# 6-(ω-GUANIDINOALKYL)- AND 6-(ω-IMIDAZOLINAMINOALKYL)--5,6,7,8-TETRAHYDRODIBENZ[*c,e*]AZOCINES

Fridrich SZEMES[a], Alfonz RYBÁR[b,*] and Eva SOLČÁNIOVÁ[c]

[a] *Drug Research Institute, 900 01 Modra*
[b] *Institute of Chemistry, Slovak Academy of Sciences, 842 38 Bratislava*
[c] *Department of Organic Chemistry, Comenius University, 842 15 Bratislava*

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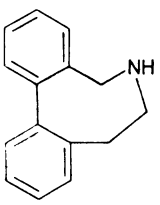
Guanidine derivatives of 5,6,7,8-tetrahydrodibenz[*c,e*]azocine *IV* and *V* were prepared by a three-step synthesis starting from 5,6,7,8-tetrahydrodibenz[*c,e*]azocine (*I*) via the corresponding 6-(ω-cyanoalkyl) *II* and 6-(ω-aminoalkyl) derivatives *III*; finally, compounds *III* were treated with either methylisothiuronium halide or methylthioimidazolinium halide.

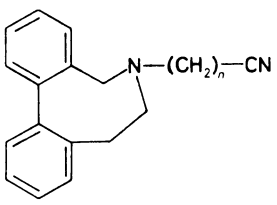
Investigation of the hitherto unknown guanidine derivatives of 5,6,7,8-tetrahydrodibenz[*c,e*]azocines *IV* and *V* was stimulated by the fact that even the unsubstituted 6-alkyl-5,6,7,8-tetrahydrodibenz[*c,e*]azocines show activity on the cardiovascular system[1,2], and 1-guanidinoethylperhydroazocine is the successfully administered antihypertensive drug guanetidine[3]. Therefore, we decided to synthesize compounds embodying both the guanidinoalkyl group and the tetrahydrodibenz[*c,e*]azocine moiety for pharmacological tests.

The starting material for this project was 5,6,7,8-tetrahydrodibenz[*c,e*]azocine[4] (*I*); its alkylation with a suitably functionalized alkylnitrile yielded the 6-(ω-cyanoalkyl) derivatives *II*. Reduction of the nitrile group led to 6-(ω-aminoalkyl)-tetrahydrodibenz[*c,e*]azocines *III*, which, on reaction with methylisothiuronium halide and methylthioimidazolinium halides afforded the final 6-(ω-guanidinoalkyl)-*IV* and 6-(ω-imidazolinaminoalkyl) derivatives *V*, respectively.

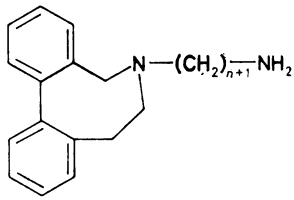
Alkylation agents for the first step of this synthesis were chloroacetonitrile, 4--chlorobutyronitrile and acrylonitrile. Alkylation with the reactive chloroacetonitrile proceeded in ethanol at reflux temperature within less than 1 h. This was not the case with 4-chlorobutyronitrile, where the reflux temperature in ethanol was unsufficient for a quantitative reaction within 8 h and therefore, the medium was replaced by dimethylformamide in which the reaction was completed at 80°C in 6 h. Potassium carbonate was the hydrogen chloride trapping reagent in both experiments. The quantitative cyanoethylation of *I* was achieved by a mild heating of the compounds in ethanol under catalysis of benzyltrimethylammonium chloride (Triton B).



