

# Radioiodination via Isotope Exchange in Pivalic Acid

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A variety of benzoic and aryl aliphatic mono and polyiodinated acids and esters (sterol, triglyceride) were radioiodinated in 55-99% radiochemical yield by isotope exchange with  $\text{Na}^{125}\text{I}$  in a melt of pivalic acid. In general, the reaction was complete in 1 h at 155°C with little or no substrate decomposition. High specific activity studies afforded  $^{125}\text{I}$ -labeled iopanoic acid with a specific activity of over 700 Ci/mmol.

## Introduction

Introduction of radioiodine into organic molecules can be accomplished by a variety of techniques depending on the structure of the compound to be labeled. Excellent reviews of radioiodination methods have recently been reported.<sup>(1,2)</sup> Aromatic compounds possessing electron donating groups (e.g. phenols and anilines) are easily radiolabeled by electrophilic iodination in the presence of radioiodine, iodine monochloride, chloramine-T, iodogen, etc.<sup>(1)</sup> A variety of methods also exist for radioiodination of unactivated aromatic rings and, in general, the method of choice is dependent on the degree of specific activity sought. If high specific activity (Ci/nmol) is desired, one approach involves exchange of an appropriate leaving group with radioiodide and subsequent separation of the substrate from the radioiodinated product. Leaving groups recently employed in this manner include aryl boronic acids,<sup>(3)</sup> aryl thallium trifluoroacetates,<sup>(4)</sup> triazenes,<sup>(5,6)</sup> and metallated arenes (tin, germanium, silicon).<sup>(7)</sup> Although very high specific activities (2000 Ci/mmol) can be achieved, radiochemical yields are typically less than 30%. Direct electrophilic radioiodination of the phenyl ring also affords high specific activity products, but in this case, isomeric mixtures frequently result which are usually difficult to separate.<sup>(8-10)</sup>

If high specific activity is not required, iodine exchange of aryl iodides with radioiodide represents a viable alternative. Advantages of the method include ease of synthesis, characterization, and handling of the stable substrate, and that no complex separation techniques are necessary since the substrate and radioiodinated product are chemically identical.

Although isotope exchange of aliphatic iodides is usually conducted in a refluxing solvent such as acetone, methyl ethyl ketone (MEK), water, or ethanol,<sup>(1)</sup> unactivated aryl iodides generally require higher reaction temperatures to effect the exchange. Accordingly, high boiling solvents such as propylene glycol have been utilized with some success.<sup>(11)</sup> In another method, the substrate and radioiodide are reacted at elevated temperatures (100-200°C) in a "melt" fashion. The molten reaction medium must possess a sufficiently high dielectric constant to solubilize both the substrate and radioiodide. Examples of such media include benzoic acid<sup>(12)</sup> (m.p. 122°C, b.p. 249°C) and acetamide (m.p. 82°C, b.p. 221°C). The latter has been used with some success by several groups,<sup>(13,14)</sup> but only with limited success in our laboratory.<sup>(15)</sup> Another method, which employs ammonium sulfate, is conducted below the melting point of both the exchange medium and the substrate. Employing ammonium sulfate in this manner also has a catalytic effect on the exchange,<sup>(16,17)</sup> which, according to the authors, is attributed to a gradual increase in the acidity of the medium as a result of *in situ* decomposition of ammonium sulfate with concomitant loss of ammonia.<sup>(16)</sup> Copper sulfate has also been used in a similar manner.<sup>(18,19)</sup>

We have examined the acetamide melt procedure quite extensively in studies with radioiodinated sterol esters.<sup>(15,20)</sup> The method generally afforded sufficient, albeit low, yields of labeled product. Utilization of ammonium sulfate also afforded low yields of radioiodinated products. This was due in part, to the formation of large amounts of volatile iodine upon addition of ammonium sulfate to the substrate/radioiodide mixture.

