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Endic Acid Diamides. Synthesis and Reactivity

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Abstract—A number of symmetric and unsymmetric *endo-cis*-dicarboxamides of the norbornene series containing dimethyl- and diethylamine, morpholine, perhydroazepine, and *p*-bromoaniline fragments were synthesized starting from endic anhydride with the aid of *N*,*N*′-dicyclohexylcarbodiimide. Oxidation of these amides with organic peroxy acids according to Prilezhaev gave *exo*-2-hydroxy-5-oxo-4-oxatricyclo[4.2.1.$0^{3,7}$]-nonane-*endo*-9-carboxylic acid salts. The structure of the obtained products was confirmed by IR and ^{1}H NMR spectroscopy.

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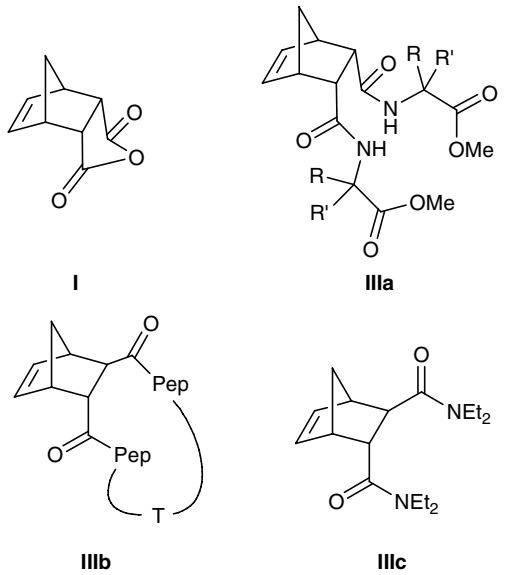
Development of methods of synthesis of dicarboximides derived from commercially available bicyclo[2.2.1]hept-5-ene-*endo*,*endo*-2,3-dicarboxylic anhydride (**I**, endic anhydride) and their reactivity were the subjects of numerous publications [1–5]. However, endic acid monoamides (amido acids) and diamides have been studied to a considerably lesser extent [5–9]. Gallo and Gellman [10] performed an IR study on NH···π hydrogen bonding in norbornenedicarboxamides having a secondary amide group. Some recent publications [11, 12] were concerned with the synthesis and conformational behavior of norbornene-containing acyclic and cyclic peptides **IIIa** and **IIIb**.



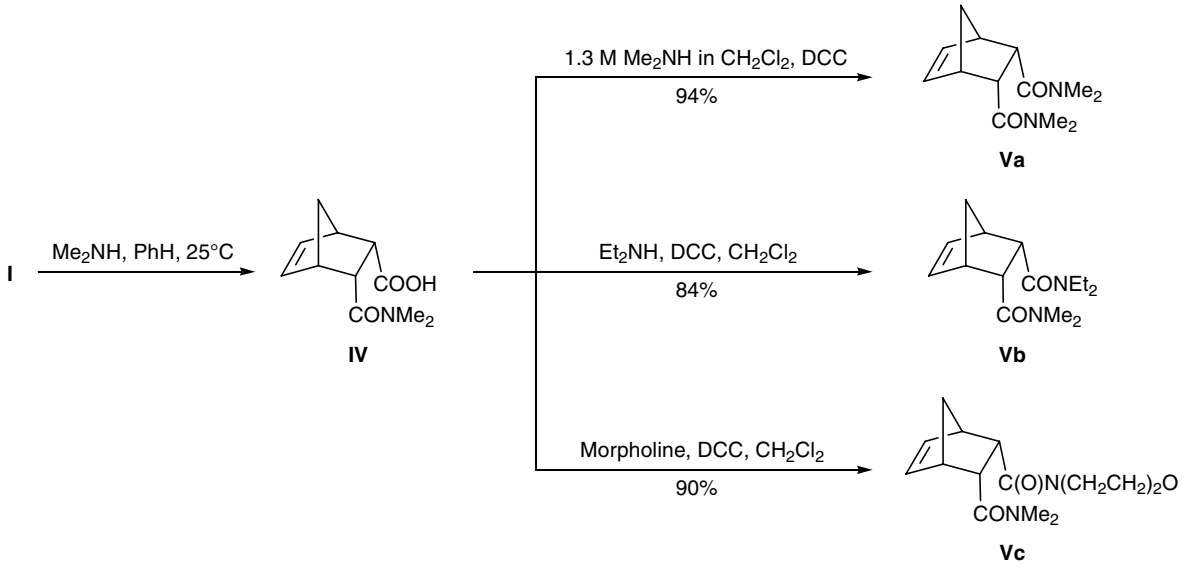
I **IIIa** **IIIb** **IIIc**

R, R′ = Alk; T = cystine/adamantane/norbornene.

