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

$R_1R_2CHP(O)(OC_2H_5)OC_6H_4NO_2$-*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	$C_{16}H_{24}NO_7P$	51.5	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	56.5	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

L. S. HAFNER, J. E. BROWN, M. V. GARRISON, AND B. H. ALEXANDER

Department of Immunochemistry, Walter Reed Army Institute of Research, Washington, D. C.

Received April 9, 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

TABLE II
DIETHYL AND MONOETHYL ALKYLPHOSPHONIC ACID ESTERS
$R_2OCHR_1P(O)(OR_3)(OC_2H_5)$

R_1	R_2	R_3	Yield, %	Purification	$n^{25}D$	Formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	Phosphorus, % Calcd.	Found
Propyl	Acetyl	H	58	DMF[a]	1.4406	$C_8H_{17}O_5P$	42.8	42.4	7.6	7.4	13.8	14.0
Butyl	Acetyl	Ethyl	75	83–85 (0.1)	1.4267	$C_{11}H_{23}O_5P$	49.6	49.3	8.7	8.9	11.6	11.2
Pentyl	Acetyl	Ethyl	39	97–100 (0.3)	1.4290	$C_{12}H_{25}O_5P$	51.4	51.1	9.0	8.9	11.1	11.2
Hexyl	Acetyl	Ethyl	71	124 (0.3)	1.4346	$C_{13}H_{27}O_5P$	53.1	53.0	9.2	9.7	10.5	10.5
Heptyl	Acetyl	Ethyl	24	115–117 (0.5)	1.4365	$C_{14}H_{29}O_5P$	54.5	54.2	9.5	9.6	10.1	9.9
Benzyl	Acetyl	Ethyl	27	118–120 (0.3)	1.4891	$C_{14}H_{21}O_5P$	56.0	56.4	7.1	7.2	10.3	10.3
Phenethyl	Acetyl	Ethyl	34	144–148 (0.25)	1.4830	$C_{15}H_{23}O_5P$	57.3	57.3	7.4	8.3	9.9	9.5
Propyl	Tosyl	Ethyl	39	Toluene[a]	1.4929	$C_{15}H_{25}O_6PS$[b]	49.5	50.2	6.9	7.5	8.5	8.5
Phenyl	Benzoyl	Ethyl	49	Xylene[a]	1.5377	$C_{18}H_{21}O_5P$	62.1	62.5	6.1	6.1	8.9	8.6

[a] Falling-film molecular still. [b] *Anal.* Calcd.: S, 8.79. Found: S, 8.62.

chymotrypsin. The synthetic routes to these compounds involve extensions to reactions previously reported.[1]

Table I reports physical constants on these compounds, and Table II describes intermediates used in their preparation.

Experimental

Diethyl α-hydroxyalkylphosphonates were prepared *via* the reaction of diethyl hydrogen phosphite with aldehydes according to the method of Kharasch.[2] The crude reaction mixtures obtained could be acetylated directly; however, better yields of the acetates were obtained if the α-hydroxy compounds were distilled. In most preparations decomposition occurred when the usual distillations were carried out. Consequently for most distillations and particularly for the distillation of the higher members of the series, a falling-film molecular still was employed; such a still separated the desired products from a considerable quantity of high-boiling residues.

Diethyl α-Acetoxyalkylphosphonates.—The α-hydroxy compounds were acetylated in the usual way with acetic anhydride.[2] The diethyl α-acetoxyalkylphosphonates were stable to distillation once the higher boiling residues had been removed.

Ethyl α-Acetoxyalkylphosphonochloridates.—The diethyl esters were chlorinated with PCl_5 as previously described by Hafner, *et al.*[1] Physical constants of the once distilled ethyl α-acetoxyalkylphosphonochloridates, *i.e.*, yields (%), index of refraction ($n^{25}D$), and boiling points [°C. (mm.)], are as follows: butyl, 68, 1.441, 77–79 (0.05); pentyl, 72, 1.444, 88–90 (0.1); hexyl, 86, 1.445, 94–95 (0.03); heptyl, 81, 1.445, molecular still (benzene); octyl, 86, 1.445, molecular still (toluene); ethyl 2-chloroethylphosphonochloridate, 53, 1.468, 112–115 (20).

