Synthetic and Mass Spectral Study of Bis Ritter Adducts from Some Dienoic Fatty Acids

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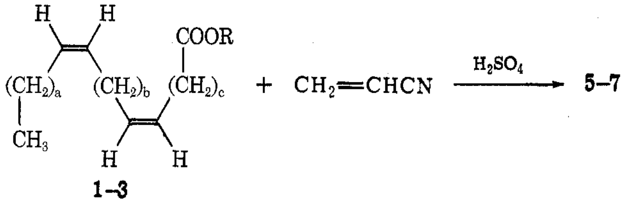
The Ritter reactions of some long-chain dienoic and hydroxymonoenic acids with acrylonitrile were investigated. The low temperature reactions of linoleic and 5,13-docosadienoic acid derivatives gave good yields of the respective bisacryloamides. In analogy to monoacrylamido fatty acid derivatives, it was possible to determine the addition sites in the Ritter products from the former dienoic fatty acids by mass spectrometry. For comparison, the synthesis and mass spectral study of 1,8-dipropionamido-*p*-menthane are also included.

In a preceding paper[1] we described the preparation and the mass spectral cracking patterns of some new Ritter adducts emerging from the reaction between acrylonitrile and long-chain monoenic fatty acids or their esters. It was shown that the assignment of the addition sites in the Ritter products is now possible by mass spectrometry.

The present investigation consists of extending the synthetic studies of the Ritter reaction to some dienoic (**1**–**3**) and hydroxymonoenic fatty acids and their esters (see Scheme I) and presenting a study of the behavior of bis Ritter adducts under electron impact. Evidence is adduced, showing that mass spectral analysis can also be applied for the assignment of the double bond positions in dienoic fatty acids.

SCHEME I

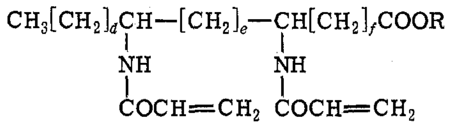


1–3

$CH_3[CH_2]_5CHOHCH_2CH{=}CH[CH_2]_7COOH$ +

4

$CH_2{=}CHCN \xrightarrow{H_2SO_4}$ **8**



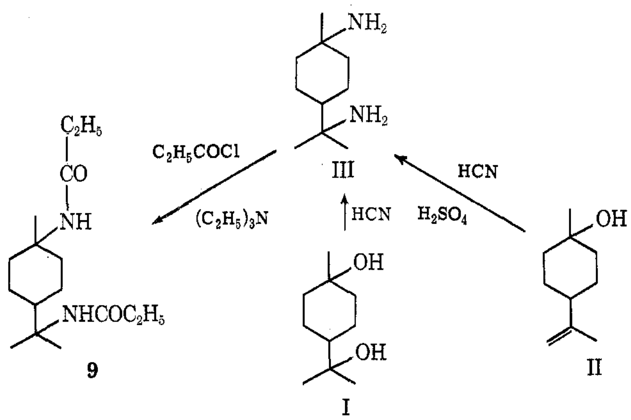
$$CH_3[CH_2]_d\underset{\underset{COCH=CH_2}{|}{NH}}{CH}-[CH_2]_e-\underset{\underset{COCH=CH_2}{|}{NH}}{CH}[CH_2]_fCOOR$$

5–8

1, $a = 4$; $b = 1$; $c = 7$; $R = CH_3$
2, $a = 4$; $b = 1$; $c = 7$; $R = C_2H_5$
3, $a = 7$; $b = 6$; $c = 3$; $R = CH_3$
5, $(d + e + f) = 14$; $R = CH_3$
6, $(d + e + f) = 14$; $R = C_2H_5$
7, $(d + e + f) = 18$; $R = CH_3$
8, $(d + e + f) = 14$; $R = CH_3$

To shed light on molecular environment influences on the primary reaction in the mass spectra of diamides structurally related to Ritter bis adducts (rupture of the C–C bond α to the amido group), we included in this study the preparation and the mass spectral fragmentation of the hitherto unknown 1,8-dipropionamido-*p*-menthane (**9**). As delineated in Scheme II, **9** was prepared by exposing the known 1,8-diamino-*p*-menthane (III) to the action of propionyl chloride in the presence of triethylamine. The terpenic diamine (III) could be obtained in good yields from the Ritter reaction of either 1,8-terpin (I) or β-terpineol (II) with hydrogen cyanide in the presence of concentrated sulfuric acid.[2]

