Esters of Lactyllactic Acid[1]

BY C. E. REHBERG AND MARION B. DIXON

The process of making esters of lactyllactic acid from lactide was discovered by Claborn,[2] who described the methyl, ethyl and butyl esters. Lactyllactates can also be made by the self-alcoholysis of esters of monomeric lactic acid.[3]

Because the acylation of lactyllactates with monocarboxylic[3] and dicarboxylic[4-6] acids yields esters useful as plasticizers, it was of interest to characterize more fully those lactyllactates which were available to us. These esters were obtained as by-products in the preparation of simple lactates on a large laboratory scale, the conversion to lactyllactate usually being 5 to 20%, depending on the ratio of alcohol to lactic acid used in the esterification.

Table I shows the esters studied and the physical properties determined

The boiling points shown were read from lines on a Cox chart. This chart was notable for the unusally low value of the Antoine constant C, its value being 183 instead of the usual 220–240. Paper graduated for $C = 273$ was converted to $C = 183$ by adding 90° to each temperature on the scale.[7]

Most of the esters in Table I are new compounds, and analytical data on those not previously described are shown in Table II.

TABLE I

PHYSICAL PROPERTIES OF LACTYLLACTATES

Lactyllactate	$n^{20}D$	$n^{40}D$	d^{20}_4	d^{40}_4	Viscosity, cps. 20°	Viscosity, cps. 40°	Boiling points at various pressures[c] 0.1 mm.	1.0 mm.	10 mm.	Solubility in water, g./100 g. (25°)
Methyl[a]	1.4314	1.4240	1.1609	1.1396	28.14	9.36	44	73	111	∞
Ethyl[a]	1.4292	1.4212	1.1136	1.0929	17.09	6.77	48	77	116	∞
n-Propyl	1.4304	1.4222	1.0764	1.0567	14.20	6.09	54	85	124	2.2
n-Butyl[a]	1.4329	1.4247	1.0622	1.0425	17.06	7.04	63	94	134	0.92
n-Hexyl	1.4362	1.4282	1.0280	1.0094	21.64	8.55	79	111	153	.08
n-Octyl	1.4396	1.4317	1.0042	0.9866	26.57	10.45	97	131	176	< .01
s-Butyl	1.4295	1.4216	1.0528	1.0332	20.10	7.58	56	86	126	1.16
2-Octyl	1.4358	....	0.9894	....	...	...	89	122	164	< .01
Allyl[b]	1.4448	1.4366	1.1172	1.0971	18.60	7.45	58	88	128	4.2
2-Butoxyethyl	1.4390	1.4312	1.0760	1.0570	30.89	11.46	91	125	169	.38
2-(2-Butoxyethoxy)-ethyl	1.4433	1.4352	1.0726	1.0531	32.09	12.81	115	150	196	.31
Tetrahydrofurfuryl	1.4578	....	1.1691	....	...	...	120 (0.3 mm.)	...		....
2-Chloroethyl	1.4540	1.4458	1.2351	1.2152	60.20	18.31	94 (0.3 mm.)	...		....

[a] Previously reported by Claborn (ref. 2). The properties he reported are in substantial agreement with ours. [b] Previously reported [Rehberg, Dixon and Fisher, *J. Org. Chem.*, 15, 560 (1950)]. [c] Values read from a Cox chart.

TABLE II

ANALYSES OF LACTYLLACTATES[a]

Lactyllactate	Saponification equivalent Calcd.	Saponification equivalent Found	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Mol. refraction Calcd.	Mol. refraction Found 20°
n-Propyl	102.1	100.7	52.9	52.7	7.9	7.9	48.60	49.04
n-Hexyl	123.2	126.2	58.5	58.6	9.0	9.1	62.45	62.68
n-Octyl	137.2	138.4	61.3	61.2	9.6	9.7	71.69	71.94
s-Butyl	109.1	109.0	55.0	55.0	8.3	8.3	53.21	53.50
2-Octyl	137.2	142.4	61.3	61.9	9.6	9.8	71.69	72.47
2-Butoxyethyl	131.2	130.4	54.9	54.8	8.5	8.6	64.09	64.11
2-(2-Butoxyethoxy)-ethyl	153.2	159.5	54.9	54.7	8.6	8.5	74.97	75.77
Tetrahydrofurfuryl	123.1	125.3	53.6	53.8	7.4	7.5	57.27	57.45
2-Chloroethyl	15.8[b]	15.8[b]	42.8	42.9	5.8	5.9	48.84	29.25

[a] The authors are indebted to C. O. Willits, C. L. Ogg, and their associates, of this Laboratory, for the analyses shown [b] Chlorine, %.

(1) Contribution from the Eastern Regional Research Laboratory, Philadelphia 18, Pennsylvania. One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) H. V. Claborn, U. S. Patent 2,371,281, March 13, 1945.

