1,3-Dipolar cycloadditions of heterocycles XVI.* Reduction of isoxazolines — a pathway to condensed oxazines

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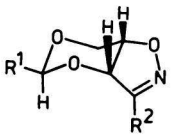
Dedicated to Professor Ing. J. Kováč, DrSc., in honour of his 60th birthday

1,3-Dipolar cycloaddition of acetonitrile oxide at substituted 1,3-dioxep-5-enes produces a diastereomeric pair of *endo* and *exo* adducts. A preparation of $n + 1$-membered heterocycles from n-membered ones *via* a simple sequence of 1,3-dipolar cycloaddition, reduction, and cyclization is described. Reduction of isoxazolines with lithium-aluminium hydride furnishes a mixture of heterocyclic *erythro* and *threo* γ-amino alcohols *VI, VII, IX, X* which upon cyclization with 4-nitrobenzaldehyde produce condensed tetrahydro-1,3-oxazine derivatives *XI, XII.*

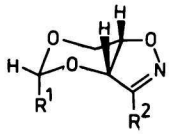
В результате 1,3-диполярного циклоприсоединения окиси ацетонитрила к замещенным 1,3-диоксеп-5-енам образуется диастереомерная пара *эндо-* и *экзо*-аддуктов. Описано получение $n + 1$-членных гетероциклов из n-членных посредством простой последовательности 1,3-диполярного циклоприсоединения, восстановления и циклизации. Восстановление изоксазолинов алюмогидридом лития приводит к образованию смеси гетероциклических *эритро-* и *трео*-γ-аминоспиртов *VI, VII, IX, X*, которые в результате циклизации с 4-нитробензальдегидом дают конденсированные тетрагидро-1,3-оксазиновые производные *XI, XII.*

Isoxazoline derivatives proved to be useful intermediates in the synthesis of γ-amino alcohols [1—3], β-hydroxycarbonyl compounds [4—6] and their derivatives. In our previous papers we have shown [7—16] that aryl-substituted isoxazolines can be photochemically converted to heterocyclic [7—14] or acyclic [15, 16] enamino aldehydes. This paper deals with 1,3-dioxepane skeleton in order to assess the role of the methyl group in the rearrangement and in the synthesis of heterocyclic γ-amino alcohols.

* For Part *XV* see Ref. [26].



II



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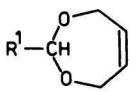
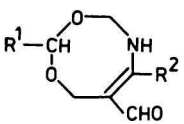


I



IV

IIa $R^1 = H$, $R^2 = C_6H_5$

IIb $R^1 = H$, $R^2 = CH_3$

IIc $R^1 = C_6H_5$, $R^2 = CH_3$

IId $R^1 = R^2 = CH_3$

IIe $R^1 = t\text{-}C_4Hg$, $R^2 = CH_3$

Scheme 1

Model isoxazolines (*II*, *III*) were prepared by 1,3-dipolar cycloaddition of acetonitrile oxide at the 2-R-substituted 1,3-dioxep-5-enes (*I*), the R being H, CH_3, phenyl, *tert*-butyl (Scheme 1). Acetonitrile oxide was generated from nitroethane by the action of phenylisocyanate, catalyzed by triethylamine, in the presence of the dipolarophile *I* [17]. We have found that in the cycloaddition of acetonitrile oxide to *I* dimerization of the *in situ* generated dipole does not present the usual problem. Yields of the cycloaddition reached 26 to 51 %, which tallies with those observed for the addition to cyclic system [18]. All substituted derivatives of *I* furnished a diastereomeric pair of *exo-II* and *endo-III* adducts. In the case where R^1 = phenyl *exo* (*IIc*) and *endo* (*IIIc*) diastereomers could be separated by column chromatography; in cases where R^1 = methyl and *tert*-butyl the separation has failed. In all cycloadditions *exo* derivatives prevailed, the $m_e : m_t$ ratio of *exo-endo* products was found to be from 56 : 44 to 80 : 20 (see Experimental), very much the same as the results found for

