

TABLE IV
 CHARACTERISTICS OF CHAULMOOGRA OILS

	<i>Hydnocarpus wightiana</i>	<i>Hydnocarpus anthelmintica</i>	<i>Taraktogenos kurzii</i>	<i>Carpotroche brasiliensis</i>	<i>Oncoba echinata</i>
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	<i>H. wightiana</i>	<i>H. anthelmintica</i>	<i>T. kurzii</i>	<i>C. Brasiliensis</i>	<i>O. echinata</i>
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 alepic 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 teresantallic 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 cardio-stimulating 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 -benzoyl-

borneol (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 camphene-carboxylic acid (VI) together with some tarry material of unknown composition and small amounts of benzonitrile which was identified as benzoic acid by hydrolysis.

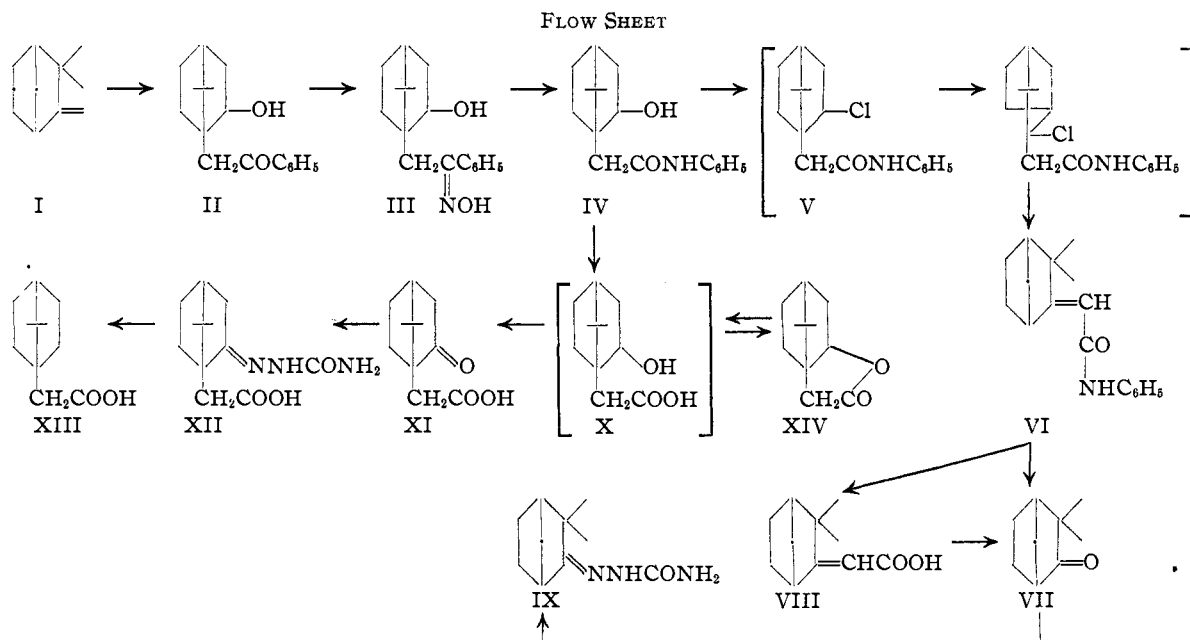
The 2-hydroxy-apocamphane-1-acetanilide was hydrolyzed with alcoholic potassium hydroxide solution. The resulting product was the lactone of 2-hydroxy-apocamphane-1-acetic acid (XIV)

(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).



together with aniline which for identification was converted into benzanilide. Attempts to isolate the intermediate hydroxy acid (X) in a pure state failed on account of the ease by which lactone formation takes place. On oxidation with alkaline potassium permanganate solution the potassium salt of 2-hydroxy-apocamphane-1-acetic acid obtained from the lactone by hydrolysis, yielded 2-keto-apocamphane-1-acetic acid (XI). This acid was identified through its semicarbazone (XII), which when subjected to the Wolff-Kishner reaction produced the apocamphane-1-acetic acid (XIII). This series of reactions shows the stability of the hydroxy group of the 2-hydroxy-apocamphane-1-acetanilide in contrast to the corresponding group in ω -benzoylborneol, which on heating is transformed into a furan derivative;⁴ this also establishes the evidence that the 2-hydroxy-apocamphane-1-acetanilide and the lactone derived therefrom have the symmetric camphor skeleton.

