4-chloroindol-3-ol (**1**) 1.7 ml (20 mmoles) of $POCl_3$ in 60 ml of C_6H_6 was carried out as described above. To a magnetically stirred solution of **2** in 60 ml of dry dioxane, cooled externally by an ice bath, was added dropwise and under N_2 a solution of 3.6 g (12.7 mmoles) of 3-*O*-acetylthymidine[6] (**7**) in 40 ml of dioxane containing 1.2 ml (14.9 mmoles) of pyridine. The work-up followed that described above for **6** omitting only the treatment with AcOH to effect detritylation. The residue, 1.98 g, derived from the column conversion (IR-120 H^+) of the product into a free acid, was dissolved in 50 ml of dry MeOH and added dropwise with magnetic stirring to a satd MeOH–NH_3 solution (20 ml) at −10°. The reaction mixture was slowly allowed to attain ambient temp and then stirred for an additional 16 hr. Traces of 5,5′-dibromo-4,4′-dichloroindigo were removed by rapid filtration and the filtrate was evapd to dryness. The greenish brown solid was dissolved in MeOH and treated with Norit and the filtered solution was evapd to dryness to give a tan, chromatographically homogeneous solid (R_f 0.71 *i*-PrOH–NH_3–H_2O, 7:2:1); wt 0.250 g (4% yield based on **1**). The latter was converted into a Ca salt in the manner described for **6**. Evaporation of the effluent gave an off-white amorphous solid: mp 229–230° dec with prior darkening at 220°; $[\alpha]^{20}D$ −17° (*c* 0.2, H_2O); uv max (pH 6) 272 nm (ε 9120), min 250 nm. *Anal.* ($C_{18}H_{17}ClBrN_3O_8P \cdot 0.5Ca \cdot 2.5H_2O$) C, H, N, P.

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Cyclohexyl Alkylphosphonofluoridates

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Ooms has shown that cyclohexyl ethyl and methylphosphonofluoridates[1] are active inhibitors of serine esterases, particularly chymotrypsin. Our continuing interest in phosphonate esters as inhibitors of serine esterases[2] prompted us to prepare a number of cyclohexyl alkyl and phenylalkylphosphonofluoridates analogous to the previously synthesized *p*-nitrophenyl alkyl and phenylalkylphosphonates.[3]

These compounds proved to be good inhibitors of serine esterases[4a] and two of the cyclohexylphosphonofluoridates, the benzyl and the phenethyl, were very potent inhibitors of chymotrypsin.[4b]

The compounds were prepared by a five-step sequence of standard reactions. Only the conversion of the alkylphosphonodichloridates into the cyclohexyl alkylphosphonochloridates proved to be more difficult and gave lower yields than anticipated.

Experimental Section

Caution.—The phosphonofluoridates are cholinesterase inhibitors and should be prepared and handled with extreme care.

Diethyl Alkylphosphonates.—The diesters were prepared by the Arbuzov–Michaelis or the Michaelis–Becker reactions.[5]

Alkylphosphonic Acids.—The esters were hydrolyzed by refluxing overnight in excess concd HCl and purified by crystallization from AcOH.

Alkylphosphonodichloridates.—The method of Doak and Freedman[6] was modified in that PCl_5 was added cautiously from an addition tube to the solid acid.

