[CONTRIBUTION NO. 17 FROM THE L. G. RYAN RESEARCH LABORATORIES OF MONSANTO CANADA LTD.]

Amino Acids. VII. N,N'-Di-(ω-carboxyalkylthiocarbamyl)- and N,N'-Di-(ω-carboxyalkylcarbamyl)-polymethylenediamines and their Derivatives

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A series of N,N'-di-(ω-carboxyalkylthiocarbamyl)-polymethylenediamines have been prepared by condensing ω-amino acids with the salts of polymethylenebisdithiocarbamates. The N,N'-di-(ω-carboxyalkylthiocarbamyl)-polymethylenediamines were converted into the corresponding N,N'-di-(ω-carboxyalkylcarbamyl)-polymethylenediamines by oxidation in alkaline solution with hydrogen peroxide. A number of esters of these dicarboxylic acid derivatives have been prepared by esterification in the presence of either sulfuric acid or dry hydrogen chloride. Glycine condensed with disodium ethylene bisdithiocarbamate to give 1,2-di-(3,3'-(2-thiohydantoinyl))-ethane. N,N'-Di-(β-carboxyethylthiocarbamyl)-ethane and -butane have been cyclized with polyphosphoric acid to 1,2-di-(3,3'-(2-thiohydrouracilyl))-ethane and 1,4-di-(3,3'-(2-thiohydrouracilyl))-butane, respectively. N,N'-Di-(β-carbomethoxyethylthiocarbamyl)-hydrazine gave 3,5-dithio-4-(β-carbomethoxyethyl)-2,3,4,5-tetrahydro-1,2,4-triazole.

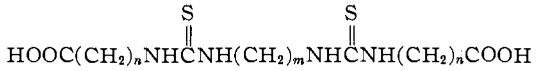
A new series of linear dibasic acids (III) have been prepared by heating aqueous solutions of the alkali metal salts of polymethylenebisdithiocarbamates with two equivalents of ω-amino acids. Disodium tetramethylenebisdithiocarbamate (II, *m* = 4) and ε-aminocaproic acid gave an 81% yield of N,N'-di-(ε-carboxypentylthiocarbamyl)-tetramethylenediamine (III, *n* = 5, *m* = 4) and a 17.8% yield of tetramethylenethiourea (IV, *m* = 4). The physical properties of the N,N'-di-(ω-carboxyalkylthiocarbamyl)-polymethylenediamines prepared during this study are described in Table I.

Methylation of the dithiourea dibasic acid derivatives III was accomplished by the use of 1% dry methanolic hydrogen chloride or by using concentrated sulfuric acid as an esterifying agent. Several of these esters are listed in Table II.

The N,N'-di-(ω-carboxyalkylthiocarbamyl)-polymethylenediamines (III) in aqueous alkaline solutions are converted in good yields into the corresponding N,N'-di-(ω-carboxyalkylcarbamyl)-polymethylenediamines (V) on oxidation with hy-

TABLE I

N,N'-DI-(ω-CARBOXYALKYLTHIOCARBAMYL)-POLYMETHYLENEDIAMINES



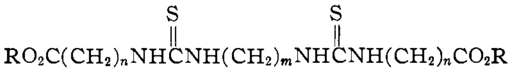
$$HOOC(CH_2)_nNH\overset{S}{\overset{\|}{C}}NH(CH_2)_mNH\overset{S}{\overset{\|}{C}}NH(CH_2)_nCOOH$$

