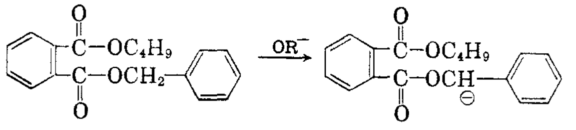
TABLE III

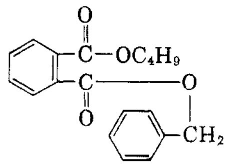
ALCOHOLYSIS OF HIGHER MOLECULAR WEIGHT ALKYL BENZYL PHTHALATES

| Starting Ester | Exchange Alcohol[a] | Catalyst % Conc. on Ester | Resulting Ester $D_{25}^{25}$ | Resulting Ester Theory yield | % of Theory ROH Removed[b] | ROH Removed $n_D^{25}$ |
|---|---|---|---|---|---|---|
| Benzyl 2-octyl phthalate | Tridecyl (oxo) alcohol | $NaOCH_3$, 0.8 | 1.0240 | 87 | 88.2 | 1.4292[c] |
| Benzyl isodecyl phthalate | Tridecyl (oxo) alcohol | $NaOCH_3$, 0.9 | 1.0232 | 81.6 | 82.8 | 1.378[d] |

[a] Exchange alcohol present in 1.2 mol. concentration per mol. of starting ester. [b] Reaction time in both cases was 4 hr., reaction conditions at end of alcoholysis was 185°/25 mm. in both cases. [c] $n_D^{25}$ pure 2-octanol, 1.4245. [d] $n_D^{25}$ commercial isodecyl(oxo)alcohol, 1.374.



It is entirely conceivable that the contribution of species like the anion shown above is pronounced in the reaction medium. Attack on this species by the alkoxide ion of the exchange alcohol should not result in attack at the carbonyl group of the benzyl ester because the required polarization would be inhibited by the already strong nucleophilic center about the benzyl anion. In addition, this anion derives resonance stabilization from the neighboring phenyl nucleus. This same inhibition to polarization of the carbonyl carbon of the benzyl ester may also be due to an inductive steric effect of the ring:



Thus, in this case the presence of the highly negative aromatic ring may, in part, negate the necessary polarization of the benzyl ester carbonyl carbon. Since this polarization is inhibited by either of the two factors already mentioned, the necessary attack by the alkoxide ion at the carbonyl carbon of the benzyl ester, which is a prerequisite of alcoholysis under these conditions, is inhibited, thereby resulting in the removal of the alkyl group only.

ST. LOUIS, MO.

---

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF UTAH]

# Compounds Related to Isopimpinellin

W. J. HORTON AND E. G. PAUL[1]

*Received July 27, 1959*

1,2,3,5-Tetramethoxybenzene (III) has been converted to 2,3-dihydroisopimpinellin in a number of steps, two of which employ selective cleavage of a methoxyl group. Acetylation of 4,6,7-trimethoxy-2,3-dihydrocoumarone (VIII) to dihydrokhellinone constitutes an improved method for this compound, an intermediate in the synthesis of khellin. The expected dehydrogenation of 2,3-dihydroisopimpinellin with a number of reagents failed to produce more than spectroscopic amounts of isopimpinellin (I).

The synthesis of furanocoumarins may employ either the appropriate coumarin or a benzofuran. Most of the published work has chosen the coumarin approach[2] due to the activity of the furan ring or the difficulty in dehydrogenation where 2,3-dihydrofuran is used. This latter problem was solved in a synthesis of khellin,[3] a furanochromone, by *N*-bromosuccinimide (NBS) dehydrogenation of an intermediate. Psoralene and related compounds have been produced by dehydrogenation over a palladium-carbon catalyst.[4]

Due to the advantages involved in benzenoid substitution in 2,3-dihydrobenzofuran, we have attempted this approach to isopimpinellin (I).[5] The synthesis was terminated when 2,3-dihydro-I failed to dehydrogenate by any of the variety of methods tried.

---

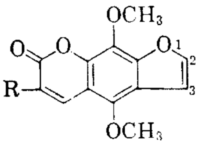
[1] From the Doctoral dissertation of E. G. Paul, National Science Foundation Cooperative Research Fellow, 1959–60.

