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THE SYNTHESIS OF KHELLIN DERIVATIVES

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Interest in the synthesis of khellin, one of the components of the Egyptian drug Ammi Visnaga, has recently been stimulated by the reports (1, 2) on its pharmacological activity and its clinical effectiveness.

The structure of khellin was established by Späth and Gruber (3). The recent synthesis of khellin by Baxter, Ramage, and Timson (6) and Clarke and Robertson (4), reported during the course of the work to be described, anticipate in general two of the approaches made by us. In view of these publications, we take opportunity to describe our work in as far as it differs in detail and to describe some related work.

2,5-Dimethoxyresorcinol on chloroacetylation gave 2,4-dihydroxy-3,6-dimethoxy-ω-chloroacetophenone (I). This was cyclized to 4,7-dimethoxy-6-hydroxy-3(2H)-benzofuranone (II) which on treatment with acetonitrile according to Hoesch gave 5-acetyl-4,7-dimethoxy-6-hydroxy-3(2H)-benzofuranone (III). On cyclizing, 3-keto-3(2H)-dihydro-6-acetylkhellin and 3-acetoxy-6-acetylkhellin wereformed.

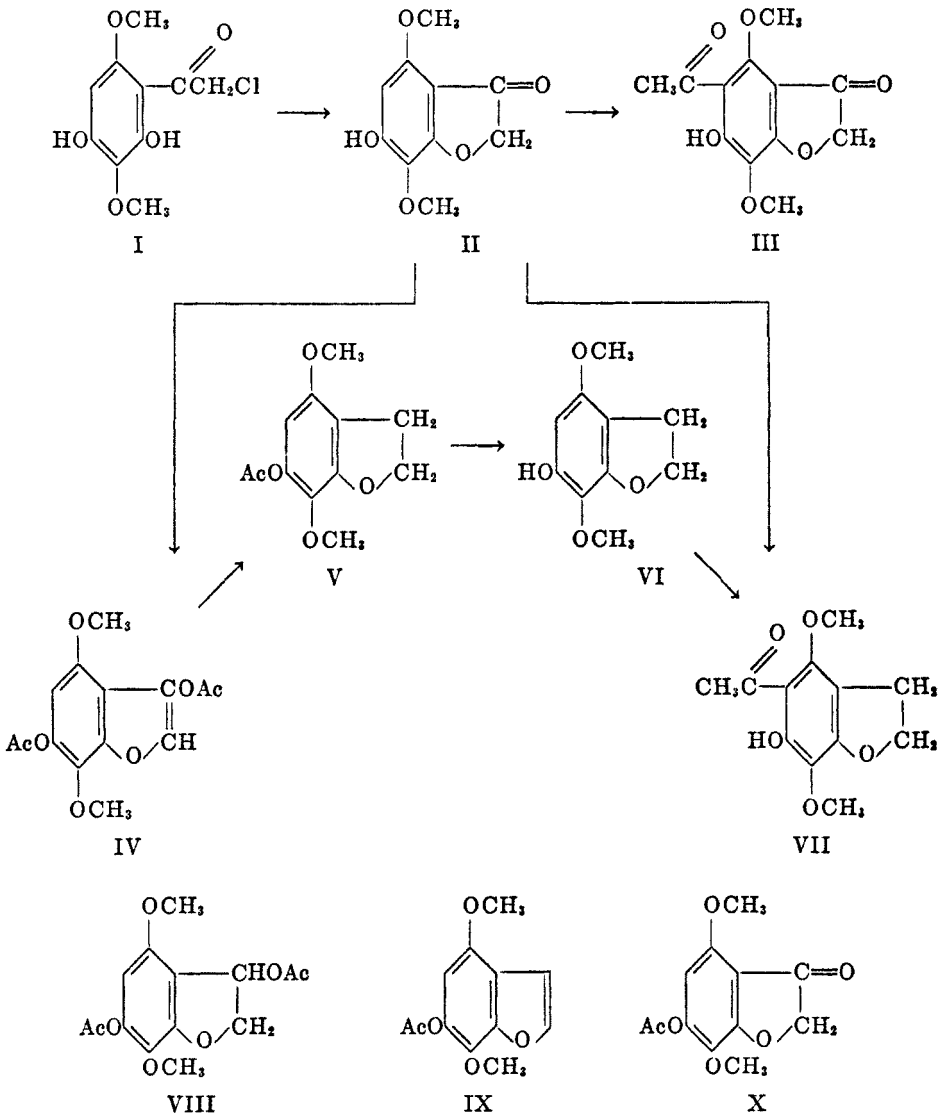
2,4-Dihydroxy-3,6-dimethoxyacetophenone on treatment with N-bromosuccinimide gave the bromo compound, 2,4-dihydroxy-3,6-dimethoxy-ω-bromoacetophenone. Although 2,4-dihydroxy-3,6-dimethoxy-ω-chloroacetophenone (I) was cyclized to 4,7-dimethoxy-6-hydroxy-3(2H)-benzofuranone (II) according to the method of Späth and Pailer (7) or Shriner and Grosser (10), the bromo derivative was not cyclized by boiling water nor sodium acetate in aqueous alcohol. Fusion eliminated hydrogen bromide, but no identifiable compound was obtained.