SCHEME II



Earlier workers have noted that, unlike the long-chain C_{18}-monoenic acids, the Ritter reaction of linoleic acid with hydrogen cyanide resulted in poor yields of an unidentified product.[3] By contrast, the similar reaction between ricinoleic acid (**4**) and hydrogen cyanide afforded the monoadduct $CH_3[CH_2]_5CHOH[CH_2]_2CH(NHCHO)[CH_2]_xCOOH$ in 80% yield.[3]

It is significant to note that the Ritter reaction of **4** seems to involve essentially the double bond, leaving the hydroxyl function intact.

This study provides the first report on the successful preparation of methyl and ethyl bis(acrylamido)stearate (**5** and **6**, respectively) in 25–32% yield from the Ritter reaction of acrylonitrile with linoleic acid, followed by treatment with the appropriate alcohols, and of methyl bis(acrylamido)docosanoate (**7**) from **3** in remarkably good yield (55%). This entailed the exposure of the appropriate substrates (**1**–**4**) to the action of acrylonitrile in the presence of concentrated sulfuric acid first at −50° and then up to −10°. Finally, it was kept at 20–27° for 45 min before being processed in the usual fashion.

In the reaction of **1** with acrylonitrile we were able to detect the formation of some isomeric monoadducts in

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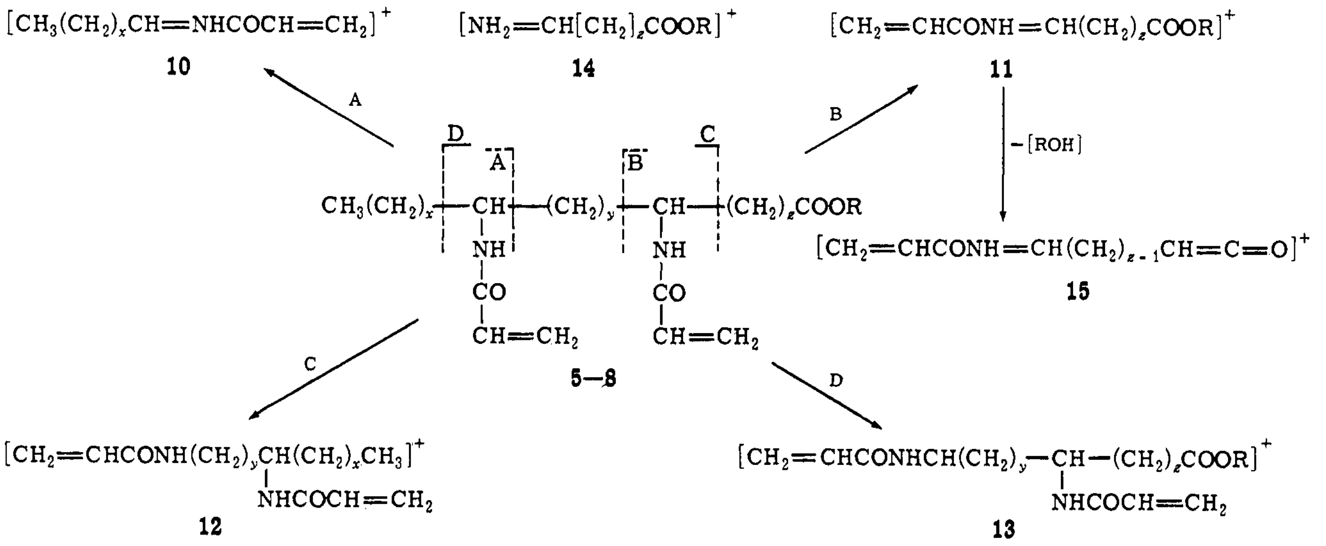
[1] S. Blum, S. Gertler, S. Sarel, and D. Sinnreich, *J. Org. Chem.*, **37**, 3114 (1972).

[2] N. M. Bortnick, British Patent 681,688; U. S. Patent 2,632,022; *Chem. Abstr.*, **48**, 727f, 4003h (1954).

