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Nuclear Medicine Progress Report for Quarter Ending September 30, 1987

F. F. Knapp, Jr.
J. F. Allred
K. R. Ambrose
A. P. Callahan
D. E. Rice
P. C. Srivastava

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Health and Safety Research Division

NUCLEAR MEDICINE PROGRESS REPORT FOR QUARTER ENDING SEPTEMBER 30, 1987

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SUMMARY

In this report the preparation of a new radioiodinated nucleoside as a potential tumor-localizing agent is described. The p-iodophenyl analogue of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICA) was prepared by a 5-step reaction sequence. The iodine-125-labeled analogue was evaluated in rats and nude mice with implanted tumors. This agent crossed the intact blood-brain barrier (0.28% injected dose/gm at 5 min) and also showed some uptake in implanted tumors (0.74% injected dose/gm at 30 min). These preliminary results demonstrate that radioiodinated nucleoside analogues are good candidates for tumor localization. The development and evaluation of similar analogues are in progress.

In order to evaluate the possible formation of 3-R,S-hydroxy-3-methyl metabolites from radioiodinated 15-(p-iodophenyl)-3-R,S-methylpentadecanoic acid ("BMIPP"), a new synthesis of 3-R,S-hydroxy fatty acids has been developed involving C-2 acylation of the ester ("Meldrum's" acid) formed by condensation of malonic acid with acetone. Treatment with acid forms the methyl ketone which is condensed under Reformatsky conditions to give the racemic β-hydroxy-β-methyl ester which is then hydrolyzed with base. In this way, the β-hydroxy analogues of BMIPP and 3-methylheptadecanoic acid have been prepared for the first time and are being used in biological studies.

Also during this period, the new radioiodinated maleimide protein labeling agent was applied to collaborators in Milwaukee and at the Oak Ridge Associated Universities. Claude Brihaye, from the University of Liege, Belgium, completed a three month assignment in the Nuclear Medicine Program.

DEVELOPMENT OF RADIOIODINATED NUCLEOSIDE ANALOGUES AS POTENTIAL TUMOR-LOCALIZING AGENTS

Radiolabeled nucleosides are desirable in cancer research as nucleic acid precursors to study their incorporation into tumors as an indication of tumor growth. The incorporation of radiolabeled thymidine into newly replicated DNA is widely used as an index of cell proliferation. Several radiolabeled 5-[^{18}F]fluorouridine analogues have also been synthesized for measuring RNA synthesis and tumor growth rates in vivo.[1] Studies have demonstrated in various cell culture systems that the ability of cells to transport nucleosides increases dramatically as an early event in changes from quiescence to a proliferative state such as in a growing tumor. Cells utilize nucleosides from their environment and the transportation of nucleosides across the plasma membrane is mediated by specific enzyme like elements of the membrane. Through the action of kinase enzymes, nucleosides are metabolically "trapped" within the cell in the form of 5'-phosphates. The relative accumulation of several radiolabeled pyrimidine nucleosides in the tumors as compared to normal tissues has been evaluated in vivo. In BDF_1 mice, bilateral transplants of P815 tumors sensitive to 1-arabinocytosine (ara-C) showed a high, specific, protracted accumulation of ^{3}H-ara-C derived radioactivity, most of which was ara-C di- and triphosphates.[2]

As another example, tissue distribution studies of [methyl-^{14}C]-thymidine in normal and tumor-bearing rats showed preferential accumulation of the radioactivity in the tumor with tumor/blood, tumor/prostate and tumor/muscle ratios of 3.09, 4.98 and 6.11, respectively.[3] The deoxyribonucleosides, 5-chloro-2'-deoxy-2'-fluoro [2-^{14}C]-uridine and 5-fluoro-2'-deoxy-2'-fluoro[2-^{14}C]uridine have been evaluated in BDF_1 mice bearing a subcutaneous Lewis lung tumor. Tissue distribution studies of 5-chloro and 5-fluoro compounds showed tumor/blood ratios of 2.5 and 7, respectively.[4]

A central premise of the foregoing discussion is the synthesis of new radiolabeled nucleosides as potential biochemical tools to study phosphorylation and nucleic acid metabolism. Because of their unique properties, radiolabeled nucleosides could serve as potential substrates for

different enzymes of nucleic acid metabolism and thereby be incorporated (trapped) into tumors as an indication of tumor activity. The localization of radiolabeled nucleosides, or more importantly, their involvement in metabolic pathways and nucleic acid synthesis, could serve as a probe for metabolism in vivo. Furthermore, the incorporation of these agents in proliferating tissue could indicate early stages of tumor growth and provide effective means for early tumor diagnosis.

