SYNTHESIS OF PIPERONYL BUTOXIDE-UL-PHENYL-^{14}C

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SUMMARY

An efficient route for the preparation of 5-[1-(2-butoxyethoxy) ethoxy]methyl-6-propyl-1,3-benzodioxole-UL-phenyl-^{14}C (piperonyl butoxide-UL-phenyl-^{14}C) is described. The synthesis consisted of 14 steps from $Ba^{14}CO_3$ and gave the title compound in overall chemical yield of 8 %. A discussion of some of the possible alternate routes is provided, including the various drawbacks to these routes. The importance of order of substitution on the benzene ring to maximize yields of the title compound is emphasized.

KEYWORDS: Piperonyl butoxide-UL-phenyl-^{14}C, 5-Bromo-1,3-Benzodioxole-UL-phenyl-^{14}C, Aniline-UL-^{14}C

INTRODUCTION

Piperonyl butoxide has been used in various mixtures as an insecticide synergist with synthetic pyrethroids, e.g. Derringer, Duracide, Grovex, Prentox, Scourge and also in combination with rotenone (1).

This paper describes a few of the possible synthetic methods for the preparation of piperonyl butoxide-UL-phenyl-^{14}C. 5-bromo-1,3-benzodioxole **(I)** is an intermediate common to each route considered, so attention is focused on its preparation. Subsequent reactions to place the propyl and polyether substituents on the benzene ring were of less concern since the primary substitution pattern on the ring was established. The introduction of the propyl substituent was carried out by reacting the Grignard reagent of 5-bromo-1,3-benzodioxole with allyl bromide to give 5-(2-propenyl)-1,3-benzodioxole (safrole) (2). Subsequent hydrogenation over Pd/C gave 5-propyl-1,3-benzodioxole (dihydrosafrole). Chloromethylation of the dihydrosafrole followed by

CCC 0362–4803/96/060511–12

Received 28 August 1995
Revised 14 November 1995

reaction with 2-(2-ethoxybutoxy)ethanol and sodium hydride introduced the polyether substituent to give piperonyl butoxide (Scheme 6.).

