

PART I

THE SELENIUM DEHYDROGENATION OF URSOLIC ACID

PART II

THE PREPARATION OF METHOXY ACETALDEHYDE

BY

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Thesis submitted to the Faculty of the Graduate School
of the University of Maryland in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy.

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ACKNOWLEDGMENT

The writer wishes to express his appreciation to Dr. N. L. Drake for suggesting these problems and for his constant advice and attention during the course of this research.

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PART II

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PART I

1. HISTORICAL INTRODUCTION

A. Ursolic acid

The earliest reference to ursolic acid recorded in the literature was made by Trommsdorf¹ in 1854. He isolated from the leaves of the bearberry (*Arctostaphylos Uva Ursi*) two crystalline compounds, one called arbutin and the other called by Trommsdorf urson. The first thorough examination of this latter compound was made by Gintl², who worked on a preparation obtained from Merk.

Ursolic acid is widely distributed throughout the plant kingdom; a list of the sources is given below^{3,4,5,6,7,8};

<i>Chimaphila umbellata</i>	<i>Ilex Aquifolium</i>
<i>Pirola rotundifolia</i>	<i>Ilex paraguariensis</i>
<i>Rhododendron maximum</i>	<i>Ilex cremata</i>
<i>Epigaea repens</i>	<i>Ilex perado</i>
<i>Gaultheria procumbens</i>	<i>Pirola umbellata</i>
<i>Calluna vulgaris</i>	<i>Vaccinium Vitis Idaea</i>
<i>Erica Tetralix</i>	<i>Erica arborea</i>
<i>Vaccinium macrocarpum</i>	<i>Pirola minor</i>
<i>Vaccinium Myrtillus</i>	<i>Erica mediterranea</i>
<i>Azalea indica</i>	<i>Erica carnea</i>
<i>Rhododendron hybridum</i>	<i>Viscum Album</i>
<i>Arbutus Andrachne</i>	Apples, pears and cranberries

In all except the last three sources, the ursolic acid occurs in the leaves of the plants mentioned. In the latter sources, the ursolic acid is found in the wax-like coating on the surface of the apple, in the skin of the pear,

and in cranberry pomace.

There are several methods of isolating ursolic acid from its natural sources. Three of these methods will be given in some detail. Nooyen³ investigated the following methods of isolation:

1. the method of Trommsdorf (1).
2. the method of VanItallie (9)
3. the method of Dodge (10).

She obtained the most satisfactory results from the third method which is described by Dodge¹⁰ in the following manner:

"200 g. of commercial Uva Ursi was thoroughly dried, pulverized, and mixed with one liter of methyl alcohol and 150 cc of 2N alcoholic potassium hydroxide, and allowed to stand several days with frequent shaking. The mixture was then filtered, and the residue washed clean with about 300 cc of methyl alcohol. The combined filtrate and washings were acidified with acetic acid and concentrated to about 300 cc. On cooling, greenish crystals, amounting to about 4 g, were deposited and on further concentrating a more impure product (7 g) was obtained. By recrystallization from alcohol, with bone black, 5 g of white crystals were obtained."

Sando⁶ used a method devised by him, which he describes thus:

"The ether-soluble extract of the dried pear skins (a 150 g. portion) was treated three times with boiling dilute aqueous sodium hydroxide, whereupon soluble and insoluble sodium salts were formed. These were separated through a Buchner funnel. The crude, water-insoluble sodium salt was dissolved in boiling 95% ethyl alcohol containing a small amount of sodium hydroxide, and an equal quantity of hot water added. The solution was maintained at the boiling point and stirred mechanically until the sodium salt had separated. The hot solution was filtered and the salt washed and dried, after which it was extracted with ether for 7 days in a Soxhlet apparatus. The insoluble salt was then recrystallized three times by the process described above. The free acid was recovered from its salt by solution of the latter in alcohol and addition of dilute hydrochloric acid. The nearly pure acid was filtered off, washed thoroughly with water, and dried. It weighed 38 g. Final purification was accomplished by several fractional crystallizations from absolute alcohol, whereby 25 g. of ursolic acid were obtained with a melting point of 282.5 - 283.5°.

Another method of isolating ursolic acid from its natural sources, suggested by the methods of Sando and of Dodge, has been devised by Dr. N. L. Drake and the author.

The details of this method are given in the experimental part of this thesis.

Below are listed the physical properties of ursolic acid as have been observed by various investigators:

Melting point⁸:

282.5-283.5°C.

Optical Properties 10,11:

$$[\alpha]_D^{24.5^\circ} = + 64.94^\circ \text{ (ursolic acid)}$$

$$[\alpha]_D^{24.5^\circ} = + 57.84^\circ \text{ (potassium ursolate)}$$

Extinction parallel
Elongation positive
Retardation, in wave lengths $1/4^{-1}$
Birefringence, from assumed thickness 0.0003
 n_D estimated 1.53-1.54
Inconvergent shows acute bisectrix
Optical angle, $2V$ $22-23^\circ$
Crystals are probably orthorhombic

Habit is characteristic, blades being present with some cleavage crosswise. These show the indices:

$$\alpha, \text{ crosswise of blades} = 1.56 \pm 0.01$$

$$\beta, \text{ lengthwise} = 1.56 \pm 0.01$$

γ , perpendicular to the blades and measurable only on rare fragments which happen to turn on edge = 1.58 ± 0.01

Between crossed nicols, interference colors of the first and second order are distinguishable.

In convergent polarized light, with crossed nicols, biaxial figures are shown with

$$2E = 130^{\circ} \pm 10^{\circ}$$

The optic sign is positive.

The crystal system is inferred to be rhombic, with the direction of the index β lying along the principal zone axis.

Solubility of ursolic acid³:

1 g. of ursolic acid at 15°C in

178 g ethyl alcohol

88 g methyl alcohol

388 g chloroform

192 g ethylene dibromide

140 g diethyl ether

Color tests shown by ursolic acid³:

1. With conc. H_2SO_4 , ursolic acid gives an orange-yellow color with a green fluorescence.
2. Liebermann test: a little ursolic acid dissolved in 2 ml. acetic anhydride gives with 8 to 10 drops of conc. H_2SO_4 a red color which changes to violet to green to blue.

For the different phases of these reactions the following absorption bands were noted⁹:

red: λ 558-593

blue: λ 632-654

green: λ 618-670

3. A little ursolic acid dissolved in CHCl_3 , when mixed with an equal volume of conc. H_2SO_4 gives directly a yellow color; with more conc. H_2SO_4 , the color later changes to brown.

The compound now known as ursolic acid was, prior to 1924, known as urson. At this time van der Haar¹², as the result of a study of the compound, showed the former name to be more consistent with its chemical nature.

There have been described in the earlier literature two compounds, malol and prunol, which van der Haar subsequently showed to be none other than ursolic acid. Malol was first reported by Sando⁶. It was shown by van der Haar¹³ in 1924 to be ursolic acid. Prunol was first reported by Power and Moore¹⁴ and in 1924 shown by van der Haar¹³ to be ursolic acid. The prunol of Power and Moore was isolated from the leaves of *Prunus serotina*.

Ursolic acid is isomeric with caryophyllin (Dodge,¹⁰) or oleanolic acid, the sugar-beet saponin (van der Haar¹⁵). Caryophyllin and oleanolic acid are the same substance.

Trommsdorf¹ assigned to ursolic acid the formula $(\text{C}_{10}\text{H}_{16}\text{O})_n$. Hlasiwetz¹⁶ and Rochleder¹⁷ also reported analyses of ursolic acid, the former finding the composition $(\text{C}_{10}\text{H}_{17}\text{O})_n$, the latter agreeing with Trommsdorf.

Gintl² also reported for ursolic acid the formula

$(C_{10}H_{16}O)_n$ where $n = 3$ as determined by a molecular weight determination. Nooyen³ obtained results in agreement with those of Gintl, i.e., $(C_{10}H_{16}O)_n$ where $n = 3$. The latter investigator found the molecular weight of ursolic acid by both the freezing point depression and the boiling point elevation methods. Dodge¹⁰ also favors the formula $(C_{10}H_{16}O)_3$; he determined the molecular weight by direct titration of the acid (he considers the compound to be a lactone, not an acid). Sando¹⁸ assigns to ursolic acid the formula $C_{30}H_{48}O_3$. He bases his formula on the statistical mean values of ninety-two analyses of ursolic acid and its derivatives.

van der Haar¹⁵, on the other hand, considers the formula to be $C_{31}H_{50}O_3$, on the basis of elementary analysis and the results of zinc dust distillation of ursolic acid in a stream of hydrogen. Power and Tutin¹⁹ found for cleanolic acid, which is isomeric with ursolic acid, the composition $C_{31}H_{50}O_3$.

By this zinc dust distillation, van der Haar obtained only carbon dioxide, water and either two different sesquiterpenes, or two molecules of the same sesquiterpene. The following equation illustrates the reaction:



According to van der Haar, if the formula for ursolic

acid were $C_{30}H_{48}O_3$, the above results would not be comprehensible. Vesterberg²⁰ considers that ursolic acid must contain only thirty carbons since it is a triterpene alcohol. But van der Haar believes this argument to be without significance. He states that ursolic acid is not a triterpene alcohol, but a monocarboxylic acid with an alcoholic hydroxyl group.

In attempting to discern between the formulas $C_{30}H_{48}O_3$ and $C_{31}H_{50}O_3$ on the basis of elementary analyses, it is to be borne in mind that ordinary carbon and hydrogen determinations, either macro- or micro-, are not sufficiently accurate to detect the difference of one methylene group in compounds of such high molecular weight. Below are given the calculated values for the carbon and hydrogen contents required by both formulas:

$C_{30}H_{48}O_3$: C, 78.88; H, 10.60

$C_{31}H_{50}O_3$: C, 79.08; H, 10.71

A critical examination of all analyses reported will show results checking as well for one formula as for the other. Any such evidence can not be considered as conclusive for either formula. Recently there has been developed by Baxter of Harvard a very sensitive method of determining carbon and hydrogen, exceeding in accuracy the ordinary methods used by any of the above investigators. Only by

this new method can the correct formula be ascertained on the basis of elementary quantitative analyses. As yet, no analyses have been made on ursolic acid by this new method, although such analyses are greatly to be desired.

Winterstein and Stein²¹ also favor the formula richer by one methylene group, namely $C_{31}H_{50}O_3$, as the correct formula for ursolic acid. In addition to elementary analyses, they have determined the titration values of both ursolic acid and monoacetyl ursolic acid. Their values are given below:

Ursolic acid:

$C_{30}H_{48}O_3$: theoretical, 456.4
 $C_{31}H_{50}O_3$: theoretical, 470.4
found: 467.4, 468.0, 462.2, 475.0
mean: 468.1

Acetyl ursolic acid:

$C_{32}H_{50}O_4$: theoretical, 498.4
 $C_{33}H_{52}O_4$: theoretical, 512.4
found: 508, 509

In consideration of the discussion given above relative to the reliability of elementary analyses for discerning the difference of one methylene group in compounds of high molecular weight, there remains only the results of van der Haar's zinc dust distillation and the titration values

of Winterstein and Stein which might lead to the acceptance of one formula in favor of the other. Of titration values it is to be observed that such values may be determined with sufficient accuracy to detect the aforementioned difference of one methylene group.

As to the structure of ursolic acid but little has been known heretofore. Dodge^{10,22} believes ursolic acid (which he still calls urson) to be a hydroxy lactone,

$C_{29}H_{47} \begin{cases} -OH \\ -O \\ -CO \end{cases}$, based on the $C_{30}H_{48}O_3$ formula, while all other investigators consider ursolic acid to be a mono-hydroxy monocarboxylic acid, either $HO.C_{29}H_{46}.COOH$ or $HO.C_{30}H_{48}.COOH$, the hydroxyl group being alcoholic.

Dodge prepared the potassium, lead and zinc salts of ursolic acid. These could be derived either from a free carboxyl group, or from a lactone group which could be hydrolyzed by the action of alkali. The potassium salt was prepared by treating an alcoholic solution of ursolic acid with alcoholic potassium hydroxide. In fact, it is possible to titrate the acid easily and accurately in this manner, using phenolphthalein as the indicator. The lead and zinc salts were prepared by the addition of alcoholic lead or zinc acetate to a 10% alkaline "urson" solution.

Further, Dodge²² was able to prepare a diacetyl ursolic acid, which he considers proof of the existence in

the molecule of two hydroxyl groups, one of which is originally present as an alcoholic hydroxyl group, the second of which is formed by hydrolysis of a lactone group.

From the diacetyl compound, there is obtained on recrystallization from ethyl alcohol the monoacetate.

Dodge grants that "the practically instantaneous neutralization by alkali in alcoholic solution, and the opening of the lactone ring on acetylation, are reactions not generally exhibited by the better known lactones. Various available lactones were examined, but they were lactones, the stable variety". He summarizes the evidence favoring the lactone structure assumed for ursolic acid, thus: "The neutrality in alcoholic solution, the tendency of salts to hydrolyze, precipitation of the free acid by CO₂, the composition of the potassium salt, and the preparation of two acetates".

Contrary to Dodge's proposal of a lactone group, Nooyen³ found evidence for the presence of a carboxyl group in ursolic acid. In addition to the ease of titration and the preparation of salts, as further evidence for the presence of the carboxyl group, she reported the preparation of a methyl ester. The latter was prepared by the action of dimethyl sulfate on the sodium salt of ursolic acid. The

compound was analyzed for $C_{29}H_{47}O.COOCH_3$ with satisfactory results. By the Zeisel method, only one methyl group was present in the compound.

The formation by ursolic acid of a diacetyl derivative has given rise to considerable discussion and uncertainty as to the actual nature of this derivative. Dodge considers the formation of such a compound as conclusive evidence for his lactone structure of ursolic acid. Other investigators, however, in view of evidence yet to be presented, which seems to exclude the possibility of the lactone formula, are hard put to it to give a satisfactory formulation for a diacetyl derivative of a monohydroxy compound.