the reaction of *I* with the benzonitrile oxide [9, 10, 13]. Structures of *exo* and *endo* adducts were assigned based on different chemical shifts of C-2 and C-6 triplets in ^{13}C NMR spectra due to the bent structure of the bicyclic adducts. *Exo* adducts *IIc—IIe* with equatorial R displayed for C-2 ($\delta = 70.25$ ppm) and C-6 ($\delta = 65.23$ ppm) values, almost identical with those of the unsubstituted derivative *IIb* ($\delta = 71.66$ ppm and 66.59 ppm). In the ^{13}C NMR spectra of *endo* derivatives on the other hand γ-effect could be observed, shifting all corresponding triplets upfields due to the influence of the axial 4-R substituent, *e.g.* for *IIIc* $\delta = 64.97$ ppm (C-2) and 62.89 ppm (C-6). Other chemical shift values found in ^{1}H and ^{13}C NMR spectra of adducts support the suggested structure of *II* and *III* (see Experimental), being in fact very similar to the spectra of the corresponding 8-phenyl-substituted derivatives [10, 13]. Referring to 8-phenyl derivatives the UV spectral maxima of 8-methyl-substituted derivatives are blue-shifted by about 10 nm.

Although the photochemistry of isoxazolines is still rather intensively studied [7—16] and [19—22], nobody has so far studied the photochemistry of isoxazolines substituted by nonaromatic chromophore. Adducts *II* and *III* were irradiated by the nearly monochromatic light with $\lambda_{max} = 253.7$ nm in methanol. The quantum yield for *IIb*, measured from the diminishing concentration of the starting compound was by 0.11 higher than that of the corresponding phenyl

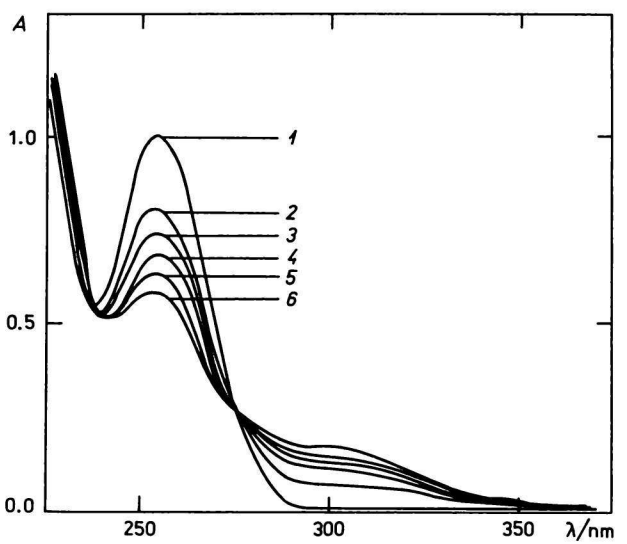


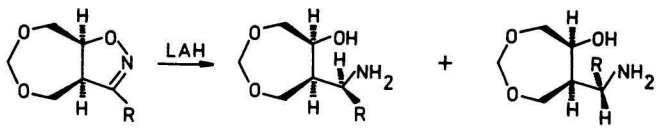
Fig. 1. Spectral changes during the irradiation of *IIb* in methanol by monochromatic light ($\lambda = 253$ nm).
t/min: *1.* 0; *2.* 15; *3.* 20; *4.* 25; *5.* 30; *6.* 35.

derivative *IIa* ($\Phi = 0.016$). The irradiation of *IIb* was monitored by periodic scans of UV spectra of the reaction mixture, where the gradual disappearance of the peak at $\lambda_{max} = 254$ nm, belonging to the starting *IIb* could be observed together with the new peak being formed at $\lambda_{max} \approx 300$ nm. The latter peak was much less intensive than that of *IIa* (Fig. 1). Preparative experiments failed to produce isolable product. In analogy with the aryl derivatives we assume that methyl derivatives rearrange to heterocyclic enamino aldehydes $II \xrightarrow{h\nu} IV$, $III \xrightarrow{h\nu} IV$, which are photochemically unstable. Even stopping the irradiation at low conversion of the starting material could not produce anything but unidentifiable material. Similar results were obained with isoxazolines containing carbonyl groups, amino groups, and two-valent sulfur [23—26].

