6-(6-SUBSTITUTED AMINO-2-HYDROXYPROPYL)-5,6,7,8--TETRAHYDRODIBENZ[*c*, *e*]AZOCINES

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Nucleophilic addition of alkyl-, cycloalkylamines, or saturated nitrogen-containing heterocycles to isolated or in situ generated 6-(2,3-epoxypropyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (*III*) afforded 6-(3-substituted amino-2-hydroxypropyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocines *IV* and their hydrochlorides. The starting 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (*I*) reacted with 1-chloro--2,3-epoxypropane to yield 6-(3-chloro-2-hydroxypropyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (*II*), which, on treatment with sodium ethoxide or an excess of an amine eliminated hydrogen chloride to give the intermediate *III*.

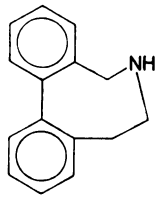
As reported[1,2] 6-alkyl,5,6-7,8-tetrahydrodibenz[*c*,*e*]azocines considered analogues of apogalanthamine showed an α-adrenolytic activity and therefore, we synthesized the so far not reported 6-(3-substituted amino-2-hydroxypropyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocines *IV* for investigation of their pharmacological effects.

The starting material for this synthesis was 5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (*I*); its preparation in a favourable yield was reported in our previous paper[3]. Alkylation of compound *I* with 1-chloro-2,3-epoxypropane furnished 6-(3-chloro-2--hydroxypropyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (*II*); the following removal of hydrogen chloride with basic reagents led to 6-(2,3-epoxypropyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (*III*). The latter and eventually *II* afforded the final 6-(3-substituted amino-2-hydroxypropyl) derivative *IV* when reacting with primary or secondary amines.

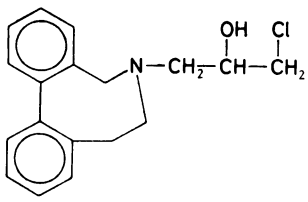
The first step of the proposed synthesis started with a moderate heating of the dibenzazocine *I* with up to 100% excess of 1-chloro-2,3-epoxypropane; this resulted in opening the oxirane ring of the alkylating reagent under formation of the 3-chloro--2-hydroxypropyl derivative *II*. Excess of the alkylating agent served for suppressing the unwanted consecutive reactions taking place with the chlorohydrin derivative *II* just being formed with a further molecule of dibenzazocine *I* to form 6-(2,3-epoxypropyl) derivative *III* and bis(5,6,7,8-tetrahydrodibenz[*c*,*e*]azocinyl)-2-hydroxy-

propane. The chlorohydrin derivative *II* was used in the next step without further purification; for analytical purposes hydrochloride *II*.HCl was prepared.

The chlorohydrin *II* was in the second step transformed into the epoxypropyl derivative *III* with triethylamine, hydroxides of alkali metals, or most favourably with sodium ethoxide in ethanol under cooling.



I



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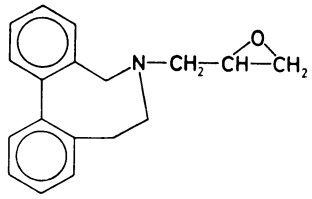
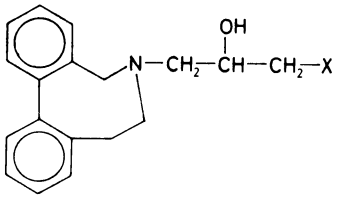


III



IV

In formula *IV*: *a*, X = $NHCH_3$ *b*, X = $N(CH_3)_2$ *c*, X = NHC_2H_5 *d*, X = $NHCH_2CH_2CH_3$
e, X = $NHCH(CH_3)_2$ *f*, X = $N(C_2H_5)_2$ *g*, X = $NHCH_2CH{=}CH_2$ *h*, X = $NHCH_2CH(CH_3)_2$
i, X = $NHC(CH_3)_3$ *j*, X = NH–  *k*, X = NH–  *l*, X = NH–  *m*, X = N 
n, X = N  *o*, X = N  CH_3 *p*, X = N  CH_3 *q*, X = N  *r*, X = N  NCH_3 *s*, X = N  $N(CH_2)_2OH$

