycoumarin).

2. 3,3'-Methylenebis-(4-hydroxycoumarin) was dehydrated to the 1,4-pyran derivative by fusing with potassium acid sulfate, by heating with red phosphorus and iodine, or by treatment with diphenylphosphoric acid chloride.

3. Various monosubstituted 3,3'-methylenebis-(4-hydroxycoumarin)s yielded the dehydration product. Heating the monomethyl ether, monobenzoate, or mono-(dimethylphosphate), and treating the last two products with sodium methoxide, all yielded the dehydration product.

4. Monomethyl ethers resulted when the 1,4-pyran ring was opened by treating the dehydration products with sodium methoxide.

MADISON, WISCONSIN

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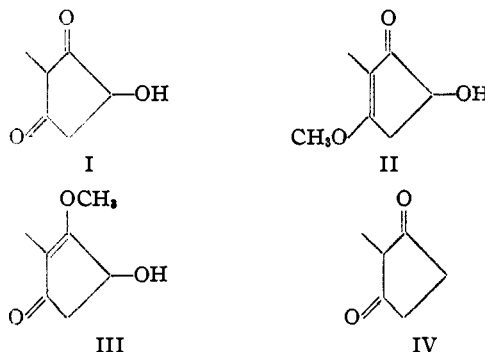
The Hydrogenation of 3-Methylcyclopentane-1,2,4-trione¹

BY MILTON ORCHIN^{1a} AND LEWIS W. BUTZ

A number of simple derivatives of methylcyclopentane, needed as intermediates in projected syntheses, are either unknown or have not been prepared by practical methods. 3-Methylcyclopentane-1,2,4-trione is readily available from 2-butanone and diethyl oxalate.² This report is concerned with the hydrogenation of the triketone in the presence of Adams catalyst at room pressure and temperature.

3-Methylcyclopentane-1,2,4-trione can be obtained anhydrous or as the monohydrate. Hydrogenation of the anhydrous triketone in ethyl acetate gave 62% of a dihydro derivative, m. p. 168°, which can be represented by formula I, although, like other 1,3-diketones with mobile hydrogen, its solutions contain enolic forms. Thus in ether it reacted with diazomethane, and two crystalline methyl derivatives, II and III, were isolated. The triketone hydrate in ethanol gave a mixture of products from which I was obtained in 39% yield and 2-methylcyclopentane-1,3-dione (IV) in 15% yield. IV has previously been obtained by the degradation of the sapo-

genin, sarcostin.³ No other products of hydrogenation were isolated.



The course of the hydrogenation is influenced by water. If traces of water are present, a small amount of 2-methylcyclopentane-1,3-dione is obtained in ethyl acetate, in addition to the hydroxy ketone. As will be shown later, the amount of hydrogen absorbed and the speed of hydrogenation were both greater in aqueous solution than in ethanol, acetic acid, or ethyl acetate. The hydroxydiketone, I, in ethanol, absorbed two moles of hydrogen very slowly. No 2-methylcyclopentane-1,3-dione could be found in the products.

(1) This work was supported by an allotment from the Special Research Fund (Bankhead-Jones Act of June 29, 1935). Not subject to copyright.

(1a) Present address: United States Bureau of Mines, Pittsburgh, Pa.

(2) Diels, Stielisch and Müller, *Ber.*, **39**, 1336 (1906).

(3) Cornforth and Earl, *J. Chem. Soc.*, 1443 (1940).