liaison V–O causé par le caractère moins donneur de Br^- que de Cl^-.
Le spectre infrarouge de (TEA)[$VOCl_3(CH_3CN)$] présente deux bandes intenses à 2297 et 2326 cm^{-1} qui sont caractéristiques de CH_3CN coordiné: elles correspondent à la vibration d'élongation de la liaison C–N et à la combinaison ν (C–C) + δ (CH_3) sym. La bande moyenne à 945 cm^{-1} correspond à la vibration de valence ν (C–C) et l'épaulement à 1025 cm^{-1} à la vibration ρ (CH_3). La bande faible située à 423 cm^{-1} peut être due à la superposition de la vibration de déformation d'angle C–C–N et d'une déformation angulaire de l'ion $(TEA)^+$. Ces indexations sont en accord avec celles faites par de nombreux auteurs en ce qui concerne les spectres de CH_3CN coordiné (références 2, 10 et références incluses).

Région spectrale <400 cm⁻¹

1) *Vibrations ν (V–Cl)* Les bandes situées respectivement à 388, 351 et 313 cm^{-1} et à 346 cm^{-1} dans les spectres infrarouge des ions [$VOCl_3(CH_3CN)$] et $VOCl_3Br^{2-}$ ont été attribuées aux vibrations de valence ν (V–Cl) par analogie à celles de l'ion monomère $VOCl_4^{2-}$ (395 et 335 cm^{-1})[8,9]. Ainsi l'absence de ponts V–Cl–V (et V–O–V) confirme que les ions [$VOCl_3(CH_3CN)$]$^-$ et $VOCl_3Br^{2-}$ sont monomères.

2) *Vibration ν (V–N) dans [$VOCl_3(CH_3CN)$]$^-$* L'attribution de la bande située à 201 cm^{-1} à une vibration de valence ν (V–N), est compatible d'une part avec l'indexation du spectre infrarouge du composé $VO(CH_3CN)_5(SbCl_6)_2$-(CH_3CN)[11] pour lequel les trois bandes de faibles intensités situées à 211, 230 et 238 cm^{-1} sont attribuables aux vibrations de valence ν (V–N) symétriques et assymétriques et d'autre part, avec les attributions faites par différents auteurs pour des vibrations de valence correspondant aux liaisons de coordination Sb–N, Nb–N et Ta–N: *Kawai* et *Kanesaka*[12] ont calculé la vibration ν (Sb–N) à 209 et 213 cm^{-1} dans $SbCl_5$(ClCN) et $SbCl_5$(BrCN); *Burgard* et *Mc. Cordick*[13] ont attribué les bandes situées à 225 et 205 cm^{-1} dans les spectres des composés $SbCl_5(CH_3CN)$ et $SbCl_5$(ClCN) aux vibrations ν (Sb–N); *Ozin* et *Walton*[14] ont calculé les vibrations ν (Nb–N) et ν (Ta–N) dans $NbCl_5(CH_3CN)$ et $TaBr_5(CH_3CN)$ à 226 et 216 cm^{-1}, vibrations observées expérimentalement à 218 et 210 cm^{-1}; une étude vibrationnelle des complexes de coordination de type $MCl_5(RCN)$[15] où M = Sb, Nb, Ta et R = C_2H_5, C_6H_5, CCl_3, CH_2Cl, $(CH_3)_3C$, CH_2=CH, met en évidence dans tous les spectres RAMAN une raie de faible intensité située entre 200 et 250 cm^{-1} et attribuable à la vibration ν (M–N).
Enfin, dans une publication récente, *Nicholls* et *Seddon*[16] attribuent les bandes faibles situées à 223 et 232 cm^{-1} dans les spectres infrarouge des composés (pyH)[$VOBr_3$-$(CH_3CN)_2$] et $VOBr_2(CH_3CN)_3$ aux vibrations ν (V–N).

3) *Vibrations ν (V–Br) dans $VOCl_3Br^{2-}$* La bande située à 295 cm^{-1} a été attribuée à la vibration de valence ν (V–Br) par comparaison à cette même vibration dans des composés à liaison V–Br: 312 et 293 cm^{-1} dans VBr_3-$(CH_3CN)_3$[2], 400 et 271 cm^{-1} dans $VOBr_3$[17] et 296 cm^{-1} dans $(TEA)_2VOBr_4$[16].

