[CONTRIBUTION FROM THE PHILADELPHIA INSTITUTE FOR MEDICAL RESEARCH IN THE PHILADELPHIA GENERAL HOSPITAL]

Some 4-(ω-Carboxyalkyl)-2-aminothiazoles and their Reaction with Acetylsulfanilyl Chloride

BY WILLIAM M. ZIEGLER

In a previous paper[1] it was shown that acetylsulfanilyl chloride would not react with 4-(α-carbethoxyalkyl)-2-aminothiazoles nor in one instance with the free acid itself. However, the 4-alkyl substituted aminothiazoles, obtained by the decarboxylation of these acids reacted readily with the chloride even though the side chain was seven carbons long. From this it was assumed that the carboxy or carbethoxy group exerted an inhibitory effect upon the amino group insofar as its reactivity with the sulfonyl chloride was concerned. Therefore, it was thought of interest to prepare several 4-(ω-carboxyalkyl)-2-aminothiazoles and to investigate their behavior toward acetylsulfanilyl chloride.

The aminothiazoles were prepared from the esters of acetodibasic acids by a method similar to the one previously reported[1] for the preparation of 4-alkyl-2-aminothiazoles. The preparation of 4-(β-carbethoxyethyl)-2-aminothiazole given herewith is typical.

To 86.5 g. (0.4 mole) of ethyl α-acetosuccinate[2] dissolved in two volumes of carbon disulfide and cooled in an ice-water mixture, 21 ml. (0.4 mole; 63 g.) of bromine was added. The flask was stoppered and allowed to stand for 18–24 hours. The solution was washed twice with water and the carbon disulfide removed under diminished pressure, holding the bath temperature at 35–40°. To this product was added 70 ml. of water, 30 g. of ice and 33 g. (0.43 mole) of thiourea, and the mixture shaken for one hour. Slightly more than the calculated quantity of ammonia water (30 ml.) was added and the mixture chilled. The crystalline product was removed by filtration, dissolved while moist in a minimum quantity of methyl alcohol and again chilled. The product thus obtained was recrystallized from 70% methyl alcohol.

Forty and eight-tenths grams (0.15 mole) of the above ester was refluxed with 30 ml. of 95% alcohol, 50 ml. of water, and 20 ml. of concentrated hydrochloric acid until the evolution of carbon dioxide had ceased (three to five hours). To the hot solution some decolorizing carbon was added, the material filtered, and a further quantity of 20 ml. of concentrated hydrochloric acid added. The solution was then evaporated at 60° until crystals separated. It was then chilled, the product removed by filtration and recrystallized from water. The mother liquors were evaporated to a small volume and worked up in the same manner. The hydrochloride of the aminothiazole was thus obtained. The free base was liberated by dissolving the hydrochloride in hot water and adding the calculated amount of sodium hydroxide solution.

In a similar manner 4-(γ-carboxypropyl)-2-aminothiazole, 4-(δ-carboxybutyl)-2-aminothiazole, and 4-(λ-carboxyundecanyl)-2-aminothiazole, were prepared from ethyl α-acetoglutarate,[3] ethyl α-acetoadipate,[4] and α-aceto-α,λ-dicarbethoxyundecane.[5] Pertinent data concerning all the compounds may be found in the table.

