mm in diameter and 30 cm in length fixed horizontally 15 cm above the platform. Male CD_1 mice were hung from the rod by their forepaws. Normal animals climb on the rod within 4 s, hanging by all four paws, whereas animals with impairment of muscular tone fall from the rod or continue to hang by the forepaws only. At the dose of 3 mg/kg ip, DZ caused muscle relaxation in nearly all the animals 30 min after treatment. Test compounds dispersed in 0.5% methocel at a volume of 10 mL/kg were administered at 10 and 20 mg/kg ip 15 min after DZ to 10 mice at each dose. Fifteen minutes later, the mice were suspended by means of their forepaws to the rod and the percentage of them falling from it was recorded.

Rotarod Test. The effect on motor coordination was determined by the method of Dunham and Miya[24] in male Wistar rats. The rod was 6 cm in diameter and 56 cm in length, fixed horizontally 15 cm above the support and was rotated at a speed of 6 rpm. The control groups treated with the solvent alone remained on the rod for at least 5 min. Ten animals per dose were placed on the rod 30 and 60 min after treatment with test compounds dispersed in 0.5% methocel at a volume of 4 mL/kg. The animals that fell off the rod during the 5-min session were recorded.

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Acute Toxicity. Test compounds were dispersed in 0.5% methocel at a volume of 10 mL/kg and administered ip to CD_1 male mice arranged in groups of three for each dose, i.e. 600–300–100 mg/kg. The animals were observed for 1–5 days, and LD_{50} values were graphically calculated.

Acknowledgment. We thank E. Gerli for his expert technical assistance in the synthetic work, A. Depaoli for the NMR spectra, and N. Corsico, M. G. Quaglia, F. Pizzocheri, and G. Colombo for the determinations of the biological activities.

Registry No. **1a**, 73351-33-4; **1b**, 96825-70-6; **1c**, 96825-71-7; **1d**, 73351-34-5; **2a**, 73351-35-6; **2b**, 96825-72-8; **2c**, 96825-73-9; **2d**, 73351-36-7; **3a**, 96825-74-0; **3b**, 96825-75-1; **3c**, 96825-76-2; **3d**, 96825-77-3; **4a**, 96825-78-4; **4b**, 96825-79-5; **4c**, 96825-80-8; **4d**, 96825-81-9; **5a**, 96825-82-0; **5b**, 96825-83-1; **5c**, 96825-84-2; **5d**, 96826-01-6; **5e**, 96825-85-3; **5f**, 96825-86-4; **5g**, 96825-87-5; **5h**, 96825-88-6; **5i**, 96825-89-7; **5j**, 96825-90-0; **5k**, 96825-91-1; **5l**, 96825-92-2; **5m**, 96825-93-3; **5n**, 96825-94-4; **5o**, 96825-95-5; **5p**, 96825-96-6; **5q**, 96825-97-7; **6a**, 96825-98-8; **6b**, 96825-99-9; **7**, 96826-00-5; dimethylamine, 124-40-3; *N*-methylethylamine, 624-78-2; *N*-methyl(2-hydroxypropyl)amine, 16667-45-1; pyrrolidine, 123-75-1; morpholine, 110-91-8; azetidine, 503-29-7; piperidine, 110-89-4.

Synthesis of High Specific Activity [^{75}Br]- and [^{77}Br]Bromperidol and Tissue Distribution Studies in the Rat

Stephen M. Moerlein* and Gerhard L. Stöcklin

Institut für Chemie 1 (Nuklearchemie) der Kernforschungsanlage Jülich GmbH, D-5170 Jülich, Federal Republic of Germany.
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A rapid synthesis of [^{75}Br]- and [^{77}Br]bromperidol with specific activity exceeding 10 000 Ci/mmol is described in which a trimethylstannylated analogue of bromperidol is used as a substrate for regiospecific no-carrier-added radiobromination. 4-[4-[4-(Trimethylstannyl)phenyl]-4-hydroxypiperidino]-4′-fluorobutyrophenone was synthesized by the reaction of (trimethylstannyl)sodium with haloperidol and purified by preparative HPLC. Subsequent radiobromination with no-carrier-added $^{75}Br^-$ or $^{77}Br^-$ and in situ oxidation using H_2O_2/CH_3COOH gave a corrected radiochemical yield of 35% with a 30-min preparation time. Tissue distribution studies in the rat show a rapid and prolonged uptake into the brain, liver, and kidneys and consistently low blood concentrations that differ quantitatively from previous studies using relatively low specific activity bromperidol. Potential clinical applications for this high specific activity radiobrominated neuroleptic are discussed.

