POTENTIAL ANTIDEPRESSANTS AND TRANQUILLIZERS: SYNTHESIS OF SOME 9-(AMINOALKOXY)-2,3,6,7-TETRAHYDRO--1*H*,5*H*-BENZO[*ij*] QUINOLIZINES AND 1-(SUBSTITUTED AMINO)--3-(1-NAPHTHOXY)-2-PROPANOLS

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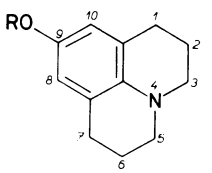
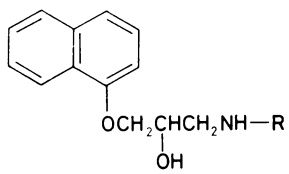
The hydrobromide of 9-hydroxyjulolidine was reacted with hydrochloride of 2-dimethylaminoethyl chloride, 2-(1-pyrrolidinyl)ethyl chloride, 2-(1-piperidinyl)ethyl chloride, and 3-dimethylaminopropyl chloride in ethanol in the presence of sodium ethoxide to give the title bases *II*—*V* which were transformed to dihydrochlorides. Heating of 1,2-epoxy-3-(1-naphthoxy)propane with 2,3,3-trimethyl-2-butylamine, 1-methylcyclopentylamine, 1-methylcyclohexylamine, 1--methylcycloheptylamine, and 10,11-dihydrodibenzo[*a*, *d*]cycloheptene-5-amine in ethanol afforded the second part of the title compounds (*VII*—*XI*), prepared also in the form of hydrochlrides. Only the ethers *II* and *V* showed indications of possible antidepressant activity.

In a recent paper[1] we pointed out the fact that the aryloxyalkylamine fragment occurs rather often in molecules of antidepressant agents and could substantiate this statement by a series of references. In the present short communication we selected as aryl the pharmaceutically neglected 2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinolizine (julolidine). To this end we used as our starting material 9-hydroxyjulolidine (*I*), described until now only as a by-product[2] of the preparation of 9-methoxyjulolidine[3]. Compound *I* has now been prepared by demethylation of 9-methoxyjulolidine[3] by refluxing with hydrobromic acid and was directly obtained in the form of the crystalline hydrobromide hemihydrate; its identity was confirmed by the mass spectrum. The hydrobromide of *I* was reacted with hydrochlorides of 2-dimethylaminoethyl chloride, 2-(1-pyrrolidinyl)ethyl chloride 2-(1-piperidinyl)ethyl chloride, and 3-dimethylaminopropyl chloride in boiling ethanol in the presence of a sufficient amount of sodium ethoxide (general method *A*). The obtained oily bases *II*—*V* were distilled (only *II* was satisfactorily homogeneous) and transformed to crystalline dihydrochlorides which were solvated with water and whose identity was corroborated by mass and IR spectra. Compounds *II*—*V*, which were prepared by the general method *A*, are assembled in Table I with the usual experimental data. Preparation of *II* is described in the Experimental as an example.



I, R = H
II, R = $CH_2CH_2N(CH_3)_2$
III, R = CH_2CH_2N⬡
IV, R = CH_2CH_2N⬡
V, R = $(CH_2)_3N(CH_3)_2$

Many 1-(substituted amino)-3-(aryloxy)-2-propanols exhibit properties of β-adrenergic blocking agents with propranolol (*VI*) as the prototype[4,5]. Compounds of this series have also some CNS activity and found use in pharmacopsychiatry especially for their tranquillizing activity[6–8]. This fact induced us to prepare the ethers *VII–X* which are analogues of propranolol (*VI*). They were obtained by heating 1,2-epoxy-3-(1-naphthoxy)propane[9,10] with 2,3,3-trimethyl-2-butylamine[11,12], 1-methylcyclopentylamine[13,14], 1-methylcyclohexylamine[13,14], 1-methylcycloheptylamine[13,14], and 10,11-dihydrodibenzo[*a*, *d*]cycloheptene-5-amine[15,16] in ethanol (general method *B*). Out of the bases *VII–XI*, only *VIII* was obtained as crystalline substance and was characterized by the UV and IR spectra. All these bases were transformed to crystalline hydrochlorides for analysis and for pharmacological testing. Compounds *VII–XI* are also assembled in Table I and the preparation of *VIII* is described in the Experimental as the example.



