Lactonization of Epoxyendic Anhydride in Reactions with Amines

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Abstract—Reactions of *exo*-5,6-epoxybicyclo[2.2.1]hept-5-ene-*endo*-2,*endo*-3-dicarboxylic anhydride (epoxy-endic anhydride) with acyclic, aromatic, heteroaromatic, and nonaromatic heterocyclic amines afforded the corresponding heterocyclization products, substituted *exo*-2-hydroxy-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-*endo*-9-carboxamides (oxabrendanes), whose structure was confirmed by the IR and ^{1}H and ^{13}C NMR (including two-dimensional) spectra. Other approaches to the tricyclic compounds were also examined, in particular via reactions of organic peroxy acids with amido acids obtained by aminolysis of endic anhydride.

Both methods of preparation and reactivity of epoxy derivatives of anhydrides containing a norbornene skeleton have been studied insufficiently, presumably because of difficulties in epoxidation of the double bond which suffers from an appreciable electron-acceptor effect of the *endo*-anhydride moiety [1]. The parent compound of this series of epoxy derivatives, *exo*-5,6-epoxybicyclo[2.2.1]heptane-*endo*-2,*endo*-3-dicarboxylic anhydride (**I**) was synthesized by oxidation of endic anhydride with trifluoroperoxyacetic [2] and *m*-chloroperoxybenzoic acids. Treatment of epoxide **I** with boiling anhydrous methanol or boiling water gave hydroxy lactones **IIa** and **IIb**, respectively (Scheme 1)

[2, 3]. 1- and 7-Alkyl-substituted epoxy anhydrides are readily converted into analogous lactones at room temperature in the presence of hydrochloric acid provided that the epoxy fragment in the substrate is additionally activated [4]. Fray and Hilton [5] obtained the corresponding hydrazide by heating compound **I** with hydrazine in boiling acetonitrile [5].

We recently showed that epoxide **I** reacts with ammonia, aniline, and benzylamine under mild conditions to give substituted oxabrendane derivatives, *exo*-2-hydroxy-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-*endo*-9-carboxamides **IIIa–IIIc** (Scheme 2) [6].

Scheme 1.

Scheme 2.

R = H (**a**), Ph (**b**), PhCH$_2$ (**c**).
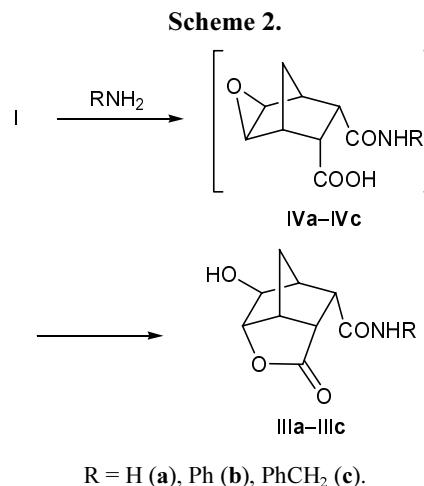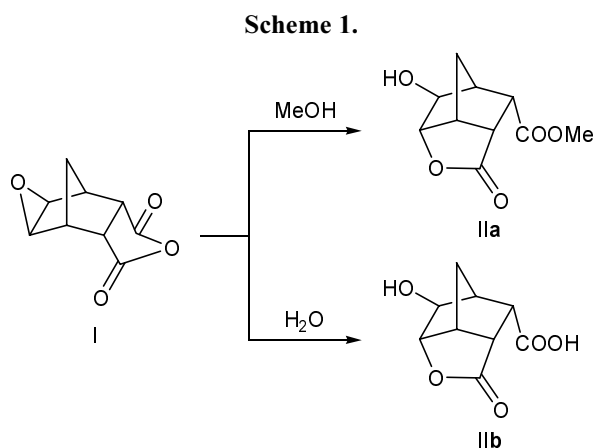
The mechanism of lactonization of amido acids **IVa–IVc** as probable intermediates was studied by PM3 quantum-chemical calculations [7] taking into account solvent effect in the macroscopic approximation (COSMO). We calculated the potential energy surfaces (PES) for heterocyclization of compounds **IVa–IVc** in favorable conformations with respect to the substituents (carboxamide and carboxy groups) at the carbon framework. The proposed heterocyclization mechanisms involved proton transfer from the carboxy group to the oxygen or nitrogen atom of the carboxamide fragment, followed by intramolecular ring closure with participation of the carboxylate oxygen atom; in all cases, the second step was rate-determining [7]. In the cyclization of epoxides **IVa–IVc**, proton transfer from the carboxy group is preferred, while cyclization at the amide rather than carboxy moiety is more favorable when proton transfer does not occur [7].

Trifluoroperoxyacetic acid was prepared by reaction of trifluoroacetic anhydride with 96% hydrogen peroxide in methylene chloride. Endic anhydride was oxidized in methylene chloride on cooling, the progress of the reaction being monitored by TLC. We examined reactions of epoxy anhydride **I** with various primary and secondary amines: acyclic amines (methylamine, dimethylamine, and *tert*-butylamine), aromatic amines (*m*-toluidine and *p*-nitroaniline), hetarylamines (2- and 3-aminopyridines, 4-amino-1,2,4-triazole, 2-aminothiazole, and 5-methyl-2-amino-1,3,4-thiadiazole), and nonaromatic heterocyclic amines (3-amino- and 3-methylaminotetrahydrothiophene 1,1-dioxides and piperazine). The reactions were carried out by stirring equimolar amounts of compound **I** and the corresponding amine in benzene at room temperature, the progress of the reactions being monitored by TLC. This procedure was proposed previously for the synthesis of unsaturated amido acids **VI** (R = alkyl, benzyl, aryl, hetaryl) by aminolysis of endic anhydride (**V**) (Scheme 3) [8, 9]. As a result, we isolated amido lactones **VII–IX** as the only products (yield 48–91%; Scheme 4). The reaction time varied from 2 days for methyl- and dimethylamine and *m*-toluidine to

Scheme 4.