[2] F. M. Dean, *Progr. in Chem. Org. Nat. Prod.*, **9**, 225 (1952).

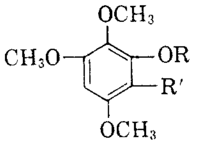
[3] T. A. Geissman and T. G. Halsall, *J. Am. Chem. Soc.*, **73**, 1281 (1951).

[4] E. C. Horning and D. B. Reisner, *J. Am. Chem. Soc.*, **72**, 1514 (1950).

[5] (a) Isopimpinellin has been obtained recently from xanthotoxin, M. E. Brokke and B. E. Christensen, *J. Org. Chem.*, **24**, 523 (1959), and earlier (b) from bergapten, F. Wessely and F. Kallab, *Monatsh. Chem.*, **59**, 161 (1932).

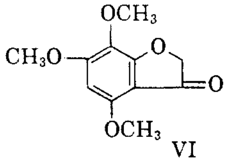


I. R = H
II. R = $CO_2H$

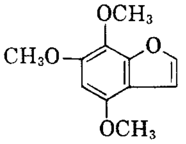


III. R = $CH_3$; R' = H
IV. R = $CH_3$; R' = $\underset{\overset{\|}{O}}{C}CH_2Cl$
V. R = H; R' = $\underset{\overset{\|}{O}}{C}CH_2Cl$

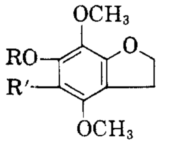
In the preparation of VI from III, the use of 1,3-bisbenzyloxy-2,5-dimethoxybenzene[3] was circumvented by the chloroacetylation of III, selective cleavage of IV by means of hydrogen bromide in acetic acid[6] to yield V and cyclization of V with sodium acetate.[7] Treatment of the coumaranone VI with lithium aluminum hydride gave the coumarone VII (77%) which was reduced over a palladium-carbon catalyst (96%) to give VIII. Reduction of the acetate of VI over platinum also gave VIII. The most convenient process was found to be the direct hydrogenation of VI over Raney nickel to VIII (89%).



VI



VII

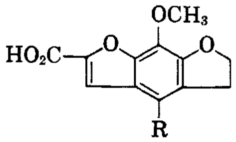


VIII. R = $CH_3$; R' = H
IX. R = $CH_3$; R' = CHO
X. R = H; R' = CHO
XI. R = H; R' = $\underset{\overset{\|}{O}}{C}CH_3$

The dihydrobenzofuran, VIII, reacted with *N*-methylformanilide to yield IX which was selectively cleaved to X by aluminum chloride. Condensation of X with cyanoacetic acid and hydrolysis of the nitrogenous product gave 2,3-dihydro-II. Decarboxylation[8] using sodium bisulfite with pyridine gave dihydro-I.

The conversion of VIII to 2,3-dihydrokhellinone in one step by acylation using boron trifluoride with simultaneous cleavage of the methoxyl at position 6 supports the proposed structure of VIII. This also constitutes a modification of Geissman's total synthesis of khellin in that dihydrokhellinone has previously been converted to khellin.[3]

Although dihydrokhellinone (as acetate) yields khellinone when treated with NBS,[3] the reagent on attempted dehydrogenation of dihydro-I gave 6-bromo-2,3-dihydro-I (52%), as did bromine in chloroform. The nature of the bromo compound was shown by conversion by base to a dihydrofuranocoumaric acid, XII.[9]



XII. R = $OCH_3$
XIII. R = H

Experiments with chloranil, lead tetraacetate, selenium dioxide, or palladium-carbon on dihydro-I gave only unreacted starting material with the last giving a minute amount of product having the ultraviolet spectra of isopimpinellin (I).[10] Similarly, 6-bromo- or 6-carboxy-2,3-dihydro-I failed to dehydrogenate with NBS. Financial support from the University Research Fund is gratefully acknowledged.

