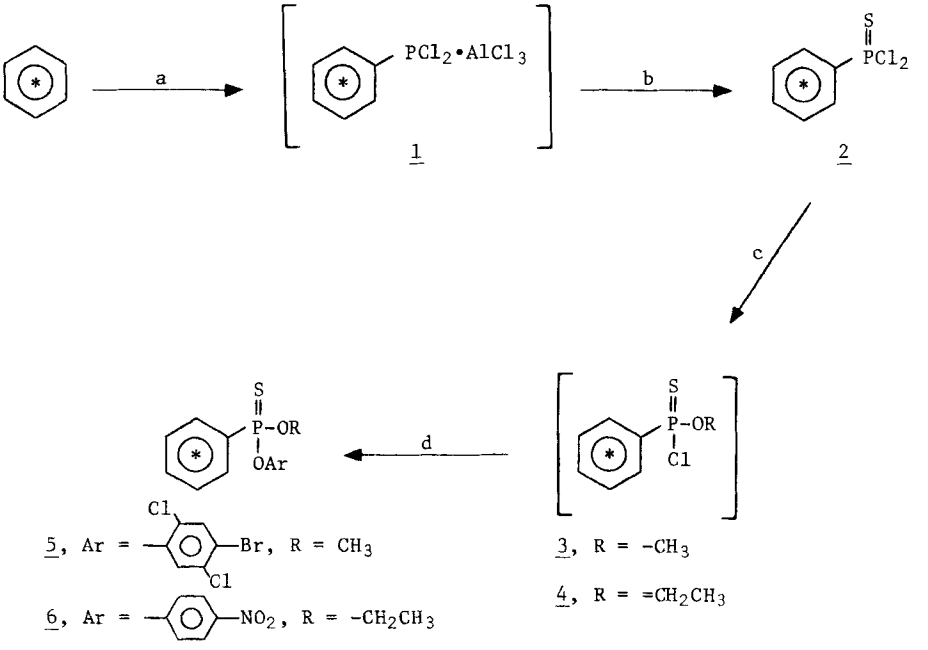
SYNTHESIS OF PHENYL-$^{14}C_6$-LABELED O-(4-BROMO-2,5-DICHLOROPHENYL) O-METHYL PHENYLPHOSPHONOTHIOATE AND O-(4-NITROPHENYL) O-ETHYL PHENYLPHOSPHONOTHIOATE USING A PHASETRANSFER PROCEDURE

A recent paper by Yoshitake et. al.[1] describing the synthesis of carbon-14 labeled optically active O-aryl O-ethyl phenylphosphonothioates prompts us to report on our preparation of two labeled substances of the same compound class, although not in their optically active form. Phosvel^{TM}, O-(4-bromo-2,5-dichlorophenyl) O-methyl phenylphosphonothioate and EPN^{TM}, O-(4-nitrophenyl) O-ethyl phenylphosphonothioate were both prepared with uniformly labeled phenyl rings in the acid moiety.

The overall synthetic scheme utilized for the preparation of both Phosvel^{TM}-(phenyl-$^{14}C_6$) 5 and EPN^{TM}-(phenyl-$^{14}C_6$) 6 is depicted below. Both compounds were prepared from the same intermediate, phenyl-$^{14}C_6$-phosphonothioic dichloride (2). Compound 2 itself was obtained in a two step one-pot reaction. Uniformly ^{14}C-labeled benzene and phosphorus trichloride in the presence of aluminum chloride[2] formed the complex 1, which was sulfurized without isolation to give intermediate 2. Reaction of 2 with the respective alcohols in the presence of 5-ethyl-2-methylpyridine[3] led to the phosphonochloridothioates 3 and 4. The final condensation of these thionophosphine ester chlorides with the appropriate phenols was run in a two phase system with the aid of a phase transfer reagent. This approach, used before for the synthesis of phosphate esters[4], simplifies this last condensation. Instead of the usual prolonged refluxing in a dry inert solvent, the mixtures were stirred at ambient temperature for the short times indicated in the experimental section.

0362-4803/81/121831-05$01.00

Received March 5, 1981



[a] PCl_3, $AlCl_3$, reflux. [b] S, 80-85°, 10 min. [c] $ØCH_3$, 2-ethyl-6-methylpyridine, R=OH, 0-5°. [d] ArOH, NaOHaq., $R_4N^+Cl^-$.

EXPERIMENTAL

Unlabeled 4-bromo-2,5-dichlorophenol and Phosvel™ (99% purity) were provided by Velsicol Chemical Corporation, Chicago, Illinois. Other unlabeled reference compounds and intermediates were purchased or synthesized, and structures were confirmed by spectroscopic methods. Benzene-$^{14}C_6$ was obtained from Pathfinder Laboratories, St. Louis, Missouri.

Phenyl-$^{14}C_6$-phosphonothioic dichloride (2).

