nated to unprotonated base for the fuchsones and isofluorenones in mixtures of concentrated sulfuric and formic acids with ratios for standard indicators in the same solvents. The indicators were *p*-nitrodiphenylamine, pK_a −2.5,[21,24] used as reference for 2-diphenylmethylene-1-naphthone, and 2,4-dichloro-6-nitroaniline, pK_a −3.3, used for the other unknowns. 2,4-Dichloro-6-nitroaniline, generously supplied by Dr. E. S. Lewis, absorbed maximally in 90% formic acid containing 1% of sodium formate at 417 mμ (log ε 3.67) (lit.[39] in acetic acid 408 (3.66)). *p*-Nitrodiphenylamine was prepared by reaction[40] of *p*-nitroacetanilide, boiling bromobenzene, potassium carbonate, potassium iodide and copper, followed by acid hydrolysis, and was advantageously crystallized from 80% acetic acid or as the solvate[41] from carbon tetrachloride. The puzzlingly wide apparent fusion range was interpreted by a polymorphic transition: the final sample melted at 133.5–134.5°, solidified at 134° and remelted at 136.5–137°. The visible absorption peak in formic acid containing 1% of sodium formate lay at 405 mμ (log ε 4.24) (lit.[42] in ethanol 390 (4.33)). The nitrodiphenylamine decomposed[43] rapidly in 97% sulfuric acid (contrary to a previous report[41]) with appearance of a deep purple color, but was stable in 70% acid.

For preparation of stock solutions, 4-hydroxy-9-phenyl-2,3-benzo-1-isofluorenone (5 mg.) was dissolved in formic acid by heat (100°, 20 minutes), and the methoxyisofluorenone and fuchsones (5–15 mg.) were each dissolved in 2 cc. of chloroform and diluted with formic acid to 50 cc.; identical solvents were used for the indicators (2–8 mg.). The absorptions of the free nitroanilines were measured in 5- to 10-cc. aliquots diluted to 25 cc. and made up to 1% in sodium formate, of the protonated fuchsones and isofluorenones in aliquots made up to approximately 17% in sulfuric acid, equivalent to H_0 −5.0 (determined roughly with 2,4-dichloro-6-nitroaniline; the anilinium ion was examined in 75% aqueous sulfuric acid). The ionization ratios were determined from optical densities at apposite wave lengths of samples diluted with stock solutions of sulfuric acid in formic acid. Solutions of *p*-nitrodiphenylamine in pure formic acid or more acidic media faded (about 4% per hour in pure acid), perhaps from acylation, and the densities were extrapolated backward in time. Correction similarly was made for decomposition of 4-methoxy-2-diphenylmethylene-1-naphthone. Two determinations of pK_a of the methoxy fuchsone cation agreed to 0.01; for the other compounds, the maximum scatter of three values at different acidities was 0.04.

HOUSTON, TEXAS

(39) H. Lemaire and H. J. Lucas, THIS JOURNAL, **73**, 5198 (1951).
(40) I. Goldberg, *Ber.*, **40**, 4541 (1907); T. L. Davis and A. A. Ashdown, THIS JOURNAL, **46**, 1051 (1924).
(41) H. Ryan and T. Glover, *Proc. Roy. Irish Acad.*, **34B**, 97 (1918).
(42) W. A. Schroeder, *et al.*, *Ind. Eng. Chem.*, **41**, 2818 (1949).
(43) L. P. Hammett and A. J. Deyrup, THIS JOURNAL, **54**, 2721 (1932).

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

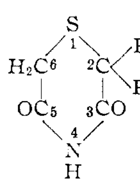
2,2-Dialkyl-3,5-thiamorpholinediones

BY GLENN S. SKINNER AND JOHN B. BICKING

RECEIVED JANUARY 4, 1954

A series of 2,2-dialkyl-3,5-thiamorpholinediones has been synthesized and subjected to pharmacological screening. All except the 2,2-diphenyl derivative have significant hypnotic activity in mice.

The synthesis of 2,2-dialkyl-3,5-thiamorpholinediones (I) was undertaken for evaluation as potentially useful hypnotics, sedatives and anticonvulsants. These compounds are isosteric with the 5,5-dialkylbarbituric acids (II) in that S replaces >C=O at position 6 (or 4) and $=CH_2$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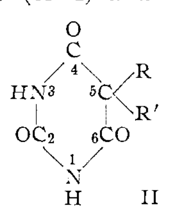
II

replaces =NH at position 1 (or 3). Thiamorpholinedione[1] was prepared by Schulze in 1866. Various alkyl derivatives[2] also are described in the literature. These alkyl derivatives are reported to be devoid of anticonvulsant activity. Derivatives corresponding to the precise pattern of two alkyls at position 2 and an unsubstituted methylene at position 6 have not been reported.

