Castor-Based Derivatives: Synthesis of Some Amides[1]

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Abstract

Various amides of ricinoleic acid and the related ricinelaidic, hydroxystearic, dihydroxystearic, and trihydroxystearic acids have been synthesized and characterized. Ester aminolysis in methanol solution with sodium methoxide catalyst at room temperature has limited utility since it suffers severe rate retardations due to steric effects with secondary amines. In addition, with primary amines and ammonia, extended reaction times are generally necessary for reasonable yields. The use of mixed carboxylic-carbonic anhydrides in amide syntheses was investigated and found applicable without interference from the secondary hydroxyl groups. Also, no appreciable steric effects were observed with most amines. This rapid, high yield method has been employed in the synthesis of a number of new amides from castor-based acids, ammonia, and primary and secondary amines.

Introduction

FATTY ACID nitrogen derivatives are recognized for their utility in many diverse industrial applications. Evaluation of certain amides of ricinoleic acid (12-hydroxy-*cis*-9-octadecenoic acid, the principal fatty acid of castor oil) as plasticizers, fungistats, and polyurethane components has been reported (1,2,3), and other end uses have been described in the patent literature. In attempting to prepare a series of amides from castor hydroxy acids for further evaluation, we briefly studied base-catalyzed ester aminolysis. This well-known technique (4) has recently been extensively studied (5), and steric effects and optimum conditions investigated. The conditions employed in our studies led to low reaction rates and, as noted (5), the utility of this method is severely limited by steric bulk in the amines used. Furthermore, the presence of alcohol functions in these acids precludes use of many carboxylic acid activation systems.

As a possible solution to the problems of alcohol function interference and steric hindrance, mixed carboxylic-carbonic anhydrides (6,7,8), which are readily prepared by reaction of carboxylic acid salts and alkyl chlorocarbonates, were investigated for utility in the synthesis of hydroxy acid amides. This method has been reported as useful for amide preparation with varying yields (35–85%) with some hydroxy amino acid derivatives (9) and with two keto-hydroxy fatty acids (10). Potential side reactions with hydroxyl functions, though not investigated (9,10), were suggested (9) as possible complicating factors in such syntheses. Also, steric bulk in amines has been reported (11) to lead to considerable urethan and carboxylic acid formation by attack of amines at the carbonic acid carbonyl group of some mixed anhydrides. Since limitations imposed by side reactions with alcohol functions and by steric effects were chief reasons for investigating the mixed anhydride method, the known carbethoxylation reactions (chloroformate plus alcohol) and esterification reactions (alcohol plus anhydride) (9) and reactions of some sterically hindered amines were studied in mixed anhydride systems involving ricinoleic acid. Another possibility considered was carbethoxylation of the hydroxyl function during anhydride formation followed by decarbethoxylation during amide formation, since reactions of alcohols with chloroformates (9) and aminolysis of carbonate esters (12) are known.

The results of these synthetic studies and of the side reactions investigated will be presented together with descriptions of the compounds prepared.

Experimental

Analytical Techniques. Infrared spectra were measured as smears, in Nujol mulls, or in 1-mm cells as *ca.* 0.5% solutions in chloroform, tetrachloroethylene, or carbon bisulfide. A Model 137 Infracord (NaCl optics) was used. References were air path or matched cells filled with solvent. These techniques were routinely used to monitor reaction and purification procedures.

Thin-layer chromatography (TLC) on chromatostrips (13) also was used as an aid in assessing purity. Detection was with 2′,7′-dichlorofluorescein in ethanol (14), and the adsorbent was Merck A.G. 7729 silica gel with 5% starch binder.

Amines. Commercially available samples were distilled prior to use and stored over KOH pellets, or used as received if anhydrous.

Methyl Ricinoleate. Samples were prepared by sodium methoxide catalyzed methanolysis of castor oil and purified by fractional distillation at reduced pressure (15).

