This invention relates to an injectable steroid hormone preparation and more particularly to an injectable progestogenic hormone preparation of high hormone concentration, said preparation being adapted to produce, on injection, a hormone depot of prolonged activity, and to a method of making same.

The hitherto most widely used method of administration of hormones is by intramuscular injection of oleaginous solutions. However, such injections must in many instances be repeated frequently at definite time intervals, corresponding to the resorption of the hormone by the organism. As this method can be extremely irksome to the patient, in many cases a method of treatment has been employed which consists in the implantation of hormone crystals of suitable size, thereby setting up a depot in the organism, from which the latter can derive its requirements over a long period. The method of crystal implantation has however, for various reasons, not always proved satisfactory in practice. A primary reason is that it is in fact a surgical operation, although only a minor one.

Attempts have therefore been made to replace the method of setting up a depot by crystal implantation by the more easily effected injection technique. Since narrow limits are placed upon the production of highly concentrated oleaginous solutions owing to the insufficient solubility of the hormones in oils, one method which has been used consists in the injection of crystal suspensions. However, this method also encounters certain difficulties particularly in relation to the production of said suspensions, and it can therefore in no wise be considered as ideal.

Some advance was made by the discovery of the so-called protracted effect which is possessed by certain esters of steroid hormones as compared with the free hormones. They rendered it possible for the first time in therapy to effect a desirable reduction in the number of the injections required, a limit still being imposed however by the relatively small size of the depot which could be set up by a single injection. The production of sufficiently highly concentrated oleaginous solutions was still rendered impossible owing to the insufficient solubility of the esters used in the customary solvents for intramuscular injection.

The present invention is in part based on the observation that it is possible to reduce the melting point of the hormones to be implanted by conversion into their low melting esters, or into low melting eutectic mixtures of esters, to such an extent that the molten hormone compounds can be directly injected without further diluent in the same manner as the known oleaginous solutions. This feature of the invention is illustrated in Examples 1 to 4 below.

The idea of injecting hormone preparations in the molten form instead of in the form of solutions is novel and steroid hormone esters with sufficiently low melting points, such as those set out in the examples below, were not hitherto known. Those hormones and derivatives thereof with high melting points which were hitherto known had, in the non-crystalline state at room temperature, in practically all cases the consistency of viscous creams or lacquers, whereas the melts produced according to the present invention, on cooling, only crystallise slowly and have the consistency of fluid oils.

It was also in no way to be expected that it is possible to produce physiologically suitable steroid hormone derivatives with such low melting point. Their application by means of a simple injection constitutes a marked simplification, as compared with implantation, in the setting up of comparatively large hormone depots in the organism.

According to a further feature of this invention, instead of mixtures of different esters of the same hormone, in cases where simultaneous application of several hormones is desired, there can be employed with particular advantage also mixtures of low melting esters of different hormones, in which case the ester-forming acyl residues may be the same or different. Instead of the esters or the enol esters others among the customary hormone derivatives are also concerned, insofar as they possess low melting points. Further additions or diluents are not absolutely necessary but they may in some cases be of advantage especially when they are of such a nature as to effect further decrease of the melting point.

Furthermore, according to this invention, it is not necessary for the production of preparations comprising mixtures of steroid hormones of low melting point to produce this effect of decreasing the melting point by admixture of other hormones or hormone derivatives, but an admixture of non-hormones may also be suitable for the same purpose.

Thus, for example, the inert steroids androstanol (M. P. 50°C.), coprostanol (M. P. 63° C.) and noncholesterol ethyl ester (M. P. 66° C.) have a strong effect in reducing the melting points of the hormone esters. However, this effect is not at all limited to substances of the steroid group. It has been shown that this effect is possessed quite generally by substances the melting points of which are relatively low, that is to say below about 65° C., insofar as they form homogeneous melts with the hormones concerned. Advantageously such substances are selected that are chemically inert to the greatest possible extent, so that they are tolerated by the body, as, for instance, hydrocarbons, alcohols and their derivatives, ketones and so on. Actual selection can be made by an expert bearing the above points in mind. As further examples of suitable substances there may be mentioned pyroctahelot monomethyl ether (guaiacol), ethyl carbamate (urethane) and phenyl salicylate (salol).

