filter. It was taken up in 2000 ml. of water at 80° with 5 g. of magnesium oxide and 5 g. of Darco G-60, filtered hot, and the filtrate was then neutralized to pH 4 and cooled to 5°. The bright yellow product was filtered, washed with water and acetone and dried at 50°. The purity, as estimated from the ultraviolet absorption curve, was about 80%. In 0.1 N sodium hydroxide solution it showed maxima at 305 and 378 mμ, a plateau at 278–285 mμ, and a minimum at 252 mμ. In 0.1 N hydrochloric acid it showed a maximum at 307 mμ, a plateau at 248–255 mμ, and a shoulder at 340–355 mμ.

Synthesis of Pteroylglutamic Acid by Anaerobic Hydrolysis of 4-Alkylamino Derivatives.—A. From 4-Dimethylaminopteroylglutamic Acid (III).—To 20 ml. of oxygen-free 1 N sodium hydroxide was added 0.200 g. of 69.6% 4-dimethylaminopteroylglutamic acid. The solution was heated on the steam-bath for five hours under nitrogen. It was then diluted to 100 ml., and poured into 45 ml. of 30% acetic acid solution. The mixture was cooled and the precipitate collected; dry weight, 0.0977 g. This material had a chemical assay of 69.9%, and a bioassay of 75% as compared to pteroylglutamic acid as a growth-stimulant for *S. faecalis* R.

B. From 4-(1-Piperidyl)-pteroylglutamic Acid (IV).—A 0.680-g. sample of 4-(1-piperidyl)-pteroylglutamic acid of 73.4% purity was treated in the same fashion as described above, yielding 0.398 g. of a product with a chemical assay of 63.5%, and a bioassay of 56.5% as growth-stimulant for *S. faecalis* R.

Summary

A series of 4-alkylaminopteroylglutamic acid derivatives has been synthesized, in which are included 4-dimethylaminopteroylglutamic acid and its 10-methyl-derivative, 4-(1-piperidyl)-pteroylglutamic acid and 4-methylaminopteroylglutamic acid.

Substitution on the 4-amino group of 4-aminopteroylglutamic acid (I), a potent antagonist for pteroylglutamic acid, produced substances of much lower toxicity.

4-Alkylaminopteroylglutamic acids were readily converted to pteroylglutamic acid by heating in alkali under anaerobic conditions.

A number of new 6-alkylaminopyrimidines were prepared as intermediates.

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n-Alkyl Lactates and their Acetates

BY C. E. REHBERG AND MARION B. DIXON

The literature contains many references to various n-alkyl lactates and their acetates (n-alkyl α-acetoxypropionates), but no comprehensive treatment of the physical constants of these esters as related to molecular structure; nor are adequate data available for such treatment. When the available data are tabulated, many wide discrepancies, as well as numerous blanks, are apparent.

Wood, Such and Scarf[2] prepared the optically active n-alkyl L-lactates from the methyl to the nonyl ester. Since they were primarily interested in optical properties, the only other property measured with precision was density. Smith and Claborn[3] reported the boiling point, specific gravity and refractive index for several n-alkyl lactates and acetoxypropionates.

In the present work, the lactates and acetoxypropionates of eleven n-alkanols having one to sixteen carbon atoms were prepared, and a systematic study of their physical properties was made. The correlation of these properties as linear functions of the number of carbon atoms in the compounds furnishes excellent checks on the purity of these esters and the accuracy of the physical measurements. These correlations are also useful for prediction of the properties of homologs not prepared and of properties at temperatures and pressures other than those studied.

Table I shows the yields and analyses of esters

TABLE I

YIELDS AND ANALYSES OF n-ALKYL LACTATES AND α-ACETOXYPROPIONATES

Ester	Yield, %	Sapn. equiv. Calcd.	Found	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
Decyl lactate	65	230.3	228.9	67.8	67.6	..	..
Tetradecyl lactate	69	286.4	286.8	71.3	70.7	12.0	11.9
Hexadecyl lactate	65	314.5	319.5	72.6	72.4	12.2	12.1
Octyl acetoxypropionate	96	122.2	121.3	63.9	63.9	9.9	10.1
Decyl acetoxypropionate	97	136.2	138.2	66.1	65.8	10.4	10.4
Tetradecyl acetoxypropionate	79	164.2	164.2	69.5	69.4	11.1	11.3
Hexadecyl acetoxypropionate	93	178.3	176.8	70.7	70.8	11.3	11.4

(1) One of the Laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

(2) Wood, Such and Scarf, *J. Chem. Soc.*, **123**, 600 (1923).

