ANTIHISTAMINE SUBSTANCES. TRICYCLIC ANALOGUES OF *N*-(4,4-DIPHENYL-3-BUTENE-1-YL)NIPECOTIC ACID AND SOME RELATED COMPOUNDS

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Alkylation of ethyl nipecotate with bromides *VII* – *X* gave amino esters *Ib* – *Vb*. Alkylation of ethyl piperazine-2-carboxylate with 4-bromo-1,1-diphenyl-1-butene afforded compound *Vb*. Final product *Ia* – *Va* were obtained by acid hydrolysis of corresponding esters *Ib* – *Vb*. Some of the compounds showed significant antihistamine and antiulcer activities.

Derivatives of dibenzo[*b*,*e*] thiepin, thieno[2,3-*c*]-2-benzothiepin and related tricyclic systems with aminoalkyl side chains proved important antihistamine activities[1 – 4]. Introduction of a hydrophilic substituent (especially carboxyl) into their molecules decreased usually their unwanted sedative effects[5], due to suppression of their penetration through the blood-brain barrier. In connection with a research after new antihistaminic substances, compounds *Ia* – *Va* were prepared fulfilling the mentioned conditions. With regard to the fact that all of these compounds are structurally related to compounds SK&F 89976 (*VI*), a GABA uptake inhibitor[6], anticonvulsant action was also expected for the new products.

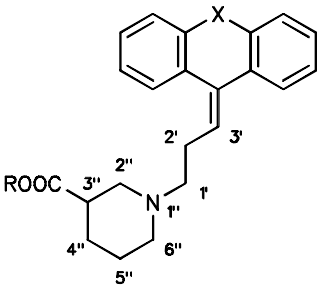
The synthesis of the carboxylic acids *Ia* – *IVa* started by alkylations of ethyl nipecotate with bromides *VII* (ref.[7]), *VIII* (ref.[8]), *IX* and *X* in acetone in the presence of potassium carbonate. The obtained amino esters *Ib* – *IVb* were hydrolyzed with dilute hydrochloric acid which resulted in the final products. The bromo compounds *IX* and *X* were prepared by Grignard reactions of cyclopropylmagnesium bromide with the corresponding tricyclic ketones and by the following reaction of the tertiary alcohols obtained with 48% hydrobromic acid in the acetic acid.

Alkylation of ethyl piperazine-2-carboxylate[9] with 4-bromo-1,1-diphenyl-1-butene[10] under similar conditions resulted in the mixture of amino esters *Vb* and *XII* which was separated by chromatography on silica gel. A similar alkylation in tetrahydrofuran in

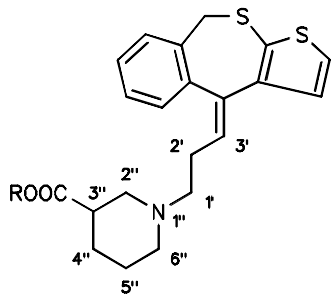
the presence of triethylamine afforded *Vb* as the single product. Its hydrolysis with dilute hydrochloric acid gave the amino acid *Va*.

For the purpose of pharmacological evaluation, amino acids *Ia* – *Va* were used in the form of water-soluble salts (hydrochlorides, hydrogen oxalates) and these were tested by methods of biochemical and behavioural pharmacology.

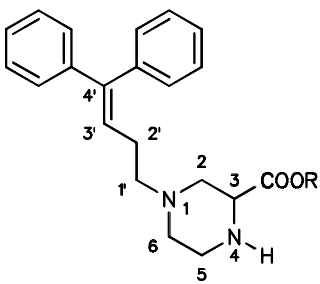
Compounds *Ia* – *Va* showed only low affinity to the GABA-ergic receptors. In the test of inhibition of binding of 10 nM [^{3}H]muscimol in the rat brain (the tested compounds were used in the concentration of 100 nM), the inhibition amounted to 80 – 90% of



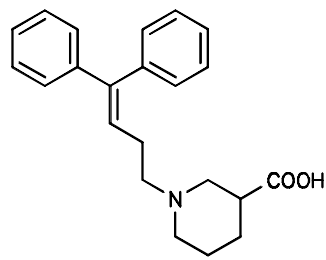
I, X = CH_2CH_2
II, X = CH_2S
III, X = S