VIIa–VIIe, VIIIa–VIIIe, IXa, IXb
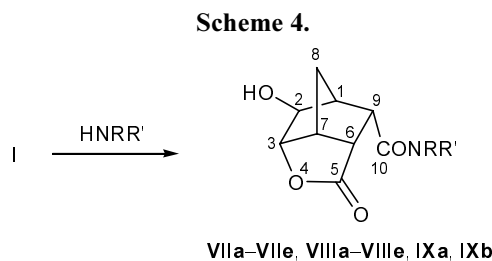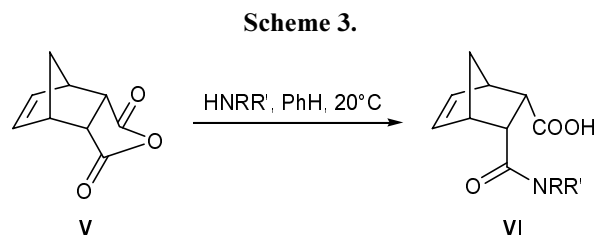
VII, R = H, R' =Me (**a**), R = R' = Me (**b**), R = H, R' = *t*-Bu (**c**), R = H, R' = *p*-MeC$_6$H$_4$ (**d**), R = H, R' = *p*-O$_2$N-C$_6$H$_4$ (**e**); **VIII**, R = H, R' = pyridin-2-yl (**a**), pyridin-3-yl (**b**), 4*H*-1,2,4-triazol-4-yl (**c**), 1,3-thiazol-2-yl (**d**), 5-methyl-1,3,4-thiadiazol-2-yl (**e**); **IX**, R = H, R' = 1,1-dioxotetrahydro-λ^6-thiophen-3-yl (**a**), R = Me, R' = 1,1-dioxotetrahydro-λ^6-thiophen-3-yl (**b**).

4–5 days for aminopyridine, 4-amino-1,2,4-triazole, 2-aminothiazole, and 2-amino-5-methyl-1,3,4-thiadiazole. The reaction of **I** with *p*-nitroaniline took 10 days. 3-Methylaminotetrahydrothiophene 1,1-dioxide reacted with compound **I** more readily than did its analog having no methyl group on the nitrogen, and the syntheses of compounds **IXa** and **IXb** required 5 and 8 days, respectively.

In the reaction of **I** with piperazine we isolated 29% of product **IXc** as a result of attack by the diamine molecule on two molecules of epoxy anhydride **I** (Scheme 5). The structure of **IXc** is confirmed by the intensity ratio of signals from the oxabrendane and piperazine moieties in the ^{1}H NMR spectrum and the absence of NH proton signals. The ^{1}H and ^{13}C NMR spectra of **IXc** contained only one proton and carbon signal from the piperazine fragment (δ 2.82 ppm, δ_C 42.7 ppm), indicating symmetric structure of the products.

Scheme 5.

IXc
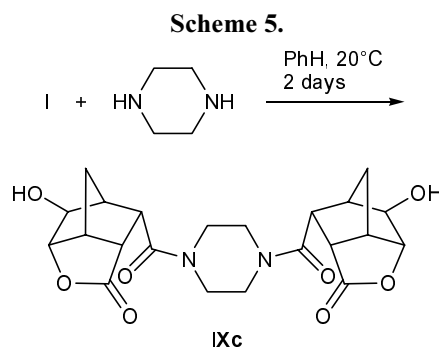
Amido lactones **VII–IX** displayed in the IR spectra absorption bands in the region 3550–3400 cm^{-1} (νOH), while those derived from primary amines also showed narrower bands in the region 3340–3330 cm^{-1} (νNH);
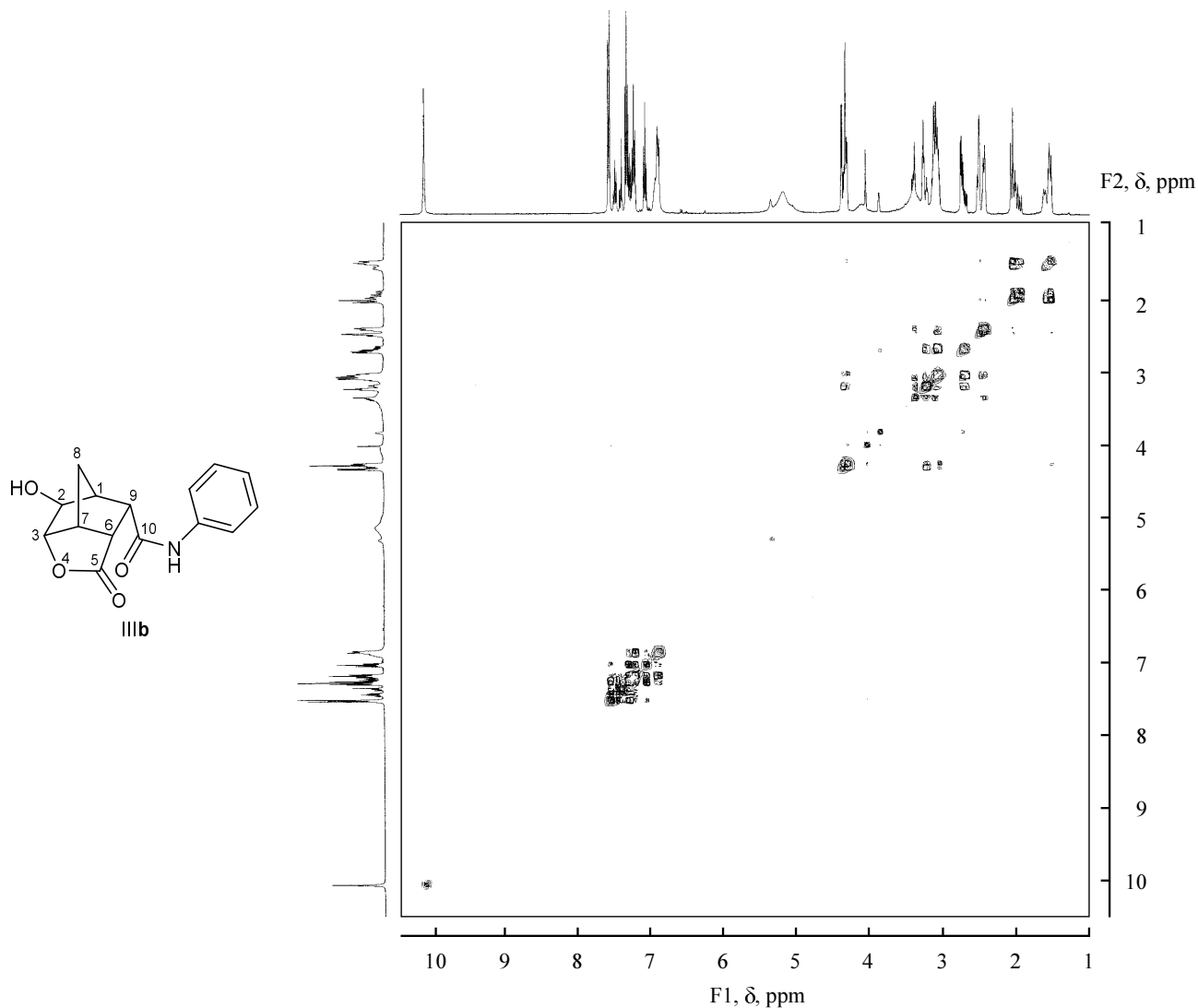
Scheme 3.

