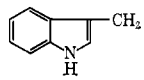
TABLE I

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	$H_2N(CH_2)_4$ NH ‖	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

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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), $n^{23}D$ 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°.

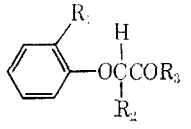
Method 3. N-Methyl-N′-2-*o*-allylphenoxypropionylpiperazine (12).—A mixture of 7.0 g (0.03 mole) of ethyl 2-*o*-allylphenoxypropionate, 3.0 g (0.03 mole) of N-methylpiperazine, and 0.1 g of sodium in 2 ml of ethanol was refluxed until no more ethanol was removed in a Dean–Stark trap (approximately 2 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.

TABLE I

PHENOXY DERIVATIVES



No.	R_1	R_2	R_3	Yield, %	Bp (mm) or mp, °C	Recrystn solvent[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	$CH_2CH{=}CH_2$	CH_3	OH	63	57	H	$C_{12}H_{14}O_2$	69.88	6.84		69.86	6.67	
2	$CH_2CH{=}CH_2$	CH_3	OC_2H_5	75	62 (0.02)		$C_{14}H_{18}O_2$	71.77	7.74		71.96	7.68	
3	$CH_2CH{=}CH_2$	CH_3	NHOH	41	76–77	B–H	$C_{12}H_{15}NO_2$	65.14	6.83	6.33	64.52	6.73	6.20
4	$CH_2CH{=}CH_2$	CH_3	NH_2	85	136–140 (0.2)		$C_{12}H_{15}NO_2$	70.22	7.37	6.82	70.48	7.42	6.90
5	$CH_2CH{=}CH_2$	CH_3	$NHCH_3$	93	52–57	H	$C_{13}H_{17}NO_2$	71.20	7.82	6.39	71.45	8.11	6.03
6	$CH_2CH{=}CH_2$	CH_3	NH-*n*-C_5H_{11}	58	130–132 (0.15)		$C_{17}H_{25}NO_2$	74.14	9.15	5.09	74.01	9.17	5.09
7	$CH_2CH{=}CH_2$	CH_3	$NHCHC_6H_4CH_2C_6H_5$	99	101–105	E	$C_{26}H_{27}NO_2$	81.01	7.06	3.63	81.05	7.10	3.86
8	$CH_2CH{=}CH_2$	CH_3	$NHCH_2COOC_2H_5$	92	160–162 (0.15)		$C_{16}H_{21}NO_4$	65.95	7.27	4.81	66.28	7.37	4.91
9	$CH_2CH{=}CH_2$	CH_3	$NHC_6H_4COOC_2H_5$	45	212–214 (0.03)		$C_{21}H_{23}NO_4$	71.37	6.56	3.96	71.24	6.94	3.73
10	$CH_2CH{=}CH_2$	CH_3		62	154–156 (0.05)		$C_{16}H_{21}NO_3$	69.79	7.69	5.09	69.43	7.83	5.16
11	$CH_2CH{=}CH_2$	CH_3	$NHNH_2$	41	71–72	Et–H	$C_{12}H_{16}N_2O_2$	65.43	7.32	12.72	65.78	7.31	12.60