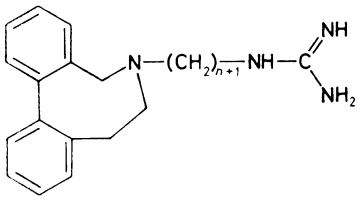

*I*



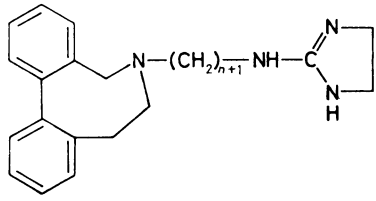

*II*




*III*




*IV*




*V*

In formulae *II*–*V*: *a*, $n = 1$; *b*, $n = 2$; *c*, $n = 3$

Nitriles *II* were reduced in the next step with lithium hydridoaluminate in tetrahydrofuran. The reaction was unambiguous with the primary amines *IIIa* and *IIIc* only. With 6-(2-cyanoethyl) derivative *IIb* a partial (c. 15%) cleavage of the intermediate to allylamine (evidenced by gas chromatography) and the starting product took place. Products of the reductive cleavage were no more observed when using alane prepared by mixing equimolar amounts of aluminium chloride and lithium hydridoaluminate for reduction. Purification of the amines by distillation under reduced pressure was restricted by thermal stability of them, which decreased with the increasing length of their side chains; therefore, only amine *IIIa* could be purified in this way. The remaining amines *IIIb* and *IIIc* were purified chromatographically.

The primary amines *III* were reacted with methylisothiuronium iodide in lower aliphatic alcohols under reflux to afford 6-(ω-guanidinoalkyl) derivatives *IV*. The reaction was through when the outflow of methanethiol generated by the reaction ceased. The 6-(ω-imidazolinaminoalkyl) derivatives *V* were prepared by an analogous procedure except the reaction time, which was by 1/3 longer.

Compounds *IV* and *V* were isolated from the mixture in form of hydroiodides. All attempts to crystallize these hydroiodides and also bases liberated failed. Crystalline final hydrochlorides *IV*.2 HCl and *V*.2 HCl were obtained by adsorption of free bases on silica gel, washing off the impurities with chloroform and methanol and liberating the products with methanolic hydrogen chloride. These hydrochlorides could be crystallized from ethanol by addition of ether.

Products of this synthesis were identified by mass spectrometry ($M^+$) of bases and by elemental analyses (as hydrochlorides). The $^1H$ NMR spectra of hydrochlorides displayed signals characteristic of the presence of $CH_2$ groups (2·8 to 4·1 ppm, m, 8 to 14 H), NH-alkyl groups (4·51–4·61, d, 1 H, $J$ = 14 Hz), hydrogens of aromatic rings (7·1–8·0, m, 8 H), NH and $NH_2$ groups (8·2–8·9, bs, 3 H).

Final guanidine-hydrochlorides *IV*.HCl and *V*.HCl were tested on antihypertensive effect (DOCA-rats). Any of the compounds tested did not exceed the antihypertensive effect of guanetidine[5].

## EXPERIMENTAL

The melting points are uncorrected. Samples for analyses were dried at 100°C/65 Pa for 8–10 h over phosphorus pentoxide. The $^1H$ NMR spectra of hexadeuterodimethyl sulfoxide solutions containing tetramethylsilane as an internal reference were measured with a Tesla 487 FTNMR apparatus operating at 80 MHz. The mass and IR spectra were recorded with AEI MS 902 S (70 eV, 100 μA) and Perkin–Elmer model 559 spectrometers, respectively. Purity of compounds was monitored by thin-layer chromatography on Silufol (Kavalier, Czechoslovakia) sheets in chloroform–1M methanolic ammonia.

6-Cyanomethyl-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (*IIa*)

A mixture of *I* (20·9 g, 100 mmol), potassium carbonate (16·0 g, 125 mmol) and chloroacetonitrile (15·1 g, 200 mmol) was refluxed in 85%-ethanol (175 ml) for 40 min. The cooled mixture was poured into water (600 ml) and the product was extracted with benzene (300 ml). The organic layer was dried over magnesium sulfate and the solvent was removed under reduced pressure. The crude product was crystallized from ethanol. Yield 22·5 g (90%), m.p. 85–87°C. For $C_{17}H_{16}N_2$ (248·3) calculated: 82·20% C, 6·50% H, 11·28% N; found: 82·45% C, 6·56% H, 11·51% N. Mass spectrum, *m*/*z*: 248 ($M^+$). IR spectrum ($CHCl_3$), $cm^{-1}$: 2 250 (C≡N).

6-(2-Cyanoethyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (*IIb*)

Acrylonitrile (11·6 g, 200 mmol) and Triton B (40%, 0·2 ml) were added to a stirred solution of compound *I* (20·9 g, 100 mmol) in ethanol at room temperature. After 2 h of stirring the mixture was concentrated and left to stand at 0–5°C for 20 h. The product was filtered off and dried under reduced pressure. Yield 23·7 g (90%), m.p. 100–101°C. For $C_{18}H_{18}N_2$ (262·3) calculated: 82·41% C, 6·91% H, 10·69% N; found: 81·81% C, 6·90% H, 10·41% N. Mass spectrum, *m*/*z*: 262 ($M^+$). IR spectrum, $cm^{-1}$: 2 250 (C≡N).