The next synthetic step involved opening the oxirane ring of 6-(2,3-epoxypropyl) derivative *III* in the sense of an S_N2 reaction with alkyl-, cycloalkylamines, dialkylamines or saturated nitrogen-containing heterocycles related to pyrrolidine, piperidine, morpholine and piperazine yielding the final 6-(3-substituted amino-2-hydroxypropyl) derivatives *IV*. An alternative formation of isomeric 6-(2-substituted amino-3-hydroxypropyl) derivatives was not observed. This phenomenon is evidently due to a bulky dibenzazocine grouping. A simplified method for preparation of final products *IV* represents the reaction of 6-(3-chloro-2-hydroxypropyl) derivative *II* with an excess of the amine (1 : 4 to 1 : 6) leading primarily to 6-(2,3-epoxypropyl) derivative *III*, which, in turn reacted in situ with another molecule of the amine to

give *IV*. The simplified method for preparation of compounds *IV* at atmospheric pressure was successfully applied with amines having their boiling points between 50 and 130°C (method *A*). Alkylamines boiling up to 50°C were reacted in a closed flask (method *B*). Method *C* was employed for the reaction of isolated 6-(2,3-epoxypropyl) derivative *III*. This method is advantageous because the great excess of the high-boiling amine need not be removed.

Purification of the final products *IV* by means of crystallization totally failed and therefore, column chromatography on silica gel was chosen as proper. The products are considerably polar and so the less polar and unpolar impurities could readily be removed. After the preceding chromatographic purification only compounds *IVa* and *IVi* could be obtained in a crystalline form. The remaining bases were transformed into the corresponding hydrochlorides *IV.n*HCl; it is worth noting that the time for a spontaneous crystallization lasted with some derivatives 1 to 3 months.

Hydrochlorides *IV.n*HCl were found hygroscopic; this property was mainly manifested with compounds *IVd*.2 HCl, *IVk*.2 HCl and *IVe*.2 HCl. Hydrochlorides *IV.n*HCl are stable in aqueous solutions. Data characterizing the final products *IV* and *IV.n*HCl are listed in Table I.

The IR spectra of free bases *IV* displayed two characteristic bands at 3 070 to 3 020 cm^{-1} associated with stretching vibrations of the C—H bonds in an aromatic ring. The symmetric and asymmetric stretching vibrations of CH groups are well discernable with most compounds *IV*: the more intensive band appeared at 2 950 to 2 930 cm^{-1}, the less intensive one at 2 860–2 820 cm^{-1}. Diagnostic is also a broad band at 3 458–3 438 cm^{-1} corresponding to an intermolecularly associated OH bond. A band at 3 348–3 338 cm^{-1} due to a stretching vibration of associated NH grouping was observed with derivatives containing an NH-alkyl group.

The ^1H NMR spectra of compounds *IV* showed, in addition to signals of characteristic groups presented in Table I, a relatively narrow multiplet at 7·10–7·50 ppm corresponding to 8 protons bound to an aromatic ring. Proton signals belonging to N—CH_2, CH_2, CH, OH and NH groups formed a rather complicated multiplet between 2·00 and 4·00 ppm.

The molecular radical ion peaks of compounds *IV* were seen in their electron impact mass spectra only at a 100 times magnified intensity. The most intensive one was assigned to a fragment with a double bond in the side chain originating from elimination of the molecule of water ($M^+ - H_2O$). Further common signals were found at *m/z* 252 ($M^+ - CH_2$—X), *m/z* 222 ($M^+ - CH(OH)$—CH_2—X) and *m/z* 208 ($M^+ - CH_2$—$CH(OH)$—CH_2—X).

