New Type of Skipped Oligoaziridines: Synthesis of New Fatty Acid Derivatives Containing Aziridine Functions

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Dedicated to Professor Walter Jansen on the occasion of his 60th birthday

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The first successful preparation of the aziridines methyl *cis*-9,10;*cis*-12,13-diepiminooctadecanoate (**3**) derived from linoleic acid, and methyl *cis*-9,10;*cis*-12,13;*cis*-15,16-triepiminooctadecanoate (**6**) derived from linolenic acid, is reported. Remarkably, the bis- and trisaziridine were obtained in a reaction sequence that consists of only two steps, using technically pure methyl esters of epoxidized sunflower and linseed oil. The conversion of methyl 9,10;12,13-diepoxyoctadecanoate (**1**), with sodium azide and ammonium chloride in ethanol in the presence of water, yielded the new diazidodihydroxy compound methyl 9(10),12(13)-diazido-10(9),13(12)-dihydroxyoctadecanoate (**2**) in the first step. **2** was obtained as a regioisomeric mixture. The reaction of **2** with triphenylphosphane led to the bisaziridine **3**. The analogous conversion of methyl 9,10;12,13;15,16-triepoxyoctadecanoate (**4**), via the new triazidotrihydroxy compound methyl 9(10),12(13),15(16)-triazido-10(9),13(12),16(15)-trihydroxyoctadecanoate (**5**), afforded trisaziridine **6**.

Aziridines can be regarded as representatives of the first and simplest of all heterocyclic systems, characterized as they are by the presence of two carbon atoms and one nitrogen atom in a three-membered ring. Interest in these small-ring heterocycles is due to the general influence of ring strain upon chemical reactivity, and the fact that the aziridine ring exhibits a great synthetic potential due to its reactivity towards a number of reagents. The system is extremely susceptible to ring cleavage and may be converted into a wide variety of functionalized compounds.[1] On the other hand, aziridines also show interesting biological properties. Most of the interest in the biological activity of aziridines has focussed on those that chemically modify DNA and show potential antitumor and insect chemosterilant activity.[2] Studies on bisaziridine and trisaziridine derivatives are not as yet well known in literature.[3] In particular studies concerning those containing the aziridine moiety and an unsubstituted NH group are quite rare.[3e,3g]

Furthermore, long-chain fatty acids containing N-heterocycles are not found in nature.[4] These nitrogen-containing fatty acid derivatives have attracted increasing interest because of their promising biological properties and great synthetic potential.[5] The first examples of long-chain fatty acid derivatives containing an internal aziridine group were reported in 1967/1968.[6] The procedure for the preparation of these compounds was the electrophilic addition of iodine isocyanate to methyl oleate (Scheme 1). The iodine isocyanate was prepared in situ from silver cyanate and iodine at −30°C. Methanolysis and basic ring closure yielded methyl *cis*-9,10-epiminooctadecanoate.[6,7] An alternative and more direct method for the preparation of fat-derived aziridines was shown to be the radical addition of *N*,*N*-dichlorourethane (DCU) to internal olefins (Scheme 1). By adding DCU to methyl oleate methyl 9,10-epiminooctadecanoate was obtained as stereoisomeric mixture ([*trans*]/[*cis*] = 60:40).[7] Another versatile route to fatty acid derived aziridines starts from the corresponding epoxy derivative[5] (Scheme 1). The ring-opening reaction involving methyl *cis*-9,10-epoxyoctadecanoate and sodium azide gave a mixture of methyl *threo*-9,10- and 10,9-azidohydroxyoctadecanoate regioisomers. Heating of the latter mixture with triphenylphosphane in dry tetrahydrofuran afforded the desired methyl *cis*-9,10-epiminooctadecanoate.

