# RELATIONSHIP OF CHEMICAL STRUCTURE AND SOLVENT TO IN VIVO SCINTIGRAPHIC DISTRIBUTION PATTERNS OF $^{11}C$ COMPOUNDS. II. $^{11}C$ AMINONITRILES

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***The preparation and scintigraphic evaluation of the distribution patterns in dogs of a series of structurally related aminonitriles labeled with $^{11}C$ is described. Carbon-11-HCN was collected in water containing carrier NaCN following 22 MeV proton bombardment of 99% $N_2$ and 1% $H_2$ gas mixture for 1 hr. Ten $^{11}C$ α-N-alkylaminophenylacetonitrile hydrochlorides and 12 $^{11}C$ α-N-arylaminoarylacetonitriles were prepared from $^{11}C$-NaCN and the corresponding Schiff base, Ar–CH=N–R(Ar). Those $^{11}C$ aminonitriles that were administered intravenously in aqueous solution showed some initial accumulation of activity in the liver followed by diffuse whole-body distribution and some small accumulation in urine. Aqueous insoluble $^{11}C$ aminonitriles, which were administered intravenously in ethanol, ether, or DMSO, showed variable initial partial retention of activity in the lungs with prominent accumulation of activity in liver and excretion in bile. Several of these compounds showed pronounced and rapid accumulation of activity in the brain. Such activity in the brain was largely cleared within 15 min. Concentration of activity in the cerebrospinal fluid following clearance from the brain was 30 times greater than blood and equivalent in concentration to that noted in bile 18 min after intravenous administration of $^{11}C$ α-anilinophenylacetonitrile in ethanol. These results suggest the possible correlation of regional brain uptake of activity of certain $^{11}C$ aminonitriles with regional brain perfusion. Use of these or similar materials could permit assessment of brain tissue morphology followed by scintigraphic imaging of the bulk flow characteristics of cerebrospinal fluid.***

In a previous article we discussed the utility of correlating the structure of $^{11}C$-labeled compounds with their scintigraphically determined in vivo distribution patterns (*1*). In our ongoing efforts in this respect, we are synthesizing and studying the in vivo distribution of a series of structurally related $^{11}C$-labeled compounds. This is being done in order to improve our understanding of structure–distribution relationships sufficiently well to design specific agents for organs, tissues, or physiologic processes. The present communication reports our development of methods for rapid synthesis of a series of 22 structurally related $^{11}C$-labeled aminonitriles and scintigraphic evaluation of their in vivo distribution patterns.

Organic nitriles are believed to be metabolized in part by loss of cyanide from the molecule, which is then metabolized to thiocyanate (*2*). Such is felt to be the case with Laetrile, a nitrile which had been used in cancer chemotherapy and whose presumed antineoplastic effects were attributed to cyanide release in tumor tissue following enzymatic attack by β-glucuronidase (*3*). Similarly, nitrile compounds used in industry, e.g., acetonitrile, acrylonitrile, malononitrile, and mandelonitrile, have been shown to liberate cyanide in vivo (*4,5*). Hydrolysis of $^{14}C$-glycinonitrile to form the corresponding carboxylic acid has been reported to occur in rats (*6*). Recent data obtained by us, but not included in the present communication, suggest that certain α-N-alkylaminonitriles prepared as the hydrochloride salt are unstable and readily dissociate, releasing cyanide, in

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aqueous solution. There also appears to be great variation in the rate of dissociation of the remaining aminonitriles not prepared as the hydrochloride salt, i.e., the α-N-arylaminoarylacetonitriles, and such variations seem to be a function of molecular composition. The relationship between molecular structure and dissociation rate of such aminonitriles resulting in release of cyanide will be the subject of a future communication.

## MATERIALS AND METHODS

Hydrogen cyanide labeled with 20.4-min $^{11}C$ was produced by cyclotron bombardment of a gas target, 99% $N_2$ and 1% $H_2$, with 22-MeV protons using procedures and equipment described previously (7). The gas stream containing $^{11}C$-HCN was passed through 10–25 ml of water containing approximately 10 mg of carrier NaCN. This resulted in $^{11}C$ labeling of the NaCN by isotopic exchange. An average of 584 mCi of $^{11}C$-NaCN (at EOB for 18 runs) was trapped in the solution following 1 hr bombardment at 25–40 μA. α-N-alkylaminophenylacetonitrile hydrochlorides labeled with $^{11}C$ were synthesized by reacting equivalent quantities of an ice-cold stirred solution of benzaldehyde and the corresponding primary aliphatic amine (2.5 mmoles reaction scale) in 5–10 ml of absolute ethanol for 5–10 min, followed by the addition of 10–25 ml of aqueous $^{11}C$-NaCN (containing 2.5 mmoles of carrier NaCN) and an equivalent quantity of acetic acid to the intermediate, e.g., imine. After a 20-min reaction period, 50 ml of cold water was added, and the aqueous solution was extracted with 100 ml of ether. The ether extract containing the α-N-alkylaminophenylacetonitrile was dried with anhydrous calcium chloride for 5 min and filtered. The ether extract was chilled and anhydrous hydrogen chloride gas was gently bubbled into the solution for 15–30 sec. After remaining in the ice-water bath for 2–3 min, the white, crystalline α-N-alkylaminophenylacetonitrile hydrochloride was filtered and washed with a solution of ether and acetone and then was dissolved in a minimum quantity of water for intravenous administration to the dog. This general procedure was followed for the synthesis of the following $^{11}C$-labeled derivatives of phenylacetonitrile hydrochloride: α-N-propylamino-, α-N-isopropylamino-, α-N-butylamino-, α-N-isobutylamino-, α-N-sec-butylamino-, α-N-tert-butylamino-, α-N-benzylamino-, and α-N-phenethylamino-. Methylamine hydrochloride was used in the preparation of $^{11}C$ α-N-methylaminophenylacetonitrile hydrochloride, and the necessity of adding acetic acid was eliminated. For the formation of $^{11}C$ α-N-ethylaminophenylacetonitrile hydrochloride, a solution of 70% ethylamine in water was used.

