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Synthesis and Biological Evaluation of (E)-19-Iodo-3,3-Dimethyl-18-Nonadecenoic Acid, A New Dimethyl-Branched Long-Chain Fatty Acid to Evaluate Regional Myocardial Fatty Acid Uptake

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SYNTHESIS AND BIOLOGICAL EVALUATION OF (E)-19-IODO-3,3-DIMETHYL-18-NONADECENOIC ACID, A NEW DIMETHYL-BRANCHED LONG-CHAIN FATTY ACID TO EVALUATE REGIONAL MYOCARDIAL FATTY ACID UPTAKE M. M. Goodman, K. R. Ambrose, K. H. Neff, and F. F. Knapp, Jr., Nuclear Medicine Group, Oak Ridge National Laboratory, Oak Ridge, TN 37831, USA.

Iodine-123-labeled structurally-modified long chain fatty acids that exhibit myocardial extraction and uptake similar to naturally occuring fatty acids, but which show prolonged retention are excellent candidates to evaluate aberrations in fatty acid metabolism that occur when the coronary arteries are normal and perfusion is not impaired. Recent quantitative autoradiographic studies in laboratory animals employing methyl-branched fatty acids have shown that hypertensive heart disease (1) and cardiomyopathies (2) are two heart disorders where there can be a dissociation between regional differences in fatty acid uptake and regional perfusion. Because of the clinical potential of using SPECT to evaluate cardiomyopathies and hypertensive disease, we have developed a variety of radioiodinated methyl-branched fatty acids (3,4). Although increased myocardial retention was achieved, these agents, however, did not demonstrate complete retention indicating catabolism was being impaired but not prevented. The goal of this study was to develop a dimethyl-branched fatty acid (5) with the radiolabel stabilized as a vinyl iodide with the objective of achieving high myocardial uptake with irreversible retention.

The synthetic method chosen for the preparation of (E)-19-iodo-3,3-dimethyl-18-nonadecenoic acid (19) involved introduction of substituents into the 2- and 5-positions of a thiophene ring followed by sulfur extrusion of a 2,5-dialkyl thiophene derivative to provide a key 3,3-dimethyl-branched fatty acid intermediate, 17-iodo-3,3-dimethylheptadecanoic acid (14) (Scheme I). Compound 14 was prepared by Friedel Crafts condensation of $CH_3O(CH_2)_7COCl$ with dimethyl-branched thiophene (7) followed by Wolff-Kishner reduction, sulfur extrusion with Raney nickel and treatment of the terminal methoxy methyl-branched intermediate (13) with $(CH_3)_3SiI$. The (E)-vinyl iodide was introduced into the terminal position of the dimethyl-branched acid by iododestannylation (Scheme II). The pivotal step in the synthesis of the (E)-iodovinyl acid involved hydrostannylation of 3,3-dimethyl-18-nonadecynoic acid (15) with $(n\text{-}Bu)_3SnH$. Iododestannylation of the stannyl intermediate 17 with I^+ followed by basic hydrolysis gave 19. Tissue distribution studies of ^{125}I-labeled 19 (Table 1) and 14 (Table 2) were performed in fasted rats. Iodine-125 19 showed 90% retention of the initial myocardial uptake (4.56% dose/g, at 2 min) after 60 min. In contrast to the prolonged myocardial retention observed with 19, iodine-125 14 showed rapid myocardial washout and significant in vivo deiodination. The significant difference in myocardial extraction and retention of the iodovinyl agent compared with the iodoalkyl derivative dramatically illustrate the enhanced stability of iodide attached to an iodovinyl moiety.

Myocardial subcellular distribution studies of the ^{125}I-labeled 19 (DMIVN) in fasted rats showed a higher association of radioactivity with the microsomes when compared to the results obtained with the 19-carbon straight chain analogue (4) (IVN) which appeared to exist primarily in the cytoplasm (Fig. 1). When the rats were nonfasted (fed) the distribution profiles of the two analogues showed differences that seemed to correlate with the differences in myocardial retention that fasting and feeding can induce.

