# Synthesis and Biodistribution of Radioiodinated Nicotine Analogs[Δ]

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## SUMMARY

Four $^{125}$I-labelled nicotine analogs were synthesized: 3-(methylpropyl-aminomethyl)-, 3-(diethylaminomethyl)-, 3-(isopropylaminomethyl)-, and 3-(diisopropylaminomethyl)-5-[$^{125}$I]-iodopyridines. 5-Bromonicotinic acid was acylated with thionyl chloride and then reacted with the appropriate primary and secondary amines to give the corresponding amides which were reduced with di-borane to the desirable amines. Radioiodination was done by halogen exchange. Biodistribution studies in rats, showed that all four labelled compounds were rapidly taken up by the brain and the adrenal gland. This was followed by rapid washout of the compounds from these organs. The most promising of these compounds, 3-(diisopropylaminomethyl)-5-[$^{125}$I]-iodopyridine, showed a brain-to-blood ratio of 6.0:1 and an adrenal-to-blood ratio of 35.9:1 at 2 minutes post administration. In vitro correlation studies showed that brain uptake of these compounds depends on both protein binding and lipophilicity, whereas adrenal uptake depends only on lipophilicity.

Keywords: Imaging, [$^{125}$I]-Nicotine analogs, Brain, Adrenal medulla.

## INTRODUCTION

In our previous study (1), we showed that $^{125}$I-labelled 5-iodonicotine (I, Figure 1) was rapidly taken up by the brain and the adrenal gland in the rat. The rapid uptake of the labelled compound was followed by rapid washout from these organs (1). In our continuous effort to search for a brain and adrenal medulla imaging agent, we synthesized four $^{125}$I-labelled nicotine analogs and studied their biodistribution in the rat. The biodistribution results were correlated with in vitro protein binding and lipophilicity studies. The compounds investigated were (IIa-d, Figure 1):

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## RESULTS AND DISCUSSION

We chose to study compounds IIa-d for the following reasons. Compound IIa

I - Iodonicotine (NIC)

II a. R = Me, R' = n-Pr 3-(Methylpropylaminomethyl)-5-[$^{125}$I]iodopyridine (MP)

b. R = R' = Et 3-(Diethylaminomethyl)-5-[$^{125}$I]iodopyridine (DIET)

c. R = H, R' = i-Pr 3-(Isopropylaminomethyl)-5-[$^{125}$I]iodopyridine (IP)

d. R = R' = i-Pr 3-(Diisopropylaminomethyl)-5-[$^{125}$I]iodopyridine (DIP)

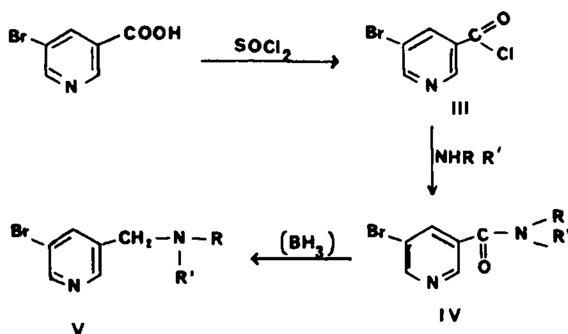
Figure 1. 5-[$^{125}$ I]-Iodonicotine and 5-[$^{125}$I]-Iodonicotine analogs

is derived from the splitting of the 2' and 3' carbon-carbon bond of the pyrrolidine ring of I. IIb is an isomer of IIa. IIc was chosen for study because Winchell et al. (2) reported that the introduction of a single isopropyl group on the amine nitrogen of p-iodoamphetamine increased the brain uptake of the resulting secondary amine. However, since the radiolabelled tertiary amines reported by Kung and Blau (3) also showed favorable brain uptake, IIc with its amine hydrogen substituted with a second isopropyl group, i.e. compound IId was also examined.

The $^{125}$I-labelled nicotine analogs were synthesized according to Scheme 1 and Scheme 2. 5-Bromonictonic acid (III) (1) was acylated with thionyl chloride and the product was reacted with the appropriate primary or secondary amine to give the the corresponding amines (IVa-d) in good yields (82.5-86.1%). However, the subsequent reduction step gave many side products, as revealed by thin layer chromatography (TLC), and hence poor yields (6.7-9.9%) of the desirable amines. Melting point, NMR and mass spectral data were used to confirm the structures of Va-d.

