acetone, and dried *in vacuo* at 78°. The spectral data are shown in Table II. The yield was 25 mg. of yellow powder that showed a correct analysis for a hemihydrate.

Anal. Calcd. for $C_{19}H_{16}FN_7O_6 \cdot 0.5H_2O$: C, 48.72; H, 4.09; N, 20 93. Found: C, 49.16; H, 4.38; N, 20.71.

Acknowledgment.—The authors are indebted to Dr. W. J. Barrett and members of the Analytical Section of Southern Research Institute for the spectral and microanalytical determination reported herein.

The Synthesis of Some Benzimidazole and Oxygen Analogs of Ethyl Pteroylglutamate

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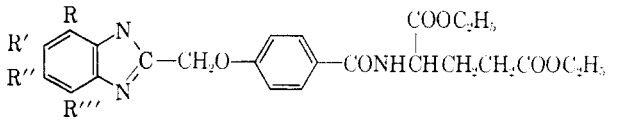
Received February 1, 1965

A series of diethyl N-(2-benzimidazolylmethoxy)benzoylglutamates (Table I) was prepared according to Scheme I.

TABLE I

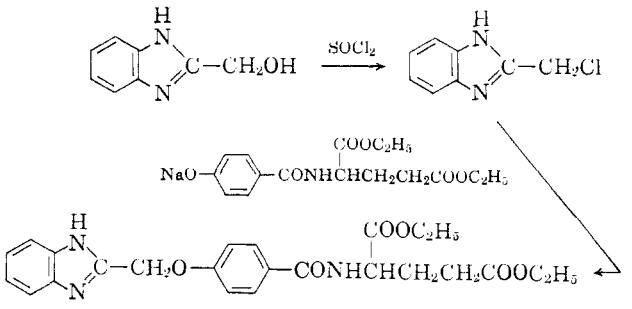
DIETHYL N-(*p*-BENZIMIDAZOLYLMETHOXY)BENZOYLGLUTAMATES



No.	R	R′	R″	R‴	Yield, %	M.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
XXII	H	H	H	H	13	156–157[a]	$C_{24}H_{27}N_3O_6$	63.56	6.00	9.27	63.68	5.89	9.03
XXIII	OCH_3	H	H	OCH_3	11	147.5–148[b]	$C_{26}H_{31}N_3O_8$	60.81	6.09	8.18	60.72	5.97	8.11
XXIV	H	OCH_3	OCH_3	H	11	80–83[c]	$C_{26}H_{31}N_3O_8$	60.81	6.09	8.18	60.52	5.83	8.27
XXV	H	H	OCH_3	H	27	118–120[c]	$C_{25}H_{29}N_3O_7$	62.10	6.04	8.69	61.94	6.27	8.52
XXVI	H	H	CH_3	H	20	126–129[c]	$C_{25}H_{29}N_3O_6$	64.22	6.25	8.99	64.35	6.38	8.76
XXVII	H	CH_3	CH_3	H	11	150.5–151[c]	$C_{26}H_{31}N_3O_6$	64.85	6.49	8.73	64.98	6.69	8.59
XXVIII	H	H	NH_2	H	9	106–115[c]	$C_{24}H_{28}N_4O_6$	61.53	6.02	11.96	61.41	6.13	11.91

[a] Recrystallized from benzene. [b] Recrystallized from ethanol. [c] Recrystallized from ethyl acetate.

SCHEME I



Experimental

All melting points were determined with a Thomas–Hoover melting point apparatus.

2-Hydroxymethylbenzimidazoles were prepared from the corresponding *o*-phenylenediamines and glycolic acid by the procedure described by Phillips.[1] Two of these are new compounds.

2-Hydroxymethyl-4-amino-6-nitrobenzimidazole was isolated in 63% yield, m.p. 256–257° dec.

