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RELATIONSHIP OF CHEMICAL STRUCTURE TO IN VIVO  
SCINTIGRAPHIC DISTRIBUTION PATTERNS OF  
 $^{14}\text{C}$  COMPOUNDS: I.  $^{14}\text{C}$ -CARBOXYLATES\*

M.B. Winstead, J.F. Lamb and H.S. Winchell\*\*

Presently available data from experiments using  $^{14}\text{C}$  labeled compounds are insufficient to adequately predict the relationship between structure of an organic compound and its in vivo distribution pattern as studied by scintigraphic techniques. This is so for several reasons. The inherent low specific activity of  $^{14}\text{C}$  labeled compounds makes  $^{14}\text{C}$  an unsuitable label for evaluation of in vivo distribution patterns of molecules whose in vivo distribution demonstrates a strong "carrier" effect in the range of the quantity of  $^{14}\text{C}$  labeled material required for the experiment. Studies of in vivo distribution patterns of  $^{14}\text{C}$  compounds requires serial sacrifice of essentially identical isogenic animals and assessment of changes in  $^{14}\text{C}$  activity in organs in vitro as a function of time after administration. This demands a priori insight in choosing the proper time intervals for such sacrifice and selection of samples of the proper tissues for in vitro assay to detect in vivo distribution behavior of interest occurring at a given time in a given tissue. Such in-

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sight is rare except in the study of metabolic behavior which is already well known and in which distribution kinetic studies offer little additional insight. The complexity of proper tissue sampling for assessment of in vivo distribution patterns using  $^{14}\text{C}$  labeled compounds cannot be underestimated. The relative accumulation of the  $^{14}\text{C}$  label in various portions of a presumed homogenous tissue may be quite disparate. For example, ubiquitous skeletal muscle, bone, and bone marrow may show wide variations in accumulation of a given substrate in samples of the tissue obtained from different sites in the body, often depending on their relative blood perfusion at the time of the study in the given animal being studied. Comparison of relative  $^{14}\text{C}$  activity in the rectus femorus muscle, the femur and femoral bone marrow with activity in brain for a given compound obtained with  $^{14}\text{C}$  in rats may provide limited insight into the contribution of activity in skull and temporalis muscle in imaging the brain of human subjects when a congener of the compound in question is synthesized incorporating a gamma emitting radionuclide. Moreover, the limited in vivo distribution data using  $^{14}\text{C}$  labeled compounds presently in the literature was obtained in a fashion which often provides little insight into prediction of distribution patterns of use in nuclear medical studies involving qualitative and quantitative scintigraphic image interpretation of in vivo radioisotope distribution in man. The methods involved in study of in vivo distribution patterns using  $^{14}\text{C}$  as a tracer are not only not applicable in man, they are usually of limited utility in any large mammal where large colonies of identical isogenic subjects are unavailable.

We believe that definition of the relationship between chemical

structure and the in vivo distribution patterns of organic compounds would have significant implications in nuclear medicine (e.g. in "designing" radiopharmaceuticals to achieve a desired result). We further believe that it would be extremely difficult to obtain such information using  $^{14}\text{C}$  as a tracer in a manner which could lead directly to its application in qualitative and quantitative scintigraphic studies in man because of the reasons noted above. Definition of the relationship of chemical structure to scintigraphically determined in vivo distribution can be achieved using  $^{11}\text{C}$  as a tracer for organic compounds as long as the in vivo behavior being studied can be defined within the time limits set by physical decay of  $^{11}\text{C}$  (i.e., at present this averages approximately 2 hours). The remarkable utility of scintigraphic images in rapidly conveying complex data to the human mind is well established in nuclear medicine. The use of  $^{11}\text{C}$  allows for such direct imaging of tissue distribution patterns in a fashion which cannot be readily matched by the indirect techniques afforded by the use of  $^{14}\text{C}$ .

We have instituted a program of systematic development of techniques for rapid synthesis of families of  $^{11}\text{C}$  labeled compounds and for serial scintigraphic evaluation of their in vivo distribution patterns. The organic synthesis methods used are modifications and time-yield optimizations of known synthetic reactions. The purposes of this effort are: a) to develop methods for making large numbers of  $^{11}\text{C}$  compounds available for present and future study; and b) to survey the in vivo distribution patterns of the compounds synthesized using nondestructive in vivo methodology most applicable to their potential use in nuclear medicine (e.g. gamma scintigraphy in intact animals).

