Solution-Dimerization of 4-Aryl-1,4-dihydropyridines

Andreas Hilgeroth,*[a] Ute Baumeister,[b] and Frank W. Heinemann[c]

Keywords: Cycloadditions / Cage compounds / Dimerizations / Steric hindrance / Photochemistry

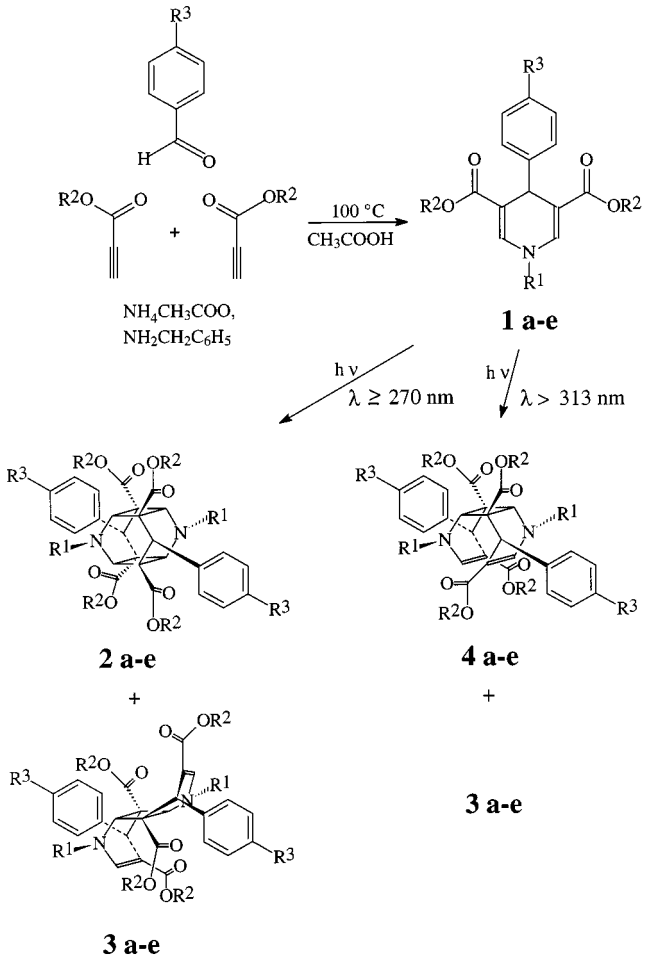
On irradiation at $\lambda \geq 270$ nm solutions of 4-aryl-1,4-dihydropyridines **1** yield cage dimers **2** as the main products beside small amounts of *anti* dimers **3**. ^{1}H-NMR data and X-ray crystal structure prove centrosymmetrical properties for both dimers with axially orientated 4-aryl substituents. Irradiation with filtered light ($\lambda > 313$ nm) leads to *syn* and *anti* dimers **4** and **3** in nearly equal yields. The poor yields of *anti* dimers **3** on irradiation with unfiltered light are demonstrated to result from a partial cleavage back to their monomeric starting materials **1**.

3,9-Diazatetraasteranes have been found as the exclusive cycloaddition products of 4-(4-methoxyphenyl)-1,4-dihydropyridines.[1] The cage formation was demonstrated to proceed via *syn*-dimeric ring-open intermediates.[1] Functionalized 3,9-diazatetraasteranes have been suggested as interesting pharmacological targets with potential anti-cancer or anti-HIV activity.[1] Moreover, the interest in these compounds has been strengthened as they were shown to be potential HIV-1 protease inhibitors by molecular modeling studies.[2][3]

As the reported solid-state synthesis was shown to be partly limited by certain conformationally determined packing restraints,[1] the photoreactivity of 4-aryl-1,4-dihydropyridines in solution had to be investigated as alternative reaction pathway to those interesting cage compounds. The given products and their stereochemical properties proved by ^{1}H-NMR data and X-ray crystal structures will be presented.

Encouraged by the molecular-modeling studies that suggested that *N*-substituted 3,9-diazatetraasteranes, especially with benzylic groups, were potential HIV-1 protease inhibitors, the corresponding 4-aryl-*N*-benzyl-1,4-dihydropyridines **1a**−**c** and NH derivatives **1d** and **e**, whose dimers could easily be functionalized by *N*-acylation, were prepared. This series of starting compounds were prepared by cyclocondensation of methyl or ethyl propiolate and aromatic aldehydes with either benzylamine or ammonium acetate, in acetic acid.[4][5]

Solution dimerization of **1a**−**e** at $\lambda \geq 270$ nm with unfiltered light of Ultra-Vitalux lamps® leads to cage-dimeric 3,9-diazatetraasteranes **2a**−**e** (ca. 75%) and small amounts of *anti* dimers **3a**−**e** (ca. 10%) (Scheme 1). ^{1}H-NMR spectra indicate symmetrical structures for both types of dimers with merely one set of signals for both 1,4-dihydropyridine subunits in the dimers (see Experimental Section).



