was again (50 and 33 g) added 1.5 and 2 h after reflux began. The cooled solution was filtered and dried (K_2CO_3), and the product was distilled: bp 105–109 °C (0.06 mm); n^{20}_D 1.5196 (not analytically pure). NMR showed that it contained 67% of the isomer designated as **26**, and the remainder was mainly the β,γ-doubly bonded ester.

Method V. Ethyl 3-Cyclohexyl-3-(4-acetylphenyl)-propionate (28). The ester **27** (56 g, 0.215 mol) was acetylated using the method which Baddeley employed for the preparation of methyl 3-(4-acetylphenyl)propionate.[14]

Method W. 1-Cyclohexyl-5-indanacetic Acid, Sodium Salt (31). The acid **30** (24.6 g, 0.09 mol) was reduced using the method [employed to prepare β-(*p*-phenoxybenzoyl)propionic acid] of ref 19 to give 1-cyclohexylindan-5-acetic acid: bp 158–162 °C (0.06 mm); n^{22}_D 1.5452. Anal. ($C_{17}H_{22}O_2$) C, H. The acid was converted to its sodium salt by adding aqueous $NaHCO_3$ to an EtOH solution of the acid, followed by evaporation.

Acknowledgment. We thank Dr. D. M. Rackham and Mr. R. C. Harden for the determination and interpretation of spectral results and Dr. D. N. B. Mallen and Mr. D. J. Osborne for the purification of compound **23**.

References and Notes

(1) For Part 2, see: J. C. Saunders and W. R. N. Williamson, *J. Med. Chem.*, **22**, see Notes section in this issue (1979).
(2) Cf. T. Y. Shen, *Angew. Chem., Int. Ed. Engl.*, 11, 460 (1972).
(3) Unpublished work.
(4) Mizushima test; for references, see p. 78 of "Antiinflammatory Agents", Vol. II (Vol. 13 of "Medicinal Chemistry"), Academic Press, New York, 1974, p 78.
(5) Cf. "Detoxication Mechanisms", R. T. Williams, Chapman and Hall, London, 1959, p 201.
(6) A. W. Pircio, M. E. Bierwagen, W. E. Strife, and W. D. Nicolasi, *Arch. Int. Pharmacodyn.*, **199**, 151–163 (1972).
(7) A. G. Anderson, Jr., and R. H. Wade, *J. Am. Chem. Soc.*, **74**, 2274 (1952).
(8) T. C. Bruice and W. C. Bradbury, *J. Org. Chem.*, **28**, 3403 (1963).
(9) W. Baker, J. F. W. McOmie, S. D. Parfitt, and D. A. M. Watkins, *J. Chem. Soc.*, 4026 (1957).
(10) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
(11) D. W. Dunwell, D. Evans, T. A. Hicks, C. H. Cashin, and E. A. Kitchen, *J. Med. Chem.*, **18**, 53 (1975).
(12) B. B. Newbould, *Br. J. Pharmacol.*, **21**, 127 (1963).
(13) E. Schwenk and D. Papa, *J. Org. Chem.*, 11, 798 (1946).
(14) G. Baddeley and R. Williamson, *J. Chem. Soc.*, 4647 (1956).
(15) C. H. Eades, Jr., C. M. Weiss, V. B. Solberg, and G. E. Phillips, *Med. Pharmacol. Exp.*, 14, 225 (1966).
(16) Cf. Irish Patent 56/65 (Boots & Co.).
(17) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **61**, 1272 (1939).
(18) D. B. Bruice, A. J. S. Sorrie, and R. H. Thomson, *J. Chem. Soc.*, 2403 (1953).
(19) D. Todd in "Organic Reactions", Vol. IV, R. Adams, Ed., Wiley, New York, 1948, p 391.

N-Alkylated 2-Aminotetralins: Central Dopamine-Receptor Stimulating Activity

Uli Hacksell,* Uno Svensson, J. Lars G. Nilsson,

Department of Organic Pharmaceutical Chemistry, Biomedical Center, University of Uppsala, S-751 23 Uppsala, Sweden

Stephan Hjorth, Arvid Carlsson,

Department of Pharmacology, University of Gothenburg, Fack, S-400 33 Göteborg, Sweden

Håkan Wikström, Per Lindberg, and Domingo Sanchez

Organic Chemistry Unit, Department of Pharmacology, University of Gothenburg, S-400 33 Göteborg, Sweden.
Received May 15, 1979

In order to define the structural requirements of N-substituents of 2-aminotetralins as central dopamine receptor agonists, a series of *N*-alkyl- and *N,N*-dialkyl-substituted 2-amino-5-hydroxy- and 2-amino-5-methoxytetralins have been synthesized and evaluated. The compounds were tested biochemically and behaviorally for dopaminergic activity. From the biochemical data it is concluded that an *n*-propyl group on the nitrogen is optimal for activity. The corresponding *N*-ethyl-substituted compounds are slightly less active, while the absence of *N*-ethyl or *N*-propyl groups give almost inactive compounds. It could be demonstrated that this is due to steric and not to lipophilic factors. It is suggested that a possible requirement for a potent agonist is that one of its N substituents must fit into a receptor cavity which, because of its size, can maximally accommodate an *n*-propyl but also smaller groups like ethyl or methyl. The active compounds appeared to give a similar relative pre- and postsynaptic stimulation and had also similar activities for the limbic system and for striatum. None of the compounds listed seemed to have central noradrenaline- or serotonin-receptor stimulating activity.

