Synthesis and Biologic Evaluation of 1-[^{11}C]-3,3-Dimethylheptadecanoic Acid

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1-[^{11}C]-3,3-dimethylheptadecanoic acid ([^{11}C]DMHDA) has been prepared for evaluation as a potential myocardial metabolism indicator based on an expected intrinsic stability toward beta-oxidative metabolic processes. Synthesis of this novel branched-chain fatty acid was accomplished by copper-catalyzed addition of tetradecylmagnesium bromide to diethylisopropylidenemalonate. Subsequent saponification and decarboxylation afforded 3,3-dimethylheptadecanoic acid (DMHDA) that was converted to the corresponding alkyl bromide by means of a modified Hunsdiecker reaction. Carboxylation of 2,2-dimethylhexadecylmagnesium bromide with $^{11}CO_2$ gave [^{11}C]DMHDA. Carbon-11 DMHDA showed moderate myocardial uptake in fasted rats, albeit lower than that reported for the 3-monomethyl analog. Considerable washout of radioactivity from the heart was also observed over the first 30 min postinjection. Imaging in dogs likewise showed disappointing heart uptake with much higher localization in the lung. These data suggest that *gem*-dimethyl substitution of the beta- position in long chain fatty acids is not only insufficient for enhanced myocardial uptake and retention, but also, may be deleterious when compared with beta-monomethylation.

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Myocardial energy demand is met primarily by fatty acid oxidation (*1*). Radiolabeled fatty acids that display efficient myocardial uptake and prolonged myocardial retention are attractive candidates for clinical evaluation of regional discrepancies in fatty acid metabolism that occur in ischemic heart disease and cardiomyopathies. For example, fatty acids labeled with carbon-11 (^{11}C) and used as adjuncts to positron emission tomography represent valuable tools for assessment of myocardial energy demands (*2–6*).

Studies with straight-chain ^{11}C-labeled fatty acids have been encouraging, but efficient myocardial extraction has been accompanied by rapid loss of radioactivity from the heart due to the beta-oxidation process. It has been shown that myocardial retention of a fatty acid can be enhanced if the beta-oxidation process is inhibited (*7–13*). Thus, in imaging studies in dogs, 1-[^{11}C]-3-methylheptadecanoic acid ([^{11}C]BMHDA), a branched-chain fatty acid analog, showed not only good myocardial uptake, but also retention of radioactivity up to 1 hr postinjection (*13*). The improved retention of [^{11}C]BMHDA compares favorably with the rapid washout of 1-[^{11}C]-heptadecanoic acid, and may be a result of its trapping in the myocardium, secondary to inhibition of fatty acid metabolism. Quite recently, several studies involving radioiodinated ω-iodophenyl fatty acids have demonstrated that dimethylation of the beta-position results in even greater myocardial retention than observed with either the beta-monomethyl- or unbranched analogs (*14–16*), presumably as a result of prevention of catabolism by alternate routes besides inhibition of beta-oxidation (*14*).

As part of our continuing research program to develop radiodiagnostic agents for imaging the myocardium, we chose to investigate the *gem*-dimethyl analog of [^{11}C]BMHDA to determine the effects of such a modification on myocardial uptake and retention. Herein is described the synthesis of this novel, radiolabeled, branched-chain fatty acid and its biologic evaluation.

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MATERIALS AND METHODS

General

Melting points were determined on an open-capillary melting point apparatus and are uncorrected. Proton nuclear mag-

netic resonance (NMR) were obtained and chemical shifts are reported relative to internal tetramethylsilane standard. Elemental analyses were performed commercially* and all values are within 0.4% of theoretic values. Thin layer chromatography analyses were done on silica gel 60 F_{254} 0.2 mm glass plates† and visualized by spraying with 1% phosphomolybdic acid in ethanol and subsequent heating. Flash chromatography was performed according to a published method (*17*) using silica gel for flash chromatography†‡.

Synthesis of 1-[^{11}C]-3,3-dimethylheptadecanoic acid [^{11}C] DMHDA) (Scheme 1).

