1.46 g (82%) of the amine, bp 97–99 °C (0.06 mm). The HCl salt was prepared by bubbling HCl through an Et_2O solution of the amine at 0 °C. The salt was collected and precipitated from absolute EtOH by the dropwise addition of Et_2O to afford small white needles, mp 136–137 °C. Anal. ($C_{13}H_{21}NO_2$·HCl) C, H, N.

Binding Affinity Studies. Sprague–Dawley rats, of either sex, weighing 200–250 g (Flow Laboratories, Dublin, Va.) were used. The rat stomach fundus preparation employed was essentially that described by Vane[29] with the following modifications: (a) the bathing solution, kept at 37 °C, was that of Armitage and Vane;[30] (b) no hyoscine was added to the bathing solution; (c) responses were recorded on a smoked drum revolving at 3 mm/min using a pendular auxotonic lever[31] with a magnification of 8 and a resting load on the muscle of 1 g; (d) two strips were cut from the same tissue and used in parallel; (e) the relative sensitivity of the two strips was determined, after a 1-h equilibration period, by the use of 5-HT doses giving submaximal contractions. Only one compound was tested per preparation.

The ability, or potency, of each agent to inhibit the contractile response to 5-HT was determined by obtaining cumulative dose–response curves to 5-HT, first in the absence of the agent in question and, then, in the presence of increasing concentrations thereof. A minimum of five dose–response curves was generated per run. The ED_{50} of 5-HT was determined for each of these curves and the apparent affinities calculated as pA_2 values by the method of Arunlakshana and Schild.[32]

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Facile Syntheses of Potent Dopaminergic Agonists and Their Effects on Neurotransmitter Release

A. S. Horn,* C. J. Grol, D. Dijkstra,

Department of Pharmacy, University of Groningen, Groningen, The Netherlands

and A. H. Mulder

Department of Pharmacology, Free University, Amsterdam, The Netherlands. *Received February 17, 1978*

The facile syntheses of important intermediates used in the preparation of the two potent dopaminergic agonists, 2-amino-6,7-dihydroxytetrahydronaphthalene (11) (referred to by some authors as ADTN) and its 5,6-dihydroxyl isomer 12, are described. Thus 6,7-dimethoxy-2-tetralone has been prepared in two steps and 5,6-dimethoxy-2-tetralone in three steps both from commercially available materials. The effects of 11, 12, and the noncatechol analogue, 2-aminotetrahydronaphthalene (ATN), on radioactive neurotransmitter release have been studied in vitro using rat brain slices. It has been shown that both 11 and 12, at a concentration of 2 μM, cause a release of [^{3}H]-DA and NA, 11 being more potent than 12 in releasing [^{3}H]-DA. ATN (2 μM) was found to be inactive in these experiments which shows the importance of the catechol function in this uptake–release process.

Although L-Dopa is currently the drug of choice for the treatment of parkinsonism its use is complicated by various side effects and problems due to metabolic loss, and there is currently great interest in finding other possible dopamine (DA) receptor agonists.[1] Two DA analogues which have attracted attention in recent years are 2-amino-6,7-dihydroxytetrahydronaphthalene (11) (referred to by some authors as ADTN) and the isomeric 2-amino-5,6-dihydroxytetrahydronaphthalene (12). A variety of neurochemical, pharmacological, and behavioral evidence