[3] E. T. Roe and D. Swern, *J. Amer. Chem. Soc.*, **77**, 5408 (1955).

SCHEME III



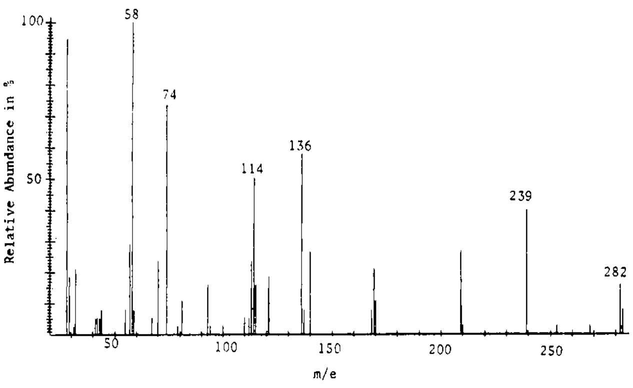


Figure 1.—Mass spectrum of 1,8-dipropionamido-*p*-mehthane.

very small yields. In the case of **3**, where the two double bonds are separated by a chain of six methylene groups, no appreciable amounts of the respective monoadducts could be observed under similar reaction conditions. The two double bonds in **3** do not appear to exhibit differences in reactivity toward acrylonitrile.

Mass Spectra.—On the basis of the electron-induced fragmentation of monoacrylamides of fatty acid esters described in a preceding paper,[1] it is expected that under electron impact each of the bisacrylamido fatty acid esters presented here (**5–8**) would generate four characteristic imidium ions (**10–13**) (see Scheme III) associated with four α cleavages (A, B, C, and D in Scheme III). It is plausible to assume that the recognition of these fragmentation products could ultimately lead to the determination of the addition sites in the Ritter reaction of long-chain dienoic acids and derivatives.

In parallel to mono Ritter adducts from monoenic fatty acid esters, the ion of highest mass-to-charge ratio in the mass spectra of fatty bisacrylamido acid esters (**5–8**) is again the acrylium ion, $CH_2{=}CH{-}{}^+C{\equiv}O$ (m/e 55) (see Tables I–IV). As expected, the most prominent peaks in the mass spectra of **5–8** correspond to ions of structures **10–13**, resulting from α cleavages at both sides of the C–N bond (fragmentation routes A to D in Scheme III). However, the intensities of iminium ions of structure **14**, resulting from expulsion of a ketene molecule from **11** or of acrylium ions of structure **15** (from ejection of an alcohol molecule from **11**) in the mass spectra of **5–8**, are relatively weak in comparison to corresponding peaks in the Ritter products from monoenic fatty acids. Most significantly, in the mass spectra of **5–8**, the intensities of peaks corresponding to ions of structure **13**, which contain all of the functional groups of the parent molecule (fragmentation type D), are notably weaker than those corresponding to ions of structure **12**, resulting from an expulsion of an ester radical $\cdot CH_2(CH_2)_{z-1}COOR$ (fragmentation type C). However, the relative abundance of ions of structure **13** in the mass spectra of **6** and **8** increases, by one order of magnitude, as the carbon chain on either moiety of the fatty acid ester increases (compare Tables I, II, and IV).

Simple analysis shows that the prominent ions in the mass spectra of **5**, **6**, and **8** could originate from mixtures of ionized molecules of structures as formulated, where the acrylamido nitrogens are preferably attached to carbons 9, 12, or 13 of the fatty acid carbon chain.

Mass spectral analysis of **7** (Table IV) suggests that this Ritter product comprises a complex mixture of positional isomers in which the site of attachment of the entering amido groups stretches from carbons 6 to 15, clustering around carbons 8 and 12 of the fatty acid long chain.