In preliminary reports we noted our results in evaluation of the first thirteen  $^{11}\text{C}$ -carboxylates we synthesized and studied (1,2). This article summarizes our results in synthesis and in vivo scintigraphy of twenty-six  $^{11}\text{C}$ -carboxylates. Forthcoming articles in this series deal with  $^{11}\text{C}$ -hydantoins,  $^{11}\text{C}$ -cyanide, cyanate and hydroxy-urea,  $^{11}\text{C}$ -D,L-amino acids,  $^{11}\text{C}$ -neurohumeral amines and their precursors, and  $^{11}\text{C}$ -nitriles.

#### MATERIALS AND METHODS

$\text{B}_2\text{O}_3$  was fused on a corrugated surface set at 30 degrees with respect to the incident beam of charged particles. When deuterons were the bombarding particles, the  $\text{B}_2\text{O}_3$  that was used was 90% enriched in the  $^{10}\text{B}$  isotope (20th Century Electronics, Ltd., New Addington, Surrey, England), and the reaction that occurred was  $^{10}\text{B}(\text{d},\text{n})^{11}\text{C}$ . When protons were the bombarding particles, natural  $\text{B}_2\text{O}_3$  containing 80.4% of the  $^{11}\text{B}$  isotope was used, and the reaction was  $^{11}\text{B}(\text{p},\text{n})^{11}\text{C}$ . When 15 MeV deuteron beam currents were greater than 10  $\mu\text{A}$ , the isolation or target foils (1-mil Al or 2-mil Pt) usually ruptured. Therefore, deuteron beam currents were kept below 10  $\mu\text{A}$ . However, up to 35  $\mu\text{A}$  of 20 MeV proton beam current could be used without rupture of the isolation or target foils. In each case the deuteron or proton beam was maximally defocused prior to bombardment. Presumably the repeated rupture of foils with the use of the deuteron beam was due to "hot spots" in the beam and greater energy loss in the foils for our deuteron than our proton beam. The  $^{11}\text{C}$  was liberated from the target by recoil primarily as  $^{11}\text{CO}$  and some  $^{11}\text{CO}_2$  and was carried from the target by a gas stream composed of dry nitrogen. A small amount of equal parts of CO and  $\text{CO}_2$  carrier

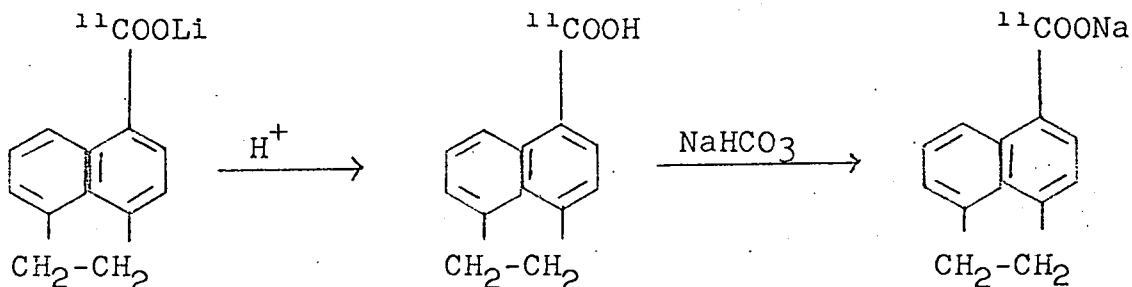
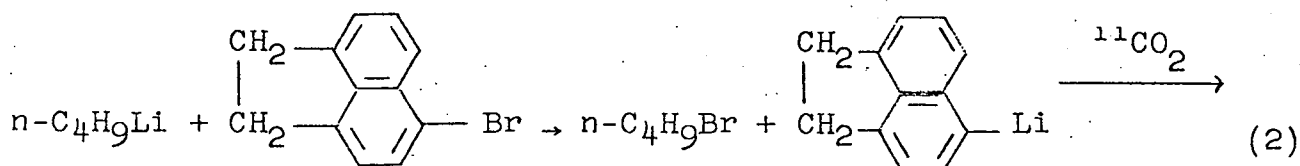
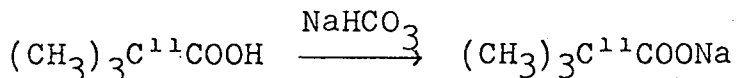
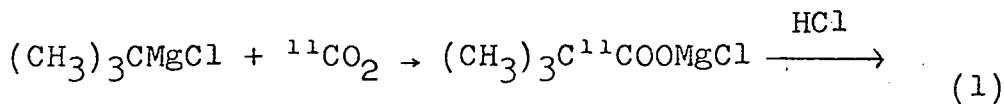
gas was introduced into the nitrogen stream. The total amount of carrier carbon as CO and CO<sub>2</sub> was estimated as 0.5 to 1.0 millimoles. The gas stream was passed over a column of Drierite<sup>®</sup> to remove water vapor, and the carbon monoxide was oxidized to carbon dioxide by passage through a 33-cm-long column packed with CuO and heated at 700°C. The gas was then cooled by passage through copper coils immersed in an iced bath. The gas flow rates were held at approximately 0.5 to 1 liter of gas per minute.

