strong bands at 11.90, 12.16, 12.93, 13.15, 13.62 and 14.31 μ.

Oxidation of 7,12-Dihydro-7-phenylpleiadene.—A solution of 0.35 g. (3.5 mmoles) of chromium trioxide in 1.5 ml. of water and 10 ml. of acetic acid was gradually added to a solution of III (0.52 g., 1.7 mmoles) in 15 ml. of warm acetic acid. After one hour on the steam-bath, the dark green solution was poured into excess ice-water and the mixture extracted once with ether and then with benzene. The extracts were combined, washed with water, 5% sodium carbonate (no solid acid obtained on acidification), water again, and then dried over sodium sulfate. After the orange solution had been concentrated to *ca.* 5 ml. it was chromatographed over alumina (20 × 1 cm. column), using benzene as eluent; 0.10 g. of III was first eluted from the column (19% recovery), this being followed by 0.35 g. (65%) of a colorless, crystalline product (VI), m.p. 198–198.5° (from ethanol–acetone). No additional products were obtained although several colored bands remained on the column.

Compound VI was characterized by infrared as a diaryl ketone,[9] showing strong bands at 6.03, 10.95, 11.99, 12.60, 13.15, 13.48, 13.78 and 14.30 mμ, and no absorption in the hydroxyl region.

Anal. Calcd. for $C_{24}H_{16}O$: C, 89.97; H, 5.04. Found[17]: C, 90.16; H, 5.10.

Unsuccessful attempts were made to prepare a 2,4-DNPH using ethanolic 2,4-dinitrophenylhydrazine hydrochloride, and a hydrazone, by refluxing VI in excess ethanolic hydrazine hydrate.

(17) Microanalysis by Dr. Alfred Bernhardt, Mulheim, Germany.

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[Contribution No. 24 from the L. G. Ryan Research Laboratories of Monsanto Canada Ltd. and Research Laboratories of Ayerst, McKenna and Harrison Ltd.]

Bacteriostats. II.[1] The Chemical and Bacteriostatic Properties of Isothiocyanates and their Derivatives

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A number of cyanoalkyl isothiocyanates, substituted benzyl isothiocyanates, substituted benzyl benzyldithiocarbamates and substituted benzyl thioureas were prepared for evaluation as bacteriostats. The preparations and relative bacteriostatic properties of these compounds are described.

A number of substituted amines were converted to the corresponding isothiocyanates which were evaluated as bacteriostats. Some of the amines were prepared by the Gabriel synthesis and the new phthalimide derivatives, which were isolated as intermediates, are described in Table I. One of the amines, (±)-3-aminobutyronitrile, was resolved into its enantiomorphs. The amines were converted into isothiocyanates by a modification of the Kaluza[4–6] procedure. The properties of these isothiocyanates are described in Table II. These isothiocyanates were further characterized by their use in the formation of substituted thioureas. The thioureas together with their physical constants are listed in Table III. When the ω-cyanoalkyl isothiocyanates were added to aliphatic diamines in an anhydrous medium, a number of N,N′-di-(substitutedthiocarbamyl)-polymethylenediamines (Table IV) were obtained. The corresponding N,N′-di-(substituted carbamyl)-hexamethylenediamines (Table V) were prepared by the addition of hexamethylene diisocyanate to two equivalents of the amine in an inert solvent.

Some of the substituted amines were converted into the corresponding urethan derivatives (Table VI) by reaction with ethyl chloroformate. 4-(2-Cyanoethyl)- and 4-(10-cyanodecyl)-thiosemicarbazides also were prepared.

A series of substituted benzyl benzyldithiocarbamates were prepared by the condensation of substituted benzyl chlorides with the triethylamine salts of substituted benzyldithiocarbamic acids. The products are described in Table VII.

Bacteriostatic Activities.—A large number of isothiocyanates have been isolated[7] from seeds of plants belonging to the Cruciferae family. They exist in plants in the combined form as glycosides. Several plants containing isothiocyanates have antibiotic properties and have been used in home remedies for a number of ailments. Allyl isothiocyanate, which is present in horse-radish, has been found[8] to have antibacterial properties. More recently Das, Kurup and Rao[9] have identified benzyl isothiocyanate as a component of the antibiotic, Pterygospermin, which was isolated from the Indian Drumstick tree (*Moringa pterygosperma*). They found that benzyl isothiocyanate possessed strong bacteriostatic properties. It proved to be more effective than either phenylethyl or phenyl isothiocyanates. In view of these observations, it is of interest to compare the bacteriostatic activities of alkyl and benzyl isothiocyanates with the new isothiocyanates described in Table II.

Table VIII lists the bacteriostatic activities of the isothiocyanates against several gram-positive and gram-negative organisms. The cyanoalkyl isothiocyanates having a two-carbon chain between the cyano and isothiocyanate groups are more effective against gram negative organisms than the

(1) Paper I: M. E. Kreling and A. F. McKay, *Can. J. Chem.*, **36**, 775 (1958).

(2) Monsanto Canada, Ltd., Ville LaSalle, Que.

(3) Ayerst, McKenna and Harrison, Ltd., Montreal, Que.

(4) (a) L. Kaluza, *Monatsh.*, **30**, 717 (1909); (b) **33**, 364 (1912).

(5) J. E. Hodgkins and M. G. Ettlinger, *J. Org. Chem.*, **21**, 404 (1956).

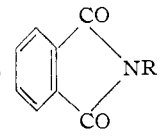
(6) D. L. Garmaise, R. Schwartz and A. F. McKay, This Journal, **80**, 3332 (1958).

(7) C. M. Suter, "Medicinal Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 245.

(8) M. J. Foter, *J. Bact.*, **38**, 353 (1939).

(9) B. R. Das, P. A. Kurup and P. L. N. Rao, *Naturwissenschaften*, **41**, 95 (1954).

TABLE I

N-SUBSTITUTED PHTHALIMIDES, 

R	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
3-Cyanopropyl	78.3	79–80[a]	$C_{12}H_{10}N_2O_2$	67.28	67.41	4.71	4.67	13.09	13.07		
4-Cyanobutyl	92.0	75.5–76.5	$C_{13}H_{12}N_2O_2$	68.40	68.86	5.30	5.14	12.28	12.03		
5-Cyanopentyl	97.6	42–44	$C_{14}H_{14}N_2O_2$	69.40	69.39	5.83	5.93	11.56	11.31		
6-Cyanohexyl	93.2	59–60	$C_{15}H_{16}N_2O_2$	70.29	70.27	6.29	6.39	10.93	11.20		
4-Cyanobenzyl	78.2	180–184[b]									
2,4-Dichlorobenzyl	97.4	181–182.5	$C_{15}H_9Cl_2NO_2$	58.85	58.94	2.96	3.08	4.57	4.71	23.17	23.60
3,4-Dichlorobenzyl	98.5	155.5–156	$C_{15}H_9Cl_2NO_2$	58.85	59.18	2.96	3.09	4.57	4.42	23.17	23.06

[a] Reported m.p. 65–66°; A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1369 (1947). [b] Reported m.p. 183–184°; H. K. Guntlier, *Ber.*, **23**, 1058 (1890).