The desired thiamorpholinediones were obtained by heating the ammonium salts or amides of the α,α-dialkylthiodiacetic acids. These compounds were prepared through the action of ethyl mercaptoacetate on the ethyl bromodialkylacetate (Fig. 1), or through the action of bromoacetic acid or chloroacetamide upon the appropriate dialkylmercaptoacetic acid or amide (Fig. 2). Diphenylmercaptoacetic acid (Fig. 3) was prepared[3] from benzilic acid with the aid of its reaction on phenyl isothiocyanate. The other dialkylmercaptoacetic acids and amides were made by alkaline hydrolysis of the 5,5-dialkyl-2-imino-4-thiazolidones.

The α-bromodialkylacetyl bromides were prepared by the successive treatment of the dialkylacetic acids with thionyl chloride and bromine.[4] In the first method (Fig. 1) the α-bromodialkylacetyl bromides were converted to the esters which reacted with the sodium salt of ethyl mercaptoacetate in alcohol to give the diethyl α,α-dialkylthiodiacetates (III) whose analyses indicated the presence of impurities. These impurities could not be removed by fractional distillation but the products could be hydrolyzed to give the pure crystalline α,α-dialkylthiodiacetic acids (IV). The diethyl α,α-dimethylthiodiacetate by the action of ammonia in alcohol gave an excellent yield of the diamide VIII but the diamides of VI and VII could not be obtained in this manner. Because of the poor yields of the acids (VI and VII) only three of the 2,2-dialkyl-3,5-thiamorpholinediones (IX, X and XI) were made by this route.

In the second method (Fig. 2) the 5,5-dialkyl-2-imino-4-thiazolidones (XII) were suitably prepared by the action of the bromodialkylacetyl bromides

(1) *Beilstein*, [4] **27**, 249 (1937).
(2) P. R. Rasenen and G. L. Jenkins, *J. Am. Pharm. Assoc.*, **38**, 599 (1949).
(3) H. Becker and H. Bistrzycki, *Ber.*, **47**, 3151 (1914).
(4) E. Fourneau and V. Nicolitch, *Bull. soc. chim.*, **43**, 1238 (1928).

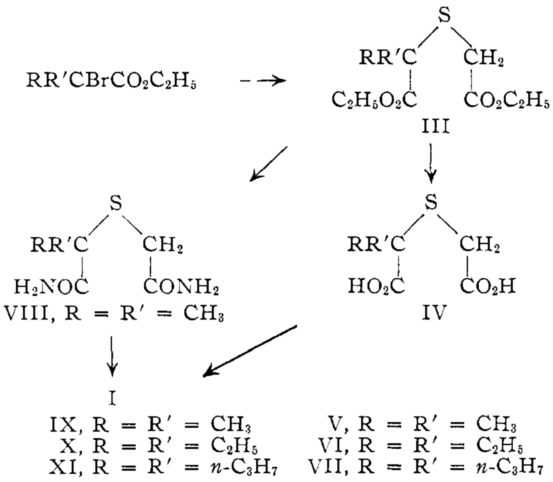

Fig. 1.—Products from bromodialkylacetic esters.

TABLE I

α,α-DIALKYLTHIODIACETIC ACIDS $HO_2C—C(R)(R')—S—CH_2CO_2H$

	R	R'	M.p., °C.	Sulfur, % Calcd.	Sulfur, % Found
V	CH_3	CH_3	106–107[b]	17.99	17.86
VI	C_2H_5	C_2H_5	92–93.5	15.54	15.49
VII	$n-C_3H_7$	$n-C_3H_7$	96–97	13.68	13.76
XIX	$n-C_4H_9$	$n-C_4H_9$	76–77	[a]	[a]

[a] Calcd. for $C_{12}H_{22}O_4S$: C, 54.93; H, 8.44. Found: C, 55.15; H, 8.62. [b] M.p. 111°. E. Larsson and K. Jönsson, *Ber.*, **67B**, 757 (1934); m.p. 106–107.5°. A. Fredga and O. Martensson, *C.A.*, **38**, 3616[6] (1944); *Arkiv. Kemi. Mineral Geol.*, Ser. B16, No. 8, 1 (1942).

