POTENTIAL ANTIPARKINSONIC AGENTS: SYNTHESIS AND PHARMACOLOGY OF SOME 4-FLUORO-4'-HALOGENOBENZHYDRYL 2-(N,N-DISUBSTITUTED AMINO)ETHYL ETHERS

Zdeněk VEJDĚLEK, Jan METYŠ, Jiří HOLUBEK, Emil SVÁTEK and Miroslav PROTIVA

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

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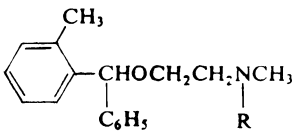
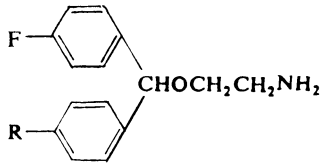
Reactions of 4,4'-dihalogenated benzhydrols and 1,1-diphenylethanols *Xab* and *XIab* with sodium hydride and 2-dimethylaminoethyl chloride and 2-pyrrolidinoethyl chloride afforded the ethers *Vab*—*VIIIab*. 2-Bromoethyl ethers *IXab*, obtained from the benzhydrols *Xab* and 2-bromoethanol by treatment with sulfuric acid, were subjected to substitution reactions with 4-phenylpiperidin-4-ol, 4-(2-tolyl)piperidin-4-ol (*XVI*), 4-(4-fluorophenyl)piperidin-4-ol and 4-(2-oxobenzimidazolin-1-yl)piperidine (*XVII*) and gave the amino ethers *XIIab*—*XIVab* and *XIXab*. The products were evaluated as potential antiparkinsonic agents and compared with flunamine (*III*). The ethers *Va*, *Vb* and *VIa* disclosed anticataleptic activity of a similar degree like that of flunamine (*III*).

With some Ar- and N-substituted benzhydryl 2-aminoethyl ethers the anticholinergic activity is more important than the antihistamine one and such compounds find practical use in the pharmacotherapy as antiparkinsonic agents. Typical from this point of view are the 2-methylbenzhydryl ethers orphenadrine (*I*) (ref.[1,2]) and tofenacine (*II*) (ref.[3,4]), the tropine derivatives benztropine[5,6] and ethylbenztropine[7,8] and finally also clofenetamine[9,10], an ether derived from 1-(4-chlorophenyl)-1-phenylethanol. In 1973–1974 there appeared the first reports on a new series of 4,4'-dihalogenobenzhydryl 2-aminoethyl ethers[11,12], represented by flunamine (*III*) (ref.[13–15]) and halonamine (*IV*) (ref.[13]). Flunamine (*III*) was first presented as a potential antiparkinsonic agent having high central dopaminomimetic activity[14]. A more recent report[16] has described flunamine (*III*) as a potential broad spectrum antidepressant. This was based on the fact that it showed a strong and almost uniform inhibition of noradrenaline, dopamine and 5-hydroxytryptamine uptake in synaptosomes from different brain areas. It was suggested that such a broad spectrum compound may have advantages over the existing more specific antidepressants because in depressions the neurotransmitter amines seem to be involved in a varying, still unpredictable degree, depending on the type of depression. The synthesis of flunamine (*III*) and several analogues was described by a Spanish author[17,18] almost simultaneously with the cited Gist–Brocades patents[11] and papers[12,14]. The Japanese

team of Sumitomo claims in a patent application[19] a broad area of structures of flunamine-like piperidines. A group of specifically N-substituted flunamine-like piperazines was described as being very potent dopamine uptake inhibitors[20]. The purpose of the present study was to synthesize and test some flunamine analogues with a tertiary amino group which are derived not only from benzhydrols but also from the corresponding 1,1-diarylethanols.

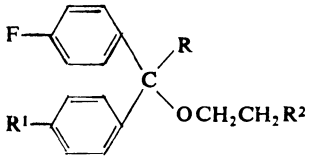


I, R = CH_3
II, R = H

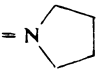


III, R = F
IV, R = Cl

In the first line there were prepared 2-dimethylaminoethyl ethers and 2-pyrrolidinoethyl ethers *Vab*–*VIIIab* derived from 4,4′-difluorobenzhydrol (*Xa*) (refs[21–23]), 4-bromo-4′-fluorobenzhydrol (*Xb*) (ref.[24]), 1,1-bis(4-fluorophenyl)ethanol (*XIa*)

