

• Technical

Difunctional Derivatives of Cyanoethylated Hydroxystearate¹

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Abstract

The conversion of the nitrile function of methyl 12-(2-cyanoethoxy)-octadecanoate II to a series of carboxylic acid derivatives has been investigated, and a series of 12 diester derivatives has been prepared. Compound II undergoes decyanoethylation in alkaline medium, and II and its derivatives degenerate in acid medium to a mixture of $\Delta 11$ and $\Delta 12$ methyl *trans*-octadecenoates by a concerted process.

Introduction

The hydrolysis of β -cyanoethyl ethers to the corresponding β -alkoxypropionic acids is complicated by the instability of the ether linkage toward hydrolytic conditions. In alkaline medium the reversibility of the cyanoethylation reaction (1) causes decyanoethylation, especially of β -cyanoethyl ethers of secondary alcohols (2-4), but exceptions have been noted (5). Aqueous acid appears to be a more favorable medium for the conversion of the nitrile to the carboxy group while ether cleavage is avoided (5-7), but yields of the desired β -alkoxypropionic acids decrease when the alkoxy group increases in size or becomes branched (4).

Our practical interest in the stability of the β -cyanoethoxy ethers stemmed from our earlier preparation of cyanoethylated hydroxy derivatives of fats (8). We used methyl 12-(2-cyanoethoxy)-octadecanoate II as a representative model compound in our study of the conversion of the nitrile group to other functions with retention of the ether linkage. In this paper we report the preparation of a series of diesters and describe a comparison of the stability toward aqueous acid and aqueous alcoholic base of II and its derivatives.

Experimental Procedures

Materials Used

For the preparation of diesters, commercially produced alcohols were redistilled. The fractions used were 99% pure by GLC.

Methyl 12-(2-cyanoethoxy)-octadecanoate II was prepared and purified as reported previously (8) and was 99% pure by GLC.

Solvents used for chromatographic procedures were Mallinckrodt Nanograde. All other reagents were commercial products which were used as received.

Procedures

Analytical Procedures. GLC of the high boiling compounds was carried out with $18 \times \frac{1}{4}$ in. stainless steel columns packed with 4% XE-60 on 60-70 mesh Gas-Chrom Z. These columns were aged for two days at 350 C, a treatment which removed a considerable portion of the liquid phase, and were capable of being operated to 400 C without excessive bleeding. The lower boiling compounds (C18:1, methyl 12-hydroxyoctadecanoate) were analyzed with 10 ft col-

umns packed with 10% diethylene glycol succinate on 45-60 mesh Chromosorb W. The alcohols were analyzed with 10 ft columns of 10% Carbowax 20M on 45-60 mesh Chromosorb W. The helium gas flow was maintained at 60 ml/min for all columns. Components representing peaks were trapped and were identified by infrared and elemental analysis. Analytical and preparatory TLC plates were coated with silica gel containing 10% binder (Adsorbosil 1) and were activated by heating at 110 C for 2 hr. Analytical plates were charred after being sprayed with a solution of potassium dichromate in aqueous sulfuric acid. Preparatory plates, after development, were sprayed with an alcoholic solution of 2',7'-dichlorofluorescein, and the bands were located under UV light. Infrared (IR) spectra were determined with a Perkin-Elmer Model 237 B spectrophotometer.

Preparative Procedures

12-(2-Carboxamidoethoxy)-Octadecanoic Acid III. To a stirred solution of methyl 12-(2-cyanoethoxy)-octadecanoate II (10 g, 0.0272 mole) in 100 ml ethanol at 10 C was added slowly a precooled (10 C) mixture of 150 ml 7% aqueous hydrogen peroxide and 100 ml 95% ethanol. The reaction mixture was adjusted to pH 10 by addition of dilute aqueous sodium hydroxide solution, was stirred at 60 C for 2 hr and then cooled to room temperature. The mixture was acidified with dilute HCl and extracted with three 250 ml portions of ether. The combined extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to 10.5 g of a semi-solid residue. The IR spectrum of the residue contained bands at 3425, 3350 and 3200 cm^{-1} (N-H), 1705 cm^{-1} (acid C=O), 1675 cm^{-1} (amide I), 1600 cm^{-1} (amide II) and 1100 cm^{-1} (C-O-C). The crude product was crystallized from a 1:1 mixture of benzene-acetone to obtain 9.1 g white solid, mp 77-79 C (theory 10.1 g). Analysis by TLC gave one spot. The developing solvent was a mixture consisting of 94% benzene, 5% methanol and 1% acetic acid.