VI, R = $-CH(CH_3)_2$
VII, R = $-C(CH_3)_2-C(CH_3)_3$
VIII, R = ⬡(CH₃)
IX, R = ⬡(CH₃)
X, R = ⬡(CH₃)
XI, R = ⬡

Compounds *II–V* and *VII–XI* were pharmacologically tested in the form of hydrochlorides, partly by methods of the general pharmacological screening. Acute toxicity in mice, LD_{50} in mg/kg: *II*, 167 p.o.; *III*, 87·3 p.o.; *IV*, 106 p.o.; *V*, 180 p.o.;

TABLE I

9-(Aminoalkoxy)julolidines and 1-amino-3-(1-naphthoxy)-2-propanols

Compound (Method/yield %)	M.p., °C or b.p., °C/kPa (solvent)	Formula (M.w.)	Calculated/Found			
			% C	% H	% N	% Cl
II	177/0·25	$C_{16}H_{24}N_2O$	73·80	9·29	10·76	—
(*A*[a]/67)		(260·4)	73·51	9·52	10·58	—
II·2HCl[b]	235—238	$C_{16}H_{26}Cl_2N_2O + H_2O$	54·70	8·03	7·97	20·20
	(ethanol)	(351·3)	54·89	8·13	7·94	20·50
III	215/0·25	$C_{18}H_{26}N_2O$	—	—	9·78	—
(*A*/70)		(286·4)	—	—	9·61	—
III·2HCl[c]	204—206[d]	$C_{18}H_{28}Cl_2N_2O + 1{\cdot}5\ H_2O$	55·97	8·07	7·26	18·35
	(ethanol)	(386·4)	56·27	7·83	7·26	18·63
IV	226—228/0·25	$C_{19}H_{28}N_2O$	—	—	9·33	—
(*A*/55)		(300·4)	—	—	9·07	—
IV·2HCl[e]	205—207[f]	$C_{19}H_{30}Cl_2N_2O + 2\ H_2O$	55·74	8·37	6·84	17·33
	(ethanol)	(409·4)	56·04	8·09	6·76	17·58
V·2HCl[c]	183—184[g]	$C_{17}H_{28}Cl_2N_2O + 1{\cdot}5H_2O$	54·55	8·34	7·48	18·95
(*A*/71)	(ethanol)	(374·3)	54·76	8·12	7·49	19·25

VII-HCl	207—208	$C_{20}H_{30}ClNO_2$	68·26	8·60	3·98	10·07
(*B*/83)	(ethanol)	(351·9)	67·96	8·50	3·99	9·92
VIII[a]	78	$C_{19}H_{25}NO_2$	76·22	8·42	4·68	—
(*B*/73)	(benzene–light petroleum)	(299·4)	76·33	8·45	4·34	—
VIII-HCl	182—183	$C_{19}H_{26}ClNO_2$	67·95	7·80	4·17	10·55
	(ethanol–ether)	(335·9)	68·04	7·94	4·30	10·62
IX-HCl	213—214	$C_{20}H_{28}ClNO_2$	68·66	8·06	4·00	10·13
(*B*/96)	(ethanol–ether)	(349·9)	68·68	8·22	4·16	10·42
X-HCl	214—216	$C_{21}H_{30}ClNO_2$	69·31	8·31	3·85	9·74
(*B*/80)	(ethanol–ether)	(363·9)	69·31	8·31	3·96	9·89
XI-HCl	207—209	$C_{28}H_{28}ClNO_2$	75·40	6·33	3·14	7·95
(*B*/90)	(ethanol)	(446·0)	75·14	6·11	3·22	8·07

