−92°, $[\alpha]^{25}_{436}$ −195° (*c* 1.13); reported:[23] $[\alpha]^{25}_{589}$ −95.1°, $[\alpha]^{25}_{436}$ −206°. It formed a picrate from ethanol, m.p. 201–202°; reported:[23] m.p. 201–202°.

Acknowledgment. We are indebted to Drs. J. Renz and D. Stauffacher of Sandoz A. G., Basel, Switzerland for authentic samples of buphanidrine and buphanamine for comparison purposes and for a very generous quantity of the latter alkaloid which enabled us to complete our structural studies. We wish to thank Dr. W. I. Taylor, Ciba Pharmaceutical Products, Inc., Summit, N. J., for a sample of his *Boöphone* alkaloid, m.p. 189°. Isolation of the crude alkaloid fraction was performed by Mr. D. L. Rogerson.

BETHESDA 14, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, CAIRO UNIVERSITY, AND THE LABORATORIES OF THE MEMPHIS CHEMICAL CO.]

Experiments with Furochromones. Synthesis of Ammiol and Khellol

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The syntheses of ammiol (Va) from khellin (Ia), and of khellol (Vb) from visnagin (Ib) are given. Treatment of the 2-formyl derivatives of 5,8-dimethoxy- (IVa) and 5-methoxyfuro-4′,5′,6,7-chromone (IVb) with ammoniacal silver nitrate solution effected their oxidation to the corresponding carboxylic acid derivatives (VIa-b) respectively.

Demethylation of Ia and of Ib is now reported to occur upon prolonged treatment with aluminum isopropoxide, to give 5-norkhellin (XIa) and 5-norvisnagin (XIb) respectively.

Khellin (Ia), visnagin (Ib), and khellol (Vb), which can be obtained from the Egyptian plants *Ammi visnaga* (L.) are now available in quantity, and a number of degradations and similar reactions have been carried out with these three substances with the view of obtaining products which may be useful as medicinals or in further syntheses.[1a–c] Recently, Seitz,[2] upon a chromatographic fractionation of a crude khellin on alumina, has succeeded in isolating a new natural furochromone derivative, ammiol (Va), which displays the same relationship to Ia as Vb to Ib.

The present investigation deals with the synthesis of 2-hydroxymethyl-5,8-dimethoxyfuro-4′,5′,6,7-chromone (Va) by an unambiguous method, and with the study of its isolation as a free constituent in the total extracts of *Ammi visnaga* (L.) grown in Egypt.

In this synthesis, namely of Va, the route applied to 2-methylchromone by Schmutz, Hirt, and Lauener[3] for the synthesis of 2-oxochromones has been followed (*cf.* Chart 1). Treatment of Ia with iodine[4] in pyridine led to the formation of 1-(4-oxo-1,4H-5,8-dimethoxyfuro-4′,5′,6,7-chromene-2-ylmethyl)-pyridinium iodide (IIa). The latter, upon treatment with sodium carbonate, gave khellinone (VIIa), and, when heated with sodium sulfite solution, 4,7-dimethoxy-6-hydroxybenzofuran-5-carboxylic acid[1a] together with VIIa. IIa was then condensed with *p*-nitrosodimethylaniline in the presence of sodium carbonate to give 5,8-dimethoxyfuro-4′,5′,6,7-chromone-2-*p*-dimethylaminophenylazomethine (IIIa).[5] Attempts to prepare the Schiff bases directly from Ia and from Ib by the Ehrlich-Sachs reaction in aqueous ethanol in the presence of sodium carbonate, as well as in anhydrous methanol in the presence of anhydrous potassium carbonate[6] did not lead to the expected products. IIIa was treated with 10*N* sulfuric acid to yield 2-formyl-5,8-dimethoxyfuro-4′,5′,6,7-chromone (IVa), which gave with the common aldehyde reagents the corresponding derivatives.

Reduction of the formyl derivative IVa with aluminum isopropoxide led to an almost quantitative yield of ammiol (Va), proved to be identical with the natural product.[7] On the other hand, reduction of IVa with zinc dust and glacial acetic acid effected the formation of a poor yield of Va, together with a sparingly soluble substance as the main product. The latter gave the correct analytical values for a glycol derivative of IVa, and its structure is under further investigation.

