POTENTIAL ANTIDEPRESSANTS: 2-(6,11-DIHYDRODIBENZO[*b*,*e*]-THIEPIN-11-YL)-4,5-DIHYDROIMIDAZOLES

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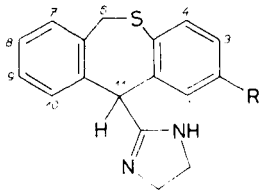
Reactions of 2-substituted 11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepins with trimethylsilyl cyanide in dichloromethane in the presence of stannic chloride afforded nitriles *IIb*—*IId* in high yields. Heating of *IIa*—*IId* with 2-aminoethylammonium toluene-4-sulfonate to 200°C gave the title compounds *Ia*—*Id* which were transformed to hydrogen maleates. Compound *Ic* (hydrogen maleate VÚFB-17 092) showed in several tests a clear thymoleptic (potential antidepressant) character.

In molecules of neurotropic substances the presence of a 4,5-dihydroimidazol-2-yl (2-imidazolin-2-yl) residue proved very often bioequivalent with the aminomethyl residue or its N-monomethyl and N-dimethyl congeners. Examples are the classical 2-benzyl-4,5-dihydroimidazole ("tolazoline") and 2-((1-naphthyl)methyl)-4,5-dihydroimidazole ("naphazoline") (ref.[1]), analogues of the adrenergic 2-(aryl)ethylamines; further the antihistaminic 2-((N-benzylanilino)methyl)-4,5-dihydroimidazole ("antazoline") (refs[2,3]), analogue of N,N-dimethyl-2-(N-benzylanilino)ethylamine ("phenbenzamine"), and 2-((benzhydryloxy)methyl)-4,5-dihydroimidazole ("diphenazoline") (refs[4–7]), analogue of N N-dimethyl-2-(benzhydryloxy)ethylamine ("diphenhydramine"). Some 2-substituted 4 5-dihydroimidazoles showed antidepressant activity (cf. ref.[8]). On the other hand 6,11-dihydrodibenzo[*b*,*e*]thiepin proved a very convenient carrier system in the molecules of antidepressants[9]. These facts led to the design of the title compounds *Ia*—*Id* considered as potential antidepres-



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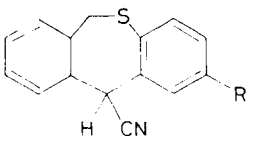

II

In formulae *I* and *II*: *a*, R = H *b*, R = CH_3 *c*, R = Cl *d*, R = Br

sants. Their open-ring analogue, 2-benzhydryl-4,5-dihydroimidazole, cannot be used for comparison because its synthesis and testing were carried out prior to the era of antidepressants[10]. On the other hand, the finding of thymoleptic properties of (6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl)methylamines[11] was encouraging. The present paper describes the synthesis and results of testing of *Ia*–*Id*.

Nitriles are the most convenient starting materials for the synthesis of 2-substituted 4,5-dihydroimidazoles. The nitrile *IIa*, whose synthesis has been rather difficult until recently[12,13], became easily accessible by aplication of the new method of cyanation of tertiary alkyl chlorides[14,15] with trimethylsilyl cyanide[16] to 11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin[17]. The same approach has now successfully been used for the transformation of 11-chloro-2-methyl-6,11-dihydrodibenzo[*b*,*e*]-thiepin[18], its 2-chloro[19] and 2-bromo[20] analogues to *IIb*–*IId*; the reactions consisted in treatment of the 11-chloro compounds with trimethylsilyl cyanide[16] in dichloromethane in the presence of stannic chloride. For preparing *Ia*–*Id* the method of Oxley and Short[21] was used; it consisted in heating *IIa*–*IId* with 2-aminoethylammonium toluene-4-sulfonate to 200°C. The crystalline bases *IIa*–*IId* were characterized by spectra and transformed to hydrogen maleates.