The camphene-carboxyanilide (VI) obtained as a by-product in the Beckmann rearrangement of the oxime of ω -benzoylborneol is a secondary product apparently formed by way of the Meerwein-Wagner retro-pinacoline rearrangement from the intermediate 2-chloro-apocamphane-1-acetanilide (V). We observed that on treating 2-hydroxy-apocamphane-1-acetanilide with phosphorus pentachloride in ether solution, the resulting product is camphene-carboxyanilide (VI). On

hydrolysis with alcoholic potassium hydroxide solution, this compound yielded camphene-carboxylic acid (VIII) and aniline identified as benzanilide. Since our product showed a higher melting point than the acid recorded by Langlois⁵ obtained from ω -bromocamphene by means of the Grignard reaction, for identification it was oxidized with potassium permanganate to camphenilone (VII) whereby oxalic acid was obtained as a by-product. The semicarbazone (IX), prepared subsequently, did not lower the melting point in the mixed melting point test with an authentic sample of camphenilone semicarbazone.

The asymmetric structure of camphene-carboxyanilide was further established by the fact that on direct oxidation with potassium permanganate, it yielded camphenilone which was identified as the semicarbazone, (IX).

Acknowledgment.—Thanks are due to Mr. Ted Calmes of the University of Florida, Gainesville, Florida, for carrying out the Wolff-Kishner reaction.

Experimental

Starting Material.—The camphene was a technical product obtained from E. I. du Pont de Nemours and Company, Wilmington, Del. This material was used in the preparation of ω -benzoylborneol and subsequently for the oxime of this product according to directions by Lipp *et al.*⁴

The Beckmann Rearrangement of the Oxime of ω -Benzoylborneol.—Thirty-five g. (0.12 mole) of the oxime

(5) Langlois, *Ann. chim.*, [IX] 12, 193, 363 (1919).

(ω -benzoylborneol: m. p. 86–87° (corr.), m. p. 85–86°, Lipp, *et al.*; oxime: m. p. 160–161° (corr.); 159–160° Lipp, *et al.*) was dissolved in 300 cc. of anhydrous ether and 77 g. (0.37 mole) of phosphorus pentachloride was slowly added over a period of one hour to the cooled solution. The temperature of the solution was kept between 20–30° throughout the course of the reaction. After terminating the reaction, the mixture was washed with cold water until the washings were no longer acid to litmus. The ether solution was separated from the water and the ether was removed. The residue was subjected to steam distillation and the distillate extracted with ether. After removal of the ether, 0.5 g. of benzonitrile was isolated and identified by hydrolyzing it to benzoic acid. It was refluxed for three hours with 10 cc. of 20% potassium hydroxide solution. During the reaction some evolution of ammonia took place. After evaporating the alcohol, the solution was acidified with dilute hydrochloric acid and the solid precipitate recrystallized from hexane, m. p. 122.5–123.5° (corr.); it did not lower the melting point when mixed with an authentic sample of benzoic acid.

The residue from the steam distillation was dissolved in a minimum amount of ethanol. After standing in an ice box overnight, a white crystalline precipitate consisting of 2-hydroxy-apocamphane-1-acetanilide was removed by filtration. After two recrystallizations from ethanol, the white rectangular needles melted constantly at 176.5–177.5° (corr.), yield 10 g. (28.2%).

Anal. Calcd. for $C_{17}H_{23}O_2N$: C, 74.9; H, 8.51. Found: C, 74.59; H, 8.72.⁶

The alcoholic mother liquors from the above reaction were evaporated on a steam-bath, leaving 17 g. of an oily residue which was refluxed for three hours with 300 cc. of a 10% alcoholic potassium hydroxide solution. After cooling, the solution was poured into 1200 cc. of ice water and the mixture extracted three times with ether. The ether solution was dried with sodium sulfate and after evaporating the ether, the brownish residue was dissolved in hexane. On standing in the ice box for four hours, a brownish crystalline precipitate was obtained which, after decolorizing with norite, was recrystallized from hexane. After two recrystallizations from hexane and one from dilute ethanol, the solid compound, camphene-carboxyanilide, melted constantly at 154.5–155.5° (corr.); fine white needles; yield 3.3 g. (10.1%).

Anal. Calcd. for $C_{17}H_{21}ON$: C, 80.00; H, 8.28. Found: C, 80.20; H, 8.34.

The hexane filtrates were evaporated, leaving 4.5 g. of a reddish viscous oil which was not identified at this time.

