HETEROCYCLES, Vol. 57, No. 6, 2002, pp. 1003 - 1016, Received, 10th December, 2001

FIRST ROTAMERIC *ANTI* DIMERS AND 3,9-DIAZATETRAASTERANES FROM UNSYMMETRICALLY SUBSTITUTED *N*-ACYL- AND *N*-ACYLOXY-4-ARYL-1,4-DIHYDROPYRIDINES

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

[a]Institute of Pharmaceutical Chemistry, Department of Pharmacy, Martin-Luther-University Halle-Wittenberg, Wolfgang-Langenbeck-Str. 4, 06120 Halle, Germany, [b]Institute of Inorganic Chemistry II, Friedrich-Alexander-University, 91058 Erlangen, Germany, [c]Institute of Physical Chemistry, Martin-Luther-University, Mühlpforte 1, 06108 Halle, Germany

Abstract - A series of unsymmetrically substituted *N*-acyl- and *N*-acyloxy-1,4-dihydropyridines (**1**) have been photochemically investigated. On irradiating the crystals of one derivative (**1a**) containing centrosymmetrical pairs of molecules with a distance of 3.894(3) Å between the potentially reacting double bonds favorable for a photodimerisation reaction, the formation of an *anti*-dimer (**2a**) was observed. Two other solid derivatives (**1b**, **c**) merely decomposed on irradiation to give substituted pyridine compound (**3**). Solution irradiation of 1,4-dihydropyridines (**1**) led to the centrosymmetric cage compounds 3,9-diazatetraasteranes (**4**) and to *anti* dimers (**2**) as main products, both existing as rotamers. Symmetric as well as rotameric properties of selected compounds (**4**) have been demonstrated by X-Ray crystal structure analysis and ^{1}H NMR spectroscopy.

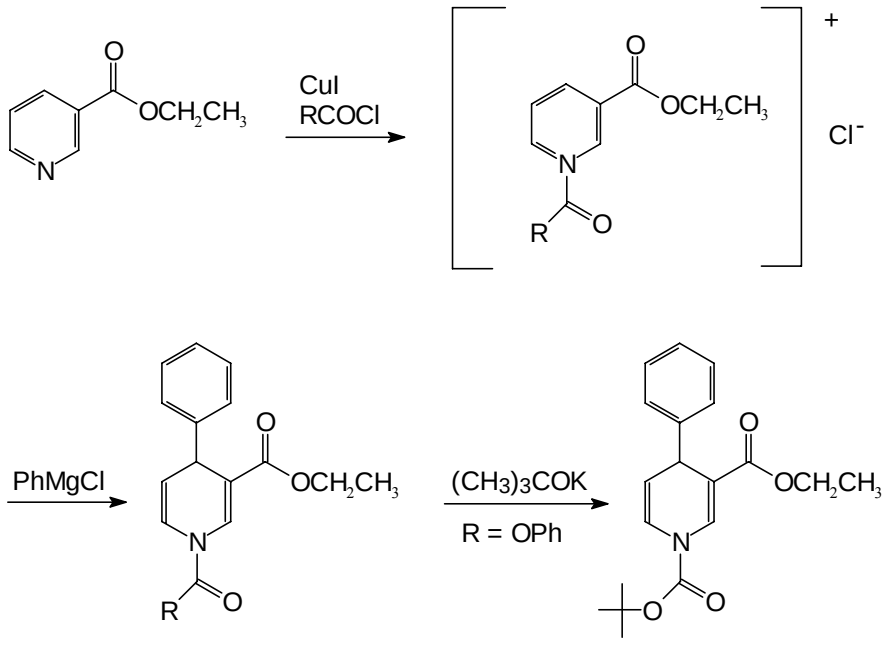
There are only very few literature reports on photochemical properties of *N*-substituted *4H*-1,4-dihydropyridines without substituents in 2- and 6-position describing pyridine oxidation products under splitting-off of the *N*-substitutent.[1] The introduction of an 4-aryl substituent was shown to stabilize the dihydropyridine ring systems towards photooxidation leading to dimeric products of *N*-substituted as well as *N*H derivatives *via* [2+2] cycloaddition reaction in the crystalline state.[2,3] Dimerizations were

controlled by the shortest distance of potentially reacting double bonds leading to either cage or *anti*-dimers as exclusive products.[3] However, these investigations have been restricted so far to symmetrically substituted derivatives, i. e. compounds with 3- and 5-carbonyl substituents. As photochemically derived cage dimeric 4-aryl-1,4-dihydropyridines with various *N*-acyl substituents have been found to be novel HIV-1 protease inhibitors,[4] we have been interested in synthetic variations of the *N*-aycl-1,4-dihydropyridine starting structure with just one carbonyl substituent in the 3-position of the dihydropyridine ring. In the following we report the photochemical reactivity of a series of *N*-acyl- and *N*-acyloxy 4-phenyl-1,4-dihydropyridines in the crystalline state as well as in solution. Solution irradiation leads to the uniform formation of both, centrosymmetrical cage compounds and *anti* dimers, besides small amounts of a photooxidized pyridine. The symmetrical constitution of the products is shown by X-Ray crystal structure analyses. Rotameric properties are demonstrated by ^{1}H NMR spectroscopy.

Results and Discussion

Starting Compounds. The 4-phenyl-1,4-dihydropyridines (**1b-c**) have been prepared by primary acylation of nicotinic acid and consequent regioselective 4-arylation of the pyridinium ring using catlytic amounts of CuI with overall yields of about 80%.[5] The *N*-Boc derivative (**1d**) was given by treatment of the crude reaction mixture of **1c** with potassium tert. butoxide.

Scheme 1

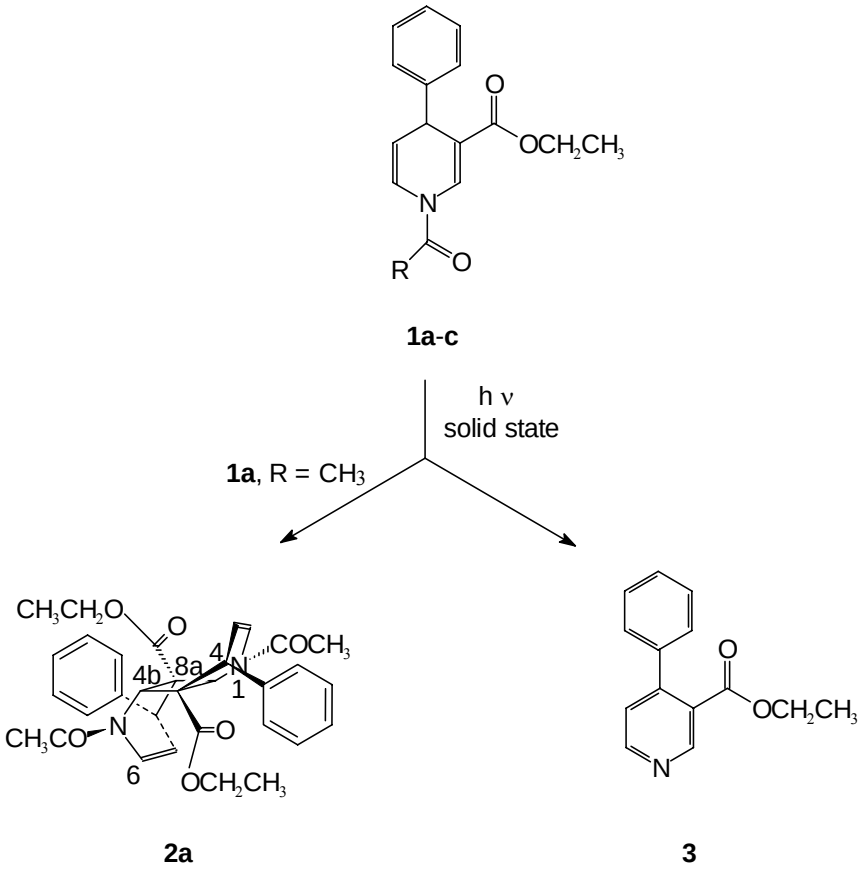


1b, R = OCH_3
1c, R = OPh

1d

Solid State Photoreactivity. On irradiation at $\lambda > 270$ nm, the crystalline compound 1-acetyl-4-phenyl-1,4-dihydropyridine (**1a**)[5] with $\lambda_{max} = 304$ nm for the dihydropyridine chromophore exclusively yielded one dimeric reaction product. Although just one ester carbonly band was found in the IR spectrum at 1724 cm^{-1} proving a symmetric molecular structure, the ^1H NMR spectrum of the recrystallized compound showed a multiplicity of signals that will be shown to result from the formation of different *N*-acyl rotamers of a common *anti* dimeric scaffold (**2a**).