## EXPERIMENTAL[11]

*2,3,4,6-Tetramethoxy-α-chloroacetophenone* (IV). To a suspension of 70 g. of freshly fused zinc chloride in 250 ml. of anhydrous ether was added slowly with stirring 98 g. (0.494 mol.) of 1,2,3,5-tetramethoxybenzene (III) and 30.3 g. (0.401 mol.) of chloroacetonitrile. Dry hydrogen chloride was passed slowly through the suspension while stirring, causing refluxing of the ether. Within 1 hr. all material in the flask had solidified to a yellow mass. Hydrogen chloride addition was continued for an additional 5 hr. and the mixture was allowed to stand overnight.

The ether was decanted from the solids and the solids were washed with dry ether. The solids were then taken up in 1 l. of water and the aqueous solution was extracted three times with ether. The aqueous solution was warmed on the water bath for 1 hr. and the oil which separated was taken up in ether and benzene, dried, and the solvents were distilled. The residual oil IV was used directly in the subsequent step.

For analysis the material from a subsequent run was distilled, b.p. 162–165° (1 mm.) and then recrystallized from petroleum ether (b.p. 65–110°). Colorless clusters of rods, m.p. 55.6–56.4° were obtained.

*Anal.* Calcd. for $C_{12}H_{15}O_5Cl$: C, 52.46; H, 5.50. Found: C, 52.90; H, 5.66.

The ether extracts, combined with the ether decanted from the solids above, were distilled, and 20 g. of starting material was recovered. The residue from the distillation of III solidified and on recrystallization from ethanol, 0.89 g. of large colorless needles m.p. 152–153° was obtained.

---

(6) W. J. Horton and J. T. Spence, *J. Am. Chem. Soc.*, **77**, 2894 (1955).

(7) R. L. Shriner, E. J. Matson, and R. E. Damschroder, *J. Am. Chem. Soc.*, **61**, 2322 (1939).

(8) R. Adams and J. Mathieu, *J. Am. Chem. Soc.*, **70**, 2120 (1948).

(9) A bromo compound was similarly obtained from 2,3-dihydroxanthotoxin. M. E. Brokke and B. E. Christensen, *J. Org. Chem.*, **23**, 589 (1958). It seems likely that this compound is 6-bromo-2,3-dihydroxanthotoxin in that these authors converted the compound by means of base to a compound, $C_{12}H_{10}O_5$, for which we suggest the structure XIII.

(10) F. Wessely and J. Kotlan, *Monatsh. Chem.*, **86**, 430 (1955).

(11) Melting points of analytically pure materials are corrected.

Further crystallization from ethanol gave material melting at 152.1–152.9°. The compound contained chlorine but no nitrogen. It melted with depression when mixed with V or VI.

*Anal.* Calcd. for $C_{11}H_{13}O_5Cl$: C, 50.68; H, 5.03. Found: C, 51.03; H, 5.11.

This material proved to be identical to *2,4,6-trimethoxyphenyl chloroacetate. 2,4,6-Trimethoxyphenol*,[12] warmed with chloroacetyl chloride, gave after crystallization from alcohol, long colorless needles m.p. 152.0–153.1°.

*Anal.* Calcd. for $C_{11}H_{13}O_5Cl$: C, 50.68; H, 5.03. Found: C, 50.63; H, 4.99.

Mixed with the above Hoesch by-product, the sample melted at 151–153°.

*2-Hydroxy-3,4,6-trimethoxy-α-chloroacetophenone* (V). The crude IV above was allowed to stand in a solution of 1.4 l. of acetic acid and 285 ml. of 30% hydrogen bromide–acetic acid at room temperature for 4.5 hr.[6] Short thick yellow rods separated after 1 hr. The solution was poured into 4 l. of ice and water, filtered, and used directly in the next step.

Recrystallization of a sample from benzene produced yellow rods m.p. 165.8–167.2°. It gave a brown color in alcohol with ferric chloride.

*Anal.* Calcd. for $C_{11}H_{13}O_5Cl$: C, 50.68; H, 5.03. Found: C, 50.20; H, 4.87.

*4,6,7-Trimethoxycoumaranone* (VI). The unpurified V was refluxed on the steam bath for 2 hr. in 300 ml. of ethanol containing 33 g. of anhydrous sodium acetate. The solution was poured into 2 l. of ice and water and allowed to stand overnight at 5°. On filtration, 42.4 g. (37% from III; 48% from unrecovered III) m.p. 142–149° was obtained. Recrystallization from ethanol gave 36.3 g. of pale tan needles, m.p. 153–155°; reported[7] m.p. 153.5–154.5°.

