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Eleostearic Acid Derivatives. I. Reactions at the Carboxyl Group

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Abstract

Nine C_1 substituted derivatives of eleostearic acid have been prepared and characterized by elemental analyses and spectrophotometric data. The preparation of two additional derivatives is indicated by infrared spectroscopy, but difficulties in purification precluded elemental analysis data. Comments are made concerning conditions for product stability and reaction environment.

Introduction

Interest in tung oil, particularly from the viewpoint of protective coatings, has prompted an investigation of the reactions of eleostearic acid (ESA), the principal fatty acid constituent of tung oil. In conducting such an investigation, the objective was to add to the already existing knowledge concerning the chemical reactions of ESA and to prepare a relatively wide spectrum of derivatives which may be of use in areas ofter than protective coatings. It has been attempted, in a qualitative manner, to establish reaction condition requirements with respect to pH, atmospheric conditions, heat, and light. In this regard it has been found advantageous to protect ESA and/or its derivatives, derived from reactions at the carboxyl group, from light and low pH mediums as well as excessive contact with the atmosphere. Any one or a combination of these conditions tends to cause product instability and subsequent polymerization initiated at the conjugated triene system. Experience shows that neutral derivatives show greater stability to heat, light, and atmospheric conditions than do those with acidic or basic functional groups. When possible, experimental conditions have been designed so that polymerization (gelation) would be inhibited. Product instability diminishes markedly when derivative formation involves destruction (usually via a typical Diels-Alder reaction) of the highly reactive conjugated triene system.

Results and Discussion

Several new derivatives, produced by reaction at the C_1 atom of ESA, have been prepared. A number of these derivatives were derived via reaction with ESA (I), and others were prepared from α-eleostearoyl chloride (II) (Figure 1).

α-Eleostearoyl chloride was prepared by the action of thionyl chloride on I. Although the acid chloride was employed in a nonpurified state, its identity was established by infrared spectroscopy. The α-eleostear-

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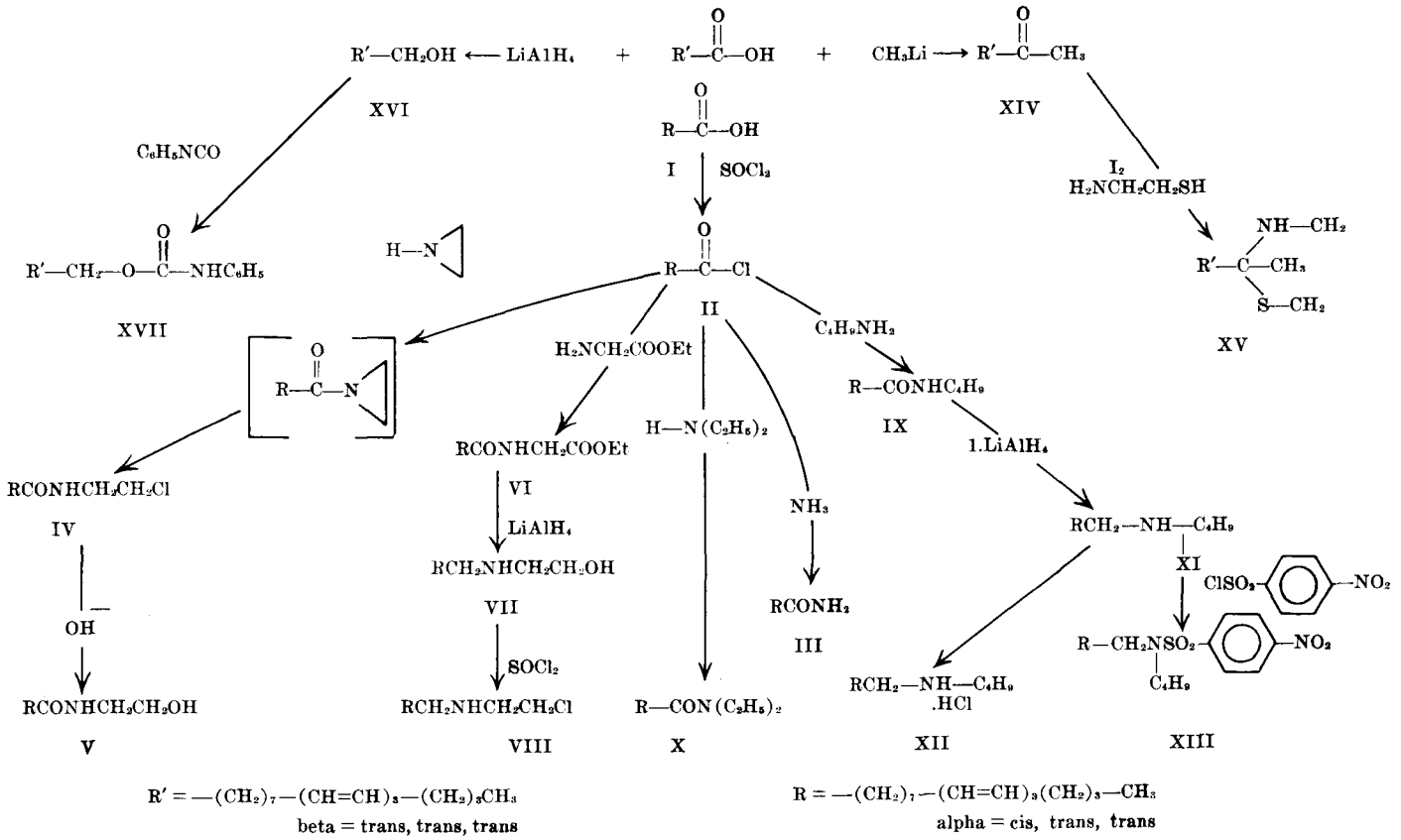

