[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

2,2,6-Trisubstituted-3,5-thiomorpholinediones. The Isolation of Racemic Intermediates

GLENN S. SKINNER AND JAMES S. ELMSLIE

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A series of 2,2,6-trisubstituted-3,5-thiomorpholinediones has been prepared. The intermediate thio ethers containing two asymmetric centers could be separated each into two racemates. Cyclization of the paired intermediates gave the identical thiomorpholinedione.

In a previous report[1] from this laboratory there has been described a series of 2,2-disubstituted-3,5-thiomorpholinediones. We now wish to report our studies involving 2,2,6-trisubstituted-3,5-thimorpholinediones (I), one of which, 2-*n*-butyl-2-ethyl-6-methyl-3,5-thiomorpholinedione (Ik, Table II), had been made in collaboration with Lovett.[2]

In our experience these compounds were best prepared (Fig. 1) by pyrolysis of either of the

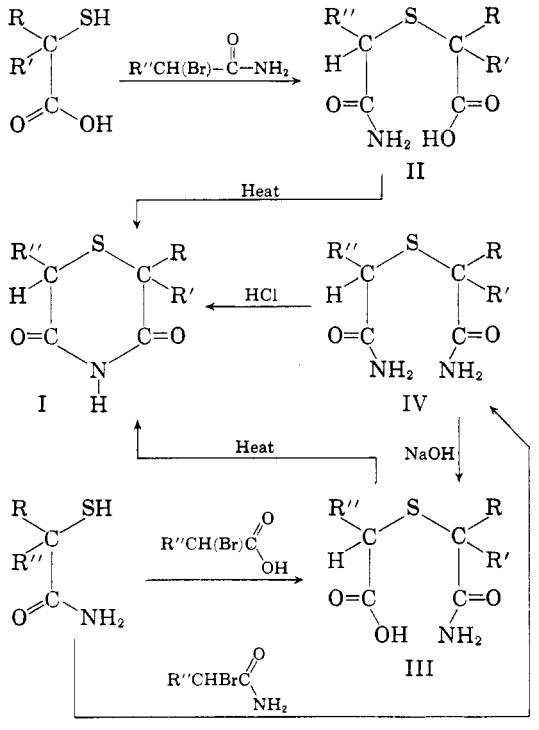


Fig. 1. Synthesis of 2,2,6-trialkyl-3,5-thiomorpholinediones

corresponding thiodiacetamic acids (II or III) or by the condensation of the thiodiacetamide (IV) in boiling hydrochloric acid. The second procedure gave better yields and cleaner products. These intermediates were prepared by condensing a disubstituted mercaptoacetic acid or amide with a monosubstitutedbromoacetic acid or amide. The mercapto acids and mercapto amides were separated[3] by before use.

Previously the condensation of α-bromoacetamides with the mercaptoacetic acids had been conducted in aqueous sodium hydroxide. In this work it was necessary to employ sodium ethoxide in ethanol since α-bromocaproamide and α-bromobutyramide were not soluble in aqueous sodium hydroxide and the amide group was partially hydrolyzed during the time required for completion of the reaction. The product could be precipitated from the ethanol solution by acidification and dilution with water. The partial hydrolysis in aqueous solution increased the difficulty of separation of the racemates.

Several of these intermediate amic acids and diamides possess two unequivalent centers of asymmetry which leads one to expect two racemates. In most cases the two racemates were separated and purified; in others there were strong indications that the two racemates were present, but only one was isolated. However, in the preparation of α-methylcarbamylmethyl-α′-mercapto-α′-ethylisocaproic acid (IId) only one product was isolated and there was no evidence that the other racemate had formed in this case. Both amic acids IIg, IIIc, and the diamide IVf related to α-ethyl-α-phenyl-α′-*n*-butylthiodiacetic acid have all been separated into their racemates. The pairs of racemates that have been separated are indicated by A and B (Table I). The thiomorpholinediones are listed in Table II.

All of the 2,2,6-trisubstituted-3,5-thiomorpholinediones (I) were stable to heat below 220° and to refluxing concentrated hydrochloric acid. They were cleaved to amic acids of type III when allowed to stand in dilute base at room temperature.