According to a still further feature of the invention, in this method of producing low melting hormone preparations not only such steroid hormone derivatives can be used as themselves possess relatively low melting points but also others, even including those which are in general used in the unesterified free form, as, for example, progesterone.

Further additions may be advantageous as diluents, especially in order to effect better dosage, since in setting up of depots which are intended to be less than about 100 mg., it is undesirable that too great a proportion of the hormone preparations remains behind in the injection syringe. As suitable inert diluents there are concerned those solvents which are known and hitherto used, for example fatty oils and higher glycols. Further additions may be important for the purposes of improving the tolerance and rendering the effect more protracted or for
increasing absorption. For these purposes wax alcohols are of advantage.

Examples 5–19 below illustrate such highly concentrated steroid hormone preparation which are suitable for injection.

The invention is based on the further observation, as a result of research on comparative solubilities of known and new hormone esters, that there exists a series of hitherto unknown esters which are distinguished by a surprisingly high solubility in the usual solvents used for injection purposes. This was not to be expected since both the previously known esters of the fatty acids and also those of the higher fatty acids which were hitherto known, have exceedingly low solubilities in the oils concerned, as is seen from the following table of their solubilities at room temperature in mg. per 1 ccm. in the case of two typical representatives of these solvents:

<table>
<thead>
<tr>
<th></th>
<th>Sesame Oil, mg.</th>
<th>Rapeseed Oil, mg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Testosterone propionate</td>
<td>less than 2</td>
<td>less than 2</td>
</tr>
<tr>
<td>Prednisone (5α) acetate (5)</td>
<td>less than 2</td>
<td>less than 1</td>
</tr>
<tr>
<td>Prednisone (5α) 16α-hemisuccinate</td>
<td>less than 1</td>
<td>less than 1</td>
</tr>
<tr>
<td>Testosterone; 16α-succinate</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Testosterone butyrate; 16α-succinate</td>
<td>25</td>
<td>20</td>
</tr>
<tr>
<td>Testosterone palmitate; 16α-succinate</td>
<td>less than 5</td>
<td>less than 5</td>
</tr>
<tr>
<td>Estradiol</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Estradiol-17β-propionate</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Estradiol-17β-propionate</td>
<td>10</td>
<td>30</td>
</tr>
</tbody>
</table>

A search for other more suitable solvents has previously produced no satisfactory result on account of the narrow limits imposed by the required tolerance.

In view of the fairly uniformly low solubilities of the hitherto known esters, among which there were represented both these of high molecular acids and also those of the low molecular acids, it could therefore not be assumed that the intermediate esters would behave in an essentially different manner.

It is the more surprising that the esters of aliphatic acids with more than three carbon atoms, especially such with 4–14 carbon atoms, which, in addition, may be more or less saturated, are distinguished by a considerably higher solubility substantially exceeding 50 mg. per cc. of solution. Moreover, here also the oil solubility of a particular hormone ester can in most cases be increased considerably by admixture of a second hormone ester. This feature is illustrated in Examples 20–23 below.

The following examples therefore illustrate the invention:

**EXAMPLE 1**

The hitherto undescribed low melting testosterone esters set forth below are introduced into ampoules for injection purposes in the manner customary for oleaginous hormone solution preparations.

(a) Preparation of testosterone caprylate

A mixture of 10 grams of testosterone, 40 cc. of pyridine and 20 cc. of caprylic acid anhydride is heated for 1½ hours at 125° C. The cooled reaction mixture is decomposed with water while stirring and cooling. After prolonged standing at a temperature below room temperature, the whole is extracted with ether and the ether solution is washed consecutively with dilute sulfuric acid, water, 5% sodium hydroxide solution, and again with water. The crude ester remaining on evaporation of the dried ether solution, after repeated recrystallisation from pentane, melts at 44.5–46.0° C.

