176. Chemistry of Succinyl Succinic Acid Derivatives. Part V[1]). On the Transesterification of Succinyl Succinates

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Summary

The unique stabilization of the ester link in dialkyl succinyl succinates is explained and a facile route to known as well as to hitherto inaccessible succinyl succinates is suggested. New representatives of this series are described.

Introduction. - Since their early discovery [2], various syntheses of succinyl succinates, starting from dialkyl succinates [3-16] or from γ-halo-acetoacetates [17-25] have been thoroughly described. Transesterification as a straightforward general route has, however, been omitted from the literature, except for two special cases [26] [27], pointing to a possible resistance of the molecule towards such transformation.

Results and discussion. - We found dimethyl succinyl succinate unaffected by boiling ethyl or allyl alcohol and believe that the observed stability of the ester link in succinyl succinates arises from its special geometry.

Diethyl succinyl succinate (DESS) was reported to be in its planar, intramolecularly hydrogen bonded form in the crystal [28], and a similar structure was inferred for the solution. The strong hydrogen bonding between enol and ester-carbonyl group shown by the lack of hydroxyl absorption in the infrared [29], prevents rotation of the ester group about its attachment axis. In being restricted to the molecular plane, the enol oxygen atom is located on the S_N2 approach axis of transesterification [30], thereby blocking an intermolecular nucleophilic attack on the ester-carbonyl group. Although small the enol furnishes an effective steric protection.

Ways to overcome this stabilisation may involve an S_N1 mechanism which is unlikely in solution, tautomerisation to the keto form of succinyl succinate, of which no direct evidence has been found, or substitution of the enolic hydrogen atom

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[1]) Part IV: [1].

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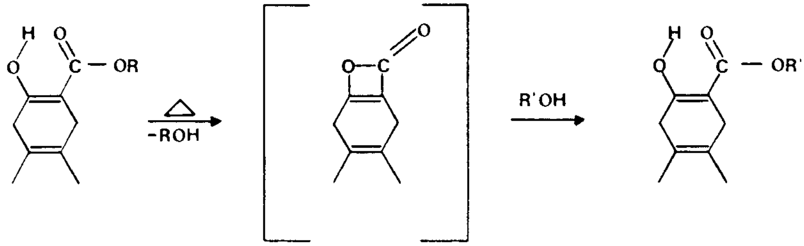
Scheme. *Transesterification of succinyl succinate through a transient four membered lactone*



by a nonchelating residue, such as acyl or alkyl, to allow rotation of the ester groups. Such an approach is, however, made difficult by the lability of enol ethers.

Hydrogenation of the cyclohexadienyl ring is expected to remove the original planarity of the molecule and produce a chair conformation, in which the steric hindrance towards transesterification is eliminated [1]. In this case activation of the ester group is attained at the expense of chelation.

Finally, transesterification with retention of the chelation is feasible probably *via* a strained lactone [31], resulting from a nucleophilic attack of the masking enol on the adjacent ester group: when carrying out the reactions at elevated temperatures, transesterification products from the nucleophiles employed are obtained *(Scheme)*. This procedure offers general access to succinyl succinic esters and for the first time[2]) allows synthesis of succinyl succinates carrying reactive ester groups, as presented in the *Table*.

Experimental Part

All reactions were carried out under N_2 to prevent oxidation of the cyclohexadienyl moiety. Chemical yields are based on DESS and are not optimized. The conversion of DESS (Diethyl succinyl succinate) could be followed by TLC. (alumina or silica gel plates with acetone/petroleum ether, using UV.-fluorescence for identification).

The alcoholates were obtained *in situ* introducing metallic sodium into the previously distilled commercial alcohols or mercaptane. Dimethyl and diethyl succinyl succinates were acquired from *Lonza AG*, Basle, and used with no further purification.

1. *Dioctyl succinyl succinate.* To 1-octanol (1040 g, 8 mol) which has been reacted with sodium (0.5 g, 0.02 mol), DESS (102.4 g, 0.4 mol) is added and the reaction mixture is stirred at 190° for 2 h, during which 45 ml of ethanol distil off. After cooling to RT. the precipitate is filtered off and crystallized from petroleum ether (50–70°) to give the title compound (90.5 g, 0.215 mol) in 54% yield.