FIG. 1.

amide (III) was prepared in 34% yield via the action of an ammonia solution with II. Kaufmann and Gulinsky (1) have recently reported the preparation of this derivative by the use of II, prepared by phosgenation of α-ESA. These workers report a melting point of 88C for III, but the authors have obtained a melting point of 112.5–114.5C. Furthermore the elemental analysis data for III agree well with theoretical values.

In an effort to prepare ESA derivatives with additional functional groups, the authors chose to react II with ethylenimine in the absence of an acid acceptor to afford the expected 2-chloroethyleleostearamide, IV. The mild alkylating potential of such a functional group coupled with the facile tendency for polymerization of the triene system indicated that this was an attractive route to a potential physiologically active polymer. Also, the reports by Overberger and co-workers (2) concerning select polymers as potential antiradiation drugs precipitated attempts to prepare such an ESA-derived polymer with a classical radioprotective moiety present. To this end, IV was reacted with a basic solution of aminoethanethiosulfuric acid in an effort to obtain the corresponding Bunte salt. The expected product was not obtained but instead a derivative the elemental analysis and spectrophotometric data of which indicate nucleophilic displacement of chloride by hydroxyl to afford α-hydroxyethyl eleostearamide, V.

It next appeared of interest to prepare a more reactive alkylating agent, such as a nitrogen mustard, characterized by a 2-chloro-ethylamino moiety. Ethyl glycinate was reacted in the usual manner with II to afford, in good yield, the corresponding amide, VI, which, when reacted with an excess of lithium aluminum hydride, gave VII. Treatment of VII with either thionyl chloride or phosphorus trichloride results in a noncrystallizable oil the infrared spectrum of which indicated the existence of VIII; however it was not possible to obtain a crystalline material from either the free base amine or its hydrochloride salt, both of which are quite unstable and rapidly polymerize on standing, even in the cold.

Treatment of II with a secondary or primary amine proceeds, as expected, to produce the corresponding amides, X and IX, respectively. The lithium aluminum hydride reduction of IX gave the corresponding amine, XI, which afforded the expected hydrochloride salt, XII, and sulfonamide, XIII, upon treatment with anhydrous hydrogen chloride and *p*-nitrobenzenesulfonyl chloride respectively.