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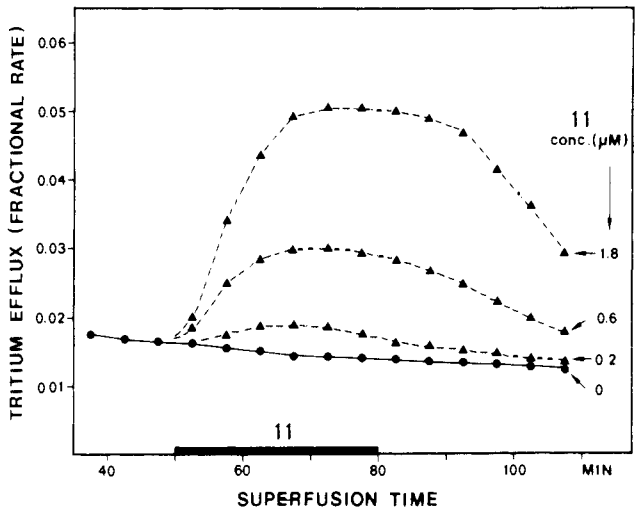


Figure 1. Dose-dependent stimulation by 11 of the tritium efflux from striatal slices previously labeled with [^{3}H]-DA. Slices were labeled by incubation with [^{3}H]-DA and subsequently superfused with KRB medium. From t = 50 to t = 80 min (indicated by solid bar) 11, in various concentrations, was present in the medium.

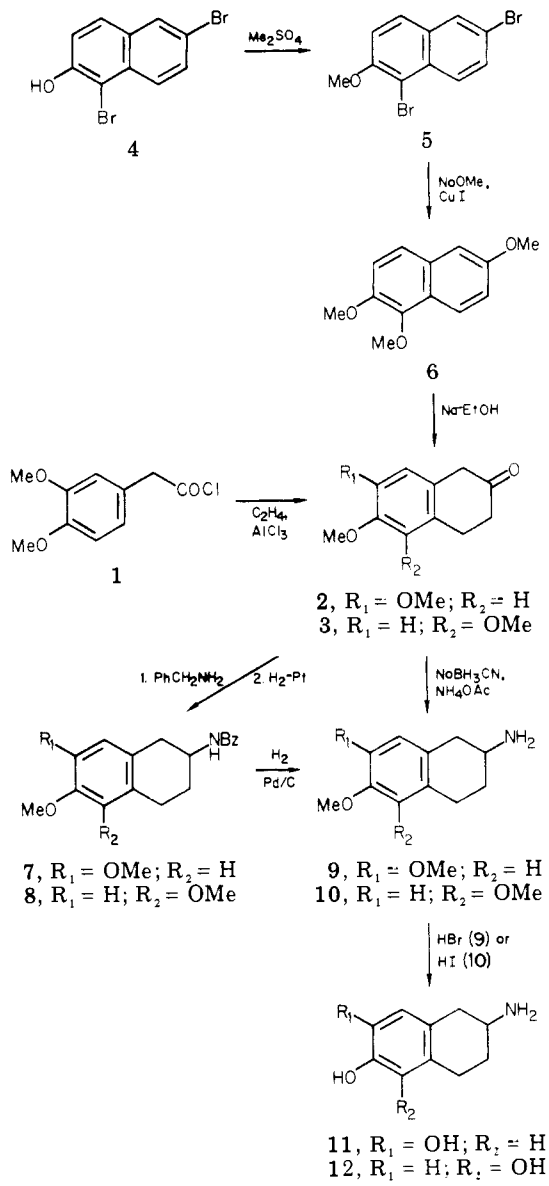
has clearly shown that these two drugs are selective, potent, and long-acting DA agonists.[2-5] One of the problems with these two compounds, however, is that due to the difficulty of synthesis they have only been available in very small amounts to a very limited number of investigators. As part of our program aimed at the development of new DA agonists and prompted by the recent publication[6] of a new synthesis of 11 and 12 we now report details of our syntheses of these drugs which we believe offer advantages over existing methods and which, therefore, may make these compounds more readily available to a larger number of research workers.

