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ORGANIC RADIOPHARMACEUTICALS

RECENT ADVANCES

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ABSTRACT

Organic radiopharmaceuticals are considered in light of accelerator and nuclide production requirements, special problems relating to the carrier-free state, including terminology,of the special technology required to prepare and manipulate these compounds and new trends in compound design and synthesis. The emphasis is on medical cyclotrons and the positron emitting radionuclides, carbon-11, nitrogen-13, oxygen-15, and fluorine-18. New routes to synthetic precursors and organic compounds of high specific activity labeled with carbon-11, fluorine-18 and iodine-123 including monosaccharides, aromatic amines, neuroleptics, fatty acids, steroids, and other classes of compounds are discussed. Some compounds are considered in terms of the development and evaluation of structure-activity relationships and including some newer concepts such as metabolic trapping.

The list of organic radiopharmaceuticals was modest and rather short as recently as 1973, especially if taken in light of known pharmaceuticals, to say nothing of physiologically active compounds and organic compounds in general. There has been a rapid increase in research and in publication in this area since 1973 (1) due to several factors, principal among which are the interest in compounds labeled with positron emitters, the development of organic compounds which probe function and metabolism in the brain, heart, liver, and adrenals, and the development of compounds tied to chelating agents which attach to technetium and other "non-organic" radionuclides. However, another factor has had a profound stimulus on synthetic work and that has been the increasing sophistication in the design of labeled compounds for studying function and metabolism *in vivo*. So, for example, structure activity relationships, the principle of metabolic trapping, the utilization of the flow-metabolism couple, and macromolecular pulse labeling among other approaches are being developed (2) to probe biochemistry and physiology in normal and pathological states.

New areas of research and application using labeled organic compounds which draw heavily on the expertise developed in radiopharmaceutical work and which may or may not relate to nuclear medicine include the quantification of drug regimen, especially in the area of chemotherapeutic agents, drug testing with relation to the enormously increased data base required by federal regulation, application to pollution problems, and studies on photosynthesis and in other living systems. It is not, however, the purpose of this paper to give an overview of application, but rather to focus on advances in recent years, and in particular to cover the period since the First International Symposium on Radiopharmaceuticals sponsored by the Society of Nuclear Medicine and held in Atlanta in 1974 on the broad aspects and problems associated with compound preparation. The labeling of organic compounds has many facets ranging from nuclide production, precursor preparation, radiopharmaceutical design, and organic synthesis to quality control, the "carrier-free" problem, and the technological side of compound production, e.g. laboratory design, assay procedures, personnel monitoring, etc. These overall questions in one form or another have been [illegible]ssed since 1974 in a number of symposia (3) and in the literature (4,5). [illegible]d, the expansion in this field has been so extensive that an in depth rev[illegible] of the whole organic area is outside the scope of this paper. The topics to be covered in this paper can be identified in the section listing given below. It must be emphasized that this review is not intended to be exhaustive in nature but rather to focus on specific examples which illustrate principles and practice. The choice is based in some measure on the informal training carried on at Brookhaven to help new groups in being exposed to the significant aspects of radionuclide incorporation with special emphasis on the positron emitting radionuclides. Many elegant procedures which have appeared in the literature since 1974 could not be covered here. However, the reader is directed to the extensive bibliographies [illegible] accelerator pr[illegible]uced nuclides for use in biology and medicine (6,7) which are complete through June, 1976 and which contain listings of organic syntheses. The third volume in this series is in preparation. In addition, other areas such as chelates, metallo-organics, labeled macromolecules, and iodination procedures are not covered.

The desirable properties and developments in compounds labeled with positron emitting radionuclides could not, however, have been brought to its present level of application without parallel development and advancement of not only positron imaging d[illegible]vices, but the successful design of positron emission transaxial

tomography (PETT) which allows the quantitative determination of radioactivity in a volume element of tissue *in vivo*. The history, theory, and capabilities of these instruments have been reviewed in depth (8). Unique characteristics of positron radiation, namely, the annihilation of the positron at the end of its track to give two photons of 511 keV each emitted in opposite direction at an ∢ of 180° ± 0.3° results in two advantages over single photon imaging. Sensitivity is increased and the imaging system is isosensitive to positron emitters along a coincidence line in the containing system. Thus, since one had labeled biomolecules whose transport, localization, metabolism, and catabolism could first be studied in animal systems in order to study basic biochemistry and physiology, two further steps could be taken; the development of compounds labeled with positron emitters labeled at levels of concentration, "carrier-free" vide infra, evoking no macro-physiological response (thus acting as "true" tracers), and the determination of dynamic properties of these compounds in a living system non-invasively and quantitatively by means of PETT. It should, however, be noted that advances in single photon tomography may ultimately lead to a similar facility in quantitative measurement of radio-activity in a volume element of tissue. Although the range of organic radiopharmaceuticals is somewhat more limited if only single photon emitters such as iodine are considered with the concomitant disadvantages of possible alteration of the bio-active compounds' functionality *in vivo* due to major structural perturbation, a major attraction is the possible wider dissemination of approach in clinical practice since the compound need not be prepared on site or in the near vicinity of a "medical cyclotron".