Fig. 1. ^{1}H–^{1}H COSY spectrum of *N*-phenyl-*exo*-2-hydroxy-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-*endo*-9-carboxamide (**IIIb**).

carbonyl absorption bands were observed at 1787–1754 (lactone) and 1688–1628 cm^{-1}(amide) [10].

Important information was obtained by analyzing the ^{1}H and ^{13}C NMR spectra. The proton signals were assigned on the basis of the two-dimensional COSY spectrum (Fig. 1) of compound **IIIb** which was described previously [6]. The ^{1}H NMR spectra contained key signals typical of intramolecular cyclization products of *exo*-epoxynorbornanes [11, 12], namely, a broadened singlet at δ 3.98–4.24 ppm from the *endo*-2-H proton and a doublet at δ 4.22–4.37 ppm ($^3J_{3,7}$ = 4.4–5.3 Hz) from 3-H. The isolated lactones also showed in the spectra two doublets from protons in the methylene bridge (C^{8}H$_2$, ^2J = 10.2–11.3 Hz) and signals from *exo*-6-H and *exo*-9-H ($^3J_{6,9}$ = 10.0–11.1 Hz) which were additionally split due to coupling

with 7-H and 1-H, respectively. The spectra also contained signals from protons in the substituents at the amide nitrogen atom (methyl and *tert*-butyl groups and aromatic rings).

In the ^{13}C NMR spectra of amido lactones (Fig. 2) two signals typical of carbonyl carbon atoms were present. The position of one of these (downfield signal, δ$_C$ 177.2–178.4 ppm) is almost independent on the amide group structure; it was assigned to the lactone carbonyl (C^5). The other signal changes its position, depending on the substituents on the nitrogen atom (δ$_C$ 168.4–173.2 ppm, C^{10}). The downfield region of the spectrum also contained signals from carbon atoms adjacent to oxygen. On the basis of published data [6, 11], we assigned signals at δ$_C$ 86.4–87.5 ppm to C^3, and those at δ$_C$ 71.9–73.1 ppm, to C^2. Signals from
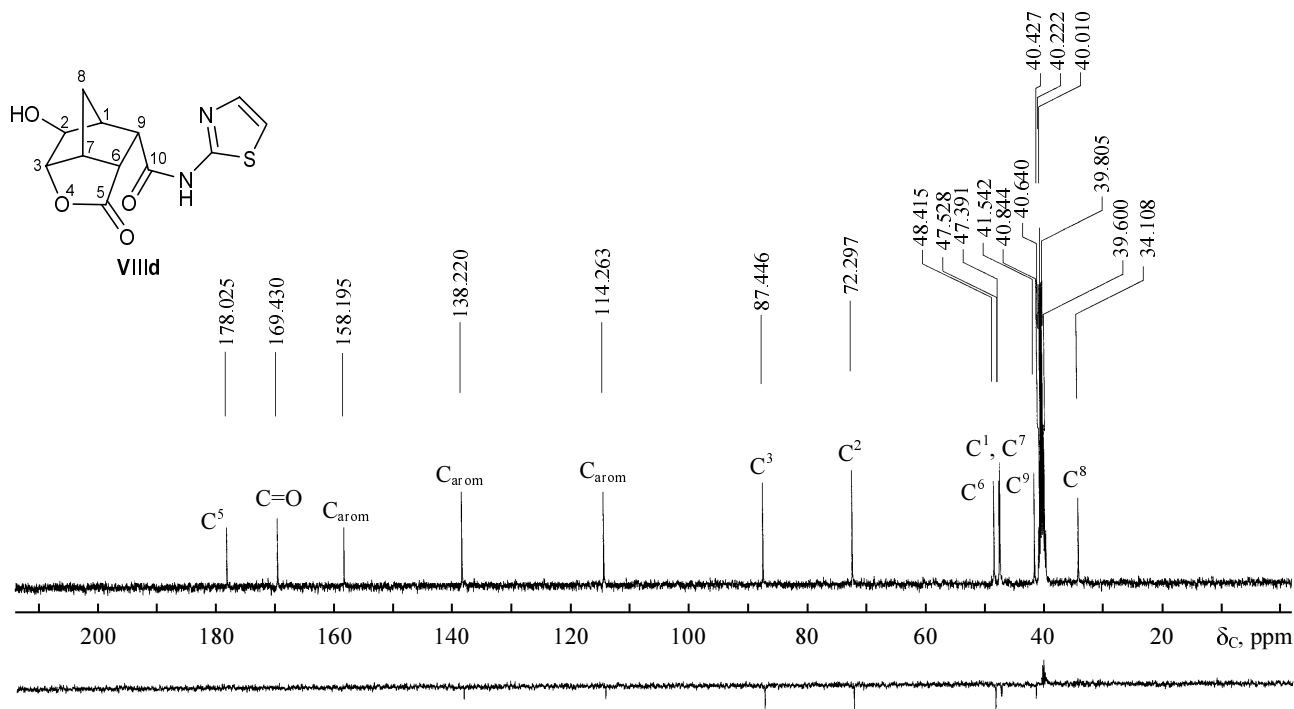
Fig. 2. ^{13}C NMR spectrum of *N*-(1,3-thiazol-2-yl)-*exo*-2-hydroxy-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-*endo*-9-carboxamide (**VIIId**) (DMSO-d_6, 100.57 MHz).

substituents on the nitrogen atom were observed at their usual positions.

