CH_3.—To 21.4 g. of *o*-bromo-cyclohexylamine hydrochloride in toluene is added 10 cc. of acetyl chloride and the mixture is refluxed for several hours. When the reaction is completed the toluene is removed *in vacuo*. The solid residue is dissolved in a small amount of warm alcohol and ice-water added. An oil separates, which crystallizes in a short while. M. p. of the acetyl derivative, 103–104°. Yield, 13.5 g. or 61%.

Subs., 0.1516: AgBr, 0.1312.
Calc. for $C_8H_{14}ONBr$: Br, 36.32. Found: 36.81.

Attempts to prepare *o*-iodo-cyclohexylamine in a manner analogous to the preparation of the chlorine and bromine compounds, using phosphorus tri-iodide in chloroform, were unsuccessful. Invariably the main products were esters of *o*-amino-cyclohexanol.

Substitution of bromine for iodine in *o*-bromo-cyclohexylamine, using potassium iodide in aqueous or alcoholic solution, has given 50% substitution, but the product is too impure for definite identification.

Summary.

Methods for obtaining cyclohexane derivatives by direct reduction of the corresponding benzene compounds have been reviewed. The method of Ipatiew for the reduction of benzene and phenol has been particularly applied.

Methods, with some modifications which are most applicable for the laboratory production of cyclohexane, cyclohexanol, cyclohexanone and its oxime, cyclohexylamine, and cyclohexene, are described.

Methods for obtaining the following *ortho* substituted cyclohexane compounds in which the *ortho* groups are dissimilar, chloro-cyclohexanone, chloro-cyclohexanol, amino-cyclohexanol, chloro-cyclohexylamine and bromo-cyclohexylamine, with certain of their derivatives, are given.

Work in this series is being continued.

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FRACTIONATION OF CHAULMOOGRA OIL.

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The material known commercially as chaulmoogra oil has assumed considerable importance in recent years. For many years, perhaps for centuries, this oil has been used in India as a palliative in leprosy. In more recent times it has had more or less use in all countries where leprosy occurs. Taken by way of the mouth its administration is frequently attended by amelioration of the disease, although the intolerance exhibited by many persons limits its usefulness, and at best the action is slow.

New interest was aroused by the results obtained by intramuscular

injections of this oil fluxed with olive oil, a line of experimentation to which the work of Heiser was especially stimulating. Leprologists believed that although chaulmoogra oil had by no means been proven a specific in leprosy, it was the most promising drug known in combating the disease.

The statements in the older literature dealing with the origin and composition of chaulmoogra oil are conflicting and unreliable. It was frequently stated to be the product of *Gynocardia odorata* and to contain "gynocardic acid" as its characteristic constituent. The true origin and nature of the oil was elucidated by Power and his collaborators in a series of papers from the Wellcome Chemical Research Laboratories.[1]

These authors showed that the true chaulmoogra oil is derived from the seeds of *Taraktogenos Kurzii* and that the oils from 2 closely related species of *Hydnocarpus* were practically identical. The oil from *Gynocardia odorata*, however, is wholly different. The outstanding feature of their work was the discovery of a new type of fatty acid present in *Taraktogenos* and *Hydnocarpus* oils. These acids are strongly dextro-rotatory and the study of their consitution indicated that they contain a 5-membered carbon ring with side chains of different length. Two acids of this series were isolated and studied; chaulmoogric acid, $C_{17}H_{31}.COOH$, and hydnocarpic acid, $C_{15}H_{27}.COOH$. Chaulmoogric acid melts at 68°, has an iodine value of 90.1, and shows a specific rotation of +56°; hydnocarpic acid melts at 59°, possesses an iodine value of 100.2, and gives a specific rotation of + 68.1°. Structural formulas believed to be consistent with their experimental results were proposed.

Brill,[2] in a series of papers from Manila, confirmed the work of Power and his collaborators by isolating both chaulmoogric and hydnocarpic acids and extended our knowledge of their distribution in several species of plants related to those examined by Power.

The following tabular statement shows some of he essential facts concerning these oils.

	Tarak-togenos*[a] Kurzii.	Hyndo. carpus*[a] Wightiana.	Hydno-carpus*[a] anthel-minticus.	Hydno-[b] carpus venenata.	Hydno. carpus-[b] alcalae.	Pangium-[b] edule.
Melting point.....	22	22	24	20	32	Cloudy at 2°
Specific gravity....	0.951 (24°)	0.958 (25°)	0.953 (25°)	0.948 (30°)	0.9502 (30°)	0.9049
Specific rotation....	+52.0°	+57.7°	+52.5°	+52.03°	+49.6°	+4.28°
Iodine value.....	103.2	101.3	86.4	99.1	93.1	113.1
Chaulmoogric acid..	+	+	+	+	(90%) +	?
Hydnocarpic acid..	+	+	+	+	—	?

[a] Power, *et al.*

[b] Brill.

[1] Power and Gornall, *J. Chem. Soc.*, **85**, 838, 851 (1904); Power and Barrowcliff, *ibid.*, **87**, 884 (1905); Barrowcliff and Power, *ibid.*, **91**, 557 (1907).

[2] H. C. Brill, *Philippine J. Sci.*, Section A, **11**, 75 (1916); **12**, 37 (1917); Brill and Williams, *Philippine J. Sci.*, Section A, **12**, 207 (1917).

Goulding and Akers[1] showed that the oil from the seeds of *Oncoba echinata*, an African plant belonging to the same family as *Taraktogenos* and *Hydnocarpus*, yielded chaulmoogric acid to the extent of 87.5% of its fatty acids.

It is therefore well established that optically active oils containing esters of acids of the chaulmoogric acid series are quite widely distributed in the seeds of members of the order *Flacourtiaceae*.

The injection of chaulmoogra oil rendered more liquid by admixture with about an equal volume of olive oil and combined with other drugs was tried at the Kalihi Leprosy Hospital in Honolulu by officers of the United States Public Health Service. The results led them to believe that there might be real value in such administration and in the fall of 1915 they came to the chemical laboratory of the College of Hawaii for assistance. On the assumption that there was some therapeutic value in the oil, the most obvious line of experimentation was that directed to the isolation of the active agent or agents and the preparation of liquids more suitable for intramuscular or intravenous injections.

