Hemimethyl Ester Acid Chloride (V).—The monoester IV (572 mg.) was covered with 5 ml. of redistilled oxyalyl chloride, cooled in an ice bath, and allowed to stand for 1 hr. The excess oxalyl chloride was removed *in vacuo*. Dry benzene was added to the residue and distilled *in vacuo* to remove last traces of chlorinating agent. This acid chloride was used in the next step without further purification.

1,2,3,4,4aα,10aβ-Octahydro-1α-(2-hydroxyethyl)-7-methoxy-2β-methyl-2α-phenanthrenecarboxylic Acid δ-Lactone (VIII).—The acid chloride V was dissolved in 15 ml. of dry ether and at once added to a solution of 35 mg. of lithium aluminum hydride in 15 ml. of dry ether maintained at $-10°$ and protected with dry nitrogen. The thick milky gel was stirred at $-10°$ and protected with dry nitrogen. The thick milky gel was stirred at $-10°$ for 1 hr. and at room temperature for an additional hour. Then 20 ml. of 1% H_2SO_4 was added with stirring and the mixture was partitioned between 200 ml. of ether and 100 ml. of 1% H_2SO_4. The ether layer was washed with 3% K_2CO_3 and water. The ether was evaporated to give 444 mg. of an oil representing a mixture of the lactone VIII and diol. While refluxing this oil in 20 ml. of ethanol, 11.2 g. of NaOH in 100 ml. of 50% ethanol was added in 25-ml. aliquots every hour for 4 hr. After most of the alcohol was evaporated, the reaction mixture was diluted with water and extracted with ether. The alkaline phase was acidified with concentrated H_2SO_4, ether was added, and the two layers were shaken intermittently to form the lactone. The aqueous phase was separated and re-extracted with ether. The combined ether phases were washed three times with water, with 5% $NaHCO_3$, and again with water, then evaporated to give 248 mg. of VIII. This lactone was recrystallized from a mixture of acetone–petroleum ether (b.p. 60–80°), aqueous ethanol, and aqueous acetone to provide colorless crystals, m.p. 170–171°.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.74; H, 7.94.

The melting point of this product was depressed 20° by admixture with the methyl ether of lactone I. On admixture with the methyl ether of lactone II the depression was 30°.

Myelographic Agents. II. Some Iodophthalates[1]

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As part of our extensive program in the field of radiopaque, diagnostic agents we have prepared series of 3- and 4-iodophthalates, 5-iodoisophthalates, and iodoterephthalates (Table I).[2] For the most part, these compounds were synthesized as potential myelographic agents. When the liquid members of these series were injected into the subarachnoid space of cats and dogs, they permitted visualization of the details of the spinal-cord structure. Many of these compounds were eliminated from the animals in periods ranging from a few weeks to a few months.

The bis esters were prepared from the iodo acids and an alcohol with an acid catalyst. The mixed esters of 3-iodophthalic acid were prepared from 3-iodophthalic anhydride. When the anhydride was refluxed with methanol or 1-butanol, a half ester was obtained. By analogy with the reactions of 3-nitrophthalic anhydride[3] and the preparation of the two half ethyl esters of 3-iodophthalic acid,[4] it is presumed that the isolated products were the 2-esters. The sodium salts were prepared from the half esters and allowed to react with an alkyl halide or tosylate; the mixed esters were obtained.

The mixed 5-iodoisophthalate esters were prepared generally by the reaction of alkyl halides, sulfates, or tosylates with the half ester sodium salts (Table II). The latter were prepared by partial hydrolysis of the bis esters.

Experimental Section

Iodophthalic Acids.—3-Iodophthalic acid was prepared from 3-aminophthalic acid by a procedure similar to that of Kenner and Mathews.[5] 4-Iodophthalic acid was prepared from 4-nitrophthalic acid. The nitro group was reduced to the amine with Raney nickel and hydrazine hydrate by the general procedure of Balcom and Furst.[6] The amine was diazotized and converted to the iodo compound by the Sandmeyer reaction. 5-Iodoisophthalic acid was prepared from 5-aminoisophthalic acid by a procedure similar to that of Grahl.[7] Iodoterephthalic acid was prepared from nitroterephthalic acid by the method used to prepare 4-iodophthalic acid.