[a] See Experimental [b] Monohydrate [c] Sesquihydrate. [d] Mass spectrum: 286 (M^+, $C_{18}H_{26}N_2O$, 2·5), 188 (10), 98 (100), 91 (3), 84 (19); UV spectrum: 253 (3·42), infl. 267 (3·34), 318 (2·91); IR spectrum (KBr): 872 (solitary Ar–H); 1 183 (Ar–O–R); 1 479, 1 599, 3 005(Ar); 2 470, 2 540, 2 605, 2 645 (NH^+); 3 445 (H_2O). [e] Dihydrate. [f] Mass spectrum: 300 (M^+, $C_{19}H_{28}N_2O$, 2·5), 188 (15), 160 (3·5), 112 (100),98 (35); IR spectrum (KBr): 872 (solitary Ar–H); 1 179 (Ar–O–R); 1 472, 1 598 (Ar); 2 470, 2 540, 2 640 (NH^+); 3 450 (H_2O). [g] Mass spectrum: 274 (M^+, $C_{17}H_{26}N_2O$, 6·5), 188 (12), 86 (100), 58 (90) UV spectrum: 256 (3·71), 316 (3·29); IR spectrum: 875 (solitary Ar–H); 1 059, 1 180, 1 290 (Ar–O–R, C–N); 1 597, 3 010 (Ar); 2 400, 2 690 (NH^+); 3 445 (H_2O).

VII, 30 i.v.; *VIII*, 25 i.v.; *IX*, 27·5 i.v.; *X*, 2 000 p.o.; *XI*, 2 500 p.o. Doses used in the screening, D in mg/kg: *VII*, 6 i.v.; *VIII*, 5 i.v.; *IX*, 5 i.v.; *X*, 300 p.o.; *XI*, 300 p.o.

Influence on the spontaneous locomotor activity in mice: compounds *II*, *III*, and *IV* in oral doses of 10 mg/kg inhibited the activity significantly. Antireserpine effects: only *II* in the oral dose of 30 mg/kg had significant antireserpine effect in the test of ptosis in mice; only *III* at 50 mg/kg orally had mild effect against reserpine-induced ulcers in rats. Potentiation of the yohimbine toxicity in mice: *II* in the oral dose of 100 mg/kg potentiated in 20% of the animals. Hypothermic effect in rats: *X* was effective in the dose D. Inhibition of binding of 4 nM [^{3}H] imipramine in the hypothalamus of the rat brain, IC_{50} in nmol l^{-1}: *II*, 3 704; *III*, 10 000; *IV*, >100; *V*, 30 000. Inhibition of binding of 4 nM [^{3}H] desipramine in the rat hypothalamus, IC_{50} in nmol l^{-1}: *II*, 807; *III*, mild inhibition at 100; *IV*, >100; *V*, 220. Spasmolytic effect against barium chloride contractions of the isolated rat duodenum: *VII* had significant effect. Influence on the blood pressure of the rat in urethane anaesthesia: significant pressoric effect of *VII*–*XI*. β-Adrenergic blocking effect in cats: mild effect with *VIII*, *IX*, and *X*, weaker than with propranolol (*VI*). Isolated rabbit heart atrium: *IX* increased heart inotropy as well as frequency. α-Adrenolytic effect on rat ductus deferens: *VIII* and *IX* had mild effect. Hypoglycaemic effect in rats: *VIII* and *XI* in doses D decreased the blood sugar level on the border of significance. Diuretic effect in mice: *X* had mild effect in the dose D. Anti-inflammatory effect in rats: *X* had significant effect in the kaolin oedema in the i.p. dose of 20 mg/kg.

In conclusion: Only *II* (VÚFB-17055) and *V* (VÚFB-17053) showed indications of potential antidepressant activity with some selectivity in favour of the adrenergic mechanism. Compounds *VII*–*XI* are weak β-adrenergic blocking agents which did not show any CNS activity in the screening.

EXPERIMENTAL

The melting points were determined in the Kofler block and were not corrected; the samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at a suitably elevated temperature. The UV spectra (in methanol, λ_{max} in nm (log ε)) were recorded with Unicam SP 700 and SP 8000 spectrophotometers, IR spectra (mostly in Nujol, ν in cm^{-1}) with a Unicam SP 200G and a Perkin–Elmer 298 spectrophotometers, and the mass spectra (m/z, %) with a Varian-MAT 44S (GC-MS) spectrometer. The homogeneity of the products and composition of the mixtures were checked by thin layer chromatography on silica gel (Silufol). The extracts were dried with Na_2SO_4 or K_2CO_3 and evaporated under reduced pressure on a rotary evaporator.