Since there was no method of testing for the curative principle except the results of injections, the plan proposed was to split the oil up into fractions, test these and follow the clues which their clinical application might furnish. The form of material for administration presented some difficulties. The mixed fatty acids from chaulmoogra oil are solid at ordinary temperatures. The physicians were adverse to using the soluble salts for intravenous injections for fear of haemolysis. On making the ethyl esters of the fatty acids we found them thin liquids and experiment showed that they were readily absorbed from intramuscular injections.

Leprosy is a slow disease and improvement, when it occurs, is a matter of months and even years. After several years' experience with ethyl esters of the fatty acids of chaulmoogra oil the working hypothesis appeared justified that the fatty acids of the chaulmoogric acid series are specific in leprosy.

Reports of the earlier part of the clinical work have been published[2] and a later report will soon appear. In brief it may be said that a considerable number of patients improved to the point of becoming clinically and bacteriologically free from leprosy and that it was impossible to identify this effect with any one of the 4 fractions of fatty acids used.

It seemed important to test out the hypothesis stated above by placing groups of lepers on treatment with the pure ethyl esters of chaulmoogric acid and hydnocarpic acid. This necessitated the preparation of con-

[1] Goulding and Akers, *Proc. Chem. Soc.*, **29**, 197 (1913).

[2] Hollmann and Dean, *J. Cutaneous Diseases*, 37, 367. McDonald and Dean, *U. S. Public Health Repts.*, Aug. 20, **1920**.

siderable quantities of the pure acids and led to the following study of methods of fractionating chaulmoogra oil.

Experimental Part.

Separation of Fatty Acids by Crystallization from Alcohol.—Five hundred g. of the mixed fatty acids from chaulmoogra oil was dissolved by warming with 1125 cc. of 92% alcohol and allowed to crystallize over night in the refrigerator, which gave an approximately 30% yield of a semi-crystalline material which, after repeated recrystallization from alcohol, gave about 18 g. of chaulmoogric acid melting at 68°.

By concentrating the mother liquors resulting from the above operations further yields of less crystalline material were obtained which on extended recrystallization from alcohol gave a few grams more of pure chaulmoogric acid, but no hydnocarpic acid. It was found that this semi-crystalline material, which may have represented a eutectic mixture of chaulmoogric and hydnocarpic acids, on recrystallization from alcohol rapidly improved in melting point until the range of 48–52° was reached, after which repeated crystallization had little effect beyond the separation of very small first crops melting at 52–54° which, if saved and combined with others of similar melting point and then recrystallized several times from alcohol, would afford fractions of a gram of pure chaulmoogric acid.

To determine whether or not a slower rate of crystallization than that obtained in the refrigerator would effect a more clean-cut separation of chaulmoogric acid and perhaps furnish the means for isolating hydnocarpic acid, the following experiment was tried.

Four hundred and seventy-nine g. of mixed fatty acids was dissolved in 1000 cc. of hot 92% alcohol, the resulting solution cooled to room temperature and slowly evaporated in a current of air from an electric fan, during which the temperature remained between 20° and 23°. As evaporation and precipitation progressed the following fractions were removed:

Fraction.	Time required to precipitate. Hours.	Yield. G.	Melting point. °C.
1.....	3	57	43–44
2.....	1	79	42–46
3.....	3	63	43–47
4.....	Overnight	139	43–45
5.....	....	40	25–35
6.....	....	100	Below 25

The fourth fraction appeared to contain a small amount of oil occluded in the solid material.

To the small amount of mother liquor from this fourth fraction water was added, which caused precipitation at first, then separation into aqueous and oily layers. The oil was taken up in ether, washed free from alcohol

and dried. On evaporating the ether an oily mass was obtained which was separated, by pressing, into about 40 g. of low melting solids and 100 g. of oil which were designated as the fifth and sixth fractions, respectively.

The first and second fractions were combined and recrystallized from 92% alcohol, which gave 35 g. of semi-crystalline material melting at 44–45°, and the mother liquor which was evaporated to dryness and combined with the original third, fourth and fifth fractions. These combined materials were recrystallized from alcohol but gave low melting solids and mother liquors from which oily materials were obtained. On account of this, and the failure of the 2 fractions to give a crystalline material of appreciably improved melting point on recrystallization, this method was abandoned.

Separation of Fatty Acids by Means of Barium Acetate.—The following experiment was undertaken to determine whether chaulmoogric and hydnocarpic acids could be obtained on the large scale from chaulmoogra oil by the barium acetate method which enabled Power and Barrowcliff to isolate hydnocarpic acid from chaulmoogra oil[1] and which they used successfully in preparing this acid from the oil derived from the seeds of *Hydnocarpus Wightiana*.[2]

Four hundred and seventy-eight g. of the mixed fatty acids from chaulmoogra oil was dissolved in one liter of 93.5% alcohol, and boiled with animal charcoal for 1.5 hours to remove the resinous matter which imparted a yellow color to the solution. After filtering off the animal charcoal, which left the solution much lighter in color, another liter of alcohol was added and the solution warmed. To this was added, with constant stirring, 62 g. of barium acetate monohydrate dissolved in the least possible quantity of hot water, this being a slight excess over the calculated amount of barium acetate necessary to precipitate $^1/_4$ of the fatty acids, figured in terms of chaulmoogric acid, $C_{17}H_{31}.COOH$. A pasty mass was immediately precipitated which did not entirely dissolve on heating. When the solution was cool, a large flocculent precipitate separated which was filtered off. To the resulting mother liquor a second and third 62-g. portion of barium acetate were added, which furnished the second and third fractions of barium salts respectively; also a final mother liquor from which the alcohol was evaporated, leaving a pasty non-crystalline mass.

The 3 fractions of barium salts were warmed with an excess of dil. sulfuric acid which caused precipitation of barium sulfate and liberation of free fatty acids which were liquid at the temperature employed and rose to the top of the aqueous layer in the form of a reddish-brown oil.

This treatment with dil. sulfuric acid had to be repeated several times,

[1] *J. Chem. Soc.*, **87**, 896 (1905).