We have been interested in the synthesis of bis- and trisaziridines derived from fats due to both their biological and chemical properties, the latter properties suggesting them as good candidates as intermediates for the synthesis of highly functionalized fatty compounds. However, the ring closure, under formation of two and three aziridine rings, is not a trivial problem. With regard to the highly functionalized precursors, if the reaction does not take place at the neighbouring groups, but at more distant groups, the formation of four- to six-membered rings would also be possible. To the best of our knowledge, skipped open-chain bis- and trisaziridines with unsubstituted NH groups have not been described in the literature. In this paper we report on our investigations to find a synthetic route for the formation of bis- and trisaziridines derived from methyl linoleate and methyl linolate.

Results and Discussion

Referring to the different preparations of methyl *cis*-9,10-epiminooctadecanoate,[5−7] we first considered the iodine

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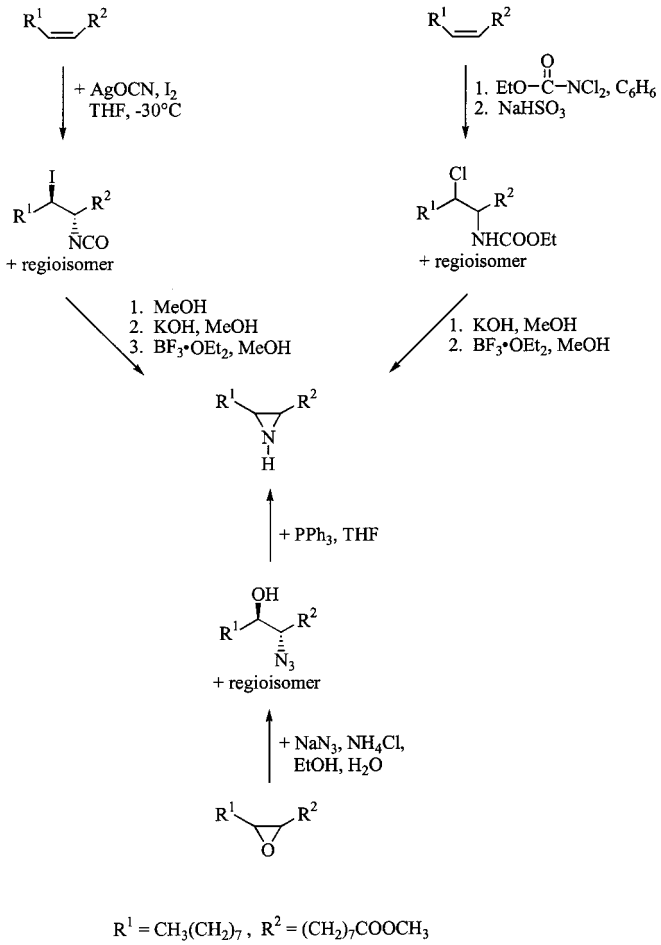
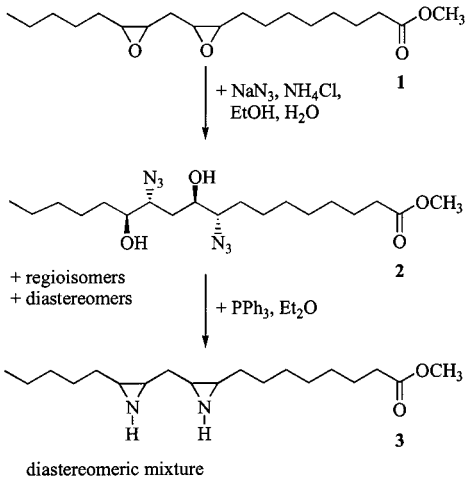