Carbon-11-labeled α-N-arylaminoarylacetonitriles were prepared by the addition of 10 ml of aqueous $^{11}C$-NaCN, containing 2–5 mmoles of carrier NaCN and an equivalent amount of acetic acid, to a stirred solution of an equimolar quantity of the corresponding Schiff base, Ar—CH=N—Ar, in 15–25 ml of absolute ethanol. In four instances, the Schiff base was prepared in situ by stirring equivalent quantities of the corresponding aromatic aldehyde and primary aromatic amine, dissolved in 8–25 ml of absolute ethanol, for 15–20 min at room temperature prior to the addition of the aqueous $^{11}C$-cyanide solution and acetic acid. In most instances, the reaction mixture was stirred for 10–20 min at temperatures of 30–60°C. Cooling in an iced salt-water bath for several minutes, with seeding being necessary in a few cases, precipitated the crystalline α-N-arylaminoarylacetonitrile derivative. The product was filtered, washed with a small quantity of cold aqueous ethanol, then dissolved in a minimum quantity of absolute ethanol, ether, or dimethylsulfoxide (DMSO), prior to being administered intravenously to dogs. The animals were fasted overnight before being surgically anesthetized with nembutal.

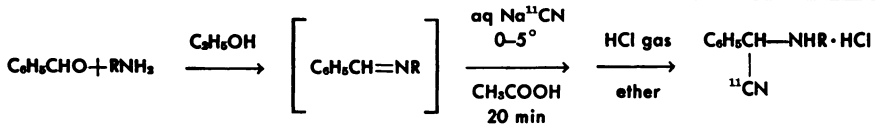
Each reaction was first performed using nonradioactive NaCN to optimize the yield at minimal reaction times. The product obtained was chemically characterized in all cases by melting point and spectroscopic methods (e.g., infrared [IR] and nuclear magnetic resonance [NMR] spectroscopy).

For the $^{11}C$ compounds intravenously administered in dogs, the in vivo distribution patterns were evaluated scintigraphically using a Searle Radiographics HP scintillation camera fitted with a pinhole collimator containing a 1-cm-diam hyperbolic aperture. Quantitative estimates of organ and tissue distribution of activity were obtained by placing the organs and tissues obtained at necropsy at fixed geometric positions in front of a thallium-activated NaI scintillation detector and analyzing detected scintillation events using routine methods.

## RESULTS

**Synthesis.** Ten α-N-alkylaminophenylacetonitrile hydrochlorides labeled with $^{11}C$ were prepared in 49–82 min total preparation time in radiochemical yields of 11–65% in activity averaging 16 mCi of product. Table 1 summarizes the results of the synthesis of these materials. The structures of the $^{11}C$-labeled products obtained from each of the α-N-alkylaminophenylacetonitrile hydrochloride reactions were confirmed by the general agreement of their respective melting points and infrared spectra with those of the corresponding unlabeled compounds. As deduced from melting point and NMR studies of each $^{11}C$-labeled compound, alkylamine

**TABLE 1. PREPARATION OF $^{11}$C-LABELED α-N-ALKYLAMINOPHENYLACETONITRILE HYDROCHLORIDES**




| Na$^{11}$CN mCi, $t_0$ | R (2.5 mmoles rx scale) | Product mCi, $t_0$ | Product mCi, $t_{inj}$ | Radiochemical yield (%) | Chemical yield (%) | Total preparation time (min) | M.P. °C d.* |
|---|---|---|---|---|---|---|---|
| 610 | $CH_3$† | 238 | 19 | 39 | 53 | 75 | 110–113‡ |
| 959 | $C_6H_5CH_2$ | 172 | 19 | 18 | 14 | 65 | 136–139§ |
| 134 | $C_2H_5$ | 87 | 6 | 65 | 33 | 82 | 146–148¶ |
| 228 | $C_6H_5CH_2CH_2$ | 34 | 4 | 15 | 6 | 65 | 121–124‖ |
| 635 | $CH_3CH_2CH_2$ | 323 | 27 | 51 | 39 | 74 | 141–144** |
| 498 | $(CH_3)_2CH$ | 57 | 11 | 11 | 26 | 49 | 142–145†† |
| 1,016 | $CH_3CH_2CH_2CH_2$ | 354 | 39 | 35 | 40 | 65 | 117–119‡‡ |
| 177 | $(CH_3)_2CHCH_2$ | 59 | 7 | 33 | 46 | 56 | 126–129§§ |
| 456 | $CH_3CH_2CH(CH_3)$ | 267 | 18 | 59 | — | 80 | 103–105¶¶ |
| 463 | $(CH_3)_3C$ | 84 | 11 | 18 | 27 | 60 | 132–135‖‖ |

* These decomposition points are those of unlabeled, recrystallized products obtained from a 4-hr 10-mmole reaction scale preparation. The structures of the $^{11}$C-labeled compounds were confirmed by the general agreement of their decomposition point and infrared spectra with those of the corresponding unlabeled compounds.

† A 5-mmole reaction scale was used in this preparation.

‡ Reported m.p. 110–112° (8); calculated for $C_9H_{11}N_2Cl$: 59.18% C, 6.07% H, 15.34% N; found 59.35% C, 6.14% H, 15.17% N.

