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A FACILE SYNTHESIS OF α,α,ω,ω-TETRAHALO-α,ω-DICARBOXYLIC ESTERS

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Abstract - The synthesis of some α,α,ω,ω-tetrachloro and tetrabromo-derivatives of the hypolipidemic 3,3,14,14-tetramethylhexadecanedioic acid from α,ω-dihalo-esters, carbon tetrahalides and lithium diisopropyl amide has been described. Interaction of α,ω-dichloro esters with CBr_4 was shown to give the expected α,ω-dibromo-α,ω-dichloro compounds, but treatment of bis(1-methylethyl) 2,15-dibromo-3,3,14,14-tetramethylhexadecanedioate with CCl_4 was found to result in halogen exchange yielding the tetrachloro-diester as the major product.

In the course of our study on long chain α,ω-dicarboxylic acids of hypotriglyceridemic and hypocholesterolemic potencies,[1,2] we found α,ω-halogenated 3,3,14,14-tetramethyl-1,16-hexadecanedioic acids of special pharmacological interest. While the syntheses of the α,ω-*di*chloro- and *di*bromo-derivatives could be accomplished simply by *N*-halosuccinimide halogenation of the acid chloride of 3,3,14,14-tetramethyl-1,16-hexadecanedioic acid (1)[3] attempts to introduce two further halogen atoms at the α and ω positions by this method, gave unsatisfactory results. The current preparations of such compounds proved either extremely tedious or low yielding. Both the methods of Shevchenko and Kukhar[4], who prepared some α,α,ω,ω-tetrachloro-α,ω-dicarboxylic esters by PCl_5-chlorination of α,ω-dinitriles followed by alcoholysis of the resulting α,α,ω,ω-tetrahaloalkylbis(phosphorimidic trichloride) derivatives, and that of De Buyck et al.[5] in which long chain carboxaldehydes are chlorinated in DMF to oxidizable α,α-dichloro-compounds, proved impractical for our sterically hindered α,ω-dicarboxylic esters. Nor did the method of Villieras et al.[6] in which dihaloacetate enolates are alkylated serve our goal, as it was shown to be usually restricted to *primary* alkyl halides.

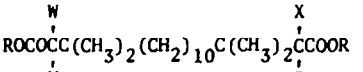
We found it, therefore, imperative to search for a simple and effective synthesis of the title compounds that is non-sensitive to steric hindrance and that can be used for large scale preparations.

RESULTS AND DISCUSSION

As carbon tetrachloride and tetrabromide were shown to induce α chlorination in some simple carboxylic esters in the presence of lithium diisopropylamide (LDA)[7], we investigated the possibility to apply this method also for diesters which have already halogen atoms in the α-positions.

When e.g., bis(1-methylethyl) 2,15-dichloro-3,3,14,14-tetramethyl-1,16-hexadecanedioate (3) [prepared by *N*-chlorosuccinimide (NCS) chlorination[8] of 3,3,14,14-tetramethyl-1,16-hexadecanedioic acid (1) in $SOCl_2$ followed by alcoholysis] was reacted with CCl_4 and LDA in THF at -78°, bis(1-methylethyl) 2,2,15,15-tetrachloro-3,3,14,14-tetramethyl-1,16-hexadecanedioate (6) was obtained in 61% yield. A trichloro-ester 4 was formed as well, as a minor side product. Likewise, the methyl ester 2 gave under the same conditions the tetrachloro-compound 5.

