✻Reaction of Methyl *trans*-2,3-epoxyhexadecanoate with Urea: Synthesis of Long Chain Fatty 2-Oxazolidones[1]

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ABSTRACT

Methyl *trans*-2,3-epoxyhexadecanoate on refluxing with urea in dimethylformamide (DMF) afforded isomeric 4(5)-tridecyl-5(4)-carbomethoxy-*cis*-2-oxazolidone (II), 5-tridecylmethylene hydantoin (II) and 2-hydroxy-3-carbamidohexadecanoic acid (III).

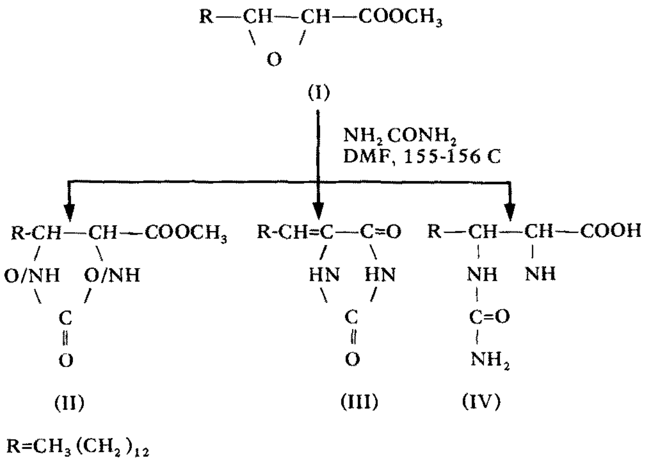
INTRODUCTION

The syntheses of 2-oxazolidones have attracted attention due to their wide range of biological and industrial applications (1). Many methods have been described for the synthesis of 2-oxazolidones from epoxides (1). 2-Oxazolidones have been prepared by the reaction of urea with epoxides (2-7). Since the reaction of urea with long chain fatty methyl 2,3-epoxy ester for the formation of 2-oxazolidones has not been reported in the literature, it is considered of interest to synthesize a long chain fatty 2-oxazolidone by the reaction of methyl *trans*-2,3-epoxy fatty ester using urea as condensing agent in dimethylformamide (DMF). It has been found that synthesis of 2-oxazolidone is successful but is complicated by the formation of side products not reported earlier (7).

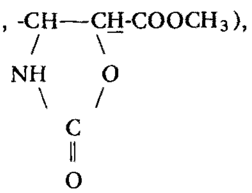
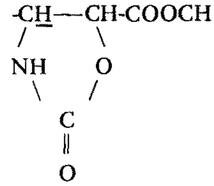
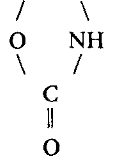
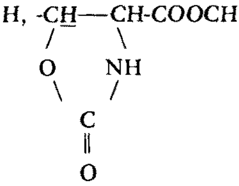
This paper reports the results of the reaction of methyl *trans*-2,3-epoxyhexahecanoate (I) with urea.

RESULTS

Methyl *trans*-2,3-epoxyhexadecanoate (I), when refluxed with urea in DMF at 155-156 C, gave three products (II, III, IV) (Scheme 1). The structures of the individual products were determined from spectral and microanalytical data.



SCHEME 1

The product (II) analyzed correctly for $C_{18}H_{33}NO_4$. Its IR spectrum gave a sharp band at 1750 cm^{-1} characteristic of 2-oxazolidone ring (8). Other characteristic absorption bands at 3335 (N-H stretch), 1730 ($\underline{C}OOCH_3$), 1455 (CH-O), 1430 (CH-N), 1220, 1085, 1065 ($\overline{C}$-O) and 700 cm^{-1} (NH wag) appeared. The ^{1}H NMR spectrum of this compound showed characteristic signals at δ 7.97 s(1H, N$\underline{H}$, slow D_2O exchangeable), 4.96 d(1H, J=8.5 Hz,  $\text{-CH—C}\underline{\text{H}}\text{-COOCH}_3$), 3.5 m(1H,  $\text{-C}\underline{\text{H}}\text{—CH-COOCH}_3$), 3.77 s(3H, $\text{-COOC}\underline{\text{H}}_3$), 1.27 br,s(chain-C$\underline{H}_2$ protons) and 0.9 t(3H, terminal-C$\underline{H}_3$). On the basis of these data, II was characterized as 4-tridecyl-5-carboxymethyl-*cis*-2-oxazolidone. The *cis*-configuration of II was established on the basis of coupling constant (J= 8.5 Hz) of 5-methine proton of ring (9,10). Appearance of weak multiplets at δ 4.0 (1H,  $\text{-CH—C}\underline{\text{H}}\text{-COOCH}_3$) and 3.7 (1H,  $\text{-C}\underline{\text{H}}\text{—CH-COOCH}_3$) suggested the formation of other isomer, 4-carbomethoxy-5-tridecyl-*cis*-2-oxazolidone in a small amount. The structure of oxazolidone II was further confirmed by mass spectral fragmentation data (Scheme 2). The mass spectrum of II gave no molecular ion peak at m/z 327 ($C_{18}H_{33}NO_4$), but 328 (M+1, 9.3), 329 (M+2, 0.2) and 326 (M-1, 1.9) peaks were observed. Other structure ion peaks were observed at m/z 296 (M-OCH3, 0.2), 295 (M-CH3OH, 4.0), 268 (M-COOCH3 or NHCOO, 18.1), 239 (8.2), 238 (44), 225 (268-43, 10.4), 213 (3.12), 211 (3.12), 210 (13.7), 195 (239-44, 3.12), 187 (16.8), 183 (2.5), 168 [144+$(CH_2)_2$, 5.0], 144 (51.25), 128 (16.5), 116 (43), 115 (48.8), 101 (32.5), 100 (32.5), 90 (42.5), 85 (144-59, 16.3), 57 (52.5), 55 (85) and 43 (100).