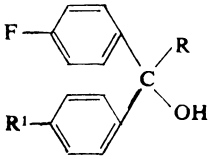


V, R = H, $R^2 = N(CH_3)_2$ *VII*, R = CH_3, $R^2 = N(CH_3)_2$

VI, R = H, R^2 =  *VIII*, R = CH_3, R^2 = 

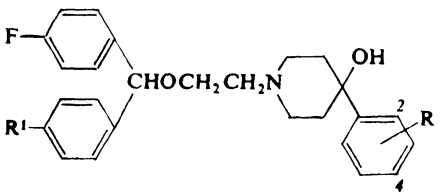
IX, R = H, R^2 = Br

In formulae *V*–*XIV*, *XIX* and *XX*: *a*, R^1 = F; *b*, R^1 = Br

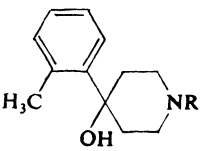


X, R = H
XI, R = CH_3

(ref.[25]) and 1-(4-bromophenyl)-1-(4-fluorophenyl)ethanol (*XIb*). The synthesis was carried out by reactions of these alcohols with sodium hydride and 2-dimethylaminoethyl chloride or 2-pyrrolidinoethyl chloride[26] in boiling benzene (method *A*). Bases *Vab*–*VIIIab* were obtained in good yields as oils, distilling *in vacuo* without decomposition, which were transformed to hydrochlorides. As a model experiment, the synthesis of N,N-dimethyl-2-(1,1-diphenylethoxy)ethylamine was carried out from 1,1-diphenylethanol[27,28], which was described by making use of sodium amide as the base[28]. For synthesis of the alcohol *Xb* (ref.[24]) the necessary 4-bromo-4′-fluorobenzophenone was obtained by reaction of 4-bromobenzoyl chloride[29] with fluorobenzene and aluminium chloride in carbon disulfide in a yield of 93% (its synthesis in a yield of only 19% was described[24] by a similar reaction of 4-fluorobenzoyl chloride with bromobenzene). Alcohol *XIb* was obtained by reaction of 4-bromo-4′-fluorobenzophenone with methylmagnesium iodide in ether; the crude oily product was successfully processed without characterization by method *A*. In the Experimental only the preparation of the ether *VIIb* is described; the other products are assembled in Table I with the usual experimental data.



XII, R = H
XIII, R = 2-CH₃
XIV, R = 4-F



XV, R = $COOC_2H_5$
XVI, R = H

In the following part the synthesis of 2-(4-aryl-4-hydroxypiperidino)ethyl ethers *XIIab*–*XIVab* is being described. These compounds are closely related to substances of the cited patent application[19]. They were obtained by reactions of the 2-bromoethyl ethers *IXa* and *IXb* with 4-phenylpiperidin-4-ol[30], 4-(2-tolyl)piperidin-4-ol (*XVI*) and 4-(4-fluorophenyl)piperidin-4-ol[30] in boiling 4-methylpentan-2-one in the presence of potassium carbonate (method *B*). Out of the oily bases *XIIab*–*XIVab* only *XIIa*, *XIIb* and *XIVa* afforded hydrochlorides without further purification; they were characterized by the IR spectra. Crude bases *XIIIa*, *XIIIb* and *XIVb* needed chromatography on alumina and only then could be transformed to oxalates. The bases, released from these oxalates, were characterized by the IR, ^{1}H NMR and ^{19}F NMR spectra. Oxalate of the base *XIVb* crystallized from a mixture of ethanol and ether as an unusually stable solvate with diethyl ether; its identity was confirmed by the mass spectrum. In the Experimental, only the synthesis of compound *XIVb* is described; the remaining products are to be found in Table I. The starting

TABLE I

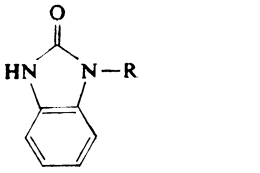
4-Fluoro-4′-halogenobenzhydryl 2-(N,N-disubstituted amino)ethyl ethers

Compound	Method (yield %)	B.p., °C/kPa or m.p., °C (ethanol–ether)	Formula (mol. wt.)	Calculated/Found				
				% C	% H	% N	% F	% Hal
Va	*A* (89)	140–142/0·13	—	—	—	—	—	
Va-HCl	—	125–126	$C_{17}H_{20}ClF_2NO$	62·27	6·16	4·28	11·59	10·82[a]
			(327·8)	62·48	6·22	4·32	11·19	10·39
Vb	*A* (85)	173–175/0·27	—	—	—	—	—	—
Vb-HCl	—	123–124	$C_{17}H_{20}BrClFNO$	52·50	5·19	3·61	4·89	9·13[a,b]
			(388·7)	52·62	5·07	3·70	4·65	8·86
VIa	*A* (91)	165–168/0·16	—	—	—	—	—	—
VIa-HCl	—	178–179	$C_{19}H_{22}ClF_2NO$	64·48	6·28	3·96	10·74	10·02[a]
			(353·8)	63·94	6·39	4·12	10·54	10·04
VIb	*A* (84)	190–193/0·20	—	—	—	—	—	—
VIb-HCl	—	157–158	$C_{19}H_{22}BrClFNO$	55·00	5·35	3·38	4·59	8·55[a,c]
			(414·8)	54·89	5·46	3·72	4·35	8·65
VIIa	*A* (79)	142–145/0·13	—	—	—	—	—	—
VIIa-HCl	—	164–165	$C_{18}H_{22}ClF_2NO$	63·24	6·49	4·10	11·12	10·37[a]
			(341·8)	62·89	6·44	4·36	10·80	10·20
VIIb	*A*[d] (89)	165–168/0·13	—	—	—	—	—	—
VIIb-HCl	—	157–158	$C_{18}H_{22}BrClFNO$	53·67	5·51	3·48	4·72	8·82[a,e]
			(402·7)	53·52	5·32	3·58	4·76	8·64
VIIIa	*A* (80)	172–175/0·16	—	—	—	—	—	—
VIIIa-HCl	—	169–170	$C_{20}H_{24}ClF_2NO$	65·30	6·57	3·81	10·33	9·64[a]
			(367·9)	64·52	6·65	4·02	9·95	9·47
VIIIb	*A* (84)	192–195/0·20	—	—	—	—	—	—
VIIIb-HCl	—	183–184	$C_{20}H_{24}BrClFNO$	56·02	5·64	3·27	4·43	8·27[a,f]
			(428·8)	56·05	5·62	3·27	4·02	7·95
XIIa-HCl	*B* (75)	164–165[g]	$C_{26}H_{28}ClF_2NO_2$	67·89	6·14	3·05	8·26	7·71[a]
			(460·0)	67·94	6·25	3·36	8·07	7·85

