TABLE I

o-, *m*-, AND *p*-(γ-L-GLUTAMYL)AMINOBENZOIC ACIDS AND DERIVATIVES

Compound	M.p., °C.	Yield, %	Empirical formula	Calculated, % C	H	N	Found, % C	H	N
(N-Carbobenzoxy-γ-L-glutamyl)aminobenzoic Acid Methyl Ester									
o-	118–120	76[a]	$C_{21}H_{23}N_3O_7$	60.86	5.35	6.76	60.89	5.55	6.78
m-	106–107	77[b]	$C_{21}H_{23}N_3O_7$	60.86	5.35	6.76	60.89	5.24	6.74
p-	155–156	83[a]	$C_{21}H_{23}N_3O_7$	60.86	5.35	6.76	60.72	5.19	6.69
(γ-L-Glutamyl)aminobenzoic Acid Methyl Ester									
o-	155–156	80	$C_{13}H_{17}N_3O_5$	55.70	5.75	10.00	55.65	5.68	9.84
m-	169–170	81	$C_{13}H_{17}N_3O_5$	55.70	5.75	10.00	55.40	5.68	10.01
p-	208–209	80	$C_{13}H_{17}N_3O_5$	55.70	5.75	10.00	55.41	5.75	10.15
(γ-L-Glutamyl)aminobenzoic Acid									
o-	258–259 (dec.)	74	$C_{12}H_{14}N_3O_5$	54.13	5.30	10.52	54.12	5.56	10.38
m-	162–163	62	$C_{12}H_{14}N_3O_5$	54.13	5.30	10.52	54.03	5.04	10.61
p-	297–300 (dec.)	53	$C_{12}H_{14}N_3O_5$	54.13	5.30	10.52	53.87	5.33	10.38
3-Phenylhydantoin of (γ-L-Glutamyl)aminobenzoic Acid									
o-	194–195 (dec.)	55	$C_{19}H_{17}N_3O_5 \cdot H_2O$	59.21	4.97	10.90	59.06	4.97	10.80
m-	201–202	91	$C_{19}H_{17}N_3O_5 \cdot H_2O$	59.21	4.97	10.90	59.24	5.05	11.05
p-	200–201	52	$C_{19}H_{17}N_3O_5 \cdot H_2O$	59.21	4.97	10.90	59.24	5.34	10.82

[a] Reflux time, 6 hr. [b] Reflux time, 48 hr.

at atmospheric pressure in the presence of 0.5 g. of palladium black catalyst. The reaction mixture was filtered to remove the catalyst, the filtrate was evaporated to dryness, and the residue was crystallized from ethanol and water. There was obtained 3.5 g. (80%) of product, m.p. 155–156°.

***o*-(γ-L-Glutamyl)aminobenzoic Acid.**—A solution of 1.0 g. of *o*-(γ-L-glutamyl)aminobenzoic acid methyl ester in 100 ml. of water was adjusted to pH 12 with saturated barium hydroxide solution, and heated on a steam bath for about 1 hr. The reaction mixture was kept at pH 12 by the addition of more barium hydroxide as required. After the pH of the reaction mixture became constant, it was cooled to room temperature, and carbon dioxide was passed through the solution until it became acid to litmus paper. Precipitation of the remaining barium ions was completed by the addition of 10% sulfuric acid. The resulting mixture was adjusted to pH 8 with 10% sodium hydroxide solution and filtered through a Celite mat. The filtrate was acidified to pH 5 with sulfuric acid, cooled, and the crystallized product which formed was filtered and dried over phosphorus pentoxide to give 0.7 g. (74%) of material which was recrystallized from water, m.p. 258–259° dec.

N-(2,4-Dioxo-3-phenyl-5-imidazolidine-L-propanoyl)-*o*-aminobenzoic Acid [3-Phenylhydantoin of *o*-(γ-L-Glutamyl)aminobenzoic Acid].—According to the general procedure of Ware[8] for the preparation of hydantoins, 148 mg. (10% molar excess) of phenyl isocyanate was added dropwise to a hot stirred solution of 300 mg. of *o*-(γ-L-glutamyl)aminobenzoic acid and 120 mg. of sodium carbonate in 15 ml. of dioxane and water (1:1). The reaction mixture was heated on a steam bath for 30 min. and kept at about pH 8 through the addition of sodium carbonate. Sufficient concd. hydrochloric acid was added to the cooled reaction mixture to give a solution of about pH 1, and this was then heated on a steam bath for an additional 15 min. After cooling in an ice bath, the precipitated product was filtered, washed with water and dried. The resulting material was recrystallized from ethanol and water to give 240 mg. of product, m.p. 194–195° dec., which gave a negative reaction to ninhydrin reagent.