§ Reported m.p. 143–145° (9), 161–164° (10); calculated for $C_{15}H_{15}N_2Cl$: 69.63% C, 5.84% H, 10.83% N; found 69.50% C, 5.69% H, 10.65% N.

¶ Calculated for $C_{10}H_{13}N_2Cl$: 61.07% C, 6.66% H, 14.24% N; found 60.79% C, 7.12% H, 14.26% N.

‖ Calculated for $C_{16}H_{17}N_2Cl$: 70.45% C, 6.28% H, 10.27% N; found 70.23% C, 6.33% H, 10.07% N.

** Calculated for $C_{11}H_{15}N_2Cl$: 62.70% C, 7.18% H, 13.30% N; found 62.51% C, 7.31% H, 13.08% N.

†† Calculated for $C_{11}H_{15}N_2Cl$: See footnote **; found 62.56% C, 7.14% H, 13.05% N.

‡‡ Reported m.p. 138° (11); calculated for $C_{12}H_{17}N_2Cl$: 64.14% C, 7.63% H, 12.47% N; found 63.86% C, 7.75% H, 12.29% N.

§§ Calculated for $C_{12}H_{17}N_2Cl$: See footnote ‡‡; found 63.72% C, 7.65% H, 12.21% N.

¶¶ Calculated for $C_{12}H_{17}N_2Cl$: See footnote ‡‡; found 63.86% C, 7.75% H, 12.29% N.

‖‖ Calculated for $C_{12}H_{17}N_2Cl$: See footnote ‡‡; found 63.86% C, 7.74% H, 12.57% N.

hydrochloride of the respective starting alkylamine was present to some extent in the final $^{11}$C-labeled product under these experimental reaction conditions. However, the in vivo studies of these compounds should be unaffected since only the desired product is labeled and capable of producing scintigraphic images.

In order to obtain analytically pure samples of the α-N-alkylaminophenylacetonitrile hydrochlorides, longer reaction times (4 hr), a larger reaction scale preparation (10 mmoles), and recrystallization of the product from acetone were incorporated. α-N-tert-butylamino-, α-N-benzylamino-, and α-N-isopropylaminophenylacetonitrile hydrochlorides were insoluble in hot acetone, but the insoluble residue was found by spectroscopic analysis to be the pure product. All ten α-N-alkylaminophenylacetonitrile hydrochlorides gave quantitative elemental analyses for carbon, hydrogen, and nitrogen that agreed within 0.5% of the respective calculated values. (Analyses were conducted by M-H-W Laboratories, Garden City, Mich.)

The infrared spectra of the purified α-N-alkylaminophenylacetonitrile hydrochlorides showed a characteristic C≡N nitrile stretch as a small absorption band or shoulder at 2,174–2,273 cm$^{-1}$ adjacent to the broad N—H$^+$ stretch of an amine salt at 2,273–3,226 cm$^{-1}$. In addition, absorption bands at 735–769 cm$^{-1}$ and 685–714 cm$^{-1}$, characteristic of a monosubstituted benzene ring, occurred in each spectrum.

The integration of the nuclear magnetic resonance spectra was found to agree with the predicted ratios. The characteristic aromatic signal accounting for five aromatic protons was observed at δ 7.3–8.0 ppm. The predicted splitting patterns for the various alkyl side chains were also observed. A sharp singlet at δ 5.9–6.1 ppm, corresponding to the benzylic proton, was found to be characteristic for this series of compounds. The N—H chemical shift was found to vary, normally occurring downfield from δ 10 to 12 ppm. The addition of $D_2O$ to the sample resulted in the disappearance of this exchangeable N—H signal.

Twelve $^{11}$C-labeled α-N-arylaminoarylacetonitriles were prepared in 35–75 min total preparation time, in radiochemical yields of 19–61%, and in activity averaging 40 mCi of product. Table 2 summarizes the results of the synthesis of these materials. All of the arylaminoarylacetonitriles have been prepared previously with the exception of α-p-chloroanilino-p-chlorophenylacetonitrile. Their melting points as reported in the literature agreed with the melting points

of both the $^{11}C$-labeled as well as unlabeled aminonitrile experimentally produced, with the exception of α-p-toluidino-p-tolylacetonitrile and α-p-toluidino-p-chlorophenylacetonitrile. In these cases the unlabeled compounds, which were recrystallized from absolute ethanol, gave quantitative elemental analyses for carbon, hydrogen, and nitrogen that agreed within 0.2% of their respective calculated value. Thus, the structures of each of the $^{11}C$-labeled α-N-arylaminoarylacetonitriles reported in Table 2 were confirmed by the agreement of their melting points and infrared spectra with those of the corresponding unlabeled compounds produced under similar experimental conditions.

Infrared and nuclear magnetic resonance spectra of each unlabeled compound in Table 2 confirmed their predicted structure. Each compound showed a N—H amine stretch as an absorption band of medium intensity at 3,226–3,448 $cm^{-1}$, and a C≡N nitrile stretching absorption band of weak intensity at 2,174–2,273 $cm^{-1}$. Characteristic absorption bands for mono- and para-substituted benzene rings occurred from 690 to 833 $cm^{-1}$. Since the infrared and nuclear magnetic resonance spectra of unrecrystallized product, as obtained directly from the experimental reaction, were almost identical to that of recrystallized product, it was apparent that the product of the rapid synthesis was essentially pure.