Chemistry. In both synthetic routes the key intermediates were the dimethoxy-2-tetralones 2 and 3. The tetralone 2 was readily synthesized in a yield of 50% from the acid chloride 1 and ethylene using a Friedel–Crafts reaction.[7,8] The acid chloride 1 was obtained[9] in a yield of 92% from the inexpensive, commercially available 3,4-dimethoxyphenylacetic acid. This is a considerable improvement on the two literature syntheses of 2 which consist of seven[10] and four[6] steps, respectively. The second tetralone 3 was prepared in three steps from the commercially available 1,6-dibromo-2-hydroxynaphthalene (4) by methylation to the known 1,6-dibromo-2-methoxynaphthalene[11] (5), followed by methoxylation using sodium methoxide in the presence of cuprous iodide[12] to the known 1,2,6-trimethoxynaphthalene[13] (6). The reduction of the latter compound to the tetralone 3 has already been described.[14] This synthesis was found in practice to be more convenient than the published methods.[6,14]

For the synthesis of the primary amines we have found that the method of Mc Dermed et al.,[14] 2 and 3 to 9 and 10 via 7 and 8, gives good yields and easily purifiable products. However, the use of the NH_4OAc + $NaBH_3CN$ method of Cannon et al.,[6] 2 and 3 to 9 and 10, shortens the Mc Dermed route by one step. Conversion of the dimethoxyamines 9 and 10 to the catecholamines 11 and 12 was carried out by either refluxing with HBr[15] or HI[14] solutions, respectively. Thus it is now possible to prepare 11 in four steps and 12 in five steps from commercially available materials. It is noteworthy that the original synthesis of 11 consisted of eight steps[15] and that of 12 of nine[16] (see Scheme I).

Neurochemical Results and Discussion. In an attempt to gain more insight into the neurochemical mode

Scheme I



of action of these compounds we have studied the effect of 11, 12, and the noncatechol analogue, 2-aminotetrahydronaphthalene (ATN), on radioactive neurotransmitter release in vitro by the method of Dismukes et al.[17] using rat brain slices. Both 11 and 12 selectively affected catecholaminergic neurons; i.e., both drugs increased tritium efflux from striatal slices labeled with [^{3}H]-DA and from cortical slices labeled with [^{3}H]-NA (Figure 1 and Table I) without having an effect on the efflux of radioactivity originating from serotonergic, GABA-ergic, or cholinergic neurons after labeling with the appropriate radioactive transmitters. ATN was completely ineffective in causing a release of [^{3}H]-DA or NA, thus indicating that the catechol function is of importance in this uptake–release process. The releasing action of 11 on dopaminergic and noradrenergic neurons, respectively, was of a similar magnitude, while 12, however, appears to be somewhat more effective on noradrenergic than on dopaminergic neurons (Table I, $p < 0.01$, Student's t test). Nomifensine, a potent inhibitor of neuronal catecholamine uptake,[18,19] at a concentration of 5 μM completely blocked the releasing effect of 1 μM 11 on striatal slices labeled with [^{3}H]-DA and on cortical slices labeled with [^{3}H]-NA. Apparently, 11 and probably 12 as well are selectively transported into catecholaminergic nerve terminals by the

Table I. Stimulation by 11 and 12 of Tritium Efflux from Striatal Slices Labeled with [^{3}H]-DA and from Cortical Slices Labeled with [^{3}H]-NA[a]

drug used (2 μM concn)	drug-stimulated overflow of tritium (as % of total tissue content)	
	[^{3}H]-DA/ striatum	[^{3}H]-NA/ cortex
11	25.1 ± 3.3 (8)	22.1 ± 2.4 (4)
12	6.5 ± 1.0 (4)	11.0 ± 1.1 (4)
2-aminotetrahydronaphthalene (ATN)	−0.7 ± 0.5 (4)	−0.3 ± 0.3 (4)

[a] In double-label experiments slices were incubated with [^{3}H]-DA or [^{3}H]-NA and [^{14}C]-GABA or [^{14}C]choline. Subsequently they were superfused and exposed for 20 min (from t = 50 min) to a 2 μM concentration of one of the drugs mentioned. No effect was detectable on ^{14}C efflux. The results are presented as the mean ± SEM with the number of determinations in parentheses.

catecholamine uptake mechanism. Radiolabeled catecholamines are then subsequently displaced from the synaptic vesicles by these drugs and released from the nerve terminals.