N-Alkylamides of cyclic dicarboxylic acids are used in medicine due to their ability to exert general restorative effect on the central nervous system. Among these, the most widely known are Neospiran, Vandid, Anacardiol, and Endomid (**IIIc**) [13, 14]. Metabolism of the latter was studied in detail in [14]. Many *trans*-diamides of the bicyclo[2.2.1]hept-2-ene and bicyclo[2.2.2]oct-2-ene series, as well as their saturated analogs, were synthesized by aminolysis of cyclopenta- and cyclohexadiene adducts with fumaroyl chloride [13, 15–17]. Some diamides were obtained by Diels–Alder reactions involving fumaric acid diamides. However, no systematic studies on the reactivity and physiological activity of these compounds were performed.

Taking into account that all attempts to obtain bicyclo[2.2.1]hept-5-ene-*endo*,*endo*-2,3-dicarbonyl dichloride were unsuccessful [treatment of endic acid (**II**) with classical chlorinating agents leads to the formation of only anhydride **I**], in the present work we developed procedures for the preparation of some symmetric and unsymmetric *endo-cis*-diamides of the norbornene series from endic acid (**II**) and its monoamides usig *N*,*N*′-dicyclohexylcarbodiimide (DCC) as condensing agent. In such a way, from monoamide **IV** we synthesized diamides **Va**–**Vc** in high yield (Scheme 1). Unsymmetrical diamide **Vd** was obtained from monoamides **VI** and **VII** which (like amido acid **IV**) were prepared by aminolysis of anhydride **I**. On the other hand, symmetric diamides **VIIIa** and **VIIIb** were synthesized in high yields from both acid **II** and the corresponding monoamides **VI** and **VII** (Scheme 2).

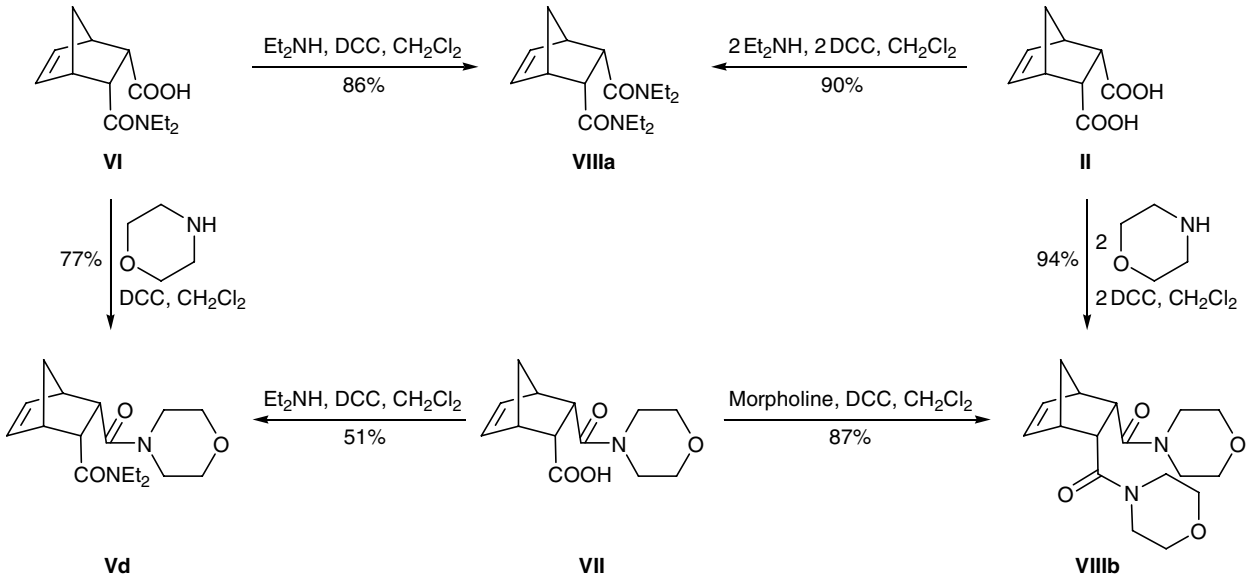
Scheme 1.