Diethyl 1,1-dimethylpentadecylmalonate (2). This diester was prepared by a procedure similar to one previously described (*18,19*). A Grignard solution was prepared from 1-bromotetradecane (8.39g, 0.03 mol), magnesium (730 mg, 0.3g-atom) and 150 ml tetrahydrofuran containing a crystal of iodine. After the slightly exothermic reaction had subsided, the reagent was added to ethyl isopropylidene malonate (1, 6.0g, 0.03 mol) (*20*) dissolved in 50 ml tetrahydrofuran containing cuprous chloride (150 mg) stirred at ambient temperature under nitrogen. After 24 hr, the reaction mixture was concentrated to a reduced volume, then poured into a mixture of ice and 3N hydrochloric acid. After stirring for 30 min, the mixture was extracted with a total of 250 ml of ether. The extract was dried ($MgSO_4$), filtered and concentrated to a yellow syrup that was flash chromatographed. Elution with 3% ethyl acetate-petroleum ether gave 3.07 g (26%) of **2** as a clear liquid. Anal. C,H; NMR(CCl_4) δ1.07–1.50(m, 41H, $(CH_3)_2C$-, CH_2-), 3.2(s, 1H, $C\underline{H}(CO_2Et)_2$), 4.17(g, 4H, $OC\underline{H}_2CH_3$).

1,1-dimethylpentadecylmalonic acid (3). A mixture of **2** (2.5 g, 6.3 mmol) and potassium hydroxide (10 g, 0.18 mol) in 10 ml water was heated at reflux for 5 hr. After cooling, the reaction mixture was acidified with 6N hydrochloric acid and extracted with ether (1 × 100 ml; 2 × 25 ml). The ether extracts were combined, washed with brine, dried ($MgSO_4$), filtered and concentrated to give 2.0 g (93%) crude **3**. Crystallization from petroleum ether gave the pure diacid, m.p.: 86.5–87.5°. Anal. C,H; NMR(CCl_4) δ0.8–1.5(m, 35H, $(CH_3)_2C$-, CH_2-1), 3.38(s, 1H, $C\underline{H}(CO_2H)_2$), 12.2(s, 2H, COOH).

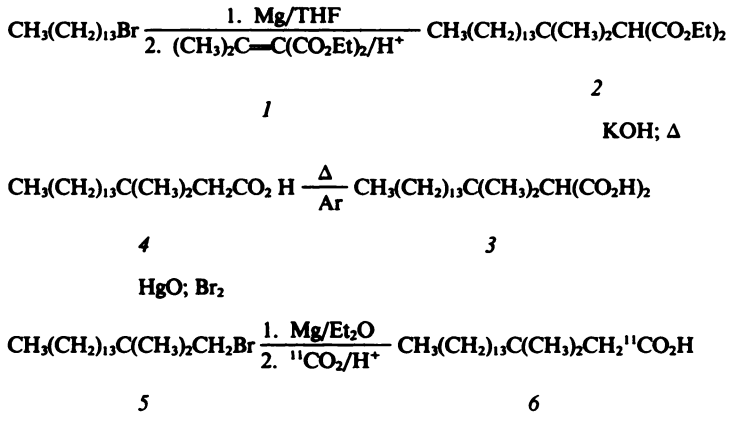
3,3-dimethylheptadecanoic acid (4). The diacid (**3**, 1.0 g, 3 mmol) was heated under argon for 2 hr at 170–190°. The waxy solid which formed upon cooling was flash chromatographed. Elution with 10% ethyl acetate-petroleum ether gave 0.78 g (90%) **4** as a waxy crystalline solid, m.p.: 39–40°. Anal. C,H; NMR(CCl_4) δ0.8–1.4(m, 35H, $(CH_3)_2C$-, CH_2-), 2.2(s, 2H, $C\underline{H}_2COOH$), 12.15(s, 1H, COOH).

2,2-dimethylhexadecyl bromide (5). The bromide was prepared by a modified Hunsdiecker reaction (*21,22*). A mixture of the acid (**4**, 1.93g, 6.5 mmol) and red mercuric oxide (705 mg, 3.25 mmol) in 24 ml 1,1,2,2-tetrachloroethane was heated to remove 12 ml of solvent and water. The heat source was removed and when the temperature of the reaction mixture had reached 70°, bromine (0.34 ml, 6.5 mmol) in 2 ml carbon tetrachloride was added dropwise to the clear yellow solution. Immediate evolution of carbon dioxide and subsequent precipitation of mercuric bromide occurred. After stirring for 24 hr at ambient temperature, the reaction mixture was filtered (Celite) and the filtrate concentrated to a pale yellow liquid which was flash chromatographed. Elution with petroleum ether gave 1.29 g (60%) of **5** as a clear liquid. Anal. C,H; NMR(CCl_4) δ1.02(s, 6H, $(CH_3)_2C$-), 1.10(m, 29H, CH_2-), 3.27(s, 2H, CH_4Br).

