

Johns melting point apparatus. Fraction 6 did not yield a bromide.

*Sylvestrene*.—Physical properties of fractions 6 and 8 suggested sylvestrene but it failed to give the sulfuric acid color reaction or a tetrabromide.

*Cineol*.—Results were negative when an attempt was made to make the resorcinol derivative using fractions 3, 10 and 21.

Table II.—Fractionation of Non-Pulegone Constituents

| Fraction | B. P., ° C.,<br>5 Mm. | B. P., ° C.,<br>760 Mm. | Sp. Gr. $\frac{25}{20}$ | $n_D^{20}$ |
|----------|-----------------------|-------------------------|-------------------------|------------|
| 1        | 34.0–34.5             | 168.0                   | 0.8401                  | 1.4698     |
| 2        | 37.5–38.0             | ...                     | 0.8391                  | 1.4690     |
| 3        | 38.5–39.0             | 171.5                   | 0.8374                  | 1.4693     |
| 4        | 39.5–40.0             | 174.5                   | 0.8440                  | 1.4694     |
| 5        | 39.5–40.0             | 175.0                   | 0.8442                  | 1.4700     |
| 6        | 42.0–42.5             | 178.0                   | 0.8519                  | 1.4741     |
| 7        | 42.5–44.0             | 178.5                   | ...                     | 1.4750     |
| 8        | 47.0–47.5             | 179.5                   | 0.8601                  | 1.4664     |
| 9        | 51.5–52.0             | ...                     | 0.8924                  | 1.4590     |
| 10       | 63.5–64.0             | 204.0                   | 0.8963                  | 1.4570     |
| 11       | 64.0–64.5             | 203.5                   | 0.8963                  | 1.4575     |
| 12       | 63.0–63.5             | 205.5                   | 0.8972                  | 1.4550     |
| 13       | 67.0–67.5             | ...                     | 0.8971                  | 1.4589     |
| 14       | 67.0–67.5             | 211.0                   | 0.8977                  | 1.4591     |
| 15       | 67.5–68.0             | 211.0                   | 0.9005                  | 1.4587     |
| 16       | 71.0–71.5             | 211.5                   | 0.9005                  | 1.4610     |
| 17       | 72.5–73.0             | ...                     | 0.9040                  | 1.4646     |
| 18       | 73.5–74.0             | ...                     | 0.9052                  | 1.4669     |
| 19       | 63.0–65.0             | ...                     | ....                    | ....       |
| 20       | 65.0–72.0             | ...                     | ....                    | ....       |
| 21       | 67.0–75.0             | ...                     | ....                    | ....       |
| 22       | 72.0–75.0             | ...                     | ....                    | ....       |

*Menthone*.—This was identified in fraction 12 by means of b. p., sp. gr.,  $n_D^{20}$  and its semicarbazone which melted at 183° C. after repeated crystallization from methyl alcohol.

*Menthol*.—The properties of Fractions 15 and 16 indicated menthol which was substantiated by preparing a phenylurethane, m. p. 107° to 108° C.,

recorded for *d*- and *l*-menthol 108° to 109° C. The stereoisomerism of the menthol was not determined.

#### SUMMARY

1. Assay method (4b) is recommended for determination of pulegone in the volatile oil of *Pycnanthemum muticum* (Michx.) Pers. which reduced time of assay from approximately 20 or more hours to five hours.

2. Pulegone content and physical properties of three different lots of oil have been determined and found to be very close.

3. Limonene has been identified, not previously reported.

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## Derivatives from Hydrogenated Castor Oil

### I. 12-Hydroxystearic Acid and Its Alkyl Esters\*

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Although 12-hydroxystearic acid was first synthesized at the beginning of the century

(1) and has been obtainable from hydrogenated castor oil since 1921 (2), little has been done until recently (3) to investigate its pharmaceutical potentialities. Nor has any extensive work been done upon the synthesis and industrial applications of its derivatives. This hydroxy acid, of relatively high melting point and molecular weight, and bearing two functional groups, should provide interesting and useful synthetic compounds. With an annual pro-

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duction in this country of over ninety million pounds of castor oil, and the commercial methods now available for the controlled hydrogenation of this oil, a ready source is provided from which 12-hydroxystearic acid may be obtained easily in high purity and in good yield.

