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ISOLATION OF FUROCOUMARINS

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This invention relates broadly to the production of coumarins and furocoumarins (psoralens) by isolation from natural sources, particularly from citrus oils, and by organic synthesis. Particular objects of the invention include the provision of processes for isolating from citrus oils such compounds as: 5-geranoxypsoralen; 7-methoxy-5-geranoxycoumarins; 5-(gamma,gamma - dimethyl) allyloxypsoralen; 7-methoxy-5-(gamma,gamma-dimethyl) allyloxycoumarin; 8-geranoxypsoralen; 5,7-dimethoxycoumarin; and 5-methoxy-8-(2,3-dihydroxy-3-methylbutoxy)-psoralen. Another object of the invention is the provision of the hitherto-unknown compound, 8-geranoxypsoralen, in pure crystalline form free from other citrus oil components. Another object of the invention is the provision of methods for converting the naturally occurring coumarins and furocoumarins into other derivatives, for example, conversion of 8-geranoxypsoralen into 8-methoxypsoralen. Further objects and advantages of the invention will be obvious from the following description.

It has recently been shown that certain derivatives of psoralen, particularly 8-methoxypsoralen, possess what is termed "photodynamic" activity in that the compounds when applied locally, or even taken internally, enhance tanning of the skin when the subject is exposed to sunlight or other radiation containing ultra-violet rays. The compounds thus serve as protective agents in that the skin becomes tanned instead of developing soreness, blisters, etc.

At present the only commercial source for 8-methoxypsoralen is the seed of *Ammi majus,* a plant grown in Egypt. Some of the furocoumarins (5-geranoxypsoralen, for instance) have been shown to be present in bergamot or other citrus fruits but known methods for recovering these compounds are not efficient and generally result in loss by decomposition of one or more of the active components.

It has now been found that the compound 8-geranoxypsoralen is present in citrus oils, particularly lemon and lime oils. This compound can be isolated from the oil by a process which involves primarily adsorption on an adsorbent material followed by elution with a suitable solvent. It has also been found that by this same isolation method, other coumarins and furocoumarins can be recovered. The isolated 8-geranoxy-psoralen can be converted into 8-methoxypsoralen or other alkyl ethers as described below. Similar syntheses can be applied to the other compounds isolated from the citrus oil. It is to be emphasized that the presence of 8-geranoxypsoralen in citrus products was not known prior hereto.

Referring now in particular to the method of extracting the citrus oil, the following procedure is used: The raw

material for this purpose is usually an oil obtained by cold pressing the peels of lemons, limes, grapefruit, bitter oranges, bergamot, etc. Citrus oils obtained by other procedures which do not involve distillation can also be used. Where the citrus oil is purified by distillation, the distillation residue (undistilled material) contains the desired compounds and can be used as the starting material. In any event, the oil is first adsorbed on a finely divided adsorbent material such as silicic acid. This material containing adsorbed oil is then eluted with a terepenophilic solvent such as hexane whereby the undesired terpene hydrocarbons originally present in the oil are selectively eluted from the adsorbent. The adsorbent is then eluted with a liquid containing both a terpenophilic solvent, such as hexane, and an oxygenated organic solvent, such as ethyl acetate. The eluate which contains the various ethereal components of the oil is collected in separate fractions as it flows out of the adsorbent column. These fractions are subjected to analytical tests and those which are rich in a particular component are combined. The combined material is then subjected to evaporation to remove at least part of the eluting solvent and the coumarin or furocoumarin is crystallized from the concentrated eluate.

The extraction and purification process is further demonstrated by the following illustrative examples:

EXAMPLE I

A. *Preparation of adsorbent column*

Powdered silicic acid was formed into a slurry with hexane and poured into a conventional chromatographic cylinder. Nitrogen gas under pressure was applied at the top of the column to force out excess hexane. There was formed a column of hexane-wetted silicic acid 3.5 inches in diameter and 10 inches long.

B. *Adsorption of oil on column*

Three hundred grams of whole, cold-pressed lemon oil was poured on top of the column and forced, by application of nitrogen gas under pressure at the top of the column, into the adsorbent column.

