organisms necessary to kill 100% of the nonmedicated mice in 4 days. Standardized bacterial cultures of *Escherichia coli* and *Salmonella choleraesuis* were suspended in 5% hog gastric mucin, and *Pasteurella multocida* was suspended in brain–heart infusion broth. Treatment (10 mice per group) was initiated 0.5 h after infection. A second treatment was administered at 4.0 h and a third at 24 h. A 50% protective dose value (PD_{50}) was calculated by the probit method.[6]

Antimicrobial Susceptibility Tests. Minimum inhibitory concentrations were determined anaerobically as previously described.[7]

Chemistry. General. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded on a Varian T-60 spectrometer with Me_4Si as internal standard. IR spectra were determined with a Perkin-Elmer Model 21 spectrophotometer. UV spectra were recorded on a Cary Model 14 spectrophotometer. Mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer. All compounds gave spectral data consistent with the proposed structure. Microanalyses were performed by the Pfizer Analytical Department.

Methyl 3-[2-(Phenylsulfonyl)ethyl]quinoxaline-2-carboxylate 1,4-Dioxide (3). To a solution of methyl 3-oxo-5-(phenylthio)pentanoate[8] (5.10 g, 0.021 mol) in 115 mL of 2-propanol/chloroform (8:1) was added benzofurazan 1-oxide (2.90 g, 0.021 mol) and calcium hydroxide (700 mg, 9.40 mmol). The reaction mixture was heated at 60 °C for 2 h, washed with water, dried (magnesium sulfate), and evaporated to give methyl 3-[2-(phenylthio)ethyl]quinoxaline-2-carboxylate 1,4-dioxide (**5**) as an oily yellow solid. Without further purification,[9] the sulfide was dissolved in 500 mL of chloroform, and a solution of *m*-chloroperbenzoic acid (7.4 g, 0.043 mol) in 50 mL of chloroform was added dropwise. The resulting solution was stirred for 0.5 h at room temperature, washed with 10% sodium bicarbonate, and evaporated to give the sulfone as a yellow solid. The crude product was purified by trituration with ether/acetone (20:1) to afford 3.3 g (40%) of **3**, mp 180–183 °C. Anal. ($C_{18}H_{16}N_2O_6S$) C, H, N.

2-Methyl-3,4-dihydropyrido[3,4-*b*]quinoxalin-1(2*H*)-one 5,10-Dioxide (1b). A solution of **3**[10] (1.0 g, 2.58 mmol) in 400 mL of acetonitrile was perfused with anhydrous methylamine gas for 20 min at room temperature. The reaction mixture was stirred for an additional 2 h and then evaporated to dryness.[11] The crude product was chromatographed (silica gel, 10:1 chloroform/MeOH as eluent) to give 540 mg (85%) of **1b**, mp 155–156 °C. The NMR spectrum ($CDCl_3$) had characteristic absorption at δ 3.15 (s, 3 H, N-CH_3), 3.60 (m, 4 H, CH_2CH_2), 7.90 (m, 2 H, H-8 and H-7), 8.60 (m, 2 H, H-6 and H-9). The infrared spectrum (KBr) had a strong lactam carbonyl band at 1666 cm^{-1}. Anal. ($C_{18}H_{16}N_2O_6S$) C, H, N.

Methyl 3-[2-(Diethylamino)ethyl]quinoxaline-2-carboxylate 1,4-Dioxide (6). Compound **6** was prepared by treating sulfone **3** with excess diethylamine in acetonitrile under conditions identical with those for the synthesis of the pyrido-[3,4-*b*]quinoxalines. The crude product was purified by chromatography (silica gel, 5% methanol/chloroform as eluent) to give **6** (40%) as a light-sensitive yellow solid, mp 100–103 °C. Anal. ($C_{16}H_{21}N_3O_4 \cdot 0.5H_2O$) C, H, N.

Acknowledgment. We thank Larry Pisko and Jan Watrous for technical assistance.

