the ether evaporated leaving an oil which solidified on prolonged cooling. Recrystallization from a small quantity of carbon tetrachloride gave 2.4 g. (46%) of white solid, m.p. 58–60°. Further recrystallizations from the same solvent gave an analytical sample, m.p. 59–61°.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.29; H, 7.38; N, 6.93.

Methyl styrylcarbamate. Methyl styrylcarbamate was prepared by a Hofmann rearrangement on cinnamamide according to the procedure of Weermann.[18]

Methyl 5-[3-carbethoxy-4-phenyl-2-isoxazolinyl]carbamate. A solution of 17.7 g. (0.10 mole) of methyl styrylcarbamate in 400 ml. of ether was added to a solution of 18.2 g. (0.12 mole) of ethyl chlorooximinoacetate[7] in 100 ml. of ether. With vigorous mechanical stirring 12.7 g. (0.12 mole) of sodium carbonate in 180 ml. of water was added dropwise over a 7-hr. period at room temperature. After the addition the mixture was stirred an additional hour. The layers were separated; the ether layer was washed with water and dried over magnesium sulfate. Filtration and evaporation of the ether left a semisolid residue, 31 g. The ester was not purified but converted directly to the hydrazide.

Methyl 5-[3-hydrazido-4-phenyl-2-isoxazolinyl]carbamate (IV). The above 31 g. of crude ester in 250 ml. of ethanol was slowly added to a solution of 25 ml. of hydrazine in 250 ml. of ethanol cooled in an ice bath. After the addition the solution was allowed to warm to room temperature over a 30-min. period. The solution was filtered from the reddish solid and tars and the solvent evaporated, leaving a solid.

The residual solid was dissolved in 100 ml. of chloroform and extracted with 100 ml. of 5% hydrochloric acid. The acid extract was washed twice with 50 ml. of chloroform, partially neutralized with 50 ml. of 10% sodium hydroxide, and made basic with 50 ml. of 5% sodium bicarbonate. This yielded, after cooling, 13 g. [47% based on methyl styrylcarbamate] of light tan solid, m.p. 127–137° sl. dec. Two recrystallizations from methanol only raised the melting point slightly, 130–140° sl. dec. Further recrystallizations from methanol-water did not raise the melting point further.

Anal. Calcd. for $C_{12}H_{14}N_4O_4 \cdot 1/2H_2O$: C, 50.18; H, 5.25; N, 19.49. Found: C, 50.27, 50.17; H, 5.22, 5.29; N, 19.48, 19.59.

The analytical sample was recrystallized from benzene-cyclohexane and dried at 0.03 mm. for 48 hr. without change. However, drying at 100° and atmospheric pressure removed the water.

Anal. Calcd. for $C_{12}H_{14}N_4O_4$: C, 51.79; H, 5.07; N, 20.14. Found: C, 51.73; H, 5.07; N, 20.11.

Methyl 5-[3-carbazido-4-phenyl-2-isoxazolinyl]carbamate. A solution of 0.50 g. (0.0072 mole) of sodium nitrite was added dropwise to a solution of 1.0 g. (0.0036 mole) of the above hydrazide (IV) in 50 ml. of 5% hydrochloric acid cooled in an ice bath. This yielded 0.94 g. (90%) of white solid, m.p. 115° vigorous dec.

A sample for analysis was prepared by dissolving in ethanol, filtering and reprecipitating with water, m.p. 120° vigorous dec.

Anal. Calcd. for $C_{12}H_{11}N_5O_4$: C, 49.83; H, 3.83; N, 24.21. Found: C, 50.10; H, 4.16; N, 24.11.

Ethyl methyl 3,5-[4-phenyl-2-isoxazolinyl]dicarbamate. The above azide (0.90 g., 0.0030 mole) was dissolved in 50 ml. of ethanol and the solution refluxed for 30 min. The solution was decolorized with Norit and evaporated to dryness. The residue was triturated with a very small amount of ether to give 0.60 g. (65%) of white solid, m.p. 173–183°. Recrystallization from ethanol-water gave an analytical sample, m.p. 183–187°.

Anal. Calcd. for $C_{14}H_{17}N_3O_5$: C, 54.72; H, 5.58; N, 13.68. Found: C, 54.68; H, 5.59; N, 13.82.

ANN ARBOR, MICH.

