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Pyrrolidine-2,3,4-tricarboxylic Anhydrides: I. Organocatalytic Synthesis and Fusion of Pyrrole Ring by the Action of *p*-Fluorobenzylamine

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Abstract—*N*-Boc-glycine effectively catalyzes 1,3-dipolar cycloaddition of maleic anhydride to *N*-benzylidene α-amino acid esters, which leads to the formation of pyrrolidine-2,3,4-tricarboxylic anhydrides. The subsequent opening of the anhydride fragment in the adducts by the action of *p*-fluorobenzylamine is regioselective, and it involves recyclization to produce polysubstituted octahydropyrrolo[3,4-*b*]pyrroles. The newly synthesized fused pyrrolidines inhibit enzymatic activity of thrombin (factor IIA) *in vitro*.

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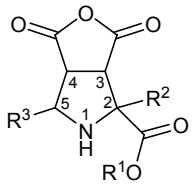
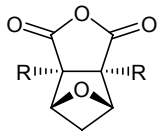
Polyfunctional organic compounds attract considerable interest from the viewpoint of creation of combinatorial libraries for biological screening. Pyrrolidine-2,3,4-tricarboxylic acid 3,4-anhydrides **I** may be regarded as promising molecular structures possessing various functional groups. Compounds like **I** contain three functional groups: a secondary amino group, anhydride fragment, and carboxy (ester) group.



I

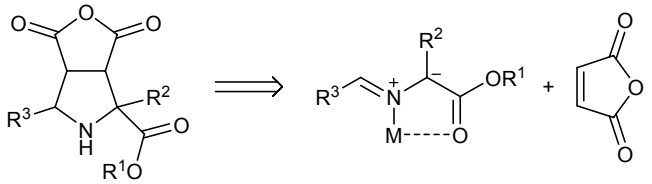


II

Consecutive and/or joint modification of the above functional groups in molecules **I** could lead to various complex low-molecular organic compounds. Heterocyclic anhydrides **I** are isostructural to cantharidin (**II**, R = Me) and norcantharidin (**II**, R = H). Cantharidin is produced as protecting agent by various beetle species, and it exhibits a broad spectrum of antitumor activity and inhibits serine/threonine protein phosphatases; the same is also typical of its synthetic analog, norcantharidin [1]. Opening of the anhydride ring in compounds **II** and their analogs by the action of nitrogen-centered nucleophiles gives dicarboxylic acid monoamides or imides which show modified biological activity as compared to parent compounds [1, 2]. The goal of the present work was to develop an effective procedure for the synthesis of heterocyclic anhydrides **I**, examine their reactions with primary amines, and test the products thus obtained for inhibitory activity toward thrombin (factor IIA).

Functionalized pyrrolidines **I** can be synthesized by 1,3-dipolar cycloaddition of maleic anhydride to azomethine ylides **A** as shown in Scheme 1.

Scheme 1.

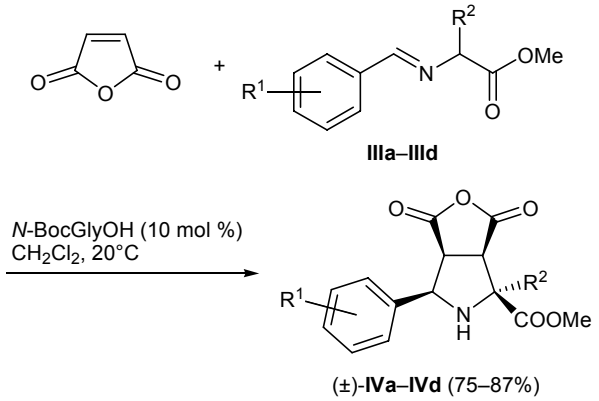


I **A**

There are some published data on the synthesis of compounds **I** via generation of 1,3-dipole **A** from the corresponding *N*-alkylidene derivatives of α-amino acid esters on heating above 100°C for a long time [3–5]. We recently developed an organocatalytic procedure for 1,3-dipolar cycloaddition of activated di-

polarophiles to azomethine ylides like **A** [6]. This procedure makes it possible to obtain polysubstituted bicyclic pyrrolidines, including those having structure like **I**, by treatment of a mixture of *N*-alkylidene α-amino acid ester and dipolarophile in methylene chloride with a catalytic amount of L-proline (L-Pro) or L-pyroglutamic acid (L-Pyr) at room temperature [6]. When the developed procedure was applied to the synthesis of heterocyclic anhydrides **I** with different substituents, in many cases the products were contaminated with the catalyst because of poor solubility of L-Pro and L-Pyr in methylene chloride. These results prompted us to search for amino acid derivatives that are readily soluble in nonpolar organic solvents. Unlike other amino acids examined in [6], the lack of free amino group in L-Pyr indicated that this functionality is not necessary for effective catalysis of 1,3-dipolar cycloaddition. α-Amino acid derivatives with the amino group protected with benzyloxycarbonyl group (*N*-Boc) are soluble in nonpolar solvents; therefore, these accessible compounds were selected as organic catalysts for the reaction shown in Scheme 2.

