traces of MeOH). The very efficient cyclization method described for 2,9-bis(bromomethyl)-1,10-phenanthrolines and aza-crown ethers to form mixed phenanthrolino-crown ether cryptates[25] has been applied to 7 and $[18]N_2O_4$ 8. The macrocycle 8 was treated under argon with an excess of cesium carbonate in refluxing dry acetonitrile before adding dropwise a suspension of the dibromide 7. After 20 h of reaction, the inorganic materials (solids) were discarded and the crystalline ligand 9 (mp 110–111 °C) was isolated in 30% yield from the organic phase by chromatography ($SiO_2/CH_2Cl_2/MeOH$). The yield of the cyclization reaction could be compared to those obtained by Lehn and co-workers who have reported up to 70% yield for this type of reactions using Na_2CO_3 as a base.[25]

The relative flexibility of our precursor (rotation around the biphenyl bond) has directed our choice toward cesium carbonate, instead of the sodium salt. For cryptates synthesis, the size of the sodium seemed to be adequate for templation of the cyclization, but in our case benefit was taken from the ability of the cesium ion to gather fragments for S_N2 reactions.[26]

From ^1H NMR data, the geometry of the ligand 9 has been approximated, and measurements are in agreement with the proposed conformation depicted in Figure 1. The signal of the ortho proton is significantly shifted to higher fields when compared to open precursors ($\Delta\delta = -0.2$ ppm), showing that the phenyl spacer is no longer coplanar with the phenanthroline ring. The second significant shift is the shielding of the benzylic protons whose signal (singlet) appears at 3.66 ppm versus 4.54 ppm in the precursor 7. This is consistent with placing the benzylic protons very close to the shielding cone of the phenyl substituents present on the phenanthroline moiety. A slight broadening of the signals has been observed at room temperature indicating a reduced mobility of the macrobicyclic framework.

Investigations concerning the complexing abilities of 9 as well as its copper(I)– and rhodium(I)–alkali complexes are under progress.

Acknowledgment. We warmly acknowledge the CNRS for financial support.

Supplementary Material Available: ^1H NMR spectra of compounds 5, 6, 7, and 9; ^{13}C NMR spectra of compounds 5 and 9; and mass spectra of compounds 5, 6, 7, and 9 (20 pages). Ordering information is given on any current masthead page.

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Articles

Synthesis of 4-Alkyl-2-iodosobenzoic Acids: Potent Catalysts for the Hydrolysis of Phosphorous Esters

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The syntheses of five new 4-alkyl-2-iodosobenzoic acids (3) are described. The iodine atom was introduced by ortho-directed lithiation of 4-alkylbenzyl alcohols followed by treatment with I_2. The catalytic effectiveness of each of the products in the hydrolysis of 4-nitrophenyl diphenyl phosphate in microemulsions was studied. The 4-methyl- and 4-ethyl-substituted products were each found to be significantly better catalysts than the standard nonalkylated 2-iodosobenzoic acid (3, R = H). These results would indicate that microemulsions of these materials may find use in detoxification procedures.

Introduction

Certain phosphate, phosphonate, and phosphinate esters are persistent acetylcholinesterase inhibitors and neurotoxic agents. Since some are used as potent pesticides and chemical warfare agents, their rates of decomposition and detoxification are of considerable importance. Efficient detoxification methods would find applications in the decontamination of environments and equipment exposed to these agents.

Many functional groups have been studied for their reactivity toward phosphate esters and, since the latter are only sparingly soluble in water, micellar and microemulsion media have often been employed. In recent years, 2-iodosobenzoic acid (IBA, 3, R = H) and several derivatives have been reported to be effective catalysts in phosphate ester decompositions.[2] Speculation on the mechanism responsible for the extraordinary reactivity of IBA has suggested that the cyclic IBA anion is the nucleophile that