The aqueous alkaline solution was evaporated to a small volume on a hot-plate, carbon dioxide being passed through the solution to prevent oxidation. After filtering, the solution was acidified with dilute hydrochloric acid and extracted with ether. After drying the ether solution with anhydrous sodium sulfate and evaporating the ether, 1.2 g. of a reddish oil was obtained. On standing for about two weeks, it slowly deposited a crystalline solid which after recrystallization from hexane melted constantly at 201.5–202.5° (corr.). It was identified as the lactone of the 2-

hydroxy-apocamphane-1-acetic acid since it did not lower the melting point in the mixed melting point test with an authentic sample.

Lactone of 2-Hydroxy-apocamphane-1-acetic Acid.—Four and five-tenths grams of 2-hydroxy-apocamphane-1-acetanilide was refluxed for six hours with 160 cc. of 20% alcoholic potassium hydroxide and, after cooling, poured into 800 cc. of ice water. The solution was then extracted five times with ether. The aqueous layer was evaporated to about 100 cc., carbon dioxide being passed through to prevent oxidation, filtered and, after cooling, acidified with dilute hydrochloric acid. The mixture was now extracted three times with ether and the ether solution dried with anhydrous sodium sulfate. After evaporating the ether, there was obtained a reddish oil which slowly deposited crystals on standing. The semi-solid mass was covered with acetyl chloride and the mixture left standing at room temperature for about fifteen minutes, then the excess of acetyl chloride removed *in vacuo*. The remaining solid was recrystallized from hexane, melting constantly at 201.5–202.5° (corr.); yield, 1.77 g. (60%).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 72.90; H, 9.45. Found: C, 73.20; H, 9.32.

The ether solution from the extraction of the original alkaline liquors was dried over anhydrous sodium sulfate and distilled, leaving minute quantities of a red oil consisting of aniline since, when treated with benzoyl chloride, it yielded benzanilide melting at 162.5–163.5° (corr.) and did not lower the melting point when mixed with an authentic sample.

2-Keto-apocamphane-1-acetic Acid.—One and seven-tenths grams of the above lactone was dissolved in 34 cc. of a 2% potassium hydroxide solution containing 1.27 g. of potassium permanganate. On refluxing the solution for about fifteen minutes, the permanganate color had disappeared and the mixture was filtered from the precipitated manganese dioxide, evaporated to a small volume on the steam-bath and after cooling to room temperature, acidified with dilute hydrochloric acid and extracted with ether three times. The ether solution was dried with anhydrous sodium sulfate and evaporated, leaving a straw colored oil which was dissolved in a small quantity of water. The precipitated solid melted constantly after three crystallizations from water at 92–93° (corr.), yield 0.6 g. (84.4%).

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.33; H, 8.22; neut. equiv., 196.2. Found: C, 67.29; H, 8.20; neut. equiv., 197.1.

Semicarbazone of 2-Keto-apocamphane-1-acetic Acid.—From 0.04 g. of the keto acid, the semicarbazone was prepared in the usual manner, giving an almost quantitative yield. The semicarbazone was recrystallized from ethanol, melting constantly at 199–200° (corr.).

Anal. Calcd. for $C_{12}H_{19}O_4N_3$: C, 56.88; H, 7.56. Found: C, 56.63; H, 7.47.

Apocamphane-1-acetic Acid.—Five-tenths gram of the semicarbazone of 2-keto-apocamphane-1-acetic acid was added to a bomb tube containing sodium ethylate prepared from 0.6 g. of sodium dissolved in 3 cc. of absolute alcohol. After closing the tube, the mixture was heated at 170–180° for fifteen hours. After cooling, the mixture was diluted

(6) All analyses for this paper were done by Mr. S. Gottlieb, Columbia University, New York, N. Y.

with water and the crude acid precipitated with dilute hydrochloric acid; yield 0.3 g. (83.2%). It was dissolved in dilute 20% ethanol, decolorized with norite and recrystallized from the same solvent. After three recrystallizations, it melted constantly at 77–78° (corr.).

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.48; H, 9.95; neut. equiv., 182.25. Found: C, 72.53; H, 10.05; neut. equiv., 182.30.

Conversion of 2-Hydroxy-apocamphane-1-acetanilide into Camphene-carboxy-anilide.—Two g. (0.007 mole) of 2-hydroxy-apocamphane-1-acetanilide was suspended in 200 cc. of absolute ether and 1.6 g. (0.007 mole) of phosphorus pentachloride was added slowly, the mixture being cooled during the reaction. The suspended compound gradually went into solution as the reaction progressed and, after completion, the ether solution was washed with cold water until the washings were no longer acid to litmus. The ether solution was dried with anhydrous sodium sulfate and evaporated, leaving a solid which on recrystallization from 85% ethanol melted at 153–154° (corr.); yield 1.2 g. (66%). It did not lower the melting point in the mixed melting point test with an authentic sample of camphene-carboxyanilide.