The 5'-phosphate of 5-amino 1-β-D-ribofuranosylimidazole-4-carboxamide (AICA riboside, 1) is a naturally occurring nucleotide and is an important precursor of de novo purine nucleotide biosynthesis.[5] A number of related nucleoside analogues such as 5-halo-1-β-D-ribofuranosylimidazole-4-carboxamide, 2-β-D-ribofuranosylthiazole-4-carboxamide (tiazofurin) and 2-β-D-ribofuranosylselenazole-4-carboxamide (selenazofurin) (Figure 1) show interesting antiviral and antitumor properties.[6] Therefore, the evaluation of biodistribution properties

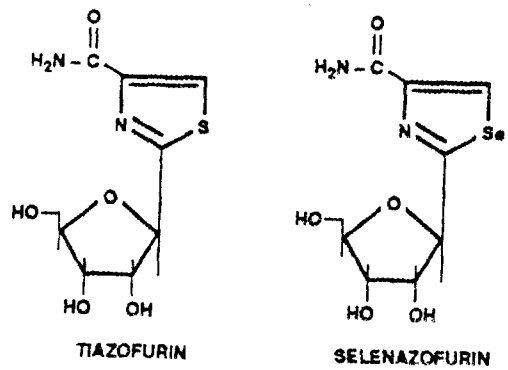

Fig. 1.

of this class of compounds is of significant biological interest. Since AICA riboside is readily available, the structural modifications of this agent for radiolabeling and biodistribution evaluation have been pursued as a model for tiazofurin and selenazofurin. This preliminary report describes the synthesis, biodistribution properties and chemical transformation of 4-N-(p-iodophenyl) analogue of AICA riboside (1).

The synthesis of the succinimide activated ester, N-succinimidyl-5-amino-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazole-4-carboxylate

(4), from AICA riboside (1) via the synthesis of 5-amino-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosylimidazole-4-carboxylic acid (3, Scheme I) has been reported.[7] A one-pot reaction has now been devised as a modification of the literature procedure for a convenient synthesis of (4). The AICA riboside (1) was hydrolyzed, acetylated and crude (3), without purification or crystallization, was coupled with N-hydroxysuccinimide in the presence of dicyclohexylcarbodimide (DCC) to yield crystalline (4).

Coupling (4) with various amino acids and admantanamine has been reported in the literature to proceed smoothly at room temperature. However, an elevated temperature (122°C ± 3°C) and a relatively prolonged reaction period (3 h) was required for the coupling of (4) with p-iodoaniline to yield the desired intermediate, 5-amino-1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)imidazole-4-[N-(p-iodophenyl)carboxamide] (5). The slow reaction could be attributed to the poor nucleophilic character of the amino group of p-iodoaniline as compared to the amino group of amino acids or admantanamine. Treatment of (5) with ammonium hydroxide provided the deacetylated product, 5-amino-1-β-D-ribofuranosylimidazole-4-[N-(p-iodophenyl)carboxamide] (6). The corresponding ([^{125}I]6) was prepared similarly by incorporating p-([^{125}I]iodo)aniline during the coupling reaction with (4). These studies were performed with the assistance of Jennifer Suggs, a 1987 Summer Student with the Oak Ridge Associated Universities.

The biodistribution of the model radiolabeled imidazole nucleoside, ([^{125}I]6), was evaluated in normal rats (Table 1) and tumor implanted nude mice (Table 2). The agent shows initial brain uptake both in normal rats and nude mice indicating the ability of this agent to cross the intact blood-brain barrier. Fairly constant levels (5.8%-17.4% dose/gm) of radioactivity over a prolonged period in the thyroid were observed indicating in vivo stability of the radiolabel. In the nude mice, the agent showed moderate initial tumor uptake, although, the uptake in the other proliferating tissues such as in the bone-marrow and intestine was approximately twice as high. [^{125}I]5, the triacetyl derivative of [^{125}I]6 showed relatively low brain uptake and higher thyroid uptake as compared to the parent nucleoside in rats.