In analogy to tetramethylated lysine ethyl ester,[4] to alicyclic amines,[5] and to propionamido fatty acid derivatives,[1] the predominant peak in the mass spectra of **9** (Figure 1) corresponds to ions of structures **18** and **19**, resulting from rupture of the C–C bond α to the amido group (**9** → **18** conversion), which upon expulsion of methylketene[5a] gives rise to the iminium ion **19** (base peak). Other prominent peaks in the mass spectrum of

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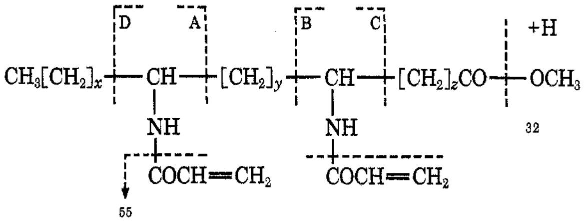
(4) K. Biemann, "Mass Spectrometry of Organic Chemical Applications," McGraw-Hill, 1962, Chapter 7B, pp 278–280.

(5) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, Chapter 8, pp 304–322.

(5a) NOTE ADDED IN PROOF.—J. A. Ballantine and R. G. Fenwick [*Org. Mass Spectrom.*, **2**, 1145 (1969)] have noted that the [M − 68] ion in the mass spectra of griseofulvin analogs results from an elimination of C_4H_4O unit ($CH_3CH{=}C{=}C{=}O$) from ring C and is often accompanied by a metastable ion.

TABLE I

RELATIVE ABUNDANCE (PER CENT) OF PROMINENT IONS (A, B, B-32, B-54, C, AND D) IN THE MASS SPECTRA OF METHYL BIS(ACRYLAMIDO)STEARATE (5)



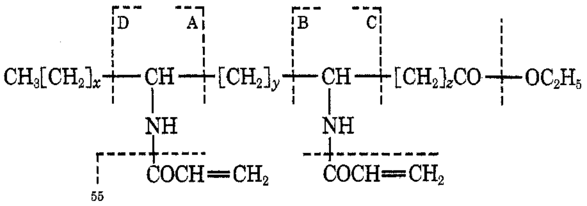
$$CH_3[CH_2]_x-\underset{\underset{COCH=CH_2}{|}}{\underset{|}{\underset{NH}{CH}}}-[CH_2]_y-\underset{\underset{COCH=CH_2}{|}}{\underset{|}{\underset{NH}{CH}}}-[CH_2]_zCO-OCH_3$$

base peak (*m/e* 55) = 100%

Site of attachment	A		D		Site of attachment	B		B-32		B-54		C	
	m/e	Rel abund	*m/e*	Rel abund		*m/e*	Rel abund	*m/e*	Rel abund	*m/e*	Rel abund	*m/e*	Rel abund
C-10	196	13	323	1.6	C-5	184	3	152	12	130	2.5	335	3
C-11	182	17	337	1.6	C-6	198	9	166	12	144	5	321	8
C-12	168	29	351	0.4	C-7	212	15	180	13	158	8	307	14
C-13	154	44	365	2.9	C-8	226	20	194	14	172	8	293	19
C-14	140	27	379	3.8	C-9	240	24	208	27	183	13	279	20
					C-10	254	10	222	14	200	4	265	12

TABLE II

RELATIVE ABUNDANCE (PER CENT) OF PROMINENT PEAKS IN THE MASS SPECTRA OF ETHYL BIS(ACRYLAMIDO)STEARATE (6)



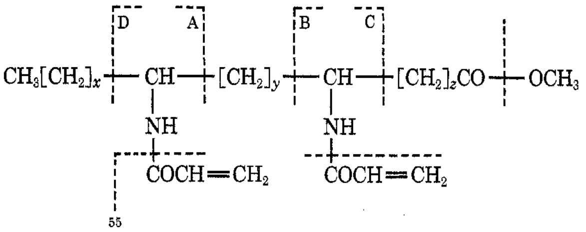
$$CH_3[CH_2]_x-\underset{\underset{COCH=CH_2}{|}}{\underset{|}{\underset{NH}{CH}}}-[CH_2]_y-\underset{\underset{COCH=CH_2}{|}}{\underset{|}{\underset{NH}{CH}}}-[CH_2]_zCO-OC_2H_5$$

base peak (*m/e* 55) = 100%

Site of attachment	A		D		Site of attachment	B		B-46		B-54		C	
	m/e	Rel abund	*m/e*	Rel abund		*m/e*	Rel abund	*m/e*	Rel abund	*m/e*	Rel abund	*m/e*	Rel abund
C 10	196		337	1	C-5	198	3	152	2	144	0.8	335	2
C-11	182	14	351	2	C-6	212	5	166	3	158	1.4	321	5
C 12	168	20	365	3	C-7	226	18	180	4	172	2.2	307	19
C-13	154	27	379	8	C-8	240	22	194	0	186	4.0	293	25
C-14	140	15	393	8	C-9	254	53	208	13	200	8.4	279	26
					C-10	268	16	222	10	214	3.8	265	13

