[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Fatty Acid Amides. VI.[2] Preparation of Substituted Amidostearic Acids by Addition of Nitriles to Oleic Acid[3]

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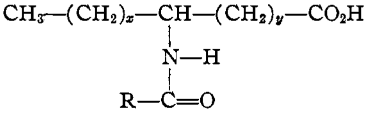
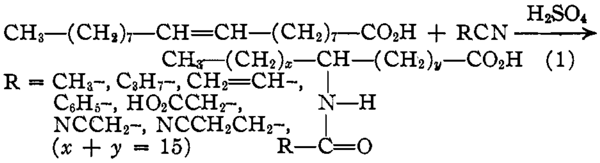


$$\begin{array}{c} CH_3\text{—}(CH_2)_x\text{—}CH\text{—}(CH_2)_y\text{—}CO_2H \\ | \\ N\text{—}H \\ | \\ R\text{—}C{=}O \end{array}$$

The addition of acetonitrile, propionitrile, acrylonitrile, benzonitrile, cyanoacetic acid, malononitrile and succinonitrile to the double bond of oleic acid in sulfuric acid solution gives good yields of substituted amidostearic acids. Best results are obtained in 95% sulfuric acid solution but other carbonium ion producers also can be employed, although yields are low. Aminostearic acid, a compound which shows typical amino acid properties, can be prepared in excellent yield from acetamidostearic acid by hydrolysis with 50% aqueous sulfuric acid. Evidence is given for supporting the carbonium ion mechanism for the addition of nitriles to oleic acid.

The reaction of nitriles with alkenes in strong acid media to yield substituted amides has been described recently by Ritter and co-workers.[4] In this paper we are describing the results obtained in applying this reaction to oleic (*cis*-9-octadecenoic) acid, a less reactive olefinic compound in general than most of those previously employed.

The reaction of nitriles with oleic acid in strong acid media is apparently general, and N-carboxyalkyl amides are obtained in good yield, as shown in equation 1.



$$CH_3\text{—}(CH_2)_7\text{—}CH{=}CH\text{—}(CH_2)_7\text{—}CO_2H + RCN \xrightarrow{H_2SO_4} CH_3\text{—}(CH_2)_x\text{—}\underset{\substack{|\\ N\text{—}H\\ |\\ R\text{—}C{=}O}}{CH}\text{—}(CH_2)_y\text{—}CO_2H \quad (1)$$

$R = CH_3\text{–}, C_3H_7\text{–}, CH_2{=}CH\text{–}, C_6H_5\text{–}, HO_2CCH_2\text{–}, NCCH_2\text{–}, NCCH_2CH_2\text{–}, (x + y = 15)$

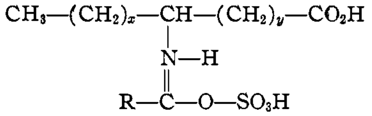
In sulfuric acid medium,[5] however, considerable isomerization occurs and the crude reaction products have broad melting ranges even though analysis shows them to be the desired products almost exclusively. Fractional crystallization permits the isolation of sharper melting, analytically pure products but the yields are then considerably reduced.

In their original paper,[4a] Ritter and Minieri proposed a reaction scheme in which sulfuric acid first adds to the double bond to form sulfate ester followed by reaction of these intermediates with the nitrile. Later,[4c] in describing the reaction of dinitriles with alkenes, they stated that carbonium ions are probable intermediates.

The formation of isomers from nitriles and oleic acid, coupled with the difficulty experienced in attempting to isolate individual isomers, suggests that a carbonium ion mechanism is probably the main one.

If in the first step sulfuric acid adds to the double bond of oleic acid and is then displaced by the nitrile, only two isomers, which should be separable, would be obtained. As confirmatory evidence that sulfate esters are not required intermediates, we have obtained the expected amides in the complete absence of sulfuric acid provided that other strong acids, such as boron fluoride and perchloric acid, are present. In these last cases, however, small yields of amides are obtained.