C. *Removal of terpenes*

Hexane (1,100 ml.) was run through the column containing the adsorbed lemon oil until essentially all the undesired terpene hydrocarbons had been washed out as an effluent containing the terpenes dissolved in hexane.

D. *Elution of coumarins and furocoumarins*

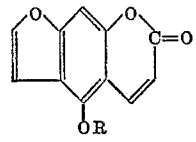
The column was then eluted with 22,500 ml. of a solution of ethyl acetate in hexane, starting with 1% ethyl acetate in hexane and increasing the proportion of ethyl acetate in each batch of about 1,000 ml. until the final concentration of ethyl acetate was 75%. The column was then eluted with 500 ml. of pure ethyl acetate and finally with 1,000 ml. of 10% ethyl alcohol in ethyl acetate. The eluate leaving the bottom of the column was collected in fractions, each containing about 25 ml., by using an automatic fraction collector. The total volume of solvent used for the elution was 24,000; 1,037 individual fractions were taken.

E. *Identification of fractions and isolation of products*

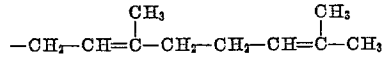
The eluate fractions were subjected to tests to determine which of them contained the same compounds. For these tests, a spot of eluate was placed on a micro-column, that is, a glass strip coated with silicic acid containing starch as a binder. The adsorbent mixture also contained a minor proportion of zinc cadmium sulphide and zinc silicate as a phosphor. The strips were then subjected to ascending development with a solvent consisting of 25% ethyl acetate in hexane. The individual compounds could then be identified by the degree of migration of the

spot (R_f value) and by the color of the spot when exposed to ultra violet light. As well known in the art, the R_f value is the ratio of the distance through which the spot migrates to the distance advanced by the solvent itself (solvent front). The particular values of R_f and color under ultra violet light for the various components of the eluate are set forth below.

(1) The first portion of the eluate contained the known compound 5-geranoxy psoralen



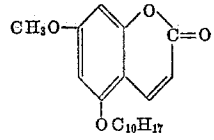
where R represents the geranyl radical:



This compound, also known as bergamottin, in the described chromatographic test, gave an R_f value of 0.68 and a purple color under ultra-violet light.

Fractions Nos. 261 to 305 of the eluate which contained this compound were combined. This composite was evaporated to a volume of about 5 ml. under vacuum in a flow of nitrogen gas. The resulting solution was allowed to stand overnight in a refrigerator whereby it deposited crystals. The crystals were removed and washed with petroleum ether. The crystals of 5-geranoxypsoralen had a melting point of 57.5 to 58.5° C. and were obtained in a yield of 280 mg. The compound was identified as 5-geranoxypsoralen by elemental analysis of it, the corresponding phenol, and corresponding acetate.

(2) The second portions of the eluate contained the known compound 7-methoxy-5-geranoxycoumarin:

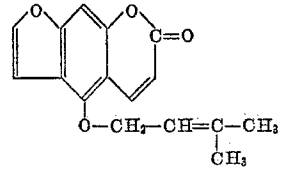


This compound in the described test gave an R_f value of 0.64 and the spot fluoresced bright blue under ultra-violet light.

Fractions Nos. 315 to 350 of the eluate which contained this compound were combined. This composite was evaporated to a volume of about 6 ml. under vacuum in a flow of nitrogen gas. The resulting solution was allowed to stand overnight in a refrigerator. The crystals which formed were separated. The product was identified as 7-methoxy-5-geranoxycoumarin by elemental analysis and by ultraviolet light and infra-red spectra.

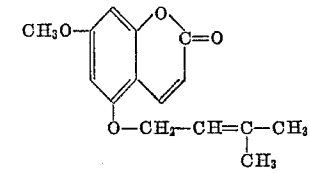
(3) The third portion of the eluate contained a compound giving an R_f value of 0.57 and a purple color under ultra violet light.