TABLE III

RELATIVE ABUNDANCE (PER CENT) OF PROMINENT IONS IN THE MASS SPECTRA OF RITTER PRODUCT (8) FROM METHYL RICINOLEATE AND ACRYLONITRILE



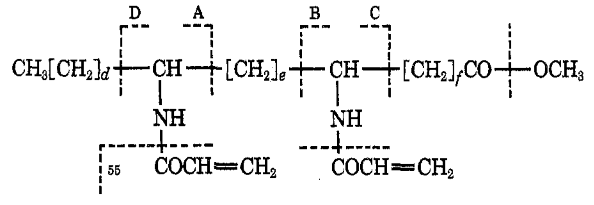
$$CH_3[CH_2]_x-\underset{\underset{COCH=CH_2}{|}}{\underset{|}{\underset{NH}{CH}}}-[CH_2]_y-\underset{\underset{COCH=CH_2}{|}}{\underset{|}{\underset{NH}{CH}}}-[CH_2]_zCO-OCH_3$$

base peak (*m/e* 55) = 100%

Site of attachment	A		D		Site of attachment	B		B-32		B-54		C	
	m/e	Rel abund	*m/e*	Rel abund		*m/e*	Rel abund	*m/e*	Rel abund	*m/e*	Rel abund	*m/e*	Rel abund
C-10	196	6	323	2	C-5	184	5	152	1	130	0.5	335	6
C-11	182	11	337	1	C-6	198	6	166	2	144	1.0	321	6
C-12	168	24	351	2.5	C-7	212	12	180	4	158	2.5	307	17
C-13	154	26	365	5	C-8	226	15	194	5	172	3.0	293	21
C-14	140	21	379		C-9	240	19	208	7	186	3.5	279	23
					C-10	254	10	222	5	200	1.5	265	8

TABLE IV

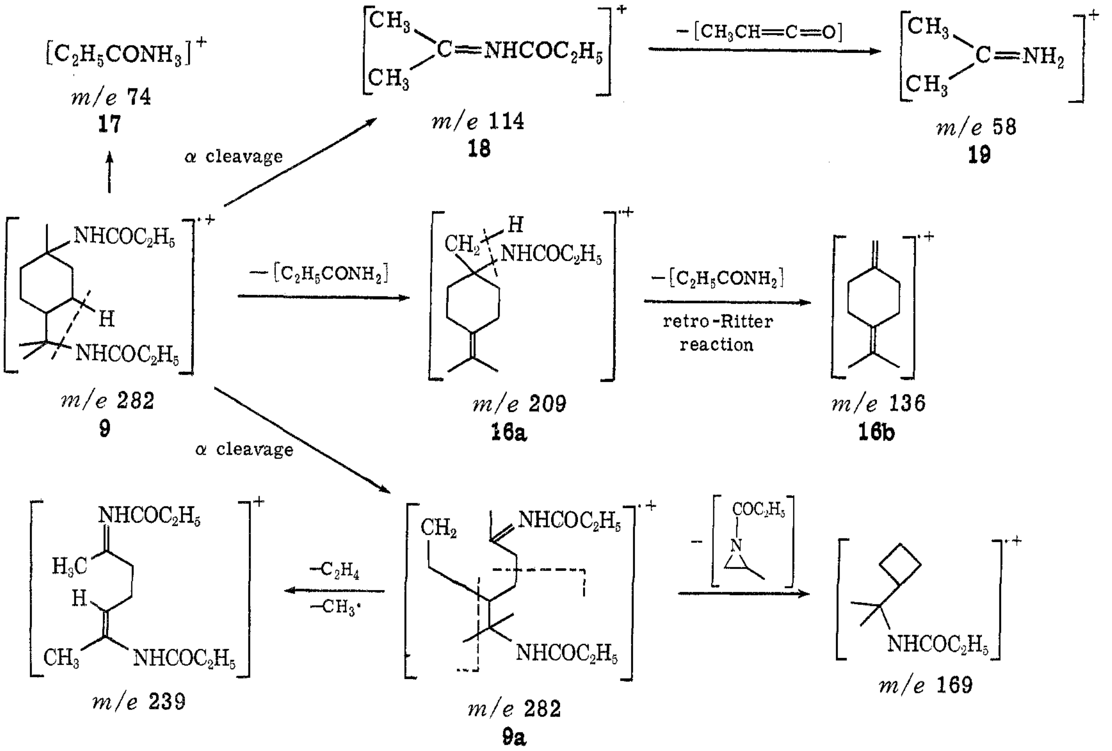
RELATIVE ABUNDANCE OF PROMINENT PEAKS (A, B, C, D, B-54, AND B-32) IN THE MASS SPECTRA OF METHYL BIS(ACRYLAMIDO)DOCOSANOATE (**7**)