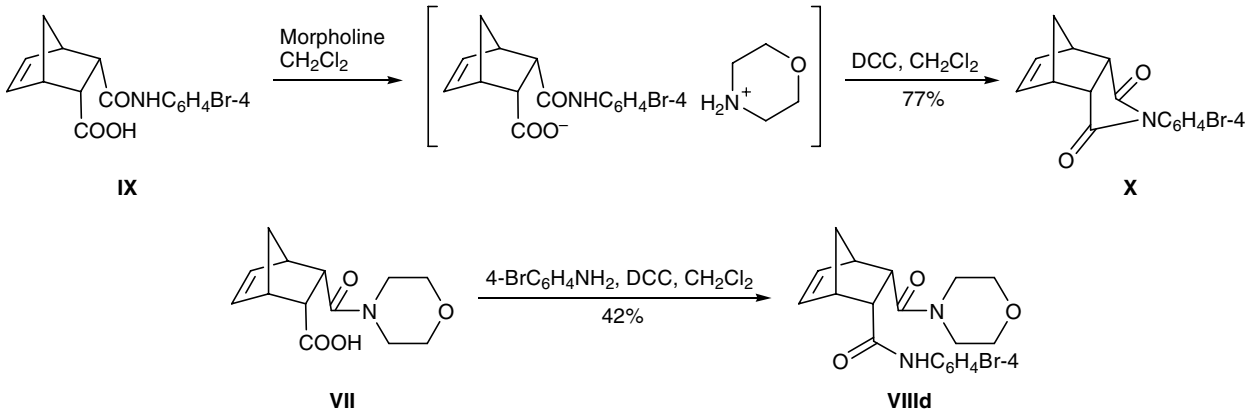
Following an analogous procedure, we synthesized symmetric diamide **VIIIc** (yield 78%) including two perhydroazepine fragments. The above reactions generally take 2–7 days (TLC data), and the yields of the target products range from 51 to 94%. The scope of the proposed procedure is limited: we failed to obtain diamide **VIIId** having a secondary amide group from amido acid **IX**; instead, we isolated previously reported [18] imide **X** in 77% yield. When amide **VII** was used as initial compound, 42% of diamide **VIIId** was obtained (Scheme 3).

Compounds **IV**, **VI**, and **VII** were described by us previously [19, 20]. Amide **IX** was synthesized by reaction of equimolar amounts of anhydride **I** and *p*-bromoaniline in benzene at room temperature. The structure of all newly synthesized compounds was confirmed by the IR and ^{1}H NMR spectra. In the IR spectra of diamides **Va**–**Vd** and **VIIIa**–**VIIId**, the carbonyl stretching vibration band appeared at 1670–1630 cm^{-1} (amide I). Compound **VIIId** displayed additional absorption bands at 1540 (δ_{N-H}, amide II) and 1278 cm^{-1} (ν_{C-N}, amide III) due to the secondary amide group [21], as well as N–H stretching vibration band at 3280 cm^{-1}. Stretching and bending vibrations of the norbornene =C–H bond appeared at 3075–3020 and 735–715 cm^{-1}, respectively [21, 22].

Scheme 2.



Scheme 3.

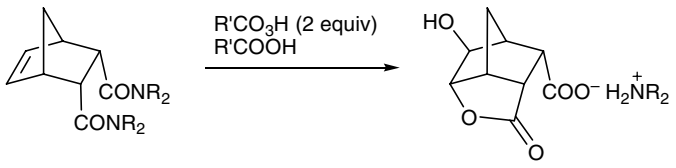


The ^{1}H NMR spectra of diamides **Va**–**Vd** and **VIIIa**–**VIIId** contained signals in the δ region 5.73–6.23 ppm from the olefinic 5-H and 6-H protons; the latter are nonequivalent in molecules of unsymmetrical diamides **Vb**–**Vd** and **VIIId** (Δδ = 0.13–0.50 ppm). Signals from protons in the bridgehead positions (1-H and 4-H) were located at δ 2.93–3.12 ppm, and 2-H and 3-H resonated at δ 3.31–3.51 ppm. Protons in the methylene bridge (*syn*-7-H and *anti*-7-H) had fairly similar chemical shifts (δ 1.18–1.38 ppm), and their signals were split with a geminal coupling constant ^2J of 7.4–8.1 Hz. In the spectrum of amide **VIIId** we also observed a downfield singlet at δ 9.73 ppm, belonging to the NH proton.