IV



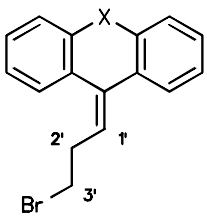
V

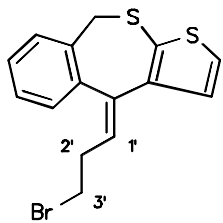


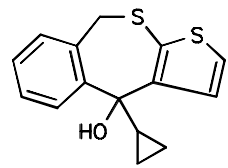
VI (SK&F–89976)

In formulae *I* – *V*: *a*, R = H; *b*, R = C_2H_5

the original binding. The inhibition of re-uptake of GABA in the rat brain (1 nM [^{3}H]GABA was as the ligand; the tested compounds were used in the concentration of 1 000 nM) amounted to 60 – 80%. Up to oral doses of 100 mg/kg, the tested compounds did not show anticonvulsant activity in mice (test with electroshock and penetrazole seizures were used). Compound *IIIa* in the oral dose of 10 mg/kg showed a weak protective action in the test of anticonvulsant activity against bicuculine convulsions in mice; the other compounds up to dose of 50 mg/kg proved inactive. The acute oral toxicity of all tested compounds in mice (approximate ID_{50} values) amounted to 500 – 1 000 mg/kg.



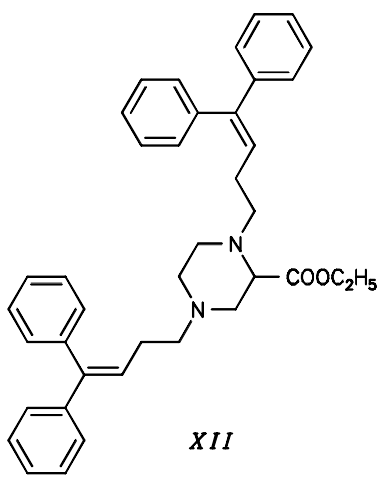




XI

VII, X = CH_2CH_2
VIII, X = CH_2S
IX, X = S

X



XII

Some of the compounds showed significant antihistamine and antiulcer activities. Histamine aerosol test in guinea pigs (per cent of protection after the dose of 1 mg/kg): *Ia*, 50; *IIa*, 37.5; *IIIa*, 25; *IVa*, 66 (in the dose of 0.1 mg/kg protection still by 33%). Test of gastric ulcers induced by indomethacin in rats (oral ED_{50} given): *Ia*, 16.0; *IIa*, 49.3; *IIIa*, 30.3; *IVa*, 33.8.

EXPERIMENTAL

The melting points of analytical samples were determined with the Mettler FP-5 or in the Kofler block and they are not corrected; the analytical samples were dried in vacuo of about 40 Pa at a room temperature or at a suitably elevated temperature. UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded with the Unicam SP 8000 spectrophotometer; IR spectra (wavenumbers in cm^{-1}) with Unicam SP 2000 or Perkin–Elmer 298 spectrophotometers, NMR spectra (in CD_3SOCD_3 unless stated otherwise) on a Tesla BS 567A (^1H at 100 MHz, ^{13}C at 25.14 MHz) or on a Varian XL-200 (^1H at 200.057 MHz, ^{13}C at 50.309 MHz), chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. The mass spectra (*m*/*z*, %) were measured on a Varian MAT-44S (GC-MS) spectrometer. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol UV_{254}). Preparative chromatographic separations were carried out on columns of silica gel (Fluka 60). The extracts were dried with Na_2SO_4 or K_2CO_3 and solvents were evaporated under reduced pressure on a rotary evaporator.

