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Preparation of Novel Heterocyclic Amino Acids from N-(Arylmethylene)dehydroalanine Methyl Esters

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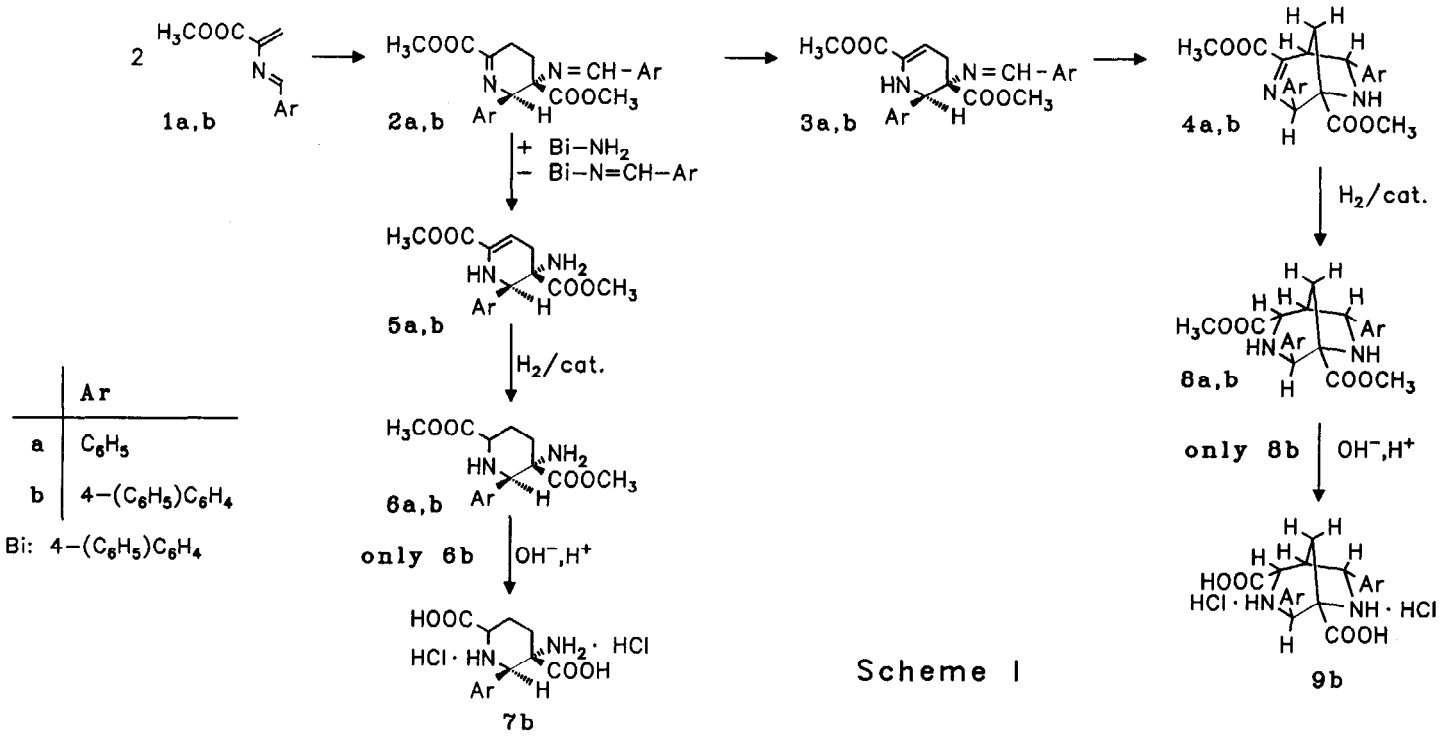
Abstract: *N-(Arylmethylene)dehydroalanine methyl esters undergo a stereoregulated dimerization reaction to produce heterocyclic α, α'-diaminodicarboxylic acid derivatives. Further transformation yields stable hydrochlorides of free α, α'-diaminodicarboxylic acids which represent either substituted 3-amino-piperidine-3,6-dicarboxylic acids or substituted 2,6-diazabicyclo[3.2.1]octane-1,5-dicarboxylic acids. These compounds represent new types of cyclic and bicyclic amino acids.*

N-(Arylmethylene)dehydroalanine methyl esters **1a** and **1b** represent highly reactive compounds first prepared by our group.[1,2] Only in the crystalline state and in solution below -15°C they are relatively stable. Earlier attempts to prepare these compounds[3] have already encountered this remarkable lability. Detailed investigations[4] elucidated the nature of the transformation reactions undergone by **1** leading to several new types of compounds.