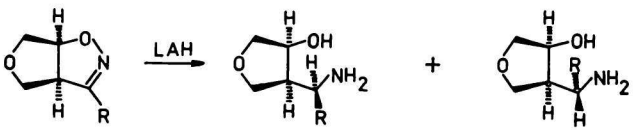
As has already been mentioned isoxazolines are precursors of γ-amino alcohols, which are extensively studied due to their pharmacological activity. Especially important are therefore synthetic procedures leading stereoselectively to γ-amino alcohols possessing a free amino group, *e.g.* amino acids and aminoglycosidic antibiotics [27, 28]. Consequently our aim has been to utilize condensed isoxazolines for the preparation of γ-amino alcohols having tetrahydrofuran and 1,3-dioxepane structure. There has been reported so far only one synthesis of 3-hydroxy-4-(1-aminoethyl)tetrahydrofuran (*IXc*, *Xc*) by the reduction of isoxazoline *VIIIc*. The reduction produced the corresponding γ-amino alcohols with three chiral centres; *erythro-IXc* and *threo-Xc* were formed in the ratio $m_e : m_t = 70 : 30$ in favour of the *erythro* derivative [29]. *Jäger et al.* have shown [30—33] that 3,5-disubstituted and 3,4,5-trisubstituted isoxazolines, prepared from alkenes or cycloalkenes and nitrile oxides, could be reduced by lithium-aluminium hydride (LAH) in ether stereoselectively to γ-amino alcohols possessing mostly *erythro* configuration ($m_e : m_t = 85 : 15$), only in case of 2,5-dihydrofuran derivative the ratio $m_e : m_t$ was only 70 : 30 [29].

Several reducing agents are capable of producing γ-amino alcohols, the outcoming ratio of diastereomers being dependent on the reducing agent [33]. For the reduction of isoxazolines *V* and *VIII* (Scheme 2) we have tested Zn/CH_3COOH and $NaBH_4/NiCl_2$. Yields fell in the range of 47—56 %, but diastereoselectivity was rather low, only the ratio $m_e : m_t \approx 55 : 45$ could be achieved. After consulting the literature we have finally opted for the system LAH—ether. With equimolar amount of LAH in refluxing ether the reaction took more than 10 days. With twofold mole excess of LAH the reduction still took 5—9 days till the maximum conversion (50—80 %) was reached (GLC control). Higher boiling point solvents (tetrahydrofuran or methyl *tert*-butyl ether) pushed the conversion to 100 % in 2 days. γ-Amino alcohols were formed as diastereomeric pairs *erythro* (*VI*), (*IX*) and *threo* (*VII*, *X*) which could not be separated. The separation also failed in already reported cases [29—33]. Struc-

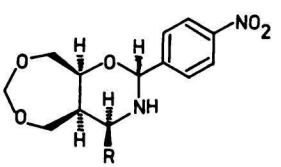
tures of the prepared alcohols were determined from spectral data, based on the finding [30—33] that in solution intramolecular hydrogen bonds enforced a chair conformation with the concomitant quasi-equatorial position of substituents in *erythro* configuration and one axial substituent in *threo* configuration. Infrared spectra of all γ-amino alcohols *VIa—VIc*, *VIIa—VIIc*, *IXa—IXc*, *Xa—Xd*, *Xf*, *Xg* displayed a broad band in the region of $\tilde{\nu} = 3280—3360\,\mathrm{cm}^{-1}$, indicating a strong intramolecular OH ··· NH_2 hydrogen bond. ^{1}H NMR spectra showed signals of OH and NH_2 protons in a multiplet at $\delta = 3.0—4.5$ ppm.



