Synthesis of [^{82}Br]Bromperidol and Preliminary Tissue Distribution Studies in the Rat

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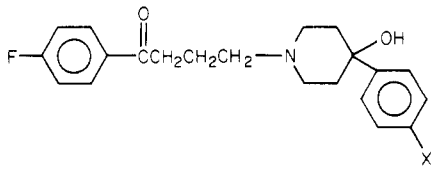
A procedure is described for the preparation of [^{82}Br]bromperidol with specific activity 440 μCi/mg. The incorporation of bromine-82 into the molecule was accomplished through Brackman and Smit's modification of the Sandmeyer reaction, during the last step of the synthetic route. This involved the formation of a complex between $Cu^{82}Br_2$ and nitric oxide gas in acetonitrile, which was then allowed to react with 4-[4-(aminophenyl)-4-hydroxypiperidinyl]-1-(4-fluorophenyl)-1-butanone (aminoperidol, **10**) to give [^{82}Br]bromperidol in about 1.5 h. Cupric [^{82}Br]bromide was prepared in situ from K^{82}Br and $CuSO_4 \cdot 5H_2O$. The radiochemical and chemical yields for the preparation of [^{82}Br]bromperidol from K^{82}Br were 10.4 and 12%, respectively. Preliminary tissue distribution studies with the labeled bromperidol in the rat showed that the uptake of radioactivity by the liver, brain, kidneys, and the lungs was very fast and was in the declining phase in the latter three organs 15 min after iv administration.

It is often assumed that therapeutic response is proportional to drug levels in blood. However, pyschotropic drugs such as the butyrophenones often provide difficulties with regard to this assumption. Some preliminary studies in rats and humans seem to indicate that the neuroleptic activity and therapeutic response of haloperidol (**2**)[1-4] and



bromperidol (1), X = Br
haloperidol (2), X = Cl

other neuroleptics[5,6] are not related to drug levels in blood. Janssen et al.[1] found that neuroleptic activity of haloperidol and several other butyrophenones correlated well with concentrations of these drugs in brain, the target organ, but suggested that blood levels need not be related to parameters of interest. Additionally, these compounds exhibit a large interpatient variation with regard to blood levels[3] and therapeutic response[2] and, consequently, the dose regiment is usually adjusted on an individual patient basis.

Possibly, the availability of butyrophenones labeled with γ-emitting radionuclides could provide an opportunity for investigators to establish a correlation between dose, blood levels, and brain levels in humans. In this connection, a synthetic route for the preparation of [^{18}F]haloperidol was developed in our laboratories[7,8] and its tissue distribution was studied in experimental animals.[8] Due to the relatively long biological half-life of these butyrophenones, it was felt, however, that more meaningful and complete pharmacokinetic data could be obtained with bromperidol (**1**), a new butyrophenone neuroleptic, labeled with ^{82}Br or ^{77}Br. These two radionuclides have relatively long half-lives of 35.4 and 56 h, respectively. Bromine-82 has an added advantage over ^{18}F in that it is commercially available. Moreover, the relatively long half-lives of ^{77}Br and ^{82}Br render [^{77}Br]- or [^{82}Br]bromperidol more amenable to studies, such as the effect of chronic administration and the administration of other psychotropic agents on the tissue (particularly brain) distribution of this compound. To date, very few studies have been done with bromperidol, which is undergoing clinical trials.[9-14] Preliminary investigations in humans and animals have shown the drug to be at least as potent as haloperidol, the prototype of the butyrophenone neuroleptics, with possibly a faster onset and longer duration of action.[10-13] Very little information is available on the tissue distribution of bromperidol.[9,14]

This paper deals with the development of a synthetic route for the labeling of bromperidol with radioactive bromine. Preliminary results regarding the tissue-distribution studies in four target organs in the rat are also reported. In this study, ^{82}Br was used for convenience since it is commercially available. The same method can be used for the synthesis of [^{77}Br]bromperidol. The nuclide of preference for external scintigraphic studies would be ^{77}Br due to its emission characteristics.[15]

