Optical Resolution of (±)-*Threo*-9,10,16-Trihydroxy Hexadecanoic Acid Using (–)Brucine

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ABSTRACT: The optical resolution of (±)*threo*-9,10,16-trihydroxy hexadecanoic acid was achieved by fractional crystallization using (–)brucine. Formation of an estolide during decomposition of the (–)brucine complex was observed to interfere with the separation of the optically pure material. This was corrected by converting the estolide to (+)-*threo*-9,10,16-trihydroxy hexadecanoic acid *via* alcoholic alkaline hydrolysis followed by neutralization. Enantiomeric purity was determined by chiral lanthanide nuclear magnetic resonance shift reagent. *JAOCS 75,* 1461–1463 (1998).

KEY WORDS: (–)Brucine, chiral NMR shift reagent, estolide, optical resolution, (±)*threo*-aleuritic acid.

Optical resolution of vicinal dihydroxy fatty acids was attempted by number of investigators for *threo*- and *erythro*-isomers (1). McGhie *et al.* (1) found that the (±)*threo*-9,10-dihydroxy octadecanoic acid can be resolved by fractional crystallization using (–)brucine from aqueous acetone. Ewing and Hopkins (2) modified McGhie and colleagues' procedure and showed that a number of dihydroxy fatty acids can be resolved using (–)brucine and (–)ephedrine. The resolution of (±)-*threo*-9,10,16-trihydroxy hexadecanoic acid (aleuritic acid) was reported to be achieved by using different bases such as (–)ephedrine (3), (–)brucine (4), and (+)cinchonine (5). The authors attempted the latter two procedures to resolve (±)aleuritic acid. Resolution by (+)cinchonine procedure failed to give any pure (+) or (–)aleuritic acid enantiomer, which was attributed to the low solubility of (+)cinchonine in methanol (6). The authors further considered the procedure *via* (–)brucine complexation reported by Eswaran *et al.* (4). However, even in this case the required purity levels were not achieved. The authors investigated this further and modified this method to achieve the pure enantiomer. In addition, a proton nuclear magnetic resonance (^{1}H NMR) procedure using europium tris[3-(trifluoromethyl-hydroxymethylene)-(+)-camphorate] shift reagent was adopted to characterize the resolved (+)aleuritic acid.

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EXPERIMENTAL PROCEDURES

All melting points (m.p.) are uncorrected. Optical rotations were measured on the Jasco DIP-20 polarimeter (Tokyo, Japan) (glass cell, length: 100 mm). Fourier transform infrared (FT-IR) spectra were recorded using BOMEM Infrared Spectrophotometer (Bomem Inc., Québec, Canada) in potassium bromide. H NMR spectra were recorded on 200.13 MHz Bruker spectrometer (Rheinstetten-Forchheim, Germany). Tetradeuteromethanol (CD_3OD) and deuterochloroform ($CDCl_3$) were used as solvents, and tetramethylsilane was the internal standard. Chemical shifts are expressed in δ-units. Aleuritic acid supplied by Pond's India Ltd. (Madras, India) was crystallized twice from 50% aqueous ethanol to give >99% pure material. (–)Brucine was purchased from British Drug House Ltd. (Poole, England).

Optical resolution of (+)aleuritic acid. Aqueous acetone (33% vol/vol, 50 mL) was added to a mixture of (±)aleuritic acid (8 g, 0.026 M) and (–)brucine (15 g, 0.038 M). The reaction mixture was refluxed for 30 min, then cooled to room temperature, filtered through cotton, and maintained at 0–5°C for 9–10 d. Crystals of (+)aleuritic acid-(–)brucine salt (I) were filtered and dried under vacuum (9.06 g, yield = 98.69%). Crude I (9.06 g) was purified by double crystallization from aqueous acetone (33% vol/vol) to give pure I [5.50 g, yield = 60.70%. I (5.5 g) was refluxed with 2 N HCl (50 mL) to give crude (+)aleuritic acid (2.23 g, yield = 93.30%). The result (2.23 g) was further purified by crystallization from ethyl acetate (20 mL) to give pure (+)aleuritic acid, II (1.50 g, yield = 67.26%). NaOH (0.65% aqueous, 10 mL) was added to a solution of II (0.50 g, 0.0016 M) in methanol (10 mL) refluxed for 1 h and cooled to room temperature. The reaction mixture was neutralized with 2 N HCl and kept overnight at 0–5°C. Crystals obtained were filtered and washed with cold water until the wash water was neutral to litmus. It was recrystallized from ethyl acetate and dried to give (+)aleuritic acid, III (0.41 g, yield = 82%).

Determination of enantiomeric purity by ^{1}H NMR spectroscopy. Two-tenths molar stock solutions of (+)methyl aleuritate, (±)methyl aleuritate, and europium tris[3-(trifluoromethyl-hydroxymethylene)-(+)-camphorate] shift reagent were prepared in $CDCl_3$. Samples having a ratio of (+)methyl aleuritate/(+)shift reagent/D_2O of 1:0.75:1 and of (±)methyl aleuritate/(+)shift reagent/D_2O of 1:0.75:1 were prepared.

