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ω-Iodophenyl Fatty Acids: A Convenient Method of Radioiodination*

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A solid-phase radioiodination technique for ω-iodophenyl fatty acids using ammonium sulfate is described. The radioiodinations are (1) regioselective, (2) high in yield (95%), (3) short in reaction time (1 h) and (4) capable of yielding high specific activity products although at lower yields. Purification is exceptionally simple: a single passage through an ion exchange column to remove unreacted $*I^-$ is all that is required. Syntheses of several ω-iodophenyl fatty acids are also described.

Introduction

In the past 4 years radiolabeled ω-phenyl fatty acids have been developed as radiopharmaceutical probes of myocardial metabolism.[1-10] As alternatives to ω-iodoheptadecanoic[11] and ω-iodohexadecanoic,[12,13] the ω-(*p*-iodophenyl) analogs offer enhanced chemical and metabolic stability due to their shorter and thus stronger carbon–iodine bond. However, in contrast to the ω-iodoalkylfatty acids which are easily radiolabeled by isotopic exchange in refluxing acetone[14] or methylethyl ketone,[12] the first reported synthesis of an ω-iodophenyl fatty acid required radiolabeling by a time consuming and technically demanding electrophilic substitution reaction.[1,3] This technique is not regioselective; extensive HPLC purification is required to separate the *ortho* (29%) and *para* (71%) isomers. A recent modification of this procedure still requires two HPLC purification procedures.[15]

Three other radioiodination techniques have been applied to the synthesis of radioiodinated ω-iodophenyl fatty acids: thallium bis(trifluoroacetate) displacement,[6-8] triazene decomposition[19-22] and interhalogen exchange.[23,24] Thallium bis(trifluoroacetate) displacement suffers from the need to prepare the thallated precursor shortly before displacement. Thallation is not regiospecific (85–90% *para* substitution is common) and purification of a mixture of isomers is again necessary on a frequent basis. The maximum radiochemical yield is 75%.[16] The second method, triazene decomposition, is regioselective but is disadvantaged by several factors: first, extensive synthetic transformations beginning with ω-phenyl fatty acid precursors are necessary to achieve the stable triazene; second, overall yields of radioiodination are low;[21,22] and third, chromatography is required to remove unreacted triazene. The last method of radioiodination, interhalogen exchange, offers the greatest potential. The process is regioselective and the precursor ω-halophenyl fatty acids are stable and can be synthesized from the respective ω-phenyl fatty acids. Such exchanges using benzoic[23] or acetic acid[24] as the exchange medium have been reported. However, the benzoic acid and acetic acids must either be eliminated (benzoic acid) or buffered to physiological pH (acetic acid) before i.v. administration of radioiodinated ω-iodophenyl fatty acid into humans.

Clearly, a direct exchange reaction employing easily synthesized, stable precursors would be desirable, especially if exchange and purification could be done quickly, in high yield, in high specific activity, and in a medium compatible with subsequent i.v. injection into humans. An added advantage would be purification via a single passage through an ion-exchange column to remove free radioiodide if present. We report here the successful solid-phase radioiodination of ω-halophenyl fatty acids by a mild halogen exchange technique recently developed in our laboratory[25] which meets these desired criteria. Reported here as well are the syntheses of some ω-iodophenyl fatty acids which were subjected to this exchange technique.

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Table 1. Solid-phase exchange radioiodination of ω-halophenyl fatty acids in the presence of ammonium sulfate[a]

ω-Halophenyl acid	Compound number	Exchange conditions			Specific activity (mCi/mg)
		Time (h)	Temp. (°C)	% Yield*	
p-I-PhCH$_2$CO$_2$H	1	1.0	145	96[b]	0.5 (0.4)
p-BrPhCH$_2$CO$_2$H[c]	2	1.7	160	34	0.1
p-I-Ph(CH$_2$)$_5$CHCH$_2$CO$_2$H CH$_3$	3	1.5	145	43[d]	1.46
p-I-Ph(CH$_2$)$_{10}$CO$_2$H	4	1.0	145	76 (55)	0.4
p-I-Ph(CH$_2$)$_{14}$CO$_2$H	5	3.0	160	95	1.72
(*p*-IPPA)		1.0	170	>95	5.4
		3.0	160	46	43.6
p-Br-Ph(CH$_2$)$_{14}$CO$_2$H[e]	6	2.5	145	<5	
		2.0	170	56	3.8

[a]Conditions: compound (0.2–2.0 mg), Na^{125}I (5–20 mCi), $(NH_4)_2SO_4$ (2–5 mg), initial volume (H_2O) 0.2–1.0 mL, solid phase.
[b]Yield based on TLC data.
[c]Radiolabeled product was ^{125}I-*p*-iodophenylacetic acid.
[d]Water was present.
[e]Radiolabeled product was ^{125}I-*p*-iodophenylpentadecanoic acid.
*Isolated yield.