Topics to be covered in sections in this overview include nuclide production, precursor preparation, the "carrier-free" problem, the design and synthesis of radiopharmaceuticals, and a short comment on technological aspects.

NUCLIDE PRODUCTION

With the increasing interest in radiopharmaceuticals labeled with positron emitters, making a proper choice in the routes used in preparing the desired nuclide become essential. This is especially true of those institutions which have not as yet put together a facility (accelerator and associated laboratories) for preparing the required nuclides. In considering the positron emitters carbon-11, nitrogen-13, oxygen-15, and fluorine-18 the nuclear reactions of choice have been clearly delineated. Table 1 lists the choices for each nuclide based on consideration of yield and target availability. Yield depends on the particle energies and currents available from the accelerator. There is at present some controversy as to which accelerator is ideal but there are some considerations which must be taken into account before a particular set of accelerator conditions is championed. The ultimate choice depends on the use to which the radionuclides are put. There is a wide gulf between an application where the main thrust is animal research and perhaps one or two human subjects/day, and an application where clinical research involving camera and/or tomograph capacity to its fullest on a daily basis is required. A further consideration is whether or not the program is based on simple gases and compounds exclusively, i.e. ^{11}CO, $^{11}CO_2$, $^{13}NH_3$, $^{13}N\text{-}N_2$, $^{15}O\text{-}O_2$, $H_2{}^{15}O$, $C^{15}O$, $^{15}O\text{-}CO_2$, etc. or is a more complex mixture of gases and radiopharmaceuticals. Going on the assumption that a broad clinical program and a program of basic research involving animals and human subjects is contemplated, the question that must be asked is whether or not sufficient quantities of radiopharmaceuticals are available at delivery for such a program. Thus, stated yields of radio-

nuclides for specific medical cyclotron types can be misleading in that they are usually based on a calculated maximum derived from excitation functions which may or may not be accurate. Furthermore, it is often the case that a yield is based on a stated maximum particle energy ignoring the fact that the material to be bombarded is in some form of container during bombardment and therefore the actual particle energy the target sees is lower than the energy of the particle impinging on the container wall. In Table 2 a list of some yields is given at energies and currents chosen to match approximately some of the specifications of currently available "low" energy machines. Factors such as optimum time and cost of enriched targets is not considered here. It must again be emphasized, however, that these are 100% recovery yields at saturation, an ideal rarely achieved in practice. Nevertheless, yields of some precursors approaching these limits are possible, especially with carbon-11. There is hardly any question that as more sophisticated engineering skills are brought to bear on production problems yields will more closely approximate theoretical maxima. Regretably to date, accelerator manufacturers have focussed on physics and not on chemistry and chemical engineering.

It is the purpose of this paper to update what is possible and to delineate new trends in organic radiopharmaceuticals. In the foregoing discussion no mention has been made of the many other accelerator produced nuclides that may be of interest. If one wishes to include such nuclides as ^{123}I, ^{76}Br, ^{77}Br, ^{68}Ga, ^{67}Ga, ^{38}K, or ^{201}Tl which can be incorporated into organic radiopharmaceuticals or used in conjunction with chelating agents, the considerations as to a suitable accelerator becomes considerably more complex. Thus, a more detailed analysis of radionuclide production problems is not germane (9). Nevertheless, careful consideration of these problems should be given by all who wish to embark on a program based on accelerator produced nuclides.

The next step in synthesis is the preparation of appropriate precursors labeled with the desired radionuclides.

PRECURSOR PREPARATION

The literature (4,10) contains many descriptions for target and precursor preparation. It is safe to say that in almost no case with the possible exceptions of ^{11}CO and $^{11}CO_2$ has the yield of precursor been optimized in the production sense. In general, methods have been described which are usually optimized for the machine parameters and other factors peculiar to the institution of origin. In any event, methods for the preparation of a wide variety of simple precursors can be found in the literature (1,3,4,5,6,7,10). A list of these precursors is given in Table 3. A number of revised, improved or new methods continue to appear in the literature.