Methyl Ricinelaidate. Methyl ricinoleate was isomerized according to McCutcheon et al. (16) and had mp 28.4–29.0C. Reported (16) 28.5–29.8C.

Ricinoleic Acid. Acid samples were prepared as required from distilled methyl ester as described (16). Preparations freed of mineral acid were stored as solids below 0C and were used without further purification.

Ricinelaidic Acid. Methyl ricinelaidate was hydrolyzed as indicated (16), and the acid was recrystallized from 20 volumes of 60–70 petroleum ether, yielding a product of mp 49.8–50.9C. Reported (16) 50.5–51.1C.

12-Hydroxystearic Acid. Distilled methyl ricinoleate was hydrogenated in ethanol containing platinum oxide at 3 atmospheres of hydrogen pressure and room temperature. The saturated esters were hydrolyzed in ethanolic-aqueous KOH to yield the acid, mp 79.5–80.0C, after acidification and recrystallization from ethanol-water. Literature value: mp 80.5–81.0C (17).

9,10-Dihydroxystearic Acid. The acid was prepared from oleic acid and performic acid on a 0.1 scale according to Swern et al. (18) and had mp 92–93C after several recrystallizations from 95% ethanol. Reported mp 94–95C (18).

9,10,12-Trihydrostearic Acid. This compound was

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prepared from castor oil using peracetic acid as described by Scanlan and Swern (19). The mixed isomers were separated by repeated crystallizations from ethanol to yield the isomer of mp 106–108C. Reported mp 108–109C (19). Calculated for $C_{18}H_{56}O_5$(332.47): C, 65.0; H, 10.9. Found: C, 65.0; H, 10.9.

Amides. Various amides were prepared by ester aminolysis or the mixed anhydride method. Representative examples of these synthetic methods and investigations of side reactions are presented in the following sections.

N,N-Dimethylricinoleamide by Ester Aminolysis. Methyl ricinoleate (16.3 g; 0.052 mole) was dissolved in 250 ml of commercial anhydrous methanol, and 97.5 g (2.17 mole) anhydrous dimethylamine (freshly opened ampoule) was added with cooling in ice. Then, 5 ml of *ca.* 1N methanolic sodium methoxide was added, and the flask was closed with a soda-lime drying tube. Samples (1 ml) were withdrawn periodically for infrared analysis. Completion of the reaction occurred in about 140 hr. Solvent and excess amine were removed *in vacuo* with a rotary evaporator. The residual oil was taken up in ether, extracted with 3N hydrochloric acid, washed with three portions of water with considerable loss in emulsions, dried over magnesium sulfate, and the solvent removed as before. The yield was 14.1 g (83.5%). An analytical sample was obtained by short-path high vacuum distillation. Analytical results and properties of this and other amides prepared by ester aminolysis are shown in Table I. Of these, only the N-methylamide was formed in about 8 hr, the remainder required several days.

Attempts to prepare N,N-diethylricinoleamide in this manner failed, even when amine and catalyst concentrations were doubled. The starting ester was recovered essentially unchanged (infrared analysis) after twelve days at room temperature.

In a similar fashion, positive results were not obtained when anhydrous sodium salts of N-methyltaurine or of sarcosine were combined with methyl ricinoleate in methanolic sodium methoxide solutions. Only the presence of starting materials could be detected after extended periods of time.

Mixed Carboxylic-Carbonic Anhydride Method. Early experiments were carried out at −60 to −70C in an attempt to suppress potential side reactions. Vaughan and Osato (20), using equimolar quantities of chloroformate, tertiary amine, and carboxylic acid, noted that the yields of amide fall off rapidly at temperatures below −20C. We found that this deficiency could be overcome by the use of 3 moles of ethyl chloroformate and triethylamine per mole of ricinoleic acid. Thus, with addition of excess amines, good yields of amides were obtained after normal anhydride formation times (*ca.* 30 min). The amides were contaminated with copious quantities of O-ethylurethans resulting from the reaction between excess chloroformate and excess amines. Relatively volatile urethans were readily removed *in vacuo* at moderate temperatures, leaving residues of quite pure amide. Non-volatile urethans were removed by extraction with suitable solvents. Since side reactions involving the hydroxyl function were not detected at −60 to −70C, they were investigated at the usual (6) reaction temperatures of −5 to 0C.