TABLE II

ISOTHIOCYANATES (RNCS)

R	Yield, %	B.p. °C.	Mm.	$n^{25}D$	d^{20}_4	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
Dodecyl	78	125–127	0.13	1.4797	0.910	$C_{13}H_{25}NS$	68.67	68.52	11.08	10.80	6.16	5.83	14.10	14.20
2-Cyanoethyl	77	84	.07	1.54243	1.166	$C_4H_4N_2S$	42.84	42.94	3.59	3.73	24.98	25.21	28.59	28.28
2-Cyanopropyl	79	71–72	.09	1.5235	1.118	$C_5H_6N_2S$	47.60	47.96	4.76	5.17	22.21	22.27	25.40	24.80
1-Methyl-2-cyanoethyl	80	67–69	.09	1.5180	1.120	$C_5H_6N_2S$	47.60	47.89	4.76	4.95	22.21	21.72		
3-Cyanopropyl	71	106	.05	1.5262	1.155	$C_5H_6N_2S$	47.60	47.79	4.76	5.18				
4-Cyanobutyl	73	131–132	.1	1.4921	1.098	$C_6H_8N_2S$	51.41	51.58	5.74	5.65	19.98	20.08	22.87	22.34
5-Cyanopentyl	74	123.5–125.5	.17	1.5159	1.092	$C_7H_{10}N_2S$	54.53	54.50	6.54	6.38	18.18	18.49	20.79	20.41
6-Cyanohexyl	73	132–133	.32	1.5090	1.052	$C_8H_{12}N_2S$	57.09	57.23	7.19	7.23	16.66	16.83	18.06	18.91
10-Cyanodecyl	80	166–168	.12	1.49435	0.984	$C_{12}H_{20}N_2S$	64.24	64.32	8.98	9.04	12.49	12.14		
4-Cyanomethylphenyl	53	123–125	.08[a]			$C_9H_8N_2S$	62.00	61.73	3.45	3.74	16.08	15.82	18.38	19.10
4-Cyanobenzyl	94	128–130	.03[b]			$C_9H_8N_2S$	62.00	62.27	3.45	3.55	16.08	16.28	18.38	18.08
2-Chlorobenzyl	79	94–98	.23	1.60914	1.282	C_8H_6ClNS[c]	52.32	52.32	3.29	3.45	7.63	8.07	17.46	16.85
4-Chlorobenzyl	78	105–108	.35	1.61114	1.291	C_8H_6ClNS[d]	52.32	52.39	3.29	3.58	7.63	7.97	17.46	16.87
4-Nitrobenzyl	62	149–151	.19[e]			$C_8H_6N_2O_2S$	49.47	50.03	3.11	3.07	14.43	14.57	16.51	16.76
2,4-Dichlorobenzyl	72	117–120	.55	1.62371	1.375	$C_8H_5Cl_2NS$[f]	44.04	44.11	2.31	2.34	6.43	6.61	14.70	14.50
3,4-Dichlorobenzyl	79	122–124	.32	1.62170	1.409	$C_8H_5Cl_2NS$[g]	44.04	44.12	2.31	2.33	6.43	6.79	14.70	14.28
3-Nitro-4-chlorobenzyl	68	144–146	.04[h]			$C_8H_5ClN_2O_2S$[i]	42.02	42.47	2.20	2.49	12.25	12.74	14.02	13.61

[a] M.p. 50–51°. [b] M.p. 73–73.5°. [c] M.p. 37–38°. [d] M.p. 58–59°. [e] Calcd.: Cl, 19.31. Found: Cl, 18.62. [f] Calcd.: Cl, 19.31. Found: Cl, 18.58. [g] Calcd.: Cl, 32.51. Found: Cl, 31.90. [h] Calcd.: Cl, 32.51. Found: Cl, 31.65. [i] Calcd. Cl, 15.51. Found: Cl, 15.30.

longer chain homologs. On the other hand, 10-cyanodecyl isothiocyanate is much more effective against gram-positive organisms than the lower homologs. A similar relationship between chain length and bacteriostatic activities has been observed[10] with the thiosulfinates.

The following alkyl and cyanoalkyl derivatives displayed no inhibition of bacterial growth with the organisms listed in Table VIII at a concentration of 1 in 10,000; *n*-propyl isothiocyanate, 14-cyanotetradecyl isothiocyanate, 4-cyanobutyl thiocyanate, 1-cyanodecyl thiocyanate, 1,3-di-(2-cyanoethyl) - thiourea, 1,3 - di - (10 - cyanodecyl) - thiourea, the N,N′-di-(ω-cyanoalkylthiocarbamyl)-polymethylenediamines, the N,N′-di-(ω-cyanoalkylcarbamyl)-polymethylenediamines, 1,3-di-(4-cyanomethylphenyl)-urea and 1-(2-cyanoethyl)-3-(5-carboxypentyl)-thiourea.

In general the benzyl isothiocyanates are much more effective bacteriostats than the cyanoalkyl isothiocyanates. The monosubstituted benzyl derivatives have about the same order of activity as benzyl isothiocyanate while 3,4-dichlorobenzyl isothiocyanate has outstanding bacteriostatic properties. It is apparent from a comparison of the activities of 4-cyanobenzyl isothiocyanate with 4-cyanomethylphenyl isothiocyanate that the benzyl derivatives are much more effective than the phenyl derivatives.

4-Chlorobenzyl 3,4-dichlorobenzyldithiocarbamate is the most effective bacteriostat for gram-positive organisms listed in Table IX. In this series the 3,4-dichlorobenzyl group is more effective when attached to nitrogen than to sulfur. Also the 4-nitrobenzyl group appeared to be more effective against gram-negative bacteria when it was attached to nitrogen rather than sulfur. These observations led to the screening of some benzylthioureas as bacteriostats. The most effective compound, which was evaluated in this series, was 1,3-di-(3,4-dichlorobenzyl)-thiourea (Table X). This work is being continued.

(10) L. D. Small, J. H. Bailey and C. J. Cavallito, THIS JOURNAL, **69**, 1710 (1947).