The second product (III) analyzed correctly for $C_{17}H_{31}N_2O_2$. It showed IR bands at 1765 cm^{-1} characteristic of hydantoin ring (11). The disappearance of the band at ~1735 cm^{-1} suggested that the ester carbonyl group participated in the formation of the hydantoin ring. Other absorption bands occur at 3200 (N-H stretch), 1675 (CH=C-$\underline{CO}$), 1455 (C-N), 1390, 1350, 1150, 1085, 1000, 750, 740, 710, 650 and 630 cm^{-1}. The ^{1}H NMR spectrum of this compound showed diagnostic signals at δ 7.71 s(2H, -N$\underline{H}$CON$\underline{H}$-, exchangeable with D_2O), 6.64 t(1H, $\text{-CH}_2\text{-C}\underline{\text{H}}$= C-), 2.49 m(2H, $\text{-C}\underline{\text{H}}_2$-CH=C-) along with usual signals of fatty acid chain. The absence of signal at ~ δ 3.77 s(3H, COOC$\underline{H}_3$) suggested the ester group participated in the formation of ring. These data suggested that product III had the 5-tridecylmethylene hydantoin structure. Structure III

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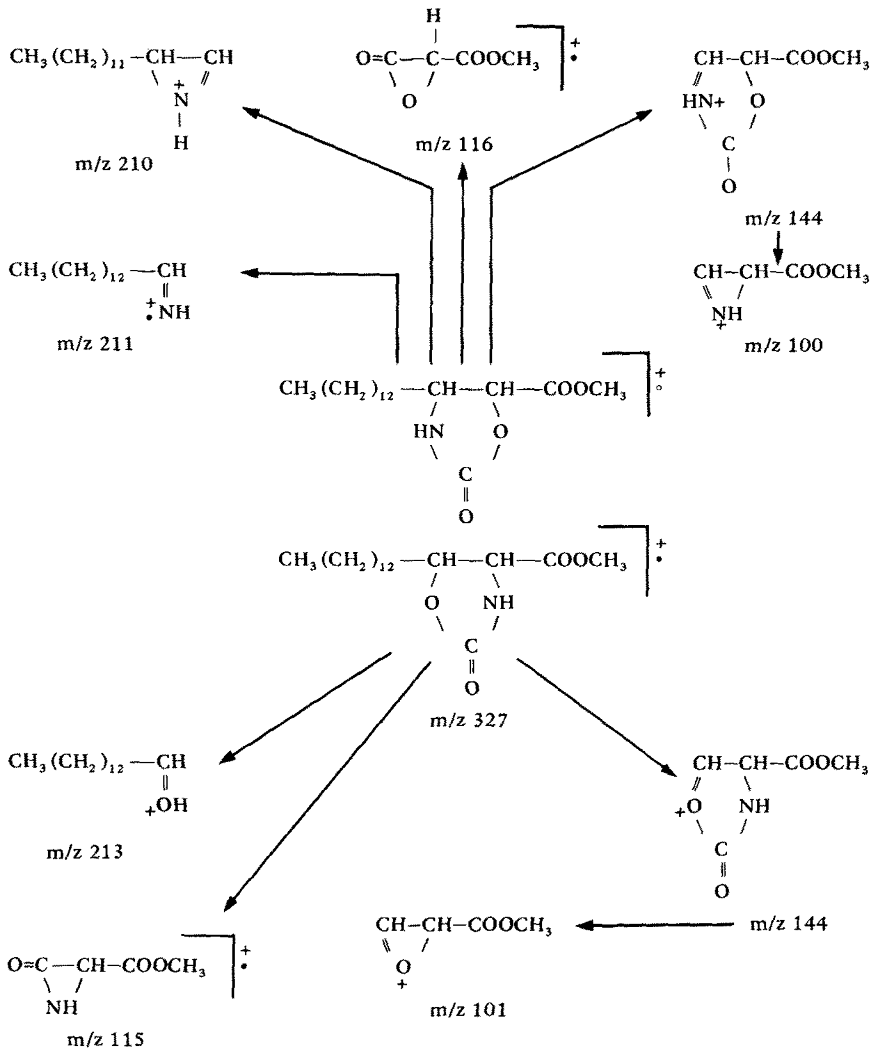


