[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF OKLAHOMA]

Synthesis of Certain Chalcones and 3-Hydroxychromones

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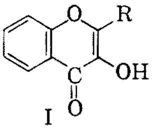
Received June 24, 1959

Certain new 3-hydroxychromones containing a heterocyclic or a polycyclic ring attached to the number 2 carbon atom of the chromone have been synthesized by preparing the corresponding hydroxychalcones, oxidizing the chalcones with alkaline hydrogen peroxide by the Algar-Flynn method, and purifying the products by column chromatography. In a few cases, the 3-hydroxychromones were also prepared directly by the Ranjorwa reaction. Properties of the purified compounds such as their ultraviolet spectra, infrared spectra, color reactions, and their melting points are recorded.

This paper reports our preparation, for biological studies, of certain new 3-hydroxychromones containing a heterocyclic or a polycyclic ring attached to the number 2 carbon atom of the chromone. The corresponding chalcones were also synthesized in every case.

Properties of the synthesized compounds, such as their ultraviolet spectra, infrared spectra, color reactions, and melting points have also been investigated.

The synthesized 3-hydroxychromones have the general formula I, where R = 9-anthracyl, 9-phenanthryl, 1-naphthyl, 2-naphthyl, 2-thienyl, 2-pyridyl, 3-pyridyl, 2-pyridyl-6-methyl, and 2-quinonyl, respectively.



I

One method tried for these syntheses was to prepare the 3-hydroxychromone in one step by the Ranjorwa reaction.[1] The Ranjorwa reaction, however, gave good results only in a few cases. The majority of the 3-hydroxychromones, therefore, were prepared by synthesizing first the corresponding chalcones and then by oxidizing the chalcones to 3-hydroxychromones by the Algar-Flynn[2] method, with alkaline hydrogen peroxide. In every case, each product obtained was purified by column chromatography. For these syntheses, 2-hydroxyacetophenone and an aldehyde of the appropriate polycyclic or heterocyclic compound were used. In one preparation only, 2-hydroxy-5-methylacetophenone was used instead of 2-hydroxyacetophenone.

EXPERIMENTAL

All melting points are uncorrected. Microanalyses were by Galbraith Laboratories, Knoxville, Tennessee.

1-(2-Hydroxyphenyl)-3-(9-anthracyl)propenone. Two general methods were employed for the preparation of this and other chalcones synthesized.

First general method for preparation of chalcones. In a 125 ml. Erlenmeyer flask, 2.06 g. (0.01 mol.) of 9-anthraldehyde and 1.36 g. (0.01 mol.) of 2-hydroxyacetophenone were dissolved in 30 ml. of 95% ethanol. To this solution, 5 ml. of 50% KOH was added in portions. The color of the solution became orange. The flask was then stoppered and kept at room temperature (approximately 25°) for 48 hr. The resulting deep red solution was diluted with water, and the chalcone was precipitated by bubbling a current of carbon dioxide through the solution. The red precipitate was crystallized from acetone, m.p. 166–167°. The yield was 1.9 g. (58%).

Second general method for preparation of chalcones. In a 125 ml. Erlenmeyer flask, 2.06 g. (0.01 mol.) of 9-anthraldehyde and 1.36 g. (0.01 mol.) of 2-hydroxyacetophenone were dissolved in 30 ml. of 95% ethanol and 5 ml. of 50% KOH was slowly added to it. The flask was shaken mechanically for 4 hr. The solution, which had now become deep red, was acidified with 5% ice cold HCl. The red precipitate formed was crystallized from acetone, m.p. 166–167°. The yield was 2.1 g. (64.8%).

The 1-(2-hydroxyphenyl)-3-(9-anthracyl)propenone obtained by both methods was purified further by column chromatography. A chromatographic column was prepared by adding a slurry of Magnesol brand magnesium silicate (Food Machinery and Chemical Corp., N. Y.) in methanol to a chromatographic tube and packing the absorbant under 10 lb. of pressure. This column of Magnesol was washed with 50 ml. of methanol. The solution of chalcone in methanol was poured onto the column, and the pressure was reduced to 5 lb. A small amount of impurity remained adsorbed on the top of the column, but most of the chalcone passed through the column. The chalcone was crystallized from acetone, m.p. 166–167°.