6-(3-Cyanopropyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (*IIc*)

A mixture of *I* (20·9 g, 100 mmol), 4-chlorobutyronitrile (20·6 g, 200 mmol) and potassium carbonate (27·6 g, 200 mmol) in dimethylformamide (80 ml) was stirred at 80°C for 6 h. The cooled mixture was poured into water (600 ml), the product was extracted with benzene (200 ml), the extract was dried with magnesium sulfate and the solvent was distilled off under diminished pressure. The product was purified by column chromatography over silica gel (100–160 μm, 300 g, eluent chloroform) and dried at 100°C/7 Pa. Yield 22·1 g (80%) (oil). Mass spectrum, *m*/*z*: 276 ($M^+$). IR spectrum (Nujol), $cm^{-1}$: 2 255 (C≡N). The hydrochloride *IIc*.HCl was obtained by treatment with 10%-methanolic hydrogen chloride, evaporation under diminished pressure

and crystallization from ethanol–ether; m.p. 193–195°C. For $C_{19}H_{21}ClN_2$ (312·8) calculated: 72·94% C, 6·76% H, 11·34% Cl, 8·96% N; found 73·06% C, 6·73% H, 11·02% Cl, 8·77% N.

6-(2-Aminoethyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (*IIIa*)

A solution of *IIa* (4·8 g, 19 mmol) in tetrahydrofuran (30 ml) was dropped into a stirred suspension of lithium hydridoaluminate (0·7 g, 38 mmol) in tetrahydrofuran (40 ml) and the mixture was refluxed for 1 h. Benzene (80 ml) was added to the cooled mixture and the excess of the hydride was decomposed with icy water (12 ml). The separated organic layer was washed with water, dried with potassium carbonate and the solvent was removed in vacuo. The oily residue was distilled at 140–142°C/21 Pa. The oil solidified by standing to a crystalline mass, m.p. 42–45°C. For $C_{17}H_{20}N_2$ (252·4) calculated: 80·91% C, 7·99% H, 11·10% N; found: 80·87% C, 7·97% H, 11·56% N. Mass spectrum, *m/z*: 252 ($M^+$).

6-(3-Aminopropyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (*IIIb*)

Aluminium chloride (20 g, 0·15 mol) in tetrahydrofuran (200 ml) was added to a stirred and by cold water cooled suspension of lithium hydridoaluminate (5 g, 0·15 mol) in tetrahydrofuran (200 ml). After 10 min powdered nitrile *IIb* (26·2 g, 0·10 mol) was added in small portions and stirring was continued at 60°C for 1 h. The mixture was cooled with icy water, benzene (500 ml) was added and the excess of the reducing agent was decomposed with icy water and aqueous sodium hydroxide (16 g, 0·40 mol, 50 ml). The organic layer was separated after 30 min of stirring, dried with potassium carbonate, the solvent was distilled off under reduced pressure and

TABLE I

6-(ω-Guanidinoalkyl)-*IV*.2 HCl and 6-(ω-imidazolinaminoalkyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]-azocine dihydrochlorides *V*.2 HCl

| Compound | Yield % | M.p., °C | Formula (M.w.) | Calculated/Found | | | | $M^{+a}$ *m/z* |
|---|---|---|---|---|---|---|---|---|
| | | | | % C | % H | % Cl | % N | |
| *IVa*.2 HCl | 71 | 236–238[b] | $C_{18}H_{24}Cl_2N_4$ (367·3) | 58·85<br>58·86 | 6·58<br>6·53 | 19·30<br>18·92 | 15·25<br>15·00 | 294 |
| *IVb*.2 HCl | 75 | 233–235[c] | $C_{19}H_{26}Cl_2N_4$ (381·3) | 59·84<br>59·58 | 6·87<br>6·79 | 18·59<br>18·95 | 14·69<br>14·43 | 308 |
| *IVc*.2 HCl | 65 | 230–233[c] | $C_{20}H_{2o}Cl_2N_4$ (395·4) | 60·75<br>60·45 | 7·14<br>7·32 | 17·93<br>17·86 | 14·17<br>13·97 | 322 |
| *Va*.2 HCl | 80 | 233–235[b] | $C_{20}H_{26}Cl_2N_4$ (393·4) | 61·07<br>61·31 | 6·66<br>6·80 | 18·03<br>18·31 | 14·24<br>14·09 | 320 |
| *Vb*.2 HCl | 60 | 239–242[c] | $C_{21}H_{28}Cl_2N_4$ (407·4) | 61·91<br>61·62 | 6·93<br>6·93 | 17·41<br>17·32 | 13·75<br>13·86 | 334 |
| *Vc*.2 HCl | 67 | 234–237[c] | $C_{22}H_{30}Cl_2Na$ (421·4) | 62·7C<br>62·91 | 7·18<br>7·29 | 16·83<br>16·55 | 13·30<br>13·28 | 348 |

