151° (1 mm.), $n^{26}D$ 1.5531. The analytical sample was taken at 149° (1 mm.), $n^{25}D$ 1.5536.

Anal. Calcd. for $C_{16}H_{20}N_2O$: N, 10.93. Found: N, 11.16.

(3) **2-(*p*-Dimethylaminoethoxyphenyl)-pyridine.**—(a) 2-(*p*-Methoxyphenyl)-pyridine was prepared in 50% yield by the reaction of *p*-methoxyphenyllithium[9] and pyridine in xylene, essentially as described for 2-(phenyl)-pyridine[7]; b.p. 127–130° (0.5 mm.), m.p. 53–54° after recrystallization from benzene–petroleum ether, literature,[10] m.p. 49–50°.

Anal. Calcd. for $C_{12}H_{11}NO$: N, 7.57. Found: N, 7.67.

(b) **2-(*p*-Hydroxyphenyl)-pyridine.**—A solution of 8 g. of 2-(*p*-methoxyphenyl)-pyridine, 25 ml. of 48% hydrobromic acid and 25 ml. of glacial acetic acid was refluxed for 20 hours. The mixture was poured on ice, made alkaline with sodium hydroxide solution and, after ether extraction, was neutralized carefully with dilute hydrochloric acid. A tan solid precipitated; m.p. 148–153°. After recrystallization from benzene, the hydroxy compound was obtained as a white crystalline solid; yield 5 g. (68%), m.p. 164–165°.

Anal. Calcd. for $C_{11}H_9NO$: N, 8.18. Found: N, 8.47.

(c) **The 2-(*p*-dimethylaminoethoxyphenyl)-pyridine** was prepared by treating 16 g. (0.093 mole) of 2-(*p*-hydroxyphenyl)-pyridine, 14 g. (0.13 mole) of dimethylaminoethyl chloride and sodamide (3 g. of sodium) in 200 cc. of xylene as described previously; yield 13 g. (58%), b.p. 176–180° (2 mm.). The oil solidified and was recrystallized from benzene–petroleum ether, m.p. 52–53°.

Anal. Calcd. for $C_{15}H_{18}N_2O$: N, 11.56. Found: N, 11.26.

(4) **2-(*p*-Dimethylaminoethoxystyryl)-pyridine.**—This ether was obtained in a yield of 88% by the reaction of *p*-hydroxy-α-stilbazole[11] with sodamide and β-dimethylaminoethyl chloride in xylene, b.p. 182–192° (1 mm.), m.p. 70–71°, from benzene–petroleum ether.

Anal. Calcd. for $C_{17}H_{20}N_2O$: N, 10.44. Found: N, 10.67.

(5) **2-(*m*-Dimethylaminoethoxystyryl)-pyridine.**—*m*-Hydroxy-α-stilbazole was prepared according to the procedure described for the para isomer[11]; yield 20%, m.p. 137–138°.

Anal. Calcd. for $C_{13}H_{11}NO$: N, 7.10. Found: N, 7.32.

The alkamine ether was prepared in the manner described for the para compound and was obtained as a yellow oil; yield 43%, b.p. 182–186° (1 mm.).

Anal. Calcd. for $C_{17}H_{20}N_2O$: N, 10.44. Found: N, 10.01.

(6) **4-(*o*-Dimethylaminoethoxy-β-phenethyl)-pyridine.**—*o*-Hydroxydihydro-γ-stilbazole was converted to the corresponding alkamine ether as described; yield 85%, b.p. 160–164° (1 mm.).

Anal. Calcd. for $C_{17}H_{22}N_2O$: N, 10.36. Found: N, 10.42.

(9) Gilman, Zoellner and Selby, THIS JOURNAL, **55**, 1252 (1933).

(10) Haworth, Heilbron and Hey (*J. Chem. Soc.*, 358 (1940)) obtained 2-(*p*-methoxyphenyl)-pyridine by the fractional crystallization of the mixed picrates of 2- and 4-(*p*-methoxyphenyl)-pyridines, the latter being obtained by the action of diazotized *p*-anisidine on pyridine.

(11) Chiang and Hartung, *J. Org. Chem.*, **10**, 21 (1945).