We also examined oxidation of diamides **VIIIa**–**VIIIc** according to Prilezhaev. Treatment of these compounds with peroxyformic or peroxyacetic acid *in situ* at 0 and 25°C, respectively, gave the corresponding ammonium *exo*-2-hydroxy-5-oxo-4-oxatricyclo-[4.2.1.0^{3,7}]nonane-*endo*-9-carboxylates **XI**–**XIII** as the only products (Scheme 4). In the reaction of peroxyacetic acid with *trans*-diamide **IIIc**, lactone **XIV** was isolated instead of the expected salt [14] (Scheme 5). We tried to synthesize amidolactone **XV** by oxidation of diamide **VIIIb** under milder conditions, using a solution of monoperoxyphthalic acid generated *in situ* in ethyl acetate at room temperature; however, only 80% of the initial compound was recovered from the reaction mixture.

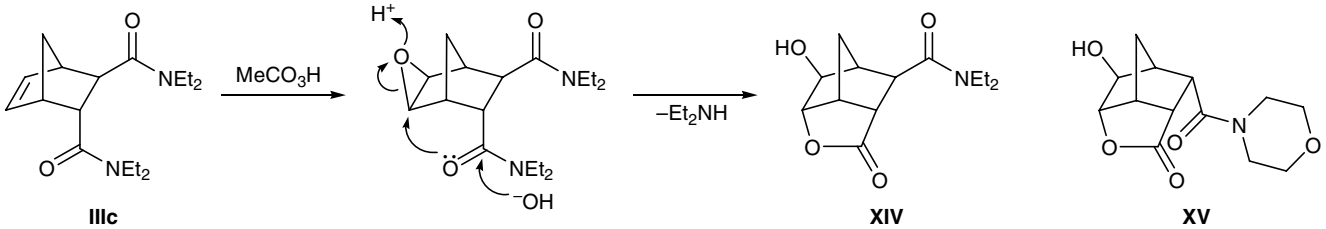
Salts **XI**–**XIII** were synthesized by us previously [19, 20] by epoxidation of amido acids obtained from endic anhydride (**I**). Scheme 6 illustrates a probable reaction mechanism. Nucleophilic attack by the oxygen atom of the carboxamide group on the nearest electro-

Scheme 4.

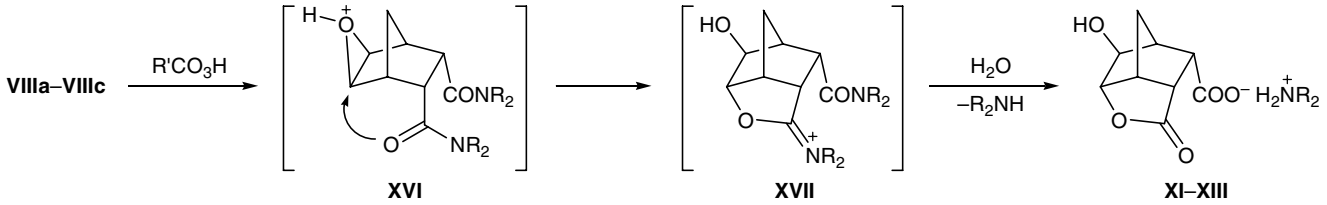


VIIIa, **XI**, R = Et; **VIIIb**, **XII**, R_2N = morpholino; **VIIIc**, **XIII**, R_2N = perhydroazepin-1-yl; R′ = H, Me.

Scheme 5.



Scheme 6.



philic carbon atom in protonated epoxy derivative **XVI** gives intermediate **XVII** which undergoes hydrolysis at the imino and amide groups to produce ammonium salts **XI**–**XIII**.