Microbial Assays.—Previously reported procedures[12,13] were used for general toxicity studies with *S. lactis* 8039 and *L. arabinosus* 17-5. The assays with *E. coli* 9723 were carried out using an inorganic salts–glucose medium[14] and a previously reported assay technique.[15] In addition to the inhibition studies, the ability of *o*-(γ-L-glutamyl)aminobenzoic acid to replace anthranilic acid or tryptophan for *L. arabinosus* 17-5 was examined in a medium[12] which was modified by omitting tryptophan and which had a total glutamic acid concentration of 20 μg./ml. In comparable studies with the *E. coli* mutant 83-1,[16] the basal medium was supplemented with 10 μg./ml. each of L-phenylalanine, L-tyrosine and L-tryptophan, and various concentration levels of *p*-(γ-L-glutamyl)aminobenzoic acid were added in an effort to induce growth. Alternately, L-phenylalanine, L-tyrosine and *p*-aminobenzoic acid (0.01 μg./ml.) were added to be basal medium, and the effect of increasing concentration levels of *o*-(γ-L-glutamyl)aminobenzoic acid (which could potentially serve as a precursor of tryptophan) was determined.

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Agents Affecting Lipid Metabolism. II. Analogs of Mevalonic Acid[1]

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Since the discovery that mevalonic acid is one of the key intermediates in the biosynthesis of cholesterol, many attempts have been made to find antimetabolites of this compound.[2-12] With the exception of the work of Daeniker and Druey,[8] none of these potential antimetabolites has involved modification of the functional

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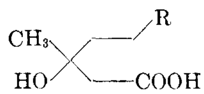
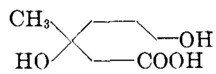
groups of mevalonic acid. We have approached the problem by preparing analogs wherein the functional groups themselves have been modified in the hope that, if these compounds would retain an affinity for the appropriate enzyme, they would behave as inhibitors of sterol biosynthesis by blocking the enzymes required for the early transformations of mevalonic acid.

Thus, these analogs of mevalonic acid were synthesized (I–IV).



I, R = $-OCH_3$
II, R = $-OC_2H_5$
III, R = $-N(CH_3)_2$



IV

3-Hydroxy-3-methyl-5-methoxypentanoic acid (I), the 5-ethoxy analog (II) and 3-methyl-3,6-dihydroxyhexanoic acid (IV) were prepared by a Reformatskii reaction of ethyl bromoacetate with 1-methoxy-3-butanone,[13] 1-ethoxy-3-butanone[14] and 1-acetoxy-4-pentanone,[15] respectively, then careful hydrolysis of the resulting β-hydroxy esters.

5-Dimethylamino-3-hydroxy-3-methylpentanoic acid (III) was prepared by a modification of the Reformatskii procedure[16] involving reaction of ethyl acetate, 1-dimethylamino-3-butanone[17] and lithium amide in anhydrous ammonia and hydrolysis of the hydroxy ester. Compound I also was prepared by this route.

The analogs were tested for their ability to inhibit the incorporation of 2-C^{14}-mevalonate into cholesterol by a rat liver homogenate. The details of our method have been described previously.[1] With final concentrations of 10^{-3} *M*, no inhibition was observed with any of the compounds.

The lack of activity in these analogs indicates an inability to form an enzyme-substrate complex, suggesting that the substrate requirements for the enzymes metabolizing mevalonic acid are quite rigid.

Experimental[18]

3-Hydroxy-3-methyl-5-methoxypentanoic Acid.—The ethyl ester of this compound was prepared by two methods: (a) 1-Methoxy-3-butanone[13] (25 g., 0.245 mole) and freshly activated zinc (28.6 g., 0.441 mole) were treated with ethyl bromoacetate (42.6 g., 0.245 mole) in anhydrous ether according to Reformatskii. The mixture was refluxed for 1 hr., cooled, poured onto crushed ice and acidified to congo red with concd. hydrochloric acid. The layers were separated, the ether washed with 5% aqueous sodium bicarbonate and then with saturated ammonium sulfate solution. The aqueous layers were combined, reacidified to congo red and extracted with chloroform. The organic extracts were combined, dried, and fractionated to yield an oil (8.0 g.), b.p. 61–62° (0.2 mm.), n^{20}D, 1.4332. The infrared spectrum had bands at 3420, 1715 and 1110 cm.$^{-1}$ attributed to hydroxyl, ester and methoxyl groups, respectively.

