

Novel glycerol derivatives, processes for the preparation thereof and also the pharmaceutical compositions which contain them.

The present invention relates to novel glycerol derivatives having pharmacological activity, to the processes for preparing these derivatives and also to the pharmaceutical and veterinary compositions which contain them.

The novel derivatives of the invention consist in the glycerol monoesters, diesters and triesters which correspond to the general formula



in which R, R₁ and R₂, which are the same or different, each represent hydrogen or an acyl radical, namely, di-n-propylacetyl, tri-n-propylacetyl, 2-ethylhexanyl, 4-n-propylheptanyl, 5-n-propyl octanyl, 2-methyl-2-ethylhexanyl, 4-methyl cyclohexylcarbonyl or di-n-propyl methoxyacetyl, on the condition that R, R₁ and R₂ are not at the same time hydrogen or di-n-propylacetyl.

As examples of compounds which are included within the scope of the present invention, it is possible to mention the esters as set out below:

Glyceryl 1-(di-n-propylacetate)

Glyceryl 1-(tri-n-propylacetate)

Glyceryl 1-(2-ethylhexanoate)

Glyceryl 1-(1-methyl cyclohexylcarboxylate)
Glyceryl 1-(2-methyl-2-ethylhexanoate)
Glyceryl 2-(di-n-propylacetate)
Glyceryl 1,2-bis-(di-n-propylacetate)
Glyceryl 1,2-bis-(2-ethylhexanoate)
Glyceryl 1,2-bis-(1-methyl cyclohexylcarboxylate)
Glyceryl 1,2-bis-(tri-n-propylacetate)
Glyceryl 1,2-bis-(2-methyl-2-ethylhexanoate)
Glyceryl 1,3-bis-(di-n-propylacetate)
Glyceryl 1-(di-n-propylacetate)-3-(1-methylcyclohexylcarboxylate)
Glyceryl 1-(di-n-propylacetate)-2,3-bis-(1-methylcyclohexyl
carboxylate)
Glyceryl 1-(di-n-propylacetate)-3-(2-methyl-2-ethylhexanoate)
Glyceryl 1-(di-n-propylacetate)-2-(1-methylcyclohexylcarboxylate)
Glyceryl 1,2,3-tri-(1-methylcyclohexylcarboxylate)
Glyceryl 1-(di-n-propylmethoxyacetate)
Glyceryl 1-(4-n-propylheptanoate)
Glyceryl 1-(5-n-propyloctanoate).

As will hereinafter be described in detail, it has been found that suitable mixtures of esters of the invention have qualities which make them particularly useful, it being possible for these mixtures also to be considered as novel compounds.

Consequently, the invention is additionally concerned with the ester mixtures of the invention, for example, mixtures of glyceryl 1,2-bis-(di-n-propylacetate)/glyceryl 1,3-bis-(di-n-propylacetate), mixtures of glyceryl 1,2-bis-(di-n-propylpropionate)/glyceryl 1,3-bis-(di-n-propylpropionate) and mixtures of glyceryl 1,2-bis-(di-n-propylmethoxyacetate)/glyceryl

1,3-bis-(di-n-propylmethoxyacetate).

The compounds of the invention have isomeric centres and can thus be produced in the form of optical isomers, position isomers or mixtures of these isomers.

If it is so desired, it is possible to separate these isomers from their mixture at the appropriate stages during the preparation of these mixtures, by methods which are known per se, in order to obtain the desired individual isomers.

These isomers, and also the mixtures of these isomers, likewise form part of the present invention.

Another object of the invention is concerned with a pharmaceutical or veterinary composition which comprises, as essential active principle, at least one ester of the invention in association with a pharmaceutical carrier or an appropriate excipient.

As will be described hereinafter in greater detail, it was found that the esters of the invention are endowed with biochemical and pharmacological properties capable of making them particularly useful in the treatment of pathological conditions which are due to a disturbance of the central nervous system and also disorders relating more particularly to neuropsychiatry.

In connection with a human being, the compounds of the invention will be able to be administered daily at the rate of 10 mg/kg to 50 mg/kg.

The documents of German Application 1 289 620, French Application 2 147 091 and German Application 2 202 535 are particularly concerned with the esters of monocarboxylic acids

of glycerol or propanediol. However, these esters, and also their properties, are different from the compounds of the present invention.

The compounds of the invention can be prepared in different ways, having regard to their chemical structure.

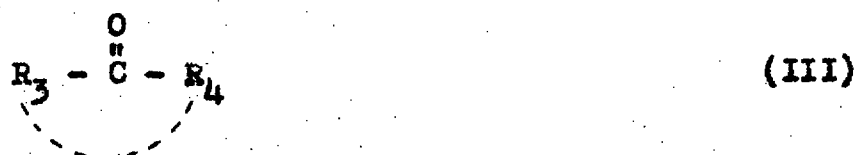
1. Monoesters

A. α-Monoesters

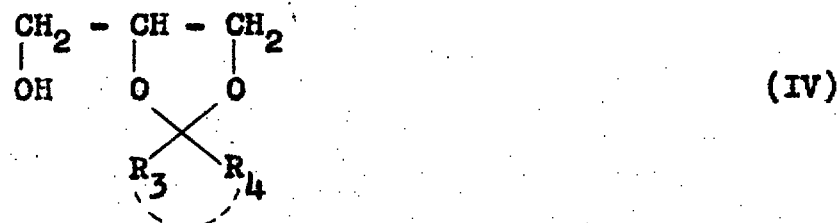
These esters, which can be represented by the general formula



in which R represents an acyl radical as defined in formula I, can be prepared by causing the reaction, under reflux, of glycerol and a ketone of general formula

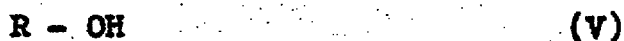


in which R₃ represents methyl, R₄ represents methyl, ethyl, 2-methylbutyl, or R₃ and R₄, when they are taken together, represent a pentamethylene radical, the reaction having taken place in the presence of p-toluenesulphonic acid as catalyst and possibly in the presence of a solvent, such as benzene, for obtaining a ketal of general formula



in which R₃ and R₄ have the same meaning as previously.

The compound of formula IV as thus obtained is then esterified in pyridine or in a mixture of dimethylformamide/pyridine at $65^{\circ}\text{C} \pm 5^{\circ}\text{C}$, with the chloride of an acid of general formula



in which R represents an acyl radical, such as defined in formula I, for obtaining a ketal of general formula



in which R represents an acyl radical such as defined in the formula I and R_3 and R_4 have the same meaning as previously, which is then hydrolysed at ambient temperature, in a hydromethanol medium and in the presence of a dilute inorganic acid, such as hydrochloric acid, sulphuric acid or acetic acid, in order to give the required compounds of the invention.

When the acid chloride of formula V is in excess, the ketal of formula IV will be subjected beforehand to a reaction with sodium or sodium hydride in N,N-dimethylformamide and the esterification will be effected in N,N-dimethylformamide or a mixture of N,N-dimethylformamide and hexamethylene phosphoramide at a temperature which is between 40° and 90°C .

B. β -Monoesters

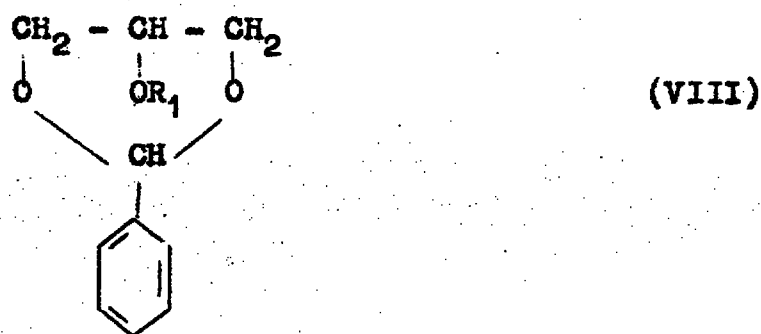
These esters, which ^{can} ~~are~~ be represented by the general formula



in which R_1 represents an acyl radical such as defined in formula I, can be prepared by causing the reaction of glycerol with benzaldehyde in the presence of a water-entraining agent and p-toluene-sulphonic acid as catalyst, so as to obtain a mixture of about 90/10 of glycerol 1,2-benzylidene and glycerol 1,3-benzylidene derivatives.

When this mixture is kept at low temperature, that is to say, in the region of 0°C , and in the presence of dry hydrochloric acid, the 1,2-benzylidene derivative is isomerised into a 1,3-benzylidene derivative.

The 1,3-benzylidene derivative in question is then esterified with the chloride of an acid of formula V at a temperature of $60^\circ\text{C} \pm 5^\circ\text{C}$ and in the presence of an acid acceptor, such as pyridine, in order to give a benzylidene derivative of general formula



in which R_1 has the same meaning as in formula VII, which is then brought into reaction with hydrogen in an alcoholic medium, for example ethanol, and in the presence of palladium charcoal as catalyst, the reaction being effected at atmospheric pressure and at ambient temperature, for giving the required compound of the invention. Instead of benzaldehyde, it is

also possible to use a derivative of the latter, substituted on the aromatic entity.

II. Diesters

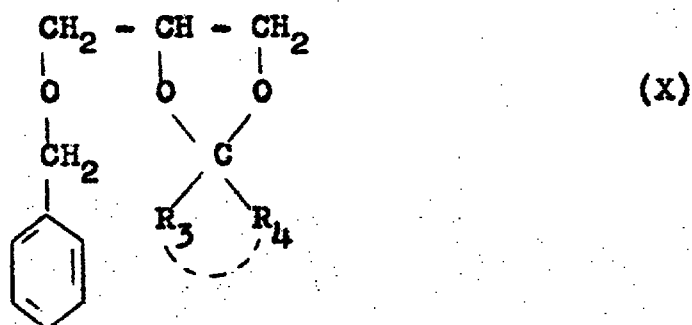
These esters, which can be represented by the general formula



in which one of the symbols R, R₁ and R₂ represents hydrogen and the other two represent an acyl radical such as defined in formula I, can be obtained as follows:

A. 1,2-Diesters

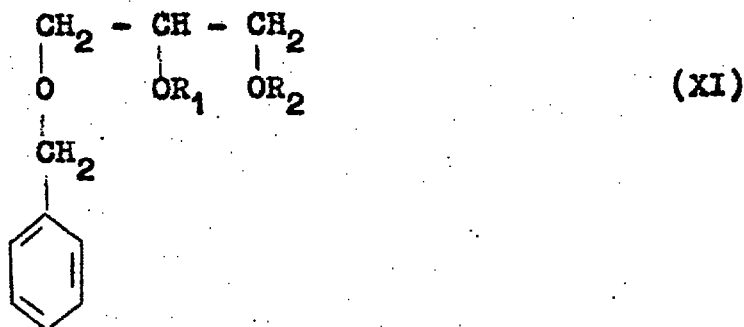
a) When R represents hydrogen and R₁ and R₂ are identical and represent an acyl radical, by reacting a ketal of formula IV with benzyl chloride in the presence of an alkali metal, for example sodium, for obtaining the benzyl ether of general formula



in which R₃ and R₄ have the same meaning as previously, the reaction being carried out under reflux in a suitable solvent, such as toluene.