A stirred mixture of 1.055 g (7.68 mmole) phosphorous trichloride, 156 mg (2.0 mmole) of benzene-$^{14}C_6$ (at 10.0 mCi/mmole) diluted with 50 µl (0.56 mmole) of "cold" benzene, and 347 mg (2.60 mmole) of aluminum chloride was refluxed for 3 hr. The resulting solution was cooled to 30°C and 84 mg (2.60 mmole) of sulfur (flowers) added. An immediate reaction occurred and the sulfur disappeared rapidly upon heating the mixture gradually to 80°C. After 10 min at 80 to 85°C, the reaction mixture was allowed to cool to room temperature and subsequently poured on cracked ice. The resulting slurry was extracted with 5 x 20 ml of petroleum ether and the combined extracts dried (Na_2SO_4), filtered, and concentrated (in vacuo), yielding a clear oily residue of 422 mg (78%) of phenyl-$^{14}C_6$-phosphonothioic dichloride; TLC, R_f 0.80 silica gel/hexanes:acetone (9:1). This material was suitable (95% radiochemical purity) for conversion to Phosvel™ and EPN™ without further purification.

O-(4-Bromo-2,5-dichlorophenyl)-O-methyl phenyl-$^{14}C_6$-phosphonothioate, Phosvel™-(phenyl-$^{14}C_6$) (5).

To a solution of 211 mg (1.0 mmole) of phenyl-$^{14}C_6$-phosphonothioic dichloride in 0.5 ml of dry toluene at 0 to 5°C was added 41 µl (1.0 mmole) of methanol in 134 µl (1.0 mmole) of 2-methyl-5-ethyl-pyridine and 300 µl of toluene in eight equal increments over a period of 1.75 hr. The resulting reaction mixture was allowed to warm to room temperature and 242 mg (1.0 mmole) of 2,5-dichloro-4-bromophenol and 100 mg of tricaprylmethylammonium chloride in 600 µl of toluene was added followed immediately by the addition of 1.0 ml 3 N sodium hydroxide. A white precipitate appeared instantly in the aqueous layer and completely disappeared in 15 min. After 30 min 25 ml of ether was added and the resulting organic layer was washed successively with 10 ml of water, 10 ml 10% H_2SO_4, 10 ml saturated Na_2CO_3 and 10 ml water. The resulting ether solution was dried (Na_2SO_4), filtered, and concentrated (in vacuo), yielding a slightly yellow

viscous oil. The oil was dissolved in a minimum amount of warm 100% ethanol and seeded. Upon standing at room temperature overnight, Phosvel^{TM}-(phenyl-$^{14}C_6$) crystallized as white rosettes. The crystals were collected and dried (in vacuo) yielding 211 mg (51.4%), 3.8 mCi at 7.4 mCi/mmole, of >99% pure Phosvel^{TM}-(phenyl-$^{14}C_6$); TLC, R_f 0.63 silica gel/hexanes:acetone (9:1). The overall radiochemical yield was found to be 38%.

O-(4-Nitrophenyl)-O-ethyl-phenyl-$^{14}C_6$-phosphonothioate, EPN^{TM}-(phenyl-$^{14}C_6$) (6).

To a solution of 211 mg (1.0 mmole) of phenyl-$^{14}C_6$-phosphonothioic dichloride in 1.5 ml of dry toluene at 0 to 5°C was added with the aid of a syringe a solution of 46 mg (1.0 mmole) of dry ethanol and 121 mg (1.0 mmole) 2-methyl-5-ethylpyridine in 1 ml of toluene in small increments over the period of 1 hr. The resulting reaction mixture was stirred at 8°C for an additional 1.75 hr and then allowed to warm to room temperature. Then 139 mg (1 mmole) p-nitrophenol and 100 mg tricaprylmethylammonium chloride were added to the stirring mixture followed immediately by the addition of 2 ml 1 N sodium hydroxide. After 1-1/2 hr the reaction had slowed down at the stage of approximately two-thirds conversion and was then completed by addition of 1 ml 1 N sodium hydroxide. After an additional 30 min stirring, the reaction was found to be complete and 40 ml ether was added. The resulting organic layer was washed successively with 2 x 25 ml water, 20 ml 10% sulfuric acid, 10 ml water, 20 ml saturated sodium bicarbonate and 20 ml water. The ether layer was dried over anhydrous sodium sulfate and concentrated (in vacuo) yielding 290 mg of a light yellow oil.

The product was purified by preparative TLC using silica gel plates and hexane-acetone 9:1 as the developing solvent yielding 156 mg (48%), 3.64 mCi at 7.5 mCi/mmole, of >98% pure EPN. The overall radiochemical yield was found to be 36.4%.

ACKNOWLEDGEMENT

We gratefully acknowledge the support of this work by the Environmental Protection Agency Contract No. 68-02-2236.

REFERENCES

1. Yoshitake, A., Mohri, Z., Kamada, T., Yasuda, T., and Nakatsuka, I. J. Labelled Compd. Radiopharm. 17:137 (1980).
2. Jenson, W. L.--U.S. Patent 2,662,917 (1951).
3. a. Hauna, D. L.--U.S. Patent 3,577,482 (1971).
   b. Shindo, N. et al.--U.S. Patent 3,327,026 (1967).
4. a. Ridgway, R. W., Greenside, H.S., and Freeman, H. H.--J. Am. Chem. Soc. 98, 1979 (1976).
   b. Freedman, H. H. U.S. Patent 3,972,887, August 3, 1976, Dow.

H. H. Kaegi* and W. P. Duncan
Midwest Research Institute
Kansas City, Missouri 64110

*present address
Bio-Organic Chemistry Laboratory
SRI International
Menlo Park, CA 94025