[2] *Ibid.*, **87**, 888 (1905).

as it was found to be difficult to remove the last of the barium salts from the oily layer. During this process the discoloration of the fatty acids increased, due probably to slight charring, in spite of the fact that the sulfuric acid used was quite dilute.

Fractions 1 and 2 were combined, dissolved in 93.5% alcohol and boiled with animal charcoal to remove charred matter, after which the solution was filtered and allowed to crystallize. The resulting material was small in amount and melted at 61°. After several recrystallizations it melted at 67-68°, and as this remained unchanged on recrystallization from a variety of solvents the material was apparently chaulmoogric acid. The yield was less than 10 g.

The third fraction and the residue from the final mother liquor were combined and treated in a similar manner. After 2 crystallizations the material melted at 62°; after 4 crystallizations it melted at 58° and after 2 more crystallizations it melted at 60°. As the yield at this point was only a little over 0.2 g., it was not practicable to recrystallize it again to determine whether the melting point had become stationary, but since a little of this material mixed with an equal part of the chaulmoogric acid obtained from the first 2 fractions melted at 55°, it was assumed that this was hydnocarpic acid rather than an impure chaulmoogric acid.

While the yields of both chaulmoogric and hydnocarpic acids could undoubtedly be increased by improved manipulation, this method was abandoned as unsuitable for producing these acids in sufficiently large quantities.

Fractional Distillation of Ethyl Esters Under High Vacuum.—The mixed ethyl esters of the acids in chaulmoogra oil were prepared by passing dry hydrogen chloride into a mixture of equal volumes of dry alcohol and the mixed, free fatty acids. The resulting esters, after being washed and dried, had a specific gravity of 0.891 at 15.5° and were reddish-brown in color. By titration it was found that they contained about 5% of uncombined acids.

The apparatus used for the distillation of these esters consisted of a 500 cc. Kjeldahl flask with a fractioning column in the neck, composed of glass beads supported by a tight roll of wire gauze placed at the bottom of the neck. This roll of gauze also served the purpose of preventing frothing over. The flask was provided with a cork stopper through which ran a thermometer, a dropping funnel and a delivery tube. The delivery tube was constructed from a meter length of ordinary glass tubing by making an approximately 80° bend in it sufficiently near one end so that the short arm would just reach through the cork.

Considerable difficulty was experienced in obtaining an air-tight joint at this point. The use of rubber stoppers was prohibited on account of the softening effect of the hot vapors. The best results were obtained by cutting a special cork on a turning lathe so that it could penetrate the

neck of the flask about $1^1/_2$ inches, making a good contact with the glass all the way, and yet be prevented from going too far by means of a shoulder left on the top of the cork. A coat of shellac over this made a fairly effective seal.

At the far end of this delivery tube, which on account of its length also acted as a condenser, was connected, by means of a short length of pressure tubing, a 3-way stopcock through which the distillate could be directed into either of 2 graduated receivers. Beyond these receivers, and connected to them by short lengths of glass tubing, was a 4-way stopcock by means of which either receiver could be connected with the outer air to release its vacuum while the other receiver was connected through a manometer to a powerful motor-driven vacuum pump. By means of this apparatus the fraction which had been collected in one of the receivers could be removed while the distillate was caught in the other, without the vacuum or the rate of distillation being disturbed.

Two 350-cc. portions of the mixed ethyl esters were subjected to fractional distillation in this apparatus, the results of which are given in tabulated form below.

Distillation of Two 350 cc. Portions of Mixed Esters Under Pressure of 3 to 4 mm.

Fraction.	Temp. range. ° C.	No. 1. Cc.	No. 2. Cc.
A-1.....	Below 185	90	90
A-2.....	185–190	80	155
A-3.....	190–195	90	40
A-4.....	Above 195	70	45
Total vol. recovered.....		330	330

As both portions of ethyl esters were from the same lot, it was assumed that fractions of approximately equal volume would be obtained in each case, when these were collected over the same temperature range. It will be noted, however, that there is a wide discrepancy between the volumes of fractions Nos. A-2, A-3 and A-4 obtained from these duplicate operations. This is accounted for by the fact that under the high vacuum employed here, slight variations in pressure, with the consequent changes in the rate of heating necessary to maintain a fairly even rate of distillation, cause variation of 6° to 8° in the temperature recorded by the thermometer in the neck of the flask.

The corresponding fractions from these duplicate operations were combined and redistilled, introducing each combined fraction into the distilling flask through the dropping funnel, as soon as the previous fraction had nearly all distilled over.

The products of this operation were classified into 4 fractions according to the temperature at which they had distilled over. The results were as follows.

Fraction.	Volume. Cc.	Temperature range. ° C.
B-1	150	Below 185
B-2	290	185–190
B-3	60	190–195
B-4	50	Above 195
Total	550	

One-g. portions of each of the above fractions were saponified, and the melting points of the free acids taken with the following results.

Fraction.	Melting point. ° C.
B-1	51–53
B-2	50–52
B-3	43–48
B-4	56–57

These 4 fractions were redistilled in the manner just described except that the pressure was reduced from 3–4 mm. to one mm. by the use of a more suitable grade of oil in the vacuum pump.

The yields and temperature ranges of the 4 fractions obtained are given herewith.

Fraction.	Volume. Cc.	Temperature ranges. ° C.
C-1	70	Below 175
C-2	340	175–180
C-3	50	180–185
C-4	70	Above 185
Total volume	530	

The results of this and the preceding distillation illustrate the wide difference in boiling-point range caused by a slight difference in the pressure.

One-g. portions from each of the above fractions were saponified and the melting points of the free acids taken, which were as follows.

Fraction.	Melting point. ° C.
C-1	50–53
C-2	52–54
C-3	55–57
C-4	59–62

These 4 fractions were redistilled once more in the same manner as described above with the following results.

Fraction.	Volume. Cc.	Temperature range. ° C.
D-1	260	Below 175
D-2	160	175–180
D-3	40	180–185
D-4	40	Above 185
Total volume	500	

The esters comprising these 4 fractions were saponified by heating with an excess of alcoholic potash and the resulting soaps decomposed with hydrochloric acid. The yields of free fatty acids and their melting points were as follows.