(3) Smith and Claborn, *Ind. Eng. Chem.*, **32**, 692 (1940).

not previously reported. Table II gives physical properties of all the esters studied.

Boiling Points and Vapor Pressures.—The boiling points at various pressures are plotted in

<div align="center">TABLE II</div>

PHYSICAL PROPERTIES OF *n*-ALKYL LACTATES AND α-ACETOXYPROPIONATES

Ester	n^{20}D	n^{40}D	d^{20}_4	d^{40}_4	Molecular refraction Found at			Viscosity, centipoises at		Soly. in water at 25°, g./100 cc.	M. p., °C.
					Calcd.^{a}	20°	40°	20°	40°		
Methyl lactate	1.4139	1.4053	1.0939	1.0708	23.67	23.77	23.84	2.94	1.71	α	..
Ethyl lactate	1.4132	1.4040	1.0348	1.0121	28.32	28.48	28.54	2.61	1.57	α	..
Propyl lactate	1.4172	1.4087	1.0035	0.9815	32.97	33.13	33.27	3.32	1.91	α	−40
Butyl lactate	1.4217	1.4128	0.9837	.9637	37.61	37.75	37.81	3.58	2.08	4.36	−28
Amyl lactate	1.4257	1.4174	.9676	.9480	42.26	42.40	42.53	4.43	2.44	1.00	−22
Hexyl lactate	1.4290	1.4201	.9540	.9351	46.91	47.09	47.16	5.49	2.87	.27	−22
Octyl lactate	1.4346	1.4264	.9361	.9183	56.20	56.34	56.49	7.71	3.89	.08	− 4
Decyl lactate	1.4397	1.4311	.9242	.9080^b	65.49	65.64	65.68	10.97	5.25	.02	8
Dodecyl lactate	1.4436^b	1.4355	.9154^b	.8988	74.79	74.92	75.09	16.44	7.50	.01	25
Tetradecyl lactate	1.4466^b	1.4384	.9087^b	.8932	84.08	84.15	84.25	22.01	9.65	..	31
Hexadecyl lactate	1.4370^c	1.4410^b	.....	.8862^c	93.38	....	93.81^c	...	..	..	41
Methyl α-acetoxypropionate	1.4092	1.4008	1.0899	1.0661	32.98	33.16	33.29	2.71	1.61	8.12	..
Ethyl α-acetoxypropionate	1.4089	1.4001	1.0460	1.0232	37.63	37.85	37.96	2.44	1.54	3.37	..
Propyl α-acetoxypropionate	1.4128	1.4041	1.0213	1.0000	42.27	42.50	42.61	2.74	1.69	.99	..
Butyl α-acetoxypropionate	1.4163	1.4080	1.0033	0.9832	46.92	47.10	47.23	3.02	1.90	.32	..
Amyl α-acetoxypropionate	1.4200	1.4118	.9890	.9694	51.57	51.75	51.89	3.53	2.11	.07	..
Hexyl α-acetoxypropionate	1.4232	1.4152	.9761	.9573	56.21	56.44	56.60	4.24	2.42	.02	..
Octyl α-acetoxypropionate	1.4284	1.4206	.9578	.9409	65.51	65.68	65.79	6.08	3.40	.01	−58
Decyl α-acetoxypropionate	1.4330	1.4254	.9440	.9272	74.80	75.00	75.17	7.84	4.17	..	−48
Dodecyl α-acetoxypropionate	1.4370	1.4295	.9336	.9169	84.10	84.31	84.56	11.08	5.70	..	−18
Tetradecyl α-acetoxypropionate	1.4403	1.4329	.9258	.9103	93.39	93.54	93.76	14.91	7.31	..	− 2
Hexadecyl α-acetoxypropionate	1.4430	1.4354	.9191	.9035	102.68	102.84	103.05	20.00	9.44	..	13

^{a} The atomic refractivities of A. Vogel, *J. Chem. Soc.*, 1833 (1948), were used. ^{b} Supercooled liquid. ^{c} At 50°.

