SYNTHESIS OF NO-CARRIER-ADDED RADIOBROMINATED N-ALKYLATED ANALOGUES OF SPIPERONE

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SUMMARY

The synthesis of a series of p-bromo-3-N-alkyl spiperone analogues is described. N-alkylation was achieved via reaction of the potassium salt of the spiperone lactam ring with alkyl iodide; subsequent reactions with elemental bromine gave the p-brominated isomers. Optimization studies using no-carrier-added (n.c.a.) $^{77}Br^-$ indicated that radiobromination of N-alkyl spiperone analogues occurs with higher yields and in shorter reaction times when dichloramine-T (DCT) is used rather than H_2O_2/acetic acid as an oxidant. The production of the title compounds in high effective specific activity with radiochemical yields of 20-30 % using n.c.a. $^{77}Br^-$ and DCT is reported.

Key words: Spiperone, brominated spiperone analogues, neuroleptic, dopaminergic receptors, no-carrier-added radiobromination, ^{77}Br.

INTRODUCTION

A variety of neuroleptics have been synthesized at the no-carrier-added (n.c.a.) level with ^{11}C(1-3), ^{18}F(4-6)

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and ^{75,77}Br(7-9) for evaluation as radiopharmaceuticals for the non-invasive mapping of cerebral dopaminergic receptor areas using positron emission tomography (PET) or single-photon emission tomography (SPECT). Of these, the in vivo localization characteristics of radiolabelled spiperone (1o,11) and its analogues (12-15) have shown particular promise for application in man.

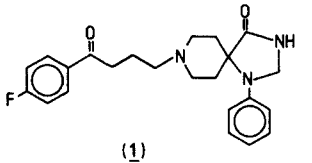
Because the molecular structure of spiperone ((1), Scheme 1) contains an amido nitrogen situated outside of the p-fluoro-butyrophenone pharmacophore (16) necessary for dopaminergic D_2-receptor binding, alkylation of radiolabelled spiperone at this site offers an opportunity for the study of the effects of lipophilicity on the in vivo receptor localization of the neuroleptic. That is, with larger alkyl groups attached to the amido nitrogen, the receptor-binding affinity should not be strongly altered, whereas such pharmacokinetic parameters as blood-brain barrier penetration, non receptor-specific binding, and plasma protein binding will differ. The results of in vivo experiments with these analogues illustrate not only the effects of lipophilicity on the tissue distribution of receptor-binding radioligands, but also indicate the optimum structural analogue of spiperone for labelling with ^{11}C, ^{18}F, or ^{75}Br. The biological results are presented elsewhere (17). This work reports the synthetic details of the radiobrominated N-alkylated analogues of spiperone used in these studies.

RESULTS AND DISCUSSION

Because most of the compounds used in this study are novel structures not yet reported in the chemical literature, standard compounds had to be synthesized and their identity

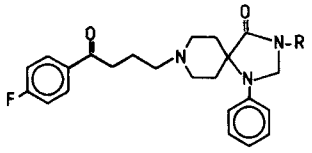
authenticated by spectral means. The synthetic pathway used for the production of non-radioactive N-alkylated and p-brominated, N-alkylated analogues of spiperone is represented in Scheme 1.

The potassium salt of the lactam was prepared by reacting spiperone with potassium metal in tetrahydrofuran. The amido nitrogen was subsequently alkylated using methyl-, ethyl-, or n-propyl iodide to give the 3-N alkylated compounds (2), (3), and (4), respectively. Overall alkylation yields of ca. 3o % were achieved in each case. Bromination of (2), (3), and (4) to give p-brominated analogues (5), (6), and (7) was readily obtained with 5o % yield using one equivalent of elemental



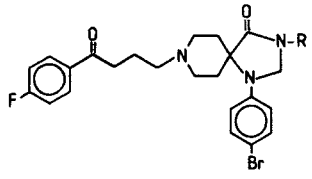
(1)