Fraction.	G.	Melting point. °C.
D-1.....	197.3	50–53
D-2.....	118.8	43–47
D-3.....	21.7	56–60
D-4.....	20.2	63–65
Total volume.....	358.0	

It was thought from the above results that the isolation of pure chaulmoogric and hydnocarpic acids simply by distillation of their mixed ethyl esters is not practicable, as the improvement in melting point between the fractions resulting from the second distillation and these resulting from the fourth distillation was so small. When, however, these fractions were recrystallized from alcohol it was at once apparent that a partial separation had been effected. The results were as follows.

	First crystallization from alcohol.		Recrystallization from alcohol.		Second recrystallization from alcohol.	
Fraction.	G.	°C.	G.	°C.	G.	°C.
D-1.....	50.4	55–56	32	58	21.2	58.5–59.5
D-2.....	74.2	48–51	61.5	48–51	20	48 –51
D-3.....	13.1	67–68	10	67–68	9.8	67.5–68
D-4.....	13.8	66–67	6	67–67.5	4.4	67.5–68

The 21.2 g. from Fraction D-1 melting at 58.5–59.5°, on being recrystallized from petroleum ether, benzene, and alcohol, respectively, gave small transparent plates melting at 59–60°, and this melting point did not change upon subsequent recrystallization. It is evident that this material was almost pure hydnocarpic acid.

Fractions D-3 and D-4 which furnished 14.2 g. of acids melting at 67.5 to 68° proved to be almost pure chaulmoogric acid, as on recrystallizing once more this material came down in the form of glistening plates melting at 68° and this melting point did not change on subsequent recrystallization.

This method was abandoned in favor of the more satisfactory method of direct fractional distillation of the fatty acids themselves, but the ester distillation method is thought to be a very promising one and will be investigated further.

Fractional Distillation of Fatty Acids.—For the distillation *in vacuo* of the fatty acids themselves, which are solid at ordinary temperatures, it was necessary to modify the apparatus used in distilling the ethyl esters described above.

The delivery tube was shortened to 35 cm. in order that the distillate

could pass through hot, and not tend to solidify. The end of the delivery tube reached through a No. 10 2-hole stopper, through the other hole of which extended a short piece of glass tubing which was connected with the vacuum line through a 3-way stopcock.

This large 2-hole stopper was inserted into a wide mouthed dropping funnel, the stem of which was cut off 5 cm. below the valve, and inserted into one of the 2 openings of a No. 11 2-hole stopper which fitted into a graduated receiver. Through the other hole of this stopper was a short piece of glass tubing which was connected to a 3-way stopcock, one branch of which communicated with the outer air, the other being connected with the 3-way stopcock in the vacuum line to which reference is made above.

By means of this apparatus, when a fraction of the desired size had collected in the graduated receiver, the valve in the stem of the dropping funnel above the receiver could be closed, the vacuum could be communicated to the connection in the dropping funnel, while air could be allowed to enter the graduated receiver through the 3-way stopcock connected to it. In this way the receiver could be removed, while the distillate meanwhile was collecting in the dropping funnel under a vacuum which had not been disturbed. Having replaced the graduated receiver and evacuated it, the one-way stopcock above it could be opened and the small amount of distillate in the dropping funnel allowed to flow down into the graduated receiver. The principle of this receiving apparatus was the same as that of the special receiver shown in Fig. 2, which was designed later to eliminate the difficulties encountered in operating this improvised apparatus, the worst of which were air leaks in the rubber connections, and clogging up of the small bores of the stopcock by condensed fatty acids.

Three hundred and fifty cc. of mixed fatty acids from chaulmoogra oil was distilled in this apparatus under a pressure of 1.5 mm. which increased to 3 mm. when the distillation was about half completed, due to an air leak. The results are given in tabulated form herewith.

Fraction.	Volume. Cc.	Temperature range. ° C.	Melting point of crude distillate. ° C.	Melting point distillate crystallized from alcohol. ° C.
1.....	40	174–199	48–49	54–55
2.....	100	199–204	49–52	54–56
3.....	100	204–211	47–49	48–49
4.....	50	211–212	42–46	67–68
Total volume....290				

Thus 290 cc. was recovered, the first 2 fractions of which, amounting to 140 cc., on being recrystallized from 93.5% alcohol 3 times gave approximately 15 g. of pure hydnocarpic acid melting at 59–60°, and the last frac-

tion, amounting to 50 cc., on being recrystallized twice, gave approximately 25 g. of pure chaulmoogric acid melting at 68°.

The third fraction, which melted at 47–49°, did not improve in melting point to any appreciable extent. It is thought to be a eutectic mixture of chaulmoogric and hydnocarpic acids.

Three separate portions of mixed fatty acids from the same lot, consisting in each case of 300 g. (325 cc.) were distilled *in vacuo*, the results of which are given below. As in the case of the ethyl esters, there is a wide discrepancy in temperature-range of the vapor for corresponding fractions, due to slight variations in the pressure and rate of heating.

		First Portion.		Second Portion.		Third Portion.	
Fraction.	Volume. Cc.	Temp. range. ° C.	Av. pres. Mm.	Temp. range. ° C.	Av. pres. Mm.	Temp. range. ° C.	Av. pres. Mm.
A-1.....	20	178–190	2.5	186–193	2.5	186–190	1.5
A-2.....	100	190–197	2.5	193–196	2.5	190–192	1.5
A-3.....	100	197–199	2.5	196–203	2.5	192–201	1.5
A-4.....	70	199–209	2.5	203–208.5	2.5	201–210	1.5

To try the effect of redistillation the corresponding fractions from these distillations were combined and redistilled, adding each fraction through the small dropping funnel in the top of the distilling flask when the previous fraction was nearly all distilled over.

The results of this redistillation and the melting points of the crude distillates, and the small portions thereof crystallized from alcohol, were as follows.

				M. p. of distillates.	
Fraction.	Volume. Cc.	Temp. range. ° C.	Average Pressure. Mm.	Crude. ° C.	Recrystallized. ° C.
B-1.....	100	160–192	3	45–47	48–51
B-2.....	300	186–193[a]	1.25	40.5–42.5	48–51
B-3.....	160	193–197	1.5	40–41	55–57
B-4.....	240	197–202.5	1.5	50–52	64–66

[a] Shut down overnight between fractions Nos. B-1 and B-2.