Anal. Calcd. for $C_8H_8N_4O_3$: C, 46.15; H, 3.87; N, 26.92. Found: C, 46.33; H, 3.95; N, 26.92.

2-Hydroxymethyl-5(6)-aminobenzimidazole Dihydrochloride.—2-Hydroxymethyl-5(6)-nitrobenzimidazole was hydrogenated over platinum in ethanol solution. After removing the catalyst, the dihydrochloride was precipitated by the addition of concentrated HCl and ether. It was recrystallized from methanol–ether; yield 45%, m.p. >350°.

Anal. Calcd. for $C_8H_{11}Cl_2N_3O$: C, 40.69; H, 4.70; N, 17.80. Found: C, 40.70; H, 4.69; N, 17.77.

2-Chlorobenzimidazoles.—The 2-chloromethylbenzimidazoles were prepared from the corresponding 2-hydroxymethylbenzimidazoles by heating with $SOCl_2$ in $CHCl_3$ solution. The addition of ether to the cooled mixture completed the precipitation of the 2-chloromethylbenzimidazole hydrochlorides. In some cases a pure product resulted and recrystallization was not necessary. In a few cases the hydrochlorides were recrystallized from ethyl alcohol.

Condensation of 2-Chloromethylbenzimidazoles with Diethyl *p*-Hydroxybenzoylglutamate. General Method.—Sodium (2 equiv.) was dissolved in dry ethanol. Diethyl *p*-hydroxybenzoylglutamate[2] (1 equiv.) in ethanol was added and then 1 equiv. of solid 2-chloromethylbenzimidazole hydrochloride was slowly added with stirring. The mixture was stirred for 2 hr. at room temperature and then refluxed for 1–4 hr. Quantitative yields of NaCl were obtained by cooling the reaction mixture. In some cases the addition of water to the filtrate gave an oil which solidified on cooling. The products were recrystallized from ethanol or ethyl acetate. A more general procedure was to evaporate the filtrate to an oil. The oil was then treated with ethanol and again evaporated. This was then repeated with dry benzene. Usually this azeotropic removal of volatile impurities caused the oil to solidify. 2-Chloromethyl-5(6)-aminobenzimidazole was used as its dihydrochloride. In this case 3 equiv. of sodium was used. The reflux time was shortened in those cases where the reaction mixture darkened too rapidly. Actually the reactions proceed at room temperature and go to completion if given enough time. The yields of the condensation products were low. It is well known that 2-chloromethylbenzimidazoles undergo self-condensation to form condensation polymers. We believe that this is the cause of the poor yields of desired products.

(1) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

(2) E. I. Fairburn, B. J. Magerlein, L. Stubberfield, and D. I. Weishlat, *J. Am. Chem. Soc.*, **76**, 676 (1954).

Myelographic Agents. I. Iodobenzoates

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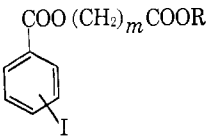
Received April 19, 1965

As part of our search for improved X-ray contrast agents we have synthesized a series of iodinated esters (Table I). These esters are oils or low-melting solids containing aromatic iodine and consequently are suitable for myelography.[1] In liquid form the esters have been injected cisternally into cats and dogs and have been found to permit visualization of details of the spinal

(1) For a review, see J. O. Hoppe in "Medicinal Chemistry," Vol. 6, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 290.

