Some New Derivatives of Lesquerolic Acid

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Abstract

A series of derivatives was prepared for evaluation purposes from lesquerolic (14-hydroxy-*cis*-11-eicosenoic) acid. Preparative procedures, isolation, and purification of these materials are reported, and the new derivatives described.

Introduction

LESQUEROLIC (14-hydroxy-*cis*-11-eicosenoic) acid is the major fatty acid (1) of lesquerella oil, obtainable from many *Lesquerellae* which have been investigated as potential replacement crops (2). As part of the exploratory work undertaken with the oil, several pure derivatives of lesquerolic acid were prepared for evaluation in certain industrial applications and as chemical intermediates. Vinyl 14-ketoeicosanoate, methyl 14-acryloxyeicosanoate, 14-ketoeicosanamide, 14-ketoeicosanitrile, and N-acetyl-14-ketoeicosanamine are new materials which have been prepared by using, for the most part, modifications of techniques previously worked out for the preparation of castor oil derivatives. Results of some of the evaluation studies will be reported elsewhere.

Experimental

Infrared (IR) spectra were obtained on a Perkin-Elmer model 137 Infracord, using thin films or Nujol mulls on NaCl plates. Thin-layer chromatography (TLC) was carried out on silica gel G strips, using ether-petroleum ether mixtures as eluting solvents. For gas-liquid chromatography (GLC) an F & M model 720 instrument was used with a 2-ft column of 20% Apiezon L on 60–80 mesh Gas-Chrom P (Applied Science Laboratories). Nuclear magnetic resonance (NMR) spectra were obtained in $CDCl_3$ by using a Varian model A60, with tetramethylsilane as reference. Melting points were taken in capillary tubes in an electrically heated block and are uncorrected.

Starting Materials

Methyl esters were obtained by sodium methoxide-catalyzed methanolysis of lesquerella oil, followed by distillation at ~0.80 mm Hg (3). The fractions which were used boiled at 193–195C. All fractions contained a minor impurity, probably a plant sterol, which could be removed only by a series of low-temperature crystallizations (4). In general, this did not interfere in subsequent reactions and was not removed.

Methyl 14-hydroxyeicosanoate was obtained by hydrogenation of methyl esters from the lesquerella oil over PtO_2 in methanol solution at 3–4 atm. The crude saturated derivative was recrystallized from acetone or Skellysolve B to yield white shiny plates of mp 59–61C [lit. 56–59C (1)]. This material had the expected IR spectrum, gave only one GLC peak, and showed a single spot on a TLC strip.

Methyl 14-ketoeicosanoate was prepared by copper chromite-catalyzed dehydrogenation of methyl 14-hydroxyeicosanoate, as previously described (4), and had mp 54–55C. Its IR spectrum and GLC analysis were satisfactory.

New Derivatives

14-Ketoeicosanoic acid was prepared by hydrolysis of the methyl ester in ethanolic KOH. After acidification of the caustic solution the precipitated keto acid was taken up in chloroform and thoroughly water-washed until free of mineral acid. The chloroform was reduced in volume on a rotary evaporator and cooled to 5C to crystallize out white needles of 14-ketoeicosanoic acid, mp 82.5–84C. IR and TLC confirmed the absence of residual ester.

Methyl 14-Acryloxyeicosanoate. Thirty-four g (0.10 mole) of methyl 14-hydroxyeicosanoate was dissolved in 150 ml of tetrahydrofuran (THF), and the acrylate derivative was prepared by the two-step procedure described for methyl 12-acryloxystearate (5): esterification with β-chloropropionyl chloride in the presence of anhydrous sodium carbonate followed by dehydrohalogenation in refluxing pyridine. The crude acrylate (37.4 g, 95% over-all yield) was a light oil of high purity as judged by TLC, GLC, and a negative Beilstein (copper wire) flame test for chlorine. The IR spectrum was quite characteristic: methyl ester carbonyl at 5.75 μ, acrylate ester carbonyl partially resolved from it at 5.8 μ, and bands at 6.15 μ, 6.2 μ, and 12.3 μ, apparently associated with terminal unsaturation and routinely found in acrylates (5). No residual hydroxyl absorption was detected. All color could be removed by passing the material (in ether solution) through neutral alumina in a sintered glass funnel. No further purification was required.