These 4 fractions of Series B were redistilled in the same way, cutting into 6 fractions.

				M. p. of distillates.	
Fraction.	Volume. Cc.	Temp. range. ° C.	Average Pressure. Mm.	Crude. ° C.	Recrystallized. ° C.
C-1.....	70	196–199.5	2	42–46	46–50
C-2.....	40	199.5–204	2.5	42–46	54–55
C-3.....	190	204–208.5	2.5	45–47	55–56
C-4.....	150	199–206.5[b]	2.5	43–45	48–50
C-5.....	250	206.5–216	2.5	47–49	65–66
C-6.....	25	216–218	4	55–56.5	65.5–66.5

[b] Shut down overnight between fractions Nos. C-3 and C-4.

Fractions C-2 and C-3, and C-5 and C-6, were combined, necessitating a new designation of the series as follows.

Fraction C-1	becomes Fraction C-*a*
Fraction C-2 and C-3,	becomes Fraction C-*b*
Fraction C-4	becomes Fraction C-*c*
Fraction C-5 and C-6,	becomes Fraction C-*d*

Each of these 4 resulting fractions was redistilled independently, dividing the distillate from each into fractions when necessary. The results are given herewith in tabulated form.

Fraction distilled.	Volume. Cc.	Fraction received.	Volume. Cc.	Temp. range. ° C.	Press. Mm.	Melting points of distillates. Crude. ° C.	Recrystallized from alcohol. ° C.
C-*a*	70	D-1	60	164–178	1.25	43–45	45–47
C-*b*	230	D-2	150	165–177	1	47–49	53–55
		D-3	60	177–180	1	47–49	52–54
C-*c*	150	D-4	100	174–178	1	45–48	51–53
		D-5	40	178–188	1	41–43	57–59
C-*d*	275	D-6	100	174–192	1	39–42	55–59
		D-7	160	192–199	1.25	51–53	63–65

In order to combine fractions of similar melting point and reduce the total number, Fraction D-1 was kept separate and designated as D-a; Fractions D-2, D-3 and D-4 were combined and designated as D-*b*; Fractions D-5 and D-6 were combined and designated as D-*c*; Fraction D-7 was kept separate and designated as D-*d*.

Fraction.	Wt. G.	Wt. obtained. G.	Substance.	M. p. ° C.
D-*a*	59	0.6	hydnocarpic acid	59–60
		1.4	material	62–63
		21.0	material	45–53
		31.0	oily material	.....
D-*b*	287	82	hydnocarpic acid	59–60
		112.5	material	45–53
		65	oily material	.....
D-*c*	130	18.4	chaulmoogric acid	67–68
		54	material	45–53
		45	oily material	.....
D-*d*	168	59.6	chaulmoogric acid	67–68
		25.4	material	45–53
		68	oily material	.....
Total for the entire 4 fractions of:				
		78	chaulmoogric acid	67–68
		1.4	unknown acid	62–63
		82.6	hydnocarpic acid	59–60
		212.9	material	45–63
		209	oily material	.....
		583.9		

Each of these resulting 4 fractions was subjected to an extended fractional crystallization from alcohol, involving from 25 to 33 recrystalliza-

tions in each case. Work was continued on each of the 4 fractions until nothing remained but pure chaulmoogric or hydnocarpic acids, or oily material, or solids which did not improve in melting point on further crystallization.

The results are briefly summarized in the preceding table.

It was found that the 212 g. of miscellaneous material from all 4 fractions, melting between 45–53°, could in each case be purified by recrystallization from alcohol until its melting point became approximately 48–52°, after which further recrystallization had little effect.

In order to determine whether this was a lower homologue of chaulmoogric and hydnocarpic acids, or a eutectic mixture of the two, 139 g. of this material melting at 48–52° was subjected to further distillation *in vacuo*. During the distillation the temperature fluctuated between 188° and 195° and the pressure between 1.5 and 3 mm. The distillate was cut into four 30-cc. fractions, on which the following data was gathered.

	1.		2.		3.		4.	
Fraction.	G.	°C.	G.	°C.	G.	°C.	G.	°C.
Melting points of crude distillates	27	49–51	27	50.5–52	27	50.5–52	27	50–51.5
Cryst. from alcohol	25	46–49	16	49.5–52	20	49.5–52	19.5	50–53
Recrystallized from alcohol	21	49.5–52	4.3	57–58	18.5	51–53	11.2	53–55
Recryst. again from alcohol	14.5	49.5–52	2.4	59–60	17	56–57	9	53–55
Recryst. again from alcohol	....	.....	...	....	6.5	58.5–59.5	....	.....
Recryst. from P. ether	4	56–57	...	....	...	.....	2	57–58

While these results are rather indeterminate, they indicate a material which approximates a eutectic mixture which neither the fractional distillation nor crystallization could separate effectively.

From the foregoing, it is apparent that the original experiment on direct fractional distillation of the mixed fatty acids, which gave 4 fractions melting at 54–55°, 54–56°, 48–49°, and 67–68° respectively, after one crystallization from alcohol, effected a separation of chaulmoogric and hydnocarpic acids which was as good, if not better, than the one just described, which involved 3 redistillations of the fractions obtained by distilling once, and gave 6 fractions melting, after one crystallization from alcohol, at 45–47°, 53–55°, 52–54°, 51–53°, 57–59°, 55–59° and 63–65° respectively. It was therefore decided to distill the mixed fatty acids only once, and to attempt to get larger yields of pure acids by making that one distillation more efficient by means of improved apparatus and by cutting into fractions at the most advantageous points.

In order to determine the best possible points for cutting fractions a

new vacuum distillation was run on a 300-g. portion of mixed fatty acids, and the distillate cut into fifteen 20-cc. fractions. The melting point of each of these fractions was taken and the fraction then crystallized from alcohol, in such a manner as to give a first crop, second crop and residue of approximately equal weights. The melting points of these 3 crops were taken and are given in graphic form herewith, together with the melting points of the crude distillates. (Fig. 1.)

