TABLE I

DIALKYLAMINOALKYLAMIDES OF PYRIDINECARBOXYLIC ACIDS

Formula[f] RC(=O)–	Method	Yield, %	B.p., °C.	Mm.	Base Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$NHCH_2CH_2N(CH_3)_2$	A	81	150–155	0.3[a]	...	..	21.74	...	..	21.12
$NHCH_2CH_2N(C_2H_5)_2$	A,B	77	173.0–173.5	.2	65.12	8.65	18.99	64.97	8.45	18.84
$NHCH_2CH_2CH_2N(C_2H_5)_2$	A	87	171–175	.2	66.34	9.00	17.86	66.37	8.80	17.40
$N(CH_3)CH_2CH_2N(C_2H_5)_2$	B	34	174–176	.2	66.34	9.00	17.86	65.65	8.36	18.03
$NHCH_2CH_2N(C_2H_5)_2$[g]	A	85	198–200	.3	70.82	7.80	15.49	69.19	7.07	14.83

Hydrochloride Yield, %	M.p., °C.	Analyses, % Calcd. N	Calcd. Cl	Found N	Found Cl
48	235–239[b]	15.79	26.64	15.56	26.46
78	110–111[c]	16.30	13.75	16.26	13.72
74	194–196[b]	14.28	24.10	14.40	23.79
62	149–152[b]	13.63	23.00	13.48	22.86
50	118–120[b]	13.63	...[d]	13.50	...
66	221–223[b,e]	12.20	20.59	11.90	20.15

[a] M.p. 104.5–106.0° (from C_6H_6). [b] Dihydrochloride. [c] Monohydrochloride. [d] Calcd.: C, 50.65; H, 7.52. Found: C, 50.75; H, 7.72. [e] German Patent 540,697 described the monohydrochloride. [f] R = 4-pyridyl. [g] R = 4-quinolyl.

solution. The colorless solid which separated was filtered and recrystallized from absolute ethanol–ether to give 10.8 g. (74% yield) of product, m.p. 194–196°.

The distilled base obtained by method B was converted in similar fashion to a **monohydrochloride**, m.p. 110–111°, alone or mixed with the **monohydrochloride** described above, or to a **dihydrochloride**, m.p. 194–196°, alone or mixed with the dihydrochloride described above.

All of the compounds, their physical properties, and analyses will be found in Table I.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WALLACE AND TIERNAN, INC.]

Some α-Amino Acids Containing a Sulfonamide Group

BY DAVID B. REISNER

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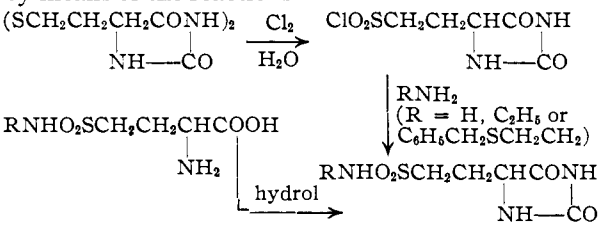
Structural analogs of glutamic acid containing a sulfonamide radical in place of the γ-carboxyl group have been synthesized and assayed as bacterial and viral growth-inhibitors.

Since the discovery by Woods[1] that sulfanilamide is an antagonist of PABA, a large number of synthetic antimetabolites has been reported in the literature. It was surprising to us that the substitution of a carboxyl group in α-amino acids by a sulfonamide radical has received little or no attention. McIlwain[2] prepared a series of α-aminosulfonic acids and included the amide of taurine but did not prepare any α-amino sulfonamides or α-amino acids possessing a sulfonamide group. As part of our researches on potential antimetabolites[3] we have prepared some *d,l*-γ-sulfamyl-α-amino acids. Since glutamic acid contains a γ-carboxyl group, our synthetic amino acids are structurally related to glutamic acid in somewhat the same manner that the sulfonamide drugs are related to PABA.