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Table I. Data on Iodinated Intermediates and Products

compound	mg (°C)	yield (%)	calcd C	calcd H	calcd I	found C	found H	found I
1 R = methyl	75.0–79.0	38						
1, R = ethyl	72.5–73.0	45	41.24	4.24	48.42	41.16	4.39	48.32
1, R = *n*-propyl	52.0–55.0	46						
1, R = *n*-pentyl	70.5–71.0	44	47.38	5.64	41.72	47.37	5.62	41.70
1, R = *n*-octyl	75.5–76.5	62	52.03	6.71	36.65	53.40	6.87	35.11
2, R = methyl	128.0–130.0 (lit. mp 126.0–127.0[a])	24						
2, R = ethyl	92.0–93.0	37	39.15	3.29	45.97	39.57	3.14	45.72
2, R = *n*-propyl	82.0–88.0	44						
2, R = *n*-pentyl	68.0–69.0	63	45.30	4.76	39.89	45.01	4.86	39.86
2, R = *n*-octyl	59.0–63.5	55	50.01	5.89	35.23	50.20	5.94	33.67
3, R = methyl	216.0–217.0	90	34.56	2.54	45.64	34.80	2.56	45.48
3, R = ethyl	212.5–213.0	82	37.01	3.11	43.45	36.65	2.95	43.26
3, R = *n*-propyl	**A** 154.5–160.0	12						
	B 168.0–169.0	88	39.23	3.63	41.46	39.44	3.68	39.88
3, R = *n*-pentyl	**A** 115.0–116.0	25	43.13	4.53	37.98	43.12	4.02	37.79
	B 188.5–189.5	90	43.13	4.53	37.98	43.19	4.52	37.63
3, R = *n*-octyl	165.5–166.5	97	47.88	5.64	33.73	47.85	5.72	33.36

[a] See ref 7.

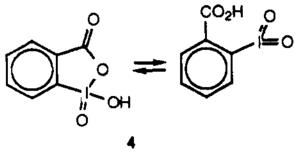
attacks phosphorous to form an acyl-type intermediate followed by hydroxide attack on this species to release the phosphoric acid derivative.

Of the several IBA derivatives that have been tested as catalysts for the hydrolysis of phosphate esters, only a few are substituted in the 4-position (with carboxy or nitro groups), but none of these substituents include the lipophilic alkyl groups. Katritzky[2] found that lipophilic substituents in the 5-position significantly enhanced the phosphate hydrolysis rates of IBA.

In the present work, five 4-alkyl-IBA's **3** were prepared for the first time and evaluated as phosphate ester hydrolysis catalysts in microemulsion systems. Somewhat surprisingly, the IBA's with smaller alkyl substituents were found to be significantly better catalysts than those with larger alkyl substituents and even better than unsubstituted IBA.

Results and Discussion

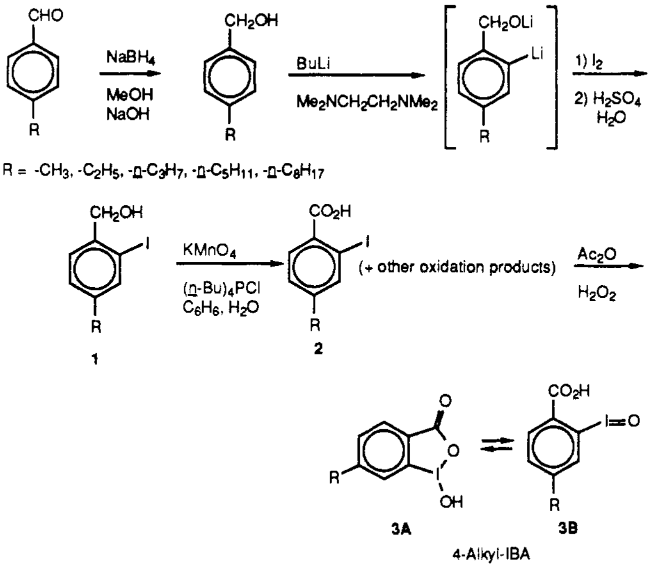
Synthesis. The products were synthesized from the commercially available *p*-alkylbenzaldehydes or -benzyl alcohols (Scheme I). The latter were lithiated at a position ortho to the hydroxymethyl group and the metal was replaced with an iodine atom to afford the 4-alkyl-2-iodobenzyl alcohols **1**. Oxidation of **1** with potassium permanganate under phase-transfer conditions yielded the corresponding carboxylic acid, **2**. The conversion to the 4-alkyl-IBA derivatives **3** was effected with a mixture of acetic anhydride and hydrogen peroxide. This procedure reportedly[3] affords both iodoso- (**3**) and iodoxybenzoic acids (**4**), but, in our hands, only the former could be isolated. Table I lists the melting points, yields, and elemental analyses of the intermediates and products prepared in this work.