1. K/THF
2. RI



(2), R = CH_3
(3), R = C_2H_5
(4), R = C_3H_7

Br_2 / CCl_4



(5), R = CH_3
(6), R = C_2H_5
(7), R = C_3H_7
(8), R = H

Scheme 1

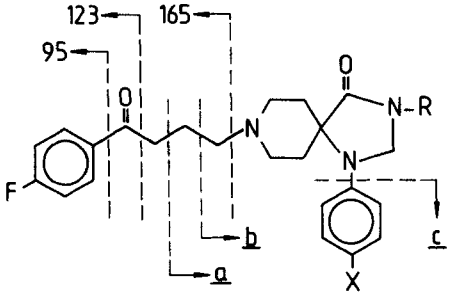


Figure 1. Mass spectral fragmentation pattern for spiperone analogues.

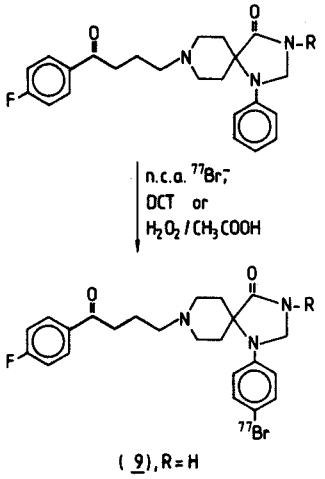
bromine. Para-bromospiperone, (8), was afforded by direct bromination of spiperone (1), as previously described (18).

Analytical verification of the molecular site of alkylation and bromination was obtained using mass spectroscopy and ^{1}H-NMR. As seen in Figure 1, the mass spectral fragmentation patterns cogently illustrate the location of alkyl groups or bromine atoms on spiperone analogues. Whereas fragments with m/e = 165, 123 and 95 were identical in the analogues and in spiperone (19), N-alkylation leads to an increase in the m/e values for fragments (a) and (b) and no change in that for fragment (c) (see Experimental section). In the 3-N alkylated, p-brominated analogues, m/e values for fragments (a), (b), as well as for (c) are increased by a quantity appropriate for the substitution.

That bromination occurs at the para position of the anilino ring in compounds (5)-(8) is shown by the ^{1}H-NMR (acetone-d_6) data. A two-proton doublet (J = 9 Hz) is seen at δ = 7.50-7.53 as well as a two-proton doublet (J = 9 Hz) at δ = 6.98-7.02. These signals can be assigned to the aromatic protons ortho to the ring bromine, and ortho to the anilino nitrogen, respectively. Alkylation of the lactam is also

shown by the ^{1}H-NMR spectra. The N-methyl group of (2) and (5) shows a three-proton singlet at δ = 2.95-3.o, the N-ethyl substitution of (3) and (6) results in a two-proton quartet at δ = 3.47-3.51 and a three-proton triplet at δ = 1.24-1.25, and the N-propyl group in (4) and (7) is indicated by a two-proton triplet at δ = 3.45 and a three-proton triplet at δ = o.95-o.97.

The standard compounds synthesized as described above were used for biological tests (17) as well as for the development of chromatographic systems for the purification of radiolabelled products. For n.c.a. radiobromination, bromination reagents other than Br_2 must be used (2o). As illustrated in Scheme 2, spiperone and its N-alkylated analogues can be radiobrominated using either dichloramine-T (DCT) or peroxide-acetic acid as in situ oxidants for n.c.a. $^{77}Br^{-}$. These oxidants differ in the kinetics of the radiobromination reaction and in the production of macroscopic



(9), R = H
(10), R = CH_3
(11), R = C_2H_5
(12), R = C_3H_7

Scheme 2

side-products. Whereas DCT generates chlorinated products during the radiobromination reaction, peroxide-acidic acid does not. As shown by the HPLC retention indices in Table 1 for the protonated, chlorinated, and brominated analogues of compounds (1)-(4), the chromatographic purification of protonated and radiobrominated products can be readily achieved, while the retention indices for the chlorinated and brominated compounds are too similar to allow high resolution, high effective specific activity isolation of radiobrominated analogues. Unfortunately, although the use of peroxide-acetic acid leads to n.c.a. radiobromination without chlorination side-products, the rate of reaction is very slow. Radiochemical yields of