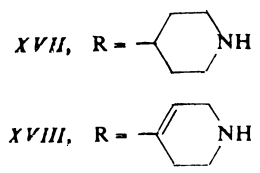
XIIb-HCl	*B* (82)	137–138	$C_{26}H_{28}BrClFNO_2$	59·95	5·42	2·69	3·65	6·81[a,h]
			(520·9)	59·49	5·44	2·85	3·61	6·89
XIIIa-HOx[i]	*B* (60)	102–103[j]	$C_{29}H_{31}F_2NO_6$	66·02	5·92	2·66	7·20	—
			(527·6)	65·68	6·18	2·50	6·88	—
XIIIb-HOx[i]	*B* (48)	95–96[k]	$C_{29}H_{31}BrFNO_6$	59·19	5·31	2·38	3·23	13·58[l]
			(588·5)	59·32	5·37	2·26	3·07	13·60
XIVa-HCl	*B* (91)	135–136[m]	$C_{26}H_{27}ClF_3NO_2$	65·32	5·70	2·93	11·93	7·42[a]
			(477·9)	65·04	5·88	3·23	11·86	7·52
XIVb-HOx[i,n]	*B*[d] (71)	80–81	$C_{28}H_{28}BrF_2NO_6$ +	57·68	5·75	2·10	5·70	11·99[l]
			+ $C_4H_{10}O$	58·03	5·53	2·23	5·74	11·97
			(666·6)					
XIXa-HOx[i]	*B* (70)	207–208[o]	$C_{29}H_{29}F_2N_3O_6$	62·92	5·29	7·59	6·86	—
			(553·5)	63·16	5·25	7·29	7·05	—
XIXb-HCl	*B* (83)	148–150[p]	$C_{27}H_{28}BrClFN_3O_2$	57·80	5·04	7·49	3·39	6·32[a,q]
			(560·9)	57·50	5·25	7·26	3·66	6·06

[a] Cl. [b] Calculated: 20·56% Br; found: 20·82% Br. [c] Calculated: 19·27% Br; found: 19·24% Br. [d] See Experimental. [e] Calculated: 19·84% Br; found: 19·71% Br. [f] Calculated: 18·64% Br; found: 18·72% Br. [g] IR spectrum: 709, 768, 828, 843 (5 and 2 adjacent Ar—H), 1 113 (R_3C—OH, R—O—R′), 1 227 (Ar—F, C—N), 1 510, 1 604 (Ar), 2 580 (NH^+), 3 305 cm^{-1} (OH). [h] Calculated: 15·34% Br; found: 15·52% Br. [i] Hydrogen oxalate. [j] Spectra of the released base. IR: 760, 832 (4 and 2 adjacent Ar—H), 1 078, 1 104 (R_3C—OH), 1 090 (R—O—R′), 1 222 (Ar—F, C—N), 1 500, 1 600, 3 040 (Ar), 2 745, 2 768 (CH_2—N), 3 150 cm^{-1} (OH). ^1H NMR: δ 6·80–7·50 (m, 12 H, ArH), 5·35 (s, 1 H, Ar_2CH—O), 3·60 (t, 2, H, CH_2O), 2·70 (t, 2 H, CH_2N in the chain), 2·60 (s, 3 H, $ArCH_3$). ^{19}F NMR: δ −115·66 (m, 2 F). [k] Spectra of the released base. IR (film): 760, 820 (4 and 2 adjacent Ar—H), 1 090 (R—O—R′, R_3C—OH), 1 485, 1 503, 1 510, 1 600 (Ar), 2 795 (CH_2—N), 3 150, 3 400, 3 513 cm^{-1} (OH). ^1H NMR: δ 6·80–7·50 (m, 12 H, ArH), 5·31 (s, 1 H, Ar_2CH—O), 3·60 (t, J = 5·0 Hz, 2 H, CH_2O), 2·72 (t, J = 5·0 Hz, 2 H, CH_2N in the chain), 2·61 (s, 3 H, $ArCH_3$). ^{19}F NMR: δ −115·39 (m). [l] Br. [m] IR spectrum: 826, 849 (2 adjacent Ar—H), 1 120 (R_3C—OH), 1 160 (R—O—R′), 1 235 (Ar—F, C—N), 1 509, 1 515, 1 606, 3 060, 3 090 (Ar), 2 530, 2 580 (NH^+), 3 305 cm^{-1} (OH). [n] Solvate with diethyl ether. [o] Spectra of the released base. IR: 730, 750, 825 (4 and 2 adjacent Ar—H), 1 089 (R—O—R′), 1 220 (Ar—F, C—N), 1 480, 1 500, 1 508, 1 600 (Ar), 1 682 (N-CO—NH in the ring), 2 735, 2 775 (CH_2—N), 3 200 cm^{-1} (NH). ^1H NMR: δ 10·60 (bs, 1 H, NH), 6·80–7·50 (m, 12 H, ArH), 5·38 (s, 1 H, Ar_2CH—O), 4·35 (bm, 1 H, CH—N), 3·61 (t, J = 5·0 Hz, 2 H, CH_2O), 2·75 (t, J = 5·0 Hz, 2 H, CH_2N in the chain). ^{19}F NMR: δ −115·55 (m, 2 F). [p] IR spectrum (KBr): 760, 820 (4 and 2 adjacent Ar—H), 1 023, 1 085 (R—O—R′), 1 489, 1 511, 1 606, 1 626 (Ar), 1 702 (N—CO—NH in the ring), 2 720 (NH^+), 3 300 cm^{-1} (NH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 10·90 (bs, 1 H, NH^+), 6·80–7·60 (m, 12 H, ArH), 5·55 (s, 1 H, Ar_2CH—O), 1·50–4·20 (m, remaining CH_2 and CH groups). [q] Calculated: 14·25% Br; found: 13·96% Br.

