CONTENTS

Part I: Compounds of Isotopic Carbon

CHAPTER 1

INTRODUCTION

A. ARRANGEMENT

As a result of the extensive utilization of isotopically labeled organic compounds as tracers in biological and medical research, and in the solution of industrial and purely academic problems, the number and variety of such compounds are necessarily large. The classification of these compounds by isotope has resulted in a logical presentation of the material in two volumes. Part I is composed entirely of the compounds of isotopic carbon. Part II contains organic compounds labeled with isotopes of hydrogen, the halogens, nitrogen, sulfur, phosphorus and oxygen.

Individual units of the text are composed of either one-step or multiple-step syntheses, and the title of each unit is the name of the end-product. The units are classified according to the labeling isotope. As indicated by the tables of contents, the units are grouped according to compound class designations, within which they are arranged according to parent structures in an increasing order of complexity. Since in any given synthesis procedure a number of labeled intermediates may be described but not represented in the synoptic tables, it cannot be overemphasized that the most efficient approach to the location(s) of a compound is through the combined index to Parts I and II. A compound which is the end-product in one synthesis may be the starting material in one or more other procedures; therefore, the preparation of an isotopic compound is indicated by a boldface page number in the index.

The section under each unit synthesis headed *Other Preparations* is rather broad in scope. It contains references to other methods of preparing the topic compound, references to similar compounds prepared essentially according to the procedures described, and, in some instances, to similar syntheses in which procedural details were lacking or inadequate.

Chemical compounds are indexed according to the Subject Index usage of *Chemical Abstracts* with the additional provision that isotopic designations appear as derivatives. The combined index to Parts I and II, with an outline of the indexing procedure, appears in Part II.

B. ISOTOPIC ORGANIC NOMENCLATURE

A collection of preparative procedures involving labeled organic compounds must, at the same time, be a collection of the names of these compounds. A book such as this which contains both a great number and a broad variety of isotopic names is an excellent proving ground for a systematic method of nomenclature. Inadequacies in one system become readily apparent under the test of repeated application; but another system which is clear and concise in its usage throughout the most difficult tests devisable for it will emerge as a welcome contribution.

Already-postulated rules for naming labeled organic compounds exist in the deuterium-tritium system of Patterson, Capell and Magill,[1] the carbon-isotope system of Collins, Crompton, Ronzio and Tolbert,[2] and in a few, less formal, published suggestions.[3,4]

The nomenclature developed for this book originated in these existing precepts, evolved during three years of study, and reached the present form when successfully applied to all names in this book.

The basic problem in isotopic nomenclature is the complexity of the molecular mixture which must be described in all stiuations involving dilute isotope and even in some cases the "pure" carrier-free nuclide. The convention for choosing the structure or combination of structures which must be named to characterize the labeled compound should constitute the first rule of the naming system.

Formulation of isotopic names is logically founded on acceptable nonisotopic nomenclature. The inherent difficulty here is the confusion of equivalent names resulting from so moderate a criterion as "acceptable." Another rule must either state the nonisotopic system of nomenclature to which one must adhere or admit chaos.

Further rules must define the mechanics for arriving at a proper isotopic name. Their invention must be governed by a requirement of general applicability and clarity along with a desire for simplicity. The fundamental decision was made for this nomenclature that simplicity would accompany the names and the mechanism for clarity would be written into the rules.

Rule I. THE ISOTOPIC NAME SHALL DESCRIBE THE *SINGLE STRUCTURE* OR *MIXTURE OF STRUCTURES*, EACH OF WHICH IS LABELED AT EVERY POSITION DICTATED BY THE PREPARATIVE METHOD FOR THE LABELED COMPOUND. THE ISOTOPIC NAME SHALL HAVE TWO PARTS: A NONISOTOPIC NAME FORMULATED IN ACCORDANCE WITH THE USAGE OF *CHEMICAL ABSTRACTS*, AND ONE OR MORE *ISOTOPIC DESIGNATIONS* WHICH PROVIDE ALL AVAILABLE INFORMATION ABOUT THE ISOTOPIC LOCATIONS IN THE LABELED COMPOUND.

This rule is based on the desire to keep the question of isotopic abundance completely separate from the assignment of names. This removes the temptation to focus attention on the most probable labeled structure and places proper emphasis on that structure or group of structures with highest isotopic multiplicity.