Radioiodination and identification of the labelled compounds were done according to the procedures reported for 5-[$^{125}$I] iodonicotine (1) with the exception that different solvent systems were used for TLC identification of the com-

Scheme 1




a. R = Me, R' = n-Pr

b. R = R' = Et

c. R = H, R' = i-Pr

d. R = R' = i-Pr

a. R = Me, R' = n-Pr

b. R = R' = Et

c. R = H, R' = i-Pr

d. R = R' = i-Pr

Scheme 2

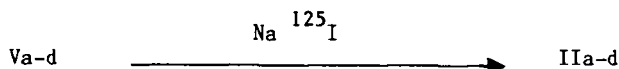



Table 1. Radiochemical yield and specific activity of $^{125}$I-labelled nicotine analogs

| Compound | Yield | Specific Activity |
|---|---|---|
| MP | 700 μCi (70.0%) | 170.1 mCi/mmole |
| DIET | 466 μCi (46.6%) | 113.2 mCi/mmole |
| IP | 750 μCi (75.0%) | 171.8 mCi/mmole |
| DIP | 600 μCi (66.0%) | 178.9 mi/mmole |

pounds. The radiochemical yield and specific activity of these compounds are shown in Table 1.

The distribution of the $^{125}$I-labelled nicotine analogs in tissues of female Sprague-Dawley rats was determined at time intervals of 2, 15, 30, 60 and 120 minutes after the administration of the compounds via tail vein injection, and the results are summarized in Table 2. The biodistribution data showed all four nicotine analogs were rapidly taken up by the brain and the adrenal gland. The accumulation of the labelled compounds in the adrenal gland is presumed to be in the adrenal medulla since Hanson and Schmiterlow have shown the $^{14}$C-nicotine accumulated in the adrenal medulla of mice (5).

Table 2. Tissue distribution of [$^{125}$I]-nicotine analogs in rats*

| Tissue | Minutes after administration 2 | 15 | 30 | 60 | 120 |
|---|---|---|---|---|---|
| | | | Compound V a (MP) | | |
| Blood | 0.08 ± 0.00 | 0.11 ± 0.01 | 0.13 ± 0.01 | 0.14 ± 0.01 | 0.05 ± 0.00 |
| Brain | 0.15 ± 0.01 | 0.07 ± 0.01 | 0.04 ± 0.00 | 0.02 ± 0.00 | 0.01 ± 0.00 |
| Adrenal | 0.51 ± 0.03 | 0.18 ± 0.02 | 0.08 ± 0.01 | 0.04 ± 0.00 | 0.02 ± 0.00 |
| Kidney | 0.23 ± 0.01 | 0.31 ± 0.03 | 0.30 ± 0.02 | 0.19 ± 0.04 | 0.19 ± 0.02 |
| Thyroid | 0.07 ± 0.02 | 0.19 ± 0.03 | 0.28 ± 0.05 | 0.43 ± 0.12 | 2.33 ± 0.60 |
| Liver | 0.25 ± 0.01 | 0.16 ± 0.02 | 0.08 ± 0.00 | 0.05 ± 0.00 | 0.03 ± 0.00 |
| | | | Compound V b (DIET) | | |
| Blood | 0.06 ± 0.00 | 0.08 ± 0.01 | 0.07 ± 0.01 | 0.09 ± 0.00 | 0.06 ± 0.01 |
| Brain | 0.17 ± 0.01 | 0.09 ± 0.00 | 0.09 ± 0.00 | 0.05 ± 0.00 | 0.03 ± 0.00 |
| Adrenal | 0.27 ± 0.01 | 0.11 ± 0.11 | 0.11 ± 0.01 | 0.06 ± 0.01 | 0.04 ± 0.01 |
| Kidney | 0.32 ± 0.02 | 0.20 ± 0.01 | 0.25 ± 0.03 | 0.30 ± 0.03 | 0.21 ± 0.02 |
| Thyroid | 0.04 ± 0.01 | 0.03 ± 0.00 | 0.04 ± 0.00 | 0.17 ± 0.10 | 0.27 ± 0.15 |
| Liver | 0.28 ± 0.01 | 0.16 ± 0.00 | 0.14 ± 0.00 | 0.09 ± 0.00 | 0.05 ± 0.01 |
| | | | Compound V c (IP) | | |
| Blood | 0.06 ± 0.00 | 0.08 ± 0.01 | 0.12 ± 0.00 | 0.13 ± 0.01 | 0.10 ± 0.01 |
| Brain | 0.24 ± 0.01 | 0.11 ± 0.01 | 0.05 ± 0.01 | 0.05 ± 0.01 | 0.01 ± 0.00 |
| Adrenal | 0.19 ± 0.01 | 0.12 ± 0.02 | 0.07 ± 0.00 | 0.07 ± 0.01 | 0.03 ± 0.00 |
| Kidney | 0.32 ± 0.02 | 0.27 ± 0.03 | 0.40 ± 0.10 | 0.44 ± 0.07 | 0.24 ± 0.03 |
| Thyroid | 0.05 ± 0.00 | 0.05 ± 0.02 | 0.05 ± 0.02 | 0.06 ± 0.00 | 0.26 ± 0.07 |
| Liver | 0.19 ± 0.01 | 0.14 ± 0.02 | 0.09 ± 0.01 | 0.09 ± 0.01 | 0.04 ± 0.00 |
| | | | Compound V d (DIP) | | |
| Blood | 0.04 ± 0.00 | 0.12 ± 0.01 | 0.11 ± 0.01 | 0.12 ± 0.01 | 0.07 ± 0.01 |
| Brain | 0.25 ± 0.02 | 0.11 ± 0.01 | 0.07 ± 0.00 | 0.04 ± 0.00 | 0.02 ± 0.00 |
| Adrenal | 1.52 ± 0.05 | 0.29 ± 0.03 | 0.12 ± 0.01 | 0.08 ± 0.01 | 0.03 ± 0.00 |
| Kidney | 0.28 ± 0.01 | 0.34 ± 0.08 | 0.34 ± 0.07 | 0.36 ± 0.07 | 0.16 ± 0.03 |
| Thyroid | 0.07 ± 0.00 | 0.07 ± 0.01 | 0.07 ± 0.02 | 0.12 ± 0.04 | 0.15 ± 0.03 |
| Liver | 0.31 ± 0.03 | 0.17 ± 0.01 | 0.12 ± 0.01 | 0.09 ± 0.00 | 0.04 ± 0.00 |