We tried to develop another procedure for the synthesis of the same lactones via epoxidation of amido acids **VI** with peroxy acids according to Prilezhaev. The possibility of using this method follows from analysis of numerous published data on lactonization of carboxylic acids of the norbornene series and their derivatives by the action of peroxy acids [1, 13]. As shown in [3, 14], epoxidation of norbornenedicarboxylic acids is accompanied by lactonization if at least one carboxy group is oriented *endo* with respect to the bicyclic carbon skeleton. Carboxy lactones were also obtained on the basis of endic anhydride using other oxidants, such as 30% hydrogen peroxide in *tert*-butyl alcohol in the presence of sodium tungstate or other catalysts [15], as well as by the action of calcium hypochlorite on endic acid or other dicarboxylic acids in water [16].

An important specific feature of epoxidation of carboxylic acid derivatives is that heterocyclization may involve amide groups in the *endo* position with respect to the carbon skeleton. This applies to lactonization of amides **X** (R = H, R' = Me; R = R' = Me; R = H, R' = Ph; R" = H, Me) [11] and *trans*-diamide **XI** by the action of peroxyacetic acid (Scheme 6) [17].

These data suggest possible concurrent participation of nucleophilic centers of the *endo*-oriented carboxy and carboxamide groups in the heterocyclization, which was confirmed by quantum-chemical calculations [7]. On the one hand, our attempts to obtain amido lactone **VIIb** by treatment of amide **XII** with peroxyformic acid (generated *in situ* from 98% formic
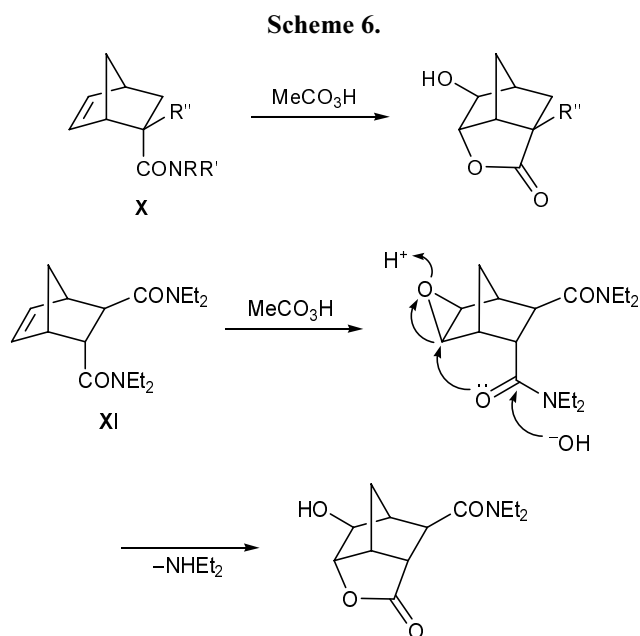
Scheme 6.
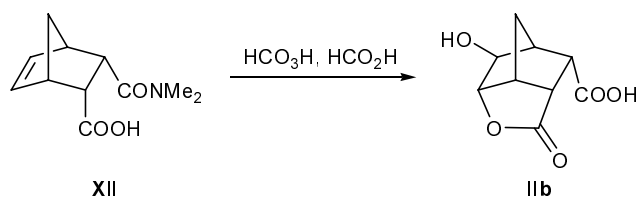
Scheme 7.

acid and 50% hydrogen peroxide) led to formation of known carboxy lactone **IIb** (Scheme 7) as the only (at 0°C) or major product (at 40 and 60°C) (the ^{1}H NMR spectrum contained no signals from carboxamide group). On the other hand, we succeeded in converting amido acid **XIII** into amido lactone **IIIc** by reaction of the former with trifluoroperoxyacetic acid (Scheme 8). The product was identical to a sample described previously [6].

Scheme 8.
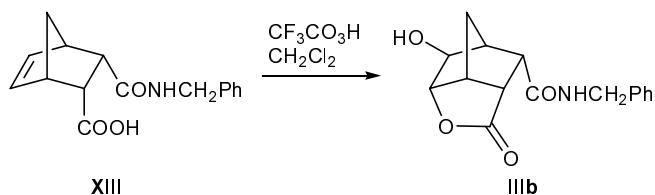
EXPERIMENTAL

The IR spectra were measured in KBr on Specord 75-IR and UR-20 spectrometers. The ^{1}H NMR spectra were recorded on Varian-VXR (200 and 300 MHz) and Gemini-BB spectrometers (400 and 500 MHz) from solutions in chloroform-d or DMSO-d_6 using TMS as internal reference. The ^{13}C NMR spectra were obtained on a Gemini-BB instrument at 100.57 MHz. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates; the chromatograms were developed with iodine vapor. The elemental compositions were determined using a Carlo Erba analyzer.

exo-5,6-Epoxybicyclo[2.2.1]heptane-*endo*-2,*endo*-3-dicarboxylic anhydride (I). A solution of trifluoroperoxyacetic acid prepared from 4.0 ml of 96% hydrogen peroxide and 29.4 ml of trifluoroacetic anhydride in 40 ml of methylene chloride was added to a mixture of 20.0 g (0.12 mol) of bicyclo[2.2.1]hept-5-ene-*endo*-2,*endo*-3-dicarboxylic anhydride (V) and 20.0 g (0.14 mol) of anhydrous sodium sulfate in 30 ml of methylene chloride, and the mixture was stirred until the reaction was complete (TLC). Volatile substances were removed under reduced pressure, and

the solid residue was recrystallized from 1,4-dioxane. Yield 52%, mp 239–241°C; published data [2]: mp 232–233°C (from acetonitrile). IR spectrum, ν, cm^{-1}: 3041, 1775, 1695, 1499, 858. ^{1}H NMR spectrum, δ, ppm: 3.26 m (2H, 5-H, 6-H), 3.22 m (2H, 2-H, 3-H), 2.96 m (2H, 1-H, 4-H), 1.64 d (1H, *syn*-7-H), 1.03 d (1H, *anti*-7-H).