The structurally related analog of Va, namely, khellol (Vb), now has been, similarly, synthesized *via* the sequence of reactions described above (*cf.*

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[1] (a) A. Schönberg, N. Badran, and N. A. Starkovsky, *J. Am. Chem. Soc.*, **75**, 4992 (1953); (b) *J. Am. Chem. Soc.*, **77**, 5390 (1955). (c) For a review on this subject, *cf.* C. P. Huttrer and E. Dale, *Chem. Revs.*, **48**, 543 (1951), and H. Schmid, *Fortsch. Chem. organ. Naturstoffe*, II, 124 (1954).

[2] G. Seitz, *Arch. Pharm.*, **287**, 79 (1954).

[3] J. Schmutz, R. Hirt, and H. Lauener, *Helv. Chim. Acta*, **35**, 1168 (1952).

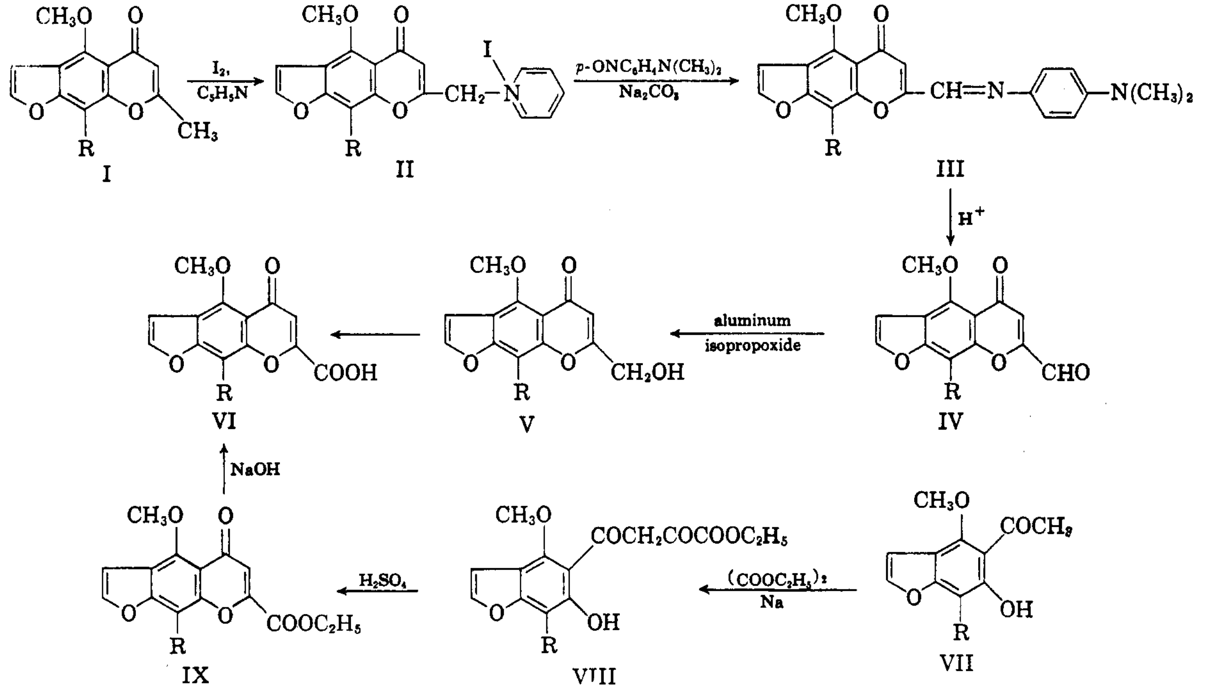
[4] *Cf.* N. A. Starkovsky, *Egyptian J. Chem.*, **2**, 111 (1959).

[5] 2-Methylchromone gives *N*-(*p*-dimethylaminophenyl)-α-(4-oxo-1,4H-benzopyran-2-yl)nitrone under similar conditions (*cf.* ref. No. 3).

[6] *Cf.* A. McGookin, *J. Appl. Chem., London*, **5**, 65 (1955).

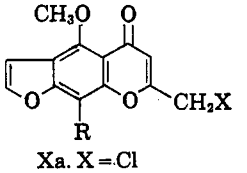
[7] Both synthetic Va as well as its structural analog Vb gave an intense violet-red color with sodium hydroxide pellets (*cf.* A. Schönberg and A. Sina, *J. Am. Chem. Soc.*, **72**, 1611 (1950).