En conclusion, on pourrait penser que (TEA)$VOCl_3$-(CH_3CN) et $(TEA)_2VOCl_3Br$ ne sont pas monomères si l'on considère que la recristallisation de ces composés dans CH_3CN ne permet pas de fixer un sixième coordinat. En effet, ceci pourrait s'interprêter en postulant l'existence de pontages par des atomes d'halogène ce qui assurerait une hexacoordinance pour le vanadium.
Cependant, les conductibilités ainsi que les spectres électroniques et vibrationnels s'interprêtent bien dans l'hypothèse d'espèces ioniques monomères et la non-fixation de CH_3CN est également observée par *Feltz*[3] pour $(TEA)_2$-$VOCl_4$ monomère[9].

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Synthesis of 19-*cis*-docosenoic, 17-*cis*-eicosenoic and 15-*cis*-octadecenoic acid

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Abstract. Large-scale syntheses of 19-*cis*-docosenoic, 17-*cis*-eicosenoic and 15-*cis*-octadecenoic acid by chain extension of 8-undecynoic acid via Kolbe's anodic synthesis, as well as by coupling of 1-butyne with n-bromoalkanoic acids were found unsuitable. Therefore, 15-octadecynoic acid was prepared on a large scale from 13-hexadecyn-1-ol by malonic ester coupling. Esterification and reduction with lithium aluminium hydride yielded 15-octadecyn-1-ol. Converting the latter into a methanesulfonate followed by malonic ester synthesis yielded 17-eicosynoic acid, which, in turn, was converted by the same sequence of reaction steps into 19-docosynoic acid. Hydrogenation of the acetylenic acids in the presence of Lindlar's catalyst yielded the title compounds.

Introduction

Dietary erucic acid (13-*cis*-docosenoic acid), a major constituent of rapeseed oil, induces lipidosis in heart and skeletal muscles of rats and several other animal species[1]. For biological tests in a systematic investigation into the metabolism of isomers and homologues of erucic acid (*U. M. T. Houtsmuller*, to be published), 100–150 g amounts of 19-*cis*-docosenoic, 17-*cis*-eicosenoic and 15-*cis*-octadecenoic acids were required.

Recently, the synthesis of 15-octadecynoic acid[2] via the route published by *Ahmad* and *Strong*[3] was described. Analogous large-scale preparation of the title compounds was not considered attractive since this includes coupling of 1-butyne with chloroiodoalkanes, the yields of which decrease with increasing chain length of the halogen compound. Therefore, alternative syntheses had to be tested for their merits for large-scale preparation.

In view of the length of the carbon chain and the almost terminal position of the double bond in these compounds synthetic routes starting from either the carboxyl or the terminal unsaturated end of the molecule were envisaged.

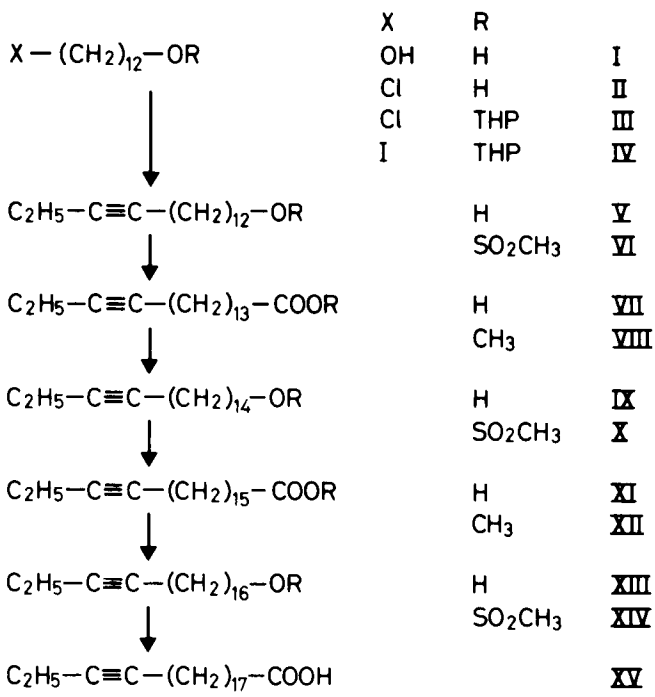
Method and results

First, a method based on *Kolbe's* anodic synthesis[4,5] was tried for the synthesis of 19-docosynoic acid. Although the yields of *Kolbe* syntheses are generally moderate, due to side-reactions of the different radical fragments, the method comprised only a few reaction steps. As starting materials were used 8-undecynoic acid prepared from 7-bromoheptanoic acid[6] and the lithium derivative of 1-butyne in a mixture of liquid ammonia and diethyl ether and tridecanedioic acid monomethyl ester, obtained by partial hydrolysis of dimethyl brassylate (tridecanedioate) with barium hydroxide[7]. Electrolysis (56 V, 0.6 A) at 50–60°C afforded a complex mixture of at least 17 components, of which methyl 19-docosynoate was a minor one. Isolation was carried out by alkaline hydrolysis to the corresponding acids, followed by fractional extraction and crystallization from light petroleum. This yielded 19-docosynoic acid in 15% yield containing varying amounts of methyl docosanoate due to reduction of methyl 19-docosynoate under the reaction conditions applied. In view of this result, this approach was abandoned.