Results and Discussion

The butyrophenone neuroleptics are usually administered in very low doses. For example, the suggested maintenance dose for bromperidol is 4–6 mg daily.[13] Thus, it is evident that in order to perform any meaningful experiments it is necessary to synthesize [^{82}Br]bromperidol with a very high specific activity. For this reason, isotope exchange reactions were considered inappropriate. An exchange reaction was nevertheless attempted,[16] without success, using the conditions described by Ndiokwere[17] for

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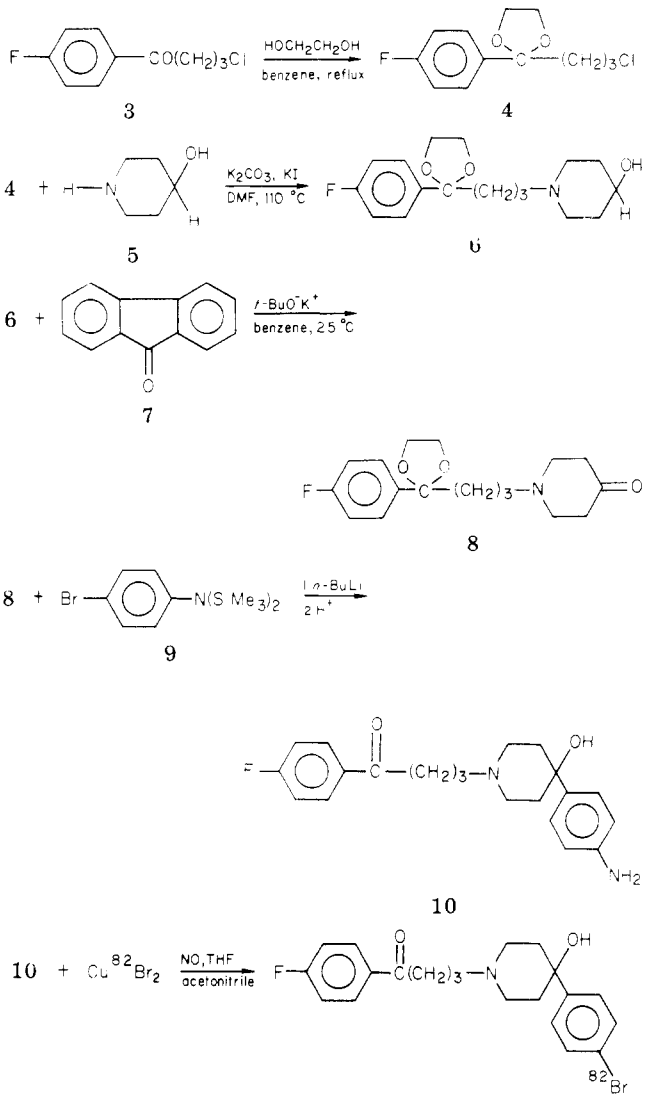
Scheme I

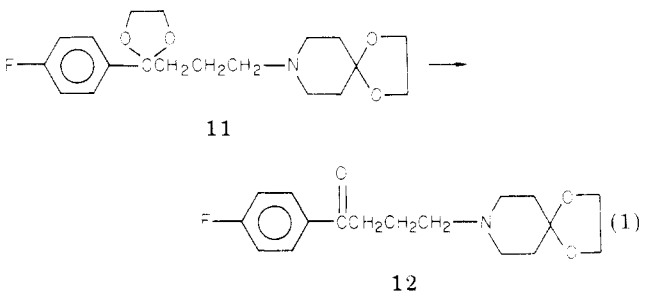


^{18}F exchange. After some preliminary investigations, direct bromination reactions with free bromine in acidic media were also excluded, mostly because of the nonspecificity of the reaction and the absence of electron-donating groups on the aromatic ring to be brominated.

