crystallization was effected from alcohol. The melting points of the picrates were sharp with decomposition occurring only after fusion was complete. Data for the picrates are collected in Table II.

Summary

Twelve new 2,3-disubstituted cinchoninic acids have been prepared from alkyl (or phenyl) propoxymethyl ketones. Certain of these derivatives have been decarboxylated and their ether grouping cleaved to produce 2-alkyl (or 2-phenyl)-3-hydroxyquinolines, thus establishing the structures as 2-alkyl (or 2-phenyl)-3-propoxycinchoninic acids.

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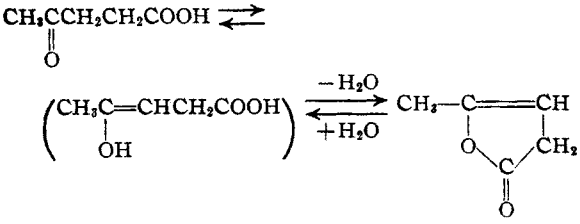
[CONTRIBUTION FROM THE RESEARCH LABORATORY OF THE A. E. STALEY MANUFACTURING COMPANY]

Pseudo Esters of Levulinic Acid

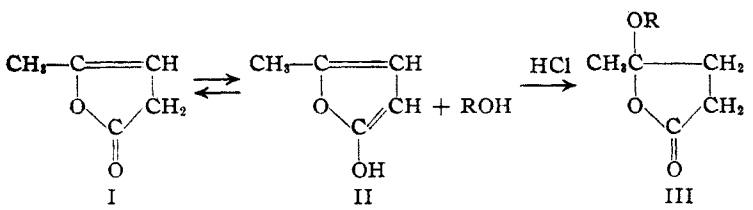
BY DAVID P. LANGLOIS AND HANS WOLFF

The dehydration of levulinic acid to α-angelica lactone is a reversible reaction. In the presence of traces of mineral acids water can be added to α-angelica lactone re-forming levulinic acid.[1] The enolic form of levulinic acid may be an intermediate in the reaction



If instead of water an alcohol is added to α-angelica lactone, the corresponding ester of levulinic acid would be expected as the reaction product. With the intention of preparing levulinic esters by this method, methanol and ethanol were added to α-angelica lactone in the presence of hydrogen chloride. The corresponding methyl and ethyl esters were obtained in quantitative yields.

Attempts to prepare cyclohexyl levulinate by this same method led to an unexpected result; an ester was obtained in 95% yield, but its physical and chemical properties differed from cyclohexyl levulinate prepared from levulinic acid and cyclohexanol by conventional methods. A further examination of the product revealed that it consisted predominately of the pseudo cyclohexyl ester of levulinic acid (III), which could result either from the addition of cyclohexanol to the double bond of α-angelica lactone (I) or from a 1–4 addition of the alcohol to the enol form of angelica lactone (II) followed by rearrangement to structure (III).



R = cyclohexyl

The presence of an enol form of α-angelica lactone is indicated by a Zerewitinoff determination in which approximately one third of a mole of methane is liberated from one mole of α-angelica lactone. Additional evidence for an enol form is given by a comparison of the ultraviolet absorption spectra of furfuryl alcohol and α-angelica lactone (Fig. 1). Furfuryl alcohol was chosen for comparison because it possesses the same molecular weight as angelica lactone and has a structure quite similar to the enol form of α-angelica lactone. The maximum of absorption at 2170 Å., indicative of two double bonds in conjugation, is common to both compounds; the considerably lower absorption of the lactone would indicate that only a partial enolization occurs.

Pseudo esters of aromatic keto acids have been described. Meyer[2] prepared pseudo methyl 2-benzoylbenzoate; Lutz[3] reported the pseudo esters of substituted benzoylacrylic acid and Newman[4] discussed the synthesis of pseudo esters of the benzoylbenzoic acid type. It appears that the pseudo esters of levulinic acid described in this paper are the first examples of pseudo esters in the purely aliphatic series.

In studying the various alcohols it was observed that secondary alcohols form pseudo esters quite readily. This is also true in the case of reactive primary alcohols such as allyl and benzyl alcohols. On the other hand, normal primary alcohols, especially the lower members, give only the normal esters of levulinic acid unless special precautions are taken. The pseudo ester of methanol can be obtained, however, if ether is used as a solvent and the quantity of hydrogen chloride is regulated carefully.