n	*m*	M.p., °C.	Yield,[a] %	Formula	Carbon, %		Hydrogen, %		Nitrogen, %		Sulfur, %	
					Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
2	2	201-202	22.3	$C_{10}H_{18}N_4O_4S_2$	37.25	37.30	5.63	6.00	17.38	17.64	19.89	20.08
3	2	161-162	29.9	$C_{12}H_{22}N_4O_4S_2$	41.12	41.28	6.33	6.43	15.99	16.30	18.30	17.92
5	2	133-134	36.0	$C_{16}H_{30}N_4O_4S_2$	47.27	46.91	7.44	7.53	13.78	14.01	15.77	16.00
3	3	128-130	40.1	$C_{13}H_{24}N_4O_4S_2$	42.84	42.58	6.64	6.42	15.37	15.45	17.59	17.66
5	3	132-133	59.4	$C_{17}H_{32}N_4O_4S_2$	48.54	48.16	7.67	7.81	13.32	13.11	15.25	15.16
2	4	165-166	41.0	$C_{12}H_{22}N_4O_4S_2$	41.12	41.05	6.33	6.31	15.99	16.27	18.30	18.47
3	4	153-154.5	61.4	$C_{14}H_{26}N_4O_4S_2$	44.42	44.26	6.93	7.05	14.80	15.13	16.94	16.97
5	4	150-152	64.9	$C_{18}H_{34}N_4O_4S_2$	49.74	49.55	7.89	8.14	12.89	13.32	14.76	14.98
3	5	138-140	18.6	$C_{15}H_{28}N_4O_4S_2$	45.89	45.88	7.19	7.06	14.27	14.35	16.34	16.00
5	5	126.5-128	42.5	$C_{19}H_{36}N_4O_4S_2$	50.86	50.75	8.09	8.19	12.49	12.94	14.29	14.38
3	6	158-159	43.9	$C_{16}H_{30}N_4O_4S_2$	47.27	47.21	7.44	7.56	13.78	13.48	15.77	15.44
5	6	144-145	46.3	$C_{20}H_{38}N_4O_4S_2$	51.91	52.08	8.28	8.46	12.11	12.13	13.86	13.73

[a] Yield of pure product.

TABLE II

ESTERS OF N.N'-DI-(ω-CARBOXYALKYLTHIOCARBAMYL)-POLYMETHYLENEDIAMINES



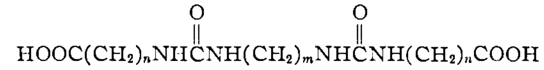
$$RO_2C(CH_2)_nNH\overset{S}{\overset{\|}{C}}NH(CH_2)_mNH\overset{S}{\overset{\|}{C}}NH(CH_2)_nCO_2R$$

R	*n*	*m*	M.p., °C.	Yield, %	Formula	Carbon, %		Hydrogen, %		Nitrogen, %		Sulfur, %	
						Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
CH_3	2	2	138-139	17(79)[a]	$C_{12}H_{22}N_4O_4S_2$	41.12	41.26	6.33	6.36	15.99	16.25	18.30	18.15
CH_3	3	2	117-118	50.9	$C_{14}H_{26}N_4O_4S_2$	44.42	44.31	6.92	6.88	14.80	14.60	16.94	17.09
CH_3	5	3	103-105	34.1	$C_{19}H_{36}N_4O_4S_2$	50.86	51.14	8.08	8.01	12.48	12.28	14.29	13.90
CH_3	2	4	94-95	37(92)[a]	$C_{14}H_{26}N_4O_4S_2$	44.42	44.20	6.92	6.88	14.80	15.11	16.94	17.27
CH_3	3	4	122-123	84.5	$C_{16}H_{30}N_4O_4S_2$	47.26	47.47	7.43	7.36	13.78	13.44	15.77	15.91
CH_3	5	4	122-123	31.0	$C_{20}H_{38}N_4O_4S_2$	51.91	51.65	8.27	8.25	12.11	12.10	13.85	13.71
n-$C_{14}H_{29}$	5	4	113-114	43.6	$C_{46}H_{90}N_4O_4S_2$	66.77	66.89	10.96	10.96	6.77	6.64	7.75	7.83
CH_3	3	6	73-74	29.5	$C_{18}H_{34}N_4O_4S_2$	49.74	49.74	7.88	7.90	12.89	12.98	14.76	14.77
CH_3	5	6	79-80	81.1	$C_{22}H_{42}N_4O_4S_2$	53.84	53.69	8.62	8.64	11.42	11.80	13.06	12.68
n-$C_{14}H_{29}$	5	6	97-98	38.4	$C_{48}H_{94}N_4O_4S_2$	67.40	67.20	11.07	10.77	6.55	6.79	7.49	7.91

[a] The higher yields were obtained in the reaction of β-carbomethoxyethyl isothiocyanate with ethylenediamine and 1,4-diaminobutane, respectively.

