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

Studies on 4-Hydroxycoumarins. XI. Cyclic Ketals of 3-(α-Acetonylbenzyl)-4-hydroxycoumarin[1]

BY MARTIN SEIDMAN AND KARL PAUL LINK

3-(α-Acetonylbenzyl)-4-hydroxycoumarin was condensed with benzyl alcohol, allyl alcohol, tetrahydrofurfuryl alcohol, ethylene glycol monoethyl ether, ethylene chlorohydrin, ethylene bromohydrin and trimethylene chlorohydrin in the presence of hydrogen chloride to form the corresponding cyclic ketals. Reaction with phenol and zinc chloride resulted in the formation of the dehydrated derivative, 2-methyl-4-phenyl-5-oxo-γ-pyrano(3,2-c)(1)benzopyran. This product was also obtained by treatment of the methyl ketal with acetic anhydride containing perchloric acid.

The new anticoagulant rodenticide 3-(α-acetonylbenzyl)-4-hydroxycoumarin (Warfarin)[2] (I) has been shown by Ikawa, *et al.*,[3] to form cyclic methyl and ethyl ketals upon being refluxed with the corresponding alcohol containing 4% hydrogen chloride. This type of reaction is rather general for δ-hydroxy ketones. The best known examples are the sugars but various other cases may be found.[4-6] As part of a study of the chemical properties of I[7] this reaction has been reinvestigated and attempted with alcohols other than the simple aliphatics. Derivatives have been prepared by reaction of I with the alcohols II–VIII.

The reaction was conducted by suspending I in approximately ten times its weight of the alcohol and passing hydrogen chloride in from a cylinder. Solution invariably resulted after about five minutes. The products were obtained by pouring the solution into an excess of ice-water after the reaction time specified in Table I and crystallizing the gum or oil which resulted. By this method the clinically useful 4-hydroxycoumarin anticoagulant number 63, 2-methyl-2-methoxy-4-phenyl-5-oxodihydropyrano(3,2-c)(1)benzopyran[8] (XVI) has been obtained in 95% yield. The previously reported yield was 83%.

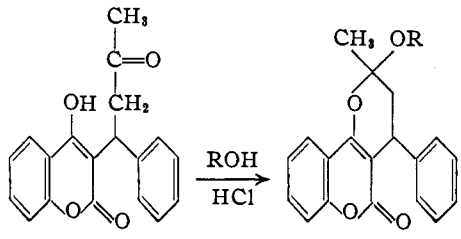
TABLE I

CYCLIC KETALS OF 3-(α-ACETONYLBENZYL)-4-HYDROXYCOUMARIN

No.	Derivatives of 2-methyl-4-phenyl-5-oxodihydropyrano (3,2-c)(1)benzopyran	Reaction time, hours	Yield, %	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
IX	2-Benzyloxy-[a]	18	12	162–163	$C_{26}H_{22}O_4$	78.39	78.34	5.76	5.82
X	2-Allyloxy-	3	12	122–123	$C_{22}H_{20}O_4$	75.86	75.67	5.75	6.02
XI	2-Tetrahydrofurfuryloxy-[b]	1/20	22	139–140	$C_{24}H_{24}O_5$	73.47	73.74	6.12	6.23
XIIA	2-(β-Ethoxyethoxy)-[c]	3	6	102–103	$C_{23}H_{24}O_5$	72.63	72.84	6.32	6.54
XIIB	2-(β-Ethoxyethoxy)-[c,d]	3	5	137–138	$C_{23}H_{24}O_5$	72.63	72.49	6.32	6.47
XIIIA	2-(β-Chloroethoxy)-	3	14	191–193	$C_{21}H_{19}O_4Cl$	68.02	68.15	5.13	5.28
XIIIB	2-(β-Chloroethoxy)-[d]	3	30	133–134	$C_{21}H_{19}O_4Cl$	68.02	68.18	5.13	5.31
XIV	2-(γ-Chloropropoxy)-	3	2	127–128	$C_{22}H_{21}O_4Cl$	68.66	68.46	5.46	5.62
XV	2-(β-Bromoethoxy)-	2	23	182–183	$C_{21}H_{19}O_4Br$	60.72	60.74	4.55	4.72

[a] Recrystallized from absolute ethanol. [b] Recrystallized from acetone. [c] Recrystallized from 95% ethanol. [d] The more soluble of the two isomers.