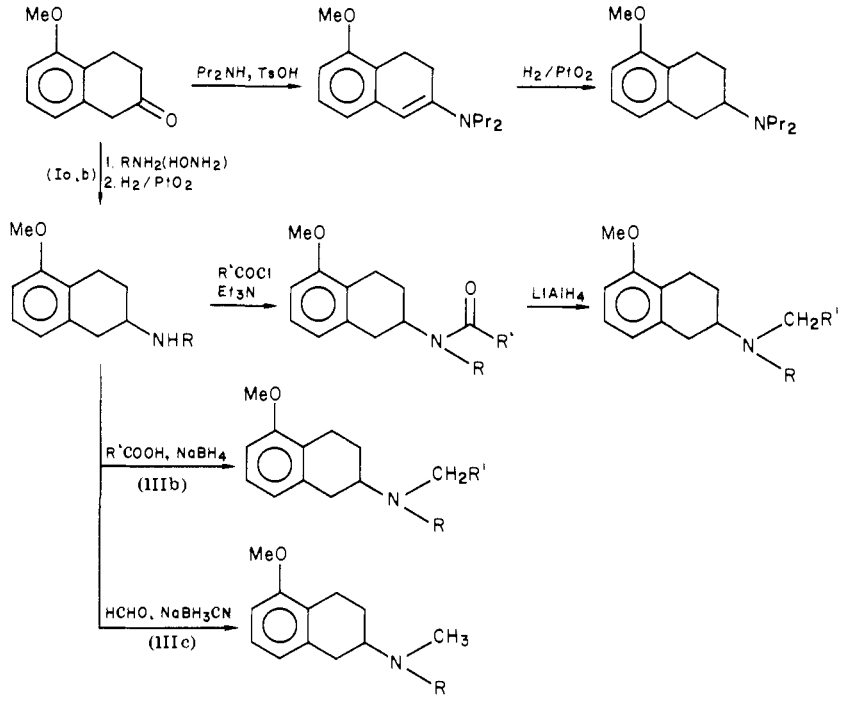
The high dopamine-receptor stimulating activity of apomorphine has been the basis of many structure–activity relationship studies. These include apomorphine derivatives[1,2] as well as various simplified structural analogues.[3-6] The bicyclic analogues 2-amino-5,6- and 2-amino-6,7-dihydroxytetralin and several of their N-alkylated derivatives have been shown to possess central dopamine-receptor stimulating activity.[5-12] Some of these compounds are even more potent than apomorphine.

The *N*-butyl or *N,N*-dibutyl derivatives of 2-amino-5,6-dihydroxytetralin, dopamine, or norapomorphine have very little or no dopaminergic activity, while the analogues carrying at least one *N*-ethyl or one *N*-*n*-propyl group possess high activity.[1,6,7,10-15] The results thus obtained in different investigations show that the structure of the *N*-alkylamino moiety of dopamine-related compounds is important for the dopamine-receptor stimulating activity. We have now investigated an extensive series of N-alkylated 2-aminotetralins in order to establish the influence of the N substituents upon the dopaminergic activity.

The monohydroxy derivative 5-hydroxy-2-(dipropylamino)tetralin has been reported to be almost equipotent to its 5,6-catechol analogue in producing stereotypy in rats and emesis in dogs.[16] This high potency of the 5-hydroxy derivative, together with the fact that monophenolic compounds are chemically more stable than catechols, induced us to choose the 2-amino-5-hydroxytetralin unit as the basic structure in our investigation. One could also expect

0022-2623/79/1822-1469$01.00/0

Scheme I



a somewhat higher metabolic stability and a longer duration of action for monophenols than for catechols (cf. ref 15).

Consequently, in the present investigation, we have synthesized a series of N-alkylated and N,N-dialkylated 2-amino-5-hydroxy- and 2-amino-5-methoxytetralins. The compounds were tested biochemically for potency and behaviorally for duration of action using methods which we have recently described.[15] The compounds synthesized and the biological data obtained are presented in Table I.

Chemistry. The primary amines **1** and **2** and the secondary amines **3**–**14** were synthesized from 5-methoxy-2-tetralone[17] via the oxime or the imines, according to pathways Ia or Ib[6] in Scheme I. The tertiary amines were synthesized via enamine formation from the same ketone, followed by catalytic hydrogenation[6] (pathway II), or from secondary amines by one of three different methods: acylation with the appropriate acid chloride, followed by $LiAlH_4$ reduction of the crude amide[18] (pathway IIIa); direct N alkylation using a $NaBH_4$–carboxylic acid complex[10,19] (pathway IIIb); reductive methylation with $NaBH_3CN$ and formalin[10] (pathway IIIc). All the ethers were cleaved using 48% HBr.

Attempts to prepare 2-(*N*-*tert*-butyl-*N*-*n*-propylamino)-5-methoxytetralin either by treating 2-(*tert*-butylamino)-5-methoxytetralin (synthesized via pathway I) with $NaBH_4$–propanoic acid or via pathway IIIa were unsuccessful.

Pharmacology. The compounds were tested biochemically for central dopamine-receptor stimulating activity and functionally for duration of action, in both cases using reserpinized rats.

In the biochemical screening method, recently published,[15] we utilize the ability of direct dopamine-receptor stimulants to reduce the Dopa-synthesis rate in the presynaptic neurons. This decreased Dopa synthesis during dopamine-receptor stimulation is caused by an inhibition of tyrosine hydroxylase mediated via negative feedback systems. The reduced Dopa accumulation (as compared to controls) is measured after in vivo inhibition (*m*-hydroxybenzylhydrazine hydrochloride, NSD 1015; 100 mg/kg) of aromatic-L-amino-acid decarboxylase. The amounts of accumulated Dopa in striatum, in the limbic forebrain, and in the remaining hemispheral portions of the rat cerebrum (mainly cortex) were determined. Since similar feedback systems seem to exist also for 5-hydroxytryptamine neurons (5-HT neurons), 5-hydroxytryptophan (5-HTP) was also measured. Dose–response curves were constructed (sc administration), and the dose required to obtain 50% of maximal Dopa or 5-HTP reduction (ED_{50}) from the corresponding control brain portions was estimated. These values are presented in Table I.

For behavioral and duration studies, reserpinized rats (10 mg/kg ip, 6 h before the experiment) were given the drug either subcutaneously or orally, and the duration of action was measured in a motility meter as previously described.[15] The doses were 2 μmol/kg for sc administration and 20 μmol/kg for po administration. The duration of action, as well as the total number of motor activity counts (area under curve, AUC) for the compounds tested, is shown in Table I.

Results and Discussion

The biochemical screening method has high sensitivity, measuring effects at very low doses of the dopamine-receptor stimulants. At doses equal to the ED_{50} values, no behavioral effects occur (gross behavioral observations). This indicates that no predominant postsynaptic receptor stimulation is involved at the doses eliciting the biochemically measured effects. Instead, specific autoregulatory, presumably presynaptic, receptors (so-called autoreceptors, cf. ref 20) are likely to be implicated. Hence, the combination of the biochemical and the behavioral test methods used in this study makes it possible to distinguish between stimulation of the two types of receptors.