TABLE III

N,N'-DI-(ω-CARBOXYALKYLCARBAMYL)-POLYMETHYLENEDIAMINES

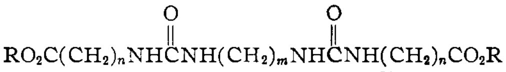


$HOOC(CH_2)_nNH\overset{O}{\overset{\|}{C}}NH(CH_2)_mNH\overset{O}{\overset{\|}{C}}NH(CH_2)_nCOOH$

n	*m*	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
2	2	209–210	81.0	$C_{10}H_{18}N_4O_6$	41.37	41.46	6.25	6.45	19.42	19.09
3	2	181–182	90.5	$C_{12}H_{22}N_4O_6$	45.27	44.92	6.97	6.91	17.60	17.70
5	2	182–183	92.1	$C_{16}H_{30}N_4O_6$	51.32	51.62	8.08	8.12	14.96	14.91
3	3	165–166	83.3	$C_{13}H_{24}N_4O_6$	46.98	47.08	7.28	7.25	16.86	16.97
5	3	170–171	91.8	$C_{17}H_{32}N_4O_6$	52.56	52.52	8.31	8.46	14.42	14.37
2	4	185–186	85.0	$C_{12}H_{22}N_4O_6$	45.27	45.49	6.97	7.36	17.60	17.78
3	4	185–186	94.0	$C_{14}H_{26}N_4O_6$	48.54	48.40	7.57	7.57	16.18	16.67
5	4	188–189	90.6	$C_{18}H_{34}N_4O_6$	53.71	53.47	8.52	8.61	13.92	13.79
3	5	168–169	87.2	$C_{15}H_{28}N_4O_6$	49.99	49.84	7.82	7.97	15.55	15.78
5	5	169–170	89.5	$C_{19}H_{36}N_4O_6$	54.79	54.87	8.71	8.71	13.45	13.58
3	6	172–173	86.0	$C_{16}H_{30}N_4O_6$	51.32	51.28	8.08	8.14	14.96	15.17
5	6	183–184	90.9	$C_{20}H_{38}N_4O_6$	55.79	55.41	8.90	8.90	13.01	12.80

TABLE IV

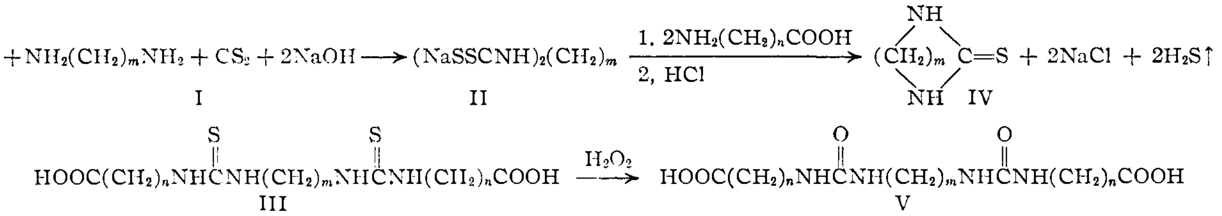
ESTERS OF N,N'-DI-(ω-CARBOXYALKYLCARBAMYL)-POLYMETHYLENEDIAMINES



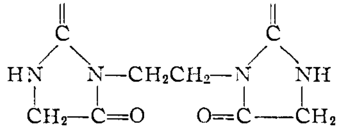
$RO_2C(CH_2)_nNH\overset{O}{\overset{\|}{C}}NH(CH_2)_mNH\overset{O}{\overset{\|}{C}}NH(CH_2)_nCO_2R$

R	*n*	*m*	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
CH_3	3	2	171–172	99.8	$C_{14}H_{26}N_4O_6$	48.54	48.67	7.57	7.60	16.17	15.67
CH_3	5	2	169–170	91.8	$C_{18}H_{34}N_4O_6$	53.71	53.81	8.51	8.53	13.92	13.72
n-$C_{14}H_{29}$	5	2	153–154	56.0	$C_{44}H_{86}N_4O_6$	68.86	69.18	11.30	11.31	7.31	7.72
CH_3	3	3	170–171	52.3	$C_{15}H_{28}N_4O_6$	49.98	49.75	7.83	7.91	15.55	15.38
CH_3	5	3	158–159	85.7	$C_{19}H_{36}N_4O_6$	54.79	54.53	8.71	8.46	13.45	13.37
n-$C_{14}H_{29}$	5	3	140–141	73.8	$C_{45}H_{88}N_4O_6$	69.16	69.07	11.35	11.05	7.17	7.08
CH_3	3	4	192–193	83.9	$C_{16}H_{30}N_4O_6$	51.33	51.27	8.08	8.28	14.96	14.72
n-$C_{14}H_{29}$	3	4	161–162	46.5	$C_{42}H_{82}N_4O_6$	68.23	67.96	11.19	10.78	7.58	7.77
CH_3	5	4	187–188	87.3	$C_{20}H_{38}N_4O_6$	55.80	55.54	8.89	8.81	13.02	13.27
n-$C_{14}H_{29}$	5	4	166–169	91.5	$C_{46}H_{90}N_4O_6$	69.46	69.21	11.41	11.21	7.05	7.54
CH_3	5	6	192–196	61.2	$C_{22}H_{42}N_4O_6$	57.61	57.43	9.23	9.36	12.22	12.61

