

UNITED STATES PATENT OFFICE

2,465,733

LECITHIN-METAL COMPOUND

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10 Claims. (Cl. 260—403)

1

This invention relates to chemical combinations of and a method or methods of combining metals with phosphatides and more particularly to combining and the combinations of lecithin with those metals having direct or indirect nutritive or medicinal advantages and effects.

At least certain of the nutritive and therapeutic values of lecithin and the choline content thereof have been recognized and are still being discovered. So also the values of certain of the metals have been recognized for their beneficent nutritional and therapeutic effects. That matter of getting particularly the beneficent metals into assimilable, beneficial and palatable form has been a continuing problem, and a corollary and sometimes separate problem has existed in measuring and controlling the dose, proportion and amount of such substances and their vehicles for administration under different circumstances.

My experiments exploring the range of beneficent uses of metal lecithinates, as my products may be conveniently designated, do not permit me to set forth all the advantages thereof nor to prophesy all the advantages that may be derived from its use in various forms. Other advantages will appear and suggest themselves in the course of the description of the instant inventions since the need for the product has been long expressed and the problem of producing it has prior to my invention remained unsolved.

Briefly and generally stated, one phase of the problem of combining metals with lecithin has been that solvents which dissolved the metal broke down the lecithin and solvents in which lecithin was safely soluble were without effect on the metals desired to be combined therewith. The desired metals and lecithin having no direct affinity, it has been my endeavor to discover and determine how they may be combined in a beneficent and useful form.

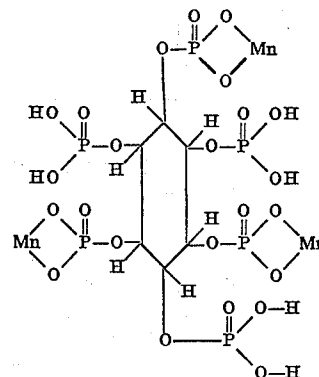
It is thus among the objects of my invention to provide a chemical combination including a phosphatide such as lecithin with metals such as iron, copper, calcium and/or manganese and to provide a method of so doing. Another object is to combine lecithin with metal phytates such as the phytates of iron, copper, calcium and/or manganese and thus include inositol of the phytate with the desired metals and the choline of the lecithin. Another object is to effect such combinations without loss of or injury to the choline part of the lecithin. Another object is to provide metal lecithin compounds and methods of producing the same in which the relative proportions and amounts of metal or metals in relation to lecithin may be controlled and determined. Another object is to provide a metal medicinal and/or nutritive compound that is palatable and beneficially assimilable. A further object is to provide a mutually beneficent ve-

2

hicle particularly for the choline part of lecithin and such metals as iron, copper, calcium and/or manganese in combination therewith. A further object is to provide a stable, palatable and assimilable compound in which more than one metal and lecithin may be included, such as iron-copper lecithinate or calcium-manganese lecithinate as the same may be conveniently designated.

Other objects and advantages will appear from the following description of certain preferred forms and examples of my invention or inventions in respect to the method and the product or article of manufacture.

In practicing my invention it is convenient and practicable to first prepare a metal phytate in which I provide the kind or kinds of metal or metals that I desire to include in the finished product. The reaction between inosite-phosphoric acid $C_6H_6(OPO_3H_2)_6$ with the acetates, hydroxides, sulphates or chlorides, for example, of the desired metals, particularly in the bivalent form, will produce the acid metal salt or metal phytate, as the same is variously known, the metal displacing the hydrogen of one or more of the phosphate radicals. For example, by providing manganese acetate or hydroxide etc. in properly proportioned amounts in relation to inosite-phosphoric acid, I can add one, two, three or more, up to six metal atoms to the phosphorylated inositol ring. In limiting and controlling the relation of the manganese acetate, hydroxide etc. in relation to the amount of the hexa-phosphoric ester I can substitute as little as one manganese atom for two hydrogen atoms in one of the six phosphate radicals and obtain a manganese phytate probably as shown in such a formula as $C_6H_6(OPO_3Mn)(OPO_3H_2)_5$. Similarly more manganese atoms in the bivalent form may be included in the phytate ring probably as shown below where three atoms are illustrated:



Similarly other metals such as iron, copper, calcium and magnesium in varying desired proportions may be attached to the ring by similar