3-Iodo-2-methoxycarbonylbenzoic Acid.—A mixture of 137 g. (0.50 mole) of 3-iodophthalic anhydride[8] and 350 ml. of absolute methanol was refluxed for 20 hr. The excess methanol was removed under reduced pressure. The residue (163 g., m.p. 125–140°) was recrystallized from dilute methanol and then benzene to give 81.4 g. (53%) of colorless, elongated prisms, m.p. 164–165°.

Anal. Calcd. for $C_9H_7IO_4$: I, 41.47; neut. equiv., 306.1. Found: I, 41.78; neut. equiv., 306.4.

Sodium 3-Iodo-2-methoxycarbonylbenzoate.—To a solution of 306 g. (1.0 mole) of 3-iodo-2-methoxycarbonylbenzoic acid in 1 l. of acetone was added 505 ml. of 2.0 *N* (1.0 mole) NaOH. Acetone was added to turbidity, and the mixture was cooled overnight. Solid separated and was collected and dried at 100° to give 209.7 g. (64%) of colorless product.

Sodium 2-butoxycarbonyl-3-iodobenzoate was prepared in a similar manner.

Sodium Alkyl (or Alkoxyalkyl) 5-Iodoisophthalates. Sodium Butyl 5-Iodoisophthalate.—A solution of 634 g. (1.6 moles) of undistilled dibutyl 5-iodoisophthalate (**46**) in 2.5 l. of dimethylformamide was cooled to 5° and a solution of 62.8 g. (1.6 moles) of NaOH pellets in 500 ml. of water was added in one batch with rapid stirring. After 2 min. the reaction had warmed to about 40° and was then heated on a steam bath at 78–85° for 0.5 hr. The solvents were removed by distillation (reduced pressure) to give a residue of diester, half ester sodium salt, and disodium salt which was stirred with about 3 l. of water at 85°. The aqueous layer was separated from the insoluble diester by decantation and was treated with Darco G60, filtered, and cooled to 5°. The crystalline half ester sodium salt crystallized and was removed by filtration and washed with pentane. The slightly damp solid was dissolved in 2.5 l. of hot water. The solution was treated with Darco G60, filtered, and cooled. The solid was removed by filtration, washed with pentane, and dried at 90° *in vacuo* to give 420 g. (73%) of colorless needles: neut. equiv., 370 (calcd., 370).

The other sodium alkyl (or alkoxyalkyl) 5-iodoisophthalates (Table II) were prepared in a similar manner.

Alkyl and Alkoxyalkyl *p*-Toluenesulfonates.—The *p*-toluenesulfonates were prepared from a number of alcohols by the general procedure of Tipson.[9] The tosylates made were the propyl,[10] butyl,[11] methoxyethyl,[9] 2-ethoxyethyl,[9] 2-butoxyethyl,[9] 3-methoxypropyl, 3-ethoxypropyl,[12] 3-propoxypropyl, 3-methoxybutyl,[13] 2-(2-ethoxyethoxy)ethyl,[14] 2-(2-butoxyethoxy)ethyl, and 1,3-diethoxy-2-propyl. These tosylates were used as intermediates to prepare mixed esters.

Most of the alcohols used for the preparation of the tosylates are commercially available (Eastman, Aldrich). 3-Methoxypropanol[15] was prepared from 3-methoxypropionitrile. Reaction of the nitrile with ethanol and concentrated H_2SO_4 gave ethyl 3-methoxypropionate which was converted to the alcohol with lithium aluminum hydride.

3-Propoxypropanol[16] was prepared from 3-propoxypropionitrile in the same manner. The nitrile was made by cyanoethylation[17] of 1-propanol.

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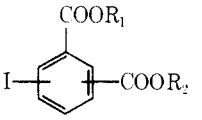
TABLE I