Scheme 2.



(±)-**IVa–IVd** (75–87%)

R^1 = H, R^2 = Me (**a**); R^1 = 4-Cl, R^2 = Me (**b**); R^1 = 4-Br, R^2 = Me (**c**); R^1 = 3-F, R^2 = $PhCH_2$ (**d**).

When an equimolar mixture of amino acid Schiff base **III** and maleic anhydride in methylene chloride was stirred for 12–24 h at room temperature in the presence of 10 mol % of *N*-Boc-glycine, the corresponding crystalline cycloaddition product **IV** partly separated from the reaction mixture (Scheme 2). Anhydride **IVa** was synthesized by us previously [6], while the structure of heterocyclic anhydrides **IVb**–**IVd** was determined by comparing their NMR spectra with those of compound **IVa** and other known analogs [4, 6]. The steric structure of *p*-chlorophenyl-substituted derivative **IVb** was unambiguously proved by

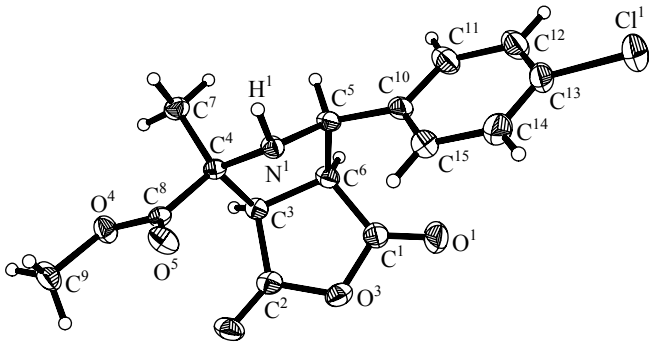


Fig. 1. Structure of the molecule of methyl (3a*R**,4*S**,6*R**,6a*S**)-6-(4-chlorophenyl)-4-methyl-1,3-dioxohexahydro-1*H*-furo[3,4-*c*]pyrrole-4-carboxylate (**IVb**) according to the X-ray diffraction data.

X-ray analysis of its single crystal, and these data confirmed our assumption concerning the steric structure of other heterocyclic anhydrides **IV** (Fig. 1, Table 1). Compounds **IV** were isolated as colorless free-flowing crystalline powders which were stable upon storage at 4°C for at least six months. Molecules **IVb** in crystals are linked to form infinite chains consisting of alternating enantiomers through intermolecular hydrogen bonds between the carbonyl oxygen atom in the anhydride fragment of one molecule and NH hydrogen atom of the other molecule (Fig. 2).

The chemical properties of heterocyclic anhydrides **I** and **IV** were studied very poorly. There are published data on the hydrolysis [5] and methanolysis [7] of

Table 1. Selected bond lengths and bond angles in the molecule of methyl (3a*R**,4*S**,6*R**,6a*S**)-6-(4-chlorophenyl)-4-methyl-1,3-dioxohexahydro-1*H*-furo[3,4-*c*]pyrrole-4-carboxylate (**IVb**)

Bond	*d*, Å	Angle	ω, deg
Cl^1–C^{13}	1.7454(15)	$C^4N^1C^5$	106.12(9)
N^1–C^4	1.4675(15)	$C^2O^3C^1$	110.36(10)
N^1–C^5	1.4697(16)	$O^3C^2C^3$	111.09(10)
N^1–H^1	0.914(17)	$O^3C^1C^6$	109.82(11)
O^1–C^1	1.1822(17)	$C^2C^3C^4$	113.21(10)
O^2–C^2	1.1933(16)	$C^1C^6C^5$	113.13(11)
O^3–C^2	1.3715(16)	$N^1C^4C^3$	101.14(9)
O^3–C^1	1.3973(17)	$N^1C^5C^6$	101.80(9)
C^1–C^6	1.5074(19)	$N^1C^5C^{10}$	113.08(10)
C^2–C^3	1.5097(18)	$N^1C^4C^8$	110.12(10)
C^3–C^6	1.5353(17)	$N^1C^4C^7$	113.56(10)
C^3–C^4	1.5575(16)	$C^5N^1H^1$	108.8(10)