Hydrochlorides of compounds *IV* were tested for a peripheric vasodilatatory effect in vitro by the isolated rabbit extremity and the isolated rabbit ear methods[4]. The most effective was found to be the morpholino derivative *IVq*.2 HCl.H_2O. This effect varied between those of xantinol nicotinate and pentoxiphylline.

TABLE I

Characterization of 6-(2-hydroxy-3-X-propyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocines *IV*

Compound	Procedure Yield, %	M.p., °C R_F[a]	Formula (M.w.)	Calculated/Found % C	% H	% Cl	% N	^{1}H NMR[a]
IVa	*B* 85	99—101[b] 0·45	$C_{19}H_{24}N_2O$ (296·4)	76·99 76·84	8·16 8·13	— —	9·45 9·14	2·48 s, 3 H (N—CH_3)
IVa.2 HCl	*D* 85	149—151[c]	$C_{19}H_{26}Cl_2N_2O$ (369·3)	61·78 61·43	7·10 7·08	19·20 19·04	7·59 7·48	
IVb.2 HCl	*C* + *D*[f] 90 + 87	130—133[d] 0·65	$C_{20}H_{28}Cl_2N_2O$ (383·4)	62·66 62·64	7·36 7·34	18·50 18·35	7·31 7·28	2·35 s, 6 H (N—CH_3)
IVc.2 HCl	*B* + *D* 83 + 85	140—144[d] 0·61	$C_{20}H_{28}Cl_2N_2O$ (383·4)	62·66 62·40	7·36 7·15	18·50 18·30	7·31 7·00	1·05 t, 3 H (CH_3, J = 6 Hz)
IVd.2 HCl	*B* + *D* 83 + 80	183—187[d] 0·65	$C_{21}H_{30}Cl_2N_2O$ (397·4)	63·46 63·25	7·61 7·41	17·85 17·65	7·05 6·90	0·93 t, 3 H (CH_3, J = 6 Hz)
IVe.2 HCl	*A* + *D* 90 + 77	148—152[c] 0·61	$C_{21}H_{30}Cl_2N_2O$ (397·4)	63·46 63·18	7·61 7·45	17·85 17·55	7·05 6·90	1·09 d, 6 H (CH_3, J = 6 Hz)
IVf.2 HCl	*A* + *D* 92 + 86	200—203[c] 0·73	$C_{22}H_{32}Cl_2N_2O$ (411·4)	64·22 63·99	7·84 7·71	17·24 16·98	6·81 6·91	1·05 t, 6 H (CH_3, J = 6 Hz)
IVg.2 HCl	*A* + *D* 85 + 69	174—178[c] 0·68	$C_{21}H_{28}Cl_2N_2O$ (395·4)	63·79 63·55	7·13 7·11	17·93 17·81	7·08 6·96	6·2—5·6 m, 1 H (CH=), 5·4—4·9 m, 2 H (CH_2=)
IVh.2 HCl	*A* + *D* 85 + 71	172—175[c] 0·74	$C_{22}H_{32}Cl_2N_2O$ (411·4)	64·22 64·36	7·84 8·02	17·24 17·28	6·81 7·00	0·92 d, 6 H (CH_3, J = 6 Hz)
IVi	*A* 90	87—89[b] 0·75	$C_{22}H_{30}N_2O$ (338·5)	78·06 78·30	8·93 8·92	— —	8·28 8·37	1·13 s, 9 H (CH_3)