Experimental

Analyses

Elemental analyses of carbon, hydrogen, iodine and bromine were performed commercially (Spang Microanalytical Laboratory, Eagle Harbor, Mich.). Proton magnetic resonance (^{1}H NMR) spectra (Varian T-60A spectrometer with $(CH_3)_4Si$ as internal standard) and infrared (i.r.) spectra (Perkin Elmer spectrometer with polystyrene as reference standard) were obtained for each compound. Melting points are uncorrected.

Chromatographic analyses

TLC analyses were performed on 2.5 × 20 cm silica gel coated glass plates (Whatman K6F) or on 2.5 × 20 cm cellulose coated glass plates (Whatman K2F). The reaction solutions were applied over a spot of 0.1 M NaI to minimize loss of volatile radioiodine by air oxidation. The plates were analyzed on a Packard Model 720 radiochromatogram scanner immediately after development and drying. Percent exchange was determined by integration of the radiochromatogram peaks (by the product of peak height × peak width at half-height) and calculated as the ratio of activity of exchanged product to the total activity chromatographed, averaged for duplicate chromatograms. The solvent systems and the respective R_f values (with variability generally within ±5%) of free iodine and iodate for each system are as follows: A, EtOH/EtOAc/concentrated NH_4OH (20/20/1): 0.60, 0.06; B, n-BuOH/AcOH/H_2O (6.5/1.5/2.5): 0.45, 0.06; C, hexane/Et_2O/HOAc (320/80/1)0.00, 0.00; R_f values for the compounds listed in Table 1 are as follows: **1**, **2**, **3**, **4** (on silica gel plates) 0.30 (A), 0.80 (B); **5**, **6** (on cellulose plates), 0.90–0.95 (C).

Chemical purity of the exchange and precursor heat stability were established for **5**. The general procedure (see below for details) for exchange radioiodination was followed except that NaI was substituted for Na^{125}I. The temperature was maintained at 170°C for 1 h. HPLC analysis of **5** before and after exchange was carried out using a Waters μ-Bondapak C-18 column (4.6 × 250 mm) with the following solvent system: MeOH/H_2O/HOAc (86/9/5) (2 mL/min flow rate).

Radiochemical purity for some of the ^{125}I-labeled compounds listed in Table 1 was confirmed by HPLC analysis. A Waters Model 272 liquid chromatograph equipped with a Radiomatic Flo-one radiactive flow detector (200-μL solid scintillator cell) was used employing simultaneous u.v. (254 nm) and radioactivity detection. The above C-18 column was used for analysis of iodephenylacetic acid isomers with the following solvent system: 3% Et_3N in H_2O titrated to pH 7.5 with H_3PO_4/acetonitrile (83/17) (1 mL/min flow rate). See Fig. 1 for an HPLC trace of this analysis.

Chemicals

The following chemicals were obtained from commercial sources: 15-phenylpentadecanoic acid (EMKA, Chemie, Markgronigen, F.R.G.), 11-bromoundecanoic acid (Aldrich Chemical Co.), 3-methylglutaric anhydride (Aldrich), 1-bromo-3-phenylpropane (Aldrich), *o*- and *p*-iodophenylacetic acid, *p*-bromophenylacetic acid. All HPLC solvents were purchased (Burdick & Jackson Labs, Inc.). Other reagents were analytical grade and used without further purification.

Synthetic procedures

It should be noted that no attempts were made to maximize synthetic yields or to purify all intermediates.

