N-Aralkylsalicylamides

GÉRARD Y. PARIS AND CLINTON H. CHAMBERS

Research Department, Abbott Laboratories Ltd., Montreal, Quebec

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The N-benzylsalicylamides described in Table I were prepared for evaluation as anthelmintics. The compounds were synthesized by the general methods which have been described for the preparation of N-arylsalicylamides,[1-5] with occasional minor modifications.

Experimental Section[6]

Method A.[1-3]—Phosphorus trichloride (1 equiv) was added dropwise to a mixture of salicylic acid (3 equiv) and the amine (3 equiv) without external cooling. After the addition was complete, the reaction mixture was heated at 180° until the evolution of HCl ceased. The product was isolated by stirring the reaction mixture in aqueous Na_2CO_3 solution.

N-Benzyl-2-mercaptobenzamide.—Phosphorus trichloride (9.2 g, 0.06 mole) was added dropwise to a mixture of thiosalicylic acid (30.8 g, 0.20 mole) and benzylamine (21.4 g, 0.20 mole). The reaction mixture was heated at 180° for 45 min and the product was isolated as previously described; yield 30.0 g (62%), mp 208–209°.

Anal. Calcd for $C_{14}H_{13}NOS$: C, 69.11; H, 5.38; N, 5.76; S, 13.18. Found: C, 68.91; H, 5.18; N, 5.89; S, 13.16.

Method B.[4]—Phenyl salicylate and the amine (1:1) were heated at 180–200° for 2 hr. The product was isolated by treatment with dilute ethanol.

N-(4-Chlorobenzyl)salicylamide was obtained by a modification[5] of method B in which 1,2,4-trichlorobenzene was used as solvent.

N-(β-Phenoxyethyl)salicylamide.—A solution of β-phenoxyethylamine (6.88 g, 0.05 mole) and phenyl salicylate (10.71 g, 0.05 mole) in 10 ml of 1,2,4-trichlorobenzene was heated at 190–200° for 30 min. Removal of solvent and phenol under vacuum yielded a residue which was treated with dilute alcohol; yield 11.0 g (85.5%), mp 115–116°. The analytical sample (mp 116–117°) was crystallized from CCl_4.

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.45. Found: C, 70.32; H, 5.81; N, 5.63.

N-Furfurylsalicylamide.—A mixture of furfurylamine (9.7 g, 0.1 mole) and phenyl salicylate (21.4 g, 0.1 mole) was shaken for 10 min at room temperature. An exothermic reaction occurred. The mixture was then heated on the steam bath for 15 min and poured into water. Acidification with HCl gave the product, 21.0 g (97%), mp 110–111°.

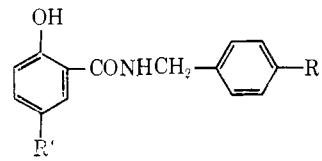
Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.34; H, 5.11; N, 6.45. Found: C, 66.19; H, 5.14; N, 6.80.

N-Furfuryl-2-mercaptobenzamide.—Reaction of phenyl thiosalicylate[7] (10 g, 0.06 mole) and furfurylamine (4.9 g, 0.05 mole) by the above method gave the product which melted at 182–183° after one crystallization from ethanol; yield 5.0 g (43%).

Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.76; H, 4.75; N, 6.00; S, 13.75. Found: C, 61.86; H, 4.61; N, 6.18; S, 13.99.