Carrying further the work on the methyl ester of ursolic acid begun by Nooyen³, van der Haar²³ has shown that the latter contains only one hydroxyl group, doing so by the Tschugaeff-Zerewitinoff method. Were ursolic acid a lactone, the formation of a methyl ester from the sodium salt of the original compound must have introduced into the ester a free hydroxyl group. But since ursolic acid itself already contains one hydroxyl group, as will be shown subsequently, and the ester contains only one hydroxyl group, then no further hydroxyl group has been introduced, and the original compound could not have been a lactone. It is to

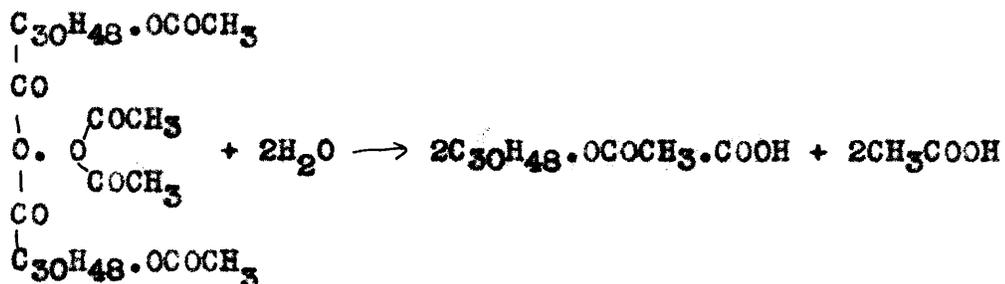
be recalled that Nooyen³ showed that the methyl ester contained only one methyl group.

As for the formation, then, of a diacetyl derivative, the following is not impossible: R-COO-COCH₃, the second acetyl group entering the carboxyl group to form a mixed acid anhydride. Such a reaction has been observed²⁴ for weak acids (such as is ursolic acid). Such acetyl derivatives are decomposed by boiling water, and it is a universally observed property of diacetyl ursolic acid that, on recrystallization from ethyl alcohol, there is never recovered the diacetyl compound, but always the monoacetyl derivative. Pichard and Riviere²⁴ represent the diacetyl derivative as a mixed acid anhydride, e.g.



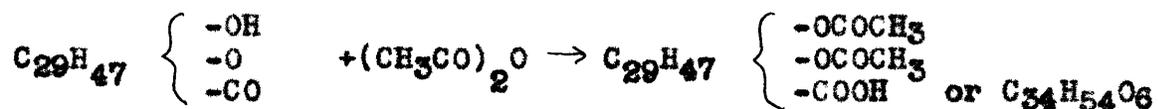
ursolic acid. The diacetyl compound, as reported by Sando¹⁸, decomposed at 200°C with evolution of gas, resolidified and melted again at about 300°C. This decomposition is interpreted by Pichard and Riviere as a resolution of the mixed anhydride into two symmetrical anhydrides: acetic anhydride which can be separated by distillation in vacuo, and the anhydride of monoacetyl ursolic acid. The latter, on hydrolysis, gives a monoacetyl derivative identical with that which is obtained by the action of boiling aqueous alcohol on the supposedly diacetyl ursolic acid. It is to be noted that

anhydride, united to form a diacetylated anhydride which crystallizes with one molecule of acetic anhydride. In a previous investigation²⁶, smaller molecules, namely benzoic acid and p-dimethyl amino benzoic acid were subjected to a similar treatment with acetic anhydride and it was found that they behaved in a manner entirely analogous to the manner of oleanolic and ursolic acids. He found no evidence of the formation of mixed acid anhydrides. When the above-mentioned acetylation product was heated with alcohol, the molecule of acetic anhydride was split out and the diacetylated anhydride split into two molecules of monoacetyl ursolic acid. These reactions van der Haar represents in the following manner, based on the $C_{31}H_{50}O_3$ formula:

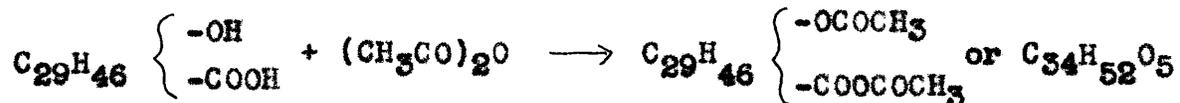


The diacetyl derivative formulated by van der Haar corresponds to two molecules of the diacetyl derivative formulated by Pichard and Riviere, when considered on a common basis (either $C_{30}H_{48}O_3$ or $C_{31}H_{50}O_3$) and hence, either compound should give the same elementary analyses, but different molecular weights. No molecular weight determination

has been recorded in the literature. However, the diacetyl derivative postulated by Dodge²² would not have an identical empirical formula, differing, on the basis of the C₃₀ formula, by one molecule of water from that of the diacetyl formula given by Pichard and Riviere and by Sando. Thus, according to Dodge, we would have:



which requires for C, 73.07 and for H, 9.75. According to Pichard and Riviere or Sando, we would have:



which requires for C, 75.50 and for H, 9.70. Elementary analyses would be sufficiently accurate to distinguish between these two formulas. Dodge was unable to obtain a pure sample of diacetyl ursolic acid and hence gave no analytical data. However, Sando¹⁸ reported results checking very well for the latter formula.

Some inconclusive work has been done on the detection of double bonds in ursolic acid. Gintl² observed a reaction between ursolic acid and bromine, which Nooyen³ misinterpreted as an addition reaction, while Gintl spoke of it as a substitution reaction since HBr was liberated.

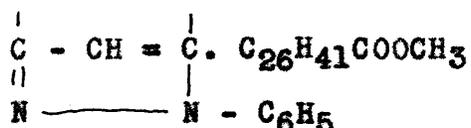
Nooyen attempted an ozonolysis of ursolic acid, and

also of its methyl ester, and since she obtained no reaction, she concluded that no double bonds were present. However, Winterstein and Stein²¹ report that tetranitro methane gives the characteristic test (formation of a yellow color) for a double bond with ursolic acid.

Neither Gintl nor Nooyen were able to hydrogenate ursolic acid by use of hydrogen.

S. Kuwada and T. Matsukawa²⁷, as the result of their investigations, claim the existence in ursolic acid of the grouping $\text{CH}_3\text{CHOHCH}_2\text{CH}_2$ -. In substantiation of their claim, they offer the following experimental data. Ursolic acid, $\text{HO.C}_{29}\text{H}_{46}.\text{COOH}$, on oxidation with CrO_3 in glacial acetic acid, yields ursonic acid, $\text{CO.C}_{29}\text{H}_{45}.\text{COOH}$. The latter is a ketonic acid as is shown by the formation of an oxime. Likewise, methyl ursolate, $\text{HOCH.C}_{28}\text{H}_{45}.\text{COOCH}_3$, may be oxidized to methyl ursonate, $\text{CO.C}_{28}\text{H}_{45}.\text{COOCH}_3$. Acetylation of ursolic acid gives acetyl ursolic acid, $\text{CH}_3\text{COOCH.C}_{28}\text{H}_{45}.\text{COOH}$, which on gentle oxidation with CrO_3 gives ketoacetyl ursolic acid, $\text{CH}_3\text{COOCH.CO.C}_{27}\text{H}_{43}.\text{COOH}$. In this oxidation the keto-group must have come from a methylene group. Methylation of ketoacetyl ursolic acid by means of diazomethane, followed by removal of the acetyl group by means of alcoholic potassium hydroxide, gives methyl ketoursolate, $\text{HOCH.CO.C}_{27}\text{H}_{43}.\text{COOCH}_3$. Oxidation of

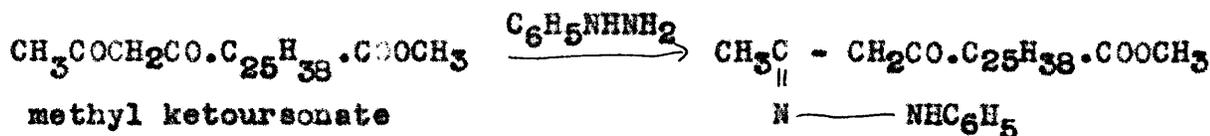
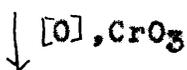
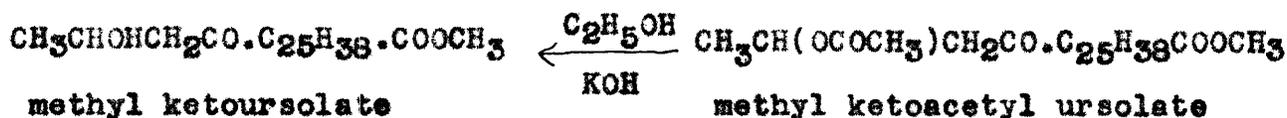
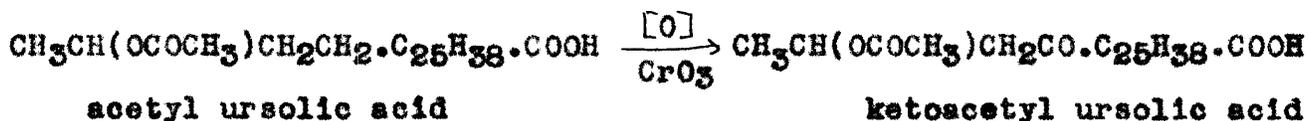
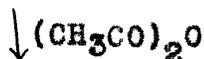
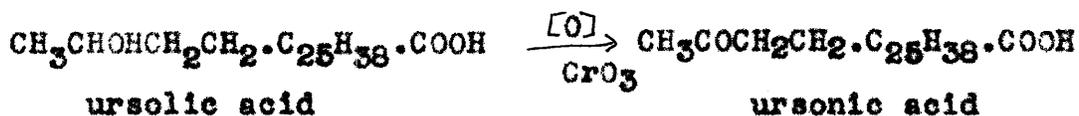
the latter compound gives^a methyl ester of a diketonic acid, methyl ketoursonate, $\text{CO}\cdot\text{CO}\cdot\text{C}_{27}\text{H}_{43}\cdot\text{COOCH}_3$. The presence of two carbonyl groups is shown by the formation of a dioxime. Methyl ketoursonate forms a monophenylhydrazone, $\text{C}_6\text{H}_5\text{NHN} = \text{C}\cdot\text{CO}\cdot\text{C}_{27}\text{H}_{43}\cdot\text{COOCH}_3$, which on reduction with sodium is converted to a phenyl pyrazole derivative,



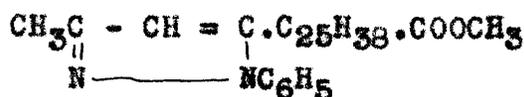
From the formation of the latter compound, it is concluded that methyl ketoursonate is a β -diketone, the two carbonyl groups being separated by a methylene group.

By oxidation of methyl ursolate with Kiliani's reagent, Kuwada and Matsukawa obtained a ketonic methyl ester, $\text{C}_{29}\text{H}_{44}\text{O}_3$. This represents a loss of C_2H_6 which they account for as a loss of a CH_3CHOH -group, with a concurrent conversion of a $-\text{CH}_2-$ group to a $>\text{CO}$ group. That is, both the hydroxyl and β -methylene groups are converted to carbonyl groups. The carbonyl group derived from the hydroxyl group is considered to be adjacent to a methyl group, and both groups are lost simultaneously during the course of the oxidation. Thus, there would have to be present in ursolic acid the chain $\text{CH}_3\text{CHOHCH}_2\text{CH}_2-$, and ursolic acid would be represented as $\text{CH}_3\text{CHOHCH}_2\text{CH}_2\cdot\text{C}_{25}\text{H}_{38}\cdot\text{COOH}$.

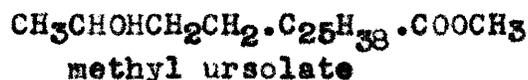
The series of reactions given above may be outlined in the following manner:



methyl ketoursonate mono-phenylhydrazone (or the other monophenylhydrazone)



phenylpyrazole derivative (or its isomer)



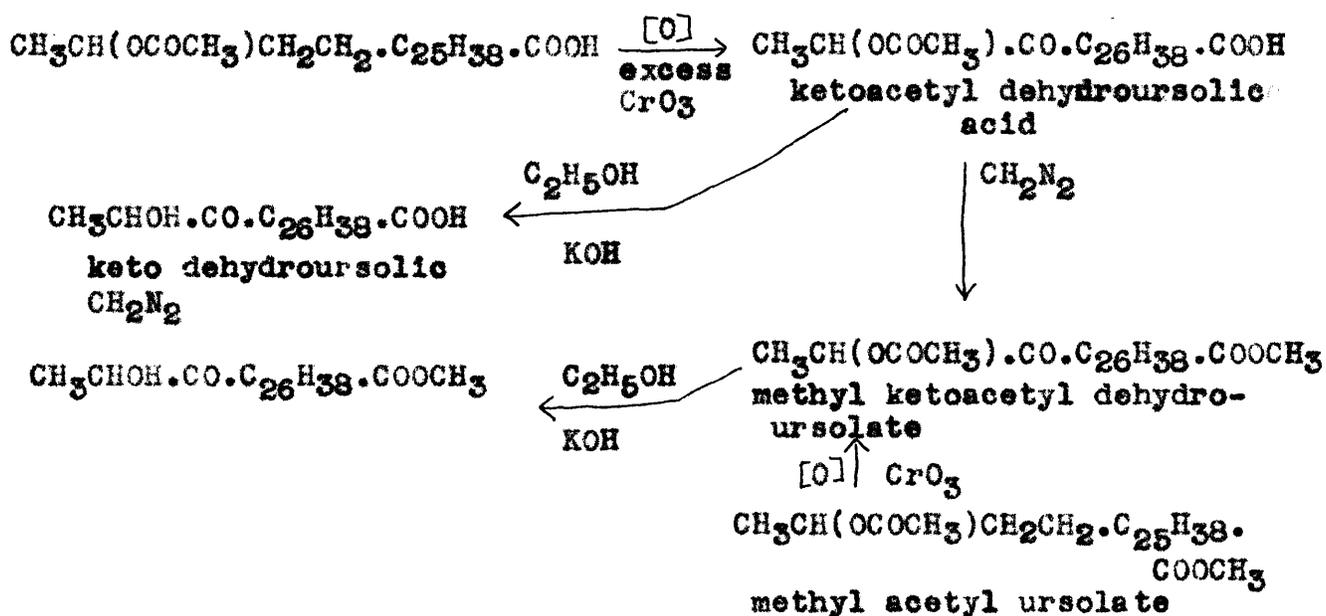
[O] ↓ Kiliani's reagent

a ketonic methyl ester, C₂₉H₄₄O₃(CH₃CO·C₂₅H₃₈·COOCH₃?)

The results of the work of Kuwada and Matsukawa with their conclusions therefrom as to the structure of ursolic are not in accord with the postulations of Ruzicka²⁸ as to the structure of oleanolic acid, an isomer of ursolic acid. The

latter work will be considered later in this thesis.