Cyclohexyl Alkylphosphonochloridate. Cyclohexyl Butylphosphonochloridate.—To a solution of butylphosphonodichloridate (63.6 g, 0.36 mole) in *ca.* 500 ml of abs Et_2O, was added a solution of cyclohexanol (36.8, 0.36 mole) in Et_3N (36.4 g, 0.36 mole), dropwise over a period of *ca.* 4 hr. with stirring. After addition, the mixture was stirred an additional 6–8 hr (in some cases the mixture, after the addition, was warmed to refluxing temperature *ca.* 2 hr and worked up). The $Et_3N \cdot HCl$ was filtered off and the Et_2O removed by distillation at a final temp of *ca.* 70° and water aspirator pressure. The residue was distilled using a still head only: yield 47%; bp 90° (0.1 mm); $n^{25}D$ 1.4680. These cyclohexyl alkylphosphonochloridates are prone to decomposition during distillation and those boiling above 100° were purified by distillation through a falling film molecular still. Constants of once distilled cyclohexyl phosphonochloridates are given in the order bp °C (mm), $n^{25}D$, yield %: Pr, 79 (0.05), 1.4688, 41; Bu, 90 (0.1), 1.4680, 47; Pent, 99 (0.1), 1.4688, 54; Hex, toluene,[7] 1.4678, 30; Ph, toluene,[7] 1.5328, 48; benzyl, BuOH,[7] 1.5309, 20; phenethyl, BuOH,[7] 1.5240, 39; phenylpropyl, xylene,[7] 1.5244, 42; phenylbutyl, xylene,[7] 1.5192, 45.

Cyclohexyl Alkylphosphonofluoridates. Cyclohexyl Phenylpropylphosphonofluoridate.—Cyclohexyl phenylpropylphosphonochloridate (35.6 g, 0.118 mole) and KF (10.4 g, 0.177 mole, 50% excess) were mixed; usually the flask became warm and the mixture was then stirred. After the flask was placed under reduced pressure (*ca.* 0.005 mm) the mixture was heated gradually in an oil bath for about 4 hr to a final temperature of 80–100°. In cases where the fluoridate distilled below 110°, it was distilled out of the reaction mixture as it was formed. The fluoridate is more stable to heat than the chloridate so higher temperature can be applied to the flask to drive out the remaining fluoridate and unreacted chloridate from the KF–KCl reaction mixture. Repeat using less KF until a constant index of refraction is obtained.

Table I

$RP(O)(OC_6H_{11})F$

No.	R	Formula[a]	Bp, °C (mm)	$n^{25}D$	Yield, %
1	Pr	$C_9H_{18}FO_2P$	43 (0.03)	1.4378	45
2	Bu	$C_{10}H_{20}FO_2P$	77 (0.15)	1.4391	58
3	Pent	$C_{11}H_{22}FO_2P$	60 (0.005)	1.4409	56
4	Hex	$C_{12}H_{24}FO_2P$	93 (0.005)	1.4424	68
5	Ph	$C_{12}H_{16}FO_2P$	94 (0.05)	1.5021	61
6	$PhCH_2$	$C_{13}H_{18}FO_2P$	96 (0.03)	1.5041	68
7	$Ph(CH_2)_2$	$C_{14}H_{20}FO_2P$	113 (0.03)	1.5001	44
8	$Ph(CH_2)_3$	$C_{15}H_{22}FO_2P$	132 (0.005)	1.4988	67
9	$Ph(CH_2)_4$	$C_{16}H_{24}FO_2P$	159 (0.03)	1.4972	33

[a] All compounds were analyzed for C, F, H, and P and were within ±0.4% of theoretical value except for **1** (F: calcd 9.12; found 8.57) and **6** (F: calcd 7.41; found 6.65).

For cyclohexyl alkylphosphonofluoridates boiling over 110°, the reaction mixture of the cyclohexyl phenylpropylphosphonofluoridate was cooled. About 60 ml of abs Et_2O was added, stirred for *ca.* 10 min, and filtered. After washing with abs Et_2O, Et_2O was removed at a water aspirator and final bath temperature of 70°: wt of syrup 29 g, $n^{25}D$, 1.4991. Add 4 g of KF to syrup and repeat: wt of syrup 30 g, $n^{25}D$, 1.4985. The final syrup from either procedure was distilled through a falling film molecular still at BuOH refluxing temp: wt 23 g, $n^{25}D$, 1.4992. The colorless distillate was distilled through a short-path distillation head at 129° (0.005 mm), yield 22 g (67%) $n^{25}D$, 1.4993.

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