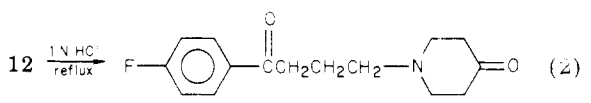
The synthetic sequence developed in our laboratory for the preparation of [^{82}Br]bromperidol is depicted in Scheme I, where the incorporation of radioactive bromine was achieved in the last step of this procedure by use of a Sandmeyer-type reaction. This work represents the first synthetic approach for the bromination of an aromatic ring with $^{82}Br^-$. Previous methods dealt with the conversion of $^{82}Br^-$ to $^{82}Br_2$ with subsequent electrophilic aromatic substitution[15,18] which, as mentioned earlier, is a nonspecific reaction. Such methods suffer from the added disadvantage that the conversion of Br^- to Br_2 is rather difficult to achieve in high yields.[18] The work described here permits the incorporation of bromine at a specific position on an aromatic ring.

A key step in the above scheme was the preparation of compound **10**, whose synthesis had not been previously reported. This involved an exchange reaction between *p*-bromo-*N*,*N*-bis(trimethylsilyl)aniline (**9**) and butyllithium, yielding 4-[*N*,*N*-bis(trimethylsilyl)]phenyllithium which reacted with monoketone **8** to give the desired product in 25% yield. The usefulness of the trimethylsilyl function for the protection of the aminophenyl group in organometallic reactions has been demonstrated.[19] Although compound **8** has been previously reported in the literature,[20,21] the synthetic details for its preparation are scanty and we therefore had to develop a new method for its synthesis. This involved the preparation of the 4-piperidine alcohol **6** from ketal **4** and 4-piperidinol (**5**) in 67% yield and its subsequent oxidation. Using UV spectroscopy, it was shown that the butyrophenone ketal function is very unstable in acidic media.[16] Thus, when the diketal **11** was subjected to 2 N HCl at room temperature, the monoketal **12** was obtained in less than 5 min (eq 1). Compound **12** was further hydrolyzed to diketone

Scheme II



13 by refluxing in 1 N HCl for 10 h (eq 2). Several at-



tempts to synthesize aminoperidol **10** from the diketone **13** by organometallic reactions failed, although literature information as well as our own experience tended to indicate that under certain conditions the piperidone carbonyl could be attacked in preference to the butyrophenone carbonyl. For example, Ikawa et al. have reported the synthesis of haloperidol by reacting diketone **13** with *p*-chlorophenylmagnesium bromide.[22]

The great lability of the butyrophenone ketal in acidic media, as well as the presence of the piperidine nitrogen and the susceptibility of the piperidine ring to oxidation,[16] necessitated the use of very mild nonacidic conditions for the oxidation of alcohol **6** to monoketone **8**. The modified Oppenauer oxidation[23-25] was found to offer the mildest conditions for this conversion, and by using 9-fluorenone as the hydride acceptor[24] at room temperature the oxida-

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Table I. Tissue Distribution of ^{82}Br Activity at Various Intervals Following an Intravenous Injection of [^{82}Br]Bromperidol[a] in Rats (% Dose/g ± SD)[b]

sacrifice time, min	blood	brain	kidneys	liver	lungs
15	0.15 ± 0.01	0.58 ± 0.07	1.63 ± 0.30	1.53 ± 0.17	5.07 ± 1.16
30	0.14 ± 0.01	0.41 ± 0.01	1.20 ± 0.18	1.66 ± 0.29	3.17 ± 0.78
45	0.14 ± 0.01	0.41 ± 0.05	1.03 ± 0.06	1.70 ± 0.13	2.75 ± 0.61
60	0.14 ± 0.02	0.32 ± 0.02	0.93 ± 0.04	1.58 ± 0.10	2.25 ± 0.45
120	0.12 ± 0.01	0.20 ± 0.01	0.61 ± 0.03	1.44 ± 0.21	1.23 ± 0.17

[a] Dose 0.2 mg/kg, 19–22 μCi. [b] The values represent the mean and standard deviation of three points.

tion product (8) was obtained in 50% yield.

The procedure described by Brackman and Smit in 1966[26] was found to be the most suitable reaction to use for the conversion of aminoperidol **10** to [^{82}Br]bromperidol (**1**). Unlike all other versions of the Sandmeyer reaction, this method is a one-vessel reaction and it involves the use of only one chemical form of bromine, namely copper(II) bromide. Thus, by slightly modifying this procedure we were able to synthesize [^{82}Br]bromperidol with a relatively high specific activity, 0.44 mCi/mg.