The benzyl ether thus obtained is then hydrolysed in a water/acetic acid mixture at the reflux temperature of this mixture or in a hydromethanolic/hydrochloric acid mixture at

ambient temperature, which yields the 1-benzyl glycerol, which is then esterified with the chloride of an acid of formula V in the presence of an acid acceptor, such as pyridine, and at a temperature which is between 50 and 95°C, in order to obtain a diester of general formula



in which R_1 and R_2 are identical and represent an acyl radical such as defined in formula I, which is then caused to react with hydrogen in an alcohol, such as ethanol in the presence of palladium charcoal as catalyst, the reaction being carried out at atmospheric pressure and at ambient temperature, which provides the required compounds of the invention.

When one or other of the radicals R_1 and R_2 is in excess, the compound of formula X will preferably be prepared, after sodation of the 1-benzyl glycerol with sodium hydride, the esterification taking place in N,N-dimethylformamide.

The glycerol 1,2-diester of the invention, in which the radicals situated in the 1- and 2-positions are identical, can also be prepared according ^{to} other processes.

In fact, experiments with other methods have been carried out in the particular case of the glyceryl -1,2-bis-(di-n-propylacetate).

For example, this diester can also be obtained by causing

the reaction of epichlorhydrin with a sodium salt, in a suitable solvent, such as for example water or a mixture of toluene and dimethylformamide and at a temperature which is between 60° and 80°C, in order to obtain the 2,3-epoxypropyl-di-n-propylacetate. This epoxy derivative is then caused to react with di-n-propylacetic acid at a temperature which is between 60° and 80°C in the presence of boron trifluoride, preferably in the form of its etherate, or in the presence of sulphuric acid, this yielding the required diester.

b) When R represents hydrogen and R₁ and R₂ are different and represent an acyl radical, by causing the reaction of epichlorhydrin with the alkali metal derivative, for example, the sodium derivative, of an acid of formula V, the reaction being carried out in a suitable solvent, such as a mixture of toluene and dimethylformamide and at a temperature which is between 60° and 80°C, for obtaining an epoxy derivative of general formula



in which R₂ represents an acyl radical as defined in formula I.

This epoxy derivative is then caused to react at a temperature which is between 60° and 80°C with a different acid of formula V in the presence of boron trifluoride, preferably in the form of its etherate or in the presence of sulphuric acid, this yielding the required ester of the invention.

B. 1,3-Diesters

a) When R and R₂ are identical and represent an acyl radical and R₁ represents hydrogen, by esterifying dihydroxy-

acetone with the chloride of an acid of formula V, this reaction being carried out under reflux, in the presence of an acid acceptor, such as pyridine, and in a solvent, such as isopropylether, for obtaining a ketodiester of general formula



in which R and R₂ represent an acyl radical such as defined in formula I, which is then reduced, at ambient temperature, with potassium borohydride in an ether, such as tetrahydrofuran, the complex as thus formed is then hydrolysed with a strong inorganic acid, such as, for example, hydrochloric acid, in order to give the required compound of the invention.

b) When R and R₂ are different and represent an acyl radical and R₁ represents hydrogen, by esterifying a diol of general formula



in which R represents an acyl radical such as defined in formula I, with the chloride of an acid of formula V, the reaction being carried out between ambient temperature and 110°C and in an acid acceptor, such as pyridine, for obtaining the required compound of the invention.

Preferably, 1 to 1.5 equivalents of acid chloride of formula V will be caused to react with 1 equivalent of diol of formula XIV.

Particularly useful mixtures of esters of the invention, containing a high percentage of diesters of the invention, can

be obtained by specific processes.

In the particular case of glycerol di-n-propylacetic esters, the following method may be used.

The esterification, at a temperature which is between -5°C and $+10^{\circ}\text{C}$, of 1 equivalent of glycerol with 2 equivalents of di-n-propylacetic acid or 2 equivalents of its chloride, in the presence of pyridine as acid acceptor, followed by a rectification of the mixture of esters thus obtained by distillation under high vacuum, by molecular centrifuging or by gaseous phase chromatography, yields a mixture of esters of di-n-propylacetic acid and glycerol, with a yield of 73 to 74 %.

This mixture comprises:

Di-n-propylacetic acid monoesters	$\leq 10 \%$
1,2- and 1,3-diesters of di-n-propylacetic acid	$\geq 88 \%$
1,2,3-Triesters of di-n-propylacetic acid, di-n-propylacetic acid, glycerol	$\leq 2 \%$

and will hereinafter be called "mixture A".

However, it has surprisingly been found that mixtures of glyceryl 1,2-bis-(di-n-propylacetate)/glyceryl 1,3-bis-(di-n-propylacetate) can be obtained, practically free from monoesters and triesters, by esterifying, in N,N-dimethylformamide as solvent, at a temperature which is between 100 and 110°C and for 5 to 10 hours, one equivalent of 1,3-dichloro-2-propanol with 2 equivalents, preferably in excess, of an alkali metal salt, preferably the sodium salt, of di-n-propylacetic acid, then by rectifying the mixture of esters thus obtained, for example, by distillation under high vacuum, molecular centrifugation or chromatography in gaseous phase, in

order to obtain a mixture of the corresponding 1,2 and 1,3-diester of the glycerol with a yield higher than 85 %.

According to preferred reaction conditions, the mixture of such 1,2- and 1,3-diester of glycerol are obtained by causing the reaction, at a temperature of 100°C and for 8 hours, and in N,N-dimethylformamide, 1,3-dichloro-2-propanol, with sodium di-n-propyl acetate, preferably in an excess of about 5 %, then rectifying the mixture of diesters thus obtained, for example, by high-vacuum distillation, molecular centrifugation or chromatography in gaseous phase, this yielding a mixture of glyceryl 1,2- and 1,3-bis-(di-n-propylacetate) with a yield of about 88 to 95 %.

When such reaction conditions are respected, a reproducible mixture of glyceryl 1,3-bis-(di-n-propylacetate)/glyceryl 1,2-bis-(di-n-propylacetate) is obtained in a ratio of 1.43 : 1 to 1.54 : 1.

This mixture comprises:

1-Monoester of glyceryl	≤ 1 %
1,2- and 1,3-Diesters of glyceryl	≥ 98 %
1,2-3-Triester of glyceryl, di-n-propylacetic acid, 1,3-dichloro-2-propanol	≤ 1 %

and will hereinafter be called "mixture B".

In the previously described process, the N,N-dimethylformamide can be used in a quantity three to five times the total quantity of reagents, without influencing the total yield in the final mixture of diesters.

Moreover, the initial sodium di-n-propylacetate may be either this latter in solid form, or an aqueous solution of sodium di-n-propylacetate prepared "in situ" from di-n-

propylacetic acid and a 50 % aqueous solution of sodium hydroxide.

It is evident that when an aqueous solution of sodium di-n-propylacetate is used as starting product, ~~the~~ water is introduced into the reaction medium. If the volume of water thus introduced is not greater than 5 % of the volume of N,N-dimethyl formamide, the yield of final mixture of diesters is not modified.

The process thus described for preparing a mixture of glyceryl 1,2- and 1,3-bis-(di-n-propylacetates) presents numerous advantages, the most important being the fact that there is obtained a final isolated mixture of high purity. The crude products do not contain triesters. After a single distillation, the content of total diesters in such a mixture ~~is~~ ^{is} ≤ 98 %.

As a consequence, the mixture of glyceryl 1,2- and 1,3-bis-(di-n-propylacetates), more particularly the "mixture B", has an undoubted commercial value: It is easily prepared in a reproducible manner, practically free from impurities and at a moderate cost price, since no separation of the constituents is required.

In addition, this mixture, like "mixture A", is of pharmacological and pharmacokinetic interest of prime importance, as will hereinafter be discussed.

The processes as described above for the preparation of mixtures of glyceryl 1,2- and 1,3-bis-(di-n-propylacetates) may also be applied to the preparation of other mixtures of diesters of the invention.

The mixtures of mono-, di- and tri-esters as thus

obtained can subsequently be separated, for example, by means of a distillation under high vacuum, a molecular centrifugation or gaseous phase chromatography, in order to obtain the desired esters in a pure form.

III. Triesters

These esters, which can be represented by the general formula



in which R, R₁ and R₂ each represent an acyl radical such as defined in formula I, can be obtained as follows:

a) When R, R₁ and R₂ represent identical acyl radicals, by esterifying the glycerol:

- either with an acid of formula V in excess at the reflux temperature of the medium and in the presence of p-toluenesulphonic acid as catalyst,

- or with the chloride of an acid of formula V in excess at a temperature of 60-70°C and in the presence of an acid acceptor, such as pyridine, so as to obtain the desired compound of the invention.

b) When R and R₁ represent identical acyl radicals and R₂ represents a different acyl radical, by esterifying a monoester of general formula



in which R₂ represents an acyl radical such as defined in formula I, with the chloride of an acid of formula V at a temperature which is between ambient temperature and 110°C

and in an acid acceptor such as pyridine, this yielding the desired compounds of the invention.

c) When R and R₂ represent identical acyl radicals and R₁, which is different, also represents an acyl radical, by esterifying a diester of general formula

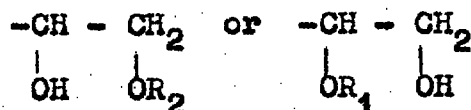


in which R and R₂ are identical and represent an acyl radical such as defined in formula I, with the chloride of an acid of formula V in the presence of an acid acceptor, such as pyridine, and at reflux temperature, so as to obtain the desired compound of the invention.

d) When R, R₁ and R₂ all represent different acyl radicals, by esterifying a diester of general formula



in which R represents an acyl radical such as defined in the formula I and A represents a radical



in which R₁ and R₂ each represent an acyl radical such as defined in formula I, with the chloride of an acid of formula V at the reflux temperature of the medium and in the presence of an acid acceptor such as pyridine, this yielding the desired compounds of the invention.

The chlorides of the starting acids of formula V can be obtained in accordance with known processes, by causing the reaction of the corresponding acid with thionyl chloride.

Likewise, the alkali metal salts of these acids are obtained by causing reaction of the acids in question with the hydroxide of the corresponding alkali metal.