The rate of reaction for each alcohol is controlled by the amount of catalyst used. The reaction is exceedingly violent if a large excess of hydrogen chloride is added at the start, and

(1) Wolff, *Ann.*, **229**, 249 (1885).

(2) Meyer, *Monatsh.*, **25**, 475 (1904).

(3) Lutz and Winne, THIS JOURNAL, **56**, 445 (1934); Lutz, *ibid.*, **56**, 1378 (1934); Lutz, *et al.*, *J. Org. Chem.*, **4**, 95 (1939); **6**, 77 and 91 (1941).

(4) Newman and McClearly, THIS JOURNAL, **63**, 1537 (1941); Newman and Lord, *ibid.*, **66**, 731 (1944).

the resulting product is largely, if not entirely, the normal ester. A pure pseudo ester can be rearranged quantitatively to the normal ester by the catalytic action of hydrogen chloride. Thus, hydrogen chloride appears to catalyze both the addition of an alcohol to the lactone and the rearrangement of the adduct to a normal ester. By carefully adjusting the amount of hydrogen chloride, it is possible to control the addition reaction without effecting an appreciable rearrangement of the pseudo ester to the normal ester.

Pseudo esters of levulinic acid can also be prepared from the alcohols and levulinyl chloride. This method of pseudo ester preparation is similar to the one employed by Meyer.[2] Levulinyl chloride has been shown to exist in the form of γ-chlorovalerolactone,[5] which may be regarded as a pseudo acid chloride.

The boiling points of the pseudo and normal esters (Table I) of any given alcohol are identical or differ only slightly. Therefore, it is not possible to separate a mixture of pseudo and normal ester by fractional distillation. However, a means for isolating some of the pseudo esters in pure form has been developed; it is based on the observation that pseudo esters do not react with carbonyl reagents whereas the normal esters give crystalline semicarbazones or 2,4-dinitrophenylhydrazones, which can be separated from the liquid pseudo esters. This procedure was successful for the preparation of pure pseudo methyl and allyl levulinate. The other pseudo esters listed in Table I contained small amounts of the normal ester which could not be separated by a carbonyl reagent on account of the slight solubility of these reagents in the reaction mixture.

TABLE I

PHYSICAL CONSTANTS OF NORMAL (N) AND PSEUDO (P) ESTERS OF LEVULINIC ACID

	B. p. °C.	Mm.	$n^{20}D$	d^{20}_4	Molecular refraction Observed	Calcd.
Methyl (N)	89–91	15	1.4225	1.0495	31.52	31.57
Methyl (P)	90–92	15	1.4390	1.1071	30.90	30.93
Isopropyl (N)	103–105	15	1.4220	0.9842	40.80	40.81
Isopropyl (P)[a]	103–105	15	1.4300	1.0151	40.22	40.16
Allyl (N)	106–108	10	1.4413	1.0277	40.03	40.34
Allyl (P)	106–108	10	1.4525	1.0677	39.46	39.70
Methyl isobutyl (P)[a]	107–108	2	1.4384	0.9828	53.56	54.02
Cyclohexyl (N)	108–110	1	1.4595	1.0308	52.43	52.46
Cyclohexyl (P)[a]	112–113	1	1.4668	1.0632	51.66	51.82

[a] Above 90% pseudo.

It will be noted in Table I that the densities and refractive indices of the pseudo esters are higher than those of the corresponding normal esters. The molecular refractions are accordingly lower. The close agreement of the observed values with the ones calculated from the Eisenlohr constants[6] furnishes a good evidence for the proposed structures of the pseudo esters. In the case of the pseudo esters an exaltation of −0.16 was introduced for the lactone ring.

(5) Helberger, *Ann.*, **522**, 269 (1936).

(6) Gilman, "Organic Chemistry," Vol. II, 1938, p. 1737.