Scheme 2



X-Ray crystal structure analysis proved one of these *anti* dimeric rotamers to have a centrosymmetrical molecular structure with differing bond lengths within the cyclobutane ring. The bonds belonging to the 1,4-dihydropyridine component (C1-C2 and C1′-C2′, respectively) were found to be shorter with 1.560(3) Å compared to those formed by the dimerization with 1.584(3) Å (C1-C2′ and C2-C1′, respectively). Phenyl substituents show pseudoaxial orientation towards the dihydropyridine ring plane.

On irradiation of two other solid 1,4-dihydropyridines (**1b**) and (**1c**) as well as the oily derivative (**1d**), decomposition was observed by TLC. Finally, the semi-solid product was proved to consist of mainly the

pyridine oxidation product ethyl 4-phenylnicotinate (**3**) (Scheme 2) .

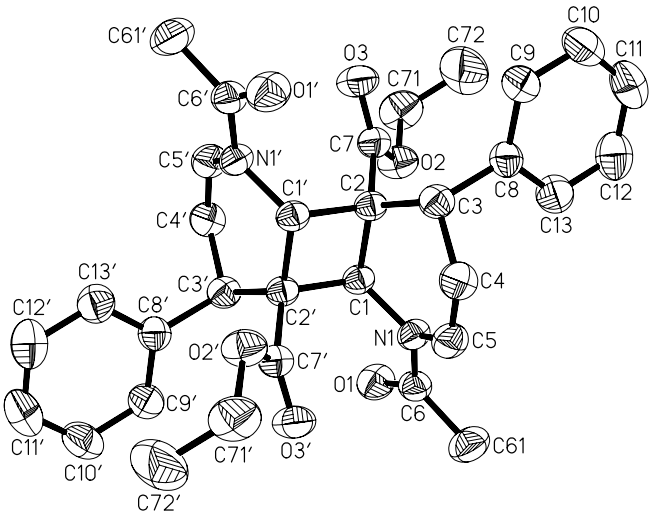


Figure 1. ORTEP drawing of *anti* dimer (**2a**) (Displacement ellipsoids at 50% probability level).

Topochemistry. Topochemically, the *anti* dimer formation in the solid state can be explained considering special packing features of the reactant molecules in the crystal. The results of an X-Ray crystal structure analysis of the reacting *N*-acetyl-1,4-dihydropyridine (**1a**)[5] show, that the molecules are arranged in one-dimensional stacks along [010].

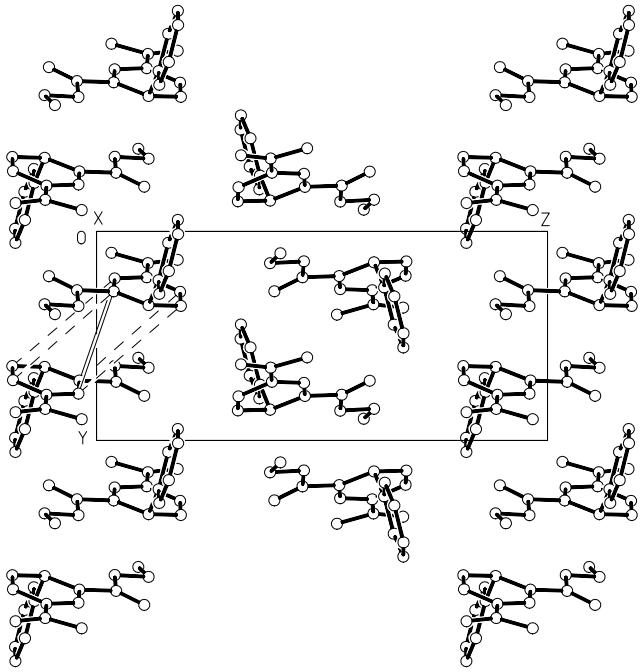
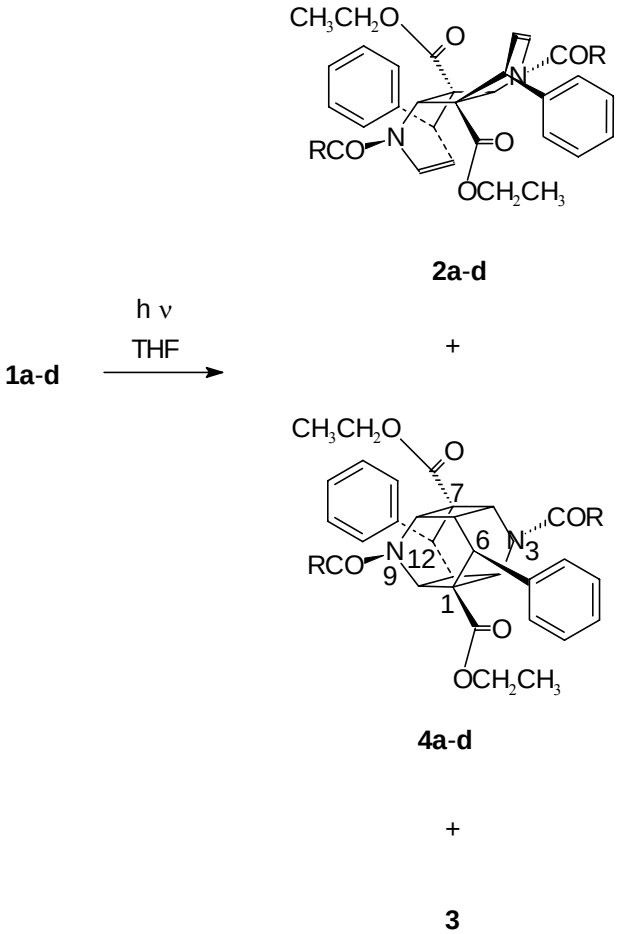


Figure 2. Packing scheme of the molecular structure of **1a** (projection along [100] with distances of potentially reacting double bonds).

Neighbouring stacks exhibit antiparallel molecular orientation due to their centrosymmetrical arrangement. The shortest distance of 3.894(3) Å between potentially reacting double bonds of such neighbouring molecules suggest an *anti* dimer formation on irradiation, as this distance makes less than the previously reported limiting distance of 4.2 Å for potentially reacting double bonds in the solid state.[6-8] An alternative *syn* dimer formation with distances of 4.836(3) Å between C2 and C5′ (and the centrosymmetric equivalent) and 4.852(3) Å between C1 and C4′(and the centrosymmetric equivalent) was unlikely as these distances exceed the reported limit of 4.2 Å and lie within the order of magnitude for non-reacting double bonds.[6-8] Thus, dimerization was proved to be topochemically controlled by the shortest distance of potentially reacting double bonds.