TABLE I

IODOBENZOATES



No.	I position	m	R	B.p. (mm.) or m.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % I	Found, % C	Found, % H	Found, % I	$n^{25}D$
1	*p*	1	C_2H_5	55.4–56.4	$C_{11}H_{11}IO_4$	39.54	3.32	37.99	39.63	3.35	37.61	
2	*p*	1	*n*-C_4H_9	126 (0.007)	$C_{13}H_{15}IO_4$	43.11	4.17	35.04	43.38	4.20	34.45	1.5520
3	*p*	*a*	*n*-C_3H_7	95 (0.007)	$C_{13}H_{15}IO_4$	43.11	4.17	35.04	43.13	4.09	35.33	1.5468
4	*o*	2	CH_3	38.6–39.4	$C_{11}H_{11}IO_4$	39.54	3.32	37.99	39.49	3.30	37.22	
5	*o*	2	C_2H_5	122 (0.03)	$C_{12}H_{13}IO_4$	41.40	3.76	36.46	41.34	3.73	36.58	1.5556
6	*o*	2	*n*-C_3H_7	124 (0.04)	$C_{13}H_{15}IO_4$	43.11	4.17	35.04	43.06	4.15	34.64	1.5478
7	*m*	2	*n*-C_3H_7	129 (0.04)	$C_{13}H_{15}IO_4$	43.11	4.17	35.04	43.25	4.05	35.00	1.5443
8	*m*[b]	2	*n*-C_3H_7	143 (0.01)	$C_{14}H_{17}IO_5$	42.87	4.37	32.36	43.08	4.19	33.00	1.5575
9	*p*	2	C_2H_5	113 (0.007)	$C_{12}H_{13}IO_4$	41.40	3.76	36.46	41.29	3.52	36.56	1.5582
10	*p*	2	*n*-C_3H_7	123 (0.02)	$C_{13}H_{15}IO_4$	43.11	4.17	35.04	43.14	4.17	34.27	1.5512
11	*p*	2	*n*-C_4H_9	137 (0.08)	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.78	4.51	34.43	1.5452
12	*p*	2	$C_2H_5OCH_2CH_2$	144 (0.03)	$C_{14}H_{17}IO_5$	42.87	4.37	32.36	43.17	4.20	31.98	1.5461
13	*p*	2	$CH_3CH(OCH_3)CH_2CH_2$	144 (0.02)	$C_{15}H_{19}IO_5$	44.35	4.71	31.24	44.58	4.58	30.94	1.5402
14	*p*	3	CH_3	43.6–45.8	$C_{12}H_{13}IO_4$	41.40	3.76	36.46	41.52	3.63	36.70	
15	*p*	3	C_2H_5	127 (0.02)	$C_{13}H_{15}IO_4$	43.11	4.17	35.04	43.40	4.06	34.77	1.5547
16	*p*	3	*n*-C_3H_7	38.8–42.0	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.49	4.47	34.50	1.5475
17	*o*	3	*n*-C_4H_9	145 (0.04)	$C_{15}H_{19}IO_4$	46.17	4.91	32.52	45.92	4.83	32.86	1.5401
18	*m*	3	*n*-C_3H_7	124 (0.01)	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.44	4.39	34.06	1.5430
19	*m*	3	*n*-C_4H_9	142 (0.03)	$C_{15}H_{19}IO_4$	46.17	4.91	32.52	46.41	4.94	32.79	1.5389
20	*m*[b]	3	*n*-C_4H_9	46.2–46.8	$C_{16}H_{21}IO_5$	45.73	5.04	30.20	45.56	5.26	30.13	
21	*p*	3	*n*-C_4H_9	143 (0.03)	$C_{15}H_{19}IO_4$	46.17	4.91	32.52	45.90	4.77	33.11	1.5427
22	*p*	3	$CH_2{=}CHCH_2$	137 (0.02)	$C_{14}H_{15}IO_4$	44.94	4.04	33.92	45.17	4.21	34.42	1.5597
23	*p*	3	$CH_3CH(CH_3)CH_2CH_2$	150 (0.03)	$C_{16}H_{21}IO_4$	47.53	5.24	31.40	47.68	5.08	31.72	1.5379
24	*p*	3	*c*	148 (0.01)	$C_{16}H_{19}IO_5$	45.95	4.58	30.35	45.87	4.44	30.29	1.5591
25	*p*	3	$CH_3OCH_2CH_2$	144 (0.009)	$C_{14}H_{17}IO_4$	42.87	4.37	32.36	42.69	4.24	32.52	1.5509
26	*p*	3	$C_2H_5OCH_2CH_2$	143 (0.009)	$C_{15}H_{19}IO_5$	44.35	4.71	31.24	44.07	4.46	31.51	1.5450
27	*p*	3	*n*-$C_4H_9OCH_2CH_2$	160 (0.01)	$C_{17}H_{23}IO_5$	47.01	5.34	29.23	47.17	5.58	29.36	1.5338
28	*p*	3	$CH_3SCH_2CH_2$	172 (0.03)	$C_{14}H_{17}IO_4S$	41.18	4.20	31.08	40.91	3.90	31.49	1.5758
29	*p*	4	*n*-C_4H_9	156 (0.01)	$C_{16}H_{21}IO_4$	47.53	5.24	31.40	47.51	4.94	32.09	1.5387
30	*p*	5	*n*-C_3H_7	169 (0.05)	$C_{16}H_{21}IO_4$	47.53	5.24	31.40	47.60	5.28	31.72	1.5386