1	R1	R2	R3
a	Bzl	C_2H_5	H
b [1]	Bzl	C_2H_5	OCH_3
c [1]	Bzl	CH_3	OCH_3
d [5]	H	C_2H_5	H
e [4]	H	CH_3	H

Scheme 1. Formation of 4-aryl-1,4-dihydropyridines and their solution-dimerization products

[a] Institut für Pharmazeutische Chemie der Martin-Luther-Universität,
Wolfgang-Langenbeck-Str. 4, D-06120 Halle, Germany
Fax: (internat.) + 49-(0)345/552-7022
E-mail: hilgeroth@pharmazie.uni-halle.de
[b] Institut für Physikalische Chemie der Martin-Luther-Universität,
Mühlpforte 1, D-06108 Halle, Germany
[c] Institut für Anorganische Chemie II der Friedrich-Alexander-Universität,
Egerlandstr. 1, D-91058 Erlangen, Germany

  1434−193X/00/0102−245 $ 17.50+.50/0

As the X-ray crystallographically determined molecular structure of cage dimer **2b** corresponds to that of the cage dimer formed by the solid-state reaction,[3] a centrosymmetrical structure for the solution dimer **2b** was confirmed (Figure 1).

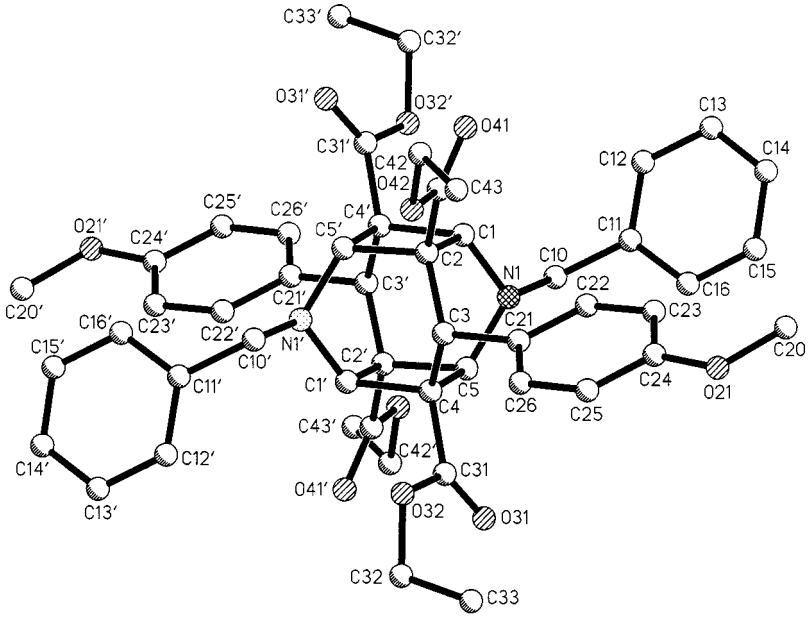


Figure 1. Molecular structure of **2b**

X-ray crystal structure analysis of *anti* dimer **3e** also proves a centrosymmetrical structure with both phenyl-substituents pseudoaxially orientated (Figure 2). The cyclobutane bonds are significantly different in length. The bonds formed by the dimerization reaction (C1−C2′ and its centrosymmetric equivalent) are longer [1.590(4) Å] than those of the 1,4-dihydropyridine subunits in the dimer (C1−C2 and its centrosymmetric equivalent) [1.553(4) Å]. In the cage dimer **2b**[6] the two longer bonds (C1−C4′ and C2−C5′ and their centrosymmetric equivalents) [1.587(3) Å and 1.589(3) Å] correspond to those formed by the dimerization reaction, while the two shorter ones (C1−C2 and C4−C5 and their centrosymmetric equivalents) [1.553(3) Å and 1.550(3) Å] represent the former 1,4-dihydropyridine bonds. This has also been reported for 3,9-diazatetraasteranes derived from the solid-state synthesis,[1] as well as for the described tetraethyl 3,9-diazatetraasterane-1,5,7,11-tetracarboxylate derived from a solution photoreaction in poor yields.[7][8] Thus, both 4-(4-methoxyphenyl) substituents show axial orientations.

With the 4-aryl substituents of the dimers both axially or pseudoaxially orientated, it had to be concluded that in solution the 1,4-dihydropyridine conformer with pseudoaxial orientation of the 4-aryl substituent predominates in relation to the conformer with the pseudoequatorially orientated 4-aryl substituent. This result corresponds well to numerous reports of solution reactions and molecular modeling studies of 4-aryl-1,4-dihyropyridines, which all prove the pseudoaxial orientation of the 4-aryl substituent to be energetically more favourable than the pseudoequatorial orientation.[9−12]

The great difference in the yields of the cage dimers **2a**−**e**, and those of the *anti* dimers **3a**−**e**, was nevertheless somehow surprising. As the formation of both types of dimers

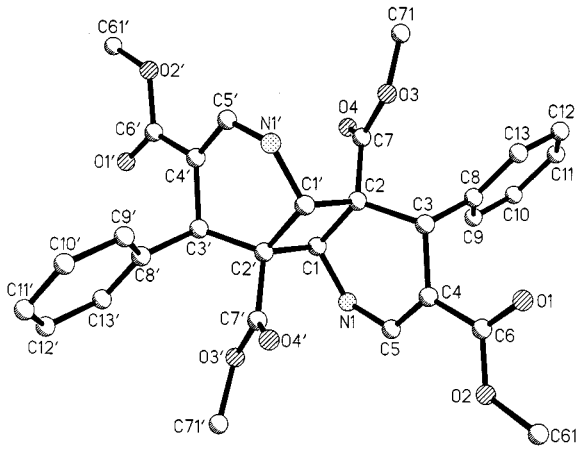


Figure 2. Molecular structure of **3e**

is not limited by conformationally determined packing restraints as in the solid state, similar yields of both possible types of dimers in solution were expected.[13]

In order to further investigate the cage dimer formation that may proceed via a *syn*-dimeric ring-open intermediate, irradiation experiments with filtered light ($\lambda > 313$ nm) were undertaken. Under these conditions, the suggested cage formation may be stopped at the stage of the *syn*-dimeric intermediate, which undergoes ring closure at lower wavelengths under excitation of the enamine chromophore with $\lambda = 272-298$ nm.