Solution Photoreactivity. Solution irradiation of the 1,4-dihydropyridine derivatives (**1a-d**) led to precipitation of crystalline products (Scheme 3).

Scheme 3



They were spectroscopically characterized as dimers with the cage structure of 3,9-diazateraasteranes (**4a-d**) by one IR ester carbonyl band. A triple set of proton signals was dedicated to three rotamers (**A-**

C), two with centrosymmetric structures (**A**, **B**) and one with a nonsymmetric structure (**C**) as shown in Figure **3** for the *N*-acetyl cage dimer (**4a**).

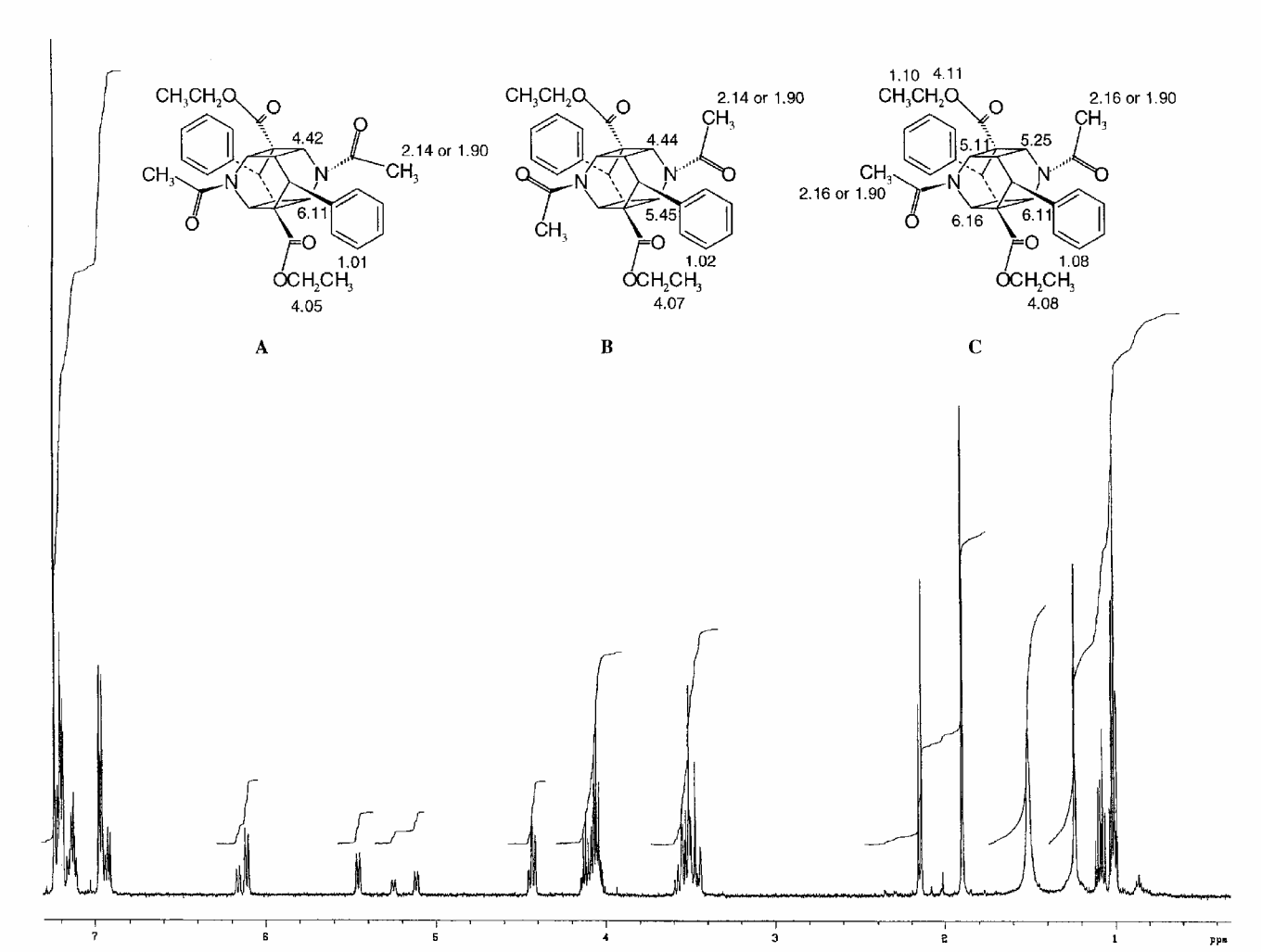


Figure 3. ^{1}H NMR spectrum of diethyl 3,9-diacetyl-6,12-diphenyl-3,9-diazahexacyclo[6.4.0.0$^{2.7}$.0$^{4.11}$.0$^{5.10}$]dodecane-1,7-dicarboxylate (**4a**) in $CDCl_3$ (500 MHz) with differing chemical shifts attached to the three rotamers **A**-**C** as discussed in the text.

The rotameric character of the dimers was demonstrated by ^{1}H NMR spectra of the *N*-phenoxycarbonyl derivative (**4c**) measured at rising temperatures in $CDCl_3$. At 50 °C corresponding signals of the rotamers show coaleszenz with resonances of equivalent protons for 5-H, 11-H at 3.70 ppm as splitted triplet, 6-H, 12-H at 3.80 as splitted singlet and 4-H, 10-H at 4.96 ppm as dublet coupling with 5-H and 11-H, respectively.[9]

The centrosymmetric character of one rotamer B was additionally demonstrated by X-Ray crystal structure analysis of the *N*-Boc compound (**4d**).[10] Besides 3,9-diazatetraasterane cage compounds (**4a-d**) *anti* dimers (**2a-d**) were yielded from the reaction mixture.