Compounds *Ia*–*Id* were tested pharmacologically in the form of hydrogen maleates; the doses given (in mg/kg) were calculated per bases. In the in vivo tests, the compounds were administered orally. The tests used were oriented towards the expected antidepressant (thymoleptic) properties. Acute toxicity in mice, LD_{50} in mg/kg: *Ic*, 162. Discoordinating effect in the rotarod test in mice: *Ia*, the dose of 25 mg/kg brought about ataxia in 20% animals; *Ib* 50 mg/kg ataxia in 30% animals; *Ic*, $ED_{50} \cong 50$ mg/kg; *Id*, $ED_{50} = 22{\cdot}7$ mg/kg. Inhibition of binding of 4 nmol l^{-1} [^{3}H]imipramine and 4 nmol l^{-1} [^{3}H]desipramine in rat hypothalamus, IC_{50} in nmol l^{-1}: *Ia*, *Ib*, and *Id*, >100, >100; *Ic*, 4 408, 1 381. Inhibition of reuptake of 10 nmol l^{-1} [^{3}H]5-hydroxytryptamine in rat brain and of 10 nmol l^{-1} [^{3}H]noradrenaline in rat brain cortex, IC_{50} in nmol l^{-1}: *Ic*, >100, >100. Potentiation of yohimbine toxicity in mice: *Ia*, doses of 3–30 mg/kg were without effect; *Ib*, doses of 5–50 mg/kg without effect; *Ic* $ED_{50} = 41{\cdot}1$ mg/kg (almost imipramine-like intensity of effect); *Id*, the dose of 50 mg/kg potentiated the toxicity significantly in 30% animals. Antireserpine effect in mice (inhibition of reserpine-elicited eyelid ptosis): *Ia*, in doses of 2·5–25 mg/kg without effect; *Ib*, 3–30 mg/kg without effect; *Ic*, significant effect at 30 mg/kg; *Id*, significant effect at 30 mg/kg. Reserpine-induced hypothermia in mice was not influenced by the dose of 50 mg/kg of *Ic*. At the same dose *Ic* did not show peripheral antiadrenergic action in mice. In conclusion: compound *Ic* (VÚFB-17 092) is the only one which showed clear thymoleptic profile.

The compounds were also tested for antimicrobial activity in vitro (microorganisms and the minimum inhibitory concentrations in μg/ml unless they exceed 128 μg/ml, are given): *Streptococcus β-haemolyticus*, *Ib* 128, *Ic* 128, *Id* 128; *Streptococcus*

faecalis, *Ib* 128, *Ic* 128, *Id* 128; *Staphylococcus pyogenes aureus*, *Ib* 128, *Ic* 64, *Id* 64; *Pseudomonas aeruginosa*, *Ib* 128, *Ic* 128, *Id* 128; *Escherichia coli*, *Ib* 64, *Ic* 64, *Id* 64; *Proteus vulgaris*, *Ia* 50, *Ib* 128, *Ic* 128, *Id* 128; *Trichophyton mentagrophytes*, *Id* 50.

EXPERIMENTAL

The melting points were determined in a Mettler FP-5 melting point recorder; 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 spectrum (in methanol, λ_{max} in nm (log ε)) was recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol, ν in cm^{-1}) were measured with a Perkin–Elmer 298 spectrophotometer, ^1H NMR spectra (in $CDCl_3$ unless stated otherwise, δ, J in Hz) with the Tesla BS 487 C (80 MHz) spectrometer, and the mass spectrum with Varian MAT 44S spectrometer (m/z and % given). The homogeneity of the substances and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

2-Methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carbonitrile (*IIb*)

Trimethylsilyl cyanide[16] (6·35 g) was added to a solution of 13·5 g 11-chloro-2-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin[18] in 80 ml dichloromethane and the stirred mixture was slowly treated with 1·5 ml $SnCl_4$, added dropwise (violent reaction after the first several drops). The mixture was stirred for 5·5 h at room temperature, allowed to stand overnight, poured into 100 ml water, and extracted with dichloromethane. The extract was washed with 100 ml 5% $NaHCO_3$, dried with $MgSO_4$, and evaporated. The inhomogeneous residue was chromatographed on 150 g silica gel (Merck 40). Benzene eluted 11·8 g (93%) of *IIb*, m.p. 180–180·5°C (ethanol). IR spectrum: 762, 815, 884 (4 and 2 adjacent and solitary Ar—H); 1 489, 3 045, 3 070, 3 080 (Ar); 2 240 (R—CN). ^1H NMR spectrum: 2·35 s, 3 H ($ArCH_3$); 3·90 d, 1 H and 4·50 d, 1 H (2 H-6; J = 13·0); 5·80 s, 1 H (H-11); 6·80–7·60 m, 7 H (7 ArH). For $C_{16}H_{13}NS$ (251·3) calculated: 76·46% C, 5·21% H, 5·57% N, 12·76% S; found: 76·68% C, 5·25% H, 5·37% N, 12·82% S.

