[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KENTUCKY]

THE PREPARATION OF SOME PHENYL SUBSTITUTED 3,5-THIAMORPHOLINEDIONES AS POSSIBLE ANTICONVULSANTS

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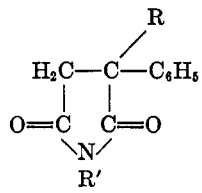
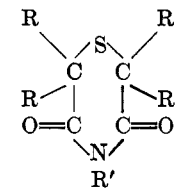
Many compounds have been found to have anticonvulsant action. The recent work of Miller and Long (1) has shown that certain substituted succinimides (I) have marked anticonvulsant activity against metrazol shock. Because of the structural similarity of succinimide and 3,5-thiamorpholinedione some phenyl substituted 3,5-thiamorpholinediones (II) have been made and their anticonvulsant activity tested.



I



II

R = H or phenyl
R′ = H or alkyl

3,5-Thiamorpholinedione was first prepared by Schulze (2) in 1866. The only substituted 3,5-thiamorpholinediones described in the literature when this work was undertaken were several alkyl substituted 3,5-thiamorpholinediones prepared by Rasanen and Jenkins (3) and they found that their compounds had no anticonvulsant activity. After this work was finished Skinner and Bicking (4) published their preparation of several 2,2-dialkyl-3,5-thiamorpholinediones some of which showed anticonvulsant activity. In this work all the possible 2- and 2,6-phenyl substituted 3,5-thiamorpholinediones have been prepared as well as some of the N-alkyl derivatives. They are listed in Table I.

It was found that the synthesis of these compounds by the distillation of the ammonium or substituted ammonium salts of the phenyl substituted thiodiacetic acids was not successful. Three general procedures were used. The first method (equation 1) involved the formation of the anhydride from the phenyl-substituted thiodiacetic acid which was converted to the amic acid by treatment with ammonia or an appropriate amine. The amic acid was then dehydrated to the 3,5-thiamorpholinedione. In using this method the anhydride and amic acid were

[1] Taken in part from a Ph.D. dissertation submitted to the Graduate School of the University of Kentucky, 1953.

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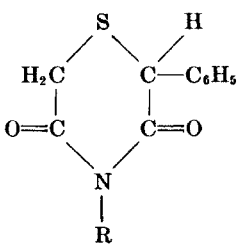
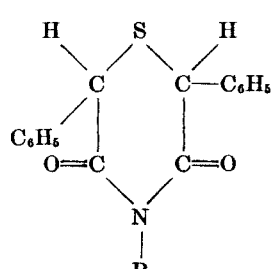
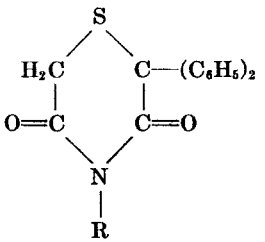
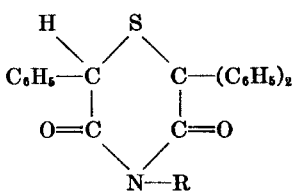
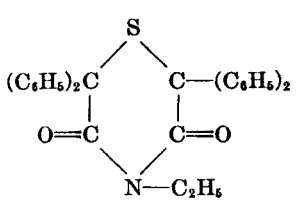
TABLE I