drogen peroxide. The properties of these N,N'-di-(ω-carboxyalkylcarbamyl)-polymethylenediamines and some of their diesters are described in Tables III and IV, respectively.

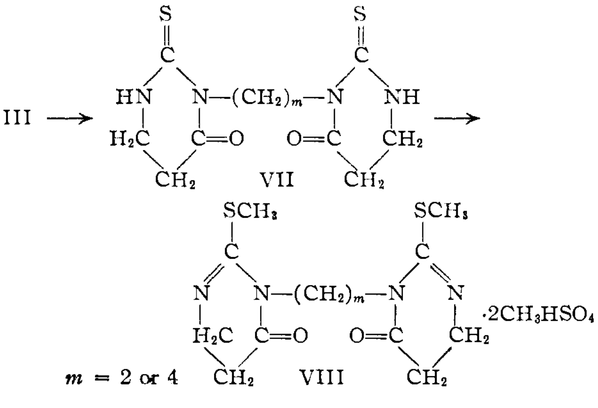


A cyclic product was obtained by heating two equivalents of glycine together with an aqueous solution of disodium ethylenebisdithiocarbamate. The analytical values for the new compound agree with those calculated for the expected 1,2-di-(3,3'-(2-thiohydantoinyl))-ethane (VI).[1]



VI

The N,N'-Di-(β-carboxyethylthiocarbamyl)-ethylenediamine (III, *n* = 2, *m* = 2) and -tetramethylenediamine (III, *n* = 2, *m* = 4) were cyclized to 1,2-di-(3,3'-(2-thiohydrouracilyl))-ethane (VII, *m* = 2) and 1,4-di-(3,3'-(2-thiohydrouracilyl))-butane (VII, *m* = 4), respectively, by



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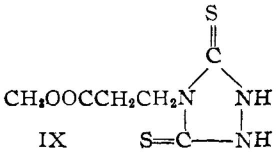
[1] The formation of thiohydantoins from substituted thioureas is discussed fully in Amino Acids. IV, *Can. J. Chem.*, **36**, 496 (1958).

heating with polyphosphoric acid. These bicyclic derivatives VII were converted into the corresponding S-methyl derivatives VIII by methylation with dimethyl sulfate. The free bases, 1,2-di-(3,3′ - (S - methyl - 2 - thiohydrouracilyl)) - ethane and 1,4 - di - (3,3′ - (S - methyl - 2 - thiohydrouracilyl))-butane, were prepared from their di-(methyl hydrogen sulfate) salts by treatment in aqueous solution with aqueous ammonia.

N,N′ - Di - (β - carbomethoxyethylthiocarbamyl)-hydrazine was prepared by treating hydrazine hydrate with two equivalents of β-carbomethoxyethyl isothiocyanate. This symmetrical hydrazine derivative on heating in the presence of polyphosphoric acid gave a new compound melting at 142°. The analytical values of this new compound are in good agreement with those calculated for 3,5 - dithio - 4 - (β- carbomethoxyethyl) - 2,3,4,5-tetrahydro-1,2,4-triazole (IX).


IX

Experimental[2]

N,N′-Di-(carboxyalkylthiocarbamyl)-polymethylenediamines.—A series of N,N′-di-(carboxyalkylthiocarbamyl)-polymethylenediamines have been prepared and their properties are listed in Table I. The methods of preparing these compounds are very similar and only the preparation of N,N′-di-(ε-carboxypentylthiocarbamyl)-tetramethylenediamine is described in detail.