It has already been established[20] that 11 is a potent inhibitor of [^{3}H]-DA uptake into striatal synaptosomes and our data clearly indicate that 11 itself is transported by the DA uptake system. This has also been confirmed using radioactive 11.[22] Our finding that 11 is a more potent releaser of [^{3}H]-DA from striatal slices than 12 provides some evidence for the recent speculations of Cannon et al.[6] and Costall et al.[4] regarding the pharmacological differences between these two drugs. In particular, it could possibly explain, to some extent, the enhanced behavioral effect seen with 11 after nialamide pretreatment.[4]

Experimental Section

Melting points were determined in open glass capillaries on a Büchi Tottoli apparatus and are uncorrected. Elemental analyses were performed in the Department of Chemistry, University of Groningen. Where elemental analyses are indicated, results obtained were within ±0.4% of the theoretical values. Infrared spectra were run on a Beckman Acculab 2. Mass spectra were obtained using a Finnigan 3300. 2-Aminotetrahydronaphthalene was purchased from E. Merck, Darmstadt, West Germany.

1,2,3,4-Tetrahydro-6,7-dimethoxy-2(1*H*)-naphthalenone (2). 3,4-Dimethoxyphenylacetyl chloride[9] (1) (40.0 g, 0.186 mol) was added dropwise over 1 h to a mixture of $AlCl_3$ (100.0 g, 0.750 mol) in 3.5 L of dichloromethane at a temperature of approximately −5 °C. After the addition was complete a rapid stream of dry ethylene was passed through the solution for 1–1.5 h and the reaction was followed by GLC (3% OV-17 on Chromosorb G.H.P., column temperature 215 °C) in order to determine exactly when the reaction was complete. The reaction mixture was cooled in an ice bath and 750 mL of ice–water was slowly added. The yellow organic layer was separated and washed with 2 N HCl and then with a saturated solution of sodium bicarbonate until neutral. The organic layer was then dried over anhydrous $MgSO_4$ and the volatiles were removed under reduced pressure to yield an oil. From the oil a bisulfite addition product was prepared. Regeneration of the tetralone from the adduct yielded a residue which, after crystallization from cyclohexane, yielded 18.6 g (50%) of white crystals: mp 85.5–86.5 °C (lit.[10] 87 °C); IR (KBr) 1715 cm^{-1} (C=O). A mass spectrum of this material exhibited a peak at m/e 206 corresponding to the molecular ion.

2-Benzylamino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (7). A solution of 1,2,3,4-tetrahydro-6,7-dimethoxy-2(1*H*)-naphthalenone (2) (6.60 g, 0.032 mol), benzylamine (4.30 g, 0.041 mol), and p-toluenesulfonic acid monohydrate (0.19 g, 0.001 mol) in 50 mL of dry benzene was refluxed 1.5 h under N_2 with continuous removal of water. The reaction is readily followed by IR spectroscopy due to the disappearance of the carbonyl peak at 1715 cm^{-1} and the appearance of a new peak at 1630 cm^{-1} (C=N). Most of the benzene was distilled off and 45 mL of ethanol was added. The solution was then transferred to a Parr reduction bottle, 50 mg of PtO_2 was added, and hydrogenation was performed at 2 atm of pressure until the reduction was complete (about 1.5–2.0 h). That the reaction had gone to completion was checked by the absence of a peak at 1630 cm^{-1} in the IR spectrum. The catalyst was filtered off and the solvent and excess benzylamine were evaporated at reduced pressure to yield an oil. The oil was diluted with 25 mL of ethyl acetate and HCl–ether was then added to yield a hydrochloride salt. After three recrystallizations from methanol–ethyl acetate 1.49 g (69%) of a white solid was obtained: mp 232.5–235 °C. Anal. ($C_{19}H_{24}ClNO_2$) C, H, N, Cl.