In a next attempt, we tried to introduce the acetylenic bond in the last stage of the synthesis by coupling of 1-butyne with the appropriate bromoalkanoic acids. To synthesize 19-docosynoic acid via this route, 18-bromooctadecanoic acid was required. Its synthesis was undertaken via *Cadiot-Chodkiewicz* coupling[8,9] of 9-bromo-8-nonyn-1-ol and 8-nonynoic acid. This afforded 18-hydroxy-8,10-octadecadiynoic acid in only 25% yield. A better yield (52%) was obtained on coupling the 9-bromo derivative[10] of 8-nonynoic acid with 8-nonyn-1-ol. Hydrogenation in the presence of Adam's catalyst yielded 18-hydroxyoctadecanoic acid. To convert this into 18-bromooctadecanoic acid with 48% hydrobromic acid and acetic acid[11], reaction temperatures higher than 120°C were required to avoid formation of oligomers. The coupling of 18-bromooctadecanoic acid with the lithium derivative of 1-butyne was tried out in dioxane, dimethylformamide and dimethyl sulfoxide. The highest yield, although only 14%, was obtained in a mixture of dioxane and dimethylformamide. Therefore, also this method was not considered suitable for large-scale preparation of the acids desired.

To prepare the title compounds, we finally chose the large-scale preparation of 15-octadecynoic acid and chain extension by repeated malonic ester synthesis. Conversion of 1,12-dodecanediol with hydrochloric acid[12–15] yielded 12-chlorododecanol, which was treated successively with 2,3-dihydro-4*H*-pyran and sodium iodide in acetone. The 2-(12-iodododecyloxy)tetrahydropyran so obtained, was coupled with the lithium derivative of 1-butyne in dioxane[16]. After removal of the protecting group, 13-hexadecyn-1-ol was obtained. Conversion with methanesulfonyl chloride yielded 13-hexadecynyl methanesulfonate which was coupled with sodium diethyl malonate. Hydrolysis and decarboxylation of the reaction product yielded 15-octadecynoic acid. Esterification followed by reduction with lithium aluminium hydride afforded 15-octadecyn-1-ol, which was converted into 17-eicosynoic acid via its methanesulfonate and malonic ester synthesis. Repeating this reaction sequence, yielded 19-docosynoic acid (Scheme). Finally, the acetylenic acids were hydrogenated in the presence of *Lindlar's* catalyst[17] to yield the title compounds.

Chain extension by repeated malonic ester synthesis although comprising many reaction steps is a suitable method for the large-scale preparation of 19-*cis*-docosenoic, 17-*cis*-eicosenoic and 15-*cis*-octadecenoic acid starting from 13-hexadecyn-1-ol. In this way, the acids were obtained in overall yields of 14.6, 23.8 and 33.8% respectively based on 1,12-dodecanediol.



Experimental

(In cooperation with Miss *J. W. Bos*, Miss *M. W. Langelaan* and Mr *L. van der Wolf*.) The compounds were analysed on a Hewlett & Packard gaschromatograph 5750 G with a 75 cm 10% SE 30 column; the purities of carboxylic acids were determined after esterification with diazomethane. For column chromatography, silica gel 0.05–0.20 mm (ex Merck) was used. The melting points were determined with a Reichert melting point microscope and are uncorrected.

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The infrared spectra were obtained with a Hilger Watts Infrascan infrared spectrometer and the mass spectra with an AEI-MS 9 spectrometer. The proton magnetic resonance spectra were obtained from solutions in carbon tetrachloride or deuteriochloroform using a Varian A-60 operating at 60 MHz and 40°C or a Varian HR-220 spectrometer operating at 220 MHz and 14°C. δ-Values are quoted in ppm downfield from internal tetramethylsilane and are accurate to within about 0.02 ppm. The coupling constants are accurate to within about 0.2 Hz.