[a] $(CH_2)_m$ = $-CH(CH_3)-$. [b] There is a 4-OCH_3 group. [c] Tetrahydrofurfuryl.

TABLE II

SOME HALOBUTYRATES

$X(CH_2)_3COOR$

X	R	B.p., °C. (mm.)	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H	$n^{25}D$
Br	*n*-Bu	133 (25)	$C_8H_{15}BrO_2$	43.07	6.78	43.27	6.51	1.4539
Br	$CH_3CH(CH_3)CH_2CH_2$	127 (14)	$C_9H_{17}BrO_2$	45.57	7.22	45.45	7.17	1.4552
Cl	$CH_3(CH_2)_3OCH_2CH_2$	166 (27)	$C_{10}H_{19}ClO_3$	53.93	8.60	53.92	8.70	1.4411
Cl	$CH_3SCH_2CH_2$	155 (27)	$C_7H_{13}ClO_2S$[a]	42.74	6.66	43.02	6.58	1.4858

[a] *Anal.* Calcd.: S, 16.30. Found: S, 16.51.

cord structure and to be eliminated from the animals in periods ranging from a few weeks to a few months.

The method of synthesis involved reaction of either a sodium iodobenzoate (method A) or an iodobenzoyl chloride (method B) with a suitably substituted aliphatic carboxylic ester. Method A was used for the acetates, butyrates, valerates, and hexanoates. Method B was used for the propionates where the use of method A led to extensive tar formation.

Experimental[2]

Iodobenzoyl Chlorides and Sodium Iodobenzoates.—Literature directions were used for the preparation of *o*-,[3] *m*-,[4] and *p*-iodobenzoyl chloride.[5] The sodium iodobenzoates are known compounds and were prepared from commercially available iodobenzoic acids by treatment with aqueous NaOH and removal of the water under reduced pressure. 3-Iodo-4-methoxybenzoyl chloride was prepared as described previously.[6]

Esters of Hydracrylic Acid.—Four of the esters of hydracylic acid used in the present work have been described by Gresham, *et al.*[7]: methyl hydracrylate, ethyl hydracrylate, *n*-propyl hydracrylate, and *n*-butyl hydracrylate. Gresham's procedure was used to prepare 2-ethoxyethyl hydracrylate, b.p. 66–67° (0.05 mm.), $n^{25}D$ 1.4348, and 3-methoxybutyl hydracrylate, b.p. 78–80° (0.05 mm.), $n^{25}D$ 1.4361, from β-propiolactone and the alcohol. The last two compounds were used as intermediates without further characterization.

Halobutyrates.—Some of these esters are shown in Table II. The chlorobutyrates of Table II were obtained from 4-chlorobutyric acid (Aldrich Chemical Co.) and the alcohol in the presence of *p*-toluenesulfonic acid monohydrate. Allyl 4-chloro-

(2) Melting points were taken in a modified Hershberg apparatus and are corrected.