Vinyl 14-Ketoeicosanoate. This derivative was prepared by vinyl interchange, essentially as previously described (6) for the synthesis of vinyl 9- and 12-hydroxystearates and vinyl 14-hydroxyeicosanoate. The procedure produced shiny white plates (75% yield), mp 53–54C. No impurities were found when this material was examined by TLC and GLC. The IR spectrum clearly showed both the vinyl ester carbonyl absorption at 5.75 μ and that for the ketone at 5.9 μ.

14-Ketoeicosanamide. The amide was prepared from 14-ketoeicosanoic acid essentially by the mixed carboxylic-carbonic anhydride method described earlier (7). The work-up procedure was modified because of the difficult solubility of this derivative in any of the common organic solvents. In this case, after the triethylammonium salt of the acid had been converted to the mixed anhydride with ethyl chloroformate in THF solution and the anhydride had been decomposed with anhydrous ammonia, the reaction mixture was diluted with copious quantities of cold distilled water and filtered. This procedure removed the triethylammonium chloride formed in the reaction and left behind the hard, white waxy amide. This was dried in a forced-draft oven, dissolved in hot chloroform, and allowed to crystallize at room temperature. Beautiful shiny flakes resulted, mp 119–120C, in 87% over-all yield. The IR of this material had ketone carbonyl absorption at 5.9 μ, amide I and II bands at 6.0 μ and 6.15 μ respectively, and two N-H stretching bands at 2.95 μ and 3.1 μ.

14-Ketoeicosanitrile. This material was prepared

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from 14-ketoeicosanamide by a dehydration procedure similar to that of Stephens et al. (8). The amide, 3.25 g (0.01 mole), was dissolved with gentle warming and stirring in an excess (75 ml) of pyridine. An excess (2.5 g) of p-toluenesulfonyl chloride was then added, also with warming and stirring; this dehydration is not exothermic, as has been reported for other series of compounds (8). After about an hour all material was in solution and the pyridine was removed in vacuo. The residue was taken up in ether and water, the aqueous layer was extracted again with ether, and the combined organic solutions were carefully washed in the usual fashion, dried, filtered, and stripped. The crude product, 2.70 g (88% of theory), showed the expected IR features for a keto fatty nitrile ($C \equiv N$ stretching vibration at 4.5μ, ketone carbonyl at 5.9 μ, absence of $N-H$) but gave two spots on a TLC strip. Only one spot was visible however after the product had been percolated through neutral alumina in several volumes of dry ether. No impurity peaks were visible in the GLC.

N-Acetyl-14-Ketoeicosanamine. Reduction of the nitrile was accomplished on a 0.01 M scale by the use of Raney nickel in acetic anhydride at 50C and 50 psig. Sodium acetate was added to help catalyze acetylation of the primary fatty amine, as it was formed, in order to prevent it from reacting further to give secondary amine (9). The crude product was isolated by filtration, removal in vacuo of acetic anhydride, and removal by water washing of excess sodium acetate. The resulting light tan powder, mp 101–102.5C, weighed 2.9 g, 83% of theoretical yield for acetylated primary amine. The material was recrystallized from Skellysolve B-ethyl acetate, and small white needles were recovered, mp 102.5–104C. The crystalline amine derivative had the anticipated IR features: ketone carbonyl at 5.9 μ, monosubstituted amide carbonyl at 6.1 μ, and NH stretch at 3.05 μ. It appeared essentially pure as judged by TLC. Elemental analysis: % C 74.9, % H 12.2, % N 3.95. Calculated for $C_{22}H_{43}O_2N$: % C 74.73, % H 12.26, % N 3.96. To determine more conclusively whether or not any disubstituted acetamide (secondary fatty amine) was present in this derivative, NMR data were obtained. The spectrum clearly showed the expected features. Resonances for the following protons were observed: terminal methyl (chain), singlet at 0.87 ppm; chain methylene, broad singlet at 1.25 ppm; methylene β to ketone carbonyl, multiplet centered at 1.51 ppm; methyl adjacent to amide carbonyl, singlet at 1.96 ppm; methylene adjacent to ketone carbonyl, triplet ($J = 7.6$) centered at 2.34 ppm; methylene adjacent to nitrogen, quartet ($J = 6.0$) centered at 3.21 ppm; proton on N, very broad singlet at 5.9 ppm. The integration curve indicated that the protons were present in the numbers to be expected for monosubstituted acetamide (acetylated primary amine) with less than 3% disubstituted derivative (from secondary amine) as a possible contaminant.

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