IODOPHTHALATES, IODOISOPHTHALATES, AND IODOTEREPHTHALATES



Compd. no.	R_1[a]	R_2[a]	M.p.[b] or b.p. (mm.), °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % I	Found, % C	Found, % H	Found, % I	Viscosity, cs. at 25°C	$n^{25}D$
				3-Iodophthalates								
1	*n*-Pr	Me	85 (0.2)	$C_{12}H_{13}IO_4$	41.40	3.76	36.46	41.14	3.81	36.82	217	1.5608
2	*n*-Bu	Me	70 (10^{-4})	$C_{13}H_{15}IO_4$	43.11	4.17	35.04	43.13	4.33	35.40	165	1.5549
3	C	Me	77 (10^{-4})	$C_{13}H_{15}IO_5$	41.29	4.00	33.56	41.33	4.20	33.07	268	1.5524
4	F	Me	116 (0.2)	$C_{14}H_{17}IO_5$	42.87	4.37	32.36	42.63	4.50	32.37	192	1.5467
5	*n*-Pr	*n*-Pr	81–86 (5×10^{-5})	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.66	4.60	33.59	109	1.5458
6	*n*-Bu	*n*-Bu	90 (5×10^{-5})	$C_{18}H_{29}IO_4$	47.53	5.24	31.40	47.30	5.03	31.08	125	1.5365
7	C	*n*-Bu	80 (10^{-4})	$C_{16}H_{21}IO_5$	45.73	5.04	30.20	45.77	5.24	30.14	112	1.5360
8	F	*n*-Bu	154 (0.1)	$C_{17}H_{23}IO_5$	47.01	5.34	29.23	46.80	5.12	29.68	156	1.5359
9	B	B	40–44	$C_{14}H_{17}IO_6$	41.19	4.20	31.09	41.47	4.22	31.2		
10	C	C	122 (10^{-5})	$C_{16}H_{21}IO_6$	44.05	4.85	29.09	43.85	4.96	29.4	160	1.5358
11	D	D	103–107 (5×10^{-5})	$C_{20}H_{29}IO_6$	48.79	5.94	25.78	48.73	5.67	26.13	98	1.5200
12	H	H	95 (2×10^{-4})	$C_{18}H_{25}IO_6$	46.56	5.43	27.34	46.60	5.59	27.33	260	1.5291
				4-Iodophthalates								
13	*n*-Pr	*n*-Pr	63–65 (10^{-5})	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.94	4.78	33.95	51	1.5482
14	*n*-Bu	*n*-Bu	67 (10^{-5})	$C_{18}H_{29}IO_4$	47.53	5.24	31.40	47.75	5.20	31.4	49	1.5378
15	D	D	167 (4×10^{-2})	$C_{20}H_{29}IO_6$	48.79	5.94	25.78	48.86	6.01	26.21	82	1.5220
16	H	H	125 (10^{-4})	$C_{18}H_{25}IO_6$	46.56	5.43	27.34	46.54	5.59	27.32	156	1.5304
17	I	I	182–184 (5×10^{-3})	$C_{20}H_{29}IO_8$	45.81	5.57	24.21	45.69	5.73	23.81	105	1.5241
				5-Iodoisophthalates								
18	Me	*n*-Pr	68 (10^{-5})	$C_{12}H_{13}IO_4$	41.40	3.76	36.46	41.36	3.85	36.7	330	1.5631
19	Me	*n*-Bu	39–42	$C_{13}H_{15}IO_4$	43.11	4.17	35.04	43.40	4.33	35.38		
20	Me	*n*-Amyl	37–43	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.79	4.76	33.12		
21	Me	C	49–57	$C_{13}H_{15}IO_5$	41.29	4.00	33.56	41.19	3.89	32.73		
22	Me	D	80–84 (5×10^{-5})	$C_{15}H_{19}IO_4$	44.35	4.71	31.24	44.70	4.47	30.79	205	1.5435
23	Me	E	93 (5×10^{-5})	$C_{13}H_{15}IO_5$	41.29	4.00	33.56	41.01	4.15	33.60	288	1.5574
24	Me	F	53 (10^{-5})	$C_{14}H_{17}IO_5$	42.87	4.37	32.36	43.11	4.37	31.89	217	1.5496
25	Me	G	143 (4×10^{-2})	$C_{15}H_{19}IO_4$	44.35	4.71	31.24	44.46	4.94	31.27	197	1.5429
26	Me	H	95 (5×10^{-5})	$C_{14}H_{17}IO_5$	42.87	4.37	32.36	42.72	4.06	32.24	318	1.5491
27	Me	I	88–95 (2×10^{-5})	$C_{15}H_{19}IO_8$	42.67	4.54	30.06	42.45	4.46	29.60	248	1.5451