2-Amino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (9). 2-Benzylamino-6,7-dimethoxy-1,2,3,4-tetrahydronaphthalene (1.66 g, 0.0056 mol) was dissolved in 50 mL of absolute ethanol, 1.0 g of 10% Pd-on-charcoal catalyst was added, and the solution was hydrogenated in a Parr bottle under 2 atm of pressure for 45 min. The catalyst was filtered off and the ethanol removed under reduced pressure to yield an oil. Preparation of an HCl salt and recrystallization from methanol–ethyl acetate gave 1.21 g (89%) of a white solid: mp 223–224 °C (lit.[6,15] mp 220–221, 228–230 °C).

1,2,6-Trimethoxynaphthalene (6). Freshly cut sodium (20.3 g, 0.87 mol) was added under N_2 to 300 mL of dry methanol. When dissolution was complete the warm solution was diluted with 140 mL of dry 2,4,6-collidine and then 28 g (0.14 mol) of vacuum-dried cuprous iodide, 42 g (0.13 mol) of 1,6-dibromo-2-methoxynaphthalene (5), and 250 mL of 2,4,6-collidine were added. The mixture was stirred under N_2 while being maintained at reflux temperature for 20 h. After cooling the solution was filtered and acidified with 2 N HCl and the mixture was extracted three times with 200 mL of ether. The combined ether extracts were washed once with 2 N HCl and once with water and then were dried over anhydrous $MgSO_4$. After evaporation of the ether under reduced pressure the product was purified by column chromatography on alumina (Merck, activity 1), using $CHCl_3$ as the eluent, to yield 22.6 g (79%) of a white powder, mp 54–55 °C (lit.[13] mp 55 °C).

1. **Labeling of Brain Slices with Radioactive Neurotransmitters.** Male Wistar rats (140–180-g body weight) were decapitated and their brains were quickly removed. Tissue slices (approximately 1.5 × 1.5 × 0.3 mm) of the corpus striatum or the occipital cortex were prepared on a McIlwain tissue chopper. The slices were incubated at 37 °C in glass vials containing 5 mL of Krebs–Ringer bicarbonate (KRB) medium and placed in a Dubnoff metabolic incubator in a 95% O_2/5% CO_2 atmosphere. After 10 min of preincubation radiolabeled transmitters or their precursors were added and incubation was continued for 15 min. Many of the experiments were carried out in a double label fashion, i.e., incubation with one ^{3}H and one ^{14}C compound.

The radiolabeled compounds used (amount and approximate final concentration in the medium in parentheses) were [^{3}H]-dopamine (5 μCi, 0.2 μM), [^{3}H]noradrenaline (5 μCi, 0.1 μM), [^{3}H]serotonin (5 μCi, 0.05 μM), [^{14}C]-GABA (1 μCi, 1 μM), and [^{14}C]choline (0.5 μCi, 2 μM).

2. **Drug Effects on Efflux of Radioactivity from Brain Slices.** After the labeling procedure the slices were transferred to superfusion cells (0.25-mL volume; 5–6 slices per cell) and superfused with KRB medium essentially as described elsewhere.[17,21] Following 50 min of superfusion the appropriate drugs were added to the medium for 20–30 min in order to determine their effect on the spontaneous efflux of radioactivity. Thereafter superfusion was continued with drug-free medium for 30 min; 5-min fractions were collected.

At the end of all experiments the radioactivity remaining in the slices was extracted with 0.1 N HCl. Radioactivity in superfusion fractions and extracts was determined by liquid scintillation counting. The data were expressed in two ways (see Dismukes et al.[17]): (a) fractional rate of efflux of radioactivity and (b) drug-stimulated overflow of radioactivity in excess of spontaneous (basal) efflux, calculated as a percentage of the total tissue content at the onset of stimulation.

