visual observation.[3]) The point F corresponds to a sharp break in the curve and is attributed to the "Krafft effect" or solubilization of the undissociated molecule by the micelle. Significantly the critical-point curve HFI intersects the precipitation curve at this point. The portion of this curve FI represents critical points as observed in supersaturated solution. Point F occurs at a temperature very near 23° and at a concentration of 0.015 *N*. The very sharp break in the precipitation curve at point F can be interpreted as indicating no appreciable formation of micelles below the critical concentration.

The slowness with which precipitation occurred in solutions whose concentration was above the critical point can be explained on the basis that orientation in the micelle is tail-to-tail, whereas in dodecylammonium chloride (and probably in the hemihydrate) it is head-to-tail.[7] Conversion of micelle to crystal would thus involve passage of the individual molecule through the solution phase.

The portion of the precipitation curve to the left of E, the eutectic at 0.006 *N*, represents the liquidus along which ice separates.

The fact that the critical concentrations pass through a minimum with respect to temperature has been observed with other colloidal electrolytes.[8]

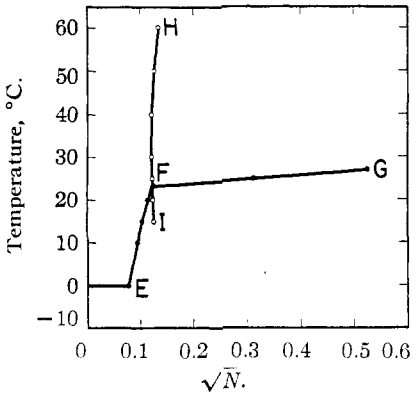


Fig. 3.—Critical points and precipitation points for aqueous solutions of dodecylammonium chloride.

Although no generalizations can be drawn, it appears evident that with dodecylammonium chloride in the range of concentrations studied micelle formation is the result of ionic aggregation plus solubilization of undissociated molecules. Further work will be directed toward a study of such solubilization and its influence on the properties of the solution.

(7) C. R. Hudgens, Abstract of Thesis, University of Illinois, 1950.

(8) A. P. Brady and H. Huff, *J. Colloid Sci.*, **3**, 511 (1948).

CHICAGO 9, ILL. RECEIVED DECEMBER 4, 1950

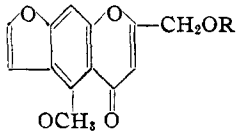
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

Chromones. IV. The Conversion of Khellol into Visnagin. Derivatives of Khellol and Visnagin

BY T. A. GEISSMAN

A number of derivatives of visnagin and khellol have been prepared for physiological studies. Khellol tosylate is a convenient intermediate for the preparation of some of these derivatives; and, in particular, by conversion into the iodo compound, followed by reduction of the latter, offers a practical means for converting khellol into visnagin.

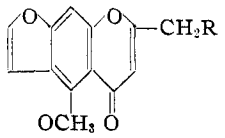
Of the three known furochromones present in the fruit of *Ammi visnaga*, khellol glucoside (I, R = $C_6H_{11}O_5$) is the most abundant.[1] While khellin, and to a lesser degree visnagin, shows therapeutic promise as a smooth muscle relaxant and coronary



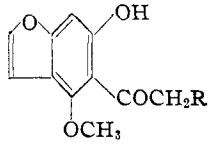
I

dilator,[2] the glucoside and the aglucone, khellol, are pharmacologically ineffective in these respects. Because of the possibility that compounds derived from khellol might prove to have physiological activity, and thus that the readily available glucoside would serve as a source of therapeutically useful khellin-like substances, a number of derivatives of khellol and visnagin were prepared for pharmacological studies.

These compounds were prepared in two ways: (1) by replacement of the hydroxyl-hydrogen atom of khellol (I, R = H) by a series of acyl residues; and (2) by the synthesis of chromones of the general structure II by partial synthesis starting from visnaginone[1b] (III, R = H) and by replacement of the hydroxyl group of khellol.



