Compounds II–IV were added to the bath, and muscle contraction was monitored for 1.5 min. Prostaglandin E_2 was used to obtain standard contraction.

REFERENCES

(1) S. T. Kam, P. S. Portoghese, J. M. Gerrard, and E. W. Dunham, *J. Med. Chem.*, **22**, 1402 (1979). S. T. Kam, P. S. Portoghese, E. W. Dunham, and J. M. Gerrard, *Prostaglandins and Medicine*, **3**, 279 (1979).

(2) N. A. Porter, J. H. Roycroft, J. Nixon, D. Gilmore, and D. B. Mengel, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 608 (1978).

(3) G. Zweifel, R. P. Fisher, J. T. Snow, and C. C. Whitney, *J. Am. Chem. Soc.*, **93**, 6309 (1971).

(4) P. G. Gassman and K. T. Mansfield, *Org. Syn.*, **49**, 1 (1969).

(5) E. L. Allred and R. L. Smith, *J. Org. Chem.*, **31**, 3489 (1966).

(6) E. J. Corey, K. C. Nicolaou, Y. Machida, C. L. Malmsten, and B. S. Samuelsson, *Proc. Natl. Acad. Sci., USA*, **72**, 3355 (1975).

(7) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed., Pergamon, Oxford, England, 1969, p. 301.

(8) H. C. Brown and G. Zweifel, *J. Am. Chem. Soc.*, **83**, 2544 (1961).

(9) M. W. Rathke, N. Inoue, K. R. Varma, and H. C. Brown, *ibid.*, **88**, 2870 (1966).

(10) E. Nagishi and S. Baba, *ibid.*, **97**, 7385 (1975).

(11) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed., Pergamon, Oxford, England, 1969, p. 289.

(12) P. S. Portoghese and D. T. Sepp, *Tetrahedron*, **29**, 2253 (1973).

(13) C. Malmsten, *Life Sci.*, **18**, 169 (1976).

(14) G. Stook and M. Isobe, *J. Am. Chem. Soc.*, **97**, 4745 (1975).

(15) J. M. Gerrard, J. D. Peller, T. P. Krich, and J. G. White, *Prostaglandins*, **14**, 39 (1977).

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Potential Organ- or Tumor-Imaging Agents XIX: Radioiodinated Antiarrhythmic Drugs as Potential Myocardial Imaging Agents

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Abstract □ Iodinated and radioiodinated analogs of propranolol and *N,N*-dimethylpropranolol were synthesized wherein an iodophenyl moiety replaced the naphthalene ring of the parent drug. These new compounds were evaluated not only for their β-adrenergic blocking and antiarrhythmic activities but also for their ability to accumulate selectively in myocardial tissue. Like propranolol, the iodinated analogs displayed comparable β-blocking and antiarrhythmic activity, and the order of potency was *ortho-* > *meta-* > *para*-iodophenyl. Quaternization of propranolol and the iodinated analogs eliminated the β-adrenergic blocking activity but retained the antiarrhythmic property of the secondary amine precursors. Among the quaternary salts, the antiarrhythmic potency was *meta-* > *ortho-* > *para*-iodophenyl. Tissue distribution of the radioiodinated derivatives revealed that only the quaternary derivatives were selectively accumulated in myocardial tissue. These results demonstrate that an iodophenyl ring can substitute for the naphthalene ring in propranolol and its quaternary salt without significant alteration of pharmacological properties. The radioiodinated quaternary derivatives may be useful pharmacological tools in experiments aimed at relating antiarrhythmic activity to myocardial uptake.