The chemical shift of the one-proton N—H signal varied from δ 3.8 to 7.6 ppm and was exchangeable with $D_2O$. The chemical shift of the benzyl proton was δ 5.3–6.0 ppm. This one-proton C—H doublet signal collapsed to a singlet in $D_2O$. The chemical shifts of the aromatic ring protons were δ 6.4–7.8

**TABLE 2. PREPARATION OF $^{11}C$-LABELED α-N-ARYLAMINOARYLACETONITRILES (5-MMOLE REACTION SCALE)**

R— —CHO + R′— —$NH_2$ $\xrightarrow{C_5H_5OH}$ R— —CH=N— —R′ $\xrightarrow[30–60°,\ 10–20\ min]{\text{aq } Na^{11}CN,\ CH_3COOH}$ R— —CH(—$^{11}$CN)—NH— —R′

| $Na^{11}CN$ | | | Product | | Radiochemical | Chemical | Total preparation | Cold chemical | |
|---|---|---|---|---|---|---|---|---|---|
| mCi, $t_0$ | R | R′ | mCi, $t_0$ | mCi, $t_{1n}$ | yield (%) | yield (%) | time (min) | yield (%) | M.P. °C* |
| 826 | H | H | 362 | 51 | 44 | 41 | 58 | 50 | 84 – 85† |
| 778 | H | Cl | 148 | 15 | 19 | 20 | 67 | 46 | 83 – 84‡ |
| 292 | H | $CH_3$§ | 178 | 39 | 61 | — | 45 | 73 | 106.5–107¶ |
| 267 | H | $CH_3O$ | 129 | 27 | 48 | 37 | 46 | 70 | 73.5– 74.5‖ |
| 415 | H | COOH§ | 107 | 15 | 26 | 51 | 60 | 65 | 166 –169** |
| 1,627 | $CH_3$§ | H | 846 | 141 | 52 | — | 53 | 55 | 84 –85.5†† |
| 567 | $CH_3O$ | H | 275 | 25 | 49 | — | 67 | 81 | 102.5–104‡‡ |
| 563 | Cl§ | H | 327 | 45 | 58 | — | 55 | 78 | 112 –113§§ |
| 462 | $CH_3$ | $CH_3$¶¶ | 249 | 49 | 54 | 66 | 38 | 77‖‖‖ | 117 –118*** |
| 683 | $CH_3O$ | $CH_3$¶¶ | 194 | 42 | 28 | 44 | 35 | 79‖‖‖ | 103.5–104.5††† |
| 377 | Cl | Cl¶¶ | 114 | 21 | 30 | 36 | 40 | 55‖‖‖ | 114 –115‡‡‡ |
| 517 | Cl | $CH_3$¶¶ | 135 | 8 | 26 | 55 | 75 | 59‖‖‖ | 84 – 85§§§ |

* These melting points are those of the unrecrystallized $^{11}C$-labeled product, as obtained directly from the reaction mixture. Each is in good agreement with the respective melting point obtained from the corresponding, optimized unlabeled reaction, as well as with the corresponding value reported in the literature. In addition, the infrared spectrum obtained for each $^{11}C$-labeled product matched that obtained for the unlabeled product.

† Reported m.p. 91° (12); 85–86° (13).

‡ Reported m.p. 81° (12).

§ The intermediate Schiff base, ArCH=N—Ar, was not isolated in this preparation.

¶ Reported m.p. 110° (12).

‖ Reported m.p. 76–77° (12).

** Reported m.p. 163–164° (13).

†† Reported m.p. 91–92° (12); 80–81° (14).

‡‡ Reported m.p. 105° (12).

§§ Reported m.p. 112–113° (13).

¶¶ A 2-mmole reaction scale was used in these preparations.

‖‖‖ This is an average yield of an optimized unlabeled 2-mmole reaction scale procedure.

*** Reported m.p. 103° (15). The product from the optimized unlabeled reaction was recrystallized from absolute ethanol and then analyzed. M.p. obtained 118–119°; calculated for $C_{16}H_{16}N_2$: 81.33% C, 6.82% H, 11.85% N; found 81.38% C, 6.82% H, 11.84% N.

††† Reported m.p. 103–104° (12).

‡‡‡ The product from the optimized unlabeled reaction was recrystallized from absolute ethanol and then analyzed. M.p. obtained 119–120°; calculated for $C_{14}H_{10}N_2Cl_2$: 60.68% C, 3.63% H, 10.10% N; found 60.74% C, 3.72% H, 9.99% N.

§§§ Reported m.p. 81–82° (13); 101–102° (15). The product from the optimized unlabeled reaction was recrystallized from absolute ethanol and analyzed. M.p. obtained 93–94°; calculated for $C_{15}H_{12}N_2Cl$: 70.18% C, 5.10% H, 10.91% N; found 70.22% C, 5.03% H, 10.97% N.