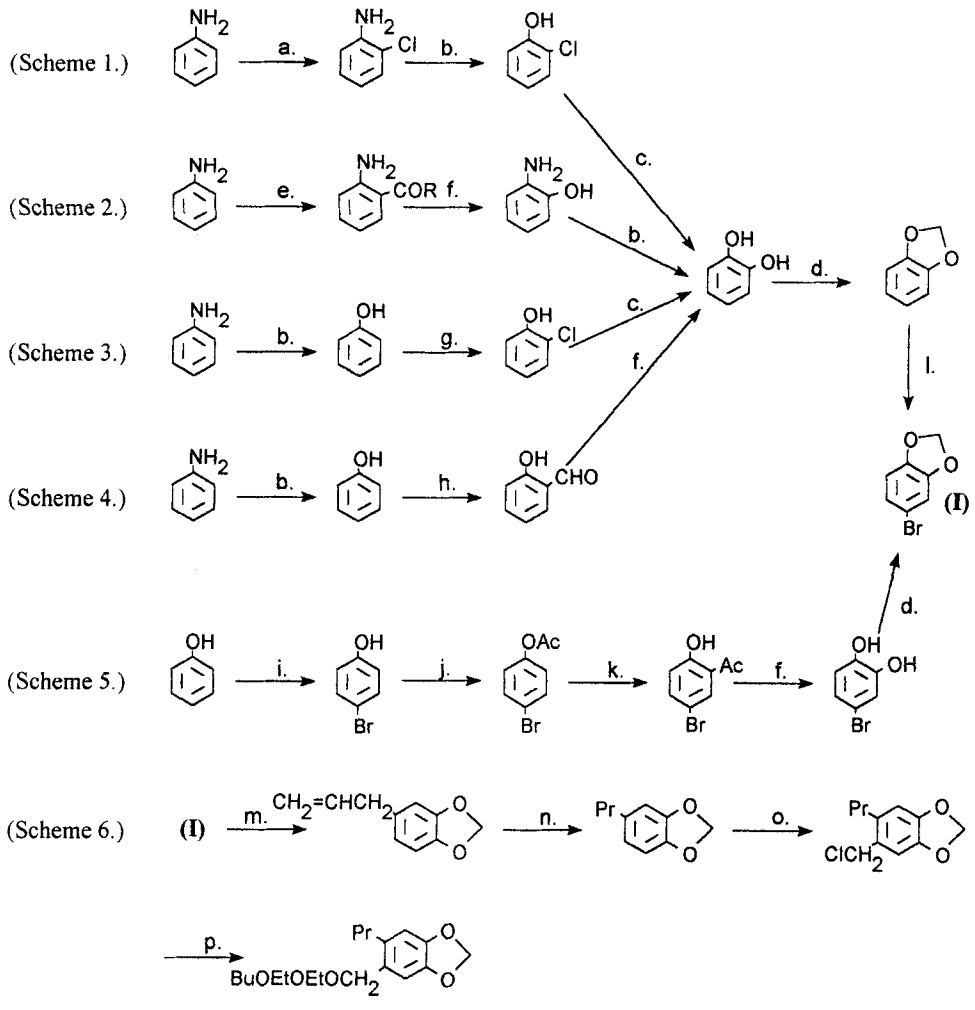
RESULTS AND DISCUSSION

This laboratory was commissioned to produce piperonyl butoxide-UL-phenyl-^{14}C for commercial purposes, therefore, the effort here reflects the need to find the most economic route to the product rather than being an effort of basic research. The conditions for each step were not optimized but were selected to satisfy the need at hand.

The possible routes considered for the preparation of the title compound all begin with aniline-UL-^{14}C and have 5-bromo-1,3-benzodioxole-UL-^{14}C as a common intermediate. The possible reaction schemes considered are given on the following page.

Our first efforts focused on obtaining catechol by chlorination of aniline with N-chlorosuccinimide (NCS) to give 2-chloroaniline followed by conversion to 2-chlorophenol via the Sandmeyer reaction. Subsequent reaction of the 2-chlorophenol with sodium hydroxide using cuprous chloride and palladium chloride as catalysts produced 1,2-dihydroxybenzene. Reaction of the catechol with dichloromethane and sodium hydride gave 1,3-benzodioxole. Bromination in acetic acid then gave 5-bromo-1,3-benzodioxole (Scheme 1.). Although chlorination of aniline with NCS gives predominantly the *ortho* isomer ($o/p \sim 2.4$), the yields of *ortho* and *para* combined amount to only 65 % (3). This results in a yield of the desired *ortho* isomer of only 46%. Indeed, repeated attempts gave crude products with o/p ratios of 2.4 - 2.7 and overall yields of 2-chloroaniline of 32 - 52 %. Chlorination of aniline with calcium hypochlorite is also reported to give predominantly the *ortho* isomer ($o/p > 3.4$), however few experimental details were given in the reference and this course was not pursued (4).

An *ortho*-specific reaction of aniline that was considered was the acylation of aniline with nitriles in the presence of aluminum chloride and boron trichloride (5). The resulting aminophenyl ketones produced could then be converted to 2-aminophenol and finally to catechol



(Scheme 2.). Although the acylation reaction leads to *ortho*-specific substitution, maximum yields of only 55 - 65 % were realized. In view of the less than desirable results with aniline, we decided to review *ortho*-specific reactions of phenol since aniline is easily converted to phenol in high yield.

One method for *ortho*-specific chlorination of phenol employs *t*-butyl hypochlorite as the chlorinating agent (6). Reported yields of 2-chlorophenol were still insufficient using this method. Another chlorination agent reported to be *ortho*-specific in the case of phenol is 2,3,4,5,6,6-hexachloro-cyclohexa-2,4-dien-1-one (7). Yields of *ortho*-chlorinated products are reported to be high (92 %), however, the long reaction time at low temperature (10 hours at -5° C) and the energy requirements (mercury lamp) were considered unsuitable.

Our attention next turned to introducing a formyl group in the *ortho* position of phenol. Several methods exist for the formylation of phenol (Vilsmeir, Gatterman-Koch, Gatterman, Reimer-Tiemann). Unfortunately, these methods either give *para* substitution or suffer from low yields. Another formylation method reported to give high yields of *ortho* formylated phenols was examined (Scheme 4.) (8). This method employs paraformaldehyde as the formylating agent as well as tin(IV) chloride as a complexing agent which directs the formyl group to the *ortho* position. A tertiary amine is also added to scavenge HCl liberated which could induce formation of phenol-formaldehyde polymer. Although this method seemed to be the most promising, the reported yield (78 %) of 2-hydroxybenzaldehyde from the formylation was never achieved in our hands. After repeated attempts either using the reported reaction conditions or by varying the acid scavenger or the stoichiometry, the best yield obtained of 2-hydroxybenzaldehyde was 54 %.