In addition to the above compounds, Kuwada and Matsukawa describe some dehydro derivatives of ursolic acid, without, however, attempting to show the location of the loss of hydrogen. Thus, acetyl ursolic acid, $\text{CH}_3\text{CH}(\text{OCOCH}_3)\text{CH}_2\text{CH}_2\cdot\text{C}_{25}\text{H}_{38}\cdot\text{COOH}$, on oxidation with excess CrO_3 yields ketoacetyl dehydro ursolic acid, $\text{CH}_3\text{CH}(\text{OCOCH}_3)\cdot\text{CO}\cdot\text{C}_{26}\text{H}_{38}\cdot\text{COOH}$. The series of reactions they describe are outlined below:



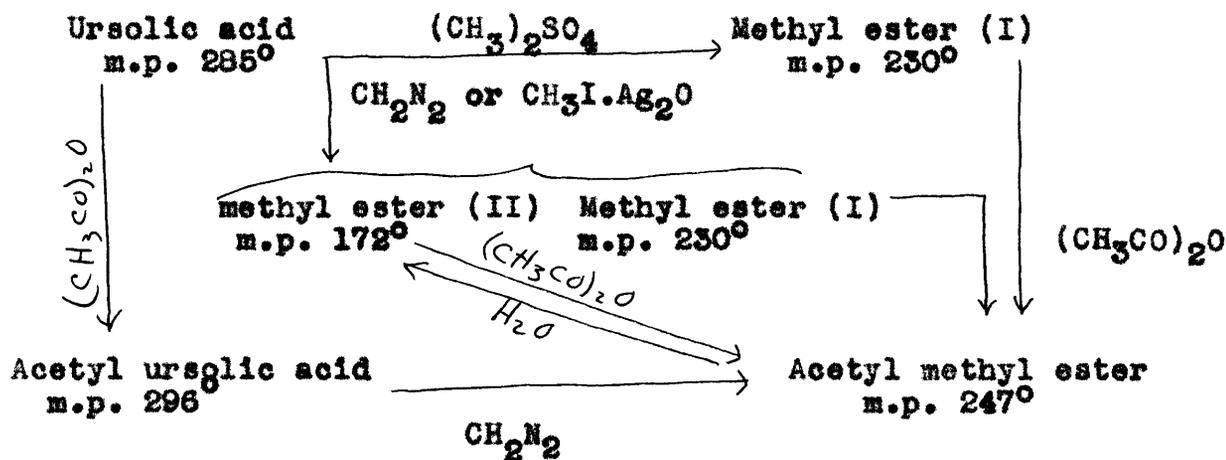
Jacobs and Fleck²⁹, in their studies on ursolic acid, have obtained results which substantiate some of those obtained by Kuwada and Matsukawa²⁷. Thus, they obtained a methyl ester of a diketonic acid, namely, methylketoursonate, $\text{C}_{31}\text{H}_{46}\text{O}_4$. This they obtained by oxidation of methyl ursolate with Kiliani's reagent. In addition, Jacobs and Fleck²⁹ were able to convert the hydroxyl group in methyl ursolate to a methylene group,

Similarly, ursolic acid was converted to desoxy ursolic acid, $\text{CH}_3\text{CH}_2\cdot\text{C}_{27}\text{H}_{42}\cdot\text{COOH}$. The latter compound does not have the same melting point as the ursanic acid prepared by Jacobs and Fleck²⁹. No explanation of this discrepancy has been given. As to the isomerism between ursolic and oleanolic acids which are now considered as stereoisomers, a comparison of desoxyursolic and desoxy oleanolic acids shows that the isomerism does not exist in the hydroxyl groups, but must lie in some other linkage.

Repeated mention has been made of the methyl ester of ursolic acid, methyl ursolate. Jacobs²⁹ and Kuwada and Matsukawa³¹ have been able to obtain two methyl esters of ursolic acid. Using dimethylsulfate as the methylating agent, the latter investigators always obtained a methyl ester having a melting point of 230°C . However, when diazomethane or methyl iodide and silver oxide were used as the methylating agent, a mixture of two methyl esters was obtained. Fractionation of the mixture with acetone results in an ester difficultly soluble in acetone, melting point of 230°C , and giving only half the theoretical value on a methoxy determination. The other ester, easily soluble in acetone, melts at $170\text{-}172^\circ\text{C}$ and gives the theoretical value on a methoxy determination.

Both methyl esters on acetylation give the same

acetyl methyl ester, melting at 246-247°C and containing one methyl group. On saponifying the acetyl methyl ester there is obtained only the methyl ester with the lower melting point, never the other methyl ester. Kuwada and Matsukawa conclude that the methyl esters are stereoisomers, and the higher melting ester is converted to the lower melting ester by the effect of acetic anhydride. The interrelationship of the two esters is shown by the following outline:



Kuwada and Matsukawa³² have isolated from the leaves of *Rhododendron hymenches* Makino an ursolic acid of melting point 290-1° (decomn.). When methylated with diazomethane, the ursolic acid yields a methyl ester melting at 170-172°C. Methylation with dimethylsulfate gives a methyl ester melting at 230°C. When, however, the ursolic acid is first treated with alkali and then methylated with either diazomethane or dimethylsulfate, only the lower

melting methyl ester is obtained. Treatment of the ursolic acid or either of the two methyl esters with acid does not change their melting points, from which these investigators conclude that the isomerization can not be wholly explained by the rearrangement of the double bond in the molecule. The ursolic acid melting at 285°C is tentatively called by Kuwada and Matsukawa α -ursolic acid, and the ursolic acid melting at 290-1°C β -ursolic acid.

Kuwada and Matsukawa³⁰ made a spectrographic study of α - and β - ursolic acid and oleanolic acid. Oleanolic and α -ursolic acids have the same general absorption spectra curves with no maxima and minima, from which they conclude there is no reason to assume the presence of any characteristic group in these substances. The curve of β -ursolic acid is different. They consider that the spectrographic study shows that the cause of isomerism lies in the $-\overset{|}{\text{C}}-\text{COOH}$ linkage, which is consistent with the behavior of the methyl esters.

B. Selenium Dehydrogenation

For the elucidation of the structure of complicated naturally occurring organic compounds use has been made during the last few years of the results of dehydrogenation methods. Those compounds to which these methods have been applied are, in general, polycyclic hydroaromatic substances. The dehydrogenation reactions convert these substances, through loss of hydrogen and often cleavage of the molecule, to aromatic compounds whose structures are either known or can be ascertained by synthesis. From the structure of the latter can be deduced the structure of the natural products, unless ring changes, other than extra ring formation involving a side chain, take place during the drastic operation which ordinarily involves heating with sulfur or selenium for some thirty-six hours at temperatures from about 280° to 360°C.

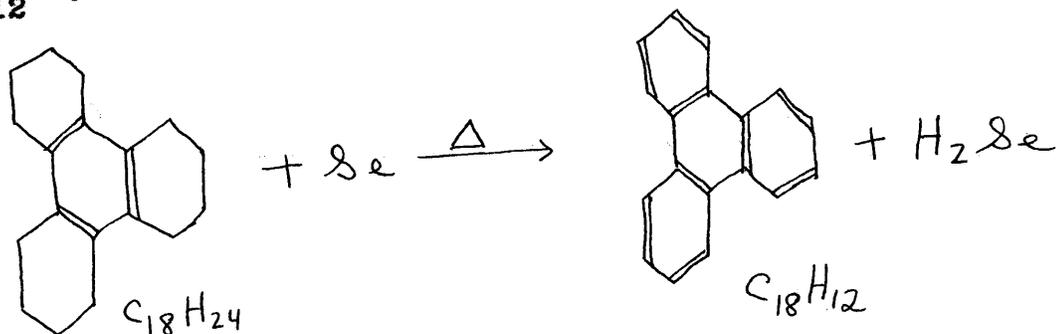
One of the earliest methods for dehydrogenation of hydroaromatic compounds is that of Vesterberg³³. He used as a dehydrogenating agent sulfur. This method was modified in 1927 by Diels³⁴, who used selenium in place of sulfur. Since that time the modified method has ^{been} largely, but not entirely, replaced the older one. Two other dehydrogenating agents worthy of note are zinc dust and palladium black³⁵, the latter being a catalytic agent.

While sulfur was the first dehydrogenating agent used, its application is restricted because this element exerts a too far reaching effect, causing in many cases carbonization and not seldom entering into the molecule concerned. Selenium, on the other hand, shows only the slightest tendency in the latter respect. In fact, there has never been isolated from the dehydrogenation products any compound containing selenium in the organic molecule. Being milder in its action, selenium affords much better yields than does sulfur, and as a corollary, effects much less carbonization.

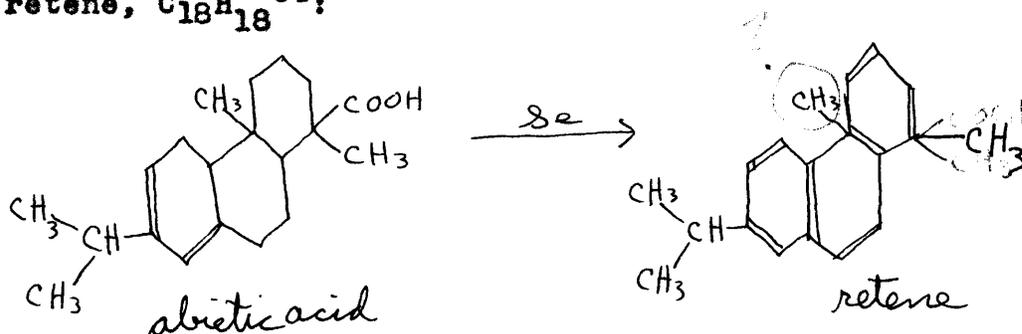
Selenium is also superior to both zinc dust and palladium black as a dehydrogenating agent, probably because it may be used for this purpose at lower temperatures than are required by the other two elements.

Although some of the effects produced by selenium during the course of a dehydrogenation are obscure and difficult to predict, several definite changes may be expected. Thus, a hydroaromatic compound will be converted to an aromatic compound, selenium combining with hydrogen removed from the original compound to form hydrogen selenide. A specific example of this simple conversion is the conversion dodecahydro - tri - o - phenylene, $C_{18}H_{24}$ to tri-o-phenylene,

$C_{18}H_{12}^{34}$:

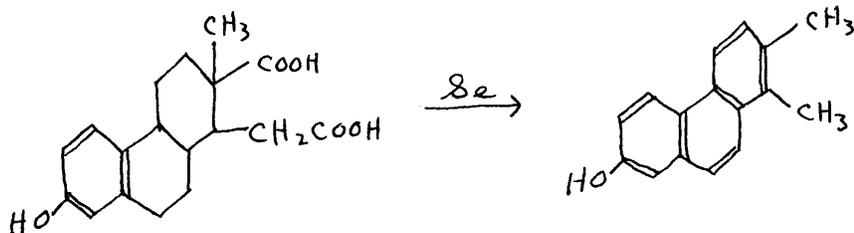


If in the original substance being dehydrogenated there are present carboxyl and hydroxyl groups, they are usually eliminated, probably as much by thermal decarboxylation and dehydration as by the effect of the dehydrogenating agent. An illustration of the fate of the carboxyl group is given by the conversion of abietic acid, $C_{19}H_{29}COOH$, to retene, $C_{18}H_{18}^{34}$:

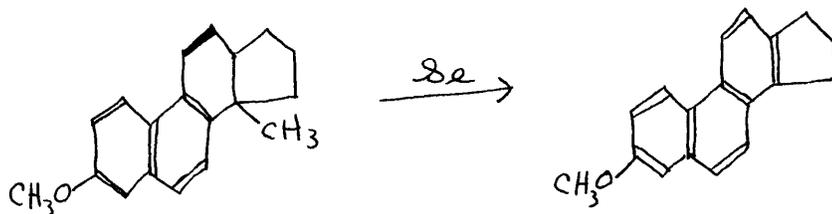


When dehydrogenating cholic acid, a trihydroxy bile acid, there is always an evolution of water during the preliminary period of heating, cholatrienic acid being formed through loss of three molecules of water³⁵. While the loss of hydroxyl groups in this manner is general, several

compounds have been isolated from the products of dehydrogenation in which the hydroxyl group is still intact. Thus, the following hydroxy bilianic acid is converted to a dimethyl phenanthrol³⁷:



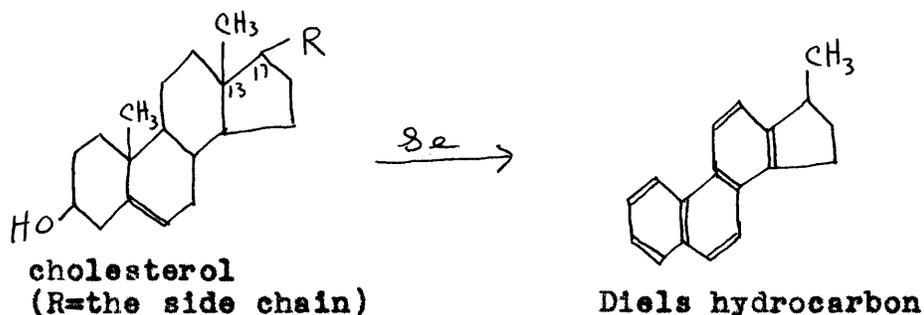
In some cases, loss of a hydroxyl group may be prevented by methylation, as in the following example³⁸:



Another interesting case of the survival of an unprotected hydroxyl group is found in the formation of a hydroxy trimethyl naphthalene during the dehydrogenation of many sapogenins containing in the original molecule one or more hydroxyl groups^{39,40,41,42}.