Attempts to catalytically reduce II directly to VI with palladium-on-carbon, platinum oxide, or Raney nickel at various pressures and temperatures in different solvents failed, although reduction of closely related compounds using palladium-black in acetic acid has been reported (7).

In analogy with Gruber (8), compound II was acetylated to yield IV, and this on reduction was expected to yield an acetylated secondary alcohol VIII which in turn was expected to lose acetic acid on vacuum-distillation, yielding an intermediate IX which might be transformed into khellinone. The reduction did not occur under Gruber's conditions. However, using platinum oxide as a catalyst, 4,7-dimethoxy-3,6-diacetoxybenzofuran (IV) was reduced to 4,7-dimethoxy-6-acetoxydihydrobenzofuran (V). The identity of this compound was established by analysis, its failure to acetylate, and its deacetylation to 4,7-dimethoxy-6-hydroxydihydrobenzofuran (VI). On vacuum-distillation V was recovered unchanged. 4,7-Dimethoxy-6-acetoxydihydrobenzofuran (V) was expected by dehydrogenation to yield the corresponding 4,7-dimethoxy-6-acetoxybenzofuran (IX), and a similar reaction was reported during the course of this work by

Baxter, Ramage, and Timson (6). The latter workers prepared VI by reduction of 6-benzyloxy-4,7-dimethoxycoumarone, reporting the same melting point as

FIGURE 1



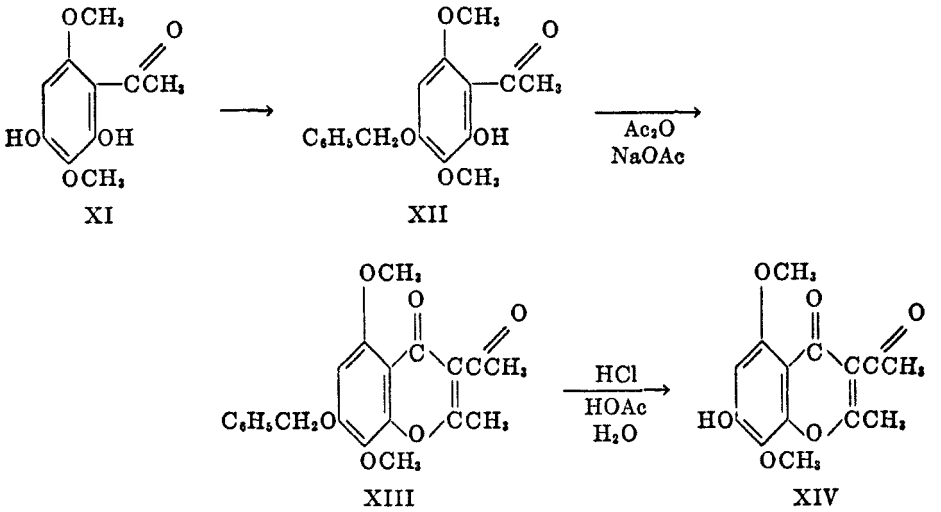
obtained in this work. This serves to confirm the unexpected reduction of IV to V.

Compounds analogous to 6-acetoxy-4,7-dimethoxy-3(2H)-benzofuranone (X) have been reported by Horning and Reisner (17) to be reduced to the dihydrobenzofuran type (V) using palladium-on-carbon. This suggests that the 3-acetoxy

group in IV is hydrolyzed, rearranged to the keto group, and reduced. However, proof of this mechanism is lacking because of the failure to synthesize X. Using the Horning and Reisner (17) method for obtaining monoacetates on 6-hydroxy-4,7-dimethoxy-3(2H)-benzofuranone (II) only the diacetoxy derivative (IV) was obtained.