*Dose 10 μCi, other tissues studied but not listed are heart, lung, spleen, and small intestine. Values represent mean % kg-dose/gm for 3 rats per time interval with ± S.E.M.

Among the four [$^{125}$I]-nicotine analogs studied, DIP (V d) showed the highest uptake in both the brain and the adrenal at 2 minutes post administration. For comparison purposes, the maximum brain-to-blood and adrenal-to-blood ratios (at 2 minutes) of these compounds, as well as that of 5-[$^{125}$I]-iodonicotine, are shown in Table 3.

Similar to 5-[$^{125}$I]-iodonicotine, the [$^{125}$I]-nicotine analogs were rapidly washed out of the brain and the adrenal after their rapid uptake by these organs.

Table 3. Maximum organ-to-blood ratios (at 2 minutes after dose administration) and $T_{\frac{1}{2}}$ of [$^{125}$I]-nicotine and analogs in the brain and adrenal of the rat.

| | Organ:blood | | $T_{\frac{1}{2}}$ (minutes) | |
|---|---|---|---|---|
| Compound | Brain | Adrenal | Brain | Adrenal |
| MP | 1.9 | 6.5 | 4 | 4 |
| DIET | 2.9 | 4.8 | 18 | 11 |
| IP | 3.7 | 3.0 | 9 | 18 |
| DIP | 6.0 | 35.9 | 13 | 9 |
| NIC | 2.4 | 4.7 | 5 | 3 |

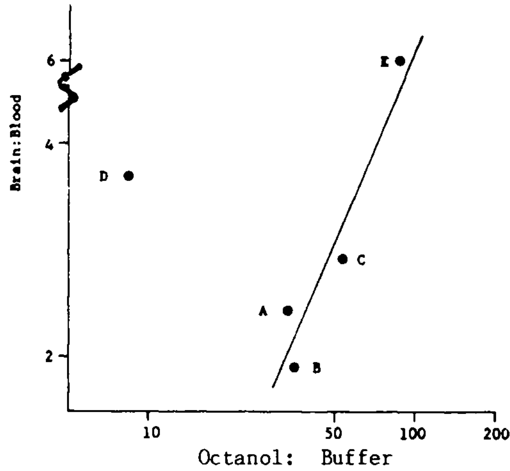
The rapid exit of these analogs from the brain and the adrenal may have resulted from the rapid metabolism of these compounds by these organs into metabolites which have lower affinity for brain and adrenal tissues. The $T_{\frac{1}{2}}$ of radioactivity in the brain and the adrenal for these tracers are compared to that of 5-[$^{125}$I]-iodonicotine in Table 3.