Scheme 1. Synthesis of the monoaziridine methyl *cis*-9,10-epiminooctadecanoate[5–7]

isocyanate pathway.[5] The reaction of two equiv. of iodine isocyanate, generated from iodine and silver cyanate, with methyl linoleate in dry THF (−30°C, stirring for 2 h) gave a β-iodoisocyanate derivative that still contained an unreacted double bond. Variation of the reaction conditions (increase of the reaction time up to 6 h and of the reaction temperature up to −10°C) gave the same disappointing results. This observation corresponds to the results of Ansari and Osman,[8] who tried to add two equiv. of iodine isocyanate to linoleic acid and identified the isolated addition product as methyl *threo*-12(13)-iodo-13(12)-isocyanato-*cis*-octadecenoate. After the failure of the iodine isocyanate method we focussed on the addition of DCU to methyl linoleate. Methyl linoleate was added to a solution of two equiv. of DCU in absolute benzene, and the temp. was maintained at 30−35°C. After refluxing the reaction mixture for 90 min, the reaction was completed by the addition of aqueous bisulfite at 5−10°C to form a β-chlorocarbamate derivative. The NMR and MS data of the crude addition product of the first reaction step indicated conversion of both double bonds, but the final basic ring closure of the supposed bisadduct, by stirring with methanolic potassium hydroxide for 3 d at room temp., only furnished product mixtures which did not contain the bisaziridine.

Finally, the bisaziridine **3** and the trisaziridine **6** were prepared starting from the corresponding epoxy derivatives. The epoxides were used as supplied (technical purity) without further purification. The methyl esters of epoxidized sunflower oil showed a proportion of 64% of methyl 9,10;12,13-diepoxyoctadecanoate (**1**). The reaction of the diepoxy compound with 7.5 equiv. of sodium azide and 7.5 equiv. of ammonium chloride was carried out in ethanol in the presence of water by refluxing for 65 h. Column chromatography of the product mixture obtained easily afforded the pure regioisomeric diazido diols methyl 9(10),12(13)-diazido-10(9),13(12)-dihydroxyoctadecanoate (**2**). The product **2** was obtained as a light yellow solid in a yield of 68%. Conversion of the latter compound **2** by heating with 2.1 equiv. of triphenylphosphane in dry diethyl ether for 21 h yielded 54% of the desired bisaziridine methyl *cis*-9,10;*cis*-12,13-diepiminooctadecanoate (**3**) as a pale yellow oil. The overall yield of **3** was 37% (Scheme 2).

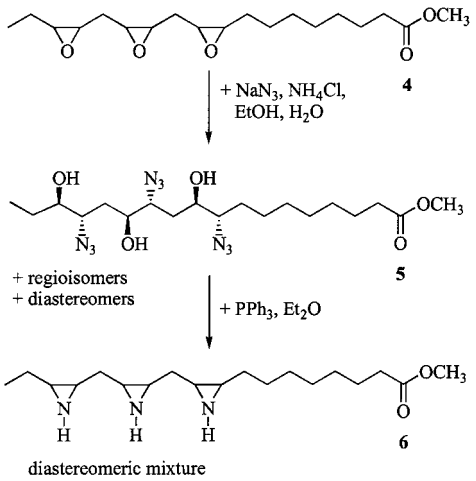
This successful preparation of the bisaziridine **3** is remarkable, since the formation of four- to six-membered rings would also be possible starting from the diazido diols. For example, azetidines can be prepared from 3-azido alcohols by reaction with triphenylphosphane under reflux in dry acetonitrile.[5] Fortunately, the analogous conversion of 2-azido alcohols to aziridines requires milder reaction conditions and proceeds via the five-membered (quite stable) 1,3,2λ^5-oxazaphospholidines as intermediates,[9] so that the formation of aziridines should be favoured compared to the formation of larger ring systems.



Scheme 2. Synthesis of the bisaziridine methyl *cis*-9,10;*cis*-12,13-diepiminooctadecanoate (**3**)

The analogous synthetic pathway was applicable for the preparation of the trisaziridine **6**. In this case the methyl esters of epoxidized linseed oil containing 53% of methyl 9,10;12,13;15,16-triepoxyoctadecanoate (**4**) served as the starting material. The regioisomeric triazido triols methyl 9(10),12(13),15(16)-triazido-10(9),13(12),16(15)-trihydroxyoctadecanoate (**5**) resulted from the reaction of the triepoxide **4** with 11.2 equiv. of sodium azide and ammonium chloride in ethanol in the presence of water by refluxing for 64 h. The product **5** was obtained after column chromatogra-

phy as an orange oil in a yield of 70%. Further conversion of **5** by heating with 3.1 equiv. of triphenylphosphane in dry diethyl ether led in 23% yield to the trisaziridine methyl *cis*-9,10;*cis*-12,13;*cis*-15,13-triepiminooctadecanoate (**6**) as an orange oil. The overall yield of **6** was 16% (Scheme 3).