Carbon disulfide was added dropwise to a stirred solution of 1,4-diaminobutane (22.0 g., 0.25 mole) in water (91 cc.) at 40° until the *p*H dropped from the original value of 12.5 to 9.3. This required about 19 g. (0.25 mole) of carbon disulfide. A solution of sodium hydroxide (20 g., 0.50 mole) in water (80 cc.) and carbon disulfide (19 g., 0.25 mole) were added simultaneously so that the temperature remained at 40–43° and the *p*H at 9.8–10.5. The final clear orange solution had a *p*H of 10.7.

A portion (87 cc.) of the above solution containing 0.1 mole of the 1,4-diaminobutane–carbon disulfide reaction product was combined with a solution of ε-aminocaproic acid hydrochloride (33.5 g., 0.20 mole) and sodium hydroxide (8.0 g., 0.20 mole) in water (100 cc.). This mixture was refluxed for 7 hours until the evolution of hydrogen sulfide had subsided. The cooled solution was filtered and the *p*H of the filtrate was adjusted to 2 with 37% hydrochloric acid solution. The resulting precipitate was removed by filtration and dried, yield 35.2 g. (81%). The product was purified by two crystallizations from methanol–water solution.

The filtrate was evaporated *in vacuo* under nitrogen to a volume of 100 cc. when crystals began to separate from the solution. These crystals melted at 174–176°, yield 2.31 g. (17.8%). One crystallization from absolute alcohol raised the melting point to 179.5–180.5°. Strack[3] reported a melting point of 177° for tetramethylenethiourea. A mixed melting point determination with a known[4] sample of tetramethylenethiourea (m.p. 177–179°) showed no depression.

The other dithiourea diacids were obtained in crude yields of 40.0 to 84.4%. The following compounds (III) were purified by straight-forward recrystallization: $n = 2$, $m = 2$ (20% ethanol–water); $n = 3$, $m = 3$ (water); $n = 5$, $m = 3$ (28% methanol–water); $n = 3$, $m = 4$ (acetone–water). The purification of III ($n = 5$, $m = 2$) required careful recrystallization conditions (20% methanol–water, 5 l./mole of ethylenediamine) in order to separate pure material. Investigation of condensation conditions to produce this compound (III, $n = 5$, $m = 2$) revealed that a 30% increase of amino acid in the reaction mixture raised the yield of pure product from 29 to 36%. The impurity (pentamethylenethiourea or its polymer) of crude III ($n = 3$, $m = 5$) was less soluble than the thiourea diacid. The desired product was obtained by concentration of the mother liquors after crystallization of the crude material from 50% methanol–water. The remaining compounds (III, $n = 5$, $m = 5$; $n = 3$, $m = 6$; $n = 5$, $m = 6$) were purified by reprecipitation with hydrochloric acid from their solutions in 5% aqueous sodium bicarbonate. The impurities (polymethylene thioureas) were insoluble in cold (10°) bicarbonate solution.

N,N′-Di-(carboxyalkylcarbamyl)-polymethylenediamines.—The N,N′-di-(carboxyalkylthiocarbamyl)-polymethylenediamines were oxidized with alkaline hydrogen peroxide solution into the corresponding N,N′-di-(carboxyalkylcarbamyl)-polymethylenediamines. The physical properties of the latter series of compounds are described in Table III.

The oxidation of one of these compounds was conducted as follows: a solution of N,N′-di-(ε-carboxypentylthiocarbamyl)-tetramethylenediamine (1.0 g., 0.0023 mole) and sodium hydroxide (0.55 g., 0.14 mole) in water (10 cc.) was treated at 20–25° with 2.40 cc. of 7.7 molar hydrogen peroxide solution. This solution was allowed to stand at room temperature overnight after which it was acidified to a *p*H of 2.5. The mixture was diluted with water (50 cc.) and the product was recovered by filtration, yield 0.82 g. (90.6%). The melting point was raised from 177–179° to 188–189° by two crystallizations from glacial acetic acid. It was relatively insoluble in water, acetone, ethanol, aqueous methanol and aqueous ethanol but it was soluble in dimethylformamide.