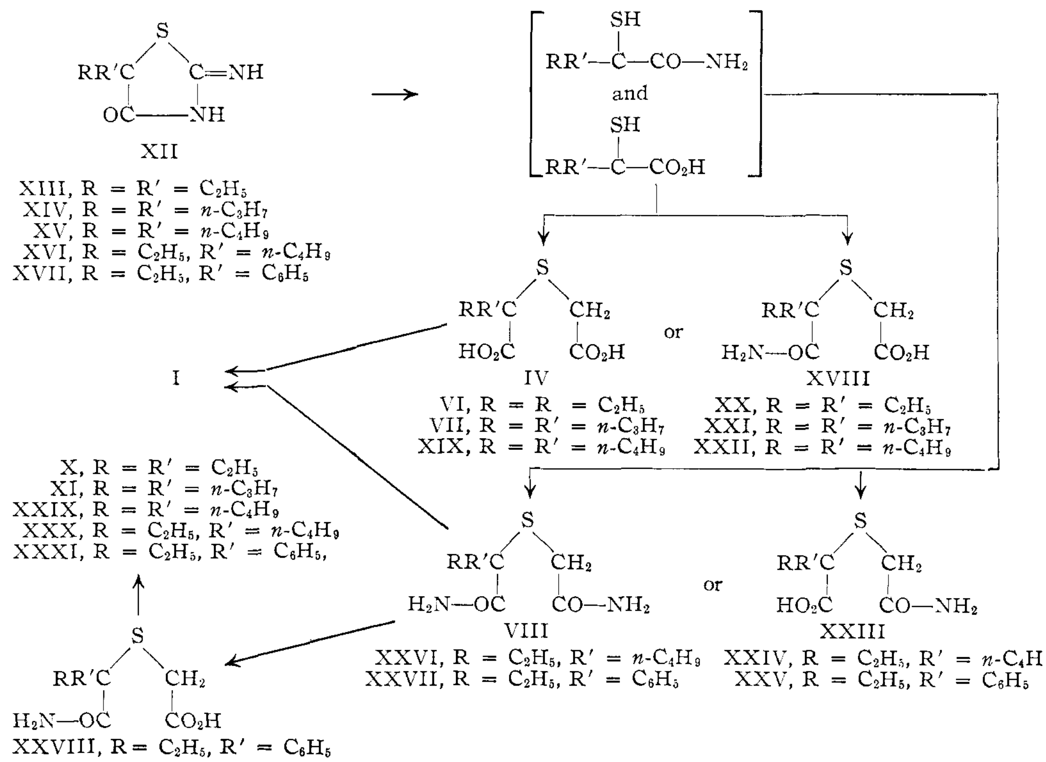

Fig. 2.—Products from dialkylthiazolidones (XII).

on an excess of thiourea in glacial acetic acid. Two (XIII and XIV) have been reported. XIII has been hydrolyzed[5] to diethylmercaptoacetamide, on longer hydrolysis, to diethylmercaptoacetic acid in unspecified yields. The product was characterized only as an oil. Our thiazolidones were all hydrolyzed to a mixture of dialkylmercaptoacetic acids and amides. When treated with bromoacetic acid and alkali each of the products gave a mixture of α,α-dialkylthiodiacetic acids (IV) and their monoamides XVIII. Likewise the similar use of chloroacetamide led to a mixture of the isomeric monoamides XXIII and the diamides VIII.

Longer periods of hydrolysis of the thiazolidones did not convert all of the amide to the acid. This is in harmony with the well-known resistance of tertiary amides toward alkaline hydrolysis. The amide group in XXIII must be primary since it is furnished by chloroacetamide. The diamide XXVII is rapidly hydrolyzed to the monoamide XXVIII isomeric with XXV indicating that the amide group remaining in the hydrolysis product of XXVII must be derived from a tertiary carboxyl.

The thiamorpholinediones are imides, which permits their ready separation from carboxylic acids with the aid of sodium bicarbonate. Better yields of the imides were obtained from the monoamides than from the ammonium salts. Alkaline hydrolysis of the diamide XXVII gave the tertiary monoamide XXVIII. While the tertiary amide in this case gave a better yield of the imide than the primary amide XXV did, a more important factor appears to be the ability of the amide to undergo

(5) E. Clemmensen and A. H. C. Heitman, *Am. Chem. J.*, **40**, 280 (1908).