EXPERIMENTAL

The IR spectra were recorded in KBr on UR-20 and Perkin–Elmer Paragon 500 FT-IR spectrometers. The ^{1}H NMR spectra were measured on Varian VXR spectrometers at 200 and 300 MHz from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using diethyl ether (A) or propan-2-ol (B) as eluent; spots were visualized by treatment with iodine vapor. The elemental compositions were determined on a Carlo Erba analyzer.

***endo*-3-(*p*-Bromophenylcarbamoyl)bicyclo[2.2.1]-hept-5-ene-*endo*-2-carboxylic acid (IX).** *p*-Bromoaniline, 3.44 g (0.02 mol), was added under stirring to a solution of 3.28 g (0.02 mol) of anhydride **I** in 25 ml of benzene, and the mixture was stirred at room temperature until the reaction was complete (TLC). The precipitate was filtered off and subjected to additional purification. Yield 6.59 g (98%), mp 152–154°C, R_f 0.74 (A). IR spectrum, ν, cm^{-1}: 3300, 3060, 1721, 1672, 1531, 1320, 1275, 714. ^{1}H NMR spectrum (300 MHz, DMSO-d_6), δ, ppm: 11.66 br.s (1H, COOH), 9.96 s (1H, NH), 7.49 d (2H, H_{arom}), 7.42 d (2H, H_{arom}), 6.19 d.d (1H, 6-H, $^3J_{5,6}$ = 5.6, $^3J_{6,1}$ = 2.9 Hz), 6.04 d.d (1H, 5-H, $^3J_{4,5}$ = 3.2 Hz), 3.32 d.d (1H, 2-H, $^3J_{2,3}$ = 10.2 Hz), 3.22 d.d (1H, 3-H, $^3J_{1,2}$ = $^3J_{3,4}$ = 3.3 Hz), 3.06 m (1H, 1-H), 3.01 m (1H, 4-H), 1.33 d (1H, *syn*-7-H), 1.27 d (1H, *anti*-7-H, ^2J = 8.4 Hz). Found, %: C 53.63; H 4.12; N 4.25. $C_{15}H_{14}BrNO_3$. Calculated, %: C 53.57; H 4.17; N 4.17.

Endic acid diamides (*general procedure*). Amido acid **IV**, **VI**, or **VII**, 0.02 mol, was dissolved in 20 ml of anhydrous methylene chloride, 0.02 mol of the corresponding amine was added (dimethylamine was used as a freshly prepared 1.3 M solution in methylene chloride), the mixture was stirred for 10–15 min, and a solution of *N*,*N*′-dicyclohexylcarbodiimide in a small amount of methylene chloride was added. The mixture was stirred at room temperature until the reaction was complete (TLC), and the precipitate of *N*,*N*′-dicyclohexylurea was filtered off, washed on a filter with anhydrous methylene chloride, and dried, The filtrate was evaporated under reduced pressure, the residue was ground with diethyl ether (to remove residual DCC), and the product was filtered off, washed, dried, and recrystallized from propan-2-ol or acetone.

***N*,*N*,*N*′,*N*′-Tetramethylbicyclo[2.2.1]hept-5-ene-*endo*,*endo*-2,3-dicarboxamide (Va).** Yield 4.44 g (94%), mp 132–134°C, R_f 0.27 (B). IR spectrum, ν, cm^{-1}: 3025, 1635, 1475, 1415, 1270, 1160, 715. ^{1}H NMR spectrum (300 MHz), δ, ppm: 5.98 m (2H, 5-H, 6-H), 3.47 m (2H, 2-H, 3-H), 2.98 m (2H, 1-H, 4-H), 2.89 s (6H, CH_3), 2.67 s (6H, CH_3), 1.36 d (1H, *syn*-7-H), 1.20 d (1H, *anti*-7-H, ^2J = 8.1 Hz). Found, %: C 66.03; H 8.51; N 11.79. $C_{13}H_{20}N_2O_2$. Calculated, %: C 66.10; H 8.47; N 11.86.