In another approach to the synthesis of khellin, 2,4-dihydroxy-3,6-dimethoxyacetophenone (XI) was benzylated to give XII which on chromone ring closure with sodium acetate and acetic anhydride gave 2-methyl-3-acetyl-5,8-dimethoxy-7-benzyloxychromone (XIII). This on debenzylation with hydrochloric acid and water in acetic acid gave 2-methyl-3-acetyl-5,8-dimethoxy-7-hydroxychromone (XIV). This latter compound could not be made to undergo a Gattermann reaction to yield a 6-aldehydo derivative.

FIGURE 2



A Gattermann reaction on 2,4-dihydroxy-3,6-dimethoxyacetophenone (XI) (12) gave 3-acetyl-2,5-dimethoxy-4,6-dihydroxybenzaldehyde on which it was then hoped to build the furan and chromone rings by known procedures. Despite many attempts, however, the yield could not be brought above 17%. Similar difficulties were experienced by Gruber and Traub (9) on compounds of closely related structures. On these grounds this approach was not further pursued. Attempts to prepare 3-acetyl-2,5-dimethoxy-4,6-dihydroxybenzaldehyde by a Hoesch condensation on 2,4-dihydroxy-3,6-dimethoxybenzaldehyde failed.

In the benzylation (4, 5, 13) of 2,4-dihydroxy-3,6-dimethoxyacetophenone, 2-benzyloxy-4-hydroxy-3,6-dimethoxyacetophenone was also obtained. The acetylated derivative was isolated in the pure state. The formation of both monobenzyloxy compounds in the benzylation of 2,4-dihydroxy-3,6-dimethoxyacetophenone (XI) is in contrast to the selective benzylation of 2,4-dihydroxy-3,6-dimethoxybenzaldehyde described by Clarke and Robertson (4).

This latter publication, which appeared during the course of this work, also described the cyclization of ethyl (5-benzyloxy-3,6-dimethoxy-2-formylphenoxy) acetate in alcohol with sodium ethoxide to yield ethyl (6-benzyloxy-4,7-dimethoxybenzofuran)-2-carboxylate. In work along similar lines in this laboratory we had saponified this ester to obtain 5-benzyloxy-3,6-dimethoxy-2-formylphenoxyacetic acid (m.p. 151°) which was cyclized and simultaneously decarboxylated with sodium acetate and acetic anhydride to give 6-benzyloxy-4,7-dimethoxybenzofuran (m.p. 51°). This compound yields khellin by routes established by Baxter, Ramage, and Timson (6) and Späth and Gruber (3).

In an attempt to prepare other coumarin derivatives which might be of pharmacological interest, the condensation of 2,4-dihydroxy-3,6-dimethoxybenzaldehyde with acetic anhydride and sodium acetate gave a small quantity of the expected 7-acetoxy-5,8-dimethoxycoumarin and a larger quantity of 4,6-diacetoxy-2,5-dimethoxybenzaldehyde diacetate.

EXPERIMENTAL

1,2,3-Tribenzyloxybenzene. This compound was prepared from pyrogallol and benzyl chloride in 65–70% yields by the addition of potassium iodide to the reaction. The use of benzyl chloride alone was reported (11) to give a 32% yield.

2,6-Dibenzyloxy-p-benzoquinone. Tribenzyloxybenzene (500 g.) was dissolved in 4 l. of warm acetic acid in a 12-l. round-bottom flask, cooled to room temperature, and with stirring 24 g. of pulverized sodium nitrite and 200 ml. of nitric acid (d = 1.19) was added. The mushy mass was kept at 4° for 4 hours with occasional *vigorous* shaking. At this time an additional 200 ml. of nitric acid (d = 1.19) was added, the mixture shaken vigorously and allowed to stand at room temperature overnight. After filtration the mother liquor was diluted with water, when further precipitation of product occurred. The latter precipitate was sludged twice with acetone, using 100 ml. each time at room temperature to remove an unidentified, uncrystallized oil. The combined crystalline material consisted of a mixture of 2,6-dibenzyloxy-*p*-benzoquinone and 5-nitro-1,2,3-tribenzyloxybenzene.