(18) R. A. Weerman, *Ann.*, **401**, 1 (1913).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

2,6-Disubstituted 3,5-Thiomorpholinediones and Related Compounds[1]

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Methods suitable for the synthesis of α,α'-dialkylthiodiacetamic acids including those with unlike radicals and their conversion to 2,6-dialkyl-3,5-thiomorpholinediones are described. The diacetamic acids could be separated into racemates but attempts to resolve the racemates to their optical isomers were unsuccessful. In the synthesis of 2,2-dialkyl-3-thiomorpholones by a previously unreported process, the intermediate dialkyl(2-aminoethylmercapto)acetic acids were isolated.

Previous workers have reported the synthesis of unsubstituted 3,5-thiomorpholinedione,[2] symmetrical 2,6-di- and 2,2,6,6-tetrasubstituted analogs,[3,4] unsymmetrical 2,2-disubstituted analogs[4–7] and unsymmetrical 2,2,6-trisubstituted analogs.[7,8]

The present series of 2,6-disubstituted 3,5-thiomorpholinediones was prepared by the scheme outlined in Fig. 1, which is equally well suited for the synthesis of compounds with unlike radicals.

5-Monoalkyl-2-imino-thiazolidinones (Series I) were prepared in yields of 80–90% which is about twice that obtained for the geminal dialkyl compounds. One previously unreported member of Series I, 5-(2-secpentyl)-2-imino-4-thiazolidinone, was prepared from its hydrobromide salt and hydrolyzed to its 2-keto derivative.

(1) Based on the Ph.D. thesis of Richard N. Macnair.

(2) Schulze, *Zeitschrift fur Chemie*, **2**, 182 (1866), through Beilstein's *Handbuch der Organischen Chemie*, ed. 4, von Julius Springer, Berlin, 1921, Vol. **27**, p. 249.

(3) P. R. Rasanen and G. L. Jenkins, *J. Am. Pharm. Assoc.*, **38**, 599 (1949).

(4) C. Barkenbus and P. Panzera, *J. Org. Chem.*, **20**, 237 (1955).

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

(6) J. R. Lovett, M.S. thesis, University of Delaware, 1955.

(7) J. R. Lovett, Ph.D. thesis, University of Delaware, 1957.

(8) G. S. Skinner and J. S. Elmslie, *J. Org. Chem.*, **24**, 1702 (1959).

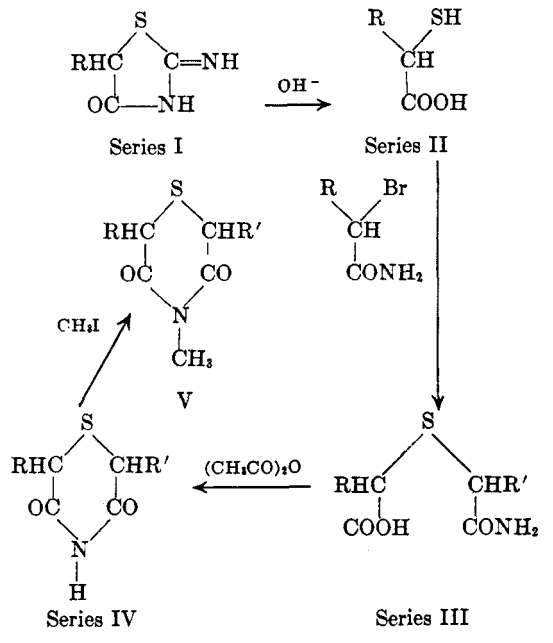


Fig. 1. Preparation of 2,6-disubstituted 3,5-thiomorpholinediones

Compounds of Series I were hydrolyzed in dilute sodium hydroxide to obtain the monosubstituted mercaptoacetic acids (Series II) in virtually 100% yield. Neither unchanged starting material nor products of partial hydrolysis were recovered. This is in direct contrast to the behavior of geminal disubstituted derivatives which gave mixtures of mercapto acid, mercapto amide, thiazolidinedione and unreacted iminothiazolidinone. The acids of Series II were very susceptible to oxidation in contrast to the disubstituted mercaptoacetic acids and amides which were readily distilled under diminished pressure. The special precaution of hydrolysis and extraction in a nitrogen atmosphere had to be adopted and purification at this stage was abandoned.