Ethyl *p*-Nitrophenyl α-Acetoxyalkylphosphonates.—The ethyl α-acetoxyalkylphosphonochloridates were treated with *p*-nitrophenol and triethylamine as previously described by Hafner, *et al.*[1]

Diethyl α-(*p*-Toluenesulfonyl)butylphosphonate.—Diethyl α-hydroxybutylphosphonate was treated with *p*-toluenesulfonyl chloride according to the procedure of Marvel.[3] The product did not crystallize and was, therefore, extracted from the HCl phase with ether. The ether solution after drying (Na_2SO_4) was filtered. The solvent was removed from the filtrate and the residue was distilled through a falling-film molecular still.

Diethyl 1-naphthylmethyl-, 2-naphthylmethyl-, and 2-chloroethylphosphonates were prepared from triethyl phosphite and the appropriate 1- or 2-naphthylmethyl chloride or 2-bromoethyl chloride *via* the usual Michaelis–Arbuzov reaction conditions.

Monoethyl α-Acetoxybutylphosphonate.—A solution of water (2.2 g., 0.124 mole) and triethylamine (12.6 g., 0.124 mole) was added dropwise to a stirred solution of ethyl α-acetoxybutylphosphonochloridate (30.1 g., 0.124 mole) and 50 ml. of ether. Another 50 ml. of ether was then added and the mixture was stirred 1 hr. It was filtered and the residue was washed with dry ether. After drying (Na_2SO_4), filtering, and removing the solvent, the residue was distilled in a falling-film molecular still using first benzene and then dimethylformamide as heating liquids.

Acknowledgment.—The authors gratefully acknowledge the help and cooperation of Dr. Elmer L. Becker and the aid of Mrs. J. C. Zufall.

(1) E. L. Becker, T. R. Fukuto, B. Boone, D. C. Canham, and E. Boger, *Biochemistry*, **2**, 72 (1963); B. H. Alexander, L. S. Hafner, M. V. Garrison, and J. E. Brown, *J. Org. Chem.*, **28**, 3499 (1963); L. S. Hafner, M. V. Garrison, J. E. Brown, and B. H. Alexander, *ibid.*, **30**, 677 (1965).

(2) M. S. Kharasch, R. A. Mosher, and I. S. Bengelsdorf, *ibid.*, **25**, 1000 (1959).

(3) C. S. Marvel and V. C. Sekera, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 366.

3-Phenylphthalimidines[1]

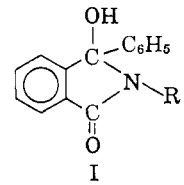
PRICE TRUITT, LINDA REEVES BRAMMER, AND LINDA TRUITT CREAGH

Chemical Laboratories, North Texas State University, Denton, Texas

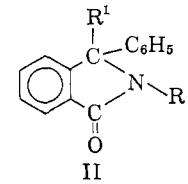
Received December 21, 1964

The recent report by Topliss and co-workers[2] of the antihypertensive effects of certain 3-hydroxy-3-phenylphthalamidines prompted us to disclose our work with similar N-substituted phthalimidines.

The method of Sachs and Ludwig[3] was utilized for the preparation of 3-hydroxy-3-phenyl-N-substituted phthalimidine (I). Other related phthalimidines (II) were prepared by the replace-



I



II

ment of the 3-hydroxyl by chloride and subsequent displacement of the reactive halogen with nucleophilic reagents.[4]

Most of the compounds prepared in this work were tested for antibacterial and antifungal activity and central nervous system effects, but none of the tests were promising.[5] The compounds substituted at the 2-position with alkyl or alkylaminoalkyl groups were toxic in the range of 125–250 mg./kg. in mice while the 2-aryl compounds were not toxic at 250 mg./kg. when administered subcutaneously in these test animals. Although the phthalimidines which were substituted with nitrogen mustard and piperidino groups in the 3-position displayed slight antitumor effects, none

(1) Supported by a grant from the National Institutes of Health (Cy-3908), a North Texas State University Faculty Grant, and a grant from Parke, Davis and Co.

(2) J. G. Topliss, L. M. Konzelman, N. Sperber, and F. E. Roth, *J. Med. Chem.*, **7**, 453 (1964).

(3) F. Sachs and A. Ludwig, *Ber.*, **37**, 388 (1904).

(4) W. von Graf, E. Girod, E. Schmid, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1085 (1959).

(5) These tests were arranged through Dr. E. Elslager of Parke, Davis and Co.