The dehydroalanine derivatives **1a** and **1b** undergo a dimerization in the form of a [4+2]-cycloaddition as the first step. In this Diels-Alder-type reaction, the 2-azabutadiene unit of **1** functions as the 4π-component whereas the C=C-double bond of a second molecule acts as the dienophile. The resulting dimer **2** can be isolated in good yield by immediate crystallization from the reaction mixture only. In solution at room temperature it undergoes a further intramolecular cyclization to yield a 3,6-diazabicyclo[3.2.1]oct-2-ene derivative **4**. The bicyclus **4** is formed via the tautomeric enamine **3**.[5] The correct configuration of the heterocycles **2**, **3**, and **4** were established by X-ray crystallographic analysis of **4b** and by detailed NMR analysis.[5]

To our knowledge, tetrahydropyridines of type **2** have not previously been described in the literature, only 3,4,5,6-tetrahydro-2-pyridinecarboxylic acid and similar compounds have been discussed as intermediates during degradation of some amino acids.[6] Structurally related compounds to the enamine **3**, with a 1,4,5,6-tetrahydropyridine ring, have been detected as constituents of flavouring matters.[7] Derivatives with the saturated ring, the pipecolinic acid system, represent a number of novel amino acids.[8] Interest in heterocyclic, non-proteinogenic amino acids is increasing as the incorporation of these amino acids into biochemically important peptides sometimes causes remarkable physiological activity.[9] Consequently there has been an upsurge in the synthesis of such less accessible compounds.[9,10]

Bicyclic amino acid derivatives of type **4** have not been described until now. There is a slight structural relationship to some rare, natural amino acids.[8] Other types of synthetic bicyclic amino acids show the ability to transport metal ions through biological membranes.[11] These examples also highlight


2
1a,b
2a,b
+ Bi–NH2
– Bi–N=CH–Ar
5a,b
H2/cat.
6a,b
only 6b
OH⁻,H⁺
7b
3a,b
4a,b
H2/cat.
8a,b
only 8b
OH⁻,H⁺
9b
Ar
a C6H5
b 4–(C6H5)C6H4
Bi: 4–(C6H5)C6H4

Scheme I

the increasing importance of non-proteinogenic amino acids.[12] Since compounds **2** and **4** are now easily available they should provide a novel access to the unusual heterocyclic α,α'-diamino dicarboxylic acids.

In order to obtain an α,α'-diamino dicarboxylic acid from **2**, this compound has to be stabilized to prevent further cyclization to **4**. Therefore the exocyclic imine bond has to be split under very mild conditions.[5] This was achieved by a transamination reaction using 4-aminobiphenyl. In this way the 4-aldehydo biphenyl and the benzaldehyde residue, respectively, could be removed by formation of the Schiff base of the added amine. The compound obtained did not contain a 3,4,5,6-tetrahydropyridine ring system as expected but instead the apparently more stable enamine tautomer **5a** and **5b** were formed.

Attempts to saponify the ester groups of **5a** and **5b** yielded some side reactions due to the labile enamine group. Therefore these compounds were hydrogenated before hand to yield the piperidine ring systems. Hydrogenation at 40°C with 15 bar H_2 pressure in methanol with 10% Pd on charcoal[13] yielded the hydrogenated compounds **6a** and **6b**. **6b** could be obtained by crystallization in 92% yield, whereas **6a** was obtained as an oil. NMR spectroscopy of both compounds **6a** and **6b** showed that only one diastereomer was formed in both cases. A definite proof for the relative configuration at the newly formed stereogenic center at C-6 cannot be given. Theoretical considerations, though, show that a cis-addition of hydrogen at the double bond of **5** should occur from the less hindered side and this is the side opposite to the aromatic ring system. Therefore both carboxyl groups should be oriented on the same side of the piperidine ring. The preferred conformation of compound **6a** and **6b** therefore should have 4 substituents in an equatorial position and only the carboxyl group at C-3 in an axial position.

Attempts to saponify the methyl esters concentrated on compound **6b**. The conditions for saponification were optimized by monitoring the hydrolysis in CD_3OD, D_2O, NaOD mixtures with the aid of ^1H NMR spectroscopy. Preparative saponification was then performed with 5% NaOH in methanol with some water. The reaction mixture was acidified with HCl and the dicarboxylic acid isolated as the dihydrochloride **7b**. The compound was only partially soluble in most solvents. The structure was elucidated by a heteronuclear correlated 2D NMR spectrum[14] and these investigations ascertained structure **7b**.

