Eur. J. Med. Chem. **23** (1988) 465—471

Short communication

2-(Substituted amino)-2-[2′-hydroxy-2′-alkyl(or aryl)]ethyltricyclo-[3.3.1.1^{3,7}]decane derivatives: a novel class of anti-hypoxia agents

Patricia A. SWIFT, Mary L. STAGNITO, George B. MULLEN, Gene C. PALMER and Vassil St. GEORGIEV*

Departments of Organic Chemistry and Pharmacology, Pennwalt Corporation, Pharmaceutical Division, Rochester, NY 14623, U.S.A.

(Received February 27, 1987, accepted November 30, 1987)

Summary — The synthesis and biological activity of a series of 2-(substituted amino)-2-[2′-hydroxy-2′-alkyl(or aryl)]-ethyltricyclo[3.3.1.1^{3,7}] decane derivatives **17**, are described. Compounds **17** represent a novel class of anti-hypoxia agents. In addition, they were found to exert anti-parkinson, anti-convulsant and analgesic activities. The degree of anti-hypoxia activity was shown to be dependent upon the length of the carbon side chain: the two most active compounds were the 2′-hexadecyl **17e** and 2′-tetradecyl **17f** analogs. The presence of an adamantyl ring and an alkyl side chain in the molecule of aminoalcohols **17** may have facilitated their penetration through the blood—brain barrier.

Résumé — **Hydroxy-2′ alkyl (ou aryl)-2′ éthyltricyclo[3.3.1.1^{3,7}]-2 décanes aminosubstitués en 2: une nouvelle classe d'agents anti-hypoxiques.** *Synthèse et activité biologique d'une série d'[hydroxy-2′ alkyl (ou aryl)-2′ éthyltricyclo[3.3.1.1^{3,7}]-2 décanes aminosubstitués en 2. Les composés 17 représentent une nouvelle classe d'agents anti-hypoxiques. De plus, les dérivés* **17** *se sont révélés être actifs comme anti-parkinsoniens, anti-convulsivants et analgésiques. Le degré de l'activité anti-hypoxique est fonction de la longueur de la chaîne latérale carbonée, les deux composés les plus actifs étant les analogues hexadécyl-2′* **17e** *et tétradécyl-2′* **17f**. *La présence d'un cycle adamantyle et d'une chaîne latérale alkyle sur la molécule des aminoalcools* **17** *peut faciliter la pénétration à travers la barrière hématocérébrale.*

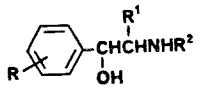
2-(substituted amino)-2-[2′-hydroxy-2′-alkyl(or aryl)]ethyltricyclo[3.3.1.1^{3,7}]decanes / spiro[isoxazolidine-3,2′-tricyclo[3.3.1.1^{3,7}]decanes], catalytic hydrogenation and zinc—acetic acid reduction of / anti-hypoxia activity / anti-parkinson activity / anti-convulsant activity / analgesic activity

Introduction

Over the years, a significant number of β-aminoalcohol derivatives **1** have been reported to possess bronchodilating activity [1]. Presently, such compounds as ephedrine **1a** [1], salbutamol **1b** [1], epinephrine **1c** [1], isoproterenol **1d** [1], isoetharine **1e** [1], metaproterenol **1f** [1], terbutaline **1g** [1], fenoterol **1h** [1], and bitolterol **1i** [2] are widely recognized as potent agents in the treatment of manifestations of bronchial asthma.

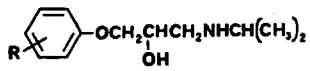
Structurally, all of derivatives **1a**—**1i** contain an α-phenyl ring, which with the exception of ephedrine is either 3,4- or 3,5-disubstituted, most notably with hydroxyl groups. There are also other β-aminoalcohol derivatives, such as alprenolol **2a** [1], oxprenolol **2b** [1] and acebutolol **2c** [1] that contain a substituted α-phenoxymethyl group instead of the phenyl ring, as well as hexoprenaline **3** [1] which represents two α-phenyl-β-aminoalcohol moieties linked together by an aliphatic hexamethylene chain.

In addition to having bronchodilating activity, many of the β-amino alcohols showed anti-inflammatory [1], analgesic [1, 3—12], hypotensive [6, 10, 12], local anesthetic [7, 9, 11], anti-spasmodic [7, 11] and CNS [4, 5, 8, 10, 12—17] activities. For example, the tricyclic compounds **4** [4] and **5** [8] have been reported to exert central nervous system (CNS)-stimulant activity, whereas derivatives **6** [14], **7** [15] and **8** [16] displayed anti-parkinson activity. Furthermore,



1a: R = H, $R^1 = R^2 = CH_3$
1b: R = 3,4-(CH_2OH)OH, R^1 = H, $R^2 = C(CH_3)_3$
1c: R = 3,4-$(OH)_2$, R^1 = H, $R^2 = CH_3$
1d: R = 3,4-$(OH)_2$, R^1 = H, $R^2 = CH(CH_3)_2$
1e: R = 3,4-$(OH)_2$, $R^1 = CH_2CH_3$, $R^2 = CH(CH_3)_2$
1f: R = 3,5-$(OH)_2$, R^1 = H, $R^2 = CH(CH_3)_2$
1g: R = 3,5-$(OH)_2$, R^1 = H, $R^2 = C(CH_3)_3$
1h: R = 3,5-$(OH)_2$, R^1 = H, $R^2 = CH(CH_3)CH_2C_6H_4OH$-4
1i: R = 3,4-(*p*-$CH_3C_6H_4CO_2)_2$, R^1 = H, $R^2 = C(CH_3)_3$

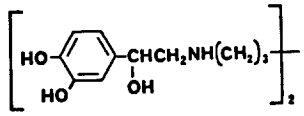
*Author to whom correspondence should be addressed.