II



III

Khellol tosylate (I, R = *p*-toluenesulfonyl) proved to be of particular interest. It can be readily prepared in excellent yield; the replacement of the tosyloxy group provides a route to 2-methyl-substituted derivatives of visnagin; and it afforded a simple and effective means of converting khellol into visnagin. Reaction of the tosylate with sodium iodide and with aniline led, respectively, to II (R = I) and II (R = NHC_6H_5). When the iodo compound was treated with zinc dust in acetic acid, visnagin (II, R = H) was formed smoothly and in good yield. The same over-all result can be

(1) E. Späth and W. Gruber, (a) *Ber.*, **71**, 106 (1938); (b) **74**, 1492 (1941); (c) **74**, 1541 (1941).

(2) See G. V. Anrep, G. S. Barsoum and M. R. Kenawy, *Am. Heart J.*, **37**, 531 (1949).

obtained by treating khellol tosylate in acetic anhydride solution successively with sodium iodide and zinc dust.

The preparation of visnagin in this way is of particular interest since, although degradation experiments[1c] have established the structure of khellol beyond reasonable doubt, the conversion of khellol into visnagin provides confirmation of a quite different kind that khellol has the structure I (R = H). The structure of visnagin as II (R = H) has been independently confirmed by total synthesis.[3]

Khellol methyl ether was prepared by the C-acylation of visnaginone with methyl methoxyacetate in the presence of sodium, followed by the ring closure of the intermediate diketone (III), R = $COCH_2OCH_3$) to the chromone (I, R = CH_3).

The results of the pharmacological examination of these compounds will be described elsewhere.

Experimental[4]

Khellol.—The hydrolysis of khellol glucoside and the purification of the resulting khellol were studied in detail after it was found that published directions for these operations were very unsatisfactory. For example, the glucoside was recovered unchanged after four hours heating at 70° with 3% sulfuric acid.[1c] Consistent yields of about 50% were obtained by refluxing for 12 hours a solution of the glucoside (20 g.) in a mixture of water (500 ml.) and concentrated hydrochloric acid (5 ml.). The use of more acid or appreciably longer periods of refluxing resulted in lower yields of less pure aglucone and in the formation of black, tarry decomposition products. The best procedure devised is as follows:

To a suspension of 5.0 g. of khellol glucoside in 450 ml. of boiling water was added a solution of 15 g. of concentrated sulfuric acid in 40 ml. of water. The glucoside dissolved at once to give a solution which was yellow at first but gradually assumed a red color. After four hours refluxing the solution was placed in the refrigerator overnight. The deep pink, crystalline deposit was collected and dried; the yield was 2.3 g. (76%).

Purification.—Purification of crude khellol by recrystallization is unsatisfactory.[5] In a typical experiment, 6.3 g. of reddish-pink material was dissolved in 15 ml. of glacial acetic acid (deep red solution) and the solution diluted with 30 ml. of methanol. The product formed deep brown-red crystals (5.15 g.), m.p. 165–170°. Concentration of the mother liquor yielded additional crops of dark-colored material.

Khellol acetate[6] is readily prepared and easily purified, and it was found that dark pink to red samples of crude khellol were readily converted to clean, colorless acetate. The red material recovered from the recrystallization of 6.3 g. of crude khellol was boiled for 10 min. with 25 ml. of acetic anhydride and 5 g. of anhydrous sodium acetate. The pale brown solution was poured over ice and after the excess acetic anhydride had decomposed the light gray, crystalline acetate was collected and recrystallized from aqueous methanol with the use of Norite and Celite. The colorless crystalline product was dissolved in 25 ml. of methanol and to the warm solution was added 18.0 ml. of 0.1 *N* aqueous potassium hydroxide. Crystallization of khellol began almost at once. The mixture was kept at 5° overnight and the product collected. The nearly colorless khellol (4.15 g.) melted at 175° (reported,[1c] 178–179° when pure) and was pure enough for use in subsequent operations.

Khellol Chloroacetate (I, R = $COCH_2Cl$).—To an ice-cooled suspension of 1.9 g. of khellol in 10 ml. of dry pyridine was slowly added 3.0 ml. of freshly-prepared chloroacetic anhydride. The mixture was swirled until a clear solution resulted, removed from the ice-bath for 5 min., and then poured onto crushed ice. The crystalline solid was collected and dried; the yield was 2.3 g. Recrystallized from ethyl acetate–petroleum ether, the compound formed tiny buff needles, m.p. 138–138.5°.