5-Nitro-1,2,3-tribenzyloxybenzene and 2,6-dibenzyloxy-p-hydroquinone. The product from the oxidation of 500 g. of 1,2,3-tribenzyloxybenzene, consisting of a dry mixture of 5-nitro-1,2,3-tribenzyloxybenzene and 2,6-dibenzyloxy-*p*-hydroquinone, was dissolved with vigorous stirring in 1.8 l. of hot acetic acid, and then 500 ml. of water was added. The temperature was held at 70°, and to the suspension 400 ml. of a saturated solution of sodium hydrosulfite ($Na_2S_2O_4$, 200 g.) was added. The mixture was stirred for 15 minutes at 50°, during which time the suspension changed from a yellow to a light cream color, and then was filtered at 50°. The residue of practically pure 5-nitro-1,2,3-tribenzyloxybenzene was crystallized from acetone. M.p. 141–142° [previously reported 139° (11)]; yield, 165 g. (30%).

Anal. Calc'd for $C_{27}H_{23}NO_5$: C, 73.5; H, 5.3.
Found: C, 73.7; H, 5.3.

The aqueous-acetic acid filtrate was cooled and substantially pure 2,6-dibenzyloxy-*p*-hydroquinone crystallized. Yield, 116 g. (29%). Yields varied from 25–40%, based on 1,2,3-tribenzyloxybenzene used in the preceding step.

Pure hydroquinone was obtained as colorless needles by recrystallizing the crude product from 80% acetic acid-water solution containing a small quantity of sodium hydrosulfite. M.p. 116–117° in accordance with previous reports (11).

The nitro group of 5-nitro-1,2,3-tribenzyloxybenzene was arbitrarily assigned to the 5-position by Baker, Nodzu, and Robinson (11). This was confirmed. 5-Nitro-1,2,3-tribenzyloxybenzene (15 g.) was heated at 65–70° for 1 hour with 100 ml. of acetic acid and 40 ml. of hydrochloric acid (d = 1.19). The reaction mixture was evaporated to dryness at 50°

in vacuo, the residue dissolved in boiling water, decolorized with Norit, and on cooling yellow needles crystallized. M.p. 203–204° [5-nitropyrogallol, reported m.p. 205° (14, 15)].

The 4-nitropyrogallol has the reported m.p. 162° (16).

1,3-Dibenzyloxy-2,5-dimethoxybenzene. This compound was prepared from 2,6-dibenzyloxy-*p*-hydroquinone in 75–95% yields in a 4-hour methylation, using sodium hydroxide and dimethyl sulfate at reflux temperatures. The previous procedure (11) required a low-temperature, 9-hour reaction.

2,5-Dimethoxyresorcinol. 1,3-Dibenzyloxy-2,5-dimethoxybenzene (11) (25.0 g.) was treated with hydrogen at 50 p.s.i. in 150 cc. of methanol, using 2 cc. of concentrated hydrochloric acid and 5.0 g. of 10% palladium charcoal at 50° until a quantitative uptake of hydrogen occurred. The catalyst was filtered off and the methanol removed by distillation. On triturating the residual oil with a little water, a white crystalline dihydrate was obtained, m.p. 62–63°. A quantitative yield was obtained. The compound has been previously prepared by acid hydrolysis (11).

2,4-Dihydroxy-3,6-dimethoxy-ω-chloroacetophenone (I). 2,5-Dimethoxyresorcinol (8.6 g.) was reacted in a modified Hoesch synthesis with 8 ml. of chloroacetonitrile and 4 g. of freshly fused zinc chloride in 200 ml. of dry ether at room temperature. Dry hydrogen chloride gas was bubbled through the reaction for 4 hours while the reaction mixture was continuously stirred. The reaction was allowed to stand overnight at room temperature. The ether layer was decanted from the oily precipitate; the oily residue was washed with ether and stirred into water. The water solution was kept at 80° for ½ hour. The crystalline acetophenone derivative separated to a major extent and after cooling was recovered by filtration. Ether extraction of the mother liquor gave a further small quantity of the compound. The 2,4-dihydroxy-3,6-dimethoxy-ω-chloroacetophenone could be recrystallized from boiling water, or after decolorization by carbon in acetone or ether, upon the addition of petroleum ether crystallized in creamy white needles. Yield, 6.3 g. (52%); m.p. 148–149°.

Anal. Calc'd for $C_{10}H_{11}ClO_5$: C, 48.8; H, 4.5.