The acids in question are either known compounds which have been published in US Patents Nos. 3 325 362, 3 958 011 and 4 025 649 and also in Belgian Patent No. 875 882, or compounds which can be obtained by the processes described in these patents. The compounds of the invention have outstanding biochemical properties, particularly a competitive inhibiting effect with respect to the γ -aminobutyric α -keto-glutaric transaminase, and also valuable neurotropic and psychotropic properties which are manifested to various degrees. These latter comprise in particular antianoxic, anticonvulsive, anxiolytic and antipsychotic properties. The compounds of the invention can also act as regulators of the central nervous system and as means for potentiating the depressants of the central nervous system.

The combined effect of these properties is capable of making the compounds of the invention particularly useful for the treatment of different varieties of central neurological disturbances and of disorders appearing more particularly with neuropsychiatry.

As examples of such central neurological disturbances or of disorders caused by a derangement of the central nervous system, it is possible to mention, convulsive states and crises, such as for example epilepsy, choreic states such as Huntington's chorea, disturbances of the memory, balance and vigilance and also neyroses and psychoses of various origins.

Aliphatic and alicyclic esters of diols or of polyols are

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known, having been described in the prior art.

From this point of view, reference will be made to Patent No. 1 289 620 of the German Federal Republic, relating to diesters useful in the field of dermatology, these diesters being formed from alcohols comprising only two hydroxyl functions. There will likewise be mentioned the French Patent No. 2 147 091, relating particularly to chemical synthesis intermediaries formed of α -monoesters of glycerol which are formed from acids comprising at most 7 carbon atoms. In addition, there will be mentioned the Patent Application No. 2 202 535 of the German Federal Republic, which relates particularly to the 1-monoester and to the 1,2-diester of glycerol and of 3-isopropyl-6-methyl cyclohexylcarboxylic acid, which are useful as agents stimulating the cold-sensitive physiological receptors. However, none of these documents was capable of permitting the forecasting of the particular properties made evident in connection with the esters of the present invention.

Likewise, reference will be made to the patent No. 3 686 238 of the United States of America, which covers glycerol derivatives having an increased and prolonged activity after oral administration.

Certain of these glycerol derivatives are formed by the glycerol of which one of the hydroxyl groups is substituted by a medicamental radical, while one or both of the remaining hydroxyl groups are substituted by a natural fatty acid having 8 to 24 carbon atoms.

It has now quite surprisingly been discovered, according to the present invention, that a slow liberation of the

medicamental entity can be obtained, starting with an ester initially formed from a therapeutically active acid of formula V as indicated ^{above} below and from glycerol, without it being necessary to substitute at least one of the OH groups of the glycerol by a natural fatty acid.

It was not possible in any way for this invention to be suggested by or deduced from the prior art.

The compounds of the above formula I represent a progress with respect to the esters of the prior art, since no natural fatty acid forms part of the molecule of the esters of the invention. It is possible, in this manner, to eliminate one stage in the synthesis, namely, the substitution of one or two hydroxyl groups of the glycerol by a natural fatty acid. The compounds of the invention thus provide a structure which is more simple than that of the compounds of the prior art.

It is consequently apparent that the fatty acyl radical forming part of the molecule of the esters of US Patent No. 3 686 238 does not offer any particular advantage. It seems that this radical only serves the part of a vehicle to the same degree as the glycerol supporting the medicamental radical.

In addition, it will be noted that no residue of medicaments appearing in the aforesaid US Patent is included in the range of the acids of the above formula V.

In addition, no proof of preparation ^{or} ~~of~~ efficacy of the derivatives of the US Patent No. 3 686 238 is mentioned therein, although this patent covers in generic form thousands of compounds.

Thus, the hydrolysis of the esters of the invention liberates, as regards an animal or a human being, the glycerol and a therapeutically active acid corresponding to the aforementioned general formula V.

Consequently, it has been observed from this hydrolysis that the compounds of the invention can be considered as a form of slow liberation of the acids in question, permitting a prolonged therapeutic level to be obtained in connection with an animal and/or a human being.

Certain acids of formula V, and likewise the derivatives of these acids, are well-known neurotropic and psychotropic agents, these properties having been published in the patents referred to above.

In addition, it was found that the esters of the invention are superior to the corresponding medicamental radical of formula V as regards their toxicity.

The esters of formula I, which are found to be particularly interesting in the treatment of central neurological disturbances, particularly epilepsy, are those in which the acyl radical represents a di-n-propylacetyl radical. These esters are useful as regards causing a slow liberation of di-n-propylacetic acid.

This acid, which is also known under the name of valproic acid, and also certain of its salts, forms one of the best antiepileptic agents which are known at the present time: moreover, it is widely used commercially in this respect.

In humans, the glyceryl 1,2-bis-(di-n-propylacetate) and the glyceryl 1,3-bis-(di-n-propylacetate) are of particular interest, as are also the mixtures of these glyceryl diesters,

as will hereinafter be discussed in detail.

Pharmacokinetic studies undertaken with the monoesters and diesters of the invention, in which the acyl radical represents a di-n-propylacetyl radical, have shown that these compounds present quite surprising differences by comparison with the glyceryl tri-(di-n-propylacetate) and the 1,2-propanediol-bis-(di-n-propylacetate).

The glyceryl tri-(di-n-propylacetate) is a known compound, having been published by MEIJER and MEINARDI in "Clinical and Pharmacological aspects of sodium valproate (Epilim) in the treatment of epilepsy", pages 71-74 (report of a Symposium held at Nottingham University, 23/24th September, 1975).

This ester was presented as "a remarkably useful substance having all the properties expected of a slow-liberation composition".

Similarly, J.W.A. MEIJER and R. KALFF conclude at the Bethel Symposium (1974 - German Federal Republic - "Antiepileptic drugs", pages 222-228, edited by Schneider-Heidelberg) that the glyceryl tri-(di-n-propylacetate) is able to behave as a form of slow liberation of the di-n-propylacetic acid. They will show that the maximum blood level in di-n-propylacetic acid obtained after administration to a human of an oral dose of glyceryl tri-(di-n-propylacetate) equivalent to 600 mg/ of di-n-propylacetic acid is approximately 30 µg/ml, 8 hours after administration.

However, the glyceryl tri-(di-n-propylacetate) cannot form a useful therapeutic agent, because the blood levels in di-n-propylacetic acid which it permits to be reached vary from 10 to 20 µg/ml, these levels being too small to

constitute therapeutic blood levels. Tests carried out within the scope of the present invention have corroborated these results when used with an animal.

These tests, effected in connection with rats which have received 600 mg/kg of glyceryl tri-(di-n-propylacetate), by oral route, would show that the di-n-propylacetic acid only appears in the blood 150 minutes after administration and that the maximum blood levels in this acid do not exceed 10 µg/ml.

The low bioavailability of this triglyceride is probably due to a poor metabolism of this product in glycerol and in di-n-propylacetic acid.

In view of these results, it seems obvious that the glyceryl tri-(di-n-propylacetate) does not have any value as a product permitting a slow liberation of the di-n-propylacetic acid, although this triester had been presented as such in the literature.

The 1,2-propanediol bis-(di-n-propylacetate), as such, is a compound covered generally by the aforesaid Patent No. 1 289 620 of the German Federal Republic.

Tests carried out on man, within the range of the present invention, have shown that the oral administration of this diester permits a slow liberation of the di-n-propylacetic acid.

Nevertheless, the blood levels in this acid as thus produced do not reach the therapeutic thresholds.

Pharmacokinetic tests carried out on the animal have shown that the glyceryl 1-(di-n-propylacetate), the glyceryl 1,2-bis-(di-n-propylacetate) and the glyceryl 1,3-bis-(di-n-propylacetate) have the qualities which are required for

causing the liberation of the di-n-propylacetic acid at a decreasing speed in the animal organism. Nevertheless, it was found, as a consequence, in quite a surprising and unforeseeable manner, that among the esters formed from di-n-propylacetic acid and from glycerol or propanediol themselves, the glycerol diesters, namely, the glyceryl 1,2-bis-(di-n-propylacetate) and the glyceryl 1,3-bis-(di-n-propylacetate) are capable of causing a slow release of the di-n-propylacetic acid in a human being to a degree permitting therapeutic blood levels in this acid to be reached.

Pharmacokinetic tests carried out within the scope of the invention have shown that the blood levels in di-n-propylacetic acid, obtained after oral administration of 950 mg of glyceryl tri-(di-n-propyl acetate) in man are too low and, in all the cases, lower than 20 $\mu\text{g/ml}$ at the maximum blood level which is reached, although the therapeutic blood levels in this acid are included between 50 and 100 $\mu\text{g/ml}$, that is to say, between about 300 and 600 $\mu\text{moles/ml}$.

This conclusion is in conformity with the results found by J.W.A. MEIJER and R. KALFF as previously referred to.

The low bioavailability of this triglyceride is probably due to a poor metabolism of this compound, as in the case of the animal. As regards the glyceryl 1-(di-n-propylacetate), the metabolism in glycerol and in di-n-propylacetic acid was found to be too fast. Similarly, the blood levels in di-n-propylacetic acid produced in man by oral administration of 1000 mg of 1,2-propanediol-bis-(di-n-propylacetate) reach a maximum lower than 15 $\mu\text{g/ml}$ (100 mmole/l), whereas 1000 mg of mixture of glyceryl 1,3-bis-(di-n-propylacetate)/glyceryl 1,2-

bis-(di-n-propylacetate) "mixture B" produces under the same conditions, high blood levels in di-n-propylacetic acid. These blood levels are about four times higher (better than 400 mmole/l) than those obtained when starting with the propanediol diester, as a result reaching therapeutic levels. There will be found hereinafter the results of some pharmacological and pharmacokinetic tests which show the particular qualities of the compounds of the present invention:

IV. Pharmacological study

The results of trials carried out with the di-n-propylacetyl derivatives of the invention, in order to determine the anticonvulsant action, are set out below.

A. Pentylenetetrazole-induced crisis.

The anticonvulsant action was determined by using pentylenetetrazole as convulsant agent.

Batches of 10 rats were treated by oral route with a dose of 600 mg/kg of glyceryl 1-(di-n-propylacetate).

At different times after the administration, the animals received an intraperitoneal dose of 125 mg/kg of pentylene-tetrazole.

The percentage of protection against the convulsive seizure or crisis at the different times in question was then determined.

A concurrent test was also carried out with 100 mg/kg of di-n-propylacetic acid.

This dose represents the amount of di-n-propylacetic acid required to provide a di-n-propylacetic acid blood-level equivalent to the maximum level obtained with 600 mg/kg of glyceryl

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1-(di-n-propylacetate).