2a R= 2-$CH_2CH=CH_2$

2b R= 2-$OCH_2CH=CH_2$

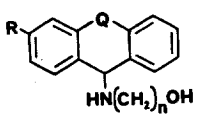
2c R= 2,4-$(COCH_3)(CH_3CH_2CH_2CONH)$



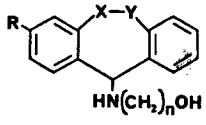
3

two other series of compounds, **9** [13] and **10** [17] were found to elicit anti-convulsant activity.

It was because of the activity of the aminoalcohols on the CNS that we decided to study, in more detail, the influence of lipophilic substituents on the ability of amino-

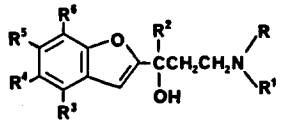


4

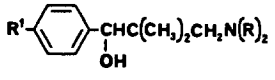


5a R= H, X= Y= CH_2

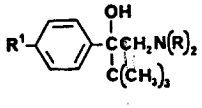
5b R= Cl, X= $S(O)_2$, Y= NCH_3



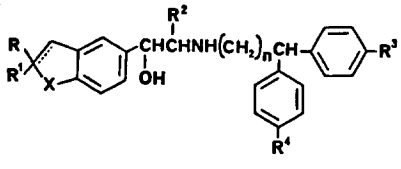
6



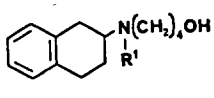
7



8

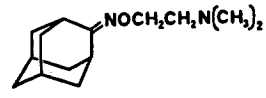


9



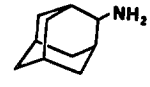
10

alcohols to permeate the blood—brain barrier and impart biological activity. The introduction of a strong lipophilic alicyclic ring system, such as adamantane, into the molecule would, undoubtedly, accelerate the penetration through the barrier. Another option in the same direction would be to alkylate the amino group and see whether the length of the chain will affect the CNS activity of the amino-alcohols. Thus, in recent years, a number of adamantane derivatives has been found to readily cross the blood—brain barrier and exert activity on the central nervous system [18—24]. One such compound, the *N,N*-dimethyl-amino-2-ethoxyimino-2-adamantane (**CM 54903**) **11** [24], when administered to rats at a dose of 40 mg/kg, produced a significant (although short-lasting) decrease in the acetylcholine content of the brain hemispheric regions, but not of the midbrain—hindbrain or cerebellum. Furthermore, the drug, which appeared to permeate the blood—brain barrier rather easily, directed its action towards the cholinergic neurons at presynaptic levels in order to compete with choline at its uptake sites [24].



11

Another adamantane derivative, the anti-viral amantadine **12** was reported to increase the dopamine release from the dopaminergic nerve terminals, [25]. This ability of amantadine to penetrate the blood—brain barrier and influence the cholinergic—dopaminergic control system allowed for its effective use in the therapy of parkinsonism [26].



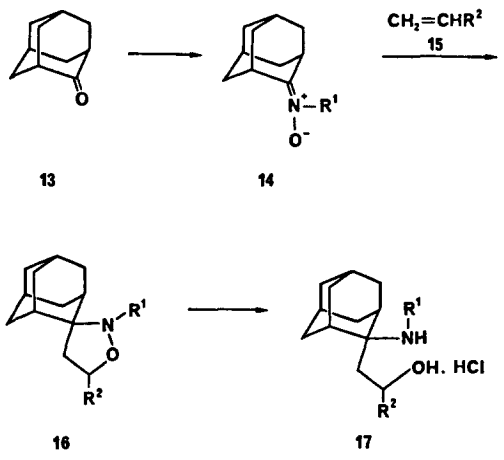
12

In the present paper, we report the synthesis and biological activity of a series of novel 2-(substituted amino)-2-[2′-hydroxy-2′-alkyl(or aryl)]ethyltricyclo[3.3.1.1^{3,7}]decane derivatives **17**. As seen from the molecule of compounds **17**, the presence of an adamantane ring system coupled with the *N*-alkyl group would certainly increase their lipophilicity, and, therefore, facilitate their permeability through the blood—brain barrier. The latter, in turn, may influence the CNS activity of derivatives **17**.

Chemistry

The synthesis of the title *N*-substituted-3-adamantyl-aminoalcohol compounds **17** was accomplished by an opening of the heterocyclic ring of the spiro[isoxazolidine-3,2′-tricyclo[3.3.1.1^{3,7}]decanes] **16** (Scheme 1). The

ring opening reaction was easily carried out by either catalytic hydrogenation in the presence of a palladium catalyst, or by a zinc—acetic acid reduction. The precursor adamantane-spiro-isoxazolidine compounds **16** were obtained by converting 2-adamantanone **13** into the corresponding nitrone derivative **14**, followed by a cyclocondensation reaction with an appropriate olefin **15**.



Scheme 1.

All of the aminoalcohol derivatives **17** prepared during the present study are listed in Table I.

was performed in order to accumulate a greater quantitation of data. The obtained behavioral testing results for compounds **17**, are summarized in Table II. In general, the drugs when given at the lowest doses (25—50 mg/kg) produced a decrease in the spontaneous motor activity, ptosis, and sometimes ataxia, mydriasis and hypothermia. If death occurred within 3 h at larger doses (50 mg/kg and over), it followed convulsions. The LD_{50} doses were determined over a 7-day period and the LD_{50} values given in Table III reflect these observations. Monitoring of behavioral signs allowed for doses to be selected empirically for testing mice for minimal neural impairment. In the latter, groups of 6 mice (for each dose level) were evaluated for their ability to right themselves on the inverted screen [29]. The lowest dose at which one or more animals failed the test was determined to be the acute minimal neural impairment dose (Table III). This dose level was then used to run the supplementary screening tests for other biological activities.

As seen from Table II, the safest compound in the series was **17g**; only large intraperitoneal doses (325 mg/kg) had effects on the neural impairment (as determined by the inverted screen test). This compound, likewise, showed the highest dose that caused death (LD_{50} = 150 mg/kg). In this regard, it should be noted that lethal doses may at times be lower than those evoking neural impairment, because the latter is evaluated at 30 min post-dose, whereas animals are observed for death over a period of 7 days. Another compound, **17f**, also appeared to possess a degree of safety relative to neural impairment, as did analog **17e**.