In general quaternary methyl groups are eliminated during dehydrogenation. Examples of this elimination have

already been given, as in the conversion of abietic acid to retene. However, a quaternary methyl group may migrate. Thus, in the dehydrogenation of cholesterol, Diels³⁵ obtained among other substances a hydrocarbon, $C_{18}H_{16}$, often referred to as Diels hydrocarbon. The structure of this hydrocarbon has been established as 3'-methyl-1, 2-cyclopentenophenanthrene by synthesis of the latter and an exhaustive comparison of the physical and chemical properties of both the synthetic and the dehydrogenation products⁴³. The conversion of cholesterol to Diels hydrocarbon is shown by the following formulas:



The explanation of this migration is given by Cook⁴⁴. "It is now possible to present a rational interpretation of the formation of 3'-methyl-1, 2-cyclopenteno-phenanthrene by dehydrogenation of sterols, bile acids and cardiac aglucones. Clearly the methyl group migration is concomitant with, and inseparable from, the elimination of the side chain, and is in no way dependent on dehydrogenation. The side chain may be regarded as being expelled from the molecule as an anion, the whole process then becomes a

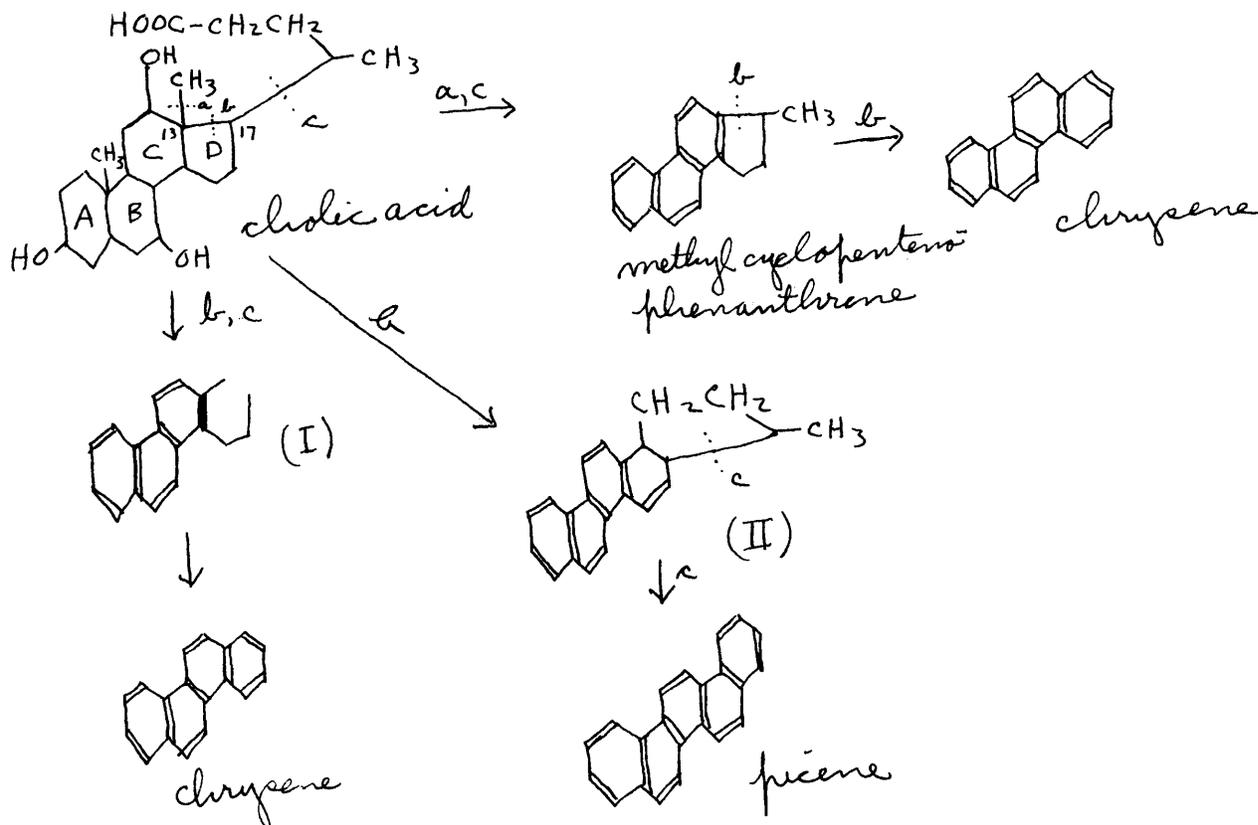
special case of the transformations which include the pinacolone and Wagner-Meerwein rearrangements. Support for this view is afforded by the observation of Diels et al, which we have confirmed, that $C_{18}H_{16}$, Diels hydrocarbon, is obtained not only by dehydrogenation of cholesterol, or better cholesteryl chloride, but also from the hydrocarbon, " $C_{19}H_{18}$ ", first observed by Mauthner and Suida⁴⁵ by pyrolysis of cholesteryl chloride. In this last process the intact side chain is eliminated, but not the methyl groups. The important point is that migration is not determined ipso facto by the dehydrogenation".

When alkyl groups, other than methyl, exist in the substances to be dehydrogenated, several fates of these groups are possible. One, they may remain intact, as in the conversion of abietic acid to retene³⁴. Methyl groups other than quaternary are seldom lost. In the example cited, an isopropyl group remains untouched during the dehydrogenation reaction. Two, the alkyl groups may be entirely eliminated, as in the conversion of cholesterol to methyl cyclopentenophenanthrene³⁵. In the case of such elimination, the side chain appears among the products of dehydrogenation as saturated and unsaturated aliphatic hydrocarbons⁴⁶. Third, the side chain may take part in the formation of a new condensed ring⁴⁷, or if the side chain is

only a methyl group, it may enter into a condensed ring already present in the molecule⁴⁷.

The third possible fate of side chain substituents takes place only when the dehydrogenation is carried out at temperatures above 400°C. Ring cleavage and extra ring formation result under the more rigorous experimental conditions. A typical illustration of this is shown in the formation of chrysene, C₁₈H₁₂, and picene, C₂₂H₁₄, from cholesterol and related substances.^{35,36,47,48}.

Ruzicka⁴⁷ has postulated mechanisms to explain the formation of both chryrene and picene. Starting with cholic acid, the steps leading to the formation of these hydrocarbons are as follows:

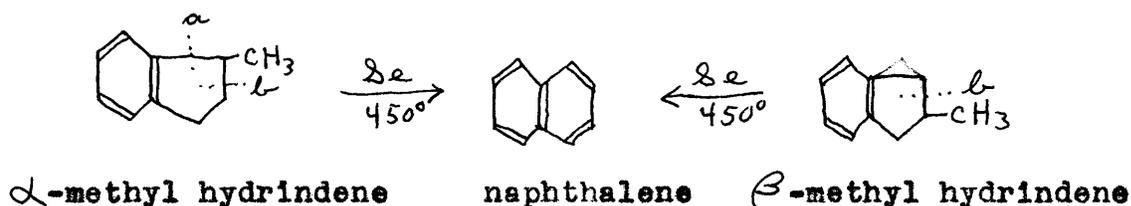


The first reaction, then, is thermal dehydration to cholatrienic acid, followed by decarboxylation of the acid to norcholatriene, after which the quaternary methyl group on C₁₀ is eliminated (these steps are not shown). Ring C is then dehydrogenated and the presence of the quaternary methyl group on C₁₃ can give rise to three possibilities. Cleavage of the side chain at c followed by migration of the methyl group to C₁₇ (formation of methyl cyclopentenophenanthrene⁴⁴) may take place. The five-membered ring (D) may then rupture at b, followed by recyclization to form a six-membered ring, resulting in chrysene.

A second possibility, splitting off of the side chain at c and rupture of ring D at b may take place simultaneously, giving rise to the intermediate hydrocarbon (I) which goes further to form, by condensation of the two alkyl groups, chrysene.

The third possibility is the rupture of ring D at b, without loss of the side chain. A condensation similar to that postulated immediately above in the second possibility will give rise to an intermediate hydrocarbon (II). Rupture at c followed by a recyclization similar to that postulated in the first possibility will result in the formation of picene.

In support of the formation of chrysene and picene by rupture of rings at b and c, respectively, followed by recyclization, is given the similar behavior of α - or β -methyl hydrindene on selenium dehydrogenation⁴⁹. Either of the latter two substances, on heating with selenium at 450°, give good yields of naphthalene thus:



The formation of naphthalene can be pictured as a rupture of the five-membered ring at a or b, followed by recyclization to form a six-membered ring.

With none of those substances mentioned above has there taken place during dehydrogenation with selenium any general rupture of the polycyclic carbon skeletons resulting in the formation of aromatic hydrocarbons of a lesser number of condensed rings. Such cleavages, however, have been widely observed in another class of polycyclic substances, namely the sapogenins and related substances. Ursolic acid is one of these latter substances. A list of these substances which have been subjected to selenium dehydrogenation is given below³⁹:

a) Triterpene alcohols

- 1. amyrrin $C_{30}H_{50}O$
- 2. betulin $C_{30}H_{50}O_2$

b) Saponins

- 3. ascigenin $C_{35}H_{58}O_7$
- 4. camelliasapogenin $C_{29}H_{44}O_5$
- 5. cyclamiretin $C_{35}H_{56}O_5$
- 6. glycyrrhetin $C_{45}H_{72}O_6$
- 7. caryocarsapogenin $C_{29}H_{44}O_4$
- 8. gypsogenin $C_{28}H_{44}O_4$
- 9. hederagenin. $C_{30}H_{48}O_4$
- 10. mimusopsapogenin. $C_{29}H_{44}O_5$
- 11. panaxsapogenin. $C_{30}H_{52}O_3 (C_{36}H_{58}O_4)$
- 12. quillajasapogenin. $C_{29}H_{46}O_5$

c) Compounds related to the triterpenes and saponins

- 13. oleanolic acid $C_{30}H_{48}O_3 (C_{31}H_{50}O_3)$
- 14. ursolic acid $C_{30}H_{48}O_3 (C_{31}H_{50}O_3)$
- 15. boswellinic acid. $C_{32}H_{52}O_4$
- 16. elemolic acid $C_{30}H_{48}O_3$
- 17. sumaresinolic acid $C_{30}H_{48}O_4 (C_{31}H_{50}O_4)$
- 18. siaresinolic acid $C_{30}H_{48}O_4 (C_{31}H_{50}O_4)$

Among other products obtained from selenium dehydrogenations, all of these substances have yielded 1,2,7-trimethylnaphthalene, sspotolene. A smaller number of these compounds, namely the pentacyclic triterpene compounds, have yielded in addition to sapotalene, also 2,7-dimethyl naphthalene, 1,2,5,6-tetramethyl naphthalene, 1,2,8-trimethyl, 7-hydroxy naphthalene, all of which have been definitely identified, and a pentacyclic aromatic hydrocarbon, $C_{24}H_{18}$ or $C_{25}H_{20}$, which is either a di- or a tri- methyl picene⁴².

Before seeking a significance of the dehydrogenation products obtained, consideration must be made of the number of condensed rings present in the substances investigated. Because of the inertia of the usual reagents on the carbon double bond, it was previously thought that these substances were saturated, in consequence of which most of those compounds mentioned above with about thirty carbon atoms were thought to contain six condensed rings. However, later evidence points to the probability that these substances are only pentacyclic, or perhaps in certain cases, tetracyclic.

Ruzicka and Huyser⁵⁰ have shown in a series of examples that tetranitromethane gives a distinct yellow color with compounds which contain a very reactive carbon double bond, while with saturated compounds, such is not the case. Since there seems to be no relationship between the intensity of the yellow color and the ease with which saturation of the double bond takes place, it is probably permissible to assume that a yellow color with tetranitromethane can also be given by such double bonds which up to now it has not been possible to saturate.

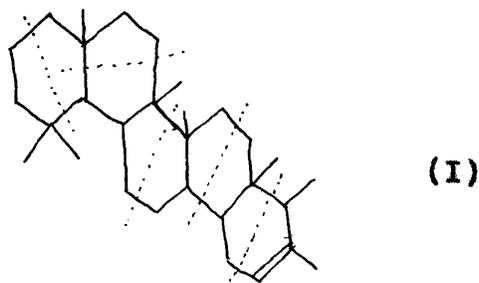
On this assumption, almost all of the natural substances enumerated above (with the exception of 4,11 and 12) were mixed in acetic acid solution with tetranitromethane,

whereby there appeared in each case a distinct yellow color. All of these substances contain, therefore, at least one less ring than one must assume on the basis of their otherwise saturated character; therefore, these substances are pentacyclic or tetracyclic compounds by the presence of only a double bond.

While catalytic dehydrogenation of several of these substances in warm acetic acid solution in the presence of the platinum oxide ^{catalyst} of Adams could not be effected with substances 3,5,9,10,13 and 14, substances 8 and 16 did give a hydrogenated product³⁹. Further support for the presence of a carbon double bond in some of these substances is given by Winterstein²¹ who obtained from substances 9,13,17 and 18 saturated bromolactones which no longer gave a yellow color with tetranitromethane. Further, Winterstein²¹ has found that the diacetyl derivative of 9 and the methyl ester of 13, when treated with perbenzoic acid, could take up approximately one atom of oxygen.

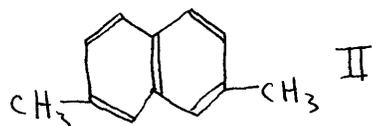
Assuming for ursolic acid the formula $C_{30}H_{48}O_3$ (rather than $C_{31}H_{50}O_3$), the parent hydrocarbon would be $C_{30}H_{50}$, which hydrocarbon may be a triterpene. Since there is present at least one double bond, the hydrocarbon is pentacyclic. Those terpenes whose structures are known possess carbon skeletons which may be resolved into isoprene units. It is plausible, therefore, to assume that the

carbon skeleton of the triterpene compounds may likewise be resolved into isoprene units. For ursolic acid and the other thirty carbon atom substances listed above, Ruzicka⁴⁵ postulates the following carbon skeleton:

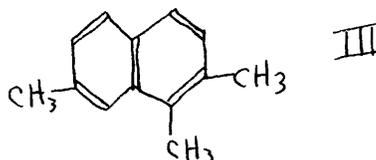


The dotted lines indicate the resolution into isoprene units.

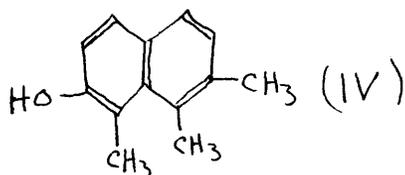
Below are given the compounds previously mentioned which have been obtained as products of dehydrogenation of the triterpene compounds and whose structures have been definitely established by synthesis⁴⁵:



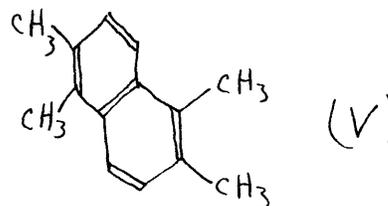
2,7-dimethyl naphthalene



1,2,7-trimethylnaphthalene



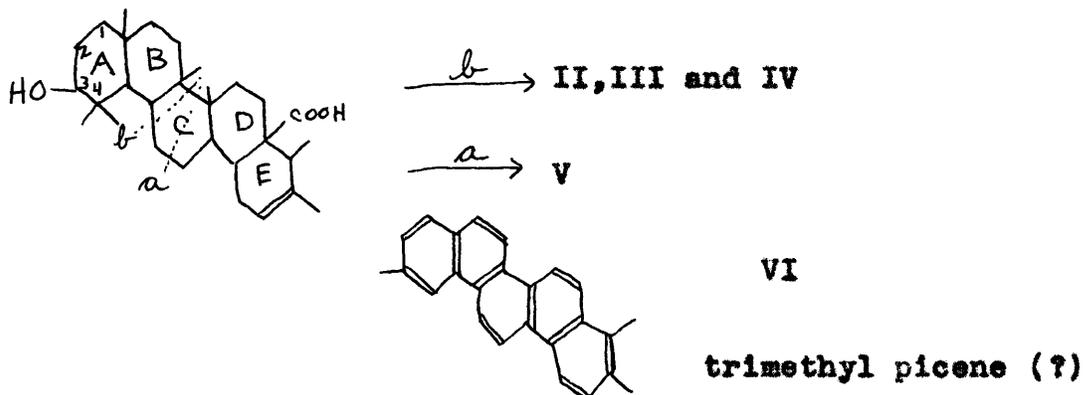
1,2,8-trimethyl-7-hydroxy naphthalene



1,2,5,6-tetramethylnaphthalene

The hydroxyl group of the triterpenes, on the basis of certain degradation reactions of hederagenin⁵⁵, must be

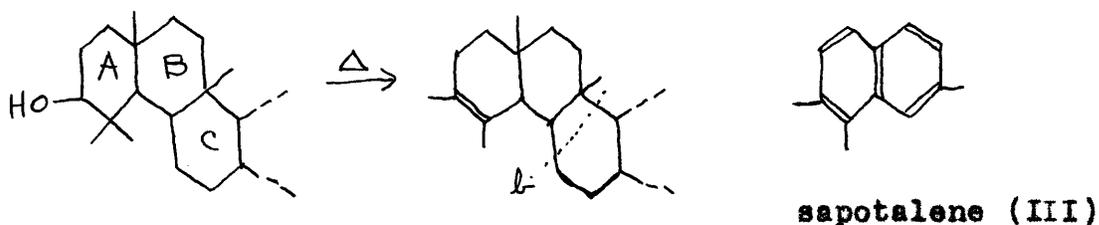
assumed to be adjacent to the carbon atom holding two methyl groups. Most probably this hydroxyl group appears in the dehydrogenation products in the trimethyl naphthol (IV).