(b) Preparation of testosterone oenanthate

By the same reaction and working up procedure, there is obtained, by the use of oleic acid anhydride, testosterone oenanthate of M. P. 36–37.5° C.

(c) Preparation of testosterone caprylate

In the same manner there is obtained, from testosterone and caprylic acid anhydride, testosterone caprylate of M. P. 44–45° C.

**EXAMPLE 2**

By melting together any two, or better three, of the esters described in Example 1, in mixture ratios which may vary relatively widely and are preferably about 1:1 or 1:1:1, respectively, clear melts are obtained which at body temperatures are still in liquid state and also at considerably lower temperatures, remain more or less fluid.

To simplify production of injection preparations according to this example, one may proceed in such a manner that the desired esters, instead of being produced individually, are produced directly in mixture with each other by esterifying testosterone, instead of with the pure carboxylic acid anhydride concerned, directly with mixtures of the desired carboxylic acid anhydrides.

**EXAMPLE 3**

The process for the manufacture of injection preparations of desoxycorticosterone is conducted in the same manner as described in Example 2. Suitable derivatives are for example the caprylate (M. P. 63–65.5° C) and the already known palmitate (M. P. 62–63° C).

After melting, solidification takes place only slowly, so that injection of the molten preparation at body temperature is possible. On melting the two esters together within a wide range of proportions, melts are obtained which solidify at still lower temperatures.

The production of such esters may be carried out in the following manner:

(a) Preparation of pregnene-5-diol-(3,21)-one-(20)-caprylate-(21) from 21-diazopregnenolone

1.72 grams of 21-diazopregnenol-3-one-(20) are dissolved in 12 cc. of caprylic acid while heating slowly to 90° C. and the whole is left for 20 minutes at this temperature until evolution of nitrogen has ceased. The unre acted caprylic acid is then distilled off in a vacuum at 135° C. After recrystallisation from hexane 1.65 grams remain. This product, in chloroform solution, is filtered over a small column of alumina, extracted by shaking with sodium bicarbonate solution and water, and recrystallised from hexane. The pregnenediolone caprylate produced has a melting point of 75–80° C.

Preparation of desoxycorticosterone caprylate from pregnene-5-diol-(3,21)-one-(20)-caprylate-(21) 750 mg. of the above produced pregnenediolone caprylate are dissolved in 60 cc. of dry toluene and mixed with 10.5 cc. of cyclohexane. To the boiling solution 3.3 cc. of aluminum isopropylate solution (about 25% isopropylate) are gradually added and the whole is maintained at boiling point for 25 minutes. Then 0.22 cc. of glacial acetic acid is added and, after cooling, the solution is subjected to steam distillation in the presence of 2.5 grams of kieselguhr. The residual liquid is filtered with suction, dried, and extracted with acetone. After distilling off the acetone, the residue is dissolved in hexane and filtered over a small column of alumina for purification. After evaporation, 550 mg. remain. This crude product is dissolved in hexane and chromatographed over a column of alumina. The desoxycorticosterone caprylate with a melting point of 62–63° C. is extracted with benzene as first eluting agent. After recrystallisation from hexane the melting point is 63–65.5° C.

(b) Preparation of a mixture of desoxycorticosterone palmitate and desoxycorticosterone caprylate from 21-diazopregnenolone

3.4 grams of 21-diazopregnenol-5-ol-(3)-one-(20), in 20 cc. of dry toluene, are heated with 12 grams of palmitic acid in a glycerol bath at 120° C. until evolution of nitrogen has ceased (for about 2 hours). The
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5 mixture is then diluted with 500 cc. of ether and allowed to stand for 15 hours over sodium hydroxide pellets. Thereupon the liquid is separated from the deposited flakes of sodium palmitate and is filtered through a layer of about 50 grams of alumina, followed by thorough washing with ether and crystallisation. There are obtained 3.1 grams of 21-palmitoxy pregnene-(5-ol)-(3)-one-(20) of M. P. 98°-102° C., which is suitable for further processing without additional purification.