BLOOMFIELD, NEW JERSEY RECEIVED SEPTEMBER 21, 1950

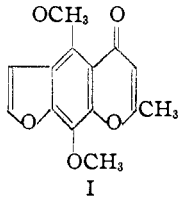
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF CALIFORNIA]

Chromones. III. A Total Synthesis of Khellin[1]

BY T. A. GEISSMAN AND T. G. HALSALL[2]

Interest in the chemistry of khellin (I) and of the related chromones which accompany it in the seeds of the umbelliferous plant *Ammi visnaga* has been heightened by the reports of the ability of khellin to produced a sustained coronary vasodilatation and to be effective in the clinical treatment of the anginal syndrome.[3] Preliminary studies indicate that the drug may be of potential usefulness in the treatment of other kinds of smooth muscle spasm.[4]

The structure of khellin has been elucidated by degradative methods by Späth and Gruber,[5] who also accomplished its partial synthesis by reconstruction of the chromone ring starting from khellinone (II), its alkaline degradation product.



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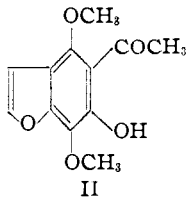


II

Because Späth and Gruber's resynthesis was not entirely unequivocal, the synthesis of khellin from khellinone was carried out by another method which established its structure as that of a 2-methylchromone.[1]

Although these results seemed to establish conclusively the structure of khellin, it appeared desirable to effect its total synthesis, partly to determine whether it might be prepared synthetically more advantageously than it could be isolated from the natural source, and partly to explore the synthetic methods with a view to the preparation of analogs. A study of the dependence of coronary activity upon structure should prove to be of considerable interest because of the nearly unique position of khellin in being a non-nitrogenous spasmolytic agent.

While the present work was in progress three reports[6,7,8] of the synthesis of khellin appeared from other laboratories. While all of these confirmed the structure I adopted for khellin, none appeared to have the potential utility as preparative routes as the method developed in this Laboratory, although the syntheses of Baxter, *et al.*, and Clarke and Robertson bear a similarity to ours in that all three proceed to khellinone by way of 2,5-dimethoxyresorcinol.[9] The elegant synthesis of Murti

(1) For the second paper in this series see Geissman and Hinreiner, THIS JOURNAL, **73**, 782 (1951).

(2) Visiting Fellow, 1949, from the University of Manchester, Manchester, England.

(3) For references to the clinical and pharmacological literature, see Anrep, Barsoum and Kenawy, *Amer. Heart. J.*, **37**, 531 (1949); Osher and Katz, *Boston Med. Quart.*, **1**, 11 (1950).

(4) Rosenman, Fishman, Kaplan, Levin and Katz, *J. Am. Med. Assoc.*, **143**, 160 (1950).

(5) Späth and Gruber, *Ber.*, **71B**, 106 (1938).

(6) Baxter, Ramage and Timson, *J. Chem. Soc.*, S30 (1949).

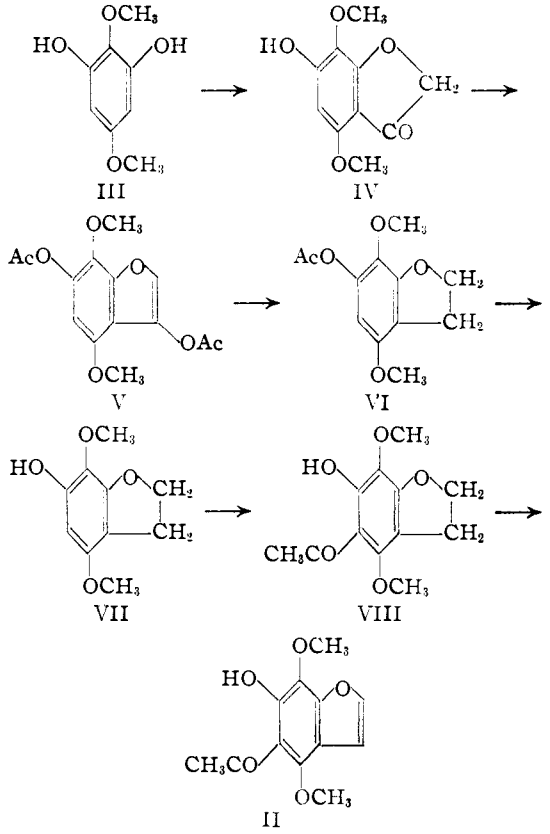
(7) Clarke and Robertson, *ibid.*, 302 (1949).

(8) Murti and Seshadri, *Proc. Indian Acad. Sci.*, **30**, 107 (1949).

(9) Baker, Nodzu and Robinson, *J. Chem. Soc.*, 74 (1929).

and Seshadri[8] follows an entirely different scheme, the *furo* ring being introduced in the last stage.