There was no evidence for the existence of two racemates of the thiomorpholinediones which have two unlike asymmetric centers. In fact, each of the racemates of α-ethyl-α-phenyl-α′-*n*-butylthiodiacetamide, namely IVf-A and IVf-B, gave the same thiomorpholinedione (Ij) by acid condensation, and this product is identical with the

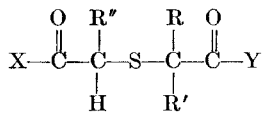
(1) G. S. Skinner and J. B. Bicking, *J. Am. Chem. Soc.*, **76**, 2776 (1954).

(2) John R. Lovett, Ph.D. Thesis, University of Delaware, 1957.

(3) G. S. Skinner, J. S. Elmslie, and J. D. Gabbert, *J. Am. Chem. Soc.*, **81**, 3756 (1959).

TABLE I

AMIDES OF TRISUBSTITUTEDTHIODIACETIC ACIDS

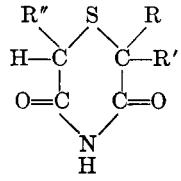


	X	Y	R	R′	R″	M.P.	Yield, %	Nitrogen, %		Carbon, %		Hydrogen, %	
								Calcd.	Found	Calcd.	Found	Calcd.	Found
IIa	NH_2	OH	CH_3	CH_3	n-C_4H_9	130–131	70	6.00	6.16	51.47	51.62	8.21	8.19
IIb	NH_2	OH	C_2H_5	C_2H_5	CH_3	170.5–171	95	6.39	6.36	49.29	49.26	7.82	7.83
IIc	NH_2	OH	C_2H_5	C_2H_5	C_2H_5	162.5–163	61	6.00	5.99	51.47	51.61	8.21	8.15
IId	NH_2	OH	C_2H_5	iso-C_4H_9	CH_3	177.5–178	82	5.66	5.64	53.41	53.33	8.56	8.35
IIe-A	NH_2	OH	C_6H_5	C_2H_5	CH_3	174.5–175		5.24	5.23	58.40	58.78	6.41	6.46
IIe-B	NH_2	OH	C_6H_5	C_2H_5	CH_3	161–161.5	69[a]	5.24	5.21	58.40	58.58	6.41	6.32
IIf	NH_2	OH	C_6H_5	C_2H_5	C_2H_5	166.5–167	52			59.76	59.87	6.81	6.86
IIg-A	NH_2	OH	C_6H_5	C_2H_5	n-C_4H_9	175–176		4.53	4.68	62.11	62.12	7.49	7.56
IIg-B	NH_2	OH	C_6H_5	C_2H_5	n-C_4H_9	173–174	68[a]	4.53	4.78	62.11	61.95	7.49	7.47
IIh	NH_2	OH	C_2H_5	n-C_4H_9	CH_3	126.5–127.5	42.5	5.66	5.61				
IIIa	OH	NH_2	C_6H_5	C_2H_5	CH_3	149	82	5.24	5.20	58.40	58.56	6.41	6.41
IIIb	OH	NH_2	C_6H_5	C_2H_5	C_2H_5	152.5–153	88			59.76	59.95	6.81	6.91
IIIc-A	OH	NH_2	C_6H_5	C_2H_5	n-C_4H_9	159–159.5	90	4.53	4.56	62.11	62.36	7.49	7.28
IIIc-B	OH	NH_2	C_6H_5	C_2H_5	n-C_4H_9	140–141	10	4.53	4.73	62.11	62.21	7.49	7.58
IVa	NH_2	NH_2	C_2H_5	C_2H_5	C_2H_5	177–177.5	100	12.06	12.00	51.69	52.20	8.68	8.54
IVb	NH_2	NH_2	C_2H_5	C_2H_5	n-C_4H_9	146.5–147	83	10.76	10.77				
IVc-A	NH_2	NH_2	C_2H_5	n-C_4H_9	C_2H_5	156–157				55.35	55.77	9.29	9.30
IVc-B	NH_2	NH_2	C_2H_5	n-C_4H_9	C_2H_5	140–141	94[a]	10.76	10.73	55.35	55.44	9.29	9.22
IVd-A	NH_2	NH_2	C_2H_5	iso-C_4H_9	C_2H_5	156–156.5		10.76	10.77	55.35	55.53	9.29	9.27
IVd-B	NH_2	NH_2	C_2H_5	iso-C_4H_9	C_2H_5	152.5–153	87[a]	10.76	10.74	55.35	55.85	9.29	9.38
IVe-A	NH_2	NH_2	C_6H_5	C_2H_5	CH_3	194–195		10.52	10.52				
IVe-B	NH_2	NH_2	C_6H_5	C_2H_5	CH_3	166–167	66[a]	10.52	10.51	58.62	59.00	6.81	7.09
IVf-A	NH_2	NH_2	C_6H_5	C_2H_5	n-C_4H_9	153–153.5		9.08	8.94	62.30	62.58	7.84	7.75
IVf-B	NH_2	NH_2	C_6H_5	C_2H_5	n-C_4H_9	160–160.5	79[a]	9.08	9.04	62.30	61.70	7.84	7.78
IVg	NH_2	NH_2	C_2H_5	n-C_4H_9	CH_3	139–140	32.5	11.37	11.18				