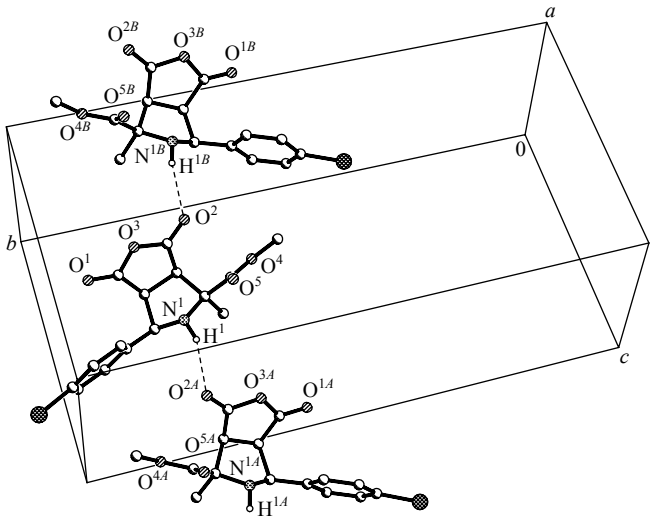


Fig. 2. Intermolecular interactions in the crystalline structure of methyl (3a*R**,4*S**,6*R**,6a*S**)-6-(4-chlorophenyl)-4-methyl-1,3-dioxohexahydro-1*H*-furo[3,4-*c*]pyrrole-4-carboxylate (**IVb**): N^1–H^1 0.914(17), $H^1\cdots O^{2A}$ 2.257(17), $N^1\cdots O^{2A}$ 3.0841(14) Å; $\angle N^1H^1O^{2A}$ 150.3(14)°.

a few compounds like **I** in acid medium. Obviously, nucleophile should react primarily at the carbonyl carbon atoms in the anhydride fragment of **I** and **IV**. Taking into account unsymmetrical structure of these substrates, formation of two regioisomers with vicinal carboxy and methoxycarbonyl groups should be expected. Thus primary products of nucleophilic addition of *p*-fluorobenzylamine to heterocyclic anhydride **IVb** should have structures **V** and **VI** (Fig. 3).

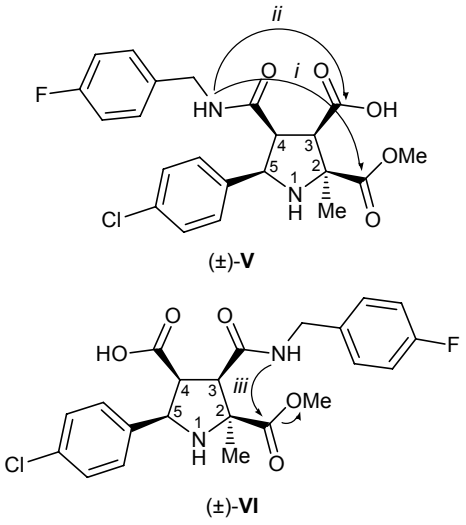
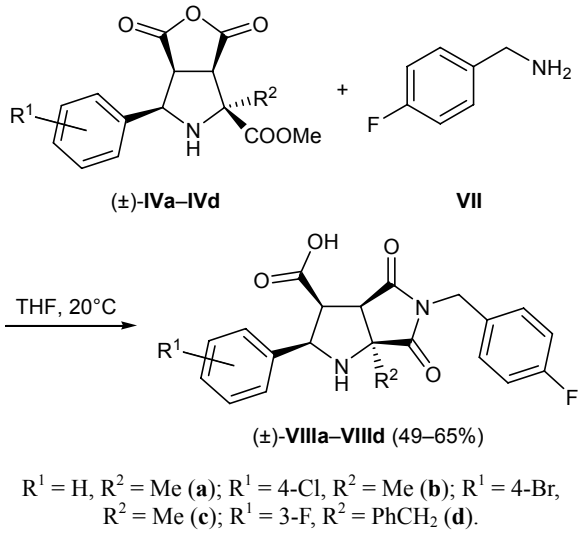


Fig. 3. Probable primary addition products of methyl (3a*R**,4*S**,6*R**,6a*S**)-6-(4-chlorophenyl)-4-methyl-1,3-dioxohexahydro-1*H*-furo[3,4-*c*]pyrrole-4-carboxylate (**IVb**) and *p*-fluorobenzylamine (**VII**) and versions of intramolecular ring closure .