28	Et	B	72–75	$C_{13}H_{15}IO_6$	41.29	4.00	33.56	41.16	3.70	33.40		
29	Et	C	48–49	$C_{14}H_{17}IO_5$	42.87	4.37	32.36	43.21	4.67	32.02		
30	Et	D	85–88 (1.2×10^{-5})	$C_{16}H_{21}IO_6$	45.73	5.04	30.20	45.83	4.87	29.75	93	1.5362
31	Et	E	58–60	$C_{14}H_{17}IO_6$	42.87	4.37	32.36	43.03	4.45	31.74		
32	Et	F	93 (1.5×10^{-4})	$C_{15}H_{19}IO_5$	44.35	4.71	31.24	44.41	4.71	30.67	142	1.5418
33	Et	G	96–98 (10^{-5})	$C_{16}H_{21}IO_5$	45.73	5.04	30.20	45.68	4.90	30.04	128	1.5362
34	Et	H	164 (4×10^{-2})	$C_{15}H_{19}IO_5$	44.35	4.71	31.24	44.19	4.73	31.41	215	1.5417
35	Et	I	80–89 (3×10^{-5})	$C_{16}H_{21}IO_6$	44.05	4.85	29.09	44.10	4.67	28.69	145	1.5377
36	*n*-Pr	*n*-Pr	84–88 (10^{-5})	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.56	4.73	33.5	151	1.5469
37	*i*-Pr	*i*-Pr	65–67	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.69	4.58	34.2		
38	*n*-Pr	C	42–44	$C_{15}H_{19}IO_5$	44.35	4.71	31.24	44.57	3.74	31.49		
39	*n*-Pr	D	100 (5×10^{-5})	$C_{17}H_{23}IO_5$	47.01	5.34	29.23	46.91	5.34	29.15	99	1.5326
40	*n*-Pr	E	43–44	$C_{15}H_{19}IO_5$	44.35	4.71	31.24	44.16	4.59	30.82		
41	*n*-Pr	F	82–85 (10^{-5})	$C_{16}H_{21}IO_5$	45.73	5.04	30.20	45.84	5.17	30.29	115	1.5367
42	*n*-Pr	G	90–95 (2×10^{-5})	$C_{17}H_{23}IO_5$	47.01	5.34	29.23	46.85	5.35	29.52	119	1.5312
43	*n*-Pr	H	142 (4×10^{-2})	$C_{16}H_{21}IO_5$	45.73	5.04	30.20	45.35	5.22	30.71	178	1.5375
44	*n*-Pr	I	100–108 (3×10^{-5})	$C_{17}H_{23}IO_6$	45.54	5.15	28.19	45.31	5.01	28.06	118	1.5331
45	*n*-Pr	K	142–144 (10^{-2})	$C_{18}H_{25}IO_8$	46.56	5.43	27.34	46.61	5.43	27.02	284	1.5250
46	*n*-Bu	*n*-Bu	90–95 (5×10^{-5})	$C_{16}H_{21}IO_4$	47.53	5.24	31.40	47.50	5.02	31.60	81	1.5374
47	*i*-Bu	*i*-Bu	41–44	$C_{16}H_{21}IO_4$	47.53	5.24	31.40	47.43	5.73	31.04		
48	*n*-Bu	A	78–81	$C_{14}H_{17}IO_5$	42.87	4.37	32.36	42.91	4.38	31.71		
49	*n*-Bu	B	40–45	$C_{15}H_{19}IO_5$	44.35	4.71	31.24	44.8	4.59	30.59		
50	*n*-Bu	C	98 (10^{-5})	$C_{16}H_{21}IO_5$	45.73	5.04	30.20	45.78	4.84	30.64	103	1.5376
51	*n*-Bu	D	112 (5×10^{-5})	$C_{18}H_{25}IO_5$	48.22	5.62	28.31	48.04	5.56	28.49	82	1.5291
52	*n*-Bu	E	115–120 (2×10^{-5})	$C_{16}H_{21}IO_5$	45.73	5.04	30.20	45.48	5.04	29.85	108	1.537
53	*n*-Bu	F	83–85 (10^{-4})	$C_{17}H_{23}IO_5$	47.01	5.34	29.23	47.03	5.20	29.51	95	1.53
54	*n*-Bu	G	96–100 (5×10^{-5})	$C_{18}H_{25}IO_5$	48.22	5.62	28.31	48.39	5.82	28.88	86	1.5
55	*n*-Bu	H	85–90 (7×10^{-5})	$C_{17}H_{23}IO_5$	47.01	5.34	29.23	46.94	5.40	29.02	133	1
56	*n*-Bu	I	90–95 (2×10^{-5})	$C_{18}H_{25}IO_6$	46.56	5.43	27.34	46.52	5.28	27.03	102	
57	*n*-Bu	J	175–180 (5×10^{-5})	$C_{29}H_{29}IO_8$	48.79	5.94	25.78	48.81	5.55	26.55	92	
58	*n*-Bu	K	158–161 (2×10^{-5})	$C_{19}H_{27}IO_8$	47.71	5.69	26.53	47.83	5.78	26.60	219	