Syntheses of the amino acids were accomplished by means of the reactions



Conversion of homocystine hydantoin[4] to 5-(β-chlorosulfonyl)-ethylhydantoin was effected by chlorinating a suspension of the disulfide in water. Treatment of the sulfonyl chloride, suspended in ether, with ammonia or appropriate amine gave the desired sulfonamido-hydantoin. Subsequent hydrolysis of the hydantoin with aqueous barium hydroxide at approximately 160° afforded the corresponding amino acid (Table I). The synthesis of 3-(*p*-aminobenzamido)-3-carboxypropanesulfonamide (V) was undertaken because of its resemblance to the α-(*p*-aminobenzamido)-glutaric acid fragment of folic acid. It was prepared by acylating I with *p*-nitrobenzoyl chloride and reducing the resulting nitrobenzamide IV with hydrogen in the presence of 5% palladium–carbon catalyst.[5]

3-Amino-3-carboxypropanesulfonamide (I) suppressed multiplication of T_2 coliphage and inhibited growth of T_2 *E. coli* at 1 p.p.m. Its activity was reversed on addition of glutamic acid or glutamine. In view of its high order of *in vitro* antibacterial activity, compound I was tested in mice which had been infected with *E. coli* according to the procedure described by Scudi, *et al.*[6] Oral doses of 10 mg. of I given daily were ineffective in protecting the animals against infection.

(1) D. D. Woods, *Brit. J. Exptl. Path.*, **21**, 74 (1940).
(2) H. McIlwain, *J. Chem. Soc.*, 75 (1941).
(3) D. B. Reisner, THIS JOURNAL, **78**, 2132 (1956).
(4) J. V. Karabinos and J. L. Szabo, *ibid.*, **66**, 649 (1944).
(5) R. Mozingo, *Org. Syntheses*, **26**, 77 (1946).
(6) J. V. Scudi, S. J. Childress and O. J. Plekss, *Proc. Soc. Exptl. Biol. Med.*, **89**, 571 (1955).

TABLE I
AMINO ACIDS, $R_1NHO_2SCH_2CH_2CHCOOH$ with NHR_2

No.	R_1	R_2	M.p., °C.	Yield, %	Formula	Nitrogen, % Calcd.	Found
I	H	H	247 d.	53.1	$C_4H_{10}N_2O_4S$[a]	15.38	15.35
II	C_2H_5	H	226.5–227.5 d.	81.0	$C_6H_{14}N_2O_4S$	13.32	13.48, 13.43
III	$C_6H_5CH_2SCH_2CH_2$	H	218–219 d.	48.4	$C_{13}H_{20}N_2O_4S_2$[b]		
IV	H	*p*-$NO_2C_6H_4CO$	188–189	91.4	$C_{11}H_{13}N_3O_7S$[c]	12.68	12.85
V	H	*p*-$NH_2C_6H_4CO$	133–134	100	$C_{11}H_{15}N_3O_5S$	13.95	13.82, 13.60

[a] Calcd.: C, 26.36; H, 5.53. Found: C, 26.24; H, 5.43. [b] This was secured from β-benzylmercaptoethylamine which was prepared *via* the condensation of β-benzylmercaptoethyl chloride and potassium phthalimide and subsequent cleavage of the phthalyl group with hydrazine. Calcd.: C, 46.98; H, 6.07. Found: C, 47.22; H, 5.86. [c] Calcd.: neut. equiv., 331. Found: neut. equiv., 330.

Acknowledgment.—The author wishes to express his appreciation to Dr. J. V. Scudi for his interest, to Dr. O. J. Plekss, Dr. P. M. Borick and Mr. H. G. Frank for microbiology data, and to Mr. E. W. Post and his staff for analytical data.

Experimental[7,8]

N-(β-Benzylmercapto)-ethylphthalimide.—A mixture of 18.7 g. (0.10 mole) of β-benzylmercaptoethyl chloride,[9] 20 g. (0.11 mole) of potassium phthalimide and 80 ml. of dimethylformamide was stirred and heated gradually to 130° during one hour. The temperature was maintained at 130° for one hour and the mixture was then cooled, diluted with 400 ml. of water and extracted three times with chloroform. The combined chloroform solutions were washed with three 100-ml. portions of 0.2 *N* sodium hydroxide and two 100-ml. portions of water. After drying over anhydrous sodium sulfate the chloroform was removed under reduced pressure, leaving an oil which crystallized after addition of 50 ml. of ether and 100 ml. of pentane. The solid was removed by filtration and washed with 200 ml. of pentane. The yield of air-dried material, m.p. 79–80°, was 20.5 g. An analytical sample was prepared by recrystallization from ether, m.p. 81–82°.