Chart 1



In all formulas: a, R = OCH_3; b, R = H

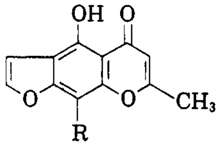
Chart 1). Thus, when 1-(4-oxo-1,4H-5-methoxyfuro-4′,5′,6,7-chromene-2-ylmethyl)pyridinium iodide (IIb), obtained either by treatment of Ib with iodine in pyridine, or by treatment of 2-iodomethyl-5-methoxyfuro-4′,5′,6,7-chromone (Xb), now prepared by the action of sodium iodide on the hitherto known 2-chloromethyl-5-methoxyfuro-4′,5′,6,7-chromone (Xa) with pyridine, was condensed with *p*-nitrosodimethylaniline, 5-methoxyfuro-4′,5′,6,7-chromone-2-*p*-dimethylaminophenylazomethine (IIIb) was obtained. Acid hydrolysis of IIIb with sulfuric acid led to the formation of 2-formyl-5-methoxyfuro-4′,5′,6,7-chromone (IVb), which readily gave the corresponding oxime derivative.



Xa. X = Cl
b. X = I

Reduction of the formyl derivative IVb gave results similar to those recorded in the case of IVa. Thus, whereas aluminum isopropoxide effected the reduction of IVb mainly to khellol (Vb); a low yield of Vb together with a sparingly soluble substance as the main product was obtained when a mixture of zinc dust and glacial acetic acid was used. The latter product gave correct analytical values for the glycol derivative of IVb and its structure is under further investigation.

The stability of the furochromone derivatives (IVa–b) under investigation, towards the reductive effect of aluminum isopropoxide (excepting attack on the formyl group), under the given experimental conditions, has now been confirmed by the recovery of Ia and of Ib when treated with the same reagent for a short time. Prolonged treatment of Ia and of Ib with aluminum isopropoxide, on the other hand, effected demethylation,[8] yielding 5-norkhellin (XIa) and 5-norvisnagin (XIb), respectively.



XIa. R = OCH_3
b. R = H

The synthesis of these new furochromone derivatives (IVa–b), starting with the easily available natural chromones (Ia–b) prompted us to undertake the study of the effect of the introduction of the solubilizing carboxylic group.[9] Thus, when

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[8] For the facile selective demethylation of furochromones in position 5, without causing undesired rearrangement, by a number of reagents—*e.g.*, magnesium iodide, arylmercaptans, etc., *cf.* (a) H. Abu-Shady and T. O. Soine, *J. Am. Pharm. Ass., Sci. Ed.*, **41**, 325 (1952); (b) S. K. Mukerjee and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **35A**, 323 (1952); (c) A. Schönberg and G. Aziz, *J. Am. Chem. Soc.*, **75**, 3265 (1953); (d) W. Asker, A. F. A. M. Shalaby, and S. M. A. Zayed, *J. Org. Chem.*, **23**, 1781 (1958); (e) A. Mustafa, N. A. Starkovsky, and E. Zaki, *J. Org. Chem.*, **25**, 794 (1960).

[9] *Cf.* J. P. Fourneau, *Ann. pharm. franc.*, **11**, 685 (1953); A. Mustafa, N. A. Starkovsky, and E. Zaki (ref. 8e).

IVa and IVb were treated with ammoniacal silver nitrate solution, 5,8-dimethoxyfuro-4′,5′,6,7-chromone-2-carboxylic acid (VIa), and 5-methoxyfuro-4′,5′,6,7-chromone-2-carboxylic acid (VIb) were obtained respectively. For the elucidation of the acid VIb, a synthesis similar to that described by Schönberg and Sina[7] for the preparation of 2-carboxyethyl-5,8-dimethoxyfuro-4′,5′,6,7-chromone (IXa) was adopted. Thus, when ethyl 4-methoxy-6-hydroxycoumarone-5-α,γ-diketobutyrate (VIIIb), obtained *via* the condensation of visnaginone (VIIb) with ethyl oxalate in the presence of sodium, was treated with sulfuric acid, it was cyclized to 2-carboxyethyl-5-methoxyfuro-4′,5′,-6,7-chromone (IXb). The latter, upon alkaline hydrolysis, gave VIb (*cf.* Chart 1). The acid VIa was proved to be identical with the product obtained by hydrolysis of the hitherto known IXa.