It may be significant that when the sulfuric acid solution is poured onto ice and water to isolate the product, an oily material is obtained. This product may require as long as 24 hours to solidify even with mixing to ensure rapid removal of sulfuric acid from the viscous, oily mass. This suggests that the initial stabilized reaction product is



$$\begin{array}{c} CH_3\text{—}(CH_2)_x\text{—}CH\text{—}(CH_2)_y\text{—}CO_2H \\ | \\ N\text{—}H \\ \| \\ R\text{—}C\text{—}O\text{—}SO_3H \end{array}$$

and it requires time to hydrolyze and then tautomerize to the amide which is the product actually isolated. The reaction product solidifies slowly when R (equation 1) is electron-releasing, that is, CH_3–, C_3H_7– and C_6H_5–, and rapidly when R is electron-attracting, $HO_2C\text{-}CH_2$–, $NC\text{-}CH_2$–, $NC\text{-}CH_2CH_2$–. The differences in the rate of solidification, however, could be caused simply by the differences in rates of crystallization.

Table I lists the substituted amidostearic acids prepared and characterized. The reactions were usually complete within 15 minutes after the reactants were mixed in concentrated sulfuric acid. In the case of α-carboxyacetamidostearic acid, crude reaction products showed high iodine numbers which suggested incomplete addition to the double bond. This conclusion could not be reconciled with the fact that the nitrogen content of the crude products was about 85% of that calculated. Quantitative microhydrogenation, however, showed almost complete absence of unsaturation and it was concluded, therefore, that the halogenating reagent used in the Wijs or Rosenmund–Kuhnhenn iodine number determination was attacking the extremely reactive methylene group between the carboxyl and amide groups. It is also noteworthy that mixtures of glacial acetic acid and sulfuric acid as reaction media, systems employed in some cases by Ritter and co-workers,[4] gave low yields in the addition of nitriles to oleic acid. Also, a study of the experi-

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[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture.

[2] For Paper V, see THIS JOURNAL, **74**, 3442 (1952).

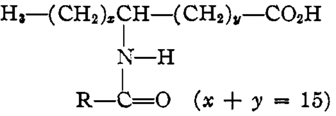
[3] Presented at the Fall Meeting of the American Chemical Society, Chicago, Illinois, September, 1953.

[4] (a) J. J. Ritter and P. P. Minieri, THIS JOURNAL, **70**, 4045 (1948); (b) J. J. Ritter and J. Kalish, *ibid.*, **70**, 4048 (1948); (c) F. R. Benson with J. J. Ritter, *ibid.*, **71**, 4128 (1949); (d) L. W. Hartzel with J. J. Ritter, *ibid.*, **71**, 4130 (1949); (e) R. M. Lusskin with J. J. Ritter, *ibid.*, **72**, 5577 (1950); (f) H. Plaut with J. J. Ritter, *ibid.*, **73**, 4076 (1951).

[5] B. B. Schaeffer, E. T. Roe, J. A. Dixon and W. C. Ault, THIS JOURNAL, **66**, 1924 (1944).

TABLE I

SUBSTITUTED AMIDOSTEARIC ACIDS,



$$CH_3—(CH_2)_xCH(NH—C(=O)—R)—(CH_2)_y—CO_2H \quad (x + y = 15)$$

R	Reaction product		Recrystallized product								
	Yield, %	N, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Neut. equiv. Calcd.	Neut. equiv. Found	Melting range, °C.
CH_3	99	3.5	4.10	3.93	70.3	70.1	11.5	11.2	342	341	70–82
CH_2=CH	89[a]	3.8	3.96	..	..	..	..	..	354	345[d]	.....
CH_3—CH_2	94	3.3	3.94	3.69	70.9	71.2	11.6	11.9	356	366	64–75
C_6H_5	97	3.1	3.47	3.30	74.4	74.5	10.2	10.3	404	406	87–90
HO_2C—CH_2	91	3.1	3.63	3.51	65.4	65.3	10.2	10.3	193	198	69–78
NC—CH_2	[b]	6.6	7.64	7.25	68.8	68.1	10.5	10.9	366	348[d]	65–72
NC—CH_2—CH_2	[c]	5.6	7.36	6.62	69.4	66.2	10.6	10.0	381	447	117–118