(b) To anhydrous ammonia (400 ml.) was added lithium (2.91 g., 0.42 mole) portionwise along with a catalytic amount of ferric nitrate. When the blue color had been discharged, ethyl acetate (17.6 g., 0.2 mole) was added and after 20 min. of stirring, 1-methoxy-3-butanone (20.4 g., 0.2 mole) was added. After stirring for an additional hr., the mixture was neutralized with ammonium chloride (22.4 g., 0.42 mole). The liquid ammonia was removed by distillation and ether (300 ml.) and water (500 ml.) were added. The ether layer yielded the ester (8.0 g.), b.p. 60–62° (0.2 mm.), n^{20}D 1.4332.

The ester (9.5 g., 0.05 mole) was dissolved in a mixture of ethanol: water (1:1) and heated to 60°. A solution of *N* sodium hydroxide (50 ml.) was added dropwise over 90 min. The alcohol was removed *in vacuo*, the mixture treated with *N* hydrochloric acid (50 ml.) at 0° and extracted with ethyl acetate to yield a colorless oil (I), b.p. 100° (0.05 mm.).

Anal. Calcd. for $C_7H_{14}O_4$: neut. equiv., 162.2. Found: neut. equiv., 159.5.

The acid was further characterized as the dibenzylethylenediammonium salt, prepared by treating an ether: methanol solution (5:1) of I with an ethereal solution of N,N′-dibenzylethylenediamine. The precipitated salt was filtered, washed with ether and crystallized from a methanol–ether mixture. It had m.p. 133–134°.

Anal. Calcd. for $C_{30}H_{48}N_2O_8$: C, 63.8; H, 8.55; N, 4.96. Found: C, 63.76; H, 8.41; N, 4.95, 4.72.

3-Hydroxy-3-methyl-5-ethoxypentanoic Acid.—The ethyl ester of this compound was prepared by the Reformatskii reaction between 1-ethoxy-3-butanone[14] and ethyl bromoacetate as described above for the methoxy analog. It was obtained in 30% yield and had b.p. 65° (0.12 mm.) and n^{22}D 1.4342. The infrared spectrum had bands at 1718 cm.$^{-1}$, 3510 cm.$^{-1}$ and 1110 cm.$^{-1}$. The ester (31.2 g.) was hydrolyzed as described for the methoxy analog. Extraction with ethyl acetate yielded an oil (13.0 g.) which was converted to the N,N′-dibenzylethylenediamine derivative. After 3 crystallizations from methanol–ether, it had m.p. 129–130° (9.5 g.).

Anal. Calcd. for $C_{32}H_{52}N_2O_8$: C, 65.14; H, 8.83; N, 4.73. Found: C, 65.16; H, 8.60; N, 5.00, 4.77.

The acid II was obtained pure, by decomposition of an aqueous solution of the salt with sodium hydroxide, removing the liberated amine by ether extraction and converting the sodium salt to the free acid by passing through a column of polystyrenesulfonic acid resin. The resulting aqueous solution was lyophilized to yield II in 98% yield as a colorless oil.

Ethyl 3-Methyl-3-hydroxy-5-dimethylaminopentanoate.—1-Dimethylamino-3-butanone[17] (9.6 g.), ethyl acetate (7.2 g.) and lithium amide (from 1.2 g. of lithium wire) reacted in anhydrous ammonia as described above. Working up the mixture yielded the ester (9.6 g.), b.p. 64–68° (0.2 mm.). A *picrate* had m.p. 79–81° on crystallization from a methanol-ether mixture.

Anal. Calcd. for $C_{16}H_{24}N_4O_{10}$: N, 12.96. Found: N, 12.40, 12.65.

3-Hydroxy-3-methyl-5-dimethylaminopentanoic Acid (III).—The amino ester (8.51 g., 0.042 mole) was dissolved in aqueous ethanol and heated to 60°. Barium hydroxide solution (128.5 ml. of 0.327 *N*) was added dropwise at such a rate that the pH of the solution did not exceed 9.0. The mixture was cooled to 0° and neutralized with sulfuric acid (43.5 ml. of 0.965 *N*). The precipitated barium sulfate was removed and the filtrate lyophilized to yield a solid (7.5 g.). After 3 crystallizations from acetonitrile it had m.p. 167–168°.