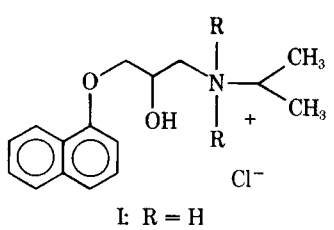
Keyphrases □ Antiarrhythmic agents—iodinated and radioiodinated analogs of propranolol and *N,N*-dimethylpropranolol, synthesis and evaluation of activity, tissue distribution of radioiodinated analogs, potential as myocardial imaging agents □ Propranolol—iodinated and radioiodinated analogs, synthesis and testing for β-adrenergic blocking and antiarrhythmic activity, tissue distribution of radioiodinated analogs, potential as myocardial imaging agents □ Radionuclide imaging—radioiodinated analogs of propranolol and *N,N*-dimethylpropranolol, tissue distribution, potential as myocardial imaging agents

The synthesis of a compound that selectively concentrates in the myocardium and that also can act as a carrier molecule for a γ-emitting nuclide has been a goal of this laboratory for several years (1–3). The approach has been to select a compound with known or suspected propensity for the target organ and then to modify the structure to allow incorporation of a γ-emitting nuclide while retaining the localizing properties of the parent compound.

BACKGROUND

One possible carrier molecule for myocardial localization is the β-adrenergic blocking agent propranolol (I). Its antiarrhythmic actions were demonstrated in a wide variety of experimentally induced arrhythmias (4, 5) as well as in clinically occurring arrhythmias (6, 7). Tissue distribution studies with [^{14}C]propranolol (8, 9) demonstrated its uptake by the heart, but not to the degree expected in view of the potent action of propranolol in blocking the cardiac effects of catecholamines (8). Instead, other tissues such as the lungs and brain contained higher levels of radioactivity (8, 9).

Previous studies in this laboratory showed that quaternization of propranolol produced a drug (II) that retained the antiarrhythmic activity but eliminated the β-adrenergic blocking property of propranolol (10). Subcutaneous administration of ^{14}C-labeled II to rats revealed a rapid and selective localization of radioactivity in the heart (23 times the blood



I: R = H
II: R = CH_3

0022-3549/80/0900-1010$01.00/0

concentration at 2 hr postinjection) with no marked concentration of radioactivity in the lungs and brain[1]. Similar results were obtained in dogs (11).

Since II and other quaternary antiarrhythmic drugs, such as bretylium, persist in the myocardium long after blood levels have declined, it is believed that the uptake and retention of these drugs by the myocardium account for their antiarrhythmic action (11, 12). In any event, it is clear that plasma levels of these drugs cannot be used to guide individualization of dosage. As a consequence, the purpose of the present study was to synthesize not only a myocardial imaging agent but also an antiarrhythmic drug whose pharmacokinetic properties could be monitored in intact animals by external counting equipment.

Most rectilinear scanners and cameras currently available are used in conjunction with γ-emitting nuclides with an energy of <500 kev. Iodine has two radionuclides, iodine 123 and iodine 131, that fulfill this requirement and that are widely used in nuclear medicine. Accordingly, the present research focused on the synthesis and biological evaluation of iodinated analogs of propranolol and *N,N*-dimethylpropranolol. Since completion of this study, two reports (13, 14) appeared concerning propranolol as a carrier for γ-emitting radionuclides for myocardial imaging.