Diesters of N,N′-Di-(ω-carboxyalkylthiocarbamyl)-polymethylenediamines. Method A.—N,N′- Di - (γ - carboxypropylthiocarbamyl)-tetramethylenediamine (2.0 g., 0.0053 mole) in 25 cc. of 1% methanolic hydrogen chloride solution was allowed to stand at 10° for 16 hours. The solvent was removed *in vacuo* and the crystalline residue was crystallized from acetone–pentane solution, yield 1.90 g. (84.5%). This crude ester (m.p. 90–95°) could not be purified easily by direct crystallization. A portion (1.03 g.) was dissolved in acetone (20 cc.) and the solution was passed through a column of neutral alumina (30 g.; 2.0 cm. dia.). The acetone eluates were combined and evaporated to dryness. After the residue was crystallized from acetone, it melted at 122–123°, yield 0.48 g.

Method B.—A mixture of N,N′-di-(ε-carboxypentylthiocarbamyl)-tetramethylenediamine (5.0 g., 0.011 mole) and myristyl alcohol (6.17 g., 0.028 mole) was heated in a wax-bath at 130° until it became molten. Sulfuric acid (0.25 cc.) was added and the clear melt was heated at 130° under a stream of nitrogen for 2 hours. After the reaction mixture had cooled to room temperature, it was triturated with ether. The insoluble ester (m.p. 105–110°) weighed 4.16 g. (43.6%). It was dissolved in chloroform (100 cc.) and the chloroform solution was passed through a column of neutral alumina (30 g.; 2.0 cm. dia.). The fractions on evaporation gave a crystalline residue which was recrystallized from ethyl acetate (25 cc.). The pure dimyristyl ester melted at 113–114°, yield 2.77 g.

Diesters of N,N′-Di-(ω-carboxyalkylcarbamyl)-polymethylenediamines. Method A.—N,N′-Di-(ε-carboxypentylcarbamyl)-trimethylenediamine (1.0 g., 0.0025 mole) in methanol (30 cc.) containing 10% by weight of dry hydrogen chloride was allowed to stand at room temperature overnight. The almost clear solution was filtered and the filtrate was evaporated to dryness. On addition of water (5 cc.) to the semi-liquid residue a crystalline product (m.p. 153–156°) was obtained, yield 0.917 g. (85.7%). Crystallization from methanol raised the melting point to a constant value of 158–159°.

Method B.—The myristyl esters of the N,N′-(ω-carboxyalkylcarbamyl)-polymethylenediamines were prepared in the same manner as described above for the preparation of the myristyl esters of the N,N′-di-(ω-carboxyalkylthiocarbamyl)-polymethylenediamines. The dimyristyl esters were purified by direct crystallization without previous passage through alumina.

Reaction of Disodium Ethylenebisdithiocarbamate with Glycine.—An aqueous solution (37 cc.) containing 0.05 mole

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[2] All melting points are uncorrected. Microanalyses were determined by Micro Tech Laboratories, Skokie, Ill.

[3] E. Strack, *Z. physiol. Chem.*, **180**, 198 (1929).

[4] A. F. McKay and M.-E. Kreling, *Can. J. Chem.*, **35**, 1438 (1957).

of disodium ethylenebisdithiocarbamate was treated with glycine (7.5 g., 0.1 mole) in water (50 cc.). This mixture was refluxed for 7 hours and the solution was cooled and filtered. The filtrate was evaporated to dryness *in vacuo* and the residue treated with concentrated hydrochloric acid (50 cc.). The resulting mixture was heated for 45 minutes on a steam-bath and the insoluble yellow product (m.p. 280° with dec.) was recovered from the cooled mixture by filtration, yield 5.72 g. (44.3%). This product was insoluble in boiling acetone, methanol, benzene, ethyl acetate, ethanol, chloroform, water and acetic acid, although it was slightly soluble in aqueous acetone and dilute acetic acid. It melted with decomposition around 280° after it was crystallized from dimethylformamide–water solution. The compound is soluble in cold dimethylformamide.

Anal. Calcd. for $C_8H_{10}N_4O_2S_2$: C, 37.19; H, 3.90; N, 21.69; S, 24.83. Found: C, 37.67; H, 3.99; N, 21.55; S, 24.45.

β-Carbomethoxyethyl isothiocyanate (b.p. 110–112° (1 mm.)) was prepared in 81% yield as previously[5] described.