The significant myocardial uptake, retention and high heart:blood ratios of agents of this type now may enable the diagnosis and management of patients with hypertensive disease and cardiomyopathies by SPECT.

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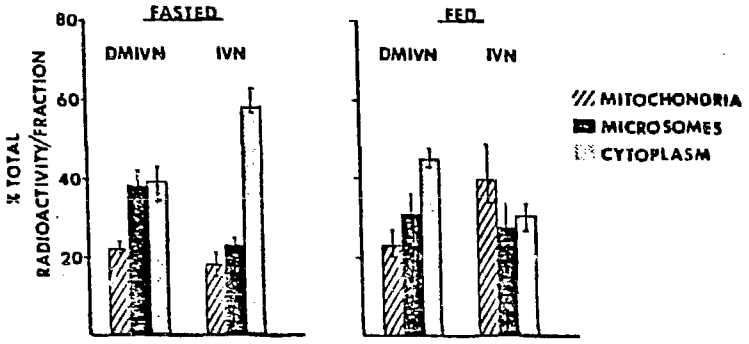
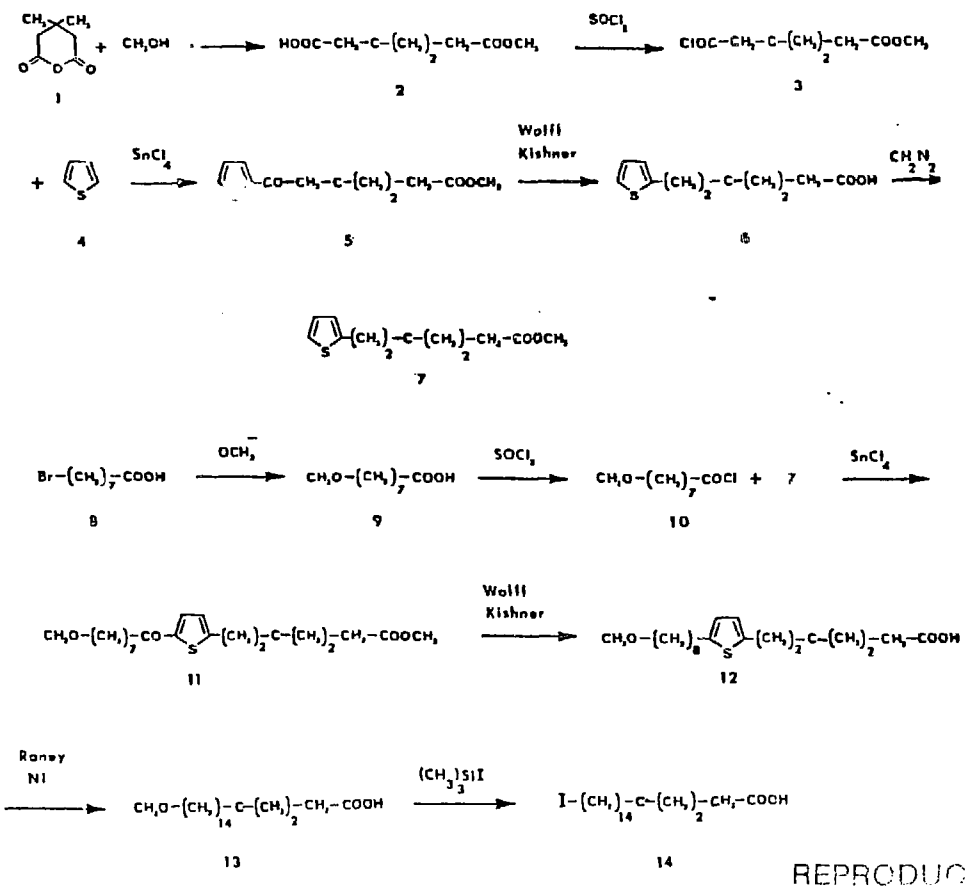


Fig. 1. Distribution (with ranges) of radioactivity in subcellular fractions from rat hearts 30 min after injection of ^{125}I-labeled DMIVN or IVN.