9-(3-Bromopropylidene)thioxanthene (*IX*)

Grignard reagent was prepared from cyclopropyl bromide (16.0 g, 0.13 mol) and Mg dust (3.3 g, 0.136 mol) in tetrahydrofuran (100 ml). After refluxing for 30 min, the mixture was cooled to room temperature and was treated over 10 min with a suspension of thioxanthone (19.0 g, 0.09 mol) in 70 ml tetrahydrofuran. It was refluxed for 5 h, after cooling decomposed with 20% aqueous NH_4Cl (added dropwise) and diluted with ether (100 ml). The organic layer was separated and evaporated. The residue (26.6 g) was dissolved in acetic acid (120 ml), the solution was treated with 48% aqueous HBr (60 ml, 0.53 mol), and the mixture was stirred for 3 h at room temperature. It was diluted with water, extracted with benzene, the extract was evaporated and the residue was chromatographed on silica gel (100 g). Elution with a mixture of benzene–light petroleum 1 : 2 gave 11.9 g (42%) of *IX*, m.p. 62.5 – 64.5 °C. Reference[11], mentioning this compound, did describe neither the method of preparation, nor characterization of the product. UV spectrum (heptane): 230 (4.50), 267 (4.16), 323 (3.58). IR spectrum (KBr): 742, 771 (ArH); 1 580, 3 000, 3 048 (Ar); 1 628 (C=C). ^1H NMR spectrum (100 MHz, $CDCl_3$): 3.02 q, 2 H (H-2′, J = 7.0); 3.48 t, 2 H (H-3′, J = 7.0); 5.91 t, 1 H (H-1′, J = 7.0); 7.20 – 7.70 m, 8 H (ArH). For $C_{16}H_{13}BrS$ (317.3) calculated: 60.57% C, 4.13% H, 25.19% Br, 10.11% S; found: 60.63% C, 4.23% H, 25.06% Br, 10.12% S.

(*E*)-4-(3-Bromopropylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin (*X*)

Grignard reagent was prepared from cyclopropyl bromide (17.0 g, 0.14 mol) and Mg dust (3.4 g, 0.14 mol) in tetrahydrofuran (100 ml). After 30 min refluxing, the mixture was cooled to room temperature and treated dropwise over 15 min with a solution of thieno[2,3-*c*]-2-benzothiepin-4(9*H*)-one[1] (21.0 g, 0.09 mol) in tetrahydrofuran (40 ml). The mixture was refluxed for 90 min, after cooling decomposed with 20% aqueous NH_4Cl (100 ml, added dropwise) and diluted with ether (100 ml). The organic layer was separated, dried, evaporated, the residue was dissolved in small amount of benzene and the solution was filtered through silica gel. Processing of the filtrate gave 20.6 g (93%)

of oily *XI*. ^{1}H NMR spectrum (100 MHz, $CDCl_3$): 0.40 – 0.95 m, 4 H (CH_2 of cyclopropoane); 1.80 m, 1 H (CH of cyclopropane); 2.12 bs, 1 H (OH); 4.45 and 4.65 AB system, 2 H (2 × H-9, J = 13.0); 7.02 d, 1 H (H-2, J = 5.8); 7.28 m, 3 H (H-6, H-7, H-8); 7.35 d, 1 H (H-3, J = 5.8); 7.65 m, 1 H (H-5).

A solution of alcohol *XI* (18.9 g, 69 mmol) in acetic acid (100 ml) was treated at 5 – 15 °C with 48% aqueous HBr (50 ml, 0.44 mol), the mixture was stirred for 5 h at room temperature, diluted with water, extracted with benzene, the extract was evaporated and the residue was chromatographed on silica gel (80 g). Elution with a mixture of benzene–light petroleum (1 : 3) gave 14.8 g (64%) of *X*, m.p. 94 – 97 °C (cyclohexane). This product is contamined by a small quantity of the *Z*-isomer (*E* : *Z* = 9 : 1). UV spectrum (heptane): 230 (4.29), 276 (3.77), 313 (3.65). IR spectrum (CS_2): 690, 709, 761, 787 (ArH); 842, 861, 872 (H in thiophene). ^{1}H NMR spectrum (signals of *E*-isomer, 100 MHz, $CDCl_3$): 2.94 q, 2 H (2 × H-2′), 3.50 t, 2 H (2 × H-3′); 6.01 t, 1 H (H-1′); 6.80 – 7.50 m, 6 H (ArH). For $C_{15}H_{13}BrS_2$ (337.3) calculated: 53.41% C, 3.88% H, 23.69% Br, 19.01% S; found: 53.55% C, 3.95% H, 23.33% Br, 18.65% S.