The stream of gas containing <sup>11</sup>C<sup>18</sup>O<sub>2</sub> and 0.5 to 1.0 millimoles of carrier <sup>12</sup>C<sup>18</sup>O<sub>2</sub> was passed for 20 to 30 minutes (or until a maximum activity reading was obtained with a radiation-detection device mounted against the outside of the iced-water bath) into a cold solution of 5 to 10 millimoles of either the appropriate Grignard reagent [R(or Ar)-MgX, X = Br or Cl] or aryl lithium reagent (ArLi) dissolved in 25 ml of anhydrous ether. Following the carbonation of the Grignard or aryl lithium reagent, the reaction mixture was hydrolyzed by the addition of 5 ml of 6N hydrochloric acid. A stream of nitrogen gas was passed through the reaction mixture during both the acid hydrolysis and subsequent bicarbonate extraction, in order to obtain adequate mixing of the reagents.

After removal of the lower hydrochloric acid layer by use of a remotely operated solenoid valve, the upper ether layer containing the <sup>11</sup>C-carboxylic acid was extracted with 25 ml of 6% aqueous sodium bicarbonate. The aqueous bicarbonate layer containing the sodium <sup>11</sup>C-carboxylate was removed and heated to boiling to remove traces of ether. The aqueous solution was then transferred to a serum bottle and sterilized prior to its administration by passing through a

millipore filter.

Representative reactions for the preparation of the sodium  $^{11}\text{C}$ -carboxylates listed in Tables I, II and III are illustrated as follows for sodium  $^{11}\text{C}$ -trimethylacetate (reaction 1) and sodium 5- $^{11}\text{C}$ -acenaphthenecarboxylate (reaction 2):



The total preparation time from the addition of hydrochloric acid to the carbonated Grignard or aryl lithium reagent to preparation of the material for administration was 15 to 20 minutes. Yields of up to 184 mCi of  $^{11}\text{C}$ -carboxylates were obtained. Prior to the preparation of each of the  $^{11}\text{C}$ -carboxylates listed in Tables I, II and III, experiments using  $^{14}\text{C}$ -labeled carbon dioxide with carrier carbon dioxide demonstrated that from 50 to more than 90% of the  $^{14}\text{C}$  introduced into the Grignard or aryl lithium reagent was converted into the corresponding sodium  $^{14}\text{C}$ -carboxylate. Essentially all the  $^{14}\text{CO}_2$  that was introduced into the system was absorbed in the solution



containing the Grignard or aryl lithium reagent, as negligible quantities of radioactivity were recovered in a 2-methoxyethanol-ethanolamine trap placed in series with the system.

Prior to the  $^{11}\text{C}$  and  $^{14}\text{C}$  carbonation reactions, the carboxylates listed in Tables I, II and III were prepared by carbonating the appropriate Grignard or aryl lithium reagent with  $^{12}\text{CO}_2$  under experimental conditions similar to those described for the preparation of the radioactive carboxylates. The resulting carboxylic acids were isolated and purified, and their yields and the melting points of the crystalline acids were ascertained as a confirmation of their respective values reported in the literature.

The distribution of  $^{11}\text{C}$ -radioisotope within the entire body of the dog following administration of the  $^{11}\text{C}$ -carboxylates was obtained by using the rapid-imaging whole-body scanner previously described by H.O. Anger (Donner Laboratory, University of California, Berkeley, California) (3). Localization of the positron-emitting  $^{11}\text{C}$  within specific regions of the animal was determined by utilizing the positron camera previously described (4) and modified by Anger to obtain tomographic visualization along six different focal planes while simultaneously obtaining standard positron scintiphotos at varying exposures.