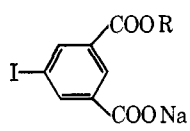
TABLE I (*Continued*)

Compd. no.	R_1[a]	R_2[a]	M.p.[b] or b.p. (mm.), °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % I	Found, % C	Found, % H	Found, % I	Viscosity, cs. at 25°	$n^{25}D$
59	*n*-Amyl	*n*-Amyl	95–100 (10^{-5})	$C_{18}H_{25}IO_4$	50.01	5.83	29.36	49.80	5.83	29.3	82	1.5305
60	*n*-Amyl	A	80–82	$C_{15}H_{19}IO_5$	44.35	4.71	31.24	44.37	4.81	30.93		
61	*n*-Amyl	C	94 (10^{-5})	$C_{17}H_{23}IO_5$	47.01	5.34	29.23	46.72	5.42	29.20	97	1.5331
62	*n*-Amyl	D	120 (2×10^{-5})	$C_{19}H_{27}IO_5$	49.36	5.89	27.45	49.24	5.81	27.36	83	1.5259
63	*n*-Amyl	F	125 (5×10^{-5})	$C_{18}H_{25}IO_5$	48.22	5.62	28.31	48.18	5.68	28.57	97	1.5302
64	*n*-Amyl	G	162–163 (10^{-2})	$C_{19}H_{27}IO_5$	49.36	5.89	27.45	49.51	5.70	27.19	101	1.5258
65	*n*-Amyl	H	98 (10^{-5})	$C_{18}H_{25}IO_5$	48.22	5.62	28.31	48.06	5.87	28.74	138	1.5298
66	*n*-Amyl	I	100–104 (3×10^{-5})	$C_{19}H_{27}IO_6$	47.71	5.69	26.53	47.98	5.62	26.50	98	1.5266
67	*n*-Amyl	J	171–175 (5×10^{-5})	$C_{21}H_{31}IO_6$	49.81	6.17	25.06	49.97	6.13	24.76	91	1.5201
68	*n*-Hexyl	*n*-Hexyl	33–36	$C_{20}H_{29}IO_4$	52.18	6.35	27.57	52.22	6.03	26.91		
69	B	B	67–69	$C_{14}H_{17}IO_6$	41.19	4.20	31.09	41.00	4.24	30.6		
70	B	D	104–108 (5×10^{-5})	$C_{17}H_{23}IO_6$	45.34	5.15	28.19	45.47	5.16	28.02	171	1.5363
71	C	C	46–49	$C_{16}H_{21}IO_6$	44.05	4.85	29.09	43.75	4.62	29.0		
72	C	D	88–92 (10^{-3})	$C_{18}H_{25}IO_6$	46.56	5.43	27.34	46.49	5.37	27.37	108	1.5295
73	C	I	167–170 (2×10^{-2})	$C_{18}H_{25}IO_7$	45.01	5.25	26.43	45.15	5.22	26.54	134	1.5308
74	D	D	120–122 (10^{-5})	$C_{20}H_{29}IO_6$	48.79	5.94	25.78	48.81	5.82	25.77	92	1.5218
75	D	F	95–100 (2×10^{-5})	$C_{19}H_{27}IO_6$	47.71	5.69	26.53	47.47	5.86	26.25	113	1.5258
76	D	G	105 (2×10^{-5})	$C_{20}H_{29}IO_6$	48.79	5.94	25.78	49.11	6.23	25.76	110	1.5231
77	D	H	185–187 (10^{-5})	$C_{19}H_{27}IO_6$	47.71	5.69	26.53	47.82	5.47	26.56	140	1.5257
78	D	K	150 (10^{-5})	$C_{21}H_{31}IO_7$	48.28	5.98	24.30	48.49	5.84	23.62	186	1.5158
79	F	F	118 (10^{-5})	$C_{18}H_{25}IO_6$	46.56	5.43	27.34	46.76	5.74	26.57	131	1.5283
80	H	H	100 (2×10^{-4})	$C_{18}H_{25}IO_6$	46.56	5.43	27.34	46.41	5.14	27.54	221	1.5290
81	H	I	42–43	$C_{19}H_{27}IO_7$	46.16	5.51	25.65	46.50	5.93	25.74		
82	I	I	204–208 (6×10^{-2})	$C_{20}H_{29}IO_8$	45.81	5.57	24.21	45.79	5.63	24.57	151	1.5232
83	I	J	183 (2×10^{-2})	$C_{22}H_{33}IO_8$	47.83	6.02	22.98	47.72	5.91	23.11	124	1.5193
84	I	K	184–186 (2×10^{-2})	$C_{21}H_{31}IO_8$	46.85	5.80	23.57	46.86	5.85	23.75	221	1.5174
85	J	J	213 (10^{-5})	$C_{24}H_{37}IO_8$	49.66	6.43	21.87	49.44	6.16	22.08	113	1.5133
86	K	K	191–195 (3×10^{-3})	$C_{22}H_{33}IO_8$	47.83	6.02	22.98	47.61	6.15	23.24	435	1.5136
			Iodoterephthalates									
87	*n*-Pr	*n*-Pr	80–85 (10^{-5})	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.85	4.58	33.5	32	1.5498
88	*n*-Bu	*n*-Bu	70–80 (5×10^{-5})	$C_{16}H_{21}IO_4$	47.53	5.24	31.40	47.65	5.36	31.2	30	1.5400
89	C	C	42–44	$C_{16}H_{21}IO_6$	44.05	4.85	29.09	44.05	4.90	28.70		
90	D	D	165–177 (2×10^{-2})	$C_{20}H_{29}IO_6$	48.79	5.94	25.78	48.83	5.86	25.26	56	1.5238