Fractions Nos. 351 to 359 of the eluate which contained this compound were combined. This composite was evaporated to a volume of about 1 ml. under vacuum in a flow of nitrogen gas. The resulting solution was allowed to stand overnight in a refrigerator whereby it deposited crystals. The crystals were removed and found to have a melting point of 94–96° C. It is believed that this compound is 5-(gamma,gamma-dimethyl) allyloxy psoralen, also known as isoimperatorin:

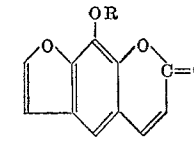


(4) The fourth portion of the eluate contained a compound giving an R_f value of 0.5 and a blue color under ultra-violet light.

Fractions Nos. 380 to 405 of the eluate which contained this compound were combined. The composite was evaporated to a volume of about 2 ml. under vacuum in a flow of nitrogen gas. The resulting solution was stored overnight in a refrigerator whereby it deposited crystals. The crystals were separated and found to have a melting point of 90–92° C. It is believed that this compound is 7-methoxy-5-(gamma,gamma dimethyl) allyloxycoumarin:



(5) The fifth portion of the eluate contained the compound 8-geranoxypsoralen:



wherein R represents the geranyl radical.

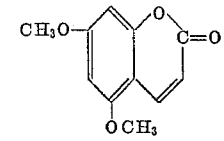
This compound in the described test gave an R_f value of 0.4 and a violet color under ultra violet light.

Fractions Nos. 406 through 475 of the eluate which contained this compound were combined. The composite was concentrated to about 3 ml. by evaporation under vacuum in a flow of nitrogen gas. The resulting solution was allowed to stand overnight at 38° F. whereby it deposited fine crystals. The crystals (178 mg.) were filtered off with suction and washed on the filter with cold petroleum ether. The yield was 0.05% based on the original lemon oil.

The compound 8-geranoxypsoralen has a melting point of 59–60° C.; it is insoluble in water, sparingly soluble in petroleum ether, moderately soluble in alcohol and ethyl ether, and quite soluble in ethyl acetate. Its ultra violet spectrum shows maxima at 217, 250, and 298 millimicrons, shoulders at 244 and 264 millimicrons, and minima at 232 and 277 millimicrons.

The crystalline compound was identified as 8-geranoxypsoralen based on the following observations: The compound gave a carbon and hydrogen analysis correct for $C_{21}H_{22}O_4$. The compound exhibited typical lactone behavior and absence of free phenol hydroxyl groups by virtue of the effect of cold caustic (no shift in spectral peaks) and heating with caustic (marked shift of spectral peaks toward red) on its ultra violet spectra. Cleavage with weak acids indicated the presence of an allylic type ether group which was confirmed to be the geranyl ether group by infra red spectral studies. Also the compound when cleaved with weak acid formed a phenol which on methylation or acetylation formed the known compounds 8-methoxypsoralen, and 8-acetoxypsoralen, respectively.

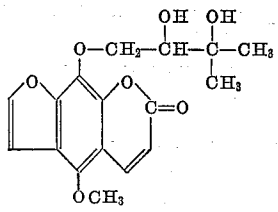
(6) The sixth portion of the eluate contained the known compound 5,7-dimethoxy coumarin, also known as limettin.



This compound in the described test gave an R_f value of 0.25 and a blue color under ultra-violet light.

Fractions Nos. 500 to 605 of the eluate which contain this fraction were combined. The composite was evaporated to a volume of about 6 ml. under vacuum in a flow of nitrogen gas. The resulting solution was stored overnight in a refrigerator. The separated crystals were removed and found to have a melting point of 147–148° C.

(7) The last portion of the eluate contained the known compound 5-methoxy-8-(2,3-dihydroxy-3-methylbutoxy) psoralen, also known as byakangelicin:



This compound in the described test gave an R_f value of zero and a lavender color when exposed to ultraviolet light.

Fractions Nos. 937 to 1037 of the eluate containing this compound were combined. The composite was evaporated to a volume of about 3 ml. under vacuum in a flow of nitrogen gas. The resulting solution was stored overnight in a refrigerator. The separated crystals were removed and found to have an ultra violet curve identical with that of an authentic sample of byakangelicin.