TABLE I

SUBSTITUTED BENZYLSALICYLAMIDES



R	R'	Method used	Yield, %	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Chlorine, % Calcd	Chlorine, % Found
H	Br	A	73	154–156[a]	$C_{14}H_{12}BrNO_2$[b]	54.91	55.01	3.95	4.02	4.58	4.76		
H	Cl	A	74	145–146[a]	$C_{14}H_{12}ClNO_2$	64.27	64.57	4.62	4.70	5.34	5.18	13.54	13.29
H	I	A	54	134–135[a]	$C_{14}H_{12}INO_2$[c]	47.61	47.65	3.43	3.30	3.98	4.16		
H	NO_2	A	87	221–223[d]	$C_{14}H_{12}N_2O_4$	61.75	61.62	4.44	4.45	10.30	10.14		
4-Cl	Br	A	35	158–159[a]	$C_{14}H_{11}BrClNO_2$[e]	49.36	49.20	3.26	3.26	4.11	4.07	10.41	10.38
4-Cl	Cl	B	63	156–158[a]	$C_{14}H_{11}Cl_2NO_2$	56.78	57.00	3.74	3.79	4.73	4.84	23.94	24.24
4-Cl	H	B	86	133–134[a]	$C_{14}H_{12}ClNO_2$	64.27	64.41	4.62	4.42	5.34	5.18	13.54	13.53
4-Cl	I	A	70	161–162[a]	$C_{14}H_{11}ClINO_2$[f]	43.40	43.60	2.85	2.78	3.62	3.51	9.15	9.33
3,4-Cl_2	Br	A	67	160–161[a]	$C_{14}H_{10}BrCl_2NO_2$[g]	44.83	44.83	2.71	2.68	3.74	3.71	18.91	18.96
3,4-Cl_2	Cl	A	73	154–156[a]	$C_{14}H_{10}Cl_3NO_2$	50.86	50.83	3.05	3.20	4.24	4.30	32.19	32.63
3,4-Cl_2	H	A	62	136–137[a]	$C_{14}H_{11}Cl_2NO_2$	56.78	56.50	3.74	3.46	4.73	4.71	23.94	23.92
3,4-Cl_2	I	A	50	174–175[a]	$C_{14}H_{10}Cl_2INO_2$[h]	39.84	40.07	2.39	2.56	3.32	3.44	16.80	16.95

[a] Recrystallized from aqueous ethanol. [b] *Anal.* Calcd: Br, 26.11. Found: Br, 26.29. [c] *Anal.* Calcd: I, 35.93. Found: I, 35.79. [d] Recrystallized from acetone–water. [e] *Anal.* Calcd: Br, 23.76. Found: Br, 23.81. [f] *Anal.* Calcd: I, 32.74. Found: I, 32.51. [g] *Anal.* Calcd: Br, 21.31. Found: Br, 21.59. [h] *Anal.* Calcd: I, 30.07. Found: I, 29.61.

N-3,4-Dichlorobenzyl-2-mercaptobenzamide.— Thiosalicyloyl chloride[8] (14.3 g, 0.08 mole) was dissolved in 150 ml of benzene and 3,4-dichlorobenzylamine (35.2 g, 0.2 mole) was added. The exothermic reaction was moderated by cooling and then allowed to stand overnight at room temperature. The solid formed was filtered, washed with ethanol, and triturated with hot water; yield 22.8 g (73.0%), mp 218–220°. One crystallization from methyl ethyl ketone raised the melting point to 224–225°.

Anal. Calcd for $C_{14}H_{11}Cl_2NOS$: C, 53.86; H, 3.55; Cl, 22.72; N, 4.47; S, 10.26. Found: C, 54.12; H, 3.74; Cl, 23.01; N, 4.35; S, 10.54.

(1) R. Wanstrat, *Ber.*, **6**, 336 (1873).
(2) H. Kupferberg, *J. Prakt. Chem.*, [2] **16**, 424 (1877).
(3) H. Hübner and Mensching, *Ann.*, **210**, 328 (1881).
(4) G. Cohn, *J. Prakt. Chem.*, [2] **61**, 544 (1900).
(5) C. F. H. Allen and J. Van Allan, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 765.
(6) All melting points were taken with a Thomas–Hoover apparatus. Elementary analyses were performed by the Microanalytical Laboratory of Abbott Laboratories, North Chicago, Ill.
(7) F. Mayer, *Ber.*, **42**, 1134 (1909).
(8) S. M. McElvain and T. P. Carney, *J. Am. Chem. Soc.*, **68**, 2592 (1946).

Synthesis of Analogs of Bacterial Cell Wall Glycopeptides

N. C. CHATURVEDI, M. C. KHOSLA, AND NITYA ANAND

Division of Medicinal Chemistry, Central Drug Research Institute, Lucknow, India

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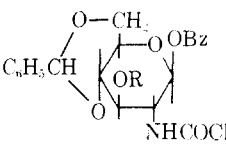
The enzymatic synthesis of the glycopeptides involved in bacterial cell wall formation by the stepwise addition of amino acids to uridine-5'-diphospho-N-acetylmuramic acid[1] offers a

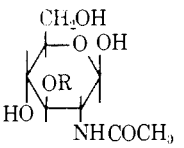
TABLE I[a]



