

UNITED STATES PATENT OFFICE

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PSEUDO ESTERS OF LEVULINIC ACID

David P. Langlois and Hans Wolff, Decatur, Ill.,
assignors to A. E. Staley Manufacturing Com-
pany, Decatur, Ill., a corporation of Delaware

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9 Claims. (Cl. 260—344)

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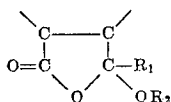
This invention relates to novel pseudo esters of gamma keto carboxylic acids. More particularly, it relates to the pseudo esters of saturated aliphatic gamma keto carboxylic acids, such as, for example, levulinic acid, and to methods for the preparation of these new chemical compounds, and the provision of such a process and the recovery of such products is a principal object of the invention.

Other objects of the invention will in part be obvious and will in part appear hereinafter.

The invention accordingly comprises the several steps and the relation of one or more of such steps with respect to each of the others thereof, which will be exemplified in the process hereinafter disclosed, and the scope of the application of which will be indicated in the claims.

By the expression "pseudo ester" is meant a compound that (1) is isomeric with a normal ester, (2) has properties unlike those of the normal ester, (3) yields the same acid and alcohol as the normal ester does when hydrolyzed, and (4) in general, can be isomerized to the normal ester.

Pseudo esters of aromatic gamma keto acids are described in the chemical literature. Reference is made to pages 445-447 of volume 56 (1934) of the Journal of the American Chemical Society for the pseudo methyl and ethyl esters of a p-bromobenzoyl acrylic acid, and to pages 1537-1541 of volume 63 (1941) of the same journal for the pseudo methyl esters of substituted benzoyl benzoic acids. Evidence is presented in both of these publications to show that the described pseudo esters may be regarded as lactones of hypothetical gamma hemiketol acids, and have the indicated common five membered ring structure I



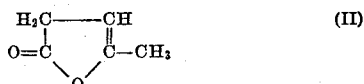
wherein R₁ and R₂ are alkyl or aryl groups.

The double bond between the 3 and 4 carbon

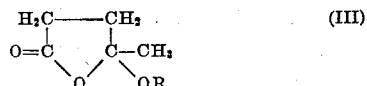
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atoms is fixed in the acrylic acid pseudo esters; in the pseudo esters of the benzoyl benzoic acids, the double bond presumably alternates with a single bond because the carbon atoms are in the benzene ring.

We have discovered that pseudo esters of levulinic acid, none of which have hitherto been reported, can be prepared by the catalytic addition of alcohols to alpha angelica lactone, which is generally regarded as having the indicated structure II



The new compounds thus obtained are formed by the addition of the alcohol (ROH) to the carbon-carbon double bond to yield structures of type III.

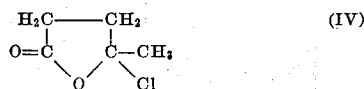


wherein R is a hydrocarbon radical selected from the group consisting of alkyl, aryl, and aralkyl radicals.

It will be noted that structure III may be regarded as a lactone of a hypothetical gamma hemiketol acid, and that its ring system is the same as that of the pseudo esters of the gamma keto acids mentioned above, except for the single bond between the 3 and 4 carbon atoms in place of a fixed or alternating double bond.

In support of this structure of the pseudo esters of levulinic acid, the following should be considered: (1) That the catalytic addition of alcohols to the aliphatic carbon-carbon double bond, though not a well-known reaction, is not an implausible one; (2) the ring structure is essentially the same as that fairly well established for the pseudo esters of other gamma keto carboxylic acids; (3) the calculated molecular refractions of the pseudo esters, based on the Auwers and Eisenlohr constants and the present ring structure, agree with the observed values; and (4) if

the acid chloride of levulinic acid, obtained by treating the acid with thionyl chloride, and which probably has structure IV,



is reacted cold with an alcohol under conditions that prevent rapid isomerization of pseudo ester to the normal form, there is obtained a pseudo ester that is identical in its physical and chemical properties with the pseudo ester obtained by catalytic reaction of the same alcohol with alpha angelica lactone in accordance with our invention.

Reference is made to page 1751 of volume 2 of the second edition (1943) of Gilman's "Organic Chemistry," published by John Wiley & Sons, for a discussion of the Auwers and Eisenlohr constants mentioned above.