[a] A = 2-hydroxyethyl, B = 2-methoxyethyl, C = 2-ethoxyethyl, D = 2-butoxyethyl, E = 3-methoxypropyl, F = 3-ethoxypropyl, G = 3-propoxypropyl, H = 3-methoxybutyl, I = 2-(2-ethoxyethoxy)ethyl, J = 2-(2-butoxyethoxy)ethyl, and K = 1,3-diethoxy-2-propyl. [b] Melting points (corrected) were taken in a Hershberg-type apparatus.

TABLE II

SODIUM 5-IODOISOPHTHALATE HALF ESTERS



R^a	Formula	Calcd., % I	Calcd., % Na	Found, % I	Found, % Na	M.p., °C.[b]
Me	$C_9H_6INaO_4$	38.68	7.09	38.6	6.86	211.4–222.6
Et	$C_{10}H_8INaO_4$	37.09	6.72	36.65	6.66	238–243
n-Pr	$C_{11}H_{10}INaO_4$	35.65	6.46	35.76	6.41	245 indef.
n-Bu	$C_{12}H_{12}INaO_4$	34.30	6.22	33.83	6.18	244–245
n-Amyl	$C_{13}H_{14}INaO_4$	33.04	6.00	32.85	5.86	239–243
D	$C_{14}H_{16}INaO_5$	30.64	5.55	30.95	5.61	143 indef.
I	$C_{14}H_{16}INaO_6$	c		c		130–140

[a] D = 2-butoxyethyl; I = 2-(2-ethoxyethoxy)ethyl. [b] All melting points are corrected and were taken in a Hershberg-type apparatus. [c] An analytical sample was not prepared.

Bis Esters of 3-Iodophthalic Acid. Bis(2-ethoxyethyl) 3-Iodophthalate (10).—A mixture of 125 g. (0.43 mole) of 3-iodophthalic acid, 84.8 g. (0.94 mole) of 2-ethoxyethanol, 5 ml. of concentrated H_2SO_4, and 300 ml. of dry benzene was refluxed for 70 hr. with a water-separatory tube. A total of 18 ml. of water s obtained. The reaction mixture was cooled in an ice bath, 250 ml. of ether was added The mixture was extracted with l. portions of 0.67 *N* NaOH until the addition of dilute the basic extracts did not give a precipitate. The organic s washed twice with water, once with 1% $KMnO_4$ solution, twice more with water, and twice with saturated NaCl. The organic layer was treated with Darco G60 and Drierite, filtered, and evaporated under reduced pressure. The residue, 142 g. of oil, was distilled to give 71.7 g. (38%) of colorless liquid, b.p. 122° (10^{-5} mm.).