After about 4 weeks of irradiation of **1a−e** the formation of nearly equal amounts of *anti* dimers **3a−e** and *syn* dimers **4a−e** could be observed, with isolated yields of about 35% in each case. In the ^{1}H-NMR spectra of NH-*anti* dimers **3d** and **3e** the NH shows coupling with both neighbouring protons, i.e. 2-H and 6-H, respectively, with J = 7 Hz (**3d**) and 4b-H and 8b-H with J = 3 Hz (**3d**), while there is only one NH coupling found in the spectra of corresponding *syn* dimers between NH and 2-H and 6-H, of J = 7 Hz (**4d**).

The increased isolated yields of the *anti* dimers **3a−e** in the dimerization process with the filtered light suggested that the *anti* dimers undergo partial cleavage to their monomeric starting materials on irradiation with unfiltered light. This would explain the lower yields in the irradiation experiments at $\lambda \geq 270$ nm. For confirmation of this assumption, solutions of *anti* dimers **3a** and **3b** have been irradiated with unfiltered light for two weeks. A fragmentation to monomeric 4-aryl-1,4-dihydropyridines **1a** and **b** was monitored by TLC, and led to final isolated yields of about 30% for both 1,4-dihydropyridines.

In summary, solution irradiation of 4-aryl-1,4-dihydropyridines offers an alternative route to 3,9-diazatetraasteranes, however with lower yields compared to the reported solid-state synthesis. The application of the solution dimerization successfully leads to 3,9-diazatetraasteranes in each case.

Experimental Section

General: Commercial reagents were used as received, without additional purification. − ^{1}H NMR: Varian Gemini 500 (500 MHz; TMS as an internal standard). − Melting points: Linström apparatus (open capillaries, uncorrected values). − Analytical TLC: Aluminium sheets coated with silica gel 60 F_{254} (Merck). − IR spectra: Bruker IFS-28 (recorded as potassium bromide disks). − UV: Diode-array spectrophotometer 8452A (chloroform). − MS: AMD 402. − Elemental analysis: Leco CHNS-932.

Diethyl 1-Benzyl-1,4-dihydro-4-phenylpyridine-3,5-dicarboxylate (1a). − Method A: Ethyl propiolate (1.96 g, 20 mmol), benzaldehyde (1.06 g, 10 mmol) and benzylamine (1.07 g, 10 mmol) were heated in 1 mL of glacial acetic acid in a steam bath for 15 min. The reaction mixture was then poured into ice/water from which **1a** crystallized on stirring. − **Method B:** The *anti* dimer **3a** (0.40 g) was dissolved in methanol/tetrahydrofuran, and the solution was irradiated as described under Method A below. After two weeks the solution was evaporated to dryness and the remaining oil was dissolved in methanol, from which **1a** was isolated by fractional crystallization. − Yield (Method A): 2.80 g (72%) [Method B gave a yield of 0.13 g (33%)], yellow powder, m.p. 145−147°C. − IR: $\tilde{\nu}$ = 1695 cm^{-1}, 1662. − UV: λ_{max} (lg ε) = 252 nm (3.44), 360 (2.81). − ^{1}H NMR ($CDCl_3$): δ = 1.17 (t, J = 7 Hz, 6 H, CH_2CH_3), 4.08 (q, J = 7 Hz, 4 H, CH_2CH_3), 4.46 (s, 2 H, NCH_2), 4.91 (s, 1 H, 4-H), 7.09−7.73 (m, 12 H, aromatic H, 2-H, 6-H). − ESI MS; *m*/*z* (%): 392 (13) [M + H$^+$]. − $C_{24}H_{25}NO_4$ (391.5): calcd. C 73.64, H 6.44, N 3.58; found C 73.27, H 6.06, N 3.52.

Diethyl 1-Benzyl-1,4-dihydro-4-(4-methoxyphenyl)pyridine-3,5-dicarboxylate (1b): The *anti* dimer **3b** (0.40 g) was dissolved in methanol/tetrahydrofuran and the solution was irradiated as described under Method A below. After two weeks, the solution was concentrated to dryness and the residue was dissolved in boiling ethanol, from which **1b** was isolated by fractional crystallization. − Yield: 0.11 g (27%) as a yellow powder, m.p. 119−121°C (ref.[1] 120−122°C).