PHENYL SUBSTITUTED-3,5-THIAMORPHOLINEDIONES

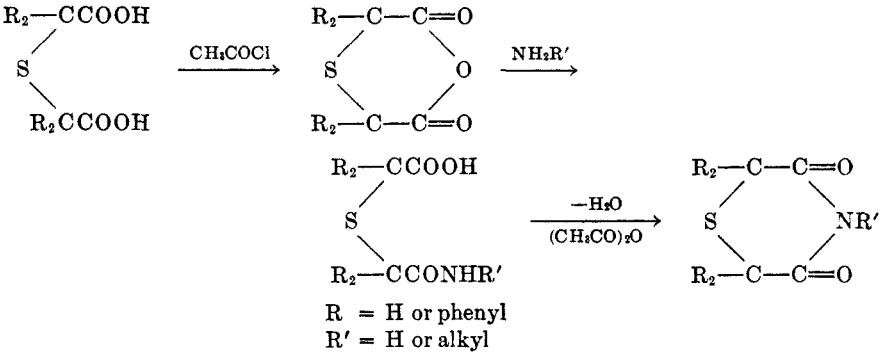
Type	R	Procedure	Yield, %	M.P., °C.	B.P., °C.	MM.	Formula	Analysis			
								Calc'd		Found	
								N	S	N	S
2-Phenyl-3,5-thiamorpholinediones 	H	1	30.3	136–138			$C_{10}H_9NO_2S$	6.76		6.60	
	Methyl	1	43.5	60–61			$C_{11}H_{11}NO_2S$	6.34		6.21	
	Ethyl	1	43.1	68–69			$C_{12}H_{13}NO_2S$	5.95		6.15	
	n-Propyl	1	41.0	60–61	165–178	1.5	$C_{13}H_{15}NO_2S$	5.62		5.68	
	Isopropyl	1	20.0	66–68	185–190	1.5	$C_{13}H_{15}NO_2S$	5.62		5.59	
	n-Butyl	1	40.0		175–178	2.5	$C_{14}H_{17}NO_2S$	5.32		5.37	
	Allyl	1	44.5	33–34	175–177	2.5	$C_{13}H_{13}NO_2S$	5.67		5.75	
2,6 - Diphenyl - 3,5 - thiamorpholinediones 	H	1	37.8	147–151			$C_{16}H_{13}NO_2S$	4.95		4.91	
	Methyl	1	51.8	70–150			$C_{17}H_{15}NO_2S$	4.71	10.78	4.86	10.67
	Ethyl	1	35.6	72–74	200–202	1	$C_{18}H_{17}NO_2S$	4.51	10.31	4.59	10.52

2,2-Diphenyl-3,5-thiamorpholinediones 	H	2	74.3	197–199[a]			$C_{17}H_{15}NO_2S$	4.71	10.78	4.80	10.92
	Methyl	2	91.0	105–106							
	Methyl	1	24.2	105–106							
	Ethyl	2	67.3	97–99			$C_{18}H_{17}NO_2S$	4.51	10.31	4.54	10.58
2,2,6-Triphenyl-3,5-thiamorpholinediones 	H	1	33.4	182–183			$C_{22}H_{17}NO_2S$	3.90	8.92	3.71	8.78
	Methyl	2	20.1	133–134			$C_{23}H_{19}NO_2S$	3.75	8.57	3.89	8.27
	Ethyl	2	10.4	163–166			$C_{24}H_{21}NO_2S$	3.62	8.29	3.72	8.41
4-Ethyl-2,2,6,6-tetraphenyl-3,5-thiamorpholinedione 		3	46.0	195–196			$C_{30}H_{25}NO_2S$		6.90		7.10

[a] Skinner and Bicking obtained a yield of 56% from the amide ester, m.p. 196–197°.

never isolated and the yields were calculated on the phenyl-substituted thiodiacetic acid used.

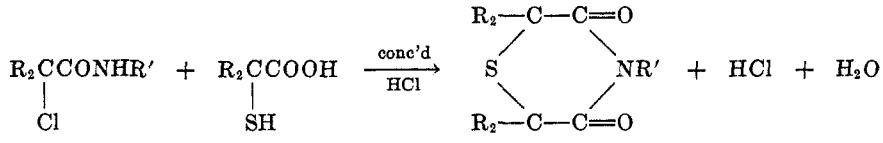
1.



R = H or phenyl
R′ = H or alkyl

The second method (equation 2) involved the formation of the amic acid by heating the appropriate α-chlorodiphenylacetamide with mercaptoacetic acid and a small amount of concentrated hydrochloric acid. Surprisingly, the resulting amic acid was dehydrated in this medium and only the 3,5-thiamorpholinedione was obtained. This method worked especially well in making 2,2-diphenyl-3,5-thiamorpholinedione. This same 3,5-thiamorpholinedione was also made by the first method for comparison. Substituting phenylmercaptoacetic acid for mercaptoacetic caused the yield of 2,2,6-triphenyl-3,5-thiamorpholinedione to be considerably smaller and some of the α-chlorodiphenylacetamide was hydrolized to α-hydroxydiphenylacetamide. When diphenylmercaptoacetic was used no 2,2,6,6-tetraphenyl-3,5-thiamorpholinedione could be isolated. This synthesis is patterned after Holmberg's (5) synthesis of α,α-diphenylthiodiacetic acid from benzilic and mercaptoacetic acid but substituting α-chlorodiphenylacetamide for benzilamide.