This acid, because it can be prepared practically free from unsaturated acids, is characterized by freedom from color, odor and any tendency toward rancidity. It provides an excellent starting point for the preparation of derivatives having similar characteristics which are so desirable in many pharmaceutical, cosmetic and industrial products. The two classes of derivatives which, it is believed, should prove most productive are those involving modification of the carboxyl and of the hydroxyl groups. In the former are included the esters obtained by combination of the acid with monohydric and polyhydric alcohols; in the latter class are the esters formed with fatty acids, the acid esters of sulfuric, pyrophosphoric and other inorganic acids, and the alkali salts of these acid esters.

In this first paper of the series, the discussion is limited to the normal primary alkyl esters of 12-hydroxystearic acid. The homologous alkyl series  $C_1$  to  $C_6$  and the even-membered derivatives from  $C_8$  to  $C_{18}$  have been prepared and characterized. Previous investigators (2, 4, 5, 6, 7, 8, 9) have prepared the lower alkyl esters,  $C_1$  to  $C_3$ , and the iso-alkyl esters,  $C_3$  to  $C_5$ . But these were made merely as confirmatory derivatives in the identification of the 12-hydroxy acid or as intermediates in its synthesis. No attempt was made to study their properties or field of application.

Such a study of an extended range of this series of esters of a high-melting hydroxylated saturated fatty acid, simulating in many characteristics the pure wax esters, should furnish an insight into the role of the waxes in pharmaceutical ointments, cosmetic creams and industrial products of similar nature, and should aid in the rationalization of formulary practice in these products.

## EXPERIMENTAL

*Isolation of 12-Hydroxystearic Acid* ( $CH_3(CH_2)_5-CHOH(CH_2)_{10}COOH$ ).—The method employed in the saponification and isolation of the free fatty acids from hardened castor oil was essentially that suggested by Jakeš and Hökl (10) for the isolation of ricinoleic acid from castor oil to avoid the usual formation of inner esters, polyricinoleic acids and similar side products.

Two hundred grams of powdered (No. 60) hydrogenated castor oil (m. p.  $86^\circ C.$ ; hydroxyl value<sup>1</sup> 152.3; saponification number 179.1; iodine number 1.14) were emulsified on a water bath with a solution of 120 Gm. of KOH dissolved in 240 cc. water in a porcelain dish. Heating and stirring were continued for two hours to complete the saponification. The soap was dissolved in one liter of hot water and the fatty acids precipitated by the addition of 400 cc. of diluted HCl (1:1) in a slow stream with constant stirring. The mixture was boiled for 10 minutes to melt the fatty acids and the aqueous layer siphoned off while the acids were still in a liquid state. One liter of boiling water was added, the mixture agitated by boiling for about two minutes and the aqueous layer removed. This washing was repeated until the aqueous layer was free from mineral acid. (About four washings were needed.) The fatty acids were chilled in a refrigerator and the cake coarsely ground in a chilled meat grinder. After drying over night at  $50^\circ C.$  the yield was 187 Gm. (97.4%) melting at  $75-77^\circ C.$