Treatment of methyl 2,15-dibromo-3,3,14,14-tetramethyl-1,16-hexadecanedioate (7)



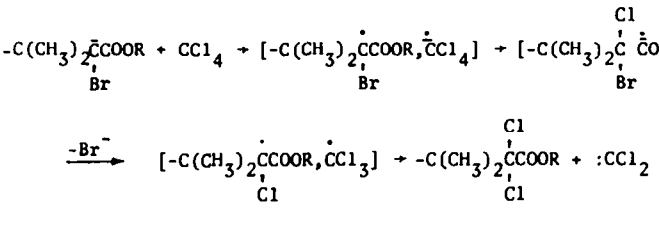
1, R = W = X = Y = Z = H
2, R = CH_3 W = X = H Y = Z = Cl
3, R = $(CH_3)_2CH$ W = X = H Y = Z = Cl
4, R = $(CH_3)_2CH$ W = H X = Y = Z = Cl
5, R = CH_3 W = X = Y = Z = Cl
6, R = $(CH_3)_2CH$ W = X = Y = Z = Cl

7, R = CH_3 W = X = H Y = Z = Br
8, R = CH_3 W = X = Y = Z = Br
9, R = CH_3 W = H X = Y = Z = Br
10, R = $(CH_3)_2CH$ W = X = Cl Y = Z = Br
11, R = CH_3 W = H X = Z = Cl Y = Br
12, R = H W = X = Y = Z = Cl

(prepared by light induced bromination of the acid chloride of 1 followed by methanolysis[3]) with CBr_4, LDA and THF at -78° afforded the tetrabromo-ester 8 in 73% yield. A tribromo by product 9 which accompanied 8 could easily be separated by column chromatography.

Interaction of the dichloro ester 3 with CBr_4 resulted in the formation of the expected bis(1-methylethyl) 2,15-dibromo-2,15-dichloro-3,3,14,14-tetramethyl-1,16-hexadecanedioate (10). However, treatment of the bis-enolate of the *dibromo*-ester 7 with CCl_4 gave 67% of the tetrachloro-compound 5 accompanied by 15% of methyl 2-bromo-2,15-dichloro-3,3,14,14-tetramethyl-1,16-hexadecanedioate (11).

Halogenation of carbanions with carbon tetrahalides was proposed to follow either an S_NX type mechanism[9] or to be initiated by a discrete electron transfer followed by halogen migration from $\dot{C}X_4$.[10] The replacement of the bromine atoms in 7 by chlorine in the presence of CCl_4 suggests, however, that in this process the single electron transfer is followed by the migration of a chlorine anion in an $S_{RN}1$ type mechanism.[11] (Scheme 1). The preferential cleavage of the C-Br rather than the C-Cl bond can be rationalized in terms of the difference in the bond energies of the two carbon-halogen linkages.



Scheme 1

EXPERIMENTAL

Bis(1-methylethyl) 2,15-dichloro- and bis(1-methylethyl) 2,2,15-trichloro-3,3,14,14-tetramethyl-1,16-hexadecanedioate (3), (4)

A soln of 1 (1.71 g, 5 mmol) in $SOCl_2$ (100 ml) was refluxed for 2.5 hr. NCS (2.67 g, (20 mmol) in the same solvent (30 ml) was added and the reflux continued for further 4.5 h. Most of the $SOCl_2$ was removed *in vacuo* and the resulting oil treated with C_6H_6 (2x) and evaporated to dryness. CCl_4 (50 ml) was added, the suspension filtered and the filtrate reacted at 0° with 2-propanol (20 ml). The mixture was stirred for 48 hr at room temperature, solvents removed *in vacuo*, and the resulting oil flash chromatographed on silica gel (mixtures of CH_2Cl_2 and hexane serving as eluent) to yield 3 (1.70 g, 69%), 4 (0.50 g, 19%) and traces of the tetrachloro-ester 6. Compound 3: colorless oil. (Found: C, 62.87; H, 9.98; Cl, 14.33. Calc. for $C_{26}H_{48}Cl_2O_4$: C, 63.03; H, 9.69; Cl, 14.34%). IR (cm^{-1}) 1743, 1724 (C=O). 300 MHz ^1H NMR ($CDCl_3$) δ 1.036 (s, 6H, CH_3), 1.057 (s, 6H, CH_3), 1.283 [m, 28H, CH_2 + $CH(CH_3)_2$], 1.432 [m, 4H, $CH_2C(CH_3)_2$], 4.122 (s, 2H, CHCl), 5.067 [hept, 2H, J = 6 Hz, $CH(CH_3)_2$]. Compound 4: colorless oil. (Found: C, 58.66; H, 8.80; Cl, 19.64. Calc for $C_{26}H_{47}Cl_3O_4$: C, 58.92; H, 8.88; Cl, 20.11%). IR (cm^{-1}) 1741, 1725 (sh) (C=O). 200 MHz ^1H NMR ($CDCl_3$) δ 1.035 (s, 3H, CH_3), 1.056 (s, 3H, CH_3), 1.201 (s, 6H, CH_3), 1.266 [m, 22H, CH_2 + $CH(CH_3)_2$], 1.336 [d, 6H, J = 6.5 Hz, $CH(CH_3)_2$], 5.103 (hept, 1H, J = 6.5 Hz, $CH(CH_3)_2$].