$CH_3[CH_2]_d-CH(NHCOCH{=}CH_2)-[CH_2]_e-CH(NHCOCH{=}CH_2)-[CH_2]_fCO-OCH_3$

base peak (*m/e* 55) = 100%; $(d + e + f) = 18$

Site of attachment	A *m/e*	A Rel abund	D *m/e*	D Rel abund	Site of attachment	B *m/e*	B Rel abund	B-54 *m/e*	B-54 Rel abund	B-32 *m/e*	B-32 Rel abund	C *m/e*	C Rel abund
C-15	182	31	337	9	C-6	198	19	144	23	166	15	377	9
C-14	196	35	351	10	C-7	212	21	158	37	180	16	363	16
C-13	210	38	365	11	C-8	226	25	172	50	194	18	349	27
C-12	224	42	379	15	C-9	240	24	186	46	208	16	335	37
C-11	238	30	393	14	C-10	254	20	200	26	222	15	321	8
C-10	252	20	407	12	C-11	268	15	214	11	236	12	307	6

SCHEME IV



9 correspond to ions of masses 239 and 169, resulting from α cleavage (**9** → **9a**) followed by either the successive losses of methyl and ethylene or the loss of propionamidomethylaziridine, and to ions of structure **16a**–**16b** and **17**, which probably emerge from the successive retrograde Ritter reactions involving the McLafferty rearrangement (**9** → **16**, **9** → **16a** → **16b**, and **9** → **17** conversions) with retention of charge by either moiety (Scheme IV). It is clear from the above discussion that the rupture of the C–C bond α to the amido groups in the diacrylamido fatty acid esters **1**–**3** occurs at a considerably faster rate than the elimination of fragment *m/e* 74 which involves the breakage of one C–C and one C–H bond (McLafferty rearrangement). Qualitatively, the situation in **9** is similar to that in **1**–**3** in the sense that the McLafferty rearrangements (**9** → **16**, **9** → **17** conversions) occur somewhat slower than the α cleavage processes, **9** → **18** → **19** and **9** → **9a** → *m/e* 239.[6]

Experimental Section

Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were taken on a Jeol C-60H spectrometer, using Me_4Si as internal standard.

Materials and Sources.—The sources for the purchased chemicals are given in parentheses. They were of "chemically pure" grade and employed as received: ethyl linoleate (**2**) (Fluka); 1,8-diamino-*p*-menthane (Fluka); and acrylonitrile (British Drug House) (bp 72–73°, 690 mm). Silicic acid (100 mesh) for chromatography (Mallinckrodt) was of analytical grade.

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(6) On the other hand, according to ref 5, p 337, the energy requirements for the McLafferty rearrangement in *n*-butyramide are considerably lower than those for α cleavage.

Methyl linoleate, (**1**), bp 164–169° (1 mm), was prepared from safflower oil by the method described.[7]

Methyl ricinoleate (**4**) was prepared from castor oil according to the literature.[8]

Methyl *cis,cis*-5,13-docosenoate (**3**), bp 180–184° (1 mm) [lit.[9] bp 153–156° (0.005 mm)], was obtained according to the literature[9] in 3–4% yield.