The steps in the presently described synthesis are represented in the chart



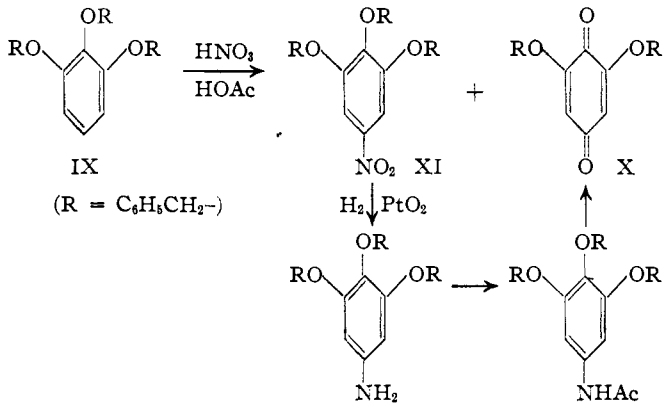
Both Baxter, *et al.*, and Clarke and Robertson proceeded to the coumarone ring *via* the aryloxyacetic ester derived from 3,6-dimethoxy-4-benzyloxysalicylaldehyde.[10,11] The former investigators then adopted a route leading to II through VIII and VII; the latter introduced the acetyl group directly into the open position of the ethyl 4,7-dimethoxy-6-hydroxycoumarone-2-carboxylate which was obtained by ring closure of the aryloxyacetic ester. Both of these routes have the disadvantage of requiring a considerable number of steps, in some of which unsatisfactory yields are obtained.

In the procedure shown in the series III → VIII → II above, the over-all yield of VIII from III is of the order of 10%. That even the improvement in the method of proceeding from III to VIII by the reduction of the coumaranone IV[12,13] is insufficient to make the production of khellin by synthesis a practicable source of the compound is clear when it is noted that the formation of III from pyrogallol[9] and the conversion of VIII into khellinone[6] involve a number of additional operations.

Considerable study was devoted to the problems involved in the preparation of 2,5-dimethoxyresorcinol (III). With the improvement in the yield of pyrogallol tribenzyl ether (IX) reported by Baxter, *et al.*,[6] the critical step in the preparation of III remains the oxidation of pyrogallol tribenzyl ether to 2,6-dibenzyloxybenzoquinone (X). Efforts were made in the present work to improve this step, but no variation in the conditions of the nitric acid oxidation or in the choice of (other) oxidizing agent used were found to lead to substantially better yields of X than those originally reported.[9] The troublesome separation of the quinone from 5-nitropyrogallol tribenzyl ether (XI), which is formed as a by-product in the oxidation of IX with nitric acid, was markedly improved by the extraction of the crude quinone with hot carbon tetrachloride. The nitro compound is selectively removed by this solvent leaving the quinone in a substantially pure state.[14]

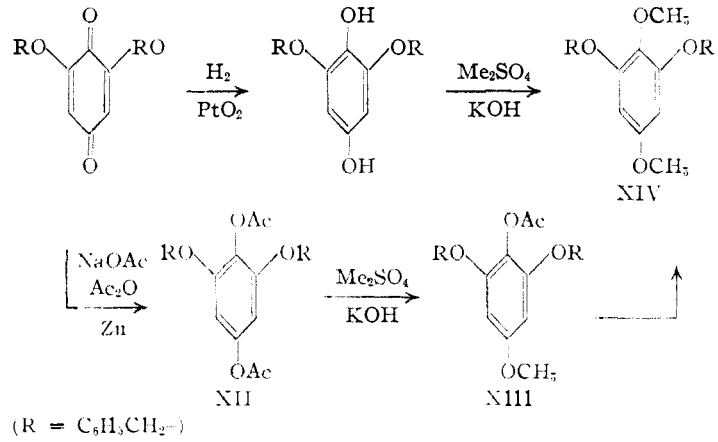
In the course of attempts to convert the otherwise useless 5-nitropyrogallol tribenzyl ether (XI) into the quinone it was found possible to isolate the latter in low yield from the oxidation of the acetylamino compound derived from XI. While no method was found to effect this conversion in practicable yields, the observation serves to substantiate the structure of XI as the 5-nitro-[9] rather than the 4-nitro derivative, an alternative not excluded on *a priori* grounds.