Reaction of β-Carbomethoxyethyl Isothiocyanate with Polymethylenediamines.—β - Carbomethoxyethyl isothiocyanate (2.7 g., 0.018 mole) was added to a solution of tetramethylenediamine (0.82 g., 0.009 mole) in absolute methanol (6 cc.). After the mixture was refluxed for 2 hours, it was cooled and then diluted with petroleum ether (90 cc.). On standing in the refrigerator for 3 hours, this solution gave 3.23 g. (95%) of crystals. The melting point of the crude N,N′-di - (β - carbomethoxyethylthiocarbamyl)-tetramethylenediamine was raised from 88–90° to 94–95° by one crystallization from acetone–petroleum ether (2:3) solution, yield 2.78 g.

A similar reaction with ethylenediamine gave a 79% yield of crude N,N′-di-(β-carbomethoxyethylthiocarbamyl)-ethylenediamine (m.p. 129–131°). Several crystallizations from acetone–petroleum ether (1:4) raised the melting point to 138–139°. N,N′-Di-(β-carbomethoxyethylthiocarbamyl)-ethylenediamine and -tetramethylenediamine are described in Table II. Alkaline hydrolysis of these diesters gave the corresponding diacids (III, $n = 2$, $m = 4$ and $n = 2$. $m = 2$) in 92–94% yields.

N,N′-Di-(β-carbomethoxyethylthiocarbamyl)-hydrazine.—A solution of β-carbomethoxyethyl isothiocyanate (2.98 g., 0.02 mole) and hydrazine hydrate (0.5 g., 0.01 mole) in methanol (10 cc.) was refluxed for 80 minutes. When the solution cooled to room temperature, it was diluted with acetone (20 cc.) and petroleum ether (70 cc.). After the mixture was cooled for 2 hours, the crystals (m.p. 169–170°) were removed by filtration, yield 2.45 g. (76%). Crystallization from acetone–petroleum ether (1:4) solution raised the melting point to 171–172°.

Anal. Calcd. for $C_{10}H_{18}N_4O_4S_2$: C, 37.25; H. 5.63; N, 17.38; S, 19.89. Found: C, 37.28; H, 5.55; N, 17.56; S, 19.78.

1,2-Di-(3,3′-(2-thiohydrouracilyl))-butane.—The polyphosphoric acid used in the following cyclization reaction was prepared by adding phosphorus pentoxide (36 g.) to 85% phosphoric acid (25 cc.). This mixture was stirred for approximately 0.5 hour until no more phosphorus pentoxide dissolved. After the solution was filtered through glass wool, it was stored in a glass stoppered flask.

N,N′-Di-(β-carboxyethylthiocarbamyl)-tetramethylenediamine (9.67 g., 0.028 mole) was mixed into a thick paste with preheated (80°) polyphosphoric acid (*ca.* 5 cc.). The paste was heated at 150–160° with occasional stirring for 15 minutes after which the reaction mixture was cooled and diluted with water (250 cc.). This diluted reaction product was allowed to stand in the refrigerator overnight, after which the crystalline product (m.p. 241–243° with dec.) was recovered by filtration, yield 74%. Three crystallizations from aqueous formic acid solution raised the melting point to 253–254° dec.

Anal. Calcd. for $C_{12}H_{18}N_4O_2S_2$: C, 45.85; H, 5.77; N, 17.82; S, 20.40. Found: C, 45.40; H, 5.88; N, 17.78; S, 20.18.

A sample of 1,4-di-(3,3′-(2-thiohydrouracilyl))-butane (1.12 g., 0.0035 mole) in dimethyl sulfate (5 cc.) was heated at 125° until a clear solution was obtained. After the clear solution was heated at 100° for 1 hour, it was cooled. The solution was diluted with acetone (25 cc.) and ether (65 cc.) and the needle-like crystals were removed by filtration, yield 1.32 g. (65.3%). The melting point was raised from 152–154° to 158–159° by one crystallization from 90% aqueous acetone. The analysis indicated that a di-(methyl hydrogen sulfate) salt of the methylated product was prepared.

Anal. Calcd. for $C_{16}H_{30}N_4O_{10}S_4$: C, 33.92; H, 5.34; N, 9.89; S, 22.63. Found: C, 33.91; H, 5.67; N, 9.91; S, 22.78.

The dipicrate of 1,4-di-(3,3′-(S-methyl-2-thiohydrouracilyl))-butane was prepared in the usual manner from water. It melted at 182–183° dec., yield 83%.

Anal. Calcd. for $C_{26}H_{28}N_{10}O_{16}S_2$: C, 38.99; H, 3.52; N, 17.49; S, 8.01. Found: C, 38.70; H, 3.71; N, 17.55; S, 7.82.

