Synthesis and Isolation of Epoxy Secondary Amides *via* Direct Amidation of *Vernonia galamensis* Seed Oil

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Vernonia galamensis **oil, containing naturally epoxidized triglycerides, was reacted with *n*-butylamine, *n*-pentylamine and *n*-hexylamine to afford high yields of epoxidized secondary amides. Three reaction conditions were investigated: (i) reflux with amines as solvents, (ii) reflux with hexane as the solvent and (iii) room temperature with the amines as solvents. Reactions with amines as refluxing solvents were completed in 1–5 h, while those with hexane went to completion within 2 to 5 d. Room temperature reactions were only *ca.* 80% complete after several days. Reactivity was increased with higher amine homologs at both reflux and room temperature reaction conditions. Isolated yields of epoxy-containing amides were about 80% with purity exceeding 96% in all cases. Spectroscopic characterization of the previously unreported alkyl-vernolamides is provided.**

KEY WORDS: N-butylvernolamide, C-13 NMR, epoxy-containing secondary amides, N-hexylvernolamide, infrared spectroscopy, mass spectrometry, N-pentylvernolamide, proton-NMR, triglycerides, *Vernonia galamensis* oil.

Vernonia galamensis oil, upon saponification, contains *ca.* 75–80% vernolic (*cis*-12,13-epoxy-*cis*-9-octadecenoic) acid, thus giving it potential as a unique raw material for industrial feedstock (1). Several recent publications have focussed on the commercial importance of this oil, including use as a reactive diluent in coatings, in plastic formulations and as a chemical intermediate (2,3). We previously reported on the nonreactivity of vernonia oil's epoxy functionality under alkaline conditions (1). Given the appropriate conditions, it is possible to derivatize vernonia oil and obtain a wide range of products. The present paper continues our effort to demonstrate the synthetic transformation of vernonia oil into various oleochemicals by direct amidation of the oil to give secondary amides, with the epoxy group being retained in the products.

Fatty amides are important chemical intermediates for commerce, with applications ranging from paper coatings and printing ink additives to slip and anti-block additives for polyethylene films (4). Industrially, secondary amides are produced from purified fatty acids and primary amines at high temperatures under moderate pressure (5). They are also produced by reacting fatty acyl chlorides with amines or, alternatively, by reacting fatty esters with amines while using sodium methoxide as a catalyst (6–8).

During the course of the present study, Haas and coworkers (9) recently reported the synthesis of tallow amide by the direct amidation of tallow with primary amines under relatively mild conditions, thus showing that primary amines are sufficiently nucleophilic to undergo mild reactions with triglycerides. This communication reports the synthesis of novel epoxy-containing fatty amides from vernonia oil by reactions of primary amines with the naturally occurring epoxy triglycerides. A discussion of the isolation and spectroscopic characterization of these new epoxidized secondary amides is provided.

EXPERIMENTAL PROCEDURES

The crude vernonia oil used in this study was obtained by mechanical pressing of enzyme-deactivated seed (10). Reactions and products were monitored and characterized with a Perkin-Elmer 983G infrared spectrophotometer (Norwalk, CT) and a Finnigan gas chromatograph (GC, model 9611) (San Jose, CA) fitted with a Supelco fused silica SPB-1 column (30 m, 0.32 mm i.d., 0.25 μm film) (Bellefonte, PA), interfaced with a Finnigan MAT 4500 automated mass spectrometer, operated in the electron impact mode with a Superincos data system (San Jose, CA). Gas chromatography-mass spectrometry (GC/MS) conditions have been previously reported (1). Proton and C-13 nuclear magnetic resonance (NMR) data were obtained with a GE QE 300 broad-band NMR spectrometer (General Electric, Fremont, CA) with the C-13 data obtained in the proton decoupled mode. Weight per epoxy (WPE) values were determined by a previously reported procedure (11). The oxirane value was determined based on the WPE by the formula: oxirane value = 16 × 100/WPE. Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, TN.