The results obtained are given in the following Table in which are shown the percentage of protection achieved at the various times indicated:

Compound	Time in hours after the pentylenetetrazol injection					
	0.5	1	2	4	8	16
Glyceryl 1-(di-n-propylacetate)	29	56	41	43	35	22
di-n-Propylacetic acid	23	0	0	0	0	0

B. Chronic cobalt-induced epilepsy

This trial was performed in comparison with sodium di-n-propylacetate. Batches of rats were given, for 14 days, either two daily intraperitoneal doses of 200 mg/kg (morning and evening) of sodium di-n-propylacetate or a daily intraperitoneal dose of 400 mg/kg (evening) of a mixture of glyceryl 1,2- and 1,3-bis-(di-n-propylacetates) ("Mixture A").

Encephalographic records were made each morning in comparison with control animals. The results are given below:

	Controls	Sodium di-n-propylacetate	Mixture of di-glycerides
Number of rats presenting at least one crisis or seizure	7/7	3/4	0/2
Number of seizures between the 7th and 14th days	3.57	1.25	0

V. Pharmacokinetic study

The results obtained from pharmacokinetic studies carried out with esters of the invention will be apparent from the

description which is to follow by reference to the annexed drawings.

A. Pharmacokinetic study in animals

The first series of Figures represent blood-levels in acid of formula V above in relation to time, this acid being either released from one of its salts or from an ester of the invention.

FIG. 1 : represents blood-levels in di-n-propylacetic acid obtained from:

- a) An oral dose to rats of 600 mg/kg :
of glyceryl 1-(di-n-propylacetate) (Curve 1)
or glyceryl 1,2-bis-(di-n-propylacetate) (Curve 2)
or glyceryl 1,3-bis-(di-n-propylacetate) (Curve 3).
- b) An intravenous dose to rats of 200 mg/kg of sodium di-n-propylacetate (Curve 4)

The curves show that, in the animal, glyceryl 1-(di-n-propylacetate), when metabolised to di-n-propylacetic acid, resists the too-rapid elimination of this acid and maintains a high blood-level in this acid.

Furthermore, the pharmacokinetic behaviour of these two diesters is very similar. The blood-levels in di-n-propylacetic acid, obtained from these esters, are very similar to those observed from the 2nd to the 24th hour after the injection of sodium di-n-propylacetate.

FIG. 2 : represents blood-levels in 2-methyl-2-ethylhexanoic acid obtained from:

- a) An oral dose to rabbits of:
596 mg/kg of glyceryl 1-(2-methyl-2-ethylhexanoate)
(Curve 1)

207 mg/kg of glyceryl 1,2-bis-(2-methyl-2-ethylhexanoate) (Curve 2)

- b) An intravenous dose to rabbits of 82.2 mg/kg of sodium 2-methyl-2-ethylhexanoate (Curve 3)

FIG 3 : represents blood-levels in 1-methyl-cyclohexylcarboxylic acid obtained from:

- a) An oral dose to rats of 600 mg/kg:
 - of glyceryl 1-(1-methyl-cyclohexylcarboxylate) (Curve 1)
 - or glyceryl 1,2-bis-(1-methyl-cyclohexylcarboxylate) (Curve 2)
 - or glyceryl 1,2,3-tri-(1-methyl-cyclohexylcarboxylate) (Curve 3)
- b) An intravenous dose to rats of 200 mg/kg of sodium 1-methyl-cyclohexylcarboxylate (Curve 4).

The results show that higher blood-levels in 1-methyl-cyclohexylcarboxylic acid can be obtained with the mono-glyceride than with the diglyceride, this latter being itself better metabolised to 1-methyl-cyclohexylcarboxylic acid and than triglyceride.

FIG. 4 : represents blood-levels in di-n-propylacetic acid obtained from:

- a) An oral dose to rabbits of 562 mg/kg of glyceryl 1-(di-n-propylacetate)-2-(1-methyl-cyclohexylcarboxylate) (Curve 1)
- b) An intravenous dose to rabbits of 200 mg/kg of sodium di-n-propylacetate (Curve 2)

FIG. 5 : represents blood-levels in 1-methyl-cyclohexylcarboxylic acid obtained from:

- a) An oral dose to rabbits of 562 mg/kg of glyceryl 1-(di-n-propylacetate)-2-(1-methyl-cyclohexylcarboxylate) (Curve 1)

- b) An intravenous dose to rabbits of 100 mg/kg of sodium 1-methyl-cyclohexylcarboxylate (Curve 2)

The results show that stable blood-levels in di-n-propylacetic acid and 1-methyl-cyclohexylcarboxylic acid can be maintained for at least 30 hours with the diglyceride.

B. Pharmacokinetic study in the human being

FIG. 6 : represents blood-levels in di-n-propylacetic acid obtained from:

- a) An oral dose of 600 mg of glyceryl 1-(di-n-propylacetate) (Curve 1)
- b) An oral dose of 476 mg of glyceryl 1,2-bis-(di-n-propylacetate) (Curve 2)
- c) An oral dose of 460 mg of sodium di-n-propylacetate (Curve 3).

The results show that the blood-levels in di-n-propylacetic acid produced by the metabolism of glyceryl 1-(di-n-propylacetate) are very close to the blood-levels obtained after administration of sodium di-n-propylacetate (460 mg of sodium di-n-propylacetate are equivalent to 600 mg of glyceryl 1-(di-n-propylacetate) with respect to the amount of di-n-propylacetyl anion).

Consequently, the oral administration of 600 mg of glyceryl 1-(di-n-propylacetate) does not present any advantage in comparison with 460 mg of sodium di-n-propylacetate.

This result proves that the monoester in question is quite inadequate for inducing a slow-release of di-n-propylacetic acid in the blood.

FIG. 7 : represents the blood-levels in di-n-propylacetic acid obtained from the oral administration of 1000 mg of glyceryl

1,2-bis-(di-n-propylacetate) every 24 hours for 4 days.

The results show that the blood-levels in di-n-propylacetic acid varied from about 300 to 550 $\mu\text{mol/l}$ (50 to 90 $\mu\text{g/ml}$).

Consequently, a single oral administration of this 1,2-diester every 24 hours is capable of maintaining therapeutic blood-levels in di-n-propylacetic acid.

This level cannot be obtained with three oral administrations per day of sodium di-n-propylacetate, each of 400 mg.

Very similar results have been recorded in the human being with glyceryl 1,3-bis-(di-n-propylacetate).

This compound even seems to present better bioavailability than that of the corresponding 1,2-diester.

FIG. 8 : represents the blood-levels in di-n-propylacetic acid obtained from:

- a) An oral dose of 1000 mg of mixtures of glyceryl 1,2-bis-(di-n-propylacetate)/glyceryl 1,3-bis-(di-n-propylacetate) ("Mixtures A and B" referred to above) (Curves 1 to 5)
- b) An oral dose of 1000 mg of sodium di-n-propylacetate (Curve 6).

The results show that the kinetics of release of di-n-propylacetic acid from the above-cited mixtures are very similar to that obtained with the 1,2-diester alone or the 1,3-diester alone.

The apparent half-life of di-n-propylacetic acid released from these mixtures was found to be 20 h 20 min. whereas that of di-n-propylacetic acid after the oral administration the sodium salt of this compound was 11 h 35 min.

From all the results of the above trials, it can be concluded that glyceryl 1,2-bis-(di-n-propylacetate), glyceryl 1,3-bis-(di-n-propylacetate) and the mixtures of glycerol di-n-propylacetic ^{di-}esters as hereabove defined present, in the human being, important advantages which can be summarised as follows:

- The high blood-levels in di-n-propylacetic acid appearing 30 min. to 1 hour after the oral administration of 300 to 500 mg of sodium di-n-propylacetate, can be avoided, which levels cause undesirable side-effects, such as dizziness,
- the dosage is rendered easier, because a single daily administration i.e. about 500 mg/25 kg of body weight/24 hours gives rise, from the fourth day after the first administration, to constant therapeutic blood-levels varying from 50 to 100 µg/ml of di-n-propylacetic acid. This advantage cannot be obtained with several daily administrations of sodium di-n-propylacetate as at present commercially available, even when this product is given in the known galenic slow-release form,
- the therapeutic protection is better, because the blood-level in di-n-propylacetic acid is more stable.

Furthermore, it has been demonstrated that the compounds of the invention are of extremely low toxicity.

The results of acute toxicity tests obtained with compounds of the invention are given below:

a) Glyceryl 1,2-bis-(di-n-propylacetate)

LD₀ in rats by oral route : > 5000 mg/kg

LD₀ in rats by intraperitoneal route : > 2000 mg/kg

Similar results were obtained in mice.

b) Glyceryl 1-(di-n-propylacetate)

LD₅₀ in rats by oral route : 2365 mg/kg

LD₅₀ in mice by oral route : 3361 mg/kg

c) Mixture of glyceryl 1,2-bis-(di-n-propylacetate)/glyceryl 1,3-bis-(di-n-propylacetate) ("Mixture A")

LD₅₀ in rats by oral route : >5000 mg/kg

LD₅₀ in rats by intraperitoneal route : 2368 mg/kg

LD₀ in mice by oral route : >5000 mg/kg

LD₅₀ in mice by intraperitoneal route : 2515 mg/kg

d) Mixture of glyceryl 1,2-bis-(di-n-propylacetate)/glyceryl 1,3-bis-(di-n-propylacetate) ("Mixture B")

LD₅₀ in rats by oral route : >5000 mg/kg

LD₅₀ in rats by intraperitoneal route : 2368 mg/kg

LD₅₀ in mice by oral route : 5597 mg/kg

LD₅₀ in mice by intraperitoneal route : 1920 mg/kg

By comparison, the LD₅₀ of sodium di-n-propylacetate by oral route in rats and mice is 1530 mg/kg and 1700 mg/kg, respectively.

The therapeutic compositions according to the invention can be presented in any form suitable for administration in human or veterinary therapy. As regards the unit of administration, this latter may take the form, for example, of a tablet, a capsule, a microcapsule, a gelatine capsule, an aqueous emulsion or a drinkable ampoule for oral administration or a solution or suspension for parenteral administration.

The unit of administration will be able to contain, for example, from 50 to 600 mg of active ingredient for the oral administration.

Depending on the administration route which is chosen, the pharmaceutical or veterinary compositions of the invention will be prepared by associating at least one of the compounds of the invention with at least one appropriate excipient or vehicle, which latter may be formed of at least one ingredient selected from the following substances: gelatine, glycerol, ethyl p-hydroxybenzoate (sodated), propyl p-hydroxybenzoate (sodated).

