When N-methylpanamine was subjected to identical air-oxidation conditions, an ether-insoluble product was obtained. This substance had the same physiological properties as oxypanamine, and it seems reasonable to conclude that analogous structural changes occurred in this case.

Reduction of oxypanamine in zinc–acetic acid gave a mixture of ether-soluble bases. It was anticipated that panamine would be among the products, but an examination of the mixture indicated four products (R_f 0.59 (major product), 0.30, 0.20 and 0.09 (trace) in system A), none of which was panamine.

Two functional groups that might be formed during air oxidation include a hydrated *t*-amine oxide group,[7] and an amide group; we are currently of the belief that the oxide group probably is present.

N-Methylpanamine.—A solution of 1.00 g. of panamine hydrate in 75 ml. of 20% acetic acid containing 5 ml. of 37% formaldehyde was subjected to hydrogenation with 0.5 g. of 10% Pd–C Catalyst; the reduction was carried out in a Parr hydrogenator at room temperature for 15 hours. After removal of the catalyst by filtration, the solution was concentrated under reduced pressure and the organic base was isolated by extraction of the alkaline solution (solid potassium carbonate was added) with chloroform. The yield was 0.75 g.; this material gave a single alkaloid spot on paper chromatography in the usual system (R_f 0.70). An analytical sample was obtained by sublimation *in vacuo;* the product formed colorless prisms, m.p. 101–102°, $[\alpha]^{25}_{436}$ +19.1°, $[\alpha]^{25}_{589}$ +5.3° (*c* 0.715, ethanol).

Anal. Calcd. for $C_{21}H_{35}N_3$: C, 76.54; H, 10.71; N, 12.75; NCH_3, 9.12 (two). Found: C, 76.47; H, 10.70; N, 12.66; NCH_3, 3.80; CCH_3, none; active H, none.

The dipicrate of N-methylpanamine was recrystallized from ethyl acetate; m.p. 130–134° dec.

Anal. Calcd. for $C_{21}H_{35}N_3 \cdot 2C_6H_3N_3O_7$: C, 50.31; H, 5.25; N, 16.00. Found: C, 50.25; H, 5.29; N, 15.75.

The diperchlorate was prepared in ethanol and recrystallized from methanol; m.p. 178–179°.

Anal. Calcd. for $C_{21}H_{35}N_3 \cdot 2HClO_4$: C, 47.55; H, 7.03; N, 7.92. Found: C, 47.44; H, 7.08; N, 7.88.

The methiodide was prepared by adding an excess of methyl iodide to a solution of N-methylpanamine in methanol. It was recrystallized from methanol–ether to yield an analytical sample with m.p. 201–202°. The same methiodide was obtained when an aqueous solution of panamine methiodide (N-methylpanamine methiodide hydriodide) was treated with 40% sodium hydroxide solution. The gummy precipitate was extracted with chloroform, and after removal of the solvent the residue was recrystallized from methanol–acetone to yield N-methylpanamine methiodide. The m.p. of 201–202° was not depressed in mixture with a sample prepared from N-methylpanamine, and the infrared spectra were identical.

Anal. Calcd. for $C_{22}H_{38}N_3I \cdot CH_3OH$: C, 54.86; H, 8.41; N, 8.35. Found: C, 54.56; H, 8.13; N, 8.17.

This methiodide was converted to the hydriodide by the addition of solid potassium iodide to a solution of the methiodide in dilute acetic acid. The product was identical (m.p., infrared spectrum) with the methiodide hydriodide prepared from panamine.

Infrared spectra were obtained with a Perkin-Elmer model 21 instrument. The spectra for ormosinine, ormosanine, panamine hydrate and N-methylpanamine were taken for reference purposes.[8]

broad weak band at 6.02 μ. This band is not present in the spectrum of the anhydrous form (E. Y. Spencer, R. D. O'Brien and R. W. White, *J. Agric. Food Chem.*, **5**, 123 (1957)).

(7) Air oxidation is not a normal reaction route for the preparation of amine oxides, but in our experience the extended manipulation of *t*-amines in air may result in oxide formation.

(8) These spectra have been deposited as Document Number 5425 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the Document number and by remitting in advance $1.25 for photoprints or $1.25 for 35 mm. microfilm, payable to Chief, Photoduplication Service, Library of Congress.

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Amino Acids. V. 1,3-Di-(ω-carboxyalkyl)-thioureas and Their Chemistry

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A series of 1,3-di-(carboxyalkyl)-thioureas have been prepared by condensing the alkali salts of amino acids with carbon disulfide. These thiourea derivatives have been oxidized to the corresponding urea derivatives with either sodium hypochlorite or hydrogen peroxide solutions. The urea and thiourea dibasic acid derivatives were esterified with various alcohols in the presence of acid catalysts. Dehydration of 1,3-di-(γ-carboxypropyl)-thiourea and 1,3-di-(γ-carboxypropyl)-urea gave, respectively, 1-(γ-carboxypropylthiocarbamyl)-2-pyrrolidone and 1-(γ-carboxypropylcarbamyl)-2-pyrrolidone. Unsymmetrical urea derivatives have been prepared by the reaction of amines with 1-nitroso-1,3-di-(ω-carboxylalkyl)-ureas. 1-Nitroso-1,3-di-(ω-carboxydecyl)-urea combines with excess hexamethylenediamine to give a new amino acid, 1-(ω-aminohexyl)-3-(ω-carboxydecyl)-urea.

Recently[1] the preparation of 1,3-di-(carboxyalkyl)-ureas by the reaction of phosgene with amino acids was reported. Prior to this work, 1,3-di-(θ-carboxyoctyl)-urea[2] (m.p. 158°) and 1,3-di-(ω-carboxyhenicosanyl)-urea[3] (m.p. 110°) were described as by-products in the preparation of θ-aminopelargonic acid and ω-aminobehenic acid, respectively. The present work describes a number of new urea and thiourea derivatives of amino acids and new procedures for their preparation.

The amino acids with the exception of 15-aminopentadecanoic acid, which were used in this investigation, were prepared by the hydrolysis of the corresponding lactams. 15-Aminopentadecanoic acid hydrochloride (VII) was synthesized from 1,14-dicarboxytetradecane (I) by the following series of reactions which were used by Triebs and Hauptmann[4] in the synthesis of ω-amino acids from dicarboxylic acids.

The 1,3-di-(ω-carboxyalkyl)-thioureas (XI) listed in Table I were prepared by condensing two equivalents of an ω-amino acid with one equivalent of carbon disulfide in the presence of two equivalents of sodium or potassium hydroxide. The hydrolysis of the lactams VIII to the amino acids IX and the condensation of the amino acids with carbon disulfide have been combined to give, in gen-

(1) Thüringsche Zellwolle German Patent Appl. T 4485.

(2) B. Flaschenträger and F. Halle, *Z. physiol. Chem.*, **192**, 253 (1930).

(3) B. Flaschenträger, B. Blechman and F. Halle, *ibid.*, **192**, 257 (1930).