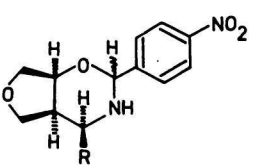
Va–Vc *VIa–VIc* *VIIa–VIIc*



VIIIa–VIIIg *IXa–IXg* *Xa–Xd, Xf, Xg*



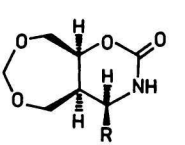
XIa



XIIa, XIIf

R

a	C_6H_5
b	4-Br–C_6H_4
c	CH_3
d	4-CH_3–C_6H_4
e	4-CH_3O–C_6H_4
f	4-Cl–C_6H_4
g	2-furyl



XIIIa

Scheme 2

The assignment was confirmed by the addition of ^2H_2O to the sample of diastereomeric pair *VIa—VIIa*, which showed a three-proton broad singlet at 3.38 ppm. ^{1}H NMR spectra showed further H-3 multiplet of 3-hydroxy-4--aminoarylalkyl tetrahydrofurans (*IX*, *X*) as well as that of H-5 of 5-hydroxy-4--aminoarylalkyl-1,3-dioxepanes (*VI*, *VII*) which were shifted apart from heterocyclic ring protons and CHN proton due to the deshielding effect of oxygen of the hydroxy group. In contrast to the starting isoxazolines *V* and *VIII*, aromatic protons of γ-amino alcohols displayed signals as a sharp singlet, indicating a free rotating benzene ring. Analogous effect was observed by photoproducts *IV* [9—13]. We could only confirm the finding of *Jäger et al.* [30—33] that *erythro* (*VI*, *IX*) and *threo* (*VII*, *X*) derivatives could not be distinguished by means of ^{1}H NMR spectroscopy.

^{13}C NMR spectroscopy on the other hand was perfectly able to distinguish the above-mentioned diastereomeric pairs. Signal assignment was performed based on multiplicity, relative intensity of *erythro* and *threo* isomers, known substituent effects, and by comparison with literature data [29—33] (see Experimental). Stereoselectivity of reduction was determined by ^{13}C NMR spectra of the reaction mixture. We have found that *erythro* : *threo* ratio depends on the character of the aromatic substituent; favouring in all cases the formation of *erythro* derivatives *VI*, *IX*. Reduction of the phenyl-substituted isoxazoline fused with 1,3-dioxepane *Va* furnished $m_e : m_t = 75 : 25$ ratio, tetrahydrofuran derivative *VIIIa* gave the ratio $m_e : m_t = 70 : 30$ in agreement with the literature data for *VIIIc* ($m_e : m_t = 70 : 30$) [29]. The following diastereomeric ratios were found for *VIIId* (4-CH_3, $m_e : m_t = 75 : 25$), *VIIIe* (4-OCH_3, $m_e : m_t = 95 : 5$), *VIIIf* (4--Cl, $m_e : m_t = 80 : 20$). In the case of *VIIIe* only *erythro* isomer *IXe* was identified.

As has already been mentioned [29—33] due to the shielding the signal of carbon adjacent to hydroxyl group shows as a doublet at $\delta = 75.79$—77.83 ppm and that of CHN moiety at $\delta = 53.79$—56.29 ppm. Structure of the prepared heterocyclic γ-amino alcohols was further confirmed by the presence of doublet of C-4 carbon in the spectra of *VI* and *VII* at $\delta = 49.64$—51.20 ppm as well as that of C-6 carbon of *IX*, *X* at $\delta \approx 52$ ppm. Triplets belonging to C-2 and C-5 carbons (*VI*, *VII*) and C-4, C-7 in *IX*, *X* were found at different δ values (see Experimental) due to the influence of the hydroxy group. Triplets of C-2 carbons of *IX*, *X* found at $\delta = 94.40$—95.12 ppm confirmed that the 1,3-dioxepane skeleton was not changed by the LAH reduction.