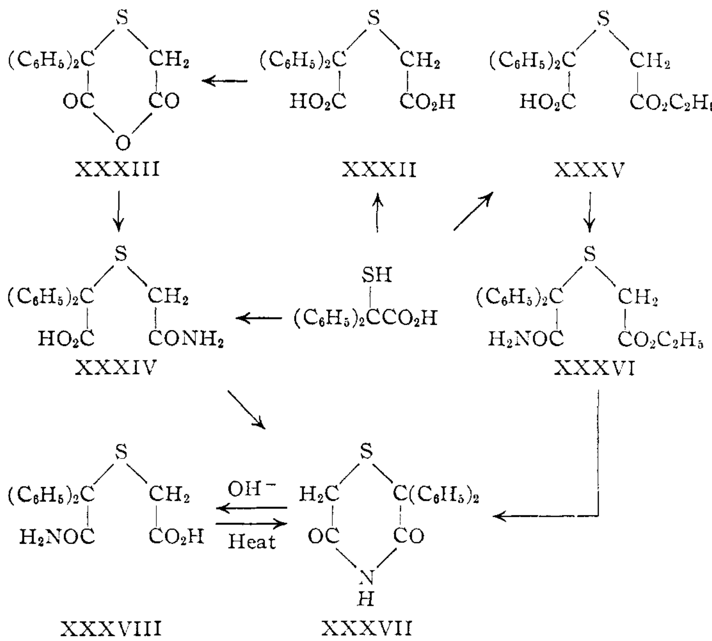

Fig. 3.—Products from diphenylmercaptoacetic acid.

the decomposition at a lower temperature. The corresponding diamide XXVII which was relatively very stable toward heat gave a very poor yield of this imide XXXI. The other diamide XXVI which decomposed at a relatively low temperature gave a relatively high yield of the imide XXX. It is also of interest that a better yield of 2,2 - diphenyl - 3,5 - thiamorpholinedione (XXXVII) was obtained from the amide-ester XXXVI under acid rather than neutral conditions.

Experimental

Ethyl α-Bromodialkylacetates.—Three of these esters were prepared by the action of an excess of alcohol upon the bromoacyl bromides that were made according to the procedure of Fourneau and Nicolitch.[4]

R	R′	Yield, %	B.p., °C.	Pressure, mm.	$n^{25}D$
CH_3[a]	CH_3	74	71–72	27	1.4410
C_2H_5[b]	C_2H_5	86	80–82	10	1.4546
n-C_3H_7[c]	n-C_3H_7	84	120–122	20	1.4538

[a] J. Volhard, *Ann.*, **242**, 161 (1887). [b] K. W. Rosenmund, *Ber.*, **42**, 4472 (1909). [c] E. Blaise and P. Bagard, *Ann. chim. phys.*, [8] **11**, 138 (1907).

5,5-Dialkyl-2-imino-4-thiazolidones (XII).—In a typical experiment 173 g. (0.55 mole) of α-bromo-α-butylcaproyl bromide was added dropwise during 20 minutes to a refluxing solution of 125 g. (1.65 moles) of thiourea in 600 cc. of glacial acetic acid.[6] After refluxing 20 minutes longer the acetic acid was removed under diminished pressure. To the residue was added 500 cc. of water and the mixture was neutralized with aqua ammonia (sp. gr. 0.90). The gummy yellow precipitate was collected on a filter and

(6) The use of acetic acid was suggested by Dr. Charles Miller and Mrs. Janice Gordon.

TABLE II

AMIDES OF DIALKYLTHIODIACETIC ACIDS Y—CO—C(R)(R′)—S—CH₂—CO—Z

	R	R′	Y	Z	M.p., °C.	Nitrogen, % Calcd.	Found
VIII	CH_3	CH_3	NH_2	NH_2	139–140	15.89	15.87
XX	C_2H_5	C_2H_5	NH_2	OH	121–122	6.83	6.73
XXI	n-C_3H_7	n-C_3H_7	NH_2	OH	125–126	6.00	5.99
XXII	n-C_4H_9	n-C_4H_9	NH_2	OH	138–139	5.36	5.26
XXIV	n-C_4H_9	C_2H_5	OH	NH_2	157–158	6.00	6.04
XXVI	n-C_4H_9	C_2H_5	NH_2	NH_2	147–149	12.06	12.03
XXV	C_6H_5	C_2H_5	OH	NH_2	133–134	5.53	5.51
XXVII	C_6H_5	C_2H_5	NH_2	NH_2	180–181	11.10	10.94
XXVIII	C_6H_5	C_2H_5	NH_2	OH	143–144	5.53	5.47
XXXIV	C_6H_5	C_6H_5	OH	NH_2	166–168 (d.)	4.65	4.63
XXXVI	C_6H_5	C_6H_5	NH_2	OC_2H_5	131.5–133	4.25	4.20
XXXVIII	C_6H_5	C_6H_5	NH_2	OH	142–143	4.65	4.63

TABLE III

2,2-DIALKYL-3,5-THIAMORPHOLINEDIONES (I)