Table 1. Distribution of radioactivity in tissues of female Fischer 344 rats following intravenous administration of [^{125}I]-5 and of [^{125}I]-6.[a]

Compound	Time after injection (min)	Mean percent injected dose/gm:tissue (range)						
		Brain	Blood	Liver	Kidneys	Heart	Lungs	Thyroid
5	5	0.19 (0.18-0.20)	0.72 (0.70-0.76)	4.37 (4.13-4.56)	4.28 (4.21-4.34)	1.34 (1.31-1.36)	1.24 (1.17-1.27)	17.94 (17.26-18.66)
	30	0.09 (0.08-0.09)	0.41 (0.38-0.46)	2.01 (1.88-2.24)	2.35 (2.21-2.43)	0.66 (0.62-0.71)	0.70 (0.65-0.78)	16.72 (15.30-19.47)
	60	0.06 (0.06-0.07)	0.30 (0.29-0.37)	1.54 (1.52-1.58)	1.44 (1.31-1.61)	0.48 (0.45-0.52)	0.52 (0.49-0.57)	26.47 (23.09-31.02)
	120	0.06 (0.05-0.06)	0.22 (0.20-0.23)	1.16 (1.02-1.28)	0.88 (0.85-0.90)	0.30 (0.27-0.32)	0.36 (0.33-0.39)	37.45 (32.67-40.07)
	240	0.04 (0.04-0.05)	0.20 (0.19-0.22)	0.99 (0.96-1.04)	0.58 (0.55-0.61)	0.21 (0.20-0.21)	0.24 (0.23-0.25)	78.95 (51.88-131.62)
6	5	0.28 (0.25-0.32)	1.40 (1.13-1.74)	2.52 (2.34-2.82)	9.56 (7.52-11.85)	0.86 (0.75-1.02)	1.10 (0.96-1.28)	11.31 (9.44-12.66)
	30	0.14 (0.13-0.16)	0.46 (0.42-0.49)	1.79 (1.77-1.81)	2.17 (2.15-2.18)	0.35 (0.31-0.40)	0.43 (0.40-0.47)	6.45 (5.04-7.51)
	60	0.06 (0.05-0.07)	0.25 (0.23-0.27)	1.31 (1.21-1.41)	1.02 (0.97-1.09)	0.19 (0.18-0.20)	0.24 (0.23-0.25)	5.86 (5.46-6.22)
	240	0.01 (0.01-0.01)	0.10 (0.10-0.10)	0.32 (0.29-0.35)	0.19 (0.18-0.20)	0.07 (0.06-0.07)	0.08 (0.08-0.09)	17.41 (12.30-24.87)

[a]Each animal (three animals per time point) received either 0.43 μCi of [^{125}I]-5 or 1.05 μCi of [^{125}I]-6 by tail vein injection.

Table 2. Distribution of radioactivity in tissues of human colorectal carcinoma implanted Sprague-Dawley nude mice following intravenous administration of [^{125}I]-6.[a]

Compound	Time after injection (min)	Mean percent injected dose/gm:tissue (range)						
		Blood	Liver	Kidneys	Heart	Lungs	Spleen	Tumor
#6	30	1.12 (0.52-1.72)	6.07 (1.98-10.17)	3.82 (1.85-5.79)	1.05 (0.51-1.59)	2.95 (0.96-4.94)	0.96 (0.46-1.45)	0.74 (0.43-1.06)
	240	0.89 (0.88-0.91)	5.88 (5.69-6.07)	2.47 (2.00-2.94)	0.79 (0.68-0.90)	2.06 (1.94-2.18)	0.72 (0.63-0.82)	0.71 (0.68-0.74)
	1440	0.10 (0.08-0.11)	0.73 (0.58-0.88)	0.35 (0.28-0.42)	0.23 (0.18-0.27)	0.41 (0.34-0.48)	0.12 (0.11-0.13)	0.10 (0.08-0.13)

[a]Each animal (two animals per time point) received 2.9 μCi of [^{125}I]-6 by tail vein injection. Other tissues analyzed include brain, small and large intestine, muscle, marrow, and femur.