The problem of the configuration of γ-amino alcohols can be approached by studying the stereochemistry of cyclic derivatives. The most often used ones are tetrahydro-1,3-oxazines. Cyclizations with acetone [31], *p*-nitrobenzaldehyde [33], *p*-chlorobenzaldehyde [34], *p*-chloroimidobenzoic acid ethyl ester [35] and

ethyl chloroformate [36] were described. Although the published cyclization with acetone proceeded with high yields, our γ-amino alcohols failed to react with acetone even after 7 days at 65 °C. Cyclization with *p*-nitrobenzaldehyde proceeded smoothly under formation of 1,3-oxazine derivatives *XIa*, *XIIa*, *XIIf* in 50—80 % yields. ^{1}H NMR spectrum of 9-(4-nitrophenyl)-11-phenyl-3,5,8--trioxa-10-azabicyclo[5,4,0]undecane (*XIa*) showed only one singlet at $\delta =$ $= 5.43$ ppm, belonging to H-9 proton, which indicated the formation of only one diastereomer out of four possible. Configuration of the chiral centre could not be elucidated from conventional spectral data; X-ray analysis was not available. 1,3-Oxazines *XIa*, *XIIa*, *XIIf* were found to be products of cyclization of *erythro* alcohols *VI*, *IX*. When ethyl chloroformate was reacted with γ-amino alcohol *VIa*, followed by the CH_3ONa treatment *XIIIa* could be isolated in low yields. The structure of *XIIIa* has been confirmed by the analysis of IR spectra, showing a carbonyl absorption at $\tilde{\nu} = 1680\ cm^{-1}$ as well as by ^{1}H NMR spectra.

Experimental

^{1}H NMR spectra of the synthesized derivatives were measured by 80 MHz Tesla BS 487 C spectrometer, ^{13}C NMR spectra were taken with a Jeol spectrometer using tetramethylsilane as internal standard. IR spectra were determined from chloroform solutions on Perkin—Elmer RB-577, UV spectra of methanolic solutions were measured in temperature-controlled cuvettes with a Perkin—Elmer spectrophotometer. Mass spectra were recorded on AEI MS 902 S spectrometer with direct inlet system at 70 eV ionizing energy. Photochemical reactions were performed in a forced circulation reactor with quartz sleeved low-pressure Hg lamp, described in [13], the reference gives also the procedure used for the quantum yield measurements. Conversion of the isoxazoline reduction was monitored by gas chromatography using Hewlett—Packard model 7620 A (10 % OV-17 column). 1,3-Dioxepanes *Ib*—*Id* were prepared according to [37] by the reaction of the corresponding aldehyde with *cis*-2-butene-1,4-diol, catalyzed by *p*-toluenesulfonic acid. Preparation of isoxazolines *Va*, *Vb* was described in [9, 10], that of isoxazolines *VIIIa*—*VIIIg* in [11].

Isoxazolines

To the solution of 1,3-dioxep-5-ene (50 mmol), phenyl isocyanate (11 cm^3; 100 mmol), and triethylamine (0.5 cm^3) in 50 cm^3 of dry ether a solution consisting of nitroethane (3.6 cm^3; 50 mmol), triethylamine (0.2 cm^3), and 50 cm^3 of dry ether was added within 2 h. The reaction mixture was then stirred at laboratory temperature for another 24 h, precipitated diphenylurea filtered off and washed with dry ether. The filtrate was then concentrated *in vacuo* and chromatographed on an aluminium oxide column to give the corresponding cycloadducts *IIb*—*IId* and *IIIb*—*IIId*.