Anal. Calcd. for $C_8H_{17}NO_3$: C, 54.84; H, 9.78; N, 7.99. Found: C, 54.93; H, 9.93; N, 7.79, 7.85.

3-Methyl-3,6-dihydroxyhexanoic Acid (IV).—1-Acetoxy-4-pentanone[15] (60.2 g.) reacted in ether with ethyl bromoacetate (72.5 g.) and zinc (49.2 g.) and on working up in the usual manner yielded an oil (73.2 g., 75%), b.p. 99–100° (0.2 mm.), n^{25}D 1.4405. The infrared spectrum had bands at 3535 and at 1720 cm.$^{-1}$. The diester (20 g.) was saponified with sodium hydroxide at 60° in the usual manner. After neutralization with hydrochloric acid, the solution was lyophilized. The residue was triturated with acetonitrile to yield, after evaporation of the solvent, 14 g. of IV. It was characterized as the N,N′-dibenzylethylenediammonium salt, m.p. 142–143° on crystallization from methanol–ether.

Anal. Calcd. for $C_{30}H_{48}N_2O_8$: C, 63.8; H, 8.56; N, 4.96. Found: C, 63.98; H, 8.40; N, 4.90, 5.03.

Acknowledgment.—The authors gratefully acknowledge the capable technical assistance of Mr. George

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Sawdyk and we thank Dr. G. Papineau-Couture and staff for spectral and analytical data.

Substituted 3-Phenyl-1,3-benzoxazine-2,4-diones and their Bacteriostatic Activity

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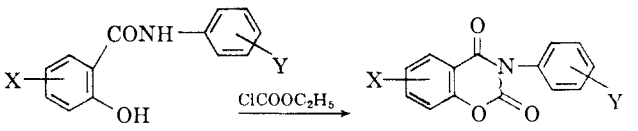
The antibacterial activity of various halo- and nitrosalicylanilides is well known.[1] Many of these compounds demonstrate good bacteriostatic activity and are substantive to skin and cotton cloth. We wish to report the preparation and antibacterial properties of some substituted 3-phenyl-1,3-benzoxazine-2,4-diones, which are heterocyclic derivatives of salicylanilides.

Only two compounds of this type have been reported in the literature. These are 3-phenyl-1,3-benzoxazine-2,4-dione[2,3] itself, prepared from salicylanilide and ethyl chloroformate, and 3-(4-bromophenyl)-1,3-benzoxazine-2,4-dione,[4] prepared by fusing phenyl salicylate with 3-(*p*-bromophenyl)-2-methyl-1-phenyl-2-thiopseudourea and hydrolyzing the resulting intermediate.[5]

Treatment of a series of halo- and nitrosalicylanilides with ethyl chloroformate in pyridine–acetonitrile[6] yielded the corresponding benzoxazinediones (Table I)



via the unisolated intermediate carbonic esters. In general, the cyclization occurred smoothly and in good yield, furnishing products easily purified by recrystallization.

The infrared spectra of a number of the benzoxazinediones were examined. As expected, two carbonyl absorptions characteristic of cyclic imides were observed. The bands occurred at 1690 cm.$^{-1}$, assigned to the carbonyl of 6-membered lactams, and at 1760 cm.$^{-1}$, assigned to the carbonyl of 6-membered lactones.[7]

The bacteriostatic activity of a number of these compounds against *Staphylococcus aureus in vitro* was determined[8] (Table II). The presence of at least two halogens is required for optimum activity, provided that both the 2- and 5-positions of the 3-phenyl ring are not substituted. The activity parallels that of the corresponding salicylanilides except for compounds 1 and 3, for which the parent anilides were more active, and compound 8, which is more active than its parent anilide.

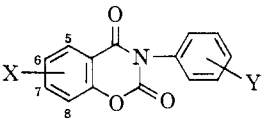
Experimental[9]

Salicylanilides.—The substituted salicylanilides corresponding to compounds 2, 3, 6 to 12, 14, 15, 17 and 18 (Table I) have been described in the literature.[1,10] The anilides required for the preparation of compounds 4 and 16 were purchased from the Aldrich Chemical Co., Inc.