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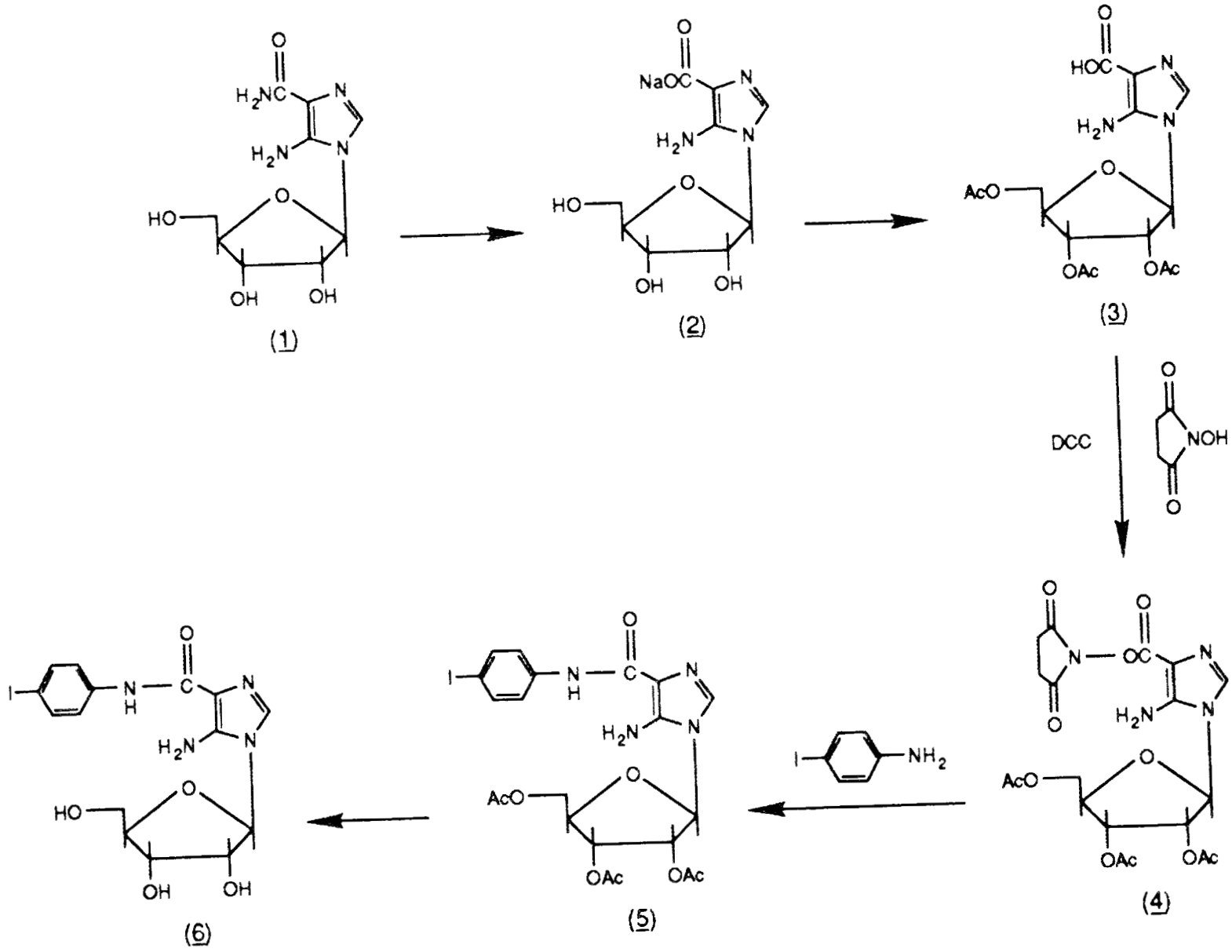


Scheme 1

Radiolabeled nucleosides are potential tools to study biochemical pathyways and metabolism of nucleic acids. The identification of radiolabeled nucleosides which show high tumor uptake relative to other proliferating tissues is of interest because such agents could potentially be used as tumor markers. The synthesis and radiolabeling of AICA riboside demonstrate that iodine can be stabilized as an N-(p-iodophenyl)carboxamide on similar nucleosides. The introduction of iodophenyl group to a carboxamide may also represent an interesting structural perturbation making the nucleoside more lipophilic and penetratable to the blood-brain barrier.

EVALUATION OF METABOLITES FROM THE RADIOIODINATED β-METHYL-BRANCHED FATTY ACID, 15-(p-IODOPHENYL)-3-R,S-METHYLPENTADECANOIC FATTY (BMIPP) — SYNTHESIS OF β-HYDROXY FATTY ACIDS

Methyl-branching in the β-position of 15-(p-iodophenyl)-3-R,S-methyl-pentadecanoic acid (BMIPP) was designed to interfere with myocardial catabolism to delay the clearance of the iodine-123 agent permitting more accurate SPECT evaluation of the regional myocardial fatty acid uptake pattern. Although the myocardial clearance of radioiodinated BMIPP in rats, dogs, and humans is considerably delayed in comparison to the IPPA straight-chain analogue, this agent does not show the irreversible retention that was anticipated from an analysis of the expected inhibitory effect of 3-methyl-branching. An alternative explanation of the delayed myocardial clearance involved initial α-hydroxylation followed by decarboxylation would form the methyl acid which could then serve as a substrate for subsequent successive cycles of β-oxidation (Figure 2).

