Synthesis of 2, 3 Fatty Aziridines

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ABSTRACT

A new route for the synthesis of 2,3-aziridines is described. The reaction of methyl 2,3-dibromohexadecanoate (II) with ammonia at 0 C gave methyl 2-bromohexadec-2-enoate (III, ca. 93%). Compound III, on further treatment with ammonia at 25 C, gave methyl 2-aminohexadec-2-enoate (IV, ca. 5%), methyl *trans*-2,3-epiminohexadecanoate (V, ca. 64%), methyl *cis*-2,3-epiminohexadecanoate (VI, ca 24%) and *trans*-2,3-epiminohexadecamide (VII, ca 3%). The structures were established with the help of elemental analyses and infrared (IR), nuclear magnetic resonance (NMR) and mass spectral analyses.

INTRODUCTION

Aziridines are a rich source of important pharmaceuticals and adrenoceptor blocking agents (1). Publications on the preparation of aziridine-2-carboxylic acid esters from short-chain 2-bromo-2,3-unsaturated or 2,3-dibromo ester are reported (2-4). Aziridine derivatives were earlier (5) prepared from *trans*-2,3-enoic esters by adding N,N-dibromobenzene sulphonamide followed by cycling the addition product. The present work describes a new route for the synthesis of 2,3-aziridines from the 2,3-dibromo ester using ammonia in methanol as the reagent.

EXPERIMENTAL PROCEDURES

Uncorrected melting points are reported. The homogeneity of the products were checked by thin layer chromatography (TLC) on silica gel plates. IR spectra were recorded on a Perkin Elmer 621 spectrophotometer (λ_{max} in cm^{-1}). The NMR spectra were obtained with a Varian A60 spectrometer, the chemical shifts (δ ppm) being obtained using tetramethylsilane as the internal reference. Mass spectra were obtained on a JEOL JMSD300 mass spectrometer, at 70eV.

MATERIAL AND METHODS

Methyl 2,3-dibromohexadecanoate (II) was prepared from methyl hexadec-*trans*-2-enoate (I) (6) by the procedure of Myers (7). To a cold solution of I (5.0 g, 0.018 mol) in dry chloroform (45 mL), bromine (8.0 g, 0.05 mol) was added by drops within 2 hr, stirred at room temperature for 6 hr and then warmed to 50 C for 12 hr. After the usual work up and evaporation of solvent under reduced pressure, it gave a solid (7.6 g) that, on crystallization from petroleum ether at low temperature, yielded II (6.9 g, ca. 91%, m.p. 36-37 C, positive Beilstein test). Analysis: calculated for $C_{17}H_{32}O_2Br_2$: C, 47.68; H, 7.53; found: C, 47.59; H, 7.50%; IR: 1740 and 650; NMR: 4.24 (m, 2H), 3.72 (s, 3H), 1.2 (br,s, chain $C\underline{H}_2$) and 0.86 (t, 3H).

Reaction of II with Ammonia at 0 C

Compound II (4.0 g, 0.007 mol) in methanol (5 mL) was added to methanol (60 mL) saturated with dry ammonia at 0 C, and the mixture was stirred for 12 hr at this temperature. Solvent was removed under reduced pressure, extracted with ether, washed with water and dried over sodium sulphate so that the solvent evaporated. The crude product (3.4 g) was passed over a silica gel (45 g) column. Elution with petroleum ether gave the starting material (II, 0.11 g, ca 3.1%). Further elution with petroleum ether/ether (99.5:0.5, v/v) gave III (3.12 g, ca 93%). Analysis: calculated for $C_{17}H_{31}O_2Br$: C, 58.78; H, 8.99; found: C, 58.65; H, 8.87%; IR (neat): 1725, 1715, 1610, 1215, 1120, 1050, 995 and 645 cm^{-1}; NMR(CCl_4): 6.61 (t, 1H, J=8 Hz), 3.78 (s, 3H), 2.5 (m, 2H), 1.3 (br,s, chain $C\underline{H}_2$) and 0.98 (t, 3H).