[a] This product was a viscous to rubbery liquid which could not be induced to crystallize. [b] See Experimental. This product was probably a mixture of α-cyanoacetamidostearic acid and malonamido-bis-stearic acid. [c] This product was probably a mixture of β-cyanopropionamidostearic acid and succinamido-bis-stearic acid. [d] Crude reaction product.

mental variables, namely, mode of addition, ratio of reactants, reaction time and temperature, showed that simultaneous addition of oleic acid and nitrile to sulfuric acid in a ratio of oleic acid: nitrile:sulfuric acid of 1:3:6 at 27–30°, and a reaction time of 15 minutes to one hour gave the best yields.

With the exception of acrylamidostearic acid, the products were white solids, insoluble in water, and soluble in warm but insoluble in cold organic solvents. Acrylamidostearic acid was a light brown viscous liquid. Its infrared spectrum contained several strong absorption bands (Table II) which were closely similar, not only in wave length but also in molar absorptivity, to the strongest bands of a commercial sample of N-*t*-butylacrylamide, m.p. 128–130°,[6] of high purity. The close similarity of these bands indicates that the functional group of the known N-*t*-butylacrylamide is also present in the product isolated from the reaction of acrylonitrile with oleic acid. Other strong bands of acrylamidostearic acid are those usually assignable to carboxyl groups and long hydrocarbon chains. It should be noted, however, that the spectra show no bands in the 2100–2400 cm.$^{-1}$ region, where the C≡N group absorbs.

TABLE II

COMPARISON OF INFRARED ABSORPTION BANDS

Acrylamidostearic acid Wave no., cm.$^{-1}$	Acrylamidostearic acid Molar absorptivity[a]	N-*t*-Butylacrylamide Wave no., cm.$^{-1}$	N-*t*-Butylacrylamide Molar absorptivity
946	54	946	10
962	71	963	65
975	115	977	130
1408	112	1402	89
1514	287	1513	385
1613	106	1614	97
1629	162	1633	142
1669	380	1674	419
3434	83	3450	97

[a] The nomenclature used is that recommended in *Anal. Chem.*, **24**, 1349 (1952).

Since acetamidostearic acid was the most convenient compound to prepare, it was selected for study of the preparation of aminostearic acid. Hydrolysis of acetamidostearic acid with refluxing 20% alcoholic potassium hydroxide or potassium hydroxide in ethylene glycol yielded unchanged starting material with the former and unidentifiable solid products with the latter. Refluxing with 50% sulfuric acid for six days gave a quantitative yield of acetic acid and a 93% yield of the sulfuric acid salt of aminostearic acid. (Ritter and Minieri[4a] reported that acid hydrolysis of their products occurred rapidly, accompanied by loss of ammonia and regeneration of the olefin instead of formation of the expected amine.) The salt was converted to aminostearic acid in excellent yield by solution in aqueous sodium hydroxide followed by acidification to *p*H 5–6. It showed typical amino acid titration characteristics (Fig. 1). Potentiometric titration in the absence of formaldehyde gave the typical curve for a zwitterion (curve A); in the presence of formaldehyde, a point of inflection could be readily observed (curve B) and, as was anticipated, the entire curve was displaced downward toward lower *p*H values.

Experimental

Starting Material.—Oleic acid was prepared from olive oil fatty acids by multiple low temperature crystallization and fractional distillation.[7] Pure aceto-, acrylo-, propio- and benzonitrile were obtained from the best commercial grades by fractional distillation through packed columns. The solid nitriles, malononitrile, succinonitrile and cyanoacetic acid, were the best commercial grades (purity 98% or better) and were used as received.

Infrared Spectra.—The infrared absorption spectra were obtained with a Beckman IR-3 spectrophotometer, using NaCl prisms.