In the area of carbon-11 precursors, post irradiation chemical methods for the preparation of ^{11}C-cyanate (11) and ^{11}C-phosgene (12) from ^{11}C-cyanide and ^{11}C carbon monoxide respectively have been described. More recently, on-line recoil syntheses of carbon-11 precursors are again being developed. ^{11}C-methyl iodide from the on-line bombardment of nitrogen-HI mixtures with protons can give radiochemical yields up to 25% (13). ^{11}C-methylamine in 45% radiochemical yield, and ^{11}C-guanidine in 49% radiochemical yield can be produced from the proton bombardment of crystalline NH_4Cl and NH_4I, respectively (14). Rapid and facile separation of these products from the target material could provide a new route to these precursors.

In the area of nitrogen-13 chemistry a method has been described for the bombardment of high pressure (~ 15 atm) O_2 targets with protons to give $^{13}N\text{-}N_2$, $^{13}N_2O$, and $^{13}NO_2$ directly in a ratio of 8:1:3.5 (15). A target system involving the utilization of the $^{16}O(p,\alpha)^{13}N$ reaction in water for preparing $^{13}NH_3$, $^{13}N\text{-}N_2$, $^{13}NO_2^-$, and $^{13}NO_3^-$ by subsequent steps has also been described (16). The preparation of $^{13}NH_3$ via reduction of the oxides of nitrogen by De Varda's alloy (17) is a convenient method for $^{13}NH_3$ preparation in good yield. Nitrous oxide ($^{13}N\text{-}N_2O$) can be prepared starting with $^{13}NO_3^-$ from the proton bombardment of water (18).

Oxygen-15 water is usually prepared by exchange of $^{15}O\text{-}CO_2$ with water. A direct recoil synthesis has been recently described involving the deuteron bombardment of $H_2\text{-}N_2$ mixtures which yields a very high specific activity product one minute after end of bombardment (19).

A patent (20) issued on the preparation of anhydrous fluorine-18 gives no experimental detail on the actual gas composition. New targetry and methodology for the preparation of on-line high specific activity anhydrous $^{18}F\text{-}F_2$ has been developed (21) utilizing the $^{20}Ne(d,\alpha)^{18}F$ reaction in high pressure neon targets containing scavenger F_2. A method for "carrier-free" $H^{18}F$ utilizing the $^{20}Ne(^3He,\alpha n)^{18}Ne$; $^{18}Ne \xrightarrow[sec]{1.5} {}^{18}F + \beta^+$ reaction in a $Ne\text{-}H_2$ mixture similar to previously described deuteron bombardments of $Ne\text{-}H_2$ mixtures has been published (22). The preparation of ^{18}F-DAST (diethylaminosulfur trifluoride) (23), ^{18}F-trifluoromethyl hypofluorite (24), and ^{18}F labeled $Cl^{18}F$ (25) have also been described.

There is little question that with the increasing interest in positron emitters for labeling organic compounds more attention will have to be paid to developing on-line production methods for the needed synthetic precursors to say nothing of wholly automated methods for compound preparation. We can expect to see more work on the refinement of procedures now in use and the development of new approaches, especially those yielding precursor at EOB or very shortly thereafter, be they by recoil or radiation synthesis, excitation labeling, or by fast chemical synthesis directly following EOB.

THE CARRIER-FREE PROBLEM

One of the important advantages of the short lived nuclides is that if the specific activity used is high enough they will act as true tracers in that their administration to whatever living system will not elicit a measurable physiological response (drug action) which may or may not perturb the purpose to which the tracer is put. In the case of carbon-14 or tritium this condition of lack of concomitant physiological response cannot always be met even if it were possible to prepare the labeled compound in the true carrier free state. Table 4 lists pertinent facts that focus on the relationships between specific activities and other physical parameters in an intercomparison of the nuclides of carbon and fluorine. If one considers the ratio of half lives the greatly superior sensitivity possible with the short lived tracer becomes quickly apparent. If one considers that many biochemical, biological, and medical experiments are carried out at the millicurie level it can be seen that for carbon-14 weighable amounts of the nuclide are involved, but that this is not the case for carbon-11 and fluorine-18. When one now considers that 1 millicurie of carbon-11 in the carrier free state is only 6.52×10^{10} atoms it