Reaction of III with Ammonia at 25 C

Compound III (2.5 g, 0.007 mol) in methanol (5 mL) was added to methanol (35 mL) saturated with ammonia at 0 C. The reaction mixture was stirred at 5 C for 3 hr and 25 C for 10 hr. After the solvent evaporation, it was worked up as described above. Evaporation of the solvent yielded a solid (2.0 g) showing 4 spots on TLC plates. The reaction mixture was fractionated on a silica gel (45 g) column using petroleum ether/ether as eluting solvent. The first elution with petroleum ether/ether (95:5, v/v) yielded a TLC homogeneous liquid product IV (0.10 g, ca 5%). Analysis: calculated for $C_{17}H_{33}NO_2$: C, 72.08; H, 11.74; N, 4.94; found: C, 71.88; H, 11.70; N, 4.45%; IR(CCl_4): 3360, 1730, 1720, 1620, 1240, 1130, 1040, 1030, 1010, 1000 and 750; NMR(CCl_4): 7.23 (t, 1H, J=7 Hz), 3.87 (s, 2H), 3.79 (s, 3H), 2.25 (m, 2H), 1.3 (br,s, chain $C\underline{H}_2$) and 0.88 (t, 3H).

Subsequent elution with petroleum ether/ether (92:8, v/v) gave a solid product V (1.28 g, ca. 64%, m.p. 39-40 C). Analysis: calculated for $C_{17}H_{33}NO_2$: C, 72.08; H, 11.74; N, 4.94; found: C, 71.90; H, 11.62; N, 4.4%; IR(KBr): 3280, 1730, 1360, 1220, 1190, 1125, 1090, 1030 and 855; IR($CHCl_3$): 3270 and 850; NMR($CDCl_3$): 3.72 (s, 3H), 2.16 (br,m, 2H), 1.98 (s, 1H), 1.3 (br,s, chain $C\underline{H}_2$) and 0.88 (t, 3H); mass: M^+ 283.

The third product VI (0.48 g, ca. 24%, m.p. 56-57 C) was collected by elution with petroleum ether/ether (90:10, v/v). Analysis: calculated for $C_{17}H_{33}NO_2$: C, 72.08; H, 11.74; N, 4.94; found: C, 71.82; H, 11.65; N, 4.81%; IR(KBr): 3170, 1735, 1410, 1370, 1180, 1135, 1015 and 845; NMR($CDCl_3$): 3.73 (s, 3H), 2.44 (d, 1H, J=6 Hz), 2.09 (m, 1H), 1.79 (s, 1H), 1.29 (br,s, chain $C\underline{H}_2$) and 0.88 (t, 3H); mass: M^+ 283.

The final elution with petroleum ether/ether/chloroform (68:30:2, v/v/v) afforded VII (0.06 g, ca. 3%, m.p. 116-117 C). calculated for $C_{16}H_{32}ON_2$: C, 71.59; H, 12.01; N, 10.43; found: C, 71.45; H, 11.90; N, 10.08%; IR(KBr): 3380, 3180, 3275, 1650, 1620, 1305, 1040 and 855; IR($CHCl_3$): 3500, 3380, 3280, 1585, 1560 and 850; mass: M^+ 268.

RESULTS AND DISCUSSION

The present study concerns the reaction of methyl 2,3-dibromohexadecanoate (II) with ammonia and is illustrated in Scheme 1.

Reaction of II with ammonia at 0 C gave III (positive Beilstein test). It was analyzed for $C_{17}H_{31}O_2Br$ and characterized as methyl 2-bromohexadec-2-enoate. The IR spectrum gave characteristic bands at 1725, 1715 and 645 assignable to the ester and C-Br functions. The NMR spectrum clearly supported the assigned structure of III by showing a triplet centered at 6.61 ascribable to a proton β to ester carbonyl,

3.78 s (3H, $-CO_2\underline{CH}_3$) and 2.5 m (2H, $-\underline{CH}_2-CH=C-$, Br).