8-Methyl-3,5,10-trioxa-9-azabicyclo[5,3,0]dec-8-ene (IIb)

The compound obtained in 51 % yield (eluant chloroform), m.p. = 88—90 °C. For $C_7H_{11}NO_3$ (M_r = 157.17) w_i(calc.): 53.49 % C, 7.05 % H, 8.91 % N; w_i(found): 53.62 % C, 6.99 % H, 9.04 % N. UV spectrum, λ_{max}/nm (log(ε/m^2 mol^{-1})): 254 (2.30). Mass spectrum: m/z = 157 ($M^{+\bullet}$). ^{1}H NMR spectrum, δ(C^2HCl_3)/ppm: 5.0 (d, J_{1-7} = 7.0 Hz, 1H, H-1), 4.48 (d, 1H, H-7), 3.84—4.95 (m, 6H, H_2-2, H_1-4, H_2-6), 2.00 (s, 3H, CH_3). ^{13}C NMR spectrum, δ(deuterated dimethyl sulfoxide)/ppm: 154.89 (s, C=N), 98.24 (t, C-4), 80.76 (d, C-1), 71.66 (t, C-2), 66.59 (t, C-6), 54.44 (d, C-7), 10.91 (q, CH_3).

exo- and endo-4-Phenyl-8-methyl-3,5,10-trioxa-9-azabicyclo[5,3,0]dec-8-ene (IIc, IIIc)

Compounds obtained by chromatography (eluant hexane—ethyl acetate, r_V = 1 : 5), crystallized from hexane. *endo*-Derivative (*IIIc*), yield = 14 %, m.p. = 94—96 °C. For $C_{13}H_{15}NO_3$ (M_r = 233.26) w_i(calc.): 66.93 % C, 6.48 % H, 6.01 % N; w_i(found): 67.03 % C, 6.45 % H, 5.91 % N. ^{1}H NMR spectrum, δ(C^2HCl_3)/ppm: 7.25—7.48 (m, 5H, H_{ar}), 5.39 (s, 1H, H-4), 4.64—4.93 (m, 1H, H-1), 3.34—4.21 (m, 5H, H_2-2, H_2-6, H-7), 1.98 (s, 3H, CH_3). ^{13}C NMR spectrum, δ(deuterated dimethyl sulfoxide)/ppm: 155.80 (s, C=N), 139.39, 128.39, 127.99, 126.05 (C_{ar}), 103.96 (d, C-4), 80.04 (d, C-1), 64.97 (t, C-2), 62.89 (t, C-6), 54.18 (d, C-7), 11.30 (q, CH_3). *exo*-Derivative (*IIc*), yield = 18 %, m.p. = 98—100 °C. For $C_{13}H_{15}NO_3$ (M_r = 233.26) w_i(calc.): 66.93 % C, 6.48 % H, 6.01 % N; w_i(found): 66.84 % C, 6.31 % H, 6.24 % N. ^{1}H NMR spectrum, δ(C^2HCl_3)/ppm: 7.20—7.43 (m, 5H, H_{ar}), 5.31 (s, 1H, H-4), 4.55—4.78 (m, 1H, H-1), 3.29—4.38 (m, 5H, H_2-6, H-7), 1.98 (s, 3H, CH_3). ^{13}C NMR spectrum, δ(deuterated dimethyl sulfoxide)/ppm: 154.83 (s, C=N), 138.14, 128.24, 127.67, 125.85 (C_{ar}), 105.84 (d, C-4), 80.56 (d, C-1), 70.25 (t, C-2), 65.23 (t, C-6), 54.18 (d, C-7), 10.48 (q, CH_3).

exo- and endo-4,8-Dimethyl-3,5,10-trioxa-9-azabicyclo[5,3,0]dec-8-ene (IId, IIId)