Scheme 3. Synthesis of the trisaziridine methyl *cis*-9,10;*cis*-12,13;*cis*-15,16-triepiminooctadecanoate

In contrast to their preparation, the purification of both the bisaziridine and the trisaziridine turned out to be more complex than expected, so that the low isolated yields had to be accepted. The difficulties arose from the similar high polarities of the aziridines and the triphenylphosphane oxide which was formed in a twofold (bisaziridine) or threefold (trisaziridine) molar excess. Furthermore the bis- and trisaziridine seemed to form associates with Ph_3PO that could not be separated by simple column chromatography as described for the monoaziridine.[5] The following procedure led to the isolation of the aziridines: First, the conversion of the azido alcohol with triphenylphosphane was carried out in diethyl ether instead of THF.[5] Then the reaction mixture was cooled to 0°C and the white precipitate of Ph_3PO was filtered off. A final column filtration on silica gel yielded the corresponding aziridines with high purity.

Bisaziridine **3** and trisaziridine **6** were obtained as diastereomeric mixtures. Both, the ring opening of the epoxide ring by nucleophilic attack of the azide anion and the cyclization of the obtained azido alcohol proceeds stereoselectively with inversion. So the overall stereochemistry of the epoxy precursor is retained. Thus, the resulting bis- and trisaziridine derivatives exhibit, respectively, the stereochemistry of the di- and triepoxy compounds used, which are formed as diastereomeric mixtures in the epoxidation of the corresponding olefins.[10]

In summary, the synthesis of new skipped bis- and trisaziridine derivatives of fatty acid methyl esters is presented. The reaction is easily performed in two steps and proceeds via new diazido and triazido alcohols, which could easily be separated by simple column chromatography. For this reason the direct use of cheap starting materials of technical purity does not appear to have a negative impact on the preparation.

Experimental Section

General: All chemicals and solvents were purchased from standard chemical suppliers. Solvents: Diethyl ether was distilled from sodium. Ethyl acetate was distilled from potassium carbonate. Methanol was refluxed over magnesium for 2 h and then distilled. Petroleum ether 60/80 was distilled. Triethylamine was refluxed over calcium hydride for 2 h and then distilled. The methyl esters of the epoxidized sunflower oil (MES) and the methyl esters of the epoxidized linseed oil (MEL) were obtained from HOBUM, Hamburg. The detailed composition (according to GC analysis) was as given in Table 1.

Table 1. Composition of the starting materials

	MES	MEL
Methyl hexadecanoate	6%	5%
Methyl octadecanoate	2%	3%
Methyl 9,10-epoxyoctadecanoate	22%	21%
Methyl 9,10;12,13-diepoxyoctadecanoate	64%	17%
Methyl 9,10;12,13;15,16-triepoxyoctadecanoate	1%	53%

The amounts of the starting epoxides used in the reactions were calculated from the proportion of the required diepoxy and triepoxy compounds. The conversions of the azido alcohols to the aziridines, and the following purifications, were carried out under nitrogen. For all liquid-chromatographic separations silica gel 60 (40−63 μm) from Merck was used.

Analytical Equipment: NMR: Bruker ARX 500, ^1H NMR (500.135 MHz), ^{13}C NMR (125.776 MHz), TMS as internal standard. − MS: Finnigan MAT 95. − Elemental analysis: Mikroanalytisches Labor Beller, 37004 Göttingen: In the case of the trisaziridine **6** it was generally difficult to obtain correct data from elemental analysis, because of its tendency to add water and carbon dioxide under cleavage of one aziridine ring.