Bis(1-methylethyl) 2,2,15,15-tetrachloro-3,3,14,14-tetramethyl-1,16-hexadecanedioate (6)

A soln of n-BuLi in hexane (3.6 ml, 4.7 mmol) was syringed dropwise under N_2 at 0° into a stirred soln of diisopropylamine (0.47 g, 4.7 mmol) in dry THF (50 ml). After 30 min at 0°, the mixture was cooled to -78° and 3 (1.17 g, 2.3 mmol) was added over a period of 30 min. The red soln was stirred for further 30 min, CCl_4 (2 ml, 20.6 mmol) was added and the mixture allowed to warm up slowly to room temperature. After 10 hr 5 N aq HCl was added at 0° to pH 1. The organic soln was concentrated under reduced pressure, the residue taken into CH_2Cl_2, washed with aq $NaHCO_3$ and water and dried (Na_2SO_4). The solvent was evaporated *in vacuo* and the resulting brown oil flash chromatographed on silica gel (mixtures of CH_2Cl_2 and hexane serving as eluent) to yield 6 (0.810 g, 61%) and 4 (0.150 g, 12%) as colorless oils. Compound 6: IR (cm^{-1}) 1740 (C=O). 60 MHz ^1H NMR ($CDCl_3$) δ 1.23 (3, 12H, CH_3), 1.30 [m, 22H, CH_2 + $CH(CH_3)_2$], 1.40 [d, 6H, J = 6 Hz, $CH(CH_3)_2$], 1.53 [m, 4H, $CH_2C(CH_3)_2$], 5.10 (hept, 2H, J = 6 Hz, $CH(CH_3)_2$]. The compound was analyzed as the free acid 12 after Newman's hydrolysis with a 1:1 mixture of H_2SO_4 and oleum (20% SO_3);[12] mp 154-154.5° (Found: C, 50.02; H, 7.24; Cl, 29.18. Calc. for $C_{20}H_{34}Cl_4O_4$: C, 50.00; H, 7.08; Cl, 29.58%).

Dimethyl 2,2,15,15-tetrachloro-3,3,14,14-tetramethyl-1,16-hexadecanedioate (5)

As for 6, the dichloro-ester 2[3] (1.12 g, 25 mmol) was reacted with CCl_4 (2 ml, 20.6 mmol) to give 5 as colorless crystals (0.75 g, 59%); mp 38.5-39°. (Found: C, 51.76; H, 7.45; Cl, 28.23. Calc for $C_{22}H_{38}Cl_4O_4$: C, 51.97; H, 7.48; Cl, 27.95%). IR ($CHCl_3$, cm^{-1}) 1742 (C=O). 200 MHz ^1H NMR ($CDCl_3$) δ 1.196 (s, 12H, CH_3), 1.276 (m, 16H, CH_2), 1.550 [m, 4H, $CH_2C(CH_3)_2$], 3.865 (s, 6H, OCH_3).