2-bromoethyl ethers *IXa* and *IXb* were prepared by reactions of benzhydrols *Xa* (ref.[21]) and *Xb* (ref.[24]) with 2-bromoethanol in boiling benzene in the presence of sulfuric acid. Benzhydryl 2-bromoethyl ether[31] was prepared similarly; the used method is an analogy of the procedure described[32] for the preparation of benzhydryl 2-chloroethyl ether. Out of the piperidine intermediates, 2-tolyl derivative *XVI* is new. It was prepared from 1-ethoxycarbonyl-4-piperidone[33] by treatment with 2-tolyl magnesium bromide in ether and by the following hydrolysis of the carbamate *XV* with potassium hydroxide in ethanol.



XVII, R =



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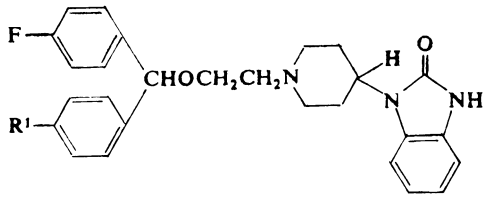
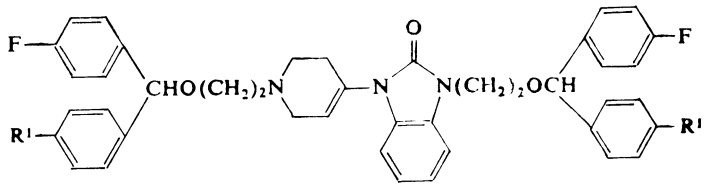


XIX



XX

4-(2-Oxobenzimidazolin-1-yl)piperidine (*XVII*) (ref.[34]) and 4-(2-oxobenzimidazolin-1-yl)-1,2,3,6-tetrahydropyridine (*XVIII*) (ref.[35]) were selected as further piperidine derivatives suitable for reactions with 2-bromoethyl ethers *IXa* and *IXb*. In the first case the use of method *B* led to compounds *XIXa* and *XIXb*, the first of which was explicitly named in the patent application[19] but none data about the characterization are available. In cases of reactions of ethers *IXa* and *IXb* with the piperideine *XVIII* (ref.[35]) it was necessary to purify the products by chromatography and only then we succeeded in transforming the homogeneous bases, obtained in low yields, to oxalates. Their analyses indicated in both cases that the compounds contain 3 nitrogen atoms per 4 atoms of halogens. In spite of the fact that both reaction components were used in approximately equivalent amounts, there evidently came also to the alkylation on the lactam NH group. The products are formulated as *XXa* and *XXb*.

In the first case the structure is supported only by the analysis of the oxalate, in the other it was fully confirmed by the ^{1}H NMR spectrum of the released base. An attempt at confirming structure *XXa* by the mass spectrum was unsuccessful: the compound with a molecular weight of 707 did not afford the molecular ion and the fragments registered were not suitable for diagnostic purposes.