The fatty acids were extracted continuously for 8 to 12 hours with petroleum ether (boiling range  $35-70^\circ C.$ ) to remove acids other than 12-hydroxystearic. The yield of the latter was 149 Gm. (77.7%) melting at  $79-80^\circ C.$ , acid value 186.0 (calculated 186.7), iodine value 0.2 (calculated 0). No attempt was made to recover 12-hydroxystearic acid from the petroleum ether extract. The melting point, after two crystallizations from acetone, was constant at  $81^\circ C.$  Previous investigators give melting points as follows:  $81-82^\circ C.$  for an acid obtained by reduction of the HBr addition product of the acetate of ricinoleic acid with zinc or tin and HCl and subsequent saponification with KOH (1);  $78^\circ C.$ ,  $81^\circ C.$  and  $80.5-81^\circ C.$  for acids obtained by the catalytic hydrogenation of methyl ricinoleate followed by saponification of the ester (4, 5, 8);  $75^\circ C.$  for a crude acid obtained from hydrogenated castor oil (5);  $83^\circ C.$  for an acid obtained from partly reduced castor oil of iodine number 12 (2);  $81-82^\circ C.$  for an acid prepared by the reduction of ricinoleic acid with hydrazine hydrate (9); and  $78-79^\circ C.$  for a completely synthetic optically inactive acid prepared by the Grignard synthesis (7).

*Preparation of the Esters of 12-Hydroxystearic Acid.*—Two general methods of esterification were used in the preparation of the series. In the esteri-

<sup>1</sup> Cf. *Ind. and Eng. Chem., Anal. Ed.*, 12 (1940), 382.

fication with the normal primary alcohols from C<sub>1</sub> to C<sub>8</sub> the customary procedure was employed: refluxing the acid with a large excess of the appropriate anhydrous alcohol containing 6% to 8% of dry HCl for about eight hours (Method A). For the higher alcohols, where a large excess of alcohol could not be used because of difficulty in its removal and recovery from the ester formed, and for reasons of economy, another method was developed. The latter method required only an equivalent or twofold excess of alcohol and was catalyzed by benzenesulfonic acid in a concentration of 5% of the acid. The reaction medium was benzene, which also served for the entrainment and continuous removal of the water formed in the esterification. A simple distillation trap<sup>1</sup> was used to collect and measure this water (Method B).

*Method A.—1. Methyl 12-hydroxystearate:* Fifty grams ( $\frac{1}{6}$  mole) of 12-hydroxystearic acid (m. p. 79–80° C.) were esterified by refluxing with 150 Gm. (about 4.5 moles) of 6% methyl alcohol-HCl for eight hours. After standing at room temperature over night, the crystalline product was filtered off on a Büchner funnel and suction continued for several hours. A second crop of ester was obtained by chilling the mother liquor in ice-salt. A yield of 47.1 Gm. (93.6%) of crude ester was obtained, melting at 55° C. (not sharp). No attempt was made to increase the yield by concentration of the mother liquor. After recrystallization from ligroin and acetone, the melting point was constant at 56.5–57.0° C. Saponification number: 181.7 (calculated 178.4); hydroxyl value: 169.5 (calculated 178.4).

2. *Ethyl 12-hydroxystearate:* Acid was esterified with a twenty-fold equivalent of 6% ethyl alcohol-HCl. Most of the ester was removed by chilling the reaction mixture in ice-salt. The filtrate was diluted with an equal volume of ether and washed successively with dilute potassium carbonate solution and water, and evaporated to dryness to obtain a small second crop of ester. Crude yield, 94.1%. Melting point, after four crystallizations from ligroin, 50.3–51.6° C.

3. *n-Propyl 12-hydroxystearate:* Esterification was carried out with a tenfold equivalent of anhydrous propyl alcohol (fraction 76–77.3° C.) containing 8% HCl. Crude yield, 86.8%. Melting point, after three crystallizations from ligroin, 48.3–49.5° C.

4. *n-Butyl 12-hydroxystearate:* A tenfold equivalent of anhydrous *n*-butyl alcohol (b. p. 116–118° C.), containing 10% HCl, was used in the esterification. Crude yield, 87.1%. Melting point, after four crystallizations from ligroin, 43.7–44.9° C.