Methyl 9(10),12(13)-Diazido-10(9),13(12)-dihydroxyoctadecanoate (2): A mixture of 5.10 g of MES (10 mmol of methyl 9,10;12,13-diepoxyoctadecanoate), 5.85 g (90 mmol) of sodium azide, 4.81 g (90 mmol) of ammonium chloride, 40 mL of water and 250 mL of ethanol was refluxed for 65 h. After the addition of 300 mL of water, the mixture was extracted with diethyl ether (4 × 100 mL). The combined organic layers were washed with 150 mL of water and dried with anhydrous sodium sulfate. Evaporation of the solvent in vacuo yielded 5.36 g of a brown oil. The product was isolated by flash chromatography (petroleum ether/ethyl acetate/methanol, 14:6:2) as a light yellow solid. − Yield: 2.83 g (68%). − ^1H NMR ($CDCl_3$): δ = 0.87 (t, 3 H, CH_3), 1.20−1.70 (m, 22 H, CH_2), 2.27 (t, 2 H, 2-H), 2.60 (m, 1 H, OH), 2.92 (m, 1 H, OH), 3.17 (m, 1 H, CHN_3), 3.51 (m, 1 H, CHOH), 3.56 (m, 1 H, CHN_3), 3.63 (s, 3 H, OCH_3), 3.73 (m, 1 H, CHOH). − ^{13}C NMR ($CDCl_3$): δ = 13.89, 13.92 (CH_3), 22.43, 22.49, 24.78, 25.36, 25.53, 25.83, 28.89, 28.95, 29.12, 29.18, 30.45, 30.48, 31.54, 31.64, 31.67 (CH_2), 33.98, 34.33, 34.39 (C-2), 51.44 (OCH_3), 63.64, 63.78, 63.79, 66.81, 66.87 (CHN_3), 73.07, 73.20, 74.36, 74.45 (CHOH), 174.37, 174.41 (C-1). − HR MS/CI (ammonia); $C_{19}H_{40}N_7O_4$ $[M + NH_4]^+$: calcd. 430.3142; found 430.3146.

Methyl *cis*-9,10;*cis*-12,13-Diepiminooctadecanoate (3): A mixture of 1.53 g (3.7 mmol) of **2** and 2.08 g (7.9 mmol) of triphenylphosphane in 50 mL of dry ether was refluxed for 21 h. The yellow solution was cooled to 0°C and the white solid (Ph_3PO) was filtered off. Evaporation of the solvent in vacuo yielded 1.57 g of a pale yellow oil. Further purification was achieved by column filtration.

Eluation with 1.5 L of ether followed by 80 mL of methanol yielded 0.64 g (54%) of the product as a pale yellow oil in the methanolic fraction. − ^{1}H NMR ($CDCl_3$): δ = 0.78 (t, 3 H, CH_3), 1.15−1.43 (m, 20 H, CH_2), 1.50 (t, 2 H 3-H), 1.88 (m, 2 H, CH), 2.05 (m, 2 H, CH), 2.18 (t, 2 H, 2-H), 3.54 (s, 3 H, OCH_3). − ^{13}C NMR ($CDCl_3$): δ = 13.90 (CH_3), 22.51, 24.77, 27.54, 27.57, 27.79, 27.82, 28.16, 28.29, 28.76, 28.87, 28.93, 29.09, 29.21, 31.64, 33.18 (CH_2), 33.92 (C-2), 34.45, 34.51, 34.69, 34.74 (CH), 51.25 (OCH_3), 174.08 (C-1). − HR MS/CI (isobutane); $C_{19}H_{37}N_2O_2$ $[MH]^+$: calcd. 325.2855; found 325.2851. − $C_{19}H_{36}N_2O_2$ (324.5): calcd. C 70.32, H 11.18, N 8.63; found C 70.62, H 11.34, N 8.52.