becomes very quickly apparent that the meaning of carrier free implies a tiny amount of material in an environment where the same material in stable (i.e. carbon-12) form may exist at levels many orders of magnitude higher than the radioactive material and still be undetectable by the usual analytical methods. To cite two examples of the problems in producing carrier free substances we can consider the preparation of $H^{11}CN$ (26) and the preparation of $H^{11}CHO$ (27) where it was possible to set upper limits on the available specific activity. It should be mentioned that no one to date has devised an experimental method that will define the proximity to the true carrier free state for carbon-11, nitrogen-13, oxygen-15, or fluorine-18 in quantitative terms when the dilution of the neat nuclide does not exceed one or two orders of magnitude. In the case of $H^{11}CN$ from $^{11}CH_4$ it was possible to obtain a maximum specific activity of 2000 Ci/mmol or a dilution of ca 5000 (26) and in the case of $H^{11}CHO$ from $^{11}CO_2$ it was possible to obtain a specific activity of 600 Ci/mmol or a dilution of ca 15,000 (27). In each case the stable carbon-12 came from traces of carbon-12 in the bombardment gas (consider for example the problem of removal of 1 ppm of $^{12}CO_2$ or $^{12}CH_4$ from commercial N_2; or the removal of 1 ppm $^{12}CO_3^=$ from boron oxide) and in the equipment and chemicals used in the subsequent steps needed to prepare the $H^{11}CN$ or $H^{11}CHO$. It can be argued that these specific activities are sufficiently high to satisfy the requirements of any trace level study. However, with the new interest in receptor site research it can be shown that near carrier free compounds are required in order to carry on meaningful experiments in many cases.

It is our contention that the question of the relation of the specific activity of the compound to that in the true carrier free state be considered in each case where it has bearing. Indeed the use, or more properly, misuse of the term carrier free is all too evident in the literature. What is almost universally meant when carrier free is used is actually no carrier intentionally added. Since it is clearly difficult to quantitate the amount of carrier in many cases and since no facile method has as yet been devised for measuring actual specific activity of the final product when no carrier has been intentionally added, we propose that a uniform nomenclature be used which will indicate to the reader of the scientific literature precisely what the condition of the product is. Thus, we propose:

1. CF to mean carrier free with evidence provided that its use is justifiable.

2. NCA to mean no carrier added and to be used for the vast majority of syntheses reported today. This term should basically replace CF since it is a more accurate designation.

3. CA to mean carrier added. This should be applied to any product where carrier is intentionally added whether or not the specific activity has been determined.

While this point may seem highly technical it will be an important issue as work with these short lived nuclides proliferates and experiments become increasingly sophisticated. We believe the use of CF, NCA, and CA will help to clarify the status of the compound for the reader of a paper and for those who depend on the accuracy of published work.

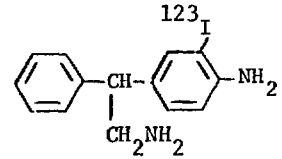
DESIGN OF RADIOPHARMACEUTICALS

Two major and related approaches have been applied in compound design, namely, (1) the targeting of a radiopharmaceutical to a particular organ by taking advantage of its unique metabolism or function, and more recently (2) to the use of labeled substrates to map metabolic activity or primary events which lead to a biological response in the case of hormones or drugs. Although the distinction here is subtle both areas of endeavor, when carried out in a scientifically thorough way contribute not only to direct application but also to forming a logical basis upon which new ideas and applications may be launched.

This section will deal with examples of some of the concepts used in radiopharmaceutical design and descriptions of the studies which support them. In many cases rather thorough studies on structure:activity relationships and metabolism have been described.

Recently a number of organ specific radiopharmaceuticals have been reported. Their design was based on their ability to elicit some physiological or biochemical response in a specific organ and they include enzyme inhibitors, receptor antagonists, adrenergic neuron blockers, and metabolic substrates or their analogs. Many of these studies include *in vitro* assays for determining factors responsible for the biodistribution of the various classes of compounds.

The successful therapeutic use of enzyme inhibitors to inhibit human adrenocortical function formed the basis for an investigation of these labeled inhibitors as agents for adrenal scanning. One of these (±)-2-(3-iodo-4-aminophenyl)-2-aminophenyl)-2-phenethylamine (an inhibitor of steroid 11 β-hydroxylase) labeled with ^{123}I (^{123}I-(±)-1) has been used to image dog adrenals (28).



^{123}I-(±)-1

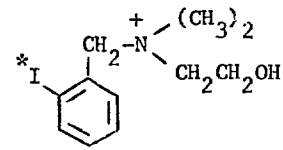
Resolution of (±)-1 into its optical isomers followed by radioiodination allowed a study of the stereoselectivity of adrenocortical enzymes. It was found that the (-)-1 enantiomer gave a 100% greater uptake in the adrenal cortex and a 3-fold increase in both the adrenal cortex/liver and adrenal cortex/medulla compared to the (+)-1 enantiomer demonstrating the possible clinical utility of a chiral radiopharmaceutical (29).

