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A CHEMICAL EXAMINATION OF THE OIL OF ERGOT.*

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Oil of ergot is obtained by extracting the drug with petroleum ether prior to the preparation of fluidextract of ergot, U. S. P. X. The fatty oil used in this investigation was contributed by Parke, Davis & Co. It was very dark colored, had a slight green fluorescence and a rancid odor.

Five lots consisting of 10 litres each were saponified by refluxing each lot with 15 litres of a 70 p. c. alcohol solution containing two Kg. of potassium hydroxide (2350 Gm. of KOH, U. S. P. X which contains 15 p. c. of water). This quantity was based upon the saponification value (182) established by saponifying a sample according to the U. S. P. X process. An additional 10 p. c. of potassium hydroxide was allowed to insure complete saponification. After refluxing 8 hours, as much as possible of the alcohol was removed by distillation. Since the soapy mixture had a tendency to froth and foam, it was possible to obtain only approximately one-half of the total volume of alcohol, the balance remaining in the soap solution.

The saponified oil was dissolved in several volumes of water, and the solution shaken repeatedly with ethyl ether to remove the unsaponifiable matter.

* Part of a thesis submitted for the degree of Doctor of Philosophy, University of Wisconsin, 1932, and read by title before the Scientific Section of the A. PH. A. at the Toronto meeting. The thesis, deposited in the University Library, contains numerous details in tabulated form not here reported.

The aqueous solution was then acidified with cold, dilute sulphuric acid. Sufficient ether had been retained by the aqueous solution to dissolve the liberated fatty acids and form a layer above the water. The ethereal solution was removed, the ether distilled off and the fatty acids obtained in the form of a brownish gray solid. Notwithstanding the fact that sufficient sulphuric acid had been used to render the solution distinctly acid, it was found that the fatty acids contained considerable soap.[1] Purification was attempted by melting the acids and pouring them in a fine stream into dilute hydrochloric acid. The mixture was stirred constantly with a mechanical stirrer for one hour. The fatty acids were collected, remelted and poured into ice water with constant stirring, to remove the hydrochloric acid retained. Since they still contained considerable soap, the entire operation of melting the fatty acids, pouring into hydrochloric acid and then remelting and pouring into water was repeated. The fatty acids, however, still contained soap.

As a result of the saponification, the following products were obtained:

1. Unsaponifiable portion of the oil.
2. The free fatty acids.
3. The glycerin solution.

1. The *unsaponifiable portion* of the oil was turned over to Kurt Bonstedt for investigation.

2. The Fatty Acids. I. Preliminary Separation of the Fatty Acids.—The lead-alcohol method of Twitchel (1) was employed to separate the solid from the liquid fatty acids. One kilogram of the mixed fatty acids was dissolved in 6 litres of hot alcohol. A hot solution of 750 Gm. of lead acetate in 6 litres of alcohol was added and the mixture shaken. No precipitate formed until the liquid became cool. After standing two days at 10° to 15°, the mixture was filtered, and the residue washed with cool alcohol. The filtrate contained the unsaturated fatty acids as lead salts.

The residue was dissolved in boiling alcohol containing 0.6 p. c. acetic acid, and the solution filtered. There was but a trace of brown-colored residue which was washed with additional hot acetic acid-alcohol. After standing two days at 10° to 15°, the mixture was filtered, and the residue, consisting of the lead salts of the saturated fatty acids, was washed with cool alcohol.

A. Saturated Acids.—The lead salts of the saturated fatty acids were treated with dilute nitric acid, which liberated the fatty acids. The solution was shaken with ether, which dissolved the fatty acids, and the ethereal solution was shaken repeatedly with water in a separatory funnel until free from nitric acid. Upon evaporation of the ether, the saturated fatty acids were obtained as a faintly straw-colored, very hard mass. The yield was 315 Gm. or 31.5 p. c. of total fatty acids. Since the iodine number was found to be 3.9, the saturated fatty acids were shown to be contaminated with 4.3 p. c. of unsaturated fatty acid (calculated as oleic). This is equivalent to 14 Gm., reducing the total saturated fatty acids to 301 Gm. or 30.1 p. c. The mixture had a melting point of 53°.