(6) H. E. Batson, "An Introduction to Statistics in the Medical Sciences", Burgess Publishing Co., Minneapolis, MN, 1957, pp 64–69.
(7) John P. Dirlam, Leonard J. Czuba, Beryl W. Dominy, Richard B. James, Richard M. Pezzullo, Joseph E. Presslitz, and Wendell W. Windisch, *J. Med. Chem.*, **22**, 1118 (1979).
(8) B. M. Trost and R. A. Fung, *J. Org. Chem.*, **39**, 2648 (1974).
(9) The crude sulfide **5** could be purified by recrystallization from methanol, mp 96–98 °C. Anal. ($C_{18}H_{16}N_2O_6S$) C, H, N.
(10) The pyrido[3,4-*b*]quinoxalines could also be obtained from sulfide **5**. However, the cyclization proceeds more rapidly and in higher yield from the sulfone (**3**).
(11) The nongaseous amines employed in the synthesis of **1d–h** were used in a tenfold molar excess. Reaction times in these cases were 24–36 h.

Synthesis and Tissue Distribution Study of Iodine-Labeled Benzyl- and Xylylamines

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Four iodine-125 labeled mono- and diamines were prepared and evaluated as potential brain-imaging agents. The diamines are analogues of the previously reported selenium-75 labeled diamines, which show high brain uptake and retention. All of the radioiodinated amines display high initial brain uptake in rats after intravenous injection (1.7–2.4% dose/organ). The xylylenediamines show prolonged brain retention ($t_{1/2} \approx 18$ h), which is desirable for brain imaging. In contrast, the benzylamine is rapidly cleared from brain tissue ($t_{1/2} \approx 15$ min).

Conventional single-photon radiopharmaceuticals currently available for clinical brain scanning are chelation compexes of ^{99m}Tc. These water-soluble complexes are excluded from normal brain tissue by the presence of an intact blood–brain barrier. Measurement of the state of the blood–brain barrier is useful in some cases. However, present emphasis in nuclear medicine is directed at the regional determination of cerebral blood flow, metabolism, and pH. The development of new lipid-soluble single-photon radiopharmaceuticals which are able to penetrate the blood–brain barrier to reflect regional blood flow would have a significant impact on the management of neurological diseases.[1]

Recently, we reported the synthesis and brain localization of a series of ^{75}Se-labeled diamines **1**.[2,3]

$$(R)_2N(CH_2)_nSe(CH_2)_nN(R)_2$$
1

The high energy γ emission of ^{75}Se (120 days, 465 keV) and the relatively high patient radiation dose limits the

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(1) T. C. Hill, *J. Nucl. Med.*, **21**, 1197 (1980).
(2) H. F. Kung and M. Blau, *J. Nucl. Med.*, **21**, 147 (1980).
(3) H. F. Kung and M. Blau, *J. Med. Chem.*, **23**, 1127 (1980).