Table III

Substituted Thioureas

Name, thiourea	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
1-Benzyl-3-octadecyl-	51	98–98.5	$C_{26}H_{46}N_2S$	74.57	74.72	11.08	10.62	6.69	6.88	7.66	8.25
1,3-Dioctadecyl-	68	88–89	$C_{37}H_{76}N_2S$	76.46	76.11	13.19	12.78	4.82	5.18	5.52	5.60
Dodecyl-	100	109–109.5	$C_{13}H_{28}N_2S$	63.88	64.04	11.54	11.76	11.46	11.56	13.12	12.95
1,3-Didodecyl-	100	78–78.5	$C_{25}H_{52}N_2S$	72.75	72.84	12.69	12.92	6.79	7.02	7.77	7.43
1-Benzyl-3-dodecyl-	100	89.5–90	$C_{20}H_{34}N_2S$	71.86	71.99	10.26	10.30	8.39	8.61	9.59	9.18
1-Phenyl-3-(4-cyanobutyl)-	82	99.5–101.5	$C_{12}H_{15}N_3S$	61.76	62.19	6.48	6.52	18.01	18.17	13.75	13.90
1-Phenyl-3-(2-carbethoxyethyl)-	74	74–75	$C_{12}H_{16}N_2O_2S$	57.11	57.37	6.39	6.58	11.11	11.16	12.71	12.62
1-Phenyl-3-(2-carbamylethyl)-	54	134.5–135	$C_{10}H_{13}N_3OS$	53.85	53.85	5.85	6.05	18.85	18.97	14.35	14.30
1,3-Di-(2-cyanoethyl)-	81	155–155.5	$C_7H_{10}N_4S$	46.13	46.51	5.54	5.63	30.74	30.70	17.59	17.70
4-Cyanomethylphenyl-	58	140–141	$C_9H_9N_2S$	56.52	56.61	4.74	4.89	21.99	21.99	16.75	16.35
1,3-Di-(2-cyanopropyl)-	94	120–126	$C_9H_{14}N_4S$	51.40	51.52	6.71	7.09	26.64	26.83	15.24	14.92
1-Benzyl-3-(2-cyanopropyl)-	80	57–58	$C_{12}H_{15}N_3S$	61.77	61.66	6.48	6.28	18.05	18.09	13.75	13.38
1-Benzyl-3-(1-methyl-2-cyanoethyl)-	71	90–93	$C_{12}H_{15}N_3S$	61.77	62.33	6.48	6.56	18.05	17.72	13.75	12.75
1,3-Di-(1-methyl-2-cyanoethyl)-	63	98–108	$C_9H_{14}N_4S$	51.40	51.49	6.70	6.77	26.64	26.36	15.24	15.11
1-Benzyl-3-(4-cyanobenzyl)-	96	149–149.5	$C_{16}H_{15}N_3S$	68.29	68.25	5.37	5.61	14.93	15.15	11.39	11.43
1,3-Di-(4-cyanobutyl)-	79	81–82	$C_{11}H_{18}N_4S$	55.42	55.85	7.61	7.56	23.51	23.35	13.46	13.25
1-Benzyl-3-(2-cyanoethyl)-	82	77–78	$C_{11}H_{13}N_3S$	60.24	60.63	5.97	5.88	19.17	19.37	14.62	14.54
1-(6-Hydroxyhexyl)-3-(2-cyanoethyl)-	93	79.5–81	$C_{10}H_{19}N_3OS$	52.37	52.70	8.35	8.35	18.32	17.90	13.98	14.01
1-Benzyl-3-(4-cyanobutyl)-	97	117.5–118.5	$C_{13}H_{17}N_3S$	63.13	63.18	6.93	6.96	16.98	16.55	12.96	13.11
1-Benzyl-3-(10-cyanodecyl)-	74	80–81	$C_{19}H_{29}N_3S$	68.84	69.17	8.82	8.64	12.67	12.49	9.67	9.52
1,3-Di-(10-cyanodecyl)-	51	56–57	$C_{23}H_{42}N_4S$	67.93	67.98	10.41	10.38	13.78	13.69	7.88	8.02
1-(2-Cyanoethyl)-3-(3-carboxypropyl)-	47	101–102	$C_8H_{13}N_3O_2S$	44.64	44.51	6.08	5.93	19.52	19.22	14.89	14.71
1-(10-Cyanodecyl-3-(6-hydroxyhexyl)-	73	57–58	$C_{18}H_{35}N_3OS$	63.29	63.48	10.33	10.13	12.33	12.23	9.38	9.00
1-(10-Cyanodecyl)-3-(5-carboxypentyl)-	89	77–78	$C_{18}H_{33}N_3O_2S$	60.81	60.70	9.36	9.25	11.82	11.48	9.02	9.20
1-(10-Cyanodecyl)-3-(3-carboxypropyl)-	78	84–85	$C_{15}H_{29}N_3O_2S$	58.70	58.77	8.92	8.83	12.83	12.53	9.79	9.45
6-Cyanohexyl-	96	130.5–131	$C_8H_{15}N_3S$	51.85	51.93	8.16	8.14	22.68	22.69	17.31	17.21
1-Benzyl-3-(6-cyanohexyl)-	97	90–90.5	$C_{15}H_{21}N_3S$	65.40	65.39	7.69	7.66	15.26	15.21	11.64	11.58
1,3-Di-(6-cyanohexyl)-	99	57.5–58.5	$C_{15}H_{26}N_4S$	61.18	61.24	8.90	8.95	19.03	19.36	10.89	10.86
5-Cyanopentyl-	75	73–75	$C_7H_{13}N_3S$	49.09	49.16	7.65	7.76	24.54	24.64	18.73	18.74
2-Chlorobenzyl-	96	127–127.5	$C_8H_9ClN_2S$[a]	47.89	47.61	4.52	4.41	13.96	14.35	15.97	15.85
1,3-Di-(2-chlorobenzyl)-	91	126.5–128.5	$C_{15}H_{14}Cl_2N_2S$[b]	55.38	55.53	4.34	4.23	8.62	8.85	9.86	9.89
4-Chlorobenzyl-	96	142.5–143	$C_8H_9ClN_2S$[c]	47.89	47.65	4.52	4.37	13.96	14.29	15.97	15.82
1,3-Di-(4-chlorobenzyl)-	69	141–143	$C_{15}H_{14}Cl_2N_2S$[d]	55.38	55.24	4.34	4.15	8.62	8.97	9.86	9.78
2,4-Dichlorobenzyl-	86	197–197.5	$C_8H_8Cl_2N_2S$[e]	40.86	40.62	3.43	3.41	11.92	12.39	13.62	13.55
1,3-Di-(2,4-dichlorobenzyl)-	96	181.5–182.5	$C_{15}H_{12}Cl_4N_2S$[f]	45.70	45.34	3.07	3.11	7.11	7.73	8.14	8.14
3,4-Dichlorobenzyl-	100	153.5–154	$C_8H_8Cl_2C_2S$[g]	40.86	40.73	3.43	3.34	11.92	12.38	13.62	13.60
1,3-Di-(3,4-dichlorobenzyl)-	71	138–139	$C_{15}H_{12}Cl_4N_2S$[h]	45.70	45.76	3.07	3.18	7.11	7.35	8.14	8.10
1-(4-Chlorobenzyl)-3-(3,4-dichlorobenzyl)-	84	111–112	$C_{15}H_{13}Cl_3N_2S$[i]	50.07	50.27	3.64	3.68	7.79	8.19	8.92	8.72
4-Nitrobenzyl-	88	113.5–115	$C_8H_9N_3O_2S$	45.48	45.72	4.29	4.22	19.94	19.78	15 18	15.32
1,3-Di-(4-nitrobenzyl)-	89	212.5–213.5	$C_{15}H_{14}N_4O_4S$	52.01	52.42	4.08	4.27	16.18	16.08	9.26	9.07
14-Cyanotetradecyl-	100	79–81	$C_{16}H_{31}N_3S$	64.60	63.73	10.50	10.40	14.13	14.39	10.77	10.70
1.3-Di-(3-nitro-4-cblorobenzyl)-	86	165–166	$C_{15}H_{12}Cl_2N_4O_4S$[j]	43.39	43.72	2.91	3.17	13.50	13.52	7.72	7.50
1-Phenyl-3-(2-cyanoethyl)-	97	123–124	$C_9H_{11}N_3S$	58.50	58.45	5.40	5.47	20.48	20.44	15.62	15.44
1-Phenyl-3-(2-carbomethoxyethyl)-	24	66.5–67	$C_{11}H_{14}N_2O_2S$	55.43	55.61	5.92	6.33	11.76	12.15	13.46	13.70

[a] Calcd.: Cl, 17.67. Found: Cl, 17.71. [b] Calcd.: Cl, 21.80. Found: Cl, 21.80. [c] Calcd.: Cl, 17.67. Found: Cl, 17.80. [d] Calcd.: Cl, 21.80. Found: Cl, 21.80. [e] Calcd.: Cl, 30.16. Found: Cl, 30.07. [f] Calcd.: Cl, 35.98. Found: Cl, 35.96. [g] Calcd.: Cl, 30.16. Found: Cl, 30.02. [h] Calcd.: Cl, 35.98. Found: Cl, 36.01. [i] Calcd.: Cl, 29.57. Found: Cl, 29.78. [j] Calcd.: Cl, 17.08. Found: Cl, 16.75.

Table IV

N,N′-Di-(substituted Thiocarbamyl)-polymethylenediamines

$$RNHCNH(CH_2)_nNHCNHR$$
(S above each C)

R	n	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
2-Cyanoethyl	2	97	144–145	$C_{10}H_{16}N_6S_2$	42.23	42.48	5.67	5.67	29.56	29.45	22.54	22.46
2-Cyanoethyl	3	95	127–128	$C_{11}H_{18}N_6S_2$	44.27	44.44	6.08	6.19	28.16	28.11	21.49	21.01
2-Cyanoethyl	4	83	143–144	$C_{12}H_{20}N_6S_2$	46.13	46.36	6.45	6.58	26.90	26.48	20.52	20.36
2-Cyanoethyl	5	54	115–117	$C_{13}H_{22}N_6S_2$	47.81	47.80	6.79	6.84	25.73	25.48	19.67	19.33
4-Cyanobutyl	2	80	165–166.5	$C_{14}H_{24}N_6S_2$	49.39	49.26	7.10	6.91	24.68	24.88	18.83	18.56
4-Cyanobutyl	4	84	170–171	$C_{16}H_{28}N_6S_2$	52.14	52.52	7.66	7.76	22.80	22.95	17.40	17.02

Experimental[11]

Amines.—3-Aminopropionitrile[12,13] and 2-methyl-3-aminopropionitrile[14] were prepared by known methods. 3-Aminobutyronitrile was prepared by the addition of ammonia to crotonitrile as described by Bruylants[15] with the modification of heating the reaction mixture for 2 hours at 125–130°.

4-Aminobutyronitrile was prepared by the following modification of the phthalimide synthesis. A solution of 4-bromobutyronitrile (25 g., 0.17 mole) and potassium phthalimide (34.4 g., 0.18 mole) in dimethylformamide (100 ml.) was stirred at 90° for 40 minutes. After dilution with water (500 ml.), the aqueous solution was extracted with chloroform (2 × 100 ml.) and the chloroform solution was washed with 0.5% sodium hydroxide solution (80 ml.) and

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

(12) S. R. Buc, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 93.

(13) A. F. McKay, G. Y. Paris and D. L. Garmaise, This Journal, **80**, 6276 (1958).

(14) J. B. Dickey, U. S. Patent 2,659,739 (1953).