5. *n-Amyl 12-hydroxystearate:* After esterification with a tenfold equivalent of anhydrous *n*-amyl alcohol (136–137° C.) containing 6% HCl and removal of about half the product by chilling in ice-

salt, the remainder of ester was obtained by evaporating the mother liquor at reduced pressure on a water bath and chilling over night. Crude yield contained considerable free alcohol. After one crystallization from ligroin the yield was 51.8% melting at 44° C. (not sharp).

*Method B.—1. n-Amyl 12-hydroxystearate:* Fifty grams ( $\frac{1}{6}$  mole) of 12-hydroxystearic acid were refluxed six hours on an oil bath at about 130° C. with 30 Gm. ( $\frac{1}{3}$  mole) *n*-amyl alcohol and 30 Gm. benzene, using 2.5 Gm. benzenesulfonic acid catalyst. The water formed was removed continuously by means of the trap described, obtaining 2.95 cc. (theoretical = 3.0 cc.). The reaction mixture was washed with dilute potassium carbonate solution and water, chilled in ice-salt and filtered, yielding 25.5 Gm. of ester. The mother liquor was evaporated on a water bath under reduced pressure, leaving a residue of 28 Gm. of impure ester. After one crystallization of the combined material from ligroin the yield was 24 Gm. (39%) melting at 44° C. (not sharp). Further recrystallization of this ester together with that obtained by Method A gave a melting point of 45.0–46.0° C.

2. *n-Hexyl 12-hydroxystearate:* The acid was esterified with twice the equivalent weight of *n*-hexyl alcohol (b. p. 156–157° C.) refluxing for five hours with the bath at about 130° C. The water separated was 3.1 cc. The reaction mixture was washed with saturated brine solution containing 3% potassium carbonate and then with saturated brine solution. (Later experiments showed that cold water could be used to replace the brine solution.) This was filtered with suction and the benzene and excess alcohol removed on a water bath under reduced pressure. The residue was chilled in an ice-chest over night and filtered with suction. Crude yield was 64 Gm. (100%—contained free alcohol). After two crystallizations from ligroin the melting point was 46.1–47.4° C.

3. *n-Octyl 12-hydroxystearate:* A 5% excess of *n*-octyl alcohol (b. p. 195–196° C. corr.) was used and refluxed over a period of four hours with the bath temperature at 110–120° C., 3 cc. water separating in that period. The reaction mixture was washed in a separatory funnel with a dilute potassium carbonate solution and then with water. The benzene was removed by warming in a vacuum evaporator on a water bath at about 40 mm. pressure and 60° C. Crude yield was 100% melting at 42–50° C. (Free *n*-octyl alcohol present.) After two crystallizations from acetone the ester melted at 49.5–51.3° C.

4. *n-Decyl 12-hydroxystearate:* The acid was refluxed during 1.25 hours at 110–120° C. with an equivalent weight of *n*-decyl alcohol (b. p. 121° C. at 16 mm.), obtaining 3.0 cc. of water. The reaction mixture was treated with 5 Gm. potassium carbonate in 200 cc. of water and the benzene removed in a vacuum evaporator. The ester was filtered off with suction and washed twice with water, pressed out on a porous plate and dried over night in a vacuum desiccator. Crude yield was 82.4% melting at 53–

<sup>1</sup> Cf. "Methods of A. O. A. C.," 5th Edition, p. 471. The volatile oil separatory trap suitable for oils heavier than water was used.

56° C. After two crystallizations from acetone the melting point was 56–57.2° C.

5. *Lauryl ester, n-dodecyl 12-hydroxystearate*: An equivalent weight of lauryl alcohol (m. p. 21–23° C.) was used, refluxing about two hours with the bath at about 110° C. and obtaining 3.0 cc. of water. The crude yield was 96.6% melting at 53–59° C. After two crystallizations from acetone the melting point was 60–61.5° C.