The pseudo esters of levulinic acid are chiefly distinguished from the normal esters by the extreme ease with which they may be saponified. In fact they saponify so readily, as compared with the normal forms, that the proportion of pseudo ester in a neutral mixture of both types can be rapidly and accurately determined by cold titration of the mixture with standard alkali solution. The physical properties of the pseudo esters differ from those of the corresponding normal esters

chloride for example, are preferred because of the ease with which they may be removed from the reacted mixture.

The acid catalysts that promote the addition of alcohols to alpha angelica lactone also accelerate the isomerization of the formed pseudo ester to the normal ester. The pure pseudo esters can be rearranged quantitatively to the normal forms by the action of the acidic catalysts. This isomerization is quite slow at room temperature with traces of the catalysts, requiring weeks for completion, but becomes progressively more rapid as the temperature and catalyst concentration are increased. For example, complete isomerization of pseudo to normal ester can be accomplished by heating the ester with the corresponding alcohol for about one hour at about 100° C. in the presence of about 1% hydrogen chloride. Under a given set of conditions, however, the rate of isomerization appears always to be less than the rate of formation of the pseudo ester.

In general, catalyst concentrations can be selected that will provide practical rates of pseudo ester formation without excessive isomerization of the pseudo ester during the reaction period. These concentrations will vary, depending upon the particular alcohol and catalyst used. Table I illustrates the relationship between kind of alcohol and near-optimum catalysts concentration when hydrogen chloride is the catalyst.

Table I

Kind of Alcohol	Gms. of Alcohol	Gms. of Lactone	Gms. of HCl	HCl in Reaction Mixture	Yield of Total Esters	Pseudo Ester in Total Esters
				Per Cent	Per Cent	Per Cent
isopropyl	20	27.5	0.006	0.013	90	90
allyl	20	27.5	0.040	0.084	92	90
n-butyl	20	27.5	0.025	0.053	90	92
sec-butyl	20	27.5	0.300	0.63	98	95
methyl isopropyl carbinol	28	27.5	0.300	0.54	92	98
methyl isobutyl carbinol	28	27.5	0.300	0.54	95	95
n-hexyl	28	27.5	0.025	0.045	90	68
cyclohexyl	28	27.5	0.038	0.069	95	90
benzyl	28	27.5	0.025	0.045	92	66
phenol	25	25	0.010	0.020	80	100

and the differences are fairly consistent. The boiling points of the pseudo esters are either about the same or slightly higher than those of the normal esters, and the densities and refractive indices of the former are consistently somewhat higher than those of the latter.

The pseudo esters of levulinic acid will find many uses in the solvents field. In particular, cyclohexyl pseudo levulinate has very powerful solvent action on paints and varnishes and makes an excellent paint remover. Most of the pseudo esters of the lower alcohols are also effective. The pseudo esters dissolve copper oxide films from copper restoring the bright metal surface without attacking the metal. The pseudo esters of the lower alcohols are compatible with nitrocellulose lacquers. The pseudo esters of the higher alcohols will be effective plasticizers for ester soluble gums and plastics.

Suitable catalysts for preparing the pseudo esters of levulinic acid in accordance with the principles of our invention are the strongly acidic ones commonly used in esterification reactions. Examples of these are hydrogen chloride, hydrogen bromide, sulfuric acid, phosphoric acid, aromatic sulfonic acids, and monochloroacetic acid. In general, any strong acid appreciably soluble in the reaction mixture is satisfactory for this purpose. The volatile catalysts, such as hydrogen

The following procedure for preparing the pseudo esters of levulinic acid from alpha angelica lactone and alcohols is applicable to the alcohols in general except for methyl, ethyl, and n-propyl alcohol. Catalyst is dissolved in the selected alcohol until the latter contains about double the concentration of catalyst that is desired in the reaction mixture of alcohol and alpha angelica lactone. An excess of the alcohol containing the catalysts is then added to a given volume of the angelica lactone at room temperature. For example, this may be about an equal volume of isopropyl and the butyl alcohols, and about one and one-half volumes of the higher alcohols, up to and including those containing eight carbon atoms. The mixture is allowed to stand. The reaction is strongly exothermic. Even when the reaction mixture is held in uninsulated glass flasks, and its volume is only about 50 ml., its temperature may rise to about 60 to 80° C. over a period of about two hours; and then drop to room temperature in about an equal period of time. Good yields of the pseudo esters are obtained when the catalyst concentration is so adjusted that the foregoing rate and extent of temperature change occurs spontaneously. Too much catalyst, causing a more rapid rise in temperature, or too little catalyst, which causes the temperature rise to lag, results in reduced yields of pseudo ester. About