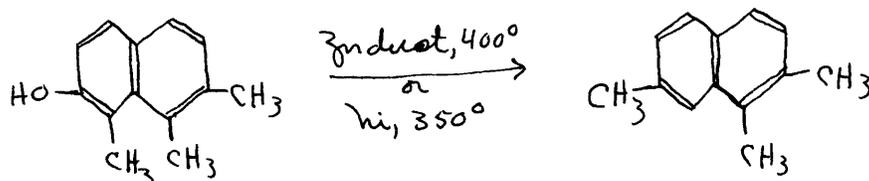
Thus, cleavage at a would result in the formation of 1,2,8-trimethyl-7-hydroxy naphthalene (IV) (rings A and B), and also 1,2,5,6-tetramethyl naphthalene (V) (rings D and E). The formation of sapotalene and 1,7-dimethyl naphthalene come from cleavage at b, but as the result of a wandering of one of the methyl groups in ring A from C₄ to C₃.

This rearrangement of one of the methyl groups, in the formation of sapotalene, is a pinacolone rearrangement⁴². A similar rearrangement has been observed in the formation of γ -methyl cyclopentenophenanthrene from cholic acid during selenium dehydrogenation⁴⁴.

Ruzicka⁴² postulates the formation of sapotalene in the following manner:

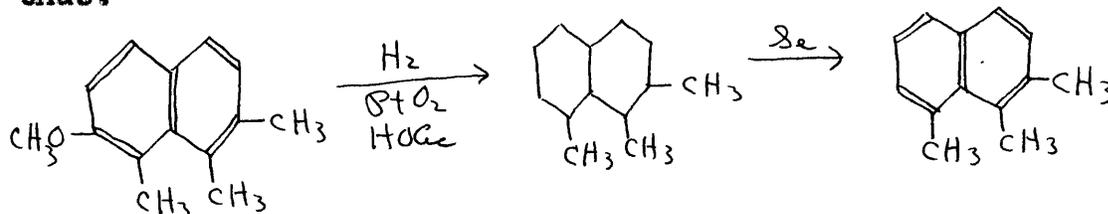


Further support of this hypothesis is found in that the trimethyl naphthol obtained as a dehydrogenation product is converted into sapotalene on treatment with zinc dust at 400° or on catalytic reduction in the presence of nickel at 300°, thus:



The possibility that the trimethyl naphthol from selenium dehydrogenation is a hydroxy sapotalene has been definitely excluded by the synthesis of the five possible hydroxy sapotalenes and a comparison of their methoxy derivatives with the methoxy derivative of the naphthol from selenium dehydrogenation. In addition, 1,2,8-trimethyl-7 hydroxy naphthalene has been synthesized and found to be identical with the naphthol obtained from selenium dehydrogenation. Furthermore, the methoxy derivative of the latter compound was completely hydrogenated, using a platinum oxide catalyst,

to a trimethyl dodecahydronaphthalene, which on dehydrogenation by selenium yielded 1,2,8-trimethyl naphthalene⁴², thus:



Ruzicka⁴² further postulates the formation of 1,7-dimethyl naphthalene in the same manner, although the dimethyl naphthol (1,8-dimethyl-7-hydroxy naphthalene) has never been isolated.

The so-called "trimethyl picene", C₂₅H₂₀(?) would be formed by conversion of the hydroaromatic triterpene compound to a pentacyclic aromatic compound, with simultaneous decarboxylation, dehydration and loss of quarternary methyl groups. As yet, it has not been possible to ascertain whether or not the picene hydrocarbon obtained by dehydrogenation of the triterpene compounds is in reality a trimethyl- or dimethyl-picene. Ruzicka⁵¹ has synthesized the trimethyl picene which should be expected on dehydrogenation, namely 3,9,10-trimethyl picene (VI). However, the synthetic preparation is not identical with the dehydrogenation product.

2. EXPERIMENTAL PART

A. Purification of Ursolic Acid

The ursolic acid used in this work was obtained from the ether extract of cranberry pomace, furnished by C. E. Sando, of the Bureau of Chemistry and Soils, United States Department of Agriculture, Washington, D. C. The writer wishes to express his indebtedness to Dr. Sando for his kindness in furnishing a liberal amount of this crude ursolic acid.

After trying several methods of purification, among which may be mentioned that of Sando⁶, as well as modifications of the latter, the following method (devised by Dr. N. L. Drake and the writer) was found to be most satisfactory.

200 g of crude ursolic acid (ether extract of the natural source) were dissolved in a hot solution of 600 ml of methyl alcohol, 300 ml of water and 50 g of potassium hydroxide. As much more methanol, water, or potassium hydroxide as might be deemed necessary was added to effect complete solution of the ursolic acid as potassium ursolate. The insoluble material which was brown and distinctly different in appearance from the original crude material was skimmed off and the solution was filtered, while still hot,

through a Buchner funnel. The hot, filtered solution was treated with decolorizing charcoal to remove a green impurity which was otherwise quite persistent. It was found that three treatments with 40 g portions of decolorizing charcoal were sufficient for this purpose. After removal of the colored impurity, the methyl alcohol-water solution of potassium ursolate was concentrated on the steam bath to remove a portion of the methyl alcohol, without resulting in any separation of solid material. 1500 ml of hot water were added to the concentrated solution, and the potassium ursolate was salted out by the addition to the solution of 50% potassium hydroxide. For this purpose about 50 g of potassium hydroxide in 50 ml of water was needed.

The precipitated potassium ursolate was collected on a Buchner funnel, after which it was dissolved in about 500 to 600 ml of hot methyl alcohol. The latter solution was filtered while still hot, and from it the free ursolic acid was liberated by the addition of about 40 ml of 6 N hydrochloric acid. Sufficient hydrochloric acid was used to leave the mother liquor acid to congo paper. The precipitated ursolic acid was transferred to a Buchner funnel. It was then transferred to a beaker and stirred with about a liter of nearly boiling water to which had been added a little 12 N hydrochloric acid. After transferring the ursolic acid to a

Buchner funnel, it was washed with an additional liter of hot water. The washed ursolic acid was then recrystallized once from ethyl alcohol, about three liters of which were needed for this purpose. The melting of the ursolic acid after the above treatments was 278-280°C (corr.). The final product was a white, crystal line substance. The free acid was white only after its liberation from the methyl alcohol solution of its potassium salt.

By the above procedure, from 2020 g of crude material there was obtained 466 g of ursolic acid melting at 278-280°C. This represents a 23% ursolic acid content of the crude material started with.

It is to be noted that unless the ursolic acid is carefully washed free of potassium chloride, it will not separate from ethyl alcohol in a crystalline form.

A portion of the ursolic acid obtained above was recrystallized a few more times, until a constant melting point of 283-284°C (corr.) was attained. This ursolic acid was then dried in an evacuated drying pistol at 175° for about three and a half hours. A redetermination on the melting point showed no change.

Analysis. Calcd. for $C_{30}H_{48}O_3$: C, 78.88; H, 10.60.

Calcd. for $C_{31}H_{50}O_3$: C, 79.08; H, 10.71.

Found: C, 79.05, 78.86; H, 10.69, 10.53.

B. Dehydrogenation Experiments

Three batches of ursolic acid were subjected to selenium dehydrogenation. The first two batches were 50 g each, while the third batch was 200 g. In each case the same procedure was followed.

The ursolic acid was mixed with one-fourth of its weight of grey, powdered selenium. The mixture was placed in a round bottom flask (200 ml for the first two batches and 500 ml for the third batch) to which was affixed an air-cooled condenser about a meter long. The latter had a side arm connection about 60 cm above the flask, through which addition of selenium could be made. The condenser was bent at a right angle about 90 cm above the flask. On the far extremity of the condenser was affixed another round bottom flask (200 ml) having a short side-arm. To the side arm of the second flask was attached a tube containing bleaching powder. This tube served as an absorber of the hydrogen selenide evolved during the course of the dehydrogenation. The reaction flask was placed in a bath of Wood's metal. The whole apparatus was set up in a hood, to insure complete removal of hydrogen selenide from the laboratory. The metal bath was maintained at a temperature of 320° to 340° throughout the course of the dehydrogenation. Selenium was introduced into the reaction flask in 5 to 10 gram portions at intervals of about thirty to sixty minutes until the total amount added

was about three times the weight of the ursolic acid. The dehydrogenation reactions took about 150 hours. Each dehydrogenation was continued until there was no further evolution of hydrogen selenide.

After the completion of a dehydrogenation, the reaction flask was removed from the metal bath, allowed to cool, and cut off from the air-cooled condenser. The flask was then cracked and its contents, a black tar, were removed and pulverized. The latter was exhaustively extracted with diethyl ether in a Soxhlet apparatus, followed by a second exhaustive extraction of the residue with benzene in a similar manner.

The extraction solvents were removed by careful evaporation on the steam bath. The residues so obtained were fractionated in vacuo. The undistilled residues from the latter operation were sublimed in vacuo.

As there was no essential difference in the manner of working with the products of dehydrogenation of the three batches, only the results from the third batch will be described. By so doing, no significant results will be omitted. Also, the products of the second and third dehydrogenations were combined and worked up together.

From 250 g of ursolic acid there was obtained after dehydrogenation, 59.5 g of material extracted by diethyl ether and 13.7 g of material extracted by benzene.

The material extracted by ether was distilled from a 200 ml flask with a sausage side-arm attached. The following fractions were obtained:

Fraction	#1	#2	#3	#4	#5	#6	#7
Temp. of bath	115°- 150°	150°- 175°	175- 200°	200- 250°	265- 285°	285- 310°	350- 365°
Pressure	12 mm	11 mm	12 mm	12 mm.	6-8 mm	2 mm	3 mm
Amount	2.5 g	3.6 g	21.1 g	8.9 g	8.0 g	7.9 g	6.1 g
Physical state	l	l	l	l	l & s	s	s

l, liquid; s, solid.

The total amount of material distilled was 58.1 g. The flask was placed in a bath of Wood's metal. The temperatures noted were the temperatures of the bath. The undistilled material was removed from the flask and combined with the material previously extracted by benzene. These combined materials were later sublimed in vacuo.

Fractions 1,2,3 and 4 were refractionated several times, using for this purpose a small Claisen flask. The results of these fractionations are summarized below:

Fraction	#8	#9	#10	#11	#12	#13	#14	#15	#16
Temperature	60- 85°	85- 110°	below 110°	110 - 120°	120- 130°	130- 140°	140- 145°	150- 153°	above 153°
-n ²⁵	1.4978	1.5110	1.5228	1.5416	1.5634	-	1.5997	1.5937	-
Amount (in g)	1.2	1.5	1.2	5.1	3.2	11.7	4.8	2.3	0.9

pressure: 11-12 mm Hg

The temperature noted is the temperature of the distilling vapors. From 36.1 g (total weight of Fractions 1, 2, 3 and 4) there was obtained in the final fractions a total amount of 31.9 g, the difference being material lost mechanically.

The largest fraction, i.e., Fraction #13, was again redistilled, using this time a fractionating column. The results of this fractionation are given below: (The column used contained Wilson rings.)⁵⁶

Fraction	#17	#18	#19	#20	#21
n ²⁵	1.5631	1.5835	1.6001	1.6038	1.5997
amount (in g)	0.8	-	2.1	2.1	1.8

pressure: 1 - 2 mm Hg

Likewise, Fractions 8, 9, 10 and 11 were refractionated through the fractionating still mentioned immediately above.

The results of this fraction are given below:

Fraction	#22	#23	#24	#25	#26	#27	#28
n ²⁵	1.5044	1.5040	1.5224	-	1.5458	1.5384	1.5443
amount (in g)	1.0	1.2	1.3	1.1	1.3	1.1	0.8

pressure: 1 - 2 mm Hg

A complete summarization of all the fractionations is given below:

Fraction	#22	#23	#24	#25	#26	#27	#28
Temperature	-	-	-	-	-	-	-
Pressure (in mm Hg)	1-2	1-2	1-2	1-2	1-2	1-2	1-2
n ²⁵	1.5044	1.5040	1.5224	-	1.5458	1.5384	1.5443
Amount (in g)	1.0	0.2	1.3	1.1	1.3	1.1	0.8

Fraction	#12	#17	#18	#19	#20	#21	#14
Temperature	120- 130°	-	-	-	-	-	140- 145°
Pressure (in mm Hg)	11-12	1-2	1-2	1-2	1-2	1-2	11-12
n ²⁵	1.5643	1.5631	1.5835	1.6001	1.6038	1.5997	1.5997
Amount (in g)	3.2	0.8	-	2.1	2.1	1.8	4.8

Fraction	#15	#16	#5	#6	#7
Temperature	150- 153°	above 153°	265- 285°(b)	285- 310°(b)	350- 365°(b)
Pressure (in mm Hg)	11-12	11-12	6-8	2	3
n _D ²⁵	1.5937	-	-	-	-
amount (in g)	2.3	0.9	3.0	7.9	6.1

b, bath temperature

Fractions #22 and 23

Fractions #22 and 23 were mobile liquids. They did not form picrates. For this reason, and because of the small amount of material, no further attempt at purification or identification was made.