exo-2-Hydroxy-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]-nonane-*endo*-9-carboxylic acid (IIb). Compound **XII**, 0.42 g (2 mmol), was dissolved in 5 ml of 98% formic acid, the solution was cooled to 0°C, 0.14 g (4 mmol) of 50% hydrogen peroxide was added under stirring, and the mixture was stirred at that temperature until the reaction was complete (TLC). Excess formic acid was removed under reduced pressure, the residue was treated with diethyl ether, and the precipitate was filtered off, dried, and recrystallized from acetone. Yield 0.34 g (85%), mp 200–202°C; published data [3]: mp 202–203°C. IR spectrum, ν, cm^{-1}: 3435, 3210, 3140, 1780, 1745, 1215, 1190, 1025. ^{1}H NMR spectrum, δ, ppm: 5.20 br.s (1H, OH), 4.29 d (1H, 3-H, $^3J_{3,7}$ = 4.8 Hz), 3.99 s (1H, 2-H), 3.19 m (1H, 7-H), 3.02 m (1H, 6-H, $^3J_{6,9}$ = 10.8, $^3J_{6,7}$ = 3.6 Hz), 2.64 m (1H, 9-H, $^3J_{9,1}$ = 4.6 Hz), 2.39 br.s (1H, 1-H), 1.93 d (1H, *syn*-8-H), 1.49 d (1H, *anti*-8-H, ^2J = 11.3 Hz).

N-Benzyl-*exo*-2-hydroxy-5-oxo-4-oxatricyclo-[4.2.1.0^{3,7}]nonane-*endo*-9-carboxamide (IIIc). A solution of trifluoroperoxyacetic acid prepared from 4.6 ml of trifluoroacetic anhydride and 0.6 ml of 96% hydrogen peroxide in 10 ml of methylene chloride was added dropwise to a solution of 2.17 g (8 mmol) of compound **XIII** in 15 ml of methylene chloride under vigorous stirring and cooling to 0°C. The mixture was stirred at that temperature until the reaction was complete (TLC), volatile substances were distilled off under reduced pressure, and the residue was purified by recrystallization. Yield 83%, mp 130–131°C. IR spectrum, ν, cm^{-1}: 3334, 1787, 1681, 1528, 1157, 1005, 686.

Reactions of *exo*-5,6-epoxybicyclo[2.2.1]heptane-*endo*-2,*endo*-3-dicarboxylic anhydride (I) with amines (*general procedure*). The corresponding amine, 5 mmol, was added under stirring to a mixture of 0.90 g (5 mmol) of epoxy anhydride **I** in 10 ml of anhydrous benzene, and the mixture was stirred until the reaction was complete. The precipitate of amido lactone **VIIa–VIIe**, **VIIIa–VIIIe**, or **IXa–IXc** was filtered off, washed with benzene, dried, and purified by recrystallization.

N-Methyl-*exo*-2-hydroxy-5-oxo-4-oxatricyclo-[4.2.1.0^{3,7}]nonane-*endo*-9-carboxamide (VIIa). Yield

91%, mp 146–148°C. IR spectrum, ν, cm^{-1}: 3345, 1780, 1719, 1688, 1587, 1273, 1161. ^{1}H NMR spectrum, δ, ppm: 7.92 s (1H, NH), 4.25 d (1H, 3-H, $^3J_{3,7}$ = 4.9), 4.20 s (1H, 2-H), 3.96 br.s (1H, OH), 3.12 m (1H, 7-H), 2.89 m (1H, 6-H, $^3J_{6,9}$ = 10.5, $^3J_{6,7}$ = 3.3 Hz), 2.51 m (1H, 9-H, $^3J_{9,1}$ = 4.6 Hz), 2.47 s (3H, CH$_3$), 2.32 br.s (1H, 1-H), 1.92 d (1H, syn-8-H), 1.34 d (1H, anti-8-H, ^2J = 10.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 178.4 (C^5), 170.7 (C=O), 87.4 (C^3), 72.1 (C^2), 48.6 (C^6), 47.7 (C^1), 47.3 (C^7), 40.9 (C^9), 34.0 (C^8), 26.3 (CH$_3$). Found, %: C 56.95; H 6.05; N 6.71. C$_{10}$H$_{13}$NO$_4$. Calculated, %: C 56.87; H 6.16; N 6.64.

N,N-Dimethyl-exo-2-hydroxy-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-endo-9-carboxamide (VIIb). Yield 52%, mp 153–155°C. IR spectrum, ν, cm^{-1}: 3550, 1782, 1706, 1587, 1268, 1204. ^{1}H NMR spectrum, δ, ppm: 5.14 s (1H, NH), 5.00 br.s (1H, OH), 4.33 d (1H, 3-H, $^3J_{3,7}$ = 5.2 Hz), 4.21 s (1H, 2-H), 3.03 m (1H, 7-H), 2.81 m (1H, 6-H, $^3J_{6,9}$ = 10.0, $^3J_{6,7}$ = 3.6 Hz), 2.72 s (6H, CH$_3$), 2.61 m (1H, 9-H), 2.35 br.s (1H, 1-H), 1.81 d (1H, syn-8-H), 1.36 d (1H, anti-8-H, ^2J = 10.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 177.7 (C^5), 168.4 (C=O), 87.5 (C^3), 73.1 (C^2), 48.0 (C^6), 47.3 (C^1), 47.1 (C^7), 41.6 (C^9), 33.9 (C^8), 29.0 (CH$_3$). Found, %: C 58.60; H 6.63; N 6.31. C$_{11}$H$_{15}$NO$_4$. Calculated, %: C 58.67; H 6.67; N 6.22.

