Epimino Derivatives from β-Iodoazides[1]

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ABSTRACT

The preparation of the epimino derivatives of oleyl alcohol and methyl oleate by a two-step procedure has been studied. The procedure utilized the addition of iodine azide to the unsaturated compound, followed by reductive cyclization to the aziridine. For the latter step, several hydride-reducing agents and direct hydrogenation over metal catalysts were investigated. Comparison of the various methods studied showed that the best yields of epimino derivatives were obtained with lithium aluminum hydride, whereas direct hydrogenation gave the poorest yield. The reaction of the β-iodoazide adducts with trimethyl phosphite was also investigated and was shown to give rise to the dialkylphosphonoaziridinyl derivative of the starting olefin.

INTRODUCTION

The preparation of fatty acid derivatives containing an internal aziridine function has been a subject of recent interest (1-4). At the present time two procedures have been developed for the preparation of these novel heterocyclic derivatives. The more extensively studied method has been the addition of iodine isocyanate to unsaturated fatty acids (1-3), while more recently the addition of N,N-dichlorourethan to unsaturated fatty acids has been employed for the preparation (4). The first formed products obtained from both addition reactions are β-halocarbamate derivatives. The latter are subsequently cyclized to the epimino derivative by reaction with alkali. When the iodine isocyanate procedure is utilized for the preparation of epimino compounds, good yields are obtained when the starting olefin has the *cis* geometry, while poorer yields of epimino derivatives are obtained when the olefin is *trans* (1,4). The dichlorourethan method of preparation gives good yields of epimino compounds with both *cis* and *trans* unsaturated fatty acids. However a disadvantage encountered with the dichlorourethan reagent is the nonstereospecific formation of epimino derivative, a complication not associated with the iodine isocyanate method (4).

As part of our continuing effort to develop newer and more facile methods for the preparation of epimino derivatives of fatty acids, the present work was undertaken. In this paper we describe the addition of iodine azide to a number of selected olefinic compounds. The products of this reaction are the β-iodoazide derivatives of the olefin. The reductive cyclization of the latter compounds to the epimino ring structure has been studied with a number of reducing agents. Also studied was the reaction of the β-iodoazide adducts with trimethyl phosphite, which gave dialkylphosphonoaziridine derivatives as the principal reaction products.

EXPERIMENTAL PROCEDURES

Materials and Equipment

cis-3-Hexene (96%) and *trans*-3-hexene (99%) were purchased from Chemical Samples, Inc., and were used as received. Methyl oleate (98%) was used as received from Applied Science Laboratories.

cis-9-Octadecene and *trans*-9-octadecene were prepared by the lithium aluminum hydride (LAH) reduction of the tosylates of oleyl and elaidyl alcohols (5). Purity, as determined by gas liquid (GLC) and thin layer (TLC) chromatography, exceeded 98%.

All other reagents were used as received from commercial suppliers except for acetonitrile, which was distilled from phosphorus pentoxide prior to use and tetrahydrofuran (THF), which was distilled from LAH prior to use.

Analytical Procedures

Titration of aziridines was carried out by a procedure developed in this laboratory (6). IR spectra were obtained on a Perkin-Elmer Model 237-B spectrophotometer with sodium chloride optics. The spectra were taken as films on sodium chloride discs. GLC was carried out on a Hewlett-Packard Model 810 gas chromatograph. Silica Gel H (Brinkmann) was used for TLC analysis. Spots were detected by heat charring after the plate was sprayed with 50% sulfuric acid.

Addition of Iodine Azide to Olefins

The procedure utilized for the addition of iodine azide to olefins has been previously described (7,10).

Threo-*3-Azido-4-iodohexane* (2a): Obtained by reaction of *cis*-3-hexene with iodine azide, the crude β-iodoazide was purified by distillation, bp 52 C at 0.5 torr (yield 83%). Purity by TLC was >98% (hexane-benzene 1:1). IR (neat): 2960, 2940, 2870, 2100 (N_3), 1460, 1380, 1275, 900 and 800 cm^{-1}. Analysis calculated for $C_6H_{12}IN_3$: C, 28.5; H, 4.78; I, 50.1; N, 16.6. Found: C, 28.6; H, 4.92; I, 49.7; N, 16.5.

Erythro-*3-Azido-4-iodohexane* (2b): Prepared from *trans*-3-hexene, the pure material was obtained by distillation, bp 47-49 C at 0.4 torr (yield 93%). Purity by TLC was >98% (hexane-benzene 1:1). IR (neat): 2980, 2960, 2870, 2100 (N_3), 1460, 1380, 1280, 1160, 1050, 925 and 800 cm^{-1}. Analysis calculated for $C_6H_{12}IN_3$: C, 28.5; H, 4.78; I, 50.1; N, 16.6. Found: C, 28.8, H, 4.80; I, 49.4; N, 16.4.