Table I. 2-(Substituted amino)-2-[2′-hydroxy-2′-alkyl(or aryl)]ethyltricyclo[3.3.1.1^{3,7}]decane] hydrochlorides **17**.

Compd.	R^1	R^2	mp °C	Recryst. solvent	Formula	Analysis
17a	CH_3	$(CH_2)_3CH_3$	181—185	ethyl acetate—methanol	$C_{17}H_{32}ClNO$	C, H, Cl, N
17b	CH_3	$(CH_2)_5CH_3$	182—185	ethyl acetate	$C_{19}H_{36}ClNO$	C, H, Cl, N
17c	CH_3	$(CH_2)_7CH_3$	162—166	ethyl acetate	$C_{21}H_{40}ClNO$	C, H, Cl, N
17d	CH_3	$(CH_2)_9CH_3$	156—158	ether (slurry)	$C_{23}H_{44}ClNO$	C, H, Cl, N
17e	CH_3	$(CH_2)_{13}CH_3$	148—152	ether (slurry)	$C_{27}H_{52}ClNO$	C, H, Cl, N
17f	CH_3	$(CH_2)_{15}CH_3$	145—149	ether (slurry)	$C_{29}H_{56}ClNO$	C, H, Cl, N
17g	CH_3	$(CH_2)_{17}CH_3$	141—145	ether (slurry)	$C_{31}H_{60}ClNO$	C, H, Cl, N
17h	CH_3	C_6H_5	>210	ethanol	$C_{19}H_{28}ClNO$	C, H, Cl, N
17i	C_2H_5	C_6H_5	241—244	ethanol	$C_{20}H_{30}ClNO$	C, H, Cl, N

Biological evaluation and Discussion

The initial goal of the biological evaluation of the title *N*-alkyl-3-adamantylaminoalcohols **17** was aimed at gathering information regarding acute bioactivity and toxicity. The test selected for this purpose was the multiparameter screen (MPS) in mice [27, 28]. The latter provides a unique insight by allowing the observation of twenty-seven variable symptoms and mortality (see Experimental protocols), following intraperitoneal or oral dosing. Next, a series of supplementary assays was carried out, and, whenever positive effects were evident, a detailed testing

The length of the alkyl chain bearing the hydroxyl group seems to play a beneficial role in determining the effects on neural impairment; the least toxic derivatives (**17e—g**) were the ones with the longest alkyl chains ($R^2 = C_{14}$—C_{18}).

All compounds studied, when administered to mice intraperitoneally at the minimal neural impairment dose (*MNID*) were found to exert a distinct anti-hypoxia activity (Table IV) [35]. There was no correlation between the *MNID* and the ability of the compounds to increase the survival time in the hypoxic environment. The protection against hypoxia at ambient temperature ranged from an 11% increase in survival time with analog **17d** to 128 and

Table II. Acute behavioral signs following intraperitoneal administration of *N*-substituted-3-adamantylaminoalcohols **17** in mice.

Compd.	Dose[a] (mg/kg)	Initial elicitation of behavioral effects[b]
17a	50	decreased SMA[c], ptosis, mydriasis, hypothermia
	100	convulsions and death
17b	25—50	decreased SMA, ptosis, decreased reactivity, catalepsy, passivity, analgesia, hypergait, hypothermia
	50	convulsions
	100	death
17c	25	decreased SMA, ptosis, mydriasis, hypothermia
	50	convulsions and death
17d	25—50	decreased SMA, ptosis, hypothermia
	50	convulsions
	100	death
17e	25	decreased SMA, ptosis, hypothermia
	50—100	hypogait, catalepsy, failed wire maneuver
	200—400	loss of pinna reflex
17f	25—50	decreased SMA, ptosis
	100—400	hypogait, ataxia, catalepsy, loss of pinna, corneal and righting reflexes
	400	death at 3 h
17g	25—50	decreased SMA, ptosis
	100	catalepsy, hypothermia
	400	death at 24 h
17h	25—50	hypogait, ataxia, catalepsy, failed wire maneuver, mydriasis, hypothermia, exophthalmia, staub tail
	100	convulsions and death
17i	25—50	decreased SMA, ptosis, ataxia, mydriasis, analgesia, hypothermia, hypergait
	100	convulsions and death

[a]Groups of 3 mice were used at each dose level.
[b]Behavioral signs are given at the dose level in which they first appeared and are, therefore, present at larger doses; mice were observed up to 3 h post-dose.
[c]SMA = spontaneous motor activity.

Table III. LD_{50} values and acute minimal neural impairment doses *(AMNID)* in mice following intraperitoneal administration of *N*-substituted-3-adamantylaminoalcohols **17**.

Compd.	Mean LD_{50} dose[a] (mg/kg) slope±SE	*AMNID*
17a	67 (60—77) 16.0±6.5	50
17b	49 (15—73) 4.2±2.0	25
17c	46[b] 5.0±2.4	10
17d	42 (38—46) 35.0±14.0	10
17e	34 (28—38) 15.0±5.5	75
17f	38[c]	125
17g	150[b] 8.0±4.4	325
17h	72 (42—134) 6.5±3.0	10
17i	58 (34—69) 9.0±4.0	35

[a]LD_{50} values between parentheses are 95% confidence limits. Groups of 5—8 animals were used at each dose and were observed over a 7-day period. Data for LD_{50} values were calculated using the AEL50 program.
[b]Dose range was too narrow to obtain confidence limits using the AEL50 program.
[c]Estimated from general behavioral screening; supplies of compound exhausted.