(15) P. Bruylants, *Bull. soc. chim. Belges*, **32**, 256 (1923).

TABLE V

N,N'-DI-(SUBSTITUTED CARBAMYL)-HEXAMETHYLENEDIAMINES

$$RNHCNH(CH_2)_6NHCNHR$$

R	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
2-Cyanoethyl	99	203–204	$C_{14}H_{24}N_6O_2$	54.54	54.18	7.84	7.67	27.33	27.24
3-Cyanopropyl	97	162–164	$C_{16}H_{28}N_6O_2$	57.13	56.86	8.39	7.92	24.77	24.80
4-Cyanobutyl	96	164.5–165.5	$C_{18}H_{32}N_6O_2$	59.30	59.34	8.85	8.45	23.06	23.06
10-Cyanodecyl	97	170.5–171.5	$C_{30}H_{56}N_6O_2$	67.64	67.47	10.60	10.28	15.77	15.98
2-Hydroxyethyl	78	182–183	$C_{12}H_{26}N_4O_4$	49.63	49.32	9.03	8.98	19.30	19.04
3-Hydroxypropyl	75	178–179	$C_{14}H_{30}N_4O_4$	52.81	52.85	9.50	9.67	17.60	17.45
6-Hydroxyhexyl	83	181.5–182.5	$C_{20}H_{42}N_4O_4$	59.68	59.37	10.52	10.09	13.92	13.89
2-Carboxyethyl	72	200–200.5	$C_{14}H_{26}N_4O_6$	48.54	48.19	7.57	7.45	16.18	15.50
2-Carbamylethyl	88	224–225	$C_{14}H_{28}N_6O_4$	48.82	48.90	8.20	8.43	24.40	24.07
3-Carbamylpropyl	67	201–202.5	$C_{16}H_{32}N_6O_4$	51.60	51.45	8.66	8.84	22.56	22.20
10-Carbamyldecyl	95	199.5–201.5	$C_{30}H_{60}N_6O_4$	63.34	63.04	10.63	10.47	14.78	14.91
2-Carbethoxyethyl	33	159–160	$C_{18}H_{34}N_4O_6$	53.71	53.95	8.51	8.59	13.92	14.21

TABLE VI

URETHAN DERIVATIVES, $RNHCOOC_2H_5$

R	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
n-Octadecyl	100	60–60.5	$C_{21}H_{43}NO_2$	73.82	73.88	12.69	12.66	4.10	4.46
2-Cyanoethyl	81[a]	31–32	$C_6H_{10}N_2O_2$	50.67	50.02	7.09	7.07	19.72	19.61
5-Cyanopentyl	59[b]		$C_9H_{16}N_2O_2$	58.70	58.27	8.75	8.68		
5-Carbamylpentyl	82	104–104.5	$C_9H_{18}N_2O_3$	53.45	53.71	8.97	8.93	13.86	13.96
5-Carboxypentyl	85	50–50.5	$C_9H_{17}NO_4$	53.16	53.37	8.42	8.59	6.92	7.41
n-Heptafluorobutyl	25[c]	31.5–32	$C_6H_8F_7NO_2$	31.00	31.35	2.97	3.07		

[a] B.p. 111–112° (0.11 mm.), $n^{25}D$ 1.4472, d^{20}_4 1.143. [b] B.p. 134–136° (0.065 mm.), $n^{25}D$ 1.4578. [c] B.p. 93–97°.

water (80 ml.). Evaporation of the dried chloroform solution gave N-(3-cyanopropyl)-phthalimide, m.p. 78–80°, yield 28.5 g. (78.3%). Crystallization from acetone–petroleum ether solution raised the melting point to 79–80°.

N-(3-Cyanopropyl)-phthalimide (40 g., 0.187 mole) and hydrazine hydrate (20 g., 0.4 mole) in ethanol (150 ml.) were allowed to stand at room temperature overnight. After the solution was diluted with water (50 ml.), it was adjusted to *p*H 3.5 with hydrochloric acid and the precipitated phthalyl hydrazide was removed by filtration. The filtrate was evaporated at 40° *in vacuo* to a small volume. The residue was cooled to 0° and then treated with 10 *N* sodium hydroxide solution (50 ml.). This basic solution was extracted with chloroform (5 × 100 ml.) and the dried chloroform extract was evaporated to dryness. The residue was extracted with ether (150 ml.) and anhydrous hydrogen chloride was passed through the ether solution to precipitate 4-aminobutyronitrile hydrochloride (m.p. 130–140°), yield 12.5 g. (56.6%). Crystallization from ethanol raised the melting point to 142–144°. The reported[16] melting point is 138–140°.

The following amines were prepared by essentially the same procedure: **5-aminovaleronitrile** (yield 35.8%, b.p. 106–110° (17 mm.), reported[17] b.p. 92–93° (12 mm.)), **6-aminocapronitrile** (yield 61.8%, b.p. 117–120° (16 mm.), reported[18] b.p. 116–118° (14 mm.)), **7-aminoheptanonitrile** (yield 39.2%, b.p. 125–128° (12 mm.), reported[18] b.p. 113–114° (9 mm.)), **11-aminoundecanonitrile** (yield 80.2%, b.p. 107° (0.1 mm.), reported[16] b.p. 136–138° (2 mm.)), **4-cyanobenzylamine hydrochloride** (yield 67.7%, m.p. 270–272°, reported[19] m.p. 274°), **2,4-dichlorobenzylamine** (yield 34.1%, b.p. 85–91° (0.5 mm.), $n^{25}D$ 1.57704, d^{20}_4 1.330; reported[20] b.p. 135° (15 mm.)) and **3,4-dichlorobenzylamine** (yield 43.5%, b.p. 89–92° (0.55 mm.), $n^{25}D$ 1.57593, d^{20}_4 1.330; reported[20] b.p. 139–140° (17 mm.)).

The properties of the intermediate N-substituted phthalimides are described in Table I.

(16) A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1369 (1947).

(17) P. Kurtz, *Ann.*, **572**, 65 (1951).

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

(19) F. Ehrlich, *Ber.*, **34**, 3368 (1901).

(20) M. Métayer and Ng. Dat-Xuong, *Bull. soc. chim. France*, 615 (1954).

2,4-Dichlorobenzylamine hydrochloride and **3,4-dichlorobenzylamine hydrochloride** were prepared from the corresponding benzyl chlorides by the following procedure. A solution of 2,4-dichlorobenzyl chloride (500 g., 2.55 moles) and hexamethylenetetramine in chloroform (3600 ml.) was refluxed for 4 hours. The solution was cooled and 2,4-dichlorobenzylhexaminium chloride (m.p. 193–195° dec.) was recovered by filtration. The filtrate on evaporation gave a second crop of the hexaminium salt, total yield 100%.

Anal. Calcd. for $C_{13}H_{17}Cl_3N_4$: C, 46.51; H, 5.11; Cl, 31.69; N, 16.69. Found: C, 46.22; H, 5.23; Cl, 32.06; N, 16.23.

2,4-Dichlorobenzylhexaminium chloride was suspended in ethanol (2500 ml.) and hydrogen chloride was passed through the suspension for 3 hours. The precipitated 2,4-dichlorobenzylamine hydrochloride melted at 273–276° after one crystallization from water (3500 ml.), yield 326 g. (60.5%). The reported[20] melting point is 275°.

3,4-Dichlorobenzylhexaminium chloride (yield 100%, m.p. 204–205° dec.) was prepared in a similar manner.

Anal. Calcd. for $C_{13}H_{17}Cl_3N_4$: C, 46.51; H, 5.11; Cl, 31.69; N, 16.69. Found: C, 46.45; H, 5.24; Cl, 32.17; N, 16.25.

Its alcoholic suspension on treatment with hydrogen chloride over a period of 7 hours gave 3,4-dichlorobenzylamine hydrochloride, m.p. 244.5–246°, in 75.5% yield. The reported[20] m.p. is 244°.