The *acetate* of VI was prepared by heating 4.5 g. with 8.2 g. of acetic anhydride and 1.6 g. of pyridine on the water bath for 2 hr. After standing overnight, the solids were dissolved by warming on the steam bath. The solution, poured into 150 ml. of ice and water gave 2.4 g. (45%; crystallized from 1:2 ethanol water) of orange-red crystals, m.p. 93–96°. Further recrystallization from ethanol water gave long amber needles, m.p. 97.4–98.0°.

*Anal.* Calcd. for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.85; H, 5.36.

*4,6,7-Trimethoxybenzofuran* (VII). Five g. of VI was added in portions to a stirred suspension of 2 g. of lithium aluminum hydride in 200 ml. of anhydrous tetrahydrofuran. The reaction mixture was stirred for an additional 15 min., refluxed with stirring for 30 min., cooled, and treated with wet ether and water. After acidification with dilute hydrochloric acid, the solution was saturated with salt and the aqueous layer was extracted with ether and with benzene. The combined ether, benzene, and THF solution was washed with saturated salt and dried over sodium sulfate. The residual oil after distillation of the solvent, was sublimed at 95° (0.5 mm.) for 19 hr. yielding 3.58 g. (77%), m.p. 45–49°. Continued sublimation gave only starting material. Recrystallization from aqueous methanol and sublimation gave colorless rods, m.p. 49.0–50.2°.

*Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.59; H, 5.74.

*4,6,7-Trimethoxy-2,3-dihydrobenzofuran* (VIII). (a) Hydrogenation of 3.45 g. of VII over 1 g. of 5% palladium carbon in 50 ml. of ethanol at slightly above atmospheric pressure gave, after crystallization from 1:1 aqueous methanol, 3.35 g. (96%) of colorless rods, m.p. 64–65°. Further crystallization from this solvent and sublimation gave rods, m.p. 64.5–65.1°.

*Anal.* Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 63.13; H, 6.66.

(b) A solution of 11.2 g. of VI in 150 ml. of absolute ethanol with 5 g. of W-2 Raney nickel hydrogenated for 6 hr. at 95° under 400 lb. initial pressure gave 9.38 g. (89%) of VIII m.p. 64–65°. (c) The acetate of VI (0.67 g.) in 50 ml. of acetic acid containing 250 mg. of platinum oxide consumed 2 mol. of hydrogen when shaken at room temperature and slightly above atmospheric pressure. The product (0.25 g.) from 1:1 aqueous methanol melted at 62–65°, unchanged when mixed with material from (a).

*4,6,7-Trimethoxy-5-formyl-2,3-dihydrobenzofuran* (IX). The reagent was prepared by combining 9.1 g. of phosphorus oxychloride and 8.1 g. of *N*-methylformanilide and allowing it to stand at room temperature for 30 min. Ten g. of VIII was then added in portions with swirling after each addition. Occasional swirling in water was required to keep the solution cool. It was then stirred for 3 hr. at room temperature, allowed to stand overnight, and poured into 150 ml. of water. After stirring for 30 min., the solution was extracted with ether and with benzene, the ether benzene was washed with aqueous sodium bicarbonate, dried over sodium sulfate, and the solvents were removed by distillation. The residual amber oil was used below without further purification.

The *semicarbazone* of IX formed colorless needles from ethanol m.p. 194.5–196.0°.

*Anal.* Calcd. for $C_{13}H_{17}O_5N_3$: C, 52.87; H, 5.80. Found: C, 53.14; H, 5.91.

*4,7-Dimethoxy-6-hydroxy-5-formyl-2,3-dihydrobenzofuran* (X). The crude oil IX in 125 ml. of anhydrous ether was treated with a solution of 6 g. of anhydrous aluminum chloride in 125 ml. of dry ether and refluxed on the water bath for 9 hr. After standing overnight at room temperature the green complex was decomposed with dilute hydrochloric acid. The product was collected by extraction with benzene and with ether, the benzene ether was washed with saturated salt solution, and the solvents were removed by distillation. The solution of the residue in hot ethanol (carbon) gave on cooling 6.83 g. (64% from VIII), m.p. 115–120°. Further crystallization from ethanol water and benzene–petroleum ether (90–120°) gave yellow needles, m.p. 118.3–118.9°. A deep red-brown color was obtained with alcoholic ferric chloride.