131% with analogs **17f** and **17e**, respectively. The majority (7 out of 9) of the compounds extended the time of survival by 60% or more. When the title derivatives were tested at the minimal neural impairment dose, compounds **17e—g** demonstrated the highest levels of protection with the optimum activity being associated with analogs having $R^2 = C_{14}$—C_{16}. One problem faced during evaluation of compounds for anti-hypoxia activity is that the resulting hypothermia has likewise been demonstrated to be a mechanism for lengthening the survival time [35]. Indeed, as revealed in Table IV, the acute hypothermia observed after the intraperitoneal administration of compounds **17** at the minimal neural impairment dose, ranged from 0 to —5°C. However, there did not appear to be a correlation between the degree of hypothermia and the percent extension of survival time. To verify further the role of hypothermia, mice were injected with compounds **17**. 15 min later the animals were placed in a QUEEG environmental chamber maintained at 35°C for 15 min prior to and during the hypoxia. Except for a few instances (compounds **17a** and **17d**) there were no remarkable differences in the percent extension of survival time between mice maintained at ambient temperature and those placed in the 35°C chamber. Control mice at ambient temperature did, however, live longer during hypoxia than did mice in the environmental chamber (5.78 and 2.14 min, respectively, $p = 0.001$; Table IV). Therefore, it may be assumed that the hypothermic effects of the *N*-substituted-3-adamantylaminoalcohols **17** in mice are not solely responsible for their anti-hypoxia properties.

During further supplementary testing for biological activity, three analogs (**17a**, **17h** and **17i**) were found to be active as potential analgesics in the prevention of writhing produced by phenyl-*p*-benzoquinone (Table V) [33]. A margin of safety for **17a**, **17h** and **17i** was then determined by calculating the corresponding index for drug safety (LD_{50}/ED_{50}: 3.2, 9.0 and 2.4, respectively; Table V). Moreover, efficacy was found following oral administration with respective ED_{50} values of 69, 33 and 69 mg/kg.

When tested for anti-convulsant activity in the maximal electroshock-induced seizures (MES) [28], **17a** and **17i**,

Table IV. Anti-hypoxia activity following intraperitoneal administration of *N*-substituted-3-adamantylaminoalcohols **17** in mice[a].

Compd.	*MNID* (mg/kg)	Anti-hypoxia activity[b]		
		ambient temperature		35°C chamber
		hypothermia	anti-hypoxia	anti-hypoxia
17a	50	−3°C	61% p = NS[c]	161%[d] p = 0.044
17b	25	−2°C	98% p = 0.048	124% p = 0.045
17c	10	−1°C	66% p = 0.004	42% p = NS
17d	10	−2°C	11% p = NS	43% p = 0.001
17e	75	−5°C	131% p = 0.004	80% p = 0.001
17f	125	−3°C	128% p = 0.004	not tested
17g	325	−4°C	87% p = 0.004	76% p = 0.021
17h	10	0	37% p = 0.016	44% p = NS
17i	35	−2°C	67% p = 0.004	52% p = 0.014

[a]Groups of 5 mice per test procedure. Statistics data analyzed by Bartlett's test of homogeneity of variances, followed by pooled t test [36] and the Wilcoxon rank sum statistic [37].
[b]The anti-hypoxia activity was measured as the percent increase in survival time. Mean±SE survival times for the controls were: ambient temperature = 5±0.16 min (10 groups of 5 mice each) *vs.* 35°C environmental chamber = 2.14±0.08 min (4 groups of 5 mice each); p = 0.001. For comparison: propranolol gave 100% extension of survival time at an *MNID* of 35 mg/kg, whereas pentobarbital at 12.5 mg/kg *(MNID)* yielded a 49% extension of survival time.
[c]NS = not significant.
[d]With removal of one outlier the value is 117% (p = 0.073).

Table V. Biological activities and safety margins of *N*-substituted-3-adamantylaminoalcohols **17** in mice.

Compd.	Biological activity		Safety margin LD_{50}/ED_{50}
	ED_{50} (mg/kg)[a] (95% confidence limits)	LD_{50} (mg/kg)	
PBQ-induced writhing[b]			
17a	21 (13—30)[c] 69 (60—80)[d]	67	3.2[e]
17h	8 (7—10)[c] 33 (26—40)	72	9.0[e]
17i	24 (19—36)[c] 69 (41—302)	58	2.4[e]
Anti-MES[f]			
17a	40 (31—60)	67	1.7
17i	12 (9—14)	58	4.8
Anti-PTZ[g]			
17e	19 (9—35)	34	1.8
17g	158 (105—287)	150	<1.0
Anti-parkinson[h]			
17a	38 (22—51)[i]	67	1.8
17e	21 (14—30)	34	1.6

[a]The ED_{50} values were calculated using the AEL50 program.
[b]PBQ = phenyl-*p*-benzoquinone[j].
[c]Subcutaneous administration.
[d]Oral administration.
[e]Subcutaneous ED_{50} value used.
[f]MES = maximal electroshock-induced seizures; intraperitoneal administration[j].
[g]PTZ = pentylenetetrazole-induced seizures; intraperitoneal administration[j].
[h]Intraperitoneal administration[j].
[i]Oral ED_{50} = 33 mg/kg (20—47).
[j]Testing consisted of 10 mice/dose with at least 5 doses used to obtain the ED_{50} value.

were active. Compound **17i** had the highest margin of safety (4.8) (Table V). In the ability to prevent the minimal seizures evoked by pentylenetetrazole (PTZ) [30], only **17e** was found to be effective enough to have a margin of safety ratio of greater than 1 (1.8). Derivative **17g** had a margin of safety that was less than 1 (Table V). **17a** and **17e** displayed effective anti-parkinson activity when assayed in the LON 954-induced tremor test [34]. A safety margin of 1.8 was determined for **17a**, while the respective value for compound **17e** was 1.6. In addition, derivative **17a** showed oral efficacy (ED_{50} = 33 mg/kg) (Table V).

When evaluated for activity in the oxotremorine-induced tremor and salivation [31] and the apomorphine-induced clinging [32] (see Experimental protocols), none of the title aminoalcohol derivatives **17** showed any effects.