[a] Total yield of A and B.

TABLE II

2,2,6-TRISUBSTITUTED-3,5-THIOMORPHOLINEDIONES



	R	R′	R″	M.P. or B.P. (Mm.)	Yield from	%	Nitrogen, % Calcd.	Nitrogen, % Found	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Ia	CH_3	CH_3	n-C_4H_9	51–52[m]		72	6.51	6.49	55.78	56.10	7.96	7.86
Ib	C_2H_5	C_2H_5	CH_3	74.5–75[m]		95	6.96	6.93	53.70	53.78	7.51	7.49
Ic	C_2H_5	C_2H_5	C_2H_5	64.5–65[m]	IVa	85	6.51	6.50	55.78	55.86	7.96	7.78
					IIc	85						
Id	C_2H_5	C_2H_5	n-C_4H_9	66.5–67[m]		97	5.76	5.74	59.22	59.37	8.70	8.75
Ie	C_2H_5	n-C_4H_9	C_2H_5	136.5–137[n] (0.35)		92	5.76	5.63	59.22	59.27	8.70	8.39
If	C_2H_5	iso C_4H_9	CH_3	127–128[n] (0.19)		69	6.11	6.01	57.61	57.47	8.35	8.29
Ig	C_2H_5	iso C_4H_9	C_2H_5	137[n] (0.23)		98	5.76	5.64	59.22	59.42	8.70	8.54
Ih	C_6H_5	C_2H_5	CH_3	108–109[m]	IIe	84	5.62	5.59	62.62	62.99	6.06	6.03
					IVe	72						
					IIIa	92						
Ii	C_6H_5	C_2H_5	C_2H_5	78–78.5[m]	IIIb	86			63.85	63.92	6.51	6.60
					IIf	63						
Ij	C_6H_5	C_2H_5	n-C_4H_9	69–69.5[m]	IVf-A	72	4.81	4.76	65.94	65.87	7.26	7.13
					IVf-B	85						
					IIg	68						
Ik	C_2H_5	n-C_4H_9	CH_3	137–139[n] (0.80)	IIh	79	6.11	5.86				

m. Melting point; n. Boiling point.

product from the pyrolysis of a mixture of the two racemic amic acids IIg-A and IIg-B.

Base hydrolysis of the same thiomorpholinedione (Ij) gave the racemic amic acids IIIc-B and IIIc-B in yields of 90% and 10%, respectively. In the separate hydrolysis of the racemic diamides IVf-A and IVf-B more of the racemic amic acid IIIc-A was produced than the racemic amic acid IIIc-B; however, the racemic diamide IVf-A gave a higher percentage of the racemic amic acid IIIc-A than did the racemic diamide IVf-B. Thus, it would appear that the formation of the higher melting racemate is favored.

Several derivatives of thiodiacetic acid previously have been separated into their racemates or into meso and DL forms.[4–6] However, no one has reported the formation of the same thiomorpholinedione from either racemate of the thiodiacetic acid derivatives. In fact, Rasenan and Jenkins[7] reported two different thiomorpholinediones upon pyrolysis of the ammonium salt of a symmetrical dialkyl derivative, α,α'-thiodipropionic acid. They believed that these were the meso and DL forms.