No.	R	Mp, °C	Yield, %	$[\alpha]_D$,[b] deg	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
I	ClH_2COOH	216–218	65	+122	$C_{24}H_{27}NO_8$	63.01	5.97	3.06	63.37	6.22	3.14
II	L-C(CH$_3$)HCOOH	264–265	68	+75.1	$C_{25}H_{29}NO_8$	63.68	6.20	2.97	63.57	6.59	3.26
III	ClH_2CO-L-Ala-OBz	172–173	74	+57.3	$C_{34}H_{38}N_2O_9$	66.01	6.19	4.53	65.91	5.99	4.33
IV	L-C(CH$_3$)HCO-L-Ala-OBz	229–230	63	+70.4	$C_{35}H_{40}N_2O_9$	66.43	6.37	4.43	65.90	6.48	4.38
V	D-C(CH$_3$)HCO-L-Ala-OBz	216	74	+100	$C_{35}H_{40}N_2O_9$	66.43	6.37	4.43	66.84	6.71	4.60
VI	ClH_2CO-L-Ala-D-Glu-(OBz)$_2$	178–179	50	+65.85	$C_{50}H_{51}N_3O_{13}$	65.94	6.13	5.01	65.67	6.40	5.27
VII	D-C(CH$_3$)HCO-L-Ala-D-Glu-(OBz)$_2$	202–203	63	+89.2	$C_{51}H_{53}N_3O_{13}$	66.25	6.27	4.93	66.63	6.51	5.14

[a] The compounds were crystallized from methanol. [b] *c* 1–2, HCONMe$_2$ between 30–35°.

TABLE II[a]



No.	R	Yield, %	$[\alpha]_D$, deg	R_f A	R_f B	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
VIII	ClH_2COOH	65	+61[b]	0.65	0.65	$C_8H_{12}NO_5$	43.04	7.32	5.01	43.32	7.47	5.23
IX	L-C(CH$_3$)HCOOH	69	+20.5[c]	0.66	0.80	$C_9H_{15}NO_5$	45.95	6.53	4.77	45.21	6.84	4.33
X	CH_2CO-L-Al-OH	81	+9.1[c]	0.44	0.72	$C_5H_{22}N_2O_4$	44.55	6.32	7.99	44.38	6.33	7.95
XI	L-C(CH$_3$)HCO-L-Ala-OH	75	−17.5[c]	0.67	0.7	$C_8H_{24}N_2O_5$	46.14	6.63	7.69	46.50	7.07	7.53
XII	D-C(CH$_3$)HCO-L-Ala-OH	70	+23.6[c]	0.58	0.81	$C_8H_{24}N_2O_5$	45.91	6.74	7.50	44.95	7.38	7.20
XIII	ClH_2CO-L-Ala-D-Glu-(OH)$_2$	75	+49[c]	0.42	0.20	$C_9H_{29}N_2O_{12}\cdot H_2O$	43.44	6.27	8.44	43.08	6.11	7.91
XIV	D-C(CH$_3$)HCO-L-Ala-D-Glu-(OH)$_2$	75	+46.22[c]	0.7	0.63	$C_9H_{31}N_3O_{12}\cdot 2H_2O$	43.07	6.66	7.03	43.51	6.15	6.83

[a] The compounds were crystallized from methanol–ethyl acetate or methanol–ether, were in general hydroscopic, did not show a sharp melting point, and sintered, darkened, and gradually decomposed above 150°. [b] *c* 1–2, MeOH at 30° within 30 min after making the solution. [c] *c* 1, H_2O at 20° within 30 min after making the solution.

new approach to the design of substances which might interfere in cell wall formation. As a first step in this direction, we reported the synthesis of L-alanyl-D-α- (and γ-) glutamyl-L-lysyl-D-alanyl-D-alanine and a partially protected L-glutamyl isomer.[2] Lanzilotti, *et al.*,[3] have reported the synthesis of Nα-[2-(2-acetamido-3-O-D-glucosyl)-D-propionyl-L-alanyl-D-α- (and γ-) glutamyl]-L-lysyl-D-alanyl-D-alanine and they have also identified the γ-glutamyl isomer with the glycopeptide of a bacterial cell wall precursor. The present communication records the synthesis of various N-acetylmuramylamino acids and peptides and their analogs.

Experimental Section[4]

The method of synthesis described below for 2-(2-acetamido-2-deoxy-3-O-D-glucopyranosyl)acetyl-L-alanine is typical of the general method followed, and the various compounds thus synthesized are described in Tables I and II.

Benzyl 2-Acetamido-2-deoxy-α-D-glucopyranoside.—The method of Kuhn, *et al.*,[5] was used except that the reaction mixture was heated at 110° for 3.5 hr, instead of refluxing it for 30 min. The product was obtained in 55% yield (lit.[5] yield 44%) and had the same melting point and rotation as reported in the literature.