After the synthesis of the monocyclic α,α'-diamino-dicarboxylic acid **7b** similar reactions were performed with the bicyclus **4**. The first step involved a catalytic hydrogenolysis[15] of the chemically sensitive cyclic imine group in **4**. Again the compound with the biphenylyl group **8b** was obtained in high yield (93%) in the crystalline state. The phenyl derivative **8a** was difficult to crystallize and to obtain pure. Spectroscopic investigations showed that compound **8a** had an analogous structure to **8b**.

Both compounds **8a** and **8b** were obtained as single diastereomers. This means that a cis-addition of hydrogen to the imine group of **4** preferentially takes place from only one side. In this case the relative configuration of the new stereogenic center at C-5 can be determined by NMR spectroscopy. The $J_{1,3}$ coupling constant of 1.8 Hz between the hydrogen at C-5 and the equatorial hydrogen at the bridgehead carbon at C-4 indicates an enlarged dihedral angle of around 70°. This is only possible if the hydrogen at C-5 is in an axial position, since in the chair conformation of the six-membered ring (C-1, C-8, C-4, C-5, N-6, C-7), the dieder angle between the equatorial hydrogen of C-4 and the axial position at C-5 is enlarged by the introduction of the two-atom bridging (C-3, N-2). The same conclusion with regard to the relative configuration at C-5 is obtained if kinetic considerations of the hydrogenation reaction are taken into account. The approach of the catalyst with the hydrogen should occur from the less hindered side of the molecule where the methylene bridge is located.

In this case too, the biphenyl derivative **8b** was further converted into the dicarboxylic acid which was isolated as the dihydrochloride derivative **9b**. Thus, it was possible to synthesize cyclic and bicyclic α,α'-diaminodicarboxylic acids of novel structure from N-(arylmethylene)dehydroalanine methyl ester. Both compounds were obtained diastereomerically pure but as racemates. Asymmetric syntheses of pure antipodes are now in progress. Interesting physiological properties of peptides containing these amino acids might be expected.

EXPERIMENTAL

General Procedure. Melting points were taken with an SMP-510 apparatus from Büchi. ^1H and ^{13}C NMR spectra were recorded on Varian EM 390 and VXR 300 spectrometers. Mass spectra were obtained with Varian MAT CH-50 and MAT 311 A. IR spectra were measured with a type 1420 instrument from Perkin-Elmer. Elemental analyses were performed in the microanalytical laboratories of the Faculty of Natural Sciences of the Heinrich-Heine-University Düsseldorf.

(2RS,3SR,6ⓡ)-3-Amino-2-(4-biphenylyl)-3,6-piperidine dicarboxylic dimethyl ester (**6b**): Compound **5b**[5] (500 mg, 1.37 mmol) was hydrogenated in methanol (130 ml) with 10% Pd on charcoal (100 mg) at 40°C in an autoclave at 15 bar H_2-pressure. After 2.5 h the catalyst was removed by filtration and the solvent evaporated. The resulting oil was crystallized at -15°C from diethyl ether. Pure compound **6b** was obtained (460 mg) in 92% yield. M.p. 111°C. ^1H NMR ($CDCl_3$): δ = 1.73-2.29 (m, 4 H, CH_2-CH_2), 3.15 (br, 2 H, NH_2), 3.57 (m, 1 H, CH-C=O), 3.62 (s, 3 H, OCH_3), 3.70 (s, 1 H, CH-Ar), 3.76 (s, 3 H, OCH_3), 4.10 (br, 1 H, NH), 7.31-7.66 (m, 9 H, aromatic H). ^{13}C NMR ($CDCl_3$): δ = 26.61 (CH_2), 36.05 (CH_2), 51.66 (OCH_3), 51.90 (OCH_3), 58.41 (quart. C), 59.21 (CH), 69.18 (CH), 126.64, 126.78, 127.17, 128.11, and 128.58 (9 aromatic C), 137.28, 140.33, and 140.57 (3 quart. aromatic C), 172.74 (C=O), 174.11 (C=O). MS: m/z = 368 (M^+). IR (KBr): γ (cm^{-1}) = 3365 (NH), 3310 (NH), 3030 (aryl-H), 2955 (CH_2), 1740 (C=O), 1725 (C=O). Anal. calcd. for $C_{21}H_{24}N_2O_4$ (368.2): C, 68.48; H, 6.52; N, 7.61. Found C, 68.24; H, 6.78; N, 7.35.