(3) L. C. Raiford and H. P. Lankelma, *J. Am. Chem. Soc.*, **47**, 1121 (1925).

(4) J. B. Cohen and H. S. Raper, *J. Chem. Soc.*, **85**, 1273 (1904).

(5) H. Meyer, *Monatsh. Chem.*, **22**, 780 (1901).

(6) S. Archer, U. S. Patent 2,572,828 (1951).

(7) T. L. Gresham, J. E. Jansen, F. W. Shaver, J. T. Gregory, and W. L. Beears, *J. Am. Chem. Soc.*, **70**, 1005 (1948).

butyrate, b.p. 97° (16 mm.), $n^{25}D$ 1.4465, was obtained by the same procedure and used without further characterization. The procedure of Linstead and Meade[8] was used to prepare propyl 4-bromobutyrate, b.p. 106° (13 mm.), $n^{25}D$ 1.4536, from γ-butyrolactone and the alcohol in the presence of HBr. This procedure also was used to prepare the bromobutyrates of Table II and the following new 4-bromobutyrates: tetrahydrofurfuryl 4-bromobutyrate, b.p. 79° (0.04 mm.), $n^{25}D$ 1.4820; 2-methoxyethyl 4-bromobutyrate, b.p. 129–132° (12 mm.), $n^{25}D$ 1.4608; 2-ethoxyethyl 4-bromobutyrate, b.p. 136–138° (12 mm.), $n^{25}D$ 1.4598.

Haloalkanoates.—Ethyl chloroacetate and butyl chloroacetate were distilled before use. Propyl 2-bromopropionate was prepared as previously reported.[9] Butyl 5-bromovalerate, b.p. 134° (15 mm.), $n^{25}D$ 1.4565, was prepared from 5-bromovaleronitrile (Aldrich Chemical Co.) and butanol in the presence of concentrated H_2SO_4 by the procedure of Adams and Thal.[10] Propyl 6-bromohexanoate, b.p. 143° (17 mm.), $n^{25}D$ 1.4525, was prepared from 6-bromohexanonitrile (Aldrich Chemical Co.) by the procedure used for butyl 5-bromovalerate.

Method A. Butyl 4-(*p*-Iodobenzoyloxy)butyrate (21).—Dimethylformamide (400 ml.) which had been dried over silica gel was placed in a flask and heated to 110°. With vigorous stirring 49.5 g. (0.183 mole) of finely powdered sodium *p*-iodobenzoate was added rapidly. In one portion 40.2 g. (0.180 mole) of butyl 4-bromobutyrate was added to the resulting suspension. Stirring and heating at 105–115° were continued for 24 hr. The cooled mixture was poured into ice water and the aqueous layer was decanted from the yellow, oily precipitate and extracted several times with hexane. The combined oil and hexane extracts were washed successively with cold water, cold 5% K_2CO_3, cold 2% HCl, 10% $NaHSO_3$, 2% $NaHCO_3$, water, and saturated NaCl. After drying over Drierite and treatment with decolorizing charcoal, the solvent was removed at reduced pressure to give 62.1 g. of yellow oil. Distillation gave 50.3 g. (71%) of product (**21**), b.p. 140–144° (0.04 mm.). An aliquot of the distillate was fractionally distilled to furnish an analytical sample.