(4) W. Triebs and S. Hauptmann, *Ber.*, **89**, 117 (1956).

$$\underset{\text{I}}{HOOC(CH_2)_{14}COOH} \xrightarrow[HCl]{EtOH} \underset{\text{II}}{EtOOC(CH_2)_{14}COOEt} \longrightarrow \underset{\text{III}}{HOOC(CH_2)_{14}COOEt} \xrightarrow{SOCl_2} \underset{\text{IV}}{ClOC(CH_2)_{14}COOEt} \xrightarrow{NH_3}$$

$$\underset{\text{V}}{NH_2OC(CH_2)_{14}COOEt} \xrightarrow[MeONa]{Br_2} \underset{\text{VI}}{MeOCONH(CH_2)_{14}COOEt} \xrightarrow{HCl} \underset{\text{VII}}{HCl\cdot NH_2(CH_2)_{14}COOH}$$

eral, good yields (82–97%) of the corresponding 1,3-di-(ω-carboxyalkyl)-thioureas (XI). This procedure has been employed also to synthesize one branched chain thiourea dibasic acid, namely, 1,3-di-(α-methyl-γ-carboxypropyl)-thiourea. The esters of these thiourea dibasic acids, which are listed in Table II, were prepared in the usual manner by acid-catalyzed esterification. 1,3-Di-(ε-carbomethoxypentyl)-thiourea also was prepared by the condensation of methyl ε-aminocaproate with carbon disulfide.

oxidation of the corresponding thiourea derivative with either sodium hypochlorite or hydrogen peroxide solutions were unsuccessful. 1,3-Di-(ω-carboxytetradecyl)-urea was prepared finally by refluxing the diethyl ester of 1,3-di-(ω-carboxytetradecyl) thiourea in an aqueous ethanol solution of silver nitrate. This method of converting thioureas into ureas, which was first described by Kjaer, *et al.*,[6] gave an 86% yield of the diethyl ester of 1,3-di-(ω-carboxytetradecyl)-urea. This diethyl ester on

TABLE I

$$HOOC(CH_2)_nNHCNH(CH_2)_nCOOH$$
$$\|$$
$$S$$

n	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
3	87.0	161–162	$C_9H_{16}N_2O_4S$	43.53	43.43	6.49	6.22	11.28	11.30	12.91	12.80
4	82.5	158–159	$C_{11}H_{20}N_2O_4S$	47.80	47.89	7.30	7.54	10.14	9.92	11.60	11.55
5	96.5	128–129	$C_{13}H_{24}N_2O_4S$	51.30	51.11	7.95	7.58	9.21	8.90	10.53	10.80
6	56.5	142–143[b]	$C_{15}H_{28}N_2O_4S$	54.19	54.58	8.49	8.77	8.43	8.73	9.65	9.61
10	89.0	136–137	$C_{23}H_{44}N_2O_4S$	62.13	61.88	9.97	10.02	6.30	6.30	7.21	7.04
14	82.0	121–122	$C_{31}H_{60}N_2O_4S$	66.85	66.36	10.86	10.65	5.03	5.32	5.76	5.57
[a]	21.0	155–156	$C_{11}H_{20}N_2O_4S$	47.80	48.01	7.30	7.61	10.14	9.87	11.60	11.51

[a] 1,3-Di-(α-methyl-γ-carboxypropyl)-thiourea. [b] Reported melting point 142–143°; German Patent 733,470, December 11 (1943).

TABLE II

$$ROOC(CH_2)_nNHCNH(CH_2)_nCOOR$$
$$\|$$
$$S$$

R	n	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
CH_3	3	80.0	48	$C_{11}H_{20}N_2O_4S$	47.80	47.56	7.29	7.12	10.13	10.00	11.60	11.55
C_2H_5	4	24.0	36–37	$C_{15}H_{28}N_2O_4S$	54.19	54.52	8.49	8.65	8.43	8.59	9.65	9.64
CH_3	5	85.0	51	$C_{15}H_{28}N_2O_4S$	54.19	53.83	8.49	8.69	8.43	8.60	9.65	9.40
C_2H_5	5	98.0	53–54	$C_{17}H_{32}N_2O_4S$	56.61	56.45	8.94	8.79	7.77	7.5	8.90	9.06
n-C_4H_9	5	11.9	29	$C_{21}H_{40}N_2O_4S$	60.54	60.73	9.68	9.75	6.72	6.59	7.69	7.51
n-C_8H_{17}	5	87.0	42	$C_{29}H_{56}N_2O_4S$	65.86	65.82	10.67	10.85	5.30	5.51	6.06	6.00
n-$C_{10}H_{21}$	5	93.0	53–54	$C_{33}H_{64}N_2O_4S$	67.75	67.89	11.03	11.06	4.79	4.69	5.48	5.31
n-$C_{14}H_{29}$	5	100.0	71	$C_{41}H_{80}N_2O_4S$	70.63	70.42	11.56	11.62	4.02	4.01	4.59	4.69
CH_3	6	73.0	46–47	$C_{17}H_{32}N_2O_4S$	56.63	56.91	8.95	8.86	7.77	7.91	8.89	8.81
C_2H_5	10	98.0	57	$C_{27}H_{52}N_2O_4S$	64.76	65.19	10.47	10.48	5.60	5.50	6.40	6.49
C_2H_5	14	86.0	75–76	$C_{35}H_{68}N_2O_4S$	68.58	68.97	11.18	11.08	4.57	4.58	5.23	5.30
C_2H_5	[a]	68.0	58	$C_{15}H_{28}N_2O_4S$	54.19	54.11	8.49	8.46	8.43	8.12	9.65	9.31

[a] Diethyl diester of 1,3-di-(α-methyl-γ-carboxypropyl)-thiourea.

The 1,3-di-(carboxyalkyl)-thioureas (XI) with the exception of 1,3-di-(ω-carboxytetradecyl)-thiourea (XI, n = 14) are converted into the corresponding 1,3-di-(carboxyalkyl)-ureas (XIV) in good yields (76–97%) by oxidation with either hydrogen peroxide or sodium hypochlorite in alkaline solution.[5] The reactions leading from the lactams to the 1,3-di-(carboxyalkyl)-ureas have been conducted without isolation of the intermediate

saponification with potassium hydroxide in [illegible] Cellosolve gave the desired 1,3-di-(ω-carbo[illegible] decyl)-urea (XIV, n = 14). The [illegible] method also was used to co[illegible] carbethoxydecyl)-thiourea [illegible] oxydecyl)-urea. Th[illegible] (carboxyalkyl)-ure[illegible] in Tables [illegible]

Table III

$HOOC(CH_2)_nNHCNH(CH_2)_nCOOH$ (C=O)

n	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
3	88	157–158	$C_9H_{16}N_2O_5$	46.54	46.47	6.94	7.01	12.07	11.62
4	76	194–195	$C_{11}H_{22}N_2O_5$	50.76	51.17	7.75	7.92	10.73	10.44
5	89	163–164[b]	$C_{13}H_{24}N_2O_5$	54.15	53.95	8.39	8.47	9.72	9.51
6	93	172–173	$C_{15}H_{28}N_2O_5$	56.94	56.76	8.92	8.89	8.85	9.05
10[a]	86	165–166	$C_{23}H_{44}N_2O_5$	64.45	64.42	10.35	10.30	6.54	6.50
14[a]	97	137–138	$C_{31}H_{60}N_2O_5$	68.83	69.02	11.18	11.20	5.18	5.28
[c]	59	164–165	$C_{11}H_{20}N_2O_5$	50.76	50.36	7.75	7.65	10.73	10.44

[a] Prepared from the ethyl esters of the corresponding thiourea dibasic acid by the silver nitrate method. [b] Reported m.p. 162–164°; P. Schlack, U. S. Patent 2,356,702, Aug. 22, 1944. [c] 1,3-Di-(α-methyl-γ-carboxypropyl)-urea.

Table IV

$ROOC(CH_2)_nNHCNH(CH_2)_nCOOR$ (C=O)