Figs. 1 and 2 as log P *vs.* $1/(t + 183)$. The usual forms of the Cox chart, where log p is plotted *vs.* $1/(t + 273)$ or $1/(t + 230)$ were unsuitable because of the strong curvature of the plotted lines. Correction was conveniently made by adding 90° to each point on the temperature scale of charts

<div align="center">TABLE III</div>

BOILING POINTS^a OF *n*-ALKYL LACTATES AND α-ACETOXY-PROPIONATES AT VARIOUS PRESSURES

Ester Lactates	Boiling points, °C., at pressures, mm.				
	0.1	1.0	10	100	760
Methyl	...	...	42	87	145
Ethyl	...	...	51	94	154
Propyl	...	...	61	108	169
Butyl	...	40	75	125	187
Amyl	...	52	89	140	206
Hexyl	34	64	103	155	221
Octyl	55	87	128	184	255
Decyl	76	109	152	211	283
Dodecyl	94	129	174	236	310
Tetradecyl	115	151	198	261	335
Hexadecyl	132	170	219	283	...
Acetoxypropionates					
Methyl	...	...	64	110	172
Ethyl	...	36	72	120	181
Propyl	...	45	82	132	196
Butyl	...	58	96	148	212
Amyl	39	69	108	162	228
Hexyl	49	79	120	175	244
Octyl	69	101	144	201	270
Decyl	89	123	167	226	296
Dodecyl	107	143	189	249	320
Tetradecyl	125	162	209	271	...
Hexadecyl	140	179	227	289	...

^{a} Taken from the originals of Figures 1 and 2. Suggested by a reviewer because of the loss of precision in reading boiling points from Figs. 1 and 2 caused by the reduction in size in the reproduced figures.

originally laid off according to $1/(t + 273)$. It can be readily shown that this is mathematically equivalent to a scale laid off according to $1/(t + 183)$. This transformation, with mathematical proof, will be reported elsewhere.[4] Table III shows the boiling points at several pressures (taken from Figs. 1 and 2).

It was found that the logarithm of the vapor pressure at any fixed temperature of either family of homologous esters was a linear function of the number of carbon atoms, x, in the compounds. These equations are listed in Table IV. All these lines pass through the common point log $P = 5.81$

<div align="center">TABLE IV</div>

EQUATIONS RELATING VAPOR PRESSURE (P) AT VARIOUS TEMPERATURES TO THE NUMBER OF CARBON ATOMS (x) IN *n*-ALKYL LACTATES AND α-ACETOXYPROPIONATES

Temp., °C.	Log $P = ax + b$		Deviations,^{a} %	
	a	b	Max.	Average
	Lactates			
50	−0.383	3.01	5	3
100	− .300	3.65	5	2
150	− .242	4.09	6	1
200	− .197	4.40	5	2
250	− .163	4.625	3	1
	Acetoxypropionates			
50	−0.369	3.08	4	2
100	− .290	3.71	5	2
150	− .233	4.14	7	2
200	− .190	4.445	4	2
250	− .157	4.69	7	3

^{a} Deviation of the calculated pressure from that read from Figs. 1 and 2; methyl and ethyl esters excluded. A change in temperature of 1° changes the vapor pressure about 5%.