Scheme I

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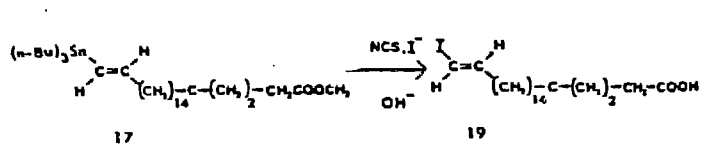

Scheme II

Table 1. Distribution of Radioactivity (% Injected Dose/Gram of Tissue) in Fasted Rats at Various Times after Intravenous Administration of 19-[^{125}I]Iodo-3,3-dimethyl-18-nonadecanoic Acid.[a]

Tissue	Time after injection; percent injected dose/gram (range)				
	2 min	5 min	30 min	1 h	2 h
Heart	4.56 (4.30-5.05)	4.66 (4.29-4.83)	4.60 (4.14-5.26)	4.10 (3.62-4.58)	3.66 (3.12-4.28)
Blood	2.44 (2.09-2.84)	1.62 (1.41-1.84)	0.74 (0.66-0.83)	0.71 (0.65-0.74)	0.70 (0.67-0.72)
Lungs	2.17 (1.96-2.35)	2.09 (1.90-2.26)	1.42 (1.27-1.57)	1.22 (1.14-1.33)	1.05 (1.01-1.08)
Liver	7.27 (6.92-8.04)	7.27 (7.18-7.46)	5.88 (4.69-6.72)	4.93 (4.67-5.39)	3.29 (3.71-4.17)
Kidneys	1.38 (1.17-1.53)	1.46 (1.31-1.61)	1.49 (1.37-1.63)	1.46 (1.35-1.56)	1.29 (1.23-1.37)
Thyroid	24.21 (21.42-25.72)	23.53 (20.60-26.37)	40.62 (33.82-44.14)	83.10 (62.11-117.75)	157.04 (122.63-209.34)
Mean Heart:Blood	1.9:1	2.9:1	6.2:1	5.8:1	5.3:1

[a]Mean and range value for five female Fischer rats.

Table 2. Distribution of Radioactivity (% Injected Dose/Gram of Tissue) in Nonfasted Rats at Various Times after Intravenous Administration of 17-[^{125}I]Iodo-3,3-dimethyl-Heptadecanoic Acid.[a]

Tissue	Time after injection; percent injected dose/gram (range)				
	2 min	5 min	15 min	30 min	1 h
Heart	2.84 (2.50-3.27)	2.06 (1.91-2.31)	1.22 (1.12-1.42)	0.84 (0.73-0.90)	0.68 (0.54-0.84)
Blood	2.59 (2.14-2.98)	1.87 (1.75-2.01)	1.36 (1.29-1.43)	1.04 (1.00-1.09)	0.83 (0.74-0.96)
Lungs	2.19 (1.93-2.38)	1.96 (1.83-2.13)	1.40 (1.34-1.44)	0.99 (0.96-1.02)	0.84 (0.07-0.82)
Liver	5.26 (4.81-5.55)	3.99 (3.66-4.35)	2.34 (2.09-2.61)	1.44 (1.41-1.50)	1.07 (0.85-1.27)
Kidneys	1.39 (1.31-1.50)	1.49 (1.45-1.54)	1.33 (1.24-1.43)	0.97 (0.93-1.03)	0.74 (0.63-0.86)
Thyroid	15.93 (13.49-23.02)	16.83 (13.55-19.04)	42.89 (29.88-57.48)	79.40 (65.29-92.69)	148.83 (130.32-138.72)
Mean Heart:Blood	1.1:1	1.1:1	0.9:1	0.8:1	0.8:1

[a]Mean and range value for five female Fischer rats.

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