2-(9-Anthracyl)-3-hydroxychromone by the Algar-Flynn reaction. One gram (0.003 mol.) of 1-(2-hydroxyphenyl)-3-(9-anthracyl)propenone was dissolved in 50 ml. of 95% ethanol, and then 20 ml. acetone and 6 ml. of $1N$ potassium hydroxide were added. This red solution was heated on a water bath, and 10 ml. of 30% H_2O_2 was added. There was a vigorous reaction, and the solution slowly turned yellow. The mixture was then heated on a water bath for 30 min. and allowed to stand for 2 hr. Yellow crystals deposited and were separated and then recrystallized from benzene, m.p. 331–332°. The yield was 0.2 g. (17.9%). From the alcoholic solution, a small amount of another yellow crystalline substance, m.p. 246–247°, was isolated. This latter compound has not been identified.

2-(9-Anthracyl)-3-hydroxychromone by the Ranjorwa reaction. In a 125 ml. Erlenmeyer flask, 2.06 g. (0.01 mol.) of 9-anthraldehyde and 1.36 g. (0.01 mol.) of 2-hydroxyacetophenone were dissolved in 30 ml. of 95% ethanol, and 5 ml. of 50% KOH was added slowly. The flask was shaken mechanically for 1 hr., with the solution exposed to air. The flask was then stoppered and kept at room temperature. The procedure was repeated daily for 30 days. At the end of the 30 days, the red sodium salt that had deposited in the flask was separated and treated with dilute HCl. The red

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[1] S. D. Limaye and D. B. Limaye, *Rasayanam*, **2**, No. 2, 41 (1952); *Chem. Abstr.*, **47**, 4879 (1953).

[2] J. Algar and J. P. Flynn, *Proc. Roy. Irish Acad.*, **42B**, 1 (1934).

TABLE I

MELTING POINTS, YIELDS, AND COLOR REACTIONS OF CHALCONES

Compound	M.P.	Yield (%)	Color Reactions	
			H_2SO_4 (Conc.)	$SbCl_5$ in CCl_4
1-(2-Hydroxyphenyl)-3-(9-anthracyl)propenone	166–167	58[a]	Dk G	Bl[b]
1-(2-Hydroxy-5-methyl phenyl)-3-(9-anthracyl)propenone	171–172	62[a]	Dk G	V[b]
1-(2-Hydroxyphenyl)-3-(9-phenanthryl)propenone	158–159	92.6	R	R-Br[b]
1-(2-Hydroxyphenyl)-3-(1-naphthyl)propenone	115–116	16.4	R	R[b]
1-(2-Hydroxyphenyl)-3-(2-naphthyl)propenone	155–156	54.9	R	R[b]
1-(2-Hydroxyphenyl)-3-(2-thienyl)propenone	99–100	58.7[a]	O	Dp O
1-(2-Hydroxyphenyl)-3-(2-pyridyl)propenone	101–102	53.3	O	R[b]
1-(2-Hydroxyphenyl)-3-(3-pyridyl)propenone	161–162	25.8	O	O
1-(2-Hydroxyphenyl)-3-(2-pyridyl-6-methyl)propenone	96–97	37.5	O	R[b]
1-(2-Hydroxyphenyl)-3-(2-quinonyl)propenone	125–126	29.0	R	R[b]

Bl = Blue; Br = Brown; Dk = Dark; Dp = Deep; G = Green; O = Orange; R = Red; V = Violet.

[a] Prepared by first method described; others were synthesized by the second method. [b] Formation of a precipitate.

salt turned yellow, and was crystallized from benzene, m.p. 331–332°.

The 2-(9-anthracyl)-3-hydroxychromone from both syntheses was purified further by chromatography. A chromatographic column was prepared by adding a slurry of Magnesol in dry benzene to a chromatographic tube. The absorbant was packed under a pressure of 10 lb. The column was washed with anhydrous benzene by pouring 50 ml. of the anhydrous benzene onto the absorbant and passing it through the column under a pressure of 10 lb. The benzene solution of the chromone was next passed through the Magnesol column, under a pressure of 5 lb. The column was developed with additional benzene. The chromone was present just at the top of the column in a yellow zone, and a chalcone appeared as an orange zone just below it. Immediately after washing the column with anhydrous benzene, the Magnesol was extruded from the top of the column, and cut by a stainless steel spatula into three portions. The top zone contained impurities and was set aside. The second zone was eluted with acetone, and the desired chromone was obtained after evaporation of the acetone. The chromone was crystallized from benzene, m.p. 331–332°.