Table I. Biodistribution in Selected Organs of Compounds 2-5

organ	% dose/organ (mean of 3 rats ± SD)			
	2	3	4	5
		2 min		
blood	3.52 ± 0.18	4.11 ± 0.38	6.42 ± 0.82	7.01 ± 0.55
heart	2.76 ± 0.49	3.19 ± 0.44	2.18 ± 0.10	0.59 ± 0.05
lungs (2)	22.63 ± 1.9	26.54 ± 5.15	31.98 ± 5.67	2.90 ± 0.27
kidneys (2)	7.69 ± 2.29	7.33 ± 1.86	6.93 ± 1.41	10.12 ± 0.78
liver	9.52 ± 1.84	12.50 ± 0.24	10.22 ± 1.90	11.81 ± 1.29
thyroid	0.28 ± 0.01	0.22 ± 0.09	0.18 ± 0.04	0.11 ± 0.027
brain	2.40 ± 0.48	1.70 ± 0.18	0.62 ± 0.10	2.42 ± 0.16
		1 h		
blood	0.83 ± 0.04	1.60 ± 0.13	1.76 ± 0.13	1.35 ± 0.06
heart	0.44 ± 0.06	0.51 ± 0.29	1.99 ± 0.29	0.06 ± 0.01
lungs (2)	4.36 ± 0.25	6.65 ± 1.46	13.02 ± 1.66	0.19 ± 0.02
kidneys (2)	6.19 ± 0.15	7.75 ± 1.16	6.71 ± 0.55	1.03 ± 0.21
liver	18.31 ± 1.54	13.51 ± 1.19	8.38 ± 0.93	1.92 ± 0.05
thyroid	0.11 ± 0.02	0.15 ± 0.02	0.27 ± 0.08	0.01 ± 0.00
brain	2.36 ± 0.20	1.47 ± 0.10	0.64 ± 0.05	0.07 ± 0.00
		6 h		
blood	0.42 ± 0.07	0.77 ± 0.11	1.33 ± 0.04[a]	0.35 ± 0.06
heart	0.19 ± 0.04	0.18 ± 0.03	0.83 ± 0.05[a]	0.014 ± 0.00
lungs (2)	1.96 ± 0.47	1.75 ± 0.34	8.71 ± 2.18[a]	0.04 ± 0.02
kidney (2)	2.98 ± 0.27	1.97 ± 0.35	3.40 ± 0.25[a]	0.34 ± 0.14
liver	7.81 ± 0.88	9.20 ± 0.78	5.17 ± 0.63[a]	0.45 ± 0.09
thyroid	0.14 ± 0.02	0.11 ± 0.01	0.45 ± 0.06[a]	0.035 ± 0.02
brain	1.51 ± 0.19	0.70 ± 0.07	0.59 ± 0.04[a]	0.022 ± 0.01

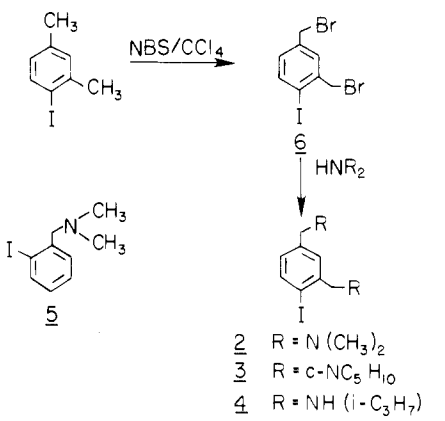
[a] Four-hour data.

use of compounds like 1 in clinical brain-imaging studies.[4] A more useful imaging agent might be realized by substituting the ^{75}Se nuclide by ^{99m}Tc or ^{123}I. The short-lived isotope ^{123}I (13.2 h, 159 keV) emits γ rays which are superior for external imaging purposes.

A number of recent reports have descrribed the brain accumulation of some iodine-labeled, centrally acting amines. The synthesis and biodistribution of 4-iodo-2,3-dimethoxyphenylisopropylamine (labeled with ^{131}I) have been reported.[5] This compound has been suggested for use in brain and lung imaging.[6] Another phenethylamine, *N*-isopropyl-*p*-[^{123}I]iodoamphetamine, has displayed high brain localization and is undergoing study as a potential in vivo diagnostic radiopharmaceutical.[7,8] The high brain uptake of 2-iodo-*N,N,N',N'*-tetramethylxylylenediamine evaluated as a prostate and pancreas localizing agent has been noted by Counsell.[9]

In connection with our efforts to develop a practical brain imaging agent for use with single-photon tomography devices, we have synthesized and evaluated four ^{125}I tertiary amines. The 4-iodoxylylenediamines (**2–4**) are analogues of the ^{75}Se-labeled diamines (**1**) in which the selenium dialkyl chain has been replaced with an aromatic ring to accomodate the iodine label. Since aromatic iodides are chemically more stable than their aliphatic counterparts, it was anticipated that this feature would minimize in vivo deiodination.[10] Compound **5** is a benzylamine labeled in the ortho position.

Scheme I



Chemistry. The synthesis of the xylylenediamines **2–4** is shown in Scheme I. Dibromination of 4-iodoxylene with *N*-bromosuccinimide in carbon tetrachloride gave an acceptable yield of α,α'-dibromo-4-iodo-*m*-xylene (**6**).[11] The dibromo compound **6** was reacted with the appropriate amine to give the 4-iodo-*m*-xylenediamines **2–4** in good yields. The monoamine **5** was prepared analogously from 2-iodobenzyl chloride.