Fractions #24,25 and 26

Fraction #25 was solid at room temperature. During the fractionation of Fractions #8,9,10 and 11, all of which were liquid at room temperature, there appeared a definitely solid fraction. As obtained in this manner, the solid melted around 37 to 40°C. After several re-crystallizations from methyl alcohol, ^{the} melting point was raised to 96.5°C. The solid was recrystallized until it

showed a constant melting point ($96.5^{\circ}\text{C}.$ (corr.)). A portion of this white, crystalline solid was converted to a picrate. The solid was mixed with the theoretical amount of picric acid and the resulting picrate recrystallized several times from methyl alcohol, until a constant melting point of $135-136^{\circ}\text{C}$ (corr.) was obtained. The picrate was light yellow in color.

A second portion of the white, crystalline solid was mixed with a theoretical amount of styphnic acid. The resulting styphnate was recrystallized until a constant melting point of $159-160^{\circ}\text{C}$ (corr.) was obtained. The styphnate was yellow-orange in color.

From Fractions #24 and 26 there was obtained by treatment of these liquid fractions with hot methyl alcohol more solid which was recrystallized to the constant melting point of 96.5°C . Mixed melting point determinations made on these solids mixed with the solid obtained from Fraction #25 showed no depression of the melting point or broadening of the melting range.

The liquid portions of Fractions #24 and #26 were converted to picrates by admixture with picric acid. After many recrystallizations from methyl alcohol, there was obtained only a small amount of pure picrate, the purity being indicated by constancy of the melting-point, which

proved to be identical with the picrate obtained from the solid described above. No other pure substances could be obtained from these three fractions.

On the basis of the melting points of the solid and its derivatives, the picrate and the styphnate, and analyses of these compounds, the solid has been identified as 2,7-dimethyl naphthalene,

substance	m.p. observed	m.p. reported in the literature ³⁹
2,7-dimethyl naphthalene	96.5°	97°
picrate	135-136°	136°
styphnate	159-160°	159

Analysis. Calcd. for $C_{12}H_{12}$: C, 92.25; H, 7.75.

Found: C, 91.93; H, 7.70.

Calcd. for $C_{18}H_{15}O_7N_3$: C, 56.09; H, 3.93.

Found: C, 56.25; H, 3.95.

Calcd. for $C_{18}H_{15}O_8N_3$: C, 53.85; H, 3.77.

Found: C, 53.84; H, 3.89.

Fractions #27, #28, #12 and #17

From Fractions #27, 28, 12 and 17 no pure compounds could be isolated or identified, although all fractions would

form picrates. Attempts were made to isolate from Fractions #27 and 28 more of the solid hydrocarbon, dimethyl naphthalene. To this end, the liquid fractions were treated with hot methyl alcohol, the same method which had been used successfully on Fractions #24 and 26. However, no solid hydrocarbon was obtained.

A portion of Fraction #27 was converted to a picrate. After eight recrystallizations from methyl alcohol, the melting point was still rising. By this time there was insufficient material for further work.

A second portion of Fraction #27 was converted to a styphnate. Repeated recrystallizations from methyl alcohol did not bring the substance to a constant melting point while there was still sufficient material with which to work.

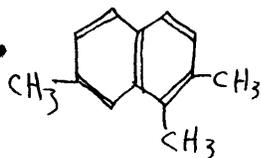
Fractions #18,19,20,21, 14 and 15

Because of the close agreement of the refractive indices of Fractions 18,19,20,21, 14 and 15 (with the possible exception of Fraction 18), all of these fractions were assumed to be principally one pure substance. A portion of Fraction #20 was converted to a picrate, which on a few recrystallizations from methyl alcohol gave a substance of constant melting point, $128-129^{\circ}\text{C}(\text{corr.})$. A picrate of the same melting point was obtained from the liquid dehydrogenation

product obtained from the dehydrogenation of the first fifty gram batch of ursolic acid. A mixed melting point of these two picrates showed no depression of the melting point and no broadening of the melting point range. From this it was concluded that both picrates were identical.

The picrate from the liquid dehydrogenation product of the first batch of ursolic acid was treated with dilute aqueous ammonia to regenerate the hydrocarbon. The latter was then converted to the styphnate in the usual manner. Four recrystallizations from methyl alcohol were sufficient to yield a substance of constant melting point, 157-157.5°C (corr.). The picrate was orange and the styphnate was yellow orange.

On the basis of the melting points of the picrate and styphnate derivatives, and analyses of these derivatives, the liquid hydrocarbon has been identified as 1,2,7-trimethylnaphthalene, otherwise known as sapotalene



substance	m.p. observed	m.p. reported in the literature ³⁹
sapotalene picrate	128-129°	129°
sapotalene styphnate	157-157.5°	157°

Analysis. Calcd. for $C_{19}H_{17}O_7N_3$: C, 57.13; H, 4.27.

Found: C, 57.42, 57.24; H, 4.53, 4.35.

Calcd. for $C_{19}H_{17}O_8N_3$: C, 54.92; H, 4.11.

Found: C, 55.19, 55.13; H, 4.19, 4.22.

Fraction #16

No work was done on Fraction #16.

Fractions 5,6 and 7

Fractions 5,6 and 7 were all solid after the first vacuum distillation of the dehydrogenation products extracted by diethyl ether. Each fraction was treated in a similar manner.

Fraction #7 contained 6.1 g of a yellow solid. It was dissolved in about 700 ml of hot benzene. Somewhat less than one gram of molecular silver was added to the solution to remove any free selenium present. One gram of decolorizing charcoal was added. The hot solution was filtered through a fluted filter and then allowed to cool slowly to room temperature, whereupon there separated in plates a white crystalline solid. Three recrystallizations from benzene were sufficient to raise the melting point of this substance to the constant melting point of $304^{\circ}C$ (corr.). The final yield of pure substance was one gram.

A similar treatment of Fractions 5 and 6 yielded small amounts of the same substance described above, as ascertained by mixed melting points.

On the basis of melting point, molecular weight determination and analyses, the hydrocarbon here described is identical with a hydrocarbon obtained by Ruzicka³⁹ from the dehydrogenation products of other triterpene compounds. Ruzicka assigns to his hydrocarbon the formula $C_{25}H_{20}$, without, however, excluding the possibility of the formula being $C_{24}H_{18}$. He describes the hydrocarbon as a di- or trimethyl picene.

The melting point of the picene hydrocarbon obtained from ursolic acid was found to be $304^{\circ}C$ (corr.). Ruzicka reports melting points of his picene hydrocarbon ranging from 299° to $307^{\circ}C$ ³⁹, without considering the picene hydrocarbons derived from different triterpene compounds to differ other than, perhaps, in degree of purity.

The following analyses were found for the picene hydrocarbon obtained from ursolic acid:

Analysis. Calcd. for $C_{25}H_{20}$: C, 93.70; H, 6.30.

Calcd. for $C_{24}H_{18}$: C, 94.09; H, 5.91.

Found: C, 94.07, 93.80; H, 5.92, 6.03.

The molecular weight of the picene hydrocarbon was determined by the Rast camphor method. The molar depression

freezing point of
of the camphor used was found by W. T. Haskins⁵² to be:

$$K_f = \cancel{3.16}^{\circ}. 31.6^{\circ}$$

Molecular weight determinations:

0.544 mg of substance dissolved in 14.705 mg of camphor gave a depression of the melting point of camphor of 3.90° (average of three readings.)

0.156 mg of substance dissolved in 4.753 mg of camphor gave a depression of the melting point of camphor of 3.50° (average of three readings).

$C_{25}H_{20}$, molecular weight: 320.2

$C_{24}H_{18}$, molecular weight: 306.1

found: 300 and 296

The analytical data found favor the formula $C_{24}H_{18}$, a dimethyl picene, over the formula $C_{25}H_{20}$, a trimethyl picene. However, one can not definitely decide between the two formulae on the basis of such data.

There is described for picene⁵³ a color test. On solution in concentrated H_2SO_4 , a green color is produced. The picene hydrocarbon obtained from ursolic acid gave a green color when dissolved in concentrated H_2SO_4 .

Further, it is possible to oxidize picene to a quinone⁵³. A successful attempt was made to convert the picene hydrocarbon from ursolic acid to a quinone. The latter derivative was then further converted to a quinoxaline

derivative. However, for want of time, neither derivatives were obtained as pure compounds and consequently were not definitely characterized.

The quinone was prepared in the following manner. 0.50 g of the picene hydrocarbon was dissolved in 800 ml of glacial acetic acid. The latter was freshly distilled from chromic anhydride. To this solution, while refluxing, was added slowly 0.31 g of chromic anhydride dissolved in glacial acetic acid. The reaction mixture was refluxed for one hour. The resultant solution was then concentrated by distilling off acetic acid, until the volume of the solution was reduced to about 150 ml. The solution was cooled and diluted with several volumes of water, whereupon there separated the quinone. The latter was orange-red in color. The yield of crude quinone obtained was 0.54 g, as compared with the theoretical yield of 0.56 g.

The quinone was converted directly to the quinoline derivative in the following manner. The quinone was dissolved in 200 ml of boiling glacial acetic acid. To this solution there was added 0.25 g of o-phenylenediamine (theoretical amount, 0.17 g). The reaction mixture was refluxed about an hour and then concentrated by distilling off most of the acetic acid. The solution was cooled and poured into several volumes of water. The aqueous reaction

Tested several fractions for solubility in abs.
- 58 - fractions above separated
(tested)

mixture was extracted with several portions of diethyl ether (1500 ml in all). The ether solution was washed with water and dilute hydrochloric acid, after which it was dried over anhydrous calcium chloride. The ether was removed by careful evaporation, leaving the quinoxaline derivative. The yield of the latter was 0.41 g, as compared with the theoretical yield of 0.65 g. The quinoxaline was yellow-brown in color.

Several recrystallizations of the quinoxaline from a chloroform-absolute ethyl alcohol solvent did not yield a pure substance. However, the formation of such a derivative shows that the quinone was a 1,2 diketone, and not a 1,4 diketone. A picene hydrocarbon would give a 1,2-diketone quinone and not a 1,4 diketone quinone.

No other pure substances could be isolated from Fractions 5,6 and 7. While isolating the above mentioned picene hydrocarbon, which proved to be only a small portion of these three fractions, there was obtained from the benzene solution filtrate an appreciable amount of a yellow, oily material. An unsuccessful attempt was made to convert this oily material to a picrate. After removal of the picric acid, by washing a benzene solution of the reaction mixture with aqueous ammonia, the recovered oily material was transferred to a molecular still. By operating at 200°C and a pressure of 0.1 mm Hg, about 2 ml of a liquid substance was

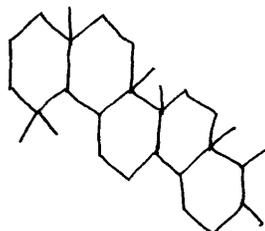
distilled over. This liquid was converted to a picrate which was brown in color. The picrate was recrystallized from methyl alcohol to which was added a few drops of a benzene solution saturated with picric acid at about 5°C. However, no pure substance could be isolated.

The solid residue from the molecular still was transferred to a sublimation apparatus⁵⁴. By operating the latter at 200°C and a pressure of about 0.1 mm Hg, there was obtained a yellow, sticky sublimate. Recrystallization of the latter from ethyl alcohol a few times and then from benzene yielded only more of the picene hydrocarbon described above.

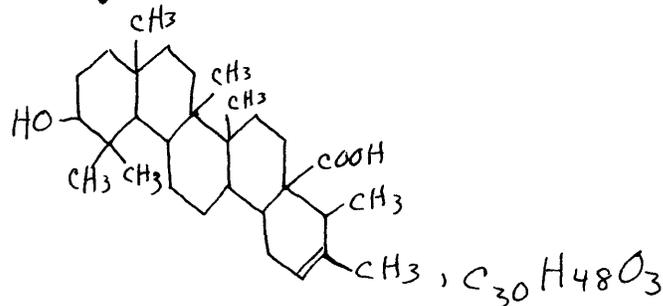
The material extracted from the original dehydrogenation reaction mass by benzene was combined with the still residues obtained from the preliminary vacuum distillation of the material extracted by ether from the original dehydrogenation reaction mass. The combined materials were transferred to the sublimation apparatus referred to above. Following the procedure described in the preceding paragraph, the only pure substance which was isolated was more of the same picene hydrocarbon.

3. DISCUSSION OF RESULTS

The identification of 2,7-dimethyl naphthalene and 1,2,7-trimethyl naphthalene and the partial identification of a picene hydrocarbon, a di- or trimethyl picene ($C_{24}H_{18}$ or $C_{25}H_{20}$) are evidence that ursolic acid belongs to the class of triterpene compounds described by Ruzicka^{39,42}, to which he tentatively ascribe the formula:



If the latter formula for the triterpene compounds is correct, then it would follow that the formula for ursolic acid may be:



The evidence found in this research, taken in conjunction with that reported by Ruzicka^{39,42}, is not to be considered as proof that the above formula does represent the structure of ursolic acid.

No attempt has been made to reconcile the findings of Kuwada and Matsukawa^{30,31,32} as to the partial structure of ursolic acid with the postulations of Kuzicka⁴² as to the structure of the triterpene compounds.

4. SUMMARY

1. A new method of isolating pure ursolic acid from the crude ether extract of its natural sources has been devised.

2. Three compounds have isolated from the products resulting from the selenium dehydrogenation of ursolic acid. 2,7-dimethyl naphthalene ^{been} has/identified on the basis of the melting points of the hydrocarbon itself, the picrate derivative and the styphnate derivatives. The hydrocarbon and the two derivatives have been identified further by carbon and hydrogen determinations.

1,2,7-trimethyl naphthalene (sapotalene) has been identified on the basis of the melting points of the picrate derivative and the styphnate derivative. These two derivatives have been identified further by carbon and hydrogen determinations.

A picene hydrocarbon has been shown, on the basis of melting point, molecular weight determinations and carbon and hydrogen determinations, to be identical with, or closely related to, the picene hydrocarbon obtained by Ruzicka³⁹ from related triterpene compounds.

The molecular weight determinations and the elementary quantitative analyses correspond more closely to a dimethyl picene than to a trimethyl picene. A quinone and quinoxaline derivative of the picene hydrocarbon have been prepared, but not characterized.

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PART II

1. INTRODUCTION

The preparation of methoxy acetaldehyde, $\text{CH}_3\text{OCH}_2\text{CHO}$, was originally intended as one of the several intermediate steps in the synthesis of 4,4 dimethyl hexanone-2, $\text{CH}_3\text{CH}_2\overset{\text{CH}_3}{\underset{\text{CH}_3}{\text{C}}} - \text{CH}_2\text{COCH}_3$. In their studies of decenes, Kline and³ Rose¹ determined the structures of the decenes by the ozonide method. One of the ketones thus obtained is thought to be 4,4 dimethyl hexanone-2. As the latter has not been described in the literature, the correctness of the assumption can be decided only by synthesizing the ketone, which was the ultimate goal of this research.