9-Hydroxy-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinolizine (*I*)

A mixture of 66·5 g 9-methoxyjulolidine[3] and 175 ml 47% hydrobromic acid was refluxed under nitrogen for 3 h, after cooling it was stirred with 200 ml acetone, the crystalline product was filtered, washed with acetone, and dried in vacuo; 63·2 g (theoretical) of hydrobromide of *I*, m.p. 255–256°C. It crystallized from aqueous ethanol as hemihydrate melting at 276–278°C.

Mass spectrm: 189 (M^+, $C_{12}H_{15}NO$, 85), 188 (100), 160 (30). For $C_{12}H_{16}BrNO + 0{\cdot}5\ H_2O$ (279·2) calculated: 51·62% C, 6·14% H, 28·63% Br, 5·02% N; found: 51·56% C, 6·19 H, 28·63% Br, 4·82% N.

The base was released with NH_4OH and isolated by extraction with chloroform, m.p. 126—128°C (benzene–hexane). Ref.[2], m.p. 123—131°C (by-product of the synthesis of 9-methoxyjulolidine).

9-(2-Dimethylaminoethoxy)-2,3,6,7-tetrahydro-1*H*,5*H*-benzo[*ij*]quinolizine (*II*) (Method *A*)

A solution of sodium ethoxide (from 3·33 g Na and 100 ml ethanol) was added to a stirred suspension of 10·8 g *I*.HBr and 8·0 g 2-dimethylaminoethyl chloride hydrochloride in 100 ml ethanol and the mixture was refluxed for 6 h. After standing overnight the precipitated NaCl and NaBr were filtered off and the filtrate was evaporated in vacuo. The residue was treated with a mixture of 20 ml 20% NaOH and 30 ml water and the product was extracted with benzene. Processing of the extract gave 8·2 g of crude *II* which was distilled; 7·0 g (67%), b.p.176—178°C/0·25 kPa. The analysis is included in Table I.

The distilled base (7·0 g) was dissolved in 25 ml ethanol and the solution was neutralized with ethanolic solution of HCl. After standing overnight in the refrigerator, the hydrocnloride was filtered, washed with a mixture of ethanol and ether, and dried; 8·2 g, m.p. 234—238°C. Crystallization from 95% ethanol gave the dihydrochloride hemihydrate, m.p. 235—238°C. Mass spectrum: 260 (M^+, $C_{16}H_{24}N_2O$, 4·5), 188 (5·3), 72 (100), 58 (18). UV spectrum: 256 (3·45), 318 (3·04). IR spectrum: 874 (solitary Ar–H); 1 184 (Ar–O–R); 1 480, 1 598, 1 609, 3 010 (Ar); 2 380, 2 480, 2 590 (NH^+); 3 390, 3 470 (H_2O). The analysis is included in Table I.

1-(1-Methylcyclopentylamino)-3-(1-naphthoxy)-2-propanol (*VIII*) (Method *B*)

A solution of 20·0 g 1,2-epoxy-3-(1-naphthoxy)propane[9,10] and 10 5 g 1-methylcyclopentylamine[11,12] in 50 ml ethanol was refluxed for 20 h. Ethanol and the unreacted amine were evaporated in vacuo, the residue was dissolved in 25 ml benzene, 180 ml light petroleum were added, and the mixture was allowed to crystallize overnight; 22·0 g (73%) of *VIII*, m.p. 78°C (benzene–light petroleum). UV spectrum: 290 (3·79). IR spectrum: 780, 801 (Ar–H in 1-monosubstituted naphthalene); 1 100 (CHOH); 1 580, 1 595, 1 627 (Ar); 2 660 (O–H···N); 3 305 (OH, NH).

Hydrochloride, m.p. 182—183°C (ethanol–ether). The analyses are included in Table I.

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