Preparation of Amidostearic Acids. Acetamidostearic Acid.—The preparation of acetamidostearic acid is typical: A mixture of 282 g. (1.0 mole) of oleic acid and 123 g. (3.0 moles) of acetonitrile in a cylindrical dropping funnel was stirred vigorously and added in 35 minutes to 338 ml. (6 moles) of 95% sulfuric acid in a 2-l. three-neck flask fitted with a thermometer and an efficient stirrer. (When the nitrile and oleic acid were miscible, stirring in the dropping funnel was unnecessary. With cyanoacetic acid and other solid nitriles, an infrared heating lamp was used to keep the contents of the dropping funnel molten.) The reaction temperature was maintained between 27 and 30° by external cooling. Fifteen minutes after addition was complete the mixture was poured with stirring onto approximately 2 l. of chopped ice and water. The soft, sirupy insoluble mass was stirred occasionally and then allowed to stand overnight in the dilute acid. The following morning stirring was continued until the product had hardened to a crumbly,

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[6] Reference 4f gives 126–128°.

[7] H. B. Knight, E. F. Jordan, Jr., E. T. Roe and D. Swern, *Biochem. Preparations*, **2**, 100 (1952).

wax-like solid, which was filtered off, washed several times with cold water and dried; yield of crude acetamidostearic acid, 339 g. (99%), m.p. 56–58°. For analysis, a small portion of this product was dissolved in ether and washed with water until free of sulfuric acid. The ether solution was dried over anhydrous sodium sulfate, filtered, and the ether was then evaporated.

Anal. Calcd. for acetamidostearic acid, $C_{20}H_{39}NO_3$: See Table I, R = CH_3. Found: N, 3.44; S, 0; neut. equiv., 362; iodine number, 6.2.

Four crystallizations from acetone at 0° (5 ml. of solvent per g. of solute) with a carbon treatment each time gave a 39% over-all yield of analytically pure acetamidostearic acid, m.p. 70–82° (Table I).

α-Cyanoacetamidostearic Acid.—A second method was found to be advantageous in small-scale procedures, and particularly where the nitrile was a solid and immiscible with oleic acid. A mixture of 7.1 g. (0.025 mole) of oleic acid and 5.0 g. (0.075 mole) of malononitrile was melted in a beaker with stirring, the beaker was then immersed in Dry Ice, and the stirring was continued until the mixture had solidified. The requisite quantity of 95% sulfuric acid (8.5 ml., 0.15 mole) was cooled to 0–10° and added all at once to the oleic acid–malononitrile mixture. It was mixed thoroughly, the Dry Ice was removed and stirring was continued until the mixture became fluid and homogeneous. The temperature rose to about 27° within about 10 minutes, and it was maintained at 27–30° for an additional 15 minutes. The reaction mixture was poured onto about 700 ml. of chopped ice and water, and the sirupy reaction product which precipitated hardened into small granular particles within 20 minutes; yield 8.7 g. of light tan solid.

Anal. Calcd. for α-cyanoacetamidostearic acid, $C_{21}H_{38}N_2O_3$: see Table I, R = NC-CH_2. Found: N, 6.63; neut. equiv., 340; iodine number, 6.1.

Three crystallizations from acetone at −25° (10 ml. of solvent per g. of solute) gave a 19% yield of a product, m.p. 65–72°, whose analysis indicated that it was mainly α-cyanoacetamidostearic acid contaminated with malonamido-bis-stearic acid (Table I).

Preparation of Acetamidostearic Acid in the Absence of Concentrated Sulfuric Acid.—A mixture of 14.1 g. (0.05 mole) of oleic acid (iodine number 89), 6.2 g. (0.15 mole) of acetonitrile and 17 ml. of acetic acid–perchloric acid (16.5 ml. of glacial acetic acid and 0.5 ml. of 70% perchloric acid) was heated for 6 hours at 90°. The dark brown solution was poured into 500 ml. of chopped ice and water with stirring. The sirupy precipitate did not solidify even after stirring for some time. It was dissolved in ether and the ether solution was washed free of acid and dried. Evaporation of the ether yielded 13.4 g. of light yellow oil (iodine number 69) which partially solidified on standing. Two crystallizations from acetone (15 ml. of solvent per g. of solute) yielded 1.4 g. (44% of acetamidostearic acid formed, based on reduction in iodine number) of acetamidostearic acid, m.p. 94.5–98.5°.