[a] Measured as bases *IV* and *V*. Crystallized from: [b] ethanol; [c] ethanol–diethylether.

the oily residue was purified by column chromatography over silica gel (100—160 μm, 360 g, eluent chloroform–50%-methanolic ammonia 20 : 1). The oily product was dried at 100°C/7 Pa. Yield 24·3 g (91%). Mass spectrum, *m/z*: 266 ($M^+$).

*Dihydrochloride* IIIb. 2 HCl prepared analogously as *IIc* had m.p. 213—215°C (ethanol–ether). For $C_{18}H_{24}Cl_2N_2$ (339·3) calculated: 63·71% C, 7·13% H, 8·26% N; found: 63·18% C, 7·17% H, 7·90% N.

6-(4-Aminobutyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine (*IIIc*)

Solution of *IIc* (10·8 g, 39 mmol) in tetrahydrofuran (40 ml) was added to a suspension of lithium hydridoaluminate (2·8 g, 75 mmol) in tetrahydrofuran (80 ml) and the mixture was stirred at 55°C for 1·5 h. To the cooled mixture benzene (100 ml) was added and the excess of the hydride was decomposed by a mixture consisting of water (5 ml) and tetrahydrofuran (10 ml) and finally with water till a white precipitate was formed. The organic layer was separated, dried with potassium carbonate, the solvent was evaporated under diminished pressure and the oily residue was purified by column chromatography over silica gel (100—160 μm, 100 g, eluent chloroform–methanolic ammonia 20 : 1). Yield of the dried (100°C/7 Pa) sirupy product was 7·8 g (71%). The crude amine can alternatively be purified by vacuum distillation at 150—160°C/11 Pa; the yield was, indeed, lower (61%). Mass spectrum, *m/z*: 280 ($M^+$). For $C_{19}H_{24}N_2$ (280·4) calculated: 81·30% C, 8·62% H, 9·99% N; found: 81·28% C, 8·65% H, 9·97% N.

Hydrochloride *IIIc*. HCl, m.p. 168—171°C (ethanol–ether).

Dihydrochlorides of 6-(ω-Guanidinoalkyl)-*IV* and 6-(ω-Imidazolinaminoalkyl)-5,6,7,8-tetrahydrodibenz[*c*,*e*]azocine *V*

Amine *III* (20 mmol) and methylisothiuronium iodide (4·36 g, 20 mmol), or 2-methylthio-2-imidazoline hydroiodide (4·88 g, 20 mmol) dissolved in methanol were refluxed for 3 and 4 h, respectively. The mixture was concentrated in vacuo, the syrup obtained was dissolved in benzene (120 ml) to which 10% sodium hydroxide (100 ml) was added and the mixture was stirred for 1 h. The organic layer was separated and dried over potassium hydroxide pellets. Silica gel (100—160 μm, 40 g) was added and the suspension was stirred for 1 h. The silica gel-sorbed product *IV* or *V* was filtered off, washed with chloroform (100 ml) and methanol (100 ml) and stirred with 0·5M methanolic hydrogen chloride (200 ml). The solution was concentrated under diminished pressure, the product was dried at 100°C/230 Pa and crystallized from ethanol to which charcoal was added. If the dihydrochloride *IV*.2 HCl or *V*.2 HCl does not crystallize within some days, ether was added to the first turbidity and the solution was left to crystallize. The final dihydrochlorides were filtered off and dried at 100°C/7 Pa. Yields and analytical data of *IV*.2 HCl and *V*.2 HCl are listed in Table I.

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