From the biological data presented in Tables II—V it appears that analog **17a** (R^2 = $(CH_2)_3CH_3$) demonstrated the most effective activity on the CNS. It showed anti-hypoxia activity (although less potent than that of **17e—g**), as well as analgesic, anti-convulsant and anti-parkinson activities. Two other analogs, **17g** and **17c** were also found active in the anti-hypoxia test, thus suggesting that alkyl substituents of relatively short length (R^2 = C_4—C_8) may also impart a beneficial effect on the anti-hypoxia activity. Both phenyl-containing analogs **17h** and **17i** exerted analgesic activity in the PBQ-induced writhing assay in addition to compound **17i** which also had the highest anti-convulsant therapeutic index and safety margin.

The overall results indicate that the presence of an adamantyl ring system and an alkyl side chain (R^2) in the molecule of the title aminoalcohols **17** may have facilitated the penetration through the blood—brain barrier. However, compounds **17** also displayed a considerable degree of toxicity, which, undoubtedly, limited their beneficial effects on the CNS. Regarding the length of the alkyl substituents R^2, two ranges (C_4—C_8 and C_{14}—C_{18}) appeared to be associated with the best overall activity on the CNS.

Experimental protocols

Chemistry

Melting points were determined on a Thomas—Hoover capillary melting point apparatus and are uncorrected. The infrared (IR) spectra

were obtained on a Nicolet MX-1 FT spectrometer as KBr discs. The ^1H nuclear magnetic resonance (^1H NMR) spectra were taken on a Varian EM-360A (60 MHz) spectrometer using tetramethylsilane as an internal standard. All spectra were consistent with the assigned structures.

*2-Methylamino-2-(2'-hydroxy-2'-*n*-hexyl)tricyclo[3.3.1.1^{3,7}]decane hydrochloride* ***17b***

Under a nitrogen atmosphere, 18.03 g (0.12 mol) of 2-adamantanone **13** and 10.34 g (0.13 mol) of *N*-methylhydroxylamine were dissolved in 300 ml of absolute ethanol. Then, sodium bicarbonate (10.99 g, 0.13 mol) was added and the resulting suspension was refluxed for 3 h. Upon cooling to room temperature, the solvent was removed under reduced pressure, then, 250 ml of toluene were added and the resulting suspension was filtered. 1-Octene (48 ml, 2.5 eq.) was added to the filtrate and the solution was refluxed under nitrogen for 40 h. Removal of the solvent provided a yellow oil which crystallized from ether saturated with hydrogen chloride, yielding 26.25 g (67%) of the hydrochloride salt of 2-methyl-5-*n*-hexyl-spiro[isoxazolidine-3,2'-tricyclo[3.3.1.1^{3,7}]decane] (**16b**: $R^1 = CH_3$; $R^2 = (CH_2)_5CH_3$) as a white solid. Recrystallization from ethyl acetate provided an analytical sample, mp: 134—136°C. Anal. Calcd for $C_{19}H_{34}ClNO$: C: 69.59; H: 10.45; Cl: 10.81; N: 4.27. Found: C: 69.21; H: 10.84; Cl: 10.66; N: 4.22.

Zinc dust was added portionwise to a solution of 6.56 g (20 mmol) of **16b** in 200 ml of 50% aqueous acetic acid. The resulting suspension was heated to 65—70°C for 7 h, then filtered and the inorganic residue was washed with hot water. The combined filtrate was neutralized with sodium bicarbonate and extracted with ether. The organic extract was dried over anhydrous magnesium sulfate and then saturated with hydrogen chloride gas in order to obtain the corresponding hydrochloride salt. Crystallization of the latter from ethyl acetate gave 5.07 g of pure **17b**, mp: 182—185°C. IR (KBr): 3230 cm^{-1} (OH), 3100—2500 cm^{-1} (NH_2^+). ^1H NMR ($CDCl_3/D_2O$): 0.70—2.40 ppm (cm, 29H, 5 × ring CH_2, 6 × chain CH_2, 4 × ring CH and C—CH_3); 2.67 ppm (s, 3H, N—CH_3); 4.10 ppm (m, 1H, C—CH—C); 5.75 ppm (bs, 1H, OH); 8.50 ppm (bs, 2H, N*H*·*H*Cl). Anal. Calcd for $C_{19}H_{36}ClNO$: C: 69.16; H: 11.00; Cl: 10.74; N: 4.25. Found: C: 69.48; H: 11.40; Cl: 10.79; N: 4.27.

2-Ethylamino-2-(2'-hydroxy-2'-phenyl)ethyltricyclo[3.3.1.1^{3,7}]decane hydrochloride ***17i***

Compound **17i** was obtained by a similar treatment of 2-ethyl-5-phenyl-spiro[isoxazolidine-3,2'-tricyclo[3.3.1.1^{3,7}]decane] hydrochloride (**16i**: $R^1 = C_2H_5$, $R^2 = C_6H_5$) with zinc dust—aqueous acetic acid. IR (KBr): 3290 cm^{-1} (OH), 3200—2700 cm^{-1} (NH_2^+). ^1H NMR ($CDCl_3/CF_3CO_2D$): 1.10—2.80 ppm (cm, 19H, 5 × ring CH_2, 4 × ring CH, C—CH_3 and CH_2—C); 3.15 ppm (m, 2H, C—CH_2—N); 5.12 ppm (m, 1H, C—C*H*—C_6H_5); 7.30 ppm (s, 5H, aromatic). Anal. Calcd for $C_{20}H_{30}ClNO$: C: 71.51; H: 9.00; Cl: 10.55; N: 4.17. Found: C: 71.27; H: 9.41; Cl: 10.57; N: 4.08.