Pharmacokinetic data for neuroleptics of the butyrophenone class are scarce.[1-3] The conventional approach to assessing butyrophenone pharmacokinetic parameters in man is to measure serum concentrations of the neuroleptic using gas–liquid chromatographic[4-8] or high-performance liquid chromatographic[9,10] methods, but these techniques unfortunately have low sensitivity (0.5–1.0 and 2–3 ng/mL, respectively). While radioimmunoassay has been suggested as an alternative analytical method,[11,12] it has an even lower sensitivity of 3–10 ng/mL[13] and has shown poor cross-correlation.[14]

The wide variation in clinical responses reported for neuroleptic serum concentrations[15] may indicate the error in assuming that the brain concentration and pharmacological activity of the butyrophenones are proportional to their blood concentration. In early reports concerning butyrophenone neuroleptics,[16] it was suggested that the

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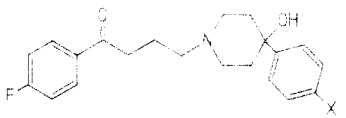
pharmacological effect of neuroleptics is better correlated with drug levels in the brain rather than drug concentrations in the blood. To further evaluate this point, a sensitive assay method is needed for the measurement of drug levels in the brain as well as in the serum. Traditionally, such information has been obtained experimentally by using a tracer technique, in which the drug is labeled with a β^--emitting radionuclide such as ^3H or ^{14}C and administered to laboratory animals, which are subsequently sacrificed and dissected to determine the organ distribution. The invasive nature of this method precludes its use in man, however, and the extrapolation to man of animal results is often invalid.

The direct measure of organ distribution and pharmacokinetics in primates (including man) can be achieved noninvasively by the use of external scintigraphy and butyrophenone neuroleptics radiolabeled with appropriate β^+- or γ-emitting radionuclides. Positron-emission computerized tomography (PET) and single-photon-emission computerized tomography (SPECT) allow for the spatial reconstruction of the radioactivity distribution in a three-dimensional manner,[17] so that organ pharmacokinetics can be measured as a function of time by selecting an appropriate region of interest within the detected field of view. PET allows the determination of local concentration (e.g., percent of administered dose per cubic centimeter), while relative organ radioactivity concentrations or organ elimination half-times can be measured accurately by using SPECT or conventional nuclear medicine γ scintigraphy. These noninvasive methods have previously been used to investigate the pharmacokinetics of various drugs with PET,[18,19] as well as conventional γ scintigraphy.[20-22]

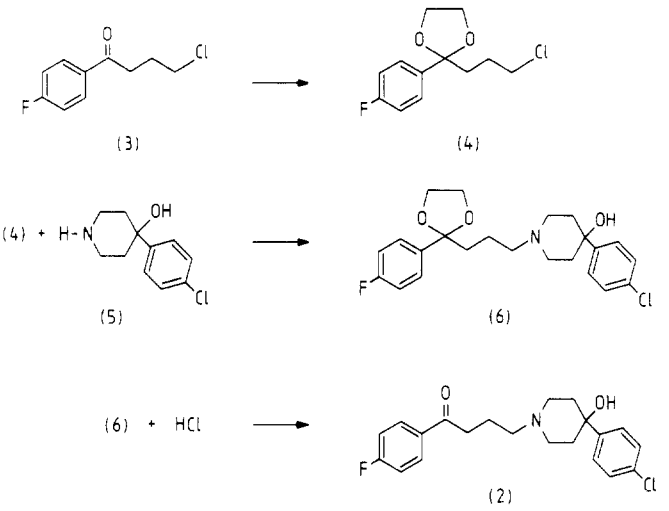
Bromperidol, 4-[4-(4-bromophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone (**1**), is a potent bu-



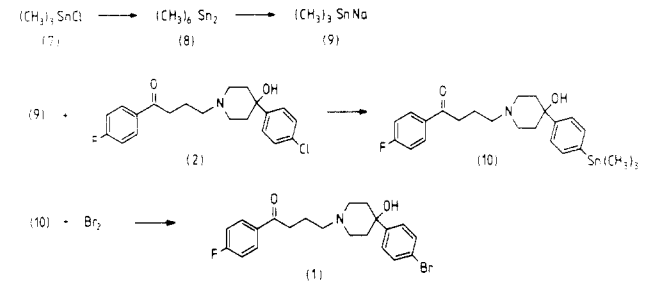
(1) X = Br
(2) X = Cl

tyrophenone neuroleptic similar to haloperidol (**2**) in structure and pharmacological effect[23,24] and has found clinical use in humans.[25] Because this neuroleptic contains bromine in its molecular structure, it can be labeled with the positron-emitter ^{75}Br ($T_{1/2}$ = 1.6 h) for quantitative pharmacokinetic studies using PET or with ^{77}Br ($T_{1/2}$ = 56 h) for longer term pharmacokinetic or metabolic investigations using conventional γ scintigraphy with high-energy collimators. This work reports the high-yield, high specific activity synthesis of [^{75}Br]- and [^{77}Br]bromperidol suitable for pharmacokinetic measurements with nuclear medicine instrumentation. Preceding studies using primates, we report here the initial tissue distribution data for high specific activity [^{77}Br]bromperidol in the rat.