Threo-*9-Azido-10-iodooctadecane* (2c): Obtained from *cis*-9-octadecene as previously described (7), the crude product, a pale yellow oil, was purified by chromatography on neutral alumina. Purity by TLC was >98% (hexane-benzene 1:1). IR (neat): 2940 (C-H), 2100 (N_3), 1460, 1380, 1260 and 720 cm^{-1}.

Erythro-*9-Azido-10-iodooctadecane* (2d): Prepared from *trans*-9-octadecene by reaction with iodine azide, the pure compound was obtained by chromatography on neutral alumina (yield 92%). Its purity as determined by TLC was >98% (hexane-benzene 1:1). IR (neat): 2950 (C-H), 2100 (N_3), 1465, 1385, 1260, 1025 and 730 cm^{-1}. Analysis calculated for $C_{18}H_{36}IN_3$: C, 51.3; H, 8.61; N, 9.97; I, 30.1. Found: C, 51.6; H, 8.68; N, 10.11; I, 29.8.

Methyl threo-*9(10)-azido-10(9)-iodooctadecanoate* (2e): Obtained from the reaction of methyl oleate and iodine azide by the procedure previously described (7), this iodoazide, a mixture of positional isomers, was isolated as an amber oil (yield, ca. 100%). Its purity as determined by TLC was >98% (hexane-benzene 50:50). IR (neat): 2930 (C-H), 2110 (N_3), 1740 (C = O), 1460, 1430, 1250, 1200 and 1160 cm^{-1}.

Reduction of β-Iodoazides

The reductive cyclization of β-iodoazides to aziridines

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[2]ARS, USDA.

TABLE I

Reduction of 9-Azido-10-Iodooctadecane (2c)

Reducing agent	Products, wt%		
	Octadecene	9-Aminooctadecane	9,10-Epiminooctadecane
$LiAlH_4$	15	28	57
$NaAlH_2(OCH_2CH_2OCH_3)_2$[a]	57	22	21
B_2H_6	11	20	52
H_2/PtO_2	78[b]	18	2

[a]Vitride.

[b]Identified as octadecane.

via LAH and diborane were carried out by modification of literature procedures (13,14). The reduction of β-iodoazides with Vitride, sodium bis (2-methoxyethoxy) aluminum hydride, was performed similarly to the LAH procedure, with the exception that the reactions were run in benzene. The hydrogenation of the β-iodoazides was run at 400 psi H_2 pressure in the presence of PtO_2 catalyst.

Product Analysis

cis-*3,4-Epiminohexane* (3a): Obtained by LAH reduction of *threo*-3-azido-4-iodohexane, the product was purified by distillation, bp 54-55 C at 45 torr (47% yield), N-*p*-nitrobenzoyl derivative mp 75-76 C (lit. mp 74-76 C [8]).

trans-*3,4-Epiminohexane* (3b): Prepared from *erythro*-3-azido-4-iodohexane in 38% yield by LAH reduction, the pure material had bp 63-65 C at 60 torr, phenylurea derivative mp 86-87 C (lit. mp 85-86 C [9]).

cis-*9,10-Epiminooctadecane* (3c): Prepared via the LAH reduction of *threo*-9-azido-10-iodooctadecane, the crude product contained 59% of the desired epimino compound as determined by aziridine titration. GLC analysis of this material indicated three products, with the epimino compound constituting 52% of the mixture. The byproducts were subsequently identified as octadecene (4) and 9-aminooctadecane (5) (see Results and Discussion section for details). Crystallization from hexane gave the pure epimino compound, mp 63-64 C (lit. mp 63.5-64.0 C [1]).

trans-*9,10-Epiminooctadecane* (3d): Obtained by LAH reduction of *erthro*-9-azido-10-iodooctadecane, the crude product was crystallized from hexane at -20 C, (27% yield), mp 46-47 C (lit. mp 48-49 C [8]).

cis-*9,10-Epiminooctadecan-1-ol* (3e): Prepared by the LAH reduction of methyl-*threo*-9-azido-10-iodooctadecanoate, the crude reduction product (52% aziridine by titration) was crystallized from acetone to give the pure epimino compound, mp 71-72 C (lit. mp 71.5-72.5 C [1]).

cis-*1-Dimethylphosphono-2,3-dioctylaziridine* (9a): To a solution of the β-iodoazide 2c (10 mmol) in hexane (25) was added trimethyl phosphite (11 mmol). The solution was stirred at ambient temperature for 18 hr, at which time the evolution of gas had ceased. The solvent was removed in vacuo, and the crude phosphonoaziridine derivative was chromatographed on Florisil to give the pure product as a colorless liquid (yield 87%, purity by titration 97%). IR (neat): 2930 (CH), 1460, 1270 (P = O), 1185, 1040 (P - O), and 850 cm^{-1}. Analysis calculated for $C_{20}H_{42}NO_3P$: C, 64.0; H, 11.3; N, 3.73; P, 8.25. Found: C, 64.2; H, 11.4; N, 3.70; P, 8.10.