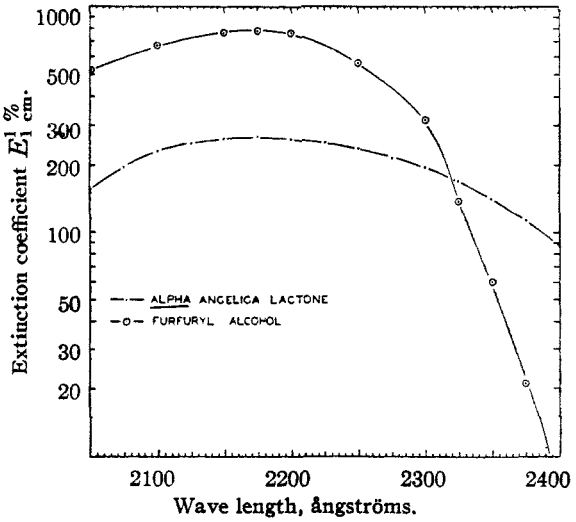


Fig. 1.—Absorption spectra of α-angelica lactone in neohexane and of furfuryl alcohol in water. Beckman Model D. V. used.

Chemically, the pseudo esters are distinguished from the normal esters of levulinic acid by their sensitivity to hydrolysis. The pseudo esters are saponified by treatment with cold 0.1 *N* sodium hydroxide. Advantage is taken of this reaction to determine the percentage of pseudo and normal esters in a reaction mixture. Total esters were determined by saponification at boiling temperature and pseudo esters by titration at room temperature. From the difference the percentage of normal esters can be determined.

Experimental

Preparation of Normal Esters of Levulinic Acid.—The method described in "Organic Syntheses" (Coll. Vol. I, p. 256) was used for the preparation of the esters. The esters were fractionated at reduced pressure, and the fractions boiling within a 2° range were collected. The foreruns and residues were small, and the esters were obtained in high yields.

Zerewitinoff Determination on α-Angelica Lactone: a sample of 0.2149 g. (0.00219 mole) of α-angelica lactone which had been standing at room temperature for several months gave 0.000777 mole of methane, corresponding to 28% of enol. A freshly distilled sample of 0.2079 g. (0.002122 mole) lactone yielded 0.000465 mole of methane; corresponding to 46% of enol.

Preparation of Pseudo Esters of Levulinic Acid.—Pseudo Methyl Levulinate: (a) From α-angelica lactone and methanol.—To a solution of 25 ml. of α-angelica lactone in 50 ml. of diethyl ether was added 25 ml. of methanol containing 0.1 g. of hydrogen chloride. The temperature of the mixture rose until the ether started to reflux. The mixture was kept at reflux in a water-bath for three hours. The ether and excess methanol were then removed under vacuum, and the residue was distilled, yielding 29 g. of a distillate, b. p. 88–92° (15 mm.).

Determination of Pseudo Ester in the Distillate.—A 0.187-g. sample was swirled in 50 ml. of water at 50° for a few minutes, then cooled and titrated with 0.1000 *N* sodium hydroxide; the cold titer found was 6.5 ml. of the 0.1 *N* sodium hydroxide. A saponification equivalent taken on the same sample required 14.4 ml. of alkali, thus

Alcohol used	Mg. HCl	Yield of ester	Pseudo, % ester in mixture	Sapn. equiv. Calcd.	Sapn. equiv. Found	Calcd. for	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Isopropyl	6	90	92	158	156	$C_8H_{14}O_3$	60.7	60.7	8.9	8.8
Methylisobutylcarbinol	300	93	96	200	200	$C_{11}H_{20}O_3$	66.0	65.5	1.0	9.7
Cyclohexyl	38	95	90	198	197	$C_{11}H_{18}O_3$	66.7	66.7	9.1	9.3
Benzyl	25	92	93	206	206	$C_{12}H_{14}O_3$	70.0	69.8	6.8	6.7

indicating the presence of 45% of pseudo ester in the mixture.

Separation of the Pseudo Ester from the Normal Ester.—To 28 g. of the ester was added 80 ml. of methanol, 14.4 g. of semicarbazide hydrochloride, and 12.8 g. of potassium acetate. After shaking the mixture for twenty-four hours, 50 ml. of ether was added, and the mixture was filtered. The residue was washed with ether, and the ether added to the filtrate. The ether and methanol were evaporated at reduced pressure, and the pseudo methyl levulinate distilled b. p. 90–92° (15 mm.). Cold titer gave a neutral equivalent of 129 (calcd. 130). *Anal.* Calcd. for $C_6H_{10}O_3$: C, 55.4; H, 7.7. Found: C, 55.0; H, 8.0.