We would like to record that we using the ordinary analytical techniques, are not in a position now to detect the presence of Va[2] in crude extracts of *Ammi visnaga* (L.) grown in Egypt, as well as in the mother liquors of crude Ia or crude khellol glucoside either before or after treatment with 4% hydrochloric acid. In paper chromatography experiments, Va gave a yellow spot with R_f = 0.47 (under ultraviolet light).

EXPERIMENTAL[10]

Synthesis of 2-hydroxymethyl-5,8-dimethoxyfuro-4′,5′,6,7-chromone (Ammiol) (Va). *1-(4-Oxo-1,4H-5,8-dimethoxyfuro-4′,5′,6,7-chromene-2-ylmethyl)pyridinium iodide* (IIa). To a solution of 12.7 g. (0.1 mole) of iodine in 16 g. (0.1 mole) of dry pyridine was added 13.0 g. (0.05 mole) of Ia; the mixture was heated (water bath) for 1 hr. After cooling, the reaction mixture was triturated with 50 ml. of acetone, and was then kept overnight in the ice-chest. The deep brown precipitate was collected, washed with acetone, and then with cold water. It was crystallized from water as dark brown crystals with metallic luster (10.5 g.), m.p. 233–235° dec.

Anal. Calcd. for $C_{19}H_{16}INO_5$: C, 49.10; H, 3.44; I, 27.41; N, 3.01. Found: C, 49.31; H, 3.44; I, 28.12; N, 2.96.

IIa is soluble in hot water, less soluble in cold water and alcohol, but dissolves readily in hot ethanol (50%). It is difficultly soluble in benzene and ligroin (b.p. 80–100°), and is sparingly soluble in acetone, dioxane and methanol. A brown solution of IIa in water turns yellow upon addition of dilute hydrochloric acid, and a red precipitate is obtained when its acidic solution is made alkaline with aqueous sodium hydroxide solution. IIa gives a purple-red color with sodium hydroxide pellets,[7] and produces a brown spot on paper with R_f = 0.35 (under ultraviolet light), turning red after spraying with alkali.

Boiling a solution of 1 g. of IIa in 50 ml. of aqueous sodium carbonate solution (15%) for 1.5 hr., followed by cooling the reaction mixture, and acidification with cold dilute hydrochloric acid gave a yellowish precipitate of VIIa, m.p. and mixed m.p. 100°.

A mixture of 1 g. of IIa and 50 ml. of aqueous sodium sulfite solution (10%) was refluxed for 15 min., and then cooled. It was acidified with cold dilute hydrochloric acid, extracted with ether, and the solvent was driven off. The bright yellow residue, so obtained, was digested with sodium carbonate solution, when 50 mg. dissolved. Acidification of the carbonate solution gave 4,7-dimethoxy-6-hydroxybenzofuran-5-carboxylic acid, m.p. 150° (m.p. and mixed m.p. [1a]). The insoluble part (*ca.* 150 mg.) was dissolved in aqueous sodium hydroxide solution, and upon acidification, followed by crystallization of the solid, yellow crystals were obtained, m.p. 100°, identical with VIIa (m.p. and mixed m.p.).

5,8-Dimethoxyfuro-4′,5′,6,7-chromone-2-p-dimethylaminophenylazomethine (IIIa). To a solution of 7 g. (0.015 mole) of IIa in hot 240 ml. of aqueous ethanol (50%) cooled to 40° was added a solution of 2.8 g. of *p*-nitrosodimethylaniline hydrochloride in 50 ml. of water. The reaction mixture was then treated dropwise, while stirring, with a solution of 2 g. of sodium carbonate in 20 ml. of water, stirred for 15 min., and then kept aside at room temperature for 4 hr. The solid that separated on addition of 400 ml. of water to the reaction mixture was extracted with chloroform, washed with dilute sulfuric acid (1%), and finally with water. The chloroform extract was dried, driven off, and the solid residue was crystallized from 2.5 l. of ethanol to give golden-yellow needles (*ca.* 2.5 g.) of IIIa, m.p. 212° dec.

Anal. Calcd. for $C_{22}H_{20}N_2O_5$: C, 67.34; H, 5.10; N, 7.14. Found: C, 67.00; H, 5.21; N, 6.95.

IIIa is difficultly soluble in water and benzene, slightly soluble in ethanol, and easily soluble in methanol and chloroform. It gives a brown-red color with sodium hydroxide pellets, and a red color turning to an orange solution when treated with concd. sulfuric acid. It is not eluted with water from its initial position on paper chromatography (red spot under ultraviolet light).