Exhaustive methylation of ammonia with methyl iodide whose carbon is 10% C^{14} will yield a mixture of five structurally distinguishable tetramethylammonium iodides. The composition of this mixture, assuming no isotope effects occur, can be calculated to be: 65.61% with no label, 29.16% with one label, 4.86% with two labels, 0.36% with three labels, and 0.01% completely labeled. These percentages depend on the original isotopic abundance in the methyl iodide. If the carbon of methyl iodide had been 90% C^{14}, the five quaternary salts would have been formed in just the opposite order of the same percentages. Application of Rule I indicates that this is a *single structure* case, regardless of the C^{14}-abundance of the methyl iodide, and that the molecule which must be described is tetramethylammonium iodide containing four C^{14} atoms.

2-Propanol labeled with C^{14} at one of the methyl groups dehydrates to give a mixture of propenes, one with C^{14} at the 1-position and the other with C^{14} at the 3-position. This is a *mixture of structures*, both of which may be described by a single isotopic name.

Artificial mixtures (mechanical, as distinguished from synthetic) may be described by a single isotopic name, when the rules permit.

This nomenclature has chosen to recognize two classes of the *mixture of structures*. The mode of distinction between these classes is characteristic of the nomenclature and not of the chemical structures involved.

A *class A mixture* is a *mixture of structures* in which every *isotopic designation* in its isotopic name completely describes one or more contributing structures. Almost every one of the mixture cases in this book is a *class A mixture*. A few examples are not in this category for two reasons: either there is a discontinuous numbering system in the nonisotopic name, or there are two or more different isotopes in the same structure.

A *class B mixture* is a *mixture of structures* which differs from a *class A mixture* in that it has a recurring label described by one or more *isotopic designations*, and takes the form of a *class A mixture* in the other *isotopic designations*. The *class B mixture* name gives the appearance of being derived from the mixture by factoring out a *single structure* and leaving a *class A mixture*.

This nomenclature does not provide a name for a mixture which is neither *class A* nor *class B*.

Rule I notes the dependence of this nomenclature on *Chemical Abstracts* as the most expedient source of nonisotopic names. Its subject index is not only a ready reference text for nomenclature but is also a repository of information on labeled compounds.

Rule II. THE COMPONENTS OF THE *ISOTOPIC DESIGNATION* SHALL BE SYMBOL, SUPERSCRIPT, SUBSCRIPT AND LOCANT. THE SYMBOL WITH ITS SUPERSCRIPT AND SUBSCRIPT IS SET OFF FROM OTHER PARTS OF THE ISOTOPIC NAME, EXCLUDING PUNCTUATION, BY MEANS OF HYPHENS. THE SYMBOL SHALL BE THE STANDARD CHEMICAL DESIGNATION OF THE ELEMENT. THE SUPERSCRIPT SHALL IMMEDIATELY FOLLOW THE SYMBOL AND SHALL BE THE MASS NUMBER OF THE ISOTOPE. WHEN *ISOTOPIC DESIGNATIONS* MUST APPEAR TOGETHER IN AN ISOTOPIC NAME, PRECEDENCE SHALL BE ESTABLISHED PRIMARILY BY ALPHABETICAL ORDER OF SYMBOL AND SECONDARILY BY NUMERICAL ORDER OF SUPERSCRIPT.

