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Carboxy Derivatives of Sulfonamidothiazoles

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A number of N^4-carboxyacyl derivatives[1] of the sulfa drugs have been found to be active antibacterial agents in the intestinal tract.[2] N^4-β-carboxypropionyl and N^4-*o*-carboxybenzoylsulfathiazole have proved particularly useful.[3] Further study of agents of this type led to the preparation of carboxy derivatives of sulfathiazole in which a carboxy group is part of the thiazole portion thus leaving the amino group of the sulfanilamide residue free. These compounds are largely carboxy or carboxymethyl derivatives[4] and are recorded in Table I together with intermediate compounds obtained in the syntheses. Related sulfonamide compounds are given in Table II and additional compounds are described in the experimental part.

TABLE I

DERIVATIVES OF SULFATHIAZOLE, 2-SULFANILAMIDO-(R)-THIAZOLE

R	M. p., (uncor.) °C.[a]	Formula	Percentage composition—Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Max. conc.[b] mg./100 cc.	In vitro[c] antibact. ratio
4-Carboxy[d]	238–242	$C_{10}H_9O_4N_3S_2$	14.03	13.96	...	...	1.9	1/1800
Hydrochloride	200	$C_{10}H_{10}O_4N_3S_2Cl$	12.50	12.71	10.55	10.25	..	....
4-Carbethoxy	192–193	$C_{12}H_{13}O_4N_3S_2$	12.83	12.99	...	...	7.8	1/5
N^4-Acetyl, 4-carbethoxy	176–178	$C_{14}H_{15}O_5N_3S_2$	11.38	11.34	...	...	..	....
5-Carboxy[e]	210–215	$C_{10}H_9O_4N_3S_2$	14.03	14.01	...	...	2.7	1/250
Hydrochloride	217	$C_{10}H_{10}O_4N_3S_2Cl$	12.50	12.45	10.55	10.52	..	....
5-Carbethoxy[f]	201–203	$C_{12}H_{13}O_4N_3S_2$	12.83	12.50	...	...	..	....
N^4-Acetyl, 5-carbethoxy[f]	225–227	$C_{14}H_{15}O_5N_3S_2$	11.38	11.50	...	...	..	....
4-Methyl-5-carboxy[f,g,h]	190–200[i]	$C_{11}H_{11}O_4N_3S_2$	13.42	13.32	...	...	8.6	1/30
Hydrochloride	230–233	$C_{11}H_{12}O_4N_3S_2Cl$	12.02	12.20	10.14	10.03	..	....
4-Carboxymethyl hydrochloride	162–163	$C_{11}H_{12}O_4N_3S_2Cl$	12.01	11.87	10.14	9.61	..	1/8900
N^4-Acetyl, 4-carbethoxymethyl[f,h]	168–169[k]	$C_{15}H_{17}O_5N_3S_2$	10.97	11.05	[j]	[j]	..	....
4-Methyl-5-carboxymethyl	238–244	$C_{12}H_{13}O_4N_3S_2$	12.84	12.70	...	...	2.5	1/3400
Hydrochloride	234–238	$C_{12}H_{14}O_4N_3S_2Cl$	11.55	11.46	9.75	9.74	..	....
4-Methyl-5-carbethoxymethyl[f]	183–184	$C_{14}H_{17}O_4N_3S_2$	11.82	11.67	...	...	4.4	1/90
N^4-Acetyl,4-methyl-5-carbethoxymethyl[f]	201–202	$C_{16}H_{19}O_5N_3S_2$	10.58	10.63	[l]	[l]	...	....
4,5-Dicarboxy	248–252	$C_{11}H_9O_8N_3S_2$	12.25	12.25	...	...	1.3[m]	1/4500
4,5-Dicarbethoxy	155–156	$C_{15}H_{17}O_8N_3S_2$	10.52	10.46	...	...	11.8	1/1200
N^4-Acetyl, 4,5-dicarbethoxy	187–189	$C_{17}H_{19}O_7N_3S_2$	9.52	9.55	...	...	...	....
4-Carboxymethyl-5-carboxy	184–186[n]	$C_{12}H_{11}O_8N_3S_2$	11.75	11.74	...	...	4.7	1/400
Hydrochloride	184–185	$C_{12}H_{12}O_8N_3S_2Cl$	10.66	10.42	9.05	9.17	...	....
N^4-Acetyl, 4-carbethoxymethyl-5-carbethoxy	245–246	$C_{18}H_{21}O_7N_3S_2$	9.22	9.12	...	...	...	....
6-Carboxybenzo	302–305	$C_{14}H_{11}O_4N_3S_2$	12.02	11.82	...	...	...	1/1400
6-Carbethoxybenzo	262–263	$C_{16}H_{15}O_4N_3S_2$	10.02	9.85	...	...	...	....

