[CONTRIBUTION FROM THE INTERNATIONAL LEPROSY CENTER, RIO DE JANEIRO, BRASIL]

Analysis of Chaulmoogra Oils. IV. *Hydnocarpus anthelmintica* Oil. V. *Taraktogenos kurzii* (Chaulmoogra) Oil

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IV. *Hydnocarpus Anthelmintica* Oil

The oil expressed from the seeds of *Hydnocarpus anthelmintica* is extensively used in the treatment of leprosy, ranking next to *H. wightiana* oil in therapeutic importance. *H. anthelmintica* occurs abundantly in Siam, Cambodia, Cochin China, and Laos. It also has been reported from Burma. The tree grows to a height of 20 to 25 meters and is generally found in valleys from sea level to 1300 meters altitude. It has been successfully cultivated in Hawaii and the Belgian Congo. The ripe fruits are more or less globular in shape and vary in size from 8 to 15 centimeters in diameter. The seeds are of approximately the same shape and size as those of *H. wightiana* (1 to 2 centimeters long) but are readily distinguished from the latter because of their smoother and thicker shell. The oil is used by the natives of Siam for cutaneous affections. The seeds form an article of export to China where they are known as Ta-fung-chi or Ta-feng-tzu.

As early as 1905 Power and Barrowcliff[1] attempted to analyze *H. anthelmintica* oil. They reported that the total fatty acids of this oil contained chaulmoogric, hydnocarpic, oleic and palmitic acids. Although several qualitative analyses have been made since, no one has succeeded in making a quantitative analysis due to the difficulty in separating the constituents. We have succeeded in analyzing *H. anthelmintica* oil by the method for chaulmoogra oils given in the first article of this series.[2] The constituents and percentage composition are given in Table I. Besides the acids previously reported as present, our analysis shows that gorlic acid and a small percentage of a lower homolog of hydnocarpic acid are also present.

TABLE I

PERCENTAGE COMPOSITION OF THE FATTY ACIDS OF *H. anthelmintica* AND *T. kurzii* OILS (FROM TABLES II AND III)

Acids	*H. anthelmintica*, %	*T. kursii*, %
Hydnocarpic	67.8	34.9
Chaulmoogric	8.7	22.5
Gorlic	1.4	22.6
Oleic	12.3	14.6
Palmitic	7.5	4.0
Lower homologs of hydnocarpic acid	0.1	0.4
Loss	2.2	1.0

(1) Power and Barrowcliff, *J. Chem. Soc.*, **87**, 884, 896 (1905).
(2) Cole and Cardoso, THIS JOURNAL, **60**, 614 (1938).

Experimental

The sample of *H. anthelmintica* oil was obtained from a 300-liter drum imported several years ago from Siam by the Departamento de Prophylaxia da Lepra da São Paulo, who generously donated the sample for our analysis. Although the oil was more than five years old, its characteristics indicate that very little decomposition had taken place. The characteristics determined at the time of the analysis were as follows: specific gravity 25/25, 0.952; F. F. A. (as % oleic) 2.9; saponification no., 203.3; iodine no. (Hanus), 89.2; specific optical rotation, $[\alpha]^{25}D$ +49.70; refractive index $[n]^{25}D$ 1.4772; unsaponifiable matter, 0.50%.

Method of Analysis.—Since the medicinal properties of chaulmoogra oils depend upon the percentage of optically active fatty acids, the analysis is reported in per cent. of the various fatty acids present. The sample of oil was saponified and the fatty acids liberated in the usual manner. The solid acids were separated from the liquid acids by crystallization from 80% ethyl alcohol. The two fractions were changed to ethyl esters and then fractionally distilled at 10 mm. in a Podbielniak Model B high temperature fractionating apparatus. The details of the separation and distillation were given in the first article of this series,[2] the only change being that the two final crystallizations for the separation of the liquid acids were made with 80% acetone to prevent the formation of ethyl esters.

Qualitative Analysis

In our analysis of the total fatty acids of *H. anthelmintica* oil we found chaulmoogric, hydnocarpic, gorlic, oleic and palmitic acids besides a very small percentage of a lower homolog of hydnocarpic acid. The acids were identified as follows.

Chaulmoogric Acid.—Pure chaulmoogric acid was obtained readily from the acids from fraction 3, Table III, by crystallization to constant melting point from 80% alcohol. It gave the correct optical rotation, iodine number, neutralization equivalent and melting point for pure chaulmoogric acid.[3]

Hydnocarpic Acid.—This acid was isolated in the pure state from fraction 2, Table III, by repeated crystallization of the acids from 80% alcohol. It gave all the correct constants for pure hydnocarpic acid.[3]

Gorlic Acid.—Ethyl gorlate was isolated by several fractional distillations of those fractions rich in ethyl gorlate such as fraction 3, Table II, by the method previously de-

(3) Cole and Cardoso, THIS JOURNAL, **59**, 963 (1937).