IVi.2 HCl	*D*	224–227[c]	$C_{22}H_{32}Cl_2N_2O$	64·22	7·84	17·22	6·81	
	88		(411·4)	63·95	7·84	16·98	6·65	
IVj.HCl	*A* + *D*	170–172[d]	$C_{23}H_{31}ClN_2O$	71·38	8·07	9·16	7·24	1·60 m, 8 H (—CH_2—)
	87 + 80	0·68	(387·0)	71·13	7·95	8·96	7·17	
IVj.2 HCl	*D*	197–200[c]	$C_{23}H_{32}Cl_2N_2O$	65·24	7·62	16·75	6·62	
	78		(423·4)	65·05	7·44	17·01	6·76	
IVk.2 HCl	*A* + *D*	238–241[c]	$C_{24}H_{34}Cl_2N_2O$	65·89	7·83	16·22	6·41	2·1–1·0 m, 10 H
	85 + 81	0·76	(437·5)	65·78	7·80	15·97	6·60	(—CH_2—)
IVl.2 HCl	*C* + *D*	161–164[c]	$C_{26}H_{38}Cl_2N_2O$	67·08	8·28	15·23	6·02	1·53 m, 14 H (—CH_2—)
	52 + 65	0·78	(465·5)	67·09	8·12	15·11	6·01	
IVm.2 HCl	*A* + *D*	139–142[d]	$C_{22}H_{30}Cl_2N_2O$	64·54	7·38	17·32	6·48	1·77 m, 4 H (—CH_2—)
	92 + 84	0·71	(409·4)	64·34	7·10	17·15	6·20	
IVn.2 HCl	*A* + *D*	238–241[c]	$C_{23}H_{32}Cl_2N_2O$	65·24	7·62	16·75	6·62	1·51 m, 6 H (—CH_2—)
	87 + 82	0·83	(423·4)	65·10	7·78	16·50	6·18	
IVo.2 HCl	*A* + *D*	226–229[c]	$C_{24}H_{34}Cl_2N_2O$	65·89	7·83	16·21	6·41	1·05 d, 3 H
	90 + 81	0·70	(437·4)	65·62	7·60	16·39	6·20	(CH_3, J = 6 Hz)
IVp.2 HCl	*A* + *D*	222–225[c]	$C_{24}H_{34}Cl_2N_2O$	65·89	7·83	16·21	6·41	0·85 d, 3 H
	90 + 78	0·80	(437·4)	65·85	7·81	16·50	6·25	(CH_3, J = 6 Hz)
IVq.2 HCl.H_2O	*A* + *D*	162–165[e]	$C_{22}H_{32}Cl_2N_2O_3$	59·59	7·28	15·99	6·32	
	92 + 83	0·82	(443·4)	59·33	7·25	15·78	6·07	
IVr.3 HCl	*C* + *D*	227–229[e]	$C_{23}H_{34}Cl_3N_3O$	58·16	7·22	22·41	8·55	2·31 s, 3 H (N—CH_3)
	86 + 79	0·59	(474·9)	58·08	7·26	22·48	8·73	
IVs.3 HCl	*C* + *D*	199–202[c]	$C_{24}H_{36}Cl_3N_3O_2$	57·20	7·00	21·11	8·34	
	75 + 87	0·44	(504·9)	57·19	6·96	21·10	8·09	

[a] For bases *IV*; crystallized from: [b] diethylether; [c] ethanol–diethylether; [d] methanol–diethylether; [e] ethanol; [f] procedure *D* = preparation of hydrochlorides of bases *IV*.

EXPERIMENTAL

Melting points are uncorrected, samples for analyses were dried at 100°C/65 Pa over phosphorus pentoxide for 8—10 h. The IR spectra of tetrachloromethane solutions and the ^{1}H NMR spectra of deuteriochloroform solutions containing tetramethylsilane as an internal reference were measured with FTS-14 (Spectra-Physics) and Tesla BS 487 (80 MHz) spectrometers, respectively. The mass spectra were recorded with an AEI MS 902 S (Manchester) apparatus at an ionizing electron energy 70 eV and 100 μA trap current. The purity of products was monitored by thin-layer chromatography on Silufol sheets (Kavalier, Czechoslovakia) in chloroform–methanolic 1M ammonia (20 : 1, compounds *IV*), or in chloroform–acetone (10 : 1, compounds *II* and *III*).