To evaluate the identity of the radioiodinated products that are released from the heart, an isolated Langendorff-perfused rat heart system has recently been used, in which a major product considerably more polar than BMIPP was identified in the out-flow tract (ORNL/TM-10531). From a comparison of the relative chromatographic mobility and chemical properties of this unknown metabolite with BMIPP, it was demonstrated that this

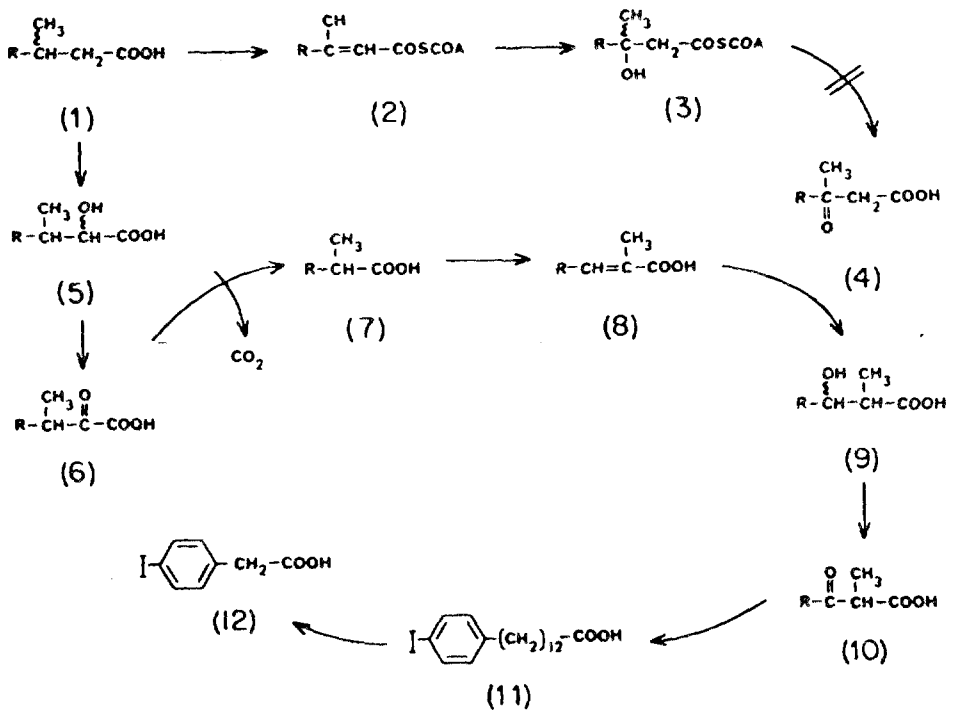
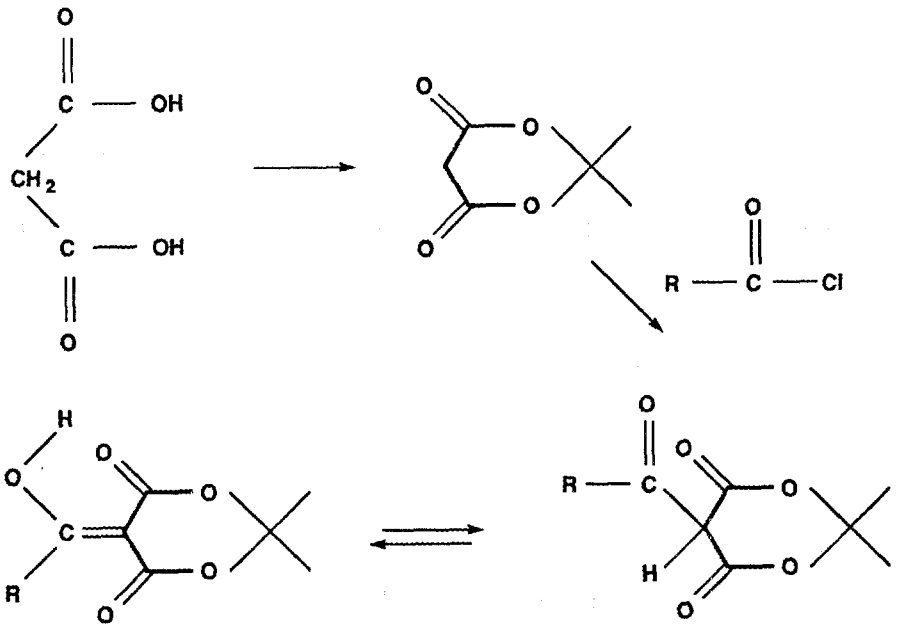


Fig. 2.

product was a carboxylic acid and the increased mobility suggested the presence of a hydroxyl moiety. The possible formation and release of BHMIPP was thus suggested from these studies.