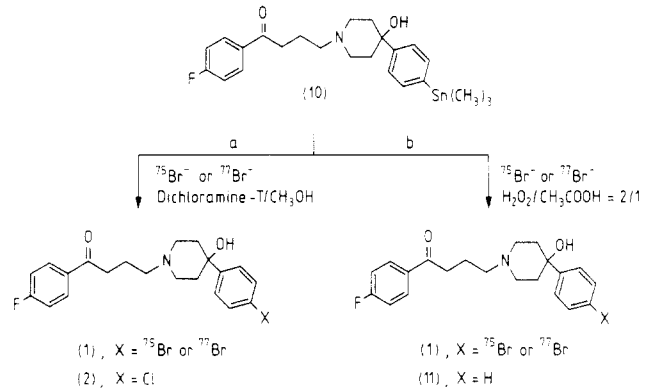
Scheme I



Scheme II



Scheme III



Results

Chemistry. 4-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone (haloperidol) (**2**) was synthesized from commercially available reagents in the three-step reaction sequence shown in Scheme I. ω-Chloro-*p*-fluorobutyrophenone (**3**) was ketalized with ethylene glycol prior to alkylation of 4-(4-chlorophenyl)-4-hydroxypiperidine (**5**). Following deketalization with HCl, the product (**2**) was purified and chemically characterized by spectral and chromatographic methods before proceeding to the following reaction sequence.

The stannylated precursor of bromperidol was a key synthetic intermediate and was prepared as shown in Scheme II. Trimethylstannyl chloride (**7**) was condensed in the presence of sodium and ammonia to form hexa-

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Table I. Tissue Distribution (Percent Injected Dose/Gram) of High Specific Activity [^{77}Br]Bromperidol in the Rat[a]

organ	time post-inj							
	5 min	15 min	30 min	1 h	2 h	4 h	6 h	8 h
blood	0.12 ± 0.01	0.11 ± 0.01	0.08 ± 0.01	0.06 ± 0.01	0.05 ± 0.01	0.06 ± 0.01	0.03 ± 0.01	0.02 ± 0.01
brain	2.26 ± 0.10	3.04 ± 0.07	2.82 ± 0.04	2.48 ± 0.03	1.85 ± 0.12	1.61 ± 0.07	1.58 ± 0.03	1.29 ± 0.02
liver	1.03 ± 0.11	2.19 ± 0.13	2.50 ± 0.16	2.99 ± 0.15	3.16 ± 0.18	4.08 ± 0.22	4.16 ± 0.13	4.33 ± 0.14
kidneys	4.96 ± 0.06	4.69 ± 0.24	5.01 ± 0.33	4.11 ± 0.24	2.93 ± 0.19	1.95 ± 0.18	1.93 ± 0.06	1.77 ± 0.13
lungs	13.6 ± 1.4	6.29 ± 0.48	5.80 ± 0.25	4.19 ± 0.34	2.10 ± 0.16	1.59 ± 0.12	1.24 ± 0.12	1.14 ± 0.14
spleen	3.02 ± 0.29	3.29 ± 0.08	4.43 ± 0.12	2.60 ± 0.16	2.69 ± 0.12	1.92 ± 0.08	1.76 ± 0.12	1.86 ± 0.10
pancreas	3.16 ± 0.42	4.72 ± 0.28	5.20 ± 0.12	4.23 ± 0.29	3.76 ± 0.14	3.51 ± 0.33	2.83 ± 0.08	2.05 ± 0.19
heart	2.29 ± 0.17	1.37 ± 0.04	1.07 ± 0.05	0.55 ± 0.12	0.46 ± 0.05	0.36 ± 0.03	0.39 ± 0.04	0.30 ± 0.03
intestines	0.39 ± 0.03	0.91 ± 0.10	0.83 ± 0.09	0.89 ± 0.06	0.82 ± 0.08	0.76 ± 0.03	0.98 ± 0.06	0.85 ± 0.14
uterus	1.91 ± 0.19	2.24 ± 0.07	3.00 ± 0.10	1.21 ± 0.10	1.07 ± 0.06	1.07 ± 0.10	1.20 ± 0.02	1.15 ± 0.01
fat	0.05 ± 0.02	0.16 ± 0.03	0.20 ± 0.02	0.22 ± 0.02	0.18 ± 0.01	0.15 ± 0.02	0.19 ± 0.02	0.18 ± 0.01
muscle	0.32 ± 0.04	0.32 ± 0.02	0.23 ± 0.03	0.18 ± 0.02	0.15 ± 0.01	0.12 ± 0.01	0.13 ± 0.01	0.10 ± 0.01
skin	0.15 ± 0.05	0.19 ± 0.01	0.20 ± 0.03	0.20 ± 0.03	0.17 ± 0.02	0.14 ± 0.02	0.14 ± 0.02	0.14 ± 0.01

[a] [^{77}Br]Bromperidol (50–100 μCi) in 0.1 mL was injected into the femoral vein of 300–320-g female Sprague–Dawley rats. Values represent the mean (percent injected dose/gram) ± standard deviation for five test animals.

methylditin (**8**). Following characterization of **8**, (trimethylstannyl)sodium (**9**) was prepared from the action of Na metal on **8** in glyme. The molarity of **9** was determined by reaction of an aliquot of the filtered supernatant with bromobenzene and the appropriate volume mixed with **2** in glyme to give a 0.5 stoichiometric excess of **9**. 4-[4-[4-(Trimethylstannyl)phenyl]-4-hydroxypiperidino]-4′-fluorobutyrophenone (**10**) was isolated from the reaction mixture by preparative HPLC. Regiospecific bromodestannylation of **10** by 1 equiv of Br_2 in chloroform produced 4-[4-(4-bromophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone (**1**), bromperidol. Product **1** was chemically characterized following workup and was found to be identical with authentic bromperidol (Janssen Pharmaceutica).