12	$CH_2CH{=}CH_2$	CH_3		57	84–88	H	$C_{17}H_{24}N_2O_2$	70.80	8.39	9.71	70.82	8.41	9.88
13	$CH_2CH{=}CH_2$	C_2H_5	OH	88	51	H	$C_{13}H_{16}O_2$	70.89	7.32		71.14	7.30	
14	$CH_2CH{=}CH_2$	C_2H_5	NHOH	99	127–128	Ea	$C_{13}H_{17}NO_3$	66.36	7.28	5.95	66.17	7.24	6.17
15	$CH_2CH{=}CH_2$	C_2H_5	NH_2	99	58–60	P	$C_{13}H_{17}NO_2$	71.20	7.82	6.39	71.52	7.60	6.14
16	$CH_2CH{=}CH_2$	C_2H_5	$NHCH_3$	99	48–50	P	$C_{14}H_{19}NO_2$	72.07	8.21	6.00	71.76	8.21	6.12
17	$CH_2CH{=}CH_2$	C_2H_5	$N(C_2H_5)_2$	40	142–146 (0.02)		$C_{17}H_{25}NO_2$	74.14	9.15	5.09	74.17	9.47	4.83
18	$CH_2CH{=}CH_2$	C_2H_5	NH-*n*-C_5H_{11}	69	52–55	P	$C_{15}H_{27}NO_2$	74.70	9.40	4.84	74.58	9.46	5.04
19	$CH_2CH{=}CH_2$	C_2H_5	$NHCHC_6H_4CH_2C_6H_5$	99	104–106	Et–M	$C_{27}H_{29}NO_2$	81.17	7.32	3.51	80.84	7.30	3.75
20	$CH_2CH{=}CH_2$	C_2H_5	$NHCH_2CH_2OH$	98	65–66	E–P	$C_{13}H_{21}NO_3$	68.41	8.04	5.32	68.33	8.22	5.01
21	$CH_2CH{=}CH_2$	C_2H_5	$NHCH_2COOC_2H_5$	49	173–175 (0.1)		$C_{17}H_{23}NO_4$	66.86	7.59	4.59	67.23	7.84	4.48
22	$CH_2CH{=}CH_2$	C_2H_5	$NHC_6H_4COOC_2H_5$	77	228–232 (0.08)		$C_{22}H_{25}NO_4$	71.91	6.86	3.81	71.76	6.78	3.95
23	$CH_2CH{=}CH_2$	C_2H_5		74	166–168 (0.03)		$C_{17}H_{23}NO_3$	70.56	8.01	4.84	70.62	8.12	4.74
24	$CH_2CH{=}CH_2$	C_2H_5	$NHNH_2$	24	173–177 (0.02)		$C_{13}H_{18}N_2O_2$	66.64	7.74	11.96	66.83	7.75	11.79
25	$CH_2CH{=}CH_2$	C_2H_5	$NHCH_2CH_2N(C_2H_5)_2$	64	168–170 (0.02)		$C_{19}H_{30}N_2O_2$	71.66	9.50	8.80	71.44	9.46	9.11
26	$CH_2CH{=}CH_2$	C_2H_5	$NH(CH_2)_3N(CH_3)_2$	51	160–162 (0.08)		$C_{15}H_{28}N_2O_2$	71.01	9.27	9.20	71.31	9.26	8.89
27	$CH_2CH{=}CH_2$	C_2H_5		59	148–150 (HCl)	Ea–E	$C_{24}H_{29}Cl_3N_2O_2$	59.57	6.04	5.79	59.86	6.45	5.73
28	C_6H_5	CH_3	OH	81	138	B	$C_{15}H_{14}O_3$	74.36	5.83		74.63	6.16	
29	C_6H_5	CH_3	NH_2	99	94–97	Ea–H	$C_{15}H_{15}NO_2$	74.66	6.27	5.81	74.44	6.66	5.70
30	C_6H_5	CH_3	NHOH	8	75–82	H	$C_{15}H_{15}NO_3$	70.02	5.88	5.44	70.09	5.79	5.20
31	C_6H_5	CH_3	$NHCH_3$	99	64–65	H–Ea	$C_{16}H_{17}NO_2$	75.27	6.71	5.49	75.72	6.77	5.77
32	C_6H_5	CH_3	$NHCH_2COOC_2H_5$	45	196–200 (0.2)		$C_{19}H_{21}NO_4$	69.70	6.47	4.28	69.85	6.51	4.26