Amidation of vernonia oil. For each of the amines (*n*-butylamine, *n*-pentylamine and *n*-hexylamine), a 250-mL round-bottom flask equipped with a reflux condenser and a magnetic stir bar was charged with 5 g (5.4 mmol, based on a molecular weight of 926), of vernonia oil (*ca.* 80% vernolic based on epoxy titration) and 50 mmol of the amine. The reactions were allowed to proceed under reflux conditions and were monitored for completion by GC/MS with squalane as an internal standard. Similar reactions were performed at room temperature, and also with 50 mL refluxing hexane. Aliquots were taken periodically and transesterified with sodium methoxide as a catalyst. Reaction completion was assumed when no esters (only amides) were present in the transesterified aliquots (see Table 1).

Isolation of N-alkylvernolamides. Each of the reaction mixtures above was transferred into a 500-mL separatory funnel to which 100 mL of water was added. Hexane (150 mL) was then added, shaken and allowed to partition (for reactions with hexane as a solvent, only 100 mL of hexane was added). After removing and discarding the aqueous layer, the organic portion was washed five times with 100-mL portions of water/methanol (1:3) solution. The aqueous/methanol washings were combined and placed in a refrigerator at −25°C for three hours. The precipitated epoxy amides were then vacuum-filtered to afford white powders, and the products were air-dried prior to melting point and WPE determination (Table 1). N-butylvernolamide was obtained in *ca.* 82% theoretical yield with a WPE value of 337 (96.2% purity, based on an oxirane value of 4.75%) and melting point of 65–66°C

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TABLE 1

Experimental Results from the Synthesis of N-Alkylvernolamides[a]

N-Alkylvernolamide	mp (°C)	WPE[b]	% Purity	% Yield	R.T. (h)	R.T.[c] (h)
N-butylvernolamide	65–66	337	96.2	82.2	4.5	112
N-pentylvernolamide	67–68	354	97.4	85.1	2.5	78
N-hexylvernolamide	64–67	366	96.6	93.6	1	54

[a] Refluxed in amine solvent; mp = melting point.

[b] WPE = weight per epoxy.

[c] Refluxed in hexane; R.T. = reaction time in hours.

(Table 1). Elemental analyses: Calculated for $C_{22}H_{41}O_2N$: C, 75.21; H, 11.68; O, 9.12; N, 3.98%. Found C, 75.32; H, 11.65; O, 8.99; N, 4.04%. N-pentylvernolamide was obtained in 85% theoretical yield and had a WPE value of 354 (97% purity, based on an oxirane value of 4.52%) with its melting point being 67–68°C (Table 1). Elemental analyses: Calculated for $C_{23}H_{43}O_2N$: C, 75.61; H, 11.78; O, 8.77; N, 3.84%. Found C, 75.16; H, 11.71; O, 9.23; N, 3.90%. For N-hexylvernolamide, the yield was 93.6% of theory with the WPE being 366.2 (96.6% purity, based on an oxirane value of 4.37%), and the compound had a melting point of 64–67°C. Elemental analyses: Calculated for $C_{24}H_{45}O_2N$: C, 75.99; H, 11.87; O, 8.44; N, 3.69%. Found C, 75.51; H, 11.66; O, 9.15; N, 3.68%.

Hydrogenation of N-butylvernolamide. For the N-butylvernolamide, a Parr hydrogenation bottle (Moline, IL) was charged with 0.176 g (0.5 mmol) of the amide along with 10 mL methanol and 0.08 g (3.27×10^{-4} mol) platinum oxide monohydrate (Adams's catalyst). The bottle and its contents were then fitted to a Parr hydrogenation system and subjected to hydrogen gas at a constant pressure of 3.0 atm for 90 min. The 90-min reaction time was determined by monitoring the products from several reactions by GC/MS. After the reaction was completed, the catalyst was removed by filtration and the methanol evaporated, giving a white powder, which was then spectroscopically characterized.