3-Nitro-4-chlorobenzylamine.—Potassium borohydride (3 g., 0.055 mole) and lithium chloride (25 g., 0.59 mole) were added to a solution of ethyl 3-nitro-4-chlorobenzoate[21] (m.p. 60–61°, 114.8 g., 0.51 mole) in tetrahydrofuran (450 ml., freshly distilled over sodium). The suspension was stirred at room temperature for 22 hours after which water (600 ml.) was added and the stirring was continued for 15 minutes. The mixture was extracted with ether (6 × 200 ml.) and the combined and dried ether extracts were evaporated to dryness. The residue (91.5 g., m.p. 55–61°) after one crystallization from water (7 liters) melted at 64–65°, yield 69 g. (68.5%). Another crystallization from water raised the melting point of the 3-nitro-4-chlorobenzyl alcohol to 66°.

(21) H. Hübner, *Ann.*, **222**, 166 (1884).

TABLE VII

ESTERS OF SUBSTITUTED BENZYLDITHIOCARBAMIC ACIDS, RSSCNHR′

R	R′	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
2,4-Dichlorobenzyl	4-Chlorobenzyl	87.5	83–84[a]	$C_{15}H_{12}Cl_4NS_2$	47.81	48.22	3.21	3.39	28.23	27.94	3.72	3.95	17.02	16.90
3,4-Dichlorobenzyl	4-Chlorobenzyl	88.9	87–88[a]	$C_{15}H_{12}Cl_4NS_2$	47.81	48.01	3.21	3.30	28.23	28.05	3.72	3.62	17.02	17.06
4-Chlorobenzyl	2,4-Dichlorobenzyl	78.5	81[a]	$C_{15}H_{12}Cl_4NS_2$	47.81	47.93	3.21	3.31	28.23	28.23	3.72	4.03	17.02	16.79
2,4-Dichlorobenzyl	2,4-Dichlorobenzyl	90	71–73[b]	$C_{15}H_{10}Cl_4NS_2$	43.82	43.96	2.70	3.02	34.49	34.29	3.41	3.65	15.59	15.20
3,4-Dichlorobenzyl	2,4-Dichlorobenzyl	77.2	58–59[a]	$C_{15}H_{10}Cl_4NS_2$	43.82	43.89	2.70	2.80	34.49	34.35	3.41	3.50	15.59	15.38
4-Chlorobenzyl	3,4-Dichlorobenzyl	63	60–61[c]	$C_{15}H_{12}Cl_3NS_2$	47.81	47.56	3.21	3.27	28.23	27.80	3.72	3.35	17.02	16.82
2,4-Dichlorobenzyl	3,4-Dichlorobenzyl	84.5	84.5–85[b]	$C_{15}H_{10}Cl_4NS_2$	43.82	44.07	2.70	2.79	34.49	33.95	3.41	3.62	15.59	15.23
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	68.8	81–82[d]	$C_{15}H_{10}Cl_4NS_2$	43.82	44.06	2.70	3.06	34.49	34.10	3.41	3.78	15.59	15.33
4-Nitrobenzyl	3,4-Dichlorobenzyl	76.5	149–150[e]	$C_{15}H_{12}Cl_2N_2O_2S_2$	46.52	46.51	3.12	3.08	18.31	18.18	7.24	7.44	16.56	16.31
4-Chlorobenzyl	4-Nitrobenzyl	68.5	137–137.5[f]	$C_{15}H_{12}ClN_2O_2S_2$	51.05	51.04	3.71	3.82	10.05	9.88	7.94	8.04	18.17	17.90
2,4-Dichlorobenzyl	4-Nitrobenzyl	69	117–117.5[f]	$C_{15}H_{12}Cl_2N_2O_2S_2$	46.52	46.60	3.12	3.37	18.31	17.73	7.24	7.56	16.56	15.87
3,4-Dichlorobenzyl	4-Nitrobenzyl	73.5	103.5[f]	$C_{15}H_{12}Cl_2N_2O_2S_2$	46.52	46.35	3.12	3.13	18.31	18.38	7.24	7.27	16.56	16.52

[a] Crystallized from ether–hexane solution. [b] Aqueous methanol. [c] Heptane. [d] 2-Propanol. [e] Ethanol. [f] Methanol.

Anal. Calcd. for $C_7H_6ClNO_3$: C, 44.82; H, 3.22; Cl, 18.90; N, 7.46. Found: C, 44.87; H, 3.33; Cl, 18.88; N, 7.26.

Thionyl chloride (81 g., 0.6 mole) was added dropwise over a period of 90 minutes to a refluxing solution of 3-nitro-4-chlorobenzyl alcohol (64 g., 0.34 mole) in dry chloroform (100 ml.). After heating under reflux for an additional 90 minutes, the chloroform was removed by evaporation. The residue on distillation *in vacuo* gave 3-nitro-4-chlorobenzyl chloride, b.p. 122° (10 mm.), $n^{25}D$ 1.58184, yield 98%.

Anal. Calcd. for $C_7H_5Cl_2NO_2$: C, 40.81; H, 2.44; Cl, 12.84. Found: C, 41.07; H, 2.58; Cl, 12.97.

3-Nitro-4-chlorobenzyl chloride (67 g., 0.325 mole) was converted through 3-nitro-4-chlorobenzylhexaminium chloride (yield 89.5%, m.p. 193–198°) into 3-nitro-4-chlorobenzylamine hydrochloride (yield 37.4%, m.p. 227–228°) by the procedure described above in the preparation of 2,4-dichlorobenzylamine hydrochloride.

Anal. Calcd. for $C_7H_8Cl_2N_2O_2$: C, 37.69; H, 3.61; Cl, 31.79; N, 12.56. Found: C, 38.04; H, 3.58; Cl, 31.98; N, 12.19.

The picrate (m.p. 208–210° dec.) was formed from water in the usual manner. One crystallization from ethanol raised the melting point to 210° dec.

Anal. Calcd. for $C_{13}H_{10}ClN_5O_9$: C, 37.56; H, 2.42; Cl, 8.53; N, 16.85. Found: C, 37.55; H, 2.64; Cl, 8.63; N, 17.12.

Resolution of (±)-3-Aminobutyronitrile.—A solution of (±)-3-aminobutyronitrile (62 g., 0.74 mole) in methanol (400 ml.) was added to dibenzoyl D-tartaric acid (278 g., 0.74 mole) in methanol (1500 ml.). The solution was allowed to stand overnight and the precipitated salt (172.1 g., m.p. 183–184°, $[\alpha]^{25}D$ −100 ± 0.6° (methanol)) was collected. Recrystallization from methanol gave the pure isomer, m.p. 183–184°, $[\alpha]^{25}D$ −101.8 ± 0.6° (methanol), yield 80.6 g. (49.5%). Addition of ether to the concentrated mother liquors gave the diastereoisomeric salt, m.p. 164.5–165°, yield 39 g. (24%). Recrystallization from methanol gave the pure isomer melting at 169–170°, $[\alpha]^{25}D$ −97.6 ± 0.6° (methanol).

The higher melting diastereoisomer (75 g., 0.17 mole) in methanol (2500 ml.) was passed through a column of Amberlite IR-120 resin (350 ml. of resin in the acid form previously washed with methanol). The column was washed with methanol (8 l.) and then the combined aminonitrile was eluted with 1% aqueous ammonia solution (800 ml.). The eluate was concentrated *in vacuo* until all the ammonia was removed and the residual solution was neutralized with hydrochloric acid. Concentration *in vacuo* gave (−)-3-aminobutyronitrile hydrochloride, m.p. 173–175°, $[\alpha]^{25}D$ −11.2 ± 0.6° (methanol), yield 12.8 g. (63%). Two crystallizations from ethanol gave the pure isomer, m.p. 183–183.5°, $[\alpha]^{25}D$ −13.7 ± 0.4° (methanol).

Anal. Calcd. for $C_4H_9ClN_2$: C, 39.83; H, 7.52; Cl, 29.40; N, 23.24. Found: C, 39.83; H, 7.51; Cl, 29.42; N, 22.94.

The lower melting dibenzoyl D-tartaric acid salt (36 g., 0.08 mole) was treated in the same manner with Amberlite IR-120 resin to give (+)-3-aminobutyronitrile hydrochloride, m.p. 170–173°, $[\alpha]^{25}D$ +8.5 ± 0.4° (methanol), yield 8.5 g. (87.5%). Four crystallizations from ethanol yielded the pure isomer, m.p. 183–183.5°, $[\alpha]^{25}D$ +13.9 ± 0.5° (methanol).