[1] Matthes and his co-workers (2, 3) have shown that this oil contains considerable ricinoleic acid. It is interesting to note that castor oil soap is readily soluble in castor oil and very difficult to remove (4).

a. Fractional crystallization. The fatty acids were dissolved in 10 parts of 95 p. c. alcohol and allowed to cool slowly. The solid fatty acids which separated were removed by filtration. Fractions were obtained at the following temperatures: 18° (fraction "A"), 16° (fraction "B"), 14° (fraction "C"), 12° (fraction "D"). Fractions "A" and "B" were immediately redissolved in alcohol and refractionated. The fractions are indicated by the following table:

Fraction.	Temperature.	Weight—Gm.	Melting Point.
A-1	20°	26.73	56.0°
A-2	12°	5.56	56.5°
A-3	4°	3.94	56.0°
B-1	20°	11.11	56.5°
B-2	12°	4.97	55.8°
B-3	4°	3.14	55.0°
C	Not refract.	11.80	55.0°
D	...	...	55.0°

No satisfactory separation was effected, probably due to the formation of eutectic mixtures of the fatty acids (5) or to the formation of ethylic esters (6).

b. Fractional precipitation. Fifty grams of the mixed solid fatty acids were dissolved in 750 cc. of alcohol and treated with a 10 p. c. solution of hydrous magnesium acetate in alcohol. The magnesium soaps did not begin to precipitate until 100 cc. of magnesium acetate solution had been added. After standing 12 hours, the magnesium soaps were separated by filtration, boiled with hydrochloric acid to liberate the fatty acids and the separated fatty acids dissolved in alcohol.

This solution was treated with 15-cc. portions of magnesium acetate solution, sufficient ammonium hydroxide being added after each precipitation to neutralize the acetic acid freed. The solution was stirred while the magnesium acetate was being added, allowed to stand for at least one hour and the magnesium soap separated by filtration. Fractions 1 to 6, inclusive, were obtained from this solution, No. 6 being the residue after removing the alcohol.

Fractions 7 to 15, inclusive, were obtained in the same manner from the filtrate obtained from the above-mentioned magnesium soaps precipitated with 100 cc. of magnesium acetate solution. Fraction 15 was the residue.

The melting points of the magnesium soaps are not satisfactory for identifying the fatty acids as becomes apparent from the following tabulation:

Myristic acid m. p. 53.8°	Mg myristate m. p. 150.4°
Palmitic acid m. p. 62.6°	Mg palmitate m. p. 121–122°
Stearic acid m. p. 69.3°	Mg stearate m. p. 132°

Therefore, the fractions were boiled with dilute hydrochloric acid, cooled, filtered and the residue washed with water. The freed acid was then recrystallized from alcohol. The following fractions of free fatty acid were thus obtained:

Fraction.	Weight—Gm.	Melting Point.
1	1.95	51.0–51.2°
2	2.44	53.8–54.0°
3	1.11	53.5–54.0°
4	4.07	55.5–56.0°
5	1.65	Softened 30°
		Melted 44°

6	12.10	(Residue)
7	1.60	55.5–55.7°
8	2.10	43.0°
9	1.20	42.0°
10	5.20	55.5–56.0°
11	7.15	56.0°
12	0.33	58.5–58.7°
13	0.50	24.0°
14	1.00	60.5-60.7°
15	6.80	(Residue)
	49.20 Gm.	

c. Fractional distillation of methyl esters. The mixed solid fatty acids (185 Gm.) were refluxed with 370 cc. of methyl alcohol containing 9 cc. of concentrated sulphuric acid. The excess methyl alcohol was recovered by distillation, and the methyl esters were dissolved in ether. This ethereal solution was washed with water until free from mineral acid. The ethereal solution was then dried with anhydrous sodium sulphate, and the esters obtained by distilling the ether.