TABLE 1
Some Physical Characteristics of (+)Aleuritic Acid Before and After Alkaline Hydrolysis[a]

Analytical test	(+)*Threo*-aleuritic acid before alkaline hydrolysis	(+)*Threo*-aleuritic acid after alkaline hydrolysis	(+)*Threo*-aleuritic acid (3)
m.p.	74–84°C	101–103°C	102.5–103.5°C
Acid value	93.59	173.34	175.6
Optical rotation $[\alpha]_D^{25°}$	23.1°	27.2°	24.6°
IR	1710 cm^{-1} 1728 cm^{-1}	1702 cm^{-1}	1700 cm^{-1}
NMR	4.06 ppm (*t*) $-CH_2-COOC\underline{H}_2-$	Absent	Absent

[a]m.p., melting point; IR, infrared; NMR, nuclear magnetic resonance.

H NMR spectra were recorded using a 4 kHz spectral width, 90° pulse, and 4.096 s acquisition rate and collecting 200 scans at 297°K.

RESULTS AND DISCUSSION

(+)Aleuritic acid (Product-II-experimental) obtained *via* fractional crystallization using (−)brucine reported by Eswaran *et al.* (4) showed the presence of an ester group (1710 cm^{-1}, 1728 cm^{-1}) in FT-IR spectra and a triplet at δ 4.06 in ^{1}H NMR. Optical rotation of the product was also found to be low at 23.1° as compared to 27° of (+)aleuritic acid. Acid value was found to be 93.59, compared to 173.34 for (+)*threo*-aleuritic acid (7). These results suggest the formation of estolide [linkage between ω-hydroxyl and the carboxyl group of (+)-aleuritic acid]. Estolide formation during decomposition of (+)aleuritic acid-(−)brucine salt (reflux with 2 N HCl for 30 min) is likely. In order to establish this, the authors refluxed (±)aleuritic acid in 2 N HCl for 30 min. The product characterized by FT-IR and ^{1}H NMR showed characteristics similar to (+)aleuritic acid (Product-II experimental). This estolide was then converted back to the (+)aleuritic acid by alkaline hydrolysis. Thus the authors modified the procedure of Eswaran *et al.* (4) by introducing a step to hydrolyze the estolide to the (+)aleuritic acid. The estolide containing (+)aleuritic acid was treated with alcoholic sodium hydroxide, and excess alkali was neutralized with HCl to regenerate the acid (under mild room temperature conditions). The product was then crystallized from ethyl acetate and characterized. The characteristics are given in Table 1. The characteristics of the product reported here agreed with the (+)aleuritic acid reported in literature (3).

The enantiomeric purity of the (+)aleuritic acid was further confirmed by ^{1}H NMR studies using a chiral NMR shift reagent (8). Due to the free carboxylic group in the molecule, the ^{1}H NMR spectrum of (±)aleuritic acid was not properly resolved after addition of the shift reagent. Hence a study was performed using (±)methyl aleuritate (9,10,16 trihydroxy methylhexadecanoate) that in turn was prepared from (±)aleuritic acid (9). When (±)methyl aleuritate, chiral NMR shift reagent, and D_2O were in the ratio of 1:0.75:1, a doublet for *R,R*-isomer at δ 8.3–9.0 and a singlet (unresolved doublet) for *S,S*-isomer at δ 8.1 were observed; for (+)methyl aleuritate, a doublet at δ 9.3–10.0 and a trace of a singlet (unresolved doublet) for *S,S*-isomer at δ 9.0 were observed. The triangulated area under the peak, considered for purity calculations, showed 98.2% enantiomeric purity for (+)(*R,R*)-methyl aleuritate with only 1.8% of (−)(*S,S*)-methyl aleuritate. The ^{1}H NMR spectra are shown in Figure 1.

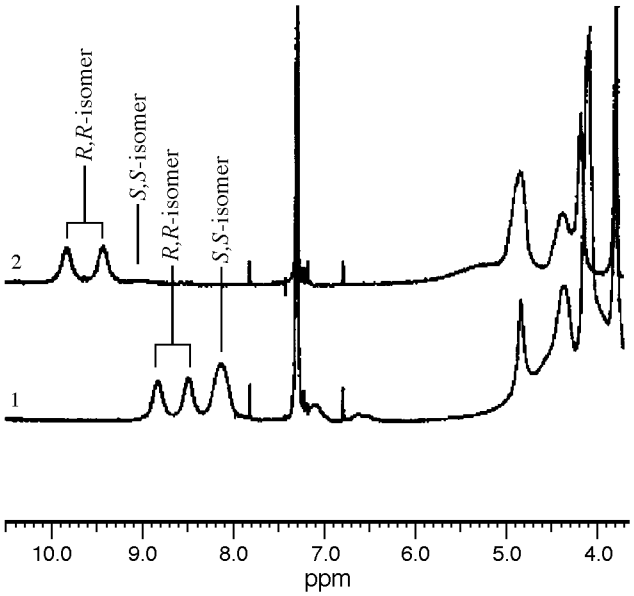

FIG. 1. Proton nuclear magnetic resonance (NMR) spectra of methyl aleuritate with chiral NMR shift reagent, 1. (±)Methyl aleuritate/NMR shift reagent/D_2O (1:0.75:1); 2. (+)Methyl aleuritate/NMR shift reagent/D_2O (1:0.75:1).

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[Received October 29, 1997; accepted June 3, 1998]