Methyl Bis(acrylamido)docosanoate (**7**). **The Ritter Reaction of Methyl *cis,cis*-5,13-Docosadienoate.**—To a stirred solution of 3 g of methyl *cis,cis*-5,13-docosadienoate (**3**) and 14 g of acrylonitrile at −50° there was added rapidly (during 3–4 min) 9 ml of concentrated sulfuric acid. The external cooling must be as efficient as to keep the internal temperature below −10° during the addition of the acid. The cooling bath was removed and the mixture was allowed to warm up to 27°. Stirring was continued for 45 min at 27°; the mixture was then cooled to 0°, 10 ml of methanol being added, and left to stand overnight at ambient temperature. The mixture was poured onto crushed ice and the resulting oil was taken up in chloroform. Upon the usual work-up, the residue was chromatographed on a column packed with a mixture of 90 g of Florisil (200–300 mesh) and 45 g of Celite, which was successively eluted by cyclohexane, benzene, ether, and methanol. The ether eluate was rechromatographed on a column packed with a mixture of 90 g of silicic acid and 45 g of Celite, using cyclohexane, benzene, benzene–ether (2:1), ether, and methanol as eluents. The first eluted fraction (benzene–ether) consisted of monoacrylamido esters, mainly of methyl 5-eicosenoate arising from contaminants present in the starting ester, and small amounts (3–5%) of the normal monoaddition of the nitrile to the dienic ester (shown by mass spectroscopy). Later fractions eluted by the benzene–ether mixture comprised the isomeric methyl bis(acrylamido)docosanoate (2.35 g, 44%) in oil form: ir 3300 (NH), 1730 (C=O ester), 1610 (C=O amide), 1650, 980, 965 cm^{-1} (vinyl); nmr ($CDCl_3$) τ 3.78 (2 H, d), 3.42 (2 H, m), 4.43 (4 H, d), 6.08 (2 H, m), 6.35 (3 H, s), 7.70 (2 H, t), 8.0–9.0 (36 H, s), 9.12 (3 H, t, J = 5 Hz). The content of the fractions was analyzed by tlc, on Kieselgel G, using chloroform–methanol (48:2) as eluent. Saturated cupric sulfate solutions containing 0.5% of potassium permangante were used as spray reagents. On tlc, methyl bis(acrylamido)docosanoate (**13**) gives an elongated green spot (the background is violet) in the range of R_f 0.19 to 0.26, suggesting that the product comprises an isomeric mixture.

Anal. Calcd for $C_{29}H_{52}N_2O_4$: C, 70.7; H, 10.5; N, 5.5. Found: C, 70.9; H, 10.8; N, 5.6.

The Ritter Reaction of Methyl and Ethyl Linoleate.—Methyl linoleate does not appear to lend itself to straightforward Ritter reaction. When it is exposed to the action of acrylonitrile in the presence of concentrated sulfuric acid at about 15°, the reaction leads to a complex product mixture. It consists of (i) Ritter adducts of mono- and bis(acrylamido)stearates, (ii) isomerization products, (iii) unidentified polymeric substances, and (iv) unchanged starting material. The formation of polymeric substances could not be subdued even at much lower reaction temperatures.

Low Temperature Ritter Reaction of Methyl Linoleate.—A well-stirred mixture of methyl linoleate (**1**) (2 g) and acrylonitrile (1 g) was cooled in solid carbon dioxide–acetone bath (*ca.* −50°) while 4.2 ml of 98% H_2SO_4 was added dropwise during 40 min. The mixture was then processed in a way described for the **3** → **7** conversion. The crude reaction product was a dark-colored oil which could be purified by three successive chromatographies on a column packed with a mixture of Florisil (50 g) and Celite (25 g), using cyclohexane, benzene, ether, and methanol as eluting solvents, in the order described above. From the ether eluted fraction, 0.55 g of a colorless powder was isolated. The main reaction product consisted of polymeric materials which did not migrate on preparative thin-layer chromatographic plates.