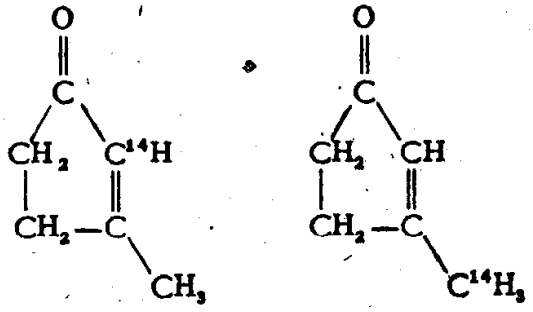
Rule III. THE SUBSCRIPT SHALL IMMEDIATELY FOLLOW THE SYMBOL AND SHALL BE AN INTEGER IN EVERY *ISOTOPIC DESIGNATION OF A SINGLE STRUCTURE* AND A FRACTION IN EVERY *ISOTOPIC DESIGNATION* OF A *CLASS A MIXTURE*. A *CLASS B MIXTURE* SHALL HAVE *ISOTOPIC DESIGNATIONS* WITH SUBSCRIPTS OF BOTH THE INTEGRAL AND FRACTIONAL VARIETY. THE INTEGRAL SUBSCRIPT SHALL STATE THE NUMBER OF LABELED ATOMS DESCRIBED BY ITS *ISOTOPIC DESIGNATION;* THE NUMERATOR OF THE FRACTIONAL SUBSCRIPT SHALL STATE THE NUMBER OF LABELED ATOMS IN EACH STRUCTURE DESCRIBED BY ITS *ISOTOPIC DESIGNATION;* AND THE DENOMINATOR OF THE FRACTIONAL SUBSCRIPT SHALL STATE THE NUMBER OF STRUCTURES DESCRIBED BY ITS *ISOTOPIC DESIGNATION.* THE INTEGRAL SUBSCRIPT "1" SHALL BE OMITTED EXCEPT IN CASES WHERE THE *ISOTOPIC DESIGNATION* DESCRIBES ONE OF TWO OR MORE EQUIVALENT LOCATIONS IN THE LABELED COMPOUND.

Examples of integral subscript usage in *single structure* cases are propane-1,2-C_2^{14} for $C^{14}H_3C^{14}H_2CH_3$ and semicarbazide-C^{13}-2-H^2-1,4-N_2^{15} for $N^{15}H_2NH^2C^{13}ON^{15}H_2$. This latter example is also an illustration of the proper order of *isotopic designations*. The discussion section of Rule V contains a name, cyclohexanecarboxylic-C^{14}-2-C^{13} acid, which is a required violation of the usual order of precedence.

It follows from Rule III that the sum of the implied and stated integral subscripts in the isotopic name of a *single structure* will be equal to the number of labeled sites in that structure.

Fractional subscript usage in *class A mixtures* is shown in the following three examples. Chlorination of naphthalene-1-C^{14} yields a mixture

of four compounds which is named 1-chloronaphthalene-1,4,5,8-$C^{14}_{1/4}$. 2,5-Hexanedione-1-C^{14} is cyclized to give the mixture:

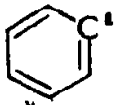


The name required is 3-methyl-$C^{14}_{1/1}$-2-cyclopenten-1-one-2-$C^{14}_{1/1}$. 2-Propanol-1-H^3_3 dehydrates to give propene-1-H^3_2 and propene-3-H^3_3. This *class A mixture* is named propene-1-$H^3_{2/1}$-3-$H^3_{3/1}$.

Nitration of benzene-C^{14}_1 with nitric-N^{15} acid, followed by reduction of the product to give aniline, yields a *class B mixture* of four compounds which is named aniline-$C^{14}_{1/4}$-N^{15}. Another example of a *class B mixture* is the combination of 1-ethyl-2-C^{14}-benzene-1-C^{14} and 1-ethyl-2-C^{14}-benzene-2-C^{14}. This is named 1-ethyl-2-C^{14}-benzene-1,2-$C^{14}_{1/2}$. The mixture, 1-ethyl-2-C^{14}-benzene-1-C^{14} and 1-ethyl-1-C^{14}-benzene-2-C^{14}, cannot be given an isotopic name with this nomenclature because of the partially repetitive numbering system of ethylbenzene. If the two structures of the last mixture were dehydrogenated to styrenes, a *class A mixture* would result, thanks to the nonrepetitive numbering system of styrene. The name, the isotopic locant system of which will be evident after Rule IV, is styrene-(α,2), (β,1)-$C^{14}_{2/2}$.

Another consequence of Rule III is that the sum of the denominators of the fractional subscripts in the isotopic name of a *class A mixture* or a *class B mixture* will be equal to the number of structures in that mixture. It also follows that the sum of the numerator-denominator products of the fractional subscripts in the isotopic name of a *class A mixture* will be equal to the number of labeled atoms in all the contributing structures. These corollaries are useful in checking the correctness of a name.