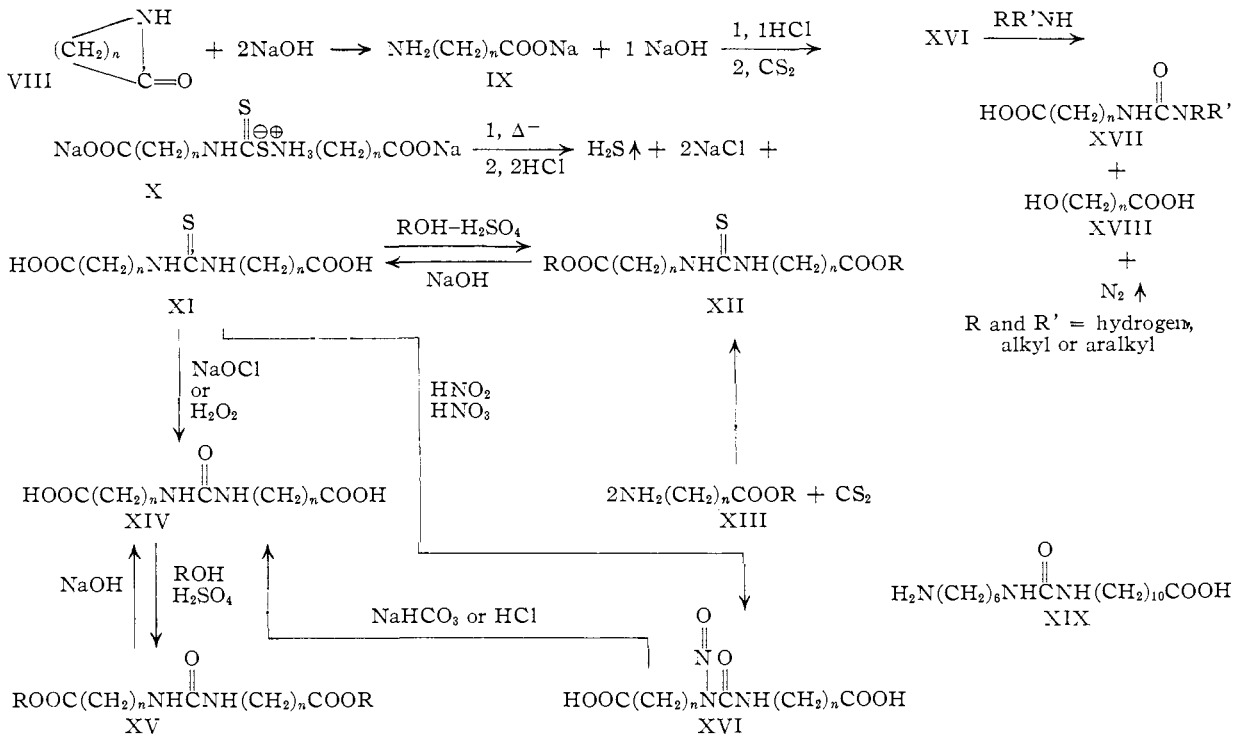
R	n	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	3	75	112	$C_{11}H_{20}N_2O_5$	50.75	50.84	7.74	7.50	10.76	10.59
n-C_4H_9	3	98	46	$C_{17}H_{32}N_2O_5$	59.27	59.37	9.36	9.45	8.13	8.01
n-C_8H_{17}	3	99	61	$C_{25}H_{48}N_2O_5$	65.75	65.86	10.31	10.61	6.32	6.02
n-$C_{10}H_{21}$	3	..	73	$C_{29}H_{56}N_2O_5$	67.92	67.81	11.09	11.18	5.46	5.31
n-$C_{14}H_{29}$	3	..	90.5	$C_{37}H_{72}N_2O_5$	71.10	71.23	11.61	11.59	4.48	4.42
CH_3	4	72	113	$C_{13}H_{24}N_2O_5$	54.15	54.25	8.39	8.36	9.72	9.70
CH_3	5	100	101.5	$C_{15}H_{28}N_2O_5$	56.93	57.00	8.92	9.06	8.86	8.85
n-C_4H_9	5	96	59.5	$C_{2\cdot}H_{40}N_2O_5$	62.96	62.99	10.06	10.16	6.99	6.80
n-C_8H_{17}	5	89	74.5	$C_{29}H_{56}N_2O_5$	67.92	67.99	11.08	11.04	5.46	5.18
n-$C_{10}H_{21}$	5	90	81.0	$C_{33}H_{64}N_2O_5$	69.66	69.46	11.34	11.35	4.92	4.71
n-$C_{14}H_{29}$	5	98	91.5	$C_{41}H_{80}N_2O_5$	72.29	71.93	11.84	11.86	4.11	4.10
CH_3	6	50	103	$C_{17}H_{32}N_2O_5$	59.28	59.06	9.36	9.41	8.13	8.39
C_2H_5	10	89[a]	97	$C_{27}H_{52}N_2O_5$	66.90	66.64	10.82	10.72	5.78	5.71
C_2H_5	14	86[a]	103	$C_{35}H_{68}N_2O_5$	70.42	70.38	11.48	11.17	4.69	4.86
CH_3	[b]	90	130	$C_{13}H_{24}N_2O_5$	54.15	54.54	8.39	8.51	9.72	9.41

[a] Prepared from the diethyl ester of the corresponding thiourea dibasic acid by the silver nitrate method. [b] Dimethyl ester of 1,3-di-(α-methyl-γ-carboxypropyl)-urea.

If the nitrosation is carried out in sulfuric acid solution, the corresponding 1-nitroso-1,3-di-(ω-carboxyalkyl)-thioureas are formed. 1-Nitroso-1,3-di-(ε-carboxypentyl)- and 1-nitroso-1,3-di-(ω-carboxydecyl)-ureas were denitrosated in acid or basic media to give the respective 1,3-di-(ε-carboxypentyl)- and 1,3-di-(ω-carboxydecyl)-ureas. The generally low yields obtained in the denitrosation reaction are considered to be partly due to the ease of scission of the C–N bond between the nitrosamide nitrogen and the carbonyl carbon. This facile rupture of the C–N bond makes these nitrosides valuable intermediates for the synthesis of urea derivatives. Thus 1-nitroso-1,3-di-
...lkyl)-ureas (XVI) combine with
...volution of nitrogen to give unsym-
...ives (XVII). A number of
...ther with some of their
...able V.
...oso-1,3-di-(ε-car-
...known[7] hydroxycaproic acid hydrazide.[8,9] Thus the other product from this reaction must be ε-hydroxycaproic acid (XVIII, $n = 5$).

A new amino acid, 1-(ω-aminohexyl)-3-(ω-carboxydecyl)-urea (XIX) was prepared in 78% yield by the reaction of 1.5 mole equivalents of hexamethylenediamine with 1-nitroso-1,3-di-(ω-carboxydecyl)-urea (XVI, $n = 10$). This amino acid was extremely insoluble in water and the common organic solvents. These reactions of the 1-nitroso-1,3-di-(ω-carboxyalkyl)-ureas are similar to those obtained in the treatment of nitrosamides with amines.[10]

An attempt to prepare unsymmetrically substituted thiourea and urea dibasic acid derivatives by the reaction of amino acids with carbon disulfide presented difficulties. The disodium salt of ε-carboxypentyldithiocarbamic acid (XX) was prepared by the method described by Cook, *et al.*,[11] for the preparation of the disodium salt of carboxymethyldithiocarbamic acid. The solution

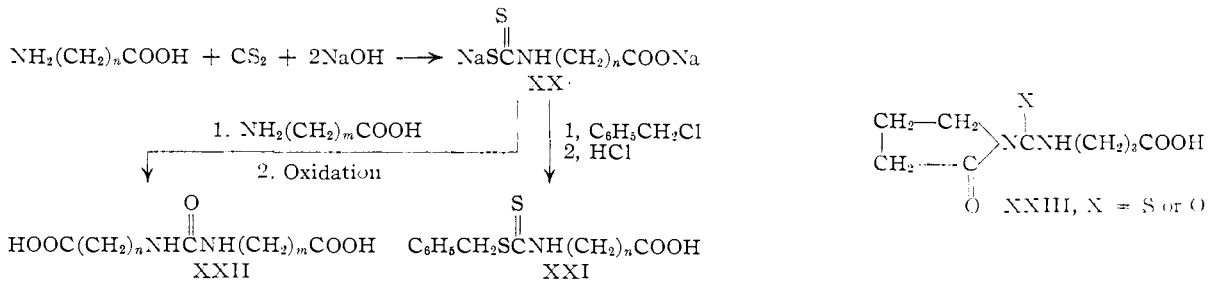


containing the disodium salt of the dithiocarbamic acid XX on refluxing with one equivalent of γ-aminobutyric acid evolved hydrogen sulfide. The final clear solution on acidification gave a mixture of thiourea dibasic acid derivatives. This mixture could not be resolved by crystallization and the complex mixture was oxidized. The crude oxidation product was separated into pure samples of 1,3-di-(ϵ-carboxypentyl)-urea and 1-(γ-carboxypropyl)-3-(ϵ-carboxypentyl)-urea (XXII, $n = 3$, $m = 5$). The yields of these products were low due to difficulties involved in their isolation. None of the 1,3-di-(γ-carboxypropyl)-urea could be isolated from the reaction mixture. In order to

