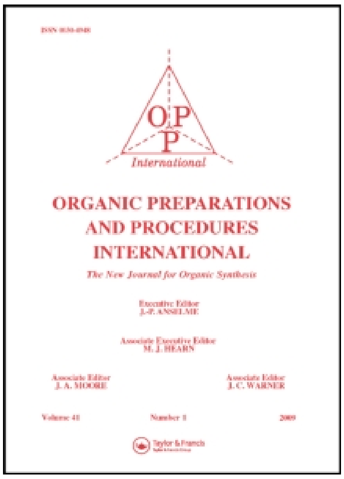

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LOWER ALIPHATIC 2-OXOACIDS AND THEIR ETHYL ESTERS FROM ETHYL ESTERS OF 2-HYDROXY ACIDS

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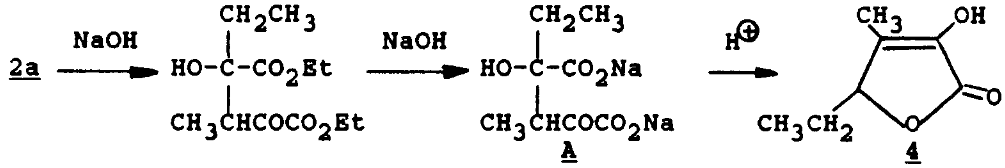
The oxidation of the readily available 2-hydroxy acids[1a,b,2a] to 2-oxoacids[3,4] often proceeds with some cleavage of carbon-carbon bonds.[4,5] Thus only individual cases of such preparations are known,[6,7] and the synthesis of 2-oxoacid esters from 2-hydroxy acid esters are also not numerous.[8-10] However, the oxidation of 2-hydroxy acid N-*tert*-butylamides, to 2-oxoacid derivatives by chromium trioxide in acetic acid was reported to be successful. These N-*tert*-butylamides were obtained by *tert*-butylation of cyanohydrins, which are prepared from aldehydes which may not be easily available. Hydrolysis of the N-*tert*-butylamides requires long reflux times (8-24 hrs) in a mixture of conc. hydrochloric and acetic acids.[11] Yields of oxidation of aliphatic 2-hydroxy acids amounted to 43%-44%,[7] and those of hydroxy esters and of hydroxy N-*tert*-butylamides were 51-85%.[8,9,11] We now describe a large-scale preparation of ethyl esters of lower aliphatic 2-oxoacids 2 and of the 2-oxoacids 3 from the readily available 2-hydroxyacid ethyl esters 1[1a-c,2a] (Table 1). Since these 2-oxoacids correspond to natural α-amino acids, *vis.*, α-aminobutyric acid, valine, leucine and isoleucine, they are useful for the synthesis of α,β-dehydroamino acids and α,β-dehydropeptides.[12-14]

$$\underset{\underline{1}}{RCH(OH)CO_2C_2H_5} \xrightarrow[CH_3CO_2H]{CrO_3} \underset{\underline{2}}{RCOCO_2C_2H_5} \xrightarrow{OH^{\ominus}/H_2O} \xrightarrow{H^{\oplus}} \underset{\underline{3}}{RCOCO_2H}$$

a) $R = CH_3CH_2$ b) $R = (CH_3)_2CH$

c) $R = (CH_3)_2CHCH_2$ d) $R = (\underline{RS})\text{-}CH_3CH_2(CH_3)CH$

The 2-hydroxyacid ethyl esters 1 were added dropwise to an acetic acid solution of CrO_3; little or no decomposition products could be detected while degradation took place if the addition was done in a reversed manner.[11] The products (2) of at least 95% purity were obtained in 84-90% yields. These esters 2 were easily hydrolyzed by aqueous sodium hydroxide to give the sodium salts of 3b-d which were stable and convenient for storage. The salt of 3b is described as an example (3b itself is no longer commercially available because of its instability[15]). Acidification of solutions of the salts with hydrochloric acid followed by extraction with an organic solvent and distillation afforded the corresponding free acids 3b-d of purity of 96% or better in yields of 81-91%. However, similar hydrolysis of 2a using NaOH or the hydrolysis with saturated Na_2CO_3 or $NaHCO_3$ solutions at 70-80° led to mixtures of various sodium salts (^{13}C-NMR) which after acidification gave 4 as the main product (yield 65%). Compound 4 formed presumably by dimerization of 2a accompanied by decarboxylation and lactonization of intermediate A which can be rationalized as follows.



That was hydrolysis of 2a at pH 7.5, acidification, distillation and crystallization which gave 3a in 39% yield (Method A). However, better results were obtained by acidic hydrolysis of 2a according to the procedure of Poisel[16] (Method B). Then, neither dimerization nor subsequent reactions were observed.