Radiochemistry. The radiolabeling reactions used to prepare high specific activity (no-carrier-added, nca) [^{75}Br]- and [^{77}Br]bromperidol are shown in Scheme III. In the radiobromination sequence, regiospecific bromodestannylation occurred by in situ generation of electrophilic bromine species, and final separation of nca [^{75}Br]- or [^{77}Br]bromperidol from reaction side products was achieved by HPLC. In reaction pathway a, dichloramine-T[26] was used as the oxidizing agent, and chlorinated side product **2** was produced in addition to high specific activity [^{75}Br]- or [^{77}Br]bromperidol (**1**). In reaction pathway b, hydrogen peroxide/acetic acid was used to oxidize $^{75}Br^-$ or $^{77}Br^-$ in situ and subsequently form radiobrominated product **1** and protonated side product **11**. For both (a) and (b), radiobromination was complete within a reaction time of 5 min, and overall radiochemical yields of 30–40% were achieved with an overall preparation time of 30 min and a specific activity exceeding 10 000 Ci/mmol. The difference between reactions a and b lies in the final HPLC purification and the ease at which high "effective" specific activity may be obtained (see Discussion).

Biological Evaluation. Preceding scintigraphic studies in primates using [^{75}Br]bromperidol, tissue distribution studies were carried out in rodents with the relatively long-lived ^{77}Br-labeled bromperidol, and serial sacrifice and dissection of the animals followed. The tissue distribution of high specific activity [^{77}Br]bromperidol in the major organs of 300–320-g female Sprague–Dawley rats is shown in Table I.

The tissue distribution of [^{77}Br]bromperidol is illustrated in Figure 1 for the lungs, liver, kidneys, brain, and blood. These data are reported as percentages of mean body concentration (see the Experimental Section) to eliminate experimental errors caused by differences in body weights and to allow for easier interspecies comparison.[27]

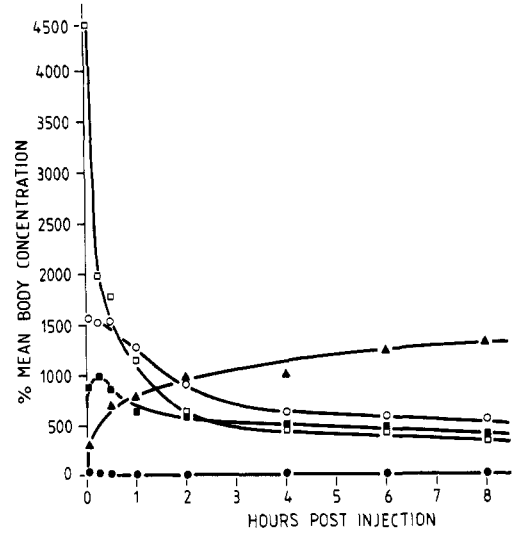

Figure 1. Tissue distribution of high specific activity [^{77}Br]-bromperidol in 300–320-g female Sprague–Dawley rats. Each point represents the mean value obtained from five animals. Key: ●, Blood; ■, brain; ▲, liver; ○, kidneys; □, lungs.

Discussion

The synthesis of [^{75}Br]- and [^{77}Br]bromperidol presents challenges in addition to those typically encountered with nca radiohalogenation methods.[28] Regiospecific halogenation is required to produce only the para-brominated isomer, and the aromatic ring to be brominated is deactivated toward electrophiles. With direct electrophilic aromatic substitution reactions, a mixture of aromatic isomers usually results, and deactivated aromatic rings can be halogenated only with radiochemical yields.

This synthetic impasse is avoided by the use of metalated precursors that promote electrophilic substitution at the aromatic site occupied by the metal moiety. Thus, regiospecificity as well as increased halogenation yields are afforded. Radiobrominated [^{82}Br]bromperidol has previously been synthesized via a metalated precursor via the Sandmeyer reaction,[29] but the preparation time (6 h) and radiochemical yield (10.4%) were unsuitable for use with