RESULTS AND DISCUSSION

By using GC to follow the reaction, it was ascertained that the amine reactivity was directly correlated to its chainlength (Table 1), an observation that was rather surprising, given the fact that there was only a one-carbon difference between the amine homologs. Haas *et al.* (9) have suggested that this might be due to the greater lipophilic nature of the higher homologs, and as such would more readily react with the triglycerides. Additionally, it is conceivable that the greater nucleophilicity of the higher amine homologs could be attributed to a greater electron donating effect of the alkyl groups due to hyperconjugation. The latter conclusion was supported by the fact that the same trend in the reactivity order was observed when hexane was used as a solvent. However, in this case, there was a dramatic difference in reaction rate (Table 1). Although the molar ratios of oil to amine (1:10) in the reactions with hexane as the solvent were the same as for the reactions with amines as refluxing solvents, lower concentration of the reactants was present in the hexane reaction medium. Also, hexane has a lower reflux temperature, which would account for the lower reaction rate. The room temperature reactions were only 80% complete as a result of the insolubility of the products, giving rise to semi-solid reaction mixtures.

The infrared spectra for the epoxy fatty amides were all similar, showing sharp absorptions at 3300 cm^{-1}, typical of secondary amides. Absorption at 1643 cm^{-1} suggested the carbonyl of the amide group, while the epoxy absorption was still present at 826 cm^{-1} and 847 cm^{-1}.

The mass spectral patterns were similar for all the N-alkylvernolamides. Mass-specxtral data for the isolated N-butylvernolamide (Fig. 1) exhibited major peaks at *m/z* 57 (70), 74 (100), 100 (19), 115 (37), 128 (35), 238 (14) and 352 (<1). The peak at *m/z* 352 represents the M + 1 ion while cleavage between C-11 and C-12 gave a fragment at *m/z* 238. Ions at *m/z* 100 and *m/z* 128 arose from simple cleavages alpha and gamma to the carbonyl group, respectively, while a McLafferty rearrangement gave the ion at *m/z* 115. Alpha cleavage of the alkyl group attached to the nitrogen gave rise to the fragment ion at *m/z* 57, and the base peak, *m/z* 74, could be due to a quaternary ammonium ion. To further confirm our spectroscopic assignments, the N-butylvernolamide was hydrogenated. The mass spectral data of the resulting products were similar

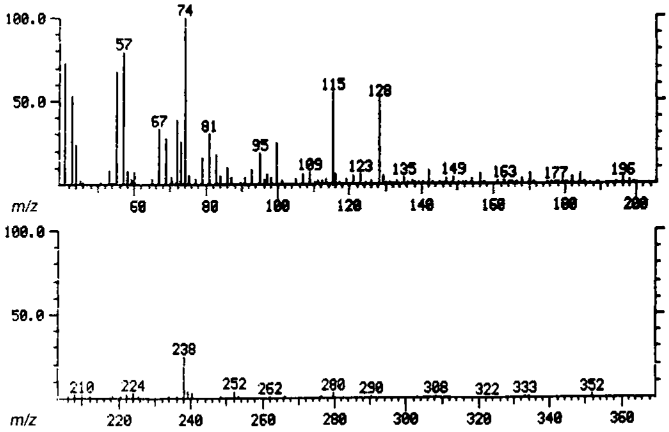

FIG. 1. Mass spectrum of N-butylvernolamide: *m/z* 352 ($M^+ + 1$), 238 ($M^+ - (CH_3(CH_2)_4\overset{\overset{O}{/\ \backslash}}{CH\text{-}CH}\text{-})$, 128 ($CH_3(CH_2)_3NH\text{-}CO(CH_2)_2\text{-}$), 115 ($CH_2\text{-}CH(OH)NH(CH_2)_3CH_3$), 100 ($CH_3(CH_2)_3NHCO$), 74 ($CH_3(CH_2)_3$), 57 ($CH_3(CH_2)_3$).

to that of the unsaturated compound, with diagnostic ions two mass units higher at *m/z* 240 and 354 compared to *m/z* 238 and 352 in the unhydrogenated product.