A part of the compounds prepared was tested in the form of salts, described in the Experimental and in Table I, in psychopharmacological animal tests (doses calculated for bases), partly in tests of the general screening. Flunamine (*III*) hydrochloride[11] was used as the standard. Acute toxicity in mice, LD_{50} in mg/kg: *III*, 35 *i.v.* (toxic symptoms are qualitatively similar like with central stimulants: tremor, excitation, convulsions); *Va*, 39 *i.v.*; *Vb*, 47·6 *i.v.*; *VIa*, 52 *i.v.*; *VIb*, 26 *i.v.*; *VIIIa*, 38·4 *i.v.*; *VIIIb*, *c.* 500 orally; *XIIa*, *c.* 250 orally; *XIVa*, *c.* 1 000 orally (with *Va*, *Vb*, *VIb*, *VIIIa*, *XIIa* and *XIVa* similar toxic symptoms like with *III*). Discoordinating effect in the rotarod test in mice was found mostly only in toxic doses (on intravenous administration maximum effect in 5–10 min after the administration, on oral administration in 15–90 min), ED_{50} in mg/kg: *III*, 15 *i.v.* (excitation); *Va*, 9·6 *i.v.*; *Vb*, 31 *i.v.*; *VIa*, 8·9 *i.v.*; *VIb* 13·5 *i.v.*; *VIIIa*, 13 *i.v.*; *VIIIb*, *c.* 200 *p.o.*; *XIIa*, <200 *p.o.* Inhibition of spontaneous locomotor activity in mice evaluated using the photo-cell method (Dews), D_{50} in mg/kg (oral administration): *III*, 26·8; *Va*, 27·7; for compounds *Vb*, *VIa* and *XIIa* $D_{50} > 50$ (slight effect); with compounds *VIb*, *VIIIa* and *VIIIb* a dose of 50 mg/kg was completely inactive. Influence on the thiopental sleeping time in mice was tested by making use of the dose of 10% of the LD_{50} (*i.v.*); the effect is expressed in percents of the sleeping time (control value 100%): *III*, 60 (the only compound in the series which reduced the thiopental sleeping time); *Va*, 510; *VIa* 880; *VIIIa*, 230; *Vb* and *VIb* without significant effect; *VIIIb*, oral dose of 25 mg/kg, 930%; *XIIa*, oral dose of 25 mg/kg, 240%; *XIVa*, oral dose of 200 mg/kg without effect. Behavioural activation in male rats after the intravenous dose of 10 mg/kg; *III*, significant effect with indication of stereotypies (chewing) and tremor; *Va* and *VIIIa*, significant effect with stereotypies more pronounced than with *III*; *Vb*, *VIa*, *VIb*, *VIIIb*, significant effect of shorter duration than with *III*. There were no signs of aggressivity after the aggregation of the animals.

Antihistamine activity in the test of histamine aerosol in guinea-pigs: *III*, *Vb*, *VIa*, *VIb* and *VIIIa* in the *i.p.* dose of 1 mg/kg were practically inactive; *VIIIb*, $PD_{50} < 10$ mg/kg *p.o.*; *XIIa*, inactive in the oral dose of 10 mg/kg. Antihistamine activity in the test of histamine detoxication in guinea-pigs (oral administration): *III*, in the dose of 10 mg/kg a weak protective effect (10–30% animals are protected); *Vb*, *VIa*, *VIb*, *XIIa* – similar like with *III*; *Va*, $PD_{50} < 10$ mg/kg (70% animals protected); *VIIIa*, $PD_{50} = 10$ mg/kg; *VIIIb*, $PD_{50} > 10$ mg/kg (40% animals protected). In general, the antihistamine activity is low. Antireserpine activity in the test of antagonism of reserpine ulcer formation in rats: An oral dose of 50 mg/kg was inactive with compounds *III*, *Va*, *Vb*, *VIa*, *VIb*, *VIIIa*, *VIIIb* and *XIIa*. Influence

on the reserpine-induced hypothermia in mice after the *i.p.* dose of 4 mg/kg: *III*, a low antagonistic effect; *Vb*, a mild but statistically significant antagonistic effect; *XIVa*, inactive in the oral dose of 200 mg/kg. Antireserpine effect in the test of ptosis in mice: *XIVa*, ED = 100 mg/kg orally. Antagonism of perphenazine-induced catalepsy in rats after oral dose of 100 mg/kg: *III*, 100% anticataleptic effect with signs of excitation (subcutaneous dose of 50 mg/kg has also full anticataleptic effect but was lethal for 20% animals); *Va*, *Vb* and *VIa*, intensive anticataleptic effect; *VIIIa*, a weak effect; *VIb*, *VIIIb* and *XIIa*, practically inactive.

With flunamine (*III*) the following further effects were found in the general screening: Antispasmodic effect towards acetylcholine in the *in vitro* test on the isolated rat duodenum; the active concentration 10 μg/ml. Antispasmodic effect towards barium chloride in the same *in vitro* test, the active concentration 1 – 10 μg/ml. Antiinflammatory effect evaluated on the basis of inhibition of the rat paw edema elicited by subplantar administration of 0·1 ml 10% kaolin suspension; ED = 10 – 30 mg/kg *p.o.* Diuretic effect in mice (dose increasing diuresis by 100% as compared with the control): ED = 1 – 5 mg/kg *p.o.* (an effect like with furosemide). Negative inotropic effect (concentration decreasing inotropy of the isolated rabbit heart atrium by 25%), 25 – 50 μg/ml.