2-Chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carbonitrile (*IIc*)

Similar reaction of 10·0 g 2,11-dichloro-6,11-dihydrodibenzo[*b*,*e*]thiepin[19] in 70 ml dichloromethane with 4·4 g trimethylsilyl cyanide[16] and 1·02 ml $SnCl_4$ gave 9·6 g (99%) homogeneous *IIc*, m.p. 191–192°C (benzene). Mass spectrum: 271 (M^+, $C_{15}H_{10}ClNS$, 36), 238 (21), 236 (22·5), 203 (100). IR spectrum: 761, 809, 880 (4 and 2 adjacent and solitary Ar—H); 1 490, 1 550, 1 579, 3 070 (Ar); 2 240 (R—CN). ^1H NMR spectrum (CD_3SOCD_3): 4·24 d, 1 H and 4·85 d, 1 H (2 H-6, J = 13·0); 6·35 s, 1 H (H-11); 7·00–7·60 m, 7 H (7 ArH). For $C_{15}H_{10}ClNS$ (271·8) calculated: 66·29% C, 3·71% H, 13·05% Cl, 5·16% N, 11·79% S; found: 65·51% C, 3·61% H, 13·21% Cl, 4·98% N, 11·75% S.

2-Bromo-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carbonitrile (*IId*)

Similar reaction of 16·1 g 2-bromo-11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin[20] in 100 ml dichloromethane with 6·45 g trimethylsilyl cyanide[16] and 1·5 ml $SnCl_4$ gave the crude product which was purified by crystallization from a mixture of 200 ml benzene and 150 ml ethanol; 15·2 g (97%) of *IId*, m.p. 195–196°C. UV spectrum: 272 (4·11). IR spectrum: 759, 806, 875 (4 and 2 adjacent and solitary Ar—H); 1 488, 1 572, 3 050, 3 070 (Ar); 2 240 (R—CN), ^1H NMR spectrum (CD_3SOCD_3): 4·25 d, 1 H and 4·85 d, 1 H (2 H-6, J = 13·0); 6·35 s, 1 H (H-11);

7·03 d, 1 H (H-4, J = 9·0); 7·40 m, 5 H (H-3,7,8,9,10); 7·70 d, 1 H (H-1, J = 2·5). For $C_{15}H_{10}$·.BrNS (316·2) calculated: 56·97% C, 3·19% H, 25·27% Br, 4·43% N, 10·14% S; found: 57·20% C, 3·28% H, 25·02% Br, 4·37% N, 10·33% S.

2-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-yl)-4,5-dihydroimidazole (*Ia*)

A mixture of 6·0 g *IIa* (ref.[17]) and 12·8 g 2-aminoethylammonium toluene-4-sulfonate was heated under stirring to 200°C for 2 h. After partial cooling it was distributed between dilute NaOH and benzene. The benzene layer deposited on standing 2·57 g (36%) of crude *Ia*, m.p. 191·5 to 195°C. Analytical sample, m.p. 193–195·5°C (benzene). IR spectrum: 743 (4 adjacent Ar—H); 1 490, 1 599, 1 608, 3 000, 3 020, 3 060, 3 090 (Ar); 1 659 (C=N), 3 115 (NH). ^{1}H NMR spectrum: 3·60 s, 4 H (NCH_2CH_2N of dihydroimidazole); 4·08 bs, 1 H (NH); 4·75 s, 1 H (H-11); 3·52 d, 1 H and 4·85 d, 1 H (2 H-6, J = 13·0); 6·90–7·50 m, 8 H (8 ArH). For $C_{17}H_{16}N_2S$ (280·4) calculated: 72·82% C, 5·75% H, 9·99% N, 11·44% S; found: 72·61% C, 5·94% H, 10·03% N, 11·23% S.

Hydrogen maleate hemihydrate, m.p. 163·5–167°C (96% ethanol–ether). For $C_{21}H_{20}N_2O_4S$ + 0·5 H_2O (405·5) calculated: 62·21% C, 5·22% H, 6·91% N, 7·91% S; found: 62·49% C, 5·42% H, 6·87% N, 8·44% S.