The correct use of the subscript "1" is demonstrated in the following examples:

$N^{15}H_2CONH_2$	urea-N^{15}_1
	benzene-C^{14}_1
$CHH^3=CH_2$	ethylene-H^3_1
$C^{13}H_2=CH_2$	ethylene-C^{13}_1
$C^{14}H_2=CHH^2$	ethylene-1-C^{14}-2-H^2_1

Rule IV. THE LOCANTS SHALL PRECEDE THE SYMBOL AND SHALL INDICATE THE LOCATIONS OF THE LABELED ATOMS. LOCANTS FOR *ISOTOPIC DESIGNATIONS* SHALL BE IDENTICAL IN KIND AND USAGE TO THOSE IN NONISOTOPIC NAMES. WHENEVER NO LOSS OF INFORMATION RESULTS FROM OMISSION OF LOCANTS, THE RESULTING SIMPLIFIED NAME SHALL BE USED. WHENEVER BOTH THE NUMERATOR AND THE DENOMINATOR OF THE SUBSCRIPT IN AN *ISOTOPIC DESIGNATION* OF A *MIXTURE OF STRUCTURES* ARE GREATER THAN 1, THE LOCANT AGGREGATE SHALL BE CONSTRUCTED OF TWO OR MORE GROUPS OF LOCANTS WITHIN PARENTHESES, THE NUMBER IN EACH GROUP BEING EQUAL TO THE NUMERATOR.

There are three classes of locants: stated, implied, and virtual. Stated locants are those expressed as numbers, Greek letters or capital-letter element designations. Implied locants are those omitted according to Rule IV. Virtual locants are missing because of lack of a locant designation in the nonisotopic name. The name 1-methyl-C^{14}-piperidine-4-C^{14}-N^{15} contains all the locant types in the order virtual, stated and implied.

There are two varieties of locant usage, one involving (a) the position at which the isotope is situated, and the other (b) the position to which the isotope is attached. This dual nature of the locant is illustrated in the following examples, after which are employed the preceding code letters for locant varieties:

$CH_3C^{14}H_2CH_3$ propane-2-C^{14} (a)

$CH_3CH_2^2CH_3$ propane-2-H_2^2 (b)

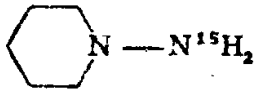
$CH_3NHCON^{15}H_2$ 1-methylurea-3-N^{15} (a)

2-methyl-2*H*-1,2,3-triazole-2-C^{13} (b)

or

2-methyl-C^{13}-2*H*-1,2,3-triazole (a)

All of these examples are strictly correct. It is traditional, however, always to employ locant type (a) for carbon isotopes. With isotopes other than carbon, ambiguity is rarely encountered. With a case such as



locant usage of type (b) gives the incorrect name: 1-aminopiperidine-1-N^{15}. 1-Amino-N^{15}-piperidine is required and uses locant type (a).

The second sentence of Rule IV is a re-emphasis of that part of Rule I pertaining to nonisotopic nomenclature. *Chemical Abstracts* uses locants in most of its major names, as evidenced by derivatives which are listed in subheadings as position-numbered substituent groups.

Other major names have no locant numbers, as inferred from the statement under their names: "for derivatives, see ....." According to Rule IV, if there is no 2-bromoisobutyric acid, then there is no "isobutyric-2-C^{14} acid," etc. Following the usage of *Chemical Abstracts*, this *isotopic name* should be 2-methylpropionic-2-C^{14} acid. "Stearic-2-C^{14} acid" should be octadecanoic-2-C^{14} acid, and "adipic-1,6-C_6^{14} acid" should be hexanedioic-1,6-C_2^{14} acid.

The anhydride of 2-chloropropionic acid is known as bis(2-chloropropionic) anhydride. Similarly, this nomenclature names the anhydride of propionic-2-C^{14} acid, bis(propionic-2-C^{14}) anhydride. Completely analogous cases are *N,N*-bis(ethyl-1-C^{14})aniline and tris(propyl-2-H_2^3) citrate.

Names like chlorobenzene, phenylhydrazine and phenylalanine do not have locants, as evidenced by the necessity to use *two* locants to describe their singly substituted derivatives. Isotopic names taking this into consideration are: 1-chlorobenzene-4-H^2, 1-phenylhydrazine-1-N^{15}, and 3-phenylalanine-1,2-C_2^{14}.