Since it is known that lipid solubility (6, 7) and protein binding (8, 9) affect the uptake of radiotracers by the brain, we determined the partition coefficient and the % protein binding of the [$^{125}$I]-nicotine analogs as well as those of 5-[$^{125}$I]-iodonicotine. Partition coefficient studies revealed that the log $P_{oct}$ (partition coefficient for octanol/buffer) values of the labelled compounds ranged from 0.92 to 2.16 well within the optimal log $P_{oct}$ values of 0.9 to 2.5 for brain uptake reported by Dischino et al. (9).

Protein binding studies showed that binding of the labelled compounds to blood proteins does not seem to be dependent on the concentrations of these compounds and when brain uptake of the tracers is correlated with the findings of partition coefficient (Figure 3) and protein binding (Figure 4) some interesting results were observed. DIP (V d), while having the highest brain uptake and the highest log $P_{oct}$ value, also exhibited the highest % protein binding among the compounds studied. These results suggested that brain uptake of these radiotracers is not governed by either lipid solubility or protein binding alone, instead, it is a result of an interplay between these two factors each of which can offset to some extent the effect of the other. Thus, the high lipid solubility of DIP (Vd) compensated for its high protein binding whereas the low protein binding of IP (Vc) compensated for its relatively low lipid solubility.

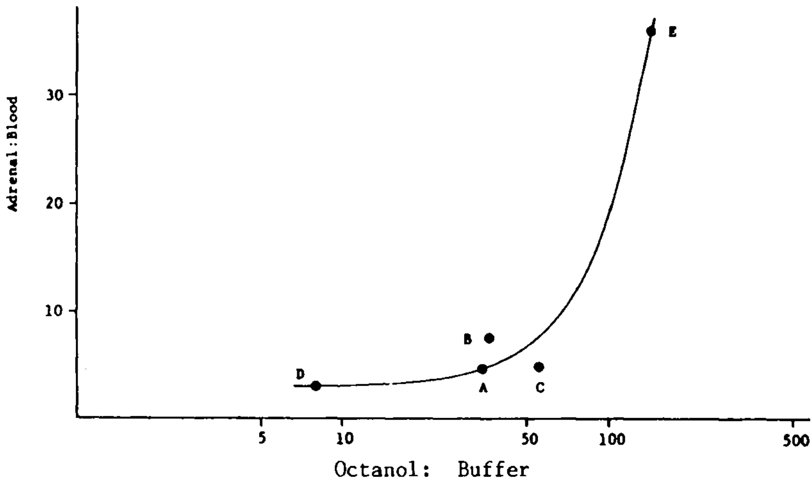
Similarly, where adrenal uptake of these tracers is correlated with parti-

Figure 3. Correlation between brain:blood ratios and partition coefficient.



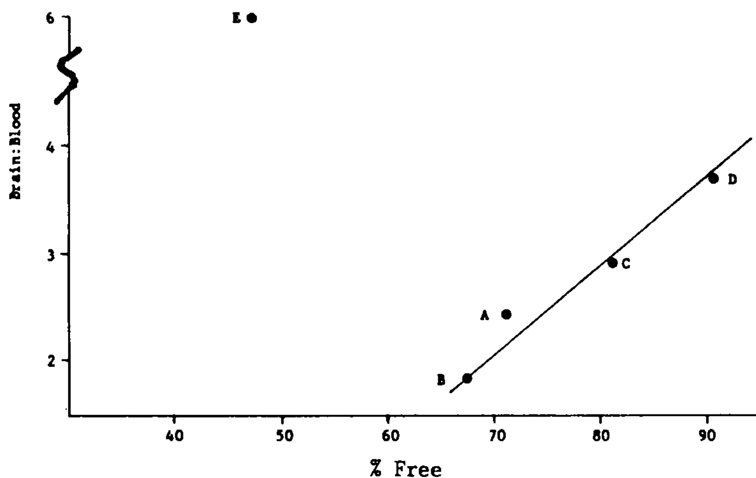

Legend: compound A: NIC B: MP C: DIET D: IP E: DIP

Figure 4. Correlation between adrenal:blood ratios and partition coefficient.