Dimethyl 2,2,15,15-tetrabromo- and dimethyl 2,2,15-tribromo-3,3,14,14-tetramethyl-1,16-hexadecanedioate (8), (9)

Treatment of 7[3] (1.056 g, 2 mmol) with CBr_4 (10.3 g, 31 mmol) gave 8 as colorless crystals (1.0 g, 73%) and 9 as a colorless oil (0.12 g (10%). Compound 8: mp 66-67°. (Found: C, 38.60; H, 5.61; Br, 46.54. Calc for $C_{22}H_{38}Br_4O_4$: C, 38.48; H, 5.54; Br, 46.65%). IR ($CHCl_3$, cm^{-1}) 1732 (C=O). 200 MHz ^1H NMR ($CDCl_3$) δ 1.280 (m, 28H, CH_2 + CH_3), 1.620 [m, 4H, $CH_2C(CH_3)_2$], 3.865 (s, 6H, OCH_3). Compound 9: (Found: C, 43.03; H, 6.39. Calc for $C_{22}H_{39}Br_3O_4$: C, 43.49; H, 6.43%). IR (cm^{-1}) 1737 (C=O). 200 MHz ^1H NMR ($CDCl_3$) δ 0.953 (s, 3H, CH_3), 1.096 (s, 3H, CH_3), 1.276 (m, 16H, CH_2), 1.612 [m, 4H, $CH_2C(CH_3)_2$], 3.751 (s, 3H, OCH_3), 3.862 (s, 3H, OCH_3), 4.196 (s, 1H, CHCl).

Bis(1-methylethyl) 2,15-dibromo-2,15-dichloro-3,3,14,14-tetramethyl-1,16-hexadecanedioate (10)

Under the conditions described for the preparation of 6, the reaction of 3 (0.99 g, 2 mmol) and CBr_4 (10.3 g, 31 mmol) gave 11 as a colorless oil (0.75 g, 58%). Found: C, 47.74; H, 7.07; Br, 23.94; Cl, 10.58. Calc for $C_{26}H_{46}Br_2Cl_2O_4$: C, 47.78; H, 7.04; Br, 24.50; Cl, 10.87%). IR (cm^{-1}) 1731 (C=O). 300 MHz ^1H NMR ($CDCl_3$) δ 1.218 (m, 22H, CH_2 + CH_3), 1.280 (s, 6H, CH_3), 1.349 [d, 12H, J = 6 Hz, $CH(CH_3)_2$], 1.648 [m, 4H, $CH_2C(CH_3)_2$], 5.098 [hept, 2H, J = 6 Hz, $CH(CH_3)_2$].

Reaction of dimethyl 2,15-dibromo-3,3,14,14-tetramethyl-1,16-hexadecanedioate (7) with CCl_4

Under the conditions described for the reaction of 3 and CCl_4, the dibromo-ester 7 (1.056 g, 2 mmol) was reacted with CCl_4 (2 ml, 20.6 mmol) to give a mixture of the dimethyl 2,2,15,15-tetrachloro- and dimethyl 15-bromo-2,2-dichloro-3,3,14,14-tetramethyl-1,16-hexadecanedioate (6 and 11, respectively) that were separated by flash chromatography on silica gel (CH_2Cl_2-hexane as eluent). Compound 6 (0.680 g, 67%) was identical with the sample obtained from 2. Compound 12: (0.15 g, 14%) colorless oil. (Found: C, 50.82; H, 7.35. Calc for $C_{22}H_{39}BrCl_2O_4$: C, 50.96; H, 7.53%). IR (cm^{-1}) 1746, 1730 (sh) (C=O). 200 MHz ^1H NMR ($CDCl_3$) δ 1.079 (s, 3H, CH_3), 1.097 (s, 3H, CH_3), 1.199 (s, 6H, CH_3), 1.274 (m, 16H, CH_2), 1.362 [m, 2H, $CH_2C(CH_3)_2$], 1.538 [m, 2H, $CH_2C(CH_3)_2$], 3.747 (s, 3H, OCH_3), 3.864 (s, 3H, OCH_3), 4.192 (s, 1H, CHBr).

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