Substituted thiodiacetamic acids (Series III, Table I) were prepared by the action of an α-bromoamide with an alkylmercaptoacetic acid in ether solution in the presence of alcoholic sodium ethoxide under nitrogen. Series III compounds, having two asymmetric centers, may exist in stereoisomeric forms. Separation of these into what appeared to be and what we shall refer to as two racemates (A and B) was accomplished by fractional recrystallization in all cases except III-4 III-5, and III-7. Each pair of racemates gave identical analyses. The 2-*sec*-pentyl group in III-4 and III-5 provides an additional asymmetric center causing four possible racemates. Only one of these racemates was obtained pure in each case but a residue of each which melted over a range was analyzed showing identical composition to the respective pure racemate. No second form of III-7 was observed.

2,6-Disubstituted 3,5-thiomorpholinediones (Series IV, Table II) were obtained by refluxing the corresponding thiodiacetamic acids of Series III with acetic anhydride. Where two asymmetric centers exist in the molecule, only one pure crystalline form was isolated. Where three asymmetric centers exist, one being in the side chain as in IV-4 and IV-5, two pure crystalline forms were obtained.

Representative members of Series III and IV were shown to have no optical activity, as expected. The infrared spectra of the amic acids including all of the isomeric pairs showed characteristic absorption bands for OH at 2.9–3.0, NH at 3.05–3.15, CH at 3.3–3.5, COOH carbonyl at 5.85–5.95 and $CONH_2$ carbonyl at 6.1–6.2 μ. The absorption curve of the isomeric amic acid A and B pairs between 6.2 and 16 μ were largely different. Both pure III A and III B forms and mixtures thereof were used to prepare Series IV compounds but only one form was obtained as stated above.

The infrared spectra of the thiomorpholinediones including the isomeric pairs of IV-4 and IV-5 showed characteristic absorption bands for NH at 3.1, CH at 3.4, and CONHR carbonyl at 5.8–6.1 μ. The absorption curve of the isomeric thiomorpholinedione A and B pairs between 6.2 and 16 μ were also largely different.

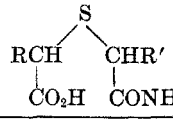
N-Methyl-2,6-disubstituted 3,5-thiomorpholinediones (Series V, Table II) were prepared by modification of the method of Loudon and Ogg for acyclic and cyclic amides.[9] The most important modifications were a decrease in the reaction temperature to room temperature and a decrease of methyl iodide to an equimolecular amount. Proof that the nitrogen was methylated lay in the absence of the NH band at 3.1 μ.

3-Thiomorpholone has been prepared unsubstituted[10] and substituted[11,12] in various positions including 2-, 4-, 5- and 6-. The 3-thiomorpholones (Series VII, Table III) prepared in this work were 2,2-disubstituted. Both 2,2-diethyl- and 2-*n*-butyl-2-ethyl-3-thiomorpholone have been prepared previously, the former by Goldberg and Lehr[11] and the latter by Gabbert.[12] Goldberg and Lehr treated ethyleneimine with the ethyl ester of mercaptodiethylacetic acid and heated the product to close the ring. Gabbert heated the product from *n*-butylethylmercaptoacetic acid and 2-bromoethylamine hydrobromide. The latter method was repeated successfully for 2-*n*-butyl-2-ethyl-3-thiomorpholone (VII-IV). This method also proved successful in the preparation of 2,2-diethyl-3-thiomorpholone (VII-2) so the procedure may very well be a general one for all compounds of this type. Another method was developed for the prepara-

(9) J. D. Loudon and J. Ogg, *J. Chem. Soc.*, 739 (1955).
(10) Herbert Bestian, *Ann.*, **566**, 210 (1950).
(11) Moses Wolf Goldberg and Hanna H. Lehr, U. S. Patent 421,680, April 7, 1954.
(12) J. D. Gabbert, M.S. thesis, University of Delaware, 1956.