	R	R′	M.p., °C.	Nitrogen, % Calcd.	Found	Pharmacological data,[d] mg./kg. LD₅₀	HD₅₀
IX	CH_3	CH_3	108–109	8.80	8.82	2600 ± 324	630 ± 55
X	C_2H_5	C_2H_5	85–86	7.48	7.39	795 ± 64	200 ± 24
XI	n-C_3H_7	n-C_3H_7	63–64	6.51	6.48	1100	360 ± 41
XXIX	n-C_4H_9	n-C_4H_9	Liq.[a]	5.75	5.63	1195	958
XXX	n-C_4H_9	C_2H_5	37–39[b]	6.51	6.50[c]	1233	201
XXXI	C_6H_5	C_2H_5	111–113	5.95	5.83	918	500
XXXVII	C_6H_5	C_6H_5	196–197	4.94	4.91	>2000	>2000

[a] B.p. 159–161° (1 mm.). [b] B.p. 156–160 (4 mm.). [c] Calcd. for $C_{10}H_{17}O_2NS$: C, 55.78; H, 7.96. Found: C, 55.92; H, 7.79 [d] Compounds administered intraperitoneally in carboxymethylcellulose suspension. These tests were made by Sharp and Dohme, West Point, Penna.

TABLE IV

PREPARATION OF 2,2-DIALKYL-3,5-THIAMORPHOLINEDIONES (I)

Product	Amide or salt	Temp., °C.	Time, min.	Yield, %	Solvent
IX	V·NH_3	190	60	40	EtOH–H_2O
IX	VIII	190	30	67	
X	VI·NH_3	190	75	37	i-C_3H_7OH–H_2O
X	XX	160–170	45	82	
XI	VII·NH_3	190	40	37	Hexane
XI	XXI	170	35	53	
XXIX	XIX·NH_3	180–190	45	32	
XXIX	XXII	140–160	40	68	See Table III
XXX	XXIV	200	40	61	Petr. ether
XXX	XXVI	160	45	80	
XXXI	XXV	180	45	44	
XXXI	XXVII	210	90	8	i-C_3H_7OH
XXXI	XXVIII	160	30	65	

washed with ether. It was recrystallized from a mixture of water and alcohol to give 57.0 g. (45%) of 5,5-dibutyl-2-imino-4-thiazolidone (XV), m.p. 216–222°. For the analysis a 1.0-g. sample twice recrystallized gave 0.6 g., m.p. 223°.

	R	R′	Yield, %	M.p., °C.	Nitrogen, % Calcd.	Found
XIII	C_2H_5	C_2H_5	65	225[a]		
XIV	n-C_3H_7	n-C_3H_7	45	235[b]		
XV	n-C_4H_9	n-C_4H_9	45	223	12.27	12.24[c]
XVI	C_2H_5	n-C_4H_9	45	203	13.99	13.86
XVII	C_2H_5	C_6H_5	51	213	12.72	12.70

[a] E. Clemensen and A. H. C. Heitman, *Am. Chem. J.*, **40**, 280 (1908), give 224°; H. Erlenmeyer and H. von Meyenburg, *Helv. Chim. Acta*, **20**, 1388 (1937), give 233–235°; W. J. Doran and H. A. Shonle, *J. Org. Chem.*, **3**, 193 (1938), give 237–238° for the pure product. [b] Erlenmeyer and von Meyenburg (see above) give m.p. 230°. [c] The authors are indebted to Kermit B. Streeter and his associates for the analytical work reported in this paper.

Dialkylthiodiacetic Acids (Fig. 1).—In a typical experiment 120 g. (1.0 mole) of ethyl mercaptoacetate and 223 g. (1.0 mole) of α-bromo-α-ethylbutyrate were mixed with a cooled solution of sodium ethoxide prepared from 23 g. of sodium and 700 cc. of alcohol. After standing under nitrogen for 4 days the alcohol was distilled. The residual oil was washed with water, dried with sodium sulfate and distilled to give 160 g. of a colorless oil, b.p. 160–164° (16 mm.). The analysis indicates that the ester is contaminated with compounds containing a higher percentage of sulfur.

Anal. Calcd. for $C_{12}H_{22}O_4S$: S, 12.22. Found: S, 14.22.

A solution of 63 g. of the oil in 250 cc. of sodium hydroxide solution (20%) and 250 cc. of methanol was heated 2.5 hours while the methanol was allowed to distil. Acidification of the cold residue gave an oil which after collection in ether and removal of the ether could not be crystallized. The oil was triturated with 35 cc. of benzylamine in ether to give a poorly crystallized salt which after two crystallizations from isopropyl alcohol gave 19.5 g. of the salt, m.p. 170–172°. The crystalline acid was liberated by sulfuric acid and crystallized from cyclohexane to give 9.0 g. (11% over-all) of the pure acid (VI, Table I).