(4) Rehberg, "Adjustment of the Temperature Scale of Cox Charts," submitted for publication in *Ind. Eng. Chem.*
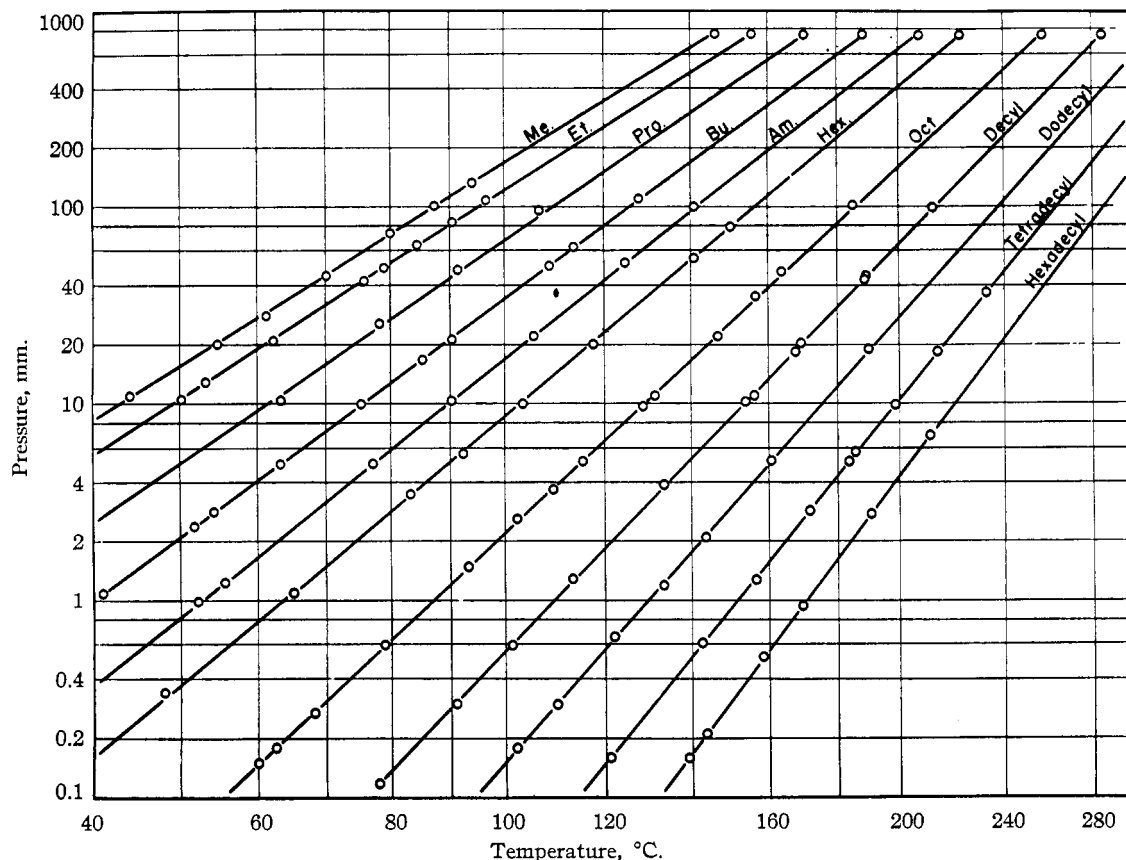
Fig. 1.—Boiling points of n-alkyl lactates.

$\pm$ 0.4 and $x = -7.5 \pm 0.3$. The slopes of the lines (numerical value of a) varies regularly with the absolute temperature

For lactates: $a = (-182/T) + 0.188$

For acetoxypropionates: $a = (-178/T) + 0.186$

The value of a for any chosen temperature can be calculated by these two equations. By using this calculated value and the common point, log $P = 5.81$, $x = -7.5$, the line relating vapor pressure at any chosen temperature to the number of carbon atoms in the compound may be determined. The precision of these correlations is about as good as the accuracy of the experimental data.

Table V contains a set of equations relating the boiling points of the esters at certain fixed pressures to the number of carbon atoms in the compounds. All these lines pass through the common point $x = -7.5$, $10^{-4}T^2 = -2.2$. The slope, a, is related to the pressure by the equations

For lactates: $a = 4.818/(5.865 - \log P)$

For acetoxypropionates: $a = 4.65/(5.865 - \log P)$

These equations for a, together with the common point, enable one to determine lines, similar to those in Table V, for boiling points at any desired pressure.

