by two recrystallizations from ethyl alcohol; m. p. 209–210°. The deep red color produced in ferric chloride solution indicated that the phenolic group was unsubstituted.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.24; H, 4.89; N, 13.59. Found: C, 58.37; H, 4.99; N, 13.49.

2-Methyl-3-hydroxy-4-cyano-5-chloromethylpyridine (VIII).—Three grams of pyridoxal oxime (II) was treated very cautiously with 15 cc. of thionyl chloride. After the vigorous exothermic reaction had subsided, the mixture stood at room temperature for ten minutes; it was then diluted with ether and filtered. After the solid material had been decolorized by treatment with Darco in hot water, the solution was filtered and cooled. The resulting crystals of 2-methyl-3-hydroxy-4-cyano-5-chloromethylpyridine were collected on a filter and washed with water; yield, 1.4 g. (47%); m. p. 167–168° dec. This material gave a precipitate of silver chloride when heated with silver nitrate solution.

Anal. Calcd. for $C_8H_7N_2OCl$: C, 52.62; H, 3.86; N, 15.34. Found: C, 52.83; H, 3.86; N, 15.65.

2-Methyl-3-hydroxy-4-carbamyl-5-hydroxymethylpyridine Hydrochloride (IX).—Thirteen cubic centimeters of water containing 0.2 g. of 2-methyl-3-hydroxy-4-cyano-5-chloromethylpyridine hydrochloride (VIII) was refluxed for forty minutes. After decolorization with Darco, the solution was concentrated to dryness under reduced pressure, and the residue was crystallized from ethyl alcohol. The crystals of 2-methyl-3-hydroxy-4-carbamyl-5-hydroxymethylpyridine hydrochloride weighed 0.1 g. and melted at 210–211° dec.

Anal. Calcd. for $C_8H_{11}N_2O_3Cl$: C, 43.94; H, 5.07; N, 12.82. Found: C, 44.30; H, 5.10; N, 12.72.

Acknowledgment.—The microanalyses were carried out by Messrs. W. K. Humphrey, J. McGregor, L. Rosalsky, E. Thornton, Mrs. Edith Meiss and Mrs. Dorothy Sellers.

Summary

Pyridoxal, isolated as the oxime, has been prepared from pyridoxine by means of manganese dioxide and sulfuric acid. Pyridoxal oxime has been dehydrated with acetic anhydride to form 2 - methyl - 3 - acetoxy - 4 - cyano - 5 - acetoxymethylpyridine. This has been converted to 4-pyridoxic acid, which has then been lactonized.

Dehydration of pyridoxal oxime with thionyl chloride has yielded 2-methyl-3-hydroxy-4-cyano-5-chloromethylpyridine.

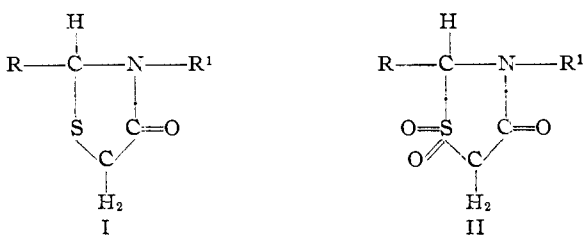
RAHWAY, N. J. RECEIVED JUNE 3, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & CO.]

The Synthesis of 2,3-Disubstituted-4-thiazolidones[1]

BY H. D. TROUTMAN AND LOREN M. LONG

During the course of our investigation concerning the synthesis of 2,3-disubstituted-4-thiazolidones, there appeared papers by Erlenmeyer and Oberlin[2] and by Surrey[3] reporting the preparation of derivatives of the same ring system. Because none of the derivatives which we have prepared corresponds to those reported by the aforesaid authors[2,3] and since some variation in preparative technique was employed, we wish to report the results of our work at this time. The compounds reported in the earlier papers[2,3] are, for the most part, 2,3-diaryl derivatives, whereas the compounds herein reported are 2-aryl-3-alkyl or 2-hetero-3-alkyl derivatives. In addition, we have oxidized a number of the derivatives listed in Table I to the corresponding 2,3-disubstituted-4-thiazolidone-1-dioxides (Formula II).