NMR spectra were consistent in all cases. The data from both the proton and C-13 NMR spectra of N-butylvernolamide (Figs. 2 and 3) provided good references for the other epoxy amides. Protons of the two terminal methyl groups were observed at 0.9 ppm. Methylene group protons gave signals between 1.0 and 1.8 ppm, except for the allylic methylenes (1.9 and 2.1 ppm), the methylene alpha to the carbonyl of the amide functionality (2.05 ppm) and the methylene adjacent to the nitrogen (3.2 ppm). The epoxy hydrogens produced signals at 2.8 ppm, while the olefinic hydrogens gave a complex signal between 5.3 and 5.6 ppm (Fig. 2). In the hydrogenated amide, the peak due to the amide proton was observed at 5.4 ppm. Carbon-13 NMR of the amide (Fig. 3) also confirmed the presence of the epoxy carbons at 56.18 and 56.81 ppm. Signals for the olefinic carbons appeared at 123.62 and 132.18 ppm, while the carbonyl carbon had a signal at 172.86 ppm.

Even though these reactions are all nucleophilic in nature, they do not result in epoxy ring opening, further confirming our earlier findings that the epoxy functionality is stable under alkaline conditions and that such hindered epoxy groups are only prone to ring opening under acidic conditions. We ascribe this selective reactivity to the steric hinderance of the oxirane group and possibly to the bulkiness of the nucleophilic agents, thereby making it possible to derivatize vernolic acid to afford a wide range of new compounds.

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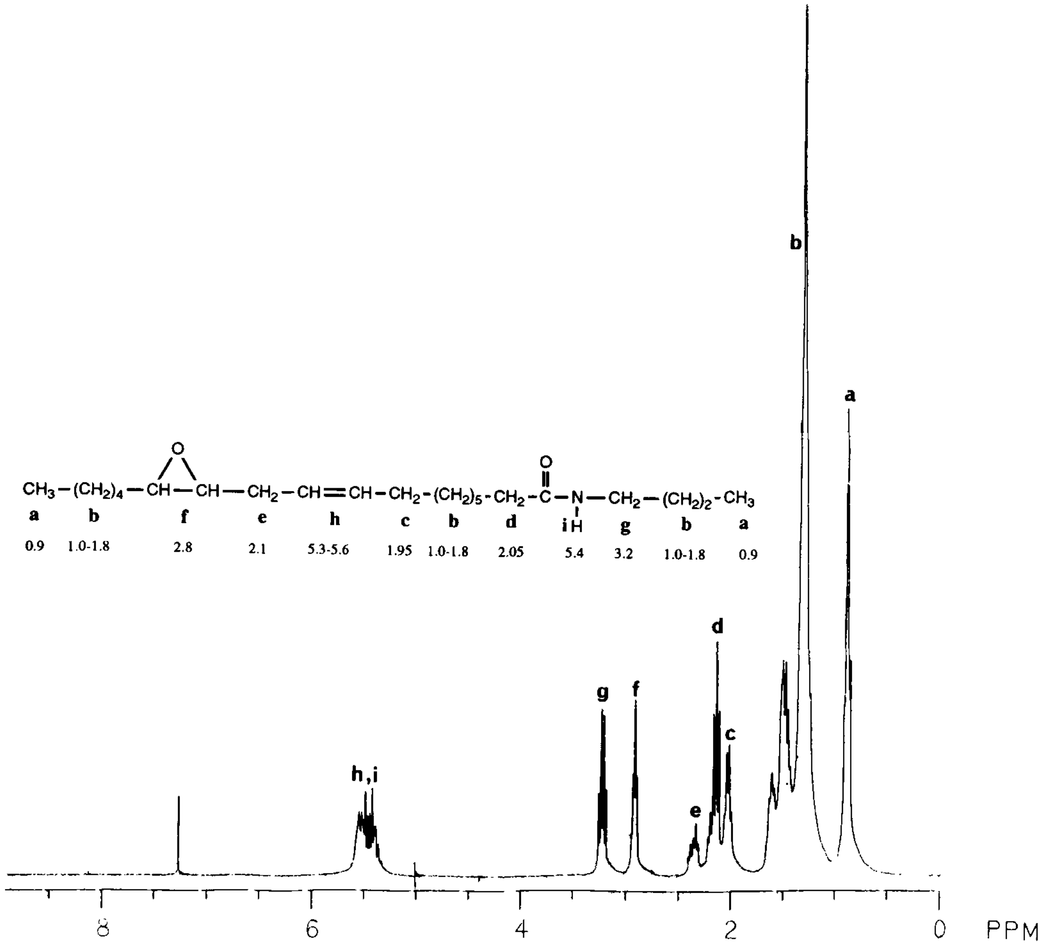

FIG. 2. Proton nuclear magnetic resonance spectrum of N-butylvernolamide; chloroform peak at 7.26 ppm.