In conclusion, the most simple 4,4'-dihalogenobenzhydryl ethers *Va*, *Vb*, *VIa* and *VIb*, show the most important similarity of pharmacodynamic effects with those of flunamine (*III*): stimulating effects of toxic doses in mice, behavioural stimulation of a higher intravenous dose in male rats with signs of apomorphine-like stereotypies, intensive anticataleptic action in higher oral doses in rats, low antihistamine and antireserpine activity.

Most of the compounds prepared were tested for antimicrobial activity *in vitro* (microorganisms and the minimum inhibitory concentrations in μg/ml given, unless they exceed 100 μg/ml): *Streptococcus β-haemolyticus*, *Vb* 50, *VIb* 12·5, *VIIa* 25, *VIIb* 24, *VIIIb* 25, *XIIa* 25, *XIIb* 12·5, *XIVa* 25, *XIXb* 12·5; *Streptococcus faecalis*, *VIb* 100, *VIIa* 100, *VIIb* 50, *VIIIb* 100, *XIIa* 50, *XIIb* 12·5, *XIVa* 25; *Staphylococcus pyogenes aureus*, *III* 100, *VIb* 50, *VIIb* 100, *VIIIb* 50, *XIIa* 50, *XIIb* 12·5, *XIVa* 12·5, *XIXb* 50; *Pseudomonas aeruginosa*, *XIXb* 50; *Escherichia coli*, *Vb* 100, *VIb* 50, *VIIb* 50, *VIIIb* 50, *XIIa* 25, *XIIb* 12·5, *XIVa* 25; *Proteus vulgaris*, *XIXb* 100; *Mycobacterium tuberculosis* H37Rv, *III* 50, *Va* 50, *Vb* 25, *VIa* 25, *VIb* 6·25, *VIIa* 50, *VIIb* 12·5, *VIIIa* 25, *VIIIb* 6·25, *XIIa* 6·25, *XIIb* 6·25, *XIVa* 6·25, *XIXb* 12·5; *Saccharomyces pasterianus*, *VIIIa* 50; *Trichophyton mentagrophytes*, *VIIa* 50, *VIIb* 50, *XIIb* 25, *XIVa* 50. The antimycobacterial effects of several compounds (*VIb*, *VIIIb*, *XIIa*, *XIIb*, *XIVa*) is worth mentioning.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. The IR spectra (mostly in Nujol) were recorded with a Unicam SP 200G spectrophotometer, ^{1}H NMR spectra (in C^2HCl_3 unless stated otherwise), the ^{19}F NMR spectra (in $CHCl_3$, $\delta_{CFCl_3} = 0$) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectrum with Varian

MAT 44S spectrometer. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). The column chromatography was carried out on neutral Al_2O_3 (activity II). The extracts were dried with Na_2SO_4 or K_2CO_3 (solutions of bases) and evaporated under reduced pressure. The oily bases for recording the spectra were released from the homogeneous salts with NH_4OH and isolated by extraction with ether.

4-Bromo-4′-fluorobenzophenone

A stirred mixture of 150 ml CS_2, 35·2 g 4-bromobenzoyl chloride[29] and 36 ml fluorobenzene was treated over 1 h with 30 g $AlCl_3$, stirred for 5 h without heating, allowed to stand overnight and refluxed for 1 h with stirring, CS_2 was evaporated, the residue was decomposed with 400 g ice and 70 ml hydrochloric acid and the mixture was extracted with 2 : 1 benzene–ether. The extract was washed with dilute hydrochloric acid and water, and processed. The residue was dissolved in 500 ml boiling hexane and the solution was allowed to crystallize; 41·7 g (93%) (including the product obtained by processing of the mother liquor), m.p. 109—110°C. Lit.[24], m.p. 107—108°C.

N,N-Dimethyl-2-(1,1-diphenylethoxy)ethylamine

A solution of 10·0 g 1,1-diphenylethanol[27,28] in 60 ml benzene was added to a suspension of 1·44 g NaH in 40 ml benzene and the mixture was refluxed for 6 h. After cooling it was treated under stirring with a solution of 5·6 g 2-dimethylaminoethyl chloride in 20 ml benzene, the mixture was stirred for 90 min at room temperature, for 30 min at 60°C and allowed to stand overnight. Under nitrogen, it was decomposed by the slow addition of 15 ml water, the organic layer was washed with water, dried and evaporated; 12·5 g (92%) oily base. Hydrochloride, m.p. 166—168°C (acetone–ether). Lit.[28], m.p. 168°C.