Analysis: Calculated for $\text{C}_{21}\text{H}_{41}\text{O}_4\text{N}$: C, 67.88; H, 11.12; N, 3.77. Found: C, 67.85; H, 11.16; N, 3.80.

12-(2-Carboxyethoxy)-Octadecanoic Acid IV. A solution of III (7.86 g, 0.0212 moles) in 200 ml of 30% aqueous HCl was allowed to reflux for 2 hr, was cooled to room temperature, and was extracted with three 100 ml portions of ether. The combined extracts were washed with water, dried over sodium sulfate, and evaporated to a white solid residue (7.80 g; theory, 7.86 g). TLC and IR analyses indicated an essentially pure compound having strong bands at 1705 cm^{-1} (acid C=O), 1100 cm^{-1} (C-O-C) and lacking amide bands. An analytical sample was recrystallized from ether and melted at 63-64 C.

Analysis: Calculated for $\text{C}_{21}\text{H}_{40}\text{O}_5$: C, 67.70; H, 10.82. Found: C, 68.13; H, 10.77.

12-(2-Chloroformylethoxy)-Stearoyl Chloride V. To a stirred solution of IV (8.35 g, 0.0224 moles) in 17 ml benzene at room temperature oxalyl chloride (5.9 ml, 0.069 moles) was added slowly. When visible gas evolution stopped, *N,N*-dimethylformamide (3 ml) was added dropwise until gas again stopped evolving.

¹ Presented at the AOCs Meeting in Washington, D.C. April 1968.
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TABLE I

Alcohol ROH	Yield ^a %	n _D ²⁵	Carbon %		Hydrogen %	
			Calculated	Found	Calculated	Found
Methanol	79	1.4484	68.96	68.98	11.07	11.12
1-Heptanol	76	1.4530	73.89	73.78	12.05	12.16
1-Dodecanol	76	1.4561	76.21	76.07	12.51	12.50
1-Octadecanol	85	1.4502 ^b	78.02	78.25	12.87	12.96
Neopentanol	84	1.4473	72.60	72.59	11.79	11.71
2,2,2-Trifluoroethanol ^c	63	1.4155	55.96	56.03	7.89	8.06
Benzyl alcohol	63	1.4978	76.04	75.98	9.48	9.46
4-Heptanol	61	1.4509	73.89	73.64	12.05	11.89
Cyclohexanol	71	1.4679	73.83	74.13	11.26	11.10
t-Butanol	62	1.4449	71.85	71.69	11.65	11.53
Phenol	81	1.4989	75.53	75.56	9.22	9.19
p-Cresol	75	1.4981	76.04	75.66	9.48	9.45

^a Overall yield from methyl 12-hydroxystearate I.

^b This refractive index was taken at 50 C.

^c Fluorine Analysis: Calculated: 21.25%, Found: 21.45%.

The mixture was stirred at room temperature for 1 hr and was then concentrated under a stream of nitrogen. The IR spectrum showed bands at 1800

cm^{-1} ($\text{C}=\text{O}$) and 1100 cm^{-1} (ether). The reaction product was dissolved in benzene and stored at 0 C until needed for the esterification reaction.

Methyl 12-(2-Carbomethoxyethoxy)-Octadecanoate VI. A solution of V (2.44 g, 0.00596 moles) in methanol (4.0 g, 0.125 mole) and pyridine (1 g, 0.0125 moles) was heated at 70 C for 2 hr and was cooled, acidified with dilute HCl, and extracted with three 25 ml portions of ether. The combined extracts were washed three times with diluted HCl and then with water. The pyridine-free extracts were dried over anhydrous sodium sulfate and evaporated to give 2.35 g yellow oil (theory 2.38 g). The product was redissolved in *n*-hexane and passed through a 30 g column of Florisil. Removal of the solvent from the hexane fractions left 1.74 g colorless oil. GLC analysis indicated that the oil contained the desired product in 95% concentration. The IR spectrum of the oil contained bands at 1745 cm^{-1} (ester C=O), and 1100 cm^{-1} (ether). Analytical data are presented in Table I.

Alkyl 12-(2-Carboalkoxyethoxy)-Octadecanoates. A series of diesters was prepared in a manner entirely analogous to the procedure for the preparation of the dimethyl ester VI. Yields and analytical data are presented in Table I.