Anal. Calcd. for $C_{17}H_{15}NO_2S$: C, 68.63; H, 5.08; N, 4.71. Found: C, 68.64; H, 4.98; N, 4.69, 4.67.

β-Benzylmercaptoethylamine.—To a warm suspension of 18 g. (0.061 mole) of N-(β-benzylmercapto)-ethylphthalimide in 200 ml. of methanol was added 7.6 ml. (0.126 mole) of 85% hydrazine hydrate. The resulting solution was heated under reflux for one hour and then cooled and diluted with 100 ml. of water. The methanol was removed *in vacuo* and concentrated hydrochloric acid (100 ml.) was added. The mixture was heated under reflux for 0.5 hour, chilled to 0° and filtered. The filtrate was treated with 200 ml. of 40% sodium hydroxide and extracted four times with ether. The combined ethereal solutions were washed with water and dried over anhydrous magnesium sulfate. The residue (7.4 g.), after evaporation of the ether, was distilled under reduced pressure to give 6.1 g. of β-benzylmercaptoethylamine, b.p. 100° at 0.8 mm.

Anal. Calcd. for $C_9H_{13}NS$: N, 8.37. Found: N, 8.15, 8.14.

5-(β-Chlorosulfonyl)-ethylhydantoin.—A cooled and stirred suspension of 25.7 g. of homocysteine hydantoin in 300 ml. of water was treated with chlorine for 80 minutes. The mixture was decanted and the solid was washed with 400 ml. of ethyl acetate. The decanted liquid was saturated with sodium chloride and extracted five times with ethyl acetate. All the ethyl acetate solutions were combined and dried over anhydrous magnesium sulfate. The dried solution was concentrated to about 250 ml. and 400 ml. of pentane was added. After chilling, the crude product was removed by filtration and dried in a vacuum desiccator over concentrated sulfuric acid. It weighed 30.0 g. and melted at 122–124° dec. An additional 2.1 g. was obtained by further addition of pentane (300 ml.) to the filtrate. Recrystallization from ethyl acetate yielded an analytical sample, m.p. 141–142° dec.

Anal. Calcd. for $C_5H_7ClN_2O_4S$: N, 12.36; Cl, 15.64. Found: N, 12.27, 12.43; Cl, 15.30.

5-(β-Aminosulfonyl)-ethylhydantoin.—A suspension of 19 g. of 5-(β-chlorosulfonyl)-ethylhydantoin in 500 ml. of anhydrous ether was stirred at room temperature and treated with ammonia (gas) for 45 minutes. The mixture was stirred for an additional 15 minutes and then filtered. The residue, after drying in a vacuum desiccator over concentrated sulfuric acid, weighed 21.2 g. It was washed with hot ethyl acetate, air-dried and then recrystallized from 25 ml. of water to give 7.9 g. of 5-(β-aminosulfonyl)-ethylhydantoin, m.p. 182–183°.

Anal. Calcd. for $C_5H_9N_3O_4S$: N, 20.28. Found: N, 19.95.

Evaporation of the ethyl acetate solution (dried over anhydrous magnesium sulfate) to about 50 ml. followed by the addition of 100 ml. of pentane gave 6.0 g. of unchanged sulfonyl chloride.

5-(β-Ethylaminosulfonyl)-ethylhydantoin.—To a suspension of 4.54 g. (0.02 mole) of 5-(β-chlorosulfonyl)-ethylhydantoin in 250 ml. of anhydrous ether was added, with stirring and cooling, a solution of 4.5 g. (0.1 mole) of ethylamine in 50 ml. of anhydrous ether. The solid cake that formed was removed by filtration and air-dried. This material (6.3 g.) was recrystallized from 20 ml. of ethanol to give 3.1 g. of the sulfonamide, m.p. 131.5–133°. Recrystallization from ethanol was repeated to provide an analytical sample, m.p. 135.5–136°.

Anal. Calcd. for $C_7H_{13}N_3O_4S$: N, 17.86. Found: N, 17.78, 17.73.