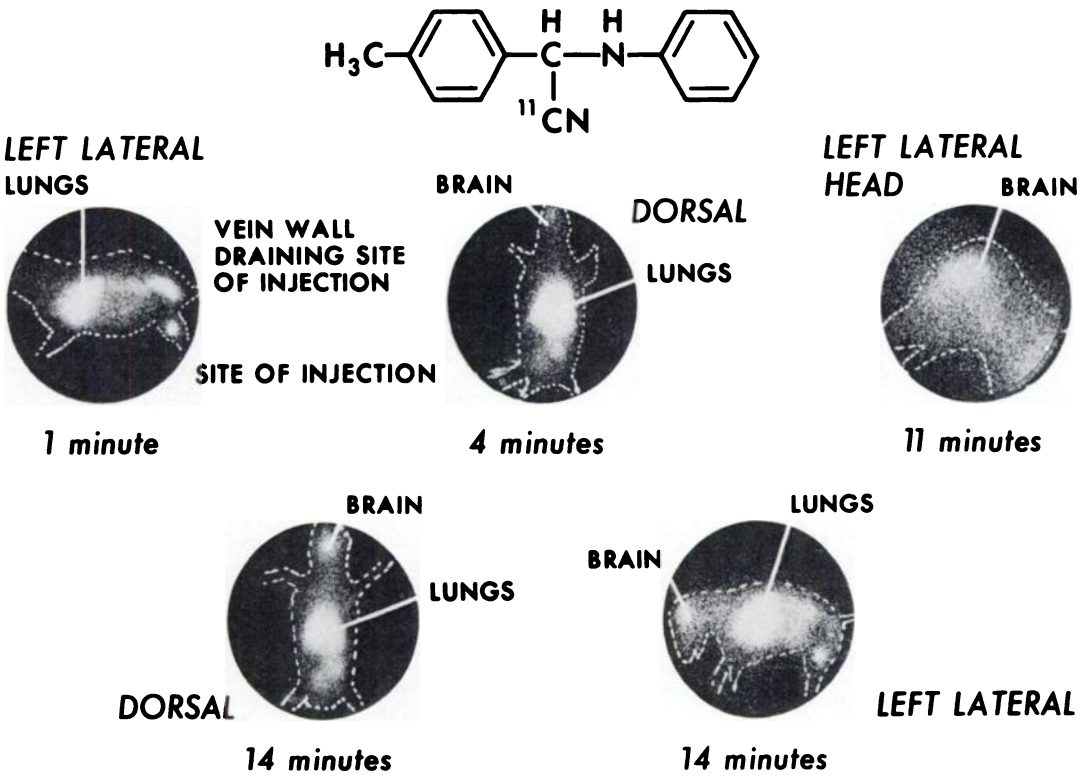
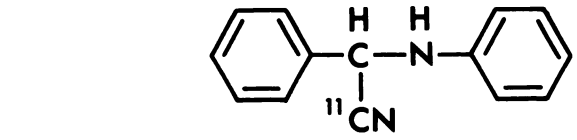



**FIG. 1.** Serial in vivo distribution patterns (whole-body views) of $^{11}C$ activity following i.v. administration of $^{11}C$ α-anilino-p-methylphenylacetonitrile in ethanol to dog. Note retention of activity in lungs, brain, and vein wall proximal to site of injection.

ppm. These signals showed the expected integration of both the mono- and disubstituted diarylaminoacetonitrile. The chemical shifts and proton integrations of all methoxy (δ 3.8–3.9 ppm) and methyl (δ 2.2–2.3 ppm) substituents on the aromatic rings agreed with the predicted values. These spectra were determined in either deuterated chloroform or deuterated dimethylsulfoxide solvent or a mixture of these two solvents.

**In vivo distribution.** Serial scintigraphic images obtained following intravenous administration of these compounds can be classified into distinct patterns dependent largely on their water solubility and solvent vehicle used in administration. All $^{11}C$ aminonitriles that were sufficiently water soluble to allow for administration in aqueous solution showed some variable initial accumulation in the liver, followed by diffuse whole-body distribution and some small accumulation in urine. The $^{11}C$ aminonitriles included in this category are all hydrocloride salts of mixed aliphatic–aromatic $^{11}C$ aminonitriles, i.e., α-N-methylamino-, α-N-ethylamino-, α-N-propylamino-, α-N-isopropylamino-, α-N-butylamino-, α-N-isobutylamino-, α-N-sec-butylamino-, and α-N-tert-butylaminophenylacetonitrile hydrochlorides, and the diarylaminonitrile, α-N-p-carboxyanilinophenylacetonitrile. All of the remaining $^{11}C$ aminonitrile derivatives were sufficiently water insoluble as to require dissolution and administration in an organic solvent (typically, ethanol). They all showed variable initial partial retention in the lungs with prominent accumulation of activity in liver and generally in brain. α-p-Methoxyanilinophenylacetonitrile and α-p-toluidinophenylacetonitrile administered in ethanol solution additionally showed scintigraphic evidence of retention in the heart. In the case of α-p-methoxyanilinophenylacetonitrile dissolved in ether, dissection at necropsy proved that such activity was principally localized in the endocardium of the right ventricle. In many of these water-insoluble compounds, significant concentration of activity was noted in the vein wall proximal to the site of injection. DMSO was used as the solvent for administration of $^{11}C$-labeled α-p-toluidino-p-chlorophenylacetonitrile, α-p-chloroanilino-p-chlorophenylacetonitrile, α-p-toluidino-p-methoxyphenylacetonitrile, and α-p-toluidino-p-tolylacetonitrile. In each case, the water-insoluble nitriles appeared to precipitate rapidly from solution as the DMSO mixed with plasma, resulting in primary deposition of activity in the lungs. Subsequently, slow release of activity from the lungs was noted with a suggestion of progressive accumulation of activity in the brain and in the liver. Scintiphotos obtained 125 min after administration of α-p-toluidino-p-chlorophenylacetonitrile showed concentration of activity in the area of the gallbladder.