The compounds were radioiodinated by exchange reaction in water (18–24 h; sealed tube, 200 °C) with no-carrier added $Na^{125}I$ (Amersham, 17 Ci/mg). The radiochemical yield varied from 30 to 60%, and the specific activity of the products were 10–100 μCi/mg. Radiochemical purity was determined to be better than 95% for all exchanged compounds by TLC in two systems.

Results and Discussion

The organ distribution in rats for compounds **2–5** is shown in Table I. The radioactivity, expressed as percent

(4) R. Wicks, H. F. Kung, R. E. Ackerhalt, J. J. Steinbach, and M. Blau, Proceedings of 3rd International Radiopharmaceutical Dosimetry Symposium, E. E. Watson, A. T. Schlafke-Stelson, J. L. Coffey, et al., Eds., Bureau of Radiological Health, FDA 81-8166, 1981, Washington, DC, pp 454–463.
(5) V. Braun, A. T. Shulgin, G. Braun, and T. Sargent, *J. Med. Chem.*, **20**, 1543 (1977).
(6) T. Sargent, T. F. Budinger, G. Braun, A. T. Shulgin, and V. Braun, *J. Nucl. Med.*, **19**, 71 (1978).
(7) H. S. Winchell, B. M. Baldwin, and T. H. Lin, *J. Nucl. Med.*, **21**, 940 (1980).
(8) H. S. Winchell, W. D. Horst, L. Braun, W. H. Oldendorf, R. Hattner, and H. Parker, *J. Nucl. Med.*, **21**, 947 (1980).
(9) C. C. Huang, N. Korn, and R. E. Counsell, *J. Med. Chem.*, **22**, 449 (1979).
(10) R. E. Counsell and R. D. Ice, in "Drug Design", Vol. VI, E. J. Ariens, Ed., Academic Press, New York, 1975, Chapter 6.
(11) A. Funke and C. O. Engeler, *Bull. Soc. Chim. Fr.*, 340 (1950).

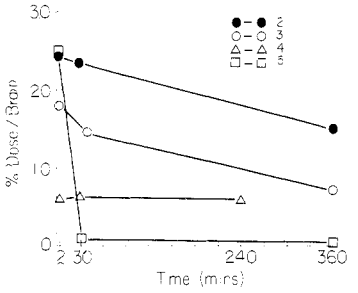


Figure 1. Brain uptake of compounds **2–5** at different times after intravenous injection.

Table II. Effect of Carrier Level on Brain Uptake of 2 in Rats[a]

carrier level, mg/kg	40	4	0.4	0.04
% dose/organ ± SD[b] (mean of 3 points)	2.43 ± 0.06	2.09 ± 0.16	3.03 ± 0.37	2.67 ± 0.14

[a] One-hour after iv injection.

dose per organ, was measured at varous times after iv injection.

At 2 min after injection, the blood concentration is already at a low level and continues to drop with time. This indicates that the compounds are rapidly extracted from blood and gain access to intracellular space. Compounds **2–4** display extraordinary high lung uptake at the early time period, followed by a relatively fast clearance. This phenomenon of amine concentration in lungs has been observed by other workers.[6,12] The lung uptake of the benzylamine **5** is lower by an order of magnitude at 2 min after injection.

The liver and kidney uptakes for compounds **2–4** are initially high and remain high for 1 h. In contrast, compound **5** shows higher initial liver and kidney activity, but this rapidly decreases with time. The other excised organs show no remarkable uptake and retention patterns worth noting; however, there is the low thyroid uptake over time which indicates that these compounds are relatively resistant to in vivo deiodination.[13]

Figure 1 is a plot of brain uptake as a function of time after injection. The uptake of monoamine **5** was 2.4% dose/organ at 2 min postinjection. This high initial uptake was followed by a rapid clearance phase with a $t_{1/2}$ of about 15 min.[14] The diamines **2–4** displayed contrasting brain accumulation curves. Compound **2** has an initial uptake of 2.4% dose/organ but also showed a high degree of retention in brain tissue. The clearance half-time for compound **2** was 18 h. Compounds **3** and **4** had similar brain retention but slightly slower initial uptake. The brain to blood concentration ratio of compound **2** was 31 at 1 h after injection.