Acetate of 2-(9-anthracyl)-3-hydroxychromone. The synthesized 2-(9-anthracyl)-3-hydroxychromone (0.5 g.) was refluxed for 1 hr. with acetic anhydride (2 ml.) and pyridine (3 drops). The resulting mixture was poured onto crushed ice. The yellow solid formed was crystallized from 95% ethanol as yellow needles, m.p. 194–195°.

Synthesis and properties of various chalcones. The various chalcones synthesized are listed in Table I. Of those listed, 1-(2-hydroxyphenyl)-3-(2-pyridyl)propenone, 1-(2-hydroxyphenyl)-3-(3-pyridyl)propenone, 1-(2-hydroxyphenyl)-3-(2-pyridyl-6-methyl)propenone, and 1-(2-hydroxyphenyl)-3-(2-quinonyl)propenone could be synthesized only by the second general method. Both methods were successful for preparation of all the other chalcones listed. Melting points, percentage yields of synthesis, and color reactions of each chalcone in concentrated H_2SO_4 and in $SbCl_5$ in carbon tetrachloride are also recorded in Table I.

Synthesis of various 3-hydroxychromones. The 3-hydroxychromones synthesized in this study are listed in Table II. All of these were prepared from the corresponding chalcone of Table I by the Algar-Flynn reaction. In only three cases as indicated in Table II, was the Ranjorwa reaction also successful. The melting points, percentage yields of synthesis by the Algar-Flynn reaction, and analytical data are also included in Table II.

The acetate of each 3-hydroxychromone was prepared. The melting point and analytical data for each acetate are also recorded in Table II.

Color reactions of 3-hydroxychromones. The color reactions produced by the synthesized chromones on treatment with common flavonoid color-producing reagents are reported in Table III.

Ultraviolet absorption spectra of 3-hydroxychromones. Ultraviolet absorption spectra of absolute ethanol solutions of the synthesized chromones were obtained using a Beckman spectrophotometer, Model DU. Two drops of 2% alcoholic $AlCl_3$ were then added to each solution and the new absorption spectrum of each recorded. The resulting shifts are given in Table III.

Infrared absorption spectra. Infrared spectra of these synthesized chromones were taken in chloroform solution on a Perkin-Elmer Infracord spectrophotometer. The absorption frequencies for the carbonyl group of the synthesized chromones were found to be between 1620 $cm.^{-1}$ and 1650 $cm.^{-1}$, and those for the hydroxyl group were between 3445 $cm.^{-1}$ and 3460 $cm.^{-1}$, as recorded in Table III. The absorption peaks for the hydroxyl group were generally not sharp, and in the case of 2-(2-pyridyl-6-methyl)-3-hydroxychromone and of 2-(2-quinonyl)-3-hydroxychromone, they were absent. Hergert and Kurth[3] reported values in the range 1627–1657 $cm.^{-1}$ and 3270–3340 $cm.^{-1}$ for the carbonyl and hydroxyl absorption frequencies, respectively, of 3 naturally occurring flavone aglycones studied. They found that the hydroxyl band was broad and not sharply defined for 2 of these 3 flavonols. For 2 naturally occurring flavonol aglycones studied, Inglett[4] found values of 1655 $cm.^{-1}$ for the carbonyl and 3160 $cm.^{-1}$ to 3340 $cm.^{-1}$ for the hydroxyl group.

The 1-naphthaldehyde used was purchased from L. Light & Co. Ltd. of England, and the other aldehydes and the acetophenone compounds used were purchased from Aldrich Chemical Co., Milwaukee, Wis.

Acknowledgment. We thank Mr. Peter Klaboe and Miss K. Lakshmi of the Physics Dept., University of Oklahoma, for assistance with the infrared determinations. We appreciate very much the support, in part, for this research by the National Institutes of Health.

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(3) H. L. Hergert and E. F. Kurth, *J. Am. Chem. Soc.*, **75**, 1622 (1953).

(4) G. E. Inglett, *J. Org. Chem.*, **32**, 93 (1958).