We previously found conditions for intramolecular condensation involving the carboxy group in *cs*-5-arylpyrrolidine-2,4-dicarboxylic acid monoamides and obtained bicyclic imides with a 3,6-diazabicyclo[3.2.1]-octane skeleton [8]. Three intramolecular condensation pathways may be proposed for regioisomeric *cis*-5-arylpyrrolidine-2,3,4-tricarboxylic acid monoamides **V** and **VI**: (*i*) [4,2]-condensation in isomer **V**, leading to 3,6-diazabicyclo[3.2.1]octane derivative; (*ii*) [4,3]-condensation in isomer **V** with formation of octahydropyrrolo[3,4-*c*]pyrrole structure; and (*iii*) [3,2]-condensation in **VI** with formation of octahydropyrrolo[3,4-*b*]-pyrrole skeleton (Fig. 3). The reactions of anhydrides **IVa**–**IVd** with *p*-fluorobenzylamine (**VII**) were carried out in THF at room temperature (Scheme 3). After 2–3 days, samples were withdrawn from the reaction mixtures and analyzed by ^{1}H NMR spectroscopy. The reaction was assumed to be complete when the two last spectra were similar. In the reaction of heterocyclic anhydride **IVb** with *p*-fluorobenzylamine the initial compounds disappeared in 3 days, and three products were detected at a molar ratio of 13 : 4 : 1. The major product was isolated as individual substance by crystallization. The ^{1}H NMR spectrum of this compound contained no signal assignable to methoxy group. Taking into account its other ^{1}H and ^{13}C NMR parameters and elemental composition, it was assigned structure **VIIIb** (Scheme 3).

Scheme 3.



R^1 = H, R^2 = Me (**a**); R^1 = 4-Cl, R^2 = Me (**b**); R^1 = 4-Br, R^2 = Me (**c**); R^1 = 3-F, R^2 = $PhCH_2$ (**d**).

Compound **VIIIb** could be formed via spontaneous [3,2]-condensation of intermediate product **VI** (Fig. 3). According to the NMR data, the minor products are likely to have structures **V** and **VI**; however, they were

not isolated. Analogous patterns were observed in the reactions of benzylamine **VII** with heterocyclic anhydrides **IVa**, **IVc**, and **IVd**. In all cases, the major products were substituted octahydropyrrolo[3,4-*b*]pyrroles **VIIIa**, **VIIIc**, and **VIIId**, indicating initial regioselective opening of the anhydride fragment. The structure of fused pyrrolidines **VIII** was proved by the X-ray diffraction data for a single crystal of compound **VIIId** (Fig. 4, Table 2). Packing of molecules **VIIId** in crystal resembles that found for anhydride **IVb**: alternating enantiomeric molecules **VIIId** are linked through intermolecular hydrogen bonds involving the nitrogen atom in the secondary amino group of one molecule and proton in the carboxy group of the other molecule (Fig. 5). The observed conformation of molecules **VIIId** is stabilized by intramolecular hydrogen bond formed by the carbonyl oxygen atom of the carboxy group and hydrogen atom in the secondary amino group (Figs. 4, 5).

Heterocyclic anhydrides **IV** and substituted octahydropyrrolo[3,4-*b*]pyrroles **VIII** synthesized in the present work were tested for inhibitory activity toward thrombin (Table 3).* Thrombin (factor IIA) is a promising biological target in the design of anticoagulants [9]. All the examined compounds are fairly readily soluble in aqueous medium. They inhibited thrombin *in vitro* (buffer solution) at a millimolar concentration up to complete suppression of its enzymatic activity (Table 3, compounds **IVa** and **IVb**).

We can conclude that 1,3-dipolar cycloaddition of maleic anhydride to azomethine ylides, followed by opening of the anhydride fragment and recyclization involving the vicinal ester fragment, provides a novel efficient synthetic approach to substituted octahydropyrrolo[3,4-*b*]pyrrole derivatives. Compounds **VIII** may be used as starting materials for subsequent transformations due to the presence of an unprotected β-amino acid moiety.

EXPERIMENTAL

The progress of reactions and the purity of products were monitored by thin-layer chromatography using Sorbfil PTSKh-AF-A-UF plates ($CHCl_3$–MeOH, 10:1). The ^1H and ^{13}C NMR spectra were recorded at 303 K on a Bruker Avance 400 spectrometer at 400 and 100 MHz, respectively, using DMSO-d_6 as solvent; the chemical shifts were determined relative to the residual proton and carbon signals of the solvent.

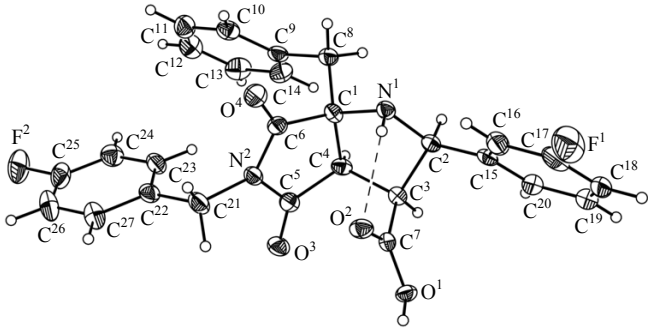


Fig. 4. Structure of the molecule of (2*R**,3*S**,3a*R**,6a*S**)-6a-benzyl-5-(4-fluorobenzyl)-2-(3-fluorophenyl)-4,6-dioxooctahydropyrrolo[3,4-*b*]pyrrole-3-carboxylic acid (**VIIId**) according to the X-ray diffraction data.