Table II shows the results of a series of experiments that test the effect of increasing carrier levels on brain uptake and retention. For compound **2**, increasing the total dose to 40 mg/kg results in no decrease in brain uptake. A 40 mg/kg dose is equivalent to a 0.3 mM concentration per whole rat brain. Since this high concentration does not effect initial brain uptake or retention, it seems highly unlikely that a specific transport system or specific binding site is involved in brain localization. However, no definitive experiments were carried out to determine the effect of nonspecific intracellular binding and/or of the pH gradient that exists between the blood and brain on retention.[2]

The brain uptake and retention of **2–4** is similar to the localization reported for the dipiperidino analogue of **1** and for 2-iodo-*N,N,N',N'*-tetramethyl-*p*-xylylenediamine.[3,9] The localization of these compounds is characterized by high brain extraction from blood, followed by slow clearance. The brain uptake of radiopharmaceuticals is a complex function of local perfusion rates, transport into cells, intracellular metabolism, and clearance from cells and from brain. The contributions of each of these processes to the localization and cerebral distribution of these agents remain to be elucidated in normal brain and various disease states.

Two of the compounds described in this report exhibit in vivo distribution patterns that suggest their usefulness as brain-imaging agents for single-photon emission tomography studies. Compounds **2** an **3** have high, rapid initial brain uptake and a stable intracerebral distribution pattern.[15] The latter is an extremely important factor, since the imaging procedure may require up to 1 h. Also, the compounds could be labeled with ^{123}I by substituting ^{123}I for ^{125}I in the radiolabeling procedure. ^{123}I has ideal physical properties in terms of imaging with single-photon emission computed tomography systems (γ ray energy = 159 keV). Also, because of its short half-life (13.2 h) and decay mode (electron capture), it delivers a low patient radiation dose.

While **2** and **3** show desirable brain localization, they are not conveniently nor ecomonically prepared. The exchange labeling with ^{123}I would require heating the reaction mixture for a period of time equal to about 2 half-lives. The expense of ^{123}I would prohibit routine synthesis. In addition, the workup involves extraction with an organic solvent and would be inconvenient to carry out in a clinical setting. It would be desirable to have an agent that can be labeled by a procedure that could be adapted to kit form.[16] Rapid and quantitative aqueous exchange reactions are ideally suited to this type of preparation, since it would involve a minimum of chemical manipulations. Further work is directed at designing compounds that will have in vivo properties similar to that of **2** and **3** and are also easily and rapidly radioiodinated by exchange reaction with ^{123}I.

Experimental Section

The melting points are reported uncorrected and were determined on a Nalge hot stage apparatus. Elemental analyses were carried out by Instranol Laboratories, Rensselaer, NY, and were within ±0.4% of theoretical values. Proton NMR spectra (Varian T-60A) and IR spectra (Perkin-Elmer 214) for KBr wafers were recorded for all compounds and were consistent with the given structures.

4-Iodo-*N,N,N',N'*-tetramethyl-*m*-xylylenediamine (2). To a solution of **6** (1.95 g, 5 mmol) in 60 mL of benzene was added dropwise an excess of anhydrous dimethylamine (4.5 mL) in 15 mL of benzene. The reaction was sealed and stirred at room temperature overnight. Water (75 mL) was added, and the benzene layer was separated and dried over Na_2SO_4. Evaporation of the solvent gave crude oil, which was dissolved in ethanol. Dry HCl gas was bubbled through the ethanol solution. The ethanol

(12) S. H. Vincent, M. B. Shambhu, and G. A. Digenis, *J. Med. Chem.*, **23**, 77 (1980).
(13) H. F. Kung, K. M. Tramposch, unpublished results; under identical experimental conditions, injection of equivalent amounts of $Na^{125}I$ results in a thyroid uptake of 0.88% dose/organ after 1 h.
(14) Graphically estimated by interpolation of plot in Figure 1.
(15) H. F. Kung, K. M. Tramposch, and M. Blau, unpublished results; autoradiographs of rat brain sections at 2 min and 1 h after iv injection of **2–4** are identically heterogeneous. This suggests that the compounds are not redistributed through the brain after initial uptake.
(16) G. H. Hinkle, G. P. Basmadjian, A. S. Kirshner, and R. D. Ice, *J. Pharm. Sci.*, **70**, 3.2 (1981).

was evaporated, leaving a white solid. Recrystallization from acetone–MeOH gave an HCl salt of **2**: yield 1.58 g (81%); mp 217–221 °C. Anal. ($C_{12}H_{19}N_2I$·2HCl) C, H, N.