[a] Most of the carboxy compounds and hydrochlorides melt with decomposition; the exact temperature varies with the condition of heating. [b] Maximum blood level attained in mice following oral administration. Unless otherwise designated, the dose was 2.5 g./kg. The maximum level was reached in all cases two hours after administration. Blood-levels for standard drugs were: sulfathiazole (1.0 g./kg.) 18.3; sulfaguanidine (1.0 g./kg.) 4.8; succinylsulfathiazole (2.5 g./kg.) 3.5. [c] Activity against *E. coli* expressed as a fraction of the activity of sulfathiazole. The activities of standard drugs were: sulfathiazole 1.0; sulfaguanidine 1/52; succinylsulfathiazole 1/5500. [d] Backer and de Jonge, *Rec. trav. chim.*, **60**, 495 (1941). [e] Harris and Finland, *Proc. Soc. Exptl. Biol. Med.*, **58**, 116 (1945). [f] Ganapathi, Deliwala and Shirsat, *Proc. Indian Acad. Sci.*, **16A**, 126 (1942). [g] British Patent 517,272. [h] Jensen and Thorsteinsson, *Dansk Tids. Farm.*, **15**, 41 (1941). [i] A sample of 2-sulfanilamido-4-methylthiazole formed by decarboxylation melted at 235–237°. [j] *Anal.* for C_2H_5O, calcd.: 11.7. Found: 11.23. [k] Obtained as monohydrate on recrystallization from dilute alcohol; m. p. 130–135°. [l] *Anal.* for C_2H_5O, calcd.: 11.32. Found: 11.16. [m] Dose 4.0 g./kg. [n] A sample of 2-sulfanilamido-4-methylthiazole formed by decarboxylation melted at 236–237°.

Most of the compounds were prepared through the reaction of the ethyl ester of the appropriate 2-aminothiazole carboxylic acid with N-acetylsulfanilyl chloride or *p*-nitrobenzenesulfonyl chlo-

(1) Moore and Miller, THIS JOURNAL, **64**, 1572 (1942).

(2) Poth, Knotts, Lee and Inui, *Arch. Surg.*, **44**, 287 (1942); Poth and Ross, *Tex. Rpt. Biol. Med.*, **1**, 345 (1943).

(3) Poth and Knotts, *Arch. Surg.*, **44**, 208 (1942); Poth, *Tex. State J. Med.*, **39**, 369 (1943); Poth and Ross, *J. Lab. Clin. Med.*, **29**, 785 (1944).

(4) Some of these compounds or derivatives have been reported in foreign literature. References are given in the footnotes to the tables. No biological data have appeared previously.