2. *Bis(2-ethylhexyl) succinyl succinate.* To 2-ethylhexanol (2.6 kg, 20 mol) treated with sodium (1 g, 0.04 mol), DESS (512 g, 2 mol) is added. The reaction mixture is stirred for 2.5 h at 170°, neutralized with acetic acid at 100° and excess 2-ethylhexanol is distilled under reduced pressure. After cooling, acetone (2 l) is added and the solution is kept over night at –20°. The precipitate is filtered off, recrystallized from acetone and dried i.V. to give the title compound (624 g, 1.47 mol) in 74% yield.

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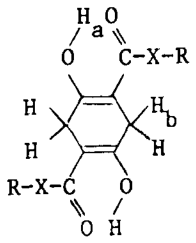
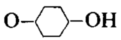
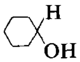
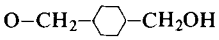
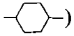
[2]) As an exception bis(6-hydroxyhexyl)-succinyl succinate was obtained from a polyester of succinic acid and 1,6-hexanediol. By this same procedure bis(2-hydroxyethyl)-succinyl succinate proved inaccessible [32].

Table. *Physical data of diverse succinyl succinates of the general formula*



Nr.	X–R	M.p. (solvent)	Anal. Found % (Calc. %)	δ (ppm) in $CDCl_3$ at RT., TMS = 0, H_a at ~ 12.0, H_b at 3.16–3.26, as *s*
1	$O-(CH_2)_7CH_3$	91–92° (petroleum ether)	C 68.1 (67.88) H 9.8 (9.51)	4.17 (*t*, $CH_2O\overset{\overset{O}{\|}}{C}$); 1.28 (*m*, CH_2); 0.87 (*t*, CH_3)
2	$O-CH_2CH(CH_2CH_3)[(CH_2)_3CH_3]$	30–33° (acetone)	C 67.8 (67.88) H 9.4 (9.51)	4.10 (*d*, $CH_2O\overset{\overset{O}{\|}}{C}$); 1.95 (*m*, CH_2; CH); 0.90 (*t*, CH_3)
3	$O-(CH_2)_{17}CH_3$	103–104° (petroleum ether)	C 74.9 (74.93) H 11.7 (11.46)	4.17 (*t*, $CH_2O\overset{\overset{O}{\|}}{C}$); 1.28 (*m*, CH_2); 0.87 (*t*, CH_3)
4[a])	$S-(CH_2)_{11}CH_3$	97–98° (petroleum ether)	C 67.6 (67.54) H 10.0 (9.94) S 11.3 (11.27)	2.96 (*t*, $CH_2S\overset{\overset{O}{\|}}{C}$); 1.26 (*m*, CH_2); 0.96 (*t*, CH_3)
5[b])	$O-CH_2CH=CH_2$	111° (acetone/petroleum ether)	C 59.8 (59.99) H 5.9 (5.77)	5.8 (*m*, $CH_2O\overset{\overset{O}{\|}}{C}$); 5.3 (*m*, =CH); 4.7 (*m*, $=CH_2$)