cis-*1-Dimethylphosphono-2-octyl-3-(7-carbomethoxyheptyl)aziridine* (9b): Prepared from the β-iodoazide adduct of methyl oleate (10 mmol) and trimethyl phosphite (10 mmol) in hexane (20 ml) as described above, the crude product was purified by chromatography on Florisil (yield 78%, purity by titration 96%). IR (neat): 2940 (CH), 1740 (C = O), 1440, 1260 (P = O), 1175, 1035 (P - O) and 840 cm^{-1}. Analysis calculated for $C_{21}H_{42}NPO_5$: C, 60.1; H, 10.1; N, 3.34; P, 7.38. Found: C, 60.4; H, 10.3; N, 3.20; P, 7.30.

RESULTS AND DISCUSSION

The model olefins selected for the present study were *cis* and *trans*-3-hexene, *cis* and *trans*-9-octadecene and methyl oleate. Conversion to their respective epimino derivatives is based on the addition of iodine azide to the olefin to give the β-iodoazide adduct, followed by selective reductive cyclization. The addition of the electrophilic pseudohalogen iodine azide, prepared in situ from sodium azide and iodine monochloride, to olefins has been shown to proceed in a stereospecific manner (10,11). Thus addition of this reagent to *cis*-3-hexene, *cis*-9-octadecene and methyl oleate (1a, c and e) yields the corresponding *threo*-β-iodoazide adducts (2a, c and e), while reaction with *trans*-3-hexene and 9-octadecene (1b and 1d) gives the *erythro* diastereomers 2b and 2d (equation 1).

$$\text{R-CH = CH-R}' \xrightarrow{IN_3} \text{R-CH(I) - CH(N}_3\text{)-R}' \qquad [1]$$

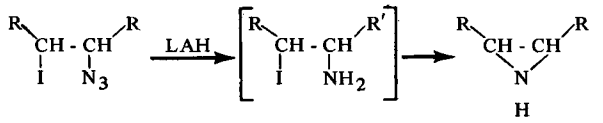
1a *cis*	2a *threo*	R=R′=C_2H_5
1b *trans*	2b *erythro*	
1c *cis*	2c *threo*	R=R′=C_8H_{17}
1d *trans*	2d *erythro*	
1e *cis*	2e *threo*	R(R′)=C_8H_{17}, R′(R)=$C_7H_{14}CO_2CH_3$

The yields of the β-iodoazide adducts were nearly quantitative—the only detectable contaminant, if any, being the starting olefin. Adducts 2a and 2b were readily purified by vacuum distillation. Since both the iodo and azide functions are heat labile substituents, the adducts derived from the higher molecular weight olefins were purified by column chromatography. Evidence for the structures of the intermediates was obtained from elemental analyses and IR spectroscopy. All of the β-iodoazides are characterized by strong absorption at 2100 cm^{-1}, which is ascribed to the asymmetric stretching vibration of the azide function (12).

The reductive cyclization of β-iodoazides to aziridines by means of metal hydrides has been previously reported by Hassner et al. (13) and Matthews (14). We have extended their method of aziridine preparation to β-iodoazides obtained from internal, aliphatic olefins. Several metal hydride-reducing agents have been employed for the preparation of aziridines from β-iodoazides; in addition, an attempt to employ catalytic hydrogenation as a means of aziridine preparation was also undertaken.

The reductive cyclization of β-iodoazides 2a to 2d with lithium aluminum hydride (LAH) gave the epimino compounds 3a to 3d (equation 2). In general the yields of epimino compounds were in the range of 30-60%. As noted previously (13) reduction of the *threo* β-iodoazide adducts yielded the epimino derivative with a *cis* geometry, while the *erythro* diastereomers gave the *trans* epimino compounds. The yields of *cis*-aziridines were slightly larger than those of the *trans* isomers—a result comparable with the

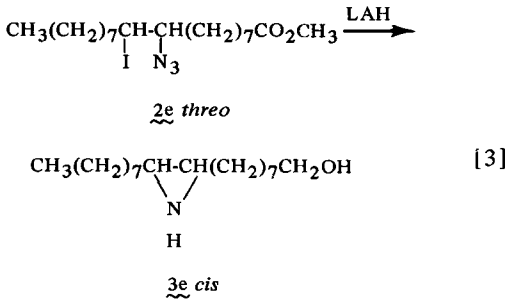
iodine isocyanate method of preparation. Reduction of iodoazide 2e with LAH produced the epimino derivative of octadecanol (equation 3) by concomitant reduction of the ester function.