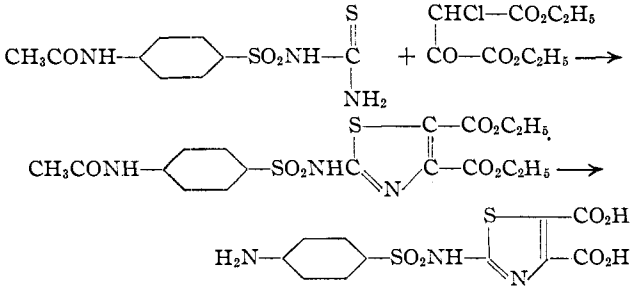
TABLE II

SULFONAMIDOTHIAZOLES

2-Sulfonamido-( )-thiazole	M. p., °C.,[a] uncor.	Formula	Nitrogen, % Calcd.	Found
2-Benzenesulfonamido-( )-thiazoles				
4-Carbethoxy	124–125	$C_{12}H_{12}O_4N_2S_2$	8.97	9.01
4-Carboxy	264–265	$C_{10}H_8O_4N_2S_2$	9.85	9.74
4-Methyl-5-carbethoxy	186–187	$C_{13}H_{14}O_4N_2S_2$	8.59	8.55
4-Methyl-5-carboxy	209–210	$C_{11}H_{10}O_4N_2S_2$	9.40	9.39
2-*p*-Nitrobenzenesulfonamido-( )-thiazoles				
4-Carbethoxy	162–164	$C_{12}H_{11}O_6N_3S_2$	11.76	11.65
4-Carboxy	268–270	$C_{10}H_7O_6N_3S_2$	12.76	12.72
4-Methyl-5-carbethoxymethyl	184–185	$C_{14}H_{15}O_6N_3S_2$	10.90	10.86
4,5-Dicarbethoxy	129–130	$C_{15}H_{15}O_6N_3S_2$	9.78	9.76
4,5-Dicarboxy[c]	210–220 250–255	$C_{11}H_7O_6N_3S_2$	10.74[b]	10.66
2-*m*-Nitrobenzenesulfonamido-( )-thiazoles				
4-Carbethoxy	125–127	$C_{12}H_{11}O_6N_3S_2$	11.76	11.63
4-Carboxy	278–281	$C_{10}H_7O_6N_3S_2$	12.76	12.77
4-Methyl-5-carbethoxymethyl	171–172	$C_{14}H_{15}O_6N_3S_2$	10.90	10.66
4,5-Dicarbethoxy	115–116	$C_{15}H_{15}O_6N_3S_2$	9.78	9.71
4,5-Dicarboxy[f]	190–195[e]	$C_{11}H_7O_6N_3S_2$	10.74[d]	10.73

[a] Most of the carboxy compounds melt with vigorous effervescence. The temperature at which this occurs depends largely on experimental conditions such as rate of heating. Many show multiple melting points due to hydrate formation or decarboxylation. [b] Monohydrate. [c] Very soluble in hot water (5.0 g. per 30 cc.) crystallized in heavy block crystals; solubility much less in dilute hydrochloric acid and on crystallization gives hair-like needles. Decarboxylates at 225–230° to give the 4-monocarboxy compound together with some 2-*p*-nitrobenzenesulfonamidothiazole; m. p. 254–256°. [d] Monohydrate. [e] Effervesces 190–195°, solidifies around 200° and remelts with effervescence 265–275°. Some samples when heated rapidly effervesced or sintered slightly around 160–165°. [f] Solubility similar to *p*-nitro compound. Heating to 200–205° caused evolution of carbon dioxide and gave the 4-monocarboxy compound which melted with effervescence at 276–280°.

ride in pyridine solution. Hydrolysis of the product of this reaction, or reduction and hydrolysis in the case of the nitro compounds, gave the desired carboxy compounds. An alternative procedure proved useful in some cases. This procedure is represented by the following scheme for the preparation of 2-sulfanilamido-4,5-dicarboxythiazole.



N-Acetylsulfanilylthiourea condensed smoothly in pyridine with halogenated keto esters. The thiazole thus formed was isolated in a high state of purity and in excellent yields. However, the relative inaccessibility of the N-acetylsulfanilylthiourea limits the usefulness of this method. Foldi, *et al.*,[5] have recently described this method for the preparation of sulfathiazole derivatives including a carboxy compound by the use of ethyl α-chloroacetoacetate.

The various sulfonamido-carboxythiazoles (Tables I and II) exhibit marked differences in stability and ease of decarboxylation depending upon the position of the carboxy group. In an effort to correlate this property with pharmacological and bacteriological results, quantitative decarboxylations were carried out in quinoline. A carboxy group attached directly to the thiazole nucleus at the 5-position was very labile; carbon dioxide was evolved readily at temperatures as low as 80° and the product was isolated and identified. However, a carboxy group in the 4-position was relatively stable; evolution of carbon dioxide occurred only when the temperature was raised to 210–225° and no identifiable product could be isolated. The 2-amino- and 2-methyl-monocarboxythiazoles, which were included for comparison, behaved similarly. 2-Sulfonamido-4,5-dicarboxythiazoles, as well as the 2-amino and 2-methyl analogs, lost only the 5-carboxy group; the corresponding 4-monocarboxy compound was identified as the product.[6] Conditions necessary for further evolution of carbon dioxide resulted in complete decomposition.