***N*,*N*-Diethyl-*N*′,*N*′-dimethylbicyclo[2.2.1]hept-5-ene-*endo*,*endo*-2,3-dicarboxamide (Vb).** Yield 4.44 g (84%), oily substance, R_f 0.18 (A). IR spectrum, ν, cm^{-1}: 3070, 1640, 1465, 1265, 1150, 730. ^{1}H NMR spectrum (300 MHz), δ, ppm: 6.16 m (1H, 5-H), 5.78 m (1H, 6-H), 3.34 m (1H, 2-H), 3.32 m (1H, 3-H), 3.30 q (2H, CH_2), 3.13 q (2H, CH_2), 2.96 m (1H, 1-H), 2.93 m (1H, 4-H), 2.80 s (3H, CH_3), 2.64 s (3H, CH_3), 1.37 d (1H, *syn*-7-H), 1.19 d (1H, *anti*-7-H, ^2J = 7.5 Hz), 1.11 t (3H, CH_3), 0.93 t (3H, CH_3). Found, %: C 68.21; H 9.13; N 10.60. $C_{15}H_{24}N_2O_2$. Calculated, %: C 68.18; H 9.09; N 10.61.

***N*,*N*-Dimethyl-*endo*-3-(morpholinocarbonyl)bicyclo[2.2.1]hept-5-ene-*endo*-2-carboxamide (Vc).** Yield 5.00 g (90%), mp 177–180°C, R_f 0.30 (B). IR spectrum, ν, cm^{-1}: 3070, 1645, 1465, 1440, 1275, 1240, 1120, 735. ^{1}H NMR spectrum (300 MHz), δ, ppm: 6.08 m (1H, 5-H), 5.90 m (1H, 6-H), 3.55–3.42 (8H, CH_2), 3.51 m (1H, 2-H), 3.46 m (1H, 3-H), 3.01 m (1H, 1-H), 2.97 m (1H, 4-H), 2.94 s (3H, CH_3), 2.70 s (3H, CH_3), 1.34 d (1H, *syn*-7-H), 1.20 d (1H, *anti*-7-H, ^2J = 8.1 Hz). Found, %: C 64.70; H 7.99;

N 10.01. $C_{15}H_{22}N_2O_3$. Calculated, %: C 64.75; H 7.91; N 10.07.

***N*,*N*-Diethyl-*endo*-3-(morpholinocarbonyl)bicyclo[2.2.1]hept-5-ene-*endo*-2-carboxamide (Vd).** Yield 4.71 g (77%), mp 168–170°C, R_f 0.58 (B). IR spectrum, ν, cm^{-1}: 3075, 1650, 1465, 1445, 1280, 1250, 1150, 735. ^1H NMR spectrum (200 MHz), δ, ppm: 6.23 d.d (1H, 5-H), 5.73 d.d (1H, 6-H, $^3J_{5,6}$ = 5.3, $^3J_{4,5}$ = $^3J_{6,1}$ = 2.7 Hz), 3.59–3.40 (8H, CH_2), 3.34 m (1H, 2-H), 3.31 m (1H, 3-H), 3.26 q (2H, CH_2), 3.14 q (2H, CH_2), 2.99 m (1H, 1-H), 2.93 m (1H, 4-H), 1.36 d (1H, *syn*-7-H), 1.20 d (1H, *anti*-7-H, ^2J 8.0 Hz), 1.12 t (3H, CH_3), 0.94 t (3H, CH_3). Found, %: C 66.60; H 8.52; N 9.19. $C_{17}H_{26}N_2O_3$. Calculated, %: C 66.67; H 8.50; N 9.15.

***N*,*N*,*N*′,*N*′-Tetraethylbicyclo[2.2.1]hept-5-ene-*endo*,*endo*-2,3-dicarboxamide (VIIIa).** Yield 5.02 g (86%), mp 133–135°C, R_f 0.22 (A), 0.67 (B). IR spectrum, ν, cm^{-1}: 3058, 1642, 1630, 1462, 1426, 1278, 1258, 1140, 718. ^1H NMR spectrum (300 MHz), δ, ppm: 5.98 m (2H, 5-H, 6-H), 3.38 m (2H, 2-H, 3-H), 3.29 q (4H, CH_2), 3.18 q (4H, CH_2), 2.93 m (2H, 1-H, 4-H), 1.38 d (1H, *syn*-7-H), 1.18 d (1H, *anti*-7-H, ^2J = 7.8 Hz), 1.08 t (6H, CH_3), 0.92 t (6H, CH_3). Found, %: C 69.91; H 9.52; N 9.64. $C_{17}H_{28}N_2O_2$. Calculated, %: C 69.86; H 9.59; N 9.59.