2a *threo*
2b *erythro*
2c *threo*
2d *erythro*

3a *cis*
3b *trans*
3c *cis*
3d *trans*

[2]

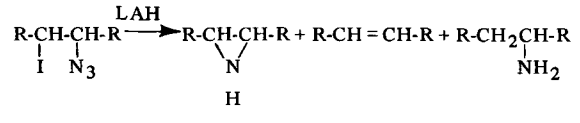


2e *threo*

3e *cis*

[3]

The reduction of the β-iodoazide derivative of 9-octadecene to the epimino derivative was studied by a number of methods with hopes of improving product yield and finding identifiable byproducts. The results are given in Table I. Measurement of the aziridine content (6) of the LAH reduction product of 9-azido-10-iodooctadecane (2c) indicated a 59% yield of the desired compound. Analysis of the crude product by GLC showed that, in addition to the epimino derivative 3c (57%), the major byproducts formed were octadecene 4 (15%) and the hydrogenolysis product 9-aminooctadecane 5 (28%) (equation 4).



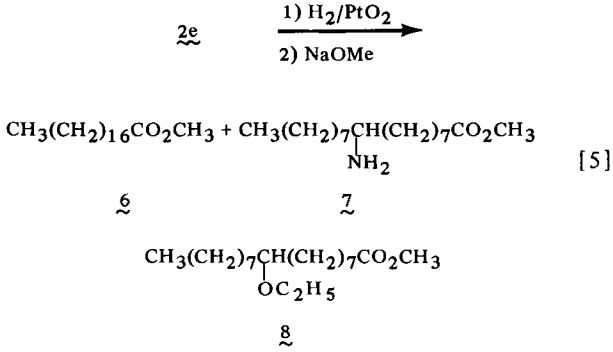
2c 3c 4 5

[4]

Use of the homogeneous hydride-reducing agent sodium bis(2-methoxyethoxy) aluminum hydride (Vitride), a benzene-soluble reducing agent, again indicated the presence of the previously identified reduction products (Table I). In this instance, however, olefin formation was observed to the extent of 57%, while the epimino compound constituted only 21% of the product. 9-Aminooctadecane (5) was present in 22% yield, an amount similar to that found in the LAH experiment.

Reaction of 9-azido-10-iodooctadecane (2c) with sodium borohydride in refluxing isopropanol gave no reduction products, the iodoazide 2c being recovered unchanged. Reduction was achieved, however, with dioborane generated from sodium borohydride and boron triflouride (15). Since this procedure is performed in acidic media, a subsequent cyclization step with base is required. GLC analysis of the diborane reduction product again indicated the presence of *cis*-9,10-epiminooctadecane (3c, 52%), 9-aminooctadecane (5, 20%) and 9-octadecene (4, 11%). Reduction of iodoazide 2e with dioborane gave a result similar to the LAH experiment in that 9,10-epiminooctadecanol (3e) was formed in only 42% yield.

As an alternative method to the hydride reduction of β-iodoazides, the catalytic hydrogenation of β-iodoazides was investigated. Reduction of iodoazides 2c and 2e to their corresponding amino derivatives (16) was carried out at 400 psi over Adams catalyst in ethanol diluent. The presumably first formed β-iodoamine derivatives were treated with caustic to form the epimino derivatives, and the crude products were analyzed by GLC. The results applicable to iodoazide 2c are given in Table I. The major product obtained was octadecane (70%). The other products were the 9-amino derivative 5 in 18% yield and the desired epimino compound 3c in only 2% yield. With β-iodoazide 2e the major products were methyl stearate (42%) and methyl 9(10)aminostearate (7, 53%). Methyl 9(10)-ethoxystearate (8, 5%) was also identified as a minor product from this latter reaction (equation 5).

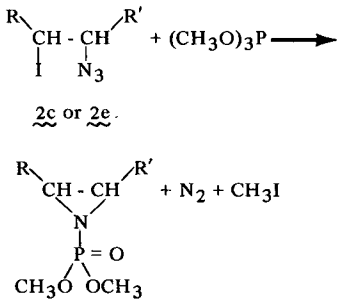


6 7

8

[5]

The versatility of the β-iodoazides as precursors in organic synthesis was demonstrated by a study of their reactions with trialkylphosphites. Mixing hexane solutions of iodoazides 2c and 2e with trimethylphosphite resulted in the immediate evolution of nitrogen gas. The products of these reactions were, respectively, dimethylphosphonoepimino derivatives 9a and 9b (equation 6). Since this rearrangement involves one inversion at carbon, the aziridines 9a and 9b have the *cis* geometry (17).



2c or 2e

9a R = R = C_8H_{17}
9b R = C_8H_{17}
R′ = $C_7H_{14}CO_2CH_3$

[6]

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