Acid Stability Tests. The following procedure is typical of the method used to determine stability toward aqueous acid. A solution of methyl 12-(2-

TABLE II
Stability in Acid Medium

Compound tested	Products obtained, %					High boiling products
	Alcohol I	Nitrile II	Amide III	Ester VI	Olefin VII	
Alcohol I	48	26	27
Nitrile II	3	34	2	38	22	1
Amide III	6	9	84	...
Acid VI	trace	55	45	...
Ester VI	2	84	11	...

TABLE III
Stability in Alkaline Medium

Compound tested	Products obtained, %			
	Alcohol I	Nitrile II	Amide III	Ester VI
Nitrile II	27	65	4	4
Amide III	64	36
Acid IV	98
Ester VI	2	93

carbomethoxyethoxy)-octadecanoate (VI, 0.100 g, 0.00025 moles) in 10 ml 40% aqueous sulfuric acid was allowed to reflux for 2 hr, was cooled to room temperature, diluted with water, and extracted with three 50 ml portions of ether. The combined ether extracts were washed with water, dried over sodium sulfate, and evaporated to a semi-solid residue (0.094 g), the IR spectrum of which indicated the presence of carboxylic acid, ester and ether bands. The residue was methylated with 20% boron trifluoride-etherate in methanol at reflux for 5 min. The reaction mixture was extracted with ether as described above to give a yellow liquid (0.092 g). IR and TLC analysis of this liquid indicated that the principal component was the dimethyl ester VI. GLC analysis and IR spectra of the components trapped from GLC gave the composition of the product mixture shown in Table II. Results of acid stability tests of compounds I, II, III and IV are also shown in Table II.

Alkali Stability Tests. The following typical procedure was used to determine stability toward alkali: A solution of methyl 12-(2-carbomethoxyethoxy)-octadecanoate VI (0.100 g, 0.00025 moles) in 6 ml of ethanolic sodium hydroxide solution (0.5% NaOH in 67% aqueous ethanol) was refluxed for 1 hr, cooled to room temperature, diluted with HCl and extracted

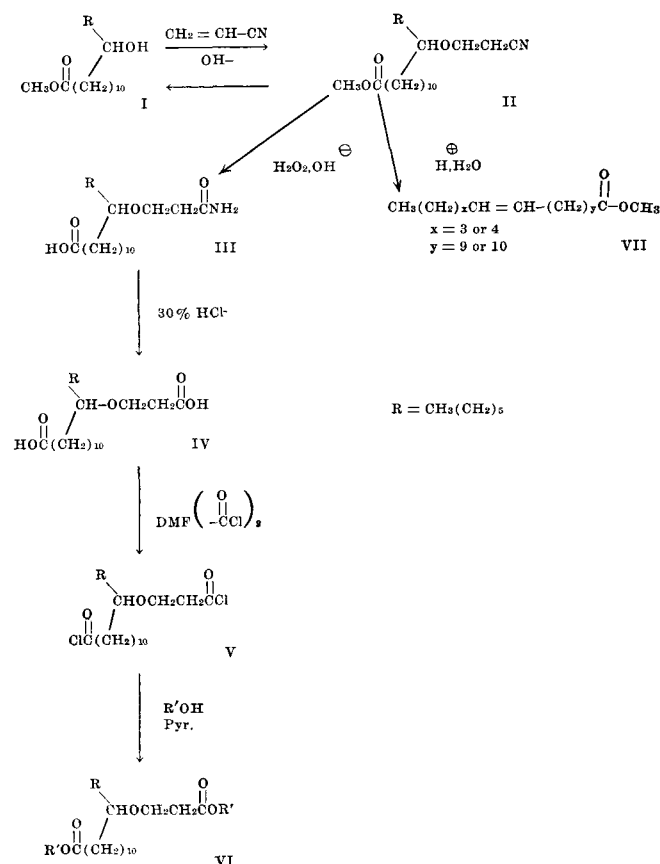


FIG. 1. Conversion of methyl 12-hydroxystearate to alkyl 12-(2-carboalkoxyethoxy)-octadecanoates.

with three 25 ml portions of ether. The combined extracts were worked up, and the crude product was methylated as described for the acid stability test above. A yellow liquid (0.089 g) was obtained. GLC analysis and IR spectra of the components trapped from GLC gave the composition of the product mixture shown in Table III. Results of alkali stability tests of compounds II, III and IV are also shown in Table III.