The methyl esters thus prepared were distilled in a modified Claissen flask on an oil-bath at a pressure of 8 mm. The following fractions were collected.

FRACTIONAL DISTILLATION I.

Fraction.	Boiling Range.	Weight—Gm.	Melting Point.
I	174–179°	31.62	28.0–28.5°
II	179–180°	46.92	26.5–27.0°
III	(Bumped over)	20.95	.....
IV	181–182°	27.05	24.8–25.2°
V	183–188°	21.14	24.0–24.2°
VI	188–196°	9.10	19.8–20.2°
VII	196–200°	5.76	28.5–29.5°
VIII	(Residue)	9.06	.....

The fractions were redistilled as follows: Nos. I and II were distilled to 178°; III and IV were then added to and distilled with 182°; V was added to and distilled with 186°; VI was added to and distilled with 190°; VII and VIII were added to and distilled with 200°. A second group of fractions was obtained as indicated by the following table:

FRACTIONAL DISTILLATION II.

Fraction.	Boiling Range.	Weight—Gm.	Melting Point.
A	173–174°	28.18	28.2°
B	175–178°	75.06	25.8-26.3°
C	178–182°	20.71	23.0–23.2°
D	182-186°	19.26	20.5–21.8°
E	186-194°	11.46	22.5–23.0°
F	194–200°	6.81	23.0–23.5°
G	(Residue)	7.92	.....

The fractions were redistilled in a similar manner and the following fractions were obtained:

FRACTIONAL DISTILLATION III.

Fraction.	Boiling Range.	Weight—Gm.	Melting Point.
1	164–168°	3.75	26.2–26.5°
2	169–171°	13.35	28.0–28.2°

Fraction.	Boiling Range.	Weight—Gm.	Melting Point.
3	172–175°	77.95	28.5–28.7°
4	176–178°	14.82	26.5–27.0°
5	179–185°	12.32	22.5–23.2°
6	186–190°	21.57	22.5–23.0°
7	190–196°	14.10	28.0–28.5°
8	197–200°	2.77	30.0–30.2°
9	201–206°	4.60	32.0–32.5°
10	(Residue)	1.73	.....

The quantitative separation of the solid fatty acids is very difficult when one considers that they differ only about 10 p. c. in molecular weight. Fractional distillation of the methyl esters, which is the most satisfactory method employed, does not yield pure fractions unless, possibly, after a large number of redistillations. The fractions obtained from ergot oil, in most cases, probably contained but two saturated fatty acids. Oleic ester, although its boiling point is near that of stearic, begins to distil below its boiling point in the presence of other methyl esters (7). Thus, small amounts of oleic ester were present in all samples except No. 1, as indicated by the iodine value. After saponification, myristic acid was isolated from No. 1, stearic acid from No. 9 and the residue, and palmitic acid from Nos. 1 to 7, inclusive. Arachidic acid was not detected. The isolation of small amounts of stearic acid in a mixture with palmitic, or vice versa, is quite difficult, since the two form an eutectic mixture (the so-called "margaric acid" is considered by some to be such a mixture).

Daturic acid was not obtained from any of the fractions. Indeed, the existence of this acid is doubted by many authorities. Jamieson's recent (1932) "Vegetable Fats and Oils" does not mention daturic (or margaric) acid, although other fatty acids are considered in detail.

The following table indicates the approximate quantitative composition of the fractions. The amount of oleic ester is calculated from the iodine value. Lead oleate is less soluble in alcohol than lead linoleate or ricinoleate, hence the iodine value of the solid acids separated by the lead-salt-alcohol method is probably due to oleic acid. The amount of saturated ester may be approximated by the molecular equivalent (based upon the saponification value), after subtracting the oleic acid content.