1-[^{11}C]-3,3-dimethylheptadecanoic acid (6). A mixture of **5** (200 mg, 0.6 mmol) and magnesium (17.1 mg, 0.7 mg-atom) in 5 ml ether (freshly distilled from LAH) containing a crystal of iodine was heated at reflux under argon for 2 hr, then transferred to the radiolabeling reaction vessel which was flushed with helium§. $^{11}CO_2$ was produced by the nuclear reaction $^{10}B(d,n)^{11}C$ in the MGH cyclotron and collected in a copper coil that was cooled in liquid nitrogen. The $^{11}CO_2$ was transferred into the reaction vessel under a gentle stream of helium. After ~5 min, the reaction mixture was poured into 3 ml 2N hydrochloric acid and agitated vigorously. The aqueous phase was removed and the ethereal solution was washed with water (2 × 2 ml). The ether was removed by heating under argon. While still warm, the residue was dissolved in 1 ml ethanol to which was added 8 ml 5% human serum albumin. The solution was filtered through a 0.22-μm Millipore filter. The radiochemical purity of the product was confirmed by thin layer chromatography (>98%).

Tissue Distribution Studies

Rats. The radiolabeled compound (10–30 μCi) was injected through a tail vein into CD Fisher rats (260–280 g). The rats were sacrificed by cervical dislocation at 5, 15, and 30 min



Scheme 1. Synthesis of 1-[^{11}C]-3,3-dimethylheptadecanoic acid.

postinjection. The appropriate organs were excised and the radioactivity measured in an automatic gamma counter.

Dogs. Two mongrel dogs were anesthetized with sodium pentobarbital (2.9 mg/kg) and 160–400 μCi of **6** was injected through a femoral vein. After 1 min, serial blood samples were taken from a femoral vein catheter to determine blood clearance rate. Two-dimensional images of the dogs were made with the positron camera.

RESULTS AND DISCUSSION

In the present study, we have evaluated the effects of *gem*-dimethyl-substitution of the beta-position of heptadecanoic acid upon myocardial uptake and retention and compared the results with those which we reported earlier for the 3-monomethyl analog, [^{11}C]BMHDA (*13*).

A general method for the synthesis of *gem*-dimethyl-substituted hydrocarbons (*18*) has been employed to synthesize [^{11}C]DMHDA from inexpensive starting materials in five steps, as outlined in Scheme 1. Cuprous ion-catalyzed addition of tetradecylmagnesium bromide to dimethyl isopropylidene malonate (**1**) provided the *gem*-diethyl-substituted ^{17}C skeleton (**2**). Basic hydrolysis of the diester to diacid **3** and subsequent thermal decarboxylation gave 3,3-dimethylheptadecanoic acid (**4**). Although **2** could be easily purified by flash chromatography, hydrolysis of the crude diester afforded, after crystallization, the malonic acid derivative in 49% yield based on **1**. 1-Bromo-3,3-dimethyl-hexadecane (**5**) was prepared from **4** through a Cristol-Firth modified Hunsdiecker reaction (*21,22*). Carboxylation of the Grignard reagent of **5** with $^{11}CO_2$ proceeded in high radiochemical purity (>98%), but in poor radiochemical yield to give the target compound **6**, 1-[^{11}C]-3,3-dimethylheptadecanoic acid ([^{11}C]DMHDA). By analogy to neopentyl halides (*23*), reduced reactivity of **5** in regard to its Grignard preparation may have contributed to the poor radiochemical yield of **6** (900–1,200 μCi/mmol).

Biodistribution studies in rats (Table 1) demonstrate the relatively poor myocardial uptake of **6** compared with that reported for its 3-monomethyl analog, (C-11)BMHDA (0.63% injected dose/gram heart tissue after 5 minutes vs 2.32 ± 0.32% for (C-11)BMHDA) (*13*). While [^{11}C]BMHDA showed essentially no washout of radioactivity from the heart after 60 min, **6** exhibited ~33% loss of activity after 30 min.