The following examples illustrate the preparation of the glycerol esters of the invention, and also a therapeutic composition containing them:

Example 1

Preparation of glyceryl (1-di-n-propylacetate)

A. 1-(Di-n-propylacetyl)-2,3-isopropylidene glycerol or 2,2-dimethyl-4-(di-n-propylacetoxymethyl)-1,3-dioxolan.

a) 1,2-Isopropylidene glycerol

Into a 1000 ml flask are introduced 92.1 g (1 mol) of glycerol, 217 g (3.75 mol) of acetone, 179 g (2.75 ml) of petroleum ether and 2.75 g (0.015 mol) of p-toluenesulphonic acid. While stirring, the mixture is heated under reflux and the water thus formed is eliminated until the end of the decantation.

This operation is completed in 25 to 30 hours. After cooling, the p-toluenesulphonic acid is neutralised by adding 1.20 g (0.009 mol) of potassium carbonate. 30 minutes later, the medium is filtered while stirring. The filtrate is transferred into a 1000 ml flask equipped with a refrigerant and the solvents are eliminated under atmospheric pressure and at a temperature of 90°C in the mass.

The concentrate is distilled under reduced pressure and the fraction boiling at $80^{\circ}\text{C} \pm 1^{\circ}$ at 12 mmHg is recovered.

In this way, there are obtained 95 g of 1,2-isopropylidene glycerol in the form of a colourless liquid.

Yield: 72 %.

Using the same method as that described above, the following compounds are prepared:

Compounds

2-Methyl-2-ethyl-4-hydroxymethyl-1,3-dioxolan.

Yield: 54.7 %

$$n_D^{20} = 1.4404$$

Infra-red spectrum (film): OH large at 3450 cm^{-1}
 CH_3, CH_2 at 2990 cm^{-1} (F)
 2950 cm^{-1} (F)
 2890 cm^{-1} (F)
C-O-C large at 1060 cm^{-1}

2-Methyl-2-isobutyl-1,3-hydroxymethyldioxolan

Yield: 75.2 %

$$n_D^{20} = 1.4432$$

Infra-red spectrum (film) : OH large at 3450 cm^{-1}
 $\text{CH}_3, \text{CH}_2, \text{CH}$ at 3000 cm^{-1}
 2970 cm^{-1} (F)
 2940 cm^{-1} (F)
 2880 cm^{-1} (F)
C-O-C at 1045 cm^{-1}

1,2-Cyclohexylidene-glycerol

Yield : 35 %

$$n_D^{20} = 1.4801$$

Infra-red spectrum (film) : OH large at 3450 cm^{-1}
 CH_3 , CH_2 at 2950 cm^{-1} (F)
 2870 cm^{-1} (m)
 C-O-C at 1100 cm^{-1} (F)

b) 1-(Di-n-propylacetyl)-2,3-isopropylidene-glycerol

Into a perfectly dry flask are introduced 132.2 g (1 mol) of 1,2-isopropylidene-glycerol, 118.7 g (1.5 mol) of pyridine and 271 g (290 ml) of N,N-dimethylformamide.

While stirring, 162.7 g (1 mol) of di-n-propylacetyl chloride are introduced. This operation lasts 30 minutes. The reaction medium is then heated to $65^\circ\text{C} \pm 5^\circ$ for 2 hours, cooled to room temperature and hydrolysed with 1200 g of distilled water. After this operation, the mixture is extracted, while stirring for 30 minutes, with two fractions each of 700 g (528 ml) of methylene chloride. The organic fractions are collected and they are washed successively with 300 g of a 5 % aqueous solution of sodium bicarbonate and three fractions, each of 300 g, of distilled water. After decantation, the mixture is dried on sodium sulphate, then filtered and rinsed with a minimum amount of methylene chloride. The solvent is eliminated under reduced pressure at a maximum temperature of 50°C . The concentrate is distilled under reduced pressure and the fraction boiling at $93^\circ\text{C} \pm 2^\circ$ under 1 mmHg is collected.

In this manner, 224.5 g of 1-(di-n-propylacetyl)-2,3-isopropylidene-glycerol are obtained in the form of a colourless liquid.

Yield : 87 %

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$$n_D^{21} = 1.4344$$

Infra-red spectrum : CH_3 , CH_2 at 2970 cm^{-1} (F)
 2940 cm^{-1} (F)
 2880 cm^{-1} (m)
 CO ester at 1740 cm^{-1} (F)
 1175 cm^{-1} (m)
 C-O-C at 1060 cm^{-1}

Using the same method as that described above, the following compounds are prepared:

Compounds

1-(Di-n-propylacetyl)-2,3-cyclohexylidene-glycerol

Yield : 74.7 %

$$n_D^{21} = 1.4583$$

Infra-red spectrum (film) : CH_3 , CH_2 at 2950 cm^{-1} (F)
 2875 cm^{-1} (F)
 CO ester at 1740 cm^{-1} (F)
 1770 cm^{-1} (F)
 C-O-C at 1100 cm^{-1} (F)

1-(Tri-n-propylacetyl)-2,3-isopropylidene-glycerol

(after sodation of 1,2-isopropylidene-glycerol in excess and esterification at $88/90^\circ\text{C}$ in N,N-dimethylformamide)

Yield : 88.7 %

$$n_D^{22} = 1.4430$$

Infra-red spectrum (film) : CH_3 , CH_2 at 2970 cm^{-1} (F)
 2945 cm^{-1} (m)
 2880 cm^{-1} (F)
 CO ester at 1735 cm^{-1} (F)
 1210 cm^{-1} (F)
 C-O-C at 1145 cm^{-1} (F)

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1-(2-Ethylhexanoyl)-2,3-isopropylidene-glycerol

Yield : 77.5 %

$$n_D^{20} = 1.4341$$

Infra-red spectrum (film) : CH_3, CH_2 at 2980 cm^{-1} (F)
 2950 cm^{-1} (F)
 2990 cm^{-1} (m)
CO ester at 1745 cm^{-1} (F)
 1175 cm^{-1} (F)
C -O-C at 1220 cm^{-1} (F)

1-(1-Methyl-cyclohexylcarbonyl)-2,3-isopropylidene-glycerol

Yield : 67.3 %

$$n_D^{20} = 1.4562$$

Infra-red spectrum (film) : CH_3, CH_2 at 3000 cm^{-1} (m)
 2950 cm^{-1} (F)
 2865 cm^{-1} (m)
CO ester at 1735 cm^{-1} (F)
 1165 cm^{-1} (m)

1-(2-Methyl-2-ethylhexanoyl)-2,3-isopropylidene-glycerol
(sodation of 1,2-isopropylidene-glycerol)

Yield : 74.3 %

Infra-red spectrum (film) : CH_3, CH_2 at 2970 cm^{-1} (F)
 2895 cm^{-1} (F)
CO ester at 1735 cm^{-1} (F)
 1160 cm^{-1} (F)

1-(Di-n-propylmethoxyacetyl)-2,3-isopropylidene-glycerol

1-(4-n-Propylheptanoyl)-2,3-isopropylidene-glycerol

1-(5-n-Propyloctanoyl)-2,3-isopropylidene-glycerol

B. Glyceryl 1-(di-n-propylacetate)

Into a flask are introduced 258.4 g (1 mol) of 1-(di-n-propylacetyl)-2,3-isopropylidene-glycerol, 410 g (520 ml) of methanol and 125 ml of 3N-hydrochloric acid. The reaction medium is maintained while stirring at room temperature for about 3 hours. After this operation, the solvents ^{are} ~~is~~ eliminated without going beyond 40°C in the mass. The concentrate is transferred into a dropping funnel and extracted with two fractions, each of 860 g (650 ml) of methylene chloride. The extracts are collected and washed successively with 2 fractions each of 390 ml of a 5 % aqueous solution of sodium bicarbonate and 2 fractions each of 400 ml of distilled water. After drying on sodium sulphate, the mixture is filtered. The solvent is evaporated out at a temperature lower than 50°C and then under vacuum of about 1 mmHg to constant weight.

In this manner, 203 g of glyceryl 1-(di-n-propylacetate) are obtained in the form of a practically colourless liquid.

$$n_D^{20} = 1.4513$$

Infra-red spectrum (film) : OH large at 3470 cm^{-1}
 CH_3 , CH_2 at 2970 cm^{-1} (F)
 2950 cm^{-1} (F)
 2890 cm^{-1} (F)
 CO ester at 1740 cm^{-1} (F)
 shoulder at 1720 cm^{-1}
 1180 cm^{-1} (m)

Using the same method as that described above, the following compounds are prepared:

Compounds

Glyceryl 1-(tri-n-propylacetate)

Yield : 92 %

$n_D^{20} = 1.4561$

Infra-red spectrum (film) : OH large at 3430 cm^{-1}
 CH_3, CH_2 at 2965 cm^{-1} (F)
 CH at 2880 cm^{-1} (F)
 CO ester at 1730 cm^{-1} (F)
 1215 cm^{-1} (F)

Glyceryl 1-(2-ethylhexanoate)

Yield : 95 %

$n_D^{22} = 1.4511$

Infra-red spectrum (film) : OH large at 3530 cm^{-1}
 CH_3, CH_2 at 2970 cm^{-1}
 2945 cm^{-1}
 2880 cm^{-1}
 CO ester at 1740 cm^{-1} (F)
 shoulder at 1725 cm^{-1}
 1180 cm^{-1} (m)

Glyceryl 1-(1-methyl-cyclohexylcarboxylate)

Yield : 87 %

$n_D^{20} = 1.4769$

Infra-red spectrum (film) : OH large at 3420 cm^{-1}
 CH_3, CH_2 at 2940 cm^{-1} (F)
 2865 cm^{-1} (F)
 CO ester at 1725 cm^{-1} (F)
 1170 cm^{-1} (F)

Glyceryl 1-(2-ethyl-2-methylhexanoate)

Yield : 92 %

$$n_D^{22} = 1.4532$$

Infra-red spectrum (film) : OH large at 3420 cm^{-1}

CH_3, CH_2 at 2970 cm^{-1} (F)

2940 cm^{-1} (F)

2880 cm^{-1} (m)

CO ester at 1730 cm^{-1} (F)

Glyceryl 1-(di-n-propylmethoxyacetate)

Yield : 40.5 %

$$n_D^{14} = 1.4593$$

Infra-red spectrum (film) : OH at 3400 cm^{-1} (F)

C=O at 1755 cm^{-1} (F)

CO ester at 1200 cm^{-1} (F)

Glyceryl 1-(4-n-propylheptanoate)

Yield : 42.6 %

$$n_D^{20} = 1.4585$$

Infra-red spectrum (film) : OH at 3400 cm^{-1} (m)

C=O at 1740 cm^{-1} (F)

CO ester at 1175 cm^{-1} (m)

Glyceryl 1-(5-n-propyloctanoate)

Yield : 67.5 %

$$n_D^{20} = 1.4595$$

Infra-red spectrum (film) : OH at 3400 cm^{-1} (F)

C=O at 1740 cm^{-1} (F)

CO ester at 1170 cm^{-1} (m)

EXAMPLE 2

Preparation of glyceryl 2-(di-n-propylacetate)

a) 1,3-Benzylidene-glycerol or 2-phenyl-1,3-dioxane-5-ol

Into a 500-ml flask are introduced 92.1 g (1 mol) of

glycerol, 78 g (100 ml) of benzene, 111.3 g (1.05 mol) of benzaldehyde and 0.2 g of p-toluenesulphonic acid.