The 2-(alkylamino)-5-hydroxytetralins were prepared from the corresponding methoxy compounds. Several related methoxy compounds have shown activity in various tests for dopamine receptor stimulation.[6] Therefore, most of the methoxy compounds prepared in this study were submitted to biological evaluation. In the biochemical model, some of these compounds showed high potency but were generally less active than their corresponding hy-

droxy-substituted analogues. In the behavioral studies, we found that the methoxytetralins have a latency period usually of about 15 min, in contrast to the almost immediate onset of action (<5 min) for the hydroxy derivatives (Table I). Furthermore, no behavioral effects have been observed after intracerebral administration of 2-amino-5,6-dimethoxy- or 2-amino-6,7-dimethoxytetralins, in contrast to the high activities found for the corresponding catechols.[7] Thus, it seems likely that the methoxytetralins are converted into active metabolites when administered peripherally.

The secondary or tertiary amines, carrying at least one *N*-ethyl or *N*-*n*-propyl group, are all very active in the biochemical test (Table I). On the other hand, derivatives lacking *N*-ethyl or *N*-*n*-propyl groups are less active or in many cases inactive. In particular, the inactivities of 2-(*n*-butylamino)- (**10**) and 2-(*n*-pentylamino)-5-hydroxytetralin (**12**) and the very low activity of 2-(*N*,*N*-di-*n*-butylamino)-5-hydroxytetralin (**42**) are noteworthy. This is analogous to what has previously been reported for 2-(alkylamino)-5,6-dihydroxy-[6,7,10,11] and 2-(alkylamino)-6,7-dihydroxytetralins,[7] as well as for N-alkylated dopamine derivatives.[13-15] The compounds carrying *N*-ethyl groups, i.e., 2-(ethylamino)- (**6**), 2-(*N*-methyl-*N*-ethylamino)- (**18**), 2-(diethylamino)- (**24**), and 2-(*N*-butyl-*N*-ethylamino)-5-hydroxytetralin (**28**), are slightly less active than the corresponding *N*-*n*-propyl analogues **8**, **20**, **26**, and **32**. The corresponding compounds with *N*-methyl instead of *N*-ethyl groups, i.e., the *N*-methyl (**4**) and *N*,*N*-dimethyl (**16**) derivatives, are considerably less active. The *N*-methyl-*N*-pentyl (**22**), *N*-ethyl-*N*-butyl (**28**) and *N*,*N*-dipropyl (**30**) compounds constitute a series in which the number of carbon atoms attached to nitrogen is constant. In this series, decreased potency is observed the more the N substituents differ from *n*-propyl. This is also seen by comparing the activities of the *N*-methyl-*N*-ethyl (**18**) with the *N*-propyl (**8**) derivative and *N*,*N*-dimethyl (**16**) with the *N*-ethyl (**6**) derivative, respectively. Apparently, steric factors, and not the lipophilicity, are responsible for the differences in the biological activity of these compounds. This is further substantiated by the observation that compounds **20** (*N*-Me,*N*-Pr), **26** (*N*-Et,*N*-Pr), **30** [*N*,*N*-(Pr)$_2$], **32** (*N*-Pr,*N*-Bu), and **34** (*N*-Pr,*N*-pentyl) have very similar activities in spite of large differences in lipophilicity.

The inactivity of 2-(isopropylamino)-5-hydroxytetralin (**14**) indicates that the *n*-propyl group at the nitrogen cannot be exchanged for a branched alkyl group without loss of activity. A comparison of the ED_{50} values for 2-(dipropylamino)- (**30**) with 2-(*N*-propyl-*N*-isopropylamino)-5-hydroxytetralin (**38**) and 2-(*N*-propyl-*N*-pentylamino)- (**34**) with 2-(*N*-propyl-*N*-neopentylamino)-5-hydroxytetralin (**40**) suggests that branched alkyl groups at the nitrogen atom decrease the activity also when one *n*-propyl group is already present.

These observations suggest that a possible requirement for a potent agonist is that one of its N substituents must fit into a cavity (or bind to a part of the receptor) which, because of its size, can maximally accomodate an *n*-propyl but also smaller groups like ethyl or methyl. The structural requirements for the other N substituent are less stringent, since even a large group like phenethyl (**36**) can be accomodated (cf. ref 21).

The lower activity of the branched *N*-propyl-*N*-isopropyl (**38**) and *N*-propyl-*N*-neopentyl (**40**) derivatives compared to the activity of their *n*-alkyl analogues **30** and **34** may be interpreted in terms of steric hindrance due to the branched groups, thus preventing the *n*-propyl group from reaching into the cavity. The piperidino derivative **44** was found to be inactive analogously to several other cyclic aminotetralin derivatives previously reported.[6] This may be explained by the absence of the necessary *n*-alkyl group.

Compounds like the primary amine (**2**) and the *N*-methyl derivative (**4**) are more hydrophilic than those with larger N substituents and may consequently have difficulties in penetrating the blood–brain barrier. Thus, the values obtained here may not reflect the true receptor-stimulating properties of these compounds (cf. ref 10). This is illustrated by the high stereotypic activity previously found for 2-amino-5,6-dihydroxytetralin on intracerebral administration[7,8,11] as compared to the inactivity of the same compound on peripheral administration.[10,11] However, it is also possible that the methyl group of, for example, **4**, due to its low lipophilicity, would bind less strongly than an ethyl or an *n*-propyl group to the proposed cavity of the receptor, thus rendering the compound a low potency.

The biochemical and behavioral results indicate similar relative pre- and postsynaptic receptor stimulation for the active compounds (Table I). In the biochemical screening, each compound also shows very similar ED_{50} values for the limbic system and for striatum. Costall et al.[7,8] have reported large variations in the behavioral effects obtained after injections of N-alkylated 2-amino-5,6-dihydroxytetralins into the nucleus accumbens or striatum. In our study, it is noteworthy that not even 2-(dipropylamino)-5,6-dihydroxytetralin (**46**) shows any difference between the limbic system and striatum in biochemical potency. It has been reported[8] that this compound (**46**) is much more potent in producing stereotypy in rats after separate administration into the nucleus accumbens than into striatum, whereas 2-(diethylamino)-5,6-dihydroxytetralin has the inverse relationship. A comparison of our results (presynaptic stimulation) with those reported by Costall et al.[7,8] (postsynaptic stimulation) may indicate that there is a greater difference between the postsynaptic limbic and striatal receptors than between the corresponding presynaptic receptors.