For oxidation, 2.9 grams of this substance are dissolved in 100 cc. of toluene, 20 cc. of cyclohexanone and 1.3 grams of aluminium isopropylate are added and the solution is boiled for 4 hours. After working up in the same manner as described for the preparation of the caprylate, 2.1 grams of desoxy corticosterone palmitate of M. P. 57°-58° C. are obtained. By recrystallisation, the melting point can be raised to 62°-63° C. By fusion of this ester together with desoxy corticosterone caprylate within a wide range of proportions, melts are obtained which solidify only at low temperatures so that they can be used for injection.

Preparation of a desoxy corticosterone palmitate-caprylate mixture

0.35 grams of desoxy corticosterone are allowed to stand for 4 hours at room temperature with a solution of 0.27 grams of palmitoyl chloride and 0.17 grams of capryl chloride in 1 cc. of pyridine. The whole is then upon treated with 500 cc. of ether, shaken with 2N-hydrochloric acid, then with sodium carbonate solution and with water, dried over sodium sulfate, filtered through a layer of 1 gram of alumina, and evaporated. The ester mixture remains as a fluid mass which can be caused to solidify at the temperature of ice.

EXAMPLE 4

One may proceed with the esters of estrone in the same manner as described in Example 2. For instance, the caprylate (M. P. 68°-70° C.) and the oenanthe (M. P. 64°-65° C.) of estrone are suitable for such use. The melting points of the mixtures, the composition of which may vary in proportion within a wide range, are so low that the melts can be injected. The preparation of these esters can be carried out as follows:

Preparation of estrone caprylate

6 grams of estrone are dissolved, while heating, in 1.5 liters of 5% potassium hydroxide solution and, after cooling to 0-5° C., shaken for 15 minutes with 7.5 cc. of capryl chloride. Further 7.5 cc. of the acid chloride are then added and shaking is continued for a further 30 minutes. The precipitated ester is filtered by suction, thoroughly washed on the filter with sodium carbonate solution and water, and dried in a vacuum desiccator.

Yield: 8.76 grams of crude caprylate of M. P. 66°-70° C. After recrystallisation from hexane and methanol the pure caprylate melts at 68°-70° C.

Preparation of estrone oenanthe

6 grams of estrone are reacted under the same conditions as described above with oenanthe chloride. 8.55 grams of crude oenanthe of M. P. 59.5°-62° C. are obtained. The pure oenanthe melts at 64°-65° C.

EXAMPLE 5

0.35 parts by weight of testosterone propionate are ground with 0.7 parts of phenyl salicylate and the mixture is molten at 38° C. A clear, easily mobile liquid is obtained which does not solidify at 0° C. and contains 350 mg. of testosterone propionate per cc. If it is desired to produce smaller dosages, weaker solutions of testosterone propionate can be prepared by increasing the proportion of phenyl salicylate.

EXAMPLE 6

1 part of progesterone is mixed with 3.5 parts of phenol salicylate and the whole is molten at 45° C. A clear, homogeneous melt remaining liquid at low temperatures, being capable of injection, and containing 250 mg. of progesterone per cc. is obtained.

EXAMPLE 7

1 part of progesterone is treated as above described with 4.5 parts of phenyl salicylate. A melt suitable for injection is obtained containing 200 mg. of progesterone per cc.

EXAMPLE 8

1 part of desoxy corticosterone acetate is mixed with 4.5 parts of phenyl salicylate and is molten at 56° C. A stable injectable preparation is produced containing 200 mg. of desoxy corticosterone acetate per cc. It is fluid at room temperature (about 18° C.).