The other bis esters of 3-iodophthalic acid were prepared in a similar manner and by the procedure described for dibutyl 5-iodoisophthalate (**46**).

Mixed Esters of 3-Iodophthalic Acid.—The mixed esters of 3-iodophthalic acid were prepared from the alkyl tosylates or halides and sodium 3-iodo-2-methoxycarbonylbenzoate or sodium 2-butoxycarbonyl-3-iodobenzoate by a process similar to that described for the preparation of butyl 3-methoxybutyl 5-iodoisophthalate (**55**).

Bis Esters of 4-Iodophthalic Acid.—The bis esters of 4-iodophthalic acid were prepared by procedures similar to those described for the preparation of the bis esters of 3-iodophthalic acid and 5-iodoisophthalic acid.

Bis Esters of 5-Iodoisophthalic Acid. Dibutyl 5-Iodoisophthalate (46).—A mixture of 292 g. (1.0 mole) of 5-iodoisophthalic acid in 500 ml. of 1-butanol was heated on a steam bath with stirring, and a slow stream of HCl was passed into the mixture. A solution resulted after about 4 hr. The heat was removed, and HCl was passed in for another hour. The cooled, two-layer reaction mixture was stirred with 25 g. of Drierite for 0.5 hr. and left overnight. The mixture was filtered, and the butanol was removed under reduced pressure. The residue was taken up in ether, washed with 2% NaOH solution until the washings were alkaline, with water until the washings were neutral, and with saturated NaCl, and treated with Drierite. The mixture was filtered and, the ether was removed under reduced pressure. The residue, 355 g. (88%) of light amber oil, $n^{25}D$ 1.5375, was distilled to give a colorless oil, b.p. 115–120° (2×10^{-5} mm.), $n^{25}D$ 1.5377.

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ison, *Org. Reactions*, **5**, 79 (1949).

The other bis esters of 5-iodoisophthalic acid were prepared by a similar procedure and that described for the preparation of bis(2-ethoxyethyl) 3-iodophthalate (**10**).

Mixed Esters of 5-Iodoisophthalic Acid. Butyl 3-Methoxybutyl 5-Iodoisophthalate.—A mixture of 420 g. (1.14 moles) of sodium butyl 5-iodoisophthalate and 323 g. (1.25 moles) of 3-methoxybutyl *p*-toluenesulfonate in 500 ml. of dimethylformamide was heated on a steam bath with stirring. In about 0.5 hr. sodium *p*-toluenesulfonate started to separate. After the mixture was heated for 20 hr., it was concentrated under reduced pressure and the residue was treated with hexane. The salt was removed by filtration and washed with hexane. The combined hexane solutions (about 3 l.) were washed with 2% NaOH solution, water, dilute $KMnO_4$ solution, water, and saturated NaCl. The hexane solution was treated with Drierite, decanted from the Drierite, stirred with Darco G60 and Drierite for 1 hr., and filtered. The hexane was removed under reduced pressure: yield 463 g. (94%) of light amber oil, $n^{25}D$ 1.5327. Distillation gave a colorless oil, $n^{25}D$ 1.5328.

Most of the other mixed esters of 5-iodoisophthalic acid were prepared by a similar procedure from the sodium 5-iodoisophthalate half esters (Table II) and alkyl (or alkoxyalkyl) tosylates, halides, or sulfates.

Butyl 2-Ethoxyethyl 5-Iodoisophthalate.—The acid chloride was prepared from sodium butyl 5-iodoisophthalate by refluxing a mixture of 163.8 g. (0.44 mole) of the sodium salt and 52.8 g. (0.44 mole) of thionyl chloride in 1 l. of CCl_4 for about 16 hr. The NaCl was removed by filtration and the CCl_4 was removed at reduced pressure. The solid residue, 162.8 g., m.p. 50–55°, of 5-iodo-3-butoxycarbonylbenzoyl chloride was heated for 5 hr. with excess 2-ethoxyethanol. The excess alcohol was removed under reduced pressure and the product was isolated by a procedure similar to that described for bis(2-ethoxyethyl) 3-iodophthalate (**10**).