The possible use of radiolabeled cardioselective β-adrenergic antagonists as agents for imaging the myocardium has recently been investigated (30,31). These β-blockers would be predicted to localize in the myocardium by virtue of their specific and high affinity interaction with β-adrenergic receptors. Thus far the compounds studied are derivatives of the β-blockers, propranolol, practolol, and acetbutylol. Although a radioiodinated derivative of practolol

showed favorable distribution characteristics for myocardial imaging, it was species dependent and in vivo displacement studies with propranolol showed the binding to be non-specific (32). A simple two-compartment equilibrium model has been developed in order to calculate the maximum target to blood ratio (33).

The observation that the presence of estrogen receptors in malignancy correlates with tumor remission after endocrine ablation suggested the importance of developing labeled ligands to bind to the estrogen-receptor and led to the investigation of several radioiodinated estrogen derivatives as candidates (34). These compounds were studied to determine their affinity for the estrogen receptor and it was found that one of these derivatives, iodohexestrol, binds to the cytosol estrogen-receptor protein. Its in vitro behavior was related to the in vivo distribution demonstrating the usefulness of the in vitro receptor assay system in predicting in vivo distribution.

Dog adrenal medullae have been imaged using ^{131}I-o-iodobenzyldimethyl-2-hydroxyethyl-ammonium (2) a radioiodinated analog of the adrenergic neuronal blocking agent bretylium (35). This study demonstrates the importance of the



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chemical structure of the cationic head of the molecule as well as the position of the iodine atom.

Since long chain fatty acids are a major energy source for the myocardium, their use for imaging the myocardium has received considerable attention (36). The successful use of ^{11}C-palmitic acid for this purpose has encouraged the development of analogs labeled with other radionuclides to extend the useful shelf life of the radiopharmaceutical. A recent study compared various long-chain fatty acids labeled with ^{11}C, ^{34m}Cl, ^{77}Br, and ^{123}I and evaluated their potential application to the measurement of myocardial metabolism in vivo. Comparative studies of the kinetics of accumulation and clearance from the heart muscle of mice showed that the extraction of ω-haloacids is more efficient than α-haloacids and that the uptake of ^{123}I-17-iodoheptadecanoic acid is nearly identical to that of ^{11}C-palmitic acid (37). A study of the chemical form of the radioactivity in the heart and blood after injection of this ω-iodo fatty acid showed that its metabolism is via β-oxidation with dehalogenation taking place only at the end (38).

The efficient incorporation of 5-fluorouridine into RNA forms the basis of another study in which ^{18}F-5-fluorouridine is used as a probe for measuring RNA synthesis in tumors. ^{18}F-5-fluorouridylate was found to be an effective precursor for RNA synthesis in mouse spleen and intestine as well as intracranial tumors (39).

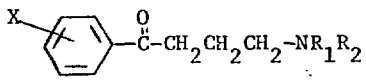
In turning to the probing of metabolism in vivo ^{18}F-2-deoxy-2-fluoro-D-glucose has been shown to be an effective tracer for quantitatively mapping the

first step of glycolysis in brain (40) and in heart (41,42). Factors responsible for the biodistribution of ^{18}FDG have been determined. Organs which show the highest uptake of activity (brain and heart) have the highest rates of ^{18}FDG-6-phosphorylation *in vitro* and show all of the radioactivity present is ^{18}FDG-6-phosphate even at one minute post-injection. The rapid clearance of ^{18}FDG from liver, lungs, and kidneys and the retention by heart and brain is the result of metabolic trapping and reflective of glucose utilization (43).

An exciting new area of research in the design and synthesis of labeled tracers has been initiated by the discovery of the existence of discrete populations of neurotransmitter receptors in brain and realization of their importance in the understanding and therapy of mental disorders. It is apparent in examining the various problems encountered in studying receptor populations (44) that the use of receptor ligands labeled with positron emitters, because of their high specific activity and decay by body penetrating radiation, can offer unique possibilities for probing the dynamics of receptor populations in normal and disease states.

The dopamine/neuroleptic receptor has received considerable attention in recent years because its blockade is the one common denominator among the many drugs which show antipsychotic activity. Therefore, it is of considerable interest to develop labeled antagonists with a high specificity for the dopamine receptor which would allow mapping these receptor populations in the brain.

Many of the most potent antagonists of the dopamine receptor are derivatives of butyrophenones and have the following general structure. The majority of these also have a halogen in the aromatic ring. Variation in the $-NR_1R_2$ substituent changes the properties of the antagonist.