The boiling points of the esters (B_e) are linearly

TABLE V

EQUATIONS RELATING BOILING POINTS $(T = {}^\circ K.)$ AT VARIOUS PRESSURES TO THE NUMBER OF CARBON ATOMS (x) IN n-ALKYL LACTATES AND ACETOXYPROPIONATES

| Pressure, mm.	$10^{-4}\,T^2 = ax + b$		Deviations in T^a	
	a	b	Max.	Average
	Lactates			
0.1	0.702	3.07	1	0.5
1.0	.823	3.97	1	.5
10	.991	5.23	1	.4
100	1.260	7.00	1	.7
760	1.616	9.92	1	.8
	Acetoxypropionates			
0.1	0.677	2.90	1	.6
1.0	.793	3.75	1	.7
10	.958	4.99	1	.6
100	1.204	6.83	1	.5
760	1.558	9.49	2	.8

^{a} Deviations from boiling points read from Figs. 1 and 2. Methyl and ethyl esters excluded.

related to the boiling points of the corresponding alcohols (B_a)

For lactates: $B_e = 0.86B_a + 87$

For acetoxypropionates: $B_e = 0.78B_a + 120$

These equations fit all the esters, including the methyl and ethyl, with maximum deviations of 3
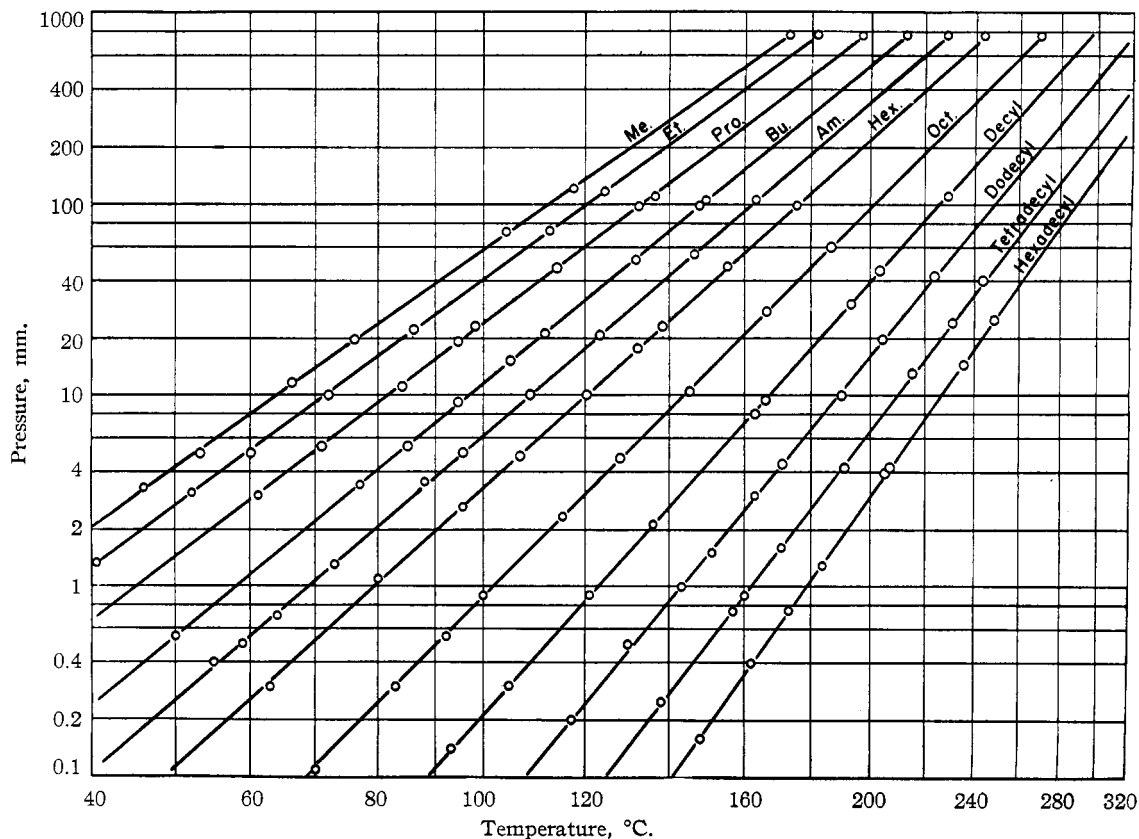
Fig. 2.—Boiling points of *n*-alkyl α-acetoxypropionates.

and 4°, respectively, and average deviations of 1°. The boiling points of the esters at reduced pressures may be similarly correlated with the normal boiling points of the alcohols. From similar correlations with other esters,[5,6] it is probable that these correlations apply, at least approximately, to branched- and secondary-alkyl, alkenyl, alkoxyalkyl, cycloalkyl and other miscellaneous esters of lactic and acetoxypropionic acids.