5-[β-(N-Benzylmercaptoethyl)-aminosulfonyl]-ethylhydantoin.—To a stirred and chilled mixture of 4.5 g. (0.027 mole) of benzylmercaptoethylamine, 3.7 ml. (0.027 mole) of triethylamine and 50 ml. of anhydrous ether 6.1 g. (0.027 mole) of 5-(β-chlorosulfonyl)-ethylhydantoin was added portionwise. An additional 50 ml. of ether was added and mixture was stirred for about ten minutes. After standing overnight at room temperature the solid was removed by filtration and washed with ether. The mixture of sulfonamide and triethylamine hydrochloride, weighing 11.8 g., was washed with *ca.* 200 ml. of water to yield 5.2 g. of material melting at 118–125°. After recrystallization from water the melting point was raised to 125.5–127.5°.

Anal. Calcd. for $C_{14}H_{19}N_3O_4S_2$: N, 11.76. Found: N, 11.75, 11.83.

3-Amino-3-carboxyethanesulfonamide.—The following procedure illustrates the general method of hydrolyzing the hydantoins.

A mixture of 3.11 g. (0.015 mole) of 5-(β-aminosulfonyl)-ethylhydantoin, 4.10 g. (0.024 mole) of barium hydroxide and 50 ml. of water was heated in a sealed tube at approximately 160° for 75 minutes. After cooling, the contents were removed and filtered. The residue was washed with water and the combined aqueous solutions were treated with 1.4 g. of ammonium carbonate monohydrate. The barium carbonate was removed by filtration and washed with warm water. The aqueous solutions were combined and evaporated to dryness *in vacuo*. The residue was triturated with 3 ml. of water and filtered to give 1.7 g. of amino acid melting with decomposition at 246°. The melting point of a sample recrystallized from water was 247° dec.

3-(*p*-Nitrobenzamido)-3-carboxyethanesulfonamide.—3-Amino-3-carboxyethanesulfonamide (0.91 g., 0.005 mole) was dissolved in 8 ml. of 2.5% sodium hydroxide and resulting solution was cooled in an ice-bath. Nitrobenzoyl chlo-

(7) The melting points and boiling points are uncorrected.

(8) All analytical samples of amino acids were chromatographically homogeneous.

(9) W. I. Patterson and V. du Vigneaud, *J. Biol. Chem.*, **111**, 393 (1935).

ride (0.93 g., 0.005 mole) and 5% sodium hydroxide (4 ml.) were added concomitantly in portions with cooling and shaking. An additional 6 ml. of 5% sodium hydroxide and ice were added and mixture was shaken occasionally for one hour; all of the solid dissolved by this time. The solution was washed with 15 ml. of chloroform, then chilled and acidified with dilute hydrochloric acid. The chilled mixture was filtered and the solid was washed with water. The air-dried solid weighed 1.6 g. and melted at 98–100° then resolidified and melted again at 187–188°. After drying *in vacuo* at 100° over phosphorus pentoxide the material melted at 188–189° without melting at the lower temperature. The melting point remained unchanged after recrystallization from ethyl acetate–pentane.

3-(*p*-Aminobenzamido)-3-carboxypropanesulfonamide.—A mixture of 662 mg. (0.002 mole) of 3-(*p*-nitrobenzamido)-3-carboxypropanesulfonamide, 215 mg. of 5% palladium–carbon catalyst and 5 ml. of absolute ethanol was shaken with hydrogen at atmospheric pressure and 25°. Reduction was complete when 147 cc. of hydrogen was absorbed (theory, 145 cc.). The mixture was filtered and solid was removed from the catalyst by washing first with warm ethanol (150 ml.) and then with warm ethyl acetate (50 ml.). The combined organic solutions were evaporated to dryness at *ca.* 55° under a current of dry nitrogen. The residue, a light tan solid, weighed 600 mg. and melted at 124–126° dec. It was recrystallized from aqueous ethanol (charcoal) in the presence of nitrogen to give 290 mg. of white solid, m.p. 133–134°.

Microbiology.—The amino acids in Table I were tested, as described by Czekalowski,[10] against T_2 bacteriophage and its host cell (*E. coli* strain at A.T.C.C. No. 11303) at *p*H 7 and 37°.

(10) J. W. Czekalowski, *Brit. J. Exptl. Path.*, **33**, 57 (1952).