Benzyl 2-Acetamido-4,6-O-benzylidene-3-O-carboxymethyl-2-deoxy-α-D-glucopyranoside (I).—A solution of 1 g of benzyl 2-acetamido-4,6-O-benzylidene-2-deoxy-α-D-glucopyranoside[6] in 30 ml of dry dioxane was treated under stirring with 400 mg of 50% NaH dispersion in oil. The stirred mixture was brought to just below the boiling point (95°), 1.5 g of chloroacetic acid in 30 ml of dioxane was added, and the temperature was allowed to come down to 60°. The mixture was stirred for an additional 30 min and treated again with 1.33 g of NaH, and the stirring was continued overnight at 60°. The mixture was then cooled to 0° and treated with excess ethanol until the effervescence was over. Solvents were removed *in vacuo*, the residue was dissolved in a large excess of water and extracted with chloroform, and the aqueous phase was acidified with cold 6 *N* HCl. The product which precipitated was taken up in ethyl acetate, and the extract was washed with water, dried ($MgSO_4$), and evaporated. The residue was taken up in excess methanol and kept overnight at 0°, and a small quantity of a compound thus precipitated, which appeared to be the β anomer [$[\alpha]^{35}D$ +37° (*c* 1.6, HCONMe$_2$). *Anal.* Calcd for $C_{24}H_{27}NO_8$: C, 63.01; H, 5.97; N, 3.06. Found: C, 63.3; H, 6.18; N, 3.10.], was discarded since the quantity was too small to be pursued. The methanolic solution on concentration gave the desired product, mp 216–218°.

L-Alanyl-D-Glutamic Acid Dibenzyl Ester.—To a stirred solution of 2.2 g of benzyloxycarbonyl-L-alanine and 3.2 g of D-glutamic acid dibenzyl ester in 100 ml of acetonitrile was added 2.06 g of dicyclohexylcarbodiimide in 10 ml of acetonitrile at −5°. The mixture was stirred for 2 hr at −5° and overnight at room temperature, and the precipitated dicyclohexylurea was filtered and washed with cold acetonitrile. The combined filtrates were evaporated *in vacuo*, the residue was extracted with ethyl acetate, and the extract was washed with 1 *N* $NaHCO_3$, H_2O, and 1 *N* HCl, dried (Na_2SO_4), and evaporated. The residue was crystallized from alcohol to give 3.3 g (73%) of benzyloxycarbonyl-L-alanyl-D-glutamic acid dibenzyl ester, mp 114.5°.

(1) E. Ito and J. L. Strominger, *J. Biol. Chem.*, **237**, 2689, 2695 (1962).

(2) M. C. Khosla, N. C. Chaturvedi, H. G. Garg, and N. Anand, *Indian J. Chem.*, **3**, 111 (1965).

(3) A. E. Lanzilotti, E. Benz, and L. Goldman, *J. Am. Chem. Soc.*, **86**, 1880 (1964).

(4) Capillary melting points were determined on Totalli's melting point apparatus (W. Büchi, Flawil, Switzerland), and are uncorrected. The homogeneity of the compounds was tested by thin layer chromatography on silica gel (200 mesh) plates employing: A, 1-butanol–acetic acid–water (4:1:5), and B, 1-butanol–acetic acid–water–pyridine (30:6:20:24) as the solvents; the blocked compounds were detected by spraying with water or by exposure to iodine vapors while final free products were detected by heating the plates at 150° for 1 hr or by spraying with ammoniacal $AgNO_3$ reagent and heating the plates at 150° for 15 min.

(5) R. Kuhn, H. H. Baver, and A. Seeliger, *Ann.*, **611**, 236 (1962).

(6) H. Sachs and L. Brand, *J. Am. Chem. Soc.*, **75**, 1668 (1953).

$[\alpha]^{30}D$ −3.5° (*c* 2, acetic acid) [lit.[6] mp 112–113°, $[\alpha]^{23}D$ −3.7° (*c* 2, acetic acid)].

A solution of 1.5 g of this ester in 7.5 ml of glacial acetic acid was treated with 7.5 ml of 4 *N* HBr–acetic acid and the mixture was kept at room temperature for 1 hr. Excess HBr and acetic acid were removed *in vacuo* at 20° and the residue, after washing with dry ether, was dissolved in water, treated with triethylamine to pH 8, and extracted with ethyl acetate, and the extract was worked up to give 0.8 g of L-alanyl-D-glutamic acid dibenzyl ester as an oil (R_f (A) 0.82) which was used for condensation without any further purification.