Reaction of III with ammonia at 25 C furnished compounds IV-VII. The presence of an amino group in IV was clearly shown by the IR spectrum exhibiting bands at 3360 and 750. A strong band at 1240 and weak band at 1040 for C-N stretching, showed the presence of a primary amine function attached with tertiary α-carbon atom (8). Two bands of equal intensity in the carbonyl region at 1730 and 1720 were observed for ester carbonyl. The splitting of the carbonyl frequency is due to the presence of an α-substituent (9). Besides the usual fatty acid ester signals, the significant NMR absorptions at

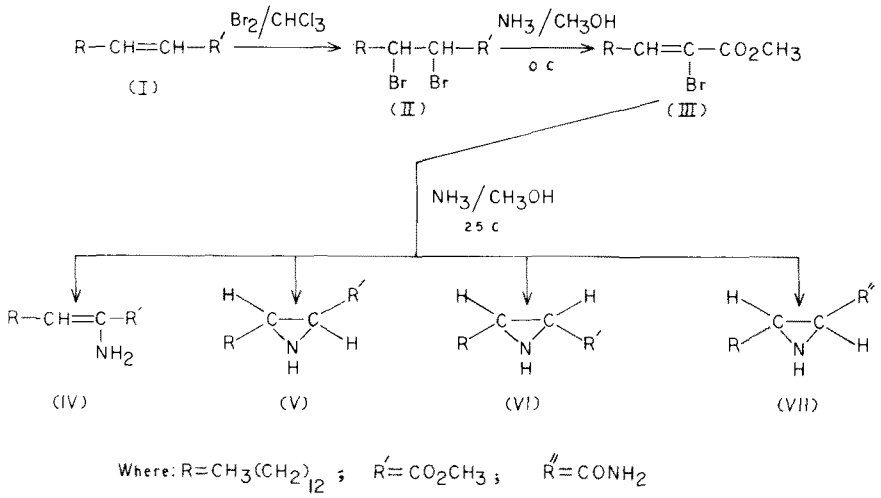
7.23 t (1H, $-\underline{CH}=C-CO_2CH_3$, J=7 Hz) and

3.87 s (2H, $-\underline{NH}_2$, D_2O exchangeable)

also supported the structure of compound IV as methyl 2-aminohexadec-2-enoate (α-dehydroamino ester).

The solid product V was characterized as methyl *trans*-2,3-epiminohexadecanoate as evidenced by the IR(KBr) bands at 3280 (weak) and 855 (strong) for the aziridine ring. When the IR spectrum was recorded in chloroform, the absorption bands characteristic of the aziridine function appeared at 3270 and 850. These bands have been ascribed to a deformation or vibration of the aziridine ring (10). The NMR showed a broad signal centered at 2.16 integrating for 2 methine protons of the aziridine ring and a singlet at 1.98 (1H, >N$\underline{H}$). The MS (Fig. 1) fragments of V at m/z 283 (M^+), 224, 210, 128 (base peak), 115, 114, 100, 88, 86 and 41 (Scheme 2) further supported the proposed structure.

Compound VI showed IR(KBr) absorption bands at 3170 and 845 for the *cis*-aziridine ring. These values are slightly different than those reported for *cis*-9,10-epiminooctadecanoate (3150 and 840) (11). The NMR spectrum clearly supported the structure of VI as methyl *cis*-2,3-epiminohexadecanoate by showing characteristic signals at