6. *Myristyl ester, n-tetradecyl 12-hydroxystearate*: Myristyl alcohol melting at 38–39° C. was used in equivalent weight, refluxing one hour with the bath temperature at 120–130° C. and obtaining 3.2 cc. water. The crude yield was 95% melting at 60–63° C. After three crystallizations from acetone the ester melted at 61–64° C.

7. *Cetyl ester, n-hexadecyl 12-hydroxystearate*: An equivalent weight of cetyl alcohol (melting 47–50° C.) was used. Refluxing was continued for 1.25 hours at 115–125° C. collecting 3.2 cc. of water (3.0 cc. were collected in one hour). The crude ester contained some NaCl from the saturated brine solution used in washing as well as a considerable amount of organic material insoluble in acetone and melting above 100° C. This latter was formed in all other cases where the esterification was continued beyond the point when the theoretical 3 cc. of water had separated. After two crystallizations from acetone the ester melted at 66.5–69.5° C.

8. *Stearyl ester, n-octadecyl 12-hydroxystearate*: The stearyl alcohol (melting at about 58° C.) was used in equivalent weight and the mixture refluxed 1.5 hours during which time 3.0 cc. of water separated. A yield of crude ester (82.8%) was obtained melting at 74–75.5° C. After one crystallization from acetone the melting point was 76–76.5° C.

#### PROPERTIES AND APPLICATIONS

*Melting Points and Solubilities*.—In the preliminary evaluation of these compounds for pharmaceutical, cosmetic and industrial uses, their melting points and their solubilities in the commonly used solvents were determined. These are summarized in Tables I and II.

Table I.—Melting Points of the Esters of 12-Hydroxystearic Acid

| Ester                   | Mol. Wt. <sup>a</sup> | Hydroxyl Value <sup>a</sup> | M. P., ° C. |
|-------------------------|-----------------------|-----------------------------|-------------|
| Methyl                  | 314.5                 | 178.4                       | 56.6–57.0   |
| Ethyl                   | 328.5                 | 170.8                       | 50.3–51.6   |
| n-Propyl                | 342.5                 | 163.8                       | 48.3–49.5   |
| n-Butyl                 | 356.6                 | 157.3                       | 43.7–44.9   |
| n-Amyl                  | 370.6                 | 151.4                       | 45.0–46.0   |
| n-Hexyl                 | 384.6                 | 145.9                       | 46.1–47.4   |
| n-Octyl                 | 412.7                 | 136.0                       | 49.5–51.3   |
| n-Decyl                 | 440.7                 | 127.3                       | 56.0–57.2   |
| n-Dodecyl (lauryl)      | 468.8                 | 119.7                       | 60.0–61.5   |
| n-Tetradecyl (myristyl) | 496.8                 | 112.9                       | 61.0–64.0   |
| n-Hexadecyl (cetyl)     | 524.9                 | 106.9                       | 66.5–69.5   |
| n-Octadecyl (stearyl)   | 552.9                 | 101.5                       | 76.0–76.5   |
| 12-Hydroxystearic acid  | 300.5                 | 186.7                       | 81.0        |
| Hydrogenated castor oil |                       | 152.3 <sup>b</sup>          | 86.0        |

<sup>a</sup> Calculated.

<sup>b</sup> Found.

The melting points of the esters appear to follow a fairly smooth curve of the pattern usually found in such a series with the minimum occurring at the butyl ester. From these data it appears that the solubility in this series of esters is a function of the melting point rather than of the molecular weight—the butyl ester, which has the lowest melting point, being in most cases the most soluble. All the esters were found to be very soluble in the hot (about 55° C.) solvents, the cetyl and stearyl esters being slightly less soluble than the others. Hot solutions of the higher esters in toluene and the oils upon cooling formed mixtures which had the appearance of gels but which were not the true gels that form from solutions of the hydroxy acid or of the hydrogenated castor oil.

Some miscibilities of the melted esters and hydroxy acid with selected pharmaceutical and industrial materials were determined.