The conversion of K^{82}Br to Cu^{82}Br$_2$ was achieved by stirring a mixture of K^{82}Br and $CuSO_4$ in acetonitrile as shown in Scheme II. The low chemical and radiochemical yields of the last reaction, 12 and 10.4%, respectively, from K^{82}Br are believed to be due to the incomplete conversion of K^{82}Br to Cu^{82}Br$_2$, since a 60% yield is obtained for the conversion of aminoperidol **10** to nonlabeled bromperidol (see Experimental Section) using $CuBr_2$ directly.

A solution of [^{82}Br]bromperidol was administered by an iv injection to 15 rats. The rats were serially sacrificed, and their major organs were removed and counted. The counts in each organ were corrected for decay.

Due to the relatively long half-life of ^{82}Br, it was not necessary to correct the counts for the dead time of the instrument. The samples were allowed to decay to approximately equal radioactivity levels (~12 000 cpm) before they were counted. At this level of radioactivity, the dead time was more or less uniform for all samples and not more than 5% of the counting time, which was 100 s.

A summary of the data obtained after iv injection of [^{82}Br]bromperidol to rats is shown in Table I. It shows concentrations of radioactivity, expressed as % dose/g, in various organs as a function of time.

As was the case with haloperidol,[8] bromperidol concentrated overwhelmingly in the lungs. This finding could be explained in terms of the great lipophilicity of these butyrophenones which might cause the retention of the drug in the lipoprotein membrane of the alveolar capillary wall. On the other hand, it is also possible that partial precipitation of the drug in the blood, due to its poor solubility, may result in trapping of radioactivity in pulmonary capillaries, causing the lung to show high concentrations of radioactivity. However, this possibility can be excluded by comparing the solubility of bromperidol in water and the concentration of the drug attained in blood after its iv injection to the rats. Bromperidol dissolves in water to the extent of 0.09 mg/mL; the dose administered to rats was approximately 0.06 mg injected into the jugular vein over a period of 1–2 min. Considering that the volume of blood of rats (300 g) is approximately 20 mL, a dose of 0.06 mg would result in blood concentrations of 3 μg/mL, well below the solubility limit of bromperidol. It should also be noted that, due to its high protein binding and its solubility in red blood cells, bromperidol is expected to be much more soluble in blood than in water.

As can be seen from Table I, the uptake of radioactivity into brain, kidneys, liver, and lungs was very fast. Fifteen minutes after iv injection of 0.2 mg/kg of ^{82}Br-labeled bromperidol, radioactivity levels in blood, brain, kidneys, and lungs were already in a declining phase. At this point, the radioactivity levels, expressed as % dose/g, in blood, brain, kidneys and lungs were 0.15, 0.58, 1.63, and 5.1, respectively. Radioactivity levels in liver were still rising and reached their peak value of 1.7% dose/g 45 min after administration. Our findings parallel those of Marcucci et al.,[27] who reported peak brain levels of haloperidol minutes after iv injection. Similar results were also obtained by Chesseaud[14] following an oral administration of specifically tritiated bromperidol to dogs and humans.

In this preliminary study, no attempts were made to determine the nature of ^{82}Br radioactivity in the various organs. However, it has been shown by Lewi et al.[28] that in the first hour after sc administration more than 80% of the total butyrophenone brain levels is due to the intact drug. The loss of bromine on the aromatic ring as the bromide ion during the brief duration of the study is unlikely. For example, Sargent et al.[15] found that following an oral and iv administration of 4-[^{82}Br]bromodimethoxyphenylisopropylamine to four human subjects, only 5% of the radioactivity excreted in the urine over 24 h was due to inorganic bromide.