The reactivity of the alcohol function alone was examined with methyl ricinoleate. This compound was treated for 15 to 30 minutes with excess ethyl chloroformate in pyridine or pyridine-tetrohydrofuran (THF) at 0C, or in triethylamine or triethylamine-THF at 0C, and the products isolated. Little or no carbethoxylation was detected by infrared analysis of smears (appearance of the typical carbonate ester band at 8.0μ with loss of the hydroxyl band at 2.75μ or by TLC with chromatostrips. The 12-O-carbethoxy derivative could be prepared, however, by allowing methyl ricinoleate and excess ethyl chloroformate to stand overnight in pyridine at 25C. This product then was used as an IR and TLC standard and as a model to determine the removability of the protecting group. The lack of change in the infrared spectrum of the carbethoxylated derivative when it was dissolved in diethylamine overnight precluded the possibility that facile removal of the carbethoxyl group (12), if present, would occur under the conditions used. Also, when the reaction conditions for amide synthesis were modified to those generally employed (6), i.e., 0.01 mole of each reactant in THF at −5 to 0C, and when amines were added, consistently good yields of hydroxy acid amides were obtained without the considerable quantities of contaminating urethan or appreciable other side reactions. This further indicates a lack of competition of the hydroxyl group for reaction with the chloroformate or mixed anhydride. The possibility of reaction of the alcohol function with mixed anhydride to form esters (9,10) was also checked by carefully examining the crude amide preparations after vacuum stripping to remove O-ethylurethans. The amides showed essentially no carbonyl bands in the ester region of their infrared spectra. This was an adequate analytical method. With model mixtures of the methyl ester or 12-O-carbethoxy methyl ester and the N,N-diethylamide of ricinoleic acid, less than 1% ester can be detected in the presence of amide when smears sufficient to give amide carbonyl absorbances (6.15μ) of about 0.7 are used.

TABLE I

Amides from Ester Aminolysis

Compound	Empirical formula	mp or (bp/μ Hg) C	n_D^{25}	Analysis					
				Calculated %			Found %		
				C	H	N	C	H	N
Ricinoleic acid:									
amide	$C_{18}H_{35}NO_2$	65.5–66.5	.....	72.7	11.9	4.71	72.4	11.7	4.69
N-methylamide	$C_{19}H_{37}NO_2$	40.5–41.5	1.4781	73.3	12.0	4.50	72.9	11.8	4.46
		(166/2)					73.6		
N-ethylamide	$C_{20}H_{39}NO_2$	(154/2.5)	1.4765	73.8	12.1	4.30		12.0	4.33
N,N-dimethylamide	$C_{20}H_{39}NO_2$	(155/2.5)	1.4773	73.8	12.1	4.30	73.5	12.0	4.39
Ricinelaidic acid:									
amide	$C_{18}H_{35}NO_2$	86.5–87.5	.....	72.7	11.9	4.71	72.5	11.9	4.62
N,N-dimethylamide	$C_{20}H_{39}NO_2$	(157/3)	1.4759	73.8	12.1	4.30	73.8	12.0	4.17

The essential absence of side reactions and the lowering of chloroformate requirement led to the adoption of the −5 to 0C method (6) as the preferred one. A typical preparation is outlined in detail in the next section.

