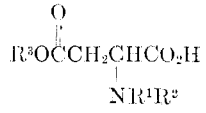
TABLE I

N-SUBSTITUTED DL-ASPARTIC ACIDS AND β-METHYL ESTERS



No.	R^1	R^2	R^3	Mp, °C	Recrystn solvent[a]	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	2-$ClC_6H_4CH_2$	H	H	216–218	A	90	$C_{11}H_{12}ClNO_4$	51.27	4.70	5.44	51.23	4.88	5.31
2	$C_6H_5CH_2CH_2$	H	H	189–190	A	90	$C_{12}H_{15}NO_4$	60.75	6.37	5.90	60.72	6.51	5.81
3	2-$ClC_6H_4CH_2CH_2$	H	H	200–201	B	33	$C_{12}H_{14}ClNO_4$	53.05	5.19	5.16	53.14	5.19	5.26
4	3,4-$(CH_3O)_2C_6H_3CH_2CH_2$	H	H	179–180	C	56	$C_{14}H_{19}NO_6$	56.56	6.44	4.71	56.36	6.48	4.92
5	$C_6H_5CH_2CH(CH_3)$	H	H	205–207	A	45	$C_{13}H_{17}NO_4$	62.14	6.82	5.57	62.08	6.77	5.98
6	2-$C_5H_4NCH_2$[b]	H	H	205–208	A	34	$C_{10}H_{12}N_2O_4$	53.57	5.39	12.50	53.32	5.40	12.80
7	3-$C_5H_4NCH_2$[b]	H	H	232–233	A	50	$C_{10}H_{12}N_2O_4$	53.57	5.39	12.50	53.29	5.59	12.90
8	C_6H_{11}[c]	C_6H_{11}[c]	H	242–243	D	59	$C_{18}H_{27}NO_4$	64.62	9.15	4.71	64.82	8.97	4.92
9	$-(CH_2)_4-$		H	176–178	E	47	$C_8H_{13}NO_4$	51.33	7.00	7.48	51.23	7.06	7.12
10	$-(CH_2)_5-$		H	183–185	A	90	$C_9H_{15}NO_4$	53.72	7.51	6.96	53.76	7.78	6.78
11	$-CH_2CH_2OCH_2CH_2-$		H	181–183	D	38	$C_8H_{13}NO_5$	47.29	6.45	6.89	47.29	6.51	6.64
12	2-$ClC_6H_4CH_2$	H	CH_3	185–186	E	42	$C_{12}H_{14}ClNO_4$	53.04	5.19	5.16	52.73	5.32	5.22
13	3-$ClC_6H_4CH_2$	H	CH_3	217–218	F	76	$C_{12}H_{14}ClNO_4$	53.04	5.19	5.16	52.85	5.22	5.39
14	4-$ClC_6H_4CH_2$	H	CH_3	223–224	A	44	$C_{12}H_{14}ClNO_4$	53.04	5.19	5.16	53.16	5.25	1.96
15	$C_6H_5CH(CH_3)$	H	CH_3	221–222	A	47	$C_{13}H_{17}NO_4$	62.14	6.82	5.58	62.16	6.50	5.17
16	$C_6H_5CH_2CH_2$	H	CH_3	238–239	E	62	$C_{13}H_{17}NO_4$	62.14	6.82	5.58	62.06	6.80	5.41
17	2-$ClC_6H_4CH_2CH_2$	H	CH_3	252–253	B	33	$C_{13}H_{16}ClNO_4$	54.65	5.65	4.90	54.79	5.54	5.09
18	4-$ClC_6H_4CH_2CH_2$	H	CH_3	240–241	B	78	$C_{13}H_{16}ClNO_4$	54.65	5.65	4.90	54.41	5.74	4.85
19	3,4-$(CH_3O)_2C_6H_3CH_2CH_2$	H	CH_3	229–230	A	31	$C_{15}H_{21}NO_6$	57.87	6.80	4.50	57.98	6.92	4.76
20	$C_6H_5CH_2CH(CH_3)$	H	CH_3	190–191	E	46	$C_{14}H_{19}NO_4$	63.38	7.22	5.28	63.42	7.15	5.62
21	$(C_6H_5)_2CHCH_2$	H	CH_3	145–147	E	67	$C_{19}H_{21}NO_4$	69.70	6.47	4.28	69.62	6.49	4.05
22	3-$C_5H_4NCH_2$[b]	H	CH_3	167–168	E	73	$C_{11}H_{14}N_2O_4$	55.45	5.92	11.76	55.33	5.73	11.90
23	4-C_5H_4N[b]	H	CH_3	217–218 dec	E	67	$C_{10}H_{12}N_2O_4$	53.57	5.39	12.50	53.64	5.37	12.60
24	$C_4H_8NCH_2CH_2$[d]	H	CH_3	167–169	D	25	$C_{11}H_{20}N_2O_4$	54.08	8.25	11.47	54.38	8.26	11.62
25	$C_6H_{11}N_2CH_2CH_2$[e]	H	CH_3	193–195	G	82	$C_{12}H_{23}N_3O_4$	52.73	8.48	15.37	52.83	8.51	15.00
26	$-(CH_2)_4-$		CH_3	152–153	H	69	$C_9H_{15}NO_4$	53.72	7.51	6.96	53.75	7.47	6.73
27	$-CH_2CH_2(CH_3)NCH_2CH_2-$		CH_3	183–184	E	75	$C_{10}H_{18}N_2O_4$	52.16	7.88	12.17	51.96	7.98	12.49