In the table below are set forth the yields of the seven compounds referred to above. The data represent the average of seven runs carried out as described above.

Compound	Name	Yield, mg. per 200 g. lemon oil
1	5-geranoxypsoralen	197
2	7-methoxy-5-geranoxy-coumarin	189
3	5-(gamma,gamma-dimethyl) allyloxy-psoralen	8
4	7-methoxy-5(gamma,gamma-dimethyl) allyloxycoumarin	9
5	8-geranoxypsoralen	96
6	5,7-dimethoxycoumarin	139
7	Byakangelicin	130

EXAMPLE II

Another run was carried out as described in Example I, parts A to D. In this instance 200 g. of cold-pressed lemon oil was adsorbed on a column of silicic acid 2.5 inches in diameter and 11 inches long. The terpenes were removed by eluting the column with 400 ml. of hexane. The column was then eluted with 15,500 ml. of a solution of ethyl acetate in hexane, starting with 0.5% ethyl acetate in hexane and increasing the proportion of ethyl acetate in each batch of about 1,000 ml. until the final concentration of ethyl acetate was 90%. The column was then eluted with 500 ml. 5% ethyl alcohol in ethyl acetate and finally with 500 ml. 25% ethyl alcohol in ethyl acetate. A total of 835 eluate fractions were collected. Fractions 425–475 were combined and the solution evaporated and 136 mg. of crystals of 8-geranoxypsoralen were obtained. The yield was 0.07% by weight based on the lemon oil.

EXAMPLE III

Another run was carried out as described in Example I, parts A to D. In this instance, 190 g. of lime oil was adsorbed on a column of silicic acid 2.5 inches in diameter and 11 inches long. The terpenes were removed by eluting the column with 1,000 ml. hexane. The column was then eluted with 7,000 ml. of a solution of ethyl acetate in hexane, starting with a solution containing 5% ethyl acetate in hexane and increasing the proportion of ethyl acetate in each batch of about 500 ml. until the final concentration of ethyl acetate was 75%. The column was then eluted with 400 ml. of 5% ethyl alcohol in ethyl acetate and finally with 500 ml. of 10% ethyl alcohol in ethyl acetate. A total of 965 fractions were collected. A number of these fractions which contained 8-geranoxy psoralen were combined and this compound recovered therefrom by evaporation and crystallization. The fractions used and the yields of the 8-geranoxy compound are listed below:

Fractions combined:	Amount of 8-geranoxypsoralen recovered, mg.
505–529	140.3
530–550	115.1
551–599	23.3
600–615	11.2
Total	289.9

The total yield of 8-geranoxypsoralen was 0.16% by weight based on the amount of lime oil.

In carrying out our process in practice we usually prefer to conduct the adsorption and elutions on a column. To this end a cylinder is packed with a finely divided solid adsorbent. Although we prefer to use silicic acid, various other adsorbents can be employed as for example, alumina, silica, magnesium oxide, magnesium hydroxide, aluminum hydroxide, bentonite, clays, diatomaceous earths, and so forth. Preferably this column is first wetted with the terpenophilic solvent whereby to minimize isomerization of reactive compounds present in the citrus oil. The expression "terpenophilic solvent" as used herein means an organic solvent which has a greater affinity for terpenes than the latter have affinity for the adsorbent. As the terpenophilic solvent, we prefer to use hexane although many other materials within this class give good results, examples being benzene, carbon disulphide, carbon tetrachloride, and mixtures of hydrocarbons such as gasoline, petroleum naphtha, petroleum ether, and so forth. Preferably the terpenophilic solvent should have a boiling point below 100° C. to facilitate its removal by distillation from the separated terpenes.