Found: C, 48.9; H, 4.6.

4,7-Dimethoxy-6-hydroxy-3(2H)-benzofuranone (II). 2,4-Dihydroxy-3,6-dimethoxy-ω-chloroacetophenone (I) (6.2 g.) was refluxed for 20 hours in 250 ml. of 95% ethanol solution with 20 g. of sodium acetate (10). The reaction mixture was concentrated to dryness at 50° under a vacuum, and the residue extracted several times with boiling acetone. After decolorization and with the addition of petroleum ether the furanone crystallized in colorless needles. Yield, 3.1 g. (59%); m.p. 177–178°.

Anal. Calc'd for $C_{10}H_{10}O_5$: C, 57.1; H, 4.8; CH_3O, 29.5.

Found: C, 57.1; H, 5.1; CH_3O 28.2.

5-Acetyl-4,7-dimethoxy-6-hydroxy-3(2H)-benzofuranone (III). 4,7-Dimethoxy-6-hydroxy-3(2H)-benzofuranone (II) (1.5 g.) was reacted in a Hoesch condensation with acetonitrile. On hydrolysis of the imino complex a yellow precipitate was obtained. This was dissolved in acetone, decolorized with carbon, and precipitated with petroleum ether. Yield, 0.8 g. (44%) of poorly crystallized, yellowish scales; m.p. 80–84°.

Anal. Calc'd for $C_{12}H_{12}O_6$: CH_3O, 24.6. Found: CH_3O, 24.8.

3-Keto-3(2H)-dihydro-6-acetylkhellin or (6-acetyl-3(2H)-4,9-dimethoxy-7-methyl-5-furo[3.2-g][1]-benzopyran-3,5-dione). 5-Acetyl-4,7-dimethoxy-6-hydroxy-3(2H)-benzofuranone (III) (0.5 g.), 100 ml. of acetic anhydride, and 6 g. of freshly fused sodium acetate were heated in an oil-bath at 180° for 60 hours. After the removal of the excess anhydride the residue was treated with water, and the aqueous suspension was then extracted several times with ether. The ether extract was decolorized with carbon and diluted with petroleum ether when a yellow, crystalline product separated. This was extracted with 5% acetic acid to remove ash, washed with water, and dried. Yield, 200 mg. (32%); m.p. 145–146° (vacuum tube).

Anal. Calc'd for $C_{16}H_{14}O_7$: C, 60.4; H, 4.5; CH_3O, 19.5.

Found: C, 60.3; H, 4.8; CH_3O, 19.0.

3-Acetoxy-6-acetylkhellin or (3-acetoxy-6-acetyl-4,9-dimethoxy-7-methyl-5-furo[3.2-g][1]-

benzopyran-5-one). The mother liquor from the crystallization of 3-keto-3(2H)-dihydro-6-acetylkhellin gave 100 mg. of material on evaporation. Extraction of this residue with boiling hexane (60–72°) gave 3-acetoxy-6-acetylkhellin which crystallized in yellow needles. M.p. 118–120° (vacuum tube); yield, 60 mg.

Anal. Calc'd for $C_{18}H_{16}O_6$: C, 60.0; H, 4.5; CH_3O, 17.2.

Found: C, 60.6; H, 4.5; CH_3O, 16.8.

3,6-Diacetoxy-4,7-dimethoxybenzofuran (IV). Two grams of 4,7-dimethoxy-6-hydroxy-3(2H)-benzofuranone (II) was refluxed with 50 ml. of acetic anhydride and 5 ml. of acetyl-chloride. The reaction mixture was concentrated to dryness, water added, the mixture extracted with ether, and the extract concentrated to an oil. This was crystallized from acetone-petroleum ether or from petroleum ether. Yield, 1.95 g. (70%); m.p. 108–109°.

Anal. Calc'd for $C_{14}H_{14}O_7$: C, 57.2; H, 4.8; CH_3O, 21.1; CH_3CO, 29.4.

Found: C, 57.5; H, 5.0; CH_3O, 21.7; CH_3CO, 29.6.