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four hours after mixing the reactants together the catalyst is either removed from the reaction mixture or inactivated. If it is a volatile one, such as hydrogen chloride, it may conveniently be removed from the reaction mixture by passing a stream of dry air through the latter. If it is a non-volatile one, such as toluene sulfonic acid, it is preferably neutralized and inactivated by shaking the reaction mixture with solid sodium carbonate. The reaction mixture, either freed of volatile catalyst by aeration, or neutralized with a weak base such as sodium carbonate to inactivate the catalyst, and filtered to remove solids, is then fractionally distilled under reduced pressure. The pseudo ester mixed with some normal ester is collected over a boiling point range of about 2° C.

To obtain substantial yields of the pseudo esters from methyl, ethyl, and n-propyl alcohol, it is necessary to modify the foregoing procedure. One satisfactory way of doing this is as follows:

The alpha angelica lactone is diluted with at least two volumes of diethyl ether, and preferably three or four, before the alcohol and catalyst are added to it. The mixture is allowed to stand under a reflux condenser until the reaction is complete, which preferably requires about four hours. No external heating is required. The mixed esters may then be separated from the catalyst, diluent, and unreacted materials as described in the preceding paragraph.

Table 2 lists the operating conditions and product yields in making the lower pseudo esters by the dilution method.

Table No. 2

Kind of Alcohol	ml. of Alcohol	ml. of Ether	ml. of Lactone	Gms. of HCl	Yield of Total Esters	Pseudo Ester in Total
					Percent	Percent
methyl.....	25	100	25	0.100	92	45
ethyl.....	25	100	25	0.050	90	50
n-propyl.....	25	100	25	0.050	92	38

Increased yields of pseudo esters from primary alcohols in general may be obtained by diluting the reaction mixture with a nonreactive low boiling liquid such as diethyl ether. Also, the use of such diluent with any alcohol is an added advantage in the large scale preparation of the pseudo esters because it suitably controls the reaction temperature. If catalytic addition of the alcohol to alpha angelica lactone on a large scale is not carried out under a reflux condenser in the presence of a relatively low boiling diluent, some other means of preventing overheating of the reaction mixture must be used.

Separation of a pseudo ester of levulinic acid from its mixture with the corresponding normal ester cannot easily be accomplished by fractional distillation because the boiling points of the two forms are so close together. Separation of one form from another in a mixture of the two can be effected, however, by taking advantage of the fact that the normal ester has a carbonyl group whereas the pseudo ester does not. Reaction of the mixture with a "carbonyl reagent" such as semicarbazide, or phenylhydrazine, preferably the former, affects only the normal ester, converting it into a derivative which can be separated from the pseudo ester because of a distinct difference in solubility or boiling point. The following procedure, using semicarbazide, is frequently successful.

A weighed sample of the mixed esters is titrated

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cold with tenth normal aqueous sodium hydroxide solution, using phenol-phthalein as indicator, to determine the proportion of pseudo ester present. The remainder is assumed to be normal ester. The mixed esters are diluted with an equal volume of the corresponding alcohol. Semicarbazide hydrochloride in amount slightly in excess of that required to combine with all of the normal ester and an equal weight of finely powdered potassium acetate are added to the alcohol-ester mixture, which is allowed to stand with intermittent shaking for about one day at room temperature. The mixture is then diluted with diethyl ether, allowed to stand for about one hour to permit complete precipitation of ether insoluble materials, and then filtered. The filtrate is fractionally distilled under reduced pressure, and pure pseudo ester, which has a higher boiling point than either the alcohol or ether, is collected over a boiling point range of about 2° C.

Purity of a pseudo ester of levulinic acid may be determined from its saponification number, cold titre, and constancy of boiling point. Cold titre and saponification number are conveniently determined by first mixing a weighed sample of the ester with a small volume of distilled water and titrating the mixture at room temperature with tenth normal aqueous sodium hydroxide solution, using phenolphthalein indicator. When the pink color end point first persists for about one minute, the titre is ready. More tenth normal alkali solution is added until there is present an excess of about 10%, based on the calculated normal ester present. The mixture is then re-

fluxed for one hour, acidified with a measured excess of tenth normal sulfuric acid, boiled gently for about two minutes to expel carbon dioxide, then quickly cooled and back titrated with tenth normal sodium hydroxide. The saponification number is calculated from the total alkali consumed during both cold and hot saponifications. If the correct saponification number is obtained for a given ester, then the ratio of cold titre to total titre is taken as the proportion of pseudo ester present.