Positron emission tomographic images in dogs were obtained after injection of **6** (160–400 μCi). The low specific activity of **6** coupled with poor myocardial uptake gave images of generally poor quality. There appeared to be considerable radioactivity in the lungs.

The data presented here do not facilitate the task of delineating the effects of structural modification upon biologic properties. It has been shown that total chain length is an important determinant of myocardial uptake of modified fatty acids (*14,19,24,25*).[1] Also, in general, when compared with straight-chain fatty acids, methylation of the beta-position has been shown to enhance myocardial uptake and retention (*9–13*). However, exceptions to this generalization have been reported. For example, when compared with its beta-methyl analog, 15-(p-[^{125}I]iodophenyl)pentadecanoic acid provided ~1.5 times greater radioactivity in the heart at 5 min (*19*). The activity decreased with time, whereas the activity of the beta-methyl analog remained nearly constant over forty minutes. Moreover, 13-[^{125}I]iodo-3-methyltridecanoic acid afforded myocardial concentrations ~30% less than those afforded by 15-[^{125}I]iodopentadecanoic acid while providing no significant improvement in myocardial retention (*24*). Of course, it can be argued that the reduced uptake may be related to chain length and the similar myocardial retention may reflect comparable deiodination due to the lability of the alkyl C-I bond.

TABLE 1
Distribution of Radioactivity (% Injected Dose/g of Tissue) in Fasted Rats at Various Times Following Intravenous Administration of 1-[^{11}C]-3,3-Dimethylheptadecanoic Acid

	Time after injection; percent injected dose/g (mean)		
Tissue	5 min	15 min	30 min
Heart	0.6258	0.4577	0.4178
Blood	0.5276	0.4889	0.3874
Lungs	8.8535	3.4328	1.1815
Liver	1.4252	1.4019	0.9259
Kidneys	0.7182	0.9459	0.8340
	n = 4	n = 4	n = 3

The effect of dimethylation of the beta-position in long chain fatty acids upon biological properties is variable. We found that *gem*-dimethylation of heptadecanoic acid was detrimental to myocardial uptake when compared with monomethylation (Table 2). The low uptake of [^{11}C]DMHDA was disappointing, but the data are consistent with results reported by Otto et al. in a study with 14-[^{125}I]iodo-3,3-dimethyltetradecanoic acid (IDTDA) (*19*). IDTDA demonstrated very low myocardial uptake which was probably related to extensive in vivo deiodination as evidence by high levels of radioactivity in the thyroid. However, it would appear that the poor uptake was also related to dialkylation of the beta-position, since 16-[^{125}I]iodo-3-methylhexadecanoic acid provided ~10 times greater levels of radioactivity in the heart. On the other hand, Knapp, et al. reported relatively high myocardial uptake for 17-[^{125}I]iodo-3,3-dimethylheptadecanoic acid accompanied by a washout which may be indicative of rapid deiodination (*16*). This same research group reported much improved myocardial extraction levels with ω-

TABLE 2
Radioactivity in the Heart (% Injected Dose/g of Tissue) of Rats at Various Times After Intravenous Administration of Radiolabeled Fatty Acid Derivatives

Compound	Time (min)	% Injected dose/g (mean)	Reference
H $CH_3(CH_2)_{12}CCH_2{}^{14}COOH$ H	5 15 60	2.65 2.04 0.89	(27)
H $CH_3(CH_2)_{13}CCH_2{}^{11}COOH$ CH_3	5 30	2.32 2.94	(13)
CH_3 $CH_3(CH_2)_{13}CCH_2{}^{11}COOH$ CH_3	5 30	0.63 0.42	
CH_3 $^{125}ICH_2(CH_2)_{13}CCH_2COOH$ CH_3	5 30	2.06 0.84	(16)
H ^{125}I $(CH_2)_{12}CCH_2COOH$ H	5 30	2.98 2.67	(9)
H ^{125}I $(CH_2)_{12}CCH_2COOH$ CH_3	5 30	4.62 3.63	(9)
CH_3 ^{125}I $(CH_2)_{12}CCH_2COOH$ CH_3	5 30	4.67 5.06	(14)

iodophenyl-β,β-dimethyl-substituted fatty acids, e.g., radioiodinated 15-(p-iodophenyl)-3,3,-dimethylpentadecanoic acid (DMIPP) (*14,15*) (Table 2).