11-(p-iodophenyl)undecanoic acid (**4**). The methyl ester of 11-phenylundecanoic acid[26] was prepared using boron trifluoride etherate in absolute methanol. The ester, identified by NMR and i.r., was used without further purification. Iodination was accomplished using the slightly modified procedure

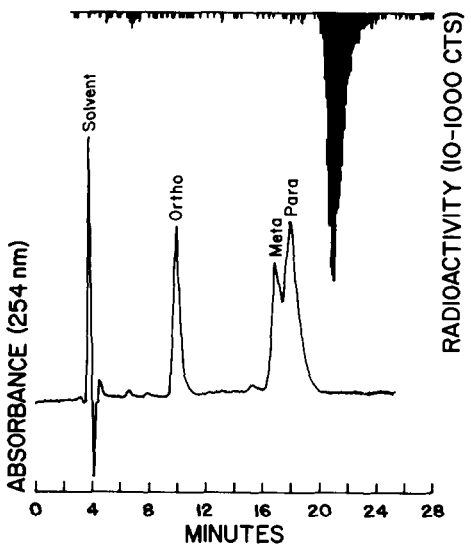

Fig. 1. HPLC of the product of ^{125}I exchange of *p*-iodophenylacetic acid spiked with a mixture of *o*-, *m*- and *p*-iodophenylacetic acids. The lower trace shows u.v. (254 nm) detection; the upper shows radioactivity detection. Analysis was performed as described in Experimental. The t_R difference between the u.v. peak for *p*-iodophenylacetic acid and the radioactive peak for *p*-[^{125}I]iodophenylacetic acid represents the time lag between the u.v. and radioactive detectors, which are in series.

of Merkushev *et al.*[27] described as follows. To a suspension of 0.83 g (3.0 mmol) of methyl 11-phenylundecanoate and 1.55 g (3.6 mmol) of bis(trifluoroacetoxy)phenyl iodine[28] in 15 mL of carbon tetrachloride was added 0.38 g (1.5 mmol) of finely divided iodine. The reaction was stirred at room temperature for 24 h. The mixture was treated with distilled water and the layers separated. The organic layer was diluted with ether, extracted twice with aqueous sodium metabisulfite and then stirred 2.5 h with aqueous sodium metabisulfite. After separation of layers the organic layer was dried with anhydrous magnesium sulfate and volatile solvents removed under reduced pressure. The ester was saponified and the resulting acid recrystallized several times from carbon tetrachloride-petroleum ether (30–60 C) to give 0.69 g (59% yield) of *p*-iodophenylundecanoic acid (>95% *para* based on NMR) m.p. 86.5–87.5; ^{1}H NMR ($CDCl_3$) δ 1.20–2.0 [envelope centered at 1.33, 16H, $(CH_2)_8$—], 2.23–2.73 (m, 4H, $PhCH_2$— and —CH_2CO_2), 7.48 (q[A_2X_2], 4H, I – C_6H_4—), 10.93 (s, 1H,—CO_2H); i.r. (CCl_4) 1700 cm^{-1} (C=O). Anal. calc'd for $C_{17}H_{25}IO_2$: C, 52.58; H, 6.49; I, 32.68. Found: C, 52.32; H, 6.40; I, 32.65.

15-(p-iodophenyl)pentadecanoic acid (**5**). The methyl ester of 15-phenylpentadecanoic acid was prepared using boron trifluoride etherate in absolute methanol. The ester was identified by NMR and i.r. and was used without further purification. Methyl 15-phenylpentadecanoate (0.33 g, 1.0 mmol) was iodinated with bis(trifluoroacetoxy)phenyl iodine and iodine as above. The ester was saponified. The crude acid (0.3 g) was a mixture of *o*- and *p*-iodophenylpentadecanoic acid which was >95% *para* by NMR. A small portion of the mixture was purified by HPLC [column: Partisil 10 ODS-2; flow rate 2 mL/min; eluent: MeOH/H_2O/acetic acid (86/9/5); $k' = 17.2$ min]; m.p. 92–94 (lit. m.p. 95[23] and 92–93[17]; ^{1}H NMR ($CDCl_3$) δ 0.8–2.0 [envelope centered at 1.26, 24H,—$(CH_2)_{12}$—]. 2.3–2.8 (m,4H,$PhCH_2$— and —CH_2CO_2), 7.42 (q[A_2X_2], 4H,I—C_6H_4—); i.r. (CCl_4) 1700 cm^{-1} (C=O). Anal. calc'd for $C_{21}H_{33}IO_2$: C,56.76; H, 7.48; I, 28.56. Found: C, 56.87; H, 7.48; I, 28.46.