After the column is formed, the citrus oil is applied thereto. By application of vacuum to the receiver attached to the bottom of the column the oil can be drawn into the adsorbent. If desired, pressure can be applied at the top of the column to force the oil into the adsorbent. The column is then ready for elution of the terpene constituents. This is accomplished by washing the column with hexane or other terpenophilic solvent as described above. In conducting this elution, it is preferable to pass the selected solvent through the adsorbent column while taking small samples of the effluent liquid and subjecting them to chromatographic or other analytical tests. By this means, one can ascertain when the effluent contains the terpenes. The terpene-containing effluent can then be collected and saved for recovery of terpenes. By continuing the tests, the point when the effluent no longer contains terpenes can also be determined. At this point the collection of the solvent can be discontinued and the column is ready for elution of the coumarin and furocoumarin derivatives. The total amount of terpenophilic solvent to be used will vary depending on the amount of adsorbent and amount of terpenes in the citrus oil. In any case by using the tests on the effluent liquor, the proper amount of solvent to use can be determined for each particular case.

The terpenes may be recovered from the effluent solution by distillation. Vacuum distillation is preferred to minimize decomposition of the terpenes.

After the terpenes have been washed out of the column, the column is eluted to remove the coumarins and furocoumarins. This elution is conducted with ethyl acetate or other oxygenated organic solvent such as diethyl ether, dioxane, acetone, ethyl alcohol, normal or iso-propyl alcohol, any of the isomeric butyl alcohols, etc. Preferably the elution is initially conducted with a solvent which contains both oxygenated organic solvent and terpenophilic solvent, for example, a solution of ethyl acetate in hexane. In this way the various oxygenated compounds adsorbed on the column are eluted more or less serially rather than in one batch containing all of them.

Usually it is preferred to increase the proportion of oxygenated organic solvent in proportion to the terpenophilic solvent to enhance this serial-wise elution effect. In the last stages of the elution, the solvent contains only the oxygenated organic solvent, for example, ethyl acetate, ethyl alcohol, or mixtures thereof.

As the eluate flows from the column, it is collected in separate fractions, for example, by the use of an automatic fraction collector as is well known in the field of chromatography. These individual fractions are then subjected to chromatographic or other tests to ascertain the presence of the desired furocoumarin. The fractions which contain this compound are then combined, subjected to evaporation to remove at least part of the solvent and allowed to stand, preferably with cooling, to allow the compound to crystallize out. The other fractions may be likewise treated to isolate the various coumarins or furocoumarins originally present in the citrus oil. The eluate fractions which contain two or more of the desired components can be re-treated to separate them. To this end the fractions are subjected to evaporation to remove solvent and the residue is adsorbed on a solid adsorbent material and eluted as previously described.

In the preferred modification of the invention, terpenes are removed from the citrus oil by elution of the adsorbed oil with hexane or similar terpenophilic solvent. Other methods can be used to eliminate the terpenes, for example, application of distillation to remove the terpenes as a vapor and leave behind the essentially non-volatile coumarins and furocoumarins. The distillation residue can then be processed as described to separate the individual components.

As briefly noted above, 8-geranoxypsoralen can be readily converted into derivatives having photodynamic activity. Such synthesis is preferably accomplished in two stages—first by splitting the 8-geranoxypsoralen to form 8-hydroxypsoralen and then reacting the latter with an etherification agent. In the first stage the 8-geranoxy compound is reacted with an ether hydrolyzing agent, for example, acetic acid, sulphuric acid, hydrochloric acid, hydroiodic acid or the like. Usually the hydrolysis is performed with glacial acetic acid which acts both as a solvent and as a hydrolytic agent. To expedite hydrolysis a minor amount of strong acid such as sulphuric is added to the reaction mixture. In general, the hydrolysis can be conducted at a temperature from about zero to 100° C. depending on the efficacy of the hydrolysis agent selected. Where the hydrolysis is conducted with the 8-geranoxy compound dissolved in an inert solvent such as ethanol, benzene, acetone, etc., and the reaction is carried out at a temperature above the boiling point of the solvent, refluxing conditions may be employed to prevent loss of solvent. In the second stage of the synthesis the 8-hydroxypsoralen is reacted with an etherifying agent, for example diazomethane, dimethyl sulphate, or methyl iodide where the aim is to prepare the 8-methoxy derivative. In the event that different ethers are desired, one may use such etherification agents as for example diethyl sulphate, ethyl iodide, dipropyl sulphate, propyl iodide, diisopropyl sulphate, isopropyl iodide, di-butyl sulphate, butyl iodide, and so forth. Where the etherification is conducted with an alkyl sulphate or halide, an alkaline agent such as potassium carbonate, sodium carbonate, potassium hydroxide, sodium hydroxide, lime, sodium ethylate, or the like is added to the reaction mixture to promote the etherification by reacting with the anion of the etherifying agent. The etherification is preferably conducted under reflux in the presence of an inert solvent such as acetone, ethanol, dioxane, etc.