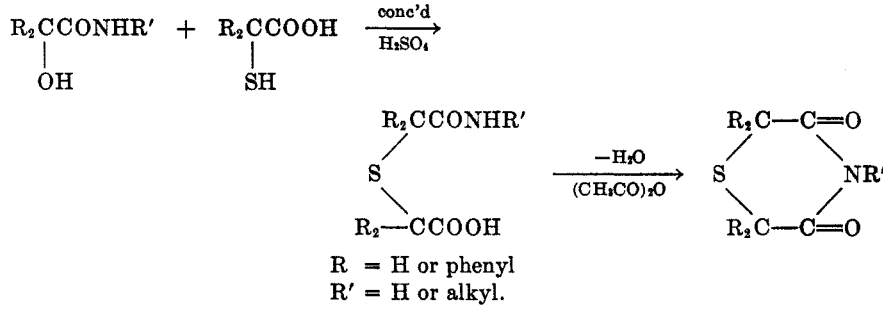
2.



R = H or Phenyl
R′ = H or alkyl

The third method (equation 3) used only in the preparation of 4-ethyl-2,2,6,6-tetraphenyl-3,5-thiamorpholenedione, consisted of synthesizing the amic acid directly from a mixture of N-ethyl-α-hydroxydiphenylacetamide and diphenylmercaptoacetic acid in the presence of concentrated sulfuric acid. Bistrazycki and Risi (6) have shown that benzilic acid and thiophenol in the presence of concentrated sulfuric acid condense in this manner. By substituting benzilic acid for the amide excellent yields of tetraphenylthiadiacetic acid can also be obtained. It was first thought that the product of the reaction was 4-ethyl-2,2,6,6-tetraphenyl-3,5-thiamorpholinedione since it was not soluble in dilute alkali but later it was found that the salts of the amic acids are very insoluble in dilute alkali but will dissolve slowly when triturated with 0.1 *N* alkali. The

resulting amic acid then was dehydrated by heating with acetic anhydride to the 3,5-thiamorpholinedione. The N-substituted 3,5-thiamorpholinediones are insoluble in cold alkali and under these conditions do not hydrolize to the amic acids.



R = H or phenyl
R′ = H or alkyl.

All the compounds listed in Table I were tested for their anticonvulsant and hypnotic activity.[3] With the exception of 4-methyl-2,2-diphenyl-3,5-thiamorpholinedione which showed slight protection towards metrazol shock, pharmacological activity was confined to the 2-phenyl-3,5-thiamorpholinedione type. The 4-methyl and 4-allyl derivatives showed 80% protection towards metrazol shock at 400 mg./kg. using rats and none towards electro shock. The 4-ethyl showed 60% protection and the 4-*n*-butyl and 4-allyl 20% protection towards electro shock at 400 mg./kg. None of the compounds showed any hypnotic activity.

EXPERIMENTAL

PREPARATION OF STARTING MATERIALS

Phenylmercaptoacetic acid. This acid was prepared according to the method of Holmberg (5) except α-chlorophenylacetic acid was used instead of α-bromophenylacetic acid.

α,α′-Diphenylthiodiacetic acid. α-Chlorophenylacetic acid (17 g., 0.1 mole) suspended in 100 ml. of water was neutralized with sodium carbonate and to this solution was added a solution of 18 g. (0.075 mole) of sodium sulfide nonahydrate in 50 ml. of water. After standing overnight the reaction mixture was filtered and acidified with concentrated sulfuric acid. The oil which separated solidified on standing. This solid was separated by filtration, washed with cold water, and dried. The crude product weighed 14.7 g. and melted over a range of 122–150°. Yield 97.3%. A fraction recrystallized from benzene melted at 167–169°. This is probably the meso isomer if analogy to the symmetrically substituted succinic acids is valid.

Anal. Calc'd for $C_{16}H_{14}O_4S$: S, 10.58; Neut. equiv., 151.2.
Found: S, 10.43; Neut. equiv., 151.5.

Attempts to effect a reasonably good separation of the racemic from the meso form were unsuccessful. The crude acid, m.p. 122–150°, was used without further treatment.