TABLE II

Melting Points, Yields, and Analyses of 3-Hydroxychromones and Their Acetates

Compound	M.P., °C.	% Yield Algar-Flynn Synthesis	Analyses		Acetate of 3-Hydroxychromone		
			Calcd.	Found	M.P., °C.	Analyses Calcd.	Analyses Found
2-(9-Anthracyl)-3-hydroxychromone[a]	331–332	17.9	C, 81.64; H, 4.17	C, 81.49; H, 4.18	194–195	C, 78.94; H, 4.24	C, 78.97; H, 4.29
2-(9-Anthracyl)-3-hydroxy-6-methylchromone[a]	305–306	34.1	C, 81.80; H, 4.58	C, 81.82; H, 4.76	283–285	C, 79.17; H, 4.60	C, 79.10; H, 4.73
2-(9-Phenanthryl)-3-hydroxychromone	248–249	16.9	C, 81.64; H, 4.17	C, 81.47; H, 4.15	179–181	C, 78.94; H, 4.24	C, 78.68; H, 4.16
2-(1-Naphthyl)-3-hydroxychromone[a]	231–232	36.1	C, 79.15; H, 4.19	C, 79.07; H, 4.06	190–192	C, 76.35; H, 4.27	C, 76.52; H, 4.43
2-(2-Naphthyl)-3-hydroxychromone	208–209	25.0	C, 79.15; H, 4.19	C, 78.98; H, 4.14	145–146	C, 76.35; H, 4.27	C, 76.41; H, 4.35
2-(2-Thienyl)-3-hydroxychromone	205–206	24.6	C, 63.92; H, 3.30; S, 13.13	C, 64.01; H, 3.34; S, 13.18	152–153	S, 11.20	S, 11.21
2-(2-Pyridyl)-3-hydroxychromone	178–179	46.1	C, 70.29; H, 3.79; N, 5.85	C, 70.04; H, 3.57; N, 5.84	138–140	N, 4.98	N, 5.08
2-(3-Pyridyl)-3-hydroxychromone	207–208	21.7	C, 70.29; H, 3.79; N, 5.85	C, 70.43; H, 3.71; N, 5.95	109–110	N, 4.98	N, 5.08
2-(2-Pyridyl-6-methyl)-3-hydroxychromone	208–209	63.4	N, 5.53	N, 5.61	118–119	N, 4.74	N, 4.87
2-(2-Quinonyl)-3-hydroxychromone	253–254	34.6	N, 4.84	N, 5.01	181–182	N, 4.23	N, 4.17

[a] Also synthesized by the Ranjorwa reaction.

TABLE III

Color Reactions, Spectral Shifts with $AlCl_3$, and Infrared Spectral Data of 3-Hydroxychromones

Compound	Color Reactions[a]					Spectral Shifts with $AlCl_3$			Infrared Spectral Data	
	5% $FeCl_3$ Soln.	H_2SO_4 (conc.)	$SbCl_5$ in CCl_4	Mg and HCl	Appearance on Paper Chromatogram under Ultraviolet	Max., mμ	Max., mμ, with $AlCl_3$	Shift, mμ, with $AlCl_3$	Hydroxyl Cm.$^{-1}$	Carbonyl Cm.$^{-1}$
2-(9-Anthracyl)-3-hydroxychromone	Y	O-R	Y	—	Bl	325	385	60	3445	1620
2-(9-Anthracyl)-3-hydroxy-6-methylchromone	Y	R-Br	Y-Br	—	Bl	322	385	57	3445	1620
2-(9-Phenanthryl)-3-hydroxychromone	Y	R-Br	G	Y	V	332	390	58	3445	1620
2-(1-Naphthyl)-3-hydroxychromone	Br	Y	Y-Br	Y	Y	333	390	57	3445	1620
2-(2-Naphthyl)-3-hydroxychromone	Br	Y	Y-Br	Y	Y	355	420	65	3445	1620
2-(2-Thienyl)-3-hydroxychromone	Y	Y	Y-Br	Y	Y	333	390	57	3445	1620
2-(2-Pyridyl)-3-hydroxychromone	Br	Y	Y	Y	Y	345	405	60	3460	1645
2-(3-Pyridyl)-3-hydroxychromone	Br	R-Br	Y	Y	G-Y	340	400	60	3440	1620
2-(2-Pyridyl-6-methyl)-3-hydroxychromone	Br	Y	Y	Y	Y-G	350	400	50	—	1645
2-(2-Quinonyl)-3-hydroxychromone	O	Y	Y-Br	Y	O	322	400	78	—	1650
Quercetin[b]						377	431	58		
Kaempferol[b]						367.5	426	58		

[a] Bl, Blue; Br, Brown; G, Green; O, Orange; R, Red; Y, Yellow. [b] Data from Jurd and Geissman [*J. Org. Chem.*, 21, 1400 (1956)].