***endo*,*endo*-2,3-Bis(morpholinocarbonyl)bicyclo[2.2.1]hept-5-ene (VIIIb).** Yield 5.57 g (87%), mp 219–220°C, R_f 0.27 (B). IR spectrum, ν, cm^{-1}: 3040, 1645, 1460, 1435, 1275, 1240, 1120, 735. ^1H NMR spectrum (300 MHz), δ, ppm: 6.01 m (2H, 5-H, 6-H), 3.52–3.42 (16H, CH_2), 3.33 m (2H, 2-H, 3-H), 2.97 m (2H, 1-H, 4-H), 1.34 d (1H, *syn*-7-H), 1.21 d (1H, *anti*-7-H, ^2J = 8.1 Hz). Found, %: C 63.81; H 7.55; N 8.69. $C_{17}H_{24}N_2O_4$. Calculated, %: C 63.75; H 7.50; N 8.75.

***endo*,*endo*-2,3-Bis(perhydroazepin-1ylcarbonyl)bicyclo[2.2.1]hept-5-ene (VIIIc).** Yield 5.37 g (78%), mp 149–151°C, R_f 0.17 (A), 0.63 (B). IR spectrum, ν, cm^{-1}: 3070, 1635, 1450, 1430, 1270, 1250, 1170, 730. ^1H NMR spectrum (300 MHz), δ, ppm: 5.98 m (2H, 5-H, 6-H); 3.41 m (2H, 2-H, 3-H); 3.29–3.16, 1.74–1.59, 1.47, 1.14–0.98 (24H, CH_2); 2.97 m (2H, 1-H, 4-H); 1.37 d (1H, *syn*-7-H); 1.18 d (1H, *anti*-7-H, ^2J = 7.4 Hz). Found, %: C 73.33; H 9.28; N 8.19. $C_{21}H_{32}N_2O_2$. Calculated, %: C 73.26; H 9.30; N 8.14.

***N*-*p*-Bromophenyl-*endo*-3-(morpholinocarbonyl)bicyclo[2.2.1]hept-5-ene-*endo*-2-carboxamide (VIIId).** Yield 3.40 g (42%), mp 182–185°C, R_f 0.21 (B). IR spectrum, ν, cm^{-1}: 3280, 3020, 1670, 1645, 1540, 1320, 1278, 1120, 735. ^1H NMR spectrum (300 MHz), δ, ppm: 9.73 s (1H, NH), 7.47–7.35 (4H, H_{arom}), 6.14 m (1H, 5-H), 6.01 m (1H, 6-H), 3.52–3.42 (8H, CH_2), 3.38 m (1H, 2-H), 3.32 m (1H, 3-H), 3.12 m (1H, 1-H), 2.97 m (1H, 4-H), 1.34 d (1H, *syn*-7-H), 1.21 d (1H, *anti*-7-H, ^2J = 7.8 Hz). Found, %: C 56.32; H 5.25; N 6.98. $C_{19}H_{21}BrN_2O_3$. Calculated, %: C 56.30; H 5.19; N 6.91.

Symmetric diamides **VIIIa** and **VIIIb** were synthesized by a similar procedure from endic acid **II** using 2 equiv of *N*,*N*′-dicyclohexylcarbodiimide and 2 equiv of the corresponding amine; yield 5.26 g (90%) (**VIIIa**), 6.02 g (94%) (**VIIIb**).

Oxidation of diamides VIIIa–VIIIc with peroxyformic or peroxyacetic acid *in situ*. Diamide **VIIIa–VIIIc**, 2 mmol, was dissolved in 5–8 ml of 98% formic or acetic acid, 0.23 ml (4 mmol) of 50% aqueous hydrogen peroxide was added dropwise under stirring at 0°C, and the mixture was stirred at that temperature until the reaction was complete (TLC). Volatile substances were removed under reduced pressure, the oily residue was treated with diethyl ether and thoroughly ground in the cold, and the precipitate was filtered off and dried. We thus isolated compounds **XI–XIII** [19, 20].

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