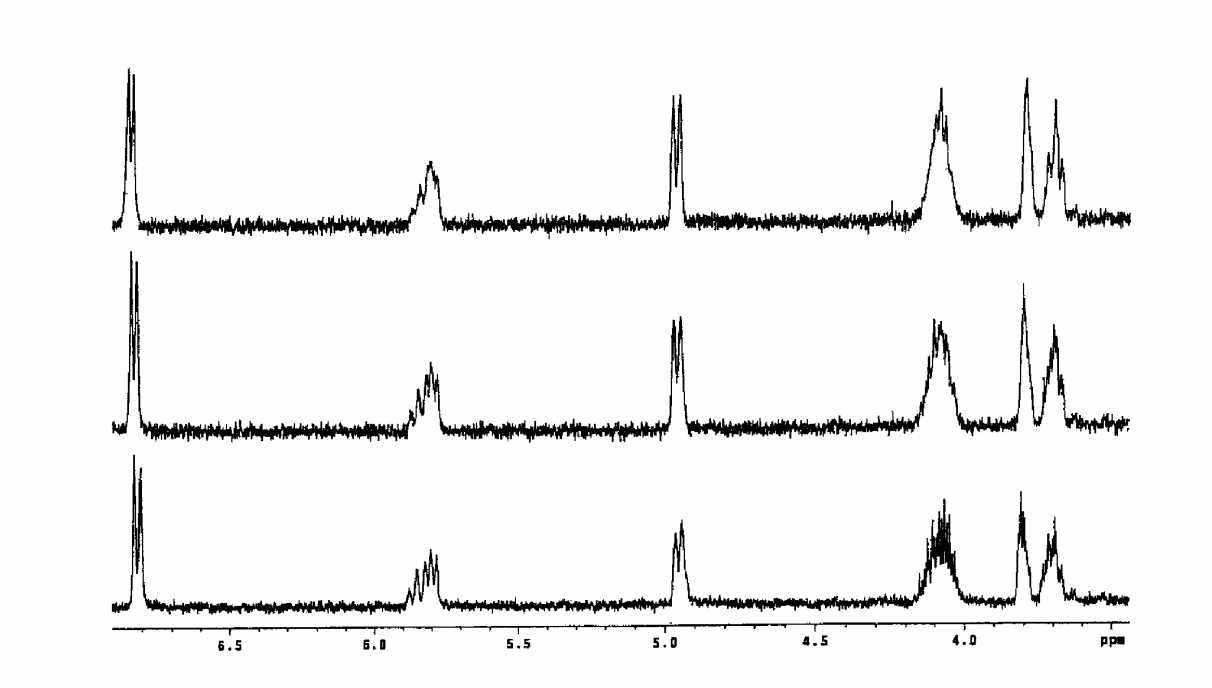


Figure 4. ^{1}H NMR spectrum of diethyl 6,12-diphenyl-3,9-diphenoxycarbonyl-3,9-diazahexacyclo[6.4.0.0$^{2.7}$.0$^{4.11}$.0$^{5.10}$]dodecane-1,7-dicarboxylate (**4c**) in $CDCl_3$ (400 MHz) measured at 50 °C (above), 40 °C (in the middle) and 27 °C (below).

Analysing the identical ^{1}H NMR spectra of **2a** derived from the solid state reaction after recrystallization and from solution reaction, the existance of all possible rotamers was shown by the triple set of proton signals corresponding to three rotamers (**A**–**C**) (see **EXPERIMENTAL**).

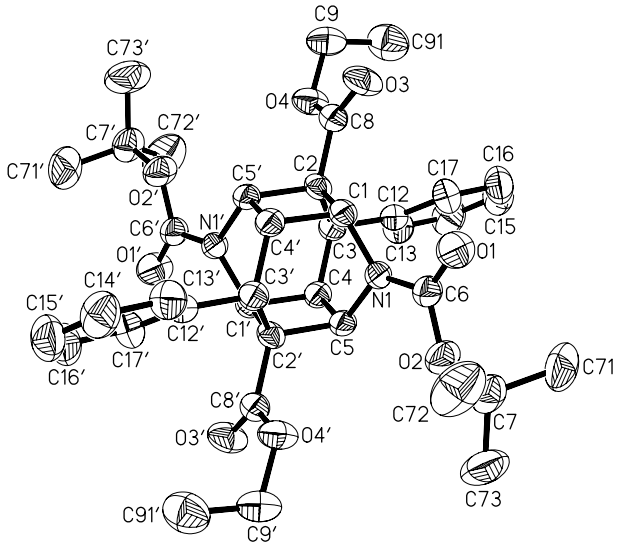


Figure 5. ORTEP drawing of diethyl 3,9-di-*tert*-butoxycarbonyl-6,12-diphenyl-3,9-diazahexacyclo[6.4.0.0$^{2.7}$.0$^{4.11}$.0$^{5.10}$]dodecane-1,7-dicarboxylate (**4d**) (Displacement ellipsoids at 50% probability level)

Finally, ethyl 4-phenylnicotinate (**3**) was characterized as the third reaction product in comparably poor yields of about 16%.

Formally, the *anti* dimer formation takes place between equivalent, i. e. the substituted sites of the 1,4-dihydropyridine molecule. The reported solid state dimerization reactions of 3,5-disubstituted derivatives have been reactions of equivalent double bonds with *head-to-tail* orientation of the reacting molecules and their dimerization products, respectively.[2,3] Thus, the observed *anti* dimer formation with the resulting *head-to-tail* orientation from the 3-substituted 1,4-dihydropyridines (**1a-d**) may presumably follow the classical [2+2] cycloaddition reaction mechanism. The formation of the 3,9-diazatetraasteranes results from the reaction of both differently substituted sites of the dihydropyridine monomer presumably *via* a *syn* dimeric intermediate as has been demonstrated for the 3,5-disubstituted derivatives.[2]

In summary, irradiation of solutions of only 3-substituted *N*-acyl- and *N*-acyloxy 4-aryl-1,4-dihydropyridines (**1a-d**) leads to the formation of both the *anti* dimers and the cage dimers 3,9–diazatetraasteranes as main reaction products besides small amounts of a pyridine oxidation product. Solid state synthesis was demonstrated to be the more attractive route to the *anti* dimer (**2a**) because of the almost quantitative yield and a uniform dimer formation. However, it is restricted to monomers with favorable crystal packing for a topochemically controlled reaction of equivalent double bonds. Otherwise, photooxidation takes place as competing reaction pathway. Both dimers, the *anti* dimers and the cage dimers show C_2 symmetric properties, thus qualifying the dimers as potential inhibitors of C_2 symmetric HIV-1 protease.

EXPERIMENTAL

Melting points were measured with a boetius apparatus and are uncorrected. IR spectra were recorded from KBr disks using a Bruker IFS-28 spectrophotometer. ^{1}H NMR spectra were measured with a Varian Gemini-400 and Varian Gemini-500 and TMS as an internal standard at 27 °C. MS was taken with an AMD 402 spectrometer. Preparative TLC was carried out with silica gel plates 60_{F254} with a layer thickness of 1 mm. Elemental analytical data were obtained with a LECO apparatus.

General Procedure for the Synthesis of *N*-Acyloxy 4-Phenyl-1,4-dihydropyridines: 1.0 g (6.62 mmol) of ethyl nicotinate were solved in anhydrous THF (30 mL). After addition of 0.06 g of CuI (0.3 3 mmol) the solution was cooled down to -8 °C. Then 6.62 mmol of the acyloxy chlorides was added dropwise to the solution over a period of 10 min. The reaction mixture was stirred for 10 min. Then a 1 M solution of phenylmagnesium chloride (6.6 mL, 6.6 mmol) was added dropwise. Stirring was contiued for 30 min at rt. Then 20% aqueous NH_4Cl (36 mL) were added, followed by the extraction with ether (3 x 150 mL). The ether phase was washed with each 40 mL of 20% mixture (1/1) of NH_3/ NH_4Cl, water, 10% HCl (2 x), water and saturated aqueous NaCl and then was dried (Na_2SO_4). After filtration ether was removed under vacuum leaving yellow powders of **1b** and **1c**.

Ethyl 1-Methoxycarbonyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (1b): Yield: 1.4 g (75%); mp 83-87 °C (ether); IR ν 1736, 1702, 1621 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (t, J = 7.1 Hz, 3 H, $COOCH_2C\underline{H}_3$), 3.92 (s, 3 H, $NCOOCH_3$), 4.10 (q, J = 7.1 Hz, 2 H, $COOC\underline{H}_2CH_3$), 4.46 (dd, J_1 = 4.4 Hz, J_2 = 0.9 Hz, 1 H, 4-H), 5,19 (dd, J_1 = 8.0 Hz, J_2 = 4.4 Hz, 1 H, 5-H), 6.86-6.89 (br s, 1 H, 6-H), 7.16-7.34 (m, 5 H, aromatic H), 8.06 (br s, 1 H, 2-H); UV ($CDCl_3$) λ_{max} (log ε) 298 (3.30), 242 (3.58); EI-MS *m/z* 287 (M^+). Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.57; H, 5.99; N, 4.82.