*2-Methylamino-2-(2'-hydroxy-2'-*n*-hexadecyl)ethyltricyclo[3.3.1.1^{3,7}]decane hydrochloride* ***17f***

2-Methyl-5-*n*-hexadecyl-spiro[isoxazolidine-3,2'-tricyclo[3.3.1.1^{3,7}]decane] hydrochloride (**16f**: $R^1 = CH_3$, $R^2 = (CH_2)_{15}CH_3$) was prepared by a procedure similar to that described in the preparation of compound **16b** starting with 2-adamantanone, *N*-methylhydroxylamine and 1-octadecene (**15f**: $R^2 = (CHs)_{15}CH_3$). The hydrochloride salt of **16f** (10.00 g, 0.2 mol) was added in one portion to a suspension of 5% palladium on carbon (1.0 g) in 200 ml of glacial acetic acid. The mixture was hydrogenated in a Parr apparatus at room temperature for 72 h. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure at 40°C. The crude oily residue was dissolved in methylene dichloride and washed sequentially with aqueous sodium bicarbonate, water and brine. The organic extract was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to yield a yellow oil which solidified on standing. Subsequent purification by flash chromatography and treatment with ether saturated with hydrogen chloride gas furnished 2.76 g of the hydrochloride salt of **17f**, mp: 145—149°C. IR (KBr): 3420—3280 and 1100 cm^{-1} (OH), 3100—2600 and 1590 cm^{-1} (NH_2^+). ^1H NMR ($CDCl_3/D_2O$): 0.85—2.50 ppm (cm, 49H, 5 × ring CH_2, 16 × chain CH_2, 4 × ring CH, C—CH_3); 2.69 ppm (s, 3H, N—CH_3); 4.09 ppm (m, 1H, C—CH—C); 5.70 ppm (bs, 1H, OH); 8.60 ppm (bd, 2H, N*H*·*H*Cl).

*2-Methylamino-2-(2'-hydroxy-2'-*n*-butyl)ethyltricyclo[3.3.1.1^{3,7}]decane hydrochloride* ***17a***

Compound **17a** was prepared by hydrogenation of 2-methyl-5-*n*-butyl-spiro[isoxazolidine-3,2'-tricyclo [3.3.1.1.^{3,7}] decane] hydrochloride (**16a**: $R^1 = CH_3$, $R^2 = n$-butyl) in the presence of 5% palladium on carbon catalyst in glacial acetic acid medium, as described for compound **17f**. IR (KBr): 3200—3100 and 1100 cm^{-1} (OH), 3080—2500 and 1590 cm^{-1} (NH_2^+). ^1H NMR ($CDCl_3/CF_3CO_2D$): 0.88—2.35 ppm (cm, 25H, 5 × ring CH_2, 4 × chain CH_2, 4 × ring CH and C—CH_3); 2.71 ppm (s, 3H, N—CH_3); 4.09 ppm (m, 1H, C—CH—C); 7.09 and 8.50 ppm (2 bs, 3H, OH, N*H*·*H*Cl partially exchanged). Anal. Calcd for $C_{17}H_{32}ClNO$: C: 67.63; H: 10.68; Cl: 11.74; N: 4.64. Found: C: 67.68; H: 10.54; Cl: 11.92; N: 4.60.

*2-Methylamino-2-(2'-hydroxy-2'-*n*-octyl)ethyltricyclo[3.3.1.1^{3,7}]decane hydrochloride* ***17c***

Derivative **17c** was synthesized by a procedure similar to that described for the preparation of compound **17f** by hydrogenating 2-methyl-5-*n*-octyl-spiro[isoxazolidine-3,2'-tricyclo[3.3.1.1.^{3,7}]decane]hydrochloride (**16c**: $R^1 = CH_3$, $R^2 = n$-octyl) in the presence of 5% palladium on carbon catalyst in glacial acetic acid medium. IR (KBr): 3220—3160 and 1100 cm^{-1} (OH), 3080—2600 and 1590 cm^{-1} (NH_2^+). ^1H NMR ($CDCl_3/D_2O$): 0.84—2.46 ppm (cm, 33H, 5 × ring CH_2, 8 × chain CH_2, 4 × ring CH and C—CH_3); 2.69 ppm (s, 3H, N—CH_3); 4.06 ppm (m, 1H, C—CH—C); 5.70 ppm (bs, 1H, OH); 8.60 ppm (bd, 2H, N*H*·*H*Cl). Anal. Calcd for $C_{21}H_{40}ClNO$: C: 70.45; H: 11.26; Cl: 9.90; N: 3.91. Found: C: 70.60; H: 11.15; Cl: 9.90; N: 3.86.

*2-Methylamino-2-(2'-hydroxy-2'-*n*-decyl)ethyltricyclo[3.3.1.1^{3,7}]decane hydrochloride* ***17d***

Compound **17d** was made by a procedure similar to that described for the synthesis of derivative **17f** by hydrogenating 2-methyl-5-*n*-decyl-spiro[isoxazolidine-3,2'-tricyclo[3.3.1.1.^{3,7}]decane] hydrochloride (**16d**: $R^1 = CH_3$, $R^2 = n$-decyl) in the presence of 5% palladium on carbon catalyst in glacial acetic acid. IR (KBr): 3260—3130 and 1100 cm^{-1} (OH), 3090—2780 and 1590 cm^{-1} (NH_2^+). ^1H NMR ($CDCl_3/D_2O$): 0.84—2.46 ppm (cm, 37H, 5 × ring CH_2, 10 × chain CH_2, 4 × ring CH and C—CH_3); 2.69 ppm (s, 3H, N—CH_3); 4.06 ppm (m, 1H, C—CH—C); 5.70 ppm (bs, 1H, OH); 8.60 ppm (bd, 2H, N*H*·*H*Cl). Anal. Calcd for $C_{23}H_{44}ClNO$: C: 71.56; H: 11.49; Cl: 9.18; N: 3.63. Found: C: 71.72; H: 11.12; Cl: 9.26; N: 3.57.