In conjunction with Gilbert Kirsch, Ph.D., a visiting professor of organic chemistry, from the University of Metz, France, the goals of the current work were to develop a chemical synthesis of 15-(p-iodophenyl)-3-R,S-methyl-3-hydroxy pentadecanoic acid (BHMIPP) and other β-hydroxy fatty acids and to compare the properties of BHMIPP with the unknown metabolite isolated from the Langendorff heart studies. The preparation of model β-hydroxy fatty acids has further importance since it is well established that such partial metabolites are formed in ischemic myocardium[8] in animal studies and thus, very probable that similar products are formed in vivo in humans. The availability of these standards will make possible an evaluation of radioiodinated fatty acid analogues in various model systems to determine their presence and relevance to the evaluation of regional myocardial fatty acid metabolic events and interpretation of time-activity data.

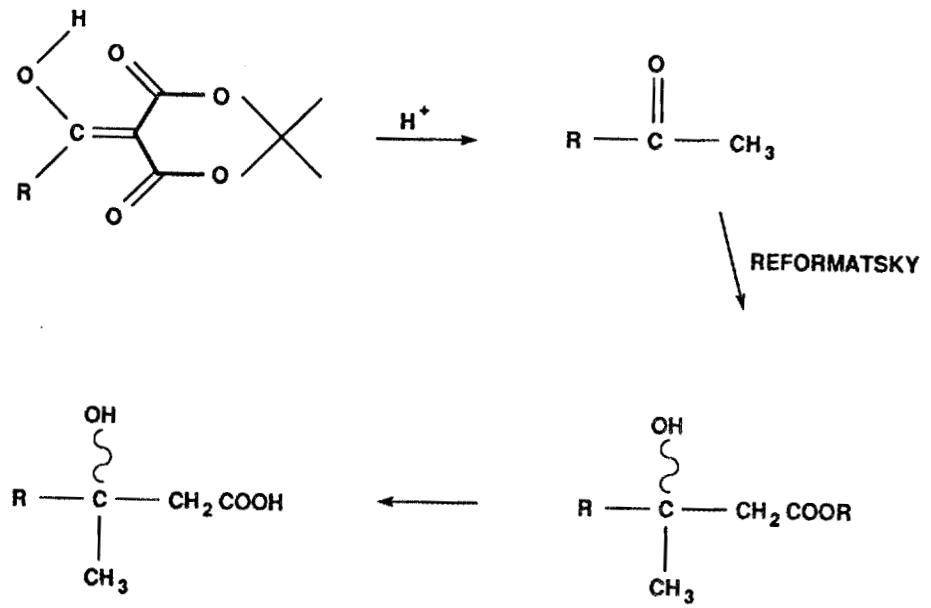
Although the reaction of the requisite aldehydes with methyl bromoacetate under Reformatsky conditions is a classical method described for the preparation of α-hydroxy fatty acids, a more versatile approach involves acylation of a masked malonic ester ("Meldrum's acid"), prepared by condensation of malonic acid with acetone (Scheme 2). By appropriate