Table 1

HPLC Retention Indices of Spiperone Analogues[a]

Compound	Retention Index (k')		
	Protonated Analogue	p-Chlorinated Analogue	p-Brominated Analogue
Spiperone (1)	6.5	11.1	14.1
3-N-Methyl-spiperone (2)	1o.o	15.6	19.o
3-N-Ethyl-spiperone (3)	14.5	17.1	25.3
3-N-Propyl-spiperone (4)	22.5	31.9	37.9

(a) Stationary phase: 4x25o mm Lichrosorb RP-18 (7 µm); mobile phase: MeOH/o.1 % $N(Et)_3$ = 7o/3o, 2.5 ml/min.

Table 2

No-Carrier-Added Radiobromination of Spiperone Analogues[a]

Compound	Radiochemical Yield (%)
(9)	68.2
(10)	60.0
(11)	47.5
(12)	35.4

(a) Reaction conditions: 1 mg bromination substrate, 100 µg dichloramine-T, 1.2 ml methanol, 200-500 µCi n.c.a. $^{77}Br^-$/25 µl H_2O, 25°C, reaction time = 2 minutes.

compounds (9)-(12) after 30 minutes were less than 10 %, in agreement with previous work concerning bromospiperone (7). We therefore concentrated on the use of dichloramine-T, since the rapid reaction kinetics are more applicable to the positron-emitting ^{75}Br($t_{1/2}$ = 1.6 h). The radiochemical yields obtained for compounds (9)-(12) in analytical tests using n.c.a. $^{77}Br^-$ and DCT with a reaction time of two minutes are summarized in Table 2. Very high radiobromination yields are seen, with only a slight influence (probably steric) caused by the N-alkyl substituent.

As Figure 2 illustrates for compound (1) as a model substrate, the macroscopic chlorination yield is dependent on the quantity of DCT used. However, the radiobromination yield is also dependent on the concentration of oxidizing agent, and rapidly decreases as the DCT concentration is made less than about 100 µg/ml. Therefore, at the DCT concentrations necessary for high radiobromination yields, chlorination side-products are unavoidable and must be chromatographically separated from the

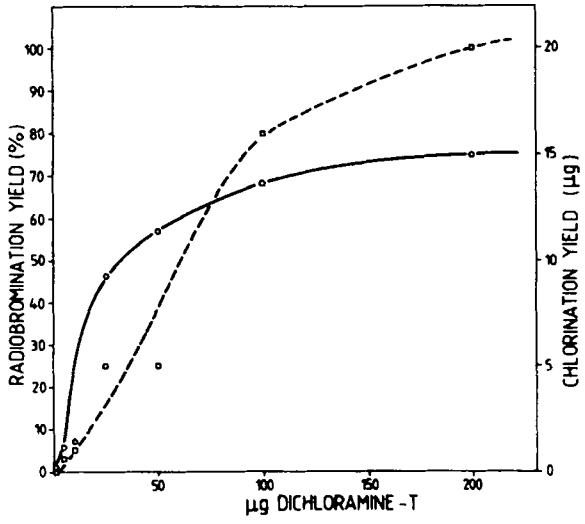


Figure 2. No-carrier-added radiobromination and macroscopic chlorination of spiperone as functions of dichloramine-T concentration. Reaction conditions: 1 mg spiperone, 1.2 ml CH_3OH, 200-500 µCi n.c.a. $^{77}Br^-$/10 µl H_2O, 25°C, reaction time = 2 minutes.

radiolabelled spiperone analogues to give high effective specific activities.