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short-lived ^{75}Br. Subsequent pharmacokinetic studies in primates with conventional γ scintigraphy[22] therefore measured only relative organ concentrations and elimination curves rather than the more useful absolute tissue concentrations that can be quantitated with ^{75}Br and PET. It should be noted in this regard that absolute tissue doses cannot be extrapolated from smaller mammals to primates due to interspecies differences in the metabolic pathways of bromperidol.[30-32] In addition to the low radiochemical yield and long preparation time, use of the Sandmeyer reaction resulted in a specific activity of 18.4 mCi/mmol,[29] which for a typical radiopharmaceutical dose of 5 mCi corresponds to 11.4 mg of bromperidol. Not only is this dose too high to qualify as a tracer of bromperidol pharmacokinetics (the therapeutic maintenance dose of bromperidol is 6 mg/day[33]), but the specific activity is too low to allow evaluation as a receptor-binding radiopharmaceutical, where specific activities in the order of several hundred Curies per millimole are required.[34]

We therefore examined alternative bromodemetalation techniques for labeling bromoperidol. Because high radiochemical yields were obtained with nca bromodestannylation using simple aromatic compounds,[35] a stannylated precursor for bromperidol was synthesized. Reaction of (trimethylstannyl)sodium reagent (**9**) directly on haloperidol (**2**) successfully resulted in the para-trimethylstannylated precursor (**10**), as shown in Scheme II. Haloperidol was used as the stannylation substrate despite the slower reaction kinetics of aryl chlorides compared with aryl bromides[36] due to ease in HPLC purification as well as to exclude traces of bromperidol in labeling precursor (**10**) (Scheme II). Stannylated compound (**10**) was readily separated in 40% yield from protonated side-product peridol (**11**) as well as unreacted haloperidol (**2**) by using preparative HPLC.

Regiospecific bromodestannylation of **10** occurred with macroscopic Br_2 as well as nca $^{75}Br^-$ and $^{77}Br^-$ oxidized in situ (Scheme II). Although the use of either dichloramine-T (a) or hydrogen peroxide/acetic acid (b) as oxidizing agents resulted in [^{75}Br]- and [^{77}Br]bromperidol in 30–40% radiochemical yield, in the former case chlorinated side-product haloperidol (**2**) was also produced. Because haloperidol is a potent neuroleptic,[23,24] its presence in the injectate results in low "effective" specific activity.[37] As shown in Figure 2a, this haloperidol impurity can be separated from radiolabeled bromperidol by using reversed-phase HPLC, but some tailing of chlorinated side product into the bromperidol peak is unavoidable.

This chromatographic difficulty can be eliminated by use of a labeling method that does not involve chlorination as a side product. Hydrogen peroxide/acetic acid has been used for the radiohalogenation of α-carbonyl carbon[37] and

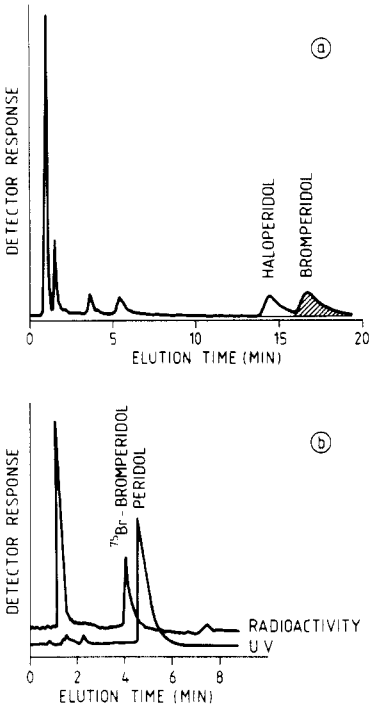

Figure 2. HPLC separation of the reaction products shown in Scheme II. (a) reaction products arising from the use of dichloramine-T (1 × 25 cm RP-18, MeOH:H_2O:Et_3N = 70:30:0.1); (b) reaction products arising from the use of H_2O_2/CH_3COOH (1.6 × 25 cm Si-60, $CHCl_3$:EtOH = 90:10).

vinyl positions[38] of steroids, and we have applied it here for aromatic bromodestannylation. Using this oxidant, protodestannylation occurs as a side reaction, rather than chlorodestannylation as when chloramines are used as oxidizing agents. Chromatographic separation of the protonated side product (peridol) and radiolabeled bromperidol is achieved by using normal-phase HPLC. As shown in Figure 2b, the tailing problem is avoided, since high effective specific activity [^{75}Br]- and [^{77}Br]-bromperidol elutes before peridol.

As seen in Table I and Figure 1, high effective specific activity [^{77}Br]bromperidol shows the pharmacokinetic profile of a lipophilic compound that has a large coefficient of distribution from the plasma into the tissues. Uptake into the lungs is high, probably due to the lipophilicity of bromperidol as well as the low pH of lung tissue, which tends to trap the basic neuroleptic. Activity clears from the lungs and kidneys with time, while that in the liver increases, possibly due to the oxidative N-dealkylative metabolic pathway common to butyrophenone neuroleptics.