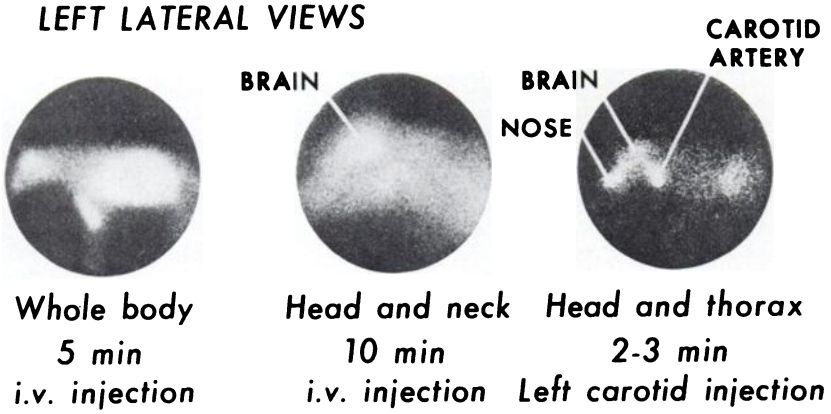
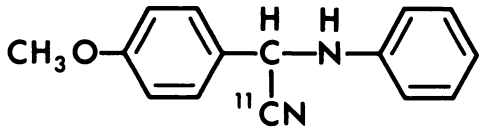




**FIG. 2.** In vivo distribution of $^{11}C$ activity following administration of $^{11}C$ α-anilinophenylacetonitrile in ethanol to dog. Note retention of activity in vein proximal to site of injection (saphenous vein in foreleg), in lungs, upper abdomen (liver), and in brain following i.v. injection (figure on left and in middle). Note retention of activity in internal carotid artery distal to site of injection, in brain, and nose following intracarotid injection.



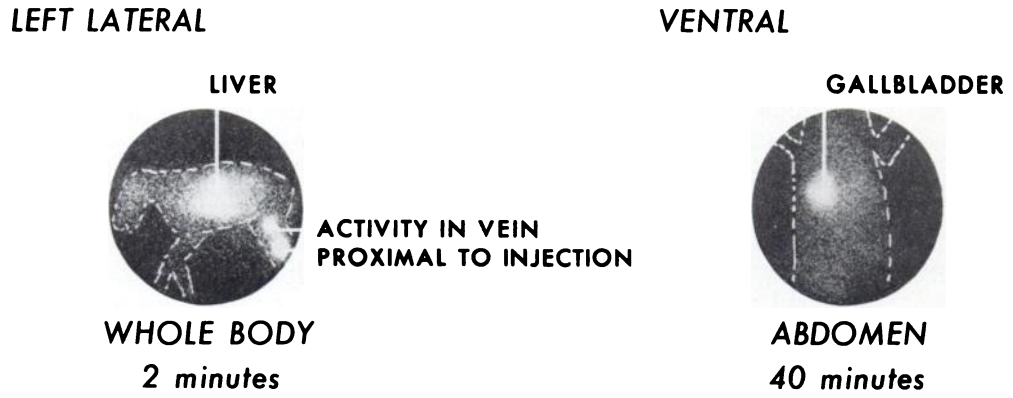




**FIG. 3.** In vivo distribution of $^{11}C$ activity following administration of $^{11}C$ α-anilino-p-methoxyphenylacetonitrile in ethanol to dog. Note prompt retention of activity in vein wall proximal to injection site in liver, followed by concentration in gallbladder.

Figures 1–4 show characteristic scintigraphic pattern variation obtained following intravenous administration of water-insoluble diaromatic aminonitriles dissolved and administered in ethanol. Figure 1 shows initial retention of activity in the vein wall distal to the site of administration, accumulation of activity in lungs and in brain, using $^{11}C$ α-anilino-p-methylphenylacetonitrile as the example. Figure 2 shows a similar pattern with more prominent accumulation of activity in the upper abdomen using $^{11}C$ α-anilinophenylacetonitrile as the example. The scintiphoto on the right of Fig. 2 shows results obtained subsequent to intracarotid injection of activity. Retention of activity in the carotid arterial wall distal to the site of injection, and in the dog's nose and brain, are noted (a dog's nose is a highly perfused organ). Figure 3 shows prominent liver uptake and biliary excretion of activity, using $^{11}C$ α-anilino-p-methoxyphenylacetonitrile as the example. Figure 4, using $^{11}C$ α-p-chloroanilinophenylacetonitrile as the example, shows rapid initial accumulation of activity in the brain, followed by washout during the ensuing 21 min associated with concentration of activity in the liver.

Table 3 shows the relative concentration of $^{11}C$ activity in various organs following intravenous administration of representative $^{11}C$ aminonitriles. All results are expressed as counts per minute per gram of tissue per counts per minute per gram of temporal muscle. The chemical formula, the time after admin-

istration when the animal was sacrificed, and the solvent used in administering the compounds are listed for each compound. The water-soluble monoaromatic α-N-methylaminophenylacetonitrile hydrochloride and α-N-sec-butylaminophenylacetonitrile hydrochloride were distributed relatively homogeneously throughout the tissues of the body. The latter showed some biliary excretion of activity at 30 min.

As illustrated in Figs. 2 and 4, the diaromatic compounds, α-anilinophenylacetonitrile and α-p-chloroanilinophenylacetonitrile, showed rapid initial accumulation of $^{11}C$ activity in the brain, followed by washout of such activity over the following 10–15 min. Such cerebral accumulation was confirmed at necropsy 5 min after injection of α-p-chloroanilinophenylacetonitrile (Table 3). However, high retention of activity is seen in lungs, and concentration of activity comparable to that in brain is noted in heart, liver, stomach, pancreas, and kidneys. In the dog sacrificed 18 min after intravenous injection of α-anilinophenylacetonitrile, the activity is noted to be largely excretion in bile. Eighteen minutes after intravenous administration of this agent, the animal showed a remarkable concentration of activity in cerebrospinal fluid, which was 30 times greater than activity in blood and approximately equal to the concentration of activity in bile (Table 3). At this time, the concentration of activity in the brain was comparable to that in blood.