Based on these results and the finding that acidic conditions facilitate the exchange (*vide infra*), we sought a new exchange medium. In fulfilling the desired requirements, it was necessary that the medium possess sufficient acidity, appropriate melt-

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ing and boiling points, and relative chemical inertness. Although acetic acid seemed to qualify, and has indeed been utilized as an exchange medium, its chemical inertness in the presence of esters was dubious. A homolog of acetic acid, pivalic acid (trimethylacetic acid), more closely fits the desired physical properties (m.p. 33°C, b.p. 164°C). Moreover, the steric hindrance associated with this acid also decreased the likelihood of it becoming a reactant or promoter of side reactions under conditions of the exchange reaction. Initial studies with pivalic acid as the exchange medium were promising and in fact afforded [<sup>125</sup>I]cholesteryl iopanoate (**5b**) in over 90% radiochemical yield with little or no ester hydrolysis. Subsequent studies with  $\omega$ -(3-amino-2,4,6-triiodophenyl)-alkanoate triacylglycerols and free acids were also successful. Based on these favorable results, we continued to study the scope of pivalic acid as an exchange medium with a variety of different substrates as shown in Tables 1–5.

### Materials and Methods

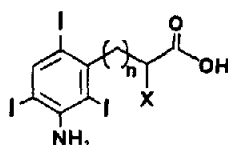
The <sup>125</sup>I used was a no-carrier-added solution of Na<sup>125</sup>I (5 mCi/0.1 mL) in reductant-free 0.1 N NaOH obtained from New England Nuclear. Radioactivity was quantified with a Searle 1185  $\gamma$ -counter. Tetrahydrofuran (THF) was distilled from LiAlH<sub>4</sub> under argon immediately prior to use. All radioiodination reactions were conducted inside a plexiglass glove box vented with a model RIT-140 radioiodine trap (Hi Q Filter Products, La Jolla, California). Thin layer chromatography (TLC) analyses were performed on Merck silica gel-60 F<sub>254</sub> polyethylene-backed plates. The plates were analyzed by u.v. and scanned for radioactivity on a Vanguard 930 autoscanner immediately after development and drying. Radiochemical yield was then determined by integration of the chromatogram peaks (by cut and weigh) and calculated as the ratio of radioactivity of exchanged product to the total radioactivity on the plate. In general, two solvent systems were used (hexane/ethyl acetate, 5:2 for esters and THF/hexane, 6:4 for acids). In both systems, the *R<sub>f</sub>* of Na<sup>125</sup>I was from 0 to 0.05. Column chromatography was performed on Merck silica gel-60 (230–400 mesh) eluted in the same two solvent systems. The HPLC system used to confirm radiochemical purity and determine specific activity of some of the compounds, consisted of an Altex 110A pump, Gilson 111 u.v. monitor (254 nm) and in-line Bicon Analyst® (Bicon Electronic Products, Newbury, Ohio) survey meter equipped with a model G1LE low energy  $\gamma$  scintillation probe and strip chart output. Columns and solvents used include a Watman Partisil 5 RAC column (9.4 × 100 mm) eluted with hexane/ethyl acetate (9:1) and an Excalibur 5  $\mu$ m (4.6 × 250 mm) C<sub>18</sub> reverse-phase column eluted with methanol.