Solution Dimerization Reactions. − Method A, Irradiation at $\lambda \geq$ 270 nm: 1,4-Dihydropyridine (**1**) (0.40 mg) was dissolved in 40 mL of methanol/tetrahydrofuran under stirring. The solution was irradiated in a quarz flask with an Ultra-Vitalux® lamp from a distance of 60 cm for 4 weeks. While the cage dimers **2** crystallize during irradiation, the *anti* dimers **3** precipitate from the solution after reduction of the solution volume. − **Method B, Irradiation at $\lambda >$ 313 nm:**[14] 1,4-Dihydropyridine (**1**) (0.40 g) was dissolved and irradiated as described above, except that irradiation was carried out in a bath of copper(II) sulfate (1.25 M). After reducing the volume of the solution, *anti* dimers **3** and *syn* dimers **4** were isolated by fractional crystallization. − The yields of the dimerization reaction are based on 0.40 mg of **1** corresponding to 100%.

Tetraethyl 3,9-Dibenzyl-6,12-diphenyl-3,9-diazahexacyclo-[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (2a): Isolated as white crystals in a yield of 0.28 g (70%), m.p. 233−235°C. − IR: $\tilde{\nu}$ = 1730 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 0.96 (t, J = 7 Hz, 12 H, CH_2CH_3), 3.96 (q, J = 7 Hz, 8 H, CH_2CH_3), 4.26 (s, 4 H, 2-H, 4-H, 8-H, and 10-H), 4.27 (s, 2 H, 6-H, and 12-H), 4.48 (s, 4 H, NCH_2), 7.05−7.31 (m, 20 H, aromatic H). − ESI MS; *m*/*z* (%): 783 (100) [M + H$^+$], 821 (7) [M + K$^+$], 805 (50) [M + Na$^+$]. − $C_{48}H_{50}N_2O_8$ (782): calcd. C 73.64, H 6.44, N 3.58; found C 73.38, H 6.24, N 3.52.

Tetraethyl 3,9-Dibenzyl-6,12-bis(4-methoxyphenyl)-3,9-diazahexacyclo-[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (2b): Isolated as white crystals, yield: 0.35 g (87%), m.p. 168−169°C (ref.[1] 170−173°C).

X-ray Diffraction Analysis of 2b:[15] A white prism-shaped crystal of $C_{50}H_{54}N_2O_{10}$ (from methanol/tetrahydrofuran), crystal size 0.48 × 0.26 × 0.14 mm, was measured at room temp. by using a STADI4 Diffractometer with Mo-K_α radiation (λ = 0.71073 Å) and a graphite monochromator. 9652 reflexions were collected in ω/2θ scanning mode in the range 3.3° ≤ 2θ ≤ 54.0°; *h*, *k*, *l* range from −10, −14, −16 to 10, 14, 16. Crystal system: Triclinic, space group $P\bar{1}$, Z = 1, a = 8.0949(8) Å, b = 11.1710(9) Å, c = 13.1761(6) Å, α = 69.686(10)°, β = 85.904(10)°, γ = 81.725(9)°; V = 1105.46(19) Å^3; D_x = 1.269 g cm^{-3}; μ = 0.097 mm^{-1}. The structure was solved by direct methods (SHELXS 97[16]) using 4826 independent reflexions. Structure refinement: Full-matrix least-squares methods on F^2 using SHELXL 97,[17] all the non-hydrogen atoms with anisotropic displacement parameters. All hydrogen atoms except H-42A, H-42B, H-43A to H-43C, that were geometrically constructed, were taken from a difference Fourier synthesis and refined isotropically. The refinement converged to a final wR^2 = 0.1371 for 4826 unique reflections and R^1 = 0.0569 for 3034 observed reflections [$I_0 > 2\,\sigma(I_0)$] and 372 refined parameters.

Tetramethyl 3,9-Dibenzyl-6,12-bis(4-methoxyphenyl)-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]dodecane-1,5,7,11-tetracarboxylate (2c): Isolated as white crystals, yield: 0.29 g (73%), m.p. 260−261°C. − IR: $\tilde{\nu}$ = 1735 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 3.53 (s, 12 H, $COOCH_3$), 3.73 (s, 6 H, C4′−OCH_3), 4.21 (s, 2 H, 6-H, and 12-H), 4.24 (s, 4 H, 2-H, 4-H, 8-H, and 10-H), 4.43 (s, 4 H, NCH_2), 6.58−7.28 (m, 14 H, aromatic H). − MS; *m*/*z* (%): 786 (< 1) [M$^+$]. − $C_{46}H_{46}N_2O_{10}$ (786.9): calcd. C 70.21, H 5.89, N 3.56; found C 70.12, H 5.79, N 3.49.

Tetraethyl 6,12-Diphenyl-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]-dodecane-1,5,7,11-tetracarboxylate (2d): Isolated as a white powder, yield: 0.31 g (78%), m.p. 208−212°C. − IR: $\tilde{\nu}$ = 3349 cm^{-1}, 1713. − ^{1}H NMR ($CDCl_3$): δ = 0.96 (t, *J* = 7 Hz, 12 H, CH_2CH_3), 2.99 (s, br., 2 H, exchangable, NH), 3.89 (s, 2 H, 6-H, and 12-H), 3.92 (q, *J* = 7 Hz, 8 H, CH_2CH_3), 4.30 (s, 4 H, 2-H, 4-H, 8-H, and 10-H), 7.01−7.50 (m, 10 H, aromatic H). − MS; *m/z* (%): 602 (1) [M$^+$]. − $C_{34}H_{38}N_2O_8$ (602.7): calcd. C 67.77, H 6.31, N 4.65; found C 67.57, H 6.31, N 4.63.