N-tert-Butyl-exo-2-hydroxy-5-oxo-4-oxatricyclo-[4.2.1.0^{3,7}]nonane-endo-9-carboxamide (VIIc). Yield 61%, mp 164–166°C. ^{1}H NMR spectrum, δ, ppm: 7.68 s (1H, NH), 5.35 br.s (1H, OH), 4.32 d (1H, 3-H, $^3J_{3,7}$ = 4.7 Hz), 3.98 s (1H, 2-H), 3.13 m (1H, 7-H), 2.89 m (1H, 6-H, $^3J_{6,9}$ = 10.7, $^3J_{6,7}$ = 3.0 Hz), 2.61 m (1H, 9-H, $^3J_{9,1}$ = 4.4 Hz), 2.47 br.s (1H, 1-H), 1.94 d (1H, syn-8-H), 1.37 d (1H, anti-8-H, ^2J = 10.7 Hz), 1.35 s [9H, C(CH$_3$)$_3$]. Found, %: C 61.72; H 7.45; N 5.49. C$_{13}$H$_{19}$NO$_4$. Calculated, %: C 61.66; H 7.51; N 5.53.

N-m-Tolyl-exo-2-hydroxy-5-oxo-4-oxatricyclo-[4.2.1.0^{3,7}]nonane-endo-9-carboxamide (VIId). Yield 87%, mp 215–217°C. IR spectrum, ν, cm^{-1}: 3450, 1763, 1684, 1560, 1283, 1198. ^{1}H NMR spectrum, δ, ppm: 7.40 s (1H, NH), 7.30–7.00 (4H, H$_{arom}$), 4.30 d (1H, 3-H, $^3J_{3,7}$ = 5.2 Hz), 4.24 s (1H, 2-H), 3.98 br.s (1H, OH), 3.16 m (1H, 7-H), 3.03 m (1H, 6-H, $^3J_{6,9}$ = 10.2, $^3J_{6,7}$ = 3.0 Hz), 2.65 m (1H, 9-H, $^3J_{9,1}$ = 4.7 Hz), 2.38 br.s (1H, 1-H), 1.91 d (1H, syn-8-H), 1.47 d (1H, anti-8-H, ^2J = 10.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 177.7 (C^5); 172.8 (C=O); 138.5, 129.2, 128.3, 120.4, 117.1 (C$_{arom}$); 87.4 (C^3); 72.8 (C^2); 49.8 (C^6); 47.7 (C^1); 46.7 (C^7); 41.5 (C^9); 33.6 (C^8); 22.0 (CH$_3$). Found, %: C 66.84; H 5.98; N 4.95. C$_{16}$H$_{17}$NO$_4$. Calculated, %: C 66.90; H 5.92; N 4.88.

N-p-Nitrophenyl-exo-2-hydroxy-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-endo-9-carboxamide (VIIe). Yield 59%, mp 227–229°C. IR spectrum, ν, cm^{-1}: 3509, 3397, 1759, 1696, 1544, 1260, 1033. ^{1}H NMR spectrum, δ, ppm: 8.60 s (1H, NH), 8.20–7.90 (4H, H$_{arom}$), 5.20 br.s (1H, OH), 4.28 d (1H, 3-H, $^3J_{3,7}$ = 5.2 Hz), 3.98 s (1H, 2-H), 3.15 m (1H, 7-H), 3.00 m (1H, 6-H, $^3J_{6,9}$ = 10.7, $^3J_{6,7}$ = 3.3 Hz), 2.63 m (1H, 9-H, $^3J_{9,1}$ = 4.7 Hz), 2.38 br.s (1H, 1-H), 1.91 d (1H, syn-8-H), 1.47 d (1H, anti-8-H, ^2J = 10.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 177.7 (C^5); 172.8 (C=O); 145.6, 136.2, 127.0, 119.5 (C$_{arom}$); 87.4 (C^3); 72.8 (C^2); 49.9 (C^6); 47.5 (C^1); 46.7 (C^7); 41.1 (C^9); 33.6 (C^8). Found, %: C 56.53; H 4.46; N 8.85. C$_{15}$H$_{14}$N$_2$O$_6$. Calculated, %: C 56.60; H 4.40; N 8.81.

N-(Pyridin-2-yl)-exo-2-hydroxy-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-endo-9-carboxamide (VIIIa). Yield 52%, mp 116–118°C. IR spectrum, ν, cm^{-1}: 3440, 1779, 1689, 1530, 1256, 1193, 1157. ^{1}H NMR spectrum, δ, ppm: 10.69 s (1H, NH); 8.36, 8.21, 7.39, 7.14 (4H, pyridine); 5.15 br.s (1H, OH); 4.35 d (1H, 3-H, $^3J_{3,7}$ = 4.4 Hz); 4.24 s (1H, 2-H); 3.60 m (1H, 6-H, $^3J_{6,9}$ = 10.9, $^3J_{6,7}$ = 3.6 Hz); 3.30 m (1H, 7-H); 2.78 m (1H, 9-H, $^3J_{9,1}$ = 4.1 Hz); 2.47 br.s (1H, 1-H); 2.01 d (1H, syn-8-H); 1.47 d (1H, anti-8-H, ^2J = 10.5 Hz). Found, %: C 61.35; H 5.14; N 10.27. C$_{14}$H$_{14}$N$_2$O$_4$. Calculated, %: C 61.31; H 5.11; N 10.22.

N-(Pyridin-3-yl)-exo-2-hydroxy-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-endo-9-carboxamide (VIIIb). Yield 48%, mp 126–129°C. IR spectrum, ν, cm^{-1}: 3500, 1756, 1686, 1552, 1280, 1012. Found, %: C 61.38; H 5.19; N 10.25. C$_{14}$H$_{14}$N$_2$O$_4$. Calculated, %: C 61.31; H 5.11; N 10.22.