TABLE V

1-ALKYL-3-(ω-CARBOXYALKYL)-UREAS RR'NCNH(CH2)nCOOR"

R	R'	R"	n	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	H	H	3	76	177–178	$C_5H_{10}N_2O_3$	41.09	41.14	6.90	6.89	19.17	19.03
C_2H_5	H	H	3	12.7	83–84	$C_7H_{14}N_2O_3$	48.26	48.15	8.10	8.07	16.08	15.74
i-C_3H_7	H	H	3	59	126–127	$C_8H_{16}N_2O_3$	51.04	50.95	8.57	8.57	14.88	14.61
i-C_3H_7	H	C_2H_5	3	44	85–86	$C_{10}H_{20}N_2O_3$	55.53	55.54	9.32	9.28	12.95	12.77
n-C_4H_9	H	H	3	60	105	$C_9H_{18}N_2O_3$	53.44	53.97	8.97	9.25	13.85	13.53
n-C_4H_9	H	C_2H_5	3	68	48–49	$C_{11}H_{22}N_2O_3$	57.36	57.16	9.63	9.49	12.17	12.36
$C_6H_5CH_2$	H	H	3	85	133–134	$C_{12}H_{16}N_2O_3$	61.00	60.81	6.83	6.53	11.86	11.57
$C_6H_5CH_2$	H	C_2H_5	3	69	58	$C_{14}H_{20}N_2O_3$	63.62	63.74	7.63	7.67	10.60	10.35
C_2H_5	C_2H_5	H	3	93	90–91	$C_9H_{18}N_2O_3$	53.44	53.48	8.97	8.95	13.85	13.41
n-C_3H_7	*n*-C_3H_7	H	3	97	132–133	$C_{11}H_{22}N_2O_3$	57.36	57.39	9.63	9.73	12.16	11.48
i-C_3H_7	*i*-C_3H_7	H	3	62	104–105	$C_{11}H_{22}N_2O_3$	57.36	57.06	9.63	9.71	12.16	12.10
$-(CH_2)_5-$		H	3	90	110–111	$C_{10}H_{18}N_2O_3$	56.05	55.82	8.47	8.48	13.08	12.86
$-(CH_2)_5-$		C_2H_5	3	65	60–61	$C_{12}H_{22}N_2O_3$	59.47	59.63	9.15	9.24	11.56	11.13
$-(CH_2)_2O(CH_2)_2-$		H	3	21	124–125	$C_9H_{16}N_2O_4$	49.99	49.82	7.46	7.44	12.96	12.68
t-C_4H_9	H	H	3	57	103–104	$C_9H_{18}N_2O_3$	53.44	53.42	8.97	9.10	13.85	13.55
t-C_4H_9	H	C_2H_5	3	61	53–54	$C_{11}H_{22}N_2O_3$	57.36	57.13	9.63	9.70	12.17	12.30
Cyclohexyl	Cyclohexyl	H	3	56	125–126	$C_{17}H_{30}N_2O_3$	65.77	66.03	9.74	9.80	9.02	8.70
H	H	H	5	98.5	176–176.5	$C_7H_{14}N_2O_3$	48.26	48.66	8.10	8.06	16.09	15.47
CH_3	H	H	5	80	125–126	$C_8H_{16}N_2O_3$	51.04	51.30	8.57	8.68	14.89	14.42
CH_3	H	C_2H_5	5	30	84–85	$C_{10}H_{20}N_2O_3$	55.53	55.94	9.32	9.36	12.95	12.40
C_2H_5	H	H	5	74.8	112–113	$C_9H_{18}N_2O_3$	53.44	53.62	8.97	8.95	13.85	13.79
n-C_4H_9	H	H	5	86	96–97	$C_{11}H_{22}N_2O_3$	57.36	57.44	9.63	9.48	12.16	11.89
n-C_4H_9	H	C_2H_5	5	86	57–58	$C_{13}H_{26}N_2O_3$	60.44	60.73	10.15	9.88	10.84	10.80
$C_6H_5CH_2$	H	H	5	96.8	133–134	$C_{14}H_{20}N_2O_3$	63.61	63.76	7.63	7.75	10.60	10.44



confirm the structure of the intermediate disodium salt XX in this type of reaction, the disodium salt of γ-carboxypropyldithiocarbamic acid was converted in 61% yield into the corresponding S-benzyl ester (XXI, n = 3) following the method of Cook, *et al.*[11]

1,3-Di-(γ-carboxypropyl)-thiourea and 1,3-di-(γ-carboxypropyl)-urea on heating in the presence of *p*-toluenesulfonic acid[5] gave 1-(γ-carboxypropylthiocarbamyl)-2-pyrrolidone (XXIII, X = S) and 1-(γ-carboxypropylcarbamyl)-2-pyrrolidone (XXIII, X = O), respectively.

Experimental[12]

Lactams.—2-Pyrrolidone and ε-caprolactam were obtained from General Aniline and Film Corporation and Badische Anilin & Soda Fabrik, respectively.

5-Methyl-2-pyrrolidone.—5-Methyl-2-pyrrolidone (b.p. 113° (5 mm.)) was prepared in 29% yield from levulinic acid by the Leuckart reaction following the procedure of Lukes and Vecera.[13] This sample had the following physical properties, $n^{25}D$ 1.4719, d_{25} 1.031 and RD 26.87 (calcd. 26.86).

α-Piperidone.—Cyclopentanone (121 g., 1.43 moles) was converted into cyclopentanone oxime (m.p. 55°) in 88% yield by the method of Fox, *et al.*[14] The oxime was rearranged to α-piperidone (b.p. 149° (26 mm.), m.p. 37–38°) in 80% yield by the method of Wallach[15] as modified by Scott, *et al.*[16]

ζ-Enantholactam.—Oximation of cycloheptanone (84 g., 0.75 mole), as described by Coffman, *et al.*,[17] gave 63 g. (97.5%) of cycloheptanone oxime (b.p. 129–130° (19 mm.)). This oxime (85 g., 0.67 mole) was rearranged in 10-g. portions into ζ-enantholactam (b.p. 155° (11 mm.), 88.2% yield) in the same manner as described by Wallach.[15]

1,14-Dicarbethoxytetradecane.—Thapsic acid (1,14-dicarboxytetradecane) (41 g., 0.152 mole) was refluxed in absolute ethanol (500 cc.) for four hours while a slow stream of dry hydrogen chloride was bubbled through the solution. After the ethanol was removed by evaporation, the residue was triturated with water and the precipitate (m.p. 37–38°) was recovered by filtration, yield 97%. The melting point reported[18] for diethyl thapsate is 38°.

Monoethyl Thapsate.—A mixture of diethyl thapsate (48 g., 0.14 mole) and thapsic acid (62 g., 0.22 mole) was converted into monoethyl thapsate in 33% yield (27 g.) by the method of Jones.[19] Two crystallizations from ethanol raised the melting point from 59–61° to 63°. Jones reported a melting point of 65–66°. Diethyl thapsate (40 g.) and thapsic acid (27 g.) were also recovered from the reaction mixture.

ω-Carbethoxypentadecanoyl Chloride.—Monoethyl thapsate (27 g., 0.086 mole) was refluxed with thionyl chloride (32 g., 0.269 mole) for 1.5 hours. The excess thionyl chloride was removed *in vacuo* and the residue was distilled. A sample of the pure product (b.p. 184–190° (0.1–0.3 mm.), m.p. 38–39°) was prepared for analysis, total yield 21 g. (73%).

Anal. Calcd. for $C_{18}H_{33}ClO_3$: C, 64.94; H, 9.99; Cl, 10.65. Found: C, 65.12; H, 10.09; Cl, 10.23.

Ethyl Thapsamate (15-Carbethoxypentadecamide).—ω-Carbethoxypentadecanoyl chloride (21 g., 0.0063 mole) was dissolved in dry benzene and dry ammonia was passed through the stirred mixture for 30 minutes under cooling. The precipitated ammonium chloride was removed by filtration and washed with benzene and chloroform. After the combined filtrate and washings were evaporated, a crystalline residue (m.p. 86–88°) was obtained. The crude material was purified by crystallization from water–ethanol solution, yield 12.7 g. (64%). It melted at 92–93°.