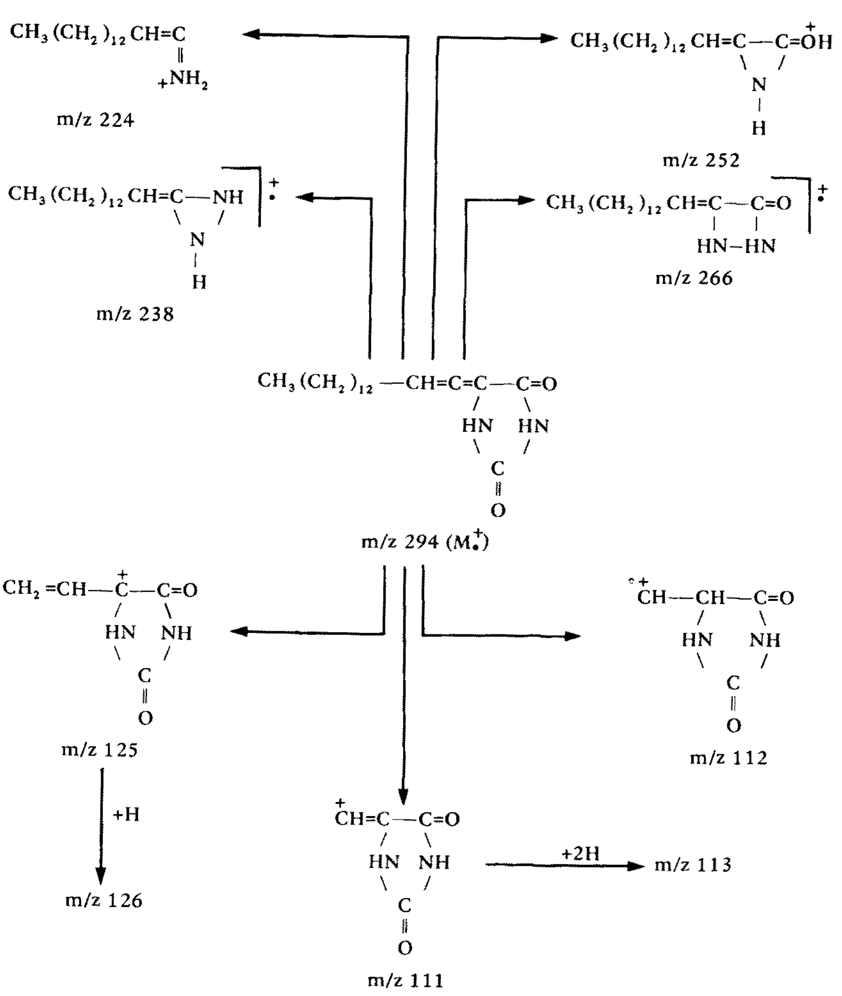
SCHEME 2

was further supported by mass spectral fragmentation data (Scheme 3). The mass spectrum of III gave a molecular peak at m/z 294 ($C_{17}H_{30}N_2O_4$, 71.5), along with (M+2) and (M+1) peaks. Other characteristic peaks were observed at m/z 266 (M-28, 2.4), 265 (M-29, 1.7), 252 (M-42, 3.2), 251 (M-43, 2.3), 238 (M-56, 4.6), 224 (5.0), 183 (5.0), 167 (7.5), 153 (12.5), 139 (33.5), 126 (125+H, 45), 125 (67.5), 113 (111+2H, >100), 112 (111+H, 42.5), 111 (125-14, 20.0), 100 (126-26, 75), 97 (125-28, 32.5), 83 (125-42, 37.5), 82 (125-43, 15) and 43 (100).