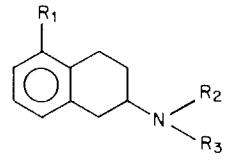
The Dopa accumulation in the hemispheral portions and the 5-HTP accumulation in any one of the three brain areas studied were not affected by the compounds tested. These results suggest that none of these compounds possesses noradrenaline- or serotonin-receptor stimulating effects at the administered doses.

In the motility studies on reserpinized rats, only the compounds with a biochemical ED_{50} value below 150 nmol/kg showed any activity at the standard dose (2000 nmol/kg sc) used here. The AUC and duration of action for the active compounds are given in Table I. For these compounds (except for the branched analogues), it seems that the duration of action increases with the number of carbon atoms on the nitrogen up to and including the *N*-butyl-*N*-propyl derivative **32**. This gives a straight-line correlation between the duration and the number of carbon atoms on the nitrogen for all the 2-(*N*-ethyl-*N*-*n*-alkylamino)- and 2-(*N*-propyl-*N*-*n*-alkylamino)-5-hydroxytetralins (Figure 1).

To verify that the reversal of reserpine sedation reflects a direct action of the drug on dopamine receptors, it was shown that compound **30** (2 μmol/kg sc) had the same duration and AUC if the rats (n = 4) were pretreated with reserpine alone or with reserpine plus α-methyltyrosine (an inhibitor of tyrosine hydroxylation, 250 mg/kg ip given 2 h prior to motility testing).

As mentioned above, prolonged duration of action could be expected for 2-amino-5-hydroxytetralins as compared to the corresponding catechols. However, no such prolon-

Table I. Physical and Biological Data of the Compounds Studied



compd	R_1	R_2	R_3[bb]	prepn method	yield, %	mp, °C	recrystn solvents[a]	formula	ED_{50},[b-d] nmol/kg limbic	ED_{50},[b-d] nmol/kg striatum	motor activity AUC,[e] counts	motor activity duration,[e] min	motor activity latency,[e] min
1	MeO	H	H	Ia[f]	52	266-267[g]	A	$C_{11}H_{15}NO\cdot HCl$	NT[h]		NT[h]		
2	HO	H	H	IV	82	252-253	A	$C_{10}H_{11}NO\cdot HBr$	I[i]		I[i]		
3	MeO	H	Me	Ia	75	210[j]	A	$C_{12}H_{17}NO\cdot HCl$	NT		NT		
4	HO	H	Me	IV	84	259-261	A	$C_{11}H_{15}NO\cdot HBr$	1100	1200	I		
5	MeO	H	Et	Ia	55	247-248[g]	A	$C_{13}H_{19}NO\cdot HCl$	NT		NT		
6	HO	H	Et	IV	75	285-288[cc]	B	$C_{12}H_{17}NO\cdot HBr$	72	66	260[k]	50[k]	3[k]
7	MeO	H	*n*-Pr	Ib	78	260-261[g]	B	$C_{14}H_{21}NO\cdot HCl$	370	430	I		
8	HO	H	*n*-Pr	IV	72	250-252	B	$C_{13}H_{19}NO\cdot HBr$	40	46	240	45	0
9	MeO	H	*n*-Bu	Ib[l]	62	210.5-211.5[g]	A	$C_{15}H_{23}NO\cdot HCl$	NT		I		
10	HO	H	*n*-Bu	IV[m]	40	130-131	A	$C_{14}H_{21}NO\cdot HBr$	I		I		
11	MeO	H	*n*-Pe	Ib	67	212-215	A	$C_{16}H_{25}NO\cdot HCl$	NT		NT		
12	HO	H	*n*-Pe	IV	87	206-207	A	$C_{15}H_{23}NO\cdot HBr$	I		NT		
13	MeO	H	*i*-Pr	Ib	68	251-253[g]	A	$C_{14}H_{21}NO\cdot HCl$	I		NT		
14	HO	H	*i*-Pr	IV	77	277-280	A	$C_{13}H_{19}NO\cdot HBr$	I		I		
15	MeO	Me	Me	IIIc	80	214-216[g]	B	$C_{13}H_{19}NO\cdot HCl$	NT		I		
16	HO	Me	Me	IV	78	226-227	B	$C_{12}H_{17}NO\cdot HBr$	390	190	I		
17	MeO	Me	Et	IIIb[n]	98	216-217[g]	B	$C_{14}H_{21}NO\cdot HCl$	NT		I		
18	HO	Me	Et	IV	78	206-207	B	$C_{13}H_{19}NO\cdot HBr$	74	53	135	31	3
19	MeO	Me	*n*-Pr	IIIc	89	151-153[g]	A	$C_{15}H_{23}NO\cdot HCl$	120	96	320	69	15
20	HO	Me	*n*-Pr	IV	87	210	A	$C_{14}H_{21}NO\cdot HBr$	23	29	380	73	0
21	MeO	Me	*n*-Pe	IIIc	78	171-172	A	$C_{17}H_{27}NO\cdot HCl$	NT		I		
22	HO	Me	*n*-Pe	IV	55	130-132	C	$C_{16}H_{25}NO\cdot HBr$	370	280	I		
23	MeO	Et	Et	IIIb	98	217-219[g]	o	$C_{15}H_{23}NO\cdot HCl$	NT		I		
24	HO	Et	Et	IV	70	233-234	B	$C_{14}H_{21}NO\cdot HBr$	77	71	250	54	0
25	MeO	Et	*n*-Pr	IIIa[p]	80	179-180[g]	A	$C_{16}H_{25}NO\cdot HCl$	65	62	630	96	13
26	HO	Et	*n*-Pr	IV[m]	43	185-186	A	$C_{15}H_{23}NO\cdot HBr$	24	17	660	82[q]	0
27	MeO	Et	*n*-Bu	IIIa[r]	70	144-145	A	$C_{17}H_{27}NO\cdot HCl$	68	79	880	140	16
28	HO	Et	*n*-Bu	IV[m]	23	153.5-154.5	A	$C_{16}H_{25}NO\cdot HBr$	30	35	820	118[q]	0
29	MeO	*n*-Pr	*n*-Pr	II	51	171[g]	A	$C_{17}H_{27}NO\cdot HCl$	13	18	810	122	15
30	HO	*n*-Pr	*n*-Pr	IV	34	188-190[s]	A	$C_{16}H_{25}NO\cdot HBr$	11	9	1090	127[q]	0
31	MeO	*n*-Pr	*n*-Bu	IIIa[r]	89	137-138	A	$C_{18}H_{29}NO\cdot HCl$	40	36	600	106	14
32	HO	*n*-Pr	*n*-Bu	IV[m]	28	144-145	A	$C_{17}H_{27}NO\cdot HBr$	11	14	1270	158[q]	0
33	MeO	*n*-Pr	*n*-Pe	IIIb[t]	46	113-114	A	$C_{19}H_{31}NO\cdot(COOH)_2$	92	101	440	93	15
34	HO	*n*-Pr	*n*-Pe	IV	48	148-150	E	$C_{18}H_{29}NO\cdot HCl$	10	19	450	75	0
35	MeO	*n*-Pr	$(CH_2)_2Ph$	IIIb[u]	51	v	A	$C_{22}H_{29}NO\cdot HCl$	290	240	I		
36	HO	*n*-Pr	$(CH_2)_2Ph$	IV	76	205-206	A	$C_{21}H_{27}NO\cdot HCl$	22	17	300	53	0