2',3'-Dichlorosalicylanilide.—This anilide was prepared from phenyl salicylate and 2,3-dichloroaniline by a procedure employed for the preparation of similar salicylanilides[10b]; m.p. 222–224° (from chlorobenzene), yield, 76%.

TABLE I

3-PHENYL-1,3-BENZOXAZINE-2,4-DIONES



Compound[c]	X	Y	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Halogen, % Calcd.	Halogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1			47	254–255[a]	$C_{14}H_9NO_3$							5.86	5.76
2		4-Cl	69	245–246	$C_{14}H_8ClNO_3$	61.4	61.1	2.95	2.90	13.0	13.1	5.12	5.10
3		4-Br	69	251–252[b]	$C_{14}H_8BrNO_3$	52.9	52.9	2.54	2.60	25.1	25.4	4.40	4.30
4	6-Cl		61	285–286	$C_{14}H_8ClNO_3$	61.4	61.7	2.95	3.05	13.0	13.1	5.12	5.00
5		2,3-Cl_2	67	195–197	$C_{14}H_7Cl_2NO_3$	54.6	54.8	2.29	2.49	23.0	23.1	4.55	4.53
6		2,4-Cl_2	70	166–167	$C_{14}H_7Cl_2NO_3$	54.6	54.5	2.29	2.44	23.0	23.0	4.55	4.34
7		2,5-Cl_2	37	176–177	$C_{14}H_7Cl_2NO_3$	54.6	54.7	2.29	2.30	23.0	23.1	4.55	4.50
8		3,4-Cl_2	77	193–195	$C_{14}H_7Cl_2NO_3$	54.6	54.5	2.29	2.50	23.0	23.4	4.55	4.71
9		3,5-Cl_2	83	183–184	$C_{14}H_7Cl_2NO_3$	54.6	54.7	2.29	2.57	23.0	23.3	4.55	4.70
10	6,8-Cl_2		73	234–235	$C_{14}H_7Cl_2NO_3$	54.6	54.7	2.29	2.39	23.0	22.8	4.55	4.45
11	6-Cl	4-Cl	30	221–222	$C_{14}H_7Cl_2NO_3$	54.6	54.8	2.29	2.38	23.0	23.2	4.55	4.44
12	6-Br	4-Cl	73	217–218	$C_{14}H_7BrClNO_3$	47.7	47.9	2.00	1.99			3.97	4.01
13		2,4,5-Cl_3	70	185–186	$C_{14}H_6Cl_3NO_3$	49.1	48.9	1.77	2.03	31.1	30.8	4.09	4.04
14	6-Cl	3,4-Cl_2	80	219–220	$C_{14}H_6Cl_3NO_3$	49.1	48.8	1.77	1.93	31.1	31.2	4.09	4.20
15	6,8-Br_2	4-Br	79	300–301	$C_{14}H_6Br_3NO_3$	35.3	35.1	1.27	1.20	50.4	50.3	2.94	3.03
16	6,8-Cl_2	3,4-Cl_2	69	261–262	$C_{14}H_5Cl_4NO_3$	44.6	44.9	1.34	1.52	37.6	37.4	3.72	3.62
17	6-NO_2	3,4-Cl_2	79	234–235	$C_{14}H_6Cl_2N_2O_5$	47.6	47.6	1.71	1.89	20.1	20.1	7.94	7.90
18	8-NO_2	3,4-Cl_2	47	166–168	$C_{14}H_6Cl_2N_2O_5$	47.6	47.5	1.71	2.18	20.1	20.3	7.94	7.86

[a] Lit.,[2] m.p. 246°. [b] Lit.,[4] m.p. 214°; only a nitrogen analysis was reported. [c] Compound 1 was recrystallized from acetone; 2, 3, 5, 7, 8, 9, 10, 12, 15, 16 and 18 from toluene; 4 from dimethylformamide; 6 and 13 from toluene–methylcyclohexane; 11 from ethyl acetate; 14 from chlorobenzene and 17 from dimethylformamide–water.

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(5) Since the melting point of our 3-(4-bromophenyl)-1,3-benzoxazine-2,4-dione (compound 3) differed by about 40° from the reported[4] value, we also employed the fusion method and obtained in low yield a product (m.p. 212–222°) which, according to elemental analysis and the infrared spectrum, was a mixture of 3-phenyl- and 3-(4-bromophenyl)-1,3-benzoxazine-2,4-dione.