2-(1-O-Benzyl-2-acetamido-4,6-O-benzylidene-2-deoxy-3-O-D-glucopyranosyl)acetyl-L-alanine Benzyl Ester (III).—To a stirred suspension of 100 mg of N-ethyl-5-phenylisoxazolium 3′-sulfonate (Woodward's reagent K)[7] in 10 ml of dry acetonitrile at 0°, a solution of 200 mg of I and 0.6 ml of triethylamine in 20 ml of acetonitrile was added. The mixture was stirred at 0° until a clear solution was obtained (40 min). A cold solution of benzyl alaninate (obtained by treating 155 mg of the *p*-toluenesulfonic acid salt of benzyl alaninate in 15 ml of acetonitrile with 0.05 ml of triethylamine) was added, and the mixture was stirred for an additional 1 hr at 0° and kept overnight at room temperature. The solvent was removed *in vacuo* and the residue was washed with 0.5% $NaHCO_3$ solution. The precipitate was extracted with ethyl acetate, the extract was washed successively with 0.5% Na_2CO_3, 5% citric acid, water, and saturated NaCl solution. The organic phase was dried ($MgSO_4$) and evaporated, and the residue was washed with ether and crystallized from ethyl acetate–petroleum ether or ethanol, mp 172–173°.

2-Acetamido-3-O-carboxymethyl-2-deoxy-D-glucose.—Unexpected difficulty was experienced in the hydrogenolytic splitting of the blocking groups and an aqueous medium seemed to be favorable for this step. In view of the insolubility of the blocked compounds in water removal of the blocking groups had to be carried out either stepwise, *i.e.*, first acid cleavage to remove the benzylidene group followed by hydrogenation in aqueous methanol, or in one step by carrying out the hydrogenation in a vigorously stirred mixture of ethyl acetate and water.

Method A. Stepwise Removal of Blocking Groups.—A solution of 340 mg of I in a mixture of 12 ml of glacial acetic acid and 8 ml of water was shaken in a closed flask for 2.5 hr at room temperature. The solvents were removed *in vacuo* at 60–70°, the residue was evaporated to dryness after adding water to remove the last traces of acetic acid, dissolved in glass-distilled water, and filtered. A part of the aqueous solution was lyophilized to give presumably benzyl 2-acetamido-3-O-carboxymethyl-2-deoxy-α-D-glucoside, mp 155–157° (from ethyl acetate); yield 70%.

Anal. Calcd for $C_{17}H_{23}NO_8$: C, 55.29; H, 6.23; N, 3.97. Found: C, 54.98; H, 6.20; N, 3.70.

The above aqueous solution was then hydrogenated using 10% Pd–C for 5–6 hr at ordinary temperature and pressure, the catalyst was filtered, and the aqueous phase was lyophilized to give the desired compound as a colorless hygroscopic powder.

In the case of compounds containing a benzyl ester as well, the compounds were first hydrogenated in methanol and subsequently in water.

Method B. One-Step Removal of Protecting Groups.—Compound I (300 mg) was dissolved in excess moist ethyl acetate (approx 200 ml), by warming if necessary, and 50 ml of distilled water and 0.3 g of 10% Pd–C were added. The mixture was vigorously stirred and hydrogenated at ordinary temperature and pressure until no more hydrogen was absorbed (5–6 hr). The catalyst was filtered and the aqueous phase was extracted twice with ethyl acetate. The aqueous extract was now stirred for 30 min with 4 g of Dowex 50 (H^+ form), the resin was filtered, the filtrate was lyophilized, and the residue was crystallized from a mixture of methanol–ethyl acetate. The compound was identical in all respects with that obtained by method A.

2-(2-Acetamido-2-deoxy-3-O-D-glucopyranosyl)acetyl-L-alanine (X) was prepared from III according to method B described above for the hydrogenolysis.

Acknowledgment.—We wish to express our thanks to Dr. M. L. Dhar, Director, for his interest in this work and to Mr. J. Saran and his associates for microanalyses.

(7) R. B. Woodward, R. A. Olofson, and H. Mayer, *J. Am. Chem. Soc.*, **83**, 1010 (1961).