It can be clearly seen from Table I that bromperidol, like haloperidol, exhibits a large coefficient of distribution with a relatively small portion of the total dose in the blood. These findings tend to support the claim that the pharmacological action of butyrophenones might be correlated better with brain levels than with blood levels.[1-4]

The synthesis of [^{82}Br]bromperidol as desceribed in this report will enable us and other investigators to undertake more detailed studies regarding the in vivo distribution of this butyrophenone neuroleptic. The specific activity of [^{82}Br]bromperidol obtained by this method is high enough to allow for external scintigraphic studies to be undertaken in humans. Such studies have been performed with ^{82}Br-labeled compounds using doses as low as 20 μCi.[15] At this level, the whole body radiation dose was estimated at 9 mrd.

Experimental Section

Melting points were determined on a Fisher-Johns (hot stage) apparatus and are uncorrected. All new compounds were characterized by NMR, IR, UV, and elemental analyses (C, H, N), which were within ±0.3% of the theoretical values unless otherwise indicated. IR spectra were determined on a Perkin-Elmer IR-567 spectrophotometer using $CHCl_3$ solutions or KBr pellets. UV

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spectra were determined on Cary Models 15 and 118 UV–visible spectrophotometers using MeOH as solvent. NMR spectra were recorded on a Varian EM-360 spectrometer using $CDCl_3$ as solvent and Me_4Si as the internal standard. All solvents used in the preparations were reagent grade and were distilled and dried before use. Solvent extracts were dried using anhydrous $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure (water pump) using a Buchi rotavapor. The *n*-butyllithium solution in hexane (Aldrich) was standardizxed before each use according to the method of Gilman and Haubein.[29] Bromine-82 was purchased from New England Nuclear in the form of $K^{82}Br$.

4-Chloro-1,1-(ethylenedioxy)-1-(4-fluorophenyl)butane (4) was prepared by treating **3** with ethylene glycol and *p*-toluenesulfonic acid in dry benzene according to Nakatsuka et al.:[30] yield 89%; ^1H NMR ($CDCl_3$) δ 1.9–2.0 (m, CH_2CH_2CCl, 4), 3.4–3.6 (t, CH_2Cl, 2), 3.7–4.1 (2 symmetrical m, OCH_2CH_2O, 4 H), 6.9–7.2 (t, Ar H, 2), 7.3–7.6 (m, Ar H, 2).

1-[4-(4-Fluorophenyl)-4,4-(ethylenedioxy)butyl]-4-hydroxypiperidine (6) was prepared by heating a mixture of **4** (13 g, 0.053 mol), 4-hydroxypiperidine (**5**; 5.4 g, 0.053 mol; Aldrich), anhydrous K_2CO_3 (8.3 g), KI (1 g), and anhydrous DMF (200 mL) at 110–120 °C for 6 h. The mixture was cooled, diluted with H_2O (150 mL), and extracted with ethyl acetate (4 × 100 mL). The organic extract was washed with H_2O (3 × 100 mL) and evaporated to dryness to give a thick yellow liquid. Trituration with benzene and petroleum ether gave a white solid (11 g, 0.036 mol, 67% yield). This was recrystallized from isopropyl ether: mp 78 °C, lit.[31] 79–81 °C; ^1H NMR ($CDCl_3$) δ 2.6–2.8 (m, CH_2N, 2), 3.0 (s, OH, 1), 3.6 (m, C*H*OH, 1), 3.7–4.1 (2 symmetrical m, OCH_2CH_2O, 4), 6.9–7.2 (t, Ar H, 2), 7.3–7.6 (m, Ar H, 2); IR ($CHCl_3$) ν_{max} 3600 and 3450 (OH); UV (MeOH) λ_{max} 256 nm (ϵ 410), 262 (610), 268 (600). Anal. ($C_{17}H_{24}FNO_3$) C, H, N.