### Radioiodine exchange in pivalic acid. General procedure

The compound to be radioiodinated (1–5 mg) was placed in a 2-mL serum vial which was then sealed with a Teflon-lined rubber septum and aluminum cap. Freshly distilled THF (100–200 mL) and aqueous Na<sup>125</sup>I (10–50  $\mu$ L) were added in succession via a microliter syringe and the vial was gently swirled to dissolve the contents and ensure homogeneity. Inlet and outlet cannuli were inserted and a gentle stream of nitrogen applied to evaporate the solvents. When the residue appeared dry, the seal was removed and solid pivalic acid (5–20 mg, dried by azeotrope with toluene and distilled under nitrogen) was added. The vial was resealed as previously described and partially immersed in a preheated (155–160°C) oil bath. When the isotope-exchange reaction was essentially complete (usually 1–2 h), the reaction vial was allowed to cool, dry THF (200  $\mu$ L) was added with a glass syringe and the vial swirled gently. A TLC sample (1–2  $\mu$ L) was removed with a 10  $\mu$ L syringe and the remaining contents were transferred to the top of a silica gel-60 column (1 × 10 cm) and subsequently eluted with the appropriate solvent system. If necessary, especially when labeling polar compounds, excess pivalic acid can be removed prior to chromatography by inserting a disposable syringe containing granulated charcoal as a trap into the reaction vial while heating and allowing the pivalic acid to distill into the trap. When eluting the column, a survey meter probe was placed at the outlet of the column to serve as a radiodetector. Fractions were collected and the radiochemical purity of each was monitored by TLC using u.v. and radioactivity detection. The appropriate fractions were combined and the solvents removed with a gentle stream of nitrogen. HPLC analysis of the final compound confirmed both chemical (u.v.) and radiochemical (radioactivity) purity, and because u.v. and radioactivity were plotted simultaneously with a two-pen strip chart recorder, calculation of specific activity was also possible by comparison of u.v. and radioactivity peak areas to preconstructed standard calibration curves. Reaction times and radiochemical yields are included in Tables 1–5. Actual isolated yields were generally 5–20% lower than shown depending on the extent of purification necessary or desired. In all cases, radiochemical purity of final compounds exceeded 95%.

### Results and Discussion

The pivalic acid exchange method reported here evolved during studies of the synthesis and evaluation of potential organ- or tumor-specific scintigraphic and CT imaging agents. Table 1 represents a series of  $\omega$ -(3-amino-2,4,6-triiodophenyl)-alkanoic acids which ironically includes both the highest and also some of the lowest yields listed. During radioiodination of acid **1a**, the reaction mixture remained

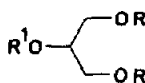
Table 1. Radioiodination of  $\omega$ -(3-amino-2,4,6-triiodophenyl) alkanic acids in pivalic acid

Compound	<i>n</i>	<i>x</i>	Time (h)	Yield (%) <sup>a</sup>
1a	0	H	2	59
1b	1	H	1	99
1c	1	Et	1	98
1d	10	H	1	99
1e	15	H	3	59 <sup>b</sup>

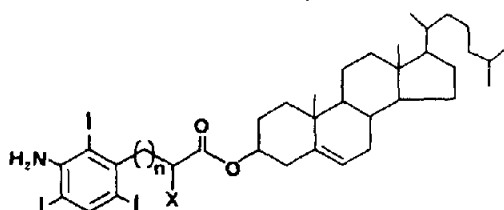
<sup>a</sup>By TLC of the reaction mixture.<sup>b</sup>Accompanied by unidentified side products (31%).

heterogeneous apparently due to lack of solubility of the substrate. This problem was eventually overcome, however, by substituting neodecanoic acid, a higher boiling (> 200°C) isomeric mixture of trialkylacetic acid (methyl, ethyl, propyl mixtures), for pivalic acid. When conducted in neodecanoic acid at 200°C, the reaction mixture was homogeneous and ultimately afforded radioiodinated 1a in 86% radiochemical yield. The low yield (59%) obtained for acid 1e was due to formation of a more polar side-product (31%).

Esterification of glycerol with acids 1a–e afforded a series of mono-, di- and trisubstituted triacylglycerols. The results obtained upon subsequent radioiodination of the intact triacylglycerols ranged from 70 to 99% radiochemical yield as shown in Table 2. Formation of hydrolysis products such as free acids, mono- and diglycerides, was quite minimal and except for 2a (11%) only ranged from 0 to 5%. High radiochemical yields (94–98%) were also obtained with cholesteryl- $\omega$ -(3-amino-2,4,6-triiodophenyl)-alkanoates (5a–c) as shown in Table 3. Moreover, the yield of 98% obtained for cholesteryl

Table 2. Radioiodination of  $\omega$ -(3-amino-2,4,6-triiodophenyl) alkanate triacylglycerols in pivalic acid<sup>a</sup>