2-Formyl-5,8-dimethoxyfuro-4′,5′,6,7-chromone (IVa). The brown solution of 1 g. of IIIa in 15 ml. of 10*N* sulfuric acid was kept aside at room temperature for 3 hr. It was then diluted with 100 ml. of cold water and the precipitate was collected and crystallized out from petroleum ether (b.p. 60–80°)–toluene mixture (3:1) as orange needles (*ca.* 350 mg.), m.p. 182–184°.

Anal. Calcd. for $C_{14}H_{10}O_6$: C, 61.31; H, 3.65. Found: C, 61.41; H, 3.68.

IVa is almost insoluble in water, but is easily soluble in ethanol, benzene, and glacial acetic acid. It gives a deep brown color with sodium hydroxide pellets, reduces ammoniacal silver nitrate solution in the cold, and gives a yellow-brown spot (under ultraviolet light) with R_f 0.50.

The following derivatives of IVa were prepared: *Oxime*, colorless crystals, from ethanol, m.p. 253–255° dec.

Anal. Calcd. for $C_{14}H_{11}NO_6$: C, 58.13; H, 3.80; N, 4.84. Found: C, 58.21; H, 3.87; N, 4.70.

Semicarbazone, colorless needles from ethanol, m.p. 245–246° dec.

Anal. Calcd. for $C_{15}H_{13}N_3O_6$: C, 54.37; H, 3.92; N, 12.69. Found: C, 54.24; H, 3.99; N, 12.13.

Phenylhydrazone, golden-yellow needles from ethanol, m.p. 218–220°.

Anal. Calcd. for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.39; N, 7.69. Found: C, 65.81; H, 4.43; N, 7.89.

2,4-Dinitrophenylhydrazone, brick-red crystals from ethanol, m.p. 320° dec.

Anal. Calcd. for $C_{20}H_{14}N_4O_9$: C, 52.86; H, 3.08; N, 12.33. Found: C, 52.70; H, 3.22; N, 12.18.

Anil, yellow needles from alcohol, m.p. 187° (orange melt).

Anal. Calcd. for $C_{20}H_{15}O_5N$: C, 68.76; H, 4.30; N, 4.01. Found: C, 68.62; H, 4.14; N, 3.56.

2-Hydroxymethyl-5,8-dimethoxyfuro-4′,5′,6,7-chromone (Va). *Reduction of* IVa *with:* (*a*) *Aluminum isopropoxide.* A

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[10] All melting points are uncorrected. For the ferric chloride reaction, a drop of an aqueous solution of ferric chloride was added to the substance dissolved in ethanol (95%). In paper chromatography experiments, Whatman paper No. 1 was used, and the ascending method technique with water as developing solvent, at 20° was followed, unless stated otherwise. Elementary microanalyses were made by Drs. Weiler and Strauss, Oxford.

suspension of 1 g. of IVa in 10 ml. of isopropyl alcohol was treated with 3 ml. of a solution of aluminum isopropoxide in the same solvent (3 equivalents), and the reaction mixture was subjected to slow distillation until collection of acetone ceased completely (10 min.). The reaction product so obtained, was poured into iced dilute hydrochloric acid, then saturated with common salt, and finally stirred for 0.5 hr. The precipitated substance was filtered, washed with water, and recrystallized from ethanol as yellowish needles (*ca.* 600 mg.), m.p. 211°.

Anal. Calcd. for $C_{14}H_{12}O_6$: C, 60.86; H, 4.31; OMe, 22.5. Found: C, 60.88; H, 4.36; OMe, 22.4.

Va is sparingly soluble in boiling water and moderately soluble in ethanol. It gives a bright red color with sodium hydroxide pellets moistened with ethanol, and a yellow color with sulfuric acid.

(*b*) *Zinc dust and glacial acetic acid.* A solution of 1 g. of IVa in 15 ml. of glacial acetic acid was shaken, at room temperature, with 2 g. of zinc dust, for 15 min., during which time a thick precipitate was obtained. The reaction mixture was poured into 1 l. of ethanol, boiled, and filtered while hot; the filtrate was then reduced to half its volume, and upon cooling, colorless crystals (*ca.* 300 mg.) m.p. 245–247° dec. were obtained.