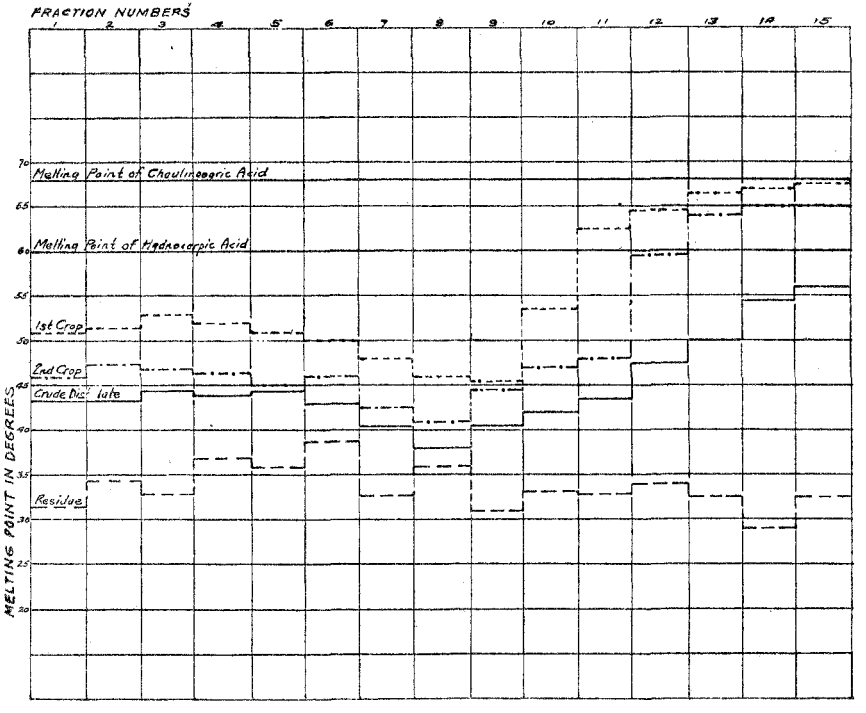

Fig. 1.

On the strength of the above melting-point diagram, Fractions 1–6 inclusive were combined and worked for hydnocarpic acid, of which they furnished 20 g. Fractions 12–15 inclusive were worked for chaulmoogric acid, of which they furnished 32 g. Fractions 7–11 inclusive were combined and crystallized from alcohol, but it was found that the melting point quickly rose to the 48–52° range, after which repeated recrystallization had little effect. This was apparently a eutectic mixture of hydnocarpic and chaulmoogric acids.

From this time up to the present the work has been severely handicapped by a radical lowering in the quality of the chaulmoogra oil coming on the American market. In place of the clear amber colored oil obtainable in the fall of 1919, it is now necessary to continue investigation on

a dark reddish-brown oil which is about 70% by volume solid matter. This inferior product has nearly the normal amount of chaulmoogric acid in it, but the hydnocarpic acid content is only about one-third as great as in previous lots.

An improved apparatus, which was first employed in making the fractional distillation next to be described, was identical with that shown in Fig. 2, except that it had a 2-liter side neck flask of the Claisen type with a fractionating column of glass beads and short lengths of glass tubing about 12.5 cm. high in the side neck.

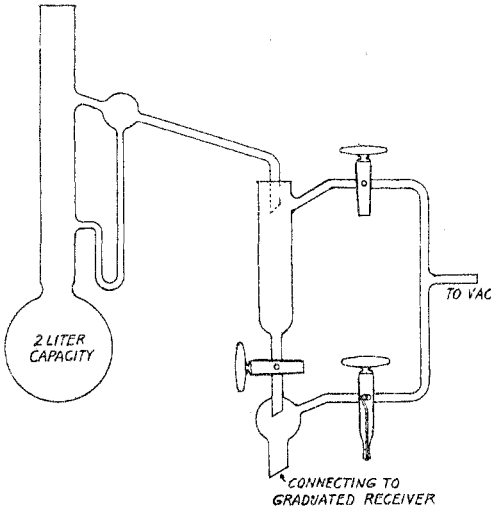

Fig. 2.

The large capacity of this flask permitted the vacuum distillations in kilogram lots of mixed acids, and up to the present time these flasks, which were made of heavy Pyrex glass, have shown no tendency to collapse under high vacuum, the only weak points being the junctures of the side and main neck, and of the side neck and delivery tube.

In order to throw more light on the character of the mixed acids from chaulmoogra oil, 1000 g. of the mixed acids (1084 cc.) was distilled and

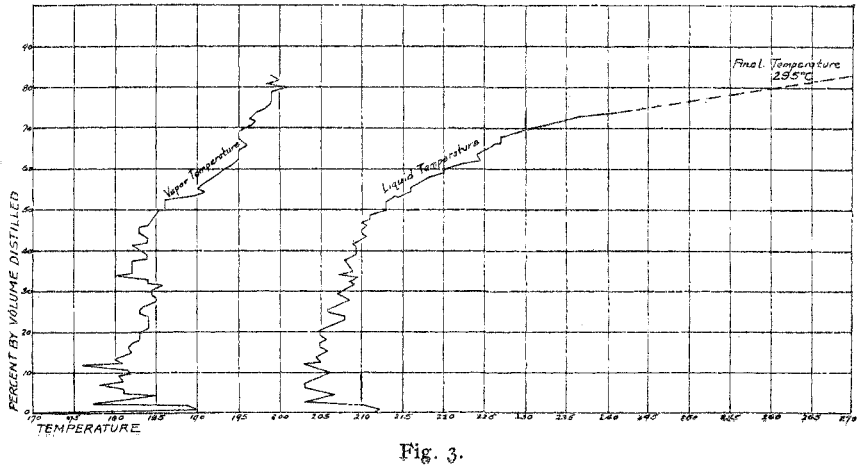

Fig. 3.

cut into 18 fractions of 50 cc. each. The temperature curves of the vapor and of the liquid in the distilling flask are given in Fig. 3. The melting points, indices of refraction, iodine numbers, specific rotations, and apparent molecular weights for each of the 18 fractions are given in Fig. 4.

Interpretation of Results.—An inspection of the data presented shows that the distillation is not effective in segregating any liquid fatty acids which may be present since all fractions solidify on cooling and require temperatures of at least 40° to liquefy them.