Instead of using the two-stage procedure outlined above, a single stage, trans-etherification may be employed. To this end the 8-geranoxy derivative may be refluxed with an excess of absolute methanol in the presence of an acid catalyst such as hydrogen chloride, sulphuric acid, etc. to obtain a replacement of the geranyl radical with the methyl radical. Similar syntheses with propyl alcohol, isopropyl alcohol or any of the isomeric butyl alcohols can be accomplished in the same general manner.

The procedures described above for the conversion of 8-geranoxy psoralen to 8-methoxypsoralen (or other 8-alkoxysporalen) can be also applied to the other derivatives isolated from citrus oil. Thus by these procedures, for example, the geranoxy or the gamma,gamma dimethyl allyloxy side chains can be converted into methoxy or other alkoxy groups. Typical examples of such syntheses are the conversion of 5-geranoxypsoralen to 5-methoxypsoralen; the conversion of 7-methoxy-5-geranoxy coumarin to 5,7-dimethoxy coumarin; the conversion of 5-(gamma,gamma-dimethyl) allyloxypsoralen to 5-methoxypsoralen; the conversion of 5-(gamma-gamma, dimethyl)-allyloxycoumarin to 5-methoxycoumarin; and so forth.

The conversion of 8-geranoxypsoralen to 8-methoxypsoralen is further demonstrated by the following illustrative examples.

EXAMPLE IV

A. *Cleavage of 8-geranoxypsoralen*

Two hundred seventy-five mg. of 8-geranoxypsoralen was dissolved with mechanical stirring in 4 ml. glacial acetic acid. After 10 minutes, one drop of concentrated sulphuric acid was added to the solution. In 4 minutes thereafter a light tan precipitate began to form. Stirring was continued for 35 minutes and the reaction mixture was refrigerated for one hour and 20 minutes. The precipitate was then removed by suction filtration and washed on the filter with glacial acetic acid followed by ice-cold ethyl ether. The product, 8-hydroxypsoralen, weighed 115 mg., that is, 74% of theory.

B. *Methylation of 8-hydroxypsoralen*

One hundred fifteen mg. of 8-hydroxypsoralen was dissolved in 10 ml. absolute methanol, an excess of diazomethane dissolved in ether was added and the mixture allowed to stand at room temperature with occasional stirring for 3 hours. The next day the reaction mixture was reduced in volume to 3 ml. by evaporation on the steam bath and the concentrate was held in a refrigerator overnight. The next day, fine needles (80 mg.) of 8-methoxypsoralen were filtered from the solution. The compound had a melting point of 145–146° C. and was obtained in a yield of 65% of theory. The product was compared with an authentic sample of 8-methoxypsoralen by mixed melting point, ultra-violet, and infra-red spectra and the two were found to be identical.

EXAMPLE V

Methylation of 8-hydroxypsoralen with methyl iodide (or sulphate)

8-hydroxypsoralen (100 mg.), methyl iodide or dimethyl sulphate (2 ml.) and anhydrous potassium carbonate (1 g.) were refluxed in acetone solution (25 ml.) for 24 hours. Inorganic material was separated, acetone was removed by distillation and water was added to the residue. The 8-methoxypsoralen which rapidly solidified was collected and crystallized from benzene-petroleum ether.

The conversion of 5-geranoxy-psoralen into 5-methoxypsoralen is further demonstrated by the following illustrative example.