(3) E. M. Filachione, E. J. Costello, T. J. Dietz and C. H. Fisher, Bureau of Agricultural and Industrial Chemistry, U. S. Department of Agriculture, AIC-295, Feb. 1951 (Processed).

(4) C. E. Rehberg, M. B. Dixon, T. J. Dietz and C. H. Fisher, *Ind. Eng. Chem.*, **42**, 1409 (1950).

(5) C. E. Rehberg and M. B. Dixon, THIS JOURNAL, **72**, 5757 (1950).

(6) C. E. Rehberg, T. J. Dietz, P. E. Meiss and M. B. Dixon, "Plasticizers from Lactic Acid. Lactate Esters Esterified with Dibasic Acids," submitted for publication in *Ind. Eng. Chem.*

(7) C. E. Rehberg, *Ind. Eng. Chem.*, **42**, 829 (1950).

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Synthesis of Δ^1-Allopregnene-17α,21-diol-3,11,20-trione-21-acetate

BY EVELYN WILSON AND MAX TISHLER

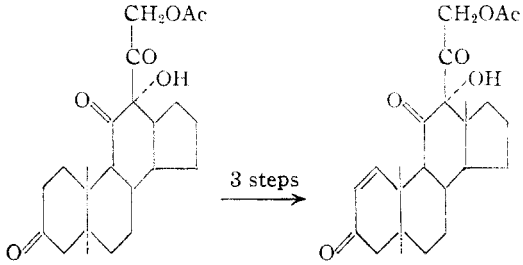
The recent publication by St. Kaufmann and Pataki[1] in which they describe the synthesis of Δ^1-allopregnene-17α,21-diol-3,11,20-trione-21-acetate ("Δ^1-allocortisone acetate") (II) has prompted us

(1) St. Kaufmann and J. Pataki, *Experientia*, **7**, 260 (1951).

to report our experiences on the synthesis of this cortisone isomer.

Our work was undertaken for the purpose of comparing the biological activity of this cortisone isomer with that of cortisone itself.

Allopregnane-17α,21-diol-3,11,20-trione-21-acetate (I), required for this synthesis, was first prepared from cortisone acetate[2] by hydrogenation in



methanol using palladium oxide and a small amount of alkali. In this reduction the desired saturated trione (I) and its C_5-epimer were formed. Separation of the two was achieved by fractional crystallization from acetone, the allo-epimer being the less soluble one.

Bromination of the allo-ketone I and dehydrobromination of the resultant 2-bromo derivative by the 2,4-dinitrophenyl hydrazine–pyruvic acid method[3] gave Δ^1-allopregnene-17α,21-diol-3,11,20-trione-21-acetate (II).

Preliminary biological testing[4] of Δ^1-allopregnene-17α,21-diol-3,11,20-trione-21-acetate showed the compound was essentially inactive in inhibiting the edema produced by the injection of an irritant into the foot of a rat. In the liver glycogen deposition test in rats the compound may have been as much as 10–20% as active as cortisone acetate.

In a preliminary test[5] Δ^1-allopregnene-17α,21-diol-3,11,20-trione-21-acetate showed some ability to inhibit the development of the Patterson lymphosarcoma in AKm. mice. At a dosage of 375 mg./kg./day for one week this cortisone isomer markedly retarded the growth of the tumor; at one-half this dose level the inhibition effect was slight. Cortisone under similar conditions causes marked inhibition at 25–37.5/mg./kg./day.

Allopregnane-17α,21-diol-3,11,20-trione-21-acetate (I) was inactive in the liver glycogen deposition and edema-inhibition tests; it was in fact antagonistic to cortisone acetate in the latter test. In its tumor-inhibiting effect allopregnane-17α,21-diol-3,-11,20-trione-21-acetate had slight, if any, activity at a dose level of 375 mg./kg./day.[5]

Experimental

***Allo*pregnane-17α,21-diol-3,11,20-trione-21-acetate (I).**—A suspension of 7.25 g. (0.018 mole) of 3,11,20-triketo-17α-hydroxy-21-acetoxy-Δ^4-pregnene (cortisone acetate) in 600 cc. of methanol was treated with 600 mg. of palladium oxide catalyst and 12 cc. of 0.001 *N* potassium hydroxide solution. The mixture was then hydrogenated at room temperature at forty pounds pressure. In about one-half hour the uptake of hydrogen stopped; the amout of hydrogen absorbed corresponded to one mole. The reaction mixture was filtered from the catalyst, and the latter was washed thoroughly with chloroform. The combined filtrates were treated with the theoretical amount of ethanolic hydrogen chloride and concentrated to dryness *in vacuo* at 40°. The residue was dissolved in chloroform, and the solution was again concentrated to dryness at 40°. The residue was crystallized twice from acetone and dried at 50° *in vacuo*. The fine white needles melted at 229–233°; wt. 3.1 g. (43%); $[\alpha]^{24}D$ +100° (0.2% chloroform); +78.5° (0.2% acetone).