[a] A = water, B = dimethylformamide, C = ethanol + water, D = ethanol, E = acetone + water, F = Methyl Cellosolve, G = isopropyl alcohol + acetone, H = *n*-propyl alcohol + hexane. [b] C_5H_4N = pyridyl. [c] C_6H_{11} = cyclohexyl. [d] C_4H_8N = pyrrolidino. [e] $C_6H_{11}N_2$ = N-methylpiperazino.

N-Substituted DL-Aspartic Acids.—The specific procedure of Zilkha and Bachi[4] was employed and the resulting product was recrystallized from a suitable solvent. The new acids prepared are listed in Table I.

N-[(4-Tolylsulfonyl)carbamoyl]amino Acids

MARVIN J. KARTEN,[1] ALLAN SCHWINN, AND WILLIAM OROSHNIK

U. S. Vitamin and Pharmaceutical Corporation, Yonkers, New York 10701

Received January 26, 1966

In our search for potential hypoglycemic agents, we were led to investigate the report by Bramanti and Di Paco[2] of possible hypoglycemic activity of N-[(4-tolylsulfonyl)carbamoyl]leucine. We wish to report the synthesis of some new N-[(4-tolylsulfonyl)-carbamoyl]amino acids. Prior synthesis[2] of such compounds involved the reaction of the ethyl esters of leucine and α-aminobutyric acid with 4-tolylsulfonyl isocyanate or 4-tolylsulfonylurethan, followed by alkaline hydrolysis. The reaction of 4-tolylsulfonylurea with amines in acetic acid and with glycine ethyl ester hydrochloride as a melt to give N-substituted N′-tolylsulfonylureas has also been reported.[3] We have found that heating 4-tolylsulfonylurea with amino acids in acetic acid affords the title compounds in fair yield. These results are summarized in Table I. The compounds showed *no* hypoglycemic activity.

Experimental Section[4]

4-Tolylsulfonylurea was prepared according to Kharag, Yavlinskii, and Savin.[5] Compounds **2–5** were prepared using the DL-amino acids. Compounds **6–8** were prepared using the L-amino acids. The optical purity of the compounds was not determined.

N-[(4-Tolylsulfonyl)carbamoyl]amino Acids.—The following example is typical of the method of preparation of compounds **1–5**, **7**, and **9** in Table I. A mixture of 0.04 mole of 4-tolylsulfonylurea, 0.08 mole of the amino acid, and 60 ml of glacial acetic acid was heated at 90–100° for 5.0 hr. After cooling, the reaction mixture was poured into 400 ml of water and refrigerated to complete precipitation of the product. The product was filtered, washed with water, dissolved in the minimum amount of 1 *N* Na_2CO_3, and filtered. Acidification of the filtrate with 3 *N* HCl gave a solid which was dried and recrystallized from a suitable solvent. With the exception of **6**, the compounds in Table I gave a negative ninhydrin[6a] test. Compound **7** also gave a positive Sakaguchi[6b] test.

N^6-Benzyloxycarbonyl-N^2-[(4-tolylsulfonyl)carbamoyl]lysine.—A mixture of N^6-benzyloxycarbonyl-L-lysine[7a] (0.04 mole, 11.2 g), 4-tolylsulfonylurea (0.04 mole, 8.56 g), and 100 ml of glacial acetic acid was heated at 90–100° for 6 hr, poured into 500 ml of water, and refrigerated. The gummy solid was filtered and dissolved in acetone, the solution was filtered, and the filtrate was evaporated *in vacuo* to give an oil. The oil was dissolved in a saturated $KHCO_3$ solution, the solution was filtered, and the filtrate was acidified with 3 *N* HCl to give a gum. The gum was washed with water, dried, dissolved in a minimum amount of ethyl acetate, and treated with petroleum ether (bp 30–60°) to give an amorphous solid which, after drying, weighed 9.3 g. An

(1) Author to whom inquiries should be addressed.