2-(2-Methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl)-4,5-dihydroimidazole (*Ib*)

Similar heating of 11·0 g *IIb* with 22·0 g 2-aminoethylammonium toluene-4-sulfonate and distribution between dilute NaOH and chloroform gave an inhomogeneous product which was chromatographed on 500 g neutral Al_2O_3 (activity II). Elution with chloroform gave 11·0 g (85%) of *Ib*, m.p. 224–226·5°C (benzene). IR spectrum: 730, 763, 804, 854 (4 and 2 adjacent and solitary Ar—H); 1 489, 3 000, 3 025 (Ar); 1 602 (C=N); 3 120 (NH). ^{1}H NMR spectrum: 2·18 s, 3 H ($ArCH_3$); 3·52 s, 4 H (NCH_2CH_2N of dihydroimidazole); 4·30 bs, 1 H (NH); 4·62 s, 1 H (H-11); 3·50 d, 1 H and 4·70 d, 1 H (2 H-6, J = 13·0); 6·60–7·30 m, 7 H (7 ArH). For $C_{18}H_{18}$·.N_2S (294·4) calculated: 73·43% C, 6·16% H, 9·52% N, 10·89% S; found: 72·95% C, 6·13% H, 9·25% N, 10·84% S.

Hydrogen maleate, m.p. 188·5–192·5°C (ethanol–ether) with decomposition. For $C_{22}H_{22}$·.N_2O_4S (410·5) calculated: 64·37% C, 5·40% H, 6·82% N, 7·81% S; found: 64·05% C, 5·39% H, 6·61% N, 7·73% S.

2-(2-Chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl)-4,5-dihydroimidazole (*Ic*)

Similar heating of 9·4 g *IIc* and 20·0 g 2-aminoethylammonium toluene-4-sulfonate and similar processing by distribution between dilute NaOH and chloroform gave by evaporation of the organic layer a crude product which crystallized from benzene; 5·5 g (51%), m.p. 196–209°C. Because further crystallization from benzene led to decomposition, the unsharply melting product was used. IR spectrum (KBr): 760, 806, 884 (4 and 2 adjacent and solitary Ar—H); 1 489, 1 595, 3 060 (Ar); 1 610 (C=N); 3 150 (NH). ^{1}H NMR spectrum: 3·68 s, 4 H (NCH_2CH_2N of dihydroimidazole); 4·00 bs, 1 H (NH); 4·60 bs, 1 H (H-11); 3·55 d, 1 H and 4·80 d, 1 H (2 H-6, J = 13·0); 6·90–7·40 m, 7 H (7 ArH). For $C_{17}H_{15}ClN_2S$ (314·8) calculated: 64·85% C, 4·80% H, 11·26% Cl, 8·90% N, 10·18% S; found: 64·90% C, 4·74% H, 11·26% Cl, 8·79% N, 10·17% S.

Hydrogen maleate, m.p. 202–205°C (ethanol–ether). For $C_{21}H_{19}ClN_2O_4S$ (430·9) calculated: 58·53% C, 4·44% H, 8·23% Cl, 6·50% N, 7·44% S; found: 58·01% C, 4·38% H, 8·60% Cl, 6·40% N, 7·14% S.

2-(2-Bromo-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl)-4,5-dihydroimidazole (*Id*)

Heating of 8·0 g *IId* with 14·0 g 2-aminoethylammonium toluene-4-sulfonate to 200°C for 2 h and distribution of the product between diluted NaOH and chloroform gave an inhomogeneous product which was chromatographed on 500 g neutral Al_2O_3 (activity II). Elution with chloroform gave 5·06 g (56%) of almost homogeneous *Id*, which crystallized from chloroform, m.p. 210–215·5°C with decomposition. IR spectrum: 751, 805, 811, 850, 880, 890 (4 and 2 adjacent and solitary Ar–H); 1 490, 1 595, 3 020, 3 060 (Ar); 1 605, 1 610 (C=N); 3 120 (NH). ^{1}H NMR spectrum: 3·55 s, 4 H (NCH_2CH_2N of dihydroimidazole); 4·25 bs, 1 H (NH); 4·60 s, 1 H (H-11); 3·50 d, 1 H and 4·78 d, 1 H (2 H-6, J = 13·0); 6·90 d, 1 H (H-4, J = 9·0); 7·20 m, 5 H (H-3,7,8, 9,10); 7·35 d, 1 H (H-1, J = 2·5). For $C_{17}H_{15}BrN_2S$ (359·3) calculated: 56·83% C, 4·21% H, 22·24% Br, 7·80% N, 8·92% S; found: 56·67% C, 4·19% H, 22·21% Br, 7·49% N, 8·95% S.

Hydrogen maleate, m.p. 199–202°C (ethanol–ether). For $C_{21}H_{19}BrN_2O_4S$ (475·4) calculated: 53·06% C, 4·03% H, 16·81% Br, 5·89% N, 6·75% S; found: 52·96% C, 3·98% H, 16·90% Br, 5·72% N, 7·03% S.

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