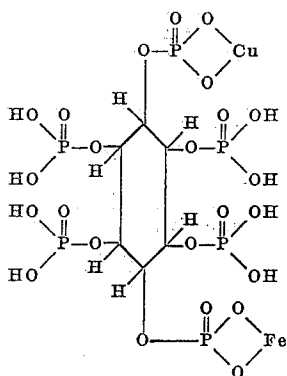
3

steps. While I have mentioned the potentiality of attaching as many as six such metal atoms in the bivalent form to the phosphorylated inositol ring, I also seek to attach to the same ring one or more lecithin molecules or groups through the same means of attachment, the OH groups of the phosphate radicals, and therefore desired to have one or more OH groups available for that purpose. In mentioning my preference for using a bivalent metal or metals in their bivalent form I have in mind that it is at least theoretically possible to attach four atoms of trivalent metal to one of the phytate rings as suggested for example in the Andrews et al. Patent No. 2,239,543, but I prefer not to do so for two reasons which are mentioned not by way of limitation but rather by way of exposition. My first reason follows from that mentioned above that the trivalent metals or the metals in the trivalent form restrict the bonds available for receiving the lecithin or phosphatide molecules or groups, and thus appear to restrict the range and flexibility of the practice of my invention. My second reason is that I believe the metals which appear to have both bivalent and trivalent forms when used in the trivalent form, will have all of their valence bonds occupied, and thus be less readily assimilable than those which upon introduction to the human body have a valence bond actually or potentially available for bodily assimilation.

At this point in the description of my invention it should be noted that one of the advantages and facilities thereof is that I may combine more than one kind of metal with the same inositol ring and thence in the same final combination. For instance having due regard to the atomic weights, ferrous acetate, $(\text{CH}_3\text{COO})_2\text{Fe}$ and cuprous acetate $(\text{CH}_3\text{COO})_2\text{Cu}$ can be proportioned to the atomic weight of the hexa-phosphoric ester to substitute, for example, one copper atom and one iron atom for the hydrogen of two of the six phosphate radicals and obtain an iron-copper phytate expressed probably as



and illustrated probably as follows:



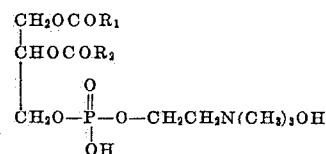
Other desired numbers and proportions of atoms of more than one metal may be similarly included in the phytate as desired within the precepts and practice of my invention. When I have added the lecithin molecule or molecules as presently to be described I will then have, following the above example, an iron-copper lecithinate or lecithin phytate which will provide an advantageous vehicle for iron and copper in the treatment, for example, an anemia. My teaching of course is not merely to use iron and copper but rather do I seek to illustrate the feasibility of producing a multi-metal lecithinate or lecithin phytate by

4

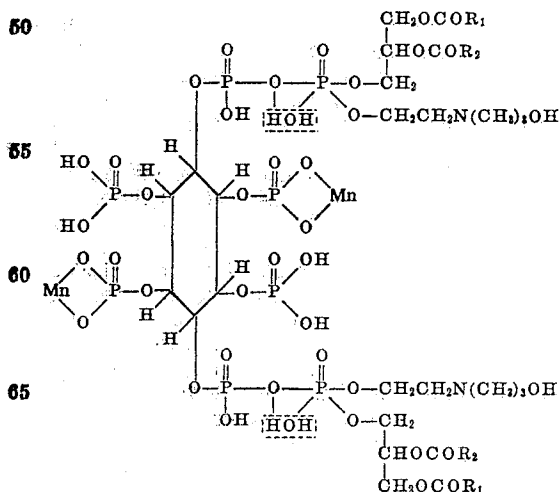
taking the steps such as are above illustrated as exemplary of the steps that may be performed at this stage in the preparation of the ultimate compound.

Both the compound having the structural formula illustrated immediately above and that having the structural formula previously shown may be described as incompletely neutralized salts of the completely phosphorylated inositol known as phytic acid, this by virtue of the fact that less than all of the hydroxyl groups of the phosphate radicals contain metal substituents.