The Ritter Reaction of Ethyl Linoleate and Acrylonitrile.—Ethyl linoleate (**2**) (3.08 g, 0.01 mol) was exposed to the action of acrylonitrile (0.03 mol) and 98% H_2SO_4 (12 g) during 40 min, below 18°, and processed as described for the **1** → **5** conversion. Column chromatography yielded the respective monooctadec-12-enoate, together with the desired ethyl bis(acrylamido)stearate (**6**), in oil forms (25% yield total). After several successive chromatographies (10:1 silica gel–Celite), it was possible to induce both **6** and the monooctadec-12-enoate to recrystallize from acetone at low temperature, with great losses of material. The bisamide (**6**) was obtained as colorless crystals of mp 107–110°; ir (KBr) 3255, 1737, 1625, 1660, 978, and 95 cm^{-1}; nmr ($CDCl_3$) τ 3.78 (2 H, α), 4.05 (2 H, m), 4.40 (4 H, d), 5.98 (2 H, m), 6.33 (3 H, s), 7.70 (2 H, t, J = 7.0 Hz), 8.2–9.0 (28 H), 9.12 (3 H, t, J = 5.0 Hz). The monoamide consisted of a wax-like material (no melting point). On tlc **6** appears at the lower region of the chromatogram, R_f 0.2–0.27, whereas the monoadduct had a higher R_f value, between 0.4 and 0.44, as expected.

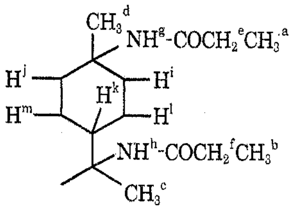
The Reaction of Methyl Ricinoleate (**4**) **with Acrylonitrile.**—A mixture of **4** (2 g) and acrylonitrile (1 g) was cooled to −50° and treated with 4.2 ml of sulfuric acid in the manner described above. The colorless reaction mixture thus obtained was subjected to chromatography, using a column packed with a mixture of 50 g of Florisil and 25 g of Celite and the same eluting solvents. The ether eluted 1.10 g of methyl bis(acrylamido)stearate (**8**) as semisolid material, ir (KBr) 3300, 1730, 1610, 1650, 980, and 965 cm^{-1}, and 0.18 g of **4**, but no monoacrylamide could be isolated.

Anal. Calcd for $C_{25}H_{44}N_2O_4$: C, 68.9; H, 10.1; N, 6.4. Found: C, 68.5; H, 10.6; N, 6.3.

Nmr ($CDCl_3$): τ 9.12 (3 H, t, J = 5 Hz), 9.0–8.2 (28 H, m), 7.70 (2 H, t, J = 7 Hz), 6.33 (3 H, m, methoxyl), 5.98 (1 H, m), 4.40–3.78 (6 H, vinylic protons), 4.05 (2 H, m, NH).

Preparation of 1,8-Dipropionamido-*p*-menthane (**9**).—To a cooled (ice) mixture of 1,8-diamino-*p*-menthane (3.4 g, 20 mmol) and 5 g (50 mmol) of triethylamine in 20 ml of dry ether was added with stirring a solution of 4.6 g (50 mmol) of propionyl chloride in 15 ml of ether. An immediate precipitate of [$Et_3N \cdot HCl$] is formed. The resulting mixture is allowed to stand overnight, filtered, and then washed with water, leaving on the funnel the crude diamide. Tlc analysis shows that the diamide thus obtained is chemically pure. An analytical sample of **9**, mp 124–126°, was obtained by preparative tlc (silica plates, chloroform as developing solvent) followed by trituration with ether.

Anal. Calcd for $C_{13}H_{30}N_2O_2$: C, 68.1; H, 10.6. Found: C, 67.9; H, 10.5.



Nmr ($CDCl_3$): τ 4.73 (1 H, broad s, $H^{g/h}$), 4.86 (1 H, broad s, $H^{g/h}$), 7.84 (2 H, q, $H^{e/f}$), J = 7.5 Hz), 7.87 (2 H, q, $H^{e/f}$), J = 7.5 Hz), 8.2–7.4 (9 H, m, H^{i-m}), 8.65 (3 H, s, H^{d}), 8.73 (6 H, s, H^{c}), 8.87 (6 H, t, $H^{a/b}$), and 8.89 (3 H, t, $H^{a/b}$).

Registry No.—**1,** 112-63-0; **2,** 544-35-4; **3,** 2566-96-3; **4,** 141-24-2; **5** or **8,** 35039-28-2; **6,** 35039-29-3; **7** or **13,** 35039-30-6; **9,** 35046-17-4; acrylonitrile, 107-13-1.

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