The reduction and methylation of the quinone (X) to 2,5-dimethoxyresorcinol dibenzyl ether (XII) can be carried out in an over-all yield of about 90%. The most practicable route involves the reduction of the quinone with Adams catalyst in methanol, followed by direct treatment of the resulting solution, after removal of the catalyst, with methyl sulfate and alkali. An alternative procedure is to reductively acetylate[15] the quinone to



the quinol diacetate (XII) and to carry out the concomitant deacetylation and methylation in a single operation.[15,16] This route has the advantage that unless a sufficiently large excess of alkali and sufficiently vigorous conditions are used the deacetylation–methylation may be incomplete. Indeed, in one run there was isolated in good yield 2-acetoxy-5-methoxyresorcinol dibenzyl ether (XIII). The reductive methylation of X was also examined,

(10) Reichstein, Oppenauer, Grüssner, Hirt, Rhyner and Glatthaar, *Helv. Chim. Acta*, **18**, 816 (1935).
(11) Howell and Robertson, *J. Chem. Soc.*, 293 (1937).
(12) Späth and Pailer, *Ber.*, **64**, 767 (1936).
(13) Horning and Reisner, THIS JOURNAL, **70**, 3619 (1948).
(14) Observation by Dr. R. M. Horowitz.
(15) Fieser, "Experiments in Organic Chemistry," 2nd Ed., D. C. Heath and Co., New York, N.Y., 1941, p. 399.
(16) Freudenberg, *Ann.*, **433**, 237 (1923).



with the use of sodium hydrosulfite, methyl sulfate and alkali. The desired ether XIV was obtained in moderate yield but the reaction was not studied in detail.

The conversion of III into the coumaranone (IV) was carried out by means of the Hoesch reaction, using chloroacetonitrile. The intermediate α-chloro-3,5-dimethoxyresacetophenone was isolated and characterized, but it was found convenient to treat the total crude product of the chloroacetylation reaction with alcoholic potassium acetate in the usual manner to complete the conversion to IV. The reduction of IV (as the acetate) was found to proceed smoothly and in good yield to VI. This coumarane, after removal of the acetyl group, was subjected to a Hoesch reaction with acetonitrile to yield dihydrokhellinone (VIII).

Dihydrokhellinone was dehydrogenated by Baxter, *et al.*,[6] by passing its vapor through a heated column of 30% palladium-on-charcoal. It was found possible in the present work to effect the dehydrogenation, although not in satisfactory yield, by the use of 30% Pd–C in refluxing Dowtherm.[17]

A new dehydrogenation procedure has been discovered in the use of N-bromosuccinimide (NBS). Treatment of dihydrokhellinone acetate with one equivalent of NBS in carbon tetrachloride yielded a non-crystalline, bromine-containing substance which after successive treatment with dimethylaniline and alcoholic alkali yielded crystalline but impure khellinone. The crude material was purified by passing its benzene solution through an alumina column, and the identity of the resulting material with khellinone established by comparison of its melting point, absorption spectrum, ferric chloride color and acetate with those of the natural material. The successful application of the NBS dehydrogenation to the synthesis of visnaginone is described in the preceding paper of this series.[18]

Experimental

Pyrogallol tribenzyl ether was prepared by Baxter, Ramage and Timson's modification[6] of the method of Baker, Nodzu and Robinson.[9] The oxidation of this ether to 2,6-dibenzyloxyquinone was carried out according to Baker, *et al.*[9]

2,6-Dibenzyloxyhydroquinone Diacetate (XII).—A mixture of 59 g. of 2,6-dibenzyloxyquinone, 30 g. of fused sodium acetate and 400 ml. of acetic anhydride was warmed on the steam-bath and to it was added in about 5-g. portions, with swirling, 50 g. of zinc dust, at such a rate as to maintain the temperature just below the boiling point (over about one-half hour). The yellow color of the quinone was discharged. After the mixture was refluxed for a further half hour it was filtered, the zinc being washed with hot glacial acetic acid. The clear, colorless filtrate was poured onto finely crushed ice and the mixture allowed to stand overnight. The precipitate of the diacetoxy compound was collected, washed thoroughly with water and dried in air. The yield was quantitative. Recrystallized from acetone, the compound forms colorless needles, m.p. 147–148°.