Continuing this general example the next step is to bring about the union of the phytate having the desired metal atoms with the desired phosphatide of which lecithin in the alpha form illustrated by way of example in the following formula in which R_1CO and R_2CO represent the acyl groups of the higher fatty acids, as follows:



Passing for the moment the detailed operations which I employ to effect this combination, the lecithin, preferably in a pure form, as represented above may be condensed with the metal phytate in pure benzene, C_6H_6 , on reflux condensation followed by evaporation or distilling off of the benzene and resulting water to produce the metal lecithin phytate or metal lecithinate. Assuming that the inositol ring was first completely phosphorylated and then two manganese atoms displaced the hydrogen of two of the phosphate radicals and that this form of manganese phytate was condensed with lecithin, the resulting compound will take the form illustrated below, assuming for illustration the alpha form of lecithin above described and assuming further that the relative proportions of lecithin to manganese phytate were such as to attach two lecithin molecules to the phytate ring. This product in this form may, as I believe, probably be illustrated as follows, the dotted rectangles indicating water of condensation:



While my teaching is not limited to the addition of particularly two lecithin molecules or groups to the metal phytate, I mention it as a satisfactory product which with the manganese above mentioned takes the form of a staple dark brown palatable substantially dry dough, readily

5

handled, measured, administered and assimilated. On the other hand limited experiments on my part have indicated less desirable physical characteristics in the form of finished product in which but one lecithin molecule is condensed with a phytate molecule, the product in this latter instance tending to be a little sticky and less easy to handle. It is also not without my teaching and understanding to use more than two lecithin molecules in a similar condensation with a metal phytate molecule, having in mind however for the purpose of the instant invention the relative undesirability, as presently advised, of bonding more lecithin to the phytate ring at the expense of the metal or metals to be bonded to the same ring, since from the formulae above written it appears that the bonds available for the metal are not available to the lecithin and vice versa. Within this range of choice however a reasonably wide range of variations and combinations between different kinds of metals and different numbers of metal atoms as compared to the numbers of groups and bonds of phosphatides can be attached to the phytate to give a corresponding range of desirable and beneficial compounds.

While I have illustrated above the lecithin groups or molecules bonded through one available OH group of two different phosphoric radicals, my experiments suggest a reasonable probability that the two lecithin molecules may bond through two OH groups of the same phosphoric radical. This presents the opportunity of bonding five bivalent atoms in five of the phosphate radicals of a completely phosphorylated inositol ring and then bonding two lecithin molecules through the two OH groups of the remaining phosphoric radical, since each lecithin molecule appears to condense with the metal phytate through a single bond.

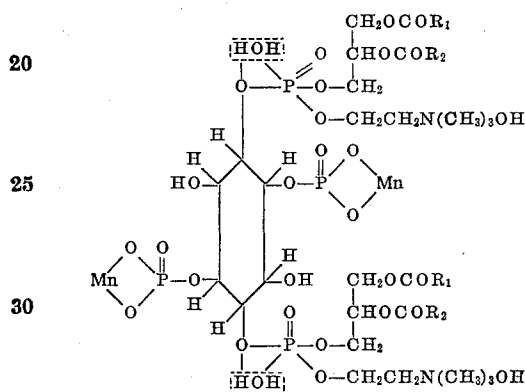
While I have indicated a preference for using benzene, C_6H_6 , as the solvent for the metal phytate and lecithin as above described, my thought has been to avoid solvents that would break off the choline from the lecithin. Along this line it is mentioned in passing that the ordinary acid impurities in commercial alcohols tend to impair or restrict the employment of such alcohols for this purpose. However, my choice of solvents is not necessarily limited to benzene and my experiments indicate that substantially any liquid neutral organic solvent of a six ring structure with sufficient H or OH groups, and in itself acting neutral, such as cyclohexanol, C_6H_{12} , or cyclohexanol, $C_6H_{11}OH$, to be illustrative of the equivalent of benzene for my purpose. Similarly the low boiling "gasolines" boiling from about $35^\circ C.$ to $70^\circ C.$, sometimes called petroleum ether or benzine, may also be used.

While I have mentioned the alpha lecithin I do not intend to exclude the beta lecithin or other beneficial phosphatides and I believe both forms of lecithin are present in commercial lecithin and act in the same or substantially the same way within the precepts and for the advantages of my invention.

In the preceding illustration I have shown the inositol or hexahydroxycyclohexane completely phosphorylated preliminary to its combination with lecithin. In this form the bond appears to run through the oxygen between two phosphorous atoms and the product contains as many more phosphorous atoms as there are lecithin molecules. I do not limit my teaching however

6

to the employment of the completely phosphorylated ring, since I have found the incompletely phosphorylated ring a satisfactory vehicle for bringing the metal into combination with lecithin and a satisfactory "bond" between the metal and lecithin, since the metal phytate, even of partially phosphorylated inositol, is soluble in the neutral organic solvents in which lecithin is also advantageously soluble. For example a double phosphorylated ring will support two bivalent metal atoms and, in a manner similar to that above described, can be condensed with lecithin in a benzene solution to produce a desirable metal lecithinate or metal lecithin phytate which I believe can be illustrated with two bivalent metal and two lecithin molecules probably as follows:



Here water is condensed out probably as shown in the dotted rectangles, the OH radicals of the inositol and lecithin yielding hydrogen and oxygen while retaining an oxygen atom through which the ring structure is bonded to the lecithin.