Anal. Calcd. for $C_{28}H_{22}O_{12}$: C, 61.09; H, 4.00. Found: C, 60.77; H, 4.14.

It is soluble in hot pyridine, less so in hot glacial acetic acid, and sparingly soluble in hot alcohol and chloroform. It gives an orange-brown color with sodium hydroxide pellets, and a yellow color with sulfuric acid.

The above alcoholic filtrate was treated with a slight excess of sodium bicarbonate and evaporated to dryness (water bath). The solid residue thus obtained was digested with hot acetone, which was filtered and evaporated leaving a residue which was crystallized from hot water, m.p. 209–210°, identified as Va; yield, *ca.* 10 mg.

Acetate of Va. A solution of 200 mg. of Va in 10 ml. of acetic anhydride containing 1 ml. of dry pyridine was refluxed for 15 min., cooled, and poured into ice cold water. The precipitate was filtered and crystallized from very dilute ethanol as yellow needles, m.p. 102–103°, yield *ca.* 150 mg.

Anal. Calcd. for $C_{16}H_{14}O_7$: C, 60.38; H, 4.40. Found: C, 60.36; H, 4.60.

Synthesis of 2-hydroxymethyl-5-methoxyfuro-4',5',6,7-chromone (khellol) (Vb). *1-(4-Oxo-1,4H-5-methoxyfuro-4',5',6,7-chromene-2-ylmethyl)pyridinium iodide* (IIb). (*a*) *From visnagin* (Ib). Treatment of 11.5 g. (0.05 mole) of Ib with iodine and pyridine, under the experimental conditions described above for IIa, gave 8.5 g. of IIb as a brown powder, m.p. 228°. Purification of IIb was effected by repeated precipitation from its methanolic solution with ether.

Anal. Calcd. for $C_{18}H_{14}INO_4$: C, 49.65; H, 3.21; I, 29.19; N, 3.21. Found: C, 49.40; H, 3.00; I, 28.60; N, 3.26.

IIb is insoluble in petroleum ether, very sparingly soluble in dioxane and acetone, and sparingly soluble in ethanol, methanol, and water. It gives a bright red color with potassium hydroxide pellets moistened with ethanol, and dissolves in sulfuric acid with an olive-green color. It produces a brown spot, R_f 0.28 (under ultraviolet light), which turns red (under ordinary light) when sprayed with aqueous sodium hydroxide solution.

(*b*) *From khellol* (Vb). A solution of 1 g. of Xa[11] in 35 ml. of hot dry acetone was treated with a solution of 2 g. of sodium iodide in 25 ml. of dry acetone. The reaction mixture was refluxed for 5 min. and, after four further hours at room temperature, was poured into 200 ml. of water. The solid thus obtained was collected, and crystallized from benzene–petroleum ether (b.p. 60–80°) mixture (1:2) to give 1.1 g. of Xb, m.p. 158°[12] dec. With potassium hydroxide powder, Xb gives a blue color slowly changing to green.

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[11] A. Schönberg, N. Badran and N. A. Starkowsky, *J. Am. Chem. Soc.*, **77**, 1019 (1955).

A solution of 1 g. of Xb in 35 ml. of acetone was treated with 0.8 ml. of pyridine, and the reaction mixture was kept aside at room temperature for 16 hr. The deep yellow product (900 mg.) so obtained was purified by repeated reprecipitation from its methanolic solution with ether; identified with IIb (melting point and mixed melting point determination, and similar behavior in paper chromatography experiments).

5-Methoxyfuro-4',5',6,7-chromone-2-p-dimethylaminophenylazomethine (IIIb). It was obtained as yellow crystals from dioxane or toluene, m.p. 206°, when IIb was treated with *p*-nitrosodimethylaniline hydrochloride and sodium carbonate, as described in the case of IIIa.

Anal. Calcd. for $C_{21}H_{18}N_2O_4$: C, 69.61; H, 4.97; N, 7.73. Found: C, 69.42; H, 5.12; N, 7.86.

IIIb is insoluble in water and soluble in hot alcohol and dioxane. It gives a brown color with potassium hydroxide pellets, and dissolves with a deep brown color in sulfuric acid. IIIb produces a red spot (under ultraviolt light) in paper chromatography, which is not eluted with water.