Entry	R	R <sup>1</sup>	Time (h)	Yield (%) <sup>b</sup>
2a	P	1a	1	92
2b	P	1b	1	80
2c	P	1c	1	80
2d	P	1d	1	71
2e	P	1e	2	97
3a	1a	P	2	83
3b	1b	P	2	96
3c	1c	P	1	94
3d	1d	P	1.5	91
3e	1e	P	2	90
4a	1b	1b	2	92
4b	1c	1c	6	70
4c	1d	1d	1.5	93
4d	1e	1e	2	80

<sup>a</sup>P = palmitate, otherwise R, R<sup>1</sup> correspond to acyl group listed in Table 1.<sup>b</sup>By TLC of the reaction mixture.Table 3. Radioiodination of cholesteryl  $\omega$ -(3-amino-2,4,6-triiodophenyl)-alkanoates in pivalic acid

Entry	<i>n</i>	<i>x</i>	Time (h)	Yield (%) <sup>a</sup>
5a	1	H	1	94
5b	1	Et	1	98
5c	10	H	3	95

<sup>a</sup>By TLC of the reaction mixture.

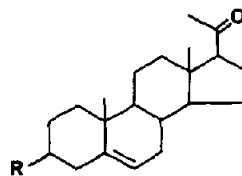
ipanoate (5b) was an improvement over the 35% yield previously reported with acetamide.<sup>(20)</sup>

The results were less consistent, however, for the pregnenolone mono- and polyiodinated benzoate esters (6a–f) and carbamate (6g) (Table 4). As may be anticipated, the triiodinated benzoates (6a, b) were labeled the most efficiently, and although yields were lower for the remaining compounds (6c–g), there was no evidence of ester hydrolysis.

To further study the scope of the reaction, we subjected a variety of different compounds to these radioiodination conditions as shown in Table 5. Radioiodination of *o*-iodohippuric acid (hippuran, 7, Fig. 1), a scintigraphic agent for assessing kidney function, had previously been reported by at least five different groups.<sup>(19)</sup> Yields ranged from 2 to 57% until Wanek *et al.*,<sup>(21)</sup> in 1977, and Hawkins *et al.*,<sup>(19)</sup> in 1982, successfully obtained [<sup>125</sup>I]hippuran in 98% radiochemical yield in the presence of copper sulfate. Employing pivalic acid as an exchange medium, radioiodination of *o*-iodohippuric acid (7) was equally successful, and thus may be applicable for use with <sup>125</sup>I.

Radioiodination of 1-(2-chlorophenyl)-1-(4-iodophenyl)-2,2-dichloroethane (9, Fig. 1), an analog of the adrenal chemotherapeutic agent *o,p'*-DDD (Mi-

Table 4. Radioiodination of pregnenolone aryl esters in pivalic acid



Entry	R	Time (h)	Yield (%) <sup>a</sup>
6a	2,3,5-triiodobenzoate	1	95
6b	3,4,5-triiodobenzoate	1	94
6c	2,5-diiodobenzoate	1	81
6d	2-iodobenzoate	1	82
6e	4-iodobenzoate	1	81
6f	2,6-dimethyl-3-iodobenzoate	1	63
6g	4-(4-iodophenyl) butyryl-carbamate	1	68

<sup>a</sup>By TLC of the reaction mixture.

Table 5. Radioiodination of miscellaneous compounds in pivalic acid

No.	Compound	Time (h)	Yield (%) <sup>a</sup>
7	<i>o</i> -iodohippuric acid	1	99
8	5-iodotubercidin	1	55
9	1-(2-chlorophenyl)-1-(4-iodophenyl)-2,2-dichloroethane	2.5	73
10	3-iodobenzoic acid	1	35 <sup>b</sup>
11	3-bromobenzoic acid <sup>d</sup>	1	15 <sup>c</sup>
12	11-iodoundecanoic acid	1	96
13	11-bromoundecanoic acid <sup>d</sup>	1	99
14	15-(4-iodophenyl) pentadecanoic acid	1	74
15	1-palmitoyl-2-iopanoyl-sn-glycero-phosphatidyl choline	1	60

<sup>a</sup>By TLC of the reaction mixture.