4

2-iodoxybenzoic acid

Scheme I



Two products were obtained in the *n*-pentyl series, each of which gave satisfactory elemental analyses for *n*-pentyl-IBA (**3**, R = *n*-pentyl). The lower melting one was obtained as a byproduct in the preparation of 2-iodo-4-*n*-pentylbenzoic acid (**2**, R = *n*-pentyl) using potassium permanganate. The second was the sole product resulting from the oxidation of **2** with acetic anhydride and hydrogen peroxide. These, apparently, are the two tautomeric forms of IBA: the lactone **3A** and the carboxylic acid **3B**, respectively. Thin-layer chromatograms of **3B** always showed a faint spot for the faster moving **3A** in addition to the more intense zone for **3B**. Also, the infrared carbonyl band of **3A** was found at a higher wavenumber (1710 cm^{-1}) compared with that of **3B** (1650). The *n*-propyl series appeared to give similar results.

Kinetics. The second-order rate constants for the catalyzed hydrolysis of *p*-nitrophenyl diphenyl phosphate were measured in a microemulsion medium consisting of 8% of the surfactant, cetyltrimethylammonium bromide, 8% of the cosurfactant, 1-methyl-2-pyrrolidinone, 4% of toluene, and 80% of a 0.03 M aqueous borate buffer by previously described techniques.[4] The results are given in Table II. The rate constants were determined in duplicate. The standard error was the 95% confidence interval for the slopes of the curves of the pseudo-first-order

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Table II. Second-Order Rate Constants for the Hydrolysis of 4-Nitrophenyl Diphenyl Phosphate by IBA and 4-Alkyl-IBA's in Microemulsion Systems

IBA catalyst, 3	k_{IBA} (s^{-1} M^{-1})
unsubstituted-IBA	12.4 ± 0.55
4-methyl-IBA	18.6 ± 0.36
4-ethyl-IBA	22.9 ± 0.38
4-*n*-propyl-IBA	0.013 ± 0.005
4-*n*-pentyl-IBA	0.026 ± 0.010
4-*n*-octyl-IBA	ref 8

rate constants versus catalyst concentration. The *n*-propyl and *n*-pentyl derivatives exhibited poor catalysis possibly due to their incorporation into the oily interior of the microemulsion aggregate. The methyl and ethyl derivatives showed significant enhancements over the catalytic activity of the unsubstituted IBA (**3**, R = H).

Experimental Section

The ^{1}H NMR spectra were obtained on a Varian EM360 spectrometer using $CDCl_3$ as the solvent and Me_4Si as the internal standard. The infrared spectra were made on a Perkin-Elmer Model 1310 spectrometer. Melting points were observed on the Thomas-Hoover apparatus and are uncorrected. Analtech precoated TLC plates (silica gel HLF, 47521) were used for the analysis of reaction products. The eluting solvents are given below for each of the reaction intermediates. Elemental analyses were performed by Schwarzkopf Analytical Laboratories, NJ.

4-Alkylbenzyl Alcohols. 4-Methylbenzyl alcohol was obtained from Aldrich and used as is from the bottle. The others were prepared as follows. A solution of 0.92 mL of 2 M NaOH, 8.3 mL of water, and 0.63 g (0.017 mol) of $NaBH_4$ was added dropwise during a 10-min period to a stirred solution of 0.04 mol of the 4-alkylbenzaldehyde in 50 mL of methanol. The temperature of the reaction mixture was maintained at 18–24 °C by means of a cooling bath. It was then stirred for 35 min at room temperature followed by distillation of the methanol at ambient pressure. The aqueous residue was diluted with a saturated salt solution and the resultant solution was extracted with benzene. The organic layer was washed with water, dried, and concentrated to a colorless oil that was essentially a homogeneous product according to TLC (70:30, hexane/EtOAc). In those cases where some starting material contaminated the product, column chromatography on E. Merck silica gel (no. 9385) successfully separated the components. IR and ^{1}H NMR were consistent with the structures of these known compounds (see supplementary material).