## RESULTS

The serial scintiphotos obtained following intravenous administration of the  $^{11}\text{C}$  labeled materials were qualitatively evaluated and a brief description of the in vivo distribution pattern as it appeared on the scintiphotos is presented in Tables I, II, and III. Each of the  $^{11}\text{C}$ -carboxylates studied was placed in one of three

groups and the results obtained for compounds within each of these three groups are described below.

A. Aliphatic Carboxylates (See Table I)

Eleven  $^{11}\text{C}$  aliphatic carboxylates were studied and these compounds are listed in order of increasing chain length in Table I.  $^{11}\text{C}$  activity of acrylate, trimethylacetate, pentanoate and cyclohexanecarboxylate was concentrated in liver and kidney.  $^{11}\text{C}$  activity of pentanoate was principally excreted in the bile and concentrated in the gall bladder while that of cyclohexanecarboxylate was largely excreted by kidneys into urine.  $^{11}\text{C}$  activity of acrylate and trimethylacetate was excreted sufficiently by both liver and kidneys to show activity in both gall bladder and urinary bladder. This was especially so for acrylate.

$^{11}\text{C}$  activity of all of the remaining aliphatic carboxylates showed a general pattern of concentration in liver and diffusely throughout abdomen, variable heart-blood pool activity and progressive diffuse whole body distribution increasing with time. Activity of acetate showed the most rapid progression to diffuse whole body distribution with time while that of butyrate showed the most prominent liver and diffuse abdominal accumulation of activity.  $^{11}\text{C}$  activity of octanoate showed some initial retention in the lungs which remained throughout the study.  $^{11}\text{C}$  activity of isobutyrate, hexanoate, heptanoate and octanoate showed the same general pattern of distribution as that obtained with the "physiologic" carboxylic acids, acetate, propionate and butyrate.

B. Benzoic Acid Derivatives (see Table II)

$^{11}\text{C}$  activity of benzoate, p-chlorobenzoate and 3,4-dimethoxy-

benzoate rapidly appeared in kidneys and was excreted in the urine.  $^{14}\text{C}$  activity of p-hydroxybenzoate and o-hydroxybenzoate (salicylate) initially appeared in the heart-blood pool and in liver and abdomen and then progressively appeared diffusely throughout the body.  $^{14}\text{C}$  activity of o-methylbenzoate (o-toluate), m-trifluoromethyl benzoate and p-phenoxybenzoate was initially seen in the heart-blood pool - followed by progressive accumulation in both liver and kidneys followed by excretion in urine and to a variable extent in the gall bladder.

C. Other Carboxylates (see Table III)

$^{14}\text{C}$  activity of phenylacetate and 2-thiophenecarboxylate was principally concentrated in kidneys and excreted in urine although some activity accumulated in liver.  $^{14}\text{C}$  activity of 3-camphorcarboxylate and 1-naphthoate accumulated in both liver and kidneys with significant excretion in urine and bile.  $^{14}\text{C}$  activity of 5-acenaphthenecarboxylate and 9-anthracenecarboxylate accumulated principally in liver and was excreted in bile.  $^{14}\text{C}$  activity of 9-phenanthrenecarboxylate was initially seen in heart-blood pool, liver and upper abdomen followed by diffuse whole body distribution after 20 minutes.

Figure I shows examples of the scintigraphically determined distribution patterns described in Tables I, II and III and alluded to in the description of results given above. The heart-blood pool activity distribution pattern is exemplified by p-phenoxybenzoate; that for liver, kidney and bladder is exemplified by trimethylacetate; that for diffuse abdominal distribution pattern by butyrate; and that for gall bladder by 5-acenaphthenecarboxylate.

Figure II shows an example of the scintigraphic evaluation of

the in vivo distribution pattern of a  $^{14}\text{C}$ -carboxylate in man. Whole body scans 2 3/4-4 1/4 min. and 8 1/2-10 min. after I.V. administration of  $^{14}\text{C}$ -benzoate are shown on the left. The rapid accumulation of activity in kidneys and excretion into bladder is apparent. The localization of activity in the brain tumor in man 60-70 min. after administration (positron camera) illustrates the normal impermeability of the blood-brain barrier to passage of most of the carboxylates studied and their accumulation in areas where the blood-brain barrier has been disturbed.