12-Chloro-1-dodecanol (II)

A mixture of 505 g (2.5 mol) 1,12-dodecanediol (I), 1300 ml concentrated hydrochloric acid, 250 ml water and 30 g copper(I) chloride was heated at 80–90°C for 40 h, while being continuously extracted with a petroleum fraction b.p. 110–120°C. After separating some unreacted I by crystallization, distillation yielded 412.5 g (74.9%) II, b.p. 117–124°C/0.01 mm, purity 89.8%.

1-Chloro-12-(2-tetrahydropyranyloxy)chlorododecane (III)

A mixture of 412.5 g (1.87 mol) II, 185 g (2.2 mol) 2,3-dihydro-4*H*-pyran and 1 ml concentrated hydrochloric acid was heated for 90 min under reflux, cooled, stirred with 10 g potassium carbonate and distilled, yielding 436.5 g (76.8%) III, b.p. 145–147°C/0.01 mm, purity 92.0%.

2-(12-Iododecyloxy)tetrahydropyran (IV)

A mixture of 758 g (2.49 mol) III and 560 g (3.75 mol) sodium iodide in 2 l acetone was heated under reflux for 40 h. After evaporation of the acetone, the residue was taken up in water and extracted with light petroleum yielding 977 g (99.2%) IV, purity 93.0%.

13-Hexadecyn-1-ol (V)

After introducing 456 g (8.5 mol) 1-butyne into a suspension of 5.6 mol lithium amide in 3 l liquid ammonia, most of the ammonia was evaporated. The residue was taken up in 2 l dioxane and heated under reflux for 4 h to expel the ammonia. Subsequently, 977 g (2.47 mol) IV was added and the reaction mixture heated under reflux for 40 h. After evaporating the dioxane, the residue was taken up in isooctane and decomposed with 500 ml water and 1 l 4 N sulfuric acid. The reaction product was heated under reflux for 5 h with 12 g *p*-toluene-sulfonic acid in 3 l methanol. This yielded 520.5 g (88.5%) V, b.p. 135–137°C/0.01 mm, purity 93.4%. Crystallization from light petroleum yielded 477.5 g (81.3%) V, being now 97.0% pure. IR: 1440 and 1325 cm^{-1} ($-CH_2-C\equiv C-$). NMR: δ 1.09 (T), J 7.5 Hz ($-CH_3$); δ 3.49 (T), J 6.5 Hz ($-CH_2-O-$).

13-Hexadecyn-1-yl methanesulfonate (VI)

To a mixture of 238 g (1.0 mol) V and 320 ml pyridine in 600 ml dichloromethane, 150 g (1.31 mol) methanesulfonyl chloride was added during 45 min at 0°C. The mixture was stirred at room temperature until V had disappeared according to GLC analysis (1.5 h). At −5°C 250 ml water was added followed by 1 l 4 N hydrochloric acid and 500 ml dichloromethane. The organic layer was washed once with water and then with 1% potassium carbonate solution until neutral. After drying, the solvent was evaporated, yielding 331.5 g (quant.) VI, purity 92.4%.

15-Octadecynoic acid (VII)

To 3.0 mol sodium diethyl malonate in 2 l super dry ethanol 659 g (<2.0 mol) VI was added within 15 min. The reaction mixture was heated under reflux for 1.5 h. The excess ethanol was evaporated, the residue poured into water, acidified with 4 N sulfuric acid and extracted with light petroleum. Alkaline hydrolysis and decarboxylation under vacuum at 140–150°C for 3 h, yielded 457.3 g (81.7%) VII, m.p. 66.0–67.0°C (from light petroleum/benzene), purity 96.0%. Lit.[2]: m.p. 65–65.5°C. IR: 1445 and 1322 cm^{-1} ($-CH_2-C\equiv C-$). NMR: δ 1.09 (T), J 7.2 Hz ($-CH_3$); δ 2.30 (T), J 7.3 Hz ($-CH_2-COOH$). An impurity of about 3% was identified by MS coupled with GLC to be 1,16-hexadecanedioic acid.

15-cis-Octadecenoic acid (VIIa)

A mixture of 157 g (0.56 mol) VII, 800 ml ethyl acetate, 13 ml quinoline and 13 g Lindlar's catalyst was hydrogenated (uptake 101.3%), yielding 140.8 g (89.3%) VIIa, m.p. 41.0–42.0°C (from acetone at −20°C), purity 97.5%. Lit.[18]: m.p. 40.5–41.5°C. IR: 3020 and 1660 cm^{-1} ($-\overset{H}{C}=\overset{H}{C}-$). NMR: δ 0.94 (T), J 7.5 Hz ($-CH_3$); δ 2.28 (T), J 7.6 Hz ($-CH_2-COOH$); δ 5.25 (C), J 11 Hz ($-\overset{H}{C}=\overset{H}{C}-$).