Attention was next turned to the reactions of β-ESA. Although various organometals are known to promote anionic polymerizations, treatment of β-ESA with methyl lithium, according to the procedure of DePuy and co-workers (3), afforded the desired methyl ketone, XIV. The incorporation of a heterocyclic moiety was attempted when XIV was reacted with mercaptoethyl amine in benzene solution. Although iodine catalysis afforded the theoretical amount of water loss, it was not possible to obtain XV in an analytically pure form, either as a free base or amine salt. The existence of XV was indicated by the lack of a carbonyl absorption in the infrared and the presence of an N-H stretch near 3.0 μ and a characteristic N-H bending vibration at 6.3 μ.

Eleostearyl alcohol, XVI, was prepared by the lithium aluminum hydride reduction of I; subsequent treatment with phenyl isocyanate resulted in the production of its urethane derivative, XVII.

Experimental Section

α-Eleostearic Acid, I

The procedure of Hoffman et al. was employed (4). A solution of α-tung oil (200 g, 0.9 moles), potassium hydroxide (60 g, 1.07 moles), 95% ethanol (500 ml), and water (50 ml) was refluxed for 30 min with constant stirring. The mixture was allowed to cool, and the soap was acidified with 2 N hydrochloric acid (1,200 ml). The liberated eleostearic acid was separated from the aqueous phase and dissolved in 95% ethanol (500 ml). This solution was kept for 24 hr at −20C for formation of α-eleostearic acid crystals. Recrystallization from ethanol produced 120 g (75%) of the pure product, which melted at 48–49C.

α-Eleostearoyl Chloride, II

The procedure of Jacobson (5) was employed. A solution of α-ESA (16 g, 0.057 moles), thionyl chloride (8.3 g, 0.1 moles), and petroleum ether was allowed to stand over-night in a flask equipped with a calcium chloride drying tube. The excess chlorinating agent and the solvent were removed in vacuo. The crude product was employed directly by assuming quantitative conversion of the acid to acid chloride. The oily product showed a strong absorption band at 5.5 μ, characteristic of an acid chloride.

α-Eleostearamide, III

Dry ether (650 ml), cooled to −10C, was treated with gaseous ammonia concurrently with the drop-wise addition of II, prepared from 0.198 moles of I. Vigorous stirring was maintained during this time and for an additional 0.5 hr. The reaction mixture was subsequently washed with three 150-ml portions of 2 N hydrochloric acid solution, then with sodium bicarbonate solution (5%). The ether layer was dried over magnesium sulfate, followed by filtration and solvent removal in vacuo to produce the crystalline product. Recrystallization from hexane afforded 16.65 g of II (34%), melting at 112.5–114.5C. Literature (1) gives 88C. The infrared spectrum was consistent with the proposed structure.

Anal. Calcd. for $C_{18}H_{31}NO$; C, 77.92; H, 11.26; N, 5.04.
Found: C, 77.72; H, 11.14; N, 4.90.

N-(2-Chloroethyl)-α-Eleostearamide, IV

A cold (−10C) ether solution (500 ml) of ethylenimine (0.413 moles) was treated drop-wise with II (0.165 moles) over a period of 1.5 hr. The rate of addition was so regulated that the reaction temperature did not exceed 0C. Subsequent to the addition of II, the mixture was stirred vigorously at ambient conditions for 1 hr, at which time washing of the reaction mixture with two 250-ml portions of 2 N hydrochloric acid, then with two 250-ml portions of saturated sodium bicarbonate solution, followed by drying of the ether solution over magnesium sulfate, was accomplished. Solvent removal in vacuo gave 36 g (74%) of crude product which, when recrystallized from hexane, melted at 86–88C. The infrared spectrum was consistent with the proposed structure.

Anal. Calcd. for $C_{20}H_{34}ClNO$; C, 70.62; H, 10.09; N, 4.13.
Found: C, 71.29, H, 9.87; N, 4.14.

N-(2-Hydroxyethyl)-α-Eleostearamide, V

The procedure of Klayman (6) was employed for the attempted preparation of 2-(aminoethanethiosulfate)-ethyl-α-eleostearamide. An ethanolic (275 ml) solution of sodium hydroxide (0.211 moles) was heated to reflux, at which time the solution was treated with a water solution (25 ml) of aminoethanethiosulfuric acid (0.211 moles), then with an ethanol (75 ml) solution of IV (0.141 moles). The addition of IV required approximately 1 hr. The reaction mixture was refluxed for an additional 4 hr, at which time the reaction solution was reduced to one-half its original volume and an equal amount of water was added. Neutralization with acetic acid and cooling over-night produced 8 g of impure product which, after crystallization from acetone and ethanol, gave 18% yield of pure product melting at 110–112C.