When the substituent group in the thiazole nucleus was carboxymethyl, the order of stability was reversed. A 5-carboxymethyl group was relatively more stable than a 4-carboxymethyl group; a higher temperature was required to bring about decarboxylation and the evolution of carbon dioxide was incomplete. 2-Sulfanilamido-4-carboxymethyl-5-carboxythiazole readily underwent complete decarboxylation at 80–100° to give 2-sulfanilamido-4-methylthiazole.

At the time these studies were initiated, the results that were reported in the literature on the decarboxylation of thiazolecarboxylic acids were conflicting.[7] All of our results are in accord with recent work[8] on other compounds and, in contrast with the earlier reports, show that the substituent in the 2-position of the thiazole ring does not influence the relative lability of the carboxy group in the 4- or 5-position.

Experimental[9]

All of the 2-aminothiazoles that were used as intermediates in this work have been described in the lit-

(5) Foldi, Gerecs, Demjen, and Konig, U. S. Patent 2,332,906 (1943).

(6) Roubleff, *Ann.*, **259**, 275 (1890), was unable to isolate any definite product from the decarboxylation of 2-amino-4,5-dicarboxythiazole.

(7) Roubleff, *ibid.*, **259**, 253 (1890); Erlenmeyer and Meyerburg, *Helv. Chim. Acta*, **20**, 204 (1937); German Patent 658,353 (*C. A.*, **32**, 4727 (1938)); Schoberl and Stock, *Ber.*, **73**, 1240 (1940).

(8) Schoberl and Stock, *ibid.*, **73**, 1240 (1940); Erlenmeyer and Morel, *Helv. Chim. Acta*, **25**, 1073 (1942); Erlenmeyer, Buchmann and Schenkel, *ibid.*, **27**, 1432 (1944); Huntress and Pfister, THIS JOURNAL, **65**, 2167 (1943).

(9) All melting points are uncorrected.

erature except 2-amino-4-carbethoxymethyl-5-carbethoxythiazole. The preparation of this compound and an improved preparation of 2-amino-4-carbethoxythiazole from commercial pyruvic acid are described below.

2-Amino-4-carbethoxymethyl-5-carbethoxythiazole.—One-tenth mole of sulfuryl chloride (13.5 g.) was added slowly to 20.2 g. (0.1 mole) of ethyl acetonedicarboxylate. The reaction mixture was stirred and cooled during the addition and finally heated on a steam-bath under reduced pressure until there was no further evolution of gases. The crude chloroester was added to a suspension of 7.6 g. (0.1 mole) of thiourea in 50 cc. of alcohol and the mixture was heated to refluxing for thirty minutes. The alcoholic solution was poured into 200–300 cc. of cold water, and the aqueous mixture made alkaline by the addition of sodium carbonate. The 2-amino-4-carbethoxymethyl-5-carbethoxythiazole was removed by filtration and dried. The yield was 21.6 g., 84%. This melted at 122°, resolidified and remelted at 127–128°. After recrystallization from benzene it melted at 122–123°, resolidified and remelted at 129–130°. Neither drying nor fusion changed the melting point behavior.

Anal. Calcd. for $C_{10}H_{14}O_4N_2S$: N, 10.83, C_2H_5O, 34.89. Found: N, 10.78, C_2H_5O, 34.67.

