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RECENT ADVANCES IN THE CHEMISTRY OF POSITRON EMITTERS

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There are at present approximately 60 institutions world-wide equipped with some type of charged particle accelerator, preponderantly "small medical cyclotrons" associated with one or more positron emission tomographs (1,2). The use of positron emitters in labeled compounds for biomedical research all but disappeared post World War II, being displaced by carbon-14 and tritium in biochemical and biological research, and by the single photon emitters primarily iodine-131 and technetium 99m in biomedical research and clinical practice. Following the introduction of a "medical cyclotron" at Hammersmith Hospital in London a number of papers again began appearing utilizing single oxygen-15 and carbon-11 labeled compounds. In 1966 a paper appeared which served as a renewed stimulus to considering positron emitters for research and clinical use (3). As the positron emission tomograph allowing quantitative determination of radionuclide (or positron emitter labeled compound) concentration in a given volume element of tissue in vivo became more readily available in the early and mid-seventies, the opportunity to use increasingly sophisticated labeled compounds and labeled biomolecules manifested itself. Compounds labeled with carbon-11, nitrogen-13 and fluorine-18 described in the literature prior to 1981 have been documented in a book on synthesis methods (4). Somewhat more recent reviews can be found in a number of book chapter (5a,b). However, no extensive review of new labeled compounds is available covering published work of the last three years. It is not the purpose of this short paper to present such a review but rather to present some of the more recent trends in labeling compounds with positron emitters.

Beginning with carbon-11 the traditional methods of preparing ^{11}C-methanol from $^{11}CO_2$ and the use of the carboxylation of a Grignard with $^{11}CO_2$ have been applied with advantage in preparing a host of labeled ethers, alcohols, ketones and hydrocarbons for use in studying the relationship between lipophilicity and brain extraction (6).

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New approaches to preparing amino acids with the label in the 3 position have been described by Langström and colleagues (7) by utilizing carbon-11. The use of chiral hydrogenation catalysts for the partial asymmetric synthesis of L-[3-^{11}C]phenylalanine (9) has also been reported by these authors. Another more recent approach to labeling amino acids is the further elaboration of the carboxylation of α lithioisocyanides by the Groningen group who have prepared DL[1-^{11}C]proline by the carboxylation of α lithio pyrrolidyl-N-tert-butylformamidine. These new and newly elaborated methods add to the amino acids accessible by the modified Bücherer-Strecker synthesis (cf. references in 4) described in the earlier literature. The importance of labeled amino acids is taking on added significance due to their more widespread use in a variety of tumor studies, a number of which are noted herein (10-13). Indeed the use of positron emitter labeled compounds for tumor detection and staging is becoming an increasingly important aspect of research and clinical application in PET. The extensive work of DiChiro and colleagues in utilizing ^{18}F-FDG for brain tumor research is well known. Another example is the use of polyamines for example the use of N-[^{11}C]methylputrescine, spermine and spermidine for prostate tumor detection (14). More recently [1-^{11}C]putrescine has been prepared (15) and is under active investigation in our laboratory for the study of primary and metastatic brain tumors.

A trend which is becoming increasingly evident is the use of carbon-11 labeled methyl iodide. The organic chemistry of this labeling agent is well understood and it has been used to label amino acids (eg. methionine) and many different agonists and antagonists for brain receptor work an early example of which was the labeling of chlorpromazine (16). A more recent example of the continued use of [^{11}C]H_3I by this group in labeling psychoactive drugs involves the synthesis of a highly specific benzodiazepine receptor drug [RO 15.1788-^{11}C] (17). Other examples of methylation using [^{11}C]H_3I, of psychoactive drugs include the preparation of 3-N-[^{11}C]methylspiperone (18) (cf. the preparation of the ^{18}F compound vide infra) and the opiate receptor binding agent, [^{11}C]carfentanil (19).

A new initiative is the development of probes for functional enzyme activity using suicide enzyme inhibitors labeled with carbon-11 via the N-methylation reaction with [^{11}C]H_3I (20,21).

A number of methods of preparation of [^{11}C]H_3I have been described. Three variations are in common use (22-24). Recently another variation using P_2I_4 as the agent to iodinate ^{11}C-methanol has been described yielding a pure product in high yield (25).

[1-^{11}C]Ethyliodide as a labeling agent has also been utilized recently (26). Before leaving comment on some recent advances in carbon-11 labeling, it is worth stressing that facile labeling can also provide compounds which

undergo facile metabolism of the labeled position in vivo. Thus demethylation of [^{11}C]methyl or decarboxylation of [^{11}C]carboxyl or indeed the labeling in any metabolically labile position with ^{11}C can render the labeled compound less useful as a tracer than a synthesis leading to a label in a stable position. An exception, of course, is the use of [^{11}C]carboxyl labeled amino acids for the quantitative measurement of regional protein synthesis (27).

Increased emphasis on fluorine-18 fluoride ion as a labeling agent is becoming apparent in the more recent literature. While a large number of fluorine-18 precursors have been made, only two ^{18}F-F_2 and ^{18}F-F^- (25) have enjoyed widespread use. Any number of syntheses of 18-FDG have appeared in the literature since its initial description in 1978 (29). Two recent syntheses (30,31) utilize [^{18}F]fluoride ion in the preparation of ^{18}FDG. High yields of a pure product can be obtained. The Hamacher (31) synthesis may prove to be the more useful because of the ready availability of the precursor and the simplicity of the reaction steps.

The use of nucleophilic aromatic substitution as a labeling method was investigated (32,33) and then applied to the labeling of fluorinated butyrophenone compounds (34) and fluorine-18 labeled N-methylspiperone (35) (cf. [^{11}C]labeled compound reference). A comparative study of fluorination with [^{18}F]fluoride ion has also been recently reported (36). Fluorinated estrogens utilizing ^{18}F fluoride ion have also been prepared (37).

Syntheses with nitrogen-13 and oxygen-15 are less common and will not be reviewed here.

CONCLUSION

With the increasing active interest in PET as a method for studying biochemistry in normal and pathological states in humans we can expect to see the development of new techniques for precursor preparation and synthesis. We have seen a doubling of the publication rate in the past three to four years over the previous three to four year period. As the need for these compounds, especially in the tumor and receptor areas, in a purely clinical setting, increases the trend towards true automation of production of the most needed compounds will accelerate. The cyclotron manufacturers all offer "black boxes" for synthesis but the optimum approach to user friendly automation yet needs to be defined.

I would again note that this paper was not intended as a comphrehensive review but rather my goal was to highlight just some of the exciting developments of the past several years. We are entering what may well be the most extensive and active period of research in the synthesis of positron emitter labeled compounds. If 1984-1985 is any gauge, many new methods and compounds will appear in the next several years.

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