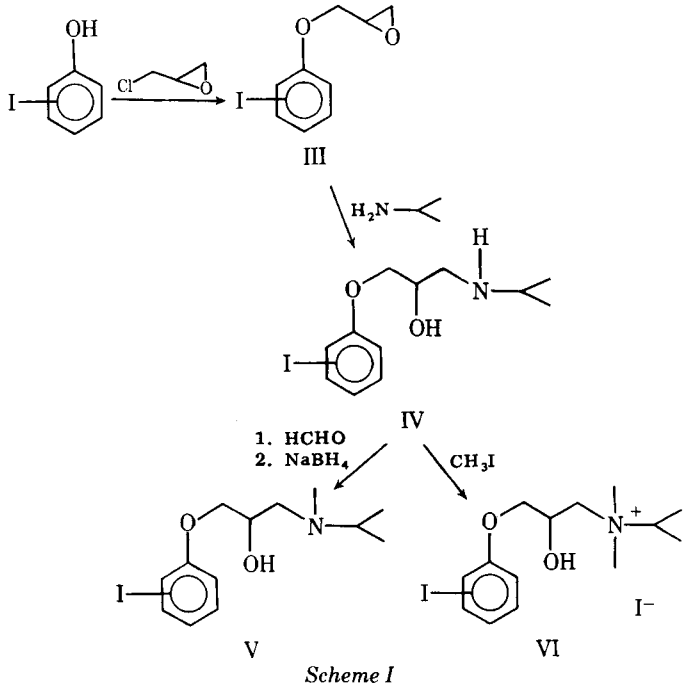
RESULTS AND DISCUSSION

Chemistry—The synthesis of the iodinated analogs of propranolol (*IV*) and their methylated congeners (V and VI) followed conventional paths as outlined in Scheme I (*a* = *ortho*, *b* = *meta*, and *c* = *para*). For synthesis of the corresponding radioiodinated derivatives, iodine 125 was selected for the initial studies because its longer half-life (60 days) and weak γ-radiation (35 kev) minimized handling and storage problems. In addition, a subsequent switch to iodine 123 or iodine 131 would represent no major change in methodology.

Radioactive iodine was introduced by the isotope-exchange method and involved refluxing an aqueous or ammonium hydroxide solution of IV or V to which the appropriate amount of sodium [^{125}I]iodide had been added. Higher yields of radioisotope incorporation usually were achieved when the exchange reactions were performed in ammonium hydroxide solution. The radioiodinated quaternary salts were obtained by treating the radioiodinated tertiary amine with methyl iodide in methanol at room temperature.

Pharmacology—The results of the pharmacological studies are summarized in Table I.

β-Adrenergic Receptor Blockade—Five of the synthesized compounds were tested for β-adrenergic receptor blocking activity against isoproterenol in isolated rabbit right atrial strips. The iodinated propranolol analogs (IV*a*–IV*c*) all showed β-adrenergic blocking activity. The order of activity was *ortho* > *meta* > *para*. The pA_2 value of 8.7 reported for propranolol by Blinks (15) was comparable to that observed for the *meta*-isomer (IV*b*). Accordingly, the *ortho*-isomer (IV*a*) was somewhat more active than propranolol as a β-adrenergic blocker. *N,N*-Dimethylpropranolol, as well as both of the iodinated analogs tested, lacked significant β-adrenergic receptor blocking activity.



Scheme I

Table I—Pharmacological Activity of Radioiodinated Analogs of Propranolol (I) and *N,N*-Dimethylpropranolol (II)

Compound	β-Adrenergic Receptor Blocking Activity, pA_2	Antiarrhythmic Activity	
		n	Dose, mg/kg
I	8.7[a]		6.1[b]
II	I(4.4)[c]		2–3[c]
IV*a*	10.0	5/5	4.8
IV*b*	8.5	5/5	5.7
IV*c*	6.6	3/3	10.0
VI*a*	I[d]	5/5	7.5
VI*b*	I	5/5	5.0
VI*c*	NT[e]	3/3	9.0

[a] Data from Ref. 15. [b] Data from Ref. 4. [c] Data from Ref. 10. [d] Inactive under conditions described under *Experimental*. [e] Not tested.

Antiarrhythmic Activity—All of the compounds tested were effective in converting the ouabain-induced ventricular tachycardia to normal sinus rhythm. Propranolol analogs IV*a*–IV*c* required doses of 4.8–10.0 mg/kg for conversion compared to 6.1 mg/kg required for propranolol (4). The iodinated analogs of *N,N*-dimethylpropranolol converted the ouabain-induced arrhythmias at doses of 5.0–9.0 mg/kg as compared to 2–3 mg/kg for the parent compound (10). In these preliminary studies, the *meta*-isomer (VI*b*) was the most potent antiarrhythmic agent among the iodinated analogs, followed in turn by the *ortho*-isomer (VI*a*) and the *para*-isomer (VI*c*).