Discussion

Attempts to convert the nitrile function of the β -cyanoethoxy ether II to the corresponding amide, acid or ester led to low product yields under a wide variety of conditions. Sulfuric acid, ranging in concentration from 30% to 70%, was tested at various temperatures and in different solvents such as water, methanol, ethanol or dioxane for a variety of time periods. In most of these experiments by-products directly traceable to ether cleavage were prominent, or the cyano group remained intact. Similar results were obtained on treatment with hydrochloric acid and with fluoboric acid in water, methanol or dioxane and with boron fluoride in methanol. In aqueous or alcoholic sodium or potassium hydroxide solutions decyanoethylation resulted in the formation of the secondary alcohol I as the principal reaction product. It was apparent, then, that the use of conditions which are vigorous enough to hydrolyze the nitrile function in a single step causes cleavage of the ether linkage.

Conversion of the nitrile group to the amide function (Fig. 1) was accomplished in excellent yield with hydrogen peroxide in weakly basic medium (6). Under these conditions the existing ester function was partially hydrolyzed, but this presented no difficulty, since the following acid hydrolysis step simply completed the conversion to the diacid.

It is of interest to note that the conversion of the 2-carboxamidoethoxy function to the corresponding carboxylic acid occurs smoothly and essentially quantitatively on treatment with refluxing 30% HCl for 2 hr. By contrast, the 2-cyanoethoxy function was unaffected (95% recovery) by the same treatment. On the other hand, 37% HCl attacked the ether linkage of the cyano compound in a manner similar to that of 40% H₂SO₄ (Table II).

The dicarboxylic acid IV was converted to the diacyl chloride cleanly and in excellent yield by treatment with oxalyl chloride in the presence of dimethyl formamide (9). The total reaction mixture

was diluted with benzene and stored at 0 C until needed for the next step, ester formation.

The series of diesters described in Table I was prepared from the diacyl chloride V and an excess of the corresponding alcohol in the presence of pyridine. The yields listed are overall yields based on methyl 12-hydroxyoctadecanoate I and represent amounts of isolated products of 95% or greater purity. The preparations were carried out without isolating or purifying intermediates. Several of the diesters of primary and secondary alcohols were also prepared by esterification of the isolated dicarboxylic acid in the presence of boron trifluoride etherate.

The indicated instability of the ether linkage of the cyano derivative II toward acid and alkaline hydrolytic conditions posed the question of the manner in which this ether function is affected. Previous workers who reported the decyanoethylation of β -cyanoethyl ethers in alkaline media (2-4) confined their studies to the observation of indirect evidence and for the most part did not isolate reaction products. We have subjected the model compound, methyl 12-(2-cyanoethoxy)-octadecanoate II and its derivatives (III, IV and VI) to arbitrarily chosen acid (40% H₂SO₄) and basic (0.5% aqueous alcoholic NaOH) hydrolysis tests in order to test the relative stabilities of the ether functions in the various compounds. To facilitate analysis, all products were re-esterified at the end of the test. Results are presented in Tables II and III.

In alkaline medium the cyano derivative II invariably gave the original alcohol I as the principal reaction product. It is apparent from the data that under the relatively mild conditions of the test the preference for ether cleavage over nitrile hydrolysis is greater than 3:1. While we did not isolate the regenerated acrylonitrile or its descendants, it seems quite clear that we are indeed dealing with a reversal of the cyanoethylation reaction, or at least that the presence of the nitrile group greatly enhances ether cleavage. Under identical hydrolysis conditions the ether functions of the amide III and the acid IV are quite stable, while that of the ester VI is affected to only a minor extent.

In acid medium the ether linkage of II, as well as those of the derivatives III, IV and VI, show a considerable degree of instability, as would be expected from ethers of secondary alcohols. This instability undoubtedly accounts for the lower yields of β -alkoxypropionic acids mentioned previously. It is quite apparent from the data of Table II that the ether function of the nitrile II is more resistant to acid hydrolysis than are the ether groups of the amide III or the acid IV. On the other hand, the ester VI may be more stable than the data indicate, since it is largely hydrolyzed to the acid during the progress of the test. The acid, apparently, is quite labile.

An important acid hydrolysis product is the *trans*-olefinic ester. Its origin gives rise to some speculation. If we may assume that the ether function of II is protonated to a high degree in 40% H₂SO₄, or if we may hypothesize, at least, that it is the protonated species which undergoes ether cleavage, then we can visualize three mechanisms by which this cleavage reaction may proceed. These are shown in Figure 2.