A small sample of 1,4-di-(3,3′-(S-methyl-2-thiohydrouracilyl))-butane di-(methyl hydrogen sulfate) (0.20 g., 0.00035 mole) in water (1 cc.) was treated dropwise with dilute ammonia solution until an alkaline reaction was obtained. The white precipitate (m.p. 185–186°) was recovered by filtration, yield 0.115 g. (92%). The melting point did not change after several recrystallizations.

Anal. Calcd. for $C_{14}H_{22}N_4O_2S_2$: C, 49.10; H, 6.48; N, 16.36; S, 18.72. Found: C, 49.31; H, 6.51; N, 16.00; S, 18.23.

1,2-Di-(3,3′-(2-thiohydrouracilyl))-ethane.—N,N′-Di-(β-carboxyethylthiocarbamyl)-ethylenediamine (9.42 g., 0.029 mole) was cyclized to 1,2-di-(3,3′-(2-thiohydrouracilyl))-ethane in 73% yield by the method described above for the preparation of 1,4-di-(3,3′-(2-thiohydrouracilyl))-butane. After crystallization from formic acid–water (1:3), the melting point was raised from 291–293° to 294–295° dec.

Anal. Calcd. for $C_{10}H_{14}N_4O_2S_2$: C, 41.95; H, 4.93; N, 19.57; S, 22.40. Found: C, 41.90; H, 4.91; N, 19.65; S, 22.27.

A sample (3.63 g., 0.013 mole) of 1,2-di-(3,3′-(2-thiohydrouracilyl))-ethane was methylated with dimethyl sulfate (initially at 160° and finally at 125°) and the product was isolated under the conditions described above for the di-(methyl hydrogen sulfate) salt of 1,4-di-(3,3′-(S-methyl-2-thiohydrouracilyl))-butane. The crude product melted at 185–190°, yield 6.60 g. (97%). Crystallization from water–acetone (1:13) solution and methanol–acetone (1:2.3) solution raised the melting point to 202–203°.

Anal. Calcd. for $C_{14}H_{26}N_4O_{10}S_4$: C, 31.22; H, 4.87; N, 10.40; S, 23.80. Found: C, 31.36; H, 4.91; N, 10.18; S, 24.13.

The dipicrate (m.p. 214–216° dec.) was formed in 74% yield from aqueous solution. The picrate was purified by solution in methanol–acetone (1:1) solution and precipitation with petroleum ether. It melted at 220–222° dec.

Anal. Calcd. for $C_{24}H_{24}N_{10}O_{16}S_2$: C, 37.31; H, 3.13; N, 18.13; S, 8.30. Found: C, 37.18; H, 3.40; N, 18.15; S, 8.17.

1,2-Di-(3,3′-(S-methyl-2-thiohydrouracilyl))-ethane di-(methyl hydrogen sulfate) was converted into its free base in 63% yield by the dropwise addition of ammonia to its aqueous solution as described above in the preparation of the butane homolog. The melting point of the free base was raised from 165–166° to 167–168° by two crystallizations from acetone–petroleum ether (1:15) solution.

Anal. Calcd. for $C_{12}H_{18}N_4O_2S_2$: C, 45.84; H, 5.77; N, 17.82; S, 20.40. Found: C, 46.03; H, 5.85; N, 17.82; S, 19.81.

3,5-Dithio-4-(β-carbomethoxyethyl)-2,3,4,5-tetrahydro-1,2,4-triazole.—A thick paste of N,N′-di-(β-carbomethoxyethylthiocarbamyl)-hydrazine (1.0 g., 0.003 mole) in polyphosphoric acid (*ca.* 5 cc.) was heated at 120° for 7 minutes. After the cooled mixture was diluted with water (100 cc.). the aqueous mixture was placed in the refrigerator for 1.5 hours. The product (m.p. 141–142°) was recovered by filtration, yield 0.3 g. (42%). The melting point was not changed by further crystallization.

Anal. Calcd. for $C_6H_9N_3O_2S_2$: C, 32.86; H, 4.14; N, 19.16; S, 29.24. Found: C, 32.78; H, 4.26; N. 19.12; S, 28.66.

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[5] D. L. Garmaise, R. Schwartz and A. F. McKay, THIS JOURNAL, **80**, 3332 (1958).