#### DISCUSSION

In the group of  $^{14}\text{C}$  aliphatic carboxylates studied (Table I), activity of acrylate, trimethylacetate, pentanoate and cyclohexanecarboxylate appeared to be largely excreted from the body by either the kidney or the liver or both, appearing in the urine or bile respectively. This suggests that these materials are treated as foreign substances and do not appreciably enter into metabolic processes in the body. The accumulation of activity in liver and diffusely in abdomen following I.V. administration of the "physiologic" carboxylates acetate, propionate and butyrate suggest that these materials largely equilibrate with lipid storage sites with high perfusion rates such as lipids in liver and mesentery. The distribution pattern of isobutyrate, hexanoate, heptanoate, and octanoate qualitatively mimics that of the "physiologic" carboxylates noted above suggesting that these acids enter into actual lipid metabolic pathways. The partial uptake of octanoate activity by the lungs may be related to the tendency of fatty acids to have decreased water solubility and increased lipid solubility as the chain length of the fatty acid is increased. The highly lipid soluble octanoate may

be retained in the lipoprotein membrane of the alveolar capillary wall on the first passage of blood containing the octanoate through the lungs. It is also possible that the amount of carrier octanoate present may have been sufficient to result in partial "fat embolization" with trapping of activity in pulmonary capillaries.

Benzoic acid is known to be conjugated with glycine to form hippurate in liver and, in some species, kidney. Hippurate and to a certain extent benzoate are excreted into urine by kidneys. The similarity of in vivo behavior of p-chlorobenzoate and 3,4-dimethoxybenzoate (veratrate) suggest that similar metabolic processes pertain to the handling of these materials. Addition of an hydroxyl group in the ortho or para position as in o-hydroxybenzoate (salicylate) or p-hydroxybenzoate alters the in vivo distribution pattern of the substituted benzoic acid markedly. Both of these hydroxy derivatives fail to show any significant renal or hepatic excretion of label. Both show a diffuse whole body pattern of activity following an initial pattern of activity in heart-blood pool, liver and abdomen. This pattern suggests some initial metabolism of these compounds in abdominal viscera or other abdominal tissue to a form having fairly uniform whole body distribution. It is possible that such metabolism may involve decarboxylation releasing the  $^{14}\text{C}$  label into the body  $\text{CO}_2\text{-HCO}_3^-$  pools.

Substitution of a methyl group in the ortho position, a trifluoromethyl group in the meta position or a phenoxy group in the para position of benzoic acid diminishes the rate of renal accumulation of activity and excretion in the urine and results in a portion of the  $^{14}\text{C}$  carboxyl activity accumulating in liver and being excreted in the bile. We believe this is due to the increased lipid

solubility resulting from the above noted substitutions with the hepatic excretion of the material occurring because of this increased lipid solubility.

All of the carboxylates listed in Table III are not normally found in the body and except for 9-phenanthrenecarboxylate are excreted from the body either by the liver or the kidneys. The more lipid soluble the carboxylate (e.g. 5-acenaphthenecarboxylate and 9-anthracenecarboxylate) the greater is the proportion of activity excreted by the liver in the bile. The greater the aqueous solubility of the carboxylate (e.g. phenylacetate and 2-thiophenecarboxylate) the greater the renal excretion. Intermediate aqueous-lipid soluble materials are excreted by both liver and kidneys. The whole body distribution noted with 9-phenanthrenecarboxylate may be due to decarboxylation in vivo with the  $^{14}\text{C}$  label entering the  $\text{CO}_2\text{-HCO}_3$  pool.

#### SUMMARY

Large quantities of  $^{14}\text{C}$ -carboxylates can be synthesized and their in vivo distribution imaged by gamma scintigraphy using positron cameras, rectilinear scanners or gamma cameras using high energy multihole or pinhole collimators. Carboxylates which are not normal body constituents are usually excreted from the body by the kidneys or the liver with excretion products appearing in urine or bile respectively. Our results do not differentiate between direct excretion by these organs or excretion after conjugation or alteration in the body. In general carboxylates containing polar moieties and possessing high water solubility are largely excreted by the kidneys while those carboxylates containing non-polar, lipid soluble moieties, are largely excreted by the liver. Whether the liver or kidney is

the organ most responsible for excretion of a given carboxylate also depends upon its degree of in vivo conjugation, a parameter which was not measured.

<sup>14</sup>C-acetate, propionate, butyrate, isobutyrate, hexanoate, heptanoate and octanoate all showed initial accumulation of activity in liver and diffusely throughout abdomen, variable retention of activity in heart-blood pool followed by an increase in homogeneous body activity with time. This distribution pattern may reflect equilibration of these materials with fatty tissue having high perfusion rates such as lipids in liver and mesentery where they may be catabolized to other moieties such as CO<sub>2</sub>.