SCHEME 1

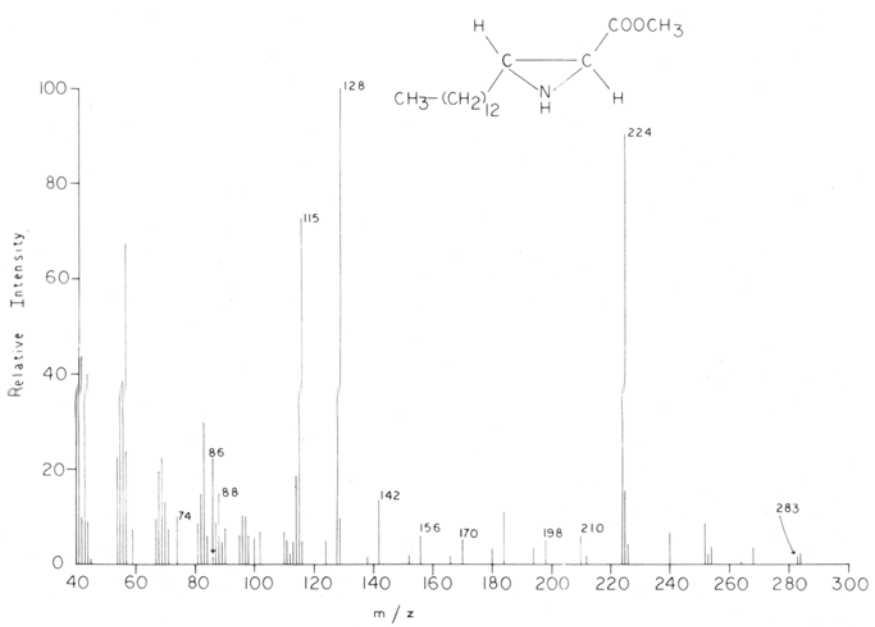
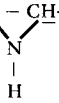


FIG. 1 MS of V

2.44 d (1H, -CH – CH-CO_2CH_3, J=6 Hz),



2.09 m (1H, -CH – CH-CO_2CH_3) and 1.79 s (1H, >NH).

The mass spectrum of VI showed a molecular ion peak at m/z 283 and a base peak at m/z 128. A similar fragmentation pattern was observed as that of *trans*-aziridine with slight differences in the intensity.

The IR(KBr) spectrum of VII showed characteristic absorption bands at 3380, 3180 (NH_2), 3275, 855 (*trans*-aziridine ring) and 1650 ($CONH_2$), 1620 (NH_2 def.). In chloroform solution these bands are replaced by bands at 3500, 3380 (NH_2), 3280, 850 (*trans*-aziridine ring), 1675 ($CONH_2$) and 1585 (NH_2 def.). These differences result from hydrogen-bonding in solution. The mass spectrum (Fig. 2) gave a molecular ion peak at m/z 268 along with 211, 210, 100, 85, 72, 71 and 56 (Scheme 3). On the basis of the above data, VII was characterized as *trans* -2,3-epiminohexadecamide.

The mechanism of the reaction is well known. That the first step in the reaction of α,β-dibromocarbonyl compounds with ammonia is dehydrohalogenation to a α-bromo-α,β-unsaturated compound, followed by 1,4-addition of the ammonia to produce the α-bromo-β-amino compound had been reported (12). The composition of the mixture of *erythro* and *threo*-α-bromo-β-amino compounds can not be determined because the component collapses immediately via intramolecular displacement of bromide to yield aziridines (V and VI). Product VII was formed by the reaction of ammonia on ester group. The possibility of the formation of amides of IV and VI in trace amounts defying detection and isolation can not be ruled out under the experimental conditions.