Compound I possesses an asymmetric carbon atom and the form used in all of these reactions is the DL-racemate. Since the synthesis of these cyclic ketals results in the formation of a second asymmetric carbon atom two diastereoisomeric racemates should be formed. The products were all obtained in very good yield as mixtures of isomers. Separation of a pure racemate was accomplished by fractional crystallization. Both racemic forms were obtained in two cases (XII and XIII).



I IX–XV

Alcohols	Products, R
II, Benzyl alcohol	IX, $-CH_2C_6H_5$
III, Allyl alcohol	X, $-CH_2CH{=}CH_2$
IV, Tetrahydrofurfuryl alcohol	XI, $-CH_2$–(tetrahydrofuryl)
V, Ethylene glycol monoethyl ether	XII, $-CH_2CH_2OCH_2CH_3$
VI, Ethylene chlorohydrin	XIII, $-CH_2CH_2Cl$
VII, Trimethylene chlorohydrin	XIV, $-CH_2CH_2CH_2Cl$
VIII, Ethylene bromohydrin	XV, $-CH_2CH_2Br$

(1) Published with the approval of the Director of the Wisconsin Agricultural Experimental Station. Supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation. Part of this work is from the thesis submitted by Martin Seidman to the faculty of the Graduate School of the University of Wisconsin in partial fulfillment of the requirements for the degree of Doctor of Philosophy, August, 1950.

(2) Warfarin, a coined name for the Anticoagulant Rodenticide Chemical 3-(α-Acetonylbenzyl)-4-hydroxycoumarin. S. A. Rohwer, U. S. Dept. Agr. Interdepartmental Comm. Pest Control, June 29, 1950. The chemical name 3-(α-acetonylbenzyl)-4-hydroxycoumarin is the systematic name used by *Chemical Abstracts*. In previous publications the name 3-(α-phenyl-β-acetylethyl)-4-hydroxycoumarin had been used.

(3) M. Ikawa, M. A. Stahmann and K. P. Link, THIS JOURNAL, **66**, 902 (1944).

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

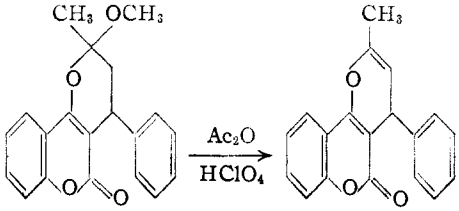
(5) N. H. Cromwell and K. C. Tsou, THIS JOURNAL, **71**, 993 (1949).

(6) R. E. Lutz and R. A. Jordan, *ibid.*, **71**, 997 (1949).

(7) Paper X in this series: M. Seidman, D. N. Robertson and K. P. Link, *ibid.*, **72**, 5193 (1950).

(8) L. D. Scheel, D. Wu and K. P. Link, Abstracts of the 116th American Chemical Society Meeting, Division of Medicinal Chemistry, Atlantic City, September, 1949. See also W. D. Battle, R. T. Capps, O. S. Orth and O. O. Meyer, *J. Lab. Clin. Med.*, **35**, 8 (1950).

The methyl ketal, XVI, was treated with acetic anhydride containing perchloric acid and the dehydrated derivative of I, 2-methyl-4-phenyl-5-oxo-γ-pyrano(3,2-c)(1)benzopyran (XVII)[7] was obtained.



This reaction parallels the formation of 2-methylchromene from 2-methyl-2-methoxychroman.[4]

When I was heated with phenol and zinc chloride in an attempt to form the phenyl ketal only XVII was isolated. An attempted reaction between I and glycolic acid in dioxane led to the recovery of unreacted I.

Experimental

Synthesis of Cyclic Ketals.—I was suspended in ten times its weight of the alcohol. Hydrogen chloride was then introduced from a cylinder. The mixture became warm and solution resulted after three to five minutes. After standing at room temperature for the time indicated in Table I the solution was poured into a large excess of ice-water with vigorous stirring. A gum or oil separated. The water was decanted and hot methanol added. Crystallization occurred readily or after refrigeration of the resulting solution. The pure racemates were obtained after fractional crystallization from methanol except as noted in Table I.