1-[4-(4-Fluorophenyl)-4,4-(ethylenedioxy)butyl]-4-piperidinone (8) was prepared by subjecting alcohol **6** to conditions of a modified Oppenauer oxidation. A mixture of alcohol **6** (7 g, 0.023 mol), 9-fluorenone (**7**; 20 g, 0.111 mol), potassium *tert*-butoxide (6 g, 0.053 mol), and anhydrous benzene (200 mL) was introduced into a flask that had been previously heated to 150 °C and cooled under nitrogen. Vacuum was applied until vigorous bubbling was observed, and the reaction mixture was stirred under vacuum in the dark, at room temperature for 2.5 h. Water (100 mL) was then added, the two layers were separated, and the aqueous layer was extracted with benzene (3 × 50 mL). The combined benzene extracts were washed with H_2O (3 × 100 mL) and extracted with ice-cold 0.06 N HCl solution (5 × 200 mL). Each acidic extract was washed with benzene (200 mL) and transferred and pooled into a flask containing 100 mL of 15% Na_2CO_3 solution. The alkaline solution was extracted with $CHCl_3$ (4 × 200 mL). The $CHCl_3$ extract was dried and evaporated to dryness, yielding 7 g of a yellow viscous oil. Trituration with isopropyl ether gave a white solid which was recrystallized from diethyl ether to give the pure product: mp 63 °C; yield 3.5 g (11.3 mmol, 50%); ^1H NMR ($CDCl_3$) δ 1.5–1.9 (m, 6), 2.3–2.7 (m, 8), 3.7–4.1 (2 symmetrical m, OCH_2CH_2O, 4), 6.9–7.2 (t, Ar H, 2), 7.3–7.6 (m, Ar H, 2); IR ($CHCl_3$) ν_{max} 1710 cm^{-1} (piperidinone C=O); UV (MeOH) λ_{max} 256 nm (ϵ 940), 268 (930). Anal. ($C_{17}H_{22}FNO_3$) C, H, N.

***p*-Bromo-*N*,*N*-bis(trimethylsilyl)aniline (9)** was prepared by a modified procedure of Walton.[19] *p*-Bromoaniline was reacted with ethylmagnesium bromide to give *N*-(*p*-bromoaniline)magnesium bromide, which was reacted with chlorotrimethylsilane to give *p*-bromo-*N*-(trimethylsilyl)aniline, which was then allowed to react with *n*-BuLi and chlorotrimethylsilane to give the desired product **9**: yield 60% (based on *p*-bromoaniline); ^1H NMR δ 0.05 (s, $SiCH_3$, 18), 6.6–6.8 (d, Ar H, 2), 7.2–7.4 (d, Ar H, 2).

4-[4-Hydroxy-4-(4-aminophenyl)piperidinyl]-1-(4-fluorophenyl)butanone (10). A solution of *p*-bromo-*N*,*N*-bis(trimethylsilyl)aniline (**9**; 5.7 g, 0.018 mol) in 10 mL of dry hexane was injected into a three-neck flask fitted with a serum cap and a reflux condenser. (The glassware had been previously heated to 150 °C and cooled under nitrogen.) The solution was degassed, placed under a nitrogen atmosphere, and cooled in an ice bath. A hexane solution of *n*-butyllithium (10.6 mL, 0.018 mol) was added, and the resulting mixture was heated at 60 °C for 5 min and then cooled in an ice bath. A solution of **8** (5 g, 0.016 mol) in purified THF (15 mL) was added, and the resulting mixture heated at 50 °C for 2.5 h. After cooling, the reaction mixture was treated with 20 mL of 4 N HCl and stirred overnight at room temperature. The pH of the solution was adjusted to about 10 and extracted with $CHCl_3$ (4 × 50 mL). The extract was dried and evaporated to dryness to give a red viscous oil. Trituration with hot benzene and petroleum ether gave 1.45 g (4.1 mmol, 25% yield) of yellowish crystals. The product was purified by recrystallization from benzene: mp 149–150 °C dec; ^1H NMR δ 1.8–3.2 (m, 15), 3.5 (br, NH_2, 2, disappeared with D_2O), 6.4–6.6 (d, Ar H, 2), 6.9–7.2 (m, Ar H, 4), 7.8–8.1 (q, Ar H, 2); IR (KBr) ν_{max} 3490, 3360, 3230 (OH and NH), 1680 cm^{-1} (butyrophenone C=O); UV (MeOH) λ_{max} 241 nm (ϵ 24 × 10^3), 280 (1.8 × 10^3, disappeared with acidification). Anal. ($C_{21}H_{26}ClFN_2O_2$) C, N; H: calcd, 6.41; found, 6.92.