The release of water incident to this bond may be enhanced when desired, by the use of an anhydrous salt in the condensing solution.

As mentioned near the outset of the specification lecithin is broken down in acid solutions and would, as I am at present advised, be adversely effected by inosite-phosphoric acid. When the inosite-phosphoric acid has been changed to a metal phytate by the substitution of metal atoms for at least part of the hydrogen atoms, as above described, the harmful influence on lecithin, when in solution therewith in a solvent such as benzene, is so reduced or so substantially eliminated as to permit the production of a desirable combination of metal and lecithin.

Since the calcium-magnesium salt of inosite-phosphoric acid known as phytin or calcium-magnesium phytate is economically available for use in the practice of my invention, I will illustrate a preferred method of making my product beginning with an illustrative sample of commercial calcium-magnesium phytate. In such a sample I have found for example 18.2% calcium, 3.4% magnesium and 19.2% phosphorous.

This can be treated to substitute whatever metal or metals is or are desired in place of the calcium and magnesium. For example, 100 gr. of calcium-magnesium phytate are suspended in 300 cc. of water to which 75 cc. of sulphuric acid (2:1) is slowly added. This reaction produces substantially inosite-phosphoric acid, calcium sulphate and magnesium sulphate which latter are then filtered out. Then 75 gr. of manganese acetate is stirred into the inosite-phosphoric acid filtrate. In the latter solution the manganese

phytate salt is precipitated and is in turn filtered off and washed and thereafter dried. I obtained yields of substantially 96.0% which upon analysis proved to have a manganese content of 21.64%. The manganese phytate at this stage takes the form of a dry white powder which as mentioned in the preceding parts of this specification is then available for condensation with lecithin. In this example substantially three phosphate radicals each carry a manganese atom, the other phosphoric groups having OH groups available to effect the bonds with the phosphatides to be added.

At this point, as presently advised, either of two series of steps may with satisfaction be practiced to condense the lecithin with the phytate. In either of the exemplary procedures I take soybean lecithin in its commercial form, as for example marketed by the American Lecithin Company under the trade name, Yelkin, a natural complex extracted from soybeans consisting of lecithin and associated phosphatides in a carrier of soybean oil. In one procedure I prefer to eliminate the carrier oil from my product before the step of condensing the lecithin with the phytate, and I may do this by extracting the oil by dissolution in acetone and flaking out the pure lecithin in a dry powdered form.

Having then in this manner the dry powdered phytate and the dry powdered lecithin I take 5.8 gr. of the above described manganese phytate and condense it with 16 gr. of the dry powdered lecithin in about 60 cc. of pure benzene, boiling the same at or about 80° C. for about 15 minutes, preferably on reflux. The resultant condensate is then dried, evaporating off the benzene and the water of condensation. The product is the manganese lecithin phytate above described and when dried thoroughly has a yellow color of dough-like constituency in which form it can be conveniently handled, measured and administered and is palatable and readily tolerated and assimilated in the human body. In the product prepared according to the above proportions the manganese content is found to be 7.88%.

Alternatively I condense 5.8 gr. of manganese phytate prepared as above described with 32 gr. of crude lecithin of which about 45% is carrier oil, and condense these ingredients in about 60 cc. of pure benzene on reflux by boiling for about 15 minutes. This product is a dark brown liquid which may be poured while still hot into an evaporation dish for the dissipation of the benzene and water of condensation at temperatures at about 110° C. During such evaporation the liquid is preferably stirred vigorously and continuously to facilitate evaporation. When most of the benzene and water has been evaporated the hot syrupy mass is permitted to cool in the air until no odor of benzene remains. At this point the semi-finished product is a yellow plastic mass containing the carrier oil of the lecithin and has utility in that form. I prefer, however, to extract the oil and do so by dissolution in acetone from which may be recovered the manganese lecithin phytate as a light yellow dough or powdery mass as above described having substantially the same manganese content of about 7.88%.

By either of these procedures the resulting compound has three bivalent manganese atoms and two lecithin molecules or groups attached to the phytate ring, as I believe, according to the structural formula hereinabove illustrated.