The addition of organic hydroxy compounds to alpha angelica lactone to yield pseudo esters of levulinic acid appears to be a general one for all such compounds that will yield normal esters of levulinic acid by a conventional method of preparing esters. This includes primary and secondary alcohols, whether monohydroxy or polyhydroxy, and whether aliphatic or aromatic. It has been observed that the secondary alcohols, such as isopropyl alcohol, cyclohexanol, and phenol, together with such reactive primary alcohols such as allyl alcohol and benzyl alcohol, form pseudo esters with alpha angelica lactone more readily than do the ordinary primary alcohols. Table No. 3 lists some physical properties of a number of pseudo esters prepared in this way. Properties of most of the corresponding normal esters are included for comparison. All of the listed esters were found to have the correct saponification numbers.

Table No. 3

Ester	Boiling Point	Refractive Index ¹	Density ⁴	Molecular Obs.	Refrac-tion Calc'd
methyl (n) ¹	89-91° C. @ 15 mm.	1.4225	1.0495	31.52	31.57
methyl (p) ²	90-92° C. @ 15 mm.	1.4390	1.1071	30.90	30.93
isopropyl (n)	103-105° C. @ 15 mm.	1.4220	0.9842	40.80	40.81
isopropyl (p)	103-105° C. @ 15 mm.	1.4300	1.0151	40.22	40.16
n-butyl (n)	112-114° C. @ 15 mm.	1.4280	0.9735	45.59	45.42
n-butyl (p)	113-115° C. @ 15 mm.	1.4343	0.9985	44.80	44.79
sec. butyl (n)	113-115° C. @ 15 mm.	1.4250	0.9670	45.51	45.42
sec. butyl (p)	113-115° C. @ 15 mm.	1.4361	1.0108	44.50	44.79
allyl (n)	106-108° C. @ 10 mm.	1.4413	1.0277	40.03	40.34
allyl (p)	106-108° C. @ 10 mm.	1.4525	1.0677	39.45	39.70
methyl isobutyl carbinol (p)	124-126° C. @ 15 mm.	1.4384	0.9823	53.56	54.02
methyl isopropyl carbinol (p)	120-121° C. @ 15 mm.	1.4435	1.0013	49.30	49.40
cyclohexyl (n)	140-142° C. @ 15 mm.	1.4595	1.0308	52.43	52.46
cyclohexyl (p)	146-148° C. @ 15 mm.	1.4668	1.0632	51.66	51.82
phenyl (n)	133-135° C. @ 3 mm.	1.5059	1.1190	50.97	51.07
phenyl (p)	130-132° C. @ 3 mm.	1.5131	1.1467	50.34	50.34

¹ Normal.² Pseudo.³ Measured at 20° C. with the D line of sodium light.⁴ Measured at 20° C. relative to water at 4° C.

The following examples will illustrate in the order given (1) the preparation of pseudo esters of levulinic acid from the acid chloride, (2) the use of p-toluene sulfonic acid to catalyze the addition of alcohols to alpha angelica lactone, (3) the use of semicarbazide to effect a separation of pseudo from normal levulinic acid ester, and (4) isomerization or molecular rearrangement of the pseudo ester into its normal form.

Example 1

Sixty grams of thionyl chloride was added dropwise to 50 grams of levulinic acid contained in a 200 ml. glass flask at such a rate that the temperature of the reaction mixture did not exceed 50° C. About one-half hour was required for the addition. The reaction mixture was then held at about 50° C. under a reduced pressure of about 30 mm. of mercury to remove hydrogen chloride, sulfur dioxide, and excess thionyl chloride. The crude levulinyl chloride thus obtained was added slowly to a vigorously stirred mixture of 125 ml. of methanol and 50 grams of finely powdered dry sodium carbonate so that the temperature of the mixture did not exceed about 30° C. nor did its pH fall below about 6. After all the levulinyl chloride was added, the mixture was stirred at room temperature for an additional thirty minutes. The reaction mixture was diluted with about 200 ml. of ether and filtered to remove the insoluble salts. The ether and excess methanol were first evaporated from the filtrate under reduced pressure and the residual ester was fractionally distilled at 15 mm. pressure. There was thus obtained in 62% yield a fraction boiling at 90-92° C. which was 92% pseudo ester. The ethyl, allyl, and n-propyl esters were also prepared in similar fashion. In all three of these latter preparations, the yield of mixed esters were low, being only 25 to 30% based on the levulinic acid taken, but the proportions of pseudo esters present ranged from 90 to 92%.

