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.

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3-Phenylphthalimidines[1]

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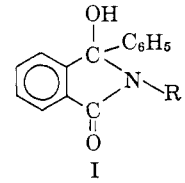
The recent report by Topliss and co-workers[2] of the antihypertensive effects of certain 3-hydroxy-3-phenylphthalamidines prompted us to disclose our work with similar N-substituted phthalimidines.

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-



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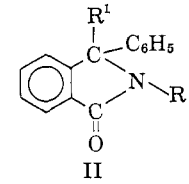


II

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.

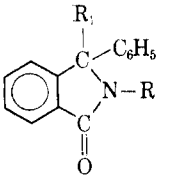
(2) J. G. Topliss, L. M. Konzelman, N. Sperber, and F. E. Roth, *J. Med. Chem.*, **7**, 453 (1964).

(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.

TABLE I
3-PHENYLPHTHALIMIDINES



R	R_1	M.p., °C.	Yield, %	Formula	N, % Calcd.	N, % Found
3-(2-Propylamino)propyl·HCl	OH	189–190	91	$C_{20}H_{25}ClN_2O_2$	7.76	7.70
3-(2-Propylamino)propyl	OH	99–102	80	$C_{20}H_{24}N_2O_2$	8.64	8.79
3-Diethylaminopropyl	OH	76–77	75	$C_{21}H_{26}N_2O_2$	8.28	8.41
2-Aminoethyl·HCl	OH	261–263	37	$C_{16}H_{17}ClN_2O_2$	9.19	9.20
3-Dimethylaminopropyl·HCl	OH	201–202	69	$C_{19}H_{23}ClN_2O_2$	8.08	8.30
Diethylaminoethyl·HCl	OH	190–192	73	$C_{20}H_{25}ClN_2O_2$	7.77	7.18
1-(3-Methoxypropyl)	OH	127–128.5	91	$C_{18}H_{19}NO_3$	4.72	4.87
Allyl	OH	145–147	85	$C_{17}H_{15}NO_2$	4.98	5.10
t-Butyl	OH	115–116	83	$C_{18}H_{19}NO_2$	4.98	5.10
Cyclohexyl	OH	224–226	92	$C_{20}H_{21}NO_2$	4.56	4.61
o-Tolyl	OH	174–175.5	45	$C_{21}H_{17}NO_2$	4.44	4.51
m-Tolyl	OH	178–180	75	$C_{21}H_{17}NO_2$	4.44	4.71
p-Tolyl	OH	222–224	89	$C_{21}H_{17}NO_2$	4.44	4.68
o-Methoxyphenyl	OH	151–153	37	$C_{21}H_{17}NO_3$	4.23	4.46
p-Methoxyphenyl	OH	191–191.5	28	$C_{21}H_{17}NO_3$	4.23	4.44
o-Nitrophenyl	OH	147.5–149	43	$C_{20}H_{14}N_2O_4$	8.09	8.24
n-Nitrophenyl	OH	197–198	41	$C_{20}H_{14}N_2O_4$	8.09	7.97
p-Nitrophenyl	OH	187–190	48	$C_{20}H_{14}N_2O_4$	8.09	8.00
m-Aminophenyl	OH	192–193	21	$C_{20}H_{16}N_2O_4$	8.86	8.92
2-Chloro-4-nitrophenyl	OH	170.5–172.5	33	$C_{20}H_{13}ClN_2O_4$	7.36	7.52
4-Propionylphenyl	OH	185–186.5	20	$C_{23}H_{19}NO_3$	3.93	4.09
4-Pyridyl	OH	211–215	34	$C_{19}H_{14}N_2O_3$	9.23	9.22
2-Pyridyl	OH	173.5–175	20	$C_{19}H_{14}N_2O_3$	9.23	9.04
2-(4-Methylpyridyl)	OH	207–208.5	40	$C_{20}H_{16}N_2O_2$	8.86	8.88
2-(6-Methylpyridyl)	OH	186–187	45	$C_{20}H_{16}N_2O_2$	8.86	8.96
2-Pyrimidyl	OH	222–223.5	41	$C_{18}H_{13}N_3O_2$	13.85	13.98
Cyclohexyl	$N(C_2H_4Cl)_2$	131–132	31	$C_{24}H_{28}Cl_2N_2O$	6.50	6.77
Phenyl	$N(C_2H_4Cl)_2$	137–139	55	$C_{24}H_{22}Cl_2N_2O$	6.59	6.65
Phenyl	Piperidino	210–212	57	$C_{25}H_{24}N_2O$	7.62	7.98
Phenyl	N-Methylpiperazino	205–207	35	$C_{25}H_{25}N_3O$	10.96	11.24
Phenyl	Ethoxyl	139–140	84	$C_{22}H_{19}NO_2$	4.25	4.22
Phenyl	$N(C_2H_5)_2$	192–194	63	$C_{24}H_{24}N_2O$	7.86	7.99
Phenyl	Morpholino	210–212	42	$C_{24}H_{24}N_2O$	7.56	7.43
Phenyl	$C_2H_5SO_2$	166–168	80	$C_{22}H_{19}NO_3S$	3.72	3.86
Phenyl	$C_6H_5CH_2SO_2$	180–192	37	$C_{26}H_{19}NO_3S$	3.18	3.14
p-Tolyl	$(NCH_2CH_2Cl)_2$	153–154	38	$C_{25}H_{24}Cl_2N_2O$	6.38	6.40
p-Tolyl	Piperidino	114–115	57	$C_{26}H_{26}N_2O$	7.32	7.58
p-Tolyl	N-Methylpiperazino	181–183	24	$C_{26}H_{27}N_3O$	10.58	10.59

of these compounds warranted further study. All of the other phthalimidines were devoid of antitumor effects.

Experimental[6]

3-Hydroxy-3-phenyl-2-substituted phthalimidines were prepared *via* previously reported procedures[3,4] and were recrystallized from methanol or methanol and water. The compounds are tabulated in Table I.

2,3-Diphenyl-3-ethylsulfonylphthalimidine.—A mixture of 9.4 g. of 3-chloro-2,3-diphenylphthalimidine[4] and 50 ml. of chloroform was cooled and added slowly to a cold, stirred solution of 3 g. of ethanethiol in 30 ml. of $CHCl_3$. The solution was stirred and allowed to reach room temperature, then evaporated *in vacuo*. The gummy solid was taken up in 50 ml. of glacial acetic acid and cooled, and 10 ml. of 30% H_2O_2 was added dropwise to the cold solution. The mixture was diluted with 100 ml. of water, and the solid was removed. Recrystallization from ethanol gave 10 g. (98%) of the expected sulfone, m.p. 166–168°.

3-Alkoxy, 3-piperidino, and 3-morpholino derivatives were prepared in the fashion described by von Graf and co-workers[4] and the data are included in Table I.

(6) Melting points, corrected, were obtained with a Thomas-Hoover apparatus.

Some Compounds Derived from 1-Cyano- and 1-Bromobenzocyclobutene

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As part of an investigation into the biological significance of benzocyclobutene derivatives,[1] we have synthesized a number of 1,1-disubstituted compounds (Table I) from the readily accessible 1-cyanobenzocyclobutene. In addition, the oxygen isostere XV of the previously described 1-aminomethylbenzocyclobutene[1] and the unique amino acid, 1-benzocyclobutenylglycine (XVI), were prepared from 1-bromobenzocyclobutene. The pharmacological evaluation of these compounds as potential antihypertensive and analgetic agents is in progress.

(1) J. A. Skorcz and J. E. Robertson, *J. Med. Chem.*, **8**, 255 (1965