In the foregoing examples, I have shown how

to remove all the calcium and magnesium from calcium-magnesium phytate for the purpose of making a metal phytate of a different metal or metals. Where it is desired that the final product contain calcium and/or magnesium when the convenient form of the raw material is the calcium and/or magnesium phytate, then I may merely remove less than all of the calcium and magnesium by restricting the amount of sulphuric acid used as in the above examples whereby to form less than all the potential amount of calcium sulphate and magnesium sulphate in the first of the steps above mentioned, leaving calcium-magnesium phytate with as few or many phosphoric acid groups attached to the inositol ring as may be desired for bonding phosphatides thereto either with or without additional metals. Thus I may form a calcium-magnesium lecithinate without additional metals or a calcium-magnesium-manganese lecithinate or still other combinations of metals and phosphatides such as lecithin through the wholly or partially phosphorylated inositol ring.

Taking for example, calcium phytate as a raw material having about 18 to 20% calcium, I might well suspend 100 gr. thereof in 300 cc. of water and then add only about 38 cc. of sulphuric acid (2:1) instead of 75 cc. H₂SO₄ (2:1) as mentioned in the examples first above given. This would leave substantially one half the calcium still in the compound and would produce for removal about one half as much calcium sulphate. To facilitate the separation of the calcium sulphate from the calcium phytate, benzol can be added in which the phytate is soluble but in which the sulphate is insoluble. Preferably such a mixture is heated and the solution of the calcium phytate in the benzol is filtered off from the calcium sulphate. Thereafter the water and the benzol are evaporated from the phytate preferably at a reduced pressure to facilitate evaporation and to employ lower temperatures. The remaining grayish-white powder comprises calcium phytate containing substantially one half calcium phosphate groups and one half phytic acid groups, the latter being available for junction with additional metal and/or lecithin by the steps hereinabove described. If it be sought to make a calcium-manganese lecithinate, the steps above described of adding manganese to certain of the phytic acid groups can be employed using, for example, proportionately reduced amounts of manganese acetate to give a calcium-manganese phytate, care being taken to leave sufficient OH groups or an OH group free in one of the phytic acid groups or on the inositol ring for subsequent condensation with the lecithin as hereinabove described.

While calcium, manganese, magnesium, copper and iron have been mentioned especially as metals combined or combinable with phosphorylated hexahydroxycyclohexane, I have referred to these metals by way of example rather than limitation. I am not aware of substantial limitation in the choice of metal or metals that may be combined with lecithin through the vehicle of the phytate within the range of affinity of any metal for the wholly or partially phosphorylated hexahydroxycyclohexane within the teachings and precepts of my invention.

While I have illustrated and described preferred forms and examples of the products and methods embracing and carrying out my invention or inventions, variations, changes and improvements will occur to those skilled in the art from the teachings and practice hereof, and I

9

do not care to be limited to the within preferred forms, methods, products or examples or in any manner other than by the appended claims.

I claim:

1. A condensation product of lecithin and an incompletely neutralized metal salt of a phosphorylated inositol. 5

2. A condensation product of lecithin and an incompletely neutralized metal salt of an incompletely phosphorylated inositol, the lecithin being bonded to the inositol ring by a phosphate radical forming part of the phosphorylated inositol. 10

3. A condensation product of lecithin and an incompletely neutralized metal salt of an incompletely phosphorylated inositol. 15

4. A condensation product of lecithin and a metal salt of an incompletely phosphorylated inositol, the lecithin being bonded by an oxygen atom to the inositol ring.

5. A condensation product of lecithin and an incompletely neutralized metal salt of phytic acid. 20

6. A condensation product of lecithin and an incompletely neutralized manganese salt of phytic acid.

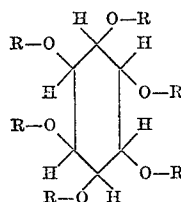
7. A condensation product of lecithin and an incompletely neutralized calcium salt of phytic acid. 25

8. A condensation product of lecithin and an incompletely neutralized magnesium salt of phytic acid. 30

9. A condensation product of lecithin and an incompletely neutralized calcium-magnesium-manganese salt of phytic acid.

10

10. The process for the production of metal-phosphatide compounds which comprises reacting a compound of the general formula



wherein at least one R represents a metal phosphate radical and the remaining R's, including at least one R, is selected from the group consisting of hydrogen and H_2PO_3 , with a phosphatide in a neutral organic solvent at a temperature of about 80°C . for about 15 minutes and drying the condensation product thus obtained.

IRENE BECKER LEVIS.

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