Example 2

One gram of p-toluene sulfonic acid was dissolved in 25 ml. of allyl alcohol, and to this solution at room temperature was added 25 ml. of alpha angelica lactone. The temperature of the mixture rose slowly to a maximum of about 80° C. over a period of about two hours and then dropped to room temperature in about an equal time. The catalyst in the reaction mixture was carefully neutralized with an equivalent amount of sodium methylete dissolved in allyl alcohol.

The neutralized reaction mixture was then fractionally distilled under reduced pressure, and 55 gms. of an ester fraction boiling at 106-108° C. at 10 mm. was collected. This fraction amounted to 92% of the theoretical yield of addition product, had a saponification number of 158, and was found to be 75% pseudo ester.

Example 3

Forty grams of the addition product obtained in Example 2, i. e., mixed pseudo and normal allyl esters of levulinic acid, was diluted with 50 ml. of allyl alcohol and then mixed with 15 grams each of powdered semicarbazide hydrochloride and potassium acetate. This mixture was allowed to stand with intermittent shaking for one day, then it was diluted with 100 ml. of ether, filtered to remove insoluble products, including the crystalline semicarbazone of normal allyl levulinate, and fractionally distilled under vacuum. After the ether and allyl alcohol were removed, 25 grams of pure pseudo allyl ester was collected at 10 mm. pressure over the boiling point range of 106-108° C. This product had a "cold" saponification number of 160, a density of 1.0677 at 20° C. (referred to water at 4° C.), and a refractive index of 1.4525 at 20° C.

Example 4

Fifty grams of pure pseudo methyl levulinate was diluted with 100 ml. of methanol containing 1 gram of hydrogen chloride, and the resulting solution was refluxed for one hour at atmospheric pressure. At the end of this time the cold alkali titre of the mixture was equal to the hydrogen chloride present. Fractional distillation of the mixture at 15 mm. pressure yielded 47 grams of pure normal methyl levulinate boiling at 89-91° C. The recovered ester had no appreciable cold alkali titre, a saponification number of 130, a density of 1.0495 at 20° C., and a refractive index of 1.4225 at 20° C.

Since certain changes may be made in carrying out the above method without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

Having described our invention what we claim as new and desire to secure by Letters Patent is: 1. The process of forming a pseudo ester of levulinic acid which comprises reacting alpha angelica lactone, in the presence of an acid catalyst, with an organic hydroxy compound of the gen-

2. A process according to claim 1 in which the catalyst used is hydrogen chloride.

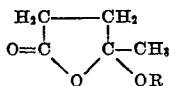
2. A process according to claim 1 in which the catalyst used is hydrogen chloride.

3. A process according to claim 1 in which the catalyst used is p-toluene sulphonic acid.

4. In the process of separating a pseudo ester of levulinic acid from a mixture of said ester with the corresponding normal ester, the improvement 10 which comprises reacting said mixture with a carbonyl reagent selected from the group consisting of semicarbazide and phenylhydrazine.

5. The process of forming a pseudo ester of levulinic acid which comprises reacting alpha angelica lactone, in the presence of hydrogen chloride and at least two volumes of diethyl ether based on the alpha angelica lactone, with an organic hydroxy compound of the general formula $R-OH$, wherein R is a hydrocarbon radical selected from the group consisting of alkyl, aryl, and aralkyl radicals.

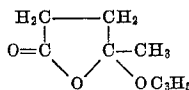
6. Pseudo esters of levulinic acid having the structure



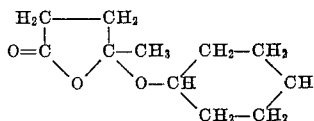
where R is a hydrocarbon radical selected from the group consisting of alkyl, aryl and aralkyl radicals, which pseudo esters are characterized by extreme ease of saponification, as compared to the corresponding normal esters, and which can be quantitatively rearranged to the corresponding normal esters by heating them with the corresponding alcohol in the presence of hydrogen chloride.

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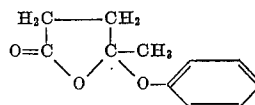
7. The pseudo allyl ester of levulinic acid having the structure



8. The pseudo cyclohexyl ester of levulinic acid having the structure



9. The pseudo phenyl ester of levulinic acid
15 having the structure



DAVID P. LANGLOIS.
HANS WOLFF.

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25 The following references are of record in the
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