#### ACKNOWLEDGEMENTS

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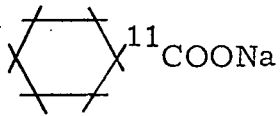
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TABLE I. ALIPHATIC CARBOXYLATES\*

<u>NAME</u>	<u>STRUCTURE</u>	<u>DISTRIBUTION PATTERN SCINTIGRAPHICALLY DETERMINED</u>
Acetate	$\text{CH}_3^{11}\text{COONa}$	Diffuse whole body distribution with some initial concentration in abdomen within 2 minutes.
Propionate	$\text{CH}_3\text{CH}_2^{11}\text{COONa}$	Activity in heart-blood pool with some concentration in abdomen within 3 to 6 minutes. Homogeneous whole body distribution of activity at 1/2 to 1 hour.
Acrylate	$\text{CH}_2=\text{CH}^{11}\text{COONa}$	Activity in liver and kidney within 3 to 5 minutes. Some activity in bladder at 10-15 minutes. Significant activity in gall bladder and urinary bladder at 60 minutes.
Butyrate	$\text{CH}_3\text{CH}_2\text{CH}_2^{11}\text{COONa}$	Concentration of activity equally in liver and throughout abdomen at $2\frac{1}{2}$ to $3\frac{1}{2}$ minutes. Some activity in heart-blood pool.
Isobutyrate	$(\text{CH}_3)_2\text{CH}^{11}\text{COONa}$	Diffuse whole body distribution of activity with some greater activity in heart-blood pool, in liver and throughout abdomen at 2-4 minutes. Homogeneous whole body distribution of activity at 30 minutes.
Trimethylacetate	$(\text{CH}_3)_3\text{C}^{11}\text{COONa}$	Activity in liver and kidney within 3 to 5 minutes. Activity in bladder at 60 minutes. Suggestion of activity in gall bladder at 80-95 minutes.

TABLE I. (cont.)

<u>NAME</u>	<u>STRUCTURE</u>	<u>DISTRIBUTION PATTERN SCINTIGRAPHICALLY DETERMINED</u>
Pentanoate	$\text{CH}_3(\text{CH}_2)_3^{11}\text{COONa}$	Activity in liver at 6 minutes. Activity in gall bladder at 40 minutes. Minimal renal clearance with minimal activity in bladder at 50 minutes.
Hexanoate	$\text{CH}_3(\text{CH}_2)_4^{11}\text{COONa}$	Activity in liver, kidneys and diffusely throughout abdomen within 2-3 minutes. Homogeneous whole body distribution of activity at 44-120 minutes.
Heptanoate	$\text{CH}_3(\text{CH}_2)_5^{11}\text{COONa}$	Activity in liver and diffusely throughout abdomen within 3 minutes. Partial redistribution to become homogeneous whole body distribution at 72-78 minutes.
Cyclohexanecarboxylate		Activity in liver, kidney and heart-blood pool at 2 minutes. Activity in bladder at 3 minutes. Large amount of activity in bladder at 30 minutes, but no activity in gall bladder as late as 98 minutes.
Octanoate	$\text{CH}_3(\text{CH}_2)_6^{11}\text{COONa}$	Activity in liver and homogeneously throughout abdomen within 4 minutes. Some activity in lungs at 4 minutes, which was still present at 56 minutes.

\* All of the compounds listed in Table I were prepared by carbonating the appropriate Grignard reagent which was obtained from either Arapahoe Chemicals, Boulder, Colorado, Alfa Inorganica, Inc., Beverly, Massachusetts or M. and T. Chemical, Inc., Rahway, New Jersey.