Anal. Calcd. for $C_{18}H_{35}NO_3$: C, 68.96; H, 11.23; N, 4.47. Found: C, 68.98; H, 11.11; N, 4.61.

Ethyl ω-Carbomethoxyaminopentadecanoate.—Ethyl thapsamate (11.74 g., 0.037 mole) in absolute methanol (150 cc.) was treated with 95 cc. of 0.875 *N* sodium methoxide in methanol. This stirred solution was cooled in an ice-water-bath while bromine (6.9 g., 0.086 mole) was added dropwise. After the precipitate had dissolved the solution was refluxed for 30 minutes. The solution was evaporated to 85 cc. and water was added. A precipitate formed after which the mixture was left in the refrigerator overnight. The precipitate (m.p. 63–65°) was removed by filtration, yielded 12.09 g. (91%). The melting point was raised to 64–65° by two crystallizations from methanol–water solution.

Anal. Calcd. for $C_{19}H_{37}NO_4$: C, 66.44; H, 10.86; N, 4.08. Found: C, 66.31; H, 10.92; N, 4.24.

15-Aminopentadecanoic Acid Hydrochloride.—Ethyl ω-carbomethoxyaminopentadecanoate (11.06 g., 0.03 mole) was refluxed in 40 cc. of concentrated hydrochloric acid solution for three hours. On cooling, a crystalline precipitate (m.p. 133–136°) separated, yield 8.31 g. (66%). Two crystallizations from water (250 cc./g.) containing 2 cc. of concentrated hydrochloric acid per 250 cc. of water gave material with a constant melting point of 152–153°.

Anal. Calcd. for $C_{15}H_{32}NO_2Cl$: C, 61.29; H, 10.98; N, 4.77; Cl, 12.06. Found: C, 61.00; H, 10.90; N, 4.80; Cl, 12.00.

Methyl ε-Aminocaproate.—A solution of caprolactam (147 g., 1.3 moles) and 115 cc. of 37% hydrochloric acid solution in water (1 l.) was refluxed for 4 hours. The solution was concentrated *in vacuo* until crystals began to appear. Acetone (1 l.) was added and the precipitated crystals of ε-aminocaproic acid hydrochloride (m.p. 132–133°) were recovered by filtration, yield 198 g. (92%).

A solution of ε-aminocaproic acid hydrochloride (105 g., 0.62 mole) in absolute methanol (125 cc.) was refluxed for 2 hours. Evaporation of the solution gave a semicrystalline mass of methyl ε-aminocaproate hydrochloride, yield 110 g. (97%). Dry ammonia was bubbled into a solution of the methyl ε-aminocaproate in chloroform solution until an excess of ammonia had been added. After removal of the ammonium chloride by filtration, the filtrate was evaporated to dryness *in vacuo*. The residual oil was distilled *in vacuo* to give 68.5 g. (78%) of methyl ε-aminocaproate (b.p. 75–78° (1 mm.)).

1,3-Di-(carboxyalkyl)-thioureas.—The 1,3-di-(carboxyalkyl)-thioureas described in Table I were prepared by the condensation of the corresponding amino acids with carbon disulfide in aqueous solution. The preparation of 1,3-di-(ε-carboxypentyl)-thiourea is described below in detail.

(12) All melting points are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(13) R. Lukes and M. Vecera, *Chem. Listy*, **46**, 94 (1952).

(14) S. W. Fox, M. S. Dunn and M. P. Stoddard, *J. Org. Chem.*, **6**, 410 (1941).

(15) O. Wallach, *Ann.*, **312**, 171 (1900).

(16) P. T. Scott, D. E. Pearson and L. J. Bucher, *J. Org. Chem.*, **19**, 1815 (1954).

(17) D. D. Coffman, N. L. Cox, E. L. Martin, W. E. Mochel and F. J. Van Natta, *J. Polymer Sci.*, **3**, 85 (1948).

(18) Bougault, *Compt. rend.*, **150**, 876 (1910).

(19) R. G. Jones, THIS JOURNAL, **69**, 2350 (1947).

ε-Caprolactam (56.5 g., 0.5 mole) in 186 cc. of water containing 40 g. (1 mole) of sodium hydroxide was refluxed for 90 minutes. After the solution cooled to room temperature, the excess sodium hydroxide (0.5 mole) was neutralized with the calculated amount of concentrated hydrochloric acid solution. To this stirred solution 21 g. (0.276 mole) of carbon disulfide was added. After this reaction mixture was stirred at 25–40° for 2 hours, the excess carbon disulfide was distilled from the solution. The remaining clear solution was refluxed for approximately seven hours until the evolution of hydrogen sulfide ceased. This solution was cooled to room temperature, after which it was acidified to a *p*H of 0.9 with concentrated hydrochloric acid solution. The crystalline precipitate (m.p. 127–128°) was removed by filtration, washed with water and dried. Several runs gave yields varying from 96–100%. The melting point of the crude product was increased to 128–129° by one crystallization from water.

1,3-Di-(carboxyalkyl)-ureas. Method A.—The methods described below for the conversion of 1,3-di-(ε-carboxypentyl)-thiourea into 1,3-di-(ε-carboxypentyl)-urea are applicable to all of the 1,3-di-(carboxyalkyl)-thioureas with the exception of 1,3-di-(ω-carboxydecyl)- and 1,3-di-(ω-carboxytetradecyl)-thioureas. The properties of 1,3-di-(carboxyalkyl)-ureas are given in Table III.

A solution of 1,3-di-(ε-carboxypentyl)-thiourea (3.04 g., 0.01 mole) and potassium hydroxide (2.24 g., 0.04 mole) in water (20 cc.) was treated at 20–25° with 37.4 cc. of 1.07 molar solution of sodium hypochlorite over a period of 7 minutes. This reaction mixture was allowed to stand at room temperature for 3 hours after which the filtered solution was acidified with hydrochloric acid solution. The crystalline precipitate (m.p. 157–158.5°) was recovered by fitration, yield 2.72 g. (94.5%). One crystallization from acetone–water solution raised the melting point to 162–163°.

Method B.—To a stirred solution of 1,3-di-(ε-carboxypentyl)-thiourea (3.04 g., 0.01 mole) and potassium hydroxide (2.24 g., 0.04 mole) in water (20 cc.) was added 16.1 cc. of 2.55 molar solution of hydrogen peroxide. During the addition period of 10 minutes, cooling was necessary to maintain the temperature at 5–10°. After this solution had remained at room temperature for several hours, it was filtered and the filtrate was acidified with 10% hydrochloric acid solution. The crystalline precipitate (m.p. 157–158°) was removed by filtration, yield 2.72 g. (94.5%). One crystallization from an acetone–water solution raised the melting point to 162–163°. A mixture melting point determination with an authentic sample of 1,3-di-(ε-carboxypentyl)-urea gave no depression.

Method C.—A solution of caprolactam (56.5 g., 0.5 mole) and sodium hydroxide (40 g., 1.0 mole) in water (166 cc.) was refluxed for 90 minutes. After the solution cooled to room temperature, the excess sodium hydroxide (0.5 mole) was neutralized with concentrated hydrochloric acid (0.5 mole) solution. Carbon disulfide (21 g., 0.276 mole) was added to this stirred solution. This reaction mixture was stirred for 2 hours at the reflux temperature of carbon disulfide after which the excess carbon disulfide was removed by distillation. The remaining solution was refluxed for 7 hours until the evolution of hydrogen sulfide ceased. After the solution cooled to room temperature it was diluted with a solution of sodium hydroxide (20 g., 0.5 mole) in water (200 cc.) and then sodium hypochlorite (1052 cc. of 0.89 *M* solution, 0.939 mole) solution was added at a temperature of 20–25°. The filtered solution was acidified to a *p*H of 2 with concentrated hydrochloric acid (68 cc.) solution and the precipitate was recovered by filtration, yield 89.0%. The melting point of the crude product (m.p. 161–162°) was raised to 163–164° by crystallizing from ethanol (4.85 cc./g.). This product did not depress the melting point of a sample of 1,3-di-(ε-carboxypentyl)-urea prepared by method A.