BUTYROPHENONE SKELETON

A general approach to the synthesis of ^{11}C-butyrophenone derivatives has been developed (45). It involves two steps using ^{11}C-cyanide as the isotopic precursor and allows the flexibility of varying the NR_1NR_2 substituent. The

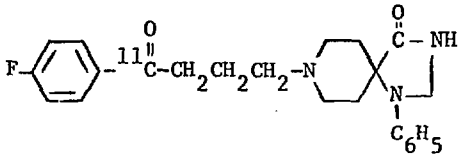
$$R_1R_2NCH_2CH_2CH_2Cl + {}^{11}CN^- \longrightarrow R_1R_2NCH_2CH_2CH_2{}^{11}CN$$

$$\xrightarrow[2)\ H^+]{1)\ ArMgBr} R_1R_2NCH_2CH_2CH_2{}^{11}\overset{O}{\overset{\|}{C}}Ar$$

carbon-11 resides in the carbonyl moiety. Since the metabolism of molecules of

this type has been shown to proceed via N-dealkylation followed by oxidation with ultimate excretion of the benzoyl moiety (46), the metabolized ^{11}C-butyrophenones (^{11}C-carbonyl) would be predicted to be rapidly excreted lowering the body background and radiation dosimetry associated with the use of this tracer.

This general synthesis of butyrophenones has been applied to the synthesis of ^{11}C-spiroperidol, a ligand with a high affinity for the dopamine receptor

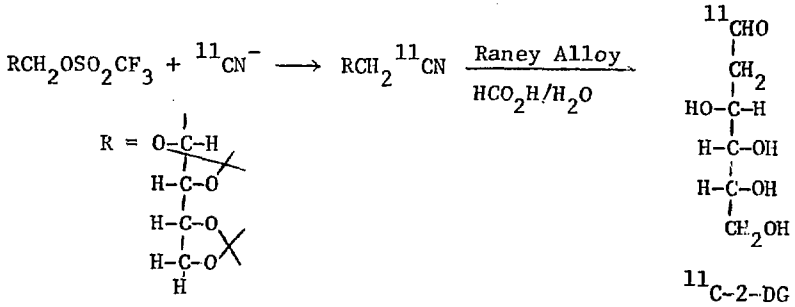


^{11}C-SPIROPERIDOL

(47). The application of this synthesis to other butyrophenones with different antagonist properties is also under investigation along with the parameters affecting no carrier added syntheses with multifunctional substrates.

NEW SYNTHESES OF RADIOPHARMACEUTICALS

Carbon-11: A new route to 2-deoxy-D-glucose has been developed (48) and applied to the synthesis of ^{11}C-2-deoxy-D-glucose (^{11}C-2-DG) (49). A particularly noteworthy feature of this sequence is the reduction of a nitrile



to an aldehyde under no carrier added (NCA) conditions.

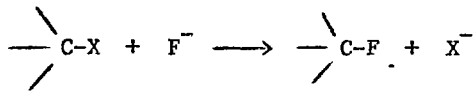
[1-^{11}C]-DL-valine has been prepared by a high temperature high pressure modification of the Bucherer-Strecker amino acid synthesis and evaluated for pancreas imaging (50). This material is produced at intervals of 1 hr or less in 100-200 mCi batches. Another amino acid, ^{11}C-DOPA (β-(3,4-dihydroxyphenyl)-D,L-α-alanine-1-^{11}C) has been synthesized by carboxylation of an α-lithio-isocyanide (51).

The preparation of ^{11}C-methyl labeled 1,1'-dimethyl-4,4'-dipyridinium diiodide (^{11}C-paraquat) has been accomplished using ^{11}C-iodomethane for use in in vivo studies of pulmonary toxicology (52).

In an unusual example of biosynthetic application ^{11}C-hippuric acid was prepared from ^{11}C-benzoic acid and glycine using rat liver mitochondria (53). The incorporation of carbon-11 into pyruvic acid, lactic acid, and L-alanine via enzymatic synthesis from $^{11}CO_2$ has been reported (54). Lactic acid and lactonitrile have also been prepared synthetically (55).

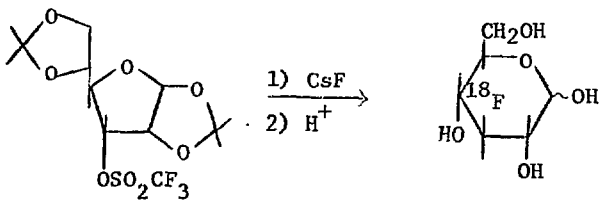
Fluorine-18: The formation of carbon-fluorine bonds is a difficult synthetic problem which is magnified when one attempts to apply known methods of carbon-fluorine bond formation to ^{18}F-labeling where it is desirable to use little or no carrier fluorine. The chemical forms of ^{18}F available for labeling can be classified as nucleophilic fluorine or electrophilic fluorine and the problems encountered with each of these forms are predictable based on the organic chemistry of fluorine.