TABLE II

FRACTIONAL DISTILLATION OF ETHYL ESTERS FROM LIQUID ACIDS OF *H. wightiana* AND *T. kurzii* OILS

Fraction	B. p., °C. (10 mm.)	Cc.	Sp. rot.	Iodine no.	% in liquid fraction: Hydnocarpate	Chaulmoograte	Gorlate	Oleate	Palmitate	Lower homologs
H. anthelmintica (17.9% of total fatty acids)										
1	153–187	1.0	36.89	...	...	...	...	...	0.69	0.61
2	187–201	36.0	36.56	82.01	27.60	...	...	16.50	2.66	..
3	201–207	25.0	36.49	94.11	16.24	...	3.20	13.00	..	..
4	207–209	8.0	35.49	98.98	4.47	...	1.66	4.26	..	..
5	209–215	4.5	38.34	104.20	...	2.52	1.53	1.81	..	..
Loss		2.5								
% in liquid fraction					48.31	2.52	6.39	35.57	3.35	0.61
% in total fatty acids					8.64	0.45	1.15	6.37	0.60	0.11
T. kurzii (41.7% of total fatty acids)										
1	161–185	2	30.59	...	...	...	...	...	1.55	0.98
2	185–201	28	34.37	94.78	14.17	...	6.09	12.97	2.20	..
3	201–207	8	40.23	112.8	3.67	...	3.24	3.22	..	..
4	207–217	39.7	48.78	138.3	...	11.87	32.20	6.24	..	..
Residue		1.3								
% in liquid fraction					17.84	11.87	41.53	22.43	3.75	0.98
% in total fatty acids					7.45	4.95	17.3	9.35	1.56	0.41

TABLE III

FRACTIONAL DISTILLATION OF ETHYL ESTERS FROM SOLID ACIDS OF *H. anthelmintica* AND *T. kurzii* OILS

Fraction	B. p., °C. (10 mm.)	Cc.	Sp. rot.	Iodine no.	% in solid fraction: Hydnocarpate	Chaulmoograte	Gorlate	Oleate	Palmitate
H. anthelmintica Oil (82.1% of total fatty acids)									
1	191–201	69	51.10	80.05	57.0	...	..	4.8	7.2
2	201–211	18	51.79	84.08	15.1	...	..	1.7	1.2
3	211–215	11	51.93	84.35	...	10.0	0.31	0.69	..
Loss		2							
% in solid fraction					72.1	10.0	0.31	7.19	8.4
% in total fatty acids					59.2	8.21	0.25	5.90	6.9
T. kurzii Oil (58.3% of total fatty acids)									
1	191–202	41.5	47.67	82.10	32.0	...	..	5.27	4.23
2	202–209	19.3	51.74	94.30	14.94	...	1.35	3.01	..
3	209–217	38.6	54.38	99.05	...	30.11	7.72	0.77	..
Loss		0.6							
% in solid fraction					46.94	30.11	9.07	9.05	4.23
% in total fatty acids					27.37	17.55	5.28	5.28	2.47

scribed.[4] The correct constants were obtained for ethyl gorlate and gorlic acid.[4]

Oleic Acid.—Oleic acid was not obtained pure but its presence was indicated in the liquid fraction by the distillation curve of the ethyl esters and by the correct iodine numbers for mixtures containing ethyl oleate in fractions 2, 3, 4 and 5 of Table II. The elaidic acid test cannot be used in the presence of gorlic acid as the latter gives a similar reaction. Hydrogenation tests were also unsatisfactory in the presence of chaulmoogric or hydnocarpic acid.

Palmitic Acid.—This acid was separated by cooling fractions of ethyl esters rich in palmitate, the latter solidifying at a higher temperature than hydnocarpate. The solid ester was separated and crystallized from ethyl alcohol to constant melting point (24°). Upon changing it to the acid and crystallizing from alcohol, the correct melting point and neutralization equivalent for palmitic acid were obtained.

Lower Homologs.—The presence of at least one homolog of hydnocarpic acid was indicated by the optical rotation and boiling point of fraction 1, Table II. The sample was too small to attempt to identify this compound.

Quantitative Analysis

The total fatty acids of *H. anthelmintica* oil when separated into liquid and solid acids by the method described by us consisted of 17.9% liquid acids and 82.1% solid acids. Although the separation is by no means complete, the breaks in the distillation curves of the ethyl esters made from these two fractions are much more distinct than when the whole esters are used. Complete separation is not necessary as the amounts of the various constituents can be computed by taking advantage of the boiling points, optical rotations and iodine numbers or absence of one or both of the two latter constants as described in Part I of

(4) Cole and Cardoso, THIS JOURNAL, **60**, 612 (1938).

this series of articles. The results of these computations are given in Tables II and III and these are summarized in Table I. Fraction 1, Table II was computed on the assumption that it was a mixture of alepric acid[5] and a saturated acid.