TABLE I

R = 4-R-2-aminothiazole	Yield, %	M. p.,[a] °C.	N Analyses, % Calcd.	N Analyses, % Found	
α,β-Dicarbethoxyethyl-	45	118–119[b]	10.3	10.1	10.3
α,γ-Dicarbethoxypropyl-	64	87– 88[b]	9.76	9.72	9.78
α,δ-Dicarbethoxybutyl-	51	83– 84[c]	9.37	9.62	9.63
α,λ-Dicarbethoxyundecanyl-	34	79– 80[d]	7.03	6.85	6.87
β-Carboxyethyl hydrochloride	75	243–245	13.4	13.3	13.3
free base	..	213–214	16.3	16.5	16.5
γ-Carboxypropyl hydrochloride	70	207–209	12.6	12.5	12.5
free base	..	125–127[e]	15.0	14.7	14.8
δ-Carboxybutyl hydrochloride	70	235–237	11.9	12.1	12.3
free base	..	202–203.5	14.0	14.2	14.3
λ-Carboxyundecanyl hydrochloride	64	178–179.5	8.36	7.99	8.00
free base	..	105–107	9.11	8.91	8.95
4-(β-Carboxyethyl)-2-sulfanilamidothiazole hydrochloride	33	277–279[f]	11.5	11.5	11.5
free base	..	143–145	12.8	12.6	12.8
4-(γ-Carboxypropyl)-2-sulfanilamidothiazole hydrochloride	11	204–206[f]	11.1	11.0	11.2
4-(λ-Carboxyundecanyl)-2-acetylsulfanilamidothiazole	40	98–100[b]	8.48	8.36	8.37

[a] All products were recrystallized from water unless otherwise stated, and all melting points are corrected. [b] Recrystallized from 70% methanol. [c] Recrystallized from 70% ethanol. [d] Recrystallized from 95% ethanol. [e] After drying at 120°. The monohydrate melts at 99–101°. [f] With partial decomposition.

Some difficulty was experienced in the isolation of products from the reaction of the amines with acetylsulfanilyl chloride. Finally the following method was used.

Nineteen grams (0.11 mole) of 4-(β-carboxyethyl)-2-aminothiazole was dissolved in 70 ml. of pyridine and 28 g. (0.12 mole) of acetylsulfanilyl chloride was added. The solution was warmed for one hour on a steam-bath and then poured into 600 ml. of 2 *N* hydrochloric acid. There was no precipitate, so the mixture was refluxed for forty minutes. The product was decolorized with Norite and

(1) Ziegler, THIS JOURNAL, **63**, 2946 (1941).

(2) Conrad, *Ann.*, **188**, 218 (1877).

(3) Emery, *Ber.*, **24**, 285 (1891).

(4) Fichter and Gully, *ibid.*, **30**, 2047 (1897).

(5) The ester used was prepared from ethyl acetoacetate and ethyl ω-bromoundecylate in the usual manner. After the removal of the unreacted ethyl acetoacetate, an aliquot of the product, which would not distill at 8 mm., was titrated with bromine to estimate the concentration of the desired dibasic ester. Using this ester to prepare 4-(α,λ-dicarbethoxyundecanyl)-2-aminothiazole, it was necessary to allow the mixture to stand for one week in the refrigerator after neutralization to obtain a solid.

filtered. It was then brought to a *p*H of 4.5–5.0 and evaporated at 60° to 300 ml., chilled and filtered. The residue was mainly sulfanilic acid. The filtrate was evaporated on a steam-bath until sodium chloride crystals appeared, and then chilled and filtered. The product obtained was recrystallized from water. The free base was obtained by treating a warm solution of the hydrochloride with the calculated amount of sodium hydroxide in a little water.

In this manner fair yields of product were obtained from 4-(β-carboxyethyl)-2-aminothiazole, and poor yields were obtained from 4-(γ-carboxypropyl)-2-aminothiazole. The mother liquors from the latter reaction were combined and evaporated to dryness. The product obtained was recrystallized from a small quantity of water. This proved to be identical with 4-(γ-carboxypropyl)-2-aminothiazole sulfanilate, which was also produced by heating the free base with sulfanilic acid in a small quantity of water and allowing it to crystallize. The product was obtained in over 50% yields in all batches. With 4-(δ-carboxybutyl)-2-aminothiazole, 75% of the amine was recovered, indicating a lack of or very little reaction. 4-(λ-Carboxyundecanyl)-2-acetylsulfanilamidothiazole was isolated from the pyridine reaction mixture of the corresponding amine and acetylsulfanilyl chloride. This product was incompletely hydrolyzed by 2 *N* hydrochloric acid, while refluxing with 2 *N* sodium hydroxide destroys it.