Ethyl 1-Phenyl-4-phenoxycarbonyl-1,4-dihydropyridine-3-carboxylate (1c): Yield: 1.9 g (83%); mp 94-97 °C (ether); IR ν 1734, 1697, 1622 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (t, J = 7.1 Hz, 3 H, $COOCH_2C\underline{H}_3$), 4.06 (dq, J_1 = 11 Hz, J_2 = 7.1 Hz, 1 H, $COOC\underline{H}_BCH_3$), 4.11 (dq, J_1 = 11 Hz, J_2 = 7.1 Hz, 1 H, $COOC\underline{H}_ACH_3$), 4.51 (d, J = 4.4 Hz, 1 H, 4-H), 5.26 (br s, 1 H, 5-H), 6.99 (d, J = 7.8 Hz, 1 H, 6-H), 7.19-7.43 (m, 10 H, aromatic H), 8.13 (s, 1 H, 2-H); UV ($CDCl_3$) λ_{max} (lg ε) 296 (3.48), 242 (3.91); CI-MS *m/z* 367 ($M + NH_4^+$). Anal. Calcd for $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.13; H, 5.43; N, 3.88.

Preparation of Ethyl 1-*tert*-Butoxycarbonyl-4-phenyl-1,4-dihydropyridine-3-carboxylate (1d): A solution of 1.5 g of potassium *tert*-butoxide (13.3 mmol) in anhydrous THF (30 mL) was added dropwise to a solution of 2.3 g of **1c** (6.7 mmol) in anhydrous THF (15 mL) at -18 °C. The mixture was stirred for 30 min at the low temperature and for additional 10 min at rt. Then water (15 mL) was added and the solution extracted with ether (2 x 40 mL). The ether phase was washed with 1 N NaOH (2 x 20 mL), water (2 x 20 mL) and saturated aqueous NaCl and finally dried over Na_2SO_4. Then ether was removed in vacuum leaving 1.5 g (69%) of **1d** as yellow oil which was purified by SC using toluene/methanol (85/15) as solvents. IR ($CDCl_3$) ν 1732, 1711, 1623 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (t, J = 7.1 Hz, 3 H, $COOCH_2C\underline{H}_3$), 1.55 (br s, 9 H, $NCOOC(CH_3)_3$), 4.02 (dq, J_1 = 10.7 Hz, J_2 = 7.1 Hz, 1 H, $COOC\underline{H}_BCH_3$), 4.08 (dq, J_1 = 10.7 Hz, J_2 = 7.1 Hz, 1 H, $COOC\underline{H}_ACH_3$), 4.44 (d, J = 4.4 Hz, 1 H, 4-H), 5,10 (br s, 1 H, 5-H), 6.81 (br s, 1 H, 6-H), 7.13-7.48 (m, 5 H, aromatic H), 8.04 (br s, 1 H, 2-H); UV ($CDCl_3$) λ_{max} (log ε) 300 (3.66), 252 (3.89); EI-MS *m/z* 329 (M^+). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 68.87; H, 6.97; N, 4.17.

Procedure for the Formation of *anti* Dimer (2a) and Ethyl 4-Phenyl-nicotonate (3) by Solid-state Irradiation: 3 Mmol of *N*-acetyl- and *N*-acyloxy 4-phenyl-1,4-dihydropyridines (**1a-d**) with a layer thickness of 1 mm were placed under an Ultra Vitalux® lamp which produces the spectrum of sunlight. Irradiation within a distance of 40 cm was carried out at 40 °C for 4 weeks. Then the mixtures were solved in boiling ethanol. The *anti* dimer (**2a**) recrystallized from the solution in white prisms. Ethanolic solutions of the other mixtures were evaporated in vaccuum leaving brownish oils which were separated by preparative TLC in toluene/methanol (85/15) using silica gel plates 60_{F254}. The main fraction

with R_f= 0.6 was worked up by washing the silica gel with acetone, which was removed in vaccum leaving an oil of ethly 4-phenylnicotinate (**3**).

Diethyl 1,5-Diacetyl-1,5,8,8bα-tetrahydro-4,8-diphenylcyclobuta[1,2-*b*:3,5-*b*´]dipyridine-4a,8aβ-(4H, 4bβH)-dicarboxylate (2a): Yield: 1.3 mmol (89%, refered to 0.81 g of **1a** as 100%); mp 275-290 °C; IR ν 1724, 1679, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (t, J = 7.0 Hz, 6 H, $COOCH_2C\underline{H}_3$, **B**), 0.83 (t, J = 7.2 Hz, 6 H, $COOCH_2C\underline{H}_3$, **A**), 0.97 (t, J = 7.2 Hz, 3 H, C4a-$COOCH_2C\underline{H}_3$, **C**), 0.90 (t, J = 7.4 Hz, 3 H, C8a- $COOCH_2C\underline{H}_3$, **C**), 2.21 (s, 9 H, *N*$COCH_3$, **A** o. **B**, 1 x **C**), 2.26 (s, 9 H, *N*$COCH_3$, **A** o. **B**, 1 x **C**), 3.53 (dq, J_1 = 10.8 Hz, J_2 = 7.2 Hz, 4 H, $COOC\underline{H}_BCH_3$, **A, B**), 3.65 (dq, J_1 = 10.8 Hz, J_2 = 7.2 Hz, 4 H, $COOC\underline{H}_ACH_3$, **A**, **B**), 3.76 (dq, J_1 = 10.8 Hz, J_2 = 7.2 Hz, 2 H, $COOC\underline{H}_BCH_3$, **C**), 3.82 (dq, J_1 = 10.8 Hz, J_2 = 7.2 Hz, 2 H, $COOC\underline{H}_ACH_3$, **C**), 3.92 (dd, J_1 = 4.2 Hz, J_2 = 2.1 Hz, 1 H, 8-H, **C**), 4.19 (d, J = 4.9 Hz, 2 H, 4-, 8-H, **B**), 4.22 (d, J = 4.9 Hz, 2 H, 4-, 8-H, **A**), 4.31 (d, J = 6.8 Hz, 1 H, 4-H, **C**), 5.04 (dd, J_1 = 8.4 Hz, J_2 = 4.2 Hz, 1 H, 7-H, **C**), 5.22 (s, 1 H, 4b-H, **C**), 5.36 (dd, J_1 = 8.4 Hz, J_2 = 4.9 Hz, 4 H, 3-, 7-H, **A**, **B**), 5.67 (s, 2 H, 8b-H, **B**), 5.67 (dd, J_1 = 8.4 Hz, J_2 = 6.8 Hz, 1 H, 3-H, **C**), 5.75 (s, 3 H, 4b-, 8b-H, **A**, 8b-H, **C**), 6.58 (d, J = 8.4 Hz, 3 H, 2-, 6-H, **A**, 2-H, **C**), 6.62 (dd, J_1 = 8.4 Hz, J_2 = 2.1 Hz, 1 H, 6-H, **C**), 6.99 (d, J = 8.4 Hz, 2 H, 2-, 6-H, **B**), 7.01-7.22 (m, 30 H, aromatic H, **A**-**C**); CI-MS *m/z* 560 ($M + NH_4^+$). Anal. Calcd for $C_{32}H_{34}N_2O_6$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.63; H, 6.35; N, 4.93.

X-Ray Diffraction Analysis of **2a**: A white prism $C_{32}H_{34}N_2O_6$ (from ethanol), crystal size 0.19 x 0.15 x 0.11 mm, was measured at a temperature of 293(2) K by using a Stoe-IPDS Diffractometer with Mo-K_α radiation (λ = 0.71073 Å) and a graphite monochromator. 13363 Reflexions were collected in the range $5.08° \leq 2\Theta \leq 50°$; *h,k,l* range from -13, -17, -14 to 13, 17, 14. Crystal system: Monoclinic, space group $P2_1/c$, Z = 2, a = 10.355(2) Å, b = 13.579(3) Å, c = 11.036(2) Å, β = 115.80(3)°; V = 1397.1(5) $Å^3$; D_x = 1.290 g cm^{-3}; μ = 0.089 mm^{-1}. The structure was solved by direct methods (SHELXS-86[11]) using 2463 independent reflections. Structure refinement: Full matrix least-squares methods on F^2 using SHELXL-93[12] all the non-hydrogen atoms with anisotropic displacement parameters. All hydrogen atoms were taken from a difference fourier synthesis and isotropically refined. The refinement converged to a final wR_2 = 0.1116 for 2463 unique reflections and R_1 = 0.0431 for 2446 observed reflections [$I_0 > 2.0\sigma(I_0)$] and 250 refined parameters.