(2RS,3SR,6ⓢ)-3-Amino-2-phenyl-3,6-piperidine-dicarboxylic-dimethyl ester (**6a**): Compound **5a**[5] (220 mg, 0.76 mmol) was hydrogenated in methanol (50 ml) with 10% Pd on charcoal (50 mg) at 40°C in an autoclave at 15 bar H_2-pressure. After 3 h the catalyst was removed by filtration and the solvent evaporated. For purification the reaction product was chromatographed on silica 60 with ethyl acetate/hexane mixtures and later methanol. **6a** was obtained in 36% yield as an oil. ^1H NMR ($CDCl_3$): δ = 1.77-2.40 (m, 6 H, CH_2-CH_2 and NH_2), 3.57 (m, 1 H, CH-C=O), 3.59 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.78 (s, 1 H, CH-Ar), 4.16 (s, 1 H, NH), 7.22-7.32 (m, 5 H, 5 aromatic H). ^{13}C NMR ($CDCl_3$): δ = 23.37 (CH_2), 35.26 (CH_2), 51.97 (OCH_3), 52.11 (OCH_3), 59.24 (CH), 60.41 (quart. C), 66.07 (CH), 127.26 (2 aromatic o-C), 128.30 (2 aromatic m-C), 128.56 (aromatic p-C), 138.83 (aromatic i-C), 172.74 (C=O), 175.10 (C=O). MS: m/z = 292 (M^+). Anal. calcd. for $C_{15}H_{20}N_2O_4$ (292.3): C, 61.63; H, 6.90; N, 9.58; Found C, 60.37; H, 6.79; N, 8.74.

(2RS,3SR,6ⓡ)-3-Amino-2-(4-biphenylyl)-3,6-piperidine-dicarboxylic acid dihydrochloride (**7b**): A solution of **6b** (450 mg, 1.22 mmol) in methanol (20 ml) was treated with 5% NaOH in methanol (25 ml) containing some water and stirred for 17 h. Afterwards three times H_2O (50 ml) were added and the mixture evaporated to 40 ml in vacuo. The resulting aqueous solution was extracted with diethyl ether and HCl was added until a pH of 2.5 was reached. Under these conditions the reaction product precipitated, it was collected by filtration and washed and dried. Yield 403 mg (80%). M.p. 275°C (dec.). ^1H NMR (CD_3OD/NaOD, D_2O): δ = 1.72 (m, 1 H, 4-H_{ax}), 1.97 (br. d, 1 H, 5-H_{eq}, 2J = 13.0 Hz), 2.08 (br. d, 1 H, 4-H_{eq}), 2.26 (m, 1 H, 5-H_{ax}), 3.35 (m, 1 H, CH-C=O), 3.61 (s, 1 H, CH-Ar), 7.28-7.60 (m, 9 H, 9 aromatic-H). ^{13}C NMR (CD_3OD/NaOD): δ = 29.19 (CH_2), 38.40 (CH_2), 59.39 (quart. C), 63.81 (CH-C=O), 69.17 (CH-Ar), 127.56, 127.78, 128.27, 129.83, and 130.48 (9 aromatic-CH), 140.36, 141.45, and 142.10 (3 quart. aromatic-C), 181.34 and 181.91 (2 COO-). MS: m/z = 342 (M-2Cl), 340 (M-2 HCl), 44 (CO_2). Anal. calcd. for $C_{19}H_{20}N_2O_4$. 2 HCl (413.3): C, 55.21; H, 5.37; N, 6.78; Found C, 55.04; H, 5.54; N, 6.63.