Uptake of [^{77}Br]bromperidol into the brain is very rapid and remains high for long periods, in general agreement with the rapid onset and duration of action of bromperidol.[23] This is in contrast to the blood levels, which remain low over the test interval in spite of high in vitro plasma binding by bromperidol.[30] These results indicate why it has been difficult to correlate blood levels with the pharmacological effect of butyrophenones[15] and corroborate that brain levels are perhaps a better monitor of clinical response.[16] This is further strengthened by our results that ca. 90% of the extractable brain radioactivity at 2 h post-injection is due to intact bromperidol.

The results in Table I are in good agreement with reports concerning bromperidol labeled with β^--emitting nuclides. [^{3}H]bromperidol labeled in the *p*-fluorobutyro-

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phenone ring shows similar pharmacokinetics in rats, but the plasma concentrations are higher.[30,39,40] Whether this is due to ^3H exchange with plasma water, because the location of the label means different metabolites are being traced, or due to other reasons is unclear. Metabolic studies using [^{14}C]bromperidol labeled in the piperidine ring unfortunately did not include tissue distribution determination.[32]

Our results also agree qualitatively with the tissue distribution of relatively low specific activity [^{82}Br]-bromperidol.[30] The latter results show a similar decrease with time of the radioactivity in the lungs and kidneys, but activity in the liver and blood remains relatively constant over the 2-h test interval. In addition, concentrations in the blood are much higher while those in the brain and liver are much lower than the results in Table I. We attribute these differences to variation in the bromperidol dose administed in each study. Although the effect of dose on the tissue distribution of bromperidol has not been investigated to date, such a study has been done for haloperidol administered subcutaneously to rats in the dose range 0.04–2.5 mg/kg.[41] It was shown that as the dose of haloperidol was decreased, the percentage of the injected dose that localized in the brain increased, that in the blood decreased, and the liver pharmacokinetics became first order. These dose effects correlate well with the differences in the distribution reported earlier for [^{82}Br]-bromperidol at a dose of 0.2 mg/kg[29] and the data shown in Table I for "infinitely diluted" (<15 ng/kg) [^{77}Br]-bromperidol.

Conclusion

This work reports the high radiochemical yield, high effective specific activity synthesis of [^{75}Br]- and [^{77}Br]-bromperidol suitable for use as a radiopharmaceutical tracer of bromperidol pharmacokinetics. Although [^{75}Br]bromperidol is not useful in primates for in vivo receptor-binding studies,[42,43] the [^{75}Br]bromperidol resulting from this synthesis can be used to quantitate absolute tissue doses in man noninvasively with PET, which is of great use for pharmacokinetic studies since metabolic differences make extrapolation from animal results to humans inappropriate. The absolute quantitation of the brain dose of bromperidol using PET can thus be used to develop correlations between plasma concentrations as well as clinical response in humans. High specific activity [^{77}Br]bromperidol prepared by this method may also be used for the determination of organ elimination half-times and metabolic studies in conjunction with conventional γ scintigraphy. In the latter case, the blood metabolites can be analyzed with great sensitivity using radio-HPLC.

In preliminary tissue distribution studies in the rat, differences were noted from a previous study[29] using relatively low specific activity radiobrominated bromperidol. These variations suggest that a future application for high specific activity [^{75}Br]- or [^{77}Br]bromperidol prepared by this method is the determination of the effect of dose (specific activity) on the tissue deposition of bromperidol. The radiosynthetic methods presented for the synthesis and purification of high effective specific activity bromperidol may find general application with alternative radiohalogenated receptor-binding radiopharmaceuticals.

Experimental Section

Unless otherwise indicated, all compounds used were of reagent grade and solvents were of analytical quality. Melting points were determined in open capillary tubes on a Mettler FP-61 melting point apparatus and were not corrected. NMR spectra were derived with a Bruker WP-80 high-resolution NMR spectrometer employing an internal standard of tetramethylsilane. IR spectra were obtained with a Perkin-Elmer Model 257 spectrophotometer using KBr pellets. Mass spectral analyses were done on an AEI Scientific Apparatus MS-30/74 mass spectrometer. Where analyses are reported by symbols of the elements, results were within ±0.4% of the calculated value.

4-Chloro-1,1-ethylenedioxy-1-(4-fluorophenyl)butane (4). A mixture consisting of ω-chloro-(4-fluorophenyl)butyrophenone (**3**) (6 mL, 36.5 mmol), ethylene glycol (6 mL, 110 mmol), and *p*-toluenesulfonic acid (500 mg) in anhydrous benzene (400 mL) was refluxed for 12 h with azeotropic distillation of water. The organic phase was successively washed with equal volumes of 5% $NaHCO_3$ and water and dried with Na_2SO_4, and the solvents were removed to leave 10.6 g (98%) of product (**4**). **4** was used for the following reaction without further purification.

4-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-1,1-ethylenedioxy-1-(4-fluorophenyl)butane (6). A mixture of product **4** (4.5 g, 18.4 mmol), 4-(4-chlorophenyl)-4-hydroxypiperidine (**5**) (3.9 g, 18.4 mmol), K_2CO_3 (9 g), and KI (210 mg) in anhydrous DMF (75 mL) was stirred at 100 °C for 17.5 h. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with water and dried with $MgSO_4$ and the solvent removed under reduced pressure to leave 6.4 g (87%) of product **6**. The subsequent reaction sequence was followed without any additional purification.