(−)-3-Aminobutyronitrile hydrochloride (7 g., 0.058 mole) in methanol (160 ml.) was passed through a column of Amberlite IRA-400 (140 ml. of resin in the basic form previously treated with methanol). The column was washed with methanol (400 ml.) and the combined eluate and washing was evaporated. The residue on distillation *in vacuo* in a collar flask gave (−)-3-aminobutyronitrile, $[\alpha]^{25}D$ −1.6 ± 0.4° (methanol), yield 4.9 g. (100%).

(+)-3-Aminobutyronitrile hydrochloride (4.5 g., 0.037 mole) was similarly converted into (+)-3-aminobutyronitrile $[\alpha]^{25}D$ +2.0 ± 0.3° (methanol), yield 3.1 g. (100%).

Isothiocyanates.—The isothiocyanates described in Table I were prepared by the same procedure so only the preparation of 2-cyanoethyl isothiocyanate is described in detail.

A solution of carbon disulfide (7.8 g., 0.1 mole) in chloroform (20 ml.) was added dropwise over a period of 30 minutes to a stirred solution of 3-aminopropionitrile (7 g., 0.1 mole) and triethylamine (10.1 g., 0.1 mole) in chloroform (30 ml.)

TABLE VIII

BACTERIOSTATIC ACTIVITIES (M.I.C., $1/X.10^{-3}$)[a] OF ISOTHIOCYANATES, RNCS

R	*M. pyogenes* var. aureus(S)	*M. pyogenes* var. aureus(R)	*Sarcina lutea*	*Strept. faecalis*	*E. coli* #198	*A. aerogenes*	*S. pullorum*	*Ps. aeruginosa*	*Pr. mirabilis*	*Pr. vulgaris*
2-Cyanoethyl	40	40	80	20	40	40	20	20	80	80
2-Cyanopropyl	20	40	80	20	80	20	20	>10	160	160
1-Methyl-2-cyanoethyl	40	40	40	40	40	20	20	>10	160	160
2-Carbomethoxyethyl[b]	20	20	80	20	20	20	10	10	40	40
4-Cyanobutyl-	40	20	80	20	40	20	10	10	80	40
10-Cyanodecyl-	160	320	160	<320	10	<10	<10	<10	10	10
Benzyl	320	320	640	160	320	40	20	20	320	160
4-Cyanobenzyl	320	320	640	160	320	20	20	10	320	160
4-Cyanomethylphenyl	20	10	20	10	10	<10	<10	<10	10	10
4-Chlorobenzyl	320	320	320	160	320	80	80	80	160	80
4-Nitrobenzyl	320	320	1280	160	320	20	40	10	320	160
2-Chlorobenzyl	320	320	160	160	80	20	20	20	80	80
2,4-Dichlorobenzyl	640	640	320	640	160	40	40	20	160	
3,4-Dichlorobenzyl	2560	5120	2560	2560	640	20	20	20	640	640
3-Nitro-4-chlorobenzyl	1280	1280	1280	640	640	40	20	10	640	640

[a] Minimal inhibitory concentration determined by serial dilution tube technique, *e.g.*, the value 40 is equivalent to a dilution of 1 part in 40,000. [b] D. L. Garmaise, *et al.*, THIS JOURNAL, **80**, 3332 (1958).

TABLE IX

BACTERIOSTATIC ACTIVITIES (M.I.C. $1/X.10^{-3}$) OF ESTERS OF SUBSTITUTED BENZYLDITHIOCARBAMIC ACIDS, RSSCNHR'

R	R'	*M. pyogenes* var. aureus-(S)	*M. pyogenes* var. aureus-(R)	*Sarcina lutea*	*Strept. faecalis*	*E. coli* #198	*A. aerogenes*	*S. pullorum*	*Ps. aeruginosa*	*Pr. mirabilis*	*Pr. vulgaris*
2,4-Dichlorobenzyl	4-Chlorobenzyl	160	160	160	80	80	20	10	10	80	80
3,4-Dichlorobenzyl	4-Chlorobenzyl	320	640	320	160	160	10	10	20	160	160
4-Chlorobenzyl	2,4-Dichlorobenzyl	80	80	80	40	20	10	10	10	20	20
2,4-Dichlorobenzyl	2,4-Dichlorobenzyl	160	160	160	80	80	10	10	10	80	40
3,4-Dichlorobenzyl	2,4-Dichlorobenzyl	320	320	640	640	160	10	10	40	80	80
4-Chlorobenzyl	3,4-Dichlorobenzyl	2560	2560	1280	2560	160	10	10	10	80	40
2,4-Dichlorobenzyl	3,4-Dichlorobenzyl	640	640	320	640	160	40	40	10	160	160
3,4-Dichlorobenzyl	3,4-Dichlorobenzyl	1280	1280	640	1280	160	20	10	10	20	40
4-Chlorobenzyl	4-Nitrobenzyl	80	80	80	40	20	10	10	10	20	20
2,4-Dichlorobenzyl	4-Nitrobenzyl	40	80	80	40	40	40	20	10	160	40
3,4-Dichlorobenzyl	4-Nitrobenzyl	80	80	160	80	80	40	40	10	640	160
4-Nitrobenzyl	3,4-Dichlorobenzyl	1280	640	80	80	40	20	20	<10	40	20

TABLE X

BACTERIOSTATIC ACTIVITIES (M.I.C., $1/X.10^{-3}$) OF THIOUREA DERIVATIVES

Compound, 3-(3,1-dichlorobenzyl)-thiourea	*M. pyogenes* var. aureus(S)	*M. pyogenes* var. aureus(R)	*Sarcina lutea*	*Strept. faecalis*	*E. coli* #198	*A. aerogenes*	*S. pullorum*	*Ps. aeruginosa*	*Pr. mirabilis*	*Pr. vulgaris*
1-(β-Chloroethyl)-	80	40	20	20	20	20	10	10	20	10
1-(3,4-Dichlorobenzyl)-	2560	2560	2560	2560	>10	>10	>10	>10	>10	>10
1-(4-Chlorobenzyl)-	640	2560	320	2560	>10	>10	>10	>10	>10	>10

at −10°. The cooling bath was removed and the reaction mixture was stirred for 5 minutes at 25°. Ethyl chloroformate was added dropwise over a period of 20 minutes at 0° and then the temperature was allowed to rise to 17° over a period of 20 minutes. A solution of triethylamine (10.1 g., 0.1 mole) in chloroform (30 ml.) was added at 17° and the solution was stirred for 30 minutes. This solution was diluted further with chloroform (100 ml.) and washed with 5% sodium hydroxide solution (2 × 60 ml.), 5% hydrochloric acid solution (2 × 60 ml.) and water (2 × 60 ml.). The chloroform solution was dried over anhydrous sodium sulfate and then evaporated to dryness. The residue on fractionation *in vacuo* gave 2-cyanoethyl isothiocyanate, yield 9.4 g. (77%).

Thioureas. Method A.—A solution of the isothiocyanate in absolute ether or absolute benzene was added to an amine in the same solvent. The precipitated thiourea derivative was recovered by filtration and crystallized from the appropriate solvent.

Method B.—The thiourea derivatives possessing a carboxyl group were prepared by the following general procedure.

A solution of 2-cyanoethyl isothiocyanate (0.56 g., 0.005 mole) in methanol (5 ml.) was added to a solution of 4-aminobutyric acid (0.52 g., 0.005 mole) and 0.98 *N* sodium hydroxide solution (5.1 ml.) in methanol (10 ml.). After 2 hours at room temperature, the solution was concentrated *in vacuo* at 25° to a volume of 5 ml. The residue was adjusted to *p*H 3 after which the product (m.p. 101–102°) crystallized slowly, yield 0.5 g. (46.6%). Crystallization did not alter the melting point.

The properties of the thioureas prepared by these procedures are listed in Table III.

N,N'-Di-(substituted carbamyl)-hexamethylenediamines.—3-Aminopropionitrile (2.8 g., 0.04 mole) in benzene (10 ml.) was added dropwise over a period of 30 minutes to a solution of hexamethylene diisocyanate (3.36 g., 0.02 mole) in benzene (40 ml.) at 25–30°. The precipitated product

(m.p. 198–201°) was recovered by filtration, yield 6.15 g. (99.4%). One crystallization from methanol raised the melting point to 203–204°.