N-Cyclohexylricinoleamide. A solution of ricinoleic acid (3.33 g; 0.011 mole) and 1.67 ml of triethylamine (0.012 mole) in THF (100 ml) was cooled to −5C in an ice-salt bath with mechanical stirring. Ethyl chloroformate (1.15 ml; 0.012 mole) was dropped in at such a rate that the temperature remained at −5C (*ca.* 10 min), and the system was stirred an additional 15 min. Cyclohexylamine (1.47 ml; 0.012 mole) was gradually added, and no temperature increase was noted. The suspension was stirred and slowly warmed to 50C in a water bath. After cooling, the solution was filtered to remove triethylamine hydrochloride. The filter cake was washed with THF, and solvent from the combined filtrates was removed with a rotary evaporator. The residual oil was taken up in diethyl ether, and washed successively with dilute hydrochloric acid, water, dilute sodium carbonate solution, and three times with water. Drying over magnesium sulfate, filtration, and solvent removal under aspirator vacuum gave 3.9 g (93%) of product that slowly crystallized at room temperature. Infrared analysis showed a monosubstituted amide with indications in the carbonyl region of contamination with N-cyclohexyl-O-ethylcarbamate. The compound responsible for this IR absorption was distilled out at 0.5 mm Hg and 165C. Recrystallization of the residue from 30 volumes of 5:1 Skellysolve F:ethylacetate gave an analytical sample weighing 2.85 g, mp 56.0–57.0C. Analytical data are presented in Table II for this

of acid. Excess amine (usually ten-fold) was necessary with more hindered secondary amines to obtain reasonable yields. After addition of amine, the reaction mixtures can be allowed to stand overnight at room temperature rather than heating to 50C. This procedure does not affect yields and may aid purity, as noted below. Purification of solid amides was carried out by heating in a vacuum to remove byproduct urethan and recrystallization from suitable solvents. The most useful pair was ethyl acetate-petroleum ether. Liquid amides were purified, after urethan removal, by short path distillation at 1–5μ Hg and temperatures below 200C.

In some instances, heating with relatively unreactive amines led to some intramolecular decomposition of the mixed anhydrides to form ethyl esters with elimination of carbon dioxide. This known reaction (9) can be avoided by using the prolonged room temperature method. If formation of esters occurs, however, small amounts of them can be readily removed from the amides by hydrolysis with limited amounts of aqueous KOH in ethanol at room temperature. This was necessary in a few cases prior to short-path distillation, since the esters and disubstituted amides were not readily separated otherwise.

N-Ricinoleyl-N-Methylglycine. The mixed anhydride (0.011 mole) was prepared at −5C as above, and 0.02 mole of sarcosine (N-methylglycine) in 20 ml of 1N sodium hydroxide solution was added rapidly with vigorous stirring, as described by Vaughan and Eichler (21) for other amino acids. After one hour at room temperature volatile materials were removed with a rotary evaporator, the solution was acidified to pH 2 with 6N hydrochloric acid, and or-