15-Octadecyn-1-ol (IX)

357.3 g (1.2 mol) methyl 15-octadecynoate (VIII; b.p. 146–152°C/0.01 mm, n_D^{25} 1.4545, purity 99%) was reduced with 32.3 g (0.85 mol) lithium aluminium hydride yielding 323.8 g (97.4%) IX, purity 99%. IR: 1440 and 1325 cm^{-1} ($-CH_2-C\equiv C-$). NMR: δ 1.09 (T), J 7.3 Hz ($-CH_3$); δ 3.47 (T), J 6.8 Hz ($-CH_2-O-$).

15-Octadecyn-1-yl methanesulfonate (X)

Proceeding as described before 323.8 g (1.22 mol) IX was converted into 417.8 g (99.8%) X, purity 90.5%.

17-Eicosynoic acid (XI)

Coupling of 417.8 g (1.21 mol) X with sodium diethyl malonate and proceeding as described before yielded 267.5 g (71.5%) XI, m.p. 71–72°C, purity 98.5%. IR: 1443 and 1323 cm^{-1} ($-CH_2-C\equiv C-$). NMR: δ 1.09 (T), J 7.3 Hz ($-CH_3$); δ 1.61 (Q), J 7.3 Hz ($-CH_2-CH_2-COOH$); δ 2.29 (T), J 7.3 Hz ($-CH_2-CH_2-COOH$).

17-cis-Eicosenoic acid (XIa)

A mixture of 164.8 g (0.54 mol) XI, 1300 ml ethyl acetate, 13 ml quinoline and 13 g *Lindlar's* catalyst was hydrogenated (uptake 106%), yielding 154.6 g (93.2%) XIa, m.p. 50–51°C (from acetone), purity 99.5%. IR: 3020 cm^{-1} ($-\overset{H}{C}=\overset{H}{C}-$). NMR: δ 0.95 (T), J 7.3 Hz ($-CH_3$); δ 1.61 (Q), J 7.3 Hz ($-CH_2-CH_2-COOH$); δ 2.29 (T), J 7.3 Hz ($-CH_2-CH_2-COOH$); δ 5.23 (C) ($-\overset{H}{C}=\overset{H}{C}-$).

17-Eicosyn-1-ol (XIII)

Proceeding as described before 355.7 g (1.10 mol) methyl 17-eicosynoate (XII; b.p. 163–169°C/0.01 mm, n_D^{25} 1.4558, purity 99%) was converted into 324.6 g (99.9%) XIII, m.p. 67–68°C, purity 99.5%. IR: 1435 and 1330 cm^{-1} ($-CH_2-C\equiv C-$). NMR: δ 1.09 (T), J 7.3 Hz ($-CH_3$); δ 3.50 (T), J 6.5 Hz ($-CH_2-O-$).

17-Eicosyn-1-yl methanesulfonate (XIV)

Proceeding as described before 162.7 g (0.56 mol) XIII gave 201.7 g (96.8%) XIV. To prevent crystallization of the 17-eicosyn-1-ol, the addition of methane sulfonylchloride was carried out at 11–14°C. On decomposition of the reaction mixture, a very stable emulsion was formed which was separated by centrifugation at 1500 rev./min.

19-Docosynoic acid (XV)

Coupling of 397.5 g (1.07 mol) XIV with sodium diethyl malonate and proceeding as described before yielded 239.8 g (67.0%) XV, m.p. 77–78°C (from ethyl acetate), purity 94.5%. IR: 1445 and 1325 cm^{-1} ($-CH_2-C\equiv C-$). NMR: δ 1.10 (T), J 7.5 Hz ($-CH_3$); δ 2.30 (T), J 7.5 Hz ($-CH_2-COOH$).

19-cis-Docosenoic acid (XVa)

A mixture of 188.2 g (0.56 mol) XV, 1800 ml ethyl acetate, 15.7 ml quinoline and 15.7 g Lindlar's catalyst was hydrogenated (uptake 104.5%), yielding 173.5 g (91.5%) XVa, m.p. 60–62°C (from acetone), purity 98.6%. IR: 3030 and 1660 cm^{-1} ($-\overset{H}{C}=\overset{H}{C}-$). NMR: δ 0.94 (T), J 7.5 Hz ($-CH_3$); δ 2.29 (T), J 7.4 Hz ($-CH_2-COOH$); δ 5.25 (C), J 11 Hz ($-\overset{H}{C}=\overset{H}{C}-$).

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