37	MeO	*n*-Pr	*i*-Pr	IIIb[t]	84	190–191	D	$C_{17}H_{27}NO\cdot HCl$	NT		NT		
38	HO	*n*-Pr	*i*-Pr	IV	82	241–242	A	$C_{16}H_{25}NO\cdot HBr$	70	87	260	55	4
39	MeO	*n*-Pr	neo-Pe	IIIa[p,w]	24	97–100	*x*	$C_{19}H_{31}NO\cdot HCl$	190	190	I		
40	HO	*n*-Pr	neo-Pe	IV	81	195–197	A	$C_{18}H_{29}NO\cdot HCl$	200	120	300	68	9
41	MeO	*n*-Bu	*n*-Bu	IIIa	65	157–158[g]	A	$C_{19}H_{31}NO\cdot HCl$	NT		NT		
42	HO	*n*-Bu	*n*-Bu	IV[m]	82	123–124	A	$C_{18}H_{29}NO\cdot HBr$	2900	2700	I		
43	MeO		$-(CH_2)_5-$	II	66	290–295[cc]	B	$C_{16}H_{23}NO\cdot HCl$	NT		NT		
44	HO		$-(CH_2)_5-$	IV	47	307–312[cc]	B	$C_{15}H_{21}NO\cdot HBr$	I		NT		
45	5,6-$(MeO)_2$	*n*-Pr	*n*-Pr	*y*	65	179–182[z]	B	$C_{18}H_{29}NO_2\cdot HCl$	57	58	NT		
46	5,6-$(HO)_2$	*n*-Pr	*n*-Pr	IV	50	220–223[aa]	B	$C_{16}H_{25}NO_2\cdot HBr$	7	7	1750	193	0
apomorphine									190	220	620	60[q]	0

[a] Recrystallization solvents: A, EtOH–ether; B, MeOH–ether; C, CH_3CN–ether; D, CH_2Cl_2–ether; E, ethanol–isopropyl ether. [b] Estimated dose giving a half-maximal decrease of the Dopa level in the rat brain part; maximal reduction of the Dopa level was empirically found to be (for all the compounds tested including apomorphine) 65% from the control level (635 ng of Dopa/g of tissue) for the limbic and 80% from the control level (1670 ng of Dopa/g of tissue) for the striatal brain portions. The shapes of the dose–response curves were all similar to those of apomorphine. [c] No effect was obtained in the hemispheral portions. [d] No reduction in the 5-HTP accumulation was obtained. [e] For definition, see Experimental Section. [f] Using NH_2OH. [g] Previously described, ref. 18. [h] Not tested. [i] Inactive; compounds with an ED_{50} value > 5000 nmol/kg have been considered as inactive. [j] Previously described, ref. 22. [k] Shown are the means of four to six recordings, SEM values were all less than 15% of the mean values. [l] The crude amine was passed through an alumina column with ether/light petroleum, 1:1. [m] Before recrystallization the salt was passed through a silica column with $CHCl_3$/MeOH, 9:1. [n] Using $NaBH_4$–AcOH. [o] No recrystallization. [p] Starting from compound 7. [q] Oral administration (20 μmol/kg): 26, 40 min; 28, 63 min; 30, 121 min; 32, 117 min; apomorphine, 33 min. [r] Starting from compound 9. [s] HCl salt, mp 204–206 °C. Reported (ref 16) mp 201–202 °C. [t] Using $NaBH_4$–propionic acid. [u] Using $NaBH_4$–phenylacetic acid. [v] Could not be crystallized. C: calcd, 73.4; found, 70.9. [w] Ether (dry) was used as solvent in the $LiAlH_4$ reduction. [x] Crystallized from the CH_2Cl_2 phase after successive partitioning between 1 M aqueous HCl/ether and 1 M aqueous HCl/CH_2Cl_2; no recrystallization. [y] Prepared analogously to method IIIb. [z] Previously reported, ref. 6. [aa] Previously reported, ref. 10. [bb] Pe = pentyl. [cc] Decomposition.

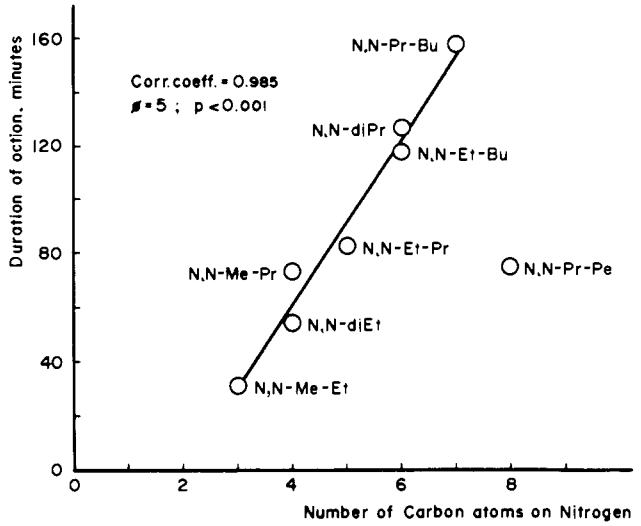


Figure 1. Straight-line correlation between the duration of action and the number of carbon atoms at the nitrogen for 2-(*N*-ethyl-*N*-*n*-alkylamino)- and 2-(*N*-propyl-*n*-alkylamino)-5-hydroxytetralins.

gation of the duration could be demonstrated when comparing compounds **30** and **46** (Table I).