Since introduction of an *ortho* substituent was presenting such difficulties, the decision was taken to place the bromine substituent on the benzene ring early in the reaction sequence. Mono-bromination of phenol in carbon disulfide gives the *para* isomer nearly exclusively. With the *para* position blocked, a variety of methods could be used to introduce the desired *ortho* substituent. The various formylation methods were considered but we found that the Fries rearrangement of 4-bromophenyl acetate to 5′-bromo-2′-hydroxyacetophenone gave considerably better results. The bromination of phenol was carried out in carbon disulfide in a manner similar to an existing procedure (9). The crude product, which contained only 3 % of

the *ortho* isomer, was purified by column chromatography and the pure 4-bromophenol was obtained in over 93 % yield. Acylation of the 4-bromophenol with excess acetyl chloride gave 4-bromophenyl acetate in 91 % yield. The Fries rearrangement of the ester to 5′-Bromo-2′-hydroxyacetophenone was first attempted using a procedure similar to that of Klarmann (10, 11). The procedure consisted of adding anhydrous aluminum chloride directly to the neat ester and heating the mixture at 150-160° C for 30 min, then quenching the reaction. Our use of this procedure, however, gave inconsistent results and frequently, incomplete reaction. A modification of a procedure employing carbon disulfide as solvent was then used which produced excellent results, giving complete conversion of the ester to the ketone (12). Dakin oxidation of the ketone to 4-bromo-1,2-dihydroxybenzene (4-bromocatechol) was carried out using the procedure of Hocking (13). This procedure proved to be unsuitable, as the ketone would fall out of solution when the reagents were mixed. We found that by increasing the level of sodium hydroxide and hydrogen peroxide and by using slightly more solvent (water), the reaction proceeded in high yield, with all starting material being consumed.

The final step of the reaction sequence to produce 5-bromo-1,3-benzodioxole (Scheme 5.) was performed according to procedure developed by Castillo (14). This procedure consisted of adding a solution of 4-bromocatechol in dry hexamethylphosphoramide (HMPA) to a suspension of sodium hydride in HMPA. After evolution of hydrogen ceased, methylene chloride was added and the mixture heated at 50° C until the reaction was complete (2-4 hrs). Quenching the reaction mixture with water and extraction with ether afforded the benzodioxole in 60 % yield. Intermolecular coupling compounds, if any were formed, remained in the basic aqueous phase during extraction. Substitution of dibromomethane or diidomethane gave 55 % and 59 % chemical yields, respectively, of the benzodioxole. Another procedure is reported to give nearly quantitative yields of benzodioxoles (15). In this procedure, a solution of the catechol and methylene chloride in DMSO is added to a solution of sodium hydroxide at 130-140° C. We found, however, that sodium hydroxide was not appreciably soluble in DMSO even with prolonged heating at 170° C, and this method was not pursued.

The overall yield of ^{14}C labelled 5-bromo-1,3-benzodioxole using this sequence of reactions (Scheme 5.) was nearly 27 % from $Ba^{14}CO_3$. Although reaction conditions were not optimized, a chemical yield of 8 % was realized for the 14 step sequence to give piperonyl butoxide-UL-phenyl-^{14}C.

EXPERIMENTAL

Reagents

All unlabelled reagents were commercially available and were used without further treatment.

Aniline-UL-^{14}C was prepared by proprietary methods developed in our laboratory from $Ba^{14}CO_3$ in overall yield of 85.2 % with a specific activity of 56 mCi/mmol.