<sup>b</sup>Accompanied by an impurity (54%).

<sup>c</sup>Accompanied by three impurities (71%).

<sup>d</sup>Radiolabeled products are [<sup>125</sup>I]3-iodobenzoic acid for 11, and [<sup>125</sup>I]11-iodoundecanoic acid for 13.

totane), and also of 5-iodotubercidin (**8**, Fig. 1), an adenosine kinase inhibitor, was also fairly successful.

In addition, 15-(4-iodophenyl)-pentadecanoic acid, a widely studied myocardial imaging agent, has been radioiodinated with <sup>123</sup>I in a melt of benzoic acid at 170°C in 95% yield by Eisenhut.<sup>(12)</sup> Although the 74% radiochemical yield presented in Table 5 was

less than expected, it was the result of a single trial and was not optimized.

In order to test the applicability of using pivalic acid to effect I for Br exchange, entries 10–13 were included. The low values obtained with 3-iodobenzoic acid (**10**) and 3-bromobenzoic acid (**11**) are in agreement with results reported by Mangner,<sup>(16)</sup> who attributed the low yield of **10** to deactivation by the electron-withdrawing carboxyl group. In contrast, interhalogen exchange in the presence of pivalic acid was easily effected with 11-bromoundecanoic acid (**13**). The nearly quantitative incorporation of radioiodide exceeds the results typically obtained by I for Br exchange of aliphatic bromides conducted in refluxing acetone or methyl ethyl ketone (80%). Moreover, routine HPLC separation of 17-[<sup>123</sup>I]iodoheptadecanoic acid from its bromo precursor by Dudczak *et al.*,<sup>(22)</sup> if applicable here, offers potential for the preparation of no-carrier-added quantities of radioiodinated fatty acids in high radiochemical yields.

In order to further investigate the reaction characteristics, several additional studies were conducted.