2-Amino-4-carbethoxythiazole.[10]—To 440 g. (2 moles) of a 40% aqueous commercial solution of pyruvic acid that was heated to 70° and stirred, 352 g. (2.2 moles) of bromine was added during a period of two and one-half hours. Heating was continued for thirty minutes or until the bromine had disappeared. To this solution was added slowly with cooling and stirring 200 g. (2.67 moles) of finely powdered thiourea. After standing overnight the hydrobromide of 2-amino-4-carboxythiazole had separated and was removed by filtration, washed with acetone and dried. The yield of crude hydrobromide was 418 g. (calcd. 380 g.). This was suspended in 1400 cc. of anhydrous ethanol containing 110 cc. of concentrated sulfuric acid and the suspension was refluxed for forty-four hours. Nine hundred cc. of alcohol was removed under diminished pressure and 700 cc. of water was added to the residue. The turbid solution that resulted was filtered and the filtrate was made alkaline with sodium bicarbonate. The white crystalline solid which separated was collected on a Buchner funnel and washed with water. After drying, the product weighed 193 g., m. p. 174.5–175.5°, and the yield, calculated from the pyruvic acid, was 56%.

Sulfonamidothiazoles.—The condensation of the sulfonyl chlorides with the 2-aminothiazoles was carried out in pyridine by a modification of the usual procedure. Attempts to use the 2-aminothiazole carboxylic acids in aqueous alkali were unsuccessful under conditions that were satisfactory for aminobenzene and aminopyridine carboxylic and sulfonic acids.[11] The following procedure using 2-amino-4,5-dicarbethoxythiazole illustrates conditions that gave good results in all cases.

2-N⁴-Acetylsulfanilamido-4,5-dicarbethoxythiazole.—A. To a solution of 12.2 g. of 2-amino-4,5-dicarbethoxythiazole in 20 cc. of dry pyridine, 13.0 g. (10% excess) of acetylsulfanilyl chloride was added slowly with stirring. The solution was allowed to stand at room temperature for sixteen hours. Heating of the reaction mixture caused excessive darkening and the production of a large amount of tar. Ten cc. of alcohol was added and the solution diluted with 20% hydrochloric acid until it was strongly acid to congo red. The brown crystalline product was removed by filtration and washed with dilute acid and water. The yield, after drying, was 11.15 g. or 50%; m. p. 181–184°. After crystallization from dilute alcohol, the melting point was 187–189°.

Unreacted 2-amino-4,5-dicarbethoxythiazole was recovered from the acid filtrate by addition of sodium hydroxide until strongly alkaline.

The yields of all of the other sulfonamidothiazoles listed in Tables I and II were 75% or more.

B. This compound was also prepared in excellent yield and in high purity from N-acetylsulfanilylthiourea and ethyl ethoxalylchloroacetate. The thiourea derivative was prepared essentially as described by Foldi.[5]

Ethyl ethoxalylchloroacetate (2.23 g., 0.01 mole) was added to 2.7 g. (0.01 mole) of acetylsulfanilylthiourea dissolved in 10 cc. of dry pyridine. After the exothermic reaction had taken place, the mixture was warmed gently on a steam-bath for a few minutes and then was diluted with an equal volume of alcohol. On acidification with hydrochloric acid and dilution with water, 4.0 g. (91%) of light yellow crystalline product separated (m. p. 183–186°). After crystallization from alcohol it melted at 187–189°.

2-Sulfanilamido-4,5-dicarboxythiazole.—The acetyl derivative was dissolved in 10% sodium hydroxide solution (5 cc. per g.) and the solution was heated for one hour on a steam-bath. An equal volume of water was added and the hot solution was neutralized with concentrated hydrochloric acid. After treatment with "Norit" decolorizing charcoal, the hot solution was made strongly acid. The precipitated product was washed with water and alcohol before drying; yield 87%, m. p. 239° with effervescence. Since this substance is very insoluble in water and organic solvents, it was purified by dissolving in sodium bicarbonate solution, treating with "Darco" decolorizing carbon and reprecipitating from the hot solution by acidification. This process was repeated several times from dilute solutions. The product melted at 251° with effervescence. This dicarboxy compound is insoluble in acids and does not form a hydrochloride. The other sulfanilamidothiazole compounds in Table I were soluble in dilute hydrochloric acid and precipitated crystalline hydrochlorides when excess acid was added to a concentrated solution. In these cases the carboxy compounds were isolated after alkaline hydrolysis by careful acidification to congo red. The addition of excess acid precipitated the hydrochloride. They were purified by recrystallization from dilute alcohol.