Anal. Found: C, 70.5; H, 11.5; N, 3.93; neut. equiv., 345; unsaturation, 0 (by hydrogen absorption).

The high and relatively sharp melting point suggests that the product is a less complicated mixture of isomers than the acetamidostearic acid obtained from sulfuric acid reaction medium.

When 10% by weight of boron fluoride (based on oleic acid), supplied by boron fluoride–acetic acid complex, was employed instead of perchloric–acetic acid, the iodine number of the oleic acid was reduced by only 5–6 units, and 45% of the acetamidostearic acid formed was isolated (16 g. of reaction product yielded 0.4 g.), m.p. 93–96°.

Anal. Found: C, 69.6; H, 11.6; N, 3.84; neut. equiv., 351; unsaturation, trace (by hydrogen absorption).

Aminostearic Acid.—Acetamidostearic acid (25.6 g., 0.075 mole) was refluxed for 140 hours with 225 ml. of 50% aqueous sulfuric acid. Steam distillation and titration of the dilute acetic acid solution showed hydrolysis to be quantitative (hydrolysis was 94% complete after 84 hours). The non-volatile product was washed free of sulfuric acid and dried. Analysis showed it to be the sulfuric acid salt of aminostearic acid (24.3 g., 93% yield).

Anal. Calcd. for $C_{36}H_{76}N_2O_8S$: C, 62.0; H, 11.0; N, 4.02; S, 4.60. Found: C, 62.2; H, 10.8; N, 3.94; S, 4.45.

The salt was dissolved in an excess of aqueous sodium hydroxide to *p*H 12 and then carefully neutralized with dilute aqueous hydrochloric acid with stirring to *p*H 5–6. The oily material which precipitated was solidified in the refrigerator, separated from the aqueous layer and washed twice by melting with hot water followed by resolidification. The dried product, m.p. 85–90° (21 g., 90% over-all yield from acetamidostearic acid), was substantially pure aminostearic acid, as shown by ultimate analysis, but contained about 1% of ash. Two crystallizations from 95% ethanol (8 ml. of solvent per g. of solute) at −20° yielded 15.2 g. (80%) of ash-free, aminostearic acid, m.p. 87–90°.

Anal. Calcd. for $C_{18}H_{37}NO_2$: C, 72.2; H, 12.5; N, 4.68; neut. equiv., 299. Found: C, 71.1; H, 11.9; N, 4.41; neut. equiv. (formaldehyde present, Fig. 1, curve B), 297.

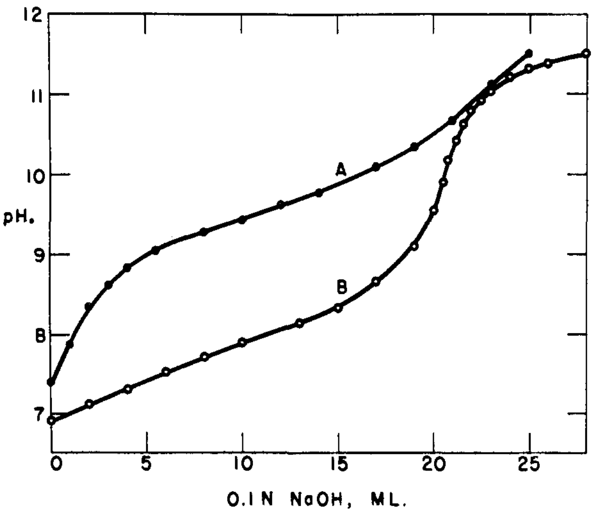

Fig. 1.—Potentiometric titration curves for aminostearic acid: A, formaldehyde absent; B, formaldehyde present; (0.6121 g. of sample dissolved in 100 ml. of 70% ethanol containing 10 ml. of neutralized 36–38% aqueous formaldehyde); neut. equiv., 297.

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