Anal. Calcd. for $C_{23}H_{32}O_6$ (404.49): C, 68.29; H, 7.97. Found: C, 68.46; H, 7.68.

From the acetone mother liquors of the allo compound the C_5-epimer, pregnane-17α,21-diol-3,11,20-trione-21-acetate, m.p. 225–230°, was obtained. The latter did not depress the melting point of an authentic specimen. A mixture of I and authentic 3,11,20-triketo-17α-hydroxy-21-acetoxypregnane melted at 214–220°.

2-Bromo-*allo*pregnane-17α,21-diol-3,11,20-trione-21-acetate.—Compound I (5.51 g., 0.0136 mole) was dissolved in 50 cc. of chloroform, and 500 cc. of reagent glacial acetic acid was added. A few drops of 1.3 *N* hydrogen bromide in acetic acid was added, and the solution was stirred while 0.0139 mole of bromine in 19 cc. of glacial acetic acid was added dropwise at room temperature. The solution was concentrated to dryness *in vacuo* at 25–35°. The residue was triturated with low-boiling petroleum ether, filtered and recrystallized from ethyl acetate, m.p. 179–185° (dec.); $[\alpha]^{24}D$ +102° (0.5% chloroform); wt. 4.5 g. (68.5%).

Δ^1-*Allo*pregnene-17α,21-diol-3,11,20-trione-21-acetate.—A mixture of 4.35 g. (0.009 mole) of bromoalloketone and 2.2 g. of 2,4-dinitrophenylhydrazine in 125 cc. of glacial acetic acid was stirred and heated at 50–55° in a nitrogen atmosphere for three hours. Then 375 cc. of distilled water was added and the mixture was chilled for two hours. The orange solid was filtered, washed well with water and air-dried. The crude hydrazone showed absorption at 3750 Å.; log *E* 4.45 (methanol). A Beilstein test was negative.

The combined filtrates from the hydrazone contained 95% of the theoretical amount of bromide ion. The crude hydrazone was mixed with 175 cc. of 90% pyruvic acid and 35 cc. of glacial acetic acid and stirred under nitrogen at 80–85° for 5.5 hours. (A clear solution is obtained in about 45 minutes.) The solution was concentrated to a small volume *in vacuo*, and the residue was diluted with a large quantity of chloroform. The solid that precipitates was filtered, and the chloroform filtrate was extracted twice with water, three times with dilute potassium bicarbonate, and finally again with water. The chloroform solution was then distilled to one-half its initial volume at atmospheric pressure. The dark solution was treated with 20 cc. of acetic anhydride and 5 cc. of pyridine. The solution was kept at room temperature overnight; it was then shaken with water. The chloroform layer was then washed successively with 2.5 *N* hydrochloric acid, water, dilute potassium bicarbonate, and then water. The solution was dried with Drierite and passed through a column of 100 g. of acid-washed alumina. The chloroform eluates were treated with Norit, filtered, and the filtrate was concentrated dry *in vacuo*. Recrystallization of the residue from ethyl acetate gave fine white needles, m.p. 253–256° (dec.), wt. 900 mg., $[\alpha]^{24}D$ +115° (0.2% chloroform); $\lambda_{max.}^{EtOH}$ 2280 Å.; log *E* 4.1; $[\alpha]^{24}D$ +123° (0.5% acetone). The material forms a solvate with one-half mole of methanol, m.p. 237–242° (dec.). An analytical sample crystallized from ethyl acetate was analyzed.

Anal. Calcd. for $C_{23}H_{30}O_6$ (402.47): C, 68.63; H, 7.51. Found: C, 68.53; H, 7.66.

The same compound was obtained when the bromoalloketone was dehydrohalogenated with γ-collidine. The yield of the Δ^1-compound, however, by this method was less.

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(2) For the partial synthesis of this compound see G. Rosenkranz, J. Pataki and C. Djerassi, THIS JOURNAL, **73**, 4055 (1951); J. M. Chemerda, E. M. Chamberlin, E. H. Wilson and M. Tishler, *ibid.*, **73**, 4053 (1951).

(3) V. R. Mattox and E. C. Kendall, *ibid.*, **70**, 882 (1950); *J. Biol. Chem.*, **185**, 601 (1950).

(4) We are indebted to Drs. C. C. Porter, R. H. Silber and C. A. Winter of the Merck Institute for Therapeutic Research for carrying out these tests for us.

(5) The tumorlytic-activity tests were kindly carried out for us by Drs. C. C. Stock and K. Sugiura at the Sloan-Kettering Institute for Cancer Research and details of this work will be reported later by them.