Butyl 2-methoxyethyl 5-iodoisophthalate was also prepared from the butyl acid chloride.

Diesters of Iodoterephthalic Acid.—The diesters of iodoterephthalic acid were prepared in a manner similar to that described for bis(2-ethoxyethyl) 3-iodophthalate (**10**).

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Book Reviews

Two Books on the History of Drugs and Experimental Therapeutics: **A. Readings in Pharmacology.** Edited by B. HOLMSTEDT and J. LILJESTRAND. The Macmillan Company, New York, N. Y. 1963. x + 395 pp. 23.5 × 16 cm. $7.50. **B. Pharmacy in History.** By J. E. TREASE. Baillière, Tindall and Cox, London. 1964. vii + 265 pp. 24 × 16 cm. $3.25.

These two quite unlike books have the same general purpose: to lead us back to the important discoveries in medicinal science so that we may get in the mood for new ventures by learning from the insight, experiments, and failures of our predecessors. The volume by Trease devotes 25 pages to the ancient history of pharmacy from Galen to early alchemy; the rest of the book (230 pages) offers a chronological review of the development of British pharmacy and is thus quite narrow in scope and in providing inspiration.

It is different in the volume of the Swedish authors. Starting with the "*Ebers papyrus*" (Egypt, 1550 B. C.), which reads astonishingly like some of our compounded prescriptions, we are led from antiquity to the rise of experimental pharmacology after Withering. An impressive list of the classical founders of pharmacology follows, arranged according to their fields of specialization. A biography is given for each of them, some background material for the state of a field of medical science at the time of their revolutionary discovery, and then the direct quotation from the paper which reported the decisive experiments and their interpretation. Most of us have read the results of these experiments in textbooks, often reinterpreted in the light of later findings. But how many of us have had the thrill of reading the original paper which heralded a completely new era of medicinal science, especially if the paper were published long before we started to read journals? By isolating the pertinent sections of these articles, a few of them in their original language, the editors have provided for their readers the sharing of the excitement that the first readers of those papers must have experienced. Indeed, in at least one photographic illustration this excitement has been transmitted to us pictorially: the snapshot shows Otto Loewi demonstrating the humoral stimulation of a perfused heart in 1926 and behind him appears the face of a man with such an expression of incredulity and joy that his wonder is communicated to us. Page after page brings us the renewed awe at the first great step forward in a previously ununderstandable situation. Not all the men thus quoted belong to a long-ago past. A considerable number of active members of the Division of Medicinal Chemistry of the American Chemical Society have joined the ranks of the outstanding pharmacologists whose works have become classic, and whose papers have been included in this volume. Many pharmacologists from other countries whose lectures have graced recent American Chemical Society meetings are also to be found.

"Readings in Pharmacology" is a book for enjoyment on a quiet evening. It will rekindle the enthusiasm which we all felt as students, and help us to relive many of the great moments of our field of work and avocation.

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Advances in Pharmacology. Volume 3. Edited by SILVIO GARATTINI and PARKHURST A. SHORE. Academic Press Inc., New York, N. Y. 1964. viii + 341 pp. 16 × 23 cm.

This volume contains the following six chapters: Experimental Approaches to the Development of Antianginal Drugs by M. M. Winbury, Pharmacological Aspects of Parkinsonism by A. H. Friedman and G. M. Everett, The Pharmacology and Biochemistry of Parasitic Helminths by T. E. Mansour, The Adrenergic System and Sympathomimetic Amines by E. Marley, Pharmacological Aspects of Drug Dependence by G. A. Deneau and M. H. Seevers, and Drugs Used in Control of Reproduction by G. Pincus and G. Bialy. Written by these experimental biologists many of whom are located in medical schools or medical research institutes, the approach to all of the topics is first an exploration of basic conditions in the tissues and organisms under discussion, of theories, and a review of working hypotheses of the authors and of those found in the literature. Even the subsequent sections which deal with therapeutic aspects of the respective agents are treated essentially from a fundamental pharmacologic point of view. Thus, virtually every page is thought provoking and not just descriptive. The editors have done an excellent job holding the discussion uniformly on a very high level.

This volume is recommended to biochemists, pharmacologists, and clinicians with a deep interest in medical science. Several of the topics have barely ever been presented in a more concise and critical way.

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