Synthesis of Bromperidol (1). The copper(II) bromide used in this reaction was either purchased from Fisher or prepared in situ by stirring a mixture of KBr (0.24 g, 2 mmol), $CuSO_4 \cdot 5H_2O$ (0.5 g, 2 mmol) and 10 mL of acetonitrile at room temperature for 6 h. In either case, the $CuBr_2$ solution was cooled in an ice bath, the system was purged with nitrogen, and nitric oxide was bubbled through the solution (1–2 bubbles/min) for 10 min. A solution of **10** (0.356 g, 1 mmol) in 7 mL of purified THF was added dropwise over a period of 5 min. The resulting mixture was stirred at 0 °C for 0.5 h, the ice bath was removed, and stirring was continued for 1 h. The nitric oxide bubbling was discontinued and 10 mL each of 8 N NH_4OH solution and $CHCl_3$ were added and mixed well. The aqueous layer was extracted with $CHCl_3$ (2 × 10 mL), and the combined $CHCl_3$ extracts were washed with H_2O, dried, and evaporated to dryness. A reddish brown solid was obtained, which was subjected to column chromatography (neutral alumina, activity stage III, 25 g). An impurity was first eluted with benzene–$CHCl_3$ (1:1). Elution with $CHCl_3$ gave 0.25 g (60% yield from **10**) of a white crystalline solid, which was shown, after one recrystallization from $CHCl_3$–ether (1:4), by mixture melting point, two-dimensional TLC [using $CHCl_3$–MeOH–concentrated NH_4OH (90:10:1) and 2-propanol–4 N NH_4OH (100:2) as solvents], and comparative spectroscopic determinations (IR, NMR, and UV) to be identical with authentic bromperidol. **Caution: Due to the highly toxic nature of NO gas it is essential to carry out the reaction in a well-ventilated hood!**

Synthesis of [^{82}Br]Bromperidol (1). A mixture of 3.8 mg of $K^{82}Br$ (3.8 mg, 0.032 mmol, 6.7 mCi), powdered $CuSO_4 \cdot 5H_2O$ crystals (7.2 mg, 0.032 mmol), and 0.8 mL of acetonitrile was stirred in a 5-mL round-bottom flask equipped with a serum cap at room temperature for 4 h. The resulting mixture was cooled in an ice bath and then nitrogen and nitric oxide gas were sequentially passed over the solution for about 1 min each. Stirring was continued for 15 min, a solution of **10** (6.1 mg, 0.017 mmol) in 0.2 mL of purified THF was added, and the mixture was stirred at 0 °C for 30 min. The ice bath was then removed and the mixture was stirred at room temperature for 1 h. Chloroform and 8 N NH_4OH (0.5 mL each) were then added, the two layers were separated, and the aqueous layer was then extracted with $CHCl_3$ (2 × 0.5 mL). The volume of the combined $CHCl_3$ extracts was reduced by applying gentle heat and a stream of nitrogen. The residue was dissolved in $CHCl_3$ (0.1 mL) and chromatographed on neutral alumina (activity stage III, 3 g, 11 × 1 cm), eluting with $CHCl_3$. Ten 1-mL fractions were collected, and the residue obtained by evaporation of pooled fractions 3–9 was dissolved in methanol, giving 1.6 mg (700 μCi) of [^{82}Br]bromperidol (12% chemical yield, 10.4% radiochemical yield from KBr). The purity and identity of the product were determined by TLC (as described for nonlabeled bromperidol) and UV spectroscopy. A radioscan before and after column chromatography of the TLC plate using $CHCl_3$–MeOH–concentrated NH_4OH (96:4:1) as eluant showed all the activity coincident with the spot of authentic bromperidol. The chemical yield was calculated using UV spectroscopy after all the radioactivity had decayed.

Animals. Fifteen male Sprague–Dawley rats weighing 300–320 g were used for the experiments. The rats had free access to food

(29) H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, **66**, 1515 (1944).
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(31) British Patent 1 120 405, July 17, 1968.

and water until the time of the experiments. All animals were anesthetized with sodium pentobarbital solution (45 mg/kg, Abbott) prior to injection with labeled drug.