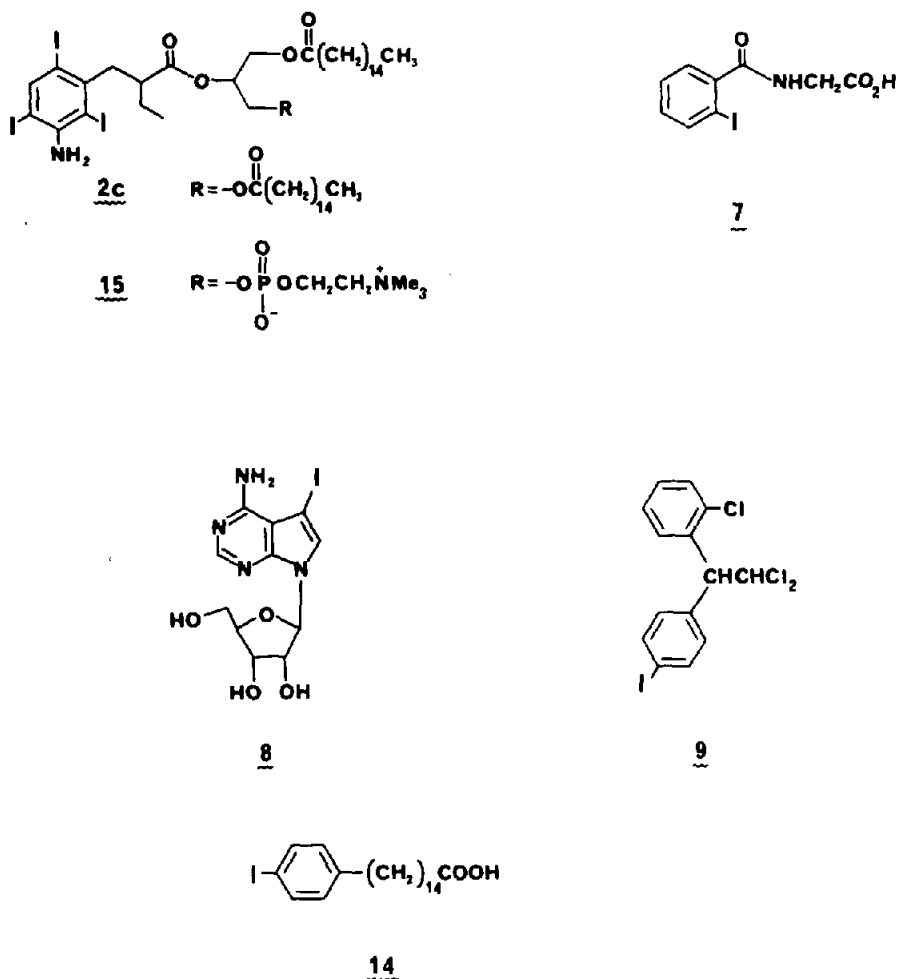


Fig. 1. Miscellaneous compounds radioiodinated by exchange in pivalic acid.

Initial time and temperature studies were performed with iopanoic acid (**1c**) and glyceryl 1,3-dipalmitoyl-2-iopanoate (**2c**) in order to ascertain the labeling efficiency of the free acid vs the ester. As can be seen in Fig. 2, radioiodination of iopanoic acid was essentially complete by 10 min at 155°C while 60 min at 100°C were required to achieve 84% radiochemical yield. Radioiodination of iopanoate ester **2c** (Fig. 3), on the other hand, was slower and was also accompanied by the formation and disappearance of an apparent transient radioactive intermediate which was less polar than **2c** by TLC (*vide supra*).

To investigate the acid catalysis of pivalic acid in the exchange reaction, a comparable study was conducted with iopanoic acid (**1c**) in neopentyl alcohol (2,2-dimethyl-1-propanol, m.p. 52°C, b.p. 114°C) at 105°C for 1 h (Table 6). A radiochemical yield of 33% was obtained along with the formation of three radioiodinated side-products (49% total) as compared to an 84% yield obtained with pivalic acid at essentially the same temperature. When an ester, cyclohexyl iopanoate, was subjected to exchange in neopentyl alcohol, a 50% yield was obtained. Addition of Amberlite, a resin containing sulfonic acid functionality often used in catalytic applications, to neopentyl alcohol resulted in an even lower yield (39%) of [<sup>125</sup>I]cyclohexyl iopanoate. By comparison, pivalic acid exchange afforded [<sup>125</sup>I]cyclohexyl iopanoate in 70% yield with no accompanying side-product formation. These results imply that in addition to its solvent role, pivalic acid apparently also has a catalytic influence on the exchange reaction.

Because exchange occurs too rapidly with iopanoic acid in pivalic acid at 155°C, cyclohexyl iopanoate was also utilized to study the relative labeling efficiencies of pivalic acid, benzoic acid, and acetamide. As seen in Table 7, the relative efficiencies of the three media were: pivalic acid > benzoic acid > acetamide.

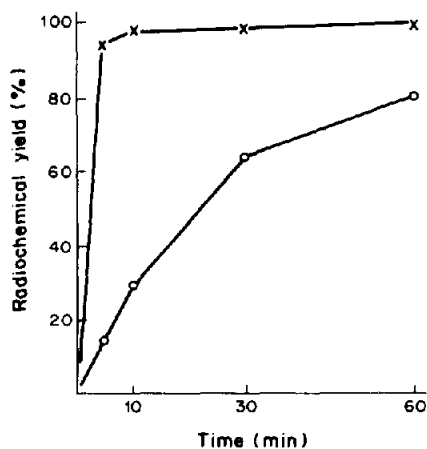


Fig. 2. Radiochemical yield of [<sup>125</sup>I]iopanoic acid (**1c**) as a function of time and temperature. 1 mg of **1c** was exchanged at 155 (x) and 100°C (o).