TABLE 1. *Yields and Characteristic Data of Ethyl Esters of 2-Oxoacids 2[a] and of the Acids 3[a]*

	Yield %	bp. (°C/Torr)	lit. bp. (°C/Torr)	n_D^{20} or mp. (°C)	lit. n_D^{20} or mp. (°C)
2a	89	70-71/20	ca.75/20[2b]	1.4135	-
2b	87	73-75/23	65-69/15[2c]	1.4110	1.4115[17]
2c	84	86-86.5/20	93/25[2d]	1.4178	1.4185[18]
2d	90	2.5-83/18	78-79/15[2d]	1.4180	-
3a	70	74-75/15	75/15[2e]	30-32	30-33[19a]
3b	91	78-84/17	65-67/10[2f]	30-31	31[2f]
3c	81	75.5-76/8	82-83/11[19b]	6-9[b]	7-9[19b]
3d	90	80-82/8	84/15[2d]	30-31	30.5[2d]

a) All compounds were characterized by ^{1}H-NMR spectra.

b) n_D^{20} = 1.4309 (lit.[19b] n_D^{20} = 1.430).

EXPERIMENTAL SECTION

2-Hydroxybutyric acid was obtained from butyric acid via bromination,[1a] and hydrolysis.[2a] Other 2-hydroxy acids were prepared from the corresponding alkylmalonic acids via bromination, decarboxylation and hydrolysis.[1b] Neither intermediates nor products were purified. Esterifications of crude 2-hydroxy acids were carried out in the presence of an ion exchanger[1c] to give the ethyl esters of purity >97%. Reactions were monitored and homogeneity of products was checked by GC using a GIEDE GCHF 18.3.6. apparatus (GDR) on a column 15%SE-30CQ 100/120, diameter 3 mm, lenght 2 m. ^{1}H- and ^{13}C-NMR: BS 567 instrument (Tesla) with $Si(CH_3)_4$ (for 2-4) or sodium 4,4-dimethyl-4-silapentane sulfonate (for sodium salts) as an internal reference. MS: MKh 1321 instrument (Nautshpribor, USSR), 70 eV, EI ionization, temperature of ion source 220°. Melting points (uncorrected): Boëtius apparatus. Microanalytical data (C,H): Perkin-Elmer.

Ethyl Esters of 2-Oxoacids (2a-d). *General Procedure*.-In a 30 L flask fitted with a stirrer, a reflux condenser and a dropping funnel, were placed 97% acetic acid (10 L) and chromium oxide (2 kg, 20 mol). The flask contents were heated to 90-100° and stirred until all the chromium oxide had dissolved. After cooling to 20°, 2-hydroxyacid ethyl ester (1a-d) (13 mol) was added dropwise over a period of 2 hrs while the temperature was kept between 25-30°. After the addition, the flask was heated to 70° and maintained at this temperature for a few minutes until the end of oxidation (monitored by GC). After cooling, the reaction mixture was poured into water (50-100 L) and extracted with methylene chloride (3-4 x 2.5-3.5 L). Water was added to the collected organic extracts and, with continous stirring, the whole was neutralized with finely powdered Na_2CO_3 until pH 7 was reached. Then, the organic phase was dried with $MgSO_4$, the solvent removed at 150 Torr and the residue distilled using a 1 m Vigreux column. Yields and analytical data are given in Table 1. The preparation of ethyl esters of 2-oxoacids can be carried out on smaller scale as well.

2-Oxoacids (3b-d). *General Procedure*.- To a vigorously stirred suspension of 2-oxoacid ester (2b-d) (7 mol) in water (1 L) in a 3 L flask, a 30% solution of NaOH was added in portions so that the temperature did not exceed 70° and until pH 12 ± 0.5 was reached and did not change over a period of 30 min. The,reaction mixture, cooled to 20°, was extracted with (3 x 400 mL) methylene chloride (2b) or benzene (2c and d). The aqueous phase was evaporated *in vacuo* (removal of ethanol), the residue dissolved in a minimum water and acidified with conc. HCl until turbidity (pH 1.3). Compound 3b was extracted with 2-butanone (3 x 0.75 L) and 3c and 3d with benzene (2 x 1 L), the organic phase dried over $MgSO_4$ and evaporated at 40 Torr. The crude 2-oxoacid was distilled using a 0.5 m Vigreux column. Yields and analytical data are listed in Table 1.