15-(p-bromophenyl)pentadecanoic acid (**6**). To a well-stirred mixture of 0.210 g (0.66 mmol) of 15-phenylpentadecanoic acid and 0.292 g (0.76 mmol) of thallium(III) acetate in 2.0 mL of carbon tetrachloride under a nitrogen atmosphere was added a solution of 0.105 g (0.66 mmol) of bromine in 2 mL of carbon tetrachloride dropwise. After the addition was complete, the mixture was heated at reflux for 30 min. The cooled reaction mixture was filtered and then thoroughly washed with aqueous sodium metabisulfite, aqueous 5% sodium carbonate and water. The organic layer was dried over anhydrous magnesium sulfate and solvent removed under reduced pressure to give 0.226 g crude product. A portion of this product was purified by HPLC (column: Partisil 10 ODS-2 reverse phase; eluent: MeOH/H_2O/acetic acid, 86/9/5; flow rate: 2.0 mL/min; $k' = 14.4$ min) to yield product as colorless crystals; m.p. 82–84, ^{1}H NMR ($CDCl_3$) δ 0.8–2.0 (envelope centered at 1.3, 24H,—$(CH_2)_{12}$—), 2.3–2.8 (m,4H, $PhCH_2$ and —CH_2CO_2), 7.4 (q[A_2X_2],4H,—C_6H_4—); i.r. (CCl_4) 1700 cm^{-1} (C=O). Anal. calc'd for $C_{21}H_{33}BrO_2$: C, 63.47; H, 8.37; Br, 20.11. Found: C, 63.38; H, 8.39; Br, 20.19.

Methyl 3-methly-5-oxo-8-phenyloctanoate. To a mixture of 6.0 g (0.034 mol) of the acid chloride of methyl 3-methylglutarate and 6.5 g (0.034 mol) of copper(I) iodide in 30 mL anhydrous tetrahydrofuran cooled to −78 under a dry, nitrogen atmosphere was added dropwise a Grignard solution prepared from 6.77 g (0.034 mol) of 1-bromo-3-phenylpropane and 0.816 g (0.034 mol) of magnesium in 25 mL absolute ether. The black reaction mixture was allowed to come slowly to room temperature and allowed to stand overnight. Ether was added and solid copper salts removed by filtration. The filtrate was dried with anhydrous magnesium sulfate and volatile solvents removed under reduced pressure to give 8.8 g of crude product. Distillation *in vacuo* (140–150 , 1–2 mmHg) yielded 3.25 g of yellow oil (36% yield) identified by 1 H NMR ($CDCl_3$) δ 0.93 (d, 3H, —$CHCH_3$), 1.3–2.8 (m, 11H, —CH— and —CH_2—), 3.7 (s, 3H, —OCH_3), 7.36 (s, 5H, C_6H_5—) and by i.r. (neat) 1740 cm^{-1} (CO_2CH_3), 1715 (C=O).

Methyl 3-methyl-8-phenyloctanoate. The oxo ester

(4.0 g, 0.015 mol) was reduced with hydrazine hydrate (2.08 g) in 7 mL diethylene glycol containing 4.0 g (0.1 mol) sodium hydroxide using the Huang-Minlon modification of the Wolff-Kishner reaction. The reaction mixture was diluted with water and extracted with ether. The aqueous layer was then acidified and extracted with ether. After drying over anhydrous magnesium sulfate, the volatile solvents were removed under reduced pressure to yield 2.95 g of crude product. The methyl ester was prepared using boron trifluoride etherate in absolute methanol; ^{1}H NMR ($CDCl_3$) δ 0.92 (d 3H, CH—C$\underline{H}_3$, J = 6 Hz), 1.1–2.0 (envelope centered at 1.33, 9H, —CH_2— and —CH—), 2.1–2.4 (m, 2H, —CH_2C=O), 2.65 (t, 2H, $C_6H_5C\underline{H}_2$—), 3.70 (s, 3H, —OCH_3), 7.37 (s, 5H, C_6H_5—); i.r. (neat) 1740 cm^{-1} (C=O). Anal. calc'd for $C_{16}H_{24}O_2$: C, 77.37; H, 9.74. Found: C, 77.33; H, 9.69.