While stirring, the mixture is refluxed and the water thus formed is eliminated. This operation takes about 4 hours. The solvent is then evaporated out under vacuum and an oily residue of about 188 g is obtained. This residue is distilled and the fraction boiling at $114 \pm 2^\circ\text{C}$ under 0.1 mm Hg is collected. Thereafter, 0.35 g of gaseous hydrochloric acid is bubbled in the distillate, the medium is homogenised and allowed to stand for 8 days in a refrigerator.

After 12 hours at 0°C , a mass is formed. This mass is dissolved by heating in about 1075 g (1500 ml) of ethyl ether. The organic layer is washed with 70 ml of an aqueous ammonia solution (1 % in NH_3), dried on sodium sulphate and crystallised at -5°C . After suction-filtration, the product is dried under vacuum at 40°C to constant weight.

In this manner, about 80 g of 1,3-benzylidene-glycerol are obtained.

Yield : about 45 %.

b) 1,3-Benzylidene-2-(di-n-propylacetyl)-glycerol

Into a flask are introduced 180.2 g (1 mol) of crude 1,3-benzylidene-glycerol and 782.5 g (1.5 mol) of anhydrous pyridine.

While stirring, 244 g of di-n-propylacetyl chloride are added at room temperature. This operation requires 20 minutes. The mixture is then heated to 60°C and maintained at this temperature for 2 hours. The pyridine in excess is then eliminated at 50°C under vacuum and the residue is taken up

in 715 g (1000 ml) ^{of} ethyl ether. The medium is extracted with a 5 % aqueous solution of potassium carbonate to obtain a pH = 7 to 8 and then with distilled water to obtain a pH = 6 to 7. After drying on sodium sulphate, the mixture is filtered, the solvent is evaporated under vacuum and the extract thus obtained is rectified by distillation. The fraction boiling between 150 and 152°C under 0.5 mm Hg is collected.

In this manner, 257 g of 1,3-benzylidene-2-(di-n-propylacetyl)-glycerol are obtained.

Yield : 83.9 %.

c) Glyceryl 2-(di-n-propylacetate)

Into a 2000 ml flask are introduced 947 g (1200 ml) of absolute ethanol, 122.6 g (0.4 mol) of 1,3-benzylidene-2-(di-n-propylacetyl)-glycerol and 8 g of 5 % palladium charcoal. The apparatus is then flushed with nitrogen. Thereafter, 18.8 l of hydrogen were bubbled at room temperature and under normal pressure. This operation lasts 7 hours. The apparatus is then cleared with nitrogen and the catalyst is filtered out. The filtrate is heated to a maximum of 50°C and to constant weight under 1 mm Hg.

In this manner, 87.7 g of glyceryl 2-(di-n-propylacetate) are obtained in the form of a colourless slightly viscous liquid.

Yield : quantitative

$$n_D^{22} = 1.4512$$

Infra-red spectrum (film) : OH large at 3450 cm⁻¹

CH₃, CH₂ at 2970 cm⁻¹ (F)

2950 cm⁻¹ (F)

2890 cm^{-1} (m)
CO ester at 1745 cm^{-1} (F)
1720 cm^{-1} (F)
C-O at 1180 cm^{-1} (m)

EXAMPLE 3

Preparation of glyceryl 1,2-bis-(di-n-propylacetate)

a) 1-Benzyl-2,3-isopropylidene-glycerol

Into a perfectly dry 2000 ml flask are introduced 500 g (575 ml) of toluene and 19.8 g (0.86 at.g.) of sodium.

The mixture is heated under reflux with vigorous stirring to obtain a good dispersion of the sodium. After this operation, the medium is cooled, always with vigorous stirring.

At a temperature of $+10/+20^{\circ}\text{C}$, 132.2 g (1 mol) of 1,2-isopropylidene-glycerol are then slowly added. This operation lasts about 30 minutes. The reaction medium is then heated under reflux for about 1 hour and after cooling to room temperature, 108.9 g of benzyl chloride are added in one portion. The medium is progressively heated to reflux for about 1 hour and the total reflux is maintained for 30 minutes. After cooling, the toluene is evaporated off under ^{reduced} pressure and 1070 g (1500 ml) of ethyl ether are added. The salts are filtered out and rinsed with 360 g (500 ml) of ethyl ether. The solvent is eliminated under reduced pressure and the concentrate is rectified by distillation. The fraction boiling at $125^{\circ}\text{C} \pm 2^{\circ}$ under 3 mm Hg is collected.

In this manner, 166.7 g of 1-benzyl-2,3-isopropylidene-glycerol are obtained.

Yield : 75 %

B.P. : $117 - 121^{\circ}\text{C}$ under 3 mm Hg.

b) 1-Benzyl-glycerol

Into a flask are introduced 222.3 g (1 mol) of 1-benzyl-2,3-isopropylidene-glycerol and 567 g of a 10 % aqueous solution of acetic acid. While stirring, the mixture is heated on a water-bath ($t^{\circ} = 95^{\circ}\text{C}$) for 1 hour. The solvents are eliminated under reduced pressure and the concentrate is rectified by distillation under vacuum. The fraction boiling between $132-135^{\circ}\text{C}$ under 0.6 mm Hg is collected in the form of a colourless liquid.

In this manner, 160 g of 1-benzyl-glycerol are obtained.
Yield: 88 %

Infra-red spectrum (film) : OH large at 3400 cm^{-1}
C-H aromatic 3080 cm^{-1} (f)
 3040 cm^{-1} (m)
 CH_3, CH_2 2930 cm^{-1} (F)
 2870 cm^{-1} (F)
C=C aromatic 1610 cm^{-1} (f)
 1590 cm^{-1} (f)

c) Benzyl-2,3-bis-(di-n-propylacetyl)-glycerol

Into a 2000 ml flask are introduced 182.2 g (1 mol) of 1-benzyl-glycerol and 978 g (1000 ml) of anhydrous pyridine.

While stirring at room temperature, 341 g (2.1 mols) of di-n-propylacetyl chloride are slowly added. The medium is heated to $50-55^{\circ}\text{C}$ and maintained at this temperature for 90 minutes. The pyridine in excess is eliminated under vacuum and the residue is taken up with 3000 g of distilled water. After extraction with two fractions each of 2500 ml of ethyl ether, the organic phase is successively washed with 3000 ml of

a 7 % aqueous solution of hydrochloric acid, 3000 ml of distilled water, 3000 ml of a 10 % aqueous solution of sodium bicarbonate and three fractions each of 2000 ml of distilled water. The mixture is dried on sodium sulphate, filtered and the solvent is eliminated under vacuum. The crude product as thus obtained is purified by chromatography on a column containing 4350 g of silica and using toluene as eluent.

In this manner, 355.2 g of ~~crude~~ 1-benzyl-2,3-bis-(di-n-propylacetyl)-glycerol are obtained.

Yield : 81.7 %

Using the same method as that described above, the following compounds are prepared:

Compounds:

1-Benzyl-2,3-bis-(2-ethylhexanoyl)-glycerol

Yield : 72 %

1-Benzyl-2,3-bis-(1-methyl-cyclohexylcarbonyl)-glycerol

Yield : 70 %

1-Benzyl-2,3-bis-(tri-n-propylacetyl)-glycerol

Yield : 51.7 %

1-Benzyl-2,3-bis-(2-ethyl-2-methylhexanoyl)-glycerol

Yield : 69.5 %.

d) Glyceryl 1,2-bis-(di-n-propylacetate)

Into a hydrogenation apparatus are introduced 4350 ml of pure ethanol, 434.3 g (1 mol) of 1-benzyl-2,3-bis-(di-n-propylacetyl)-glycerol and 26 g of 5 % palladium charcoal. The apparatus is cleared with nitrogen and then hydrogen is bubbled for 9 hours at room temperature and under atmospheric

pressure (22.4 l of hydrogen at 0°C/760 mm Hg). The apparatus is again cleared or flushed with nitrogen and the catalyst is filtered out.

The filtrate is heated at 50°C and then under vacuum (1 mm Hg) to dryness. In this manner, 344.g of glyceryl 1,2-bis-(di-n-propylacetate) are obtained in the form of a colourless liquid.

Yield : quantitative

$$n_D^{20} = 1.447$$

Infra-red spectrum (film) : OH large at 3500 cm^{-1}

CH₃, CH₂ at 2995 cm^{-1} (F)

2890 cm^{-1} (F)

2880 cm^{-1} (F)

CO ester at 1745 cm^{-1} (F)

1170 cm^{-1} (F)

Using the same method as previously, the following compounds are prepared:

Compounds

Glyceryl 1,2-bis-(2-ethyl-hexanoate)

Yield : quantitative

$$n_D^{20} = 1.4468$$

Infra-red spectrum (film) : OH large at 3500 cm^{-1}

CH₃, CH₂ at 2975 cm^{-1} (F)

2950 cm^{-1} (F)

2890 cm^{-1} (F)

CO ester at 1745 cm^{-1} (F)

shoulder at 1725 cm^{-1}

1175 cm^{-1}

Glyceryl 1,2-bis-(1-methyl-cyclohexylcarboxylate)

Yield : quantitative

$$n_D^{20} = 1.4773$$

Infra-red spectrum (film) : OH large at 3520 cm^{-1}

CH_3, CH_2 at 2940 cm^{-1} (F)

2870 cm^{-1} (F)

CO ester at 1735 cm^{-1} (F)

1175 cm^{-1} (F)

Glyceryl 1,2-bis-(tri-n-propylacetate)

Yield : quantitative

$$n_D^{20} = 1.4561$$

Infra-red spectrum (film) : OH large at 3500 cm^{-1}

CH_3, CH_2 at 2970 cm^{-1} (F)

2950 cm^{-1} (F)

2885 cm^{-1} (F)

CO ester at 1735 cm^{-1} (F)

1210 cm^{-1} (m)

Glyceryl 1,2-bis-(2-ethyl-2-methylhexanoate)

Yield : 78.7 %

$$n_D^{22} = 1.4519$$

Infra-red spectrum (film) : OH large at 3530 cm^{-1}

CH_3, CH_2 at 2975 cm^{-1} (F)

2950 cm^{-1} (F)

2890 cm^{-1} (F)

CO ester at 1735 cm^{-1} (F)

1150 cm^{-1} (F)

EXAMPLE 4

Preparation of glyceryl 1,3-bis-(di-n-propylacetate)

a) 1,3-bis-(di-n-Propylacetoxy)-acetone

Into a perfectly dry flask are introduced 680 g (935 ml) of isopropyl ether, 173.7 g (2.2 mols) of anhydrous pyridine and 90.1 g (1 mol) of dihydroxyacetone. While stirring at room temperature, 349.7 g (2.15 mols) of di-n-propylacetyl chloride are introduced in 30 minutes to 1 hour. The reaction medium is then refluxed at 65°C and maintained at this temperature for 3 hours. After cooling, the mixture is hydrolysed with 500 ml of iced distilled water. The organic layer is washed with a dilute hydrochloric acid solution to pH = 1 and then with water to neutrality. After drying on sodium sulphate, the solvent is evaporated at 50°C under vacuum.