Table II.—Comparative Solubilities of the Esters of 12-Hydroxystearic Acid at 25° C.

| Ester           | Cc. of Solvent Needed to Dissolve 1 Gm. of Ester |         |         |         |             |                |
|-----------------|--|---------|---------|---------|-------------|----------------|
|                 | Ethanol  | Acetone | Ligroin | Toluene | Mineral Oil | Cottonseed Oil |
| C <sub>1</sub>  | 3  | 5       | 20      | 2       | ..          | 20             |
| C <sub>2</sub>  | 2  | 3       | 10      | 1       | 40          | 20             |
| C <sub>3</sub>  | 2  | 3       | 4       | 1       | 40          | 20             |
| C <sub>4</sub>  | 1  | 1       | 2       | 1       | 30          | 10             |
| C <sub>5</sub>  | 1  | 2       | 2       | 1       | 30          | 20             |
| C <sub>6</sub>  | 2  | 3       | 2       | 1       | 30          | 20             |
| C <sub>8</sub>  | 10   | 5       | 5       | 2       | 50          | 30             |
| C <sub>10</sub> | 50   | 20      | 20      | 3       | ..          | 40             |
| C <sub>12</sub> | 150  | 50      | 50      | 5       | ..          | 50             |
| C <sub>14</sub> | 200  | 80      | 50      | 5       | ..          | 50             |
| C <sub>16</sub> | ...  | 450     | 200     | 20      | ..          | ..             |
| C <sub>18</sub> | ...  | ...     | 450     | 50      | ..          | ..             |
| Acid            | 5  | 20      |         | 200     |             |                |
| Oil             | 200  | 200     |         | 150     |             |                |

It was found that Peru balsam was only incompletely miscible with these compounds at their respective melting points, and similarly ichthammol was only slightly miscible. However, the hydroxy acid appeared to react chemically with the ichthammol and formed a homogeneous mixture in all proportions. Tetrabromofluorescein, a representative of a group of certified cosmetic colors, was only poorly soluble in the melted esters although the latter were definitely tinted. On the other hand, both crude oil and coal tar were miscible in all proportions. Carbitol was miscible in all proportions with the hydroxy acid and with the melted esters, C<sub>1</sub> to C<sub>4</sub>, somewhat less miscible with those from C<sub>5</sub> to C<sub>12</sub>, and from 10 to 20 volumes of solvent were needed to form a clear solution of the esters of the C<sub>14</sub> to C<sub>15</sub> alcohols. The esters were less miscible in propylene glycol, the extent of miscibility being a function of the molecular weight of the esters rather than of their melting point. The acid and the methyl ester were miscible in all proportions while the butyl ester, although completely miscible with an equal weight of glycol at 75° C., was only partially miscible at its melting point and required 20 volumes of glycol to make a clear solution at that temperature. The stearyl ester was immiscible with up to 50 volumes of propylene glycol. All the members of the series including the hydroxy acid were found to be immiscible with glycerine but miscible in all proportions with petrolatum and with lanolin.

According to a recent research on commonly used natural waxes (11), a comparison of the chemical compositions of these

waxes shows that, in general, they consist of similar components; in fact, beeswax, carnauba, candelilla and montan contain compounds with identical composition, *i. e.*, acids, alcohols and hydrocarbons with 24 to 34 carbon atoms. The characteristic properties of these waxes which determine their individual applicability to specific uses result from variation in proportions of acids, alcohols and hydrocarbons, differences in chain length of the two components of the ester, and the presence of small amounts of additional distinctive components such as resin-like substances and ketones. It appears probable that, without any attempt at actual duplication of composition, waxes can be made to definite specifications by rational combinations of such a series of esters as have been prepared, both with each other and with appropriate acids, alcohols and hydrocarbons. Such products would have the desirable absence of color, odor and tendency toward rancidity as well as predetermined definite and permanent compositions.