8-(p-iodophenyl)-3-methyloctanoic acid (**3**). The methyl ester (0.75 g, 3.0 mmol) was iodinated with 1.55 g (3.6 mmol) of bis(trifluoroacetoxy)phenyl iodine and 0.38 g (1.5 mmol) of finely divided iodine in 15 mL of carbon tetrachloride according to the procedure above. Extraction and treatment with aqueous sodium metabisulfite as above yielded 0.90 g of pale yellow oil. Saponification of a portion of the ester (0.20 g, 0.5 mmol) resulted in 0.1 g (55% yield) of acid as a yellow oil. A small portion was purified by HPLC (column: Partisil 10 ODS-2 reverse phase; eluent: MeOH/H_2O/acetic acid, 86/9/5; flow rate: 1 mL/min; $k' = 7.2$ min) to yield acid as a colorless oil; ^{1}H NMR (CCl_4) δ 0.95 (d, 3H, —CHC$\underline{H}_3$), 1.0–1.6 (envelope centered at 1.3, 9H, —CH_2— and —CH—), 2.1–2.36 (m, 2H, —CH_2C=O), 2.6 (t, 2H, $C_6H_4C\underline{H}_2$—), 7.35 (q[A_2X_2], 4H, —C_6H_4—), 12.1 (s, 1H, CO_2H); i.r. (CCl_4) 1710 cm^{-1} (C=O). Anal. calc'd for $C_{15}H_{21}IO_2$: C, 50.03; H, 5.84; I, 35.24. Found: C, 50.02; H, 5.80; I, 35.20.

Exchange radioiodinations

The ^{125}I used in this study was a no-carrier-added solution of Na^{125}I (*ca.* 500 mCi/mL) in reductant-free 0.1 N NaOH obtained from New England Nuclear. Radioactivity was quantified with a Capintec Model CRC-2 radioisotope calibrator or a Packard Model 5260 autogamma counter. Both instruments were calibrated against an NBS standard solution of Na^{125}I.

General procedures. Solid-phase reactions were performed in 1 or 5 mL septum-closed multidose vials with a disposable glass syringe as the distillate condenser and receptacle. The experiments were carried out under a flow of air (*ca.* 5–10 cm^3/min) introduced via an 18 gauge needle through the septum of the reaction vessel. Heating was accomplished with an oil bath, and the temperature reported for non-refluxing reactions are those of the equilibrated oil bath. At appropriate time intervals, TLC analysis and pH measurement (via combination microelectrode) were carried out either directly (refluxing solutions) or after redissolution of the reaction medium in a volume of solvent equal to the initial volume (solid-phase reactions).

For preparative radioiodide exchange of the compounds listed in Table 1, 0.2–2.0 mg of substrate, 5–20 mCi of Na^{125}I, and 2–5 mg of ammonium sulfate were dissolved in 0.4–1.0 mL of water or aqueous alcohol, the mixture was heated to dryness, and the dry reaction mixture was maintained at 145–170 C (below the melting point of the substrate) for 1–4 h. The reaction mixture was then dissolved in 1–4 mL of water. Passage of the resulting solution through a Cellex-D (Bio-Rad) anion-exchange column (1 × 4 or 1.5 × 5 cm), and elution with 5% acetic acid in ethanol removed the unbound radioiodide from the final preparation. The product concentration of the eluent from the Cellex-D column was determined by u.v. absorption at its λ_{max} and calculated from a standard curve of unlabeled compound generated on a Bausch and Lomb Spectronic 70 spectrophotometer against a blank of acetate buffer. Specific activity of the exchanged product was then determined from the specific concentration obtained by u.v. spectroscopy or by estimation based on starting quantities of substrate and final radiochemical yield.

Results and Discussion

The syntheses of nonradioactive compounds **3**, **4** and **6** are reported for the first time. Synthesis of **5** by different iodination procedures has been reported.[17,23] As syntheses employed standard chemical transformations which were achieved without difficulty, no further remarks are necessary.

Six ω-halophenyl fatty acids of varying chain length were exchange-labeled under solid-phase conditions. The results of these exchanges are compiled in Table 1. It should be noted that percent yield and temperature were optimized only for **5**, *p*-IPPA, as it is the ω-iodophenyl fatty acid of current clinical interest.