General Procedure for the Preparation of Amino Acids *Ia – IVa*

A mixture of respective bromopropylidene compounds (15 mmol), ethyl nipecotate (2.7 g, 17 mmol), K_2CO_3(2.9 g, 21 mmol) and acetone (100 ml) was stirred and refluxed for 16 h. The mixture was filtered, the filtrate was evaporated, the residue distributed between 5% $NaHCO_3$ and benzene and the organic layer was evaporated. The residue (the crude ester) was dissolved in 10% aqueous hydrochloric acid (100 ml, 0.29 mol) and the solution refluxed for 16 h. After cooling, the clear solution was separated from semisolid crude product by decantation, the product was dissolved in acetone, the solution was filtered with active carbon and the filtrate was evaporated. The residue, representing the hydrochloride of the product, was purified by crystallization from a mixture of ethanol and ether. In some cases, the crude hydrochloride was decomposed with aqueous ammonia, the base was isolated by extraction with ether and transformed to the hydrogen oxalate by treatment with oxalic acid in acetone.

1-[3-(10,11-Dihydrodibenzo[a,d]cycloheptene-5-ylidene)propyl]piperidine-3-carboxylic acid (Ia). The bromopropylidene derivative[7] *VII* (4.7 g, 15 mmol) afforded by reaction with ethyl nipecotate (2.7 g, 17 mmol) and hydrolysis 1.9 g (28%) *Ia* hydrogen oxalate, m.p. 125 – 135 °C (ethyl acetate–ether). ^{1}H NMR spectrum (200 MHz): 1.46 m, 1 H (H-5a″); 1.78 – 1.96 m, 3 H (H-5e″, 2 × H-4″); 2.82 m, 5 H (2 × H-2′, H-3″, H-2a″, H-6a″); 3.11 m, 4 H (2 × H-10, 2 × H-11); 3.20 – 3.49 m, 4 H (2 × H-1′, H-2e″, H-6e″); 5.90 t, 1 H (H-3′, J = 7.1); 6.98 – 7.50 m, 8 H (ArH); 9.12 bs, 3 H (3 × COOH). ^{13}C NMR: 21.7 t (C-5″), 24.2 t (C-2′), 25.4 t (C-4″), 34.1 t and 34.8 t (C-10, C-11), 38.5 d (C-3″), 51.2 t (C-6″), 55.8 t (C-1′), 61.1 t (C-2″), 122.8 d (C-3′), 125.4 d, 126.3 d, 126.9 d, 127.2 d, 127.4 d, 127.8 d, 128.7 d, 130.4 d (Ar), 134.1 s (C-5), 137.0 s, 137.6 s (C-9a, C-11a), 140.9 s, 141.3 s (C-4a, C-5a), 164.3 s (COOH in oxalate), 171.4 s (COO^- in oxalate), 173.1 s (COOH). For $C_{26}H_{29}NO_6$ (451.5) calculated: 69.16% C, 6.47% H, 3.10% N; found: 68.60% C, 6.82% H, 3.00% N.

1-[3-(6,11-Dihydrodibenzo[b,e]thiepin-11-ylidene)propyl]piperidine-3-carboxylic acid (IIa). The bromopropylidene derivative[8] *VIII* (5.0 g, 15 mmol) gave by reaction with ethyl nipecotate (2.7 g, 17 mmol) and the following hydrolysis 2.2 g (34%) of *IIa* hydrochloride hemihydrate, m.p. 163.5 – 165.5 °C. IR spectrum (Nujol): 768 (ArH); 876, 1 204, 1 721 (COOH); 1 588, 3 050 (Ar); 2 530, 2 615, 2 670 (NH^+); 3 420 (OH). ^{1}H NMR spectrum (200 MHz): 1.41 m, 1 H (H-5a″); 1.74 – 1.92 m, 3 H (H-5e″, 2 × H-4″); 2.35 m, 2 H (H-2a″, H-6a″); 2.75 – 3.18 m, 7 H (H-2e″, H-6e″, H-3″, 2 × H-2′, 2 × H-1′); 3.68 d, 1 H and 4.76 d, 1 H (2 × H-6, J = 13.8); 5.90 t, 1 H (H-3′, J = 7.2); 6.93 – 7.40 m, 8 H (ArH); 11.2 bs, 1 H (COOH). ^{13}C NMR spectrum: 21.8 t (C-5″), 23.9 t (C-2′), 25.1 t (C-4″), 32.2 t (C-6), 38.5 d (C-3″), 51.2 t (C-6″), 55.5 t (C-1′), 60.9 t (C-2″), 125.1 d