Similarly 94.5 g. (0.5 mole) of ethyl α-bromoisobutyrate gave 101 g. of colorless oil, b.p. 139° (12 mm.).

Anal. Calcd. for $C_{10}H_{18}O_4S$: C, 51.26; H, 7.75. Found: C, 50.12; H, 7.83.

In this case 11.7 g. of the oil yielded an acid which crystallized directly and could be recrystallized from a mixture of cyclohexane and ethyl acetate to give 5.2 g. (50%) of pure V. A solution of 28.0 g. of the oil was heated under pressure with 170 cc. of alcoholic ammonia (12.5%) at 65–70° for two weeks. The amide precipitated from the cold solution and was recrystallized from a mixture of benzene and alcohol to give 16.7 g. (79%) of the pure diamide VIII. The esters of VI and VII did not yield the diamides in this way.

Likewise 25.1 g. (0.10 mole) of ethyl α-bromo-α-propylvalerate gave 13.5 g. of an oil, b.p. 165–167° (11 mm.). Saponification of 5.6 g. of this oil gave a crystalline acid which after crystallization from a mixture of hexane and benzene and then from water gave 1.45 g. (16% over-all) of the pure acid VII. VI and VII were identical with the acids prepared from the corresponding thiazolidones (XII, Fig. 2).

Hydrolysis of 5,5-Dialkyl-2-imino-4-thiazolidones.—The solutions of the thiazolidones in aqueous sodium hydroxide were heated under reflux as detailed below. The resulting solutions were acidified with sulfuric acid to precipitate an oil which was collected in ether. The residue from the removal of the ether was used directly in the subsequent reactions with bromoacetic acid and chloroacetamide.

Thiazolidone	NaOH soln. %	Cc./g. compd.	Time, hr.
XIII	15	6	76
XIV	15	6	46
XV	15	6	40
XVI	15	6	48
XVII	5	15	92

Reaction of the Hydrolysates of the Thiazolidones with Bromoacetic Acid.—The product from the hydrolysis of 51.6 g. (0.30 mole) of 5,5-diethyl-2-imino-4-thiazolidone (XIII) was dissolved in 240 cc. of 10% sodium hydroxide solution. To this was added a solution of 41.7 g. (0.30 mole) of bromoacetic acid in 120 cc. of 10% sodium hydroxide. After 30 minutes, the resulting solution was acidified. The oily precipitate was collected in ether and dried over sodium sulfate. The residue from the distillation of the ether was dissolved in a hot mixture of 200 cc. of cyclohexane and 90 cc. of isopropyl alcohol. Cooling in ice gave 9.8 g. of impure amide XX, m.p. 116–121°, which by recrystallization gave 8.6 g. (14%) of pure XX. The oil remaining after the removal of the solvents from the filtrate from impure XX slowly crystallized. It was triturated with a little petroleum ether and sucked dry on a filter; yield of impure acid VI 28.4 g., m.p. 77–87°. This product was dissolved in 200 cc. of hydrochloric acid (sp. gr. 1.19) and refluxed for 4 hours. On cooling the solution deposited 25.6 g. (41%) of the pure acid VI identical with that obtained by the plan shown in Fig. 1. In an attempt to hydrolyze XIII completely to the acid it was found that the ratio of the acid to amide in aliquots taken at intervals of 48, 72 and 81 hours was about the same. Amide was still present after 120 hours and the yield of products was poor indicating other decomposition.

The similar acidic product from 34.5 g. (0.173 mole) of XIV gave 10.8 g. of impure amide XXI by chilling a petroleum ether solution. Recrystallization from a mixture of cyclohexane and isopropyl alcohol gave 8.2 g. (20.3%) of pure XXI. The residue from the distillation of the petroleum ether was crystallized from 70 cc. of hexane to yield 16.5 g. of the impure acid VII. This was refluxed 36 hours in a mixture of 125 cc. of hydrochloric acid (1.19) and 65 cc. of glacial acetic acid. The acid from the ice-cold solution weighed 13.2 g. which after crystallization from 300 cc. of water gave 8.5 g. (21.2%) of pure VII.

The impure amide XXII obtained, similarly to XXI, from 22.8 g. (0.100 mole) of XV weighed 8.3 g. Recrystallization from cyclohexane gave 6.3 g. (24.1%) of pure XXII. The residue from the first filtrate was crystallized from 30 cc. of petroleum ether to give 9.7 g. of the impure acid XIX. The product obtained after refluxing 16 hours with a mixture of 90 cc. of hydrochloric acid and 60 cc. of acetic acid was recrystallized from a mixture of cyclohexane and petroleum ether to give 8.0 g. (30.5%) of pure XIX.