(1RS,3SR,4RS,5RS,7SR)-3,7-Bis(4-biphenylyl)-2,6-diazabicyclo-[3.2.1]octane-1,5-dicarboxylic-dimethyl ester (**8b**): 750 mg of **4b**[5] (1.41 mmol) in methanol/benzene (5:1) (60 ml) were hydrogenated at 10% Pd on charcoal at 40°C with 15 bar H_2 pressure for 7 h. After filtration and evaporation the residue was recrystallized from dichloromethane/n-pentane. Yield 700 mg (93%), m.p. 152°C. ^{1}H NMR (C_5D_5N): δ = 2.45 (d, 1 H, HCH, 2J = 11.6 Hz), 2.53 (dd, 1 H, HCH, 3J = 4.5 Hz), 3.25 (s, 3 H, OCH_3), 3.27 (m, 1 H, CH-CH_2), 3.72 (s, 3 H, OCH_3), 4.25 (d, 1 H, CH-C=O, 3J = 1.8 Hz), 4.84 (s, 1 H, Ar-CH-C-N), 4.92 (d, 1 H, Ar-CH-CH), 5.00-5.40 (br, 2 H, 2 NH), 7.35-7.92 (m, 18 H, 18 aromatic H). ^{13}C NMR ($CDCl_3$): δ = 35.50 (CH_2), 44.20 (bridgehead-CH), 51.66 (OCH_3), 52.17 (OCH_3), 58.14, 62.83, and 65.88 (3 CH-N), 69.19 (quart. bridgehead-C), 126.64, 126.89, 126.96, 126.97, 127.27, 127.65, 128.06, 128.74, and 128.79 (18 aromatic CH), 137.85, 139.77, 139.90, 140.02, 140.60, and 140.77 (6 quart. aromatic C), 170.97 and 173.75 (2 C=O). MS: m/z = 532 (M^+). Anal. calcd. for $C_{34}H_{32}N_2O_4$ (532.6): C, 76.67; H, 6.06; N, 5.26; Found C, 76.14; H, 5.93; N, 5.61.

(1RS,3SR,4RS,5RS,7SR)-3,7-Diphenyl-2,6-diazabicyclo[3.2.1]-octane-1,5-dicarboxylic dimethyl ester (8a): **4a**[5] was hydrogenated as described for **4b**. Yield 50%, m.p. 175°C. ^{1}H NMR ($CDCl_3$): δ = 2.30 (m, 2 H, CH_2), 3.14 (s, 3 H, OCH_3), 3.61 (s, 3 H, OCH_3), 3.73 (m, 1 H, CH-CH_2), 4.02 (d, 1 H, CH-C=O, 3J = 1.8 Hz), 4.52 (s, 1 H, Ar-CH-C-N), 4.76 (d, 1 H, Ar-CH-CH, 3J = 4.2 Hz), 7.21-7.65 (m, 10 H, 10 aromatic H). MS: m/z = 380 (M^+).

(1RS,3SR,4RS,5RS,7SR)-3,7-Bis(4-biphenylyl)-2,6-diazabicyclo-[3.2.1]-octane-1,5-dicarboxylic acid dihydrochloride (**9b**): **8b** (100 mg, 0.19 mmol) in methanol/dichloromethane (9:1) (20 ml) was treated with 5% NaOH in methanol containing some water (10 ml). After 24 h stirring at room temperature two times water (15 ml) were added to the reaction mixture and evaporated to about 20 ml. The aqueous solution was extracted with dichloromethane and then acidified with HCl to a pH of 2.0 whereupon a white substance precipitates. This was collected, washed and dried. Yield 40 mg (37%), m.p. above 230°C. ^{1}H NMR (CD_3OD): δ = 2.51 (dd, 1 H, HCH, 2J = 13.0 Hz, 3J = 4.0 Hz), 2.63 (d, 1 H, HCH), 3.38 (m, 1 H, CH-CH_2), 4.53 (br. s, 1 H, CH-C=O), 7.33-7.87 (m, 18 H, 18 aromatic H). (The two signals of the CH-aryl grouping could not be identified due to overlap with the broad peak of the solvent (4.80-5.08 ppm).) ^{13}C NMR (CD_3OD): δ = 31.12 (CH2), 42.75 (bridgehead-CH), 55.10, 57.10, and 62.17 (3 CH-N), 73.40 (quart. bridgehead-C), 127.92, 127.96, 128.01, 128.26, 128.32, 128.55, 128.70, 128.80, 129.49, 129.90, 129.97, 130.02, and 130.13 (18 aromatic CH), 137.91, 141.45, 141.49, 141.64, 142.71, and 143.11 (6 quart. aromatic C), 171.09 and 175.28 (2 C=O). MS: m/z = 577 (M^+), 504 (M - 2 HCl). Anal. calcd. for $C_{32}H_{28}N_2O_4$. 2 HCl (577.5): C, 66.55; H, 5.24; N, 4.85; Found C, 66.40; H, 5.21; N, 4.72.

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