N,N-Dimethyl-2-[1-(4-bromophenyl)-1-(4-fluorophenyl)ethoxy]ethylamine (*VIIb*)

Grignard reagent prepared from 1·82 g Mg and 10·7 g methyl iodide in 45 ml ether was treated with stirring over 30 min with a solution of 19·0 g 4-bromo-4′-fluorobenzophenone in 45 ml benzene at room temperature. The mixture was refluxed for 90 min, cooled and decomposed with ice and 90 ml 20% NH_4Cl. The aqueous layer was extracted with a mixture of benzene and ether, the organic layers were combined, washed with 50 ml 5% Na_2CO_3, dried and evaporated; 19·5 g (97%) crude oily *XIb*.

Method A: A solution of 9·15 g crude *XIb* in 40 ml benzene was added to a stirred suspension of 1·1 g NaH in 30 ml benzene and the mixture was refluxed for 4 h. After cooling it was treated with stirring with a solution of 4·9 g 2-dimethylaminoethyl chloride in 20 ml benzene over 5 min and the mixture was refluxed for 4 h. After cooling it was decomposed with 15 ml water, added dropwise, the organic layer was washed with 5% NaCl, dried and evaporated. The residue was distilled; 10·0 g (89%), b.p. 165—168°C/0·13 kPa. Hydrochloride, m.p. 157—158°C (ethanol–ether). Analytical data, *cf.* Table I.

Benzhydryl 2-Bromoethyl Ether

A mixture of 35 ml benzene, 56·5 g 2-bromoethanol and 2·5 g H_2SO_4 was heated to 65—70°C and treated under stirring with a warm solution of 55 g benzhydrol in 65 ml benzene over 35 min. It was refluxed for 4 h, cooled, diluted with 35 ml benzene, washed with water, dried with $CaCl_2$ and evaporated. The residue was distilled; 72·9 g (84%), b.p. 169—173°C/0·33 kPa. Lit.[31], b.p. 169—172°C/0·27 kPa.

4,4′-Difluorobenzhydryl 2-Bromoethyl Ether (*IXa*)

The reaction of 8·6 g 2-bromoethanol with 10·0 g 4,4′-difluorobenzhydrol[21] in 16 ml benzene in the presence of 1·5 g H_2SO_4 was carried out similarly and the reaction mixture was similarly processed; 13·3 g (93%), b.p. 168—170°C/0·2 kPa, n_D^{23} 1·5512. For $C_{15}H_{13}BrF_2O$ (327·2) calculated: 24·43% Br, 11·62% F; found: 23·86% Br, 11·38% F.

4-Bromo-4′-fluorobenzhydryl 2-Bromoethyl Ether (*IXb*)

A similar reaction of 8·6 g 2-bromoethanol, 12·8 g 4-bromo-4′-fluorobenzhydrol[24] and 1·5 g H_2SO_4 in 18 ml benzene gave 16·2 g (92%) *IXb*, b.p. 193—195°C/0·27 kPa, n_D^{23} 1·5875. ^{1}H NMR spectrum: δ 6·80—7·70 (m, 8 H, ArH), 5·33 (s, 1 H, Ar_2CH), 3·71 (m, 2 H, CH_2O), 3·50 (m, 2 H, CH_2Br). ^{19}F NMR spectrum: δ −115·0 (m). For $C_{15}H_{13}Br_2FO$ (388·1) calculated: 46·41% C, 3·38% H, 41·19% Br, 4·89% F; found: 46·70% C, 3·52% H, 40·91% Br, 4·69% F.

1-Ethoxycarbonyl-4-(2-tolyl)piperidin-4-ol (*XV*)

Grignard reagent, prepared from 5·84 g Mg and 41·4 g 2-bromotoluene in 180 ml ether (a grain of I and 0·6 ml ethyl iodide used for starting the reaction), was treated under stirring with a solution of 34·0 g 1-ethoxycarbonyl-4-piperidone[33] in 200 ml ether, added dropwise over 40 min. The mixture was stirred for 1 h at room temperature, refluxed for 90 min, after cooling decomposed with 200 ml 20% NH_4Cl, dried and evaporated. The residue was dissolved in 120 ml warm hexane and allowed to crystallize; 33·0 g (63%), m.p. 118—119°C (ethanol–hexane). IR spectrum: 777 (4 adjacent Ar—H), 1 031, 1 156, 1 199, 1 250, 1 279 (C—O), **1 110** (R_3C—OH), 1 354, 1 388, 1 444, 3 460 (O—H), 1 484 (Ar), **1 670** cm^{-1} ($CONR_2$). For $C_{15}H_{21}NO_3$ (263·3) calculated: 68·41% C, 8·04% H, 5·32% N; found: 68·15% C, 8·27% H, 5·48% N.

4-(2-Tolyl)piperidin-4-ol (*XVI*)

A mixture of 38·3 g *XV*, 42 g KOH and 52 ml ethanol was stirred and refluxed (bath temperature 120—130°C) for 5 h, after cooling diluted with 300 ml water and extracted with dichloromethane. The extract was dried and evaporated. The residue crystallized from 40 ml boiling acetone; 13·5 g (49%), m.p. 141—142°C (benzene–hexane). IR spectrum: 732, 764 (4 adjacent Ar—H), 1 119 (R_3C—OH), 1 494, 1 610, 3 030 (Ar), 3 120, 3 300 cm^{-1} (OH, NH). For $C_{12}H_{17}NO$ (191·3) calculated: 75·35% C, 8·96% H, 7·32% N; found: 74·76% C, 9·05% H, 7·41% N.