EXAMPLE 9

There is produced according to Example 4 a melt from 1 part of testosterone propionate and 1 part of phenyl salicylate, 1 part of ethyl lactate and 2.5 parts of sesame oil are added thereto, yielding an oelaginous injection liquid which contains 200 mg. of testosterone propionate per cc. By varying the fatty oil proportion, solutions of higher or lower hormone content can be obtained.

EXAMPLE 10

By the method according to Example 4, 1 part of progesterone is molten with 2 parts of phenyl salicylate. 0.5 part of ethyl lactate and 2 parts of sesame oil are then added to the melt whereby an injection solution is obtained which contains 200 mg. of progesterone per cc.

EXAMPLE 11

1 part of testosterone propionate and 1 part of phenyl salicylate are molten together according to Example 5. To the melt there are also added 0.5 part of cetyl alcohol, 0.5 part of benzyl alcohol, 1 part of ethyl lactate and 1.4 parts of sesame oil. A salve-like preparation is obtained which is transparent blow 25° C. and which at about 30° C. becomes sufficiently fluid for injection purposes. It contains 200 mg. of testosterone propionate per cc.

EXAMPLE 12

1 part of desoxy corticosterone acetate and 2 parts of phenyl salicylate are molten according to Example 5. 0.6 part of cetyl alcohol are introduced into the melt, yielding a preparation which can be injected at body temperature and contains 300 mg. of desoxy corticosterone acetate per cc.

EXAMPLE 13

2 parts of testosterone propionate are molten together with 5 parts of urethane at about 50° C. The melt remains liquid at 44° C. 1 cc. of this melt contains 300 mg. of testosterone propionate.

EXAMPLE 14

2 parts of progesterone are molten together with 5 parts of urethane. The melt remains fluid at 38° C. 1 cc. of this melt contains 300 mg. of progesterone.

EXAMPLE 15

Melts as in Examples 13 and 14 are diluted with suitable injectable liquids. They constitute injection fluids which are stable at a temperature considerably below room temperature. For example, 2 parts of testosterone propionate are molten with 5 parts of urethane and the melt is diluted with 3 parts of ethyl lactate and 3 parts of propylene glycol. 1 cc. of these melts contains 200 mg. of testosterone propionate.

EXAMPLE 16

1 part of guaiacol (M. P. 28° C.) is molten with 2 parts of testosterone propionate. The melt remains liquid.
The dried ether solution is evaporated and the oily residue is triturated with hexane, whereby crystallisation gradually sets in. The crystalline paste is filtered with strong suction and the crystallisate is purified by repeated recrystallisation from hexane-acetone. The pure 17-ethyl estradiol monopropionate melts at 124–125° C.

**EXAMPLE 21**

In the case of the testosterone esters, as set forth in the table above, the solubility of the monopropionate in 1 cc. of sesame oil at room temperature is 12 mg. and that of the monobenzoate less than 2 mg. On the other hand, the solubility of the caproate is more than 550 mg., that of the oenanthate more than 900 mg. and that of the caprylate more than 600 mg. These solubilities are further considerably increased by mixing the various esters. A triester mixture is obtained which possesses practically unlimited solubility in sesame oil.

The preparation of the caproic, caprylic and oenanthic esters of testosterone is described in Example 1.

**EXAMPLE 22**

In the case of desoxycorticosterone the solubility maximum which is reached in the case of the esters of the acids of average molecular weight, is likewise clearly recognizable on reference to the table above, the solubility of the caprylate in 1 cc. of sesame oil at room temperature being 75 mg.

To prepare the hitherto unknown caprylate of desoxycorticosterone, the latter compound is esterified in the same manner as described in previous examples. In addition, for instance, the process described in Example 3 may be used.