Reaction of the Hydrolysates of the Thiazolidones with Chloroacetamide.—The product from the hydrolysis of 48.5 g. (0.242 mole) of 5-n-butyl-5-ethyl-2-imino-4-thiazolidone (XVI) and 22.6 g. (0.242 mole) of chloroacetamide were dissolved in 200 cc. of a 10% sodium hydroxide solution. After 30 minutes the solution was acidified to precipitate 58.5 g. of crystalline product. The finely powdered material was stirred with 400 cc. of a saturated solution of sodium bicarbonate. The undissolved material weighed 20.6 g. (36.7%) and consisted solely of the diamide XXVI, m.p. 147–149°. The product precipitated from the filtrate by acid was recrystallized from isopropyl alcohol to give 15.1 g. (26.7%) of the amide XXIV.

The product from the hydrolysis of 8.0 g. (0.036 mole) of 5-ethyl-5-phenyl-2-imino-4-thiazolidone (XVII) and 3.4 g. (0.036 mole) of chloroacetamide were dissolved in 60 cc. of 5% sodium hydroxide solution. After 5 minutes the solution was acidified and 1.3 g. (14%) of the diamide XXVII, m.p. 180–181°, was separated as above. The product precipitated from the filtrate by acid was crystallized twice from a mixture of acetic acid and water to give 2.9 g. (32%) of pure XXV.

Hydrolysis of a Diamide XXVII.—A mixture of 7.7 g. (0.031 mole) of α-ethyl-α-phenylthiodiacetamide and 50 cc. of 10% sodium hydroxide solution was refluxed for 5 minutes. The cooled solution was acidified and the precipitate was recrystallized from isopropyl alcohol to give 6.4 g. (83%) of the tertiary amide XXVIII isomeric with the primary amide XXV.

2,2-Dialkyl-3,5-thiamorpholinediones (Table III).—These compounds were prepared by heating the ammonium salts or amides of the thiodiacetic acids. Details of these decompositions are summarized in Table IV and further depicted by the examples given below.

a. **From a Dicarboxylic Acid.**—To a solution of 16.3 g. (0.075 mole) of α,α-di-*n*-propylthiodiacetic acid (VII) in 60 cc. of dry ether was added 20 cc. of a 10% solution of ammonia in absolute alcohol. The salt which precipitated was dried and placed in a Claisen flask fitted with a capillary boiling tube and having a receiver fused to the sidearm. The salt was heated in a metal-bath at 190–200° (80 mm.) for 40 minutes. The imide was then slowly distilled at a bath temperature of 230° (20 mm.). The yellow oil was triturated with a 5% sodium bicarbonate solution to give 8.2 g. of soft crystalline product. After three crystallizations from hexane there was obtained 5.5 g. (37%) of the pure imide XI.

b. **From a Monoamide.**—α-Butyl-α-ethyl-α-carbamylmethylmercaptoacetic acid (XXIV) (15.0 g., 0.0645 mole) was heated 40 minutes at 200° (40 mm.). Distillation gave 11.9 g. of yellowish viscous oil, b.p. 160–163° (5 mm.). The product crystallized slowly and melted at 35–39°. Crystallization from petroleum ether gave 8.5 g. (61%) of the pure imide (XXX).

c. **From a Diamide.**—α-Butyl-α-ethylthiodiacetamide (25.0 g., 0.108 mole) melted and decomposed vigorously when heated at 160–165° (40 mm.). After 45 minutes the product was distilled to give 18.7 g. (80.5%) of viscous colorless oil, b.p. 156–160° (4 mm.). It crystallized upon standing overnight to give XXX, m.p. 37–39°. The melting point was not changed by crystallization from petroleum ether and the substance was analyzed directly.

d. **By Heating in an Inert Liquid.**—A solution of 10 g. of α-carbamylmethylmercapto-α,α-diphenylacetic acid (XXXIV, Fig. 3) in 100 cc. of *o*-chlorotoluene was boiled 75 minutes while 60 cc. of solvent was allowed to distil. The solution was cooled and mixed with 100 cc. of hexane to precipitate a soft crystalline material which was filtered and stirred with sodium bicarbonate solution. The solid was recrystallized twice from a mixture of benzene and acetone to give 2.5 g. (27%) of pure XXXVII.

e. **From an Amide Ester.**—A solution of 6.2 g. (0.019 mole) of XXXVI (Fig. 3) in a mixture of 25 cc. of hydrochloric acid (sp. gr. 1.19) and 35 cc. of glacial acetic acid was heated at 100° for 10 minutes whereupon crystals began to separate. The crystalline precipitate from the ice-cold mixture was recrystallized from a mixture of benzene and acetone to give 3.0 g. (56%) of XXXVII.