Anal. Calcd. for $C_{20}H_{35}O_2N$; C, 74.72; H, 10.93; N, 4.35; mol. wt., 321.5.
Found: C, 74.82; H, 11.03; N, 4.51; mol. wt., 311.

N-(Carboethoxymethyl)-α-Eleostearamide, VI

Ethyl glycinate hydrochloride (0.25 moles) and pyridine (0.35 moles) were placed in dry ether (300 ml) and cooled to −5C, at which time II (0.161 moles) was added drop-wise over a period of 1 hr. After complete addition, the mixture was refluxed for 1 hr, at which time it was washed with 200 ml of 2 N hydrochloric acid, 500 ml of water, 100 ml of 5% potassium hydroxide solution, and 50 ml of water, in that order. The ether layer was dried over magnesium sulfate and concentrated in vacuo; the solid was crystallized in ethyl alcohol to give 48 g (82%) of crude product, which subsequently melted at 85–86C after additional crystallizations from ethanol.

Anal. Calcd. for $C_{22}H_{37}O_3N$; C, 72.69; H, 10.26; N, 3.85.
Found: C, 72.38; H, 10.10; N, 3.90.

N-(2-Hydroxyethyl)-α-Eleostearylamine, VII

An ethereal (240 ml) slurry of lithium aluminum hydride (0.025 moles) was treated drop-wise with VI (0.0047 moles), dissolved in ether (125 ml), over a period of 1 hr and subsequently refluxed for 120 hr. The excess lithium aluminum hydride was destroyed with a water-saturated ether solution. The reaction mixture was washed with 15% potassium hydroxide solution, and the inorganic salts were removed by filtration. The ether solution was dried over magnesium sulfate and concentrated in vacuo to give VI (70%), which had a melting point of 68–70C after recrystallization from a petroleum ether-ethanol mixture.

Anal. Calcd. for $C_{20}H_{37}ON$; C, 78.11; H, 12.13; N, 4.56.
Found: C, 78.01; H, 12.24; N, 4.71.

N-(2-Chloroethyl)-α-Eleostearylamine, VIII

An ether solution (25 ml) of VII (0.0019 moles) was added drop-wise to 2 ml of thionyl chloride previously cooled to 0C. Subsequent to the addition, the reaction temperature was raised to 30C for 1 hr, at which time the excess thionyl chloride was destroyed by the addition of ethanol (25 ml). Solvent removal in vacuo produced an oily material which defied crystallization but the infrared spectrum of which indicated the presence of VIII. Furthermore a positive chloride test was obtained with silver nitrate reagent. Treatment of VIII with an ether solution of hydrogen chloride did not afford a crystallizable derivative.

N-(n-Butyl)-α-Eleostearamide, IX

To an ethereal solution (100 ml) of *n*-butyl amine (0.112 moles) was added eleostearoyl chloride (0.05 moles), dissolved in ether (50 ml). After addition,

the solution was allowed to stand at ambient temperature for 1 hr, when the precipitated amine hydrochloride was dissolved with 2 N hydrochloric acid (50 ml). The aqueous layers were discarded, and the ether layer was treated with cold portions of water (50 ml) and finally with a 5% sodium bicarbonate solution. The ethereal layer was dried over magnesium sulfate, and the solvent was removed in vacuo to produce a crystalline product which, when recrystallized from heptane, gave 10.5 g (61%) of the desired product melting at 81.5 to 82.5C. Infrared and ultraviolet spectrophotometric data were consistent with the proposed structure.

Anal. Calcd. for $C_{22}H_{38}NO$; C, 79.82; H, 11.71.
Found: C, 77.85; H, 11.49.

N,N-Diethyl-α-Eleostearamide, X

A procedure identical to that employed for the preparation of IX was employed; II (0.057 moles) and diethylamine (0.143 moles) gave 9.8 g (52%) of X, which distilled at 132C/0.6 mm Hg. The infrared and ultraviolet spectra were consistent with the proposed structure.