Tissue Distribution—Based on the pharmacological results, the *meta*-iodinated analogs of propranolol and *N,N*-dimethylpropranolol were radioiodinated. The results of tissue distribution studies with these compounds are summarized in Table II. Administration of propranolol analog IV*b* resulted in no selective accumulation of radioactivity in myocardial tissue. On the other hand, there was marked uptake of activity in the lungs and liver. However, administration of the quaternary ammonium salt (VI*b*) resulted in selective concentration of radioactivity in rat myocardial tissue. Adrenal, lung, and thyroid tissues also showed high levels of uptake. The high levels of activity seen in the thyroid were believed to be due to *in vivo* deiodination of the compounds.

These results indicate that replacement of the naphthalene ring system in propranolol and *N,N*-dimethylpropranolol with an iodophenyl moiety does not markedly modify the pharmacological properties of the parent compounds. The iodinated analogs of propranolol all possessed β-adrenergic receptor blocking activity. However, the position of the iodine on the phenyl ring altered the potency of this activity. The β-blocking activities of propranolol and the *meta*-iodinated analog (IV*b*) were about equal and intermediate between the activities noted for the *ortho*-isomer (IV*a*) and the *para*-isomer (IV*c*).

This relationship also was observed for the antiarrhythmic activity of the three propranolol analogs. The doses needed to convert the ouabain-induced arrhythmia were about equal for propranolol (6.1 mg/kg) and the *meta*-iodinated analog, whereas lower and higher doses were required for the *ortho*- and *para*-isomers, respectively. Thus, the antiarrhythmic activity of these compounds paralleled their β-adrenergic receptor blocking activity. Since other drugs without β-adrenergic activity have antiarrhythmic properties, there may be no relationship between these two effects in the propanolol series; the antiarrhythmic action may be due to a direct membrane effect (5).

The absence of any significant localization of radioactivity in the heart following injection of radioiodinated IV*b* also paralleled the absence of marked localization of radioactivity in the myocardium reported after injection of ^{14}C-labeled propranolol (8). Similarly, other radioiodinated analogs of β-adrenergic antagonists have failed to demonstrate appreciable myocardial uptake and retention of radioactivity (13, 14).

Similar to the parent compound, the iodinated analogs of *N,N*-dimethylpropranolol (VI) were devoid of β-adrenergic receptor blocking activity. However, these analogs retained the antiarrhythmic activity of *N,N*-dimethylpropranolol, although larger doses of the analogs were

[1] A. Buswink, M. Johnson, F. Kniffen, and R. E. Counsell, unpublished data.

Table II—Tissue Distribution Profiles of Radioiodinated Analogs of Propranolol and *N,N*-Dimethylpropranolol after Subcutaneous Administration to Rats

Tissue	Percent of Administered Dose per Gram of Tissue[a]			
	IV*b*		VI*b*	
	2 hr	6 hr	2 hr	6 hr
Adrenal	0.362 ± 0.035	0.121 ± 0.016	1.680 ± 0.134	0.996 ± 0.224
Blood	0.140 ± 0.012	0.172 ± 0.009	0.422 ± 0.027	0.261 ± 0.030
Brain	0.318 ± 0.033	0.033 ± 0.010	0.037 ± 0.003	0.013 ± 0.002
Heart	0.166 ± 0.004	0.068 ± 0.012	—	—
Auricle	—	—	2.755 ± 0.320	0.604 ± 0.095
Ventricle	—	—	4.254 ± 0.201	1.013 ± 0.041
Kidney	0.621 ± 0.025	0.390 ± 0.065	0.854 ± 0.069	0.330 ± 0.015
Liver	1.211 ± 0.110	0.345 ± 0.051	0.776 ± 0.093	0.237 ± 0.016
Lung	1.048 ± 0.068	0.195 ± 0.061	1.190 ± 0.121	0.479 ± 0.020
Skeletal muscle	0.111 ± 0.005	0.044 ± 0.004	0.190 ± 0.041	0.114 ± 0.019
Thyroid	—	—	7.762 ± 1.452	9.016 ± 1.595

[a] Values represent the mean ± *SEM*; $n = 3$.