TABLE II. BENZOIC ACID DERIVATIVES

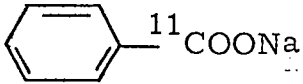
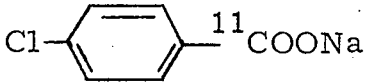
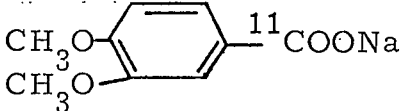
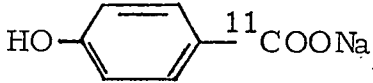
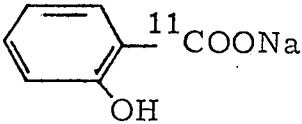
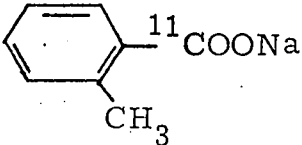
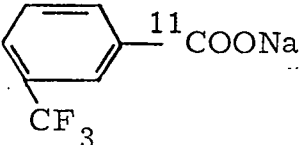
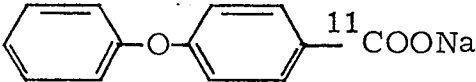
<u>NAME</u>	<u>STRUCTURE</u>	<u>DISTRIBUTION PATTERN SCINTIGRAPHICALLY DETERMINED</u>
Benzoate <sup>a/</sup>		Rapid clearance of activity by kidneys and excretion into urine. Behavior very similar to hippurate.
p-Chlorobenzoate <sup>a/</sup>		Rapid clearance of activity by kidneys and excretion into urine. Similar to benzoate.
3,4-Dimethoxybenzoate <sup>b/</sup> (Veratrate)		Rapid appearance of activity in kidneys within 2 minutes and considerable activity in bladder at 9 minutes. Similar to benzoate.
p-Hydroxybenzoate <sup>c/</sup>		Activity in heart-blood pool, liver and homogeneously throughout abdomen at 2-3 minutes, becoming homogeneous whole body distribution within 20 minutes. (no urinary excretion).
o-Hydroxybenzoate <sup>d/</sup> (Salicylate)		Activity in heart-blood pool, liver and upper abdomen at 2-3 minutes, becoming diffuse whole body with some activity in kidneys at 33 minutes and in bladder at 40 minutes.
o-Toluate <sup>a/</sup>		Activity in heart-blood pool, liver and kidneys within 2 minutes. Slow progressive increase in liver and kidney uptake and soft tissue clearance. Activity in bladder noted at 21 minutes, and activity in gall bladder at 96 minutes.

TABLE II. (cont.)

NAME	STRUCTURE	DISTRIBUTION PATTERN SCINTIGRAPHICALLY DETERMINED
m-Trifluoromethylbenzoate <sup>e/</sup>		Activity in heart-blood pool, liver and kidneys within 3 minutes. Slow increase in accumulation of activity in kidneys with time. Some activity in bladder at 11 minutes. Some activity in gall bladder at 61 minutes. More activity excreted by kidneys and less by liver than with o-toluate.
p-Phenoxybenzoate <sup>f/</sup>		Activity in heart-blood pool with slow partial accumulation in liver by 11 minutes. Slight amount of activity in kidneys and bladder at 79-101 minutes. Heart-blood pool activity still present at 62-76 minutes.

- a/ This compound was prepared by carbonating the appropriate Grignard reagent which was obtained from either Arapahoe Chemicals, Boulder, Colorado or Alfa Inorganics, Inc., Beverly, Massachusetts.
- b/ This compound was prepared by carbonating at -60° C. 3,4-dimethoxyphenyl lithium, which was prepared from 4-bromoveratrole and n-butyl lithium [M. Calvin, C. Heidelberger, J. C. Reid, B. M. Tolbert, and P.F. Yankwich, Isotopic Carbon (John Wiley & Sons, New York 1949), pp. 183-184].
- c/ This compound was prepared by carbonating the aryl lithium intermediate which was obtained from the reaction of p-bromophenol with n-butyl lithium [H. Gilman and C.E. Arnitzer, J. Am. Chem. Soc., 69, 1537 (1938)].
- d/ This compound was prepared by carbonating the aryl lithium intermediate, which was obtained from the reaction of o-bromophenol with n-butyl lithium [H. Gilman and C.E. Arnitzer, J. Am. Chem. Soc., 69, 1537 (1938)].
- e/ This compound was prepared by carbonating m-trifluoromethylphenyl lithium, which was prepared from m-bromobenzotrifluoride and n-butyl lithium [H. Gilman and L.A. Woods, J. Am. Chem. Soc., 66, 1982 (1944)].
- f/ This compound was prepared by carbonating p-phenoxyphenyl lithium, which was prepared from p-bromophenyl phenyl ether and n-butyl lithium [W. Langham, W.Q. Brewster and H. Gilman, J. Am. Chem. Soc., 63, 547 (1941)].