The concentrate is rectified by distillation and the fraction boiling between 155-160°C under 0.2/0.3 mm Hg is collected.

In this manner, 205 g of crude 1,3-bis-(di-n-propyl-acetoxy)-acetone are obtained.

Yield : 60 %.

b) Glyceryl 1,3-bis-(di-n-propylacetate)

Into a flask are introduced 342.48 g (1 mol) of 1,3-bis-(di-n-propylacetoxy)-acetone, 2490 g (2800 ml) of tetrahydrofuran and 59.3 g (1.1 mol) of potassium borohydride. Thereafter, 880 g of distilled water and 110 g (1.1 mol) of 36 % hydrochloric acid are added, so that the pH of the medium remains between 7 and 8.

This operation lasts about 1 hour. If necessary, the pH is adjusted to 7-8. The medium is allowed to stand for 1 hour and then heated to dryness, while keeping the temperature below 45-50°C. The residue is taken up in ethyl ether,

washed with water to eliminate the salts, dried on sodium sulphate and heated to dryness. The residue is taken up in toluene and passed through a column containing about 3000 g of silica. The residual ketodiester is eluted with toluene and the desired product with chloroform. The chloroform fractions containing the desired compound are heated to dryness at a temperature below 50°C and then under vacuum, while not exceeding 50°C.

In this manner, 200 g of glyceryl 1,3-bis-(di-n-propylacetate) are obtained in the form of a pale yellow liquid.

Yield : 58 %

$n_D^{20} = 1.4472$

Infra-red spectrum : OH large at 350 cm^{-1}

CH_3, CH_2 at 2980 cm^{-1} (F)

2950 cm^{-1} (F)

2890 cm^{-1} (F)

CO ester at 1740 cm^{-1} (F)

EXAMPLE 5

Into a 500 ml flask are introduced 269 g (275 mol) of pyridine and 18.2 g (0.2 mol) of glycerol. While stirring, 100 g (0.623 mol) of 1-methyl-cyclohexylcarbonyl chloride are added in about 15 minutes. The reaction medium is progressively heated to 65/70°C in one hour and maintained at this temperature for 3 hours. After this operation, the mixture is refluxed for 2 hours and then cooled. The pyridine in excess is eliminated under vacuum and at a temperature of 60°C.

The pasty mass is taken up in 250 g of distilled water and extracted with two fractions, each of 250 ml of ethyl ether.

The organic extracts are collected and are washed successively with dilute hydrochloric acid to $\text{pH} = 1$, with water, with a 5 % aqueous solution of sodium carbonate to $\text{pH} \geq 10$ and finally with water to neutrality. After being dried on sodium sulphate, the mixture is heated to dryness and the oil thus obtained is taken up in toluene. It is passed through a column containing 730 g of silica and the fraction corresponding to the pure triglyceride is taken up in about 500 ml of ethyl ether. This solution is treated with 3 g of active charcoal, the solution obtained is filtered and heated to dryness at a temperature of $60-70^\circ\text{C}$ and under a pressure of 0.5-1 mm Hg.

In this manner, 50 g of glyceryl tri-(1-methyl-cyclohexylcarboxylate) are obtained in the form of a yellowish slightly viscous liquid.

Yield : 54 %

$n_D^{17} = 1.4812$

Infra-red spectrum (film) : CH_2 at 2940 cm^{-1} (F)

2860 cm^{-1} (m)

CO ester at 1740 cm^{-1} (F)

1205 cm^{-1} (F)

1160 cm^{-1} (F)

EXAMPLE 6

Preparation of glyceryl 1-(di-n-propylacetate)-3-(methyl-1-cyclohexylcarboxylate)

Into a perfectly dry flask are introduced 1000 ml of pyridine and 218 g (1 mol) of glyceryl 1-(di-n-propylacetate).

While stirring, 240 g (1.5 mol) of 1-methyl-cyclohexyl-

carbonyl chloride are progressively added at room temperature. Thereafter, the medium is heated to 40°C for 4 hours and then to 70°C for 6 hours. After cooling, the reaction mixture is hydrolysed by adding 5000 ml of distilled water. The medium is extracted with three fractions, each of 1000 ml of ethyl ether. The ethereal fractions are collected and washed successively with distilled water, a 2 % aqueous solution of hydrochloric acid and once again with distilled water. After drying on sodium sulphate, the ether is eliminated under reduced pressure, while not exceeding the temperature of 40°C.

The oil so obtained is passed through a column containing silica and eluted with a hexane/ethyl ether mixture.

In this manner, 88 g of glyceryl 1-(di-n-propylacetate)-3-(methyl-cyclohexylcarboxylate) are obtained.

$$n_D^{21} = 1.4608$$

Infra-red spectrum (film) : OH at 3500 cm^{-1} (m, f)

C=O at 1740 cm^{-1} (F)

Using the same procedure as previously described, the following compound is prepared:

Compound

Glyceryl 1-(di-n-propylacetate)-3-(2-methyl-2-ethylhexanoate)

$$n_D^{21} = 1.4490$$

Infra-red spectrum (film) : OH at 3500 cm^{-1} (f)

CH₃, CH₂ at 2970 cm^{-1} (F)

2940 cm^{-1} (F)

2880 cm^{-1} (F)

CO ester at 1730 cm^{-1} (F)

1150 cm^{-1} (f)

EXAMPLE 7

Preparation of glyceryl 1-(di-n-propylacetate)-2,3-(1-methyl-cyclohexylcarboxylate)

This compound is obtained (199.2 g) in addition to the glyceryl 1-(di-n-propylacetate)-3-(1-methyl-cyclohexyl-carboxylate in Example 6.

$$n_D^{20} = 1.4569$$

Infra-red spectrum (film) : CH_3 , CH_2 at 2970 cm^{-1}
 2940 cm^{-1} (F)
 2870 cm^{-1} (F)
 CO ester at 1740 cm^{-1} (F)
 1160 cm^{-1} (m)

EXAMPLE 8

Preparation of glyceryl 1-(di-n-propylacetate)-2-(1-methyl-cyclohexylcarboxylate)

a) 2,3-Epoxy-propyl di-n-propylacetate

Into a flask are introduced 70 g (0.48 mol) of di-n-propylacetic acid, 250 ml of toluene and 30 ml of N,N-dimethyl-formamide. After this operation, 40 g of 50 % aqueous solution of sodium hydroxide are added. This mixture is heated to $60^\circ\text{--}80^\circ\text{C}$ and 138.7 g (1.5 mol) of epichlorhydrin are introduced. The reaction medium is maintained under reflux for 6 hours at $70\text{--}80^\circ\text{C}$ and then concentrated in a rotary evaporator. After extraction with ethyl ether, the organic fractions are collected and distilled under 1 mmHg, recovering the fraction boiling between 76 and 78°C . In this manner, 2,3-epoxypropyl-di-n-propylacetate is obtained in the form of a limpid colourless liquid.

$$n_D^{21} = 1.4351$$

Infra-red spectrum (film) : CH_3 , CH_2 at 2975 cm^{-1} (F)
 2950 cm^{-1} (F)
 2890 cm^{-1} (F)
 CO ester at 1745 cm^{-1} (F)
 1180 cm^{-1} (F)
 $\text{CH}-\text{CH}_2$ at 1260 cm^{-1} (m)



b) Glyceryl 1-(di-n-propylacetate)-2-(1-methyl-cyclohexylcarboxylate)

4 g (0.02 mol) of 2,3-epoxypropyl-di-n-propylacetate and 5.6 g (0.04 mol) of 1-methyl-cyclohexylcarboxylic acid are heated in a flask at 70°C for 90 minutes. After this operation, a few drops of boron trifluoride etherate are added. The mixture is allowed to return to room temperature and is extracted with ethyl ether. The organic fractions are washed with sodium carbonate and the ether is evaporated off. The mixture of 1,2- and 1,3-diester as thus obtained is then purified by chromatography on a column containing silica.

In this manner, glyceryl 1-(di-n-propylacetate)-2-(1-methyl-cyclohexylcarboxylate) is obtained.

EXAMPLE 9

Preparation of a mixture of glyceryl 1,2- and 1,3-bis-(di-n-propylacetates) (Mixture A)

Into a perfectly dry flask are introduced 9.1 kg (9.3 l) of pyridine and 1.229 kg (13.36 mols) of glycerol.

With vigorous stirring, the mixture is cooled to $0/-5^\circ\text{C}$. Thereafter, 4.340 kg (26.72 mols) of di-n-propylacetate

chloride are added, care being taken to keep the reaction medium below 10°C. This operation takes 3 h 30 min. The temperature of the medium is then allowed to return to room temperature and the medium is allowed to stand for about 15 hours. Under reduced pressure and without exceeding 50°C, the pyridine is then distilled off.

After cooling, 3.5 l of water and 3.5 l of benzene are added.

The aqueous phase containing the pyridine hydrochloride is decanted and is again extracted with 3 l of benzene. The fractions are collected and successively washed with a 36 % aqueous solution of hydrochloric acid to pH = 1 and then with distilled water until neutral.

The benzene is eliminated by distillation under reduced pressure without exceeding 50°C in the mass. The crude ester is then rectified in fractions, each of 700 to 800 g, and the fraction boiling between 130°C/0.5 mm Hg and 135°C/0.1 mm Hg is collected.

In this manner, 3.420 kg of a mixture of glyceryl 1,2- and 1,3-bis-(di-n-propylacetates) ("Mixture A") are obtained.