Table III—Experimental Data

Compound	Boiling Point (mm Hg) or Melting Point (Solvent)	Yield, %	Formula	Analysis, %		
					Calc.	Found
III*a*	118–123° (0.2)	44	$C_9H_9IO_2$	C	39.16	39.08
				H	3.28	3.13
III*b*	125° (0.3)	64	$C_9H_9IO_2$	C	39.16	39.00
				H	3.28	3.47
III*c*	120° (0.2)	64	$C_9H_9IO_2$	C	39.16	39.12
				H	3.28	3.12
IV*a*	97–98° (acetone)	60	$C_{12}H_{18}INO_2$	C	43.00	43.02
				H	5.41	5.13
IV*b*	89–90° (acetone)	60	$C_{12}H_{18}INO_2$	C	43.00	42.79
				H	5.41	5.36
IV*c*	112–113° (acetone)	83	$C_{12}H_{18}INO_2$	C	43.00	43.04
				H	5.41	5.44
V*a*	116–117° (methanol–ether)	68	$C_{13}H_{21}ClINO_2$	C	40.48	40.33
				H	5.49	5.51
V*b*	131–132° (methanol–ether)	70	$C_{13}H_{21}ClINO_2$	C	40.48	40.74
				H	5.49	5.60
V*c*	114–116° (methanol–ether)	70	$C_{13}H_{21}ClINO_2$	C	40.48	40.84
				H	5.49	5.72
VI*a*	153–155° (acetone)	82	$C_{14}H_{23}INO_2$	C	34.23	34.15
				H	4.72	4.54
VI*b*	165–166° (acetone)	81	$C_{14}H_{23}INO_2$	C	34.23	34.16
				H	4.72	4.65
VI*c*	215–216° (methanol–acetone)	78	$C_{14}H_{23}INO_2$	C	34.23	34.22
				H	4.72	4.68

required to convert the ventricular tachycardia to normal sinus rhythm. The tissue distribution profile of radioiodinated VI*b* was comparable to that of II. At 2 hr after administration to rats, the heart to lung ratio of VI*b* was 3.6 whereas the ratio for the parent drug was 2.7. Studies are in progress using VI*b* labeled with iodine 131 as a probe for relating the antiarrhythmic activity of these quaternary drugs to their uptake and retention in the myocardium.

EXPERIMENTAL[2]

General procedures are described for the synthesis of III–VI, and experimental data are furnished in Table III.

1-(*o*-Iodophenoxy)-2,3-epoxypropane (III*a*)—Epichlorohydrin (2.7 g, 30 mmoles) was added dropwise at room temperature to a stirred solution of *o*-iodophenol (4.4 g, 20 mmoles) in 5% NaOH (25 ml). The reaction mixture was allowed to stir overnight. The oily layer that resulted was extracted with chloroform. This extract was washed with water and dried over anhydrous sodium sulfate. Removal of the solvent gave an oily residue which, upon distillation *in vacuo*, afforded a colorless oil (2.5 g).

1-(*o*-Iodophenoxy)-3-isopropylamino-2-propanol (IV*a*)—A solution of I*a* (5.4 g, 20 mmoles) and isopropylamine (8 ml) in isopropanol (60 ml) was stirred overnight at room temperature. The solution was evaporated to dryness, redissolved in 10% HCl, and washed with ether. The aqueous layer was made basic with sodium hydroxide and extracted with ether. The extract was washed with water, dried over anhydrous sodium sulfate, and concentrated to yield a solid. Upon recrystallization from acetone, this solid afforded a colorless solid (4.0 g).

1-(*o*-Iodophenoxy)-3-methylisopropylamino-2-propanol (V*a*)—Formaldehyde solution (37%, 0.8 ml) was added with stirring to a solution of II*a* (0.67 g, 2 mmoles) in absolute methanol (10 ml), and the reaction mixture was stirred at room temperature for 2 hr. Sodium borohydride (1.2 g) was added with stirring at ice bath temperature. The mixture was allowed to come to room temperature and then was poured into ice–water (100 ml). The mixture was extracted with ether, and the ether layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness *in vacuo*. The residue was dissolved in methanol–hydrochloric acid and diluted with ether. Filtration resulted in the hydrochloride salt (0.48 g), which was recrystallized from methanol–ether.