This phenomenon has been observed in the succinimide series by Linstead and co-workers.[8–10] Dry distillation of the ammonium salt of either racemate of a substituted succinic acid which has two asymmetric centers produced only one succinimide. In the case of unsymmetrical disubstituted succinic acids, the imide which formed has been shown to be the one in which the two substituent groups are trans to each other.

Pharmacological screening tests indicate that the 2,2,6 - trisubstituted - 3,5 - thiomorpholinediones possess anticonvulsant activity.[11]

EXPERIMENTAL

Ethylisobutylmercaptoacetic acid and amide. 5-Ethyl-5-isobutyl-2-imino-4-thiazolidone (50 g., 0.25 mole) was dissolved in a 5% solution of sodium hydroxide (1.00 mole) and the mixture was refluxed for 30 hr. The products were separated by method A[3] (Ref. 3):

Ethylisobutylmercaptoacetic acid, yield 11 g. (25%), b.p. 111.5–112° (0.53 mm.), n_D^{28} 1.4730.

Anal. Calcd. for $C_8H_{16}O_2S$: C, 54.51; H, 9.15; S, 18.19. Found: C, 54.64; H, 8.93; S 18.10.

Ethylisobutylmercaptoacetamide, yield 22 g. (51%), b.p. 108° (0.50 mm.), n_D^{28} 1.4946.

(4) J. M. Loven and R. Ahlberg, *Ber.*, **54**, 228 (1921).
(5) R. Ahlberg, *Ber.*, 61B, 811, 827 (1928).
(6) R. Ahlberg, *Svensk Kem. Tidskr.*, **44**, 48 (1932).
(7) P. R. Rasenan and G. L. Jenkins, *J. Am. Pharm. Assoc.*, **38**, 559 (1949).
(8) R. P. Linstead and M. Whalley, *J. Chem. Soc.*, 3722 (1954).
(9) G. F. Ficken, R. B. Johns and R. P. Linstead, *J. Chem. Soc.*, 2280 (1956).
(10) J. H. Golden and R. P. Linstead, *J. Chem. Soc.*, 1732 (1958).
(11) Tests by Merck, Sharp and Dohme, West Point, Pa.

Anal. Calcd. for $C_5H_{17}NOS$: C, 54.81; H, 9.79; N, 7.99. Found: C, 54.20; H, 9.62; N, 7.88.

Dimethylmercaptoacetic acid. 5,5-Dimethyl-2-imino-4-thiazolidone (28.8 g., 0.20 mole) was dissolved in a 3.5% solution of sodium hydroxide (0.63 mole) and the mixture was refluxed for 17 hr. The hydrolysate was cooled and acidified with sulfuric acid. No oil separated. The mixture was distilled under diminished pressure. The water was removed from the aqueous distillate by passing air over the liquid at room temperature. The residue was dimethylmercaptoacetic acid, yield 6.8 g. (34%), m.p. 56–57°. Biilmann[12] reported that the melting point of this compound was "not sharp" at 47°. Our product was converted to the amic acid IIa and the thiomorpholinedione Ia.

Monosubstituted-α-bromoacetamides. In a typical experiment α-bromopropionyl bromide (21.6 g., 0.100 mole) was added rapidly dropwise to a stirred cold saturated solution of dry ammonia in petroleum ether, instead of benzene[13] in which the amides are more soluble. Ammonia was passed into the mixture through an adapter with a wide outlet during the addition and for 1 hr. longer. The solid mixture of α-bromopropionamide and ammonium bromide was filtered and washed first with petroleum ether and then carefully with water to remove the ammonium bromide. Recrystallization from benzene gave the pure amide, yield 92%, m.p. 128–129°. α-Bromobutyramide and α-bromocaproamide were prepared in similar yields.

Condensation of a disubstituted mercaptoacetic acid with a monosubstituted-α-bromoacetamide. In a typical example in which only one racemate would be expected, 7.3 g. (0.049 mole) of diethylmercaptoacetic acid was dissolved in a solution of sodium ethoxide prepared from 2.5 g. (0.108 mole) of sodium and 100 cc. of ethanol. To the stirred mixture was added 8.0 g. (0.053 mole) of α-bromopropionamide all at once. The solution became cloudy and solidified after 15 min. After standing 30 min. more the mixture was cooled in ice, diluted with water and acidified with concentrated hydrochloric acid. The solid which precipitated was collected and recrystallized from ethanol to yield the pure amic acid IIb.