The other N,N'-di-(cyanoalkylcarbamyl)- and N,N'-di-(hydroxyalkylcarbamyl)-hexamethylenediamines listed in Table V were prepared in the same manner and purified by crystallizing from methanol.

N,N'-Di-(2-Carboxyethylcarbamyl)-hexamethylenediamine.—A solution of hexamethylene diisocyanate (8.4 g., 0.05 mole) in acetone (20 ml.) was added dropwise over a period of 40 minutes to a stirred solution of β-alanine (8.9 g., 0.1 mole) and sodium hydroxide (4 g., 0.1 mole) in water (100 ml.). Acidification of the solution yielded the product, m.p. 196–197°, yield 14.5 g. (83.8%). Crystallization from glacial acetic acid raised the melting point to 200–200.5°.

A portion (2.0 g., 0.0058 mole) of N,N'-di-(2-carboxyethylcarbamyl)-hexamethylenediamine in 8% ethanolic hydrogen chloride solution (100 ml.) was allowed to stand at room temperature for 18 hours. The residue from the evaporated solution was extracted with chloroform (100 ml.) and the chloroform extract was washed with 5% sodium hydroxide solution (2 × 100 ml.) and water. The dried chloroform solution on evaporation gave a crystalline residue of N,N'-di-(2-carbethoxyethylcarbamyl)-hexamethylenediamine, yield 0.77 g. (33%). Crystallization from ethanol gave a constant melting point of 159–160°.

N,N'-Di-(2-Carbamylethylcarbamyl)-hexamethylenediamine. Method A.—A solution of N,N'-di-(2-cyanoethylcarbamyl)-hexamethylenediamine (1.23 g., 0.004 mole) in concentrated sulfuric acid (7.4 g.) was allowed to stand at room temperature overnight. The solution was poured into ice-water (100 ml.) and the diamide (m.p. 224–225°) was recovered by filtration, yield 1.22 g. (88.4%).

The other N,N'-di-(carbamylalkylcarbamyl)-hexamethylenediamines listed in Table V were prepared in the same manner.

Method B.—N,N'-Di-(2-carbethoxyethylcarbamyl)-hexamethylenediamine (0.32 g., 0.0008 mole) and sodium (0.018 g., 0.0008 mole) in methanol (30 ml.) saturated with ammonia were allowed to stand at room temperature for 4 days. N,N'-Di-(2-carbamylethylcarbamyl)-hexamethylenediamine (m.p. 221–223°) separated from the solution, yield 0.21 g. (75.7%).

N,N'-Di-(substituted thiocarbamyl)-polymethylenediamines.—2-Cyanoethyl isothiocyanate (0.67 g., 0.006 mole) was added to a solution of ethylenediamine (0.18 g., 0.003 mole) in absolute ethanol (5 ml.). The reaction was exothermic and the product (m.p. 144–145°) separated from the cooled solution, yield 0.83 g. (94.5%). The melting point was not altered by further crystallization.

The N,N'-di-(substituted thiocarbamyl)-polymethylenediamines in Table IV were prepared by this procedure.

N-2-Cyanoethylurethan.—Ethyl chloroformate (10.9 g., 0.1 mole) was added dropwise over a period of 30 minutes to a stirred solution of 3-aminopropionitrile (7 g., 0.1 mole) and sodium hydroxide (4 g., 0.1 mole) in water (50 ml.) at 5–10°. The stirring was continued for 10 minutes at room temperature after which the solution was extracted with chloroform (100 ml.). The dried chloroform solution was evaporated to dryness and the residue was distilled *in vacuo*. The distillate (b.p. 111–112° (0.11 mm.)) solidified (m.p. 31–32°) on standing, yield 11.4 g. (80.5%).

N-*n*-Octadecylurethan and N-*n*-heptafluorobutylurethan were prepared by the same method. These urethans are described in Table VI.

N-5-Carboxypentylurethan.—Ethyl chloroformate (44.5 g., 0.41 mole) was added dropwise over a period of 90 minutes to a stirred solution of ε-aminocaproic acid (52.5 g., 0.4 mole) and sodium hydroxide (32 g., 0.8 mole) in water (300 ml.) at 8–12°. After the solution was stirred for an additional 15 minutes at 12°, it was acidified with hydrochloric acid solution. The acidified solution was extracted with chloroform (200 ml.) and the dried chloroform extract was taken to dryness. The residual N-5-carboxypentylurethan (m.p. 48–50°) was obtained in 85.4% (69.4 g.) yield. Two crystallizations from ether–petroleum ether solution raised the melting point to 50–50.5°.

N-5-Carbamylpentylurethan.—A solution of N-5-carboxypentylurethan (10.2 g., 0.05 mole) in thionyl chloride (11.9 g., 0.10 mole) was maintained at 40–45° for 90 minutes. The solution was evaporated to dryness *in vacuo* and the residue was extracted with ether (50 ml.). A saturated solution of ammonia in ether (250 ml.) was added and the suspension was filtered. The precipitate was extracted with chloroform (150 ml.) and the chloroform on evaporation gave N-5-carbamylpentylurethan (m.p. 98–100°) in 82.2% (8.3 g.) yield. One crystallization from acetone raised the melting point to 104–104.5°.

N-5-Cyanopentylurethan.—A mixture of N-5-carbamylurethan and phosphorus oxychloride (4.92 g., 0.032 mole) was heated at 70–75° for 2 hours. Water (20 ml.) was added and the solution was extracted with ether (3 × 20 ml.). The residue from the ether extract on distillation *in vacuo* gave N-5-cyanopentylurethan (b.p. 134–136° (0.065 mm.)), yield 6.9 g. (59%).

4-(2-Cyanoethyl) thiosemicarbazide.—2-Cyanoethyl isothiocyanate (1.1 g., 0.01 mole) was added to hydrazine hydrate (0.5 g., 0.01 mole) in ethanol (10 ml.) at 0°. The product (m.p. 142–142.5°) separated out immediately, yield 0.84 g. (52%). The melting point was not altered by recrystallization from methanol.

Anal. Calcd. for $C_4H_8N_4S$: C, 33.32; H, 5.59; N, 38.86. Found: C, 33.69; H, 5.89; N, 38.62.

A solution of 4-(2-cyanoethyl) thiosemicarbazide (0.29 g., 0.002 mole) and benzaldehyde (0.3 g., 0.0024 mole) in ethanol (10 ml.) was refluxed for 15 minutes. On cooling, the solution deposited crystals of 4-(2-cyanoethyl)-benzal thiosemicarbazone (m.p. 193–195°), yield 0.4 g. (88.4%). Crystallization from absolute ethanol raised the melting point to 195°.

Anal. Calcd. for $C_{11}H_{12}N_4S$: C, 56.90; H, 5.21; N, 24.12; S, 13.80. Found: C, 56.83; H, 5.45; N, 24.15; S, 13.76.

A solution of 4-(2-cyanoethyl) thiosemicarbazide (0.29 g., 0.002 mole) and phenyl isothiocyanate (0.29 g., 0.002 mole) in ethyl acetate (10 ml.) was refluxed for 10 minutes. The concentrated solution on cooling gave 1-phenyl-6-(2-cyanoethyl)-bithiourea, m.p. 163–163.5°, yield 0.41 g. (78.6%).

Anal. Calcd. for $C_{11}H_{13}N_5S_2$: C, 47.29; H, 4.70; N, 25.10; S, 22.92. Found: C, 46.91; H, 4.67; N, 25.42; S, 23.03.

4-(10-Cyanodecyl) thiosemicarbazide, m.p. 86.5–87°, was prepared in 72.4% yield by the method used in the preparation of 4-(2-cyanoethyl)thiosemicarbazide.

Anal. Calcd. for $C_{12}H_{24}N_4S$: C, 56.30; H, 9.44; N, 21.88; S, 12.50. Found: C, 56.60; H, 9.53; N, 22.01; S, 12.46.

Substituted Benzyl Benzyldithiocarbamates.—The substituted benzyl benzyldithiocarbamates described in Table VII were prepared by the same method which is described below for the preparation of 2,4-dichlorobenzyl 3,4-dichlorobenzyldithiocarbamate. Yields recorded in Table VII are based on the formation of the ester from the triethylamine salt of the dithiocarbamic acid.