Esterification of 1,3-Di-(carboxyalkyl)-thioureas and 1,3-Di-(carboxyalkyl)-ureas.—The esters of 1,3-di-(carboxyalkyl)-thioureas and 1,3-di-(carboxyalkyl)-ureas listed in Tables II and IV, respectively, were prepared by heating these thiourea and urea derivatives with alcohols in the presence of catalytic amounts of concentrated sulfuric acid. Since all of these preparations are very similar, only the preparation of the didecyl ester of 1,3-di-(ε-carboxypentyl)-thiourea is described.

A mixture of excess *n*-decyl alcohol and 1,3-di-(ε-carboxypentyl)-thiourea (5.52 g., 0.018 mole) in the presence of concentrated sulfuric acid (0.58 g.) was heated on a steam-bath for 5 hours. This solution on standing in the refrigerator overnight deposited crystals (m.p. 51–52°), yield 9.86 g. (93%). One crystallization from methanol raised the melting point to a constant value of 53–54°.

1-Nitroso-1,3-di-(ε-carboxypentyl)-urea. Method A.—A solution of 12 cc. of 18% nitric acid and 20 mg. of sodium nitrite was cooled to 15° and 1,3-di-(ε-carboxypentyl)-thiourea (3.04 g., 0.01 mole) was added portionwise over a period of 15 minutes. The temperature of the stirred solution was held at 15–20° for a further period of 2.5 hours after which the yellow product (m.p. 104–106°) was removed by filtration and air-dried, yield 2.95 g. (93%). Two crystallizations from acetone–water solution raised the melting point to 106–106.5°.

Anal. Calcd. for $C_{13}H_{23}N_3O_6$: C, 49.20; H, 7.30; N, 13.24. Found: C, 49.28; H, 7.41; N, 13.33.

Method B.—1,3-Di-(ε-carboxypentyl)-urea (0.5 g., 0.0017 mole) suspended in 35% nitric acid solution (15 cc.) was treated at 0° with a solution of potassium nitrite (0.148 g., 0.0017 mole) in water (2 cc.). After this reaction mixture was held at 0–5° for 30 minutes, it was allowed to stand overnight at room temperature. The solid (m.p. 106–106.5°) was removed by filtration and dried, yield 0.46 g. (84.5%). This material did not depress the melting point of a sample of 1-nitroso-1,3-di-(ε-carboxypentyl)-urea prepared by method A.

1-Nitroso-1,3-di-(γ-carboxypropyl)-urea.—1-Nitroso-1,3-di-(γ-carboxypropyl)-urea (m.p. 103–104°) was prepared in 70% yield in dilute sulfuric acid medium by method B for the preparation of 1-nitroso-1,3-di-(ε-carboxypentyl)-urea.

Anal. Calcd. for $C_9H_{15}N_3O_6$: C, 41.38; H, 5.79; N, 16.08. Found: C, 41.12; H, 6.14; N, 16.06.

1-Nitroso-1,3-di-(10-carboxydecyl)-urea.—1,3-Di-(10-carboxydecyl)-thiourea[1] (0.514 g., 0.0011 mole) was added portionwise to a cold solution of potassium nitrite (0.05 g., 0.0005 mole) in concentrated nitric acid solution (30 cc.). This reaction mixture, which was cooled with an ice-bath, was stirred for 15 minutes. Water (100 cc.) was added to the solution and the product (m.p. 73–75°) was recovered by filtration, yield 0.54 g. (100%). One crystallization from benzene–petroleum ether (1:1) solution (50 cc.) raised the melting point to 89–90°.

Anal. Calcd. for $C_{23}H_{43}N_3O_6$: C, 60.37; H, 9.47; N, 9.18. Found: C, 60.32; H, 9.79; N, 8.95.

1-Nitroso-1,3-di-(ε-carboxypentyl)-thiourea.—1,3-Di-(ε-carboxypentyl)-thiourea (48 g., 0.158 mole) was added portionwise over a period of 25 minutes to a stirred ice-cooled solution of potassium nitrite (15 g., 0.177 mole) in 70% acetic acid solution (280 cc.). During the addition of the thiourea a further quantity of potassium nitrite (15 g., 0.177 mole) was added. This mixture was stirred for 30 minutes after which the product (m.p. 94–95°) was recovered by filtration, yield 45 g. (86%). One crystallization from benzene–petroleum ether (1:1) solution raised the melting point to 95–96°.

Anal. Calcd. for $C_{13}H_{23}N_3O_5S$: C, 46.83; H, 6.95; N, 12.60; S, 9.62. Found: C, 46.98; H, 6.80; N, 12.31; S, 9.81.

1,3-Di-(ε-carboxypentyl)-urea from 1-Nitroso-1,3-di-(ε-carboxypentyl)-urea. Method A.—A solution of 1-nitroso-1,3-di-(ε-carboxypentyl)-urea (0.5 g.) in 10 cc. of 10% hydrochloric acid was refluxed for 10 minutes. This reaction mixture was cooled and the precipitate (m.p. 159–160°) was recovered by filtration, yield 0.286 g. (63%). This product after crystallization from water melted at 162–163° alone and on admixture with an authentic sample of 1,3-di-(ε-carboxypentyl)-urea.

Method B.—1-Nitroso-1,3-di-(ε-carboxypentyl)-urea (1.0 g., 0.003 mole) was dissolved in 8 cc. of 5% potassium hydroxide solution. This solution was warmed on the steam-bath for 60 minutes, although gas evolution had ceased after 10 minutes. When the solution was acidified with 10% hydrochloric acid solution, 0.356 g. (39.2%) of 1,3-di-(ε-carboxypentyl)-urea (m.p. 158–159°) was obtained. One crystallization from water–acetone solution raised the melting point to 161.5–162.5°. The product was identified by a mixed melting point determination with an authentic sample of 1,3-di-(ε-carboxypentyl)-urea.

The filtrate from the 1,3-di-(ε-carboxypentyl)-urea was evaporated to dryness *in vacuo* and the solid residue was ex-

tracted with absolute ethanol (30 cc.). The ethanol solution on evaporation gave a colorless oil which was crystallized from acetone, yield 81 mg. These crystals (m.p. 122–125°) were purified by solution in ethanol and precipitation with acetone. The pure product (m.p. 129–130°) did not depress the melting point of a sample of ϵ-aminocaproic acid hydrochloride (m.p. 130.5–131.5°) prepared from caprolactam.

A similar experiment using sodium bicarbonate instead of potassium hydroxide gave a 45.4% yield of 1,3-di-(ϵ-carboxypentyl)-urea (m.p. 157–159°).

1,3-Di-(ω-carboxydecyl)-urea.—1-Nitroso-1,3-di-(ω-carboxydecyl)-urea (0.183 g., 0.0004 mole) was suspended in water (5 cc.) and 5% aqueous sodium bicarbonate solution (3 cc.) was added. This mixture was heated on a steam-bath for 10 minutes after which it was acidified with hydrochloric acid solution. The product (m.p. 153–154°) was removed by filtration and dried, yield 0.139 g. (80%). One crystallization from ethanol raised the melting point to 164–166°. A mixture melting point with a sample of 1,3-di-(ω-carboxydecyl)-urea prepared by the oxidation of 1,3-di-(ω-carboxydecyl)-thiourea was not depressed.

Ammonolysis of 1-Nitroso-1,3-di-(ϵ-carboxypentyl)-urea.—A suspension of 1-nitroso-1,3-di-(ϵ-carboxypentyl)-urea (20 g., 0.0631 mole) in 13.5% ammonia solution (200 cc.) was heated on a steam-bath for 30 minutes. The clear solution was cooled in an ice-bath and then acidified with 10% hydrochloric acid solution. After the mixture had remained for 1 hour in the ice-bath, the product (m.p. 174–175°) was collected by filtration, yield 9.66 g. (84%). One crystallization from ethanol (200 cc.) raised the melting point to 175–176°. Thomas and Goerne[7] report a melting point of 174–178° for 1-(ϵ-carboxypentyl)-urea. The mother liquor from the crude 1-(ϵ-carboxypentyl)-urea was extracted with ether in a continuous extractor for 12 hours. After the ether extract was dried over anhydrous sodium sulfate, the ether was removed *in vacuo* without heating. The residue was a viscous liquid, yield 5.75 g. A portion (4.45 g.) of this product was distilled *in vacuo* giving a viscous liquid ($n^{26}D$ 1.4428, d^{26}_4 1.029), yield 2.60 g. The observed molar refractivity from the above experimental data for ϵ-caprolactone is 29.40, while the value calculated for ϵ-caprolactone is 29.37. Van Natta, *et al.*,[8] reported the following physical properties for ϵ-caprolactone; $n^{24}D$ 1.4608 and d^{24}_4 1.0698.