It is interesting to note (Table I) that, in spite of the different biochemical potencies, most of the active hydroxy- and corresponding methoxytetralins have similar AUC and similar duration of action, respectively. The reason for this is presently not understood.

Four of the most active compounds (**26**, **28**, **30**, and **32**) were also tested orally with a standard dose of 20 μmol/kg, and all were active.

Experimental Section

Chemistry. Melting points (uncorrected) were determined in open glass capillaries on a Thomas-Hoover apparatus. ^1H NMR spectra, recorded on a Varian EM-360 spectrometer or on a Perkin-Elmer R 12B spectrometer, were in agreement with expected data. The elemental analyses (C, H, N) for the new substances (Elementaranalystjänst, Chemical Center, Lund, Sweden or the Microanalytical Laboratory, Agricultural College, Uppsala, Sweden) were within 0.4% of the theoretical values. For purity tests, TLC was performed on fluorescent silica gel plates developed in at least two different solvents. For all the compounds, only one spot (visualized by UV light and I_2 vapor) was obtained.

2-(Methylamino)-5-methoxytetralin (3). Method Ia. 5-Methoxy-2-tetralone[17] (1.76 g, 10 mmol) was dissolved (N_2 atmosphere, room temperature) in ethanol (50 mL) and methylamine hydrochloride (1.34 g, 20 mmol) dissolved in water (20 mL) and NaOH (2.0 g, 50 mmol) dissolved in water (20 mL) were added under stirring. After stirring for 15 min, the mixture was poured onto ice (100 g) mixed with concentrated HCl (20 mL). The acidic solution was hydrogenated catalytically over PtO_2 (500 mg) in a Parr apparatus (2 h). The catalyst was filtered off and the filtrate was extracted with methylene chloride. The aqueous phase was made alkaline with 10% Na_2CO_3 and extracted with ether. The extract was dried (Na_2SO_4) and **3** was precipitated as the hydrochloride and recrystallized from ethanol/ether.

2-(Propylamino)-5-methoxytetralin (7). Method Ib. To a solution of 5-methoxy-2-tetralone[17] (12.5 g, 71 mmol) in absolute ethanol (200 mL) were added acetic acid (12.8 g, 213 mmol), *n*-propylamine (12.6 g, 213 mmol) and 4Å molecular sieves. The mixture was stirred at room temperature (N_2 atmosphere) for 2 h, the molecular sieves were filtered off, and the solution was hydrogenated in a Parr apparatus using PtO_2 (500 mg) as catalyst. After filtration and evaporation, compound **7** was precipitated as the hydrochloride and recrystallized from ethanol/ether.

2-(Dipropylamino)-5-methoxytetralin (29). Method II. A solution of 5-methoxy-2-tetralone[17] (20.0 g, 114 mmol), dipropylamine (50.5 g, 500 mmol), and *p*-toluenesulfonic acid (2.5 g) in dry benzene (700 mL) was refluxed (N_2 atmosphere) for 48

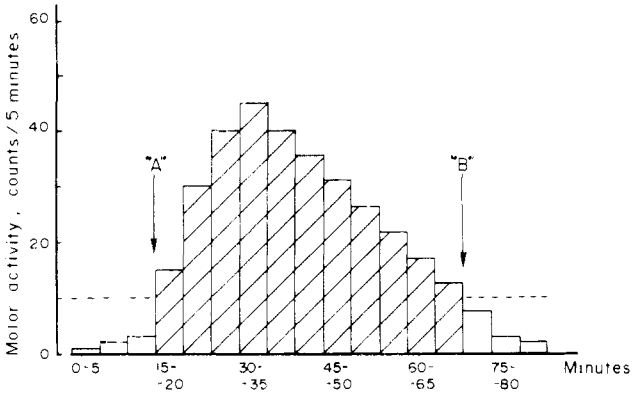


Figure 2. Duration of action is defined as the time interval between "A" and "B". Area under curve (AUC) is the total number of motor-activity counts summated over the entire duration of action period (shaded area).

h. The solution was transferred to a Parr flask, absolute ethanol (400 mL) and PtO_2 (1.0 g) were added, and the solution was hydrogenated. The catalyst was filtered off, the solvent was evaporated, and the residue (35.9 g) was dissolved in methylene chloride and passed through an alumina column (3 × 25 cm). The solvent was evaporated and the residue dissolved in dry ether, whereupon **29** was precipitated as the hydrochloride and recrystallized from ethanol/ether.

2-(*N*-Butyl-*N*-propylamino)-5-methoxytetralin (31). Method IIIa. Propionyl chloride (2.05 g, 22 mmol) in dry toluene (5 mL) was slowly added at 5 °C to a solution of 2-(butylamino)-5-methoxytetralin (**9**) (5.0 g, 22 mmol), triethylamine (2.2 g, 22 mmol), and dry toluene (45 mL). The mixture was stirred at room temperature for 30 min, whereupon the triethylammonium chloride formed was filtered off and the solvent evaporated. The residue (6.2 g) dissolved in dry tetrahydrofuran (30 mL) was added to a suspension of $LiAlH_4$ (0.84 g, 21 mmol) in dry tetrahydrofuran (30 mL) under nitrogen. After stirring under reflux for 3 h, the mixture was hydrolyzed, the precipitate was filtered off, and the solvent was evaporated. The residue, dissolved in light petroleum, was passed through an alumina column, and **31** was precipitated as the hydrochloride and recrystallized from ethanol/ether.