2-Sulfanilamido-4,5-dicarbethoxythiazole was obtained by refluxing the N-acetyl derivative with 2.5 *N* hydrochloric acid in 50% alcohol until solution was complete and, after dilution with water and chilling, precipitating the product with sodium bicarbonate. The mono-carbethoxy derivatives were prepared in a similar manner or by the esterification of the corresponding acid using sulfuric acid in dry ethanol. The esters were purified by crystallization from alcohol or alcohol and water.

Decarboxylations.—One to two millimoles of the carboxy compound and 3–5 cc. of purified synthetic quinoline were placed in an alkoxyl apparatus. The mixture was immersed in an oil-bath and heated slowly. A rapid stream of carbon dioxide-free nitrogen was used to carry the evolved carbon dioxide into standard barium hydroxide. The lowest temperature at which precipitation of barium carbonate appeared was observed and the heating then continued above this temperature. The extent of decarboxylation was determined by titration of the barium hydroxide with standard acid at various intervals. The products of the decarboxylation were isolated from these runs or from larger runs which were carried out for the purpose in the same manner.

2-(*p*-Nitrobenzenesulfonylimino)-3-methyl-2,3-dihydro-4-carboxythiazole.—To 3.3 g. (0.01 mole) of the 2-(*p*-nitrobenzenesulfonamido)-4-carboxythiazole suspended in 25 cc. of water, sufficient 20% sodium hydroxide was added to dissolve the solid and then a two-fold excess of sodium hydroxide added. With vigorous stirring, 1.5 g. (0.012 mole) of dimethyl sulfate was added dropwise over a period of fifteen minutes, maintaining strong alkaline conditions by addition of more 20% sodium hydroxide as necessary. Stirring was continued for an additional fifteen minutes, after which a small amount of insoluble material was removed. Acidification caused the precipitation of about 3 g. of crude material melting at 237–240°. Recrystallization from dilute alcohol gave 1.4 g. (40%) of product, m. p. 255.5–256° with effervescence.

(10) Steude, *Ann.*, **261**, 26 (1891).

(11) Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2217 (1938); Ewins, *et al.*, U. S. Patent 2,259,222 (1941), 2,275,354 (1942), 2,335,221 (1943); Kolloff, THIS JOURNAL, **60**, 950 (1938).

Anal. Calcd. for $C_{11}H_9O_6N_3S_2$: N, 12.24, neut. equiv., 343.3. Found: N, 12.25, neut. equiv. 344.6, (phenolphthalein indicator).

No attempt was made to locate definitely the methyl group in this compound or any of the compounds that were derived from it. The structure is assigned through analogy with the results obtained when sulfathiazole and related compounds are methylated under similar conditions.[12]

2-Sulfanilylimino-3-methyl-2,3-dihydro-4-carboxythiazole.—Two and one-half grams of 2-(*p*-nitrobenzenesulfonylimino)-3-methyl-2,3-dihydro-4-carboxythiazole was suspended in 50 cc. of alcohol and 90 cc. of 0.057 *N* sodium hydroxide was added. One gram of moist Raney nickel was added to the solution and hydrogenation carried out at low pressure. Absorption of hydrogen ceased when the theoretical amount had been taken up. The catalyst was filtered off, the filtrate concentrated to half its volume, and the product precipitated by neutralization; yield 1.8 g. (82%) of crude product, m. p. 230–231° with effervescence. Recrystallization from dilute alcohol raised the melting point to 235–236°.

Anal. Calcd. for $C_{11}H_{11}O_4N_3S_2$: N, 13.41. Found: N, 13.39.

2-(N-β-Carboxypropionylsulfanilimido)-3-methyl-2,3-dihydro-4-carboxythiazole.—Three and one-tenth grams (0.01 mole) of 2-sulfanilimido-3-methyl-2,3-dihydro-4-carboxythiazole and 1 g. of succinic anhydride were heated under reflux for twenty minutes in 20 cc. of dioxane. Soon after all the solid had dissolved the product began to crystallize. The suspension was chilled and filtered. The yield was 3.5 g. (87%) of product, m. p. 185–188°. Recrystallization from ethanol gave an alcoholate which when dried for four hours at 140° *in vacuo* gave a product melting at 208–210° with effervescence.