(C-3′), 2 × 127.1 d, 127.7 d, 127.8 d, 128.2 d, 128.4 d, 128.7 d, 131.0 d (Ar); 133.8 s (C-11), 136.4 s and 136.6 s (C-4a, C-6a), 138.8 s (C-11a), 143.0 s (C-10a), 173.0 s (COOH). For $C_{23}H_{26}ClNO_2S$ + 0.5 H_2O (425.0) calculated: 65.00% C, 6.40% H, 8.34% Cl, 3.30% N, 7.54% S; found: 65.14% C, 6.61% H, 8.42% Cl, 3.83% N, 7.31% S.

1-[3-(Thioxannnthene-9-ylidene)propyl]piperidine-3-carboxylic acid (IIIa). Reaction of *IX* (4.8 g, 15 mmol) with ethyl nipecotate (2.7 g, 17 mmol) and the following hydrolysis resulted in 2.9 g (42%) of *IIIa* hydrogen oxalate, m.p. 155 – 160 °C (acetone–ether). ^{1}H NMR spectrum (200 MHz): 1.49 m, 1 H (H-5a″); 1.82 – 1.97 m, 3 H (H-5e″, 2 × H-4″); 2.86 m, 5 H (H-2a″, H-6a″, 2 × H-2′, H-3″); 3.23 – 3.54 m, 4 H (H-2e″, H-6e″, 2 × H-1′); 5.90 t, 1 H (H-3′, *J* = 7.0); 7.31 – 7.54 m, 8 H (ArH); 8.80 bs, 3 H (3 × COOH). ^{13}C NMR spectrum: 21.8 t (C-5″, 24.3 t (C-2′), 25.2 t (C-4″), 38.8 d (C-3″), 51.4 t (C-6″), 55.5 t (C-1′), 60.8 t (C-2″), 125.9 d and 126.1 d (C-3′, Ar), 126.8 d, 126.9 d, 127.3 d, 2 × 127.5 d, 128.0 d, 128.9 d (Ar), 130.9 s (C-9), 132.5 s and 132.8 s (C-4a, C-10a), 136.6 s and 137.6 s (C-9a, C-8a), 164.6 s (COOH in oxalate), 171.6 s (COO^- in oxalate), 173.3 s (COOH). For $C_{24}H_{25}NO_6S$ (455.5) calculated: 63.28% C, 5.53% H, 3.08% N, 7.04% S; found: 63.55% C, 6.09% H, 3.18% N, 7.18% S.

In this case, the intermediate crystalline ester *IIIb*, i.e. ethyl 1-[3-(thioxanthene-9-ylidene)propyl]-piperidine-3-carboxylate, was isolated as hydrochloride, m.p. 161 – 164 °C (benzene). IR spectrum (Nujol): 740, 770 (ArH), 1 221, 1 309, 1 736 (COOR); 1 581, 1 666, 3 043 (Ar); 2 523, 2 608 (NH^+). ^{1}H NMR spectrum (100 MHz): 1 22 t, 3 H (CH_3, *J* = 7.0); 1.60 – 3.60 m, 13 H (CH and CH_2); 4.13 q, 2 H (OCH_2, *J* = 7.0); 5.94 t, 1 H (H-3′, *J* = 7.0); 7.30 – 7.60 m, 8 H (ArH). For $C_{24}H_{28}ClNO_2S$ (430.0) calculated: 67.04% C, 6.56% H, 3.26% N, 8.25% Cl, 7.46% S; found: 67.09% C, 6.71% H, 3.31% N, 8.50% Cl, 7.25% S.