Legend: compound A: NIC B: MP C: DIET D: IP E: DIP

tion coefficient (Figure 5) and protein binding (Figure 6) we notice that the higher the protein binding of the tracer, the higher is its uptake by the adrenal gland. On the other hand, correlation between adrenal uptake and partition coefficient of the tracers showed that the higher the lipid solubility of the tracer, the higher the adrenal uptake. Hence, it appears that the uptake of the tracers by this organ is not affected by protein binding, but is dependent on their lipid solubility. The lack of effect of protein binding on organ uptake of radiotracers has been observed by Tramposch, King and Blau (10).



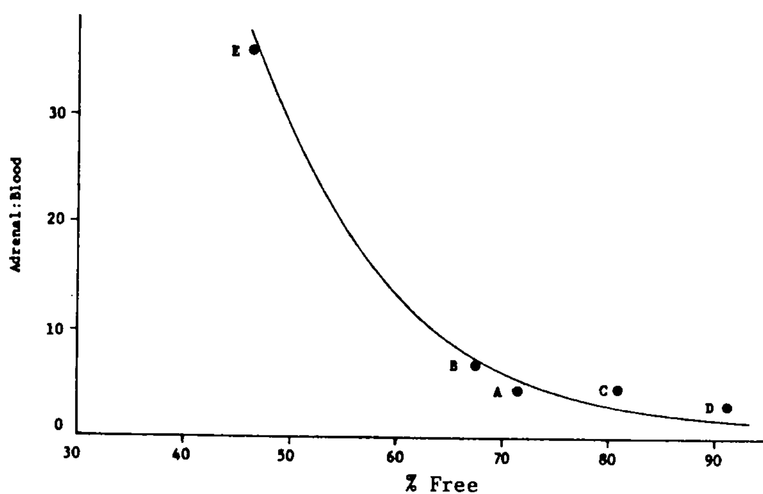

Legend = Compound A = NIC B = MP C = DIET D = IP E = DIP

Figure 5. Correlation between brain: blood ratios and protein binding.

## EXPERIMENTAL

### MATERIALS AND METHODS

All reagents were purchased from Aldrich Chemical Company. Na $^{125}I$ was purchased from ICN Chemical and Radioisotope Division. Human Serum Albumin was purchased from the Oklahoma Blood Institute. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. $^{1}H$-NMR spectra were




Legend: compound A: NIC B: MP C: DIET D: IP E: DIP

Figure 6. Correlation between adrenal:blood ratios and protein binding.

recorded on a Varian EM360A NMR spectrometer (60 MHz). Chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane internal standard. Mass spectra were obtained with a CELLO double-focusing mass spectrometer. Radiochromatograms were recorded on a Vanguard Model 930 auto scanner. Radioactivity in tissue samples were assayed with a Beckman Gamma 9000 gamma counter. Protein binding studies were performed by using Amicon's Model MPS-1 micropartition system.

## SYNTHESIS OF [$^{125}$I]-NICOTINE ANALOGS

**5-Bromonicotinic acid alkyl amides (IVa-d).** 5 Bromonicotinic acid (10 gm, 49.5 mmole) was dissolved in thionyl chloride (20 ml, 274 mmole) and the mixture was dried under vacuum to leave a residue which was dissolved in 50 ml of dry THF. An appropriate primary or secondary amine was added until no white fumes of hydrogen chloride gas were given off. 100 ml 4N KOH was then added to the mixture. The aqueous fraction was extracted with ether. The ether extract was combined with the THF fraction, dried over anhydrous $MgSO_4$, and evaporated under vacuum. The solids were recrystallized from benzene, and the liquids were distilled under reduced pressure.

IVa, yield 84.3%, b.p. 133-135°C (0.4 mm Hg); $^1$H-NMR ($CDCl_3$), $\delta$ 0.47-1.20 (s, 3H, propyl-$CH_3$), 1.20-2.01 (m, 2H, -$CH_2$-), 2.8-3.17 (s, 3H, N-$CH_3$), 3.17-3.87 (s, 2H, N-$CH_3$), 7.83-8.0 (t, 1H, 6-Ar), 8.53-8.67 (d, 1H, 4-Ar), 8.67-8.80 (d, 1H, 2-Ar).