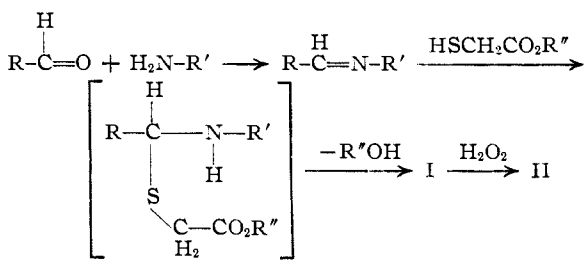
I II

R = phenyl or substituted phenyl
thienyl
furyl

R′ = alkyl or substituted alkyl

It was thought that the synthesis of 4-thiazolidones as represented by I and the corresponding dioxides as represented by II might possibly lead to compounds possessing anticonvulsant activity. The fact that various amides, sulfides and sulfones exhibit such activity has been indicated in numerous publications by various authors, and the results of pharmacological testing summarized by Merritt and Putnam.[4]

The following scheme represents the method which was used in the preparation of all of the 4-thiazolidones listed in Table I. It will be noted



that the method of choice recommended by Surrey[3] involves the use of thioglycolic acid instead of an ester of thioglycolic acid as shown above. Surrey reports that in an attempt to prepare 2,3-diphenyl-4-thiazolidone from the corresponding Schiff base and ethyl thioglycolate only an 8%

(1) Presented before the Division of Medicinal Chemistry, Chicago, Ill., April 21, 1948.

(2) Erlenmeyer and Oberlin, *Helv. Chim. Acta*, **30**, 1329 (1948).

(3) Surrey, THIS JOURNAL, **69**, 2911 (1947).

(4) Merritt and Putnam, *Epilepsia*, **3**, 51 (1945).

TABLE I

2,3-DISUBSTITUTED-4-THIAZOLIDONES

R	R′	Yield, %	M. p., °C.	Formula	Analyses, %[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Phenyl	Methyl	66	Oil[b]	$C_{10}H_{11}NOS$	62.14	61.80	5.74	5.64
Phenyl	Ethyl	53	54–55	$C_{11}H_{13}NOS$	63.72	64.06	6.32	6.47
Phenyl	*n*-Propyl	72	67–68	$C_{12}H_{15}NOS$	65.10	65.38	6.84	6.78
Phenyl	*n*-Butyl	48	56.5–57.5	$C_{13}N_{17}NOS$	66.32	66.42	7.29	7.29
Phenyl	Allyl	55	48–49	$C_{12}H_{13}NOS$	65.72	65.95	5.97	6.20
Phenyl	Benzyl	89	153–154	$C_{16}H_{15}NOS$	71.34	71.58	5.61	5.84
Phenyl	β-Diethylamino ethyl	67	Oil[c]	$C_{15}H_{22}N_2OS$	64.70	64.99	7.96	7.76
3-Nitrophenyl	Benzyl	50	113–114	$C_{16}H_{14}N_2O_3S$	61.13	61.26	4.49	4.64
3-Aminophenyl	Benzyl	81	132–133	$C_{16}H_{16}N_2OS$	67.57	67.19	5.67	5.86
4-Chlorophenyl	Methyl	70	Oil[d]	$C_{10}H_{10}ClNOS$	52.74	52.17	4.43	4.21
4-Chlorophenyl	Ethyl	67	69–70	$C_{11}H_{12}ClNOS$	54.65	54.80	5.01	5.39
4-Chlorophenyl	*n*-Propyl	50	64–65	$C_{12}H_{14}ClNOS$	56.35	56.39	5.52	5.45
2-Furyl	Methyl	67	78	$C_8H_9NO_2S$	52.44	52.56	4.95	4.73
2-Thienyl	Methyl	84	65–66	$C_8H_9NOS_2$	48.21	48.34	4.55	4.50

[a] The analytical data reported in this paper were determined by A. W. Spang of this Laboratory. [b] B. p. 147–149° (1.9 mm.). [c] B. p. 165–168° (2 mm.). [d] B. p. 184–185° (3 mm.).