1,4-Dimethoxy-2,6-dibenzyloxybenzene (XII).—(A) To a warm, stirred suspension of 74 g. of 2,6-dibenzyloxyhydroquinone diacetate (XII) in 600 ml. of methanol was added 200 ml. of dimethyl sulfate. To the mixture was added a solution of 224 g. of potassium hydroxide in 800 ml. of 50% aqueous methanol at such a rate as to maintain vigorous refluxing. After all of the alkali had been added the heating was discontinued and the solution was stirred overnight. Most of the methanol was removed by distillation and water was added to precipitate the dimethyl ether as an oil, which crystallized on cooling. The product was collected and recrystallized from acetone–methanol. The yield was 50.5 g. (79%). In other runs, yields were generally of the order of 85%. The melting point of the purified 1,4-dimethoxy-2,6-dibenzyloxybenzene was 80° (lit.,[6] 82–83°) but products melting from about 76 to 78° were sufficiently pure for use in succeeding steps.

(B) A warm (50°) suspension of 16 g. of 2,6-dibenzyloxyquinone in 150 ml. of 95% ethanol was hydrogenated at slightly above atmospheric pressure in the presence of 200 mg. of Adams catalyst. Hydrogen uptake was rapid, being complete in about three minutes (about 20 minutes when carried out at room temperature), with the formation of a colorless solution. The solution was filtered into a nitrogen-filled flask containing 100 ml. of water, and 27 ml. of 28% aqueous sodium hydroxide was added with stirring. Thirty-one and one-half ml. of dimethyl sulfate was then added slowly, followed by 16.5 ml. of the sodium hydroxide solution. After about 3 hours a further 50 ml. of the alkali was added and the stirring was then continued overnight. Most of the alcohol was removed by distillation and water was added to the residue. The oil which precipitated crystallized on cooling. This was removed and the filtrate extracted with ether. There was obtained 14.0 g. (80%) of the dimethyl ether, m.p. 80°.

In a repetition of this experiment, 32.0 g. of the quinone (in two batches of 16.0 g. each) yielded 31.5 g. (90%) of the dimethyl ether, m.p. 80°.

2,5-Dimethoxyresorcinol (III) was produced in essentially quantitative yield by the catalytic (10% palladium–charcoal) debenzylation of XII. Since purification of the resorcinol was difficult to carry out without substantial losses, the crude material was used directly in the next step (Hoesch acylation). In one instance, however, it was characterized as the diacetate, **1,4-dimethoxy-2,6-diacetoxybenzene**; white needles from dilute methanol, m.p. 64°.

Anal. Calcd. for $C_{12}H_{14}O_6$: C, 56.67; H, 5.56. Found: C, 56.84; H, 5.97.

4,7-Dimethoxy-6-hydroxycoumaranone-3 (IV).—The dimethoxyresorcinol from the catalytic debenzylation of 35 g. of 1,4-dimethoxy-2,6-dibenzyloxybenzene was dissolved in 250 ml. of dry ether. To the solution were added 10.5 g. of chloroacetonitrile and 10 g. of fused, powdered zinc chloride. Dry hydrogen chloride was passed in for 3.5 hours, with vigorous stirring and ice–salt cooling. At the end of the first 90 minutes a solid began to separate. The ether was removed by decantation and the pale yellow solid washed with two portions of dry ether. The solid was dissolved in water and the resulting solution heated on the steam-bath for 1 hour. During this period a white solid appeared and then dissolved. Ten ml. of 6 *N* sulfuric acid was added and the heating continued for 90 minutes. The solution was decanted from a small amount of solid (A) and cooled. The solid (A) was retreated in the same manner. The precipitate (B) from the main solution was combined with the

(17) Horning and Reisner, THIS JOURNAL, **72**, 1514 (1950), have recently reported the dehydrogenation of dihydropsoralene with Pd-charcoal in diphenyl ether.

(18) Geissman and Hinreiner, *ibid.*, **73**, 782 (1951).

product from the retreatment of (A) and the total (15 g.) refluxed for 75 minutes with a solution of 20 g. of potassium acetate in 250 ml. of methanol. After removal of about half of the methanol by distillation the residual solution was cooled. The solid which separated was dissolved in water and the resulting solution extracted with ether (twice), ethyl acetate (twice) and chloroform (twice). The dried (calcium chloride) extracts were evaporated and the residual solid recrystallized from chloroform. The yield of 4,7-dimethoxy-6-hydroxycoumaranone-3, m.p. 181°, was 9.6 g. (46%).

Anal. Calcd. for $C_{10}H_{10}O_5$: C, 57.13; H, 4.80. Found: C, 56.95; H, 5.16.

4,7-Dimethoxy-3,6-diacetoxycoumarone (V).—A mixture of 5.9 g. of the coumaranone (IV), 6 g. of fused sodium acetate and 50 ml. of acetic anhydride was refluxed for 1.5 hours. After decomposition of the excess acetic anhydride with ice the solid (7.0 g.) was collected and recrystallized from aqueous methanol. The compound formed colorless plates, m.p. 108°.