TABLE I

2,6-DISUBSTITUTED THIODIACETAMIC ACIDS

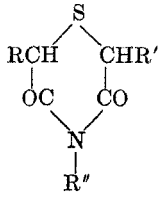


No.[a]	R	R′	M.P.,°	C		H		N		Solvent
				Calcd.	Found[b]	Calcd.	Found	Calcd.	Found	
III-1A	C_2H_5	CH_3	144	43.96	44.18	6.85	6.62	7.32	7.31	Nitromethane
III-1B	C_2H_5	CH_3	101–102	43.96	44.20	6.85	7.18	7.32	7.23	*n*-Hexane
III-2A	*n*-C_4H_9	CH_3	143–144	49.29	49.15	7.81	7.94	6.38	6.40[c]	Ethanol/water (1:1)
III-2B	*n*-C_4H_9	CH_3	82–83	49.29	49.52	7.81	7.90	6.38	6.25[d]	Cyclohexane
III-3A	*n*-C_4H_9	C_2H_5	151–152	51.48	51.13	8.21	8.04	6.00	5.96	Ethanol/water (1:1)
III-3B	*n*-C_4H_9	C_2H_5	95–96	51.48	52.03	8.21	8.32	6.00	5.94	Cyclohexane
III-4A	2-*sec*-C_5H_{11}	CH_3	162–163	51.48	51.51	8.21	8.16	6.00	5.96	Ethanol/water (1:1)
III-4B	2-*sec*-C_5H_{11}	CH_3	88–94	51.48	51.61	8.21	8.49	6.00	5.88[e]	*n*-Hexane
III-5A	2-*sec*-C_5H_{11}	C_2H_5	144–145	53.41	53.54	8.56	8.44	5.66	5.62	Ethanol/water (1:1)
III-5B	2-*sec*-C_5H_{11}	C_2H_5	83–88	53.41	53.54	8.56	8.98	5.66	5.70	*n*-Hexane
III-6A	C_6H_5	C_2H_5	182–183	56.90	56.90	5.97	6.20	—	—	Ethanol
III-6B	C_6H_5	C_2H_5	153–154	56.90	56.96	5.97	6.31	5.53	5.40	Acetone
III-7	C_6H_5	CH_3	160–161	55.21	55.56	5.48	5.47	5.85	5.95	Isopropyl alcohol

[a] The letters A and B designate racemates of the same composition. [b] These and all subsequent analyses were performed by Sharp and Dohme Division of Merck, Inc. [c] S Calcd. 14.62; found 14.49. [d] S Calcd. 14.62, found 14.81. [e] S Calcd. 13.74, found 13.54.

TABLE II

2,6-DISUBSTITUTED AND 2,4,6-TRISUBSTITUTED 3,5-THIOMORPHOLINEDIONES



No.	R	R,	R″	M.P.,° or B.P.,° (mm.)	Yield, %	C		H		N		Solvent
						Calcd.	Found	Calcd.	Found	Calcd.	Found	
IV-1	C_2H_5	CH_3	H	97–98	81	48.53	48.34	6.40	6.27	8.08	8.05	Isopropyl alcohol
IV-2	*n*-C_4H_9	CH_3	H	85–86 117/0.25	88.4	53.70	53.66	7.51	7.46	6.96	6.89	*n*-Hexane distilled
IV-3	*n*-C_4H_9	C_2H_5	H	93–94	49	55.78	55.49	7.96	7.92	6.50	6.48	Isopropyl alcohol
IV-4A	2-*sec*-C_5H_{11}	CH_3	H	100–101	68.5[a]	55.78	55.78	7.96	8.31	6.50	6.29	*n*-Hexane
IV-4B	2-*sec*-C_5H_{11}	CH_3	H	109–111 (0.15)		55.78	55.54	7.96	8.16	6.50	6.36	Distilled
IV-5A	2-*sec*-C_5H_{11}	C_2H_5	H	120–121	63.6[b]	57.61	57.51	8.35	8.60	6.10	6.08	*n*-Hexane
IV-5B	2-*sec*-C_5H_{11}	C_2H_5	H	116 (0.14)		57.61	57.49	8.35	8.58	6.10	6.09	Distilled
IV-5C	2-*sec*-C_5H_{11}	C_2H_5	H	94–95		57.61	57.73	8.35	8.78	6.10	5.97	*n*-Hexane
IV-6	C_6H_5	C_2H_5	H	123–124	78.3	61.25	61.21	5.57	5.69	5.95	5.88	Ethanol
IV-7	C_6H_5	CH_3	H	114–115	65.8	59.71	59.89	5.01	5.17	6.33	6.34	Isopropyl alcohol
V-1	*n*-C_4H_9	C_2H_5	CH_3	101–102[c] (0.23)		57.61	57.35	8.35	8.93	6.10	5.85	Distilled
V-2	C_6H_5	C_2H_5	CH_3	129–131[d] (0.10)	75.3	62.62	61.87	6.06	6.14	5.62	5.61	Distilled

[a] Includes A and B. [b] Includes A, B, and C. [c] n_D^{25} 1.4990. [d] n_D^{25} 1.5666.