6	$O{-}CH_2(CH_2)_7CH{=}CH(CH_2)_7CH_3$	62° (acetone)	C 74.8 (75.36) H 11.1 (10.95)	4.17 (*t*, $CH_2O\overset{O}{\overset{\|}{C}}$); 5.3 (*t*, =CH); 2.0 (*m*, $CH_2{-}C{=}C$); 1.29 (*m*, CH_2); 0.87 (*t*, CH_3)
7	$O{-}CH_2CH_2OH$	138-139° (tetrahydrofuran)	C 50.1 (49.99) H 5.7 (5.61)	4.3 (*m*, $CH_2O\overset{O}{\overset{\|}{C}}$); 3.9 (*m*, CH_2OH); 1.85 (*s*, OH)
8	$O{-}CH_2CH_2CH_2OH$	98-100° (2-propanol)	C 53.3 (53.15) H 6.6 (6.39)	4.37 (*t*, $CH_2O\overset{O}{\overset{\|}{C}}$); 3.73 (*t*, CH_2OH); 1.95 (*t*, CH_2); 1.80 (*s*, OH)
9	$O{-}CH_2(CH_2)_2CH_2OH$	110° (toluene)	C 55.8 (55.80) H 7.0 (7.04)	4.22 (*t*, $CH_2O\overset{O}{\overset{\|}{C}}$); 3.68 (*t*, CH_2OH); 1.72 (*m*, CH_2); 1.80 (*s*, OH)
10	$O{-}CH_2C(CH_3)_2CH_2OH$	144-145° (ethanol)	C 57.9 (58.04) H 7.8 (7.59)	4.07 (*s*, $CH_2O\overset{O}{\overset{\|}{C}}$); 3.30 (*s*, CH_2OH); 2.03 (*s*, OH); 0.96 (*s*, CH_3)
11[c])	$O{-}CH_2(CH_2)_4CH_2OH$	96-97° (toluene)	C 59.9 (59.97) H 8.3 (8.07)	4.19 (*t*, $CH_2O\overset{O}{\overset{\|}{C}}$); 3.65 (*t*, CH_2OH); 1.47 (*m*, CH_2); 1.43 (*s*, OH)
12[d])		155-160° (acetone/petroleum ether)	C 60.5 (60.58) H 7.7 (7.13)	5.0 (*m*, $CHO\overset{O}{\overset{\|}{C}}$); 3.75 (*m*, ); 1.7 (*m*, ring CH_2)
13		156-158° (acetone)	C 63.5 (63.69) H 8.1 (8.03)	4.0 (*d*, $CH_2O\overset{O}{\overset{\|}{C}}$); 3.45 (*d*, CH_2OH); 0.75-2.10 (*m*, ); 1.33 (*s*, OH)

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[a]) H_a at 13.0 ppm. [b]) Lit. [2d]: m.p. 115°. [c]) Lit. [32]: m.p. 96°. [d]) Isomer mixture; H_a at 3.16 and 3.20

3. *Dioctadecyl succinyl succinate.* To 1-octadecanol (1624 g, 6 mol) reacted with sodium (0.5 g, 0.02 mol), DESS (76.8 g, 0.3 mol) is added and allowed to react at 200° for 2 h. Part of the evolved ethanol (28 ml) distils off. The reaction solution is cooled to 80°, diluted with ethanol (4 l) and filtered warm. Recrystallization from pet. ether 50-70° gives the title compound (82.5 g, 0.12 mol) in 40% yield.

4. *Didodecyl thiosuccinyl succinate.* To 1-dodecyl mercaptane (404 g, 2 mol) an ethanolic solution of sodium ethylate (100 mg sodium in 20 ml ethanol) is added. DESS (25.6 g, 0.1 mol) is introduced and the reaction is stirred 15 h at 160° and additional 6 h at 180°. After cooling, the precipitate is filtered and crystallized from pet. ether 50-70° to give the title compound (12.5 g, 0.022 mol, 22% yield).

5. *Diallyl succinyl succinate.* Sodium (0.2 g) is reacted with allyl alcohol (58 g, 1 mol) and the resulting solution is introduced into a glass lined autoclave charged with DESS (51.2 g, 0.2 mol). After deaeration the mixture is pressurised at 165° for 8 h (max. press 15 atm.). After cooling, the precipitate (30 g, 0.11 mol, 54% yield) is crystallized from acetone/petroleum ether to give the title compound.

6. *Dioleyl succinyl succinate.* Oleyl alcohol (1.96 kg, 7.3 mol) is reacted with metallic sodium (1.2 g, 0.05 mol) at 120°. To the resulting solution DESS (373 g, 1.45 mol) is added and the mixture is stirred at 180° for 1.5 h, during which evolved ethanol distils off. The mixture is then cooled to RT., diluted with 5 l acetone, neutralized with aqueous HCl-solution and further cooled to 5°. The precipitate is filtered off and washed with cold acetone to give the title compound (590 g, 0.85 mol) in 58% yield.