α,α-Diphenylthiodiacetic acid. This acid was prepared by Holmberg (7) but a modification of his procedure proved more successful. Benzilic acid (4.6 g., 0.02 mole) and 1.48 g. (0.02 mole) of mercaptoacetic acid were dissolved in 15 ml. of glacial acetic acid and the mixture was kept at approximately 40° during the drop-wise addition of 8 ml. of concentrated sulfuric acid. The reaction mixture was poured onto a small portion of crushed ice and stirred until the product crystallized. The solid was separated by filtration, washed

[3] The pharmacological tests were made by the pharmacological division of Eli Lilly and Company.

with cold water, and then dissolved in a warm 3% sodium hydroxide solution. The alkaline solution was treated with charcoal, filtered, and the filtrate was acidified with concentrated hydrochloric acid. The precipitated acid was filtered, washed with cold water, and dried. It weighed 4.6 g. (76.2%) and melted at 194–195° (lit. 194–196°).

α,α,α'-Triphenylthiodiacetic acid. This acid was prepared in the same manner as α,α-diphenylthiodiacetic acid by using benzilic acid and phenylmercaptoacetic acid. The crude acid was crystallized from 50% acetic acid and gave a product melting at 208–210° (dec.). Yield 59.5%.

Anal. Calc'd for $C_{22}H_{18}O_4S$: S, 8.45; Neut. equiv., 189.2.
Found: S, 8.49; Neut. equiv., 190.5.

Tetraphenylthiodiacetic acid. This acid was prepared in the same manner as above but starting with benzilic acid and diphenylmercaptoacetic acids. Yield 80.5%. An analytical sample was obtained by crystallizing a small amount of the crude product from glacial acetic acid in which it is very sparingly soluble. M.p. 202° dec.

Anal. Calc'd for $C_{28}H_{22}O_4S$: S, 7.05. Found: S, 7.21.

α-Chlorodiphenylacetamide. This amide was prepared by the method used by Stevens and French (7) to prepare the N-phenyl derivative except that ammonia was used instead of aniline. From 5 g. (0.019 mole) of α-chlorodiphenylacetyl chloride and 0.68 g. (0.040 mole) of ammonia dissolved in anhydrous ether there was obtained 3.6 g. (78.4%) of a product melting at 111–114° (lit. 111–114°). It melted at 112–115° after one crystallization from ether-petroleum ether.

N-Methyl-α-chlorodiphenylacetamide. M.p. 105–107°, yield 96%.

Anal. Calc'd for $C_{15}H_{14}ClNO$: N, 5.39. Found: N, 5.50.

N-Ethyl-α-chlorodiphenylacetamide. M.p. 97–98°, yield 83.5%.

Anal. Calc'd for $C_{16}H_{16}ClNO$: N, 5.11. Found: N, 5.24.

PREPARATION OF PHENYL SUBSTITUTED 3,5-THIAMORPHOLINEDIONES

Procedure 1. 4-Methyl-2-phenyl-3,5-thiamorpholinedione. This procedure is typical for the preparation of those compounds listed in Table I as having been prepared by Procedure I. Phenylthiodiacetic acid (22.6 g., 0.1 mole) and 100 ml. of acetyl chloride were refluxed for 2 hours. The acetic anhydride formed and the excess acetyl chloride were removed by heating at 100° under a water pump vacuum. The remaining crude phenylthiodiacetic anhydride was dissolved in 50 ml. of anhydrous benzene and this solution was added slowly to an ice-cooled solution of 7.0 g. (0.225 mole) of monomethylamine in 50 ml. of anhydrous benzene. Most of the benzene was decanted from the viscous amic acid salt and 150 ml. of water was added. The aqueous salt solution was separated from the remaining benzene with a separatory-funnel and acidified with concentrated hydrochloric acid. The precipitated N-methyl-α-phenylthiodiacetamic acid was filtered, washed with cold water and, after drying, was refluxed for 2 hours with 100 ml. of acetic anhydride. After the removal of about 75 ml. of acetic anhydride by distillation, the residue was poured onto a small quantity of crushed ice and stirred until the crude oil solidified. The product was filtered, washed with cold water, and dried. One crystallization from alcohol gave 8.0 g. of white crystals melting at 60–61°. By concentrating the alcoholic mother liquor an additional 1.6 g. was obtained making the total yield 9.6 g. (43.5%).