The X-ray diffraction data for compounds **IVb** and **VIIId** were acquired on a Bruker Smart Apex II diffractometer (MoK_α irradiation, λ 0.71073 Å, graphite monochromator) at 150 and 100 K, respectively. Both structures were solved by direct methods (SHELXS-86) [10] and were refined with respect to F^2 by the least-squares procedure in full-matrix anisotropic

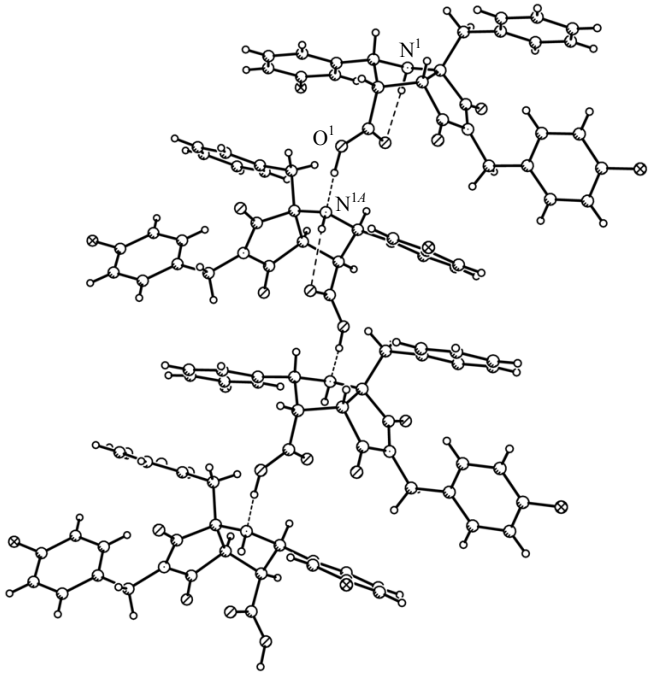


Fig. 5. Intermolecular interactions in the crystalline structure of (2*R**,3*S**,3a*R**,6a*S**)-6a-benzyl-5-(4-fluorobenzyl)-2-(3-fluorophenyl)-4,6-dioxooctahydropyrrolo[3,4-*b*]pyrrole-3-carboxylic acid (**VIIId**): N^1–H^{1N} 0.91(4), $H^{1N}\cdots O^2$ 2.20(3), $N^1\cdots O^2$ 2.812(4) Å; $\angle N^1H^{1N}O^2$ 124(3)°; O^1–H^{1O} 0.93, $H^{1O}\cdots N^{1A}$ 1.65, $O^1\cdots N^{1A}$ 2.573(4) Å; $\angle O^1H^{1O}N^{1A}$ 175°.

* Biological tests were performed at the Physical Biochemistry Laboratory, Hematological Research Center, Russian Academy of Medical Sciences, Moscow (Head of the laboratory Prof. F.I. Ataullakhanov).

Table 2. Selected bond lengths and bond angles in the molecule of (2*R**,3*S**,3a*R**,6a*S**)-6a-benzyl-5-(4-fluorobenzyl)-2-(3-fluorophenyl)-4,6-dioxooctahydropyrrolo[3,4-*b*]pyrrole-3-carboxylic acid (**VIIId**)

Bond	*d*, Å	Angle	ω, deg
N^1–C^2	1.491(5)	$C^2N^1C^1$	104.3(3)
N^1–C^1	1.498(4)	$N^1C^1C^6$	110.8(3)
C^1–C^4	1.546(5)	$N^1C^1C^8$	109.3(3)
C^2–C^3	1.546(5)	$N^1C^1C^4$	106.2(3)
C^3–C^4	1.551(5)	$N^1C^2C^{15}$	114.4(3)
C^4–C^5	1.504(5)	$N^1C^2C^3$	103.5(3)
C^1-C^6	1.524(5)	$C^2C^3C^4$	100.5(3)
N^2–C^6	1.380(5)	$C^1C^4C^3$	105.7(3)
N^2–C^5	1.387(5)	$C^5C^4C^3$	113.6(3)
F^1–C^{17}	1.331(5)	$C^5C^4C^1$	105.1(3)
F^2–C^{25}	1.372(5)	$C^6C^1C^4$	103.9(3)
N^2–C^{21}	1.458(5)	$C^6N^2C^5$	113.2(3)

approximation for all non-hydrogen atoms (SHELXL-97) [11]. All hydrogen atoms were localized by the Fourier difference syntheses, and their positions were refined in isotropic approximation.