Sodium Salt of 3b.- To the neat stirred ester 2b (369.5 g, 2.56 mol) in a 2 L flask, a 30% NaOH solution was added dropwise so that the temperature and pH did not exceed 70° and 7.5 respectively. After 30 min, when the last portion of the base was added, the flask was cooled to 20° and its content extracted with methylene chloride (3 x 150 mL). The aqueous phase was removed by distillation at 40 Torr, the residue crushed and dried to a constant weight (342 g, 96%) at 100°/0.5 Torr, mp. 205-208°, lit.[19c] mp. 220-230°. ^{1}H-NMR (D_2O): δ 1.20, 1.22 (d,d <7,7> 6H), 3.05 (q <7> 1H)

Anal. Calcd for $Na[C_5H_7O_3].1/8H_2O$: C, 42.78; H, 5.21

Found: C, 42.70; H ,5.08

5-ethyl-3-hydroxy-4-methyl-2-oxo-3-oxolen (4).- The alkaline solution resulting from the hydrolysis of 2a (286 g, 2.2 mol) [according to the general procedure for 2-oxoacids (3b-d)] was acidified with conc. HCl to pH ≈1, saturated with NaCl and extracted with 2-butanone. The organic layer was dried over $MgSO_4$ and evaporated at 40 Torr. The residue was distilled using a 0.5 m Vigreux column and two fractions were collected with the following characteristics:

Compd	bp. (°C/Torr)	Yield (%)	mp. (°C)	tlc (R_f^{a})	^{1}H-NMR Spectra (δ) <J in Hz> ($CDCl_3$)
3a	68-80/16	4.5	28-31	0.25	1.00 (t <7> 3H), 2.85 (q <7> 2H), 10.65 (s, 1H)
4b	79-80/0.1	65.0	30-31	0.82	0.80 (t <7> 3H), 1.45 (m, 2H), 1.80 (s, 3H), 4.90 (m, 1H), 7.65 (s, 1H)

a) Silica gel plates (Merck no 5553; FRG) in chloroform/methanol (5:1), visualized with fluorescein-bromine. b) Compound is of 98% purity and is hygroscopic. It reacts with bromine (with HBr evolution and the resulting product oxidizes HI to I_2), $FeCl_3$, CH_2N_2, $(CH_3O)_2SO_2$ and $NaHCO_3$ (with CO_2 evolution) but not with 2,4-dinitrophenylhydrazine.- IR (film) (Specord IR 71, C. Zeiss, GDR): 3380 cm^{-1} (OH), 3000, 2840 (CH), 1730 (C=O), 1560 (C=C), 1145 (C-O).- MS: m/z (%) = 142 (M^+; 37).

Anal. Calcd for $C_7H_{10}O_3 \cdot 0.5H_2O$: C, 55.64; H, 6.67

Found: C, 55.96; H, 7.03

Methyl Ether of 4: ^{1}H-NMR (CCl_4): δ 0.90 (t <7> 3H), 1.45 (m, 2H), 1.84 (s, 3H), 3.90 (s, 3H), 4.65 (m, 1H).- MS: m/z (%) = 156 (M^+; 23), 127 (M^+; 26).

2-Oxobutanoic Acid (3a). *Method A*.- To a vigorously stirred suspension of ethyl ester 2a (130g, 1 mol) in water (100 mL) in an ice-cooled 0.5 L flask, was added dropwise a 30% solution of NaOH so that the temperature and pH did not exceed 20° and 7.5 respectively. The reaction mixture was extracted with methylene chloride (3 x 100 mL) and the aqueous phase was evaporated to dryness at 40° at 1 Torr. The residue (130 g), dissolved in water (300 mL), was acidified with 2 N HCl to pH 1.3, saturated with NaCl and extracted with 2-butanone (3 x 500 mL). After drying over $MgSO_4$, the solution was evaporated at 40 Torr and the residue distilled to yield 33 g (50%) of 3a, bp. 76-80°/18 Torr, (92% purity by GC). The product was dissolved in a hot CCl_4-hexane mixture (1:3) and the solution was decolorized with active charcoal. The solution was then cooled to -20° and the resulting crystals collected at this temperature, washed with cold hexane and dried at 20°/5 Torr to yield 25.7 g (78%) of 3a (98% purity by GC), mp. 30-32°.

Method B.- In a 10 L flask fitted with a stirrer, ethyl ester 2a (130 g, 1 mol) was heated with 1 N HCl (4 L) for 2 hrs at 65-70°. After cooling to 20°, the solution was saturated with NaCl and extracted with diethyl ether (10 x 500 mL). The collected organic extracts were dried over $MgSO_4$, evaporated at 150 Torr and the residue was distilled. Yield and analytical data are listed in Table 1.

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