Densities and Refractive Indices.—These constants were determined at 20° and at 40° (Table II). When refractive index or density was plotted *versus* $1/(x + C)$, where x = number of carbon atoms and C is a constant, a straight line resulted when the proper value of C was used. Since this value of C was not highly critical, it was determined by trial and error, three trials usually being sufficient. As with most such correlations, the methyl esters deviated considerably from the linear relationship. Table VI shows the equations of these straight lines.

Wood, Such and Scarf,[2] who have reported the most extensive work in this field, determined the densities of the *n*-alkyl lactates from the methyl to the nonyl ester over a temperature range of about 0–140°. When these data were plotted on a density *versus* temperature chart, straight lines

(5) Rehberg, Dixon and Fisher, *J. Org. Chem.*, **13**, 254 (1948).
(6) Fein and Fisher, *ibid.*, **13**, 749 (1948).

TABLE VI

RELATIONSHIP OF DENSITY AND REFRACTIVE INDEX TO THE NUMBER OF CARBON ATOMS (*x*) IN *n*-ALKYL LACTATES AND α-ACETOXYPROPIONATES

Equations	—Deviations[a]—	
	Max.	Average
Lactates		
$1/x = 1.12d^{20}{}_4 - 0.9585$	0.0011	0.0005
$1/x = 1.193d^{40}{}_4 - 1.006$	.0015	.0008
$1/(x + 9) = 0.96n^{20}{}_D + 1.4275$	.0006	.0002
$1/(x + 9) = -0.94n^{40}{}_D + 1.3908$	.0006	.0003
Acetoxypropionates		
$1/x = 0.75d^{20}{}_4 - 0.6416$	.0008	.0004
$1/x = 0.80d^{40}{}_4 - 0.6752$	.0008	.0004
$1/(x + 9) = -0.844n^{20}{}_D + 1.2512$	.0005	.0002
$1/(x \times 9) = -0.821n^{40}{}_D + 1.2119$	.0004	.0002

[a] Methyl esters excluded.

were obtained for each ester. From these lines, $d^{20}{}_4$ for the esters were taken, and used to determine the equation representing these densities as a function of the number of carbon atoms in the esters. This equation is $1/x = 1.12d^{20}{}_4 - 0.9560$. It is seen that this line parallels that determined by the first equation in Table VI, but each value of $d^{20}{}_4$ is 0.0022 lower than is found by use of the equation in Table VI. It is notable that Wood, Such and Scarf's data agree closely with the above equation, paralleling our data, up to the octyl es-

ter. Here, however, the deviation is 0.0045; for the nonyl ester, it is 0.0090. It seems likely, therefore, that these two esters were not pure. Their octyl lactate boiled at 137° (11 mm.) and had d^{20}_4 0.9302 (interpolated), whereas ours boiled at 131° (11 mm.) and had d^{20}_4 0.9361. Wassmer and Guye[7] reported b. p. 126–128° (11 mm.), and d^{20}_4 0.936 (interpolated).

The temperature coefficient of density of our lactates agreed, within experimental error, with those of Wood, Such and Scarf. Since the latter coefficients were determined from data covering a much wider temperature range than ours, they should be much more accurate, because small amounts of impurities, which appreciably affect density, have negligible effect on the temperature coefficient of density. By using coefficients calculated from Wood, Such and Scarf's data, it was found that the temperature coefficient of density, m, is related to the molecular weight of the lactates M, according to the equation:[8] $10^4 m = 670/M + 5.35$.

Molecular Refractions.—The calculated values shown in Table II were computed from Vogel's constants. At 20° all the esters showed a rather constant exaltation above the calculated values of about 0.18, whereas at 40° the exaltation was about 0.30. Refractivities calculated from Eisenlohr's constants agreed closely with observed values for the lower esters, but showed increasing differences as the molecular weight of the ester increased. For esters below the octyl members, Eisenlohr's constants gave better agreement; for those above the octyl esters, Vogel's constants were better.