TABLE II

2,3-DISUBSTITUTED-4-THIAZOLIDONE-1-DIOXIDES

R	R′	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Phenyl	Methyl	40	123–124	$C_{10}H_{11}NO_3S$	53.30	53.67	4.92	5.18
Phenyl	Ethyl	49	100–101	$C_{11}H_{13}NO_3S$	55.19	55.36	5.48	5.42
Phenyl	*n*-Propyl	38	108–110	$C_{12}H_{15}NO_3S$	56.89	56.84	5.97	6.15
Phenyl	*n*-Butyl	53	86–87	$C_{13}H_{17}NO_3S$	58.38	58.67	6.41	6.37
Phenyl	Benzyl	70	127–128	$C_{16}H_{15}NO_3S$	63.77	63.91	5.02	5.27
4-Chlorophenyl	Methyl	54	155–156	$C_{10}H_{10}ClNO_3S$	46.24	46.23	3.88	3.91
4-Chlorophenyl	Ethyl	50	145–146	$C_{11}H_{12}ClNO_3S$	48.26	48.50	4.42	4.52

yield of the thiazolidone was obtained after refluxing in Skellysolve E for sixteen hours. Our results confirm this report since we obtained only starting materials when equivalent quantities of benzylidene aniline and ethyl thioglycolate were mixed, heated on the steam-bath for two hours and distilled at reduced pressure.

However, the situation is changed when benzylidene alkylamines are employed in place of the aniline derivatives. Aliphatic amines form amides with esters much more readily than do aromatic amines; and as a result, the intermediate ester shown in the scheme above loses alcohol with ease to form the corresponding 4-thiazolidone.

In no case was the intermediate ester isolated. By the simplest procedure, equivalent quantities of benzylidene alkylamine and a thioglycolic ester were mixed together in a flask. Appreciable amounts of heat were evolved. The resulting solution was then heated almost to reflux for several hours and then distilled at reduced pressure.

In a variation of this procedure equivalent quantities of benzylidene alkylamine and ethyl thioglycolate were mixed together and heated. The temperature of the solution reached a maximum and then started to drop, indicating formation of alcohol. When the temperature of the solution ceased to fall, water was added and the mixture was steam distilled until the distillate was clear. The product was then isolated from the residue.

As indicated in Table I, thenylidene and furfurylidene alkylamines were employed as well as benzylidene and substituted benzylidene alkylamines. There was no essential difference in the behavior of these intermediates in the reaction or in the yield of final product.

Table II summarizes the 4-thiazolidone-1-dioxides obtained from the 4-thiazolidones by oxidation with hydrogen peroxide in a solution of acetic anhydride and glacial acetic acid. The procedure was similar to that reported for the oxidation of 5-R-thiomethyl-5-phenylhydantoins[5] and 8-R-thiocaffeine derivatives.[6]

Pharmacology.—Although pharmacological testing of the compounds listed in Tables I and II is in the preliminary stage, a general idea of the anticonvulsant activity of the two series may be obtained from the results to date. Animal experiments with these compounds are under the direction of Chen of this Laboratory.

Of the derivatives tested as inhibitors of electrically induced convulsions, 2-phenyl-3-methyl-4-thiazolidone and 2-phenyl-3-ethyl-4-thiazolidone have proved to be the most effective. Both compounds give complete protection at an oral dosage of 100 mg./kg. in cats. However, as the dosage is

(5) Long, THIS JOURNAL, **68**, 2159 (1946).
(6) Long, *ibid.*, **69**, 2939 (1947).

decreased, the activity falls to a much lower level of protection at 50 mg./kg. 5,5-Diphenylhydantoin (Dilantin) gives complete protection at 50 mg./kg.[7] Oxidation of the 2-phenyl-3-methyl- and 2-phenyl-3-ethyl-4-thiazolidones to the corresponding 4-thiazolidone-1-dioxides leads to an appreciable decrease in activity. This result is similar to that obtained when 5-R-thiomethyl-5-phenylhydantoins are oxidized to the corresponding sulfones.[5]