In the production of ^{77}Br-labelled compounds (9)-(12) for application in receptor-binding studies in animals, separation of the radiobrominated products with minimal chlorinated side-product contamination was achieved by a two-column HPLC system in which the radiobrominated analogues (plus some p-chlorinated by-product) eluted from an HPLC column was further purified by elution through a second HPLC column ("column switching" - see Experimental section). The trace impurities of chlorinated products were thereby effectively eliminated. Using this technique, the title compounds (9)-(12) in injectable saline solution were prepared in 70-90 minutes with overall radiochemical yields of 20-30 % and containing less than 10 pmol of macroscopic contaminant.

EXPERIMENTAL

Syntheses of Standard Compounds.

The alkylation and subsequent bromination techniques used for all compounds were identical. 5oo mg Spiperone (1) (Janssen Pharmaceutica, Beerse, Belgium) was dissolved in 2o-3o ml THF, and was refluxed with freshly-cut pieces of potassium metal for 2o minutes. The resulting yellow solution was decanted off and reacted with one equivalent of methyl-, ethyl-, or n-propyl iodide at 65°C for 45 minutes. The potassium iodide precipitate was filtered off, the solvent removed under reduced pressure, and impurity spiperone recrystallized from a methanol solution. The alkylated spiperone analogues were isolated from the mother liquors using preparative HPLC (4x25o mm Lichrosorb RP-18 (7 µm); MeOH/o.1 % NEt_3 = 7o/3o). Final chromatographic purification (2.5x65 cm Kieselgel; MeOH) resulted in compounds (2)-(4) in overall yields of 35 %.

Inactive macroscopic brominations were performed as previously described (18). To solutions of (1)-(4) in 3 ml methylene chloride was added dropwise 1 equivalent of bromine in carbon tetrachloride. The solution was stirred at 0°C for thirty minutes, after which the mixture was shaken with 1o ml 5% NH_4OH/1 % $Na_2S_2O_3$, and the phases allowed to separate. The organic layer was removed, the solvent evaporated off under reduced pressure to leave an oily residue. Compounds (5)-(8) were subsequently isolated in 5o % yield using preparative HPLC (4x25o mm Lichrosorb RP-18 (7 µm); MeOH/o.1 % NEt_3 = 7o/3o) followed by column chromatography (5x3o cm Kieselgel; MeOH).

Spectra Data.

^{1}H-NMR spectra were derived with a Bruker WP-8o High Resolution NMR spectrometer using an internal standard of tetramethyl-

silane. IR spectra were obtained with a Perkin-Elmer Model 257 spectrophotometer using KBr pellets. Mass spectral analyses were done using an AEI Scientific Apparatus MS-3o/74 mass spectrometer.

3-N-Methylspiperone (2).

TCL (Kieselgel Si-6o; MeOH): R_f = o.44.

^{1}H-NMR ($CDCl_3$): δ = 1.5-2.1 (m,4H); 2.3-3.1 (m,13H); 4.7 (s,2H); 6.7-7.4 (m,7H); 8.o-8.3 (q,2H).

IR(KBr): υ_{max} = 835, 99o, 112o, 1155, 123o, 13oo, 137o, 15o5, 16oo, 1685, 171o cm^{-1}

MS: m/e = 4o9 (M^+), 391 (M-18, 17 %), 271 (a, 2o %), 258 (b, 1oo %), 165 (18 %), 123 (59 %), 95 (32 %), 77 (c, 67 %).

3-N-Ethylspiperone (3).

TLC (Kieselgel Si-6o; MeOH): R_f = o.46.

^{1}H-NMR ($CDCl_3$): δ = 1.3 (t,3H), 1.5-2.2 (m,4H); 2.4-3.2 (m,1OH); 4.6 (q,2H); 4.8 (s,2H); 6.8-7.4 (m,7H); 8.1-8.4 (q,2H).

IR(KBr): υ_{max} = 84o, 1155, 1235, 1295, 138o, 147o, 15oo, 1595, 169o cm^{-1}.

MS: m/e = 4o5 (M-18, 28 %); 285 (a, 23 %); 272 (b, 1oo %); 165 (25 %); 123 (63 %); 95 (43 %); 77 (c, 65 %).