2-Formyl-5-methoxyfuro-4',5',6,7-chromone (IVb). A suspension of 100 mg. of IIIb in 20 ml. of 10*N* sulfuric acid was occasionally stirred at room temperature (28°) for 3 hr. The mixture was then poured into 100 ml. of water and extracted with chloroform. Evaporation of the solvent gave *ca.* 50 mg. of yellow crystals of IVb which, upon recrystallization from benzene–petroleum ether (b.p. 60–80°) mixture melted at 173–174° (red melt).

Anal. Calcd. for $C_{13}H_8O_5.H_2O$: C, 59.54; H, 3.84. Found: C, 59.59; H, 3.88.

IVb crystallized with one molecule of water of crystallization and was soluble in ethanol. Its crystals gave a pale brown color with potassium hydroxide pellets, and a red color with concd. sulfuric acid.

Oxime of IVb was obtained as pale yellow crystals, m.p. 244–245° dec.; yield, *ca.* 80%. It gives an intense violet color with sulfuric acid and a pale yellow color with sodium hydroxide pellets.

Anal. Calcd. for $C_{13}H_9NO_5$: C, 60.23; H, 3.47; N, 5.40. Found: C, 60.24; H, 3.82; N, 5.12.

2-Hydroxymethyl-5-methoxyfuro-4',5',6,7-chromone (Vb). *Reduction of* IVb *with* (*a*) *aluminum isopropoxide.* Under the same experimental conditions as described for the reduction of IVa, IVb gave shining colorless needles of Vb (from dilute ethanol), m.p. 178–180°; identified by melting point and mixed melting point with an authentic specimen of Vb, obtained by acid hydrolysis of the natural product khellol glucoside.[13] It gives a violet-red color with sodium hydroxide pellets.

(*b*) *Zinc dust and glacial acetic acid.* One gram of IVb was treated with zinc dust and glacial acetic acid, as described in the case of IVa. The reduction product crystallized from alcohol as colorless needles, m.p. 253–255° dec.

Anal. Calcd. for $C_{26}H_{18}O_{10}$: C, 63.70; H, 3.70. Found: C, 63.30; H, 3.92.

It is insoluble in water, very sparingly soluble in ethanol, and moderately soluble in hot glacial acetic acid. It gives a yellow-brown color with sodium hydroxide pellets, and a yellow color with sulfuric acid.

Action of ammoniacal silver nitrate solution on: (*a*) IVa. A mixture of 100 mg. of IVa and 10 ml. of 5% ammoniacal silver nitrate solution was refluxed for 5 min., cooled, and acidified with excess of 5% sulfuric acid. The solid thus obtained was collected and purified by reprecipitation from its solution in aqueous sodium bicarbonate. It was crystallized from acetic acid in yellow crystals (*ca.* 60 mg.), m.p. 277–279° dec.

Anal. Calcd. for $C_{14}H_{10}O_7$: C, 57.9; H, 3.46. Found: C, 57.82; H, 3.56.

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[12] T. A. Geissman, *J. Am. Chem. Soc.*, **73**, 3356 (1951) gave m.p. 158–159° for Xb.

[13] E. Späth and W. Gruber, *Ber.*, **74**, 1549 (1941).

VIa is insoluble in water, sparingly soluble in ethanol, and soluble in hot glacial acetic acid; it gives a red color with concd. sulfuric acid.

One gram of IXa[7] was dissolved in hot 20% aqueous sodium hydroxide solution, and the solution was immediately cooled and acidified with dilute sulfuric acid. The crystals so obtained (*ca.* 900 mg.), m.p. 275–279°, were identified as VIa (melting point and mixed melting point).

(*b*) IVb. Similarly, treatment of IVb with ammoniacal silver nitrate solution under the above conditions led to VIb, which crystallized as pale yellow needles from glacial acetic acid, m.p. 256°.

Anal. Calcd. for $C_{13}H_8O_6$: C, 60.00; H, 3.40. Found: C, 59.92; H, 3.44.

VIb is insoluble in water, very sparingly soluble in benzene, and freely soluble in hot glacial acetic acid. It reacts with sodium bicarbonate solution with the separation of a sparingly soluble crystalline sodium salt. Crystals of VIb turn red when treated with concentrated sulfuric acid.

Synthesis of VIb. *Ethyl 4-methoxy-6-hydroxycoumarone-5-α,γ-diketobutyrate* (VIIIb). It was obtained after the procedure of Schönberg and Sina by the condensation of visnaginone (VIIb) with diethyl oxalate in the presence of sodium; colorless needles from ethanol, m.p. 95° (red melt); yield, *ca.* 25%.