Tetramethyl 6,12-Diphenyl-3,9-diazahexacyclo[6.4.0.0^{2,7}.0^{4,11}.0^{5,10}]-dodecane-1,5,7,11-tetracarboxylate (2e): Isolated as white crystals, yield: 0.33 g (83%), m.p. 265−267°C. − IR: $\tilde{\nu}$ = 3329 cm^{-1}, 1728. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.40 (s, 12 H, $COOCH_3$), 3.86 (s, 2 H, 6-H, and 12-H), 4.04 (d, *J* = 3 Hz, after D_2O addition s, 4 H, 2-H, 4-H, 8-H, and 10-H), 4.64 (s, *J* = 3 Hz, 2 H, exchangable, NH), 7.13−7.41 (m, 10 H, aromatic H). − ESI MS; *m/z* (%): 569 (100) [M + Na$^+$]. − $C_{30}H_{30}N_2O_8$ (546.6): calcd. C 65.93, H 5.49, N 5.13; found C 65.65, H 5.63, N 5.07.

Tetraethyl 1,5-Dibenzyl-1,5,8,8bα-tetrahydro-4,8-diphenylcyclobuta-[1,2-*b*:3,4-*b*′]dipyridine-3,4aα,7,8aβ(4*H*,4bβ*H*)-tetracarboxylate (3a): Isolated as a white powder, yield (Method A) 0.03 g (8%), (Method B) 0.13 g (32%), m.p. 231−236°C. − IR: $\tilde{\nu}$ = 1729 cm^{-1}, 1690, 1609. − UV: λ_{max} (lg ε) = 242 nm (4.23), 302 (4.64). − ^{1}H NMR ($CDCl_3$): = 1.11 (t, *J* = 7 Hz, 6 H, C4a,C8a−$COOCH_2CH_3$), 1.16 (t, *J* = 7 Hz, 6 H, C3,C7−$COOCH_2CH_3$), 3.58 (q, *J* = 7 Hz, 4 H, C4a,C8a−$COOCH_2CH_3$), 3.94 (AMX_3, *J* = 11 Hz, *J* = 7 Hz, 2 H, C3,C7−$COOCH_MCH_3$), 4.06 (AMX_3, *J* = 11 Hz, *J* = 7 Hz, 2 H, C3,C7−$COOCH_ACH_3$), 4.17 (s, 2 H, 4-H, and 8-H), 4.39 (d, *J* = 15 Hz, 2 H, NCH_B), 4.52 (s, 2 H, 4b-H, and 8b-H), 4.67 (d, *J* = 15 Hz, 2 H, NCH_A), 6.94−7.42 (m, 20 H, aromatic H), 7.46 (s, 2 H, 2-H, and 6-H). − MS; *m/z* (%): 782 (< 1) [M$^+$]. − $C_{48}H_{50}N_2O_8$ (782): calcd. C 73.64, H 6.44, N 3.58; found C 73.38, H 6.55, N 3.32.

Tetraethyl 1,5-Dibenzyl-1,5,8,8bα-tetrahydro-4,8-bis(4-methoxyphenyl)cyclobuta[1,2-*b*:3,4-*b*′]dipyridine-3,4aα,7,8aβ(4*H*,4bβ*H*)-tetracarboxylate (3b): Isolated as white scales, yield (Method A) 0.06 g (15%), (Method B) 0.15 g (38%), m.p. 143−147°C. − IR: $\tilde{\nu}$ = 1716 cm^{-1}, 1674, 1616. − UV: λ_{max} (lg ε) = 240 nm (4.30), 304 (4.52). − ^{1}H NMR ($CDCl_3$): δ = 0.09 (t, *J* = 7 Hz, 6 H, C4a,C8a−$COOCH_2CH_3$), 1.10 (t, *J* = 7 Hz, 6 H, C3,C7−$COOCH_2CH_3$), 3.59 (q, *J* = 7 Hz, 4 H, C4a,C8a−$COOCH_2CH_3$), 3.69 (s, 6 H, C4′−OCH_3), 3.93 (AMX_3, *J* = 11 Hz, *J* = 7 Hz, 2 H, C3,C7−$COOCH_MCH_3$), 4.05 (AMX_3, *J* = 11 Hz, *J* = 7 Hz, 2 H, C3,C7−$COOCH_ACH_3$), 4.10 (s, 2 H, 4-H, and 8-H), 4.36 (d, *J* = 15 Hz, 2 H, NCH_B), 4.47 (s, 2 H, 4b-H, and 8b-H), 4.65 (d, *J* = 15 Hz, 2 H, NCH_A), 6.51−7.39 (m, 18 H, aromatic H), 7.42 (s, 2 H, 2-H, and 6-H). − ESI MS; *m/z* (%): 865 (7) [M + Na$^+$]. − $C_{50}H_{54}N_2O_{10}$ (842): calcd. C 71.26, H 6.41, N 3.33; found C 71.16, H 6.50, N 3.42.