4-Alkyl-2-iodobenzyl Alcohols 1. This procedure was essentially that which Meyer and Seebach[5] used to prepare 2-iodobenzyl alcohol. A molecular sieve(4A)-dried solution of 0.035 mol of the 4-alkylbenzyl alcohol, 72 mL of petroleum ether (30–60 °C), and 10.93 mL (8.42 g, 0.072 mol) of tetramethylethylenediamine was stirred under a nitrogen atmosphere while 48.05 mL of a 1.5 M solution of *n*-butyllithium (0.072 mol) in hexane was added in two portions during a 10-min period. The clear light yellow solution changed first to a turbid milky solution and then became dark in color. It was heated to the reflux temperature for 11 h and stirred at room temperature for 13 h. The reaction mixture was cooled to −78 °C and 6.27 g (0.0247 mol) of iodine was added. The result was stirred and allowed to warm to room temperature for 1 h. Ten percent H_2SO_4 (53 mL) was added in order to acidify the reaction mixture, the layers were separated, and the aqueous layer was extracted with ether. The organic solutions were combined, washed with water, and dried. Removal of the solvents under reduced pressure left a dark oil, which contained much free iodine. This was chromatographed on an E. Merck silica gel column (no. 9385, 100 g) using 95:5 hexane/EtOAc. Several of the mid fractions were pooled and the solvent was removed to afford a solid residue, which was easily recrystallized from low-boiling petroleum ether or from hexane. Spectral and elemental analysis data may be found in Table I Spectral data is included in the supplementary material.

4-Alkyl-2-iodobenzoic Acids 2. The procedure reported by Herriott and Picker[6] for the oxidation of benzyl alcohol was used with minor modifications. A mixture of 4.8 g (0.03 mol) of $KMnO_4$ and 50 mL of water was stirred vigorously for 10 min and then cooled in a water bath while 0.011 mol of the 4-alkyl-2-iodobenzyl alcohol **1**, 30 mL of benzene, and 0.47 g (0.0016 mol) of tetrabutylphosphonium chloride were added sequentially. The mixture was stirred for 3 h at room temperature after which some sodium bisulfite was added to discharge the residual permanganate color. Ether, 80 mL, was added and the resultant mixture was acidified with 50% H_2SO_4 and filtered through a pad of Celite. The aqueous layer was extracted 3 times with ether. The organic solutions were combined, washed with saturated salt solution, and dried. The solvent was removed at reduced pressure to leave a residual mixture of an oil and solid. This was chromatographed on 90 g of silica gel (E. Merck, 9385) using a stepwise gradient of eluting solvents beginning with 79:20:1 hexane/EtOAc/HOAc and ending with 95:5 EtOAc/HOAc. The separated components were treated somewhat differently as described below.

2-Iodo-4-methylbenzoic Acid. Tetrabutylammonium bromide was used in place of tetrabutylphosphonium chloride as the phase-transfer agent. The product mixture contained three components. The fastest moving product was identified as 2-iodo-4-methylbenzaldehyde: yield, 64%; IR (KBr) 2860, 1700 (shoulder), 1684, 1598, 1209, 1040, 872, 860, 822, 700; ^{1}H NMR ($CDCl_3$) 10.1 (CHO), 7.2–7.9 (Ar), 2.35 (CH_3); positive (2,4-dinitrophenyl)hydrazine test for aldehyde. The second fastest component was 2-iodo-4-methylbenzoic acid (see tables for data) and the slowest product was not immediately identified. The above 2-iodo-4-methylbenzaldehyde was again treated with potassium permanganate in benzene-water, but this time, tetrabutylphosphonium chloride was used and the benzaldehyde was completely oxidized. The yield of 2-iodo-4-methylbenzoic acid from benzaldehyde was 39%. This intermediate was the only iodinated compound prepared in the project that has been previously reported in the literature. It has been synthesized in 75% yield by the treatment of *p*-toluic acid with thallium (III) trifluoroacetate followed by the reaction of the resulting arylthallium bistrifluoroacetate with potassium iodide.[7]