The third sentence of Rule IV allows the following simplified names: propane-C_3^{14} instead of propane-1,2,3-C_3^{14}; benzene-C_6^{14} instead of benzene-1,2,3,4,5-C_6^{14}; cyclopentane-1,2,4-H_6^3 instead of cyclopentane-1,1,2,2,4,4-H_6^3; propene-1-$H_{2/1}^3$-3-$H_{3/1}^3$ instead of propene-1,1-$H_{2/1}^3$-3,3,3-$H_{3/1}^3$; and aniline-$C_{1/4}^{14}$-N^{15} instead of aniline-1,2,3,4-$C_{1/4}^{14}$-N^{15}. The name "acetone-H_6^2" is not allowed because it is a contraction of the incorrect name "acetone-1,3-H_6^2." Acetone has no locants, and the correct name is 2-propanone-H_6^2.

The last sentence of Rule IV establishes a basis for the form used for a multiply-labeled *mixture of structures*. The mixture

$CH_2{=}C^{14}HC^{14}H_2CH_2CH_2CH_2OH$ and $CH_2{=}CHCH_2C^{14}H_2C^{14}H_2CH_2OH$

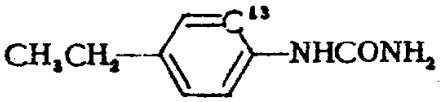
is named 5-hexen-1-ol-(2,3),(4,5)-$C_{2/2}^{14}$. The chlorination product of benzene-1,2,3-C_3^{14} is a mixture of four structures and is named 1-chlorobenzene-(1,2,3),(1,2,6),(2,3,4),(3,4,5)-$C_{3/4}^{14}$.

Before this discussion of components of the *isotopic designation* is ended, a frequently used naming method which circumvents these rules must be mentioned. This is a purely descriptive means of locating the isotope which, for example, gives the singly O^{18}-labeled structures of ethyl acetate the names: ethyl acetate carbonyl-O^{18} and ethyl acetate alcohol-O^{18}. This book prefers to avoid all such descriptive *isotopic designations* and names these ester cases 3-oxa-2-pentanone-2-O^{18} and 3-oxa-2-pentanone-3-O^{18}.

Rule V. WHENEVER THE POINT OF LABEL CAN BE LOCATED IN THE NONISOTOPIC NAME, THE *ISOTOPIC DESIGNATION* SHALL FOLLOW THAT PART OF THE NONISOTOPIC NAME WHICH IT MODIFIES. THE PREFERRED POSITION FOR THE *ISOTOPIC DESIGNATION* SHALL BE AT THE END OF A WORD. WHENEVER LOCANT AMBIGUITY MAKES THIS IMPOSSIBLE, THE *ISOTOPIC DESIGNATION* SHALL APPEAR AT THE END OF THE RADICAL IN WHICH THE LABEL RESIDES. WHENEVER THE LOCANT OF AN *ISOTOPIC DESIGNATION* DOES NOT DEFINE WHICH OF TWO OR MORE PRECEDING SECTIONS OF THE ISOTOPIC NAME IS MODIFIED BY THAT *ISOTOPIC DESIGNATION*, THE *ISOTOPIC DESIGNATION* SHALL APPLY TO THAT SECTION IMMEDIATELY PRECEDING IT. WHENEVER THE LABEL IS IN A SUBSTITUENT GROUP WHICH HAS NO POSITION NUMBER AND WHICH APPEARS IN THE NAME OR RADICAL AS A FUNCTIONAL GROUP SUFFIX, PLACEMENT OF THE *ISOTOPIC DESIGNATION*, WITH NO LOCANT, IMMEDIATELY AFTER THE NAME OR RADICAL SHALL BE TAKEN TO MEAN LOCATION OF THE LABEL IN THAT SUBSTITUENT GROUP.

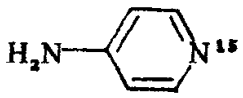
Rule V clearly separates isotopic from nonisotopic usage for the substituent or modifying group. Complexity in the rules is required to bring about simplicity in the isotopic name which carries a subsequent *isotopic designation*.