Tetramethyl 1,5-Dibenzyl-1,5,8,8bα-tetrahydro-4,8-bis(4-methoxyphenyl)cyclobuta[1,2-*b*:3,4-*b*′]dipyridine-3,4aα,7,8aβ(4*H*,4bβ*H*)-tetracarboxylate (3c): Isolated as white crystals, yield (Method A) 0.04 g (11%), (Method B) 0.15 g (37%), m.p. 253−260°C. − IR: $\tilde{\nu}$ = 1710 cm^{-1}, 1689, 1615. − UV: λ_{max} (lg ε) = 243 nm (4.84), 280 (4.83), 302 (4.77). − ^{1}H NMR ($CDCl_3$): δ = 3.13 (s, 6 H, C4a,C8a−$COOCH_3$), 3.43 (s, 6 H, C3,C7−$COOCH_3$), 3.64 (s, 6 H, C4′−OCH_3), 4.01 (s, 2 H, 4-H, and 8-H), 4.34 (s, 2 H, 4b-H, and 8b-H), 4.50 (d, *J* = 15 Hz, 2 H, NCH_B), 4.59 (d, *J* = 15 Hz, 2 H, NCH_A), 6.51−7.44 (m, 18 H, aromatic H), 7.52 (s, 2 H, 2-H, and 6-H). − MS; *m/z* (%): 786 (< 1) [M$^+$]. − $C_{46}H_{46}N_2O_{10}$ (786.9): calcd. C 70.21, H 5.89, N 3.56; found C 70.12, H 5.83, N 3.47.

Tetraethyl 1,5,8,8bα-Tetrahydro-4,8-diphenylcyclobuta[1,2-*b*:3,4-*b*′]-dipyridine-3,4aα,7,8aβ(4*H*,4bβ*H*)-tetracarboxylate (3d): Isolated as white crystals, yield (Method A) 0.04 g (10%), (Method B) 0.11 g (28%), m.p. 235−237°C. − IR: $\tilde{\nu}$ = 3352 cm^{-1}, 1733, 1662, 1628. − UV: λ_{max} (lg ε) = 240 nm (3.37), 280 (4.34). − ^{1}H NMR ($CDCl_3$): δ = 0.81 (t, *J* = 7 Hz, 6 H, C4a,C8a−$COOCH_2CH_3$), 1.08 (t, *J* = 7 Hz, 6 H, C3,C7−$COOCH_2CH_3$), 3.43 (AMX_3, *J* = 11 Hz, *J* = 7 Hz, 2 H, C4a,C8a−$COOCH_MCH_3$), 3.58 (AMX_3, *J* = 11 Hz, *J* = 7 Hz, 2 H, C4a,C8a−$COOCH_ACH_3$), 3.80 (AMX_3, *J* = 11 Hz, *J* = 7 Hz, 2 H, C3,C7−$COOCH_MCH_3$), 3.90 (AMX_3, *J* = 11 Hz, *J* = 7 Hz, 2 H, C3,C7−$COOCH_ACH_3$), 3.95 (s, 2 H, 4-H, 8-H), 4.31 (d, after D_2O addition s, *J* = 3 Hz, 2 H, 4b-H, and 8b-H), 7.01−7.18 (m, 10 H, aromatic H), 7.31 (dd, *J* = 7 Hz, *J* = 3 Hz, 2 H, exchangable, NH), 7.39 (d, after D_2O addition s, *J* = 7 Hz, 2 H, 2-H, and 6-H). − FD MS; *m/z* (%): 602 (100) [M$^+$]. − $C_{34}H_{38}N_2O_8$ (602.7): calcd. C 67.77, H 6.31, N 4.65; found C 67.61, H 6.34, N 4.61.

Tetramethyl 1,5,8,8bα-Tetrahydro-4,8-diphenylcyclobuta[1,2-*b*:3,4-*b*′]-dipyridine-3,4aα,7,8aβ(4*H*,4bβ*H*)-tetracarboxylate (3e): Isolated as white crystals, yield (Method A) 0.03 g (7%), (Method B) 0.17 g (42%), m.p. 310−320°C. − IR: $\tilde{\nu}$ = 3364 cm^{-1}, 1739, 1665, 1626. − ^{1}H NMR ([D$_6$]DMSO): δ = 3.07 (s, 6 H, C4a,C8a−$COOCH_3$), 3.40 (s, 6 H, C3,C7−$COOCH_3$), 3.95 (s, 2 H, 4-H, and 8-H), 4.29 (d, after D_2O addition s, *J* = 2 Hz, 2 H, 4b-H, and 8b-H), 7.01−7.13 (m, 10 H, aromatic H), 7.34 (dd, *J* = 6 Hz, *J* = 2 Hz, 2 H, exchangable, NH), 7.41 (d, after D_2O addition s, *J* = 6 Hz, 2 H, 2-H, and 6-H). − MS; *m/z* (%): 546 (< 1) [M$^+$]. − $C_{30}H_{30}N_2O_8$ (546.6): calcd. C 65.93, H 5.49, N 5.13; found C 65.91, H 5.59, N 5.06.