6-(3-Chloro-2-hydroxypropyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (*II*)

Compound *I* (5·22 g, 25 mmol) and 1-chloro-2,3-epoxypropane (4·60 g, 50 mmol) in ethanol (40 ml) were stirred at 40°C for 30 min, the solvent was distilled off under reduced pressure and the product was dried at 80°C/7 Pa. Yield of the crude product in form of waxy white mass was 5·60 g (98%). IR spectrum (cm^{-1}): 3 435 (assoc. OH). The product was characterized as hydrochloride, m.p. 177—179°C. For $C_{18}H_{24}ClNO$ (338·3) calculated: 63·91% C, 6·26% H, 20·96% Cl, 4·14% N; found: 63·77% C, 6·34% H, 21·00% Cl, 4·20% N. IR spectrum (cm^{-1}): 3 435 (assoc. OH). ^{1}H NMR spectrum (ppm): 7·10—7·50 m, 8 H (H_{arom}); 2·00—4·00 m, 12 H (CH_2,CH,OH).

6-(2,3-Epoxypropyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (*III*)

Compound *II* (7·56 g, 25 mmol) dissolved in anhydrous ethanol (40 ml) was introduced into a stirred and to 0°C cooled solution of sodium ethoxide in anhydrous ethanol (0·57 g Na, 25 mmol, 100 ml). After 10 min the mixture was left to stand at 5°C for 3 h, the separated sodium chloride was filtered off and the solvent was evaporated under diminished pressure to dryness and the residue was dried at 80°C/7 Pa for 8 h. Yield 6·40 g (97%) of a yellowish waxy substance, R_F 0·57.

The analytically pure *III* was obtained from the hydrochloride *II*. HCl and a double amount of sodium ethoxide as a vitreous mass. Mass spectrum (*m*/*z*): 265 (M^+). IR spectrum (cm^{-1}): 1 258, 927, 847 (epoxyde). ^{1}H NMR spectrum (ppm): 7·10—7·45 m, 8 H (H_{arom}); 2·10—4·05 m, 11 H (CH_2, CH).

6-(3-Substituted Amino-2-hydroxypropyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (*IV*)

Method A: A mixture of *II* (7·56 g, 25 mmol) and a primary or secondary amine (100 mmol) was refluxed for 2 h. The mixture was cooled to 5°C and allowed to stand for 1 h, the separated hydrochloride of the amine employed was filtered off, the filtrate was concentrated in vacuo and the oily residue dissolved in benzene (50 ml) was washed with an aqueous sodium hydroxide (2 mol l^{-1}, 50 ml), dried with potassium carbonate and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, 100—160 μm, 60—80 g). Impurities were first eluted with chloroform–acetone–methanol (10 : 1 : 0·5) and the product was flown out by addition of diethylamine (1—3%) to the eluent. The eluate was concentrated and the oily residue *IV* was dried at 80°C/7 Pa.

Method B: Compound *II* (7·56 g, 25 mmol), an anhydrous low-boiling amine (150 mmol) and anhydrous ethanol (40 ml) were heated at 95—100°C in a pressure glass vessel for 1 h. The mixture was then cooled to 5°C for 3 h, the separated amine hydrochloride was filtered off and the solute was worked out as with method *A*.

Method C: A high-boiling amine (25 mmol) and the solution of *III* (6·20 g, 25 mmol) in ethanol (40 ml) were refluxed for 4 h, the solvent was evaporated under diminished pressure and the crude compound *IV* was partially freed from the excess of the amine by heating at 90°C/7 Pa. The product was then chromatographically purified as with method *A*.

Hydrochlorides of Bases *IV*

The chromatographically purified compound *IV* was dissolved in a minimal amount of ethanol and with stirring slightly acidified with methanolic hydrogen chloride (c. 1 mol l^{-1}). The crystalline foam, obtained by removal of the solvent under reduced pressure was purified with charcoal and crystallized from methanol or ethanol. If the hydrochloride *IV*.*n*HCl resisted crystallization for some days ether was added to the first turbidity and the solution was left to spontaneous crystallization. The microcrystalline hydrochloride *IV*.*n*HCl was filtered off and dried at 100°C/ /2·7—4·0 kPa for 2—3 h and then at c. 7 Pa for additional 5 h.

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