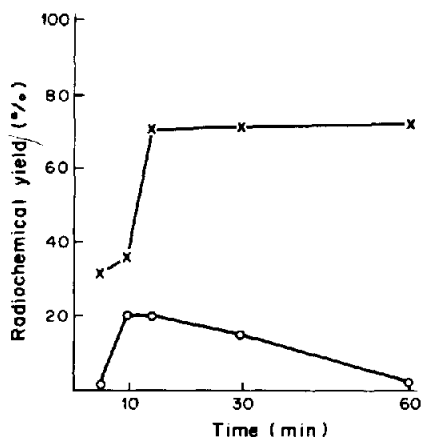


Fig. 3. Radiochemical yield of [<sup>125</sup>I]-**2c** (x) and transient intermediate (o) as a function of time at 155°C.

Throughout these studies high specific activity was not a goal and generally not considered achievable by isotope exchange under the described conditions. However, by increasing the amount of Na<sup>125</sup>I (2.5 mCi) and decreasing the amount of iopanoic acid (1 μg), we were able to obtain [<sup>125</sup>I]iopanoic acid with a specific activity of over 700 Ci/mmol in roughly 60% radiochemical yield (Table 8). Of interest was the appearance of a slightly less polar radioactive im-

Table 6. Apparent catalytic effect of pivalic acid at 105°C for 1 h

Substrate	Conditions	Yield (%)	
		Desired	Other <sup>a</sup>
Iopanoic acid	Neopentyl alcohol	33	49
Cyclohexyl iopanoate	Neopentyl alcohol	50	14
Cyclohexyl iopanoate	Neopentyl alcohol plus Amberlite	39	23
Cyclohexyl iopanoate	Pivalic acid	70	0

<sup>a</sup>Total radioactive side-products excluding unreacted Na<sup>125</sup>I.

Table 7. Effect of various media on radioiodide exchange between Na<sup>125</sup>I and cyclohexyl iopanoate<sup>a</sup>

Medium	Yield (%) <sup>b</sup>
Acetamide	9
Benzoic acid	65
Pivalic acid	78

<sup>a</sup>Conditions: 3 mg cyclohexyl iopanoate, 10–12 mg of media, 2 μL aq. Na<sup>125</sup>I (200 μCi), 155°C for 1 h.

<sup>b</sup>by TLC of reaction mixture

Table 8. High specific activity study with iopanoic acid<sup>a</sup>

Amount (μg)	Na <sup>125</sup> I (mCi)	Rad. Yield (%) <sup>b</sup>		Spec. act. Ci/mmol
		desired	transient	
100	1.0	95	0	5.4
10	1.0	90	0	51.4
1	1.5	59	22	498 <sup>c</sup>
1	2.5	56	40	778 <sup>c</sup>

<sup>a</sup>Conditions: substrate (1–100 μg), aq. Na<sup>125</sup>I (1–2.5 mCi, 2–5 μL) and pivalic acid (1 mg) at 155°C for 1 h in a Wheaton micro V-vial (0.3-mL).

<sup>b</sup>by TLC of reaction mixture (silica gel, THF/hexane (6:4), iopanoic acid *R<sub>f</sub>* = 0.50, transient *R<sub>f</sub>* = 0.64).

<sup>c</sup>calculated by comparison of HPLC radioactivity trace vs a standardized radioactivity calibration plot and quantity of starting iopanoic acid. Since we were unable to see iopanoic acid by u.v. at 254 nm at this scale, this represents a minimum specific activity.

purity much like that formed with glyceryl iopanoate **2c** at 105°C (*vide infra*). An important difference, however, was that in the previous case the substrate (**2c**) was present in a very large excess on a molar basis relative to Na<sup>125</sup>I. At the highest specific activity level (1 µg of iopanoic acid, 2.5 mCi of high specific activity Na<sup>125</sup>I, 17.4 Ci/mg Na<sup>125</sup>I) the molar ratio of substrate to radiiodide was only about 1.85. Radioactive side-products have been reported<sup>(23,24)</sup> upon ω-iodination of fatty acids by halogen exchange with Na<sup>123</sup>I and Na<sup>131</sup>I in MEK, and in one case, was found by GC-MS analysis to be butyl iodide.<sup>(24)</sup>