Anal. Calcd. for $C_{15}H_{15}O_7N_3S_2$: N, 10.16. Found: 10.14.

2-(N-Acetylsulfanilylimino)-2,3-dihydro-3,4-dimethyl-5-carbethoxymethylthiazole was prepared by dissolving 4 g. (0.01 mole) of 2-N-acetylsulfanilamido-4-methyl-5-carbethoxymethylthiazole in dilute sodium hydroxide solution and adding 1.5 g. (0.012 mole) of dimethyl sulfate dropwise with stirring while chilling the reaction mixture in an ice-bath. The product precipitated from solution. The yield was 2.0 g. (50%); m. p. 190–194°. Recrystallization from 70% alcohol yielded a product melting at 202–203°.

Anal. Calcd. for $C_{17}H_{21}O_5N_3S_2$: N, 10.21. Found: 10.14.

Hydrolysis of this product in dilute sodium hydroxide did not give a well defined product.

Biological Data[13]

The blood concentrations following the oral administration to mice (Table I) and to dogs[14] indicate that the introduction of a carboxy group into the heterocyclic nucleus of sulfathiazole greatly reduces the absorption from the gastrointestinal tract. The antibacterial activity, as measured *in vitro* (Table I), is reduced to a fraction of the activity of sulfathiazole and is comparable to the activity of the N^4-carboxyacyl derivatives, although in these latter compounds the amino group is blocked. In spite of this lowered *in vitro* antibacterial activity, many of the compounds have shown a marked activity in lowering the number of coliform bacteria in the intestinal tracts of rats and dogs. The 4,5-dicarboxy compound was particularly interesting because of the low blood and urine levels and the lack of toxicity.

Although no exact correlation of the biological results with the ease of decarboxylation to the highly active and readily absorbable sulfathiazole or sulfamethylthiazole can be made, the most labile compounds gave slightly higher blood levels and exhibited greater antibacterial activity. The extreme ease with which the 4-methyl-5-carboxy compound undergoes decarboxylation undoubtedly accounts for the high blood level and relatively high activity of this compound. The instability makes difficult the preparation of material completely free of sulfamethylthiazole and also probably results in the formation of sulfamethylthiazole during the tests. Of the two dicarboxy derivatives, the greater lability of the 4-carboxymethyl-5-carboxy compound results in a higher activity and greater absorption than is the case for the 4,5-dicarboxy derivative. The very low activity of the 4-carboxymethyl compound, which is also very easily decarboxylated, is unexpected.

On oral administration to mice with experimental streptococcal or pneumococcal infections, none of these sulfanilamido-carboxythiazoles showed therapeutic activity; the esters were slightly active against the streptococcal infections.

Summary

Derivatives of sulfathiazole having carboxy or carboxymethyl groups in the thiazole nucleus have been prepared.

The carboxy derivatives showed a much lower antibacterial activity than sulfathiazole when tested *in vitro*. Certain of the compounds gave low blood levels following oral administration to animals and exhibited marked antibacterial activity in the intestinal tracts.

Decarboxylation studies showed that a carboxy group in the 5-position or a carboxymethyl group in the 4-position of the thiazole ring is very labile. A 4-carboxy or a 5-carboxymethyl group is relatively stable. Substituents in the 2-position do not influence the relative lability of a 4- or 5-carboxy group.

GLENOLDEN, PA. RECEIVED NOVEMBER 17, 1945

(12) Druey, *Helv. Chim. Acta*, **24**, 226 (1941); Hartman and Druey, *ibid.*, **24**, 536 (1941); Jensen, *ibid.*, **24**, 1249 (1941); Jensen and Thorsteinsson, *Dansk Tids. Farm.*, **15**, 41 (1941); Shepherd, Bratton and Blanchard, THIS JOURNAL, **64**, 2532 (1942).

(13) We are indebted to the Departments of Bacteriology and Pharmacology of these Laboratories and to Dr. E. J. Poth, University of Texas Medical Branch, Galveston, Texas, for these data.

(14) Poth and Ross, *J. Lab. Clin. Med.*, **30**, 843 (1945).