IVb, yield 82.5%, b.p. 147-149°C (0.9 mm Hg); $^1$H-NMR ($CDCl_3$), $\delta$ 0.92-1.40 (t, 3H, -$CH_3$), 3.03-3.86 (s, 2H, -$CH_2$-), 7.80-7.93 (t, 1H, 6-Ar), 8.50-8.60 (d, 1H, 4-Ar), 8.63-8.76 (d, 3H, 2-Ar).

IVc, yield 86.1%, m.p. 104°C; $^1$H-NMR ($CDCl_3$), $\delta$ 1.23-1.30 (s, 3H, -$CH_3$), 1.33-1.43 (s, 3H, -$CH_3$), 4.00-4.60 (m, 1H, -CH-), 6.20-6.73 (s, 1H, -NH-), 8.15-8.32 (t, 1H, 6-Ar), 8.70-8.82 (d, 1H, 4-Ar), 8.82-8.92 (d, 1H, 2-Ar).

IVd, yield 83.7%, m.p. 141-142°C; $^1$H-NMR ($CDCl_3$), $\delta$ 0.75-1.03 (s, 6H, -$CH_3$), 1.03-1.27 (s, 6H, -$CH_3$), 3.00-3.67 (m, 2H, -CH-), 7.50-7.67 (t, 1H, 6-Ar), 8.23-8.33 (d, 1H, 4-Ar), 8.43-8.57 (d, 1H, 2-Ar).

**3-(Alkylaminomethyl)-5-bromopyridines (Va-d).** These compounds were synthesized according to the method of Brown and Helm (4) with slight modifications. The appropriate 5-bromonicotinic acid alkyl amide (IV a-d) (4 gm), dissolved in 30 ml of methylene chloride, was added to 50 ml (excess) 1M $(CH_3)_2S \cdot BH_3$ at ice bath temperature. The reaction mixture was refluxed for 1 hour and was then allowed to cool to room temperature. Hydrochloric acid (50 ml, 10%) was added

slowly through a dropping funnel. The organic layer was discarded. The aqueous fraction was made strongly basic by the addition of 4N KOH (100 ml) and extracted with ether. The ether was dried over anhydrous $MgSO_4$ and evaporated. The crude residue was dissolved in acetate buffer (pH 4) and extracted with ether. The product was further purified by preparative thin layer chromatography.

Va, yield 9.9%, b.p. 100°C (1.0 mm Hg); $^1$H-NMR ($CDCl_3$), $\delta$ 0.77-1.13 (t, 3H, propyl $CH_3$), 1.33-1.80 (m, 2H, $-CH_2-$), 2.17-2.53 (m, 5H, $-CH_2-N-CH_3$), 3.43-3.60 (s, 2H, py-$CH_2$-N), 7.77-7.97 (t, 1H, 6-Ar), 8.40-8.52 (d, 1H, 4-Ar), 8.52-8.63 (d, 1H, 2-Ar); M.S., m/e (rel. int), 244 (4.1), 215 (77.9), 213 (80.5), 186 (5.7), 184 (5.3), 170 (100), 86 (22.1).

Vb, yield 10.2%, b.p. 65°C (0.3 mm Hg); $^1$H-NMR ($CDCl_3$), $\delta$ 0.90-1.23 (t, 3H, $-CH_3$), 2.30-2.77 (9, 4H, ethyl-$CH_2$-), 3.50-363 (s, 2H, py-$CH_2$-), 7.77-7.93 (t, 1H, 6-Ar), 8.40-8.48 (d, 1H, 4-Ar), 8.48-8.60 (d, 1H, 2-Ar); M.S., m/e (rel. int), 242 (18.5), 229 (95.8), 227 (100), 172 (18.9), 170 (22), 86 (43).

Vd, yield 8.0%, b.p. 85°C (0.4 mm Hg); $^1$H-NMR ($CDCl_3$), $\delta$ 0.93-103 (s, 6H, $-CH_3$), 1.06-1.13 (s, 6H, $-CH_3$), 2.73-3.27 (m, 2H, $-CH_2-$), 3.57-3.70 (s, 2H, py-$CH_2$-), 7.80-7.93 (t, 1H, 6-Ar), 8.40-8.57 (d, 2H, 4-, 2-Ar); M.S., m/e (rel. int), 257 (84.9), 255 (77.9), 172 (100), 170 (84.9), 80 (12), 78 (11).

