[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

THE PREPARATION OF 2-METHYL-6,7-BENZOCHROMONES

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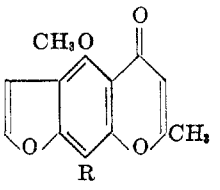
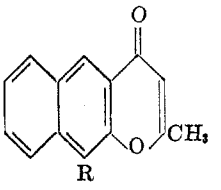
The natural product khellin (I) has attracted considerable interest in the medicinal field because of its potent coronary vasodilation and antispasmotic properties. It has been reported to be effective in the treatment of angina pectoris and bronchial asthma (1).

Numerous variants of khellin have been prepared in an effort to find simpler derivatives with comparable activity (2) and to study the relationship between structure and physiological activity (3). As yet no compound has been found with greater activity than that of khellin.

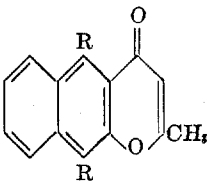
In this work syntheses are reported for two variants of khellin, 2-methyl-6,7-benzochromone (II) and 2-methyl-8-methoxy-6,7-benzochromone (III), in which



I. R = OCH_3
Ia. R = H



II. R = H
III. R = OCH_3



IV. R = OCH_3

the furano ring is replaced by a benzenoid nucleus. Reactions which would have led to a third possibility, 2-methyl-5,8-dimethoxy-6,7-benzochromone (IV), were complicated and are being studied further. Data on the effect of such a structural change on physiological activity are not available in the literature. The reverse replacement of a phenyl group by a furyl grouping causes in general a decrease in the physiological activity of a compound (4).

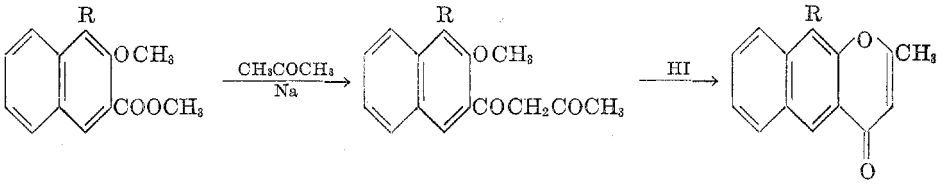
The chromones were prepared by the series of reactions listed on page 1420.

The synthesis starting with methyl 2-methoxy-3-naphthoate (V) proceeded normally and gave 2-methyl-6,7-benzochromone (II) in an over-all yield of 15%. The 2-methylchromone structure was demonstrated by its facile condensation with benzaldehyde to 2-styryl-6,7-benzochromone (X).

Methyl 1,2-dimethoxy-3-naphthoate (VI) which was prepared from 1,2-dihydroxy-3-naphthoic acid by a two step methylation process, condensed with acetone in the desired fashion.Cyclization of the diketone (VIII) with hydriodic acid gave products which depended upon the time of refluxing. A period of seven hours gave a mixture of 2-methyl-8-hydroxy-6,7-benzochromone (IX) and 2-methyl-8-methoxy-6,7-benzochromone (III). Complete demethylation was achieved only after 24 hours of heating. The product (IX) could ce reconverted

[1] Abstracted in part from the Ph.D. thesis of H. A. Ready, June 1952.

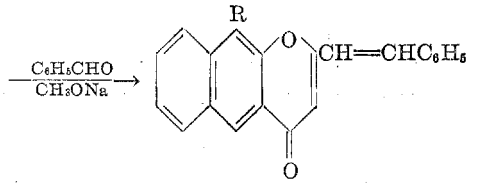
to the methyl ether (III) by diazomethane. The 2-methylchromone structure in the latter was demonstrated by the formation of a 2-styryl derivative (XI).



V. R = H
VI. R = OCH_3

VII. R = H
VIII. R = OCH_3

II. R = H
III. R = OCH_3
IX. R = OH



X. R = H

XI. R = OCH_3

Because of the numerous steps involved in preparing methyl 1,2-dimethoxy-3-naphthoate (VI), the more readily available ethyl 1,3-dihydroxy-2-naphthoate was studied as a starting material for the closely related 5-hydroxy-6,7-benzochromone. The condensation of ethyl 1,3-dimethoxy-2-naphthoate with acetone, however, gave a red glass which could not be crystallized or distilled.

The conversion of 2-methyl-8-hydroxy-6,7-benzochromone (IX) to 2-methyl-5,8-dimethoxy-6,7-benzochromone (IV) was tried in a similar manner to that used for making khellin (I) from visnagin (Ia) (5) but was not successful. Nitration of IX produced a mixture of mononitro compounds which could not be separated by crystallization. Coupling of IX with diazotized sulfanilic acid gave a blue, water-soluble azo dye. Reduction of this product with stannous chloride gave a compound which could not be freed from inorganic salts by either dissolving in alkali and reprecipitating or by oxidation with ferric chloride. This series of reactions is being studied further.

The physiological activity of the chromones will be reported later.