Anal. Calcd. for $C_{14}H_{14}O_8$: C, 57.13; H, 4.80. Found: C, 57.09; H, 5.12.

4,7-Dimethoxy-6-acetoxycoumarane (VI).—A solution of 7.8 g. of the acetoxycoumaranone (V) in 150 ml. of glacial acetic acid was hydrogenated at atmospheric pressure and room temperature in the presence of 3 g. of 10% palladium–charcoal. The theoretical amount of hydrogen was absorbed in 6 hours. The solution was filtered and evaporated under reduced pressure. The residual oil (6.4 g., 87%) crystallized on cooling. Recrystallization from methanol afforded colorless prisms, m.p. 87–88.5°.

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.60; H, 5.95. Found: C, 60.41; H, 6.18.

4,7-Dimethoxy-6-hydroxycoumarone (VII) was prepared by saponification of the acetate (VI). The compound melted at 112.5–113° (Baxter, *et al.*,[6] report m.p. 114°). Although the compound was not new, a sample was analyzed.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.40; H, 6.16. Found: C, 61.55; H, 6.44.

Dihydrokhellinone (VIII).—(A) The Hoesch reaction with the dimethoxyhydroxycoumarane (VII) was carried out substantially as was done by Baxter, Ramage and Timson.[6] The product was recrystallized from aqueous methanol yielding pale yellow platelets, m.p. 102–103°. Dihydrokhellinone prepared from khellinone (from khellin[6]) melted at 102–103°, and a mixture of the natural and synthetic compounds melted at the same temperature.

(B) A solution of 1.29 g. of khellinone in 75 ml. of 95% ethanol was hydrogenated in the presence of 0.1 g. of Adams catalyst under slightly more than atmospheric pressure. The calculated amount of hydrogen was absorbed in 40 minutes, but the uptake had not stopped at this point. The reduction was interrupted, the solvent removed, and the crystalline residue recrystallized from aqueous methanol. The pale yellow product (1.02 g.) melted at 102–103°.

Anal. Calcd. for $C_{12}H_{14}O_6$: C, 60.45; H, 5.93. Found: C, 60.25; H, 5.76.

A sensitive test for the presence of khellinone in dihydrokhellinone depends upon the behavior of the two compounds with concentrated sulfuric acid. To about 1 mg. of khellinone in a 3-in. test-tube is added 5–6 drops of glacial acetic acid and 2 drops of concentrated sulfuric acid. The originally deep orange solution on standing overnight changes to a deep ink-blue solution. Dihydrokhellinone, treated in the same way, gives an initially pale yellow solution which is unchanged after 24 hours. Traces of khellinone in dihydrokhellinone give final colors which range from greenish-yellow to blue.

Khellinone (II). Dehydrogenation Experiments.—(A) Numerous experiments were performed in an attempt to devise a method of dehydrogenating dihydrokhellinone (a) with no solvent and (b) in a solvent. No khellinone could be isolated when the dehydrogenation of dihydrokhellinone was attempted in the following ways: (1) treatment with lead tetraacetate in hot acetic acid solution; (2) heating for 3 hours at 230° with 10% palladium–charcoal; (3) heating with 10% palladium–charcoal in refluxing mesitylene; (4) heating with 30% palladium–charcoal[19] in α-methylnaphthalene or α-bromonaphthalene.

(19) Linstead and Thomas, *J. Chem. Soc.*, 1127 (1940); catalyst-d.

(B) A mixture of 40 ml. of "Dowtherm" 405 mg. of dihydrokhellinone and 390 mg. of 30% palladium–charcoal[9] was boiled under reflux for 21 hours. The solution was cooled and filtered, the catalyst was washed with benzene, 1 *N* potassium hydroxide was added and the mixture steam distilled to remove benzene. The mixture was cooled, the alkaline layer was separated from the Dowtherm, again steam distilled to remove traces of Dowtherm, acidified and extracted with ether. Removal of the ether left a residue of oily crystals which was recrystallized from aqueous methanol. The crystallizate melted at 90–93° (mixed with khellinone, m.p. 92–95°; mixed with dihydrokhellinone, m.p. 80–89°); 65 mg. (16%) was obtained. After another recrystallization the product melted sharply at 95°. From absorption spectra measurements it was shown that this product is at least 95% pure khellinone.

Acetylation yielded khellinone acetate, m.p. 74–74.5°, not depressed on admixture with authentic khellinone acetate,[6] m.p. 75–76°.