EXAMPLE VI

A. *Clevage of 5-geranoxypsoralen*

Four hundred and ninety milligrams of 5-geranoxypsoralen was dissolved in 5 cc. glacial acetic acid. One drop of concentrated sulphuric acid was added and the reaction mixture stirred for 2 hours. A tan colored

precipitate was formed which was filtered off. A yield of 278 mg. of 5-hydroxypsoralen was obtained—77% of theoretical.

B. *Methylation of 5-hydroxypsoralen*

Forty mg. of 5-hydroxypsoralen, 20 ml. of anhydrous acetone, 0.2 g. of potassium carbonate and 1 ml. of dimethyl sulphate were refluxed for 3 hours. The reaction mixture was allowed to cool and 50 ml. of water added. Fine needles formed which were filtered off and recrystallized from alcohol. A yield of 14 mg. of 5-methoxypsoralen was obtained.

Having thus described the invention, what is claimed is:

1. A process for isolating coumarins and furocoumarins from a citrus oil which comprises adsorbing the citrus oil on a solid adsorbent material, eluting the adsorbent material with a liquid comprising an oxygenated organic solvent, collecting the resulting eluate in a series of fractions containing individual coumarins and furocoumarins, and individually recovering the coumarins and furocoumarins from the fractions.

2. A process for isolating a furocoumarin from a citrus oil which comprises adsorbing the citrus oil on a solid adsorbent material, eluting the adsorbing material with a liquid comprising an oxygenated organic solvent, collecting the resulting eluate in a series of fractions, separating the fractions containing the furocoumarin, and recovering the furocoumarin therefrom.

3. The process of claim 2 wherein the furocoumarin is 5-geranoxypsoralen.

4. The process of claim 2 wherein the furocoumarin is 8-geranoxypsoralen.

5. The process of claim 2 wherein the furocoumarin is 5-(gamma,gamma-dimethyl) allyloxypsoralen.

6. The process of claim 2 wherein the furocoumarin is 5-methoxy-8(2,3-dihydroxy-3-methylbutoxy)psoralen.

7. A process for isolating furocoumarins from a citrus oil which comprises adsorbing a citrus oil on a solid adsorbent material, extracting the adsorbent material with a terpenophilic solvent to remove terpene constituents, eluting the adsorbent material with a liquid comprising a terpenophilic solvent and an oxygenated organic solvent then with an oxygenated solvent alone, collecting the resulting eluate in a series of fractions containing individual furocoumarins, and individually recovering furocoumarins from the fractions.

8. The process of claim 7 wherein the furocoumarins include 5-geranoxypsoralen.

9. The process of claim 7 wherein the furocoumarins include 8-geranoxypsoralen.

10. The process of claim 7 wherein the furocoumarins include 5-(gamma,gamma-dimethyl)-allyloxypsoralen.

11. The process of claim 7 wherein the furocoumarins include 5-methoxy-8(2,3-dihydroxy-3-methyl butoxy)-psoralen.

12. A process for isolating 5-geranoxypsoralen from citrus oil which comprises adsorbing the citrus oil on a solid adsorbent, extracting the adsorbent with hexane to remove terpene components, eluting the adsorbent with initially a liquid containing a minor proportion of ethyl acetate dissolved in hexane, then with a series of liquids containing increasing proportions of ethyl acetate to hexane, then with ethyl acetate alone, and finally with a liqud containing ethyl acetate and ethanol, collecting the eluate in a series of separate fractions, combining the fractions which contain 5-geranoxypsoralen and recovering the 5-geranoxypsoralen therefrom.

13. A process for isolating 8-geranoxypsoralen from citrus oil which comprises adsorbing the citrus oil on a solid adsorbent, extracting the adsorbent with hexane to remove terpene components, eluting the adsorbent with initially a liquid containing a minor proportion of ethyl acetate dissolved in hexane, then with a series of liquids containing increasing proportions of ethyl acetate to hexane, then with ethyl acetate alone, and finally with a liquid containing ethyl acetate and ethanol, collecting the eluate in a series of separate fractions, combining the fractions which contain 8-geranoxypsoralen and recovering the 8-geranoxypsoralen therefrom.

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