α,α-Diphenylthiodiacetic Anhydride (XXXIII, Fig. 3).—Diphenylmercaptoacetic acid[3] was prepared in 66% yield. A solution of 20.5 g. (0.084 mole) of the acid in 135 cc. of 5% sodium hydroxide was added to 11.7 g. (0.084 mole) of bromoacetic acid in 70 cc. of 5% sodium hydroxide solution. After 15 minutes, the solution was acidified to give 24.8 g. (98%) of the crude acid XXXII, m.p. 185–190° dec., which was used without further purification. The recorded melting point[7] is 194–196°. A mixture of 12.3 g. (0.041 mole) of XXXII and 20 cc. (0.28 mole) of acetyl chloride was refluxed for 1.5 hours. The liquid was diluted with 50 cc. of cyclohexane and the solution was chilled. The precipitate was recrystallized twice from a mixture of benzene and cyclohexane to give 6.3 g. (54%) of the pure anhydride XXXIII, m.p. 108–109°. The quite pure sample of XXXII from the hydrolysis of the anhydride had m.p. 188–190° either in an open or a sealed tube.

Anal. Calcd. for $C_{16}H_{12}O_3S$: C, 67.59; H, 4.26. Found: C, 67.43; H, 4.43.

α-Carbamylmethylmercapto-α,α-diphenylacetic Acid (XXXIV).—To an ice-cold solution of 5 cc. of liquid ammonia in 100 cc. of ether was added a solution of 7.4 g. (0.026 mole) of XXXIII in 200 cc. of ether. The ammonium salt was filtered and dissolved in 25 cc. of water. The solution was acidified to give 6.2 g. (80%) of product, m.p. 157–161° dec. The decomposition point was not lowered by an analytically pure sample prepared as follows.

To a solution of 24.0 g. (0.099 mole) of diphenylmercaptoacetic acid in 160 cc. of 5% sodium hydroxide solution was added 9.4 g. (0.10 mole) of chloroacetamide. After 15 minutes the solution was acidified and the precipitate was recrystallized from a mixture of isopropyl alcohol and water to give 19.3 g. (65%) of pure XXXIV.

α-Carbethoxymethylmercapto-α,α-diphenylacetic Acid (XXXV).—A mixture of 22.4 g. (0.092 mole) of diphenylmercaptoacetic acid, 300 cc. of 5% sodium bicarbonate solution and 16.0 g. (0.096 mole) of ethyl bromoacetate became homogeneous after being shaken for 20 minutes. The crystalline precipitate obtained by acidification was crystallized twice from a mixture of benzene and cyclohexane to give 15.4 g. (51%) of the acid ester, m.p. 141–143°. For the analysis, 1.5 g. was recrystallized again from the above solvent mixture to give 1.4 g. of pure XXXV, m.p. 142–143°.

Anal. Calcd. for $C_{18}H_{18}O_4S$: C, 65.43; H, 5.49. Found: C, 65.33; H, 5.39.

α-Carbethoxymethylmercapto-α,α-diphenylacetamide (XXXVI).—A solution of 6.8 g. (0.21 mole) of XXXV in 25 cc. of thionyl chloride was refluxed for 30 minutes. After removal of the excess of thionyl chloride under diminished pressure the residue was stirred with 30 cc. of ice-cold aqua ammonia (sp. gr. 0.90). The crystalline product was crystallized three times from alcohol to give 4.6 g. (68%) of pure XXXVI.

α-Carboxymethylmercapto-α,α-diphenylacetamide (XXXVIII).—A solution of 1.9 g. (0.0067 mole) of XXXVII in 25 cc. of 5% sodium hydroxide was allowed to stand at room temperature for 5 hours. The sodium salt which had separated was dissolved by the addition of 125 cc. of water. Acidification of the solution gave a precipitate which when recrystallized from a mixture of isopropyl alcohol and water gave 1.4 g. (69%) of pure XXXVIII.

Conversion of XXXVIII to XXXVII.—XXXVIII (0.6 g., 0.002 mole) was heated at 160° for 20 minutes under a pressure of 60 mm. The amide decomposed vigorously to give a residue which was stirred with cold sodium bicarbonate solution. The insoluble material was crystallized from a mixture of benzene and acetone to give 0.30 g. (53%) of pure XXXVII.

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(7) B. Holmberg, *J. prakt. Chem.*, **141**, 93 (1934).