ACKNOWLEDGMENTS

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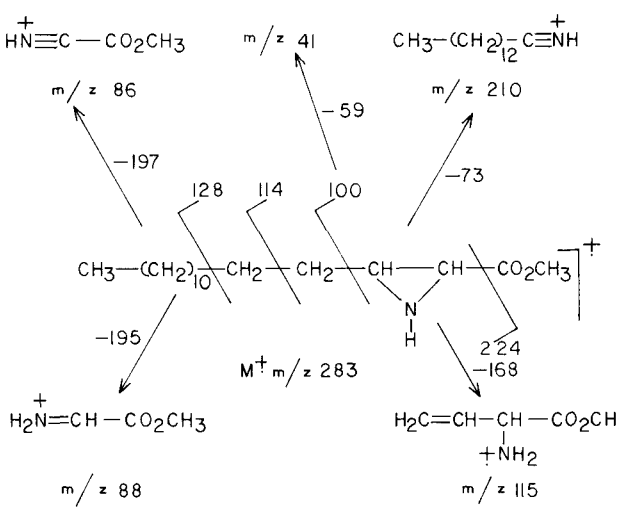
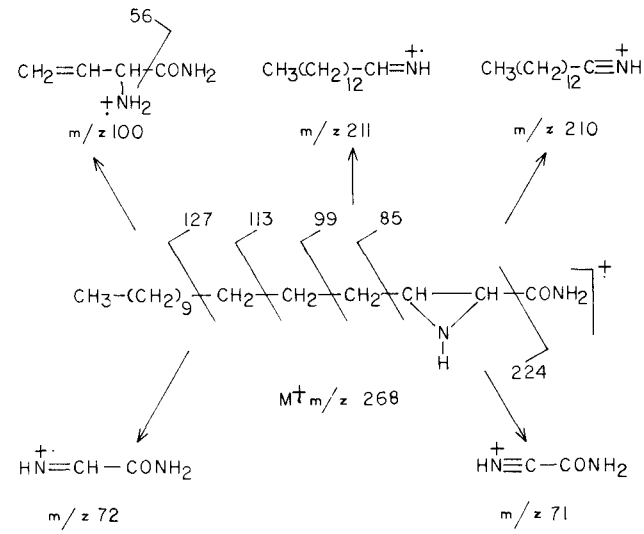


SCHEME 2



SCHEME 3

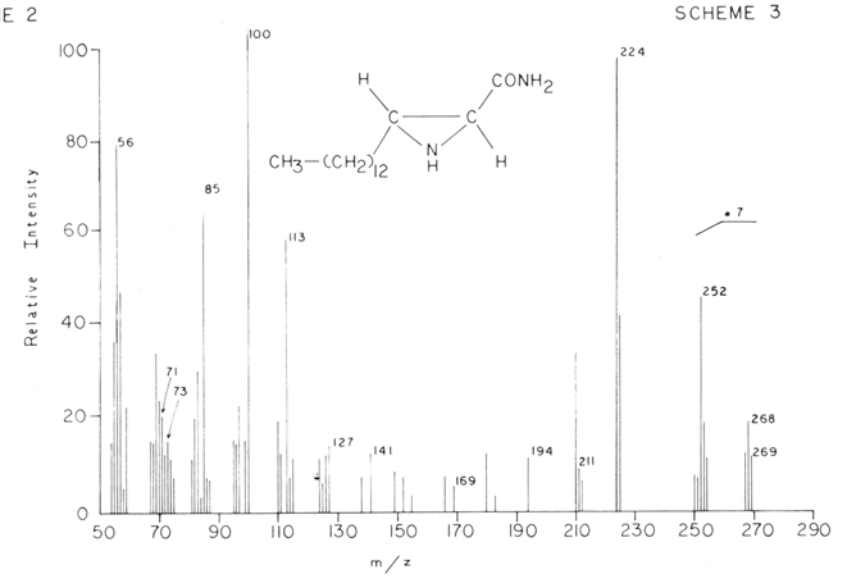


FIG. 2 MS of VII

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ERRATUM

In the Letter to the Editor by Robert R. Allen on page 1897 of the November 1983 *JAOCS*, an error occurred in line 330 of the program. The second **S3** in line 330 was printed as **83**. The line should read:

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330 Fl=S3*AA*AB*(EK-GK)-S3*AA*AC*(FK-GK)+SL*AC*(FK-GK)+SO*GK
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