Anal. Calcd. for $C_{15}H_{11}O_6Cl$: C, 55.82; H, 3.44; Cl, 10.99. Found: C, 55.86; H, 3.43; Cl, 10.83.

Khellol Iodoacetate (I, R = $COCH_2I$).—One gram of khellol chloroacetate was dissolved in 10 ml. of a 30% solution of sodium iodide in acetone. The solution was allowed to stand overnight and poured into a mixture of water and ether. The product was only slightly soluble in ether and separated in crystalline form. The solid was collected, combined with a further small amount obtained by evaporation of the ether layer, and recrystallized from ethyl acetate–petroleum ether and from benzene–petroleum ether. The pale yellow needles (0.80 g.) melted at 150–151°.

Anal. Calcd. for $C_{15}H_{11}O_6I$: C, 43.48; H, 2.67. Found: C, 43.78; H, 2.87.

Khellol Piperidinoacetate Picrate (I, R = $COCH_2N(CH_2)_5 \cdot HOPic$).—A solution of 1.0 g. of khellol chloroacetate and 1 ml. of piperidine in 20 ml. of dry benzene was allowed to stand for two days. The solution was diluted with ether and extracted with dilute aqueous hydrochloric acid. The addition of alkali to the acid extract resulted in the formation of an amorphous material which became gummy when dried. This was dissolved in methanol, the solution treated with dry hydrogen chloride and diluted with ether. The oily precipitate crystallized on standing but proved to be very hygroscopic. It was converted to the crystalline picrate by the addition of saturated aqueous picric acid to its aqueous solution. A sample of the picrate recrystallized from ethanol formed bright yellow needles, m.p. 214–215°.

Anal. Calcd. for $C_{20}H_{19}O_6N \cdot C_6H_3O_7N_3$: N, 9.37. Found: N, 9.55.

Khellol Acid Succinate (I, R = $COCH_2CH_2COOH$).—A solution of 0.5 g. of khellol, 0.5 g. of succinic anhydride in 5 ml. of dry pyridine was kept at room temperature overnight. The addition of water and dilute acid resulted in the formation of a crystalline precipitate. The product (0.6 g.) was recrystallized from dilute acetic acid; m.p. 196.5–197.5°.

Anal. Calcd. for $C_{17}H_{14}O_8$: C, 58.94; H, 4.08. Found: C, 58.29, 58.45; H, 4.24, 4.23.

Khellol Benzoate (I, R = COC_6H_5).—A mixture of 0.50 g. of khellol, 0.5 ml. of benzoyl chloride and 4 ml. of pyridine was refluxed for 5 min. and poured onto ice. The crystalline product (0.51 g.) was recrystallized twice from dilute methanol, from which it formed pale yellow needles, m.p. 144–145°.

Anal. Calcd. for $C_{20}H_{16}O_6$: C, 68.57; H, 4.05. Found: C, 68.73; H, 4.36.

Khellol *p*-Nitrobenzoate (I, R = $COC_6H_4NO_2$-*p*).—To a dry mixture of 1.7 g. of khellol and 2.0 g. of freshly prepared *p*-nitrobenzoyl chloride was added, with ice cooling, 10 ml. of dry pyridine. The mixture was warmed cautiously until solution was complete, then cooled in ice and diluted to 40 ml. with ether. The crystalline precipitate was collected (2.15 g.) and recrystallized from glacial acetic acid. The colorless silky needles turned pale yellow on drying at 56° (20 mm.) overnight, but the m.p. (210–211°) did not change.

Anal. Calcd. for $C_{20}H_{13}O_8N$: C, 60.75; H, 3.32; N, 3.54. Found: C, 60.71; H, 3.62; N 3.64.