Maleic anhydride was preliminarily purified by recrystallization from chloroform. Initial Schiff bases **III** were synthesized according to the procedures described in [6, 12].

Pyrrolidine-2,3,4-tricarboxylic acid 3,4-anhydrides IVa–IVd (*general procedure***).** A solution of 14 mmol of compound **III** in 25 ml of methylene chloride and 0.25 g (1.4 mmol) of *N*-Boc-glycine were added in one portion to a solution of 1.37 g (14 mmol) of maleic anhydride in 15 ml of methylene chloride. The mixture was stirred for 24–48 h at room temperature (TLC), the precipitate was filtered off, the filtrate was evaporated by half under reduced pressure and cooled to –20°C, and the precipitate was filtered off. If necessary, 5 ml of hexane was added to initiate crystallization.

Table 3. Inhibitory effect of compounds **IVa**–**IVd** and **VIIIa**–**VIIId** on the hydrolysis of specific substrate with thrombin in aqueous buffer

Compound no.	Reduction of the rate of hydrolysis of thrombin substrate, %	Inhibitor concentration, mmol/l
IVa	92	5.33
IVb	90	2.40
IVc	71	1.36
IVd	55	0.52
VIIIa	29	3.48
VIIIb	35	1.97
VIIIc	23	1.63
VIIId	47	0.96

Methyl (3a*R,4*S**,6*R**,6a*S**)-4-methyl-1,3-dioxo-6-phenylhexahydro-1*H*-furo[3,4-*c*]pyrrole-4-carboxylate (IVa).** Yield 79%, colorless crystals, mp 208–210°C. ^{1}H NMR spectrum, δ, ppm: 1.50 s (3H, CH_3), 3.48 br.s (1H, NH), 3.65 d (1H, 3a-H, J = 8.0 Hz), 3.71 s (3H, OCH_3), 3.92 d.d (1H, 6a-H, J = 8.8, 8.0 Hz), 4.78 d (1H, 6-H, J = 8.8 Hz), 7.23–7.28 m (1H, H_{arom}), 7.31–7.38 m (4H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 22.92, 50.50, 52.38, 55.85, 61.10, 67.47, 127.65 (2C), 128.14, 128.51 (2C), 139.07, 170.29, 172.17, 172.68. Found, %: C 62.00; H 5.34; N 4.99. $C_{15}H_{15}NO_5$. Calculated, %: C 62.28; H 5.23; N 4.84.

Methyl (3a*R,4*S**,6*R**,6a*S**)-6-(4-chlorophenyl)-4-methyl-1,3-dioxohexahydro-1*H*-furo[3,4-*c*]pyrrole-4-carboxylate (IVb).** Yield 87%, colorless crystals, mp 164–165°C. ^{1}H NMR spectrum, δ, ppm: 1.50 s (3H, CH_3), 3.55 d (1H, NH, J = 3.4 Hz), 3.65 d (1H, 3a-H, J = 8.0 Hz), 3.71 s (3H, OCH_3), 3.94 d.d (1H, 6a-H, J = 8.8, 8.0 Hz), 4.80 d.d (1H, 6-H, J = 8.8, 3.4 Hz), 7.40 s (4H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 22.93, 50.37, 52.41, 55.69, 60.28, 67.45, 128.55 (2C), 129.44 (2C), 132.55, 138.30, 170.44, 172.08, 172.60. Found, %: C 55.71; H 4.38; N 4.43. $C_{15}H_{14}ClNO_5$. Calculated, %: C 55.65; H 4.36; N 4.33. X-Ray diffraction data: monoclinic crystals, space group $P2_1/n$; a = 6.3454(4), b = 22.4276(13), c = 10.7282(6) Å; β = 104.849(1)°; V = 1475.77(15) Å^3; Z = 4; d_{calc} = 1.457 g/cm^3; F(000) = 672. Intensities of 13257 reflections (3528 of which were independent, R_{int} = 0.0286) were measured by ω-scanning in the range 1.82 < θ < 28.00° (–8 ≤ h ≤ 7, –29 ≤ k ≤ 29, –14 ≤ l ≤ 14). The final divergence factors were R_1 = 0.0370, wR_2 = 0.0924 for 2940 reflections with I > 2σ(I). The complete set of crystallographic parameters of compound **IVb** is available from the authors upon request.