TABLE III. OTHER CARBOXYLATES

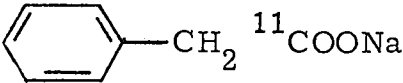
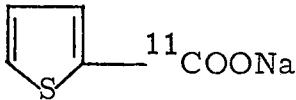
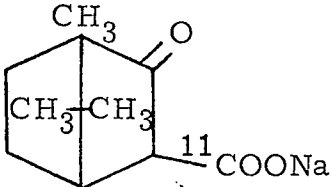
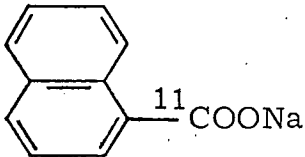
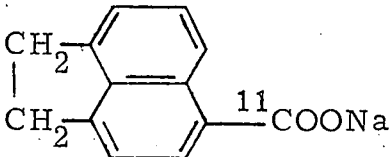
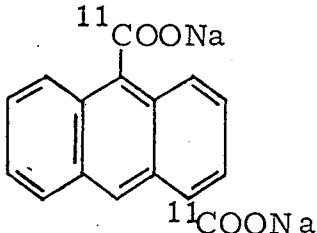
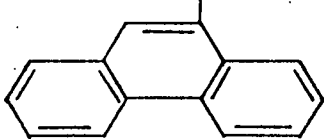
<u>NAME</u>	<u>STRUCTURE</u>	<u>DISTRIBUTION PATTERN SCINTIGRAPHICALLY DETERMINED</u>
Phenylacetate <sup>a/</sup>		Activity in liver and kidney in 4 minutes. Major excretion of activity in urine but residual activity in liver and kidneys at 1½ hours.
2-Thiophenecarboxylate <sup>b/</sup>		Activity principally in kidneys and some in liver within 6 minutes. Major excretion in urine but significant diffuse whole body background at 60 min.
3-Camphorcarboxylate <sup>c/</sup>		Activity in liver and kidneys within minutes with activity noted in bladder and gall bladder at ½-¾ hr.
1-Naphthoate <sup>d/</sup>		Activity in liver and kidneys within minutes. Activity in bladder within 8 minutes and in gall bladder within 110 minutes.
5-Acenaphthenecarboxylate <sup>e/</sup>		Activity in liver within 3 minutes. Some activity in kidneys within 11 minutes, with some excretion into urine. Significant activity in gall bladder at 37 minutes which increased by 100 minutes.
9-Anthracenecarboxylate <sup>f/</sup>		Activity in liver within 6 minutes, negligible renal activity or urinary excretion. Significant activity in gall bladder by 60 minutes.
9-Phenathrenecarboxylate <sup>g/</sup>		Activity in heart-blood pool, liver and upper abdomen within 10 minutes, followed by homogenous whole body distribution of activity after 20 minutes.

TABLE III. FOOTNOTES

- a/ This compound was prepared by carbonating the appropriate Grignard reagent which was obtained from either Arapahoe Chemicals, Boulder, Colorado or Alfa Inorganics, Inc., Beverly, Massachusetts.
- b/ This compound was prepared by carbonating 2-thienylmagnesium bromide, which was prepared from 2-bromothiophene and magnesium (D. A. Shirley, Preparation of Organic Intermediates, John Wiley & Sons, New York, 1951, p. 282).
- c/ This compound was prepared by carbonating 3-camphor lithium, which was prepared from 10 mmoles of 3-bromocamphor dissolved in 15 ml of ether and 20 mmoles of n-butyl lithium. Nitrogen gas was bubbled into the room temperature solution for one hour prior to the carbonation reaction at iced-bath temperature.
- d/ This compound was prepared by carbonating 1-naphthyl lithium, which was prepared from 1-bromonaphthalene and n-butyl lithium [H. Gilman and F.W. Moore, J. Am. Chem. Soc., 62, 1843 (1940)].
- e/ This compound was prepared by carbonating 5-acenaphthene lithium, which was prepared from 5-bromoacenaphthene and n-butyl lithium similar to the method described for preparing 4-acenaphthenecarboxylic acid [H. Gilman, W. Langham, and F.W. Moore, J. Am. Chem. Soc., 62, 2327 (1940)].
- f/ This compound was prepared by carbonating 9-anthracene lithium, which was prepared from 9-bromoanthracene and n-butyl lithium similar to the method described for preparing 9-phenanthrenecarboxylic acid [H. Gilman, and T.H. Cook, J. Am. Chem. Soc., 62, 2813 (1940)].
- g/ This compound was prepared by carbonating 9-phenanthrene lithium, which was prepared from 9-bromophenanthrene and n-butyl lithium [H. Gilman and T.H. Cook, J. Am. Chem. Soc., 62, 2813 (1940)].

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