*Anal.* Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 59.25; H, 5.53.

*2,3-Dihydro-6-carboxyisopimpinellin.* A suspension which contained 40 ml. of ethanol, 75 ml. of 20% aqueous sodium hydroxide, 6.8 g. of X, and 9.7 g. of cyanoacetic acid was warmed on the steam bath for 30 min. during which time the solids dissolved. After standing overnight at room temperature, the solution was poured into 200 ml. of 6*N* hydrochloric acid and diluted to 750 ml. This was refluxed with stirring for 40 min., cooled, and filtered. The yellow solid obtained weighed 7.60 g. (91%), m.p. 278–287°. Crystallization from ethanol produced microscopic yellow needles, m.p. 292–293.5°.[13]

*Anal.* Calcd. for $C_{14}H_{12}O_7$: C, 57.54; H, 4.14. Found: C, 57.35; H, 4.37.

*2,3-Dihydroisopimpinellin* (*dihydro-I*). A suspension of 2.2 g. of the above carboxylic acid in 20 ml. of 25% sodium bisulfite, 1 ml. of pyridine, and a trace of copper powder[8] was warmed on the water bath with occasional stirring until the solids dissolved and the yellow color had disappeared. After stirring for an additional 5 min. and boiling over a burner for 30 sec., 17 ml. of 50% potassium hydroxide was added dropwise causing the solution to boil. The solution was then boiled for 10 sec., cooled in an ice bath, and acidi-

---

[12] *2,4,6-Trimethoxyphenol* was prepared in 48.4% yield from III according to the method of C. D. Hurd and H. E. Winberg, *J. Am. Chem. Soc.*, 64, 2085 (1942). It formed colorless long thin prisms from cyclohexane-benzene, m.p. 61.9–63.5°. Alcoholic ferric chloride gave a brown color. *Anal.* Calcd. for $C_9H_{12}O_4$: C, 58.68; H, 6.57. Found: C, 59.14; H, 6.62. The *benzoate* formed colorless plates from methanol m.p. 97.0–98.4°. *Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.65; H, 5.60. Found: C, 66.78; H, 5.69.

[13] Taken on a Fisher-Johns Melting Point Block.

fied with concentrated hydrochloric acid. After cooling at −5° for 2 hr., filtration gave material which was crystallized from 250 ml. of 25% aqueous ethanol by concentration of the solution until the solid appeared. In this manner 1.48 g. (79%) of nearly colorless long needles m.p. 145–153° was obtained. Recrystallization from ethanol water gave long colorless needles, m.p. 156.6–157.4°; $\lambda_{\max}^{\text{alc}}$ 253, 262, 326 mμ (log ε, 3.82, 3.83, 4.17).

*Anal.* Calcd. for $C_{13}H_{12}O_5$: C, 62.90; H, 4.88. Found: C, 63.19; H, 4.86.

*6-Bromo-2,3-dihydroisopimpinellin.* (a) A solution of 1.0 g. of dihydro-I and 2.1 g. of bromine in 35 ml. of chloroform was evaporated to dryness on the steam bath. The residual solid in 500 ml. of ethanol was concentrated to the crystallization point. On cooling, 1.15 g. (87%) of light tan needles, m.p. 223–230°, was obtained. Crystallization from ethanol and again from benzene gave small light yellow needles, m.p. 231.2–233.0°.

*Anal.* Calcd. for $C_{13}H_{11}O_5Br$: C, 47.73; H, 3.39; Br, 24.43. Found: C, 47.73; H, 3.66; Br, 25.0.

The bromo compound was not effected by stirring with potassium iodide in acetone, by refluxing in ethanolic sodium acetate nor by refluxing in dimethylaniline. (b) After 90 min. refluxing of a solution of 250 mg. of dihydro-I in 10 ml. of dry carbon tetrachloride containing 0.09 ml. of pyridine, 200 mg. of NBS, and a trace of benzoyl peroxide, the cooled solution was filtered and the solid product was recrystallized to produce 130 mg. (52%), m.p. 227–232°, undepressed when mixed with material in (a).