Various theoretical methods are at hand for the complete synthesis of 4,4 dimethyl hexanone-2. Of the methods, the two which seemed most feasible have received investigation in their first steps in this laboratory. One of these investigations has been described by Jenkins²; the other is described below.

Previous Work

No mention of either methoxy acetaldehyde or its preparation has been made in the literature. The most logical attempt to prepare a new compound is that one which

is based on a workable method already in use for the preparation of compounds of the general class to which the one in question belongs. For aldehydes, the first consideration is catalytic dehydrogenation of the corresponding primary alcohols, and the experience of others recommends the method of Bouveault³, who used a copper catalyst. Another method described by Adkins, Komms, Struss and Dasler⁴ has recently appeared in the literature. It is a modification of Bouveault's method and for some alcohols much better. The catalyst is copper-chromium oxide.

Chemical oxidation of primary alcohols to the corresponding aldehydes is more theoretical than practical. The chief difficulty is that the aldehyde is so much more easily oxidized than the alcohol. The method is applicable in those cases in which the aldehyde formed is highly volatile as in the preparation of acetaldehyde from ethyl alcohol, according to the method of Gatterman⁵. A later improvement on this method by Adams⁶ in which the yield was improved from 22 to 43% made it seem worthwhile to try to extend the method to the preparation of methoxy acetaldehyde.

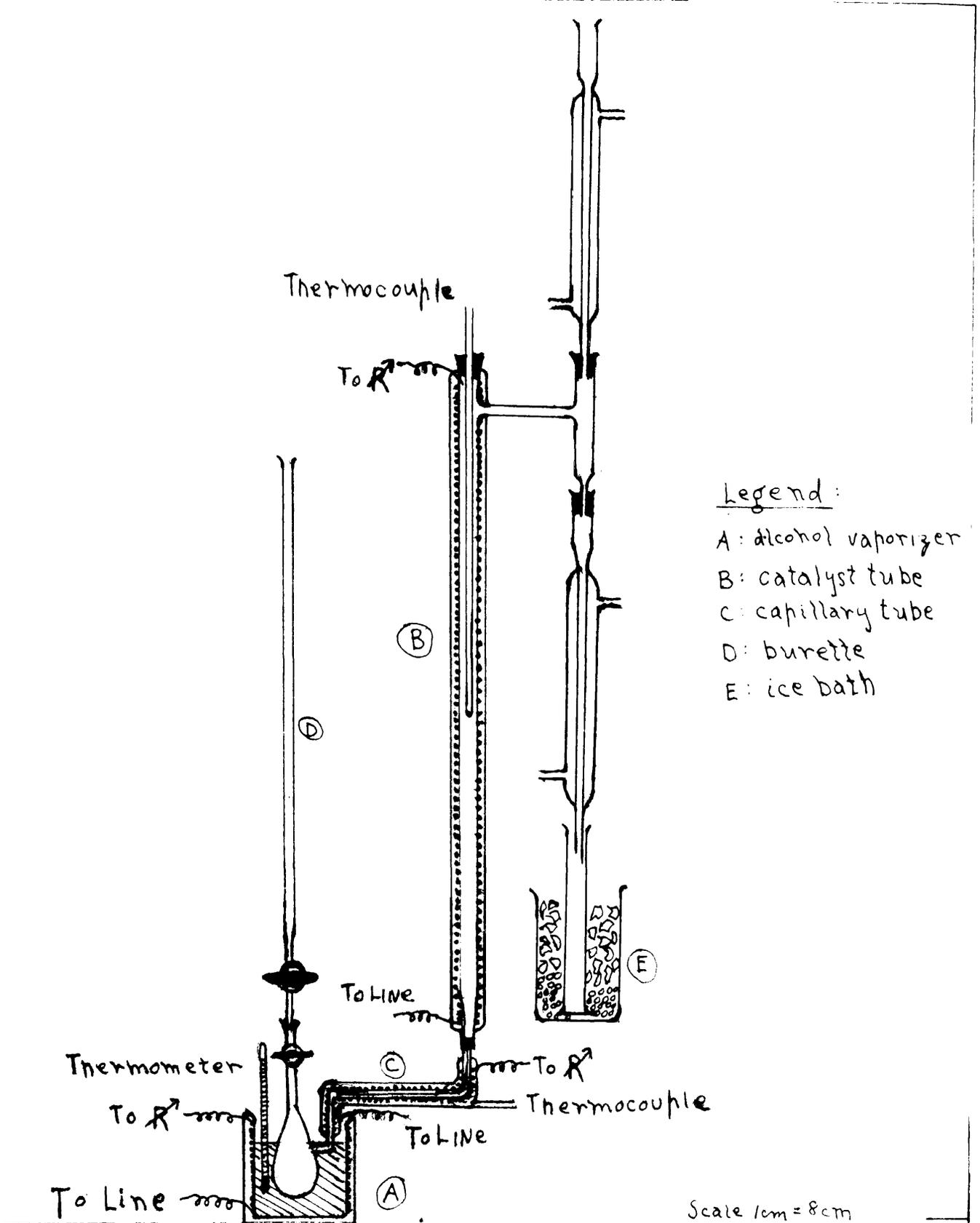
Regardless of whether dehydrogenation or oxidation is made, the alcohol needed is ethylene glycol monomethyl ether.

This alcohol is an inexpensive commercial product sold under the trade name of methyl cellosolve. Other methods of preparing aldehydes are generally more complex and less satisfactory than the two mentioned here. In addition, they would require the use of compounds not as readily available as methyl cellosolve.

Methods and Apparatus Used

Several attempts were made to prepare methoxy acetaldehyde by catalytic dehydrogenation of methyl cellosolve. The different catalysts used were reduced copper, zinc-chromium oxide, and copper-chromium oxide. The preparation of these catalysts is described below. The apparatus used in these experiments varied from that of Bouveault³ first used, to a final modification adopted in this laboratory. An illustration of the final apparatus is to be found below.

In Bouveault's apparatus, the rate of passage of the vapors of the alcohol over the catalyst is dependent largely on the boiling of the alcohol in the flask. It is consequently difficult to maintain a steady rate of flow as boiling is affected by the slightest drafts in the laboratory or the smallest variations in the gas pressure feeding the burner. It is not sufficient to shield the boiling flask from the drafts of the laboratory. It was



Legend:

- A: alcohol vaporizer
- B: catalyst tube
- C: capillary tube
- D: burette
- E: ice bath

Scale 1cm = 8cm

found necessary to choose some other method of introducing the alcohol vapors to the catalyst column, a method more capable of being controlled.

The method adopted was one already in use in this laboratory⁷. The alcohol was placed in a small round bottom flask, in this work a 125 cc flask. It was fitted with a vertical tube carrying a stop-cock through which the alcohol was admitted to the flask. The flask bore a side arm sealed directly to a capillary tube which led into the catalyst column. The capillary was heated electrically and well lagged with asbestos. During passage through this tube, complete volatilization was insured. The flask was placed in a Crisco bath which was heated electrically. By means of a rheostat the temperature of the bath was easily controlled. The alcohol was boiled from the flask into the capillary and thence into the catalyst column. The rate of flow was determined by the temperature of the Crisco bath.

The rate of flow throughout a run was not quite constant, being higher at the beginning of the run. However, it was possible to reproduce rates on successive runs and little attention was required to do so.

The original apparatus of Bouveault³ was modified in a second respect. The fractionating column and the return tube from the lower end of the fractionating column

to the boiling flask for the return of the unreacted alcohol were taken out of the apparatus. It was found that such a fractionating column as could be incorporated conveniently into the set-up was not capable of making a satisfactory separation of the alcohol and aldehyde. With this modification the alcohol made only a single passage over the catalyst.

The products of the runs were fractionated as a separate operation. The column used greatly exceeds the ordinary laboratory fractionating columns in efficiency. It is described by Jenkins². The apparatus is a decided modification of Podbielniak's column⁸. Very little work was done in determining its actual efficiency, but the following example will give an idea of its efficacy. A mixture of 16 cc of benzene and 17 cc of toluene was separated by a single fractionation into 15.5 cc of benzene and 11.8 cc of toluene, each boiling over a one degree range. There was an intermediate fraction of 1.4 cc, with a hold-up of 3.2 cc and a loss of 1.1 cc. The distillation required two hours. Such sharp separations were not obtained with the dehydrogenation products; these were more complex mixtures than the two-component mixture, benzene-toluene.

One attempt was made to prepare methoxy acetaldehyde from methyl cellosolve by chemical oxidation. The

method of Adams⁶ referred to above was used, such modifications as necessary to the particular case being made. 172 g of concentrated H_2SO_4 and 312 cc of water were placed in a one liter three necked flask fitted with a condenser set for distillation, a dropping funnel, and an efficient mechanical stirrer provided with a mercury seal. The solution was heated nearly to its boiling point. Through the dropping funnel was added with stirring a solution of 100 g of methyl cellosolve, 131 g of $Na_2Cr_2O_7 \cdot 2H_2O$ and 131 cc of water. The rate of addition was slow enough to allow the oxidation products to distill over as rapidly as they were formed. Distillation was continued about fifteen minutes after all the methyl cellosolve had been added. The results are given below.

Preparation of Catalysts

Copper Catalyst

For the preparation of one mole of the copper catalyst, 242 g of $Cu(NO_3)_2 \cdot 3H_2O$ was dissolved in three liters of water. The solution was transferred to a five liter three necked round bottom flask fitted with a mechanical stirrer, a dropping funnel, and a thermometer. The solution was heated to 50° with stirring. To the hot solution through the dropping funnel was added 340 cc of 10.47% NH_3 (aqueous solution, sp.gr. 0.958) over a period

of about half an hour, stirring all the while. The mixture was maintained at 50° and stirred for two hours, at the end of which time heating and stirring was ceased and the precipitate allowed to settle, which required about eight hours. The supernatant liquid was siphoned off. The precipitate was washed by decantation three times. Each time the flask was filled with water, heated to 50° while stirring and stirred for an additional two hours. The precipitate was finally transferred to suction flask and washed with two liters of water at 50° . The precipitate was then sucked nearly dry and run through a sodium press. The worms so formed were dried overnight at 110° , then cut into small pieces and placed in the catalyst column. The mixture of copper oxide and hydroxide was reduced in a slow stream of hydrogen at 300° .

Several precautions had to be observed in the above preparation. It was important to not heat the precipitate of copper hydroxide above 50° as it was unstable at higher temperatures and was readily converted into the black oxide which was a form not easily workable. The precipitate had to be dried to a plastic paste before it could be put through a sodium press. The proper degree of dryness could best be determined experimentally. It was here that the oxide was not workable. It was impossible to put it through^a sodium press. Even three washings would not remove the last traces

of nitrates. In the reduction of the catalyst fumes of nitrogen dioxide were always given off. The catalyst had to be brought up to 300° slowly.

Zinc-chromium oxide catalyst

The preparation of the zinc-chromium oxide was as described in the thesis of William P. Campbell⁹ and the patent of Lazier¹⁰. 126 g of $(\text{NH}_4)_2\text{Cr}_2\text{O}_7$ and 189 g of $\text{Zn}(\text{NO}_3)_2$ were dissolved in three liters of water. The solution was placed in a five liter flask fitted as described in the preparation of the copper catalyst. The solution was heated to 50° and maintained at this temperature throughout the precipitation. 694 cc of NH_4OH (sp.gr.0.979) were added with stirring over a period of about an hour. The stirring was continued for forty-five minutes. The precipitate was allowed to settle and the supernatant liquid was siphoned off. The precipitate was washed two times by decantation, using three and a half liter portions of water each time. In washing, the water added was heated to 50° and stirred forty-five minutes at that temperature. The precipitate was filtered on a suction filter and washed with several portions of water. It was dried to a plastic mass and run through a sodium press. The worms were dried overnight in an oven at 110°. The dried worms were cut into small pieces and placed in the catalyst column. The basic zinc ammonium

chromate was decomposed by heating it at the temperature at which it was to be used.

Copper-chromium oxide catalyst

The copper-chromium oxide catalyst prepared was the one described by Adkins¹¹ as catalyst 3ORAC. 10.8 g of $\text{Ba}(\text{NO}_3)_2$ dissolved in 100 cc of boiling water, 75.6 g of $\text{Cr}(\text{NO}_3)_3 + \text{Aq}$ dissolved in 900 cc of warm water, and 200 g of $\text{Cu}(\text{NO}_3)_2 \cdot 3 \text{H}_2\text{O}$ dissolved in 300 cc of water were mixed together at room temperature. To the combined solutions was added a solution of 188.8 g of $(\text{NH}_4)_2\text{CO}_3 \cdot \text{H}_2\text{O}$ dissolved in 1070 cc of water. The voluminous precipitate was filtered on a suction filter and washed with two 100 cc portions of water. It was dried overnight in an oven at 110° , pulverized and decomposed in four portions by heating in an open evaporating dish. The catalyst was then leached by allowing it to stand for one hour in 200 cc of 10% acetic acid. It was not possible to put this catalyst through a sodium press, but it could be made into small pills using an ordinary pill machine. The pills should be of such size as to weigh about 0.15 g each.

In the original article it was prescribed to use for this quantity of catalyst 77.2 g of $\text{Cr}_2(\text{NO}_3)_6 \cdot 15 \text{H}_2\text{O}$. The use of 75.6 g of $\text{Cr}(\text{NO}_3)_3 + \text{Aq}$ should accomplish the same purpose as the amount of chromium is the same in either

case. The $\text{Cr}(\text{NO}_3)_3 + \text{Aq}$ was found by Smith¹² to contain 23.42% chromium.

Materials Used

The methyl cellosolve used was purchased from the Carbide and Carbon Chemicals Corporation. It was carefully distilled through a 24 cm fractionating column packed with beads and well lagged with asbestos. The fraction boiling from 122.7-123.7° (at 760.3 mm) was used. 900 cc of commercial methyl cellosolve gave a forerun of 25 cc, an 840 cc fraction between 122.7-123.7°, and a small residue above the latter temperature. Of the 840 cc, the major part boiled constantly at 123.7°. The boiling point of methyl cellosolve is given in Beilstein as 124.9° at 767.5 mm. This boiling point was never realized under ordinary conditions.

The materials used for the preparation of the catalysts were of analytic reagent quality, purchased from the Mallinckrodt Chemical Company.

Investigation of Catalysts

Three copper catalysts were prepared. The first one was prepared from 50 g of wet copper oxide spread on rolls of copper wire gauze 15 cm long and 10 mm in diameter. The total length of the wire gauze was 70 cm. In the first run 300 cc of methyl cellosolve were run through the catalyst

column using Bouveault's method. The run required ten hours. 187 g of a mixture of aldehyde and alcohol were obtained. An unknown amount of methyl cellosolve was lost due to a leak in the apparatus near the end of the run. The 187 g mixture obtained was carefully fractionated through a 24 cm fractionating column packed with beads and well lagged with asbestos. In all subsequent fractionations the more efficient fractionating column mentioned above was used. Twenty-two grams of methoxy acetaldehyde boiling from 86-87° (p = 762.2 mm) was the final yield, a 12% yield based on 187 g of mixture and overlooking the methyl cellosolve lost as explained above.