2-(*N*-Ethyl-*N*-methylamino)-5-methoxytetralin (17). Method IIIb. $NaBH_4$ (1.60 g, 42 mmol) was added portionwise to a stirred solution of acetic acid (8.28 g, 138 mmol) in dry benzene (100 mL) under N_2, keeping the temperature below 20 °C. After 1 h, 2-(methylamino)-5-methoxytetralin (**3**; 1.61 g, 8.4 mmol) was added, and the mixture was refluxed for 5 h and then treated with 2.5 M NaOH (150 mL). The benzene layer was dried (Na_2SO_4) and the solvent was evaporated. The residue was dissolved in ether, and **17** was precipitated as the hydrochloride and recrystallized from ethanol/ether.

2-(*N*-Methyl-*N*-propylamino)-5-methoxytetralin (19). Method IIIc. A mixture of 2-(propylamino)-5-methoxytetralin hydrochloride (**7**; 9.2 g, 36 mmol), 37% formalin (18 mL, 180 mmol), $NaBH_3CN$ (7.5 g, 120 mmol), and 3Å molecular sieves (20 g) in methanol (250 mL) was stirred (N_2) for 5 days at room temperature. The molecular sieves were filtered off and the solvent was evaporated. The residue was dissolved in 10% HCl (200 mL), and the solution was extracted with methylene chloride several times. The organic layer was dried (Na_2SO_4) and the solvent was evaporated. The oily residue was crystallized by cooling and stirring with diisopropyl ether (100 mL). Recrystallization from ethanol/ether gave the pure hydrochloride **19**.

Demethylation of Methoxytetralins. Method IV. The hydroxytetralins were obtained by heating the appropriate 5-methoxytetralin in 48% HBr for 3 h at 125 °C under nitrogen. The hydrobromic acid was evaporated and the residue (usually crystalline) was recrystallized from ethanol/ether, yielding the pure 5-hydroxytetralin hydrobromide.

Pharmacology. Animals used in the experiments were male rats of Sprague–Dawley strain (Anticimex, Stockholm), weighing 200–350 g. All substances to be tested were dissolved in saline immediately before use. Injection volumes were always 10 mL/kg, and injection solutions had neutral pH.

Biochemistry. The biochemical experiments and the spectrophotometric determinations of Dopa and 5-HTP were performed as previously described.[15] The experiments were always carried out at 9–12 a.m. Separate dose–response curves for each substance (based on four to six dose levels) and each brain area were constructed. The dose of the drug yielding a half-maximal decrease of the Dopa level (Table I, footnote *b*) was estimated; these values (ED_{50}) are presented in Table I.

Motor Activity. The motor activity was measured by means of photocell recordings ("M/P 40 Fc electronic motility meter", Motron Products, Stockholm) as previously described.[15] Six hours prior to the motility testing (carried out between 1 and 6 p.m.), the rats were intraperitoneally injected with 10 mg/kg of reserpine. The agents to be screened for central dopamine-receptor stimulating activity were then administered sc in the neck region or po via a stomach tube. Doses of tested substances were always 2 μmol/kg sc and 20 μmol/kg po. Immediately following drug administration, the animals were placed individually in the test cages and put into the motility meters. Motor activity was then followed and recorded for each 5-min period until the drug effects ceased (<10 counts/5 min). Each box was equipped with a semitransparent mirror that allowed gross behavior observations of the animals during the recordings. Reserpinized rats, injected with vehicle only, gave control values ranging from 0 to 5 counts/5 min over the entire motor activity test period.

The area under the curve (AUC), the duration of action, and the latency were calculated for all the active compounds according to the following definitions.

Latency (until onset of action) is defined as the time interval preceding three (or more) consecutive 5-min intervals, each with motor activity counts >10 ("A" in Figure 2).

Duration of action is defined as the time interval from the end of the latency period ("A") up to and including the last 5-min interval preceding three (or more) consecutive 5-min intervals, each with motor-activity counts <10 ("B" in Figure 2).

Area under curve (AUC) is the total number of motor-activity counts summated over the entire "duration of action" period (shaded area in Figure 2).

Acknowledgment. The authors thank Mrs. Inger Nilsson and Mrs. Inger Weijdling for their assistance in the synthetic work and Mrs. Ingrid Bergh and Mrs. Lucia Gaete-Walderrama for their assistance in the pharmacological testing. The financial support from AB Hässle, Mölndal, Sweden, AB Astra, Södertälje, Sweden, the Swedish Board for Technical Development, and the Medical Faculty of the University of Gothenburg are gratefully acknowledged.

References and Notes

(1) E. R. Atkinson, F. J. Bullock, F. E. Granchelli, S. Archer, F. J. Rosenberg, D. G. Teiger, and F. C. Nachod, *J. Med. Chem.*, **18**, 1000 (1975).
(2) J. L. Neumeyer, F. E. Granchelli, K. Fuxe, U. Ungerstedt, and H. Corrodi, *J. Med. Chem.*, **17**, 1090 (1974).
(3) J. Z. Ginos, G. C. Cotzias, E. Tolosa, L. C. Tang, and A. LaMonte, *J. Med. Chem.*, **18**, 1194 (1975).
(4) A. Misiorny, S. B. Ross, and N. E. Stjernström, *Acta Pharm. Suec.*, **14**, 105 (1977).
(5) J. G. Cannon, J. C. Kim, M. A. Aleem, and J. P. Long, *J. Med. Chem.*, **15**, 348 (1972).
(6) J. D. McDermed, G. M. McKenzie, and A. P. Phillips, *J. Med. Chem.*, **18**, 362 (1975).
(7) B. Costall, R. J. Naylor, J. G. Cannon, and T. Lee, *Eur. J. Pharmacol.*, **41**, 307 (1977).
(8) B. Costall, R. J. Naylor, J. G. Cannon, and T. Lee, *J. Pharm. Pharmacol.*, **29**, 337 (1977).
(9) G. N. Woodruff, K. J. Watling, C. D. Andrews, J. A. Poat, and J. D. McDermed, *J. Pharm. Pharmacol.*, **29**, 422 (1977).
(10) J. G. Cannon, T. Lee, H. D. Goldman, B. Costall, and R. J. Naylor, *J. Med. Chem.*, **20**, 1111 (1977).
(11) J. G. Cannon, B. Costall, P. M. Laduron, J. E. Leysen, and R. J. Naylor, *Biochem. Pharmacol.*, **27**, 1417 (1978).
(12) P. Seeman, J. L. Tedesco, T. Lee, M. Chau-Wong, P. Muller, J. Bowles, P. M. Whitaker, C. McManus, M. Tittler, P.