(2) G. Bramanti and G. F. Di Paco, *Ann. Chim.* (Rome), **51**, 1202 (1961).

(3) A. G. Georgiev, *Compt. Rend. Acad. Bulgare Sci.*, **14**, 603 (1961); *Chem. Abstr.*, **58**, 5546*b* (1963).

(4) Melting points were taken on a Fisher-Johns block and are corrected. Analyses are by Midwest Microlab, Inc., Indianapolis, Ind.

(5) I. M. Kharag, M. D. Yavlinskii, and B. M. Savin, U.S.S.R. Patent 128,015 (1960); *Chem. Abstr.*, **55**, 3523*b* (1961).

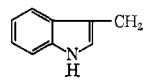
(6) I. Smith in "Chromatographic and Electrophoretic Techniques," Vol. 1, I. Smith, Ed., 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1960: (a) p 95; (b) p 97.

(7) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley and Sons, Inc., New York, N. Y., 1961: (a) pp 893, 1057; (b) pp 906, 932.

TABLE I

N-[(4-TOLYLSULFONYL)CARBAMOYL]AMINO ACIDS

$$\begin{array}{l} RCHCO_2H \\ | \\ NHCONHSO_2C_6H_4CH_3\text{-}4 \end{array}$$

No.	R	Mp, °C	Recrystn solvent[a]	Purified yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	H[b]	199–201	A	47	$C_{10}H_{12}N_2O_5S$	44.11	4.44	10.29	43.86	4.79	9.96
2	CH_3	177–178	A–B	23	$C_{11}H_{14}N_2O_5S$	46.15	4.93	9.79	46.49	5.07	9.64
3	$(CH_3)_2CH$	177–178	A–B	55	$C_{13}H_{18}N_2O_5S$	49.68	5.77	8.91	49.89	5.81	9.02
4	$C_6H_5CH_2$	180–182	A–B	31	$C_{17}H_{18}N_2O_5S$	56.34	5.01	7.73	56.19	5.26	7.45
5		189–190	C	23	$C_{19}H_{19}N_3O_5S$	56.85	4.77	10.47	56.88	4.93	10.67
6	$H_2N(CH_2)_4NH$	173–175	D	14	$C_{14}H_{21}N_3O_5S\cdot 0.5H_2O$	47.71	6.29	11.92	48.01	6.26	11.68
7	$H_2NCNH(CH_2)_3$	189–190	B	22	$C_{14}H_{21}N_3O_5S\cdot 0.5H_2O$	44.20	5.83	18.41	44.35	6.05	18.50
8	$HO_2C(CH_2)_2$	178–179	B	59[c]	$C_{13}H_{16}N_2O_7S$	45.34	4.68	8.14	45.35	4.64	8.21
9	...[d]	131–132	A–B	47	$C_{14}H_{20}N_2O_5S$	51.21	6.14	8.53	51.09	6.18	8.59

[a] A = ethanol, B = water, C = dissolved in NaOH and reprecipitated with HCl, D = methanol–water–ether. [b] Identical with the compound prepared by alkaline hydrolysis of N-[(4-tolylsulfonyl)carbamoyl]glycine ethyl ester.[3] [c] In this case the ester was employed as indicated in the Experimental Section. [d] The compound is N-[(4-tolylsulfonyl)carbamoyl]-6-aminocaproic acid.

analytical sample was prepared by recrystallizing a small portion of the solid twice from ethyl acetate and benzene; mp 139–141°.

Anal. Calcd for $C_{22}H_{27}N_3O_7S$: C, 55.34; H, 5.70; N, 8.80. Found: C, 55.62; H, 5.92; N, 8.88.

N^2-[(4-Tolylsulfonyl)carbamoyl]lysine (6).—The crude N^6-benzyloxycarbonyl-N^2-[(4-tolylsulfonyl)carbamoyl]lysine (9.0 g), prepared above, was dissolved in a mixture of 200 ml of methanol and 50 ml of water containing 1 ml of glacial acetic acid. The mixture was shaken with 0.8 g of 10% Pd–C in a Parr apparatus until 1 mole of hydrogen/mole of compound was absorbed (1 hr). The mixture was filtered, the filtrate was evaporated *in vacuo* to almost dryness, and acetone was added to yield a white solid which was dried to give 3.7 g of product, mp 170°. Recrystallization from methanol–water–ether yielded 1.9 g, mp 173–175°. Further recrystallization did not raise the melting point.