***N,N*-Dimethyl-1-(*o*-iodophenoxy)-3-isopropylamino-2-propanol Iodide (VI*a*)**—A mixture of IV*a* (3.35 g, 10 mmoles), sodium carbonate (1.1 g), and methyl iodide (5 ml) in absolute methanol (50 ml) was refluxed with stirring for 1 day. Additional methyl iodide (5 ml) was added, and refluxing was continued for 2 days. The solvent was removed under reduced pressure, and the resulting oily residue was washed with water. The residue was triturated with ethyl acetate and allowed to stand overnight. The resulting solid was filtered, washed with ethyl acetate,

[2] Melting points were taken on a Fisher-Johns melting-point apparatus and are corrected. Elemental analyses were performed by Midwest Microlab, Indianapolis, Ind., or by Spang Microanalytical Laboratory, Ann Arbor, Mich. IR spectra (Perkin-Elmer 337 spectrophotometer, either neat or as potassium bromide pellets) and NMR spectra (Varian A-60 spectrometer, taken in deuterated chloroform or dimethyl sulfoxide) were consistent with the proposed structures. TLC analyses were run on silica gel plates (Eastman Kodak), and spots were detected under UV light. Radiochemical purity of radioiodinated compounds was confirmed by TLC analysis, and they were scanned with an Atomic Associates RCS-363 radiochromatogram scanner. The corresponding authentic nonradioactive compound was cochromatographed with the radioiodinated compounds. Total radioactivities were determined with a Picker nuclear isotope calibrator.

Table IV—Isotope-Exchange Conditions and Results

Parameter	Compound IV*b*	Compound V*b*
Starting material, mg	200	200
Sodium [^{125}I]iodide, mCi	5	6
Solvent (ml)	Water (4.5)	Ammonium hydroxide (2.0)
Temperature	100°	100°
Reaction time	48 hr	5 days
Extract solvent	Chloroform	Ether
Resulting compound, mg	200	160
Total activity, μCi	600	2500
Percent exchange	12.0	41.7

and dried. Recrystallization from acetone or methanol–acetone afforded a colorless solid (3.0 g).

Isotope Exchange—Radioactive iodine was incorporated by heating a solution of the secondary (IV) or tertiary (V) amine in the presence of sodium [^{125}I]iodide. Table IV lists the experimental data. The quaternary derivative (VI) was formed by refluxing a methanolic solution of V in the presence of excess methyl iodide for 2 hr. Radiochemical purity was ascertained by TLC analysis of the compounds on silica gel plates[3] developed in ether–methanol (5:1) for IV and V or chloroform–methanol (3:1) for VI.

Pharmacology—*β-Adrenergic Receptor Blocking Activity*—Chronotropic concentration–effect curves to isoproterenol in spontaneously beating rabbit atrial strips were obtained using the procedure described by Schuster *et al.* (10). Probit analysis (16) was used to compute the median effective dose (ED_{50}) for each concentration–effect curve, and these values then were used to calculate the pA_2 values for the compounds tested according to the method described by Schild (17). The pA_2 value is defined as the negative logarithm of the antagonist concentration that doubles the agonist concentration required to achieve a given effect.

Antiarrhythmic Activity—Arrhythmias were induced in anesthetized male mongrel dogs (9–13 kg) with ouabain according to the procedure described by Schuster *et al.* (10). After establishment of ventricular tachycardia, a saline solution of the test material was administered intravenously until conversion to normal sinus rhythm was attained for at least 30 min with failure of right vagal stimulation to expose automatic ectopic ventricular activity during vagal-induced sinoatrial nodal arrest.

Tissue Distribution—Radioiodinated IV*b* and VI*b* were given by subcutaneous injection to male Sprague–Dawley rats[4], 180–330 g. The doses of radioactivity ranged from 22 to 25 μCi/rat (1.8–8.0 mg/rat) in 0.25 ml of vehicle. The vehicle was saline for VI*b* and 0.1 *N* HCl for IV*b*. At 2 and 6 hr after administration of the compounds, groups of three rats were killed by exsanguination while under ether anesthesia. Adrenal, blood, brain, heart, kidney, liver, lung, muscle, and thyroid samples were removed. Tissue samples were placed in liquid scintillation vials and weighed. Duplicate samples were taken.