3-N-Propylspiperone (4).

TLC (Kieselgel Si-6o, MeOH): R_f = o.46.

^{1}H-NMR ($CDCl_3$): δ = 1.o (t,3H); 1.6-2.2 (m,6H); 2.4-3.2 (m,1OH); 3.5 (t,2H); 4.8 (s,2H); 6.8-7.4 (m,7H); 8.1-8.3 (q,2H).

IR(KBr): υ_{max} = 83o, 99o, 1125, 1155, 123o, 1295, 1375, 15o5, 16oo, 168o, 17o5 cm^{-1}.

MS: m/e = 437 (M^+); 419 (M-18,32 %); 3oo (a,17 %); 286 (b,75 %); 165 (32 %); 123 (1oo %); 95 (52 %); 77 (c,68 %).

p-Bromo-3-N-Methylspiperone (5).

TLC (Kieselgel Si-6o, MeOH): R_f = o.46.

^{1}H-NMR ($CDCl_3$): δ = 1.8-2.1 (m,4H); 2.4-3.2 (m,13H); 4.7 (s,2H); 6.9 (d,2H); 7.2-7.6 (m,6H); 8.2 (q,2H).

IR(KBr): υ_{max} = 83o, 99o, 116o, 123o, 1295, 1375, 1495, 16oo, 1685, 17o5 cm^{-1}.

MS: m/e = 488/9o (M^+); 47o/2 (M-18,12 %); 35o/2 (a, 15 %); 336/8 (b, 49 %); 165 (35 %); 155/7 (c, 15 %); 123 (1oo %), 95 (51 %).

p-Bromo-3-N-Ethylspiperone (6).

TLC (Kieselgel Si-6o, MeOH): R_f = o.5o.

^{1}H-NMR ($CDCl_3$): δ = 1.2 (t,3H); 1.5-2.2 (m,4H); 2.4-3.2 (m,1OH); 3.5 (q,2H); 4.6 (s,2H); 7.6 (d,2H); 7.2-7.6 (m,4H); 8.2 (q,2H).

IR(KBr): υ_{max} = 8oo, 85o, 99o, 115o, 121o, 13oo, 1375, 1495, 1595, 168o, 171o cm^{-1}.

MS: m/e = 5o2/4 (M^+); 484/6 (M-18, 16 %); 364/6 (a, 15 %); 35o/2 (b, 78 %); 165 (33 %); 155/7 (c, 23 %); 123 (1oo %); 98 (53 %).

p-Bromo-3-N-Propylspiperone (7).

TLC (Kieselgel Si-6o, MeOH): R_f = o.53.

^{1}H-NMR ($CDCl_3$): δ = o.9 (t,3H); 1.5-2.2 (m,6H); 2.4-3.2 (m,1OH); 3.4 (t,2H); 4.7 (s,2H); 6.8 (d,2H); 7.1-7.6 (m,4H); 8.2 (d,2H).

IR(KBr): υ_{max} = 8oo, 83o, 99o, 116o, 123o, 13oo, 138o, 1495, 16oo, 1695, 171o cm^{-1}.

MS: m/e = 498/5oo (M-18, 52 %); 478/8o (a, 18 %); 464/6 (b, 67 %); 165 (43 %); 155/7 (c, 13 %); 123 (1oo %); 95 (41 %).

p-Bromospiperone (8).

TLC (Kieselgel Si-6o, MeOH): R_f = o.44.

^{1}H-NMR ($CDCl_3$): δ = 1.6-2.2 (m,4H); 2.4-3.2 (m,1OH); 4.7 (s,2H); 6.8 (d,2H); 7.2-7.6 (m,4H); 8.2 (q,2H).

IR(KBr): υ_{max} = 835, 122o, 1375, 1495, 16oo, 1685, 171o cm^{-1}.

MS: m/e = 474/6 (M^+); 456/8 (M-18, 5 %); 336/8 (a, 23 %); 322/4 (b, 61 %); 165 (43 %); 155/7 (c, 13 %), 123 (1oo %); 95 (53 %).