Yield : 78 %

$$n_D^{20} = 1.4461$$

Infra-red spectrum (film) : OH large at 3490 cm⁻¹

CH₃, CH₂ at 2950 cm⁻¹ (F)

2880 cm⁻¹ (F)

CO ester at 1730 cm⁻¹ (F)

1150 cm⁻¹ (F)

and large

The mixture thus obtained contains:

- about 90 % of glyceryl 1,2- and 1,3-~~di~~-(di-n-propylacetates) i.e. about 70 % of 1,3-diester and about 30 % of 1,2-diester
- about 7 % of glyceryl 1-(di-n-propylacetate)
- about 2 % of glyceryl tri-(di-n-propylacetate)
- about 1 % of impurities i.e. glycerol and di-n-propylacetic acid.

EXAMPLE 10

Preparation of a mixture of glyceryl 1,2- and 1,3-bis-(di-n-propylacetates) ("Mixture B")

Into a 2-l flask equipped with a reflux condenser are introduced 893 g (900 ml) of N,N-dimethylformamide, 77.4 g (0.6 mol) of 1,3-dichloro-2-propanol and 206.4 g (1.24 mol + 3 %) of sodium di-n-propylacetate. Under nitrogen atmosphere and with vigorous stirring, the medium is brought to 100°C and this temperature is maintained for 8 hours. The maximum quantity of solvent is then distilled off under reduced pressure ($\sim$ 20 mm Hg) and 893 g of a distillate is recovered.

To the residue as thus obtained ($\sim$ 350 g) are added 300 g of distilled water and 537 g (620 ml) of toluene. The organic phase is successively washed with 300 g of distilled water, a solution of 30 g of sodium carbonate in 400 g of distilled water and finally with as many fractions of 300 g of distilled water as required to obtain a neutral pH. After drying on sodium sulphate, the solvent is eliminated under reduced pressure with a rotary evaporator, in order to obtain a crude mixture of final products ($\sim$ 201 g; $\sim$ 97.3 %). This mixture is rectified under high vacuum and the fraction

boiling at 152°C under 0.2 mm Hg is collected. In this manner, a mixture of glyceryl 1,2- and 1,3-bis-(di-n-propylacetates) ("Mixture B") is obtained in the form of a colourless liquid.

$$n_D^{20} = 1.4476$$

Glyceryl 1,3-bis(di-n-propylacetate)/glyceryl 1,2-bis-(di-n-propylacetate) = 1.54

Glyceryl 1-(di-n-propylacetate) : about 1 %

Glyceryl tri-(di-n-propylacetate) : not detected (< 0.5 %)

1,3-Dichloro-2-propanol : 0.002 %.

Following the same procedure as previously, the following mixtures of diesters are prepared :

Mixtures

Glyceryl 1,2-bis-(di-n-propylpropionate) and glyceryl 1,3-bis-(di-n-propylpropionate)

B.P. : 172-180°C under 0.4 mm Hg.

$$n_D^{23} = 1.4567$$

Infra-red spectrum (film) : OH at 3480 cm^{-1} (m)

C=O at 1740 cm^{-1} (F)

C-O at 1170 cm^{-1} (m)

Glyceryl 1,2-bis-(di-n-propylmethoxyacetate) and glyceryl 1,3-bis-(di-n-propylmethoxyacetate)

$$n_D^{14} = 1.4556$$

Infra-red spectrum (film) : OH at 3480 cm^{-1} (m)

C=O at 1755 cm^{-1} (F)

COO at 1100-1200 cm^{-1} (m)

Other tests for the preparation of a mixture of glyceryl 1,2- and 1,3-bis-(di-n-propylacetates) were carried out in accordance with the process described above, while respecting

the following working conditions:

Esterification		Excess of sodium di- n-propyl acetate (in %)	Dimethylformamide	Yield (in %)
T (°C)	Time (h)		Water	
110	9	-	no water	88.8
100	8	5(*)	no water	93.9
100	5	-	95/5	90.7
100	7	-	95/5	94

(*) dimethylformamide used in amounts equivalent to 5 times the total amount of the reagents.

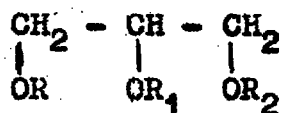
EXAMPLE 11

In accordance with known pharmaceutical techniques, a capsule, containing the following ingredients, was prepared:

<u>Ingredient</u>	<u>mg</u>
Mixture of glyceryl 1,2- and 1,3-bis- (di-n-propylacetates) ("Mixture B")	500
Gelatin	212
Glycerol	83
Ethyl p-hydroxybenzoate (sodium salt)	4
Propyl p-hydroxybenzoate (sodium salt)	2
Titan ^{um} _u dioxide	4.4

CLAIMS

1. Glycerol monoesters, diesters and triesters, corresponding to the general formula:



in which R, R₁ and R₂, which are identical or different, each represent hydrogen or an acyl radical, namely, di-n-propylacetyl, tri-n-propylacetyl, 2-ethylhexanoyl, n-4-propylhexanoyl, n-propyl-5-octanoyl, 2-methyl-2-ethylhexanoyl, 1-methylcyclohexylcarbonoyl or di-n-propylmethoxyacetyl, on the condition that R, R₁ and R₂ are not simultaneously hydrogen or di-n-propylacetyl.

2. Glyceryl 1-(di-n-propylacetate).
3. Glyceryl 1-(tri-n-propylacetate).
4. Glyceryl 1-(2-ethylhexanoate).
5. Glyceryl 1-(1-methyl-cyclohexylcarboxylate).
6. Glyceryl 1-(2-methyl-2-ethylhexanoate).
7. Glyceryl 2-(di-n-propylacetate).
8. Glyceryl 1,2-bis-(di-n-propylacetate).
9. Glyceryl 1,2-bis-(2-ethylhexanoate).
10. Glyceryl 1,2-bis-(1-methyl-cyclohexylcarboxylate).
11. Glyceryl 1,2-bis-(tri-n-propylacetate).
12. Glyceryl 1,2-bis-(2-methyl-2-ethylhexanoate).
13. Glyceryl 1,3-bis-(di-n-propylacetate).
14. Glyceryl 1-(di-n-propylacetate)-3-(1-methyl-cyclohexylcarboxylate).
15. Glyceryl 1-(di-n-propylacetate)-2,3-bis-(1-methyl-

cyclohexylcarboxylate).

16. Glyceryl 1-(di-n-propylacetate)-3-(2-methyl-2-ethylhexanoate).

17. Glyceryl 1-(di-n-propylacetate)-2-(1-methyl-cyclohexylcarboxylate).

18. Glyceryl 1,2,3-tri-(1-methyl-cyclohexylcarboxylate).

19. Glyceryl 1-(di-n-propylmethoxyacetate).

20. Glyceryl 1-(4-n-propylheptanoate).

21. Glyceryl 1-(5-n-propyloctanoate).

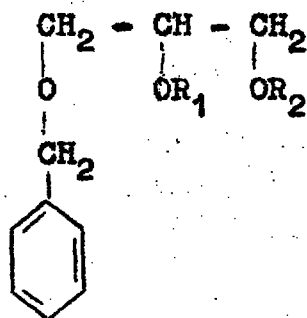
22. Mixture of glyceryl 1,3-bis-(di-n-propylacetate)/glyceryl 1,2-bis-(di-n-propylacetate) in a ratio of about 1.43:1 to 1.54:1.

23. Pharmaceutical or veterinary composition comprising, as essential active ingredient, at least one mono-, di- or tri- ester according to any of the Claims 1 to 21, in association with a pharmaceutical carrier or an appropriate excipient.

24. Pharmaceutical or veterinary composition comprising, as essential active ingredient, a mixture of glyceryl 1,3-bis-(di-n-propylacetate)/glyceryl 1,2-bis-(di-n-propylacetate) according to Claim 22, in association with a pharmaceutical carrier or an appropriate excipient.

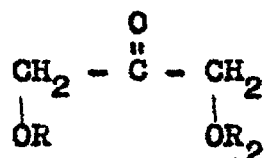
25. Process for preparing glycerol 1,2-diester^s according to Claim 1, in which R represents hydrogen and R₁ and R₂ are identical and represent an acyl radical, wherein a diester of general formula

(16)



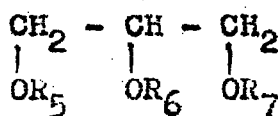
in which R_1 and R_2 are identical and represent a previously defined acyl radical, is reacted with hydrogen in alcoholic medium and in the presence of palladium carbon as catalyst, the reaction being carried out at atmospheric pressure and at ambient temperature.

26. Process for preparing glycerol 1,3-diester according to Claim 1, in which R and R_2 are identical and represent an acyl radical and R_1 represents hydrogen, wherein a keto diester of general formula



in which R and R_2 are identical and represent a previously defined acyl radical, is reduced at ambient temperature with potassium hydroboride in an ether and then the complex as thus formed is hydrolysed with a strong inorganic acid.

27. Process for preparing mixtures of glycerol 1,2-diester and glycerol 1,3-diester corresponding to the general formula



in which R_5 represents a di-n-propylacetyl, di-n-propylmethoxy-

acetyl or di-n-propylpropionyl radical, and R_6 and R_7 , which are different, each represent hydrogen or a di-n-propylacetyl radical, di-n-propylmethoxyacetyl radical or di-n-propylpropionyl radical, R_5 and R_6 or R_5 and R_7 being identical, wherein an equivalent of 1,3-dichloro-2-propanol is esterified, in N,N-dimethylformamide as solvent, at a temperature which is between 100 and 110°C and for 5 to 10 hours, with 2 equivalents, preferably in excess, of an alkali metal salt of di-n-propylacetic acid, di-n-propylmethoxyacetic acid or di-n-propylpropionic acid and then the mixture of esters thus obtained is rectified.

28. Process for preparing mixtures of glyceryl 1,3-bis-(di-n-propylacetate)/glyceryl 1,2-bis-(di-n-propylacetate) in a ratio of 1.43 to 1.54, wherein an equivalent of 1,3-dichloro-2-propanol is esterified in N,N-dimethylformamide as solvent, at a temperature which is between 100 and 110°C and during 5 to 10 hours, with two equivalents, preferably in excess, of an alkali metal salt of di-n-propylacetic acid and then the mixture of esters thus obtained is rectified.

29. Process according to Claim 27 to 28, wherein the alkaline metal salt is the sodium salt.

30. Process according to Claim 27 or 28, characterised in that the alkali metal salt is in an excess of 5 % as a maximum.

31. Process according to Claim 27 or 28, wherein the temperature is 100°C and the esterification is carried out for 8 hours.

32. Mixture of glyceryl 1,3-bis-(di-n-propylacetate)/

1,2-bis-(di-n-propylacetate), obtained by application of the process according to any one of Claims 27 to 31.