Weinreich, W. C. Friend, and G. M. Brown, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 130 (1978).
(13) J. Z. Ginos, G. C. Cotzias, and D. Doroski, *J. Med. Chem.*, **21**, 160 (1978).
(14) J. G. Cannon, F.-L. Hsu, J. P. Long, J. R. Flynn, B. Costall, and R. J. Naylor, *J. Med. Chem.*, **21**, 248 (1978).
(15) H. Wikström, P. Lindberg, P. Martinson, S. Hjorth, A. Carlsson, U. Hacksell, U. Svensson, and J. L. G. Nilsson, *J. Med. Chem.*, **21**, 864 (1978).
(16) J. D. McDermed, G. M. McKenzie, and H. S. Freeman, *J. Med. Chem.*, **19**, 547 (1976).
(17) J. N. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949).
(18) D. E. Ames, D. Evans, T. F. Grey, P. J. Islip, and K. E. Richards, *J. Chem. Soc.*, 2636 (1965).
(19) P. Marchini, G. Liso, A. Reho, F. Liberatore, and F. M. Moracci, *J. Org. Chem.*, **40**, 3453 (1975).
(20) A. Carlsson, *Adv. Biochem. Psychopharmacol.*, **16**, 439 (1977).
(21) B. R. Thomas, "Polynucleotide Biology", Thomas, Lund, Sweden, 1976, pp 55–82.
(22) Y. C. Martin, C. H. Jarboe, R. A. Krause, K. R. Lynn, D. Dunnigan, and J. B. Holland, *J. Med. Chem.*, **16**, 147 (1973).

N-[(Tetrahydrofuryl)alkyl] and *N*-(Alkoxyalkyl) Derivatives of (-)-Normetazocine, Compounds with Differentiated Opioid Action Profiles

Herbert Merz* and Klaus Stockhaus

Department of Medicinal Chemistry and Department of Pharmacology, C. H. Boehringer Sohn, D-6507 Ingelheim, Federal Republic of Germany. *Received March 2, 1979*

In modification of the *N*-(tetrahydrofurfuryl) substitution of the opioid κ-agonist **5a-1**, a series of *N*-(alkoxyalkyl) derivatives **5** of (-)-normetazocine were synthesized and evaluated pharmacologically for opioid properties and, in part, toxicities in mice. Three groups of compound **5** may be distinguished: (a) morphine-like agonists, (b) non-morphine-like agonists, and (c) nalorphine-like agonist–antagonists. Analgesic activity (either morphine-like or not) is related to the position of the ether oxygen in the N substituent, maximum potency being obtained if nitrogen and oxygen are linked by a 2-carbon chain. The action profile of those compounds with a 2-carbon chain between nitrogen and oxygen is governed by the degree of branching of carbon C-2″ in the β position to the nitrogen, unbranched C-2″ affording compounds of type a and branched C-2″ affording those of type b or c depending on the nature of the branching. If diastereomeric pairs arise from those branchings, the 2″*S* forms are by far more potent analgesics than their 2″*R* counterparts, which may even be inactive. Different receptor interactions due to the degree and nature of branching of C-2″ are proposed to account for the differentiated opioid action profiles observed. Non-morphine-like agonists attaining analgesic potencies of more than 100 times that of morphine and having unusually favorable therapeutic ratios might be major advances in the search for strong analgesics with low abuse potential.

Recently, we have shown[1] that certain stereoisomeric *N*-(tetrahydrofurfuryl)normetazocines [5,9-dimethyl-2′-hydroxy-2-(tetrahydrofurfuryl)-6,7-benzomorphans] possess action profiles distinctly different from those of morphine and other classical opiates. In particular, they do not elicit the Straub tail phenomenon in mice nor do they substitute for morphine in morphine-dependent monkeys, although analgesic potencies up to more than 100 times that of morphine are attained. Obviously, it is the *N*-(tetrahydrofurfuryl) group that induces the unique action profiles of these opioid analgesics. Thus, it was tempting to modify the crucial *N*-(tetrahydrofurfuryl) substituent of those compounds systematically and to see what changes of their pharmacological properties would result. Consequently, we have prepared a series of *N*-[(tetrahydrofuryl)alkyl] and *N*-(alkoxyalkyl) derivatives (**5**) of (-)-normetazocine and studied their opioid actions in mice. We now report on the results of these chemical and pharmacological studies and discuss structure–activity relationships.[2] This report also includes a revision of the stereochemistry of the *N*-(tetrahydrofurfuryl)normetazocines[1] and results of advanced pharmacological studies with one of those stereoisomers.

Chemistry. The compounds to be discussed are represented by the general formula **5**. All are derived from (-)-5,9α-dimethyl-2′-hydroxy-6,7-benzomorphan[3] [(-)-normetazocine] which has been shown[4] to have the 1*R*,5*R*,9*R* configuration. Thus, they will be designated as 2-substituted (1*R*,5*R*,9*R*)-5,9-dimethyl-2′-hydroxy-6,7-benzomorphans.[5] With regard to the nature of the N substituent, they may be subdivided into *N*-[(tetrahydrofuryl)alkyl] derivatives **5a** with cyclic ether functions and *N*-(alkoxyalkyl) derivatives **5b** with open-chain ether functions. Chirality of the N substituent gives rise to the existence of pairs of 2″*R* and 2″*S* diastereomers. Configurational assignments follow from unequivocal syntheses generating the chiral N substituent from enantiomeric precursors of known absolute stereochemistry, as described in detail under the Experimental Section. Starting from (-)-normetazocine (**1**), the compounds **5** were synthesized (Scheme I) either directly by alkylation with the bromides **2** (method A) or by acylation with the acids or acid derivatives **3**, followed by reduction of the amide intermediates **4** with $LiAlH_4$ (method B). Compounds **5** with chiral N substituents were obtained either as stereochemically homogenous substances (from enantiomeric **2** or **3**) or as diastereomeric mixtures (from racemic **2** or **3**). Separation

Scheme I