The characteristics of various combinations of the esters of 12-hydroxystearic acid were determined, using fused mixtures of equal parts of two of the esters. After refrigeration for 12 hours, the mixtures were examined to ascertain the nature of their structure, the type of fracture and the melting point. The results are summarized in Table III.

No broad generalizations can be made from this table, but it appears that unless the two components differ from each other by at least two carbon atoms the mixture retains the crystalline structure of the origi-

Table III.—Characteristics of Ester Mixtures

| Mixture         | Structure        | Fracture    | M. P., ° C. <sup>a</sup> |
|-----------------|------------------|-------------|--------------------------|
| Methyl-ethyl    | Crystalline      | Crystalline | 48.3                     |
| Methyl-propyl   | Semi-crystalline | Crystalline | 44.0                     |
| Methyl-decyl    | Waxy             | Conchoidal  | 44.0                     |
| Ethyl-propyl    | Crystalline      | Crystalline | 47.4                     |
| Propyl-butyl    | Crystalline      | Crystalline | 43.0                     |
| Propyl-amyl     | Waxy             | Conchoidal  | 39.2                     |
| Butyl-amyl      | Crystalline      | Crystalline | 42.0                     |
| Butyl-hexyl     | Waxy             | Conchoidal  | 37.5                     |
| Butyl-decyl     | Waxy             | Conchoidal  | 42.0                     |
| Octyl-decyl     | Waxy             | Conchoidal  | 47.3                     |
| Decyl-lauryl    | Waxy             | Conchoidal  | 52.4                     |
| Lauryl-myristyl | Waxy             | Conchoidal  | 56.0                     |
| Myristyl-cetyl  | Semi-crystalline | Crystalline | 60.3                     |
| Cetyl-stearyl   | Crystalline      | Crystalline | 73.0                     |

<sup>a</sup> Determined by the U. S. P. method for materials belonging to Class II. ("United States Pharmacopœia XI," p. 455.)

nal pure esters. Even in such cases, if the esters are too near the extremes of the series, the resultant mixture is not amorphous as is indicated in the methyl-propyl, myristyl-cetyl and cetyl-stearyl pairs, which remain more or less crystalline. The most satisfactory pairs were the decyl-lauryl and lauryl-myristyl, although others, as indicated, had the amorphous wax-like structure and brittle conchoidal fracture sought for. It was further found that addition of 10% of free alcohol or 10% of hydroxy acid or 5% of each to the higher esters produced crystalline mixtures of slightly lower melting point while similar additions to amorphous ester pairs did not alter their waxy structure.

It appears likely that esters of 12-hydroxystearic acid prepared with some of the standard mixtures of homologous higher alcohols (saturated *n*-primary) commercially available would have the desired wax-like character without further admixture.

*Ointments and Cosmetic Creams.*—Mixtures of white petrolatum containing 10% of the ester as a hardener were prepared by fusion with each of the esters in the series. All the esters as well as the hydroxy acid were completely compatible with the petrolatum, forming homogeneous mixtures and imparting a degree of hardness depending on the melting point of the ester. It is obvious, therefore, that these esters permit a degree of flexibility in the compounding of ointments. For example, by use of a high-melting ester greater amounts of liquids such as pine tar may be incorporated without producing too soft a product.

The esters *per se* were not suitable in place of beeswax as hardeners in beeswax-borax type cosmetic creams. Preliminary attempts to induce emulsification in this type of cream by the addition of 10% of free 12-hydroxystearic acid were unsuccessful. On the other hand, tri-isopropanolamine produced satisfactory cosmetic creams. The two formulas which follow gave creams of good appearance, consistency and stability.