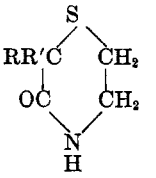
tion of Series VII compounds which consisted in treating a mercaptoacetamide with 2-bromoethylamine hydrobromide and subsequently pyrolyzing the intermediate amino amide. 2-*n*-Butyl-2-ethyl-3-thiomorpholone (VII-IZ) was prepared in this manner and was identical with VII-IY by comparison of boiling points, refractive indices, and infrared spectra. The previously uncharacterized intermediate dialkyl(2-aminoethylmercapto)acetic acids (Series VI) were isolated.

Pharmacological screening tests performed on members of Series IV, V, and VII showed no promise of anticonvulsant activity.[13] Thus it ap-

(13) These tests were performed by Sharp and Dohme Division of Merck, Inc., West Point, Pa.

TABLE III

2,2-DIALKYL 3-THIOMORPHOLONES



No.	R	R′	M.P., ° or B.P., °/mm.	n_D^{25}	Yield, %
VII-1Y	*n*-C_4H_9	C_2H_5	143/0.85	1.5148[a]	78.4
VII-1Z	*n*-C_4H_9	C_2H_5	143–145/1.1	1.5138[a]	60.1
VII-2	C_2H_5	C_2H_5	57–58[b,c]		60.0

[a] J. D. Gabbert, M.S. thesis, University of Delaware, 1956; found b.p. 155°/5.5 mm., n_D^{26} 1.5148. [b] M. W. Goldberg and H. H. Lehr, U. S. Patent 421,680. [c] $C_8H_{15}NOS$: C, 55.47; H, 8.73; N, 8.09; S, 18.51. Found: C, 55.62; H, 8.48; N, 8.01, 8.03; S, 18.46.

pears that the same groups in the 2,6- positions are less effective than they are in the 2,2- position. In addition to this comparison it is interesting to note that where the same two groups are concerned, geminally substituted 3,5-thiomorpholinediones melt lower than their 2,6-disubstituted analogs.[5,7]

EXPERIMENTAL

5-(2-sec-Pentyl)-2-imino-4-thiazolidinone hydrobromide. This compound separated in a crude yield of 46.8% by application of the procedure previously used for the preparation of 5,5-dialkyl-2-imino-4-thiazolidines.[6] It was washed with ether and recrystallized from isopropyl alcohol, m.p. 211–212°.

Anal. Calcd. for $C_8H_{15}BrN_2OS$: C, 35.96; H, 5.65; Br, 29.91; N, 10.48. Found: C, 35.96; H, 5.65; Br, 29.58; N, 10.41.

5-(2-sec-Pentyl)-2-imino-4-thiazolidinone. This substance was prepared by dissolving 2 g. of the hydrobromide salt in an excess of hot water and treating this solution immediately with an excess of solid sodium bicarbonate. The product precipitated quantitatively and was recrystallized from ethyl alcohol, m.p. 202–203°.

Anal. Calcd. for $C_8H_{14}N_2OS$: C, 51.61; H, 7.58; N, 15.04. Found: C, 52.00; H, 7.50; N, 15.01.

5-(2-sec-Pentyl)-2,4-thiazolidinedione. This product was prepared by refluxing 5.0 g. (0.027 mole) of the above hydrobromide with 48 cc. of 2*N* hydrochloride acid for 8 hr. The insoluble oil was extracted with ether and this solution was washed with water and saturated sodium bicarbonate solution. The ether was evaporated to yield 2.7 g. (54%) of an oil which was distilled under diminished pressure to give 1.6 g. of a liquid, b.p. 103°/0.15 mm., n_D^{25} 1.5155.

Anal. Calcd. for $C_8H_{13}NO_2S$: C, 51.32; H, 6.99; N, 7.48. Found: C, 51.34; H, 7.10; N, 7.35.

Mercaptoacetic acids of series II. A substituted 2-imino-4-thiazolidinone, 0.2 mole, in a stainless steel flask with a 10% solution containing 0.9 mole of sodium hydroxide was refluxed for at least 1 hr. while nitrogen was passed through the vessel. The product was obtained quantitatively by acidification of the mixture with concd. hydrochloric acid followed by ether extraction. No bicarbonate-insoluble products were obtained. A nitrogen atmosphere was maintained as much as possible during the acidification and ether extraction and the ether solution of the product was continuously bathed with nitrogen while being dried over magnesium sulfate before use.