Radiobromination Studies.

The ^{77}Br used in these experiments was produced via the $^{75}As(\alpha,2n)^{77}Br$ reaction using the Jülich CV-28 compact cyclotron, removed from the target material using a dry distillation technique, and dissolved as n.c.a. radiobromide in triply-distilled water (21,22).

Synthetic optimization studies were performed using dichloramine-T and peroxide-acetic acid as oxidizing agents. All solvents used in these radiobromination experiments were of reagent grade. Dichloramine-T (DCT) was prepared from chloramine-T (E. Merck, Darmstadt) as described in the literature (23). For experiments with DCT, 2oo-5oo mCi (1o-25 µl) of aqueous n.c.a. $^{77}Br^-$ was added to a 2 ml reaction vial containing 1 mg of compound (1), (2), (3) or (4) in 1 ml methanol. DCT (5oo µg/ml methanol) was then added to the mixture to initiate the oxidative n.c.a. radiobromination reaction. Following reaction at 25°C for two minutes, the entire reaction vessel contents were removed and analyzed using radio-HPLC (4x25o mm Lichrosorb RP-18 (7 µm); MeOH/o.1 % NEt_3 = 7o/3o, 2.5 ml/min). One-minute fractions of the HPLC eluate were collected and the radioactivity measured in an automated NaI(Tl) well-type scintillation counter. The radioactivity in the fractions corresponding to compounds (5)-(8) (cf. Table 1) were compared to that in a standard sample of the injectate to allow calculation of the radiobromination yields shown in Table 2 and in Figure 2. In Figure 2, the chlorination yields were determined by comparison of the

UV absorbance of the injected sample with a UV absorbance-mass calibration curve.

Radiobromination experiments using peroxide-acetic acid were performed with 2oo-5oo µCi n.c.a. $^{77}Br^-$ in 2o µl H_2O and 1 mg compound (1), (2), (3), or (4). 5oo µl of glacial acetic acid/35 % H_2O_2 = 1/2 was added and the reaction mixture stirred at 25°C for thirty minutes. The reaction vessel contents were removed and extracted with 4 ml 5 % Na_2SO_3 and 4 ml $CHCl_3$. A 1oo µl aliquot of each phase was removed and the radioactivity content determined using a NaI(Tl) scintillation counter to allow calculation of the % organic yield for the reaction. A 1oo µl sample of the organic phase was analyzed by radio-HPLC as described above to determine the yield of radiobrominated spiperone analogue. The radiochemical yields after thirty minutes were less than 1o % for compounds (9)-(12).

Preparation of Radiobrominated Compounds for In-Vivo Application.

Based on the optimization studies which show that high radiochemical yields are rapidly obtained using DCT, this oxidizing agent was also employed in the preparative syntheses of radiolabelled compounds for *in vivo* studies. 1o mCi n.c.a. $^{77}Br^-$ in 1 ml H_2O was dried under reduced pressure, followed by reaction of 1 mg compound (1), (2), (3), or (4) in 1 ml MeOH containing 1oo µg DCT for 1o m at 25°C. The reaction vessel contents were then removed and injected onto a 4x25o mm Lichrosorb RP-18 (7µm) HPLC column eluted with a mobile phase of MeOH/o.1 % NEt_3 = 7o/3o, 5.o ml/min. The fraction of the eluent corresponding to compound (9)-(12) was eluted through a second 4x25o mm Lichrosorb RP-18 (7 µm) column to minimize tailing of

chlorinated side-products into the radiobrominated compound peak. The product fractions were collected and the solvent removed at reduced pressure. The high effective specific activity radiobrominated compounds (9)-(12) were re-dissolved in physiological saline solution containing 10 % absolute ethanol. Overall radiochemical yields of 20-30 % were achieved with a total preparation time of 70-90 minutes, and a specific activity exceeding 2000 Ci/mmol as determined by UV absorption.

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