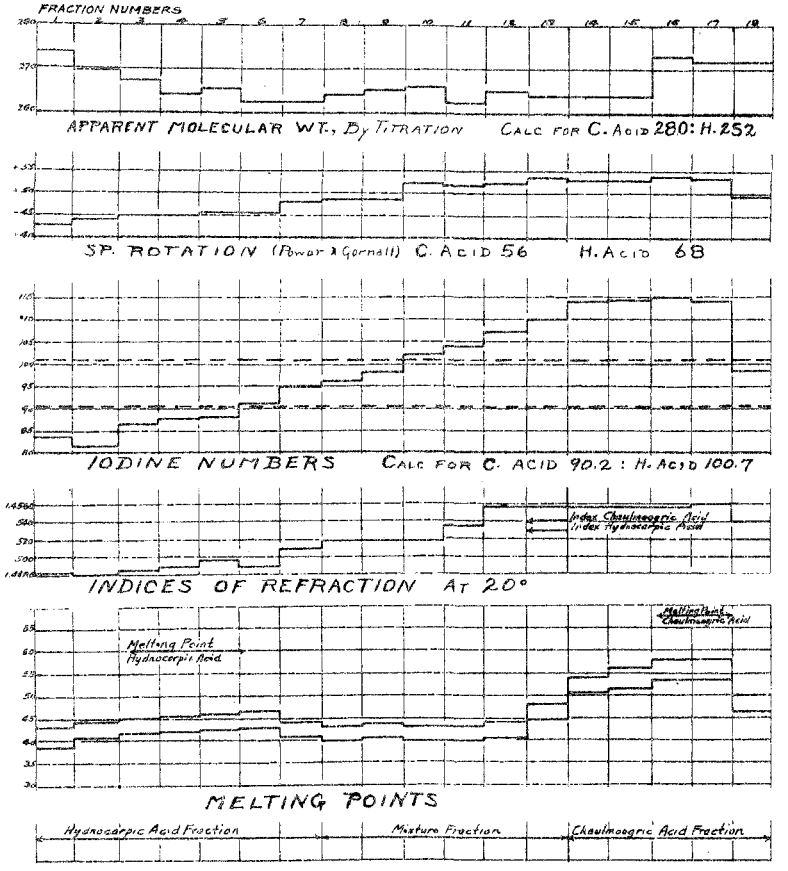

Fig. 4.

The higher boiling fractions give evidence of being much nearer to pure chaulmoogric acid than the lower fractions to hydnocarpic. Evidently the lower fractions contain material of higher molecular weight, lower or no rotatory power, lower iodine absorption, and lower indices of refraction. Oleic and palmitic acids, both of which were identified by Power in chaulmoogra oil, would have the effects indicated. With the

chaulmoogric acid fractions there appears to be relatively little optically inactive material, but some materials which raise both the iodine value and the indices of refraction, indicative of more highly unsaturated acids.

No evidence of any members of the chaulmoogric series below hydnocarpic acid nor above chaulmoogric appears.

After a careful consideration of the probable composition of each of the 18 fractions, based on data shown in Fig. 4, Fractions 1–6 inclusive were combined and worked for hydnocarpic acid, of which they gave 48 g.; Fractions 14–18 inclusive were combined and worked for chaulmoogric acid, of which they gave 110 g.

Fractions 7–13 inclusive were combined and redistilled to determine whether this would afford a separation of the hydnocarpic and chaulmoogric acids which they were thought to contain in the form of a eutectic mixture. The results of this distillation are given herewith.

Fraction.	Volume. Cc.	Temp. range of vapor. ° C.	Average pressure. Mm.	Melting points of distillates. ° C.
1	50	186–196	3.25	43–49
2	50	196–198.5	3.5	43–49
3	50	198–201.5	4	42–46
4	50	201–209	4.5	32–49
5	30	209–210	4.5	50–57

A comparison of the melting points of these fractions with those of the 7 fractions from which the distillation was made, 41–44°, 40–43°, 41–43.5°, 40–43°, 40–43°, 41–44° and 45–48° respectively, shows very plainly that a partial separation was effected by this second distillation. This was confirmed by the extraction of a small amount of hydnocarpic acid from the combined Fractions 1 and 2, and a small amount of chaulmoogric acid from Fraction 5. The greater part, however, of the products of this distillation improved in melting point on recrystallization until the 48–52° range was reached, after which further crystallization had little effect.

This shows that it is unprofitable to redistill the mixture fraction *by itself*. It has been found, however, that the addition of the mixture fraction to the next lot of mixed fatty acids to be distilled increases very materially the yield of hydnocarpic and chaulmoogric acids which can be obtained from such distillations.

Reference to Fig. 4 will show that the portion of the distillate designated as the hydnocarpic acid fraction consisted of the first 300 cc. distilled off from one kg. (1084 cc.) of mixed fatty acids; that the mixture fraction consisted of the next 350 cc. to distill over, while the chaulmoogric acid fraction included all the remainder of the distillate (approximately 250 cc.).

It has been found lately that in the case of low grade chaulmoogra oil better results are obtained by cutting the distillate from one kg. of material

(300 cc. of mixture fraction from previous distillation plus sufficient crude mixed fatty acids to make 1000 g.) as follows.

Hydnocarpic acid fraction....	First	350 cc.
Mixture fraction.....	Next	300 cc.
Chaulmoogric acid fraction...		250 cc.

Having established a satisfactory procedure for carrying out the fractional distillation of the mixed fatty acids, attention was turned to the second phase of the separation, namely, fractional crystallization. An extended investigation of the relative efficiency of a variety of solvents in various proportions to the weights of the material being crystallized brought out the following facts.

For the chaulmoogric acid fraction the most effective solvent is 80% alcohol in the proportion of 20 cc. of solvent to 5 g. of solute.

For the mixture fraction no solvent has been found which will effectively separate the 2 acids.

For the hydnocarpic acid fraction 80% alcohol in the ratio of 20 cc. of solvent to 5 g. is the most efficient for solutes whose melting point is below 35°. After this point has been passed the most satisfactory solvent is petroleum ether, in the ratio of 30 cc. of solvent to 5 g. of solute.