4-Iodo-α,α′-dipiperidino-*m*-xylene (3). To a solution of **6** (2.65 g, 6.8 mmol) in 60 mL of benzene was added piperidine (2.38 g, 28 mmol) in 40 mL of benzene. The mixture was stirred at room temperature overnight. The product was isolated as in **2**. Recrystallization from benzene–MeOH gave an HCl salt of **3**: yield 1.91 g (59%); mp 213–216 °C. Anal. ($C_{18}H_{27}N_2I$·2HCl) C, H, N.

4-Iodo-*N*,*N*′-isopropyl-*m*-xylylenediamine (4). To a solution of **6** (1.00 g, 2,56 mmol) in 30 mL of benzene was added isopropylamine (0.62 g, 10.5 mmol) in 25 mL of benzene. The reaction was stirred at room temperature overnight. Workup as in the preparation of **2**. Recrystallization from acetone–hexane gave an HCl salt of **4**: yield 0.68 g (63%); mp 202–205 °C. Anal. ($C_{14}H_{21}N_2I$·2HCl·0.5H_2O) C, H, N.

2-Iodo-*N*,*N*-dimethylbenzylamine (5). To a solution of 2-iodobenzyl chloride (2.05 g, 8.1 mmol) was added 3.5 mL of anhydrous dimethylamine. The reaction mixture was sealed and stirred at room temperature overnight. The salt that formed was filtered, and the filtrate was washed twice with saturated NaCl. The organic layer was dried over Na_2SO_4 and evaporated to give a brown oil. The oil was dissolved in hexane–ether and passed through a short pad of silica gel. The solvent was evaporated, and the clear oil was transformed into its dihydrochloride salt in the usual way. Crystallization from acetone–MeOH gave an HCl salt of **5**: yield 0.95 g (39%; mp 195–197 °C. Anal. ($C_9H_{12}NI$·HCl) C, H, N.

α,α′-Dibromo-4-iodo-*m*-xylene (6). 4-Iodo-*m*-xylene (8.7 g, 37.5 mmol) and *N*-bromosuccinimide (15 g, 84.3 mmol) were suspended in 100 mL of CCl_4. Benzoyl peroxide (0.3 g) was added in portions, and the reaction mixture was heated at gentle reflux for 18 h. The succinimide was filtered off, and the CCl_4 filtrate was evaporated in vacuo to leave a brown oil. The oil was chromatographed on silica gel and eluted with petroleum ether (bp 30–60 °C) to give 3.51 g (24%) of dibromo compound **6**. A small sample was crystallized from hexane, mp 102–105 °C. Anal. ($C_8H_7IBr_2$) C, H.

General Radiolabeling Procedure. The ^{125}I-labeled compounds were prepared by exchange reaction with $Na^{125}I$ (Amersham, 17 Ci/mg). To 5–10 mg of the amine salt (**2–5**) in 0.5 mL of water was added 200–500 μCi of $Na^{125}I$ (no carrier added in NaOH, pH 7–11). The mixture was transferred to a glass tube, sealed, and placed in a water-filled bomb. The bomb was heated at 200 °C for 18–24 h. The mixture was allowed to cool and was made basic by the addition of 0.1 N NaOH. The aqueous phase was extracted twice with 1.5-mL portions of $CHCl_3$. The organics were combined, dried over Na_2SO_4, and evaporated under a stream of nitrogen. The residue was dissolved in acidic normal saline (0.6 N HCl) to give a solution of the radioiodinated amine. The purity was determined to be greater than 95% by TLC in two systems: (1) Gelman ITLC eluted with $CHCl_3$–hexane–diethylamine (4:6:0.1) and (2) silica gel 60 F-254 (Merck), $CHCl_3$–EtOH–NH_4OH (8.5:1:0.5). In all cases, the radioactivity was coincident with the R_f values of the authentic cold compound run side by side. The isolated radiochemical yields on typical runs for the compound were **2**, 32%; **3**, 30%; **4**, 39%; **5**, 61%.