(b) **From Levulinyl Chloride and Methanol.**—To 50 g. of levulinic acid 60 g. of thionyl chloride was added dropwise with stirring; the reaction temperature was not allowed to exceed 50°. The mixture was then maintained at 50° under reduced pressure in order to remove hydrogen chloride, sulfur dioxide and excess thionyl chloride. The levulinyl chloride was then added under vigorous stirring to a mixture of 125 ml. of methanol and 50 g. of sodium carbonate. The addition rate was carefully controlled in order to keep the *p*H of the reaction mixture above 6 and avoid warming of the mixture above 30°. The mixture was stirred for thirty minutes after all levulinyl chloride had been added. Approximately 200 ml. of ether was then added, and the mixture was filtered. After evaporating the ether and excess methanol *in vacuo*, the ester b. p. 90–92° (15 mm.) was obtained in 62% yield; it titrated for 92% of the pseudo ester.

Pseudo Allyl Levulinate: To 25 ml. of α-angelica lactone 25 ml. of allyl alcohol containing 0.4 g. of hydrogen chloride was added. The temperature of the reaction mixture rose gradually to 60°. After allowing to stand for three hours the mixture was distilled yielding 36.5 g. of ester. Cold titer and saponification equivalent indicated the presence of 10% of normal ester in the distillate. Addition of 70 ml. of allyl alcohol, 5 g. of 2,4-dinitrophenylhydrazine and one drop of glacial acetic acid, shaking the mixture for twelve hours followed by filtration removed the normal ester. On distillation 25 g. of pseudo allyl levulinate was obtained b. p. 93° (3 mm.); sapn. equiv. calcd. 156, found 153 (cold titer 98% of sapn. equiv.). *Anal.* Calcd. for $C_8H_{12}O_3$: C, 61.5; H, 7.7. Found: C, 61.4; H, 7.5.

Pseudo Isopropyl, 4-Methyl-2-pentyl, Benzyl, and Cyclohexyl Levulinate: These esters were prepared from 25 ml. of α-angelica lactone and 35 ml. of the corresponding alcohol. The amount of hydrogen chloride used, yields obtained, and analytical data found are given in the table.

Rearrangement of Pseudo Esters to Normal Esters.—The pseudo ester was diluted with the corresponding alcohol containing a small amount of a mineral acid. As little as 0.3% hydrogen chloride was sufficient. The mixture was heated to boiling until the cold titer became constant and equal to the mineral acid present. The pure normal ester was obtained in a quantitative yield.

Summary

1. Alcohols add to α-angelica lactone to form pseudo esters of levulinic acid.

2. The pseudo esters of levulinic acid are quantitatively converted to the normal esters by heating in the presence of a mineral acid.

3. Pseudo esters do not form carbonyl derivatives and may thus be separated from the normal esters.

4. Pseudo esters of levulinic acid are readily hydrolyzed by cold water.

5. Several pseudo esters of levulinic acid have been prepared, and their properties are tabulated.

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(7) Original manuscript received January 15, 1947.

[CONTRIBUTION FROM STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

The Dipole Moments of Thiouracil and Some Derivatives

BY W. C. SCHNEIDER AND I. F. HALVERSTADT[1]

In certain molecules where oxygen or sulfur atoms are attached to carbon atoms adjacent to heterocyclic ring nitrogens, the amide-iminoalcohol, $-\overset{O}{\overset{\|}{C}}-NH- \rightleftarrows -\overset{OH}{\overset{|}{C}}=N-$, type of tautomerism may exist. The relative contributions of these tautomeric forms will be affected by changes in substituents, solvents, temperature, state, etc.

The thiouracil molecule contains two such groups, both of which are usually shown in the amide form. Classical structural formulas can be assigned to those derivatives in which the labile hydrogens of the amide groups have been replaced by alkyl, aralkyl, etc., substituents, but occasionally these formulas may not adequately represent the properties of the compound. In some of these cases the assumption of tautomeric forms having a separation of charge has proved helpful.

The structure of 2-thiouracil was of interest to us because of its marked antithyroid activity. Certain dipole moment and infrared absorption data on thiouracil and a large number of derivatives are reported in this paper. On this basis a tentative classification of the compounds according to classical structure is made.

(1) Associated with Cutter Laboratories, Berkeley, California.