Anal. Calcd. for $C_{22}H_{38}NO$; C, 79.28; H, 11.71.
Found: C, 78.13; H, 11.38.

N-(n-Butyl)-α-Eleostearylamine, XI. The procedure of Micovic and Mihailovic was employed (7). An ether (200 ml) slurry of lithium aluminum hydride (0.079 moles) was treated drop-wise with an ether (80 ml) solution of IX (0.02 moles). After addition, the reaction mixture was refluxed for 130 hr, at which time the excess reducing agent was decomposed by treatment with a water-saturated ether solution. The resulting mixture was washed with potassium hydroxide solution (15%), and the decomposition products were removed by filtration. The ether layer was concentrated in vacuo to yield the crude crystalline product. Recrystallization from hexane gave 0.95 g (35%) of the amine melting at 33–34C. The infrared spectrum was consistent with the proposed structure. *N-(n-Butyl)-α-eleostearylamine hydrochloride, XII,* was prepared by treatment of XI with an ether solution of hydrogen chloride. The pure product gave a decomposition temperature of 95C after purification from a mixture of methanol and ether.

Anal. Calcd. for $C_{22}H_{39}NCl$; C, 74.26; H, 11.81; N, 3.96; Cl, 9.98.
Found: C, 74.40; H, 11.81; N, 4.14; Cl, 9.18.

N-Butyl-N-α-Eleostearyl-p-Nitrobenzenesulfonamide, XIII

A mixture of XI (0.00093 moles), *p*-nitrobenzenesulfonyl chloride (0.0011 moles), and sodium carbonate (0.0011 moles) were placed in a solution of ethanol (25 ml) and water (10 ml). The reaction mixture was heated to reflux and maintained there for 10 min, at which time the reaction mixture was cooled to allow XIII to crystallize in 60% yield after purification from an ethanol-water mixture to give a melting point of 70–71C.

Anal. Calcd. for $C_{28}H_{44}SN_2O_4$; C, 66.58; H, 8.80.
Found: C, 66.36; H, 8.91.

trans-10, trans-12, trans-14-Nonadecatrien-2-one, XIV

An ether (100 ml) solution of β-I (0.24 moles) was contained in a flask, fitted with a drying tube, reflux condenser, and True-Bore stirrer. To this solution, under nitrogen, was added drop-wise methyl lithium (0.48 moles) at such a rate as to maintain a gentle reflux. After complete addition, the reaction mixture was treated drop-wise with saturated ammonium chloride solution. Two layers subsequently formed; the ether layer was separated and washed with water and dried over magnesium sulfate. The solvent was removed in vacuo, and the residue was crystallized from 95% ethyl alcohol to give 22 g (70%) of XIII with a melting point of 56–56.5C.

Anal. Calcd. for $C_{19}H_{32}O$; C, 82.60; H, 11.59.
Found: C, 82.48; H, 11.70.

2-Methyl-2-β-Eleostearyl-Thiazolidine, XV

The procedure of Mills and Bogert was employed (8). A benzene solution of XIV (0.1 moles) and mercaptoethylamine (0.1 moles) was treated with 0.1 g of iodine and refluxed until the theoretical amount of water was removed via use of a Barrett trap. At this time the solvent was removed and an infrared spectrum was obtained. The oily residue showed the lack of a carbonyl band and the presence of an N-H stretching-, and N-H bending-vibration as well as the *trans, trans* absorption peak at 10.1 microns. Attempted crystallization with numerous solvents failed as did attempts to prepare a crystalline hydrochloride salt.

β-Eleostearyl Alcohol, XVI

The method of Lighthelm et al. (9) was employed to prepare XVI in 60% yield with a melting point of 56–58C.

β-Eleostearylphenylurethane, XVII

β-Eleostearyl alcohol, XVI (0.0089 moles), and phenyl isocyanate (0.0089 moles) were heated for 5 min on a steam bath and cooled for 1 hr, at which time a white solid crystallized. Recrystallization from petroleum ether afforded 0.65 g (45%) of XVII, which gave a melting point of 79–80C.

Anal. Calcd. for $C_{25}H_{37}NO_2$; C, 68.72; H, 9.89.
Found: C, 69.17; H, 9.97.

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