7. *Bis(2-hydroxyethyl) succinyl succinate.* To 1,4-dihydroxyethane (7.44 kg, 120 mol) metallic sodium (4.6 g, 0.2 mol) is added. After dissolution, DESS (1.536 kg, 6 mol) is introduced and stirred at 150° for 6 h, during which 640 ml distillate are collected. The mixture is then poured into 7 l water containing 20 ml conc. hydrochloric acid. The precipitate is filtered off, dried in *vacuo* at 50° and crystallized in tetrahydrofuran (THF) to give the title compound (760 g, 2.6 mol, 44% yield).

8. *Bis(3-hydroxypropyl) succinyl succinate.* Into 1,3-dihydroxypropane (912, 12 mol) reacted with metallic sodium (0.7 g, 0.03 mol), DESS (154 g, 0.6 mol) is added. The mixture is stirred at 170° for 3.5 h, cooled and poured into 10 l water. The precipitate is washed with water, dried over night in *vacuo* at 50° and crystallized from 2-propanol to give the title compound (33 g, 0.1 mol, 17% yield).

9. *Bis(4-hydroxybutyl) succinyl succinate.* To 1,4-butanediol (2.7 kg, 30 mol) reacted with sodium (0.75 g, 0.03 mol), DESS (256 g, 1 mol) is added. The mixture is stirred at 160° for 5 h during which 60 ml ethanol distil off. The contents are then poured into 2.7 l water containing 4 ml conc. hydrochloric acid, cooled to RT. and filtered over cloth. The crude product is dried over P_2O_5 and crystallized from toluene to give the title compound (115 g, 0.33 mol, 33% yield).

10. *Bis(2,2-dimethyl-3-hydroxypropyl) succinyl succinate.* To neopentylglycol (3.12 kg, 30 mol) reacted with sodium (1.72 g, 0.07 mol), DESS (384 g, 1.5 mol) is added and the mixture is stirred at 160° for 4 h, during which part of the evolved ethanol distils off. The solution is then poured into 6 l water acidified with 15 ml conc. hydrochloric acid, the precipitate is filtered off and crystallized from ethanol to give the title compound (336 g, 0.97 mol) in 64% yield.

11. *Bis(6-hydroxyhexyl) succinyl succinate.* To 1,6-hexanediol (4.602 kg, 39 mol) reacted with sodium (1 g, 0.04 mol), DESS (333 g, 1.3 mol) is added and the mixture is stirred at 160° for 5.5 h followed by pouring into 5 l water acidified with 4 ml conc. hydrochloric acid. The precipitate is thoroughly rinsed with water, dried over P_2O_5 and crystallized from toluene to give the title compound (146 g, 0.36 mol, 28% yield).

12. *Bis(4-hydroxycyclohexyl) succinyl succinate.* To 1,4-cyclohexanediol (232 g, 2 mol, isomer mixture) reacted with 100 mg sodium, DESS (25.6 g, 0.1 mol) is added and the mixture is stirred at 170° for 4 h. After cooling to RT. the solution is poured into 700 ml water, the precipitate is filtered off, dried over night in *vacuo* at 60° and crystallized from acetone/petroleum ether to give the title compound (32 g, 0.08 mol, 80% yield).

13. *Bis[4-(hydroxymethyl) cyclohexylmethyl] succinyl succinate.* To 1,4-bis(hydroxymethyl)-cyclohexane (288 g, 2 mol) reacted with metallic sodium (75 mg), DESS (25.6 g, 0.1 mol) is added at 140°. The temp. is raised to 170° and the mixture is stirred for 5 h. The solution is cooled to RT. and poured into 800 ml water. The precipitate is filtered off and crystallized from acetone to give a product (32.7 g, 0.07 mol, 70% yield) of m.p. 153-156°. Recrystallization gives the title compound.

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