A second run was made, using the same catalyst and apparatus, the latter being modified in that the fractionating column was heated electrically to 80° in order to improve its fractionating efficiency. 300 cc of methyl cellosolve were placed in the flask and run over the catalyst. After the run had continued two hours no aldehyde had been produced. The catalyst had suddenly lost its activity; it was removed and a new one prepared.

The second catalyst was prepared by reducing 200 g of wet copper hydroxide spread on wire gauze as described above. The modified apparatus described above was used in all subsequent experiments. Eleven runs were made to determine the optimum temperature for the dehydrogenation of methyl cellosolve over a copper catalyst. The results are given in

table I. The amounts of aldehyde, and consequently the expression of yields, are approximations. The products of the runs were not fractionated to pure components, but to nearly pure components. This procedure was followed as a matter of convenience. The combined aldehyde fractions of several runs were fractionated to give pure methoxy acetaldehyde. However, the approximations can be made with sufficient accuracy to show the trend of the results.

Table I
Determination of Optimum Temperature

Run #	Amt. of methyl cello-solve	Temp. of catalyst	Amt. of aldehyde	yield	
1	10 cc	300°	-	-) not fractionated length of runs: 240 minutes
2	10	300	-	-	
3	50	300	2 cc	4%	
4	50	300	2	4	
5	50	325	2	4	
6	50	325	3	6	
7	50	350	4	8	
8	50	375	8	16	
9	50	400	11	22	
10	50	425	12	24	
11	50	475	7	14	

Optimum Temperature :425°

Three more runs were made at 425° to determine the optimum rate, but only a negligible amount of aldehyde was formed in any of the runs. The catalyst had lost its activity. A third catalyst was prepared; 160 g of reduced

copper was prepared from copper hydroxide in the form of worms mentioned above. The worms were dumped into the column and after reduction filled little more than half the column. Six runs were made to check the optimum temperature of 425° with respect to the new catalyst. The results are given in Table II.

Table II

Check on Optimum Temperature of 425° with Respect to New Catalyst

Run #	Amt. of methyl cello-solve	Temp. of catalyst	Amt. of aldehyde	Yield
1	10 cc	300°	-	- not distilled
2	50	300	7.0 cc	14%
3	50	375	4.6	9%
4	50	400	5.2	10%
5	50	425	9.2	18%
6	50	425	7.2	14%

Optimum Temperature: 425°

These results check those found for the second copper catalyst, with the possible exception of run #2 at 300° in which a yield equalling that of run #6 was obtained. The results also foreshadow a decline in activity of the catalyst, as proved to be the case within the course of eight more runs. The next three runs were made to determine the effect on the yield of the rate of passage of the alcohol over the catalyst. The results are

given in Table III.

Table III
Effect of Rate on Yield at 425°

Run #	Amt. of methyl cello-solve	Temp. of bath	Length of run	Amt. of aldehyde	Yield
1	50 cc	130°	200 min.	6 cc	12%
2	50	135	120	3 cc	6%
3	50	140	75	1 cc	2%

Five runs were made at the optimum temperature and rate to determine the life of the catalyst. The results are given in Table IV.

Table IV
Life of Catalyst at Optimum Temperature and Rate

Run #	Amt. of methyl cello-solve	Amt. of aldehyde	Yield
1	50 cc	3.5 cc	7%
2	50	2	4
3	50	2	4
4	50	1	2
5	50	-	- Run not completed

The catalyst soon lost its activity. It was oxidized and again reduced at 300° in order to restore its activity. In view of its short life at 425°, it was decided to make several runs at 300° to study the life and activity of the catalyst at a lower temperature. Thirty runs were

made at this temperature. The results are given in Table V. The aldehyde fractions of the thirty runs were combined and fractionated to obtain the aldehyde in a pure form. To summarize the thirty runs, 1500 cc, or 1454 g of methyl cellosolve were used. 1135 g were recovered unreacted. From the 319 g which were decomposed there was obtained 130 g of methoxy acetaldehyde. The rest of the reacted alcohol was converted into secondary products, none of which were isolated and identified, most of which were highly volatile liquids or gases. The process gave a net yield of 9.2% based on the 1454 g of methyl cellosolve used, or a yield of 41.9% based on the methyl cellosolve recovered.

In this work very few of the secondary products were isolated and identified for two reasons. The by-products were chiefly highly volatile liquids or gases. The problem was primarily the preparation of methoxy acetaldehyde and not the catalytic decomposition of methyl cellosolve.

Table V
Use of Copper Catalyst at 300°

Run #	Amt. of methyl cello-solve	Temp. of bath	Length of run	Amt. of alde-hyde	Yield
1	50 cc	130°	140 mm	7 cc	14%
2	50	130	145	6	12
3	50	130	130	5	10
4	50	130	140	6	12
5	50	130	140	5	10
6	50	130	140	5	10
7	50	130	138	5	10
8	50	130	120	5	10
9	50	130	120	5	10
10	50	130	120	5	10
11	50	130	120	5	10
12	50	130	120	4	8
13	50	130	120	4	8
14	50	130	120	4	8
15	50	130	120	4	8
16	50	130	120	4	8
17	50	130	120	4	8
18	50	130	120	4	8
19	50	130	120	4	8
20	50	130	120	4	8
21	50	130	120	4	8
22	50	130	120	4	8
23	50	130	120	4	8
24	50	130	120	4	8
25	50	130	120	4	8
26	50	130	120	3	6
27	50	130	120	3	6
28	50	130	120	3	6
29	50	130	120	3	6
30	50	130	120	3	6

Two zinc-chromium oxide catalysts were used in attempts to dehydrogenate methyl cellosolve. The quantity of the first one used was 34 g, an amount which filled the

catalyst tube to a depth of 40 cm. One run, using 300 cc of methyl cellosolve, was made over this catalyst at 425°. The original set-up was used. 210 cc of crude distillate and considerable gaseous products were formed. CO₂ and H₂ were identified as two of the gases liberated. The crude distillate was fractionated and yielded 120 cc of unreacted methyl cellosolve. Of the decomposition products less than ten cc of the desired aldehyde was obtained, and that not in a pure state. At the time this run was made suitable apparatus for the fractionation of small quantities of liquids was not at hand.

Sixty percent of the methyl cellosolve used was catalytically decomposed. The yield of methoxy glycolic aldehyde was less than three percent on the basis of methyl cellosolve used, or less than five percent on the basis of methyl cellosolve recovered. The remainder of the decomposition products were largely gases.

In spite of such unfavorable results a second zinc-chromium oxide catalyst of 95 g was used, this time in the apparatus as finally modified. Five runs were made. The results are given in Table VI.

Table VI

Run #	Amt. of methyl cello-solve	Temp. of catalyst	Length of run	Amt. of aldehyde	Yield
1	50 cc	325°	120 min.	less than 1 cc	2%
2	50	350	150	1	2%
3	50	375	150	2	4%
4	50	400	112	2	4%
5	50	425	120	2	4%

The zinc-chromium oxide catalyst is evidently not a satisfactory catalyst for the dehydrogenation of methyl cellosolve to methoxy acetaldehyde.

The copper-chromium oxide catalyst of Adkins et al⁴ was used in but one set of runs. 60 g of the catalyst in the form of pills was placed in the catalyst tube. The results of four runs are given in Table VII.

Table VII

Run #	Amt. of methyl cello-solve	Temp. of catalyst	Length of run	Amt. of aldehyde	Yield
1	50 cc	300°	150 min.	1 cc	2%
2	50	325	135	2	4
3	50	350	120	2	4
4	50	375	127	2	4

The results obtained are not such as the original article would predict, especially in comparison with results obtained using a copper catalyst. For this reason the

catalyst was tested with one of the alcohols mentioned in the original article to see if the fault was in the particular catalyst prepared in this laboratory or in the catalyst in general. Fifty cc of n-butanol were run over the catalyst at 300° in 125 minutes. 14.2 cc of n-butyraldehyde were obtained, a yield of 29.5% based on the alcohol used. This result is consonant with those obtained by Adkins and showed the particular catalyst to be satisfactory for some alcohols, but unsatisfactory for the dehydrogenation of methyl cellosolve.

One attempt was made to prepare methoxy acetaldehyde by the chemical oxidation of methyl cellosolve. The method has been described. The result was most unsatisfactory. From the 100 g of methyl cellosolve used there was obtained 10 g of methoxy acetaldehyde, a yield of less than 10%. No methyl cellosolve was recovered; that which was not oxidized to the aldehyde, was further oxidized to some secondary product, one of which was identified as formaldehyde.

Characterization of Methoxy Acetaldehyde

The methoxy acetaldehyde prepared in this laboratory was a clear water-white liquid, more viscous than water. It possessed the sharp odor characteristic of volatile aliphatic aldehydes. The physical properties given are only indicative,

as repeated measurements of the physical constants of the aldehyde show that it has not been obtained in the pure form. This observation has been confirmed in the research laboratories of the Carbide and Carbon Chemicals Corporation, where it has been shown that methoxy acetaldehyde forms a constant boiling mixture with water. This azeotropic mixture is formed during the catalytic preparation of the aldehyde. It may be separated into its components by fractional distillation with benzene.

The boiling point, density and refractive index were measured on the methoxy acetaldehyde prepared in this laboratory. These measurements were made on a sample of the constant boiling mixture and on anhydrous methoxy acetaldehyde furnished by the research laboratories of the Carbide and Carbon Chemicals Corporation. The results are tabulated below.

	Azeotropic Mixture prepared in this laboratory	Azeotropic mixture furnished by Carbide & Carbon	Anhyd. Methoxy Acetaldehyde furnished by Carbide & Carbon
Boiling point	89.6°C (765.5 mm)	88.8°C (769.6 mm)	92.3°C (769.6 mm)
d_4^{25}	1.110	1.116	1.005
n_D^{25}	1.4246	1.4270	1.3950
R calcd.	-	-	17.66 (17.78, theo.)

The boiling points were determined in a Cottrell boiling-point apparatus using a calibrated thermometer. The densities were measured and checked in a pycnometer calibrated against distilled water. The refractive indices were measured in an Abbe refractometer. The source of light for these latter measurements was a "Day-light", i.e., one containing a blue bulb.

The following results were obtained from carbon and hydrogen analyses run ^{on} the samples furnished by the Carbide and Carbon Chemicals Corporation.

Analysis:

Azeotropic mixture, $\text{CH}_3\text{OCH}_2\text{CHO} - \text{H}_2\text{O}$

Found: C, 42.53, 42.37; H, 8.85, 8.59

Anhydrous methoxy acetaldehyde

Calcd. for $\text{C}_3\text{H}_6\text{O}_2$: C, 48.62; H, 8.17.

Found: C, 48.80; H, 8.29.

Attempts were made to prepare the following derivatives of methoxy acetaldehyde: semicarbazone, methyl phenylhydrazone, thiosemicarbazone, 4,4-diphenyl semicarbazone, p-nitrophenyl hydrazone, and 2,4-dinitrophenylhydrazone. In only the latter two cases were the attempts successful. With p-nitrophenylhydrazone and 2,4-dinitrophenyl hydrazine no trouble was experienced in obtaining pure crystalline derivatives.

p-Nitrophenylhydrazone

0.50 g of p-nitrophenylhydrazine (free base) was dissolved in 0.5 ml of concentrated hydrochloric acid and 25 ml of water. The undissolved hydrazine (less than 0.05 g) was filtered out of the solution. To the latter was added 0.5 cc of methoxy acetaldehyde where upon a yellow precipitate was formed immediately in about an eighty-three percent yield. The derivative was recrystallized from alcohol to a constant melting point, 115.0-115.5°C. The methoxy acetaldehyde p-nitrophenylhydrazone was analyzed for carbon and hydrogen.

Analysis. Calcd. for $C_9H_{11}O_3N_3$: C, 51.63;
H, 5.30.

Found: C, 51.72, 51.84, 51.71; H, 5.33, 5.34,
5.50¹

2,4-Dinitrophenylhydrazone

0.25 g of 2,4-dinitrophenylhydrazine (free base) was dissolved in 25 ml of ethyl alcohol by refluxing. To the saturated solution thus prepared was added 0.10 cc of

1. The writer wishes to express his indebtedness to Dr. Sterl A. Shrader for the micro carbon and hydrogen analyses.

methoxy acetaldehyde and the mixture was carefully heated to boiling. One drop of concentrated HCl was added; the mixture was heated for two minutes, after which water was added drop by drop to incipient cloudiness. On cooling a yellow precipitate separated which was filtered and recrystallized from alcohol to a constant melting point, 124-125°C. The yield was seventy-five percent of the theoretical. The methoxy acetaldehyde 2,4-dinitrophenylhydrazone was analyzed for carbon and hydrogen.



Analysis. Calcd. for $\text{C}_9\text{H}_{10}\text{O}_5\text{N}_4$: C, 42.50;

H, 3.97. Found: C, 42.56; H, 3.88²

2. The writer wishes to express his indebtedness to Dr. J. R. Spies for the micro carbon and hydrogen analyses.

CONCLUSION

Methoxy acetaldehyde has been prepared by the catalytic dehydrogenation of methyl cellosolve. Three catalysts have been investigated, copper, zinc-chromium oxide and copper-chromium oxide. The latter two have been shown to be unsatisfactory for the dehydrogenation of methyl cellosolve to methoxy acetaldehyde. Copper has been shown to be a fairly satisfactory catalyst for dehydrogenation, a result in accordance with the results of previous investigators. Further in accordance with their results, it has been found that copper readily loses its catalytic activity at elevated temperatures. While the greatest activity was found at 425°C, the life of the catalyst was so short, subsequent work showed the advantage of a lesser activity at 300°C, combined with a much longer life of the catalyst.

The chemical oxidation of methyl cellosolve, using $\text{Na}_2\text{Cr}_2\text{O}_7$ and H_2SO_4 as the oxidizing agent, has been shown to be unsatisfactory as a method of preparing methoxy acetaldehyde.

The methoxy acetaldehyde obtained in this laboratory has been shown by the work done in the research laboratories of the Carbide and Carbon Chemicals Corporation to be an azeotropic mixture of the aldehyde and water. The physical

constants of the azeotropic mixture and the anhydrous methoxy acetaldehyde have been measured.

Two solid derivatives of methoxy acetaldehyde, the p-nitrophenylhydrazone and 2,4-dinitrophenylhydrazone, have been prepared. Their melting points have been recorded.

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