(C) A solution of 386 mg. of dihydrokhellinone, 255 mg. of N-bromosuccinimide and a trace of benzoyl peroxide in 15 ml. of carbon tetrachloride was refluxed for 5 minutes. During this period the solution became brown, then colorless, and succinimide separated. The filtered solution was evaporated, leaving a nearly colorless oil (454 mg.). To this was added 8 ml. of purified dimethylaniline and the resulting solution was heated for 3 hours in a metal-bath at 210°. After cooling, the solution was added to ether and washed several times with 3 *N* sulfuric acid. The ether was removed and the residual oil heated on the steam-bath for 30 minutes with a solution of 1 g. of potassium hydroxide in 15 ml. of aqueous (1:1) methanol. The methanol was removed by distillation, water was added and the solution washed with ether and then acidified. Ether extraction, followed by removal of the ether, led to the isolation of an oil which slowly crystallized. The oil was dissolved in benzene and passed through a column of alumina, which removed some dark-colored impurities in a narrow, firmly-adsorbed band at the top of the column. From the eluate was obtained 72 mg. (22%) of khellinone, m.p. and mixed m.p. 92–94°. The admixture of dihydrokhellinone lowered the m.p. to 71–94°.

5-Aminopyrogallol Tribenzyl Ether.—The hydrogenation of 5-nitropyrogallol tribenzyl ether in ethyl acetate in the presence of Adams catalyst afforded a quantitative yield of the amino compound, m.p. (white needles from ethanol), 90–91°.

Anal. Calcd. for $C_{27}H_{25}O_3N$: C, 78.83; H, 6.08; N, 3.41. Found: C, 78.63; H, 6.17; N, 3.53.

5-Acetaminopyrogallol Tribenzyl Ether.—The amine (1.8 g.) was acetylated by refluxing for one-half hour with acetic anhydride (7.5 ml.), acetic acid (7.5 ml.) and a trace of zinc dust. The solid (1.95 g.) remaining after the decomposition of the acetic anhydride with ice-water was recrystallized from methanol: white needles, m.p. 124–125°.

Anal. Calcd. for $C_{29}H_{27}O_4N$: C, 76.79; H, 6.01; N, 3.09. Found: C, 76.83; H, 6.14; N, 3.19.

Oxidation Experiments with 5-Acetaminopyrogallol Tribenzyl Ether.—Oxidation with chromic acid in acetic acid and nitric acid in acetone resulted either in recovery of the starting material or extensive oxidation. In one experiment, 0.5 g. of the acetamino compound was dissolved in 15 ml. of glacial acetic, 5 drops on 6 *N* nitric acid was added and the solution was heated for 5 hours on the steam-bath. The solution was poured into water, ether was added and the yellow solid which separated (at the interface) was removed and recrystallized. The compound was shown (m.p. and mixed m.p.) to be 2,6-dibenzyloxyquinone.

NOTE ADDED IN PROOF.—Since this paper was submitted for publication, the preparation and reduction of the coumarone V has been described by Gardner, Wenis and Lee, *J. Org. Chem.*, 15, 841 (1950).

Acknowledgment.—The authors gratefully acknowledge the generosity of the Smith, Kline and French Laboratories and the S. B. Penick Co., who have furnished financial support and supplies of some of the materials used in this work. Analyses were performed by Mrs. Beatrice Kent

(U.C.L.A.) and the Clark Microanalytical Laboratories, Urbana, Illinois.

Summary

1. The total synthesis of khellinone has been carried out.

2. The nitro compound obtained as a by-product in the nitric acid oxidation of pyrogallol tribenzyl ether has been shown to be 5-nitropyrogallol tribenzyl ether.

3. The conversion of dihydrokhellinone to khellinone has been accomplished with the use of N-bromosuccinimide.

LOS ANGELES, CALIFORNIA RECEIVED JUNE 28, 1950

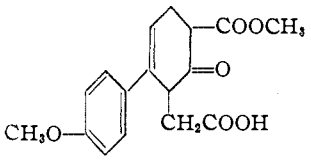
[CONTRIBUTION FROM THE CHARLOTTE DRAKE CARDEZA FOUNDATION, JEFFERSON MEDICAL COLLEGE]

Cyclized Products from the Stobbe Condensation with δ-Keto-esters

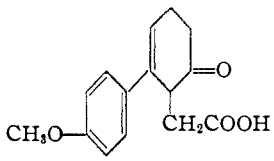
BY D. L. TURNER

The Stobbe condensation with methyl γ-anisoylbutyrate gives in addition to the normal products, a cyclized half-ester I, which can be converted to IIIb an important intermediate for a potential estrone synthesis. The normal Stobbe products are utilized to produce the same ester IIIb by a longer route. Similar cyclization occurs in the Stobbe condensation with methyl γ-benzoyl-β-phenylbutyrate. Finally, some furyl substituted benzoylbutyric acids are described.