	M. E.	Weight—Gm.	I. V.	Fatty Acid.	P. C.	Weight—Gm.
1.	253.2	3.75	0.0	Myristic	44.3	1.66
				Palmitic	55.7	2.09
2.	265.9	13.35	2.5	Myristic	16.6	2.22
				Palmitic	80.5	10.74
				Oleic	2.9	0.39
3.	267.0	77.95	2.8	Myristic	13.6	10.60
				Palmitic	83.1	64.75
				Oleic	3.3	2.60
4.	270.0	14.82	4.3	Myristic	5.0	0.74
				Palmitic	90.0	13.44
				Oleic	5.0	0.74
5.	273.0	12.32	6.0	Palmitic	86.2	10.41
				Stearic	6.8	0.84
				Oleic	7.0	0.87
6.	276.0	21.57	9.0	Palmitic	79.9	17.25
				Stearic	9.6	2.06
				Oleic	10.5	2.26

7. 279.5	14.10	13.2	Palmitic	61.7	8.70
			Stearic	22.9	3.23
			Oleic	15.4	2.17
8. 292.5	2.77	20.4	Palmitic	17.8	0.49
			Stearic	58.4	1.65
			Oleic	23.8	0.63
9. 295.0	4.60	26.2	Palmitic	4.9	0.23
			Stearic	64.4	2.96
			Oleic	30.7	1.41
	165.23 Gm.				

Summary of Solid Fatty Acids.

Myristic acid	15.32 Gm.	9.9 p. c.
Palmitic acid	78.00 Gm.	83.1 p. c.
Stearic acid	10.74 Gm.	7.0 p. c.

or

Myristic acid	3.0 p. c. of total fatty acids
Palmitic acid	25.0 p. c. of total fatty acids
Stearic acid	2.1 p. c. of total fatty acids

B. Unsaturated Acids.—The alcoholic solution of lead salts of the unsaturated fatty acids (see above) was concentrated to one-half of its volume and treated with hydrogen sulphide until no more lead sulphide precipitated. The mixture was then warmed to coagulate the lead sulphide and filtered. The residue was washed with alcohol, and the mixed filtrates concentrated in an atmosphere of carbon dioxide. The unsaturated fatty acids remained as a yellow-colored, oily liquid. Yield—624.5 Gm. or 62.45 p. c. of total fatty acids.

The unsaturated fatty acids were separated from each other according to the method of Rosenthaler (8). They were dissolved in ten volumes of glacial acetic acid and two volumes of ether. At a temperature not exceeding 8°, this solution was treated with a solution consisting of one part of bromine and two parts of glacial acetic acid until the bromine was in excess.

The mixture was then kept at 5° for 6 hours, and the precipitate removed by decantation and filtration. This precipitate, a brownish gray solid, proved to be alpha-linolenic hexabromide, m. p. 181°. It was present in very small quantities, only 0.12 Gm. being obtained, corresponding to 0.006 p. c. of the total liquid acids.

The filtrate was added to five volumes of water. A red, oily liquid separated to the bottom. The water was decanted and shaken out with ether. The separated oily liquid was then dissolved in the ethereal solution, dried with anhydrous sodium sulphate and the ether recovered. The residue consisted of 1032 Gm. of red, oily liquid.

This liquid was dissolved in one litre of petroleum ether, allowed to stand at 0° for several hours and filtered. A small amount of black residue was obtained. The filtrate was then diluted with two litres of petroleum ether and allowed to stand over night at −3° to −6°. A small quantity of dark brown, viscous, oily liquid separated to the bottom. After separation of this layer, the petroleum-ether solution was washed thoroughly with water to remove the trace of acetic acid which was retained by the ether solution (see above). After standing at −3° to −6° for several days, more oily liquid separated, making a total of 163 Gm. This liquid,

according to Matthes and Schuetz (2), is dibromricinoleic acid. The 163 Gm. of dibromide correspond to 89.7 Gm. of ricinoleic acid.