X-ray Diffraction Analysis of 3e:[15] A colourless prism-shaped crystal of $C_{30}H_{30}N_2O_8$ (from methanol/tetrahydrofuran), crystal size 0.34 × 0.3 × 0.12 mm, was measured at room temp. by using a Siemens P4 diffractometer with Mo-K_α radiation (λ = 0.71073 Å) and a graphite monochromator. 3393 reflexions were collected in ω scanning mode in the range 4.92° ≤ 2θ ≤ 52.0°; *h*, *k*, *l* range from −10, −1, −14 to 1, 15, 14. Crystal system: Monoclinic, space group $P2_1/n$, *Z* = 2, *a* = 9.718(2) Å, *b* = 12.392(1) Å, *c* = 11.106(1) Å, β = 91.75(1)°; *V* = 1336.8(3) Å^3; D_x = 1.353 g cm^{-3}; μ = 0.099 mm^{-1}. The structure was solved by direct methods (SHELXTL 5.03[18]) using 2621 independent reflexions. Structure refinement: Full-matrix least-squares methods on F^2 using SHELXTL 5.03,[18] all the non-hydrogen atoms with anisotropic displacement parameters. All hydrogen atoms were taken from a difference Fourier synthesis and a common isotropic displacement was kept fixed during the refinement. The refinement converged to a final wR^2 = 0.1300 for 2621 unique reflections and R^1 = 0.0597 for 1361 observed reflections [$I_0 > 2\ \sigma(I_0)$] and 227 refined parameters.

Tetraethyl 1,5-Dibenzyl-1,5,8,8bβ-tetrahydro-4,8-diphenylcyclobuta-[1,2-*b*:3,4-*b*′]dipyridine-3,4aβ,7,8aβ(4*H*,4bβ*H*)-tetracarboxylate (4a): Isolated as a white powder, yield 0.14 g (36%), m.p. 138−145°C. − IR: $\tilde{\nu}$ = 1734 cm^{-1}, 1698, 1617. − UV: λ_{max} (lg ε) = 240 nm (4.66), 298 (4.37). − ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 7 Hz, 6 H, C4a,C8a−$COOCH_2CH_3$), 1.15 (t, *J* = 7 Hz, 6 H, C3,C7−$COOCH_2CH_3$), 3.58 (AMX_3, *J* = 11 Hz, *J* = 7 Hz, 2 H, C4a,C8a−$COOCH_MCH_3$), 3.63 (AMX_3, *J* = 11 Hz, *J* = 7 Hz, 2 H, C4a,C8a−$COOCH_ACH_3$), 3.99 (AMX_3, *J* = 11 Hz, *J* = 7 Hz, 2 H, C3,C7−$COOCH_MCH_3$), 4.05 (s, 2 H, 4-H, and 8-H), 4.06 (AMX_3, *J* = 11 Hz, *J* = 7 Hz, 2 H, C3,C7−$COOCH_ACH_3$), 4.46 (s, 2 H, 4b-H, and 8b-H), 4.59 (d, *J* = 15 Hz, 2 H, NCH_B), 4.71 (d, *J* = 15 Hz, 2 H, NCH_A), 6.88−7.40 (m, 20 H, aromatic H), 7.61 (s, 2 H, 2-H, and 6-H). − MS; *m/z* (%): 782 (< 1) [M$^+$]. − $C_{48}H_{50}N_2O_8$ (782): calcd. C 73.64, H 6.44, N 3.58; found C 73.34, H 6.41, N 3.43.

Tetraethyl 1,5-Dibenzyl-1,5,8,8bβ-tetrahydro-4,8-bis(4-methoxyphenyl)-cyclobuta[1,2-*b*:3,4-*b*′]dipyridine-3,4aβ,7,8aβ(4*H*,4bβ*H*)-tetracarboxylate (4b): Isolated as white prisms, yield 0.14 g (35%), m.p. 191−194°C (ref.[1] 195−197°C).

Tetramethyl 1,5-Dibenzyl-1,5,8,8bβ-tetrahydro-4,8-bis(4-methoxyphenyl)cyclobuta[1,2-*b*:3,4-*b*′]dipyridine-3,4aβ,7,8aβ(4*H*,4bβ*H*)-tetracarboxylate (4c): Isolated as white needles, yield 0.13 g (33%), m.p. 212−223°C. − IR: $\tilde{\nu}$ = 1737 cm^{-1}, 1680, 1627. − UV: λ_{max} (lg ε) = 240 nm (4.30), 284 (4.37). − ^1H NMR ([D_6]DMSO): δ = 3.07 (s, 6 H, C4a,C8a−$COOCH_3$), 3.43 (s, 6 H, C3,C7−$COOCH_3$), 3.66 (s, 6 H, C4′−OCH_3), 3.79 (s, 2 H, 4-H, and 8-H), 4.15 (s, 2 H, 4b-H, and 8b-H), 4.48 (d, *J* = 15 Hz, 2 H, NCH_B), 4.87 (d, *J* = 15 Hz, 2 H, NCH_A), 6.60−7.43 (m, 18 H, aromatic H), 7.79 (s, 2 H, 2-H and, 6-H). − MS; *m*/*z* (%): 786 (< 1) [M^+]. − $C_{46}H_{46}N_2O_{10}$ (786.9): calcd. C 70.21, H 5.89, N 3.56; found C 69.91, H 5.79, N 3.47.