With nucleophilic fluorine, displacement reactions are usually envisioned



for C-F- bond formation. The success of a displacement reaction is strongly affected by the presence or absence of water in the reaction mixture because the high hydration energy of fluoride causes the energetics of C-F bond formation to be very unfavorable in protic media (56).

Several approaches to increasing the reactivity of fluoride ion have been applied to labeling with ^{18}F. The use of anhydrous $H^{18}F$ from the Ne + H_2 target is the most successful and has been applied to the synthesis of ^{18}F-3-deoxy-3-fluoro-D-glucose (57). In other studies where $^{18}F^-$ from the water target is



^{18}F-3-Deoxy-3-Fluoro-D-Glucose

used, the reactivity of the ^{18}F-fluoride (after careful drying) is increased by using hindered cations or by using crown ethers. For example, ^{18}F-6-deoxy-6-fluoro-α-D-galactopyranose has been prepared using tetraethylammonium fluoride-^{18}F in acetonitrile (58). The use of $K^{18}F$ and 18-crown-6 has been applied to the synthesis of ^{18}F-21-fluoroprogesterone (59,60), as well as to the ^{18}F for F exchange on benzotrifluoride (61). ^{18}F-β-D-glucosyl fluoride has been prepared by the reaction of tetra-O-acetyl-α-D-glucosyl bromide with $Ag^{18}F$ in acetonitrile (62).

Electrophilic fluorination using $^{18}F_2$ has found continued application in the synthesis of ^{18}F-2-deoxy-2-fluoro-D-glucose (63). The use of $^{18}F_2$ is considerably simplified by purchasing a premixed cylinder of 1% F_2 in neon as

the source of F_2 carrier in the target gas. This is far safer than handling pure fluorine and eliminates the need for a high vacuum line for measuring small quantities of pure F_2.

Nitrogen-13: A procedure has been described for the preparation of millicurie quantities of ^{13}N-bis(2-chloroethyl)nitrosourea labeled in the nitroso group (64).

TECHNOLOGY

The application of β^+-emitters to many areas of research has generated considerable interest in the physical set-up of cyclotrons and adjacent chemistry laboratories which are capable of safely handling Curie levels of short-lived nuclides. Therefore, some of the important aspects of laboratory design, shielded work areas, radioactivity monitoring and experimental set-ups which have proved workable from our experience and which often use commercially obtainable or easily constructed components are summarized below.

The spatial relationship of the cyclotron vault to the chemistry laboratory is an important one, in that the delivery of target gases or liquids is generally most easily accomplished when the distance between the target and the area where the radionuclide is to be used is as short as possible. When the chemistry lab is adjacent to the vault, there is, of course, a heavy shielding wall between these areas with strategically placed ports to contain delivery lines.

Target gases as well as liquid or solid forms of labeled precursors are most safely and conveniently handled in a shielded hood or some form of hot cell. The simplest shielded work area can be obtained by modifying a commercially available laboratory hood. After providing structural support of the floor of the hood, lead plate is placed on the floor of the hood. Along the entire front face of the hood a short wall of lead bricks is built up. On the top of the wall a high density (6.2 gm/cc) lead glass window (65) (16.5 in high x 16.5 in wide) is installed on a track so that it slides across the front face of the hood. This provides a reasonably well shielded work area, especially when modular shielding is used within the hood. For example, lead shielding of various traps in which the nuclide is trapped as well as small lead shields for various reaction vessels, when used inside the modified commerical hood provides reasonably inexpensive and effective protection for manipulations which need to be carried out during synthesis. The use of remotely controlled equipment during synthesis as well as extension tools for performing various manipulations is also very effective. The automation of a radiopharmaceutical synthesis has recently been reported and includes all steps of precursor preparation, compound preparation, chromatography, and sterilization. The facility is enclosed within a hot cell (66).

Monitoring the amount of radioactive precursor delivered from a target to the synthesis laboratory is conveniently carried out using an ionization chamber with digital readout (67) in a shielded fixed geometry. This allows one to measure the accumulated radioactivity at any time during target gas delivery. Such a system is in use in our $^{18}F_2$ production. Monitoring the distribution of radioactivity during synthesis is conveniently done using a shielded ionization chamber with a large ($\sim$ 2 7/8 inch) diameter well. This unit is installed in the shielded hood already described and allows direct measurement of radioactivity of different vessel sizes and shapes (67).