2-Methyl-2-methoxy-4-phenyl-5-oxodihydropyrano(3,2-c)(1)benzopyran (XVI).—Sixty grams of I was suspended in 300 ml. of methanol and hydrogen chloride passed in. The mixture became warm and a clear solution resulted. A mass of crystals then appeared. After cooling, the product was filtered off and washed with methanol and dilute sodium hydroxide solution. The mother liquor and the washings were then poured into an excess of water and the solid which precipitated was filtered off. The combined precipitates were recrystallized from benzene; yield 59 g., m.p. 163–164°.

Conversion of XVI to XVII.—Two grams of XVI was suspended in 20 ml. of acetic anhydride and two drops of perchloric acid added. The mixture was heated on a steam-bath for one hour giving a green solution. After being cooled the solution was poured into 200 ml. of ice and water to give a pink precipitate. After two recrystallizations from methanol 0.8 g. of XVII was obtained, m.p. 144–145°. The melting point of a mixture of this product with authentic XVII was 144.5–146°.

Reaction of I with Phenol and Zinc Chloride.—Fifteen grams of phenol was melted and 10 g. of I and 4 g. of anhydrous zinc chloride added. The mixture was heated at 70° for 15 minutes. After cooling, the melt was poured into 1 l. of ice-water and the gum which formed was dissolved in 95% ethanol. Dropwise addition of water caused a precipitate to form. After filtration the crystals were washed with 10% sodium hydroxide solution and recrystallized from ethanol. Three grams of material melting at 127–135° was obtained. After two more recrystallizations from methanol the melting point was 145–146°.

Acidification of the sodium hydroxide washings precipitated a small amount of unreacted I.

Attempted Reaction of I with Glycolic Acid.—Into a mixture of 10 g. of I and 10 g. of glycolic acid in 150 ml. of dioxane was introduced hydrogen chloride from a cylinder. Solution occurred in a few minutes. After standing 14 hours at room temperature the solution was poured into 600 ml. of ice-water giving a gum. The gum was dissolved in 100 ml. of boiling 95% ethanol and the solution refrigerated. After five days the crystals which had formed were separated by filtration; yield 6.0 g., m.p. 145–152°. Recrystallization from acetone-water raised the melting point to 159–161°. The melting point of a mixture of this product with authentic I was 159–161°.

MADISON 6, WISCONSIN RECEIVED OCTOBER 20, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

Reactions of Unsaturated Compounds with Iodine–Amine Complexes. I. Reactions of Benzalacetophenone and Benzalacetone

BY PHILIP L. SOUTHWICK AND DAVID R. CHRISTMAN[1]

Complexes of iodine with ammonia, cyclohexylamine, benzylamine, morpholine and piperidine have all been found to react readily with benzalacetophenone. When sufficient additional amounts of ammonia or the amine are present, good yields can usually be obtained of 2-phenyl-3-benzoylethylenimines from ammonia or the primary amines, and of α,β-diaminobenzylacetophenones from the secondary amines. Benzalacetone reacts with the iodine–morpholine and iodine–piperidine complexes to yield α,β-diamino benzylacetones, but apparently does not yield ethylene imine ketones with iodine–ammonia or primary amine complexes. The products from both ketones are often obtained chiefly in the configurations which are not predominant in the similar products obtained by reactions of these amines with the corresponding ketone dibromides.

Recent work in this Laboratory[2] has shown that N-bromosuccinimide is capable of attacking the carbon to carbon double bond of certain β-phenyl-α,β-unsaturated ketones. The result of this attack which in most instances occurred only in the presence of catalytic amounts of benzoyl peroxide, was either the addition of two bromine atoms to the double bond, the substitution of a bromine atom for hydrogen on the α-carbon atom, or simply conversion of the ketone into its geometric isomer. However, efforts to elucidate the mechanisms of these reactions were largely unsuccessful.[2]

One of the questions raised by the results obtained with N-bromosuccinimide concerned the possibility that the bromo derivatives resulted not from the direct action of N-bromosuccinimide on the ketones, but from the action of the elementary bromine which might have been formed by the decomposition of the N-bromosuccinimide. Although there was reason for believing that free bromine was not involved in these reactions, it nevertheless became of interest to test the effect on α,β-unsaturated ketones of an N-halogen amide or amine the decomposition of which could not liberate a halogen capable of attacking the double bond. Benzalacetophenone, benzalacetone and similar α,β-unsaturated ketones do not form stable

(1) Institute Graduate Fellow in Organic Chemistry, 1950–1951.

(2) P. L. Southwick, L. A. Pursglove and P. Numerof, THIS JOURNAL, **72**, 1600, 1604 (1950).