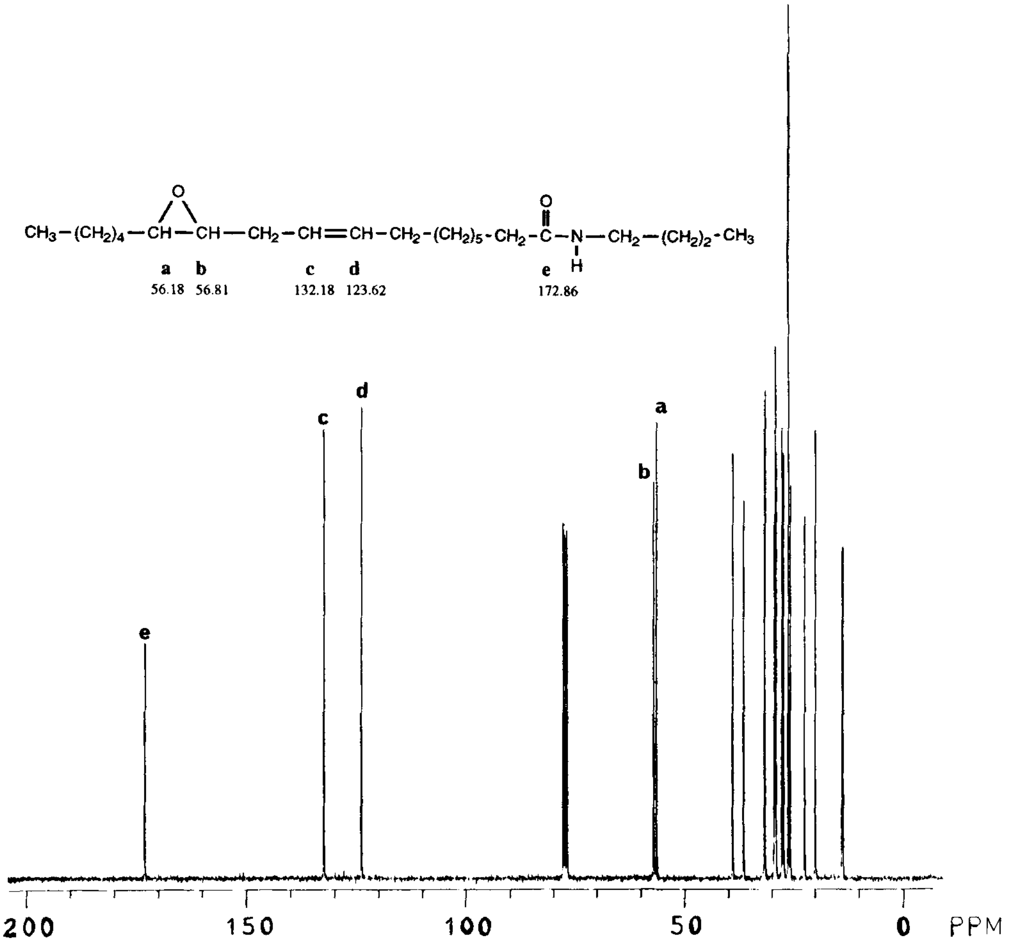

FIG. 3. C-13 nuclear magnetic resonance spectrum of N-butylvernolamide methyl carbons 12.1 ppm, methylene carbons 20–40 ppm, epoxy carbons 56.18 and 56.81 ppm, olefinic carbons 123.62 and 132.18 ppm, carbonyl carbon 172.86 ppm.

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