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Phenanthridine Syntheses via the Diels–Alder Reaction. A New Route to 6(5)-Phenanthridinone

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Starting from isoprene and *o*-nitrobenzenediazonium chloride, by 9-methyl-6(5)-phenanthridinone (IX) has been prepared *via* a seven-step reaction sequence. An alternate route to IX by Diels–Alder condensation of isoprene with *o*-nitrocinnamic acid, followed by reductive cyclization and catalytic dehydrogenation, gave in addition the isomeric 8-methyl-6(5)-phenanthridinone (XIII). The latter method was employed for a new, three-step synthesis of 6(5)-phenanthridinone (XVII) from butadiene and *o*-nitrocinnamic acid.

Although many synthetic methods for the preparation of phenanthridine derivatives have been developed,[3,4] the potentialities of utilizing the Diels–Alder reaction have received little attention.[5–9] The present paper describes several Diels–Alder phenanthridine syntheses which have made possible the preparation of two new methyl 6(5)-phenanthridinones, and a new route to 6(5)-phenanthridinone.

o-Nitrobenzenediazonium chloride (I) was treated with isoprene under Meerwein conditions according to the method described by Braude and Fawcett[9] for the analogous condensation with butadiene, and the intermediate chloro compound II was dehydrochlorinated with methanolic potassium hydroxide. That the product of this reaction sequence was 1-(*o*-nitrophenyl)-3-methyl-1,3-butadiene (IV) rather than the isomer 1-(*o*-nitrophenyl)-2-methyl-1,3-butadiene was shown by ozonolysis of the chloro adduct II, followed by hydrogen peroxide oxidation to give *o*-nitrophenylacetic acid (III) identical with an authentic sample. This structural assignment was subsequently confirmed by conversion of IV to 9-methyl-6(5)-phenanthridinone (IX) (*vide infra*).

(1) Frick Chemical Laboratory, Princeton University, Princeton, N. J.

(2) Parke, Davis and Company Fellow, 1952–1954.

(3) R. S. Theoband and K. Schofield, *Chem. Revs.*, **46**, 171 (1950).

(4) L. P. Walls, in "Heterocyclic Compounds," ed. by H. Gilman, Vol. 4, John Wiley and Sons, Inc., New York, N. Y., 1952, p. 564.

(5) S. Sugasawa, K. Kodama and S. Hara, *J. Pharm. Soc. Japan*, **60**, 138 (1940).

(6) S. Sugasawa and K. Kodama, *Ber.*, **72B**, 675 (1939).

(7) L. H. Mason and W. C. Wildman, THIS JOURNAL, **76**, 6194 (1954).

(8) W. C. Wildman and W. T. Nortou, *ibid.*, **76**, 152 (1954).

(9) E. A. Braude and J. S. Fawcett, *J. Chem. Soc.*, 3113 (1951).

It proved to be impossible to purify either II or IV sufficiently for correct, reproducible analyses. Both products were obtained crude as dark red oils. Attempts to distil II *in vacuo* gave small amounts of an impure red liquid with large amounts of a dark, tarry substance remaining in the pot. An attempt to obtain a solid ester derivative by the addition of potassium benzoate to the crude intermediate chloro compound was unsuccessful. Corresponding oils which could not be purified were obtained when iodine was substituted for chlorine. Similarly, the diene IV could not be purified completely by distillation or by chromatography. However, a comparison of the ultraviolet absorption spectrum of distilled IV with the spectrum of authentic 1-(*o*-nitrophenyl)-1,3-butadiene (see Table I) showed the product to be substantially

TABLE I

COMPARISON OF ULTRAVIOLET ABSORPTION SPECTRA (SOLVENT: 95% ETHANOL)

1-(*o*-Nitrophenyl)-1,3-butadiene[9]		Cmpd. IV (1-(*o*-nitrophenyl)-3-methyl-1,3-butadiene)	
λmax in Å.	log εmax	λmax in Å.	log εmax
2175	5.04	2180	5.19
2230	5.05	2230	5.21
2625	4.50	2640	4.47
3350	3.58	3350	3.30

pure, even though microanalytical values were unsatisfactory. Attempts to prepare a solid dibromo derivative of IV gave only tars. In contrast to the ease with which 1-(*o*-nitrophenyl)-1,3-butadiene undergoes the Diels–Alder reaction,[9] no product could be isolated from the reaction of IV with methyl acrylate, methyl vinyl ketone or N-(*p*-nitrophenyl)-maleimide. However, the