**EXAMPLE 23**

The same excellent solubility of the esters of aliphatic carboxylic acids of medium number of carbon atoms is found in the case of estrone. Thus, for instance, more than 100 mg. of the oenanthate and more than 75 mg. of the caprylate are soluble at room temperature in 1 cc. of sesame oil. Moreover it was found that a mixture of the two esters is still more readily soluble. Also by mixing esters of different steroid hormones the solubility is increased. The specified, hitherto partly unknown, esters, are prepared for instance, as described in Example 4. Other hormone derivatives of low melting point which can be practiced in using this invention are, for instance, certain hormone ethers, enol ethers, and acetals, especially those of lower molecular, preferably straight chain aliphatic alcohols. Especially suitable compounds of this type are, for instance, the 3-enol butyrate of testosterone-17-butyrate having a melting point of 67–69° C. and a solubility in sesame oil of 80 mg. per cc., and the 3-enol valerate of testosterone-17-valerate having a melting point of 76–79° C. and a solubility in sesame oil of 135 mg. per cc. Such and other enol esters of testosterone and other steroid hormones containing keto groups are obtained, for instance, by heating the ketonic steroid hormone with the corresponding acylating agent at a temperature of at least about 100° C. for a sufficient time to form an enol derivative which is acylated at the enolic hydroxyl group. Thus, the 3-enol butyrate of testosterone-17-butyrate is obtained by heating a mixture of 1 part of testosterone-17-n-butyrate, 2 parts of sodium butyrate, and 40 parts of n-butyric acid anhydride to boiling under reflux for about 5 hours. The reaction mixture is then poured into water and the reaction product is extracted with ether. After the ethereal extract has been washed with dilute sodium carbonate solution, dilute caustic alkali solution, and water, it is dried by means of sodium sulfate and the solvent is evaporated. The residue is recrystallized from alcohol. The 3-enol valerate of testosterone-17-valerate is obtained in an analogous manner. In general, enol esters of testosterone-17-esters with aliphatic carboxylic acids having at least 4 carbon atoms.

**EXAM**

A mixture of 5 grams of 17-ethyl estradiol, 20 cc. of pyridine, and 10 cc. of propionic acid anhydride is heated for 1½ hours to 115° C. The cooled reaction mixture is decomposed with water, while stirring and cooling. After stirring at room temperature for several hours, the mixture is extracted with ether and the ether solution is washed consecutively with dilute sulfuric acid, water, dilute sodium carbonate solution, and again with water.
in their molecule are suitable compounds of relatively high solubility in customary steroid hormone solvents and having a relatively low melting point.

The term “steroid hormone” as used herein and in the claims annexed hereto comprises not only the free hormones of steroid structure themselves or mixtures of the same but also their derivatives as they are mentioned herein or mixtures of the same with the free hormones or with other hormones or with other derivatives or with derivatives of other hormones.

We claim:

1. An injectable concentrated, substantially water-free repository hormone composition, fluid at body temperature, which composition consists of an ester of a steroid hormone selected from the group consisting of estrogensic, androgenic, progestational, and adrenocortical steroid hormones, said steroid hormone ester having a melting point above body temperature, and a non-toxic substance selected from the group consisting of guaiacol, phenyl salicylate, and urethane, said substance having a melting point below about 65° C. and forming, on melting together with said steroid hormone ester, a homogeneous molten mixture therewith, said steroid hormone ester and said organic substance being present in said repository hormone composition in the form of a molten homogeneous mixture remaining stable in its fluid form, the steroid hormone ester content of said mixture substantially exceeding 50 mg. per g. thereof.

2. In a process for the manufacture of an injectable concentrated, water-free repository hormone composition, the step which comprises melting together an ester of a steroid hormone selected from the group consisting of estrogenic, androgenic, progestational, and adrenocortical steroid hormones, said steroid hormone ester having a melting point above body temperature, and a non-toxic substance selected from the group consisting of guaiacol, phenyl salicylate, and urethane, to form a homogeneous molten mixture of said steroid hormone ester and said organic substance, said mixture being fluid at body temperature, said steroid hormone ester being added in an amount sufficient to yield a composition of a hormone content substantially exceeding 50 mg. per g. thereof.

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