The oily liquid was debrominated with zinc, saponified with potassium hydroxide, and neutralized with hydrochloric acid to yield the free fatty acid. This acid was then exactly neutralized with sodium hydroxide, and treated with an excess of 1.5 p. c. ice cold potassium permanganate solution. The excess permanganate was reduced with sulphur dioxide which also liberated the free fatty acids. Two trihydroxides were obtained, melting at 110° and 115°. Matthes and Kuerschner (3) obtained these two trihydroxides from ricinoleic acid from ergot oil in addition to one melting at 140–142°.

The petroleum-ether solution, after separation of dibromricinoleic acid, was concentrated and allowed to stand for 24 hours at 0° to −6°. A solid, yellow-colored precipitate formed which melted at 103°. After crystallization from petroleum ether, it melted at 113° (uncorr.). The original petroleum-ether solution was allowed to stand again for 24 hours, and additional yellowish white crystals separated. These melted at 113°. These indicated alpha-linoleic tetrabromide, m. p. 114°. The yield, 21.14 Gm., corresponds to 7.47 Gm. of linoleic acid.

The filtrate was again concentrated and allowed to stand for several days at 0° to −23°. A yellow, fatty substance (m. p. 57°) separated. This substance was separated, dissolved in acetone, and cooled with freezing mixture, when linoleic tetrabromide (m. p. 114°) separated. This was filtered and the mother liquid evaporated. The oily residue was dissolved in petroleum ether from which a red, oily liquid (ricinoleic dibromide) separated on cooling. The acid value (585) indicated that the yellow substance was a mixture of 90 p. c. linoleic and 10 p. c. ricinoleic bromides.

The filtrate from which the yellow solid originally separated was evaporated. The residue consisted of 391 Gm. of an oily liquid. Oxidation with dilute permanganate, after first debrominating with zinc (see oxidation of ricinoleic acid, above), yielded a dihydroxystearic acid which melted at 135° (dihydroxystearic acid from oleic acid melts at 133° to 136.5° (9)).

Thus it was found that the unsaturated fatty acids consisted of linolenic, linoleic, ricinoleic and oleic acids. The amount of linolenic was so small that for practical purposes it may be considered negligible so that the actual quantities of the other acids may be computed without it.

The acetyl value of the mixed fatty acids (59.1) indicates 35.8 p. c. of ricinoleic acid. Since the fatty acids contained 69.9 p. c. of liquid (unsaturated) fatty acids (after accounting for those which separated with the solid acids), 34.1 p. c. of the unsaturated fatty acids consisted of oleic and linoleic. The iodine value of the mixed fatty acids (73.5) indicates an iodine value of 105 for the unsaturated fatty acids. After accounting for the ricinoleic acid, the quantities of oleic and linoleic may thus be calculated. The approximate quantitative composition of the unsaturated fatty acids is indicated in the following table:

Oleic acid	30 p. c. of the unsaturated acids
Ricinoleic acid	51 p. c. of the unsaturated acids
Linoleic acid	19 p. c. of the unsaturated acids
Linolenic acid	Traces

or

Oleic acid	20.9 p. c. of total fatty acids
Ricinoleic acid	35.8 p. c. of total fatty acids
Linoleic acid	13.2 p. c. of total fatty acids
Linolenic acid	Traces

II. Study of About 18 Kilos of Fatty Acids. A. By Fractional Crystallization.—The fatty acids were crystallized from a relatively concentrated (25 to 33 p. c.) alcoholic solution at various temperatures. The various fractions were then recrystallized from a more dilute solution in acetone, since a certain amount of ethyl ester was produced when alcohol was used. It was found, however, that solid fatty acids could not be satisfactorily separated from the liquid acids by this method.