The contents of each vial were digested overnight in 0.3–0.5 ml of 2.5 *N* NaOH. The vials were heated at 40–60° for 5–10 min to complete digestion. Four drops of hydrogen peroxide (30% solution) were added to each cooled vial to decolorize the samples. Enough 0.9–1.1 *M* acetic acid to neutralize the base and 10 ml of scintillation cocktail[5] were added to each sample, and the vials were shaken on a vortex mixer. The samples were assayed for radioactivity in a liquid scintillation counter[6] for 5 min or until enough counts had accumulated to reduce the counting error to 1%. Maximum counting error for samples that counted the full 5 min was 7%. Efficiency for iodine 125 was 45%.

Results are expressed as the percentage of the administered dose per gram of tissue and were calculated from:

$$\frac{\text{sample dpm} \times 1000\ \text{mg/g}}{\text{sample weight (mg)} \times 2.22 \times 10^6\ \text{dpm/}\mu\text{Ci} \times \text{dose (}\mu\text{Ci)}} \times 100$$

REFERENCES

(1) R. E. Counsell, T. Yu, V. V. Ranade, and A. Buswink, *J. Med. Chem.*, **16**, 1038 (1973).

(2) R. E. Counsell, T. Yu, V. V. Ranade, A. A. Buswink, E. A. Carr, Jr., and M. Carroll, *J. Nucl. Med.*, **15**, 991 (1974).

(3) R. E. Counsell, V. V. Ranade, W. Kline, B. H. Hong, and A. A. Buswink, *J. Pharm. Sci.*, **65**, 285 (1976).

(4) B. R. Lucchesi, L. S. Whitsitt, and N. L. Brown, *Can. J. Physiol. Pharmacol.*, **44**, 543 (1966).

(5) B. R. Lucchesi, L. S. Whitsitt, and J. L. Stickney, *Ann. N.Y. Acad. Sci.*, **139**, 940 (1967).

(6) D. J. Rowlands, G. Howitt, and P. Markman, *Br. Med. J.*, **1**, 891 (1965).

(7) D. C. Harrison and J. R. Griffin, *Ann. N.Y. Acad. Sci.*, **139**, 997 (1967).

(8) D. Masuoka and E. Hansson, *Acta Pharmacol. Toxicol.*, **25**, 447 (1967).

(9) A. Hayes and R. G. Cooper, *J. Pharmacol. Exp. Ther.*, **176**, 302 (1971).

(10) D. P. Schuster, B. R. Lucchesi, N. L. Nobel, M. N. Mimnaugh, R. E. Counsell, and F. J. Kniffen, *ibid.*, **184**, 213 (1973).

(11) J. K. Gibson, N. J. Korn, R. E. Counsell, and B. R. Lucchesi, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **38**, 697 (1979).

(12) D. H. Namm, C. M. Wang, S. El-Sayad, F. C. Copp, and R. A. Maxwell, *J. Pharmacol. Exp. Ther.*, **173**, 344 (1975).

(13) A. Bobik, E. A. Woodcock, C. I. Johnston, and W. J. Funder, *J. Labelled Compd. Radiopharm.*, **12**, 605 (1977).

(14) V. W. Jiang, R. E. Gibson, W. J. Rzeszotarski, W. C. Eckelman, R. C. Reba, F. Vieras, and P. O. Alderson, *J. Nucl. Med.*, **19**, 918 (1978).

(15) J. R. Blinks, *Ann. N.Y. Acad. Sci.*, **135**, 673 (1967).

(16) A. Goldstein, "Biostatistics: An Introductory Text," Macmillan, New York, N.Y., 1964, pp. 153–174.

(17) H. O. Schild, *Br. J. Pharmacol.*, **2**, 189 (1957).

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[3] Eastman Kodak, Rochester, N.Y.
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