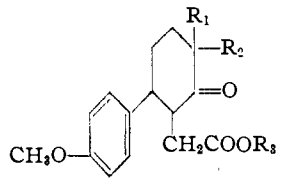
The Stobbe condensation with methyl γ-anisoylbutyrate, when carried out at a higher temperature, has been found to give, in addition to the normal product studied by Johnson, Jones and Schneider,[1] the cyclized ester I in a yield of about 15%. The isolation of this half-ester was facilitated by the insolubility of its potassium salt in *t*-butyl alcohol, the reaction medium. Hydrolysis of the half-ester proceeded as expected with the loss of the carbomethoxy group activated by the adjacent carbonyl group to give the acid II.



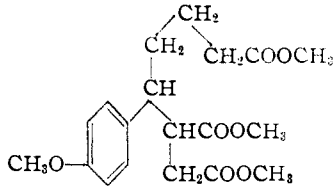
I



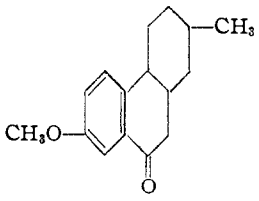
II



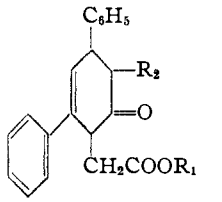
IIIa, R_1 = H, R_2 = $COOCH_3$, R_3 = CH_3
IIIb, R_1 = CH_3, R_2 = $COOCH_3$, R_3 = CH_3
IIIc, R_1 = CH_3, R_2 = R_3 = H



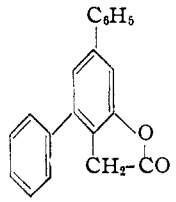
IV



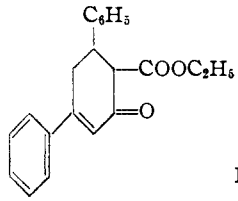
V



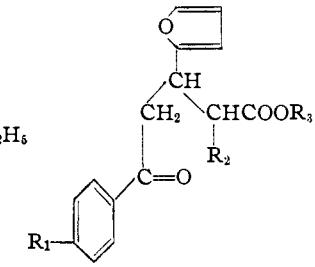
VIa, R_1 = H, R_2 = $COOCH_3$
VIb, R_1 = CH_3, R_2 = $COOCH_3$
VII, R_1 = R_2 = H



VIII



IX



X

The location of the double-bond in I is discussed below. The residual structure was conclusively shown by the following experiments. The unsaturated ester I was hydrogenated using palladium-on-strontium carbonate (2%) as catalyst[2,3] and esterified. The resulting keto-ester IIIa could not be obtained in crystalline form; however, methylation gave the crystalline homolog IIIb. This same product was also obtained by an alternative route utilizing the non-crystalline part of the half-esters from the Stobbe condensation. Reduction and esterification gave dimethyl β-carbomethoxy-γ-anisylsuberate (IV), which was cyclized and methylated to IIIb. W. S. Johnson[4] has prepared IIIb from the trimethyl ester of pure β-carboxy-γ-anisylsuberic acid[1] and has kindly established the identity of his product with the material described here.

The structure of IIIb was shown by conversion to 2-methyl-7-methoxyphenanthrene, identified as the trinitrobenzene complex by comparison with an authentic sample.[5] This conversion was effected by Clemmensen reduction of the crystalline hydrolysis product IIIc, followed by cyclization of the acid chloride by the Friedel–Crafts method

(1) W. S. Johnson, A. R. Jones and W. P. Schneider, THIS JOURNAL, **72**, 2395 (1950).

(2) A. Koebner and R. Robinson, *J. Chem. Soc.*, 1994 (1938).

(3) W. S. Johnson and H. Posvic, THIS JOURNAL, **69**, 1361 (1947).

(4) Private communication from Professor W. S. Johnson.

(5) I wish to thank Professor W. E. Bachmann, who kindly provided a sample of the trinitrobenzene complex of 2-methyl-7-methoxyphenanthrene.