In order to gain insight into the nature of the transient intermediate, it was isolated from the 2.5 mCi high specific activity reaction mixture by HPLC and portions subjected to the following experimental conditions:

(1) High specific activity Na<sup>125</sup>I and pivalic acid were heated in the usual manner without iopanoic acid. A large radioactive peak (88%) with  $R_f = 0.61$  (THF/hexane, 6:4) and possessing no u.v. absorbance by TLC was formed. Further treatment of the reaction mixture with excess sodium thiosulfate resulted in total conversion of radioactivity with  $R_f = 0.61$  to the origin (Na<sup>125</sup>I), thus implying the formation of some oxidized form of iodide which is much less polar than Na<sup>125</sup>I itself. Accordingly, a portion of the transient intermediate fraction was treated with sodium thiosulfate in a similar manner to see if it also could be "reduced" back to Na<sup>125</sup>I. There was no change, however, indicating that the intermediate formed in the presence of iopanoic acid was not the same one seen previously upon heating Na<sup>125</sup>I and pivalic acid.

(2) When the transient intermediate fraction was reheated in the presence of additional iopanoic acid and pivalic acid, all of the radioactivity became associated with the iopanoic acid. The result was inconclusive, however, because it was not known whether the transient intermediate had radioiodinated the new iopanoic acid or was actually an intermediate iopanoate-iodine species which upon further heating was converted to [<sup>125</sup>I]iopanoic acid. In response to this uncertainty, a final experiment was conducted in which another portion of the transient intermediate was simply reheated in the presence of pivalic acid. The radioactivity was indeed converted to [<sup>125</sup>I]iopanoic acid. Therefore, based on these preliminary studies, it appears that the transient "impurity" may actually be an iopanoic acid-radioiodine complex which upon further heating can be converted to labeled iopanoic acid. Further assessment of mechanistic detail is difficult in view of the non-classical behavior of iodine in very small (nmol) quantities, where for instance, oxidation species like HIO and HIO<sub>2</sub> are known to be quite stable.<sup>(1,16,23,24)</sup> Nevertheless, the implication of the involvement of an oxidized iodine species coupled with the poor results obtained with compounds containing electron

withdrawing groups such as 3-iodobenzoic acid, seems to favor an electrophilic rather than a nucleophilic mechanism.

### Conclusions

A variety of benzoic and aryl aliphatic mono and polyiodinated acids and esters, as well as 5-iodotubercidin, an analog of *o,p'*-DDD (Mitotane), and 11-bromoundecanoic acid were radioiodinated by isotope exchange with Na<sup>125</sup>I in a melt of pivalic acid at 155°C. In general, the reaction was complete in 1 h with little or no substrate decomposition. Radiochemical yields were good to excellent (55–99%) except for 3-iodo- and 3-bromobenzoic acids, which were apparently deactivated by the electron-withdrawing effect of the carboxyl group. In addition, I for Br exchange with 11-bromoundecanoic acid afforded almost quantitative yields of [<sup>125</sup>I]iodoundecanoic acid which, if separated from the bromo substrate according to a recently reported method,<sup>(22)</sup> could give rise to carrier-free ω-iodoalkanoic acids. Radioiodination of cyclohexyl iopanoate in pivalic and benzoic acids as well as acetamide resulted in the following relative labeling efficiencies: pivalic acid > benzoic acid >> acetamide. Additional high specific activity studies afforded [<sup>125</sup>I]iopanoic acid with a specific activity of over 700 Ci/mmol. Because of its rapidity, the method is appropriate for use with <sup>123</sup>I ( $t_{1/2} = 13.3$  h), currently the iodine nuclide of choice for scintigraphic imaging. Finally, because the method is most successful with lipophilic substrates, it is very complimentary to the ammonium sulfate method,<sup>(16)</sup> which is best suited toward water-soluble compounds, and as such, provides the radiochemist with an efficient method of radioiodinating a wide variety of compounds.

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