Phenol-UL-^{14}C Aniline hydrochloride-UL-^{14}C (1.278 g, 9.71 mmol, 544 mCi) was dissolved in 40 ml of 6N H_2SO_4 in a 100 ml single neck flask equipped with a magnetic stir bar. The flask was cooled in an ice bath and a solution of sodium nitrite (0.70 g, 10.2 mmol) in 20 ml of water was added dropwise through a pressure equalizing dropping funnel (PEDF) over 40 min. The mixture was stirred an additional 20 min in the ice bath. Urea (97 mg) was added to destroy any excess nitrous acid and the diazonium solution added to 97 ml of 50 % H_2SO_4 heated to 140-150° C with stirring. The diazonium solution was kept in an ice bath during the addition and added portionwise (1-2 ml) to a PEDF and dripped quickly into the acid solution. The addition was completed in 20 min. The product was then steam distilled into a receiver chilled in an ice bath until 50-60 ml were collected. The distillate was saturated with NaCl and extracted with Et_2O to remove all radioactivity. The combined extracts were dried over $MgSO_4$ and filtered. The solvent was stripped at the rotary evaporator under aspirator vacuum at a bath temperature of 25° C. The residue weighed 1.184 g. G.C. analysis (packing: OV-101, 10 %, temp.: 120° C) showed the residue to contain only phenol-UL-^{14}C and diethyl ether. By calibration with standard solutions of phenol in Et_2O, it was determined that the residue contained approximately 67 % phenol-UL-^{14}C by weight (0.794 g, 8.26 mmol, 463 mCi, 85 % chemical yield from the aniline).

4-Bromophenol-UL-^{14}C The solution of phenol-UL-^{14}C from above was transferred to a 25 ml 2-necked flask equipped with a magnetic stir bar and thermometer, using 6 ml of CS_2. The flask was cooled in an ice bath and a solution of bromine (1.33 g, 8.23 mmol) in 2 ml CS_2 was added using a 10 ml PEDF. The bromine solution was added dropwise over 30 min to maintain the temperature below 5° C. The mixture was stirred an additional 30 min in the ice bath, then transferred to a 50 ml single-necked flask with an ether rinse. The solvents were stripped at the rotary evaporator under aspirator vacuum in a 30° C bath. The residue was redissolved in 15 ml of ether and washed with 5 ml of 10 % sodium metabisulfite, 5 ml saturated sodium bicarbonate and 2 ml water. The organic phase was dried over $MgSO_4$ and filtered. Solvent was stripped at the rotary evaporator under aspirator vacuum at 30° C. The colorless liquid residue (1.096 g) was determined by G.C. (packing: OV-101, temp.: 150° C), using calibration as before, to contain 72.3 % 4-bromophenol-UL-^{14}C (1.38 g, 7.89 mmol) and 3.3 % 2-bromophenol-UL-^{14}C (62.6 mg, 0.36 mmol). The crude product was purified by column chromatography (~150 g silica gel, 60-100 mesh, 60 A, 4 cm i.d. x 48 cm column) eluting with 100 % CH_2Cl_2. The *ortho* isomer was eluted first and fractions containing the 4-bromophenol-UL-^{14}C were combined and concentrated using a rotary evaporator as before to give 2.206 g residue. G.C. analysis as previously described showed the residue to contain 59.9 % product by weight (1.32 g, 7.55 mmol, 423 mCi, 91.4 % chemical yield from phenol).

4-Bromophenyl acetate-UL-ring-^{14}C The flask containing the product from the previous reaction was cooled in an ice bath and 2.5 ml acetyl chloride added with stirring. The flask was stoppered and stirred an additional 5 min in the ice bath. The mixture was then allowed to stir at ambient temperature for approximately 16 hr. The excess acetyl chloride was stripped at 30° C. The residue was dissolved in 10 ml ether and washed with 4 ml each of 5 % sodium bicarbonate and water. The product solution was then dried, filtered and concentrated as before to give 2.432 g of colorless liquid. G.C. analysis at 120° C showed the residue to contain 61.3 % product by weight (1.49 g, 6.87 mmol, 384 mCi, 91 % chemical yield from 4-bromophenol-UL-^{14}C. The residual solvent was removed under high vacuum to give the crude product as a solid.

A portion of this material (0.775 g, 3.57 mmol, 200 mCi) was carried on without further purification.

5′-Bromo-2′-hydroxyacetophenone-UL-ring-^{14}C The 200 mCi of ester from above was dissolved in 3.5 ml CS_2 and added dropwise using a 10 ml PEDF to a stirred suspension of anhydrous $AlCl_3$ (0.96 g, 7.2 mmol) in 7 ml CS_2. The mixture was stirred 15 min at ambient temperature and then the solvent was distilled off. The mixture was heated for 2 hr at 150-160° C and gradually thickened, making stirring difficult. The mixture was cooled to ambient temperature and treated with 3.5 ml ice water and 4.5 ml 1N HCl with stirring. After an additional 5 min of stirring, the product was extracted with Et_2O (3 x 10 ml). The product solution was dried, filtered and concentrated as before to give 0.933 g of residue. G.C. analysis at 150° C showed the residue to contain 73.7 % product (0.727 g, 3.35 mmol, 188 mCi, 93.8 % chemical yield from the ester), the remainder was Et_2O and small amounts of 2 unidentified impurities.