Khellol *p*-Toluenesulfonate (I, R = $SO_2C_6H_4CH_3$-*p*).—To a mixture of 3.46 g. of khellol and 4.0 g. of *p*-toluenesulfonyl chloride was added 10 ml. each of dioxane, water and 6 *N* sodium hydroxide. The mixture was cooled in ice and shaken; the solids gradually dissolved and after a few minutes crystals began to appear. Water was added and after thorough cooling the product was collected, washed with water and dried. The crude material (5.3 g.) was recrystallized from acetic acid (30 ml.)–water (20 ml.). The buff platelets melted at 151–152° (4.35 g., 81%). A sample recrystallized from ethyl acetate formed nearly colorless leaflets, m.p. 152–153°.

Anal. Calcd. for $C_{29}H_{16}O_7S$: C, 60.00; H, 4.02. Found: C, 59.89; H, 4.09.

(3) W. Gruber and K. Horváth, *Monatsh.*, **80**, 874 (1949); J. S. H. Davies and W. L. Norris, *J. Chem. Soc.*, 3195 (1950); T. A. Geissman and E. H. Hinreiner, THIS JOURNAL, **73**, 782 (1951).

(4) Melting points are those observed on a 70 mm. immersion thermometer and may be regarded as "corrected."

(5) P. Fantl and S. I. Salem, *Biochem. Z.*, **226**, 166 (1930).

2-Anilinomethylnorvisnagin (II, R = NHC_6H_5).—A mixture of 1.0 g. of khellol tosylate, 2 ml. of purified aniline and 2 ml. of methanol was warmed until a clear solution resulted. Upon the addition of 10 ml. of ether and cooling the product separated as a crystalline powder. Recrystallized from glacial acetic acid, the compound forms tiny, nearly colorless prisms, m.p. 211–212°. The compound is insoluble in dilute aqueous acids, but when to a suspension of a small sample in methanol was added a drop of 6 *N* hydrochloride acid a clear solution resulted. This solution remained clear when diluted with water but became cloudy when a drop of dilute alkali was added.

Anal. Calcd. for $C_{19}H_{15}O_4N \cdot 0.5H_2O$: C, 69.07; H, 4.88; N, 4.24. Found: C, 68.97; H, 4.71; N, 4.70.

2-Iodomethylnorvisnagin (II, R = I).—To a warm solution of 1.0 g. of khellol tosylate in 20 ml. of dry acetone was added 2.0 g. of sodium iodide dissolved in 10 ml. of acetone. A thick crystalline magma formed at once. The mixture was warmed on the steam-bath for 5 min., allowed to stand overnight and poured into a water–ether mixture. The solid which separated (0.58 g.) and that recovered by evaporation of the ether layer (0.17 g.) were recrystallized from ethyl acetate. The tiny, pale yellow needles melted at 158–159° (dec.).

Anal. Calcd. for $C_{13}H_9O_4I$: C, 43.82; H, 2.55. Found: C, 43.95; H, 2.64.

Visnagin (II, R = H) **(A) from 2-Iodomethylnorvisnagin.**—To a solution of 280 mg. of the iodo compound in 5 ml. of glacial acetic acid, zinc dust was added in small portions while the solution was kept at the boiling point. The color of the solution went from yellow to brown and then to pale yellow. The zinc was removed by filtration, the filtrate poured into an ether–water mixture, and the ether solution separated, washed, dried and evaporated. The crystalline residue (155 mg.) was recrystallized from aqueous methanol and then from ethyl acetate–petroleum ether. The stout, colorless prisms melted at 139–140° alone or mixed with a sample of authentic visnagin. The absorption spectrum of the product showed maxima at 243 mμ (log ε 4.58) and 322.5 (log ε 3.71). A sample of synthetic visnagin (prepared from visnaginone) is reported to show a log ε of 4.59 at 244 mμ (the second maximum was not reported).[6] The absorption spectrum of khellol glucoside was determined for comparison, and showed maxima at 245 mμ (log ε 4.47) and 324 mμ (log ε 3.65).

(B) From Khellol Tosylate.—To a solution of 500 mg. of khellol tosylate in 5 ml. of acetic anhydride was added a hot solution of 1.0 g. of sodium iodide in 10 ml. of acetic anhydride. To the resulting brown solution (containing a colorless precipitate) was added zinc dust until the color changed to pale yellow. The mixture was filtered into a slurry of ice and water; as the acetic anhydride decomposed fine silky needles formed. After the mixture had stood overnight (at 5°) the product was collected and recrystallized from ethyl acetate–petroleum ether and from ethyl acetate. The colorless prisms melted at 138–140°, and did not depress the m.p. of authentic visnagin.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.80; H, 4.38. Found: C, 67.87, 67.70; H, 4.37, 4.67.