Tissue Distribution Studies. Sprague–Dawley male rats (220–300 g) under light ether anesthesia were injected intravenously with 0.2 mL of a saline solution containing 0.5–2.0 μCi of test compound. At different time periods after injection the animals were put under ether anesthesia and killed by cardiectomy. The organs of interest were excised, weighed, and counted in a Beckman automatic γ counter (Model 4000).

The percent dose per organ was determined by comparison of tissue radioactivity levels to suitably diluted aliquots of the injected dose. The approximate percent dose per gram of wet tissue or organ can be calculated by dividing the percent dose per organ by the mean organ weight (mean weights: heart, 0.85 g; brain, 1.65 g; blood, 18 g; liver, 9 g; kidneys, 1.9 g; lungs, 1.6 g). The brain to blood concentration ratios were calculated from the percent dose per gram of wet tissue.

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Hydrogen Bonding and Anesthetic Potency†

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Hydrogen bond strengths in terms of the proton chemical shifts of five potent inhalation anesthetics containing acidic hydrogen were measured in cyclohexane and in methanol using the proton magnetic resonance spectroscopic method. The purpose of this study is to quantitatively compare the relative polar character of potent anesthetics. The hydrogen bond shift (Δppm) of each anesthetic is the difference in the chemical shifts of the infinitely diluted unassociated anesthetic in cyclohexane and that of the infinitely diluted hydrogen bonded anesthetic in methanol. It was found that the hydrogen bond shifts (in Δppm) are as follows: methoxyflurane, 0.72; chloroform, 0.75; halothane, 1.06; isoflurane, 1.38; enflurane, 1.44. There is a good correlation between the hydrogen bond shifts and the clinical potencies (minimum alveolar concentration in man). The conclusion from this study is that the acidic halogenated inhalation anesthetics are more potent if they form weaker hydrogen bonds.

In tabulating and comparing the thermodynamic activities (as suggested by Ferguson), Suckling,[1] one of the halothane inventors, found that the presence of acidic hydrogen on the halocarbons tends to increase anesthetic potency. This discovery was later confirmed by Poznak and Artusio, Jr.,[2] when they tested the halocarbons and halo ethers synthesized by Larsen.[3] Terrell et al.,[4] in reporting their synthesis of 36 halogenated methyl ethyl ethers as anesthetic agents, also confirmed that effective anesthetics, in general, contain at least one acidic hydrogen. Davies et al.[5] examined 45 halocarbons containing from 1 to 4 carbon atoms and concluded that anesthetics are more potent if they contain more acidic hydrogens. Two other groups of investigators[6,7] also found that a polar

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(1) C. W. Suckling, *Br. J. Anaesth.*, **29**, 466 (1957).
(2) A. van Poznak and J. F. Artusio, Jr., *Toxicol. Appl. Pharmacol.*, **2**, 363 (1960).
(3) E. R. Larsen, *Fluorine Chem. Rev.*, **3**, 1 (1969).
(4) R. C. Terrell, L. Speers, A. J. Szur, J. Treadwell, and T. R. Ucciardi, *J. Med. Chem.*, 14, 517 (1971).
(5) R. H. Davies, R. D. Bagnall, and W. G. M. Jones, *Int. J. Quantum. Chem., Quantum Biol. Symp.*, 1, 201 (1974).
(6) C. Hansch, A. Vittoria, C. Silipo, and P. Y. C. Jow, *J. Med. Chem.*, 18, 546 (1975).
(7) T. DiPaolo, L. B. Kier, and L. H. Hall, *Mol. Pharmacol.*, 13, 31 (1977).

0022-2623/82/1825-0873$01.25/0