B. By Fractional Distillation of Methyl Esters.—The fatty acids were then esterified with methyl alcohol and submitted to the fractional distillation process of Gruen and Janko (10). This consists in treating the methyl esters (in petroleum ether or chloroform solution) with bromine solution at 0° to 5°. After the fatty acids are entirely brominated, the mixture was washed with aqueous sodium bicarbonate solution and dried with anhydrous sodium sulphate.

The solvent was recovered, and the methyl esters subjected to fractional distillation at a pressure of 8 to 15 mm. There was considerable decomposition as was indicated by clouds of more volatile material produced below the boiling point of the esters. The first fractions obtained were straw colored, but after redistillation they were colorless. The iodine value, however, ranged from 15 to 50 indicating the presence of unsaturated fatty acids. This method was not satisfactory, possibly due to the oxidized condition of the original fixed oil.

SUMMARY.

The solid fatty acids may be separated from each other more satisfactorily by fractional distillation of the methyl esters than by either fractional crystallization from alcohol or by fractional precipitation with magnesium acetate.

The approximate quantitative composition of the mixed fatty acids from the fatty oil of ergot is herewith tabulated:

	P. C. of Total Fatty Acids.
Myristic acid	3.0
Palmitic acid	25.0
Stearic acid	2.1
Oleic acid	20.9
Ricinoleic acid	35.8
Linoleic acid	13.2
Linolenic acid	Traces

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A CHEMICAL STUDY OF MA HUANG.*[1]

BY ALICE H. HAYDEN[2] AND C. B. JORDAN.

HISTORICAL.

Ma Huang presents one of the most interesting histories found in drug lore. Its antiquity, its varied rôles throughout the centuries and its recent spectacular rise to its present position in modern medicine weave a fascinating story for those interested in drugs and the relationship of pharmacognosy and chemistry to the development of medical science.

Early Chinese records (1) indicate that Ma Huang was known and used as early as the third century, B. C. The Chinese employed the drug to allay coughing, to promote sweating, to stimulate heart action, to relieve post-partem difficulties and to control fevers. Chen (2) reports that Ma Huang was usually prescribed with other crude drugs and made into a decoction and taken by the patient as such.

Ma Huang means astringent yellow. The taste is very astringent; this has been attributed to a high tannin content. There seems to be some doubt, however, as to just what is the exact application of the word "Huang" or "yellow." Some writers, Chen (3) and Nielsen (4), believe that the word yellow applies to the appearance of the dried stem, but Read (5) is of the opinion that the early literature refers to "Huang" as the color of the flower.

Ma Huang belongs to the seventh division of the Gymnospermous plants, the Gnetales. The exact botanical identity of this drug has been a subject of much confusion and discussion. The earlier investigators referred to it as *Ephedra vulgaris*, **var,** *helvetica*. However, recent investigations indicate that this term is now obsolete and should be dropped. The modern tendency is to consider Ma Huang as a generic term applying to various ephedrine-bearing species of Ephedra growing in China (5).

The drug is imported in large bales. There is no true grading of the product; oftentimes a single bale will contain several species of Ephedra. During the processes of collecting, drying, compressing and transporting, the plants become badly broken and most of the berries, flowers and bracts drop off so that a complete separation of the different species is practically impossible.

As far as can be ascertained, the first chemical investigation of the plant was carried out by Yamanshi, who, in 1885, isolated an alkaloid in an impure state. After the death of the discoverer, Nagai (1887) (6) with the assistance of Hori, continued the study, purified the product and named it ephedrine. It is interesting to note, however, that the term ephedrine was first used by Loew (1875) to desig-

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* Scientific Section, A. PH. A., Toronto meeting, 1932.

[1] An abstract based upon a thesis by Alice H. Hayden submitted to the Faculty of Purdue University in partial fulfilment of the requirements for the degree of Doctor of Philosophy. The original thesis is accompanied by a bibliography of over one thousand references.

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