Camphene-carboxylic Acid.—Eight-tenths gram of camphene-carboxy-anilide was refluxed for thirty-six hours with 100 cc. of 20% alcoholic potassium hydroxide. After cooling, the solution was poured into ice water which was extracted with ether. The aqueous solution was evaporated to about 20 cc. while carbon dioxide was being passed through, filtered and after cooling acidified with dilute hydrochloric acid and extracted with ether. The ether solution was dried with sodium sulfate and evaporated, leaving a brownish solid which was dissolved in hexane, decolorized with norite and recrystallized from the same solvent; melting point 126–127° (corr.); yield, 0.13 g. (23.2%).

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.32; H, 8.95; neut. equiv., 180.23. Found: C, 73.41; H, 9.15; neut. equiv., 180.70.

The ether solution obtained by extracting the original alkaline liquors was dried with anhydrous sodium sulfate and evaporated, leaving a residue which partly solidified on cooling. It was washed with a small amount of hexane, leaving a white solid which proved to be identical with the original material; yield 0.282 g. (35%). The hexane washings were evaporated, leaving minute quantities of a residual reddish oil which consisted of aniline since the benzoyl derivative prepared in the usual manner melted at 162.5–163.5° (corr.), and did not lower the melting point when mixed with an authentic sample of benzanilide.

Camphenilone Semicarbazone.—Two and five-tenths grams of camphenicarboxylic acid was dissolved in 75 cc. of water containing 2.61 g. of potassium hydroxide. To this solution was slowly added a solution of 4.38 g. of potassium permanganate solution while steam distilling. A volatile oil of camphoraceous odor was taken up in ether, the solution being dried with anhydrous sodium sulfate. After distilling off the ether, there was obtained 1.5 g.

(79%) of camphenilone which was immediately converted into the semicarbazone prepared in the usual manner; yield of semicarbazone 1.8 g. It was recrystallized from dilute ethanol, yielding fine white needles melting at 223–224° (corr.) and did not lower the melting point in the mixed melting point test with an authentic sample.

Anal. Calcd. for $C_{16}H_{17}ON_3$: C, 61.53; H, 8.78. Found: C, 61.34; H, 8.89.

The manganese dioxide was filtered from the aqueous solution, which was evaporated to a small volume, acidified with dilute hydrochloric acid and the precipitate removed by filtration. After recrystallizing from hexane, the acid melted at 126–127° (corr.). The mixed melting point test with the original material showed no lowering; recovery, 0.2 g. A solution of calcium chloride was added to the aqueous solution made alkaline with ammonia after removal of the original acid. The precipitate responded to the usual tests for calcium oxalate.

Three and seven-tenths grams of camphene-carboxyanilide was added to a solution of 6.4 g. of potassium permanganate and 0.8 g. of potassium hydroxide in 230 cc. of water. The mixture was shaken on a machine for fifteen hours and then steam distilled; 200 cc. of distillate was collected to which was added 1 g. of semicarbazide hydrochloride and 1 g. of sodium acetate. On standing *in vacuo* for three days, a crystalline precipitate was separated and recrystallized from ethanol, m. p. 224–225° (corr.). When mixed with an authentic sample of camphenilone semicarbazone, it did not lower the melting point.

Summary

1. When subjected to the Beckmann rearrangement, ω -benzoylborneoloxime yielded 2-hydroxy-apocamphane-1-acetanilide and as secondary product camphene-carboxyanilide, formed apparently by the Meerwein-Wagner rearrangement, and small amounts of benzonitrile, together with some tarry material of unknown composition.

2. The composition of 2-hydroxy-apocamphane-1-acetanilide was established by a series of new ω -homocamphor derivatives: lactone of hydroxy-apocamphane-1-acetic acid, 2-keto-apocamphane-1-acetic acid, semicarbazone of 2-keto-apocamphane-1-acetic acid and apocamphane-1-acetic acid.

3. The Meerwein-Wagner retro-pinacolone rearrangement on 2-hydroxy-apocamphane-1-acetanilide yielded camphene-carboxyanilide, which was characterized through its oxidation to camphenilone and hydrolysis to camphene-carboxylic acid.

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