Scheme 2

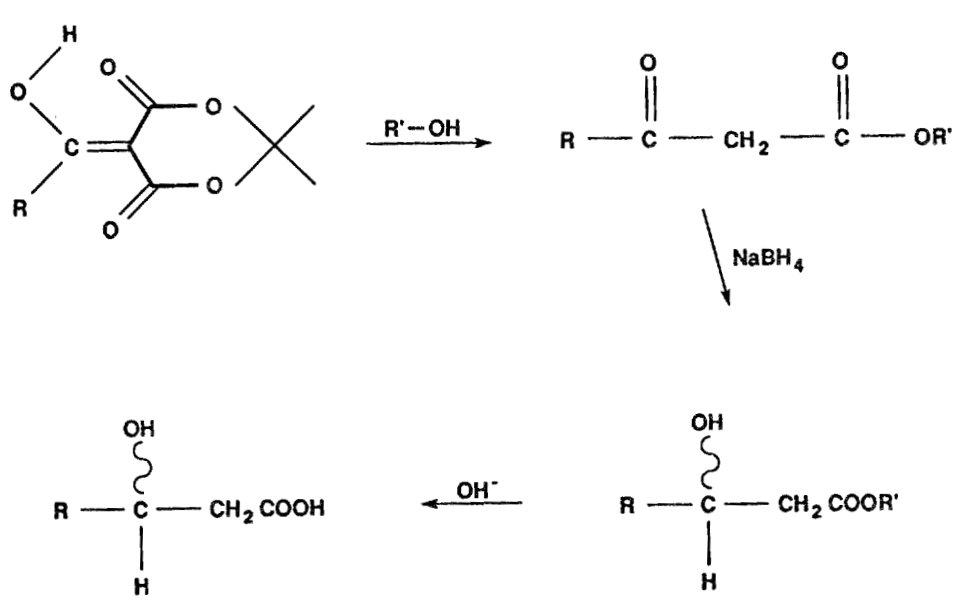
choice of the acyl fragment, a variety of α-ketone fatty acid esters can be fabricated by subsequent hydrolysis of the substituted malonic ester (Scheme 3). Following sodium borohydride reduction and basic hydrolysis of the esters, the racemic 3-R,S-hydroxy products are readily formed. Using this approach, the α-hydroxy derivatives of palimtic, myristic and heptadecanoic acids have been prepared. Future work will study the metabolism of these fatty acids in ischemic tissue.

The "Meldrum's" acid is also a useful intermediate for the synthesis of β-hydroxy-β-methyl fatty acids. Rather than treatment with alcohol, acid hydrolysis in the presence of an alcohol is a convenient method for



Scheme 3

generation of the methyl ketone (Scheme 4). In this way a broad spectrum of methyl ketone substrates can be prepared. Reformatsky treatment followed by basic hydrolysis of the ester yields the racemic 3-R,S-hydroxy fatty acids. Using this approach, several β-hydroxy-β-methyl fatty acids have



Scheme 4

been prepared, as shown in Figure 3. These compounds are now being used as standards or markers to evaluate the formation of metabolites from the methyl-branched fatty acids in vivo and in the isolated heart systems. This method is also useful for introduction of isotopes of carbon into the hydroxy fatty acids by use of bromoacetic acid radiolabeled in the C-1 or C-2 positions.

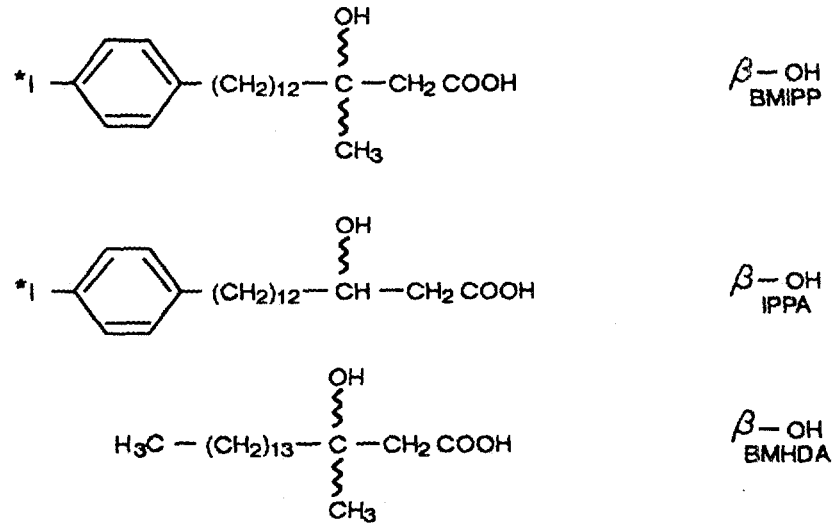


Fig. 3. Structures of racemic β-hydroxy-β-methyl fatty acids prepared by the "Meldrum's" acid approach.

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AGENTS FOR MEDICAL COOPERATIVES

Osmium-191

One shipment of osmium-191 was made during this period. The new activated carbon osmium-191/iridium-191m radionuclide generator was supplied to collaborators at the UCLA Medical Center, Torrance, California (I. Mena, M.D.).

Radioiodinated Agents

Two shipments of iodine-125 labeled agents were made to collaborators. One shipment was supplied to the Oak Ridge Associated Universities, Oak Ridge, Tennessee (J. Crook, M.D., Ph.D.) and one shipment was made to the Blood Center of Southeastern Wisconsin, Milwaukee, Wisconsin (T. J. Kunicki, Ph.D.).