TABLE II

Amides from Mixed Anhydride Synthesis

Compound	Crude yield %	Empirical formula	mp (bp/μ Hg) C	n_D^{25}	Analysis					
					Calculated %			Found %		
					C	H	N	C	H	N
Ricinoleic acid: amide[a,b]	90	$C_{18}H_{35}NO_2$	66.0–66.3[c]	.....	72.7	11.9	4.71	72.8	11.7	4.67
N-methylamide[a,b]	84	$C_{19}H_{37}NO_2$	30.5–31.5 (161/3–4)	1.4781	73.3	12.0	4.50	73.1	12.0	4.44
N-isopropylamide	89	$C_{21}H_{41}NO_2$	36–37 (178/1–2)	.....	74.3	12.2	4.12	74.2	12.2	4.23
N-β-hydroxyethylamide	71	$C_{20}H_{39}NO_3$	55.5–57.5	.....	70.3	11.5	4.10	70.3	11.4	4.08
N-*n*-butylamide	95	$C_{22}H_{43}NO_2$	28–29 (187/1)	.....	74.7	12.3	3.96	74.5	12.2	4.18
N-isobutylamide	90	$C_{22}H_{43}NO_2$	32–33 (191/8.5)	.....	74.7	12.3	3.96	74.3	12.2	4.15
N-*sec*-butylamide[b]	89	$C_{22}H_{43}NO_2$	38.5–39.5 (174/1)	.....	74.7	12.3	3.96	74.5	12.2	3.90
N-t-butylamide[b]	92	$C_{22}H_{43}NO_2$	(149/4.5)	1.4740	74.7	12.3	3.96	74.5	12.1	3.96
N-hexadecylamide	...	$C_{34}H_{67}NO_2$	65.5–66.0	.....	78.2	12.9	2.68	78.2	13.0	2.67
N-cyclohexylamide	93	$C_{24}H_{45}NO_2$	56–57	.....	75.9	12.0	3.69	76.0	12.1	3.66
N-β-phenethylamide	90	$C_{26}H_{43}NO_2$	51.5–52.5	.....	77.8	10.8	3.49	77.5	10.8	3.48
N-phenylamide[a,b]	83	$C_{24}H_{39}NO_2$	70.5–71.5	.....	77.2	10.5	3.75	77.4	10.6	3.75
N,N-diethylamide[a,b]	68	$C_{22}H_{43}NO_2$	(169/6.5)	1.4749	74.7	12.3	3.96	74.5	12.1	3.88
N,N-di-*n*-propylamide[a,b]	81	$C_{24}H_{47}NO_2$	(158/4)	1.4735	75.5	12.4	3.67	75.3	12.3	3.70
N,N-diisopropylamide[a,b]	89	$C_{24}H_{47}NO_2$	(148/7)	1.4735	75.5	12.4	3.67	75.2	12.3	3.60
N,N-di-*n*-butylamide[a,b]	89	$C_{26}H_{51}NO_2$	(159/2.5)	1.4720	76.2	12.6	3.42	76.0	12.6	3.29
N,N-diisobutylamide[b]	69	$C_{26}H_{51}NO_2$	(162/1)	1.4711	76.2	12.6	3.42	76.1	12.6	3.20
N,N-dicyclohexylamide[b]	64	$C_{30}H_{55}NO_2$	(191/1)	1.4949	78.0	12.0	3.03	77.8	12.1	2.98
N-pentamethylenylamide[a,b]	85	$C_{23}H_{43}NO_2$	(178/4)	1.4885	75.6	11.9	3.83	75.4	11.8	3.70
N-methyl-N-phenylamide[a,b]	80	$C_{25}H_{41}NO_2$	(166/6)	1.5050	77.5	10.7	3.61	77.2	10.6	3.73
Ricinelaidic acid: amide[a,b]	70	$C_{18}H_{35}NO_2$	86.5–87.5	.....	72.7	11.9	4.71	72.6	11.8	4.81
12-Hydroxystearic acid: N,N-dimethylamide[a,b]	86	$C_{20}H_{41}NO_2$	56.0	.....	73.3	12.6	4.28	73.5	12.7	4.22
9,10-Dihydroxystearic acid: N,N-diethylamide	89	$C_{22}H_{45}NO_3$	31.5–32.5	.....	71.1	12.2	3.77	71.2	12.2	3.76
9,10,12-Trihydroxystearic acid: N,N-diethylamide	78	$C_{22}H_{45}NO_4$	76.0–77.0	.....	68.2	11.7	3.61	68.3	11.7	3.58

[a] At −70C; see text.
[b] Excess amine used.
[c] No depression on admixture with authentic sample.

and other preparations synthesized in much the same fashion. At lower reaction temperatures (i.e., −60 to −70C), 3 molar proportions of choloroformate, triethylamine, and amine reactant were used per mole

ganic materials were extracted into chloroform. Washing with water to remove mineral acid, drying over magnesium sulfate, and heating *in vacuo* gave a good yield of thick oil showing absorbance in the infrared

for disubstituted amide (6.2μ) and carboxylic acid (5.8μ). Attempted crystallization was unsuccessful. Chromatostrip analysis showed the absence of ricinoleic acid, but this does not clearly establish this preparation to be a single compound.