When the 80% alcohol is used the best results are obtained by allowing the solution to stand overnight in an ordinary refrigerator (about 16°). When petroleum ether is used the treatment is the same until nearly pure hydnocarpic acid has been obtained, which crystallizes best at ordinary room temperature, the time required being 1 to 3 hours.

A scheme for the systematic fractional crystallization of chaulmoogric and hydnocarpic acid fractions has been worked out which has given excellent results. For the chaulmoogric acid fraction 10 receptacles of appropriate size were placed in a rack and the receptacles marked consecutively for material melting: (1) below 25°; (2) 25–35°; (3) 35–45°; (4) 45–50°; (5) 50–55°; (6) 55–60°; (7) 60–63°; (8) 63–65°; (9) 65–67°; (10) pure chaulmoogric acid 68°.

A corresponding set of receptacles was devoted to the hydnocarpic fraction, marked for the following melting point, temperature ranges (1) below 25°; (2) 25–30°; (3) 30–35°; (4) 35–40°; (5) 40–45°; (6) 45–50°; (7) 50–53°; (8) 53–56°; (9) 56–59° (10) pure hydnocarpic acid 60°.

In carrying out a fractional crystallization the crude distillate is first allowed to crystallize from the proper solvent in such a way that a first and second crop, amounting in each case to approximately $1/3$ of the original weight of the material are obtained. The final mother liquor is washed with hot water to remove alcohol and the resulting oil dried. This gives a first crop, second crop and residue, which, after taking their melting points, are placed in the receptacles whose indicated melting point ranges cover that of the product as nearly as possible.

All three of these are recrystallized simultaneously from the appropriate solvent, producing 3 first crops, 3 second crops and 3 residues, which are classified according to their melting points. Thus it frequently results that a first crop from low melting material and a second crop from material of intermediate melting point and a residue from high melting material will all melt at about the same point, and since they will be put in the same receptacle, they will automatically be combined and recrystallized together in the next operation.

Thus with a minimum amount of time and effort the pure acids move to one end of the series of receptacles, the liquid material moves to the opposite end, while any other solid acids of definite melting point will automatically accumulate in one of the intermediate receptacles.

Up to the present time no such solid acids have been definitely isolated, but there is reason to believe that several such exist, and this subject, together with the composition of the liquid portions, will be dealt with in a later paper.

As the greater part of this paper has been devoted to tracing the development of this work, with frequent references to the present practise, it is thought worth while at this point to give in some detail the complete method in use at the present time, for the practically quantitative extraction of chaulmoogric and hydnocarpic acids from chaulmoogra oil.

Two hundred and forty g. of sodium hydroxide is dissolved in one liter of hot water and thoroughly mixed with 1500 g. of chaulmoogra oil in a 5-liter, round-bottom flask, and heated in an autoclave under 15 pounds of steam pressure for one hour. Loss by frothing is prevented by inserting a loosely fitting wooden plug or stopper in the neck of the flask through which runs a piece of 16 mm. i. d. glass tubing, which extends about 35 cm. above the flask, where 2 right angle bends lead it into an 800 cc. beaker, which is placed on a shelf in the autoclave. A piece of cheesecloth tied over the top of the beaker, through which the bent tube projects, effectively prevents loss from spattering.

After removing the flask containing the sodium soaps from the autoclave, the contents are poured into about 3 or 4 liters of hot water in a large precipitating jar, and stirred until dissolved.

The soap solution is now acidified with commercial hydrochloric acid, and the liberated fatty acids rise to the top of the water in the form of a thick oily layer. By means of a siphon the aqueous layer, which contains sodium chloride and glycerol, is drawn off and discarded. The remaining oil is washed with successive portions of hot water and finally transferred to a hot-water funnel, where, in the course of one to two hours heating all the water separates from the liquefied fatty acids. The latter are strained through linen of fine mesh before being allowed to solidify. The usual yield of crude mixed fatty acids is between 1350 and 1400 g.

One kg. (1084 cc. when liquefied) of these mixed fatty acids was subjected to vacuum distillation in the apparatus shown in Fig. 2.[1]

The vacuum is applied before the temperature of the liquid in the flask rises above 100°, otherwise serious frothing-over may result. It is best to have both of the 3-way stopcocks open for the vacuum, also the one-way stopcock between the receiving chamber and the graduated receiver. There is usually a tendency for a little of the fatty acid vapor to solidify in the stopcocks, interfering with the vacuum. This difficulty may be obviated by playing a jet of steam against the stopcock. As the stopcocks must remain air-tight, even while hot, it is best to use a mixture of vaseline and talcum powder as a lubricant in them.

The first 350 cc. which distill over is worked for hydnocarpic acid. The next 300 cc., composing the mixture fraction, is set aside to be redistilled as part of the next lot of mixed fatty acids. The rest of the distillate is worked for chaulmoogric acid.

The chaulmoogric acid fraction is recrystallized from 80% alcohol, using the proportions of 20 cc. to 5 g. of the acids, and following the systematic scheme for recrystallizing given above.

The hydnocarpic acid fraction is treated in the same way, except that material which melts above 35° is recrystallized from petroleum ether, using 30 cc. of solvent to 5 g. of solute.

The amounts of chaulmoogric and hydnocarpic acids present vary largely according to the quality of the oil, but from even low grade oil, starting with 1000 g. of mixed acids, this method will give at least 50 g. of pure hydnocarpic acid and 100 g. of pure chaulmoogric acid.

HONOLULU, T. H.

[1] It has been found that a very effective column for the neck of the flask is obtained by locating 4 diaphragms of 3 mm. mesh wire gauze at intervals of about 37 mm., the lowest being at the bottom of the neck and the highest being about 5 cm. below the outlet into the delivery tube. Resting on the lowest of these diaphragms are as many 25-mm. lengths of glass tubing, 5.5 mm. inside diameter, placed vertically, as the neck of the flask will accommodate. On the next diaphragm a similar set of 4 mm. tubes; on the next a set of 2.5 mm. tubes, while on the highest diaphragm are placed 8 mm. glass beads to a thickness of about 25 mm. The large tubes at the bottom take care of the heavy back-flow of liquid at that point. The increasing density of the column near the top gives an increasingly thorough washing to the up-coming gases. The breaks between sectors in the column prevent the gas pressure from below forcing condensed liquid up through the column.