N-[(4-Tolylsulfonyl)carbamoyl]glutamic Acid (8).—A mixture of 0.046 mole (11.1 g) of L-glutamic acid diethyl ester hydrochloride[7b] and 0.02 mole (4.3 g) of 4-tolylsulfonylurea was heated at 100–110° for 3.0 hr. The resulting oil was taken up in 150 ml of water, extracted with three 75-ml portions of ether, dried (Drierite), and evaporated to give an oil. The oil was taken up with 1 *N* Na_2CO_3 and extracted with ether. The aqueous layer was acidified with 3 *N* HCl and extracted with ether, and the ether was evaporated to give an oil which, upon treatment with water, yielded 13.4 g of a solid. The solid was treated with 100 ml of a 10% ethanolic KOH solution at 0° and then allowed to stand overnight at room temperature. The mixture was concentrated *in vacuo*, the residue was dissolved in 100 ml of water and acidified to congo red with concentrated HCl to yield a solid. The solid was dissolved in a saturated K_2CO_3 solution, reprecipitated with 3 *N* HCl, and recrystallized from water to give 4.1 g of product, mp 178–179°. Further recrystallization did not raise the melting point.

Substituted 2-Phenoxypropionic and -butyric Acids and Derivatives

E. MAGNIEN, F. TESTA, AND S. L. SHAPIRO

U. S. Vitamin and Pharmaceutical Corporation, Yonkers, New York 10701

Received January 26, 1966

We have prepared a series of α-phenoxy-substituted propionic and butyric acid derivatives. Among the derivatives are the esters, acids, hydroxamates, and amides. These compounds were tested for possible use as hypocholesteremic agents. Some of these compounds had moderate activity in lowering of serum cholesterol in guinea pigs. The most active compounds were **8, 12, 13, 17, 37, 39, 43,** and **51** (Table I).

Experimental Section[1]

Preparation of Esters and Acids.—The esters were prepared by refluxing equimolar amounts of the phenol, α-bromo ester, and K_2CO_3 in acetone. The esters were obtained by vacuum distillation. The acids were obtained by hydrolysis of the esters in refluxing 2 *N* NaOH for 1 hr followed by neutralization and filtration of the insoluble acids.

The amides were prepared by three methods.

Method 1. N-(4-Carbethoxy)phenyl-2-*o*-allylpropionamide (9).—To a solution of 6.6 g (0.04 mole) of ethyl *p*-aminobenzoate in 30 ml of dry ether was added 4.5 g (0.02 mole) of 2-*o*-allylphenoxypropionyl chloride while maintaining the solution at 0°. After 2 hr, the amine hydrochloride was filtered off. The filtrate was evaporated to dryness and the product distilled to obtain 3.2 g of bp 212–214° (0.03 mm), $n^{25}D$ 1.5714.

Method 2. N-(4-Pyridyl)-2-*o*-phenylphenoxybutyramide (51).—A mixture of 2.5 g (0.01 mole) of 2-*o*-phenylphenoxybutyric acid, 0.94 g (0.01 mole) of 4-aminopyridine, and 2.1 g (0.01 mole) of dicyclohexylcarbodiimide in 40 ml of acetonitrile was stirred for 3 hr at 25°, then allowed to stand overnight. The dicyclohexylurea (2.3 g) was filtered off, and the filtrate was evaporated to dryness *in vacuo*. The amber-colored residue was dissolved in dry ether, and excess HCl was passed into the solution. The crude hydrochloride (2.0 g) was crystallized from ethanol–ether to give 1.6 g, mp 176–178°.

Method 3. N-Methyl-N′-2-*o*-allylphenoxypropionylpiperazine (12).—A mixture of 7.0 g (0.03 mole) of ethyl 2-*o*-allylphenoxypropionate, 3.0 g (0.03 mole) of N-methylpiperazine, and 0.1 g of sodium in 2 ml of ethanol was refluxed until no more ethanol was removed in a Dean–Stark trap (approximately 2 hr). The mixture was cooled and partitioned between ether and 3 *N* HCl. The water extract was saturated with K_2CO_3, and the product was extracted into ether. After removal of the ether, the product was distilled to yield 4.9 g of material with bp 142–144° (0.04 mm). This product solidified on standing and was crystallized from hexane to yield 2.3 g, mp 84–88°.

2-*o*-Allylphenoxybutyrohydroxamic Acid (14).—A solution containing 0.02 mole of hydroxylamine was prepared from 1.39 g (0.02 mole) of hydroxylamine hydrochloride and 0.46 g (0.02 g-atom) of sodium in 50 ml of ethanol. After removal of the NaCl, 2.48 g (0.01 mole) of ethyl 2-*o*-allylphenoxybutyrate was added. The solution was allowed to stand at room temperature for 40 days. The solvent was removed *in vacuo* leaving a solid residue of 2.5 g, mp 111–118°. Two crystallizations from ethyl acetate–hexane gave analytically pure material of mp 127–128°.

(1) Melting points were determined on a calibrated Fisher-Johns apparatus. Elemental analyses were determined by Drs. Weiler and Strauss, Oxford, England.