A sample (1.06 g.) of the crude extraction product was heated for 12 hours with hydrazine hydrate (0.6 cc., 0.012 mole). At the end of the reaction, ethanol (2 cc.) was added and the mixture was left overnight in the refrigerator. The crystalline white precipitate (m.p. 110–112°) was collected by filtration, yield 0.13 g. One crystallization from ethanol (4 cc.) raised the melting point to 114°. The melting point reported in the literature[9] for ϵ-hydroxycaproic acid hydrazide is 114–115°.

Anal. Calcd. for $C_6H_{14}N_2O_2$: C, 49.29; H, 9.65; N, 19.16. Found: C, 49.45; H, 9.60; N, 18.90.

Reaction of Amines with 1-Nitroso-1,3-di-(ω-carboxyalkyl)-ureas.—The 1-nitroso-1,3-di-(ω-carboxyalkyl)-ureas in the presence of 3.25 to 5.7 equivalents of amine or aqueous amine solution were heated on a steam-bath for 15 to 30 minutes until the evolution of nitrogen ceased. The product precipitated from the cooled solution on acidification with dilute hydrochloric acid solution. After the product was recovered by filtration, it was purified by crystallization from suitable organic solvent. No precipitate or an oil was obtained on the acidification of some reaction mixtures. In these cases the acidified reaction mixture was extracted with chloroform or petroleum ether. The product was obtained on evaporation of the organic solvent. The unsymmetrical urea derivatives prepared in this manner are listed in Table V.

Reaction of Hexamethylenediamine with 1-Nitroso-1,3-di-(ω-carboxydecyl)-urea.—Hexamethylenediamine (1.15 g., 0.01 mole) was added to a suspension of 1-nitroso-1,3-di-(ω-carboxydecyl)-urea (3.0 g., 0.0065 mole) in water (20 cc.) and the mixture was heated on the steam-bath for 15 minutes. After the reaction mixture had remained for 2 hours at room temperature, the precipitate (m.p. 177–180° dec.) was recovered by filtration and dried, yield 1.75 g. (78%). The product was very insoluble in water and organic solvents. A portion (100 mg.) was crystallized from water (2000 cc.) to give crystals melting at 203–204° dec.

Anal. Calcd. for $C_{18}H_{37}N_3O_3$: C, 62.94; H, 10.86; N, 12.23. Found: C, 62.88; H, 10.87; N, 12.34.

The picrate formed in the usual manner from water melted at 110–113°. Three crystallizations from acetone–petroleum ether solution lowered the melting point to 96–97°.

Anal. Calcd. for $C_{24}H_{40}N_6O_{10}$: C, 50.34; H, 7.04; N, 14.68. Found: C, 50.74; H, 7.11; N, 14.38.

A sample (0.4 g., 0.0011 mole) of crude 1-(ω-aminohexyl)-3-(ω-carboxydecyl)-urea in methanol (250 cc.) was refluxed for 2 hours while dry hydrogen chloride was passed through the solution. The solution was taken to dryness *in vacuo* and the residue was dissolved in water. On treating with saturated aqueous picric acid solution, a 73% yield of a crystalline picrate (m.p. 82–83°) of 1-(ω-aminohexyl)-3-(ω-carbomethoxydecyl)-urea was obtained. One crystallization from ethanol–water (1:4) solution and two from acetone–water (1:6) solution raised the melting point to 96–97°. These crystals on admixture with 1-(ω-aminohexyl)-3-(ω-carboxydecyl)-urea picrate (m.p. 96–97°) depressed the melting point to 91–92°.

Anal. Calcd. for $C_{25}H_{42}N_6O_{10}$: C, 51.18; H, 7.22; N, 14.33. Found: C, 51.03; H, 7.43; N, 14.06.

Esterification of the Unsymmetrical Urea Derivatives.—All the esters listed in Table V were prepared by the same method, which is described below in the preparation of 1-*n*-butyl-3-(ϵ-carbethoxypentyl)-urea.

1-*n*-Butyl-3-(ϵ-carboxypentyl)-urea (0.833 g., 0.0036 mole) was dissolved in absolute ethanol (100 cc.) containing 12% dry hydrogen chloride and the solution was allowed to stand at room temperature overnight. After the solvent was removed by evaporation *in vacuo*, a crystalline residue (m.p. 54–55°) was obtained, yield 0.8 g. (86%). Crystallization from aqueous ethanol (50%) raised the melting point to 57–58°.

1,3-Di-(ϵ-carbomethoxypentyl)-thiourea.—Methyl ϵ-aminocaproate (88.9 g., 0.613 mole) and carbon disulfide (45.6 g., 0.6 mole) in absolute methanol were allowed to stand at room temperature overnight. The reaction mixture was diluted with absolute methanol (300 cc.) and then refluxed for 17 hours. This solution was cooled and filtered to remove a small amount (0.87 g.) of impurity after which the filtrate was evaporated to a volume of 150 cc. This solution on cooling gave 26.8 g. of product (m.p. 50–51°). The mother liquor on concentration gave an additional 37.6 g. of product (m.p. 48–51°). The total yield was 64.4 g. (63.4%). Crystallization from 75% aqueous methanol raised the melting point to 50–51°. The analytical values for this ester are reported in Table II.

S-Benzyl Ester of γ-Carboxypropyldithiocarbamic Acid.—A solution of 2-pyrrolidone (17.0 g., 0.2 mole) and sodium hydroxide (16 g., 0.4 mole) in water (50 cc.) was refluxed for 90 minutes. Carbon disulfide (15.2 g., 0.2 mole) was added to the cooled (15°) solution and the mixture was stirred at 15–20° until all of the carbon disulfide had dissolved. To this clear solution was added benzyl chloride (26.0 g., 0.20 mole) and then the stirring was continued for an additional 2 hours. A slight heat of reaction was observed and a yellow precipitate separated. The precipitate redissolved on adjusting the *p*H to 9.0. After the clear yellow solution was acidified, a gummy yellow solid separated. This precipitate was redissolved in one liter of water containing 90 g. of sodium bicarbonate. On acidification with concentrated hydrochloric acid solution, pale yellow crystals (m.p. 95–100°) separated, yield 32.7 g. (60.8%). One crystallization from benzene raised the melting point to 115–116°, yield 23.1 g.

Anal. Calcd. for $C_{12}H_{15}NO_2S_2$: C, 53.50; H, 5.61; N, 5.20; S, 23.81. Found: C, 53.85; H, 5.60; N, 5.49; S, 23.72.

1-(γ-Carboxypropyl)-3-(ϵ-carboxypentyl)-thiourea and -urea.—Caprolactam (22.6 g., 0.2 mole) and sodium hydroxide (16.0 g., 0.4 mole) in water (60 cc.) was refluxed for 1 hour. This solution was cooled and treated with carbon disulfide (15.2 g., 0.2 mole). The mixture was stirred at 15–20° for 1 hour and at room temperature for 2 hours after which a clear solution of disodium ϵ-carboxypentyldithiocarbamate was obtained. To this solution was added γ-aminobutyric acid (20.6 g., 0.2 mole) in water (66 cc.) and the mixture was refluxed for seven hours. The solution was cooled and filtered through a sintered glass filter. The

filtrate on acidification to a *p*H of 2.0 gave 46 g. (83.2%) of crude 1-(γ-carboxypropyl)-3-(ε-carboxypentyl)-thiourea (m.p. 96–100°).