N-Ricinoleyl-N-Methyltaurine. Proceeding as with sarcosine did not yield an acidic product, because the sulfonic acid was not extractable from the aqueous solution. A product was isolated as the sodium salt by evaporation, and this could be converted to the free acid (a viscous oil)with methanolic HCl. Attempted purification was inconclusive, except that the absence of ricinoleic acid was again demonstrated by TLC, and the infrared spectrum showed disubstituted amide and sulfonic acid bands.

Surface tensions were measured at room temperature in the usual manner with a du Noüy tensiometer. These values were found to be 43.6 and 53.9 dynes/cm for 0.01% aqueous solutions of crude N-ricinoleylsarcosine and N-ricinoleyl-N-methyltaurine. Distilled water had a surface tension of 72.5 dynes/cm with this apparatus.

Discussion

Although attractive in its simplicity, base-catalyzed ester aminolysis is severely retarded by steric hindrance and is limited as a synthetic method. Higher temperatures, increased pressures, and optimum concentrations have been reported to improve this situation (5), but even these expedients fail in some cases. Under the mild conditions selected here (dilute methanol solutions at ambient temperatures and pressures), the rates observed with methyl ricinoleate and several amines were usually measured in days rather than hours. Furthermore, this method failed with a relatively simple disubstituted amine, diethylamine. Side reactions in the presence of strongly basic solutions seem possible, but have not been investigated. The main deterrents to the use of this method are low reaction rates and high steric sensitivity.

While not as simple a technique as ester aminolysis, mixed carboxylic-carbonic anhydride syntheses provide a relatively rapid, high yield process with reduced effects of steric bulk in the amines used. Although steric effects were not systematically studied, results (Table II) with hindered amines show that this method is considerably less sensitive to steric bulk in amines than is ester aminolysis. Steric hindrance is not completely lacking. For example, with most hindered secondary amines such as di-iso-propyl- and di-iso-butylamine, both an excess (ten-fold) of amine and an overnight reaction period were necessary for complete decomposition of the anhydride. Also, the crude products were of lower purity as judged by yield and infrared analysis. These results cannot be directly compared to those of Tarbell and coworkers, since they generally used equimolar quantities of amines with other mixed anhydrides (11), but the side reaction noted (9,11) leading to cleavage at the carbonic acid carbonyl group probably also accounts for the increased urethan and lowered amide yields observed with hindered amines and ricinoleic acid. The effects of steric hindrance noted here, however, are of relatively little consequence and do not appreciably detract from the general utility of the mixed anhydride method with these hydroxy fatty acids.

It appeared unlikely that alcohol functions of the hydroxy acids would be entirely inert during the mixed anhydride synthesis, particularly in view of known carbethoxylation and esterification reactions (9). The use of such anhydrides with 9,12-dioxo-10, 11-dihydroxy- and 10,11-dihydroxy-12-oxo-octadecanoic acids was noted earlier (10). This report, however, did not discuss potential side reactions or the widely variable yields obtained with these hydroxy acids. Furthermore, Albertson (9) suggested that hydroxyl group interference is of consequence when hydroxy amino acids are used in mixed carboxylic-carbonic anhydride systems and indicated precautions to be observed. It was found with the hydroxy acids studied here that reaction of the hydroxyl function with either ethyl chloroformate or the mixed anhydride was very slow or absent at 0C. Under the conditions used, these rates were negligible compared to the rates of anhydride formation or of decomposition to amides.

Another advantage of this method is its use with aqueous systems for the preparation of otherwise unobtainable derivatives such as those from N-methyltaurine and sarcosine. Such compounds were not readily obtained by ester aminolysis, and usually are prepared through acid chlorides.

The mixed carboxylic-carbonic anhydride method has permitted preparation of many new hydroxy acid amides that would be unobtainable with other methods except through elaborate schemes of hydroxyl masking. The lack of interference from the alcohol functions coupled with speed, simplicity, applicability, and low steric sensitivity offers an opportunity for the rapid preparation of amide bonds with unbranched, aliphatic, carboxylic acids and amines of considerable steric bulk under mild conditions and in good yields.

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