4-[4-(4-Chlorophenyl)-4-hydroxypiperidino]-4′-fluorobutyrophenone (Haloperidol) (2). A 5-g portion (11.2 mmol) of product **6** and concentrated HCl (5 mL) in methanol (60 mL) were refluxed for 2 h. The reaction mixture was diluted with ethyl acetate and successively washed with 5% aqueous ammonia and water. The solution was dried with $MgSO_4$, and the solvents were removed by evaporation under reduced pressure. The residue was eluted through a silica gel column using a mobile phase of $CHCl_3$:MeOH = 9:1, and the major peak was recrystallized twice from ethyl acetate to yield 4.0 g (65%) of solid product **2**: mp 148.6 ± 0.1 °C; ^1H NMR (acetone-d_6) δ 8.1 (dd, J = 3, 6 Hz, 2 H, Ar H), 7.4 (m, 6 H, Ar H), 3.2–1.5 (m, 15 H, alk H); IR (KBr) 1675 (Ph–CO), 1595 (Ph), 1215 (C–OH), 1550 (Ph–F), 990 (pyr), 830 (1,4-disubstituted Ph) cm^{-1}; MS m/e 376 (M^+). Anal. ($C_{21}H_{23}FClNO_2$) C, H, N.

Hexamethylditin (8). Compound **8** was synthesized as previously described.[44] Trimethyltin chloride (**7**) (20 g, 100 mmol) was dissolved in 35 mL of absolute hexane and the resultant mixture cooled to −80 °C in a round-bottomed flask equipped with stirrer and dry ice cold finger. Ammonia (100 mL) was condensed into the flask, and 2.35 g (100 mmol) of Na was added in small pieces over a 30-min period with stirring. The ammonia was then evaporated off, and the mixture was filtered under an argon atmosphere through glass wool. The filtrate was fractionally distilled to isolate 12.6 g (77%) of product (**8**): bp 84–85 °C (45 mm) (lit.[44] mp 61 °C (12 mm)); ^1H NMR (CCl_4) δ 0.21 (s).

(Trimethylstannyl)sodium (9). On the basis of the same report,[45] a 1 M solution of **9** in absolute glyme was prepared. A 2-mL portion of this solution was stirred with 115 mg (5.0 mmol) of finely cut Na and 4 mL of absolute glyme at 0 °C under an argon atmosphere. Stirring was continued for 2 h, at which time the same amount of black precipitate remaining was allowed to settle. The light yellow supernatant was filtered through glass wool, and the concentration of **8** in the filtrate was determined[44]

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to be 0.6 M. This solution was used immediately in the following reaction.

4-[4-[4-(Trimethylstannyl)phenyl]-4-hydroxypiperidino]-4'-fluorobutyrophenone (10). A 750-mg sample (2 mmol) of product **2** was dissolved in 20 mL of absolute glyme and the resultant mixture cooled to 0 °C under an inert atmosphere. Five milliliters (3 mmol) of a 0.6 M solution of **9** in absolute glyme was added and the resultant mixture allowed to stand at −10 °C for 14 h. The supernatant was removed, and the solvent was evaporated off at reduced pressure. The residue was dissolved in 40 mL of $CHCl_3$ and washed twice with 40 mL of water. The organic layer was separated, and the solvents were removed to leave a solid residue consisting of unreacted **2**, side product **11**, and product **10**. These products were separated by using preparative HPLC (1 × 25 cm RP-18; MeOH:H_2O:Et_3N = 80:20:0.1); k' = 2.8, 3.2, and 5.0 for **11**, **2**, and **10**, respectively. The solvents were removed from the third fraction to yield 432 mg (0.9 mmol, 43%) of product (**10**): mp 221.0 ± 0.1 °C; ^{1}H NMR ($CDCl_3$) δ 8.15 (dd, 2 H, Ar H), 7.5 (m, 6 H, Ar H), 3.1–1.8 (m, 15 H, alk H), 0.28 (s, 9 H, $SnCH_3$); IR (KBr) 1665 (Ph–CO), 1595 (Ph), 1220 (C–OH), 1150 (Ph–F), 990 (pyr), 825 (1,4-disubstituted Ph), 760 (Ph–Sn) cm^{-1}; MS *m/e* 504 (M^+). Anal. ($C_{21}H_{32}FNO_2Sn$) C, H, N.