The thiourea (10 g., 0.036 mole) was oxidized in the usual manner with sodium hypochlorite to give 7.5 g. (79.6%) of crude urea derivative (m.p. 120–155°). This crude material was subjected to triangular crystallization starting with 60 cc. of acetone–water. The least soluble material (1.45 g., m.p. 154–158°) was obtained after two crystallizations. This was crystallized again to give 1.24 g. of 1,3-di-(ε-carboxypentyl)-urea (m.p. 161–162°). The most soluble material (2.25 g., m.p. 125–130°) was dissolved in 50 cc. of 10% methanolic hydrogen chloride and methylated at room temperature overnight. The methanol was evaporated *in vacuo* at room temperature. The residue was dissolved in chloroform and the extract was washed with 5% sodium bicarbonate solution and water. The dried solution on evaporation gave a crystalline residue which, after one crystallization from benzene, yielded 1.98 g. (80%) of diester, m.p. 87–88°. It gave a depression in melting point on admixture with 1,3-di-(γ-carbomethoxypropyl)-urea (m.p. 112–113°) or 1,3-di-(ε-carbomethoxypentyl)-urea (m.p. 101–102°). The dimethyl ester melting at 88–89° was shown on analysis to be 1-(γ-carbomethoxypropyl)-3-(ε-carbomethoxypentyl)-urea.

Anal. Calcd. for $C_{13}H_{24}N_2O_5$: C, 54.15; H, 8.39; N, 9.72. Found: C, 54.27; H, 8.53; N, 9.54.

A mixture of 1-(γ-carbomethoxypropyl)-3-(ε-carbomethoxypentyl)-urea and sodium hydroxide (507 mg.) in water (10 cc.) was refluxed for 30 minutes. The solution on cooling and acidification to *p*H 2.0 gave 782 mg. (86.6%) of 1-γ-carboxypropyl)-3-(ε-carboxypentyl)-urea (m.p. 127–131°). Two crystallizations from water raised the melting point to 135–136°.

Anal. Calcd. for $C_{11}H_{20}N_2O_5$: C, 50.76; H, 7.74; N, 10.77. Found: C, 50.74; H, 7.85; N, 10.94.

1,3-Di-(ω-carbethoxytetradecyl)-thiourea.—1,3-Di-(ω-carboxytetradecyl)-thiourea (0.95 g., 0.017 mole) was suspended in absolute ethanol (80 cc.) containing 1.5% hydrogen chloride and the mixture was shaken for 8 hours at room temperature. After the reaction mixture had remained standing overnight at room temperature, a small amount of insoluble material was removed by filtration. The filtrate was diluted with water (100 cc.) and the white precipitate was recovered by filtration, yield 0.90 g. (86%). The melting point was raised from 74–76° to 75–76° by crystallizing from ethanol.

1,3-Di-(ω-carbethoxytetradecyl)-urea and 1,3-Di-(ω-carbethoxydecyl)-urea.—Both 1,3-di-(ω-carbethoxytetradecyl)-thiourea and 1,3-di-(ω-carbethoxydecyl)-thiourea were converted into the corresponding urea derivatives by a process similar to that described by Kjaer, *et al.*[6] Since both compounds were prepared by the same method only the preparation of 1,3-di-(ω-carbethoxytetradecyl)-urea is given in detail.

1,3-Di-(carbethoxytetradecyl)-thiourea (305 mg., 0.00048 mole) was dissolved in hot ethanol (5 cc.) and a solution of silver nitrate (190 mg., 0.0011 mole) in 83% ethanol was added. A precipitate of silver sulfide formed immediately. The mixture was refluxed for 20 minutes after which it was filtered hot. The filtrate was diluted with several volumes of water and the precipitate was collected on a sintered glass filter, yield 255 mg. (86%). The melting point (100–102°) of the crude product was raised to a constant value of 102–103° by two crystallizations from ethanol. The purified yield was 212 mg. (71%).

1,3-Di-(ω-carboxytetradecyl)-urea.—An attempt to saponify the diethyl ester of 1,3-di-(ω-carboxytetradecyl)-urea by refluxing for 4 hours with a large excess of aqueous potassium hydroxide solution failed. The hydrolysis was accomplished successfully by dissolving the diethyl ester (520 mg., 0.0009 mole) in methyl Cellosolve (100 cc.) containing 2.5 cc. of 1.037 *N* potassium hydroxide solution and refluxing for three hours. The solution was concentrated to 20 cc., acidified with hydrochloric acid and then diluted with water (60 cc.). The precipitate (m.p. 130–133°) was removed from the cooled reaction mixture by filtration, yield 490 mg. (97%). Three crystallizations from ethanol (71.5 cc./g.) raised the melting point to 137–138°.

1,3-Di-(α-methyl-γ-carboxypropyl)-thiourea.—5-Methyl-2-pyrrolidone (12.8 g., 0.129 mole) was converted into the sodium salt of γ-aminovaleric acid which was condensed with carbon disulfide under the conditions described above for the preparation of 1,3-di-(ω-carboxyalkyl)-thioureas. However, the solution on acidification remained clear. It was concentrated *in vacuo* to 100 cc. and then placed in the refrigerator overnight. A crystalline precipitate (m.p. 148–150°) was obtained, yield 5 g.

The filtrate on concentration *in vacuo* gave an oil which was recovered by extraction with chloroform and ethyl acetate. Evaporation of the combined extracts gave an amorphous residue. This residue in water (50 cc.) was heated for 30 minutes with excess alkali. The solution was decolorized with Norite, cooled in ice and acidified with 10% hydrochloric acid solution. Removal of most of the solvent *in vacuo* gave 3.7 g. of crystals melting at 148–150°. The total yield was 8.7 g. (52%).

1,3-Di-(α-methyl-γ-carboxypropyl)-thiourea (2.2 g.) was dissolved in 40% aqueous methanol (75 cc.) at room temperature. This solution was filtered and then concentrated to half volume *in vacuo*. On cooling overnight in the refrigerator white platelets separated from the solution, yield 1.7 g. The melting point (155–156°) was not altered by repeated crystallizations.

1-(γ-Carboxypropylthiocarbamyl)-2-pyrrolidone.—A mixture of 1,3-di-(γ-carboxypropyl)-thiourea (2 g., 0.008 mole) and *p*-toluenesulfonic acid monohydrate (0.2 g.) was heated at 180–195° *in vacuo* (30 mm.) for approximately 10 minutes. After the melt cooled, it was crystallized from water (5 cc.), yield 1.09 g. (58.8%). The melting point was raised from 127–128° to 128.5–129.5° by one crystallization from acetone–water solution.

Anal. Calcd. for $C_9H_{14}N_2O_3S$: C, 46.94; H, 6.13; N, 12.17; S, 13.92; neut. equiv., 230. Found: C, 46.51; H, 6.25; N, 12.21; S, 13.63; neut. equiv., 227.

1-(γ-Carboxypropylcarbamyl)-2-pyrrolidone.—A mixture of 1,3-di-(γ-carboxypropyl)-urea (1.0 g., 0.004 mole) and *p*-toluenesulfonic acid monohydrate (0.1 g.) was heated *in vacuo* (10 mm.) until frothing ceased. The cooled melt was dissolved in water (4 cc.). On cooling, 0.49 g. (53.2%) of crystalline product (m.p. 116.5–117.5°) was obtained. The melting point was not raised by further crystallization.

Anal. Calcd. for $C_9H_{14}N_2O_4$: C, 50.46; H, 6.59; N, 13.08; neut. equiv., 214.22. Found: C, 50.51; H, 6.51; N, 12.80; neut. equiv., 214.

VILLE LASALLE, QUEBEC, CANADA

COMMUNICATIONS TO THE EDITOR

17,20;20,21-BISMETHYLENEDIOXY STEROIDS

Sir:

The sensitivity of the dihydroxyacetone side chain of adrenocortical hormones to reagents such as lithium aluminum hydride, bromine, Grignard reagents, and strong acids and base is well known. Two methods have been generally used for protection of the side chain: (1) formation of the C_{20} dioxolane,[1] which renders the side chain inert to essentially all the above reagents except acid; (2)

(1) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell, and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953), and subsequent papers by Bernstein and co-workers summarize most of the syntheses utilizing 20-dioxolanes.