Although it has not been proved that compounds which protect animals against metrazol induced convulsions will necessarily inhibit the attacks which are typical of petit mal epilepsy, this test remains the only one in common use in the laboratory. The strongest evidence in favor of the test is, perhaps, the fact that 3,5,5-trimethyl-2,4-oxazolidone[8] which is effective against petit mal epilepsy in clinical studies is also effective in preventing convulsions when metrazol is administered to animals.

Several of the compounds reported in this paper are quite effective in preventing metrazol induced convulsions. 2-(4-Chlorophenyl)-3-methyl-4-thiazolidone gives complete protection in rats at an oral dosage of 125 mg./kg. 2-(2-Furyl)-3-methyl-4-thiazolidone gives complete protection at 250 mg./kg. The activity decreases as the number of carbons in the 3-substituent is increased. These results compare well with those obtained by Chen in our laboratory with 3,5,5-trimethyl-2,4-oxazolidone. This compound exhibits complete protection against metrazol at 500 mg./kg.

Experimental

Benzylidene Alkylamines.—The preparation of these intermediates was carried out by the method of Zaunschirm.[9] The product was distilled in each case to give yields in excess of 80%.

Methods.—Although the variations in the following procedures are not great, the particular procedure employed for each type of derivative is given.

2-Phenyl-3-methyl-4-thiazolidone.—Sixty grams (0.5 mole) of ethyl thioglycolate was added to 59.5 g. (0.5 mole) of benzylidenemethylamine in a small flask fitted with a reflux condenser. The addition was made portionwise with intermittent swirling of the flask. The solution became quite warm as heat was evolved during the reaction.

After the addition of the ester was completed, the solution was gently refluxed for one hour. The slightly yellow solution was then distilled at reduced pressure through a short Vigreux column. Considerable time was required for the removal of ethanol and lower boiling materials. The product distilled over as a pale yellow oil at 147–149° (1.9 mm.).

2-(3-Nitrophenyl)-3-benzyl-4-thiazolidone.—To 120 g. (0.5 mole) of 3-nitrobenzylidene benzylamine[10] in a 500-ml., three-necked flask fitted with a mechanical stirrer, a dropping funnel and a reflux condenser was slowly added with stirring 55 g. (0.52 mole) of methyl thioglycolate.[11] The clear solution was stirred for one-half hour after all of the ester had been added. The dropping funnel was then replaced by a nitrogen inlet tube and nitrogen was passed through the solution which was heated by means of a Glascol mantle to an internal temperature of 165°. As the reaction proceeded and methanol was formed, the temperature of the solution dropped to 120°. Heating was continued for a total of six hours.

The semi-solid mass which resulted when the solution was cooled to room temperature was refluxed with 700 ml. of methanol, 25 g. of Norite and 10 g. of Super-Cel and filtered while hot. The crystalline product which precipitated when the filtrate was cooled in an ice-bath was filtered off, washed with cold methanol and dried *in vacuo* at 75°.

2-(3-Aminophenyl)-3-benzyl-4-thiazolidone.—To a mixture of 60 g. (0.2 mole) of 2-(3-nitrophenyl)-3-benzyl-4-thiazolidone, 440 g. of zinc dust, 290 ml. of water and 1330 ml. of 95% ethanol was added a solution of 15 g. of calcium chloride in 25 ml. of water. The mixture was refluxed overnight. The filter-cake from the hot mixture was washed with with 200 ml. of hot 95% ethanol. The combined filtrates were concentrated to 1 l. and poured into 2 l. of water. The solid product was filtered off and dried at 60°. Recrystallization from 95% ethanol did not change the melting point.