Ethyl 4-Phenylnicotinate (3): Yield: 0.47 g (70%) from **1b**, 0.44 g (65%) from **1c** and 0.54 g (80%) from **1d**; mp (picrate) 125-126 °C (lit.,[5] 126-129 °C).

General Procedure for the Formation of *anti* Dimers (2a-d) and Cage Dimers (4a-d): 1.5 Mmol of *N*-acetyl- and *N*-acyloxy 4-phenyl-1,4-dihydropyridines (**1a-d**) were solved in a quarz flask in anhydrous THF (30 mL). The solution was placed under an Ultra Vitalux® lamp with a distance of 40 cm. Irradiation was carried out for 4 weeks at a temperature of 40 °C. During the irradiation the cage compounds

(**4a-d**) precipitated from the solution and were finally filtered off from the solution. After reduction of the solution volume the *anti* dimers (**2a-d**) crystallized and were filtered off. The mother liquid was then worked up by evaporation under vaccum leaving yellow oils that were separated by TLC as described above leading to the isolation of ethyl 4-phenylnicotinate (**3**).

Diethyl 1,5-Diacetyl-1,5,8,8bα-tetrahydro-4,8-diphenylcyclobuta[1,2-*b*:3,5-*b´*]dipyridine-4a,8aβ(4H, 4bβH)-dicarboxylate (2a): Yield: 0.23 mmol (30%, refered to 0.41 g of **1a** as 100%); mp 280-295 °C (methanol).

Diethyl 1,5,8,8bα-Tetrahydro-1,5-dimethoxycarbonyl-4,8-diphenylcyclobuta[1,2-*b*:3,5-*b´*]dipyridine-4a,8aβ(4H,4bβH)-dicarboxylate (2b): Yield: 34% (refered to 0.43 g of **1b** as 100%); mp > 350°C (methanol); IR ν 1732, 1716, 1654 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, *J* = 7.0 Hz, 3 H, $COOCH_2C\underline{H}_3$, **C**), 0.86 (t, *J* = 7.1 Hz, 6 H, $COOCH_2C\underline{H}_3$, **B**), 0.92 (t, *J* = 7.1 Hz, 6 H, $COOCH_2C\underline{H}_3$, **A**), 0.96 (t, *J* = 7.1 Hz, 3 H, $COOCH_2C\underline{H}_3$, **C**), 3.47 (dq, J_1 = 12.0 Hz, J_2 = 7.1 Hz, 2 H, $COOC\underline{H}_BCH_3$, **A** o. **B**), 3.50 (dq, J_1 = 10.7 Hz, J_2 = 7.1 Hz, 2 H, $COOC\underline{H}_BCH_3$, **A** o. **B**), 3.54 (dq, J_1 = 10.7 Hz, J_2 = 7.1 Hz, 2 H, $COOC\underline{H}_ACH_3$, **A** o. **B**), 3.58 (dq, J_1 = 12.0 Hz, J_2 = 7.1 Hz, 2 H, $COOC\underline{H}_ACH_3$, **A** o. **B**), 3.70-3.83 (m, 4 H, $COOC\underline{H}_2CH_3$, **C**), 3.76 (s, 6 H, *N*$COOCH_3$, **A** o. **B**), 3.83 (s, 3 H, *N*$COOCH_3$, **C**), 3.86 (s, 9 H, *N*$COOCH_3$, **A** o. **B**, **C**), 3.96 (d, *J* = 5.0 Hz, 2 H, 4-, 8-H, **A**), 3.96 (d, *J* = 5.0 Hz, 1 H, 4-H, **C**), 4.14 (d, *J* = 5.5 Hz, 1 H, 8-H, **C**), 4.25 (d, *J* = 5.8 Hz, 2 H, 4-, 8-H, **B**), 4.97 (dd, J_1 = 8.5 Hz, J_2 = 5.0 Hz, 2 H, 3-, 7-H, **A**), 5.23 (dd, J_1 = 8.0 Hz, J_2 = 5.8 Hz, 2 H, 3-, 7-H, **B**), 5.23 (dd, J_1 = 8.0 Hz, J_2 = 5.0 Hz, 1 H, 3-H, **C**), 5.32 (s, 3 H, 4b-, 8b-H, **B**, 4b-H, **C**), 5.42 (s, 2 H, 4b-, 8b-H, **A**), 5.44 (dd, J_1 = 8.5 Hz, J_2 = 5.5 Hz, 1 H, 7-H, **C**), 5.47 (s, 1 H, 8b-H, **C**), 6.74 (d, *J* = 8.0 Hz, 1 H, 2-H, **C**), 6.81 (d, J_1 = 8.5 Hz, 2 H, 2-, 6-H, **A**), 6.92 (d, *J* = 8.5 Hz, 1 H, 6-H, **C**), 6.93 (d, *J* = 8.0 Hz, 2 H, 2-, 6-H, **B**), 7.08-7.24 (m, 30 H, aromatic H, **A**-**C**); CI-MS *m/z* 592 ($M + NH_4^+$). Anal. Calcd for $C_{32}H_{34}N_2O_8$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.84; H, 6.04; N, 4.78.

Diethyl 1,5,8,8bα-Tetrahydro-4,8-diphenyl-1,5-diphenoxycarbonylcyclobuta[1,2-*b*:3,5-*b´*]dipyridine-4a,8aβ(4H,4bβH)-dicarboxylate (2c): Yield: 34% (refered to 0.52 g of **1c** as 100%); mp 158-161 °C (methanol); IR ν 1730, 1691, 1664 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (t, *J* = 7.0 Hz, 3 H, $COOCH_2C\underline{H}_3$, **C**), 1.01 (t, *J* = 7.2 Hz, 6 H, $COOCH_2C\underline{H}_3$, **B**), 1.05 (t, *J* = 7.2 Hz, 6 H, $COOCH_2C\underline{H}_3$, **A**), 1.07 (t, *J* = 7.2 Hz, 3 H, $COOCH_2C\underline{H}_3$, **C**), 3.72 (dq, J_1 = 10.4 Hz, J_2 = 7.2 Hz, 4 H, $COOC\underline{H}_BCH_3$, **A**, **B**), 3.78 (dq, J_1 = 10.4 Hz, J_2 = 7.2 Hz, 4 H, $COOC\underline{H}_ACH_3$, **A**, **B**), 3.81 (dq, J_1 = 9.8 Hz, J_2 = 7.2 Hz, 1 H, $COOC\underline{H}_BCH_3$, **C**), 3.82 (dq, J_1 = 10.8 Hz, J_2 = 7.2 Hz, 1 H, $COOC\underline{H}_BCH_3$, **C**), 3.86 (dq, J_1 = 9.8 Hz, J_2 = 7.2 Hz, 1 H, $COOC\underline{H}_ACH_3$, **C**), 3.93 (dq, J_1 = 10.8 Hz, J_2 = 7.2 Hz, 1 H, $COOC\underline{H}_ACH_3$, **C**), 4.15 (d, *J* = 5.3 Hz, 2 H, 4-, 8-H, **B**), 4.15 (d, *J* = 4.2 Hz, 1 H, 4-H, **C**), 4.24 (d, *J* = 5.3 Hz, 1 H, 8-H, **C**), 4.31 (d, *J* = 6.5 Hz, 2 H, 4-, 8-H, **A**), 5.14 (dd, J_1 = 8.3 Hz, J_2 = 4.2 Hz, 1 H, 3-H, **C**), 5.35 (dd, J_1 = 8.4 Hz, J_2 = 5.3 Hz, 2 H, 3-,