Anal. Calcd. for $C_{15}H_{14}O_7$: C, 58.82; H, 4.57. Found: C, 58.67; H, 4.83.

VIIIb gives a reddish-brown color with ferric chloride and dissolves in aqueous sodium hydroxide solution (4%) with a yellow color.

2-Carboxyethyl-5-methoxyfuro-4′,5′,6,7-chromone (IXb). A solution of 1 g. of VIIIb in hot 20 ml. of ethanol was treated with 0.5 ml. of sulfuric acid and 10 ml. of ethanol. The reaction mixture was kept for 24 hr. at room temperature (25°). The yellow crystals (0.80 g.) melted at 167–168°.

Anal. Calcd. for $C_{15}H_{12}O_6$: C, 62.50; H, 4.16. Found: C, 62.38; H, 4.26.

IXb is sparingly soluble in water, insoluble in aqueous sodium hydroxide solution (4%), and soluble in benzene, chloroform, and glacial acetic acid. It gives a deep red color with sulfuric acid.

5-Methoxyfuro-4′,5′,6,7-chromone-2-carboxylic acid (VIb). When a mixture of 0.5 g. of IXb and 2.5 ml. of aqueous sodium hydroxide (4%) was gently heated (water bath, 65°), the solid went into solution in a few minutes. The solution was immediately diluted with water, and acidified with dilute sulfuric acid to give 0.4 g. of yellow crystals, m.p. 252–254°, identified as VIb (melting point and mixed melting point with a specimen prepared as above).

Action of aluminum isopropoxide on: (*a*) *khellin* (Ia). To a solution of 3.2 g. of Ia in 20 ml. of hot isopropyl alcohol was added a solution of aluminum isopropoxide (prepared from 1 g. of aluminum foil, 50 mg. of mercuric chloride, 20 ml. of isopropyl alcohol, and 0.2 ml. of carbon tetrachloride). The reaction mixture was refluxed for 2 hr. and was then distilled to half its volume. It was poured into 400 ml. of iced dilute hydrochloric acid, and the copious yellow precipitate thus obtained was collected and crystallized from ethanol to give 2 g. of 5-norkhellin (XIa), m.p. 197–200° (not depressed by admixture with an authentic specimen of XIa prepared by demethylation of Ia with hydrochloric acid or hydrobromic acid.[8a]

(*b*) *Visnagin* (Ib). 5-Norvisnagin (XIb) was obtained, upon treatment of Ib with aluminum isopropoxide as described above, m.p. 154–156° (not depressed by admixture with an authentic specimen of XIb, prepared by demethylation of Ib with hydrochloric acid.[14]

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Experiments with Chromeno-α-pyrone. Reactions of Provismine (Visnadin)

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3′-Keto-3′,4′-dihydroseselin (II) now has been obtained in 40% yield by the controlled hydrolysis of provismine (visnadin) (I) with alcoholic sulfuric acid. Mild treatment of I with the same reagent led to the formation of khellactone (IV) which can be smoothly converted to II by heating with 10*N* sulfuric acid.

II reacts readily with common ketonic group reagents to give the corresponding derivatives (VIa–d), and reacts in the enolic form with acetic anhydride to form 3′-acetoxyseselin (V). It undergoes condensation reactions with the 4′-methylene group to give the condensation products VIe–g and VII.

Reduction of II with aluminum isopropoxide gives 3′-hydroxy-3′,4′-dihydroseselin (IXa), which is readily converted to seselin (X) upon sublimation with phosphorus pentoxide.

Ammi visnaga L., a plant indigenous to the Mediterranean regions, has been used in Egypt for centuries as a home remedy and spasmolytic.[1]

That the seeds contain biologically active substances other than the chromones, khellin, visnagin, and khellol glucoside[2] has been shown by Samaan,[3] whose "visnagan" fraction (the oil remaining after removal of all crystalline material) evidenced considerable vasodilatory activity. Visnagan was subsequently investigated by Cavallito and Rockwell,[4] Smith, Pucci, and Bywater,[5a] and later, by

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[1] For a complete review on the subject, *cf.* H. Schmid, *Fortschritte der chemie organische Naturstoffe*, Vienna, L. Zechmeister (Ed.), **11**, 124 (1954).

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