V. *Taraktogenos kurzii* (Chaulmoogra) Oil

Chaulmoogra is the native name for *Taraktogenos kurzii* oil which has been used for centuries in Burma and India in the treatment of leprosy. In recent years, however, the word "chaulmoogra" has been used generically to indicate any oil containing chaulmoogric acid which might be used in the treatment of leprosy, such as *H. wightiana* or *C. brasiliensis* oil. *Taraktogenos kurzii* is a tree widely distributed in Burma. It is also found in Siam, Eastern Bengal and Assam. *T. kurzii*, called by the Burmese, kalaw, grows to a height of 15 to 20 meters in dense forests. The fruits are globular, varying in size from 8 to 15 cm. in diameter. The seeds are larger than those from *H. wightiana* with a smoother and thicker shell. Bears are very fond of the white flesh of the fruit (in which the seeds are imbedded) and large numbers of them are said to roam the forests in search of the kalaw fruits. Collecting the seeds is very dangerous on account of tigers, bears and other wild animals. The fruit ripens in June or July, falls in the rainy season and is usually no longer fresh when gathered. For this reason and because of the long time necessary for transportation to a press for expression of the oil the true chaulmoogra oil of commerce is almost always of poor quality with a very high free fatty acid content. It is often adulterated and other hydnocarpus oils are frequently sold as chaulmoogra oil. Because of these disadvantages its use in leprosy treatment has been largely superseded by authentic *H. wightiana* and *H. anthelmintica* oils, which are cheaper and of better quality. Plantations would eliminate these disadvantages. In fact the oil for this analysis was obtained from a plantation at Vicosa, Minas Geraes, where Dr. Rolfs has succeeded in acclimatizing *T. kurzii* to Brazil. It flourishes there, producing heavy crops of fruits.

The first analysis of chaulmoogra oil was made by Power and Gornall[6] in 1904. They reported that the oil contained both chaulmoogric and hydnocarpic as well as a small amount of palmitic and linolic acids. Other investigators have added very little to our knowledge of chaulmoogra oil. No quantitative analysis has ever been made. We have made an analysis of this oil by the method described in the first article of this series.[2] The constituents and percentage composition of chaulmoogra oil are given in Table I. Besides the acids mentioned by Power and Gornall, we have found that the oil also contains gorlic and oleic acids and a small amount of a lower homolog of hydnocarpic acid. No linolic or linolenic acid was found. The high iodine numbers of certain fractions which led previous investigators to suspect the presence of linolic or linolenic acid are due to the presence of gorlic acid, which has two double bonds. If gorlic acid should prove to be of greater value in leprosy treatment than the other optically active fatty acids, then the true chaulmoogra oil would be preferable to the other oils we have analyzed since it contains the highest percentage of this acid (see Table V).

Previous statements that the oil does not keep well are not true. The bad reputation of the oil is due to the fact that the oil is practically never expressed from fresh dried seeds as mentioned above. Oil from old seeds is always irritating. *T. kurzii* oil which we cold-pressed from fresh, dried seeds has changed very little after standing for three years and is still non-irritating upon injection. We have found this generally true of all the chaulmoogra oils we have analyzed.

Experimental

The sample of oil was obtained by cold pressing of fresh, dried seeds kindly donated by the Escola Superior de Agricultura at Vicosa, Minas Geraes. The sample of oil was three years old before it was analyzed but the characteristics of the oil had changed only very slightly in that time. The characteristics of the oil made at the time of analysis were as follows: specific gravity 25/25, 0.952; F.F.A. (as % oleic), 1.3; saponification no., 200.6; iodine no. (Hanus), 101.5; specific optical rotation $[\alpha]^{25}D$ +49.80; refractive index $[n]^{25}D$ 1.4790; unsaponifiable matter 0.29%.

The analysis was made on the total fatty acid content of the oil since the medicinal properties of the oil depend upon the percentage of the optically active acids present and was made in the same manner as that of *H. anthelmintica* oil.

Qualitative Analysis.—The fatty acids of *T. kurzii* oil were found to contain chaulmoogric, hydnocarpic, gorlic, oleic and palmitic acids with a very small percentage of a lower homolog of hydnocarpic acid. The acids were identified in the same manner as those from *H. anthelmintica* oil.