7-H, **B**), 5.48 (s, 1 H, 4b-H, **C**), 5.52 (dd, J = 8.2 Hz, J_2 = 6.5 Hz, 2 H, 3-, 7-H, **A**), 5.64 (s, 3 H, 4b-, 8b-H, **B**, 8b-H, **C**), 5.71 (s, 2 H, 4b-, 8b-H, **A**), 6.83 (d, J = 8.2 Hz, 2 H, 2-, 6-H, **A**), 6.98 (d, J = 8.4 Hz, 2 H, 2-, 6-H, **B**), 7.00 (d, J_1 = 8.3 Hz, 1 H, 2-H, **C**), 7.01 (d, J = 8.4 Hz, 1 H, 6-H, **C**), 7.07-7.49 (m, 60 H, aromatic H, **A**-**C**); ESI-MS *m/z* 721 ($M + Na^+$). Anal. Calcd for $C_{42}H_{38}N_2O_8$: C, 72.19; H, 5.48; N, 4.01. Found: C, 71.73; H, 5.56; N, 3.87.

Diethyl 1,5-Di-*tert*-butoxycarbonyl-1,5,8,8bα-tetrahydro-4,8-diphenylcyclobuta[1,2-*b*:3,5-*b*´]dipyridine-4a,8aβ(4H,4bβH)-dicarboxylate (2d): Yield: 31% (refered to 0.49 g of **1d** as 100%); mp 170-180 °C (methanol); IR ν 1728, 1705, 1652 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (t, J = 7.5 Hz, 18 H, $COOCH_2C\underline{H}_3$, **A**-**C**), 1.54, 1.67 (2 x s, 54 H, $C(CH_3)_3$, **A**-**C**), 3.63 (dq, J_1 = 10.6 Hz, J_2 = 7.5 Hz, 6 H, $COOC\underline{H}_BCH_3$**A**-**C**), 3.70 (dq, J_1 = 10.6 Hz, J_2 = 7.5 Hz, 6 H, $COOC\underline{H}_ACH_3$, **A**-**C**), 3.96 (d, J = 5.7 Hz, 2 H, 4-, 8-H, **B**), 4.00 (d, J = 5.7 Hz, 2 H, 4-, 8-H, **A**), 4.12 (d, J = 5.7 Hz, 1 H, 8-H, **C**), 4.15 (d, J = 6.5 Hz, 1 H, 4-H, **C**), 5.15 (d, J = 8.5 Hz, 1 H, 3-H, **C**), 5.19 (dd, J_1 = 7.6 Hz, J_2 = 5.7 Hz, 1 H, 7-H, **C**), 5.26 (dd, J_1 = 9.0 Hz, J_2 = 5.7 Hz, 4 H, 3-, 7-H, **A**, **B**), 5.37 (s, 1 H, 4b-H, **C**), 5.40 (s, 2 H, 8b-H, **B**), 5.49 (s, 1 H, 8b-H, **C**), 5.55 (s, 2 H, 4b-H, **A**), 6.68 (d, J = 8.6 Hz, 2 H, 2-, 6-H, **A**), 6.70 (d, J = 8.5 Hz, 1 H, 2-H, **C**), 6.85 (d, J = 8.6 Hz, 2 H, 2-, 6-H, **B**), 6.87 (d, J = 7.6 Hz, 1 H, 6-H, **C**), 7.08-7.20 (m, 30 H, aromatic H, **A**-**C**); ESI-MS *m/z* 681 ($M + Na^+$). Anal. Calcd for $C_{38}H_{46}N_2O_8$: C, 69.28; H, 7.04; N, 4.25. Found: C, 68.95; H, 6.68; N, 3.90.

Ethyl 4-Phenylnicotinate (3): Yield: 0.041 g (12%) from **1a**, 0.051 g (15%) from **1b**, 0.061 g (18%) from **1c** and 0.068 g (20%) from **1d**.

Diethyl 3,9-Diacetyl-6,12-diphenyl-3,9-diazahexacyclo[6.4.0.$0^{2.7}$.$0^{4.11}$.$0^{5.10}$]dodecane-1,7-dicarboxylate (4a): Yield: 27%; mp 208-214 °C (methanol); IR ν 1727, 1652 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (t, J = 7.0 Hz, 6 H, $COOCH_2C\underline{H}_3$, **B**), 1.02 (t, J = 7.1 Hz, 6 H, $COOCH_2C\underline{H}_3$, **A**), 1.08 (t, J = 7.2 Hz, 3 H, C7-$COOCH_2C\underline{H}_3$, **C**), 1.10 (t, J = 7.2 Hz, 3 H, C1-$COOCH_2C\underline{H}_3$, **C**), 1.90 (s, 9 H, 2 x $NCOCH_3$, **A** o. **B**, 1 x $NCOCH_3$, **C**), 2.14 (s, 6 H, 2 x $NCOCH_3$, **A** o. **B**), 2.16 (s, 3 H, $NCOCH_3$, **C**), 3.44-3.59 (m, 12 H, 5-, 6-, 11-, 12-H, **A**-**C**), 4.05 (q, J = 7.0 Hz, 4 H, $COOC\underline{H}_2CH_3$, **B**), 4.07 (q, J = 7.1 Hz, 4 H, $COOC\underline{H}_2CH_3$, **A**), 4.08 (q, J = 7.2 Hz, 2 H, C7-$COOC\underline{H}_2CH_3$, **C**), 4.11 (q, J = 7.2 Hz, 2 H, C1-$COOC\underline{H}_2CH_3$, **C**), 4.42 (dd, J_1 = 9.0 Hz, J_2 = 1.7 Hz, 2 H, 4-, 10-H, **A**), 4.44 (d, J = 10.9 Hz, 2 H, 4-, 10-H, **B**), 5.11 (d, J = 9.5 Hz, 1 H, 4-H, **C**), 5.25 (d, J = 8.3 Hz, 1 H, 10-H, **C**), 5.45 (d, J = 9.0 Hz, 2 H, 2-, 8-H, **B**), 6.11 (dd, J_1 = 9.8 Hz, J_2 = 1.8 Hz, 2 H, 2-, 8-H, **A**), 6.11 (d, J = 9.8 Hz, 1 H, 8-H, **C**), 6.16 (d, J = 9.2 Hz, 1 H, 2-H, **C**), 6.91-7.25 (m, 30 H, aromatic H, **A**-**C**); EI-MS *m/z* 542 (M^+). Anal. Calcd for $C_{32}H_{34}N_2O_6$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.53; H, 6.53; N, 5.12.