4-Bromocatechol-UL-^{14}C Glassware pretreatment: To a 25 ml, 2-necked flask was added 2 ml of 30 % H_2O_2. The flask was then filled with 0.1N NaOH and magnetically stirred for a moment, then stoppered and allowed to stand overnight at ambient temperature. Immediately before use, the pretreatment solution was discarded and the flask and stir bar rinsed thoroughly with distilled water.

The ketone from the previous step was dissolved in a solution of sodium hydroxide (0.32 g, 8 mmol) in 16 ml water and transferred to the pretreated flask. A thermometer was placed in the side neck and 30 % aqueous hydrogen peroxide (1.09 g, 9.6 mmol) was added in one portion with rapid stirring. Some solid dropped out momentarily but rapidly redissolved. The temperature increased from 32 to 46° C at which point the flask was lowered into a water bath. When the temperature dropped to 45° C, the bath was removed. The mixture, which had darkened slightly, was then stirred for 17 hr at 25-30° C. The reaction mixture was acidified to pH 5 with glacial acetic acid. The aqueous solution was saturated with sodium chloride and

extracted with ether. The combined extracts were dried and filtered as before. TLC analysis on silica gel (CH_2Cl_2:MeOH, 95:5, UV detection) showed a single major spot at R_f~0.45 co-eluting with standard 4-bromocatechol, as well as 3 well-resolved faint spots of unknown identity. No starting material was recovered or observed. Radioscan of the plate with a Berthold LB 2838 Automatic TLC-Linear Analyzer showed the product to be 82.5 % radiochemically pure. The solvent was completely stripped at the rotary evaporator to give a light brown solid. The crude product was purified by column chromatography (~150 g silica gel, 60-100 mesh, 60 A, 4 cm i.d. x 48 cm column) eluting with 3 % MeOH in CH_2Cl_2. Combining the pure product fractions, stripping the solvent and drying under high vacuum to constant weight gave 0.505 g, 2.64 mmol of pure 4-bromocatechol-UL-^{14}C (148 mCi, 78.8 % chemical yield from the ketone precursor). TLC showed the product to be 99 % radiochemically pure.

5-Bromo-1,3-benzodioxole-UL-phenyl-^{14}C Sodium hydride (60 % dispersion in mineral oil, 0.32 g, 7.92 mmol) was placed in a 25 ml 2-necked flask equipped with a magnetic stir bar, a septum on the side neck and reflux condenser. A drying tube containing $CaSO_4$ was placed on top of the condenser and 5 ml hexamethylphosphoramide (HMPA) was added to the flask. The product from above in 2 ml HMPA was then added via syringe through the septum over 10 min. The mixture turned from colorless to green almost immediately. Methylene chloride (0.336 g, 3.96 mmol) was then added through the septum over 10 min and the reaction mixture heated 4 hr at 50° C. The mixture was cooled and added to 45 ml ice water with stirring. The mixture was extracted with 3 x 10 ml ether, the extract washed with 10 ml water, dried over $MgSO_4$ and filtered. The solvent was stripped to give 0.51 g of colorless liquid. G.C. analysis (10 % C20M, 150° C) with calibration as before showed the residue to contain only solvent and product (0.323 g, 1.59 mmol, 89 mCi, 60 % chemical yield from starting 4-bromocatechol-UL-^{14}C).