Dose and Route of Administration. Immediately after synthesis [^{82}Br]bromperidol was dissolved in 10.0 mL of the injection mixture, which consisted of propylene glycol–ethanol–water (40:20:40) and had its pH adjusted to 4 using concentrated HCl. An aliquot of the solution was counted to determine the exact dose of ^{82}Br radioactivity. Each animal received an intravenous bolus injection in the jugular vein of 19–22 μCi (0.2 mg/kg) of [^{82}Br]bromperidol.

Collection and Counting of Tissue Samples. After injection of [^{82}Br]bromperidol, rats were sacrificed by cardiac puncture at time intervals of 15, 30, 45, 60, and 120 min. A sample of blood was first collected with a syringe, followed by removal of liver, kidneys, lungs, and brain. All samples were placed in preweighted glass scintillation vials and counted in a Packard γ counter by monitoring the 777-keV peak. Counts were corrected for decay, and all samples were weighed after counting.

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Notes

Glycerides as Prodrugs. 2. 1,3-Dialkanoyl-2-(2-methyl-4-oxo-1,3-benzodioxan-2-yl)glycerides (Cyclic Aspirin Triglycerides) as Antiinflammatory Agents[1]

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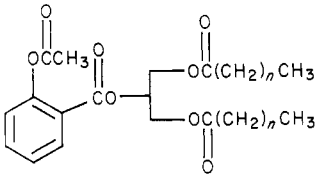
A series of 1,3-dialkanoyl-2-(2-methyl-4-oxo-1,3-benzodioxan-2-yl)glycerides ("cyclic aspirin triglycerides") was synthesized. They demonstrated essentially all the systemic antiinflammatory activity associated with aspirin in the carrageenin-induced rat paw edema test. Examination of the rat stomachs showed that the 1,3-didecanoyl derivative did not cause gastric lesions.

The antiinflammatory activity and the absence of gastric irritation properties of a series of 1,3-dialkanoyl-2-(*O*-acetylsalicyloyl)glycerides (1) having aspirin at the 2

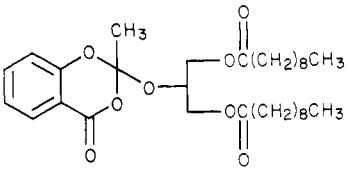


1

position of glycerol and fatty acids at the 1 and 3 positions have been reported in a previous paper.[3]

The most active member of this series was the 1,3-didecanoyl derivative (**1**, $n = 8$). During the purification of this compound by column chromatography, a byproduct was isolated and characterized as 1,3-didecanoyl-2-(2-methyl-4-oxo-1,3-benzodioxan-2-yl)glyceride (**2b**).

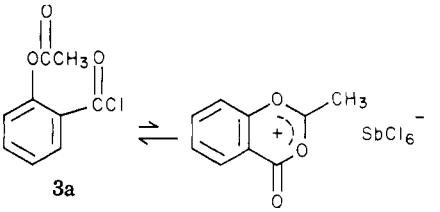
We now report the synthesis and the pharmacological properties of a series of glycerides in which aspirin in **1** is replaced by a 2-methyl-4-oxo-1,3-benzodioxan-2-yl moiety in the 2 position. For convenience, we will refer to this



2b

series of compounds as the "cyclic aspirin triglycerides".

Chemistry. It was reported by Brinkman and Rüchardt in 1972[4] that *O*-acetylsalicyloyl chloride (**3a**) exists as an



3a 3b

equilibrium mixture with the cyclic structure **3b**, which was isolated as the hexachloroantimonate salt.

In 1974, Rüchardt and Rochlitz[5] reported the isolation of the cyclic compound 4 as the main product obtained when a solution of *O*-acetylsalicyloyl chloride and alcohol (or phenol) was heated in tetrahydrofuran in the presence of a base.

(1) This work has been presented in part at the 176th National Meeting of the American Chemical Society, Miami Beach, Fla., Sept 11–15, 1978.
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