N-(1,2,4-Triazol-4-yl)-exo-2-hydroxy-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-endo-9-carboxamide (VIIIc). Yield 85%, mp 173–175°C. IR spectrum, ν, cm^{-1}: 3300, 3158, 1754, 1695, 1531, 1172. ^{1}H NMR spectrum, δ, ppm: 7.67 (2H, triazole), 7.54 s (1H, NH), 5.38 br.s (1H, OH), 4.32 d (1H, 3-H, $^3J_{3,7}$ = 4.9 Hz), 3.98 s (1H, 2-H), 3.13 m (1H, 7-H), 2.88 m (1H, 6-H, $^3J_{6,9}$ = 10.4, $^3J_{6,7}$ = 3.0 Hz), 2.60 m (1H, 9-H, $^3J_{9,1}$ = 4.4 Hz), 2.43 br.s (1H, 1-H), 1.94 d (1H, syn-8-H), 1.47 d (1H, anti-8-H, ^2J = 10.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 177.8 (C^5), 169.5 (C=O), 87.4 (C^3), 72.7 (C^2), 50.9 (C^6), 47.4 (C^1), 47.1 (C^7), 41.4 (C^9), 34.3 (C^8). Found, %: C 49.93; H 4.62; N 21.18. C$_{11}$H$_{12}$N$_4$O$_4$. Calculated, %: C 50.00; H 4.55; N 21.21.

***N*-(1,3-Thiazol-2-yl)-*exo*-2-hydroxy-5-oxo-4-oxa-tricyclo[4.2.1.0^{3,7}]nonane-*endo*-9-carboxamide (VIIId).** Yield 61%, mp 234–236°C. IR spectrum, ν, cm^{-1}: 3536, 3169, 1761, 1685, 1579, 1275, 1028. ^{1}H NMR spectrum, δ, ppm: 12.30 s (1H, NH), 7.48 and 7.23 (2H, thiazole), 5.25 br.s (1H, OH), 4.37 d (1H, 3-H, $^3J_{3,7}$ = 5.0 Hz), 4.23 s (1H, 2-H), 3.26 m (1H, 7-H), 3.23 m (1H, 6-H, $^3J_{6,9}$ = 10.6 Hz), 2.80 m (1H, 9-H, $^3J_{9,1}$ = 4.6 Hz), 2.51 br.s (1H, 1-H), 2.03 d (1H, *syn*-8-H), 1.51 d (1H, *anti*-8-H, ^2J = 10.9 Hz). ^{13}C NMR spectrum, δ$_C$, ppm: 178.0 (C^5); 169.4 (C=O); 158.2, 138.2, 114.3 (C, thiazole); 87.4 (C^3); 72.3 (C^2); 48.4 (C^6); 47.5 (C^1); 47.4 (C^7); 41.5 (C^9); 34.1 (C^8). Found, %: C 51.49; H 4.35; N 10.06. C$_{12}$H$_{12}$N$_2$O$_4$S. Calculated, %: C 51.43; H 4.29; N 10.00.

***N*-(5-Methyl-1,3,4-thiadiazol-2-yl)-*exo*-2-hydroxy-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-*endo*-9-carboxamide (VIIIe).** Yield 58%, mp 190–192°C. IR spectrum, ν, cm^{-1}: 3553, 3381, 1781, 1683, 1530, 1353, 1312, 1253, 1199, 1019. ^{1}H NMR spectrum, δ, ppm: 7.00 s (1H, NH), 5.26 br.s (1H, OH), 4.37 d (1H, 3-H, $^3J_{3,7}$ = 5.2 Hz), 4.19 s (1H, 2-H), 3.42 m (1H, 7-H), 3.26 m (1H, 6-H, $^3J_{6,9}$ = 10.4, $^3J_{6,7}$ = 3.3 Hz), 2.82 m (1H, 9-H, $^3J_{9,1}$ = 4.3 Hz), 2.61 s (3H, CH$_3$), 2.44 br.s (1H, 1-H), 2.03 d (1H, *syn*-8-H), 1.51 d (1H, *anti*-8-H, ^2J = 10.7 Hz). ^{13}C NMR spectrum, δ$_C$, ppm: 177.9 (C^5); 169.7 (C=O); 160.0, 158.7, 153.9 (C, thiadiazole); 87.4 (C^3); 72.3 (C^2); 48.4 (C^6); 47.4 (C^1); 47.2 (C^7); 41.6 (C^9); 34.1 (C^8); 16.0 (CH$_3$). Found, %: C 48.85; H 4.47; N 14.29. C$_{12}$H$_{13}$N$_3$O$_4$S. Calculated, %: C 48.81; H 4.41; N 14.24.

***N*-(1,1-Dioxotetrahydro-λ^6-thiophen-3-yl)-*exo*-2-hydroxy-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonane-*endo*-9-carboxamide (IXa).** Yield 54%, mp 186–188°C. IR spectrum, ν, cm^{-1}: 3476, 1773, 1628, 1534, 1399, 1173, 1160, 1123. ^{1}H NMR spectrum, δ, ppm: 4.29 d (1H, 3-H, $^3J_{3,7}$ = 5.3 Hz); 4.04 s (1H, 2-H); 4.00 s (1H, NH); 3.96 br.s (1H, OH); 3.65, 3.26, 3.05, 2.25, 1.88 (7H, CH$_2$, CH, thiophene); 3.18 m (1H, 7-H); 2.99 m (1H, 6-H, $^3J_{6,9}$ = 10.7, $^3J_{6,7}$ = 3.3 Hz), 2.62 m (1H, 9-H, $^3J_{9,1}$ = 4.6 Hz), 2.40 br.s (1H, 1-H), 1.93 d (1H, *syn*-8-H), 1.49 d (1H, *anti*-8-H, ^2J = 10.7 Hz). ^{13}C NMR spectrum, δ$_C$, ppm: 178.0 (C^5); 173.1 (C=O); 87.2 (C^3); 72.8 (C^2); 59.0, 51.6, 49.4, 31.8 (CH$_2$, CH, thiophene); 48.5 (C^6); 47.3 (C^1); 46.9 (C^7); 40.9 (C^9); 33.6 (C^8). Found, %: C 49.58; H 5.46; N 4.51. C$_{13}$H$_{17}$NO$_6$S. Calculated, %: C 49.53; H 5.40; N 4.44.