Anal. Calc'd for $C_{11}H_{11}NO_2S$: N, 6.34. Found: N, 6.21.

Procedure 2. 4-Methyl-2,2-diphenyl-3,5-thiamorpholinedione. This procedure is typical for the preparation of those compounds listed in Table I as having been prepared by Procedure 2. N-Methyl-α-chlorodiphenylacetamide (5.2 g., 0.02 mole), 2.6 g. (0.02 mole) of a 70% water solution of mercaptoacetic acid, and 12 drops of concentrated hydrochloric acid were stirred and heated on a steam-bath for 4 hours. The reaction mixture was allowed to stand overnight during which time the viscous mass solidified. The solid was broken into fine particles, washed with 10% sodium hydroxide or 5% sodium bicarbonate in the case of the nitrogen unsubstituted thiamorpholinedione, filtered, and finally washed with

cold water and dried. A product weighing 5.6 g. (94%) and melting at 104–105° was obtained. It melted at 105–106° after one crystallization from alcohol.

Anal. Calc'd for $C_{17}H_{15}NO_2S$: N, 4.71. Found: N, 4.80.

Procedure 3. (*A*). *N-Ethyl-α-hydroxydiphenylacetamide.* Monoethylamine (3.7 g., 0.082 mole) of monoethylamine in 100 ml. of cold anhydrous ether was added dropwise to a cooled solution of 10 g. (0.38 mole) of α-chlorodiphenylacetyl chloride. After standing 3 hours at room temperature the precipitated amine hydrochloride was filtered off and the ether solution evaporated until the N-ethyl-α-chlorodiphenylacetamide precipitated out. This product was placed in 100 ml. of water and heated on steam-bath with stirring for 4 hours. The mixture was cooled and the solid filtered off. It was crystallized from 50% ethyl alcohol; 7.2 g. (70.6%), m.p. 104–104.5°.

Anal. Calc'd for $C_{16}H_{17}NO_2$: N, 5.48. Found: N, 5.37.

(*B*). *N-Ethyltetraphenylthiodiacetamid acid.* In 4 ml. of acetic acid at 60° was dissolved 1.2 g. (0.005 mole) of N-ethyl-α-hydroxydiphenylacetamide and 1.2 g. (0.05 mole) of diphenylmercaptoacetic acid. The solution was allowed to cool to 45° prior to the dropwise addition of 2 ml. of concentrated sulfuric at a rate sufficient to maintain the temperature at 45–50°. A precipitate formed and the solution became red. After standing at room temperature for 1 hour, sufficient crushed ice was added to give about 50 ml. of total reaction mixture. The red color disappeared leaving a white waxy solid which was filtered off and washed with water. This was triturated with 20 ml. of 20% sodium hydroxide solution and filtered. The solid then was triturated with 100 ml. of 0.1 *N* sodium hydroxide. The small amount of undissolved residue was removed by filtration and the filtrate was extracted with benzene. The alkaline solution then was acidified with hydrochloric acid and 1.48 g. (61%) of a white solid was obtained. M.p. 122–125°, crystallized from benzene, it had m.p. 125–126° dec.

Anal. Calc'd for $C_{30}H_{27}NO_3S$: N, 2.90, S, 6.66.
Found: N, 2.81, S, 6.80.

(*C*). *4-Ethyl-2,2,6,6-tetraphenyl-3,5-thiamorpholinedione.* N-Ethyltetraphenylthiodiacetamic acid (2.9 g., 0.006 mole) was dissolved in 30 ml. of acetic anhydride and refluxed for 3 hours. The pale red-brown solution, when cooled with ice yielded 1.1 g. of white solid, m.p. 187–195°. Addition of a small amount of water precipitated an additional 0.18 g. The yield was 46% after two crystallizations from toluene, m.p. 195–196° dec.

Anal. Calc'd for $C_{30}H_{25}NO_2S$: S, 6.90. Found: S, 7.10.

SUMMARY

The preparation of several phenyl substituted 3,5-thiamorpholinediones have been prepared in order to test their anticonvulsant activity. Two new methods of preparing 3,5-thiamorpholinediones are described.

LEXINGTON, KENTUCKY

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