Path "a" indicates elimination of a β -hydrogen, located either at C₁₁ or C₁₃, and leads directly to a *trans*-olefin, expectedly a mixture of about equal parts of Δ^{11} and Δ^{12} isomers. Eliminative attack at C₂

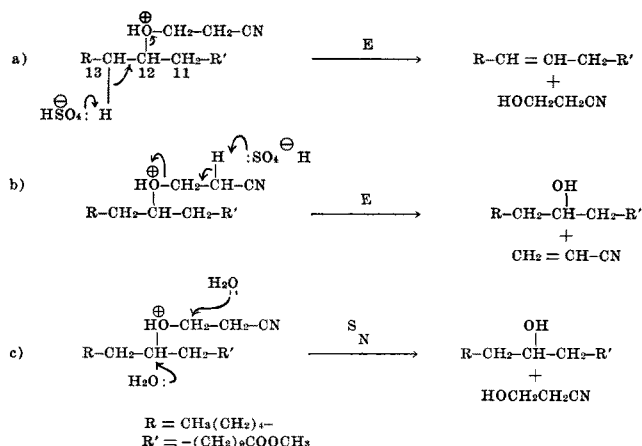


FIG. 2. Pathways in the H₂SO₄-catalyzed ether cleavage of methyl 12-(2-cyanoethoxy)-octadecanoate.

of the side chain (path b) causes the formation of a secondary alcohol, methyl 12-hydroxystearate in this case, and acrylonitrile. Most probably this is the path which in basic medium leads to decyanoethylation. Nucleophilic substitution, mono- or bimolecular, at the carbon atoms flanking the ether link (path c) results in the formation of the secondary alcohol and of β -hydroxy propionitrile. If paths b and c are operative then the olefin which is isolated experimentally must be formed by the acid-catalyzed dehydration of methyl 12-hydroxystearate.

It is conceivable that all of the paths of Figure 2 are utilized in the production of the observed products, but it would seem likely that one path predominates. One would expect the favored mechanism to be b since eliminative attack occurs at the more acidic hydrogen and since a conjugated olefin is formed by this pathway.

Actually, experimental evidence indicates that the predominant course of the reaction is by direct formation of the olefin (equation a). Intermediacy of 12-hydroxystearate in olefin formation, required by paths b and c, is unlikely in the face of the following evidence. Methyl 12-hydroxystearate under acid hydrolysis conditions gives a majority of I and lesser amounts of the olefin VII (Table II), while ether cleavage produces major amounts of VII and only minor quantities of I. Furthermore, acid hydrolysis of I is accompanied by the formation of considerable amounts of material of low volatility (probably dimers). A similar material has been observed only in minor amounts in the cleavage of II and not at all in the cleavage of III and IV.

To resolve the problem, the olefinic esters obtained from the acid hydrolysis of the cyanoether II and the alcohol I have been isolated and the position of the double bond has been determined by ozonolysis. The olefin resulting from the cleavage of II had the following double bond distribution: $\Delta 10 = 3.1\%$, $\Delta 11 = 50.9\%$, $\Delta 12 = 42.5\%$ and $\Delta 13 = 3.6\%$. The

olefinic material derived from the acid hydrolysis of I had essentially random double bond distribution, and none of the positional isomers was present in greater than 15% concentration. In view of these results, hydroxystearate is ruled out as an intermediate in the formation of the *trans*-olefin. Furthermore, the confinement of double bond locations to the $\Delta 11$ and $\Delta 12$ positions indicates that ether cleavage proceeds by a concerted, though not necessarily synchronous process.

Finally it should be mentioned that treatment of nitrile II with a 60% methanolic solution of boron trifluoride etherate at reflux over an extended period of time gave as the principal product the dimethyl ester VI. The two principal by-products formed were the olefin VII and a new material identified as a methoxystearate. The *trans*-octadecenoate in this case can only have been formed by an elimination reaction such as path a in Figure 2. The methyl ether, on the other hand, may be either a nucleophilic substitution product (Figure 2, path c), or it may be the result of BF_3 -catalyzed secondary addition of methanol to the olefin formed first.

ACKNOWLEDGMENTS

Elemental analyses were performed by Marta Tatomyr and Laverne H. Scroggins.

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[Received June 6, 1968]