α-Methylcarbamylmethyl-α'-mercapto-α'-ethylisocaproic acid (IId). Ethylisobutylmercaptoacetic acid (4.4 g., 0.025 mole) was dissolved in a solution of sodium ethoxide prepared from 1.3 g. (0.057 mole) of sodium and 35 cc. of ethanol. To this stirred solution was added 3.8 g. (0.025 mole) of α-bromopropionamide. The solution became cloudy and liberated heat. The mixture was cooled to room temperature and stirred for 30 min., at which time the entire solution appeared to solidify. This was cooled in ice, diluted with water until the solid dissolved, and then acidified. A finely divided white solid formed which was filtered, washed with water, and dried, m.p. 177–178°. One recrystallization from ethanol gave the pure product.

α-Methylcarbamylmethyl-α'-mercapto-α'-phenylbutyric acid (IIe-A and IIe-B). To a stirred solution of sodium ethoxide prepared from 0.5 g. (0.022 mole) of sodium and 25 cc. of ethanol were added in succession 2.0 g. (0.01 mole) of ethylphenylmercaptoacetic acid and 1.6 g. (0.01 mole) of α-bromopropionamide. In 3 min. the solution became cloudy. After stirring for 2 hr. at room temperature the mixture was cooled and acidified. An oily solid formed which was separated by decantation. Trituration of the solid with ethanol afforded 0.25 g. of solid, m.p. 170–171°. Recrystallization from isopropyl alcohol produced pure IIe-A. Dilution of the supernatant liquid with water produced 1.6 g. of another solid, m.p. 135–141°. Recrystallization of this from ethanol gave pure IIe-B.

α-Ethylcarbamylmethyl-α'-mercapto-α'-phenylbutyric acid (IIf). Ethylphenylmercaptoacetic acid (1.4 g., 0.0072 mole) was dissolved in a solution of sodium ethoxide prepared from 0.40 g. (0.017 mole) of sodium and 30 cc. of ethanol. To the stirred solution was added 1.25 g. (0.0075 mole) of α-bromobutyramide all at once. After stirring for 3 hr. the solution was cooled in ice, acidified and diluted with water until a solid precipitated, m.p. 135–145°. Recrystallization from ethanol afforded pure IIf.

α-n-Butylcarbamylmethyl-α'-mercapto-α'-phenylbutyric acids (IIg-A and IIg-B). To a stirred solution of sodium ethoxide prepared from 4.6 g. (0.20 mole) of sodium and 100 cc. of ethanol were added in succession 19.6 g. (0.10 mole) of ethylphenylmercaptoacetic acid and 19.4 g. (0.10 mole) of α-bromocaproamide. The mixture became cloudy immediately and a solid slowly precipitated. After stirring for 2 hr. the mixture was cooled, acidified, and diluted with water. The solid dissolved and a second solid formed which was treated with boiling isopropyl alcohol. About half of this solid did not dissolve. It had m.p. 160–161.5°. Thorough washing with hot ethanol and recrystallization from dimethylformamide-water (1:1) produced pure IIg-A. As the filtrate cooled another solid precipitated, m.p. 163–165°. Recrystallization of this from ethanol produced pure IIg-B. A melting point of a mixture of the two pure racemates was 162–167°. Each racemate was dissolved in dimethylformamide and tested for optical activity. Both were optically inactive as expected.

Condensation of a disubstituted mercaptoacetamide with a monosubstituted-α-bromoacetamide. In a typical example in which only one racemate was expected, diethylmercaptoacetamide (6.0 g., 0.041 mole) was dissolved in a solution of sodium ethoxide prepared from 1.2 g. (0.052 mole) of sodium and 50 cc. of ethanol. α-Bromobutyramide (7.0 g., 0.042 mole) was added all at once to the stirred solution. The mixture became cloudy and liberated heat. A water bath was used to keep the temperature near 25°. In 5 min. the product solidified. After standing for 1 hr. the mixture was cooled in ice, diluted with water until the solid dissolved, and then acidified. Upon further dilution a solid formed which was filtered. Recrystallization from ethanol produced only the pure diamide IVa.