α-p-Toluidinophenylacetonitrile and α-p-methoxyanilinophenylacetonitrile administered in ether were retained largely in the lungs. A high concentration of $^{11}C$ activity in bile at 73 and 39 min, respectively, after administration of these compounds suggests the biliary route of excretion as the primary one. It is noteworthy that, at 39 min, the concentration of activity from α-p-methoxyanilinophenylacetonitrile in mesenteric fat was 2.3 times that in blood.

Tissue distribution of $^{11}C$ activity from α-anilino-p-chlorophenylacetonitrile, 60 min after its intravenous administration, was high in bile, again suggesting biliary excretion as the principal route of excretion from the body. Similar results were obtained with $^{11}C$ α-anilino-p-methylphenylacetonitrile.

## DISCUSSION

In the present studies, $^{11}C$-labeled aminonitriles containing only one benzene ring, which were soluble in both aqueous and organic solvents, rapidly distributed themselves fairly uniformly throughout the body in a fashion similar to that seen with antipyrine. Some of these showed subsequent excretion of activity in bile and urine. While the chemical identity of the activity in the bile and urine was not determined, it could represent the corresponding carboxylic acid arising from hydrolysis of the nitrile. Such biliary excretion of carboxylic acids possessing lipid solubility has been described (*1*).

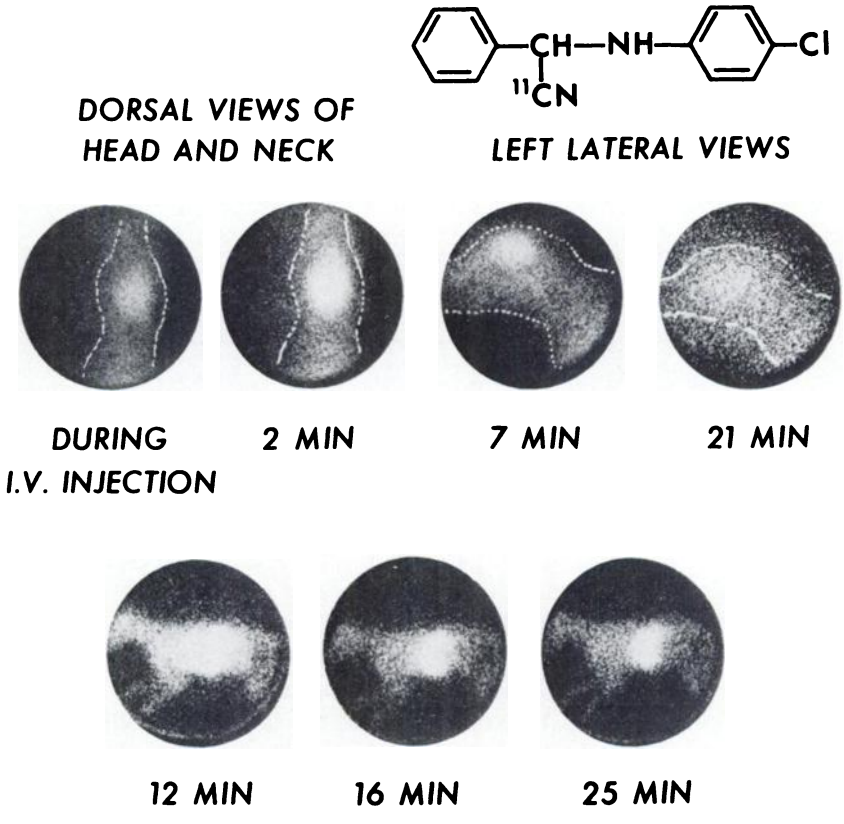
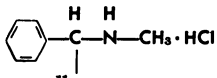
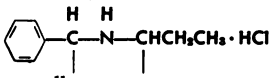
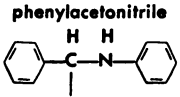
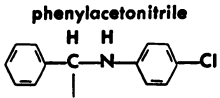
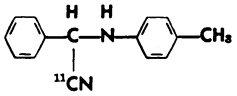
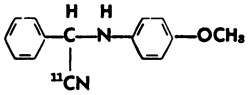
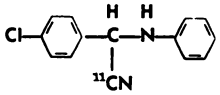
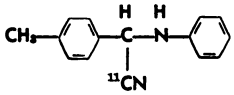



**FIG. 4.** Clearance of $^{11}C$ activity from brain and concentration in liver following i.v. administration of $^{11}C$ α-p-chloranilinophenylacetonitrile in ethanol to dog.

**TABLE 3. RELATIVE CONCENTRATION OF $^{11}C$ ACTIVITY IN ORGANS FOLLOWING I.V. ADMINISTRATION OF $^{11}C$ AMINONITRILES (CPM/GM TISSUE/CPM/GM TEMPORAL MUSCLE)**