It is reasonable to assume that the prolonged myocardial retention observed with most beta-methylated fatty acid derivatives derives from an inhibition of beta-oxidative catabolism. As shown in Figure 1, monoalkylation of the beta-position would allow a fatty acid to undergo initial dehydrogenation to the trans-enoylSCoA (2) and subsequent hydration to the beta-hydroxy derivative (3). Further dehydrogenation to the

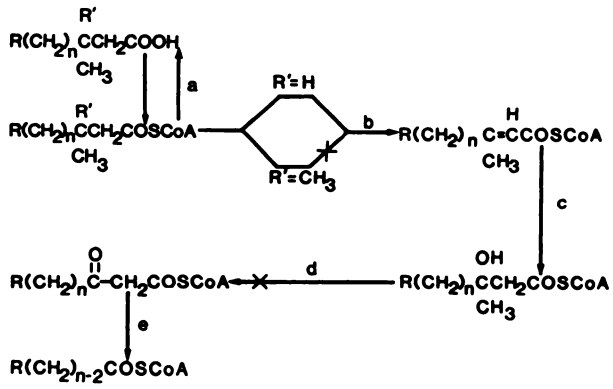


FIGURE 1
Beta-oxidative metabolic pathway for fatty acids: a = thiokinase; b = dehydrogenase; c = enoylhydratase; d = dehydrogenase; e = thiolase.

TABLE 3
Relative Lipophilicities of β,β-Dimethylated Fatty Acids

R		Δ Lipophilicity*
H	$-(CH_2)_{14}C(CH_3)_2CH_2COOH$	
I	$-(CH_2)_{14}C(CH_3)_2CH_2COOH$	+1.00
I—CH=CH	$-(CH_2)_{14}C(CH_3)_2CH_2COOH$	+1.72
I—	$-(CH_2)_{12}C(CH_3)_2CH_2COOH$	+2.25†

* Δ Lipophilicity is the difference in lipophilicity relative to (C-11)DMHDA, which reflects the contribution to total lipophilicity made by R based on Hansch hydrophobic (π) constants.
† $=(p\text{-}IC_6H_4)^{-2}=(CH_2)$

beta-ketoacylSCoA derivative (4) cannot occur. Thus, the beta-methyl fatty acid derivative can be trapped in the myocardial cell secondary to inhibition of oxidative catabolism. By analogy, dialkylation of the beta-position would not be expected to provide a derivative with enhanced myocardial retention. The *gem*-dimethyl fatty acid derivative would be an anti-metabolite, i.e., not able to function as a substrate for the initial dehydrogenation reaction (*19,26*). Therefore, one would expect a priori the kind of fairly rapid myocardial washout we observed. Of course, the poor retention of [^{11}C]DMHDA may be related to factors other than that discussed above. For example, the compound may not undergo active fatty acid transport, nor may it be a suitable substrate for acylCoA synthetase. If the compound is a substrate for acylCoA synthetase, hydrolysis and back diffusion or unknown metabolic pathways may ensue. Experiments designed to address these possibilities may provide valuable data regarding fatty acid transport and metabolism.

The prolonged myocardial retention reported for DMIPP has not been adequately explained and may be entirely unrelated to metabolic processes. It is interesting that the β,β-dimethyl fatty acid derivatives which have been reported to possess higher myocardial uptake and retention compared with [^{11}C]DMHDA also possess increased lipophilicity (Table 3). Perhaps more weight should be given to this physicochemical parameter in future studies concerning myocardial uptake and retention of modified fatty acids.

The absolute effect of beta-dimethylation of fatty acids upon biological properties remains a clouded issue. It may be of benefit, perhaps, to evaluate 1-[^{11}C]-3,3-dimethyl-17-phenylheptadecanoic acid in order to shed light on this problem. Such a study would provide information regarding the influence of an unsubstituted aromatic ring upon myocardial extraction and retention of a beta-*gem*-dimethyl-branched fatty acid.

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NOTES

* Schwarzkopf Microanalytical Laboratory, Woodside, NY.

† EM, Industries.

‡ J.T. Baker Chemical Co.

§ Based on the amount of unreacted metal recovered, ~76% of the theoretical amount of magnesium had been consumed.

¶ We have also observed this, inasmuch as 1-[^{11}C]-3,3-dimethyl-pentadecanoic acid ([^{11}C]DMPDA) showed ~40% lower myocardial uptake than [^{11}C]DMHDA.

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