4-[4-(4-Bromophenyl)-4-hydroxypiperidino]-4'-fluorobutyrophenone (Bromperidol) (1). A 51-mg sample (100 mmol) of product **10** was dissolved in 100 mL of $CHCl_3$, and 16 mg (100 mmol) of Br_2 in 25 mL of $CHCl_3$ was added dropwise while stirring. Following an additional 30 min of stirring, the mixture was removed and washed twice with 100 mL of water. The organic phase was dried with Na_2SO_4 and the solvent evaporated at reduced pressure. The residue was recrystallized from ethyl acetate to yield 33 mg (79%) of product (**1**): mp 155.0 ± 0.1 °C; ^{1}H NMR δ 8.1 (dd, 2 H, Ar H), 7.4 (m, 6 H, Ar H), 3.1–1.6 (m, 15 H); IR (KBr) 1675 (Ph–CO), 1595 (Ph), 1220 (C–OH), 1150 (Ph–F), 990 (pyr), 925 (1,4-disubstituted Ph) cm^{-1}; MS *m/e* 420 (M^+). Anal. ($C_{21}H_{23}BrFNO_2$) C, H, N.

Radiosynthesis of [^{75}Br]- or [^{77}Br]Bromperidol (1). The bromine radioisotopes were produced via the ^{75}As(^{3}He, 3 n)^{75}Br reaction or ^{75}As(α, 2 n)^{77}Br reaction using the Jülich CV-28 compact cyclotron.[45]

By reaction pathway a (Scheme III), 15 mCi of $^{77}Br^-$ in aqueous solution was dried under reduced pressure at 100 °C. A 2-mg sample of **10** was then added with 1 mL of methanol, the mixture was stirred to dissolve the stannylated butyrophenone, and 2 mg of dichloramine-T was added to begin the oxidative bromination reaction. After 5 min at 25 °C, the entire contents were removed and separated by HPLC (1 × 25 cm RP-18, MeOH:H_2O:Et_3N = 80:20:0.1; k' = 3.4) to yield 6 mCi (40% radiochemical yield) of [^{77}Br]bromperidol.

By reaction pathway b (Scheme III) and a radioisotope production yield of 12 mCi of $^{77}Br^-$, the aqueous solution of radiobromide was dried under reduced pressure at 100 °C in a sealed vessel. A 2-mg portion of compound **10** was added with 1 mL of 35% H_2O_2/CH_3COOH (2:1) and the reaction mixture stirred at 25 °C for 10 min. The mixture was then cooled in an ice bath and made basic by dropwise addition of ice-cold 33% aqueous NH_3. Following addition of base, the organic products were extracted into 1.5 mL of $CHCl_3$. The entire organic phase was injected onto an HPLC column (1.6 × 25 cm Si-60; $CHCl_3$:EtOH = 90:10) to isolate [^{77}Br]bromperidol (k' = 6.2) from peridol (k' = 7.0). The elution fraction corresponding to bromperidol was dried in vacuo and redissolved in 2–5 mL of 0.9% aqueous NaCl, pH 3.0. Sterile filtration resulted in 4.3 mCi of [^{77}Br]bromperidol suitable for in vivo administration. Overall corrected radiochemical yields of 35% were obtained following a total synthesis and purification time of 30 min, with a specific activity exceeding 10 000 Ci/mmol as determined by using a bromperidol mass–UV absorbance curve. The radiosynthetic yields for [^{75}Br]bromperidol were very similar, the major difference being that higher starting radioactivities (ca. 150–200 mCi of $^{75}Br^-$) were used.

Tissue Biodistribution Studies. Female Sprague–Dawley rats weighing 300–320 g were allowed free access to food and water during the course of these experiments. [^{77}Br]bromperidol (50–100 μCi) in 0.1 mL of 0.9% NaCl, pH 3, was injected into the femoral vein of each animal after light ether anesthesia. Following a predetermined test interval, the animals were sacrificed in groups of five by decapitation, immediately following extraction of a blood sample via cardiac puncture. The organs shown in Table I were removed by surgical dissection, blotted dry, and weighed, and the radioactivity was determined by counting in a NaI(Tl) well-type γ-scintillation counter. The results were calculated in terms of percent injected dose per gram of tissue using a standard sample of the injectate. For the major organs of interest (brain, blood, liver, kidneys, lungs), these values were recalculated as percentages of the mean body concentration (% MBC) using the equation % MBC = [organ dose/organ weight]/[total injected dose/total body weight] × 100.

Cerebral Metabolism. For animals sacrificed at 2 h post-injection, brain samples were homogenized in distilled water and 20 mL of the homogenate was mixed with 100 mL of aqueous solution of bromperidol (1 mg/mL, pH 3). The solution was adjusted to pH 10 and extracted into 100 mL of $CHCl_3$. The phases were separated, 1-mL aliquots were removed from each phase, and the percent organic extraction of radioactivity was determined by counting in a γ-scintillation detector. The organic phase was concentrated by evaporation at reduced pressure, and a 50-μL aliquot was separated by two-dimensional TLC (Kieselgel Si-60; MeOH:acetone = 12:88; MeOH:c-C_6H_{12}:AcOEt = 18:33:49). The stationary phase was cut in a grid pattern and the radioactivity content of each region of the TLC plate determined by counting in a γ-scintillation detector. The percentage of total TLC plate radioactivity that comigrated with a standard solution of bromperidol was multiplied by the percent organic extraction to give an average value of 87.2 ± 6.4% for the total brain activity due to intact bromperidol in five animals.

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