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

BY JOHN H. BILLMAN AND JOHN L. RENDALL[2,3,4]

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-

TABLE I

AMIDES AND ESTERS

Compound	I[a]	II[b]	M. p., °C., uncor.	B. p., °C.	Pressure, mm.	Yield, %	Analyses, % Calcd.	Found
Benzyl dibenzylacetate[5]	+	0	81.5			53.0		
Benzyl α,β-diphenylpropionate[6]	0	0		197–201	1	73.2		
Benzyl levulinate[7]	−	+		148–150	3	85.0		
Benzyl 2-pyrrolidone-5-carboxylate	0	+		202–204	2	68.5	N, 6.39	6.06
β-Diethylaminoethyl γ-diethylamino-α-phenylbutyrate	0	0		170–173	1	62.5	N, 8.38	8.47
β-Diethylaminoethyl acetoacetate	−	−		113	2	51.8[c] 59.0[d]	N, 6.97	6.95
β-Diethylaminoethyl 2-pyrrolidone-5-carboxylate	0	0		183–184	3	26.1	N, 12.28	12.44
β-Diethylaminoethyl nicotinate[8]	0	0		130–132	2	50.0		
Benzyl urea[9]	−	+	147.5			100.00		
N-Triphenylmethyl-N′-benzylurea	+	0	228			18.0	C, 82.65	82.97
							H, 6.17	6.66
p-Dibenzylacetaminobenzophenone	0	0	60			15.0	N, 3.34	3.38
p-Dibenzylacetaminoacetophenone	+	0	135-6			50.0	C, 80.67	81.30
							H, 6.49	6.66

[a] Anticonvulsant activity: 0, inactive; +, poor; ++, moderate; +++, good; −, no test reported to date. [b] Antispasmodic activity: same symbols. [c] Prepared from diketene and β-diethylaminoethanol. [d] Prepared from acetoacetic ester and β-diethylaminoethanol by *trans*-esterification.

benzylacetate was prepared by the action of dibenzylacetyl chloride on benzyl alcohol in pyridine.

General Procedure for Amides.—The amides were prepared by the reaction of the acid chloride with the amine in pyridine.

2-Pyrrolidone-5-carboxylic Acid.—2-Pyrrolidone-5-carboxylic acid was prepared by heating glutamic acid at 170° for two hours similar to the procedure described by Haitinger.[10]

Benzyl 2-Pyrrolidone-5-carboxylate.—A mixture of 14.7 g. (0.10 mole) of 2-pyrrolidone-5-carboxylic acid and 72.0 g. (0.655 mole) of benzyl alcohol in 100 ml. of xylene was refluxed for eight hours, the water evolved being caught in a water trap. Distillation *in vacuo* yielded 15.0 g. (68.5% of theoretical) of the ester boiling at 202–204° (2 mm.).

p-Dibenzylacetaminoacetophenone.—Fourteen grams (0.058 mole) of dibenzylacetic acid and 16.9 g. (0.14 mole) of thionyl chloride were mixed and allowed to stand ten hours. The mixture was heated for two hours in a water-bath maintained at 50°. The excess thionyl chloride was removed *in vacuo*. A solution of 10.0 g. (0.074 mole) of p-aminoacetophenone in 10 g. of pyridine was added slowly to the acid chloride (cooled in ice.). The reaction mixture was heated in a water-bath at 40–5° for three hours and then added to a mixture of ice and water. The semisolid which formed was crystallized twice from alcohol yielding 8.5 g. (50.0% of theoretical) of the amide melting at 35–36°.

Benzyl Urea.—Benzyl urea was prepared in a quantitative yield by heating an aqueous solution of benzylamine hydrochloride with potassium cyanate.

N-Triphenylmethyl-N′-benzylurea.—A solution of 18.0 g. (0.0644 mole) of triphenylchloromethane and 9.68 g. (0.0644 mole) of benzyl urea in 75 ml. of pyridine was refluxed for five hours and then added to a mixture of ice and water. The solid which formed was recrystallized from absolute alcohol twice to give 4.9 g. (18.0% of theoretical) of product melting at 228°.

(5) Delépine, *Compt. rend.*, **190**, 878 (1930).
(6) Ramart and Haller, *ibid.*, **178**, 1583 (1924).
(7) Sah, Lei and Fang, THIS JOURNAL, **55**, 4727 (1933).
(8) Ingersoll and Robbins, *ibid.*, **48**, 2449 (1926).
(9) Schiff, *Ber.*, **9**, 81 (1876).
(10) Haitinger, *Monatsh.*, **3**, 228 (1882).

Summary

Twelve miscellaneous esters and amides have been prepared and tested for antispasmodic and anticonvulsant activity.

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