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In Vitro Antiplaque Properties of a Series of Alkyl Bis(biguanides)

Robert A. Coburn,*

Department of Medicinal Chemistry, School of Pharmacy

Pamela J. Baker, Richard T. Evans, Robert J. Genco,

Department of Oral Biology, School of Dentistry

and Stuart L. Fischman

Department of Oral Medicine, School of Dentistry, State University of New York at Buffalo, Buffalo, New York 14260.
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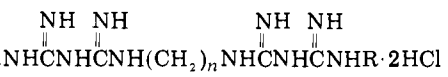
A series of eight alkyl bis(biguanide) analogues of alexidine, N,N''''-1,6-hexanediyl bis[N'-(2-ethylhexyl)imidodicarbonimidic diamide] (1), was prepared. Five of these analogues constituted a series isolipophilic with 1 but with varying bridge length between biguanide moieties. The compounds were evaluated in vitro for antibacterial and antiplaque properties against *Streptococcus mutans*, *Actinomyces viscosus*, and *Actinomyces naesludii*. One analogue, N,N''''-1,6-hexanediyl bis[N'-(*n*-octyl)imidodicarbonimidic diamide], appeared to be more effective than either 1 or chlorhexidine against this spectrum of dental plaque forming microorganisms.

In the search for chemotherapeutic agents for the control of dental diseases, the bis(biguanides) **1–10**, especially



1–10

chlorhexidine (**10**, R = *p*-chlorophenyl, n = 6), have received much attention.[1-8] The effectiveness of chlorhexidine in controlling the formation of dental plaque in humans has been ascribed to its antibacterial properties and substantivity in the oral cavity.[3,5,9]

Although studies by Davies[10] indicated that optimal antibacterial properties were associated with bis(biguanides) with hexamethylene bridges, Cutler[11] has shown that lipophilicity was the principal property correlating with this activity. Gjermo[6] evaluated a series of 1,6-bis(biguanidohexanes) for both in vitro antibacterial and in vivo antiplaque properties and found an alkyl derivative (R = cyclohexylmethyl) superior to chlorhexidine. Variations of bridge length, n = 2–12, of bis(biguanides) with *p*-chlorophenyl terminal groups were examined by Warner[7] who found comparable antibacterial activity in vitro among members in this series, while n = 2 or 10 resulted in lower antiplaque activity against *Streptococcus mutans* in vitro. Recently, a series of eight hexamethylene bridged alkyl bis(biguanides) was evaluated for in vitro antiplaque properties employing a bioassay involving preformed plaques on nichrome wires with drug solution contact for 30 min.[12]

In this study an isolipophilic series of alkyl terminal group bis(biguanides) of various bridge lengths was prepared and evaluated, as their dihydrochloride salts, for in vitro antibacterial and antiplaque activity against *Actinomyces viscosus*, *A. naesludii*, and *S. mutans*. The lipophilicity of members in this series (compounds **2–6**) was chosen to be nearly equal to that of alexidine (**1**, R = 2′-ethylhexyl, n = 6) which has been reported to be clinically effective in decreasing plaque scores.[13-15] Three other alkyl bis(biguanides) (**2–9**) with slightly different lipophilicity were also tested. Chlorhexidine (**10**) was included for purposes of comparison.

In these previous studies involving the variation of bridge length with constant terminal groups, both the lipophilicity and separation of cationic centers varied simultaneously, thereby potentially obscuring the relationship of antiplaque properties upon antibacterial properties vs. binding abilities. The rationale for this study was the expectation that while only small differences in antibacterial activities among compounds of comparable lipophilicity may be observed, larger variations in antiplaque properties may reflect differences in binding ability which may be produced by changes in spatial separation of cationic centers.[9]

The synthesis of the analogues listed in Table I followed the method of Rose and Swain[16] wherein an α,ω-di-

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