CONCLUSION

This short paper was intended to update current trends and directions in the design and preparation of organic radiopharmaceuticals, particularly those labeled with positron emitters. Associated concerns such as nuclide production, specialized technology, and a presentation of problems engendered by the increasing need for carrier free or near carrier free materials were also addressed. The debate over whether or not accelerator produced radionuclides will impact in a major way on health care will no doubt continue but it is now becoming clear that the discussion is no longer based on utility but rather on economics. The coming years will surely bring major advances in cyclotron technology, focussing mostly on simplicity and reliability of operation, automated (computerized) control, and hopefully reduced cost in the sense of cost per watt of beam. Automation of nuclide production and ultimately radiopharmaceutical production (black box approach) according to sound engineering practice is a concurrent goal. While it is not feasible to suggest an accelerator in every hospital it is worth considering regional centers based on levels of activity and types of nuclides required. Oxygen-15, nitrogen-13, potassium-38, and probably carbon-11, etc. i.e. nuclides with half lives of less than one hour and the compounds in which they are incorporated will have to be produced at or near the site of use. However, nuclides such as fluorine-18 and its compounds could serve a wider geographic area. We have not addressed the utility of generator produced nuclides since they are covered in detail in other papers at this symposium.

Some accelerator produced radionuclides, especially ^{67}Ga, ^{201}Tl, and ^{81}Rb-^{81m}Kr in the U.S. (and ^{123}I in Europe) have already impacted in a major way on health care. The utility of the simple gases containing ^{13}N, ^{15}O, and ^{11}C and labeled organic compounds, metallo-organics, and organic complexes are now receiving intensive study worldwide with notable breakthroughs in the area of *in vivo* metabolic studies and the flow-metabolism couple. Thus, one can expect to see major advances in the coming years with accelerator nuclides taking their place in the pursuit of basic biochemical and biological research and in the armamentarium of nuclear medicine practice.

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TABLE 1

Positron Emitters for Labeled Organic Radiopharmaceuticals

Nuclide	Reactions of Choice	Threshold (MeV)	Energy at Cross Section Max (MeV)	Maximum Cross Section (millibarns)
Carbon-11	$^{10}B(d$ $)$	0	2.3	260
	$^{11}B(p,n)^{11}C$	3.0	6.5	400
	$^{14}N(p,\alpha)^{11}C$	3.1	7.6	253
Nitrogen-13	$^{13}C(p,n)^{13}N$	3.2	6.6	276
	$^{12}C(d,n)^{13}N$	0.3	4.7	150
Oxygen-15	$^{15}N(p,n)^{15}O$	3.7	6.3	380
	$^{14}N(d,n)^{15}O$	0	2.5	200
Fluorine-18	$^{18}O(p,n)^{18}F$	2.6	5.1	700
	$^{20}Ne(d,\alpha)^{18}F$	0	-	194

TABLE 2

Carbon-11 and Fluorine-18 Yields

Nuclide	Reaction	Energy of Particle (p or d) on Target			
		8	10	12	14
		Yield in mCi/uA at Saturation			
Carbon-11	$^{14}N(p,\alpha)^{11}C$	29	45	66	93
Fluorine-18	$^{18}O(p,n)^{18}F$	110	147	187	216
	$^{20}Ne(d,\alpha)^{18}F$	46	63	75	84

TABLE 3

Precursors for Synthesis of Compounds Labeled with Positron Emitters

Carbon-11

CO CO_2 CN^- CH_2O CH_3I CH_3OH

C_2H_2 C_2H_4 C_2H_5OH $CH_3\text{-}COOH$ $NH_2\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH_2$

Nitrogen-13

NO NO_2 N_2O N_2 HCN NH_3

Oxygen-15

O_2 H_2O CO CO_2

Fluorine-18

F_2 F^-

Salts of Fluorine

$(C_2H_5)_4N^+F^-$ or Crown Ether salts

NOF ClF CF_3OF $(C_2H_5)_2NSF_3$

SbF_3 $LiBF_4$ $FClO_3$ BiF_3 etc.

TABLE 4

Carbon, Fluorine, and Tritium as Tracers

	Carbon-11	Fluorine-18	Tritium	Carbon-14
Half-life	20.4 min	110 min	12.3 yrs	5700 yrs
Ratio of Specific Activities Carbon-14 = 1	1.5×10^{8}	2.7×10^{7}	464	1
Curies/mol (atomic state)	9.22×10^{9}	1.71×10^{9}	2.92×10^{4}	62.8
Atoms/Curie	6.52×10^{13}	3.52×10^{14}	2.06×10^{19}	9.6×10^{21}