Substituted thiodiacetamic acids of series III. A freshly prepared mercaptoacetic acid, 0.2 mole, in a dry ether solution was placed in a three necked flask through which nitrogen was passed continuously. To this was added 0.2 mole of an α-bromoamide. The mixture was stirred while a dry sodium ethoxide solution containing 9.2 g. (0.40 mole) of sodium in 160 cc. of absolute ethanol was added dropwise during approximately 1 hr. The mixture was transferred to a beaker and the solvent allowed to evaporate to about 1/8 its volume. The residue was diluted with up to 500 cc. of water and acidified stepwise with concd. hydrochloric acid. The precipitated fractions were filtered and dried under vacuum to constant weight. The yields in these preparations ranged from 74–100% before separation into racemates.

Separation of series III *compounds into racemates.* In general, two or more fractions of impure product were obtained from the above preparation. The mixtures were fractionally recrystallized from appropriate solvent pairs which are noted in Table I. Two racemates, A and B, were obtained. The higher melting A was obtained first from one solvent. This solvent was then removed from the mother liquor and a second solvent was used on the residue to obtain the lower melting B. This procedure was repeated with alternation of the solvents until the separation was effected.

2,6-Disubstituted 3,5-thiomorpholinediones of series IV. These were prepared by refluxing 0.02 mole of a Series III amic acid with 60 cc. (64.8 g.) of freshly distilled acetic anhydride for 45 min. The product was precipitated by decomposing the excess acetic anhydride in iced water. The mixture was diluted with water as necessary to precipitate the product completely. If the product was crystalline, it was filtered. If it was oily, the acid was neutralized with solid sodium bicarbonate and the product was extracted with ether. The average yield of crude product was 74%. Purification was effected by recrystallization from the solvent stated in Table II or by distillation.

In two specific examples of this procedure using pure amic acids III-3A, m.p. 151–152°, and III-3B, m.p. 95–96°, a single 3,5-thiomorpholinedione (IV-3) was obtained, m.p. 93–94°, and a mixture of the product from III-3A with that from III-3B also melted at 93–94°.

Racemates of IV-4. Separation was effected by first recrystallizing 20.6 g. of the crude product from *n*-hexane to give 0.45 g. of a solid which was recrystallized once more to yield a small amount of solid, m.p. 100–101° (IV-4A). The residue was an oil which was distilled under diminished pressure, b.p. 109–111°/0.15 mm., n_D^{25} 1.5143 (IV-4B). This oil solidified while standing for a month.

Racemates of IV-5. Separation was effected by first recrystallizing 32.7 g. of crude material above from *n*-hexane yielding 2.5 g. of a solid which was recrystallized several times from 150-cc. portions of *n*-hexane, to give 1.25 g. of white plates, m.p. 120–121° (IV-5A). The oily residue (30.2

g.) was distilled under diminished pressure into fractions which completely solidified within a few days. The purest fractions were redistilled, b.p. 116°/0.14 mm., n_D^{25} 1.5101, (IV-5B) which resolidified. A representative portion of the solidified product, 4.3 g., was readily soluble in warm *n*-hexane and was purified by fractional precipitation of high melting material by cooling until the melting point range narrowed to 1°. At this point it was recrystallized once to yield 0.15 g. of a white solid, m.p. 94–95° (IV-5C). Infrared spectra indicated that the liquid, B, was probably a mixture of the two solids, A and C. IV-5C was thought to predominate in this mixture due to the solubility difference in *n*-hexane between IV-5A and IV-5C and the solubility similarity in *n*-hexane between IV-5B and IV-5C.

N-Methyl-2,6-disubstituted 3,5-thiomorpholinediones. Series V). These were most conveniently prepared by treating 0.02 mole of the corresponding Series IV thiomorpholinedione with 0.05 mole (2.8 g.) of potassium hydroxide in 90 cc. of acetone while stirring at 0°. To this was added 1.25 cc. (2.84 g., 0.02 mole) of methyl iodide. The stirred mixture was allowed to warm to room temperature. After 1 hr. the liquid was decanted from the solid and the acetone was evaporated. The residue was diluted with water and the oil was extracted with ether yielding 2.0 g. of the cyclic imide after evaporation of the ether. This oil was insoluble in sodium bicarbonate solution.