6-Acetoxy-4,7-dimethoxydihydrobenzofuran (V). 3,6-diacetoxy-4,7-dimethoxybenzofuran (IV) (2.0 g.) in acetic acid was reduced at 50 p.s.i. with hydrogen at 30° using a platinum oxide catalyst. The theoretical amount of hydrogen required to saturate the double bond in the furan ring was taken up in 1 hour. The catalyst was removed and the product concentrated to an oil. This was crystallized from ethanol-petroleum ether, and on recrystallizing twice from the same solvents, fine, colorless needles were obtained, m.p. 89–90°. Mixed melting point with the starting compound, m.p. 108–109°, gave a depression, m.p. 72–78°. Yield, 0.4 g. (23%). In the experiments the yield varied from 0–40%.

Anal. Calc'd for $C_{12}H_{14}O_5$: C, 56.3; H, 6.2; CH_3O, 24.2; CH_3CO, 16.8.

Found: C, 56.6; H, 5.8; CH_3O, 24.4; CH_3CO, 16.1.

4,7-Dimethoxy-6-hydroxydihydrobenzofuran (VI). 6-Acetoxy-4,7-dimethoxy-3-hydroxy-dihydrobenzofuran (V) (0.8 g.) was saponified in 50 ml. of ethanol with 10 ml. of 5% sodium hydroxide solution at 70° for 3 hours. The recovered product was crystallized from acetone and petroleum ether. Yield, 0.5 g. (82%); m.p. 114–115° [reported m.p. 114° (6)].

Anal. Calc'd for $C_{10}H_{12}O_4$: C, 61.2; H, 6.2; CH_3O, 31.6.

Found: C, 61.3; H, 6.2; CH_3O, 30.7.

Acetylation of 4,7-dimethoxy-6-hydroxydihydrobenzofuran (VI) gave the 6-acetoxy-4,7-dimethoxydihydrobenzofuran monohydrate (V); m.p. 88–89°.

5-Acetyl-6-hydroxy-4,7-dimethoxydihydrobenzofuran (VII). 4,7-Dimethoxy-6-hydroxy-dihydrobenzofuran (VI) (200 mg.) was reacted in a Hoesch condensation with acetonitrile. The imino complex was hydrolyzed with water at 80° for 1 hour. On cooling, a yellow, crystalline compound separated which was recrystallized from acetone and petroleum ether. Yield, 120 mg. (50%); m.p. 104–104.5° [reported m.p. 105° (6)].

Anal. Calc'd for $C_{12}H_{14}O_5$: CH_3O, 26.1. Found: CH_3O, 25.9.

2-Benzyloxy-4-hydroxy-3,6-dimethoxyacetophenone and 4-benzyloxy-2-hydroxy-3,6-dimethoxyacetophenone (XII). 2,4-Dihydroxy-3,6-dimethoxyacetophenone (XI) (10.8 g.), 21.5 g. of powdered potassium carbonate, and 6.5 g. of benzyl bromide were refluxed in 120 ml. of dry acetone for 1½ hours. The reaction was filtered and the acetone solution concentrated to dryness. A small quantity of water was added and the oily residue crystallized. It was washed with water and dried. Crude yield, 10.5 g. (68%); m.p. 103–105°. Purification and recrystallization from acetone and petroleum ether gave colorless needles with m.p. 105–107°. The mixture could not be separated.

Anal. Calc'd for $C_{17}H_{18}O_5$: C, 67.5; H, 6.0.

Found: C, 68.0; H, 6.2.

2-Benzyloxy-4-acetoxy-3,6-dimethoxyacetophenone and 3-acetyl-7-benzyloxy-5,8-dimethoxy-2-methylchromone (XIII). The mixture of benzyloxyhydroxydimethoxyacetophenones (10.6 g.), obtained in the preceding experiment, was refluxed at 170° (oil-bath) with 400 ml. of acetic anhydride and 50 g. of fused sodium acetate for 70 hours. The excess anhydride was removed under a vacuum, water was added to the residue, the mixture was extracted with ethyl acetate, and the extract concentrated to an oil. This slowly crystallized from ethyl acetate containing an excess of petroleum ether. Crude yield, 11.0 g.

A 6.5-g. sample of the crude mixture obtained above was extracted three times with 100-

ml. portions of hot hexane (60–72°). The first extract, 1.5 g. of 2-benzyloxy-4-acetoxy-3,6-dimethoxyacetophenone, was repeatedly decolorized in ethyl acetate solution and crystallized from hot petroleum ether as colorless needles. M.p. 113–114°.

Anal. Calc'd for *2-benzyloxy-4-acetoxy-3,6-dimethoxyacetophenone* $C_{19}H_{20}O_6$: C, 66.1; H, 5.8; CH_3O, 18.1.