COLD CREAM (ALMOND OIL TYPE)

|                      |          |
|----------------------|----------|
| Ester + 10% acid     | 24.5 Gm. |
| Almond oil           | 56.0     |
| Tri-isopropanolamine | 1.2      |
| Water                | 18.3     |

COLD CREAM (MINERAL OIL TYPE)

|                      |          |
|----------------------|----------|
| Ester + 10% acid     | 16.2 Gm. |
| Mineral oil          | 58.0     |
| Tri-isopropanolamine | 0.8      |
| Water                | 25.0     |

The creams were made by adding the tri-isopropanolamine dissolved in the water to the melted ester, acid and oil, with vigorous mechanical stirring. After emulsification occurred, the cream was stirred occasionally until cold and congealed. It was found that both the low-melting and high-melting esters gave creams of poor quality with these formulas, the former because they did not impart sufficient hardness and the latter because they formed granular creams. The C<sub>8</sub> to C<sub>12</sub> esters were satisfactory, the decyl ester proving the best. A combination of two esters melting in this middle range (*e. g.*, lauryl-myristyl) was even better. Increasing the amount of ester made a somewhat stiffer but not a better cream. Increasing the amount of free acid with the ester to 20% made no improvement unless the amount of tri-isopropanolamine was correspondingly increased.

Emulsified cosmetic creams of the water-miscible type were prepared using Aerosol OT as the emulsifying agent according to the following formula:

|                          |        |
|--------------------------|--------|
| Cetyl ester              | 20 Gm. |
| Mineral oil              | 40     |
| Water                    | 20     |
| Aerosol OT (10% aqueous) | 20     |

The melted ester and oil were added to the Aerosol OT in water with vigorous stirring until emulsification occurred and the cream stirred occasionally until cooled and congealed. This type of cream had by far the finest texture and properties. By introducing free cetyl alcohol and free 12-hydroxystearic acid, the appearance of the finished cream was varied as follows: Addition of 10% cetyl alcohol to the cetyl ester (*viz.*, 2% of the total weight) produced a high luster cream; addition of 10% 12-hydroxystearic acid to the cetyl ester produced a matte cream of harder consistency; addition of 5% each of alcohol and acid produced a cream of medium luster and medium consistency. These creams proved very stable but permitted the addition of

only limited quantities of 10% solutions of aluminum chloride or of tannic acid without being materially altered. This limitation in the addition of electrolytes and acidic substances is due more to the characteristics of the emulsifier than to the ester used. Because of the neutral character of the esters, incompatibility with dilute acids, alkalies and electrolytes should not be encountered.

Physical limitation precludes the preparation of the large number of possible combinations of the 12-hydroxystearic acid esters in varying proportions with related fatty alcohols and acids. But the examples cited should suffice to show the adaptability of these esters to formulations involving wax-type components. The desirable qualities of these esters invite further studies of their pharmaceutical and industrial applications. The problem of making synthetic products which approximate or even improve upon the natural waxes is indeed a complex one, but it is believed that a satisfactory approach has been made through the synthesis of these esters of 12-hydroxystearic acid.

#### SUMMARY

Methods have been given for the isolation of 12-hydroxystearic acid from commercial hydrogenated castor oil, and for the syntheses of a series of twelve of its esters with normal primary alcohols. A number of

their physical properties have been evaluated and some of their applications to ointments and similar bases have been suggested. The results indicate the possibilities of utilizing these esters in the formulation of waxes having reproducible properties and whose qualities should prove superior to the natural waxes in respect to stability and freedom from color, odor and rancidity.

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## A Phytochemical and Pharmacological Study of the Berries of *Phytolacca americana* Linné (Fam. Phytolaccaceae)

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The berries of *Phytolacca americana* (*decandra*) have been known in clinical medicine for many years. Phytochemical

and pharmacological investigations have consisted of a few incomplete reports. The present work was undertaken with the purpose of making a more complete study.

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#### EXPERIMENTAL

##### A. PHYTOCHEMICAL INVESTIGATION

*Preliminary Study.*—*Moisture Determination:* The moisture content was determined by the volatile immiscible solvent method of the United States