Elemental analysis of the product (IV) corresponded to the composition $C_{17}H_{34}N_2O_4$. It gave characteristic IR bands at 3420 (weak, COOH), 3370 (NHCONH$_2$), 3360-3200 (broad band, NHCONH$_2$, -OH), 1710 (COOH), 1685 (NHCONH$_2$) with a notch at 1610 (NH$_2$ def.), 1450 (C-N), 1370, 1280, 1070 (C-O) and 750 cm^{-1} (NH$_2$ wag). Absence of band at ~1730 and appearance of band at 1710 cm^{-1} suggested the ester group changed into carboxyl group. The ^{1}H NMR spectrum of this compound gave signals at δ 8.09 d (J=6 Hz, -NHCO-), 7.52 s(2H, -NHCONH$_2$), 4.35 m(1H, $-\underset{\underset{OH}{|}}{C}H\text{-COOH}$), 3.69 m(1H, $-\underset{\underset{-NH}{|}}{C}H\text{—}\underset{\underset{OH}{|}}{C}H\text{-}$), 2.25 m(1H, $-\underset{|}{C}H\text{-OH}$, disappeared readily on D$_2$O shake) along with 9.2 br,s (COOH) and other usual signals of fatty acid chain. On the basis of these data, the compound (IV) was characterized as 2-hydroxy-3-carbamidohexadecanoic acid. The structure of IV was confirmed further from mass spectral fragmentation data (Scheme 4). The mass spectrum of IV gave no molecular ion peak at m/z 330 ($C_{17}H_{34}N_2O_4$). The parent ion peak observed was at m/z 313 (M-OH, 0.9) followed by 312 (M-H$_2$O, 1.5). The other characteristic structure revealing ions were observed at 296 (M-2×OH, 1.2), 295 (M-35, 1.3), 294 (M-36, 1.1), 285 (M-COOH, 1.0), 280 (296-NH$_2$, 2.6), 279 (295-NH$_2$, 3.6), 269 (313-NH$_2$CO, 2), 268 (313-COOH, 5), 267 (312-COOH, 1.9), 255 (2), 253 (271-H$_2$O, 1.8), 252 (268-NH$_2$, 1.8), 251 (268-17, 1.0), 240 (285-CONH$_3$, 2.8), 225 (268-43, 4.5), 224 (268-CONH$_2$, 4.0), 223 (8.8), 213 (3.4), 212 (4.0), 211 (4.75), 183 (3.3), 161 (147+CH$_2$, 2), 149 (147+2H, 98.75), 147 (4.5), 75 (60) and 46 (100).

DISCUSSION

The reaction of methyl *trans*-2,3-epoxy ester (I) with urea in DMF gave 2-oxazolidone (II) along with side products III and IV not reported by Huth and Frost (7). They carried out the reaction of urea with ethyl 3-aryl-*trans*-2,3-epoxypropanoate and reported the formation of four isomers of



SCHEME 3

2-oxazolidones, i.e. the *cis*- and *trans*-4-aryl and *cis*- and *trans*-5-aryl isomers, respectively. In our case only two isomeric *cis*-products (II) in the form of their mixture could be isolated. The two *trans*-isomers are assumed to be formed from NMR data but could not be isolated. The product (IV) was isolated as an individual homogeneous compound. It may be assumed that its isomeric product, i.e. 2-carbamido-3-hydroxyhexadecanoic acid, was formed in low yield but reacted further by formation of 5-tridecyl-2-oxazolidone (II) and hydantoin (III). The latter resulted due to the participation of ester group.

EXPERIMENTAL PROCEDURES

All melting points were observed on a Kofler hot plate apparatus and are uncorrected. Infrared (IR) spectra were obtained with a Perkin-Elmer 621 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained on a Varian A60 spectrometer. Chemical shifts are reported as δ (ppm) relative to tetramethylsilane. The samples were run as 10% solution in CCl_4/DMSO-d^6. Mass spectra (MS) were obtained on an AEIMS-902 mass spectrometer. The figures in parentheses denote the postulated source of the ions along with intensity relative to the base peak.