Found: C, 65.9; H, 5.6; CH_3O, 18.1.

The second extract, 2.5 g., was a mixture and was not investigated further.

The third extract, 1.0 g., was taken up in hot petroleum ether, decolorized with carbon, and cooled. The pale yellow crystals obtained were washed several times with ethyl ether to yield almost colorless plates. Yield, 0.4 g. of 3-acetyl-7-benzyloxy-5,8-dimethoxy-2-methylchromone (XIII); m.p. 149–150°.

Anal. Calc'd for *3-acetyl-7-benzyloxy-5,8-dimethoxy-2-methylchromone* (*XIII*) $C_{21}H_{20}O_6$: C, 68.4; H, 5.5; CH_3O, 16.8.

Found: C, 68.0; H, 5.6; CH:O, 16.8.

3-Acetyl-5,8-dimethoxy-7-hydroxy-2-methylchromone (XIV). Due to the difficulty of separation, 1.0 g. of the crude mixture of 2-benzyloxy-4-acetoxy-3,6-dimethoxyacetophenone and 3-acetyl-7-benzyloxy-5,8-dimethoxy-2-methylchromone (XIII) was treated with 25 ml. of acetic acid and 7 ml. of concentrated hydrochloric acid at 70–80° for 1 hour. The reaction mixture was concentrated to dryness under a vacuum and the residue taken up in ethyl acetate. The addition of petroleum ether caused crystallization of a mixed product. The chromone was less soluble in ethyl acetate at 25° than the debenzylated by-product. Repeated extractions of the mixed crystals with cold ethyl acetate and final recrystallization from hot ethyl acetate and petroleum ether gave colorless plates of the chromone (XIV). Yield, 100 mg.; m.p. 219–220°.

Anal. Calc'd for $C_{14}H_{14}O_6$: C, 60.4; H, 5.0; CH_3O, 22.3.

Found: C, 60.4; H, 4.8; CH_3O, 21.6.

7-Acetoxy-5,8-dimethoxycoumarin. 2,4-Dihydroxy-3,6-dimethoxybenzaldehyde (10 g.), fused sodium acetate (15 g.), and 150 ml. of acetic anhydride were refluxed for 16 hours at an oil-bath temperature of 180°. The excess anhydride was evaporated off *in vacuo*, and the residue was treated with 0.5% sodium hydroxide solution. The resulting solid (8 g.) was dissolved in ethanol; after decolorizing, the solution gave three crystalline fractions.

Fraction (A) was identified as the *coumarin*, m.p. 181–183°, which was recrystallized twice from ethanol. Yield, 2.3 g. (18%); m.p. 186–186.5°.

Anal. Calc'd for $C_{13}H_{12}O_6$: C, 59.1; H, 4.6; CH_3O, 23.5.

Found: C, 59.1; H, 4.5; CH_3O, 22.9.

4,6-Diacetoxy-2,5-dimethoxybenzaldehyde diacetate. Fraction (B) in the preceding synthesis was recrystallized from ethanol. Yield, 1.6 g. (8%); m.p. 131–131.5°.

Anal. Calc'd for $C_{17}H_{20}O_{10}$: C, 53.2; H, 5.2; CH_3O, 16.2; CH_3CO, 44.7.

Found: C, 53.6; H, 5.2; CH_3O, 16.2; CH_3CO, 45.8.

Fraction (C) was impure fraction (B), 4.2 g. (22%).

3-Acetyl-2,5-dimethoxy-4,6-dihydroxybenzaldehyde. 2,4-Dihydroxy-3,6-dimethoxyacetophenone (XI) (3.0 g.), zinc cyanide (6.0 g.), and potassium chloride (0.45 g.) were suspended in 100 ml. of dry ether. Anhydrous aluminum chloride (6 g.) in 150 ml. of dry ether was added. Dry hydrogen chloride gas was passed in for 4 hours and the product worked up as for (I). A small quantity crystallized from water. Recrystallization from ether-petroleum ether gave colorless needles. Yield, 0.6 g. (17%); m.p. 86–87°. Yields varied from 0–17%, and replacement of part of the ether by ethyl acetate did not increase the yield.

Anal. Calc'd for $C_{11}H_{12}O_6$: C, 55.0; H, 5.0.

Found: C, 55.1; H, 5.6.