Tetraethyl 1,5,8,8bβ-Tetrahydro-4,8-diphenylcyclobuta[1,2-*b*:3,4-*b*′]-dipyridine-3,4aβ,7,8aβ(4*H*,4bβ*H*)-tetracarboxylate (4d): Isolated as white needles, yield 0.15 g (38%), m.p. 157−163°C. − IR: $\tilde{\nu}$ = 3332 cm^{-1}, 1734, 1661, 1630. − UV: λ_{max} (lg ε) = 242 nm (4.18), 272 (4.55). − ^1H NMR ($CDCl_3$): δ = 0.84 (t, *J* = 7 Hz, 6 H, C4a,C8a−$COOCH_2CH_3$), 1.08 (t, *J* = 7 Hz, 6 H, C3,C7−$COOCH_2CH_3$), 3.52 (AMX_3, *J* = 11 Hz, *J* = 7 Hz, 2 H, C4a,C8a−$COOCH_MCH_3$), 3.63 (AMX_3, *J* = 11 Hz, *J* = 7 Hz, 2 H, C4a,C8a−$COOCH_ACH_3$), 3.82 (AMX_3, *J* = 11 Hz, *J* = 7 Hz, 2 H, C3,C7−$COOCH_MCH_3$), 3.91 (s, 2 H, 4-, 8-H), 3.99 (AMX_3, *J* = 11 Hz, *J* = 7 Hz, 2 H, C3,C7−$COOCH_ACH_3$), 4.48 (s, 2 H, 4b-H, and 8b-H), 6.95−7.11 (m, 10 H, aromatic H), 7.25 (d, *J* = 7 Hz, after D_2O addition s, 2 H, 2-H, and 6-H), 7.69 (d, *J* = 7 Hz, 2 H, exchangable, NH). − MS; *m*/*z* (%): 602 (1) [M^+]. − $C_{34}H_{38}N_2O_8$ (602.7): calcd. C 67.77, H 6.31, N 4.65; found C 67.47, H 6.45, N 4.64.

Tetramethyl 1,5,8,8bβ-Tetrahydro-4,8-diphenylcyclobuta[1,2-*b*:3,4-*b*′]-dipyridine-3,4aß,7,8aβ(4*H*,4bβ*H*)-tetracarboxylate (4e): Isolated as a white powder, yield 0.19 g (48%), m.p. 234−237°C (ref.[1] 238−240°C).

Acknowledgments

The authors are grateful for the support of their work by the German Pharmaceutical Society (DPhG) and the Fonds der Chemischen Industrie.

[1] A. Hilgeroth, U. Baumeister, F. W. Heinemann, *Eur. J. Org. Chem.* **1998**, 1213−1218.
[2] R. Zöllner, A. Hilgeroth, *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, Suppl. 1, 31.
[3] A. Hilgeroth, R. Fleischer, M. Wiese, F. W. Heinemann, *J. Comput. Aid. Mol. Des.* **1999**, *13*, 233−242.
[4] T. Chennat, U. Eisner, *J. Chem. Soc., Perkin Trans. 1* **1975**, *10*, 926−929.
[5] V. K. Lusis, G. Y. Dubur, *Khim. Geterotsikl. Soedin.* **1982**, *8*, 1068−1071.
[6] Although the structure of **2b** was found identical to that of the recently presented solid-state dimerization product it has to be discussed here, because the former molecular structure has merely been used as starting geometry for moleclar modeling but not been discussed concerning its molecular properties, e. g. bond lengths.
[7] U. Eisner, J. R. Williams, B. W. Matthews, H. Ziffer, *Tetrahedron* **1970**, *26*, 899- 909.
[8] W. M. Bright, D. A. Langs, J. V. Silverton, H. Ziffer, U. Eisner, *Cryst. Struct. Commun.* **1974**, *3*, 1−4.
[9] A. Hilgeroth, K. Kuna, U. Kuckländer, *Heterocycles* **1998**, *48*, 1649−1658.
[10] J. J. Baldwin, D. A. Claremon, P. K. Lumma, D. E. McClure, S. A. Rosenthal, J. R. Winquist, E. P. Faison, G. J. Kaczorowski, M. J. Trumble, G. M. Smith, *J. Med. Chem.* **1987**, *30*, 690−695.
[11] R. A. Janis, D. J. Triggle, *J. Med. Chem.* **1983**, *26*, 775−785.
[12] A. Hilgeroth, Dissertation, Heinrich-Heine-Universität Düsseldorf, **1994**, p. 101−104.
[13] Alternatively to the dimers **2**, **3** and **4** with *head-to-tail* conjunction of the monomeric 4-aryl-1,4-dihydropyridines, the formation of the corresponding *head-to-head*-connected derivatives seems unlikely, at least for the possible *syn* dimers, due to steric hindrance of both ester groups at one cyclobutane bond.
[14] G. Adembri, D. Donati, St. Fusi, F. Ponticelli, *Heterocycles* **1985**, *23*, 2885−2889.
[15] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100853. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
[16] G. M. Sheldrick, *SHELXS-97*, Universität Göttingen, **1997**.
[17] G. M. Sheldrick, *SHELXL-97*, Universität Göttingen, **1997**.
[18] *SHELXTL 5.03 for Siemens Crystallographic Research Systems*, Siemens Analytical X-ray Instr., Madison, Wisconsin, U.S.A., **1995**.

Received June 2, 1999
[O99316]