*6-Carboxy-4,8-dimethoxy-2,3-dihydro[1,2-b,5,4-b′]difuran* (XII). Heating a mixture of 350 mg. of 6-bromo-2,3-dihydro-I and 20 ml. of sodium hydroxide for 90 min. on the steam bath gave, after cooling and acidification with hydrochloric acid, a yellow solid. This was redissolved in 5% aqueous sodium bicarbonate, reprecipitated with dilute sulfuric acid, and crystallized from aqueous ethanol to give 220 mg. (77%) of long yellow needles, m.p. 251–253°. Further crystallization from ethanol water gave light yellow needles, m.p. 247.0–247.2° (sealed cap).

*Anal.* Calcd. for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 59.31; H, 4.90.

*Attempted dehydrogenations.* (a) A solution of 100 mg. of dihydro-I and 110 mg. of chloranil in 10 ml. of xylene was refluxed on a sand bath for 12 hr. On cooling, the crystals which appeared melted, after purification with 25% ethanol water, at 157–159°, undepressed with the original material. From the xylene filtrate only dihydro-I could be found. The total recovery was 47 mg. (b) Dihydro-I (100 mg.) with 200 mg. of lead tetraacetate in 10 ml. of dry benzene at the reflux point for 30 hr. gave a yellow solid which was purified with difficulty. Crystallization from ethyl acetate gave an orange colored material, m.p. 125–145°, which was brought to m.p. 145–150° by crystallization from ethanol water and did not depress the melting point of the original compound. (c) Heating 148 mg. of dihydro-I with 150 mg. of 30% palladium carbon under nitrogen at 250° for 10 min. and at 320° for 5 min. gave material which melted at 141–145° after three crystallizations from ethanol and melted at 130–133° when mixed with 2,3-dihydroisopimpinellin. This material in ethanol gave maxima at 223, 240, 248, 266–271, and 311 mμ and nearly identical values in dioxan; reported for isopimpinellin[10] in dioxan, 242, 250, 268, and 308 mμ. Larger amounts of catalyst, temperatures above 250°, and extended time resulted in noncrystallizable material. Repeated chromatography on alumina with removal by means of 0.5–3% *tert*-butyl alcohol in benzene did not change the melting point of material melting at 138–142°. (d) The action of 45 mg. of selenium dioxide with 94.5 mg. of dihydro-I in 10 ml. of acetic anhydride refluxed for 2 hr. lead to the recovery of 63 mg. of material, m.p. 155–158°, with an ultraviolet spectra identical to dihydro-I.

*2,3-Dihydrokhellinone.* A stream of boron trifluoride was passed into a solution of 2.63 g. of VIII in 50 ml. of acetic acid and 3 ml. of acetic anhydride. The temperature was held to 35° and after 45 min., 38.5 g. of the gas had been absorbed. After standing at room temperature overnight, the solution was poured into 500 ml. of ice and water. The precipitated solid was crystallized from methanol water whereupon 1.9 g. (64%) was obtained as yellow plates m.p. 103–106°. Additional crystallizations from aqueous methanol gave large yellow plates, m.p. 103.5–104.5°; reported[3] m.p. 102–103°. A mixture with authentic material melted undepressed.[14]

*Anal.* Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.00; H, 5.85.

The *acetate* formed colorless plates from methanol-water, melting partially at 86° and completely at 96–97°. Sublimation produced colorless material m.p. 95.2–95.6°, not changed when mixed with an authentic sample.[14]

*Anal.* Calcd. for $C_{14}H_{16}O_6$: C, 59.99; H, 5.76. Found: C, 60.20; H, 5.71.

The *benzoate* formed colorless diamond shaped crystals from methanol m.p. 139.9–140.9°.

*Anal.* Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.88; H, 5.43.

SALT LAKE CITY 12, UTAH

---

[14] Samples of 2,3-dihydrokhellinone (m.p. 102–103°) and its acetate (m.p. 95–96°) were very generously supplied by Prof. T. A. Geissman.