2-(2-Thienyl)-3-methyl-4-thiazolidone.—To 75 g. (0.6 mole) of thenylidene methylamine (b.p. 73–74° (11 mm.)) was slowly added with stirring or frequent shaking 63.6 g. (0.6 mole) of methyl thioglycolate. The solution was stirred for one-half hour and then heated under reflux while nitrogen was passed through the flask. The addition of a few pieces of anhydrous calcium chloride at the start of this period seemed to initiate the reaction so that the temperature remained lower than in a number of similar reactions in which calcium chloride was not added. The solution was heated for a total of two and one-half hours.

The reaction mixture was cooled somewhat and 200 ml. of water was added. Steam distillation was then carried out until 2 l. of distillate had been collected. The residue was extracted with 200 ml. of benzene. The resulting benzene solution was concentrated *in vacuo*. The residue solidified on cooling. Recrystallization was accomplished by solution in hot ethyl acetate followed by the addition of an equal volume of ligroin.

2-(2-Furyl)-3-methyl-4-thiazolidone.—To 76.3 g. (0.7 mole) of furfurylidene methylamine[12] (b.p. 59–60° (22 mm.)) was added dropwise with stirring 74.2 g. (0.7 mole) of methyl thioglycolate. The resulting solution was stirred for one-half hour and then heated at 165° in an atmosphere of nitrogen for six hours. Distillation of the product through a short Vigreux column yielded a yellow, viscous oil, b.p. 134–140° (3 mm.). The product solidified after standing for a short time. The analytical sample was recrystallized from equal parts of ethyl acetate and ligroin.

2-(4-Chlorophenyl)-3-ethyl-4-thiazolidone.—Fifty-three grams (0.5 mole) of methyl thioglycolate was added slowly to 83.8 g. (0.5 mole) of 4-chlorobenzylideneëthylamine (b.p. 101–107° (13 mm.)) and the mixture stirred for one-half hour. A few pieces of anhydrous calcium chloride were added and the mixture heated to 145° under nitrogen for four and one-half hours.

The product was cooled somewhat, mixed with 200 ml. of water and steam distilled until 3 l. of distillate had been collected. The oily residue was dissolved in 250 ml. of benzene and the resulting solution concentrated *in vacuo*. The residue solidified on cooling and was recrystallized from 700 ml. of ligroin.

2-Phenyl-3-(β-diethylaminoethyl)-4-thiazolidone.—Fifty-three grams (0.5 mole) of methyl thioglycolate and 102 g. (0.5 mole) of benzylidene β-diethylaminoethylamine were mixed together and stirred for one-half hour. The solution was then heated under reflux in an atmosphere of nitrogen for two and one-half hours. The temperature of the solution reached a maximum of 120° and then dropped to 94° as methanol was formed. The product was distilled at reduced pressure.

(7) Putnam and Merritt, *Science*, **85**, 525 (1937).

(8) Lennox, *J. Am. Med. Assoc.*, **129**, 1069 (1945).

(9) Zaunschirm, *Ann.*, **245**, 279 (1888).

(10) Ingold and Piggott, *J. Chem. Soc.*, **121**, 2385 (1922).

(11) Baker, *et al.*, *J. Org. Chem.*, **12**, 144 (1947).

(12) Schwabbauer, *Ber.*, **35**, 410 (1902); Litterscheid, *Ann.*, **335**, 371 (1904).

2-Phenyl-3-*n*-butyl-4-thiazolidone-1-dioxide.—The following procedure is typical of the method used for the preparation of the 1-dioxides listed in Table II. To a mixture of 59 g. (0.25 mole) of 2-phenyl-3-*n*-butyl-4-thiazolidone, 500 ml. of glacial acetic acid and 125 ml. of acetic anhydride was added in one portion 125 ml. of 30% hydrogen peroxide. The temperature of the mixture slowly increased to 55°. At this point the flask was intermittently immersed in cold water so as to keep the temperature below 60°. When the evolution of heat had apparently ceased, the solution was allowed to stand for several hours at room temperature. It was then concentrated *in vacuo* on a water-bath at 65° until practically all of the solvent had been removed. The residue was mixed with 200 ml. of methanol and 300 ml. of water, heated for a short time on a steam-bath and cooled. The solid product was filtered off and recrystallized from 275 ml. of methanol.