1-[3-(4,9-Dihydrothieno[2,3-c]-2-benzothiepin-4-ylidene)propyl]piperidine-3-carboxylic acid (IVa). The bromopropylidene compound *X* (5.1 g, 15 mmol) was reacted with ethyl nipecotate (2.7 g, 17 mmol) and the crude product gave by hydrolysis and further processing 3.0 g (41%) of *IVa* hydrogen oxalate hemihydrate, m.p. 95 – 105 °C (acetone–ether). ^{1}H NMR spectrum (200 MHz): 1.47 – 1.96 m, 4 H (2 × H-4″, 2 × H-5″); 2.41 m, 2 H (H-2a″, H-6a″); 2.80 m, 3 H (H-3″, 2 × H-2′); 3.16 m, 4 H (H-2e″, H-6e″, 2 × H-1′); 3.93 d, 1 H and 4.58 d, 1 H (2 × H-9, J = 13.2); 6.00 t, 1 H (H-3′, *J* = 6.5); 7.05 d, 1 H (H-3, *J* = 5.4); 7.15 – 7.38 m, 5 H (ArH), 9.25 bs, 3 H (3 × COOH). ^{13}C NMR spectrum: 21.7 t (C-5″), 24.2 t (C-2′), 25.0 t (C-4″), 34.2 t (C-9), 38.6 d (C-3″), 51.6 t (C-6″), 55.3 t (C-1′), 60.8 t (C-2″), 122.1 d (C-3′), 2 × 127.6 d, 127.8 d, 128.1 d, 128.7 d, 129.0 d (Ar), 134.1 s (C-4), 135.9 s (C-3a), 137.2 s and 137.6 s (C-8a, C-10a), 143.6 s (C-4a), 164.6 s (COOH in oxalate), 172.0 s (COO^- in oxalate), 173.4 s (COOH). For $C_{23}H_{25}NO_6S_2$ + 0.5 H_2O (484.6) calculated: 57.00% C, 5.41% H, 2.89% N; found: 57.12% C, 5.75% H, 2.72% N.

Ethyl 1-(4,4-Diphenyl-3-butene-1-yl)piperazine-3-carboxylate (*Vb*)

A) A mixture of ethyl piperazine-2-carboxylate[9] (3.0 g, 18.9 mmol), 4-bromo-1,1-diphenylbutene[10] (5.6 g, 18.9 mmol), triethylamine (1.9 g, 18.9 mmol) and tetrahydrofuran (45 ml) was refluxed for 24 h. The precipitated triethylamine hydrobromide was filtered off, the filtrate was evaporated, the residue was dissolved in ether and the solution neutralized with HCl in ether; yield 5.5 g (63%) of *Vb* dihydrochloride hydrate, m.p. 167 – 169 °C. IR spectrum: 703, 744 (ArH); 1 261, 1 290, 1 308, 1 329, 1 743 (COOR); 1 490, 1 542, 3 010 (Ar); 1 630 (C=C); 2 400, 2 540, 2 635 (NH^+); 3 440 (NH). Mass spectrum: 364 (M^+, $C_{23}H_{28}N_2O_2$, 0.05), 291 (1.6), 171 (100), 128 (10), 98 (17), 97 (21), 91 (8), 56 (10), 44 (12). ^{1}H NMR spectrum (200 MHz): 1.24 t, 3 H (CH_3, *J* = 6.8); 2.53 m, 2 H (H-2a, H-5a); 3.38 – 3.58 m, 7 H (H-2e, H-5e, H-6a, 2 × H-1′, 2 × H-2′); 3.84 d, 1 H (H-6e, *J* = 10.8); 4.25 q, 2 H (OCH_2, *J* = 6.8); 4.81 d, 1 H (H-3, *J* = 7.2); 6.17 t, 1 H (H-3′, *J* = 6.2); 7.17 – 7.44 m, 10 H (ArH); 10.40 bs, 1 H (NH^+). ^{13}C NMR spectrum: 14.0 q (CH_3), 24.3 t (C-2′),