When the point of label can be located in the nonisotopic name, there are four discernible variations of the placement of the *isotopic designation*: (a) end of word and no locant ambiguity; (b) end of radical and no locant ambiguity; (c) end of word and more than one possible preceding location; and (d) end of radical and more than one possible preceding location. One example of each type follows, along with the code letters:

$C^{14}H_3NHNH_2$	methylhydrazine-C^{14}	(a)
$C^{13}H_3NHCONH_2$	methyl-C^{13}-urea	(b)
$C_6H_5CH_2C^{14}OOH$	phenylacetic-1-C^{14} acid	(c)
	(*p*-ethylphenyl-2-C^{13}) urea	(d)

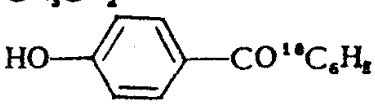
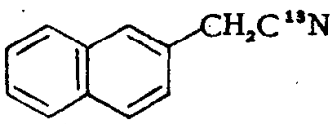
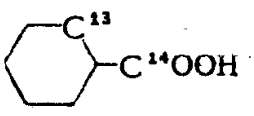
The third sentence of Rule V removes the ambiguity from names of types (c) and (d). This might also have been done by the use of parentheses: phenyl(acetic-1-C^{14}) acid and [*p*-ethyl(phenyl-2-C^{13})]urea. However, proper use of Rule V makes these parentheses unnecessary.

Improper use of the rule could give the structure



the incorrect name, 4-aminopyridine-N^{15}, with the thought that the N^{15} applies to the immediately preceding pyridine nitrogen and not to the amine nitrogen. The correct name, using the available locant, is 4-aminopyridine-1-N^{15}.

Rule V provides for the many cases in which the label has no assignable locant. Examples of the useful application of this rule follow:

$C_6H_5C^{14}OOH$	benzoic-C^{14} acid
$CH_3CH_2OH^3$	ethanol-H^3
	4-hydroxybenzophenone-O^{18}
	2-naphthaleneacetonitrile-C^{13}
	cyclohexanecarboxylic-C^{14}-2-C^{13} acid

Rule VI. WHENEVER THE POSITION OF LABEL IS UNKNOWN OR WHENEVER NO LOCANT USAGE IS POSSIBLE, THE *ISOTOPIC DESIGNATION* SHALL PRECEDE THAT PART OF THE NONISOTOPIC NAME WHICH IT MODIFIES. WHENEVER THIS INDEFINITE *ISOTOPIC DESIGNATION* APPEARS WITHIN A WORD, CLARIFYING PARENTHESES MUST BE USED TO CONNECT IT WITH THE INVOLVED SUBSEQUENT PORTION OF THE NONISOTOPIC NAME.

Rule VI allows for indefinite naming with an *isotopic designation* from which locants necessary for complete clarity are missing. This condition may be due to a trivial name without locants or to a case in which the location of labeling is in doubt. If subscript information is known, it is given according to Rule III. Representative examples are H^3_4-hexestrol and C^{14}_1-erythromycin.

Rule VI provides that there shall be no confusion with Rule V when the indefinite *isotopic designation* occurs in the middle of a word. 1-Methyl-C^{14}-naphthalene is labeled in the methyl group, and 1-methyl(C^{14}-naphthalene) is labeled an unknown number of times at unknown positions in the naphthalene ring.

C. PROPERITIES AND PROCUREMENT OF ISOTOPES

A number of factors must be considered in the selection of a suitable isotope for labeling a particular organic compound. The most obvious are those imposed by the composition of the compound, its intended use and the chemical difficulties of introducing the isotope. Other factors which must be considered are: availability and half-life of the isotope, specific activity desired, the sensitivity of available methods of detection or assay, stability of the labeled molecule and cost. Physical data and other information that should be useful in selection of an isotope for a particular labeling problem are given in Table I, 1.

Comar[5] has presented specific information on a number of isotopes which are useful experimentally in biology and agriculture. These data include availability, physical properties, methods of assay, chemistry involved in isotopic detection, and typical experimental procedures for the use of isotopes. A comprehensive compilation of useful data, including the availability of radioactive and nonradioactive isotopes and of labeled compounds, both inorganic and organic, has been presented in the Isotope Index.[6] Information on prices, availability, procurement procedures, and properties of radioactive isotopes is given in the Oak Ridge National Laboratory's Catalog and Price List.[7]

D. SOME SPECIALIZED TECHNIQUES IN ISOTOPIC SYNTHESES

1. Semimicro Techniques and Vacuum Systems

A considerable number of standard reactions and practices of organic chemistry have been used in synthesizing labeled compounds. However, most of these have been modified in order to increase the yields and decrease the scale of essential operations.