4-Ethyl-2-iodobenzoic Acid. In the ethyl series, the reaction was run for 4 h instead of 3 h and three products were isolated. The first, an oil having the largest TLC R_f (59:40:1 hexane/EtOAc/HOAc), was identified as 4-ethyl-2-iodobenzaldehyde. It gave a positive 2,4-dinitrophenylhydrazine test. IR (neat): 2960, 2930, 2870, 2750, 1685, 1591, 1030, 885, 851, 835, 765. ^{1}H NMR ($CDCl_3$): 9.9 (CHO), 7.2–7.9 (Ar), 2.8 ($ArCH_2C$), 1.4 (CCH_3); yield, 12%. The second component was the desired product, **2**, R = ethyl, and gave the middle TLC zone (see tables for data). The third component (slowest TLC zone) had a high mp, 287.5–291.0 °C dec. It could not be purified adequately for a reliable elemental analysis, but its limited solubility and infrared spectrum indicated it to be 2-iodoterephthalic acid: IR (KBr) 3200–2400, 1705, 1550, 1475, 1405, 1250, 1120, 1030, 910, 845, 820, 775, 746, 721, 689; yield, 44%.

2-Iodo-4-*n*-propyl- and 2-Iodo-4-*n*-pentylbenzoic Acid. Only a trace of what appeared to be 4-alkyl-2-iodobenzaldehyde (a yellow oil with a positive DNPH test) was isolated. The title products had TLC R_f's (59:40:1 hexane/EtOAc/HOAc) slightly smaller than that of the starting materials. They were recrystallized from hot aqueous EtOH. A third product was the 4-alkyl-2-iodosobenzoic acid **3A** by elemental analysis. It had the smallest TLC R_f and was recrystallized from hot aqueous EtOH. See Table I for data and the discussion section.

2-Iodo-4-*n*-octylbenzoic Acid. The TLC spot usually associated with the benzaldehyde byproduct was observed in this experiment, but the material was not isolated. The desired product exhibited a mid-R_f TLC value and it was recrystallized from warm petroleum ether (30–60 °C).

4-Alkyl-2-iodosobenzoic Acids 3. The procedure followed here has been reported[3] to afford both iodoso- and iodoxybenzoic acids. In our hands, only the former were isolated. Acetic an-

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[5] Meyer, N.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 521.

[6] Herriott, A. W.; Picker, D. *Tetrahedron Lett.* **1974**, *16*, 1511.

[7] Carruthers, W.; Pooranamoorthy, R. *J. Chem. Soc. Perkin Trans. I* **1974**, 2405.

[8] Could not be solubilized as the sodium salt.

hydride, 9.6 mL, and 2.4 mL of 30% H_2O_2 were stirred at 40 °C for 4 h. The 4-alkyl-2-iodobenzoic acid, 4.8 mmol, was added in one portion and the resultant mixture was stirred at 40 °C. A solution occurred after a few minutes, quickly followed by the precipitation of a white solid. The reaction mixture was diluted with 96 mL of water after 20 h of heating. The resultant mixture was stirred at room temperature for 1 h. It was filtered and the white crystalline solid was washed with water and dried. Purification was accomplished by recrystallization from hot EtOH except for 2-iodoso-4-*n*-pentylbenzoic acid **3B**, which was recrystallized from hot acetone. 2-Iodoso-*n*-pentyl- and -4-*n*-propylbenzoic acids **3A** were also obtained as byproducts from the $KMnO_4$ oxidation of 2-iodo-4-*n*-pentyl- and -4-*n*-propylbenzyl alcohols 1 (see discussion section).