Method B. Propyl 3-(*p*-Iodobenzoyloxy)propionate (10).—A solution of 174.0 g. (0.652 mole) of *p*-iodobenzoyl chloride in 1 l. of benzene was prepared. A solution of 86.9 g. (0.658 mole) of propyl hydracrylate and 90.5 ml. (0.75 mole) of triethylamine in 50 ml. of benzene was added dropwise over 10 min. to the stirred solution. An exothermic reaction occurred and the reaction mixture grew cloudy. Refluxing with stirring was continued for 40 hr. After cooling, the white precipitate was filtered off and washed with a little benzene. The combined benzene solutions were extracted with cold water and cold 5% K_2CO_3 solution until the acidified aqueous wash showed no white precipitate. The benzene solution was further washed once with cold 2% HCl and several times with water, dried (Na_2SO_4), treated with decolorizing charcoal, and concentrated at reduced pressure to give 207 g. of pale yellow oil. Distillation gave 177 g. (75%) of product (**10**), b.p. 87° (2×10^{-5} mm.). An aliquot of the distillate was fractionally distilled to furnish an analytical sample.

(8) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 943 (1934).

(9) M. S. Newman and F. J. Evans, Jr., *J. Am. Chem. Soc.*, **77**, 946 (1955).

(10) R. Adams and A. F. Thal, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 270.

TABLE I
ETHYL *p*-NITROPHENYL ALKYLPHOSPHONATES
$R_1R_2CHP(O)(OC_6H_4)OC_6H_4NO_2$-*p*

R_1	R_2	Yield, %	Purification[a]	$n^{25}D$	Formula	Carbon, %, Calcd.	Carbon, %, Found	Hydrogen, %, Calcd.	Hydrogen, %, Found	Nitrogen, %, Calcd.	Nitrogen, %, Found	Phosphorus, %, Calcd.	Phosphorus, %, Found
n-Propyl	Acetoxy	63	Xylene	1.5059	$C_{14}H_{20}NO_7P$	48.7	48.6	5.8	5.9	4.1	3.6	9.0	8.6
n-Butyl	Acetoxy	87	Xylene	1.5016	$C_{15}H_{22}NO_7P$	50.1	50.3	6.2	6.1	3.9	4.2	8.6	8.6
n-Pentyl	Acetoxy	56	DMF	1.4954	$C_{16}H_{24}NO_7P$	51.3	51.7	6.5	6.8	3.8	3.8	8.3	8.2
n-Hexyl	Acetoxy	63	DMF	1.4997	$C_{17}H_{26}NO_7P$	52.8	52.6	6.8	6.5	3.6	3.3	8.0	8.1
n-Heptyl	Acetoxy	51	DMF	1.4976	$C_{18}H_{28}NO_7P$	53.9	53.9	7.0	7.2	3.5	3.3	7.7	7.9
Phenyl	Acetoxy	13	Ethanol	73–74[b]	$C_{17}H_{18}NO_7P$	53.8	54.7	4.8	5.1	3.7	3.7	8.2	8.4
Benzyl	Acetoxy	13	Aniline	1.5438	$C_{18}H_{20}NO_7P$	55.0	55.1	5.1	5.0	3.6	3.5	7.9	7.6
Phenethyl	Acetoxy	48	Dimethyl sulfoxide	1.5391	$C_{19}H_{22}NO_7P$	56.0	56.3	5.4	5.7	3.4	3.4	7.6	7.4
Chloromethyl	H	10	Ether	55–56[b]	$C_{10}H_{13}ClNO_5P$	40.9	41.0	4.5	4.5	4.8	4.9	10.6	10.4
1-Naphthyl	H	13	Aniline	1.6090	$C_{19}H_{18}NO_5P$	61.5	60.2	4.9	5.1	3.8	3.8	8.3	7.9
2-Naphthyl	H	12	Ethyl benzoate	1.6090	$C_{19}H_{18}NO_5P$	61.5	61.4	4.9	4.9	3.8	3.5	8.3	8.6

[a] Falling-film molecular still. [b] Melting point, °C.

The Synthesis of Ethyl *p*-Nitrophenyl α-Acetoxyalkylphosphonates

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Received April 20, 1965

A series of ethyl *p*-nitrophenyl α-acetoxyalkylphosphonates were synthesized in order to ascertain their inhibitory action on various enzymes such as acetylcholine esterase, trypsin, and