***N*-Methyl-*N*-(1,1-dioxotetrahydro-λ^6-thiophen-3-yl)-*exo*-2-hydroxy-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]-nonane-*endo*-9-carboxamide (IXb).** Yield 62%, mp 145–147°C. IR spectrum, ν, cm^{-1}: 3527, 3485, 1770, 1551, 1350, 1336, 1285, 1126. ^{1}H NMR spectrum, δ, ppm: 5.01 br.s (1H, OH); 4.25 d (1H, 3-H, $^3J_{3,7}$ = 5.0 Hz); 3.99 s (1H, 2-H); 3.18, 3.14, 2.02, 1.95 (7H, CH$_2$, CH, thiophene); 3.12 m (1H, 7-H); 2.98 m (1H, 6-H, $^3J_{6,9}$ = 10.8, $^3J_{6,7}$ = 3.1 Hz); 2.60 m (1H, 9-H, $^3J_{9,1}$ = 4.6 Hz); 2.36 br.s (1H, 1-H); 2.23 s (3H, CH$_3$); 1.92 d (1H, *syn*-8-H); 1.45 d (1H, *anti*-8-H, ^2J = 11.0 Hz). ^{13}C NMR spectrum, δ$_C$, ppm: 177.2 (C^5); 172.3 (C=O); 86.4 (C^3); 71.9 (C^2); 56.1, 55.7, 50.7, 33.3, 28.1 (CH$_2$, CH, thiophene); 47.4 (C^6); 46.4 (C^1); 46.2 (C^7); 40.3 (C^9); 33.3 (C^8); 25.0 (CH$_3$). Found, %: C 51.12; H 5.72; N 4.28. C$_{14}$H$_{19}$NO$_6$S. Calculated, %: C 51.06; H 5.78; N 4.26.

***N,N′*-Bis(*exo*-2-hydroxy-5-oxo-4-oxatricyclo[4.2.1.0^{3,7}]nonan-9-ylcarbonyl)piperazine (IXc).** Yield 29%, mp 204–206°C. IR spectrum, ν, cm^{-1}: 3420, 1765, 1630, 1570, 1284, 1165, 1010. ^{1}H NMR spectrum, δ, ppm: 5.25 br.s (2H, OH), 4.22 d (2H, 3-H, $^3J_{3,7}$ = 5.0 Hz), 4.08 s (2H, 2-H), 3.08 m (2H, 7-H), 2.83 m (2H, 6-H, $^3J_{6,9}$ = 11.1, $^3J_{6,7}$ = 3.4 Hz), 2.82 (8H, CH$_2$, piperazine), 2.50 m (2H, 9-H, $^3J_{9,1}$ = 4.7 Hz), 2.32 br.s (2H, 1-H), 1.85 d (2H, *syn*-8-H), 1.42 d (2H, *anti*-8-H, ^2J = 10.4 Hz). ^{13}C NMR spectrum, δ$_C$, ppm: 177.9 (C^5), 173.2 (C=O), 86.5 (C^3), 72.0 (C^2), 49.4 (C^6), 46.6 (C^1), 46.3 (C^7), 42.7 (CH$_2$, piperazine), 40.6 (C^9), 32.7 (C^8). Found, %: C 59.12; H 5.86; N 6.31. C$_{22}$H$_{26}$N$_2$O$_8$. Calculated, %: C 59.19; H 5.83; N 6.28.

***endo*-3-(Dimethylcarbamoyl)bicyclo[2.2.1]hept-5-ene-*endo*-2-carboxylic acid (XII).** Endic anhydride (**V**), 3.28 g (0.02 mol), was dissolved in 10–15 ml of benzene, and 2.73 g (0.02 mol) of 33% aqueous dimethylamine was added under stirring. The mixture was kept at room temperature until the reaction was complete (TLC), and the precipitate was filtered off, washed with benzene, dried, and purified by recrystallization from benzene. Yield 2.72 g (78%), mp 150–151°C (from benzene). IR spectrum, ν, cm^{-1}: 3460, 2950, 1758, 1685, 1530, 1330, 1240, 728. ^{1}H NMR spectrum, δ, ppm: 6.21 d (2H, 5-H, 6-H), 3.22 d (2H, 2-H, 3-H), 3.02 m (2H, 1-H, 4-H), 2.62 s (6H, CH$_3$), 1.44 d (1H, *syn*-7-H), 1.31 d (1H, *anti*-7-H). Found, %: N 6.78. C$_{11}$H$_{15}$NO$_3$. Calculated, %: N 6.70.

***endo*-3-(Benzylcarbamoyl)bicyclo[2.2.1]hept-5-ene-*endo*-2-carboxylic acid (XIII)** was synthesized in a similar way from 3.28 g (0.02 mol) of compound **V** and 2.14 g (0.02 mol) of benzylamine. Yield 4.88 g (90%), mp 118–120°C (from benzene). IR spectrum, ν, cm^{-1}: 3280, 3030, 1770, 1650, 1514, 1486, 1267, 1207, 745. ^{1}H NMR spectrum, δ, ppm: 7.26 m (5H, C$_6$H$_5$),

6.69 s (1H, NH), 6.32 d (1H, 5-H), 5.98 d (1H, 6-H, $^3J_{5,6}$ = 5.2, $^3J_{4,5}$ = $^3J_{6,1}$ = 3.0 Hz), 4.26 d and 4.06 d (1H each, C**H**$_2$C$_6$H$_5$), 3.16 d (1H, 2-H), 3.11 d (1H, 3-H, $^3J_{2,3}$ = 10.0, $^3J_{2,1}$ = 3.0 Hz), 3.01 m (1H, 1-H), 2.96 m (1H, 4-H), 1.35 d (1H, *syn*-7-H), 1.20 d (1H, *anti*-7-H, ^2J = 8.5 Hz). Found, %: N 5.24. C$_{16}$H$_{17}$NO$_3$. Calculated, %: N 5.17.

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