*2-Methylamino-2-(2'-hydroxy-2'-*n*-tetradecyl)ethyltricyclo[3.3.1.1^{3,7}]-decane hydrochloride* ***17e***

Derivative **17e** was prepared by a procedure similar to that described for the synthesis of compound **17f** by hydrogenating 2-methyl-5-*n*-tetradecyl-spiro[isoxazolidine-3,2'-tricyclo[3.3.1.1.]^{3,7}decane] hydrochloride (**16e**: $R^1 = CH_3$, $R^2 = n$-tetradecyl) in the presence of 5% palladium on carbon catalyst in glacial acetic acid. IR (KBr): 3420—3280 and 1100 cm^{-1} (OH), 3100—2600 and 1590 cm^{-1} (NH_2^+). ^1H NMR ($CDCl_3/D_2O$): 0.85—2.47 ppm (cm, 45H, 5 × ring CH_2, 14 × chain CH_2, 4 × ring CH and C—CH_3); 2.70 ppm (s, 3H, N—CH_3); 4.09 ppm (m, 1H, C—CH—C); 5.70 ppm (bs, 1H, OH); 8.63 ppm (bd, 2H, N*H*·*H*Cl).

*2-Methylamino-2-(2'-hydroxy-2'-*n*-heptadecyl)ethyltricyclo[3.3.1.1^{3,7}]-decane hydrochloride* ***17g***

Compound **17g** was obtained by a procedure similar to that described for the preparation of analog **17f** by hydrogenating 2-methyl-5-*n*-heptadecyl-spiro[isoxazolidine-3,2'-tricyclo[3.3.1.1.^{3,7}]decane] hydrochloride (**16g**: $R^1 = CH_3$, $R^2 = n$-heptadecyl) in the presence of 5% palladium on carbon catalyst in glacial acetic acid. IR (KBr): 3400—3240 and 1100 cm^{-1} (OH), 3100—2800 and 1590 cm^{-1} (NH_2^+). ^1H NMR ($CDCl_3/D_2O$): 0.84—2.45 ppm (cm, 53H, 5 × ring CH_2, 18 × chain CH_2, 4 × ring CH and C—CH_3); 2.69 ppm (s, 3H, N—CH_3); 4.10 ppm (m, 1H, C—CH—C); 5.70 ppm (bs, 1H, OH); 8.60 ppm (bd, 2H, N*H*·*H*Cl). Anal. Calcd for $C_{31}H_{60}ClNO$: C: 74.73; H: 12.14; Cl: 7.12; N: 2.81. Found: C: 74.76; H: 12.11; Cl: 7.30; N: 2.81.

2-Methylamino-2-(2'-hydroxy-2'-phenyl)ethyltricyclo[3.3.1.1^{3,7}]decane hydrochloride ***17h***

Compound **17h** was synthesized by a procedure similar to that described

for the preparation of analog **17f** by hydrogenating 2-methyl-5-phenylspiro[isoxazolidine-3,2′-tricyclo[3.3.1.1^{3,7}]decane] hydrochloride (**16h**: R^1 = CH_3, R^2 = phenyl) in the presence of 5% palladium on carbon catalyst in glacial acetic acid. IR (KBr): 3250 and 1100 cm^{-1} (OH), 3080-2500 and 1590 cm^{-1} (NH_2^+). ^1H NMR ($CDCl_3/CF_3CO_2D$): 1.80—2.51 ppm (cm, 16H, 5 × ring CH_2, 4 × ring CH and CH_2—C); 2.79 ppm (m, 3H, N—CH_3); 5.13 ppm (d, 1H, C—CH—C); 6.90 and 8.46 ppm (2 bs, 3H, OH, N*H*·*H*Cl partially exchanged). Anal. Calcd for $C_{19}H_{27}ClNO$: C: 70.90; H: 8.77; Cl: 11.01; N: 4.35. Found: C: 71.15; H: 9.16; Cl: 11.02; N: 4.37.

Pharmacology

Multiparameter screen (MPS) in mice

Male CF-1 mice obtained from Charles River Laboratories weighing 20—30 g were housed under a 12 h light/dark cycle, at a temperature of 20—24°C and relative humidity of 30—50%. Standard (Purina lab chow) food and water were available *ad libidum* until the time of drug testing. Prior to the test procedures, mice that exhibited any abnormal behavior, reduction in body weight and/or signs of ill health were discarded. All animals were housed in in-house facilities for at least 5 days prior to initiation of experiments. Groups of mice were examined at various times after the administration of graded doses (25—400 mg/kg) of the test compounds. The MPS technique is an examination of symptomatology and is used to evaluate the drug action with regard to acute bioactivity or toxicity [27, 28]. In this test, 5 groups of 3 mice each were treated with graded doses of the test compounds. A 6th group received the vehicle and served as a control. The groups were evaluated for 27 symptoms plus mortality immediately, and at 0.5, 3 and 24 h after intraperitoneal (i.p.) or oral (*p.o.*) dosing.

A series of supplementary procedures were then run, beginning with a drug dose that was 1/4 of the approximate LD_{50} dose. The doses (5 mice/dose) were initially run, and whenever positive effects were evident, a detailed testing was performed for a greater quantitation of data (5 doses at 10 mice/dose). Testing was performed on all compounds at 30 min post-dose. Control mice were run with each test compound. The tests consisted of the following:

Inverted screen procedure. The test is designed to determine the minimal dose that produces an acute neural impairment. The latter is usually related to a therapeutic dose in order to assess the drug's specificity. The test is a measure of impaired motor function [29].

Anti-convulsant activity vs. *pentylenetetrazole (PTZ)-induced convulsions* [30].

Maximal electroshock seizures [30].

Oxotremorine-induced tremor and salivation. Compounds with central activity usually would also show antagonism to the peripheral effects of oxotremorine. Compounds which antagonize salivation, but do not affect tremor, are considered to have peripheral activity only [31].

Apomorphine-induced clinging. Compounds which antagonize this behavior can be considered to possess eventually an anti-psychotic activity [32].

Phenyl-p-benzoquinone (PBQ)-induced writhing. The test detects non-opiate, non-steroidal compounds with potential analgesic/anti-inflammatory activity [33].

N-Carbamoyl-2-(2,6-dichlorophenyl)acetamide hydrochloride (LON 954)-induced tremor. LON-954-induced tremor detects compounds that possess a potential anti-parkinson (dopamine receptor-stimulant) activity [34].