Quantitative Analysis.—The total fatty acids of *T. kurzii* oil when separated into liquid and solid fatty acids by the method described by us consisted of 41.7% liquid acids and 58.3% solid acids. After distillation of the ethyl esters made from these two fractions, the amounts of the various constituents present were computed as previously

(5) Cole and Cardoso, THIS JOURNAL, **61**, 2349 (1939).
(6) Power and Gornall, *J. Chem. Soc.*, **85**, pt. II, 838, 851 (1904).

TABLE IV

CHARACTERISTICS OF CHAULMOOGRA OILS

	Hydnocarpus wightiana	*Hydnocarpus anthelmintica*	*Taraktogenos kurzii*	*Carpotroche brasiliensis*	*Oncoba echinata*
Specific gravity 25/25	0.955	0.952	0.952	0.955	...
Free fatty acid (as % oleic)	2.7	2.9	1.3	3.6	4.3
Saponification number	201.0	203.3	200.6	201.8	193.7
Iodine number (Hanus)	98.4	89.2	101.5	108.0	96.4
Spec. optical rotation $[\alpha]^{25}D$	55.0	49.7	49.8	53.8	51.7
Refractive index $[n]^{25}D$	1.4799	1.4772	1.4790	1.4790	...
Unsaponifiable matter, %	0.25	0.50	0.29	....	...

TABLE V

PERCENTAGE COMPOSITION OF TOTAL FATTY ACIDS OF CHAULMOOGRA OILS

Acids	*H. wighti-ana*	*H. anthel-mintica*	*T. kurzii*	*C. Brasili-ensis*	*O. echi-nata*
Hydnocarpic	48.7	67.8	34.9	45.0	None
Chaulmoogric	27.0	8.7	22.5	24.4	74.9
Gorlic	12.2	1.4	22.6	15.4	14.7
Lower homologs of hydnocarpic	3.4	0.1	0.4	?	?
Oleic	6.5	12.3	14.6	6.3	2.2
Palmitic	1.8	7.5	4.0	6.6	7.8
Loss	0.4	2.2	1.0	2.3	0.4

described. The results of these computations are given in Tables II and III and these are summarized in Table I. Fraction 1, Table II, was computed on the assumption that only alepric and palmitic acids were present as the sample was too small to be separated further.

Summary

The qualitative and quantitative analyses of *Hydnocarpus anthelmintica* and *Taraktogenos kurzii* (chaulmoogra) oils have been made by the methods described in the first article of this series. They are the first quantitative analyses that have been made of these two important medicinal oils.

The percentage compositions of these oils are given in Table I.

A summary of the characteristics and percentage compositions of the five oils of the chaulmoogra group so far analyzed in this series of articles is given in Tables IV and V.

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Studies in the omega-Camphor Series. I. On the Synthesis of 2-Keto-apocamphane-1-acetic Acid

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Some time ago one of the authors of this paper described the reaction involved in the formation of the Semmler and Bartelt lactone from teresantalic acid and the synthesis of *cis*-2-keto-apocamphane-7-π-carboxylic acid,[1] the corresponding *trans* acid being previously synthesized.[2] In view of the fact that camphor itself does not exert the cardiostimulating action, but certain π-camphor derivatives,[3] derived therefrom, do, it was of interest to synthesize some corresponding ω-2-substituted camphane derivatives.

The present paper deals with the synthesis of the novel 2-keto-apocamphane-1-acetic acid, some derivatives of it and with the reactions involved in its preparation.

As starting material we used the ω-benzoylborneol (II) of Lipp, *et al.*,[4] who obtained this compound from camphene (I) by combining it with benzoyl chloride by means of the Friedel-Crafts synthesis, whereby the asymmetric camphene nucleus is converted into the symmetric camphor skeleton by the Meerwein–Wagner rearrangement.

On subjecting the oxime of ω-benzoylborneol (III) to the Beckmann rearrangement, we obtained a mixture of 2-hydroxy-apocamphane-1-acetanilide (IV) and the anilide of camphenecarboxylic acid (VI) together with some tarry material of unknown composition and small amounts of benzonitrile which was identified as benzoic acid by hydrolysis.

The 2-hydroxy-apocamphane-1-acetanilide was hydrolyzed with alcoholic potassium hydroxide solution. The resulting product was the lactone of 2-hydroxy-apocamphane-1-acetic acid (XIV)

(1) (a) Hasselstrom, THIS JOURNAL, **53**, 1099 (1931); (b) Asahina and Ishidate, *Ber.*, **66**, 1675 (1933).

(2) (a) Wedekind, *Ber.*, **55**, 1557 (1923); (b) Hasselstrom, *Ann. Acad. Finn.*, **30**, 12 (1929).

(3) Tamura, *Imp. Acad. Japan*, **11**, 4 (1935).

(4) Lipp, Küppers and Holl, *Ber.*, **60**, 1575 (1927).