Methyl (3a*R,4*S**,6*R**,6a*S**)-6-(4-bromophenyl)-4-methyl-1,3-dioxohexahydro-1*H*-furo[3,4-*c*]pyrrole-4-carboxylate (IVc).** Yield 75%, colorless crystals, mp 168–169°C. ^{1}H NMR spectrum, δ, ppm: 1.50 s (3H, CH_3), 3.55 br.s (1H, NH), 3.65 d (1H, 3a-H, J = 8.0 Hz), 3.70 s (3H, OCH_3), 3.93 d.d (1H, 6a-H, J =

8.6, 8.0 Hz), 4.80 d (1H, 6-H, J = 8.6 Hz), 7.33 d (2H, H_{arom}, J = 8.3 Hz), 7.54 d (2H, H_{arom}, J = 8.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 22.93, 50.32, 52.41, 55.68, 60.33, 67.45, 121.13, 129.80 (2C), 131.46 (2C), 138.73, 170.44, 172.06, 172.59. Found, %: C 49.04; H 3.81; N 4.02. $C_{15}H_{14}BrNO_5$. Calculated, %: C 48.93; H 3.83; N 3.80.

Methyl (3a*R,4*S**,6*R**,6a*S**)-4-benzyl-6-(3-fluorophenyl)-1,3-dioxohexahydro-1*H*-furo[3,4-*c*]-pyrrole-4-carboxylate (IVd).** Yield 82%, colorless crystals, mp 180–181°C. ^{1}H NMR spectrum, δ, ppm: 2.85 d (1H, NH, J = 3.8 Hz), 3.17 d and 3.26 d (1H each, C**H**$_2$Ph, J = 14.0 Hz), 3.72 s (3H, OCH_3), 3.92 d (1H, 3a-H, J = 8.0 Hz), 4.06 d.d (1H, 6a-H, J = 9.4, 8.0 Hz), 5.07 d.d (1H, 6-H, J = 9.4, 3.8 Hz), 7.07–7.19 m (4H, H_{arom}), 7.21–7.32 m (4H, H_{arom}), 7.34–7.42 m (1H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 50.43, 52.29, 55.13, 59.72, 71.82, 114.20 d (J = 8.0 Hz), 115.10 d (J = 8.0 Hz), 123.70, 127.54, 129.08 (2C), 130.08 (2C), 130.62 d (J = 4.0 Hz), 135.65, 141.73, 162.50 d (J = 96.0 Hz), 170.01, 170.83, 171.85. Found, %: C 65.98; H 4.76; N 3.75. $C_{21}H_{18}FNO_5$. Calculated, %: C 65.79; H 4.73; N 3.65.

Substituted octahydropyrrolo[3,4-*b*]pyrrole-3-carboxylic acids VIIIa–VIIId (*general procedure*). Compound **IVa–IVd**, was dissolved in 50 ml of THF, 0.338 g (0.310 ml, 2.7 mmol) of *p*-fluorobenzylamine was added in one portion, and the mixture was stirred for 48–72 h at room temperature (TLC). The mixture was then concentrated under reduced pressure, and the residue was recrystallized from ethyl acetate–hexane.

(2*R,3*S**,3a*R**,6a*S**)-5-(4-Fluorobenzyl)-6a-methyl-4,6-dioxo-2-phenyloctahydropyrrolo[3,4-*b*]-pyrrole-3-carboxylic acid (VIIIa).** Yield 61%, colorless crystals, mp 248–250°C. ^{1}H NMR spectrum, δ, ppm: 1.48 s (3H, CH_3), 3.47–3.56 m (2H, 3-H, 3a-H), 4.46 d and 4.60 d (1H each, 4-FC_6H_4C**H**$_2$, J = 15.2 Hz), 4.83 d (1H, 2-H, J = 4.3 Hz), 7.08–7.17 m (2H, H_{arom}), 7.17–7.43 m (7H, H_{arom}), 12.00 br.s (1H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 22.63, 41.33, 52.33, 54.60, 65.93, 66.26, 115.46, 115.67, 127.46 (2C), 127.88, 128.24 (2C), 130.00, 130.09, 132.75, 138.94, 161.90 d (J = 96.0 Hz), 172.10, 176.13, 179.07. Found, %: C 65.80; H 5.09; N 7.26. $C_{21}H_{19}FN_2O_4$. Calculated, %: C 65.96; H 5.01; N 7.33.