In general, the synthesis of compounds labeled with stable isotopes such as C^{13}, H^2, N^{15} and O^{18} can be accomplished in the usual type of laboratory glassware. However, the use of semimicro techniques and equipment is often advantageous because of ease of handling, conservation of the compounds involved and the time consumed in making the synthesis. Micro and semimicro equipment and methods are essential to the synthesis of radioactively labeled compounds in which high specific activities are desired. Such methods and their application to isotopic synthesis are discussed in detail by others.[8,9]

The synthesis, manipulation and storage of small amounts of radioactive materials, especially those of low molecular weight and high volatility, can usually be accomplished most efficiently and safely in vacuum-type apparatus. The nature of the reactions and materials frequently requires inert atmospheres, and it is not unusual to use a vacuum manifold to carry out several steps of a multiple-step synthesis

involving numerous transfers. A number of figures demonstrating versatile and unusual designs of vacuum systems and semimicro apparatus used in isotopic syntheses are dispersed throughout the text.

Information on the design and manipulation of high vacuum apparatus[8,9] has been presented in numerous textbooks.

2. Methods of Isotopic Measurement

Labeled organic compounds are always synthesized for the specific purpose of using the measurement of the isotope as a means of quantitation. Although the organic chemist may not be the ultimate user of a labeled compound, he may find it essential to make isotopic measurements in studies of reaction mechanisms, in following the course of a labeling synthesis, or in providing an isotopic assay of the final product.

a. Stable Isotopes

Some methods now available for determination of stable isotopes require only apparatus and instruments which are generally available in many chemical laboratories, and the procedures are seldom more complicated than ordinary analytical techniques. All isotopes of an element can be measured on the basis of mass ratios, and the mass spectrometer provides the most generally applicable method. Conversion of the material being analyzed to the analytical sample depends on its nature and on the elemental species of the isotope. Often the conversion methods applicable to radioactive isotopes are adaptable also to stable isotopes and *vice versa*.

Deuterium.—Assay of the stable hydrogen isotope generally proceeds from the initial conversion of the sample to water by Pregl technique or by sealed-tube combustion.[11,20-22] The water may then be analyzed for deuterium content by infrared spectroscopy,[20,21,23] optical spectroscopy,[24] or density determination by the falling drop method.[11,22,25,26] The water may be converted to hydrogen[11,27,28] or to a hydrocarbon[11,29,30] and mass spectrometric methods applied.

Carbon-13.—Analysis for C^{13} invariably involves conversion of the sample to carbon dioxide, which then can be subjected to mass spectrometric methods[11,31,32] or infrared gas analysis,[23,33] or converted to acetylene for analysis by a potentially useful method of flame spectrophotometry.[34]

Nitrogen-15.—Nitrogen-15 may be analyzed in the mass spectrometer in the form of nitrogen gas which is obtained by the Dumas method,[11,35] by ampoule combustion,[31,32,36] or by hypobromite oxidation of ammonia from the Kjeldahl method.[11,37,38] Infrared gas analysis of nitrous oxide[33] and ultraviolet photometry of nitrogen gas excited by electrodeless discharge[39] have been described.

TABLE I, 1

Isotopes of Elements Most Common to Organic Compounds

Isotope	Half-life or % nat. abundance	Modes of decay and energy of radiations (Mev)		Form supplied	Specific act. or conc.
		beta[a] (%)	gamma		
H^2	0.0156%	–	–	gas or water	99.6%
H^3	12.26 yr.	β^- 0.0176	none	gas, carrier-free	2.95 c./cc. at STP
C^{11}	20.4 min.	β^+ 0.968	none	–	–
C^{12}	98.89%	–	–	C	99.9–99.96%
C^{13}	1.11%	–	–	C, $BaCO_3$	69%, 60%
C^{14}	5600 yr.	β^- 0.1585	none	$BaCO_3$	160–1200 mc./g. C
N^{15}	0.365%	–	–	NH_4Cl	60%
				NH_4NO_3	7–60%
				NH_4OH	60%
O^{18}	0.206%	–	–	water	10%
F^{18}	112 min.	β^+ 0.65	none	fluoride soln.	–
P^{32}	14.3 d.	β^- 1.712	none	H_3PO_4 in HCl soln.	~40 c./g. P
				H_3PO_4 in HCl soln.	carrier-free
S^{35}	87.1 d.	β^- 0.165	none	H_2SO_4 in HCl soln.	carrier-free
				BaS in $Ba(OH)_2$ soln.	>10,000 mc./g. S
				S in benzene soln.	>1000 mc./g. S