To avoid extensive chromatographic purification, the exchange should yield a single radioactive product in addition to unreacted radioiodide. Figure 1 shows an HPLC analysis of the product of the exchange procedure using *p*-iodophenylacetic acid, **1**, as precursor. As can be seen from the trace of radioactivity, a single radioactive product corresponding to ^{125}I-labeled **1**, was obtained. In addition, the exchange method should not produce either dehalogenated or rearranged products, i.e. the precursor and the product should be stable to the conditions of the exchange. Product stability is established in part by detection of a single radioactive product. Precursor stability was established by subjecting **5** to the conditions of the exchange except for the substitution of NaI for Na^{125}I. HPLC analysis of **5** before and after exchange showed the presence of **5** only (t_R of **5** = 9.97, t_R of PPA = 7.18); thus re-

arrangement and/or dehalogenation of precursor does not occur.

For interhalogen exchange radioiodinations to be useful on a routine, clinical basis, the ideal purification would be a single passage through a disposable ion exchange column to remove unreacted radioiodide. To avoid using HPLC for purification the exchange must be regiospecific, i.e. the exchange must yield a single product of known structure. The regiospecificity of iodine for iodine exchange was established by HPLC analysis of exchange products using *p*-iodophenylacetic acid (**1**). The iodophenylacetic acid isomers can be separated by HPLC ($t_0 = 9.58$; $t_m = 16.33$; $t_p = 17.30$). Only *para* for *para* exchange was observed. Similar results were obtained for *o*-, *m*- and *p*-iodobenzoic acids.[25] Thus, interiodine exchange in the presence of ammonium sulfate is regiospecific.

The regiospecificity of iodine for bromine exchange was also established by HPLC analysis of exchange products using *p*-bromophenylacetic acid, **2**. The only radioiodinated product had $t' = t_p$, above. Although I for Br exchange is regiospecific, it is not as useful for routine use. For example at 170°C I for *I exchange to yield *p*-*IPPA required 1.0 h to achieve greater than 95% exchange but Br for *I exchange as for **6** was only 50% complete at 2.0 h. Thus not only are the percent exchange rates lower, the length of reaction time is also increased.

The need for an acidic environment for aryl iodide exchange has been demonstrated.[23,25,29] We have confirmed that exchange is negligible for pH > 7.0 for ω-iodophenyl fatty acids. The sodium hydroxide usually present in commercially available radioiodide solutions poses a problem which can be solved in two ways. Neutralization of hydroxide and acidification of the reaction medium can be achieved either by adding a sufficient quantity of fatty acid to be exchanged, or by adding an alternative source of protons. The former approach severely limits the specific activity of the product which can be achieved[23] and is therefore of little utility. The latter approach using benzoic[23] or acetic acid[24,29] is successful, but the presence of these acids requires additional steps in the workup procedures prior to human use. Ammonium sulfate is an excellent alternative. It provides an acidic reaction mixture, and since both ammonium and sulfate ions are compatible with human use, it requires no removal prior to injection. We report here a 95% yield for **5** (*p*-IPPA) using ammonium sulfate which is identical to that reported for *p*-IPPA using benzoic acid.[24] Ammonium sulfate thus gives comparable yields of a clinically useful fatty acid while simplifying purification.

High specific activity syntheses are also possible using ammonium sulfate solid-phase exchanges. An exchange at 170° for **5** produced *p*-*IPPA with a specific activity of 5.4 mCi/mg, a value comparable to that reported by Eisenhut.[23] A specific activity of 43.6 mCi/mg was achieved in one experiment but the isolated yield was reduced.

The major advantage of this direct halogen exchange lies in the purification. As the exchange employs no metals or solvents incompatible with human use and yields a single product of known structure, purification requires minimal effort. The reaction mixture is merely dissolved in warm aqueous solution and passed through a short anion exchange column to remove free radioiodide. The solution is now ready for formulation for human use. The entire reaction can be performed in a closed system thus making it a viable approach for large-scale, routine production of ^{123}I-or^{131}I-labeled ω-iodophenylpentadecanoic acid.

In conclusion, solid phase radioiodinations of ω-iodophenyl fatty acids in the presence of ammonium sulfate are advantageous for six reasons: (1) the exchanges are regioselective, (2) the exchanges yield a single product (3) percent yields of 95% are routinely available, (4) specific activities up to 40 mCi/mg can be achieved, but with a decrease in yield, (5) reaction times are relatively short and (6) human use purification involves only a single passage through an ion-exchange column.

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