Safrole-UL-phenyl-^{14}C The product from above was diluted with 0.645 g, 3.21 mmol of unlabelled 5-bromo-1,3-benzodioxole to adjust the specific activity from 56 to 18.5 mCi/mmol. To a 25 ml single-necked flask equipped with a magnetic stir bar and reflux condenser was

added 4.8 mmol, 117 mg of powdered Mg (-50 mesh) and 3.5 ml anhydrous THF. The flask and condenser were swept with nitrogen and the flask heated to 55° C. Two drops of 1,2-dibromoethane were added to initiate the Grignard reaction, followed by the diluted product from above in 250 ul increments over 25 min. The mixture was heated an additional 45 min after the addition was complete. The Grignard solution was then added over 5 min to 15 ml of refluxing allyl bromide. The mixture was stirred an additional 5 min, cooled to room temperature, and quenched with 8 ml water, 1.2 g ammonium chloride and 1 ml of 29 % ammonium hydroxide. The lower organic layer was removed and the clear aqueous layer was washed with 2 x 7 ml ether. The combined organic solution was dried over $MgSO_4$ and filtered. The solvents were stripped at 40° C to give 1.002 g of colorless liquid. G.C. analysis (10 % OV-101, 160° C) showed that the residue contained safrole-UL-phenyl-^{14}C, allyl bromide and 1,3-benzodioxole-UL-phenyl-^{14}C. The residue contained 46.6 % product by weight (0.467 g, 2.88 mmol, 60.1 % chemical yield from 5-bromo-1,3-benzodioxole-UL-phenyl-^{14}C).

Dihydrosafrole-UL-phenyl-^{14}C The residue from above was dissolved in 15 ml MeOH and added to a 250 ml Parr bottle containing a stir bar and 100 mg of MeOH moistened 10 % Pd/C. The bottle was pressurized with 30 psi H_2 until uptake ceased (~15 min). Stirring under pressure was continued for an additional 15 min. The bottle was evacuated, pressurized with N_2 to 30 psi and evacuated again. The catalyst was removed by filtration and washed with MeOH. The solvent was stripped at 40° C. The residue separated into 2 phases and was partitioned between ether and water (10 ml each) and stirred. The upper organic layer was removed and dried over $MgSO_4$. After filtration and stripping of the solvent, 0.633 g residue was obtained. G.C. analysis (10 % C20M, 160° C) showed the residue to contain 66.6 % by weight of product (0.442 g, 2.69 mmol, 49.8 mCi), as well as 16 % by weight of 1,3-benzodioxole-UL-phenyl-^{14}C. The crude product was purified by preparative G.C. (183 x 0.77 cm i.d. column, 10 % C20M, 210° C). A total of 0.298 g (1.82 mmol, 33.7 mCi, 63 % chemical yield from safrole-UL-phenyl-^{14}C) was recovered that was 99 % pure by G.C.

5-chloromethyl-6-propyl-1,3-benzodioxole-UL-phenyl-^{14}C The dihydrosafrole was transferred to a 10 ml Wheaton Reactivial with Et_2O. The solvent was removed under vacuum and a micro stir bar was added to the vial. Formaldehyde (37 % aqueous solution, 0.177 g, 2.18 mmol) was added followed by 1.7 ml of concentrated HCl. The vial was sealed and stirred for 23 hr at 25-30° C. Water (4 ml) was then added and the mixture extracted with ether. The extract was dried and filtered and the solvent stripped to give 0.378 g, 1.77 mmol of crude product which was used without further purification in the final step.

Piperonyl butoxide-UL-phenyl-^{14}C Sodium hydride (60 % dispersion in mineral oil, 0.212 g, 5.31 mmol) was placed in a 10 ml single-necked flask equipped with a micro stir bar. The flask was cooled in a water bath and 2-(2-butoxyethoxy)ethanol (1.72 g, 10.6 mmol) was added with stirring. After the bubbling subsided, the product from above in 1.5 ml of 2-(2-butoxyethoxy)ethanol was added dropwise over 2-3 min. The mixture was stirred under a nitrogen blanket for 3 hr at 115-120° C. After another 16 hr at 25-30° C, the reaction was quenched with 5 ml water and transferred to a 50 ml flask with the aid of an additional 15 ml water. The aqueous solution was extracted with 3 x 10 ml hexane. The combined extracts were washed with 5 ml water, dried and filtered. The solvent was stripped to yield 0.828 g of colorless oil. TLC analysis on silica gel eluting with hexane:diethyl ether, 2:1 showed the product to have radiochemical purity of 82.5 %. The product was purified on a column of silica gel (3 x 24 cm), eluting with petroleum ether (30-60° C):diethyl ether, 3:1. The pure fractions were combined and the solvents stripped to give 0.490 g of piperonyl butoxide-UL-phenyl-^{14}C (1.45 mmol, 27.8 mCi, 89 % from the crude chloromethyl precursor), which had a radiochemical purity of 98.4 % by TLC.

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