Anti-hypoxia screen. Groups (5 controls and 5 experimentals) of mice were initially tested at ambient temperature. The mice were treated with a drug or a vehicle and 30 min later were placed in a plastic chamber consisting of 5 interconnected compartments. A gas mixture composed of 96% nitrogen and 4% oxygen was allowed to enter the individual compartments at a pressure of 10 lbs/sq. inch and a flow rate of 0.01 M^3/min. The time to last gasp was monitored with an electric timer [35]. In order to rule out the possibility of hypothermia produced by the test compounds (as the mechanism of the observed anti-hypoxia action [35]), a second group of mice received the test compound and 15 min later were placed in the hypoxia apparatus, which in turn, was placed in an environmental QUEEG chamber maintained at 35°C. The mice remained in the QUEEG chamber for 15 additional min and throughout the period of hypoxia. The time to the last gasp was evaluated by an observer viewing the animals through a glass door.

Acknowledgments

The authors gratefully acknowledge the technical assistance of Rosemary Harvey, Marilyn A. Knowles, Sherri L. Phippen and Lou A. Steiner in running the biological assays.

References

1 Georgiev V. St. (1983) *in: Survey of Drug Research in Immunologic Disease* Vol. 2, S. Karger, Basel, pp. 225—509
2 Georgiev V. St. (1987) *in: Survey of Drug Research in Immunologic Disease.* Vol. 8, Karger, Basel, pp. 322—324
3 Melandri M., Buttini A., Carminati G. & Galimberti P. (1966) *Chim. Ther.* 1, 212—220
4 Malen C., Desnos M. & Poignant J. C. (1972) German Patent 2,154,867
5 Robba M. & Duval D. (1973) *Chim. Ther.* 8, 22—31
6 Hirsch B., Lohmann D. & Froemmel H. (1972) German (East) Patent 92,924
7 Igarashi H. (1974) *Yakugaku Zasshi* 94, 126—137
8 Malen C., Desnos M. & Poignant J. C. (1975) U.S. Patent 3,872,102
9 Vlasenko E. V., Roitman I. R. & Azlivyan A. S. (1975) *Biol. Zh. Arm.* 28, 18—20
10 Muro T., Nakao T., Ogawa K., Oka T. & Yaoka O. (1976) Japan Patent 76 141,829
11 Igarashi H., Kawasaki T., Hamada S., Endo H., Takita Y. & Urai J. (1977) *Yakugaku Zasshi* 97, 1125—1130
12 Muro T., Nakao T., Ogawa K., Oka T. & Yaoka O. (1978) Japan Patent 78 59,675
13 Yuki H., Nakao T. & Setoguchi S. (1977) Japan Patent 77 03,052
14 Ravina E., Montanes J. M., Seco M. C., Calleja J. M. & Zarzosa M. (1973) *Chim. Ther.* 8, 182—184
15 Garoufalia S., Foscolos G. B., Tsatsas G., Costakis E., Galanopoulou P., Karageorgiou C., Petounis A. & Varonos D. (1981) *Ann. Pharm. Fr.* 39, 519—527
16 Tsatsas G., Garoufalia S., Foskolos G. B., Costakis E., Galanopoulou N., Karageorgiou C., Petounis A. & Varonos D. (1981) *Prakt. Akad. Athenon* 55, 382—394
17 Isoda S., Kaneo M. & Ichikawa Y. (1980) Japan Patent 80 17,345
18 Fahn S., Graddock G. & Kumin G. (1971) *Arch. Neurol.* 25, 45—48
19 Rinne U. K. (1972) *Acta Neurol. Scand. (suppl.)* 51, 59—103
20 Hirschmann J. (1973) *Med.-Welt.* 24, 976—979
21 Gilbert J. C. (1975) *Br. Med. J.* 4, 33—35
22 Tomatis R., Salvadori S., Menegatti E. & Guarneri M. (1979) *Farmaco Ed. Sci.* 34, 496—506
23 Liubimov B. I., Skoldinov A. P., Boiko S. S., Rodionov A. P. & Mozhaeva T. (1980) *Farmakol. Toksikol.* 43, 408—411
24 Vezzani A., Zatta A., Ladinsky H., Caccia S., Garattini S. & Consolo S. (1982) *Biochem. Pharmacol.* 31, 1693—1698
25 Bailey E. V. & Stone J. W. (1975) *Arch. Int. Pharmacodyn. Ther.* 216, 244—262
26 Parkes J. D., Zilka K. J., Calver D. M. & Knill-Jones R. P. (1970) *Lancet* 1, 259—262
27 Irwin S. (1968) *Psychopharmacologia* 13, 222—254
28 Campbell D. E. S. & Richter W. (1967) *Acta Pharmacol. Toxicol.* 25, 345—363
29 Coughenour L. L., Mclean J. R. & Parker R. B. (1977) *Pharmacol. Biochem. Behav.* 6, 351—353
30 Porter R. J., Cereghino J. J., Gladding G. D., Hessie B. J., Kupferberg H. J., Scoville B. & White B. G. (1964) *Clev. Clin. Q.* 51, 293—305
31 Lesley G. B. & Maxwell D. R. (1964) *Nature* 202, 97—98
32 Protais P., Custentin J. & Schwartz J. C. (1976) *Psychopharmacology* 50, 1—6
33 Okun R., Liddon S. C. & Lasagna L. (1963) *J. Pharmacol. Exp. Ther.* 139, 107—109
34 Coward D. M., Doggett N. S. & Sayers A. C. (1977) *Arzneim. Forsch.* 27, 2326—2332
35 Artru A. A. & Michenfelder J. D. (1981) *Anesth. Analg.* 60, 867—870
36 Winer B. J. (1971) *in: Statistical Principles in Experimental Design.* 2nd edn., MacGraw-Hill, New York, pp. 208—209 and 834—837
37 Ferguson G. A. (1966) *in: Statistical Analysis in Psychology and Education.* 2nd edn., McGraw-Hill, New York, pp. 360—361