The aqueous solution from above was acidified with concd. hydrochloric acid and the oil thus precipitated was extracted with ether and washed with sodium bicarbonate solution. This aqueous solution was washed with ether and then acidified to reprecipitate the oil which was extracted once more with ether, 4.7 g. after the ether was removed. Distillation of this acid portion under diminished pressure gave the identical cyclic imide.

n-Butylethyl(2-aminoethylmercapto)acetic acid (VI-2). This compound was prepared from 8.28 g. (0.047 mole) of *n*-butylethylmercaptoacetic acid dissolved in a cold 10% solution containing an equimolecular amount of sodium hydroxide (1.88 g., 0.047 mole). To this cold solution were added simultaneously an aqueous solution of 9.6 g. (0.047 mole) of 2-bromoethylamine hydrobromide and a 10% solution containing 3.76 g. (0.047 mole) of sodium hydroxide. The addition took place during a period of 45 min. with constant stirring which was continued for 1 hr. The solution was neutralized with glacial acetic acid and evaporated under diminished pressure to precipitate 7.6 g. (73.8%) of a crystalline product which was recrystallized from a 1/1 mixture of ethanol and water, m.p. 180–181° dec.

Anal. Calcd. for $C_{10}H_{21}NO_2S$: C, 54.76; H, 9.65; N, 6.38. Found: C, 54.75; H, 9.43; N, 6.34.

Diethyl(2-aminoethylmercapto)acetic acid (VI-1). This was prepared similarly in a 97.7% yield and was recrystallized from 95% ethanol, m.p. 233–234° dec.

Anal. Calcd. for $C_8H_{17}NO_2S$: C, 50.22; H, 8.96; N, 7.32. Found: C, 50.17; H, 9.10; N, 7.23.

2-n-Butyl-2-ethyl- and 2,2-diethyl-3-thiomorpholone (VII-1Y *and* VII-2). These were prepared from 2-bromoethylamine hydrobromide[12] with the results as shown in Table III.

2-n-Butyl-2-ethyl-3-thiomorpholone (VII-2Z). In a manner similar to that described above, 5.19 g. (0.029 mole) of *n*-butylethylmercaptoacetamide was treated with 6.0 g. (0.029 mole) of 2-bromoethylamine hydrobromide. The reaction mixture was made strongly basic with sodium hydroxide to precipitate the product which acted like an extremely deliquescent solid and was not purified but was immediately pyrolyzed to produce 3.58 g. (60.1%) of VII-1Z which was redistilled, b.p. 143–145°/1.1 mm., n_D^{25} 1.5138. Infrared spectra showed this to be identical with VII-1Y.

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[CONTRIBUTION FROM THE DIVISION OF STEROID RESEARCH, THE JOHN HERR MUSSER DEPARTMENT OF RESEARCH MEDICINE, UNIVERSITY OF PENNSYLVANIA, AND THE RESEARCH LABORATORIES, THE UPJOHN CO.]

Investigations on Steroids. XXXI. Preparation of 19-Hydroxycorticosterone[1,2]

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By the action of the fungus *Cunninghamella blakesleeana*, 19-hydroxycortexone (II) has been converted into a crystalline compound interpreted to be 19-hydroxycorticosterone (III). Contrary to expectations, acetylation of III gave a mixture of products, from which as main component the crystalline 11β,19,21-triacetate (VI B) was isolated. Benzoylation of III gave the crystalline 19,21-dibenzoate (V). III possesses little, if any, glucocorticoid activity and is devoid of mineralocorticoid action. Although there appears to be no doubt that III and its benzoylation product are identical with compounds described in the literature,[9] discrepancies exist regarding the acetylation and the physiological activity of III.

The syntheses of 19-hydroxy analogs of a number of steroid hormones were done at the University of Pennsylvania.[5a-d] The preparation of 19-hydroxycortexone[5a,6] (II) coincided with the elucidation of the structure of aldosterone by the combined efforts of a Swiss-British team.[7] II was subsequently found to occur in adrenal tissue.[8,9] We immediately considered it desirable to synthesize

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(2) The findings of this paper were presented on September 5, 1958, at the 4th International Congress of Biochemistry in Vienna {*cf.* Maximilian Ehrenstein: Biochemistry of the Corticoids, Proceedings of the Fourth International Congress of Biochemistry, Vol. 4 [Symposium: Biochemistry of Steroids], Pergamon Press, p. 259 (1959)}.

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