EXPERIMENTAL[2]

3-Methoxy-2-naphthoylacetone (VII). To a stirred suspension of powdered sodium (5.2 g.) in dry ether (200 ml.) at 0–5° was added freshly distilled methyl 2-methoxy-3-naphthoate (6) (VI) (24.5 g.) in dry toluene (50 ml.) and then acetone (6.8 g.). The latter was added in the course of a five-minute period. After 30 minutes the ice-bath was removed and the stirring continued at room temperature for 40 hours. After this period, a small amount of methanol

[2] Melting points and boiling points are not corrected.

was added to decompose the excess sodium and the solution was added to water (200 ml.), extracted with two 50-ml. portions of ether, and acidified with dilute hydrochloric acid. Extraction with ether gave a solution of the diketone and 3-hydroxy-2-naphthoic acid which were separated by dissolving in 5% potassium hydroxide and precipitating the diketone with excess carbon dioxide. The crude 1,3-diketone (9.2 g.) (33% yield) after one recrystallization from ethanol melted at 81–82°.

Anal. Calc'd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82.
Found: C, 74.11; H, 5.64.

2-Methyl-6,7-benzochromone (II). A solution of 2-methoxy-3-naphthoylacetone (VII) (5.0 g.) in a mixture of acetic anhydride (25 ml.) and 55% hydriodic acid (25 ml.) was refluxed for four hours and after cooling poured into 300 ml. of ice-cold 2% sodium bisulfite solution. Extraction with ether gave after washing with cold 1 *N* potassium hydroxide and removal of the solvent 2-methyl-6,7-benzochromone (II). Recrystallization from ligroin (b.p. 86–100°) gave pale yellow needles (2.0 g.) melting at 134–135°.

Anal. Calc'd for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79.
Found: C, 79.72; H, 4.66.

2-Styryl-6,7-benzochromone (X). A solution of 2-methyl-6,7-benzochromone (II) (0.2 g.), benzaldehyde (0.5 ml.), and sodium methoxide (from 0.1 g. of sodium) in methanol (8 ml.) was heated for ten minutes at 100° and then allowed to stand for 12 hours at room temperature. The resulting solid melted at 168–169° after one recrystallization from ethanol.

Anal. Calc'd for $C_{21}H_{14}O_2$: C, 84.54; H, 4.69.
Found: C, 84.19; H, 4.53.

1,2-Dimethoxy-3-naphthoic acid. 1,2-Dihydroxy-3-naphthoic acid (7) (40 g.) in 20% sodium hydroxide (400 ml.) containing sodium hydrosulfite (2 g.) was shaken with two 40-ml. portions of methyl sulfate and then refluxed for three hours. The mixture was treated twice with 30 ml. of methyl sulfate and 30 g. of sodium hydroxide in 80 ml. of water and refluxing was continued for 20 hours. (The resulting solution should have been alkaline at this point. If this was not the case, 30 g. more of sodium hydroxide in 200 ml. of water was added and refluxing continued for two hours.) The resulting solution was poured onto ice (400 g.) and acidified with concentrated sulfuric acid (120 ml.). The acid formed crystallized upon stirring and was purified by redissolving in 5% sodium bicarbonate solution. The solution after clarification with sodium hydrosulfite gave upon acidification a pale yellow solid which melted at 118–122° after one crystallization from 80% ethanol; yield, 35 g. This product, which was suitable for the next reaction, formed colorless needles melting at 123–124° when recrystallized a second time from ethanol.

Anal. Calc'd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21.
Found: C, 67.41; H, 5.11.

Methyl 1,2-dimethoxy-3-naphthoate (VI). A solution of 1,2-dimethoxy-3-naphthoic acid (20 g.) in ether (250 ml.) and methanol (20 ml.) was cooled in a salt-ice mixture, and treated with diazomethane (0.15 mole) in ether (150 ml.) and then allowed to stand for 12 hours. After decomposition of the excess diazomethane with acetic acid, removal of the solvent gave a pale yellow oil, b.p. 126–127°/0.5 mm.; yield, 18.6 g.

Anal. Calc'd for $C_{14}H_{14}O_4$: C, 68.28, H, 5.73.
Found: C, 68.65; H, 5.58.

1,2-Dimethoxy-3-naphthoylacetone (VIII). Methyl 1,2-dimethoxy-3-napthoate (30 g.) was treated with sodium and acetone in a manner similar to that used with methyl 2-methoxy-3-naphthoate. The product obtained by precipitation with carbon dioxide was purified by distillation at reduced pressure and boiled at 145°/0.5 mm.; m.p. 75–76°; yield, 10 g.

Anal. Calc'd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92.
Found: C, 70.99; H, 5.92.

Acidification of the filtrate from the carbon dioxide precipitation with hydrochloric acid gave 1,2-dimethoxy-3-naphthoic acid (10.5 g.).

8-Hydroxy-2-methyl-6,7-benzochromone (IX). 1,2-Dimethoxy-3-naphthoylacetone (VIII) (2 g.) was refluxed with acetic anhydride (6 ml.) and constant-boiling hydriodic acid (6 ml.) stabilized with hypophosphorous acid for 24 hours. After cooling the solid was filtered, washed with water (50 ml.) containing sodium sulfite (0.2 g.), and purified by refluxing with ethanol (25 ml.) for 15 minutes. The yellow crystals (1.3 g.) obtained melted at 268–273°d.