Microemulsion Components. The surfactant, cetyltrimethylammonium bromide (CTAB), was purchased from Sigma Chemical Co. (98% pure) and was used as received. The kinetic data obtained in microemulsions that had been prepared with unpurified CTAB was the same as the kinetic data obtained in microemulsions that had been prepared with CTAB that had been recrystallized from methanol.

The cosurfactant, 1-methyl-2-pyrrolidinone (MP), was received as a gift from BASF Corp. Toluene (Baker) was used as the hydrophobic phase without further purification.

The borate buffer was prepared from sodium tetraborate decahydrate ($Na_2B_4O_7{\cdot}10H_2O$; Fisher; 0.0095% impurities) and glass-distilled, deionized water (conductivity ≤2 msiemens). A Corning water purifier LD-5 and a Corning AG Pyrex still were used to purify the water. A 0.03 M borate buffer, pH 9.4, was used as the aqueous phase in the kinetic studies.

The catalyst standard, 2-iodosobenzoic acid (IBA), was obtained from Sigma Chemical Co. A mixture of the acid form of IBA and water was adjusted with dilute NaOH to pH 9–9.5, or until all of the acid had dissolved. The solution was dried with gentle heating under vacuum (≤0.01 mm) on a rotary evaporator. The sodium salt of IBA was then allowed to dry under vacuum overnight. A 0.06 M solution of it in 0.03 M borate buffer was prepared.

Known weights of 4-alkyl-IBA derivatives **3** were added to 4 mL of distilled water. A molar equivalent of standard 0.2 N NaOH solution was added. The solutions were allowed to stand overnight or until conversion to the sodium salt was complete.

The substrate, 4-nitrophenyl diphenyl phosphate (PNDP), was prepared as a custom synthesis by Biomol Research Laboratories, Inc., according to the method of Gulick and Geske. ^{31}P and ^{13}C NMR results indicated that the PNDP was greater than 99.5% pure. PNDP was dissolved in acetonitrile (Aldrich; 99.9% pure) before use.

Measurement of Hydrolysis Rate Constants. The measurement and analysis of rate data have previously been described.[4] The software for measuring absorbances of the product (*p*-nitrophenoxide) of the hydrolysis of *p*-nitrophenyl diphenyl phosphate and for the analysis of the data, Precise Input 1.72 and Auto Algernon, respectively, was developed by Dr. Barry L. Knier.

Acknowledgment. Grateful acknowledgment is made for the support of this work by the National Research Council and the U.S. Army Chemical Research, Development, and Engineering Center through a senior resident research associateship for C.A.P.

Registry No. 1 (R = Me), 126156-20-5; 1 (R = Et), 126156-21-6; 1 (R = Pr), 126156-22-7; 1 (R = *n*-pentyl), 126188-98-5; 1 (R = *n*-octyl), 126156-23-8; **2** (R = Me), 1829-21-6; **2** (R = Et), 126156-24-9; **2** (R = Pr), 126156-25-0; **2** (R = *n*-pentyl), 126156-26-1; **2** (R = *n*-octyl), 126156-27-2; **3a** (R = Pr), 126156-33-0; **6a** (R = *n*-pentyl), 126156-34-1; **3b** (R = Me), 64297-88-7; **3b** (R = Et), 126156-29-4; **3b** (R = Pr), 126156-30-7; **3b** (R = *n*-pentyl), 126156-31-8; **3b** (R = *n*-octyl), 126156-32-9; PNDP, 10359-36-1; 4-methylbenzyl alcohol, 589-18-4; 4-ethylbenzyl alcohol, 768-59-2; 4-*n*-propylbenzyl alcohol, 82657-70-3; 4-*n*-pentylbenzyl alcohol, 81720-37-8; 4-*n*-octylbenzyl alcohol, 40016-25-9; 2-iodo-4-methylbenzaldehyde, 126156-28-3; 4-ethyl-2-iodobenzaldehyde, 126156-36-3.

Supplementary Material Available: ^{1}H NMR and IR spectral data of many of the intermediates and products presented in tabular form and NMR spectra of 1 (4 pages). Ordering information is given on any current masthead page.