Summary

A series of 2,3-disubstituted-4-thiazolidones has been prepared for testing as possible anticonvulsants. Several of the compounds have been oxidized to the corresponding 2,3-disubstituted-4-thiazolidone-1-dioxides.

Preliminary results indicate that certain of the derivatives are effective in giving protection against electrically induced convulsions while other members of the series inhibit metrazol induced convulsions. Oxidation of the 4-thiazolidones leads to less active derivatives.

DETROIT, MICHIGAN RECEIVED APRIL 7, 1948

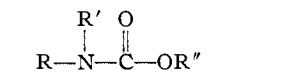
[CONTRIBUTION FROM THE ABBOTT RESEARCH LABORATORIES]

Carbamate Antimalarials

BY MARLIN T. LEFFLER AND EDWARD J. MATSON

In the broad antimalarial screening program sponsored by the Committee on Medical Research, there were, among the samples submitted by Abbott Laboratories, a number of compounds with the carbamate linkage. These carbamates were tested at Johns Hopkins University under the direction of E. K. Marshall, Jr., and it was observed that one of them in particular, *p*-carbobutoxyphenyl carbanilate (SN-1285), showed definite antimalarial effect against *P. lophurae* in ducks. The activity appeared to be in the neighborhood of one-tenth that of quinine. While this order of activity was not striking, the lead did seem unique in that these compounds bore little resemblance to previously known antimalarials, and for this reason a more extensive investigation of the series was desirable.

In this study the substituents on the carbamate moiety were varied as follows



where, as seen in Table I, R and R′ are hydrogen, alkyl, aryl or heterocyclic groups, while R″ is usually a substituted aryl group. In general, two methods of synthesis were used: the carbamates were formed either from the chloroformates and amines (method A), or through the isocyanates with or without a solvent (methods C and B, respectively).

In method A, it developed that pyridine was an ideal solvent for the condensation with aromatic amines and could easily be removed from the product at the end of the reaction by dilution with cold water. However, when more basic amines such as dimethylamine were employed, pyridine was unsatisfactory and two moles of the amine in an inert solvent were necessary.

When isocyanates were used, a trace of triethylamine catalyst[1] greatly increased the rate of the addition reaction. Many of the carbamates described in Table I were made in this manner using a reaction temperature of about 200° in the absence of a solvent (method B); however, it is worth special mention that, in certain instances, this simple procedure gave only low yields of the desired carbamates and produced instead rather significant amounts of the corresponding ureas. In fact, in some cases (SN-4178, SN-3231, Table I) urea formation predominated, and in the case of 2,4-dinitrophenol, only diphenylurea resulted. While the mechanism by which ureas are formed is not clearly understood, it was found that the amount of urea produced could be influenced to a considerable degree by varying the reaction temperature. It was for this reason that the low temperature procedure with a solvent (method C) was employed for the preparation of a number of the carbamates herein reported. By using a mixed solvent of dioxane and toluene, it was possible to effect a complete solution of most of the isocyanate–phenol combinations that were used and, when the temperature was controlled at about 10–15°, urea formation in most cases was diminished or completely avoided. In this instance also, triethylamine was added as a catalyst.

Antimalarial Activity.—The details of the tests and activities of these compounds will be found in the monograph, "A Survey of Antimalarial Drugs 1941–1945."[2] The results may be summarized by saying that the introduction of carbobutoxy or sulfamyl groups on the phenyl in R″ (Table I) and the *p*-methoxy substitution in the phenyl R′ when R was hydrogen increased the activity against *P. lophurae*. Other groups were not so effective. However, highly active

(1) Tarbell, Mallatt and Wilson, THIS JOURNAL, **64**, 2229 (1942).

(2) F. Y. Wiselogle, "A Survey of Antimalarial Drugs 1941–1945," J. W. Edwards, Ann Arbor, Michigan, 1947.