Myelographic Agents III. Glycol Iodobenzoates[1]

JAMES E. SIGGINS AND JAMES H. ACKERMAN

Sterling-Winthrop Research Institute, Rensselaer, New York

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In continuation of our study of contrast agents for X-ray visualization of the spinal cord, we have prepared some reverse esters (Table I) analogous to the series previously reported.[2] We were able to realize our hope that this small molecular modification would permit rapid elimination from the spinal canal. After cisternal administration into cats and dogs, the esters enabled details of the spinal canal to be visualized and were eliminated from the animals in periods ranging from a few weeks to a few months.

Experimental Section[3]

o-Iodobenzoyl chloride and sodium *p*-iodobenzoate were prepared as previously described[2] from commercially available iodobenzoic acids. Aliphatic acid chlorides, ethylene chlorohydrin, and trimethylene chlorohydrin were commercial products used as obtained. Tetramethylene chlorohydrin (Matheson Coleman and Bell) was distilled before use, bp 82–84° (11 mm), $n^{25}D$ 1.4511.

2-Hydroxyethyl acetate (Eastman Kodak Co., practical) was stirred with ice-cold 25% aqueous K_2CO_3 and the mixture was extracted with chloroform. Washing with water, drying (Na_2SO_4), removal of solvent, and distillation gave 2-hydroxyethyl acetate satisfactory for our purposes, bp 98° (23 mm), $n^{25}D$ 1.4190.

Chloroalkyl Alkanoates.—The standard reaction between an acid chloride and an alcohol was used to prepare these compounds, with the exception of 3-chloropropyl 2-methoxyacetate.[4] The latter was prepared by the toluenesulfonic acid catalyzed reaction between methoxyacetic acid and trimethylene chlorohydrin.

The reaction of hexanoyl chloride with trimethylene chlorohydrin in hexane gave a 74% yield of 3-chloropropyl hexanoate, bp 134° (23 mm), $n^{25}D$ 1.4373.

Anal. Calcd for $C_9H_{17}ClO_2$: C, 56.10; H, 8.89; Cl, 18.40. Found: C, 56.42; H, 9.07; Cl, 18.78.

1-Chloro-2-propyl Valerate.—Commercial 1-chloro-2-propanol (Matheson Coleman and Bell) was fractionally distilled through a 15-cm Vigreux column to give a forerun, bp 49–51° (28 mm), which was discarded and a colorless fraction, bp 51° (28 mm), $n^{25}D$ 1.4355. Forty-seven grams (0.5 mole) of this alcohol was added dropwise to a stirred solution of 59 ml (0.5 mole) of butyryl chloride in hexane. After evolution of HCl had subsided, the mixture was heated under reflux for 2 hr, cooled, washed with 5% $NaHCO_3$, and dried (Na_2SO_4). The solvent was removed and the oil was fractionally distilled through a 15-cm Vigreux column to give 54.8 g (80%) of the ester, bp 110° (30 mm), $n^{25}D$ 1.4290.

Anal. Calcd for $C_8H_{15}ClO_2$: C, 53.77; H, 8.46; Cl, 19.84. Found: C, 53.54; H, 8.56; Cl, 19.80.

Method A. 2-Acetoxyethyl *p*-Iodobenzoate (1).—To a solution of 62.0 g (0.250 mole) of *p*-iodobenzoic acid in 360 ml of dimethylformamide was added 35 ml (0.25 mole) of triethylamine, followed by 30.8 g (0.252 mole) of 2-chloroethyl acetate. The brown mixture was stirred 24 hr at 115°. After cooling and removal of $Et_3N \cdot HCl$ by filtration, the mixture was poured into water and the aqueous phase was extracted with $CHCl_3$. The combined organic extract was washed successively with cold 5% K_2CO_3, H_2O, cold 3% HCl, H_2O, and saturated NaCl. Drying over Drierite, decolorizing with charcoal, and removal of solvent gave an oil which amounted to 42.8 g (51%) of 1 after distillation. This product solidified after cooling in Dry Ice.

(1) Paper II: J. H. Ackerman, V. Akullian, C. Moore, and A. A. Larsen, *J. Med. Chem.*, **9**, 165 (1966).

(2) J. E. Siggins, J. H. Ackerman, and A. A. Larsen, *ibid.*, **8**, 728 (1965).

(3) Melting points were taken in a modified Hershberg apparatus and are uncorrected.

(4) Einar J. Salmi and R. Leimu, *Suomen Kemistilehti*, **20B**, 43 (1947); *Chem. Abstr.*, **42**, 4031*g* (1948).