Isotope	Half-life or % nat. abundance	Modes of decay and energy of radiations (Mev)		Form supplied	Specific act. or conc.
		beta[a] (%)	gamma		
Cl^{35}	75.53%	–	–	NaCl, AgCl	89.7–95.7%
Cl^{36}	3.08×10^5 yr.	β^- 0.714 (98%)	–	HCl	>0.1 mc./g. Cl
Cl^{37}	24.4%	–	–	NaCl, AgCl	60.5–66.3%
Cl^{38}	1 sec.	–	0.66[b]	–	–
Cl^{38}	37.3 min.	β^- 4.81 (53%)	–	–	–
		β^- 1.11 (31%)	1.60, 2.15	–	–
		β^- 2.77 (16%)	2.15	–	–
Br^{80}	4.58 hr.	–	0.049[b]	–	–
Br^{80}	18.5 min.	β^- 1.99 (85%)	–	–	–
		β^- 1.38 (15%)	0.620	–	–
Br^{82}	25.7 hr	β^- 0.465	0.535, 0.750 1.02	KBr in HCl soln.	>1000 mc./g. Br
I^{128}	25.0 min.	β^- 2.12 (76%)	–	–	–
		β^- 1.67 (16%)	0.46	–	–
I^{129}	1.72×10^7 yr.	β^- 0.15	0.038	NaI in basic Na_2SO_3	0.2 μc./mg. I
I^{131}	8.05 d.	β^- 0.606 (87%)	0.364 (81%)	NaI in basic Na_2SO_3	carrier-free

[a] Expressed as maximum energy
[b] Isomeric transition

Oxygen-18.—The mass spectrometric method has almost completely supplanted that depending on the determination of density differences of water.[40] Water is assayed by equilibration with carbon dioxide, which is then used for determination of the isotopic ratio.[41,42] The method of Schütze-Untersaucher[43] for the determination of oxygen in organic compounds by conversion to carbon dioxide has been adapted for isotopic purposes.[44,45] Ampoule combustion techniques may also be employed.[31,32] Equilibration of a variety of organic substances with carbon dioxide by use of a sulfuric acid catalyst has been found possible.[46] It seems likely that infrared spectral methods may soon be applied to routine determinations.[40]

b. Radioactive Isotopes

(1) Assay Methods.—The quantitative determination of radioactive isotopes is based on well known methods of detecting the energetic particles they emit during radioactive decay. Ionization chambers, Geiger counters, proportional counters and various modifications of scintillation detectors (liquid, plastic and crystal) are the usual detectors employed. No single device is best for measurement of radiations of all types, but each instrument has its particular sphere of usefulness. Table I, 2 summarizes the types of detectors and their applications to the assay of labeled compounds.

The choice of an assay method for a radioactive isotope depends on a number of factors, the most important of which are the type and energy of the emitted radiation. Isotopes that emit weak beta particles (e.g., H^3, C^{14}, S^{35}) are best measured by methods that maximize geometrical efficiency and minimize absorption of the radiations in the sample and in the walls of the detector. Gas-phase Geiger and proportional counters, ionization chambers (into which the sample is introduced as a gas), and more recently, various modifications of the liquid scintillation detector appear to be the methods of choice for samples having relatively low specific activities. If the specific activity of the sample is adequate, weak beta-emitting isotopes can be assayed in solid and liquid phase with internal proportional and Geiger counters and with conventional thin-window Geiger tubes.

Isotopes that emit energetic beta particles (e.g., P^{32}, F^{18}, Cl^{36}, I^{131}) may be measured with any of the detectors mentioned previously. The choice of method may be made on the basis of availability and convenience. Geiger and proportional counters are most frequently used.

Gamma-emitting isotopes (e.g., I^{131}, Br^{82}, Cl^{36}) can be measured efficiently with the sodium iodide (thallium-activated) crystal scintillation counter. Good efficiency is obtained as a result of the high stopping power of the sodium iodide, and excellent energy resolution results from the significant fraction of gammas which enter into the photoelectric process. Equipped with a double gate discrimination circuit, this de-