OTHER NUCLEAR MEDICINE GROUP ACTIVITIES

A "Workshop" organized by F. F. Knapp, Jr. in conjunction with the ORNL Technology Applications Office was held on July 16 to discuss the development and applications of the new osmium-191/iridium-191m radionuclide generator system developed at ORNL in conjunction with

collaborators at the University of Liege, Belgium (Drs. C. Brihaye and M. Guillaume). The U.S. patent has been waived by DOE to Martin Marietta Energy Systems and one goal of the "Workshop" was to grant an exclusive license. A second goal of the "Workshop" was to discuss other agents being developed by the ORNL Nuclear Medicine Program. A total of 18 representatives from 12 companies, including the major radiopharmaceutical manufacturers, attended.

F. F. Knapp, Jr. chaired a technical session and presented a paper at the "European Nuclear Medicine Congress 1987" and co-authored three other papers describing clinical applications of iodine-123-labeled fatty acids in Budapest, Hungary on August 24-28. He also presented invited seminars at the Nuclear Medicine Department at the University of Bonn, West Germany.

Reske, S. N., Nitsch, J., and Knapp, F. F., Jr. "Calcium Channel Blocker (CCB) Mediated Improvement of Regional Cardiac Free Fatty Acid Utilization During Exercise,"

Knapp, F. F., Jr., Kohlen, S., Kolkmeier, J., Reske, S. N., Cunningham, E. B., Rice, D. E., Callahan, A. P., and Ambrose, K. R. "Formation of Catabolites from Methyl-Branched Fatty Acids by Isolated Langendorff Rat Heart System,"

Kropp, J., Joch, M., Knapp, F. F., Jr., and Reichmann, K. "Thallium-201 Scintigraphy in Comparison to [I-123]Iodophenylpentadecanoic Acid (IPPA) to Detect CHD,"

Kropp, J., Joch, M., Knapp, F. F., Jr., and Biersack, H. J. "Myocardial Metabolism Before and After Bypass Surgery (BS) Evaluated by I-123 Phenylpentadecanoic Acid (IPPA).

The poster presented at the European Nuclear Medicine Congress in Budapest, Hungary entitled "Abberations of Cardiac Free Fatty Acid Metabolism After Submaximal Exercise" (S. N. Reske, F. F. Knapp, Jr., L. Lange, J. Nitsch, H. J. Biersack, J. Kropp and K. Reichman), was presented an award for the outstanding poster in the Cardiology/Hematology sections.

P. C. Srivastava participated in the "Vth International Conference on the Chemistry of Selenium and Tellurium" held in Oak Ridge on August 24-28, 1987, and presented a technical paper describing the development of telluro fatty acids.

Srivastava, P. C., Knapp, F. F., Jr., and Kabalka, G. W. "New Radiohalogenated Alkenyl Tellurium Fatty Acids."

The patent for the new generator entitled "Osmium-191/Iridium-191m Radionuclide Generator" (F. F. Knapp, T. A. Butler and C. Brihaye) has been granted by the U.S. Patent Office, No. 4,683,123, Official Gazette, July 28, 1987.

P. C. Srivastava served as an ad hoc committee member for a study section for the National Institutes of Health on September 21-24 for the review of proposals on development of therapeutic agents for the treatment of Acquired Immune Deficiency Syndrome.

K. R. Ambrose is a co-recipient of an IR-100 Award entitled "Fiber-Optics Fluoroimmuno Sensor," in a joint effort with members of the Advanced Monitoring Development Group (T. Vo-Dinh, M. J. Sepaniak, G. D. Griffin, K. R. Ambrose, and B. J. Tromberg). This work involved the development of a portable fiber-optics sensor that can sensitively and selectively measure human exposure to traces of hazardous chemicals or infectious agents.

Visitors

Sheri L. Blystone, from the Chemistry Department at Case Western Reserve University, presented a seminar on September 21 describing the organometallic synthesis of chiral molybdenum species. She will join the Nuclear Medicine Program as a postdoctoral fellow in January 1988.

On August 20, 1987, 28 physicians and other health care professionals from the ORAU/REAC/TS "Medical Planning and Care in Radiation Accidents" program toured the Nuclear Medicine facilities. On August 31-September 1, 1987, three administrative executive staff members from Duke University visited the Nuclear Medicine facilities for a program overview.

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