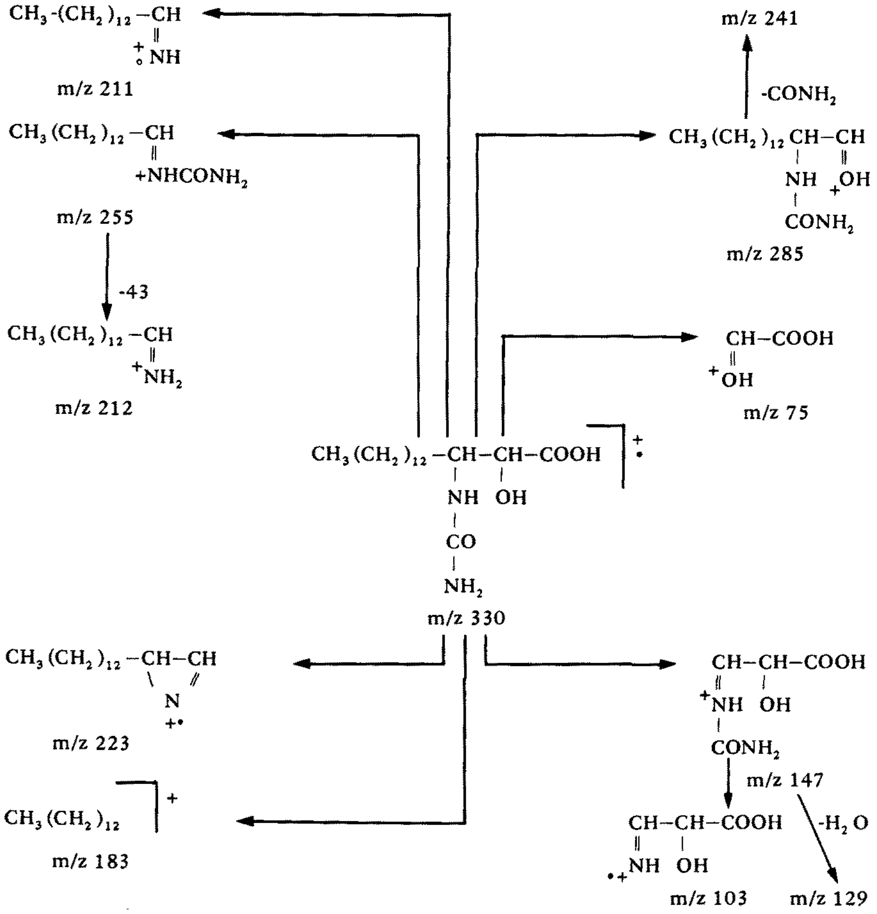
Analytical thin layer chromatography (TLC) was done on glass plates (20× 5 cm) with a layer of silica gel G (0.25 mm thickness). Mixtures of petroleum ether/diethyl ether/acetic acid (70:30:1, v/v/v) were used as developing solvents. The components were made visible on TLC plates by spraying with an aqueous solution (20%) of perchloric acid and heating at 120 C.

MATERIALS AND METHODS

Methyl *trans*-2,3-epoxyhexadecanoate (I) (mp 35-36 C) was prepared by the m-chloroperbenzoic acid epoxidation of methyl *trans*-2-hexadecenoate following the procedure of Gunstone and Jacobsberg (12). Methyl *trans*-2-hexadecenoate was prepared by the reaction of *trans*-2-hexadecenoic acid with anhydrous methanol in the presence of a catalytic amount of sulphuric acid (1-2 drops). *trans*-2-Hexadecenoic acid was prepared from palmitic (hexadecanoic) acid by the method of Palameta and Prostenik (13).

Reaction of Methyl *trans*-2,3-epoxyhexadecanoate (I) with Urea

A solution of I (2 g, 0.007 M) in DMF (30 ml) was refluxed with urea (0.42 g, 0.007 M). The reaction was com-



SCHEME 4

plete in one hr as revealed by TLC. The reaction mixture was diluted with water, extracted with diethyl ether. The ether layer was washed successively with water to remove the final traces of urea and DMF and dried over Na_2SO_4. Solvent was removed under reduced pressure to give a viscous oil (1.93 g). TLC analysis showed three distinct spots. The reaction mixture was chromatographed using silica gel (40 g) column chromatography. The elution with petroleum ether/ether (74:26, v/v) afforded II as solid, 1.08 g (ca. 56%, crystallized from methanol, mp 71-72 C); Found: C, 65.54; H, 9.71; N, 4.11; Calcd. for $C_{18}H_{33}NO_4$: C, 66.02; H, 10.15; N, 4.11%. Further elution with petroleum ether/ether (69:31, v/v) gave III as solid, 0.31 g (ca. 16%, crystallized from methanol, mp 148-149 C); Found: C, 68.81; H, 10.21; N, 9.13; Calcd. for $C_{17}H_{31}N_2O_2$: C, 69.11; H, 10.57; N, 9.48%. Further elution with petroleum ether/ether (74:26, v/v) gave IV as viscous liquid, 0.5 g (ca. 26%); Found: C, 61.28; H, 9.91; N, 8.21; Calcd. for $C_{17}H_{34}N_2O_4$; C, 61.74; H, 10.36; N, 8.54%.

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