In the case of 3-(**isopropylaminomethyl**)-5-**bromopyridine** (Vc), the reduction was performed by using dry THF as solvent and 1M THF·$BH_3$ (50 ml) as the reducing agent. After the addition of 10% HCl, the THF was distilled off at atmospheric pressure. The aqueous fraction was made alkaline and the rest of the procedure was the same as above.

Vc, yield 6.7%, b.p. 97°C (1.0 mm Hg); $^1$H-NMR ($CDCl_3$), $\delta$ 1.00-1.07 (s, 3H, $-CH_3$), 1.13-1.20 (s, 3H, $-CH_3$), 2.60-3.10 (m, 1H, -CH-), 3.75-3.85 (s, 2H, py-$CH_2$), 7.53-7.67 (t, 1H, 6-Ar), 8.47-3.57 (d, 1H, 4Ar), 8.57-8.67 (d, 1H, 2-Ar); M.S. m/e (rel. int.) 229 (12.8), 213 (100), 172 (89.7), 91 (29.4), 77 (6.2), 72 (12.8), 58 (12.6).

## BIODISTRIBUTION STUDIES OF [$^{125}$I]-NICOTINE ANALOGS

Biodistribution studies were performed according to procedures reported for 5-[$^{125}$I]-iodonicotine (1) with one modification. The [$^{125}$I]-nicotine analogs were converted to the dihydrochloride salts by the addition of a few drops of ether saturated with HCl (the ether was evaporated) before the compounds were formulated in saline.

## PARTITION COEFFICIENT STUDIES

The method followed closely the procedure reported by Kung et al. (11). A labelled compound (1-2 µCi) was mixed with 2 gm each of 1-octanol and phosphate buffer (pH 7.4) in a test tube. The tube was vortexed (3 x 1 min.) at room

temperature and then centrifuged for 10 minutes. Two 0.5 gm samples of each of the 1-octanol and buffer layers were counted in a gamma counter. The procedure was performed in duplicate for each labelled compound.

## PROTEIN BINDING STUDIES

Serial dilution using physiological saline was done to obtain 14, 7, and 3.5 nmole/0.1 ml of a mixture of 5-bromo and 5-[$^{125}$I]-iodo compounds from a starting concentration of 28 nmole/0.1 ml of a batch of a labelled compound. To 0.1 ml of each concentration in a test tube was added 0.8 ml of 25% human serum albumin and sufficient phosphate buffer (pH 7.4) to give a final volume of 10 ml and a final concentration of 2% of human serum albumin. The mixtures were incubated with constant shaking for 30 minutes at 37°C in a water bath. Two aliquots (0.1 ml each) of each mixture were counted in a gamma counter for 'total' counts. An aliquot (1 ml) of each mixture was placed in an Amicron's Model MPS-1 micropartition system and centrifuged for 10 mintues. Two aliquots (0.1 ml each) of each filtrate were counted in a gamma counter for 'free' counts.

## REFERENCES

1. Chan S.M., Basmadjian G.P., Marten D.F., Sadek S.A., Magarian R.A., Grunder J.R. and Ice R.D. - J. Label. Cmpds. Radiopharm. 20: 1017 (1983)
2. Winchell H.S., Baldwin R.M. and Lin T.H. - J. Nucl. Med. 21: 940 (1980)
3. Kung H.F. and Blau M. - J. Nucl. Med. 21: 147 (1980)
4. Brown H.C. and Helm P. - J. Org. Chem. 38: 912 (1973)
5. Hansson E. and Schmiterlow G.G. - J. Pharm. Exp. Ther. 137: 91 (1962)
6. Rapaport S.I., Ohno K. and Pettigrew K.D. - Brain Res. 172: 354 (1979)
7. Oldendorf W.H. - Proc. Soc. Exp. Biol. Med. 147: 813 (1974)
8. Loberg M.D., Corder E.H., Fields A.T. and Callery P.S. - J. Nucl. Med. 20: 1181 (1979)
9. Dischino D.D., Welch M.J., Kilbourn M.R. and Raichle M.E. - J. Nucl. Med. 24: 1030 (1983)
10. Tramposch K.M., Kung H.F. and Blau M. - J. Med. Chem. 26: 121 (1983)
11. Kung H.F., Tramposch K.M. and Blau M. - J. Nucl. Med. 24: 66 (1983)