In a typical example in which two racemates were separated ethylphenylmercaptoacetamide (9.8 g., 0.050 mole) and α-bromocaproamide (9.7 g., 0.050 mole) were added in succession to a solution of sodium ethoxide prepared from 1.3 g. (0.056 mole) of sodium and 75 cc. of ethanol and the solution was stirred for 2 hr. After 5 min. the solution became cloudy and a finely divided solid precipitated. The mixture was cooled in ice, acidified, and diluted with water. As the water was added the solid dissolved and another solid precipitated. This solid was filtered and washed with methanol, m.p. 143–144°. Upon addition of more water to the filtrate a second crop of solid formed, m.p. 152–155°. A mixture of the two crops melted at 134–144°. Recrystallization of the first crop from isopropyl alcohol produced the pure diamide IVf-A. Recrystallization of the second crop from dimethylformamide-water (1:1) afforded the pure diamide IVf-B.

In a similar manner ethylphenylmercaptoacetamide was condensed with α-bromopropionamide. Upon acidification and solution with water an oil formed which was separated by decantation. Upon standing in 5% sodium hydroxide solution the oil solidified. When this solid was treated with hot ethanol about half of it dissolved. The ethanol insoluble portion, m.p. 191–193°, was recrystallized from dimethylformamide-water (1:1) producing the pure diamide IVe-A. The ethanol solution, upon concentration, yielded another solid, m.p. 162–167°. Recrystallization of this from dimethylformamide-water (1:1) produced the pure diamide IVe-B. A mixture of the two pure racemates melted at 158–170°.

α-Ethyl-α-phenylcarbamylmethyl-α'-mercaptopropionic acid (IIIa). A mixture of the diamides IVe-A and IVe-B (4.3 g., 0.016 mole) was added to 14 cc. of 5% sodium hydroxide and heated for 2 hr. The solid slowly dissolved and ammonia was liberated. Upon acidification of the cooled solution an oil formed which was dissolved in sodium bicarbonate solution and extracted with ether. The sodium bicarbonate layer

(12) E. Biilman, *Ann.*, 348, 129 (1906).

(13) C. A. Bischoff, *Ber.*, **30**, 2310 (1897).

was then cooled, acidified and extracted with ether. Concentration of the ether solution produced a solid product, m.p. 133–140°. Recrystallization from dimethylformamide-water (1:1) and then from ethanol-water (1:1) yielded the pure amic acid IIIa.

α-Ethyl-α-phenylcarbamylmethyl-α'-mercaptobutyric acid (IIIb). Ethylphenylmercaptoacetamide (3.0 g., 0.015 mole) was dissolved in 32 cc. (0.08 mole) of 10% sodium hydroxide solution. α-Bromobutyric acid (2.7 g., 0.016 mole) was added dropwise to the stirred solution. After stirring for 1 hr. the mixture was cooled and acidified. The oil which formed was taken up in ether and the ether solution was extracted with sodium bicarbonate. The bicarbonate layer was cooled, acidified and extracted with ether. Concentration of the ether layer produced a solid, m.p. 142–144°. Repeated recrystallization from dimethylformamide-water (1:1) and then from ethanol-water (1:1) produced the pure amic acid IIIb.

α-Ethyl-α-phenylcarbamylmethyl-α'-mercaptocaproic acids (IIIc-A and IIIc-B). *From* IVf-A. This diamide (1.0 g., 0.0027 mol.) was dissolved in 3 cc. of 5% sodium hydroxide solution (0.0037 mol.) and heated to 70° for 1 hr. Upon cooling and acidifying a gunky white precipitate formed which hardened on standing, m.p. 140–150°. Recrystallization from isopropyl alcohol produced 0.8 g. of pure IIIc-A. By working up the filtrates and recrystallizing from ethanol a small amount of impure IIIc-B was obtained.

From IVf-B. This diamide was treated similarly. The solid which precipitated was filtered and washed with water. It was then recrystallized from isopropyl alcohol; first crop, m.p. 157–158° (IIIc-A); second crop, m.p. 135–142° (mostly IIIc-B).