That the sluggishness of reaction is a characteristic of the amine rather of the other reactants or some possible conditions is supported by the following facts. The sulfonyl chloride used was of a good grade and gave excellent yields of sulfanilamide and sulfanilanilide. Further, the 4-(δ-carboxybutyl)-2-aminothiazole did not react with *p*-toluenesulfonyl chloride in the refluxing pyridine; 70% of the amine was recovered unchanged. That the acetylsulfanilamide may have been formed and hydrolyzed[6,7] does not seem probable since no hydrolysis was run in the reaction with the *p*-toluenesulfonyl chloride just mentioned; nor did a sample of 4-(γ-carboxypropyl)-2-sulfanilamidothiazole change when refluxed for two hours with 2 *N* hydrochloric acid.

(6) Winterbottom, THIS JOURNAL, **62**, 160 (1940).

(7) Lur'e, Starobogatov, and Nikitskaya, *J. Gen. Chem.* (U. S. S. R.), **11**, 545 (1941); *C. A.*, **35**, 6938 (1941).

Thus, since 2-amino-4-propylthiazole and 2-amino-4-amylthiazole react well with acetylsulfanilyl chloride, it seems that the conversion of the end carbon in the chain to the carboxy group had a decided inhibitory effect upon the reaction. Also, this effect varies greatly with the position of the carboxy group in the chain. Very striking is the fact that, except for the acetic acids, the interference increases as the carboxy group is moved outward from the ring, to a maximum at five or possibly six carbons and then probably decreases, since the carboxyundecanyl derivative gave yields comparable to the carboxyethyl compound.

The 4-(β-carboxyethyl)-2-sulfanilamidothiazole was found ineffective against experimental streptococcus and pneumococcus infections in mice.

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Summary

1. Several 4-(ω-carboxyalkyl)-2-aminothiazoles were prepared from the ethyl esters of α-acetodibasic acids.

2. The yields of sulfonamides from these aminothiazoles decreased as the alkyl group increased, to a certain point, from two to four carbons, increasing again when it contained eleven carbons.

3. It is concluded that the conversion of the end carbon of a 2-amino-4-alkylthiazole to a carboxy group has a decided inhibitory effect upon the reaction of that amine with acetysulfanilyl chloride and the interference increases as the chain increases to five or possibly six carbons, then decreases.

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Antispasmodics and Anticonvulsants. III.[1] Miscellaneous Amides and Esters

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A large portion of the work that has been done in the field of antispasmodics and anticonvulsants has been concerned with the preparation and testing of amides and esters. As we were interested in a study of compounds having the above physiological activity, we decided to prepare a number of miscellaneous esters and amides in an attempt to find some compounds not previously reported as having antispasmodic or anticonvulsant activity. Since benzyl alcohol and 2-diethylaminoethanol have been used frequently in making active esters, we treated these alcohols with a number of different substituted acids.

(1) II, John H. Billman and John L. Rendall, THIS JOURNAL, **66**, 540 (1944).

(2) Submitted to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree, Doctor of Philosophy, in the Department of Chemistry, Indiana University.

(3) Eli Lilly Fellow for the years 1941–3.

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At the same time we decided to prepare *p*-dibenzylacetaminoacetophenone and *p*-dibenzylacetaminobenzophenone. It was felt that these amides might be active inasmuch as they are derivatives of acetophenone or benzophenone, which are both active by themselves. Two benzyl substituted ureas were prepared and submitted for testing.

The compounds which have been prepared are listed in Table I.

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Experimental

General Procedure for Esters.—The esters with the exception of benzyl dibenzylacetate were prepared by refluxing a xylene solution of the acid and alcohol and measuring the water evolved in a calibrated water trap to ascertain the extent of completion of the reaction. Benzyl di-