Diethyl 3,9-Dimethoxycarbonyl-6,12-diphenyl-3,9-diazahexacyclo[6.4.0.$0^{2.7}$.$0^{4.11}$.$0^{5.10}$]dodecane-1,7-dicarboxylate (4b): Yield: 31%; mp > 350°C (methanol); IR ν 1712, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ

1.05 (t, J = 7.2 Hz, 18 H, $COOCH_2C\underline{H}_3$, **A**-**C**), 3.47-3.57 (m, 6 H, 5-, 11-H, **A**-**C**), 3.57 (s, 9 H, $N$$COOCH_3$, **A** o. **B**, **C**), 3.59 (br s, 9 H, $N$$COOCH_3$, **A** o. **B**, **C**), 3.75 (s, 6 H, 6-, 12-H, **A**-**C**), 4.06 (q, J = 7.2 Hz, 12 H, $COOC\underline{H}_2CH_3$, **A**-**C**), 4.64 (d, J = 11.0 Hz, 1 H, 4-H, **C**), 4.66 (d, J = 9.0 Hz, 2 H, 4-, 10-H, **A**), 4.82 (d, J = 11.0 Hz, 1 H, 10-H, **C**), 4.84 (d, J = 9.5 Hz, 2 H, 4-, 10-H, **B**), 5.51 (d, J = 8.8 Hz, 1 H, 8-H, **C**), 5.56 (d, J = 8.8 Hz, 2 H, 2-, 8-H, **B**), 5.67 (d, J_1 = 7.8 Hz, 2 H, 2-, 8-H, **A**), 5.70 (d, J = 9.5 Hz, 1 H, 2-H, **C**), 6.99-7.24 (m, 30 H, aromatic H, **A**-**C**); CI-MS *m/z* 592 ($M + NH_4^+$). Anal. Calcd for $C_{32}H_{34}N_2O_8$: C, 66.89; H, 5.96; N, 4.88. Found: C, 66.57; H, 5.99; N, 4.82.

Diethyl 6,12-Diphenyl-3,9-diphenoxycarbonyl-3,9-diazahexacyclo[6.4.0.0$^{2.7}$.0$^{4.11}$. 0$^{5.10}$]dodecane-1,7-dicarboxylate (4c): Yield: 28%; mp 286-287 °C (methanol); IR ν 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.99 (t, J = 7.1 Hz, 3 H, C7-$COOCH_2C\underline{H}_3$, **C**), 1.02 (t, J = 7.3 Hz, 3 H, C1-$COOCH_2C\underline{H}_3$, **C**), 1.03 (t, J = 7.1 Hz, 6 H, $COOCH_2C\underline{H}_3$, **B**), 1.05 (t, J = 7.1 Hz, 6 H, $COOCH_2C\underline{H}_3$, **A**), 3.67-3.73 (m, 6 H, 5-, 11-H, **A**-**C**), 3.80-3.82 (m, 6 H, 6-, 12-H, **A**-**C**), 4.02-4.16 (m, 4 H, $COOC\underline{H}_2CH_3$, **C**), 4.06 (dq, J_1 = 10.3 Hz, J_2 = 7.1 Hz, 4 H, $COOC\underline{H}_BCH_3$, **A**, **B**), 4.11 (dq, J_1 = 10.3 Hz, J_2 = 7.1 Hz, 4 H, $COOC\underline{H}_ACH_3$, **A**, **B**), 4.96 (d, J = 9.2 Hz, 4 H, 4-, 10-H, **A**-**C**), 5.80 (d, J = 8.9 Hz, 2 H, 2-, 8-H, **B**), 5.81 (d, J = 8.0 Hz, 2 H, 2-, 8-H, **A**), 5.84 (d, J = 8.0 Hz, 1 H, 8-H, **C**), 5.87 (d, J = 9.0 Hz, 1 H, 2-H, **C**), 6.82-7.39 (m, 60 H, aromatic H, **A**-**C**); ESI-MS *m/z* 721 ($M + Na^+$). Anal. Calcd for $C_{42}H_{38}N_2O_8$: C, 72.19; H, 5.48; N, 4.01. Found: C, 72.25; H, 5.60; N, 3.97.

Diethyl 3,9-Di-*tert*-butoxycarbonyl-6,12-diphenyl-3,9-diazahexacyclo[6.4.0.0$^{2.7}$.0$^{4.11}$.0$^{5.10}$]dodecane-1,7-dicarboxylate (4d): Yield: 34%; mp 325-326 °C (methanol); IR ν 1726, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J = 7.1 Hz, 18 H, $COOCH_2C\underline{H}_3$, **A**-**C**), 1.32, 1.48 (2 x s, 54 H, $C(CH_3)_3$, **A**-**C**), 3.42-3.58 (m, 12 H, 5-, 6-, 11-, 12-H, **A**-**C**), 4.04 (q, J = 7.1 Hz, 12 H, $COOC\underline{H}_2CH_3$, **A**-**C**), 4.62 (d, J = 8.9 Hz, 4 H, 4-, 10-H, **A**, **C**), 4.86 (d, J = 8.2 Hz, 2 H, 4-, 10-H, **B**), 5.44 (d, J = 8.5 Hz, 1 H, 8-H, **C**), 5.48 (d, J = 8.6 Hz, 1 H, 2-H, **C**), 5.63 (d, J = 9.4 Hz, 4 H, 2-, 8-H, **A**, **B**), 7.02-7.20 (m, 30 H, aromatic H, **A**-**C**); ESI-MS *m/z* 681 ($M + Na^+$). Anal. Calcd for $C_{38}H_{46}N_2O_8$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.11; H, 7.28; N, 4.27.

X-Ray Diffraction Analysis of **4d**: A white prism $C_{38}H_{46}N_2O_8$ (from ethanol), crystal size 0.19 x 0.15 x 0.11 mm, was measured at a temperature of 298(2) K by using a Stoe-IPDS Diffractometer with Mo-K_α radiation (λ = 0.71073 Å) and a graphite monochromator. 12256 Reflexions were collected in the range 5.64° ≤ 2Θ ≤ 50°; *h,k,l* range from -16, -9, -27 to 16, 8, 27. Crystal system: Monoclinic, space group $P2_1/c$, Z = 2, a = 12.318(4) Å, b = 6.820(1) Å, c = 21.150(6) Å, β = 101.00(3)°; V = 1744.1(8) Å^3; D_x = 1.254 g cm^{-3}; μ = 0.088 mm^{-1}. The structure was solved by direct methods (SHELXS-86[11]) using 2463 independent reflections. Structure refinement: Full matrix least-squares methods on F^2 using SHELXL-93,[12] all the non-hydrogen atoms with anisotropic displacement parameters. All hydrogen atoms were ta-

ken from a difference fourier synthesis and isotropically refined. The refinement converged to a final wR_2 = 0.1312 for 2967 unique reflections and R_1 = 0.0495 for 2942 observed reflections [$I_0 > 2.0\Phi(I_0)$] and 310 refined parameters.

REFERENCES

1. A. Sausins and G. Dubur, *Khim. Geterotsikl. Soedin.*, 1993, **5,** 489 and references therein.
2. A. Hilgeroth and F. W. Heinemann, *Eur. J. Org. Chem*., 2000, 245.
3. A. Hilgeroth, U. Baumeister, and F. W. Heinemann, *Heterocycles*, 1999, **51**, 2367.
4. A. Hilgeroth and A. Billich, *Arch. Pharm. Pharm. Med. Chem*, 1999, **332**, 380.
5. A. Hilgeroth, K. Brachwitz, and U. Baumeister, *Heterocycles*, 2001, **55**, 661.
6. M. D. Cohen and G. M. J. Schmidt, *J. Chem. Soc.*, 1964, 1996.
7. M. D. Cohen, G. M. J. Schmidt, and F. I. Sonntag, *J. Chem. Soc.*, 1964, 2000.
8. G. M. J. Schmidt, *J. Chem. Soc.*, 1964, 2014.
9. Coaleszenz of equivalent protons of the *N*-acetyl compound (**4a**) in $CDCl_3$ could not be demonstrated because this temperature lies above the boiling point of the solvent. The derivative did not solve in solvents with higher boiling points like DMSO-d_6.
10. The *N*-Boc compound was the only one from which acceptable crystals for X-Ray crystal structure analysis were yielded.
11. G. M. Sheldrick, *Acta Crystallogr.*, 1990, **A46**, 467.
12. G. M. Sheldrick, SHELXL-93, Program for the Refinement of Crystal Structures, Universität Göttingen, Germany, 1993.