(2*R,3*S**,3a*R**,6a*S**)-2-(4-Chlorophenyl)-5-(4-fluorobenzyl)-6a-methyl-4,6-dioxooctahydropyrrolo[3,4-*b*]pyrrole-3-carboxylic acid (VIIIb).** Yield 65%, colorless crystals, mp 234°C. ^{1}H NMR spectrum, δ, ppm: 1.47 s (3H, CH_3), 3.46–3.54 m (2H, 3-H, 3a-H), 4.45 d and 4.59 d (1H each, 4-FC_6H_4C**H**$_2$, J = 15.2 Hz), 4.84 d (1H, 2-H, J = 4.3 Hz), 7.11–7.15 m (2H, H_{arom}), 7.32–7.38 m (6H, H_{arom}), 12.00 br.s (1H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 22.48, 41.32, 52.14, 54.30, 65.44, 65.77, 115.46, 115.67, 128.19 (2C), 129.39 (2C), 130.01, 130.09, 132.16, 132.75, 138.27, 161.85 d (J = 96.8 Hz), 171.86, 176.07, 179.02. Found, %: C 60.32; H 4.28; N 6.74. $C_{21}H_{18}ClFN_2O_4$. Calculated, %: C 60.51; H 4.35; N 6.72.

(2*R,3*S**,3a*R**,6a*S**)-2-(4-Bromophenyl)-5-(4-fluorobenzyl)-6a-methyl-4,6-dioxooctahydropyrrolo[3,4-*b*]pyrrole-3-carboxylic acid (VIIIc).** Yield 56%, colorless crystals, mp 232°C. ^{1}H NMR spectrum, δ, ppm: 1.47 s (3H, CH_3), 3.48–3.55 m (2H, 3-H, 3a-H), 4.46 d and 4.59 d (1H each, 4-FC_6H_4C**H**$_2$, J = 15.2 Hz), 4.83 d (1H, 2-H, J = 4.5 Hz), 7.13 t (2H, H_{arom}, J = 8.7 Hz), 7.28–7.38 m (4H, H_{arom}), 7.47 d (2H, H_{arom}, J = 8.3 Hz), 11.82 br.s (1H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 22.48, 41.32, 52.09, 54.30, 65.48, 65.78, 115.46, 115.67, 120.72, 129.76 (2C), 130.01, 130.09, 131.10 (2C), 132.72, 138.70, 161.85 d (J = 96.0 Hz), 171.84, 176.06, 179.02. Found, %: C 54.39; H 4.10; N 6.00. $C_{21}H_{18}BrFN_2O_4$. Calculated, %: C 54.68; H 3.93; N 6.07.

(2*R,3*S**,3a*R**,6a*S**)-6a-Benzyl-5-(4-fluorobenzyl)-2-(3-fluorophenyl)-4,6-dioxooctahydropyrrolo-[3,4-*b*]pyrrole-3-carboxylic acid (VIIId).** Yield 49%, colorless crystals, mp 254°C. ^{1}H NMR spectrum, δ, ppm: 3.04 d and 3.18 d (1H each, PhC**H**$_2$, J = 12.9 Hz), 3.46 d.d (1H, 3-H, J = 9.2, 6.0 Hz), 3.61 d (1H, 3a-H, J = 9.2), 4.18 d and 4.41 d (1H each, 4-FC_6H_4C**H**$_2$, J = 15.0 Hz), 4.77 d (1H, 2-H, J = 6.0 Hz), 6.88 d.d (2H, H_{arom}, J = 8.5, 5.6 Hz), 6.93–7.03 m (3H, H_{arom}), 7.08–7.19 m (7H, H_{arom}), 7.25–7.31 m (1H, H_{arom}), 11.95 br.s (1H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 41.04, 41.28, 50.28, 52.43, 65.58, 70.24, 114.01 d (J = 8.0 Hz), 114.61 d (J = 8.0 Hz), 115.27, 115.49, 123.76, 127.44, 128.96 (2C), 129.75, 129.83, 130.23 d (J = 4.0 Hz), 130.36 (2C), 132.17, 135.43, 142.24 d (J = 2.0 Hz), 161.70 d (J = 96.0 Hz), 162.37 d (J = 96.0 Hz), 171.74, 175.86, 178.16. Found, %: C 68.21; H 4.64; N 6.07. $C_{27}H_{22}F_2N_2O_4$. Calculated, %: C 68.06; H 4.65; N 5.88. X-Ray diffraction data: monoclinic crystals, space group $P2_1/c$; a = 11.4149(12), b = 11.4458(14), c = 20.509(2) Å; β = 100.028(2)°; V = 2638.6(5) Å^3; Z = 4, d_{calc} = 1.382 g× cm^{-3}; F(000) = 1140. Intensities of 21561 reflections (4430 independent reflections, R_{int} = 0.0519) were measured by ω-scanning in the range $2.02 < \theta < 24.62°$ ($-13 \le h \le 13$, $-13 \le k \le 13$, $-24 \le l \le 24$). The final

divergence factors were $R_1 = 0.0731$, $wR_2 = 0.2069$ for 3300 reflections with $I > 2\sigma(I)$. The complete set of crystallographic parameters of compound **VId** was deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 761401).

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