1-[2-(4-Bromo-4′-fluorobenzhydryloxy)ethyl]-4-(4-fluorophenyl)piperidin-4-ol (*XIVb*) (Method *B*)

A mixture of 40 ml 4-methylpentan-2-one, 3·60 g 4-(4-fluorophenyl)piperidin-4-ol[30], 7·4 g *IXb* and 3·1 g K_2CO_3 was stirred and refluxed for 4 h, cooled, diluted with ether, washed with water, dried and evaporated. The residue was chromatographed on a column of 160 g Al_2O_3. Chloroform eluted 6·6 g (71%) oily homogeneous base. The oxalate crystallized from a mixture of ethanol and ether as a solvate with diethyl ether, m.p. 80—81°C. Mass spectrum. *m/z*: 501 (M^+ corresponding to $C_{26}H_{26}BrF_2NO_2$), 208 (base peak), 263. The analysis, *cf.* Table I.

Spectra of the free base *XIVb*. IR: 812, 830 (2 adjacent Ar—H), 1 068 (R—O—R′), 1 088 (R_3C—OH), 1 220 (Ar—F, C—N), 1 480, 1 500, 1 510, 1 600 (Ar), 2 798 (N—CH_2), 3 160, 3 374 cm^{-1} (OH). ^{1}H NMR: δ 6·80—7·60 (m, 12 H, ArH), 5·30 (s, 1 H, Ar_2CH), 3·60 (t, J = = 5·0 Hz, 2 H, CH_2O), 2·71 (t, J = 5·0 Hz, 2 H, CH_2N), 1·30—2·80 (m, remaining CH_2 groups). ^{19}F NMR: δ −115·35 (m, 1 F), −116·87 (m, 1 F).

1-[2-(4,4′-Difluorobenzhydryloxy)ethyl]-4-(3-[2-(4,4′-difluorobenzhydryloxy)ethyl]--2-oxobenzimidazolin-1-yl)-1,2,3,6-tetrahydropyridine (*XXa*)

A mixture of 40 ml 4-methylpentan-2-one, 4·15 g *IXa*, 2·80 g *XVIII* (ref.[35]) and 1·95 g K_2CO_3 was stirred and refluxed for 5 h. It was cooled and distributed between water and ether. The organic layer was treated with a slight excess of HCl in ether, the oily hydrochloride was separated by decantation, treated with NH_4OH and the crude base was extracted with benzene. Processing of the extract gave 5·0 g oil which was chromatographed on 100 g Al_2O_3. Elution with chloroform gave 1·2 g (13%) homogeneous base which was neutralized with oxalic acid in a mixture of ethanol and ether. The hydrogen oxalate formed is a solvate with water; m.p. 84–85°C (ethanol–ether). For $C_{44}H_{39}F_4N_3O_7 + H_2O$ (815·8) calculated: 64·78% C, 5·07% H, 9·32% F, 5·14% N; found: 64·35% C, 5·12% H, 9·41% F, 4·62% N.

1-[2-(4-Bromo-4′-fluorobenzhydryloxy)ethyl]-4-(3-[2-(4-bromo-4′-fluorobenzhydryloxy)ethyl]--2-oxobenzimidazolin-1-yl)-1,2,3,6-tetrahydropyridine (*XXb*)

A similar reaction of 4·7 g *IXb*, 2·60 g *XVIII* (ref.[35]) and 1·82 g K_2CO_3 in 40 ml 4-methylpentan-2-one and similar processing gave 2·32 g (23%) homogeneous base. Hydrogen oxalate monohydrate, m.p. 99–100°C (96% ethanol–ether). For $C_{44}H_{39}Br_2F_2N_3O_7 + H_2O$ (937·6) calculated: 56·36% C, 4·41% H, 17·05% Br, 4·05% F, 4·48% N; found: 56·59% C, 4·22% H, 16·86% Br, 4·07% F, 4·37% N. Spectra of the released base. IR: 750, 816 (4 and 2 adjacent Ar—H), 1 070, 1 079, 1 092 (R—O—R′), 1 220 (Ar—F, C—N), 1 482, 1 502, 1 508, 1 600 (Ar), 1 705 cm^{-1} (N—CO—N). ^1H NMR: δ 6·80–7·60 (m, 20 H, ArH), 5·95 (bm, 1 H, CH=C of piperideine), 5·35 and 5·25 (2 s, 1 + 1 H, 2 Ar_2CH), 4·11 (t, J = 5·0 Hz, 2 H, CH_2NCO), 3·74 and 3·68 (2 t, J = 5·0; 5·0 Hz, 2 + 2 H, 2 CH_2O), 2·85 (t, J = 5·0 Hz, 2 H, remaining CH_2N in the chain). ^{19}F NMR: δ −115·28 (m).

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