33	C_6H_5	CH_3		99	98–100	E	$C_{19}H_{21}NO_3$	73.29	6.80	4.50	73.73	6.56	4.23
34	C_6H_5	CH_3	$NHCH_2CH_2N(C_2H_5)_2$	10	76–79 (HCl)	E	$C_{21}H_{29}ClN_2O_2$[b]	66.92	7.75	7.43	66.42	7.93	7.05
35	C_6H_5	CH_3	$NH(CH_2)_3N(CH_3)_2$	34	76–78	P	$C_{20}H_{26}N_2O_2$	73.59	8.03	8.58	73.67	7.96	8.45
36	C_6H_5	CH_3		45	166–168 (HCl)	Et–E	$C_{26}H_{18}ClN_3O_2$	67.70	5.40	7.90	67.89	5.41	7.77
37	C_6H_5	C_2H_5	OH	87	149–149.5	Et–W	$C_{16}H_{16}O_3$	74.98	6.29		74.80	6.57	
38	C_6H_5	C_2H_5	OC_2H_5	82	143–148 (0.2)		$C_{18}H_{20}O_3$	76.03	7.09		76.43	7.05	
39	C_6H_5	C_2H_5	NHOH	99	131–132	E	$C_{15}H_{17}NO_3$	70.83	6.32	5.16	71.14	6.29	4.97
40	C_6H_5	C_2H_5	NH_2	99	105–107	Ea–H	$C_{15}H_{17}NO_2$	75.27	6.71	5.49	74.90	6.65	5.72
41	C_6H_5	C_2H_5	$NHCH_3$	52	102–105	Ea	$C_{17}H_{19}NO_2$	75.81	7.11	5.20	75.97	6.90	5.42
42	C_6H_5	C_2H_5	NHC_2H_5	57	132–136 (0.03)		$C_{18}H_{21}NO_2$	76.29	7.47	4.94	76.33	7.28	4.52
43	C_6H_5	C_2H_5	$NH(C_2H_5)_2$	99	57–59	B–H	$C_{20}H_{25}NO_2$	77.13	8.09	4.50	76.78	8.09	4.66
44	C_6H_5	C_2H_5	NH-*n*-C_5H_{11}	55	190–192 (0.2)		$C_{21}H_{27}NO_2$	77.50	8.36	4.30	77.20	8.00	3.86
45	C_6H_5	C_2H_5	$NHCH_2CH_2C_6H_5$	75	212–214 (0.15)		$C_{24}H_{25}NO_2$	80.19	7.01	3.90	79.95	6.83	4.37
46	C_6H_5	C_2H_5	$NHCHC_6H_4CH_2C_6H_5$	55	240 (0.05), 94–95	H	$C_{30}H_{29}NO_2$	82.72	6.71	3.22	82.64	6.48	2.96
47	C_6H_5	C_2H_5	$NHCH_2CH_2OH$	63	202–204 (0.002)		$C_{18}H_{21}NO_3$	72.21	7.07	4.68	72.15	6.96	4.81
48	C_6H_5	C_2H_5	$NHCH_2COOC_2H_5$	44	200–204 (0.1)		$C_{20}H_{23}NO_4$	70.36	6.79	4.10	70.77	6.64	4.39
49	C_6H_5	C_2H_5	$NH(CH_2)_3N(CH_3)_2$	83	55–56	P	$C_{21}H_{28}N_2O_2$	74.08	8.29	8.23	73.72	8.06	8.36
50	C_6H_5	C_2H_5		41	215–218 (0.15)		$C_{21}H_{26}N_2O_2$	74.52	7.74	8.28	74.30	7.43	8.50
51	C_6H_5	C_2H_5		60	176–178 (HCl)	Et–E	$C_{21}H_{21}ClN_2O_2$	68.38	5.74	7.60	68.62	5.82	7.95

[a] B = benzene, E = ether, Ea = ethyl acetate, Et = ethanol, H = hexane, M = methanol, P = pentane, W = water. [b] *Anal.* Calcd: Cl, 9.41. Found: Cl, 9.48.