C-Methoxyacetylvisnaginone (III, R = $COCH_2OCH_3$).—To 2.0 g. of powdered sodium, covered with 20 ml. of dry ether, was added a solution of 3.0 g. of visnaginone in 10 ml. of methyl methoxyacetate. The vigorous reaction caused the ether to distil from the reaction flask, leaving a brown sirup. The addition of 20 ml. of dry ether to this sirup caused it to set to a yellow paste. After 12 hours at room temperature the reaction mixture was decomposed by the addition of ice, the aqueous layer was separated and washed with ether, and acidified. The mixture was extracted with ether and the ether solution dried and evaporated to 50 ml. Buff crystals separated on cooling, and a second crop was obtained by further concentration of the filtrate. The product was recrystallized from aqueous methanol (with the use of decolorizing carbon) and formed pale yellow, blunt needles, m.p. 127–128° (1.90 g.).

Anal. Calcd. for $C_{14}H_{14}O_5$: C, 60.43; H, 5.02. Found: C, 60.20; H, 5.32.

Khellol Methyl Ether (I, R = CH).—To a suspension of 500 mg. of the above diketone in 5 ml. of methanol was added 0.5 ml. of concentrated hydrochloric acid. The compound dissolved on warming to give a clear orange-yellow solution which was heated to boiling for about 2 min., cooled, and diluted with water. The excess acid was neutralized with dilute alkali and the solution (*ca.* 15 ml.) cooled. The nearly colorless, soft needles (430 mg.) were collected and recrystallized from ethyl acetate–petroleum ether. The compound formed soft, white needles, m.p. 124–125°.

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.65; OCH_3, 23.84. Found: C, 64.62; H, 4.76; OCH_3, 23.75.

Acknowledgment.—The author wishes to thank the Smith, Kline and French Laboratories and S. B. Penick and Company for financial assistance and for supplies of the khellol glucoside used in this work.

LOS ANGELES, CALIF. RECEIVED JANUARY 31, 1951

(6) Private communication from Drs. G. E. Ullyot and P. N. Craig.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

A Dodecitol from the Alkaline Electroreduction of D-Glucose[1,2]

BY M. L. WOLFROM, W. W. BINKLEY, C. C. SPENCER AND B. W. LEW

A crystalline substance, designated atlitol and obtained as a by-product in the commercial alkaline electroreduction of D-glucose, has been characterized as an optically active unbranched dodecitol.

The Atlas Powder Co. of Wilmington, Delaware, operates a process for producing D-mannitol by the electroreduction of D-glucose.[3,4] In a factory run made in 1939 a high melting material was obtained from the centrifuge in a recrystallization of D-mannitol. The substance was sent to this Laboratory for characterization. It was a crystalline, non-reducing, optically active, high melting substance of low water solubility that was unchanged by acid treatment. It formed a crystalline acetate whose analysis (and that of the parent body) and molecular weight indicated a dodecitol. Periodate assay showed the consumption of essentially 11 moles (per mole of substance) of oxidant with the production of 10 moles of formic acid and 2 moles of formaldehyde; carbonic, oxalic or glycolic acids were not detected in the oxidation mixture. The substance showed a tendency to over-oxidize slightly and to analyze somewhat low on formic acid. Nevertheless, it is believed that the cited figures are essentially correct and it is to

(1) A preliminary report of this work is recorded in *Abstracts Papers Am. Chem. Soc.*, **119**, 6Q (1951).

(2) Paper No. 5 in the series entitled "Sugar Interconversion under Reducing Conditions"; previous communication, M. L. Wolfrom, B. W. Lew, R. A. Hales and R. M. Goepp, Jr., THIS JOURNAL, **68**, 2342 (1946).

(3) H. J. Creighton, U. S. Patent 1,990,582 (1935).

(4) H. J. Creighton, *Trans. Electrochem. Soc.*, **75**, 289 (1939).