| Organ | $^{11}C$-α-N-methylamino-phenylacetonitrile hydrochloride  ~15–20 min after i.v. administration (in water) | $^{11}C$-α-N-sec-butylamino-phenylacetonitrile hydrochloride  30 min after i.v. administration (in water) | $^{11}C$-α-anilino-phenylacetonitrile  18 min after i.v. administration (in ethanol) | $^{11}C$-α-p-chloroanilino-phenylacetonitrile  5 min after i.v. administration (in ethanol) |
|---|---|---|---|---|
| Brain | 0.54 | 0.77 | 1.99 | 16.93 |
| Lungs | 0.56 | 2.13 | 2.76 | 98.13 |
| Heart (washed) | 0.32 | 1.57 | 2.24 | 18.00 |
| Temporal muscle | 1.00 | 1.00 | 1.00 | 1.00 |
| Liver | 0.14 | 2.23 | 4.47 | 20.67 |
| Bile | 0.88 | 10.90 | 64.67 | 0.47 |
| Spleen | 0.05 | 3.23 | 1.08 | 1.40 |
| Stomach | — | 1.70 | 1.75 | 11.73 |
| Pancreas | 0.46 | 1.73 | 3.21 | 10.53 |
| Kidneys | — | 3.26 | 2.86 | 15.47 |
| Blood | 0.24 | 3.40 | 1.86 | 5.87 |
| Mesenteric fat | 0.19 | 1.23 | — | 2.07 |
| Urine | 1.47 | 6.70 | 0.93 | — |
| Cerebrospinal fluid | — | — | 56.51 | — |

| Organ | $^{11}C$-α-p-toluidino-phenylacetonitrile  73 min after i.v. administration (in ether) | $^{11}C$-α-p-methoxyanilino-phenylacetonitrile  39 min after i.v. administration (in ether) | $^{11}C$-α-anilino-p-chloro-phenylacetonitrile  ~60 min after i.v. administration (in ethanol) | $^{11}C$-α-anilino-p-methyl-phenylacetonitrile  ~55 min after i.v. administration (in ethanol) |
|---|---|---|---|---|
| Brain | 1.20 | 1.33 | 1.00 | 1.06 |
| Lungs | 8.60 | 28.94 | 3.00 | 12.48 |
| Heart (washed) | 2.20 | 2.83 | 1.00 | 1.59 |
| Temporal muscle | 1.00 | 1.00 | 1.00 | 1.00 |
| Liver | 1.00 | 6.11 | 1.00 | 3.81 |
| Bile | 18.00 | 175.08 | 78.00 | 31.66 |
| Spleen | — | 2.11 | 1.00 | 2.09 |
| Stomach | — | 2.14 | 1.00 | 1.50 |
| Pancreas | — | 2.42 | 2.00 | 1.89 |
| Kidneys | — | 2.97 | 3.00 | 3.44 |
| Blood | — | 1.75 | — | 2.81 |
| Mesenteric fat | — | 4.08 | — | 2.68 |
| Urine | — | 2.28 | — | 6.77 |
| Cerebrospinal fluid | — | — | — | 0.79 |

Those $^{11}C$-labeled aminonitriles that were very water insoluble, e.g., the arylaminoarylacetonitriles, precipitated from the solvent used as the vehicle for injection after the solvent was diluted with blood. Such precipitated material was partially retained in the vein wall proximal to the site of injection, in certain cases in the endocardial lining of the right ventricle, and in the lungs. Such precipitation following injection, with prominent retention of activity in the lungs, was most marked with those compounds injected using DMSO as the solvent. Thus, the use of ethanol as a solvent would appear to decrease the rate of precipitation, or the coarseness of the precipitate formed, following intravenous administration of the agent in this solvent when compared to the use of DMSO as the solvent. In carrier experiments dilution of the water-insoluble compound into an aqueous solution resulted in the rapid production of a grossly visible precipitate. It is anticipated that such a dense precipitate would be mechanically trapped in the pulmonary capillary bed following intravenous administration of the agent. Such mechanical trapping of particulate material in the lungs may not be the sole mechanism for retention of these highly lipid-soluble materials in the lungs. The large surface area of lipoprotein cell membrane in the pul-

monary capillary bed may represent a substantial sink for dissolution and retention of highly lipid-soluble substances. Most of these $^{11}C$ arylamino-arylacetonitriles showed remarkably rapid accumulation in the brain (e.g., α-anilinophenylacetonitrile and α-p-chloroanilinophenylacetonitrile). Such activity in the brain was largely cleared within 10–15 min. However, activity in the cerebrospinal fluid following such clearance was 30 times greater than in the blood and equivalent in concentration to that noted in bile 18 min after administration of $^{11}C$ α-anilinophenylacetonitrile. It is possible that the aminonitrile was the form accumulating in brain, where it possibly dissociated, releasing cyanide, or underwent hydrolysis to the amino acid, or both. The partition coefficient of the more water-soluble cyanide or amino acid would be expected to favor distribution of the $^{11}C$-labeled cyanide or amino acid in cerebrospinal fluid or blood. If this reasoning is correct, one could potentially correlate brain uptake of certain $^{11}C$ aminonitriles with brain perfusion, and the subsequent clearance of activity from the brain with processes related to nitrile dissociation or metabolism. Clearance of activity from the cerebrospinal fluid should correlate with cerebrospinal fluid resorption kinetics. In either case, use of these or similar materials could allow for assessment of brain metabolism followed by imaging of the bulk flow characteristics of cerebrospinal fluid.

## SUMMARY

These results demonstrate that in dogs aminonitriles that show both aqueous and lipid solubility distribute themselves diffusely throughout the body in a fashion somewhat similar to that noted with antipyrine. Aqueous-insoluble aminonitriles injected intravenously in ethanol, ether, or DMSO often show rapid accumulation in the brain followed by almost complete clearance of activity from this organ over the ensuing 10–15 min. With at least one compound (α-anilinophenylacetonitrile), a high concentration of activity was noted in cerebrospinal fluid (30 times that in blood) 18 min after intravenous injection of the material and following clearance of activity from the brain. These results suggest the possible correlation of regional brain perfusion with regional brain uptake of activity. Potentially, brain tissue metabolism and bulk flow of cerebrospinal fluid may be scintigraphically imaged when the agent is first localized in the brain and then accumulates in cerebrospinal fluid, respectively.

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