Methyl 9(10),12(13),15(16)-Triazido-10(9),13(12),16(15)-trihydroxyoctadecanoate (5): A mixture of 6.42 g of MEL (10 mmol of methyl 9,10;12,13;15,16-triepoxyoctadecanoate), 8.78 g (135 mmol) of sodium azide, 7.22 g (135 mmol) of ammonium chloride, 50 mL of water and 300 mL of ethanol was refluxed for 64 h. After addition of 300 mL of water, the mixture was extracted with diethyl ether (4 × 150 mL). The combined organic layers were washed with 200 mL of water and dried with anhydrous sodium sulfate. Evaporation of the solvent in vacuo yielded 7.39 g of a dark brown oil. The product was isolated through flash chromatography (petroleum ether/ethyl acetate/methanol, 14:6:2) as an orange oil. − Yield: 3.28 g (70%). − ^{1}H NMR ($CDCl_3$): δ = 1.02 (t, 3 H, CH_3), 1.25−1.98 (m, 18 H, CH_2), 2.27 (t, 2 H, 2-H), 3.15 (m, 2 H, CHN_3), 3.54 (m, 2 H, CHOH), 3.63 (s, 3 H, OCH_3), 3.77 (m, 1 H, CHN_3), 3.85 (m, 1 H, CHOH). − ^{13}C NMR ($CDCl_3$): δ = 10.51 (CH_3), 23.66, 23.79, 23.85, 24.71, 25.48, 25.90, 28.81, 28.87, 29.02, 30.57, 30.63 (CH_2), 33.94 (C-2), 34.79, 34.96, 35.15 (CH_2), 51.44 (OCH_3), 63.96, 64.24, 66.69, 67.36, 67.48, 68.28, 68.92, 69.03 (CHN_3), 69.57, 69.94, 70.02, 70.07, 70.25, 70.31 (CHOH), 174.48 (C-1). − HR MS/CI (ammonia); $C_{19}H_{39}N_{10}O_5$ $[M + NH_4]^+$: calcd. 487.3105; found 487.3097.

Methyl *cis*-9,10;cis-12,13;*cis*-15,16-Triepiminooctadecanoate (6): A mixture of 2.31 g (4.9 mmol) of **5** and 3.99 g (15.2 mmol) of triphenylphosphane in 70 mL of dry ether was refluxed for 24 h. The orange solution was cooled to 0°C and the white solid (Ph_3PO) was filtered off. Evaporation of the solvent in vacuo furnished 4.04 g of an orange oil. Further purification was achieved by column filtration. Successive eluation with 1.5 L of ether followed by 150 mL of ether/methanol (1:1) and 150 mL of methanol afforded 0.70 g of the product in the ether/methanol fraction. Finally column chromatography (methanol/triethylamine, 10:1) yielded 0.35 g (23%) of the pure product as an orange oil. − ^{1}H NMR ($CDCl_3$): δ = 0.93 (t, 3 H, CH_3), 1.15−1.50 (m, 16 H, CH_2), 1.52 (t, 2 H, 3-H), 1.92 (m, 2 H, CH), 2.12 (m, 4 H, CH), 2.20 (t, 2 H, 2-H), 3.57 (s, 3 H, OCH_3). − ^{13}C NMR ($CDCl_3$): δ = 12.00 (CH_3), 21.97, 22.11, 24.80, 27.81, 28.15, 28.26, 28.37, 28.74, 28.85, 28.95, 29.11, 29.24, 32.93, 33.21, 33.26 (CH_2), 33.96 (C-2), 34.49, 34.77, 36.05, 36.32 (CH), 51.31 (OCH_3), 174.16 (C-1). − HR MS/CI (isobutane); $C_{19}H_{36}N_3O_2$ $[MH]^+$: calcd. 338.2807; found 338.2806. − $C_{19}H_{35}N_3O_2$ (337.5): calcd. C 67.62, H 10.45, N 12.45; found C 65.23, H 10.01, N 11.20.

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