From the thiomorpholinedione Ij (Table II). This compound (1.0 g., 0.0034 mole) was dissolved in 10 cc. of 1.5% sodium hydroxide solution (0.0037 mol.). The mixture was allowed to stand at room temperature for 24 hr. All of the solid had dissolved after standing for 16 hr. The solution was cooled in ice and acidified. The precipitate was collected, m.p. 145–148°. Recrystallization from isopropyl alcohol-water (5:1) gave pure IIIc-A. A second crop from the filtrate of the first recrystallization was obtained, m.p. 137–140°. Repeated recrystallization of this from ethanol-water (5:1) gave pure IIIc-B. The melting point of a mixture of the two isomers was lower (*ca.* 135°).

2,2,6-Trisubstituted-3,5-thiomorpholinediones. From an amic acid type III. The amic acid IIIb (5.6 g., 0.020 mol.) was heated at 150–155° for 1 hr. while being evacuated. Water was evolved vigorously at first. Upon cooling an oily solid residue remained which was triturated with sodium bicarbonate solution leaving a solid, m.p. 67–70°. Recrystallization from an isopropyl alcohol–water mixture produced pure 2,6-diethyl-2-phenyl-3,5-thiomorpholinedione.

From an amic acid type II. In a typical example a mixture of IIg-A and IIg-B (8.1 g., 0.026 mol.) was placed in a distilling flask and heated at 180–190° for 90 min. under a vacuum. The oil which remained on cooling was taken up in isopropyl alcohol and cooled. Water was added until the solution became cloudy. The crystalline product was collected and recrystallized from isopropyl alcohol producing pure 6-*n*-butyl-2-ethyl-2-phenyl-3,5-thiomorpholinedione.

From the diamide. In a typical example IVa (7.6 g., 0.033 mol.) was dissolved in 20 cc. of concentrated hydrochloric acid and refluxed for 1 hr. Upon cooling, white needles formed. Recrystallization from ethanol gave pure 2,2,6-triethyl-3,5-thiomorpholinedione.

From the racemic diamide IVf-A. This diamide (7.6 g., 0.025 mol.) was dissolved in 20 cc. of hydrochloric acid (S.G. 1.18) and the solution was refluxed for 1 hr. When cooled an oil separated which would not crystallize. Distillation of the oil under diminished pressure gave a viscous colorless oil which solidified on standing. Recrystallization from isopropyl alcohol produced pure 6-*n*-butyl-2-ethyl-2-phenyl-3,5-thiomorpholinedione.

From the racemic diamide IVf-B. This diamide (1.5 g., 0.0049 mol.) was dissolved in 5 cc. of hydrochloric acid (S.G. 1.18) and the solution was refluxed for 75 min. Upon gradual cooling, finally in ice, a solid formed. One crystallization of this from isopropyl alcohol gave the identical 6-*n*-butyl-2-ethyl-2-phenyl-3,5-thiomorpholinedione.

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NEWARK, DEL.

[CONTRIBUTION FROM THE MORLEY CHEMICAL LABORATORY, WESTERN RESERVE UNIVERSITY]

Reactions of Perfluoroalkyl Isocyanates with Amines

RALPH L. DANNLEY, DONALD YAMASHIRO,[1] AND ROBERT G. TABORSKY[2]

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Perfluoroalkyl isocyanates react with stoichiometric quantities of primary amines at low temperatures to form perfluoroalkyl ureas. These ureas readily undergo replacement of the alpha fluorine atoms to yield perfluoroacyl ureas. Solvolysis of the ureides to remove the perfluoroacyl group can be accomplished by refluxing with excess amine. The reaction of the perfluoroalkyl isocyanates with secondary amines could not be controlled and produced perfluoroacyl amidines.

It has been reported[3] that perfluoroalkyl isocyanates react abnormally with amines to yield compounds of undetermined structure instead of the expected ureas. These isocyanates also react abnormally with alcohols but by observing proper

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(2) Present address, Roswell Park Memorial Institute, Buffalo, N.Y.

(3) A. Ahlbrecht, D. Husted, T. Reid, and O. Smith, Contribution No. 34 of Central Research Department, Minnesota Mining and Manufacturing Co., St. Paul, Minn., "Chemistry of Perfluoro Acids and Their Derivatives. IV. Fluoroalkyl Isocyanates."