Anal. Calc'd for $C_{14}H_{10}O_3$: C, 74.32; H, 4.45.

Found: C, 73.99; H, 4.30.

Refluxing for only seven hours gave in addition varying amounts of 8-methoxy-2-methyl-6,7-benzochromone (III). This product was separated by treating the mixture with 2% potassium hydroxide and melts at 162–163°. Acidification of the alkaline filtrate gave the 8-hydroxychromone (IX).

8-Methoxy-2-methyl-6,7-benzochromone (III). 8-Hydroxy-2-methyl-6,7-benzochromone (IX) (1 g.) when treated in ether (10 ml.) and methanol (20 ml.) at 0° with diazomethane (0.02 mole) in ether (55 ml.) for 12 hours gave upon removal of most of the solvent the methyl ether (III). Crystallization from methanol (10 ml.) gave pale yellow needles (0.7 g.) melting at 162–163°. This sample did not lower the melting point of the product obtained by cyclization.

Anal. Calc'd for $C_{15}H_{12}O_3$: C, 74.98; H, 5.03.

Found: C, 75.13; H, 4.77.

The 8-methoxy-2-styryl-6,7-benzochromone (XI) prepared in the same way as the 2-styryl-6,7-benzochromone (X) gave pale yellow needles from ethanol melting at 165–166°.

Anal. Calc'd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91.

Found: C, 80.18; H, 4.92.

Nitration of 8-hydroxy-2-methyl-6,7-benzochromone (IX). To a stirred suspension of 8-hydroxy-2-methyl-6,7-benzochromone (IX) in glacial acetic acid was added nitric acid (7 drops, $d = 1.42$) in acetic acid (5 ml.) at 20°. After five minutes the mixture was diluted with water (30 ml.), cooled to 0°, and filtered. The crude product upon purification by refluxing with ethanol (25 ml.) gave a yellow powder (1.0 g.) m.p. 202–210° d. Insolubility in most solvents prevented further purification of this compound.

Anal. Calc'd for $C_{14}H_9NO_5$: C, 61.97; H, 3.70.

Found: C, 61.61; H, 3.39.

Coupling of 8-hydroxy-2-methyl-6,7-benzochromone (IX) *with diazotized sulfanilic acid.* A solution of the 8-hydroxychromone (IX) (1.0 g.) in water (40 ml.) containing potassium hydroxide (1 g.) when treated with diazotized sulfanilic acid gave a purple solution which was allowed to stand at 0° for 45 minutes. Unreacted chromone was removed by acidification and filtering. The filtrate was refluxed with a mixture of stannous chloride (4 g.) and concentrated hydrochloric acid (10 ml.) for 30 minutes. After cooling to 10° a yellow powder (0.4 g.) was obtained which left a white residue on ignition. Treatment of the tin complex with dilute alkali in the absence of air gave a yellow solution from which tin-free products could not be precipitated with dilute hydrochloric acid, tartaric acid, or a mixture of ammonium chloride and oxalic acid. Oxidation with ferric chloric gave no definite compound.

Ethyl 1,3-dimethoxy-3-naphthoate. A mixture of ethyl 1,3-dihydroxy-2-naphthoate (8) (15 g.), anhydrous potassium carbonate (20 g.), and methyl iodide (45 ml.) was refluxed in dry acetone (250 ml.) for 72 hours and filtered. Removal of the solvent followed by the addition of water, extraction with ether, and removal of unreacted ester with alkali gave a yellow oil (10 g.), b.p. 160–162°/1 mm. A sample in aqueous ethanol gave no color with ferric chloride.

Anal. Calc'd for $C_{15}H_{16}O_4$: C, 69.21; H, 6.19.

Found: C, 69.38; H, 6.16.

Condensation of this ester with acetone and sodium gave a red oil which could not be distilled or crystallized.

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SUMMARY

The preparation of 2-methyl-6,7-benzochromone and 2-methyl-8-methoxy-6,7-benzochromone from methyl 2-methoxy-3-naphthoate and methyl 1,2-dimethoxy-3-naphthoate respectively is described.

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LITERATURE REFERENCES

(1) HUTTRER AND DALE, *Chem. Revs.*, **48**, 543 (1951).
(2) SCHMITZ, LAUENER, HIRT, AND SANZ, *Helv. Chem. Acta*, **34**, 767 (1951).
(3) SCHÖNBERG AND SINA, *J. Am. Chem. Soc.*, **72**, 1611, 3396 (1950).
(4) MORTON, *The Chemistry of Heterocyclic Compounds*, McGraw Hill Book Co., New York, 1946, p. 13.
(5) SCHÖNBERG AND BADRAN, *J. Am. Chem. Soc.*, **73**, 2960 (1951).
(6) LESSER, KRANEPUHL, AND GAD, *Ber.*, **58**, 2119 (1925).
(7) SPRUIT, *Rec. trav. chim.*, **67**, 285 (1948).
(8) MEYER AND BLOCH, *Org. Syntheses*, **25**, 73 (1945).