A solution of 3,4-dichlorobenzylamine (26.4 g., 0.15 mole) and triethylamine (15.7 g., 0.15 mole) in ether (150 ml.) was treated at −10° with carbon disulfide (12.5 g., 0.165 mole). The triethylamine salt of 3,4-dichlorobenzyldithiocarbamic acid separated from solution as colorless crystals (m.p. 117–119° dec., yield 50.2 g. (94.6%)). In a similar manner the triethylamine salts of 4-chlorobenzyl- (m.p. 113° dec.), 2,4-dichlorobenzyl- (m.p. 122–123.5° dec.) and 4-nitrobenzyldithiocarbamic acids (m.p. 83–85° dec.) were prepared in 93, 91 and 78% yield, respectively. The salt (22 g., 0.006 mole) in methanol (75 ml.) was treated with 2,4-dichlorobenzyl chloride (13.7 g., 0.07 mole). After removal of the methanol, the residue was dissolved in ether (500 ml.) and the ether solution was washed with 5% hydrochloric acid solution, 5% aqueous sodium hydroxide solution and water. The dried ether solution was evaporated to dryness and the residue was crystallized from heptane (500 ml.). The crystals of 2,4-dichlorobenzyl 3,4-dichlorobenzyldithiocarbamate melted at 84.5–85°, yield 21.7 g. (84.5%).

ω-Cyanoalkyl Thiocyanates.—The following procedure was used in the preparation of all of the cyanoalkyl thiocyanates.

A solution of 11-bromoundecanitrile (7.38 g., 0.03 mole) and potassium thiocyanate (3 g., 0.03 mole) in acetone (50 ml.) was refluxed for 90 minutes. The suspension was filtered and the filtrate was evaporated to dryness. The residue was extracted with benzene (100 ml.) after which the benzene extract was evaporated. Fractional distillation

of the residual oil gave 4.48 g. (66.6%) of 10-cyanodecyl thiocyanate. A purified product (b.p. 160–162.5° (0.08 mm.), d^{20}_4 0.982, $n^{25}D$ 1.4806) was obtained by redistillation.

Anal. Calcd. for $C_{12}H_{20}N_2S$: C, 64.25; H, 8.99; N, 12.49; S, 14.29. Found: C, 64.26; H, 9.32; N, 12.58; S, 14.08.

3-Cyanopropyl thiocyanate, b.p. 112.5–115° (0.06 mm.), d^{20}_4 1.100, $n^{25}D$ 1.4968, was prepared in 76.5% yield from 4-bromobutyronitrile.

Anal. Calcd. for $C_5H_6N_2S$: C, 47.59; H, 4.79; N, 22.21; S, 25.41. Found: C, 47.57; H, 4.86; N, 22.61; S, 25.30.

4-Cyanobutyl thiocyanate, b.p. 131–132° (0.1 mm.), d^{20}_4 1.098, $n^{25}D$ 1.4921, was prepared from 5-bromovaleronitrile in 72.8% yield.

Anal. Calcd. for $C_6H_8N_2S$: C, 51.40; H, 5.75; N, 19.98; S, 22.87. Found: C, 51.74; H, 5.93; N, 17.51; S, 22.50.

VILLE LA SALLE, QUEBEC

CONTRIBUTION FROM THE FATTY ACID PRODUCERS' COUNCIL OF THE ASSOCIATION OF AMERICAN SOAP AND GLYCERINE PRODUCERS, INC., AND THE EASTERN REGIONAL RESEARCH LABORATORY[1]

Phosphorus Derivatives of Fatty Acids. VI.[2] ω-Dialkyl Phosphonoundecanoates

BY RICHARD SASIN,[3] ROSE MARIE NAUMAN[3] AND DANIEL SWERN

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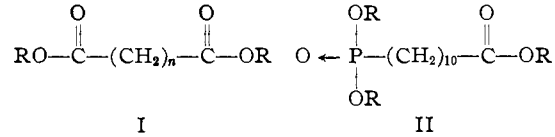
A series of ω-bromoundecanoates has been prepared in 55–96% yield from ω-bromoundecanoic acid and alcohols or phenol: $Br(CH_2)_{10}COOH + ROH \rightarrow Br(CH_2)_{10}COOR + H_2O$ where R = CH_3, C_2H_5, n-C_4H_9, n-C_6H_{13}, 2-ethylhexyl, n-$C_{12}H_{25}$, C_6H_5. By heating the ω-bromoundecanoates with trialkyl phosphites, the corresponding ω-dialkyl phosphonoundecanoates were prepared in 53–87% yield: $Br(CH_2)_{10}COOR + (R'O)_3P \rightarrow O \leftarrow P(OR')_2(CH_2)_{10}COOR + R'Br$. Trialkyl ω-phosphonoundecanoates prepared include: R = R′ = CH_3, C_2H_5, n-C_4H_9, n-C_6H_{13}, 2-ethylhexyl, n-$C_{12}H_{25}$. Mixed ω-dialkyl phosphonoundecanoates prepared include: R = C_2H_5, R′ = n-C_4H_9; R = 2-ethylhexyl, R′ = n-C_4H_9; R = $C_{12}H_{25}$, R′ = n-C_4H_9; R = C_6H_5, R′ = n-C_4H_9; R = n-C_4H_9; R′ = 2-ethylhexyl; R = 2-ethylhexyl, R′ = C_2H_5; R = C_2H_5, R′ = 2-ethylhexyl. The compounds in which R = 2-ethylhexyl and R′ = C_2H_5; and R = C_2H_5 and R′ = 2-ethylhexyl were prepared by another synthetic method. The ω-dialkyl phosphonoundecanoates are colorless, odorless, thermally stable liquids, insoluble in water and soluble in organic solvents.

In this Laboratory, recent research on the preparation of pure derivatives from fats has been directed mainly toward the correlation of structure with important physical properties desired in plasticizers and also in synthetic lubricants. Groups containing the phosphorus atom, for example, are known to impart useful properties to plasticizers, and a number of phosphorus-containing plasticizers are commercially available.

For the past four years we have been systematically preparing long-chain phosphorus compounds of various types. These are trialkyl phosphates,[4] dialkyl acyloxyalkyl phosphates,[4] dialkyl acyloxyalkylphosphonates[5] and alkyl (α-dialkylphosphono)-alkanoates.[6]

Since most low temperature plasticizers are dialkyl esters (I) of dicarboxylic acids, such as adipates, azelates and sebacates, it was decided to prepare a series of compounds similar to these dibasic esters but containing a dialkylphosphono group in place of one carboxylic ester group. The ω-dialkyl phosphonoundecanoates (II) are such a series of compounds; their preparation is described here. No reports on the preparation and study of the physical and chemical properties of the ω-dialkyl phosphonoundecanoates could be found in the literature.



I II

n = 4, 7, 8

This paper also describes the preparation and properties of a series of ω-bromoundecanoates, used as intermediates in the preparation of II. They were prepared from ω-bromoundecanoic acid and alcohols or from the acid chloride and phenol. The esters prepared include: methyl, ethyl, n-butyl, n-hexyl, 2-ethylhexyl, n-dodecyl and phenyl. All of these compounds are colorless liquids at room temperature, insoluble in water and soluble in organic solvents. The physical properties, yields obtained and analyses of the ω-bromoundecanoates are summarized in Table I.

By heating the ω-bromoundecanoates with a 100% molar excess of trialkyl phosphite at elevated temperature for several hours, the ω-dialkyl phosphonoundecanoates were prepared in 53–87% yield. After the unused trialkyl phosphite was removed, the residue was distilled under diminished pressure.

The trialkyl ω-phosphonoundecanoates prepared include: trimethyl, triethyl, tri-n-butyl, tri-n-hexyl, tri-2-ethylhexyl and trilauryl. The mixed ω-phosphonoundecanoates synthesized include: ethyl ω-di-n-butyl, 2-ethylhexyl ω-di-n-butyl, lauryl ω-di-n-butyl, phenyl ω-di-n-butyl, n-butyl ω-di-2-ethylhexyl, 2-ethylhexyl ω-diethyl and ethyl ω-di-2-ethylhexyl. The last two compounds were prepared from 2-ethylhexyl undecenoate and diethyl phosphonate, and ethyl undecenoate and di-2-ethylhexyl phosphonate under free radical

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