2,4-Diacetoxy-3,6-dimethoxyacetophenone. 2,4-Dihydroxy-3,6-dimethoxyacetophenone (XI) (5.0 g.), acetic anhydride (100 ml.), and sodium acetate (10.0 g.) were heated together in an oil-bath (180°) for 2 hours. The reaction mixture was cooled, poured into water, and after 4 hours extracted with ether. The ether extract deposited two compounds on concentration. One was a yellow, amorphous material which was very soluble in ether. The

solid mixture was washed with cold ether, and the residue was a white, crystalline product which was recrystallized from petroleum ether. Yield, 0.7 g. (10%); m.p. 79–80°.

Anal. Calc'd for $C_{14}H_{16}O_7$: C, 56.8; H, 5.4; CH_3O, 20.9.
Found: C, 57.0; H, 5.8; CH_3O, 20.0.

This compound did not give a reliable acetyl analysis.

2,4-Dicarboxymethoxy-3,6-dimethoxyacetophenone. 2,4-Dihydroxy-3,6-dimethoxyacetophenone (XI) (3.0 g.), ethyl monobromoacetate (3.0 g.), and potassium carbonate (5.0 g.) in 50 ml. of acetone were refluxed for 3 hours and filtered. The residue was extracted with boiling acetone and concentrated *in vacuo* to an oil. The oil was purified by exhaustive precipitation successively from ether-petroleum ether and ethyl acetate. The final precipitate was heated with 5% sodium hydroxide solution and acidified with hydrochloric acid. The purified oil was then crystallized as colorless masses from ethyl acetate-ethyl alcohol by the addition of petroleum ether. Yield, 0.48 g. (10%); m.p. 96°; resolidifies and remelts 143–150° with decomposition.

Anal. Calc'd for $C_{14}H_{16}O_9 + \frac{1}{2}\ C_2H_5OH$: C, 51.2; H, 5.4; apparent CH_3O, 20.9.
Found: C, 51.4; H, 5.2; apparent CH_3O, 21.1, 20.7.

2,4-Dihydroxy-3,6-dimethoxy-ω-bromoacetophenone. 2,4-Dihydroxy-3,6-dimethoxyacetophenone (XI) (4.0 g.) and N-bromosuccinimide (4.0 g.) were refluxed in 100 ml. of carbon tetrachloride for 2 hours. The reaction mixture was concentrated to dryness *in vacuo*, dissolved in ethanol, and poured into an excess of water. The alcohol was distilled off, and the product crystallized directly from water. It was decolorized in acetone solution and recrystallized from water, m.p. 158–159°; from acetone and an excess of petroleum ether, m.p. 159–160°; yield, 3.5 g. (64%).

Anal. Calc'd for $C_{10}H_{11}BrO_5$: C, 41.3; H, 3.8; CH_3O, 21.3.
Found: C, 41.5; H, 3.7; CH_3O, 21.1.

2,4-Dihydroxy-3,6-dimethoxypropiophenone. This compound was obtained in 63% yield from a Hoesch condensation, using propionitrile (15.0 ml.) and 2,5-dimethoxyresorcinol (12.0 g.), m.p. 126–127°.

Anal. Calc'd for $C_{11}H_{14}O_5$: C, 58.4; H, 6.2; CH_3O, 27.4.
Found: C, 58.0; H, 6.2; CH_3O, 26.3.

3,4,5-Tribenzyloxyaniline hydrochloride. 5-Nitro-1,2,3-tribenzyloxybenzene (50.0 g.) was added to 200 ml. of boiling ethanol, and 50 ml. of a saturated solution of sodium hydrosulfite ($Na_2S_2O_4$) was added. The suspension was then boiled ½ hour with stirring and filtered into water containing concentrated hydrochloric acid. The hydrochloride crystallized as colorless needles and was recrystallized by solution in boiling ethanol, decolorization with carbon, and filtration into 50 ml. of concentrated hydrochloric acid. Yield, 33.5 g. (66%); m.p. 165–169°.

Anal. Calc'd for $C_{27}H_{25}NO_3 \cdot HCl$: C, 72.3; H, 5.8; N, 3.2.
Found: C, 72.1; H, 5.9; N, 3.3.

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SUMMARY

Two new analogs of khellin, 3-keto-3(2H)-dihydro-6-acetylkhellin and 3-acetoxy-6-acetylkhellin, some new benzofuranones, dihydrobenzofurans, and some new chromones have been prepared.

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