38.2 t (C-6), 47.0 t (C-5), 48.5 t (C-2), 52.0 d (C-3), 55.1 t (C-1′), 63.0 t (OCH_2), 123.8 d (C-3′), 127.2 d (2 Ar), 127.6 d and 127.7 d (C-4 of Ph), 128.5 d, 128.8 d, 129.5 d (2 Ar), 139.0 s (C-4′), 141.7 s and 143.7 s (C-1 of Ph), 164.8 s (CO). For $C_{23}H_{30}Cl_2N_2O_2 + H_2O$ (455.4) calculated: 60.65% C, 7.08% H, 15.57% Cl, 6.15% N; found: 60.23% C, 6.73% H, 15.69% Cl, 6.02% N.

B) A mixture of ethyl piperazine-2-carboxylate[9] (0.50 g, 3.16 mmol), 4-bromo-1,1-diphenylbutene[10] (0.91 g, 3.16 mmol), K_2CO_3 (0.87 g, 6.3 mmol), KI (12 mg, 0.07 mmol) and acetone (10 ml) was refluxed for 24 h, filtered, the filtrate was evaporated, and the residue was chromatographed on silica gel (20 g). Elution with chloroform and then chloroform–ethanol (20 : 1) recovered first 0.14 g of the starting 4-bromo-1,1-diphenylbutene and then gave 0.17 g (19%) of ethyl 1,4-bis-(4,4-diphenyl-3-butene-1-yl)piperazine-2-carboxylate (*XII*), oil. ^{1}H NMR spectrum (100 MHz): 1.22 t, 6 H ($2 \times CH_3$, J = 7.2); 2.0 – 3.3 m, 15 H (aliphatic CH and CH_2); 4.14 q, 4 H ($2 \times OCH_2$, J = 7.2); 6.04 t, 2 H (CH=); 7.1 – 7.5 m, 20 H (ArH). Dihydrochloride hemihydrate, m.p. 124 – 126 °C (ethyl acetate–ethanol). Mass spectrum: 570 (M^+, $C_{39}H_{42}N_2O_2$, 0.1), 497 (2), 377 (100), 303 (6), 129 (26), 115 (18), 111 (17), 97 (17), 91 (40). For $C_{39}H_{44}Cl_2N_2O_2 + 0.5\ H_2O$ calculated: 71.76% C, 6.95% H, 10.86% Cl, 4.29% N; found: 71.48% C, 6.79% H, 10.83% Cl, 4.25% N.

Conclusion of the chromatography by elution with chloroform–ethanol (20 : 1) gave finally 0.48 g (42%) of *Vb* identical with the product prepared by method *A*.

1-(4,4-Diphenyl-3-butene-1-yl)piperazine-3-carboxylic Acid (*Va*)

A solution of *Vb* (4.4 g, 12 mmol) in 6 M HCl (180 ml) was refluxed for 14 h. After cooling, the precipitate was filtered, dissolved in water, the solution was filtered with active carbon while hot, the filtrate was evaporated and the residue crystallized from 5% hydrochloric acid; 3.2 g (62%) of *Va* dihydrochloride hydrate, m.p. 158 – 162 °C. ^{1}H NMR spectrum (200 MHz): 2.42 m, 2 H (H-2a, H-5a); 3.30 – 3.52 m, 7 H (H-2e, H-5e, H-6a, H-2′, H-1′); 3.77 d, 1 H (H-6e, J = 11.3); 4.57 d, 1 H (H-3, J = 9.8); 6.10 t, 1 H (H-3′, J = 5.7); 7.16 –7.44 m, 10 H (ArH); 10.1 super bs, 1 H (COOH). ^{13}C NMR spectrum: 24.3 t (C-2′), 38.2 t (C-6), 47.0 t (C-5), 48.8 t (C-2), 52.4 d (C-3), 55.1 t (C-1′), 123.9 d (C-3′), 127.2 d, 128.4 d, 128.8 d, 129.5 d ($2 \times$ C-2 and C-3 of Ph), 127.55 d and 127.65 d (C-4 of Ph), 139.0 s (C-4′), 141.7 s and 143.6 s ($2 \times$ C-1 of Ph), 166.2 s (CO).

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