Viscosity.—When the viscosities shown in Table II were plotted as log η versus carbon atoms (x), straight lines were obtained, the equations of which are shown in Table VII.

TABLE VII

RELATION OF VISCOSITY (CPS.) TO NUMBER OF CARBON ATOMS (x) IN n-ALKYL LACTATES AND α-ACETOXYPROPIONATES

t, °C.	Log $\eta = ax + b$		Deviations, cps.[a]	
	a	b	Max.	Average
	Lactates			
20	0.0782	0.026	0.64	0.21
40	.0670	− .146	.27	.08
	Acetoxypropionates			
20	0.069	−0.135	.60	.17
40	.060	− .275	.22	.07

[a] Methyl esters excluded.

Solubility.—The solubility of the esters in water at room temperatures was determined by the method of Fordyce and Meyer.[9] Table II shows the results.

(7) Wassmer and Guye, J. Chim. Phys., 1, 257 (1903).

(8) Griswold and Chew, Ind. Eng. Chem., 38, 364 (1946), have shown a similar relationship for hydrocarbons.

(9) Fordyce and Meyer, ibid., 32, 1053 (1940).

When log S was plotted versus carbon atoms (x), the lactates and acetoxypropionates, with the exception of those having infinite solubility, fell approximately on the same straight line. The equation of this line is

Log $S = -0.433x + 3.52$

The authors are grateful to C. O. Willits and C. L. Ogg of this Laboratory for the analytical data.

Experimental

Materials.—Methyl, ethyl and butyl lactates are commercially available. The technical esters were used after a careful fractional distillation. The other lactates were prepared by direct esterification[8] or, preferably, by the alcoholysis of methyl lactate. For the latter method, 1.5 or 3.0 equivalents of the higher alcohol were used with the methyl lactate. About 0.5 g. of sulfuric acid per mole of methyl lactate was used as catalyst, and the reaction was conducted under reflux in a still having a fractionating efficiency of 5 to 10 theoretical plates. The pot temperature was kept below 150–160°, reduced pressure being sometimes required in the preparation of the higher lactates. Methanol was distilled continuously as fast as formed. When liberation of methanol had virtually ceased (three to six hours), the catalyst was neutralized, and excess alcohol and the product were distilled at the lowest practicable pressure. It is essential that the temperature be kept as low as possible during this distillation if formation of large amounts of lactide and polylactic esters is to be avoided. The esters thus obtained were fractionated under low temperature and pressure before use. Separation of lactide from hexyl, octyl and decyl lactates by distillation was difficult. However, lactide can be titrated with 0.1 N sodium hydroxide, toward which it behaves as a free monobasic acid; hence its detection and estimation are easy.

Most of the acetoxypropionates were made by treating the lactate with a 10% excess of acetic anhydride containing a little sulfuric acid. The tetradecyl ester was made from the alcohol and acetoxypropionyl chloride,[10] in the presence of pyridine. The octyl and cetyl esters were made by both methods. All the esters were fractionally distilled before use.

Physical Constants.—Refractive indices were measured with an Abbe type refractometer. Densities were determined with a Sprengel type pycnometer holding about 10 cc. Viscosities were measured with modified Ostwald pipets which had been calibrated with oils furnished by the Bureau of Standards. The constant temperature bath for all these measurements was set to ±0.1° and controlled to ±0.02°.

Boiling points at various pressures, used in the construction of Figs. 1 and 2, were determined by distillation of the compounds in an alembic type still, which was continuously agitated.[11]

Summary

The lactates and α-acetoxypropionates of eleven n-alkanols having one to sixteen carbon atoms were prepared and carefully purified. Densities, refractive indices and viscosities of these esters at 20 and 40° are reported. Solubilities in water at 25° and melting points are also included.

Linear equations are shown relating vapor pressures, boiling points, refractive indices, densities, viscosities and solubilities of the compounds to the number of carbon atoms in the compounds.

(10) Filachione, Lengel and Fisher, THIS JOURNAL, 66, 494 (1944).

(11) Ratchford and Rehberg, Anal. Chem., 21, 1417 (1949).