Elution with hexane—ethyl acetate (r_V = 1 : 5) furnished a crystalline solid — a mixture with m_e : m_t = 4 : 1 excess of the *exo*-derivative *IId*, yield = 26 %. ^{1}H NMR spectrum, δ(C^2HCl_3)/ppm: 5.05—5.25 (m, 1H, H-1 *endo*), 3.28—4.95 (m, 13H, 2 × H_2-6, 2 × H-7, 2 × H-4, H-1 *exo*), 1.95 (s, 6H, 2 × CH_3), 2.03 (d, 3H, CH_3 *endo*), 1.26 (d, 3H, CH_3 *exo*). ^{13}C NMR spectrum, δ(C^2HCl_3)/ppm: *endo-IIId*: 155.29 (s, C=N), 105.38 (d, C-4), 76.67 (d, C-1), 70.17 (t, C-2), 64.97 (t, C-6), 54.83 (d, C-7), 21.05 (q, CH_3), 11.43 (q, CH_3); *exo-IId*: 154.51 (s, C=N), 99.02 (d, C-4), 84.59 (d, C-1), 71.21 (t, C-2), 66.40 (t, C-6), 55.27 (d, C-7), 21.05 (q, CH_3), 11.43 (q, CH_3).

exo- and endo-4-(tert-Butyl)-8-methyl-3,5,10-trioxa-9-azabicyclo[5,3,0]dec-8-ene (IIe, IIIe)

Compounds *IIe*, *IIIe* (crystalline solid) were obtained by elution with hexane—ethyl acetate ($r_V = 1:5$) in the ratio $m_e:m_t = 36:64$ in favour of the *exo*-derivative *IIe*, yield = 28 %. ^{1}H NMR spectrum, $\delta(C^2HCl_3)$/ppm: 5.60—5.80 (m, 1H, H-1 *endo*), 3.98—4.75 (m, 13H, 2 × H_2-2, 2 × H_2-6, 2 × H-7, 2 × H-4, H-1 *exo*), 1.23 (s, 9H, $(CH_3)_3$—C *endo*), 0.90 (s, 9H, $(CH_3)_3$—C *exo*), 1.15 and 1.30 (s, s, 6H, 2 × CH_3).

General procedure for the reduction of isoxazolines

To the solution of isoxazoline (10 mmol) in 100 cm^3 of dry ether lithium-aluminium hydride was portion-wise added under the nitrogen atmosphere (1.1 g; 26 mmol). Reaction mixture was then 19 h refluxed and subsequently stirred at laboratory temperature 5 more days. After the TLC check indicated the end of reaction the excess hydride was removed by the addition of 1 : 1 cm^3 of water, 0.75 cm^3 of 20 % NaOH and another 1.5—3.5 cm^3 of H_2O to the stirred reaction mixture until the precipitate bleached white. The precipitate was then filtered off, washed with 50 cm^3 of ether and 30 cm^3 of chloroform. Combined organic filtrates were concentrated *in vacuo* and distilled at 0.66 Pa (bath temperature 100 °C). The oil thus obtained was then stored in desiccator over KOH.

erythro- and threo-5-Hydroxy-6-(1-phenyl-1-aminomethyl)-1,3-dioxepane (VIa, VIIa)

Isoxazoline *Va* gave colourless oil ($m_e:m_t = 3:1$) in 85 % yield. For $C_{12}H_{17}NO_3$ (M_r = 223.26) w_i(calc.): 64.55 % C, 7.68 % H, 6.27 % N; w_i(found): 64.66 % C, 7.57 % H, 6.33 % N. IR spectrum; $\tilde{\nu}/cm^{-1}$: 3360, 3300 (NH, OH). ^{1}H NMR spectrum, $\delta(C^2HCl_3)$/ppm: 7.27 (s, 5H, H_{ar}), 4.71 (s, 2H, H_2-2), 4.17 (d, $J_{5,6}$ = 6.0 Hz, 1H, H-5), 3.67—3.90 (m, 6H, H_2-4, H_2-7, H-6, CHN), 3.38 (s-br, 3H, OH, NH_2). ^{13}C NMR spectrum, $\delta(C^2HCl_3)$/ppm: *erythro-VIa*: 144.45, 140.21, 137.93 (C_{ar}), 94.40 (t, C-2), 76.86 (d, C-5), 71.66 (t, C-4), 69.78 (t, C-7), 56.26 (d, CHN), 52.10 (d, C-6); *threo-VIIa*: 144.45, 140.21, 137.93 (C_{ar}), 95.12 (t, C-2), 76.86 (d, C-5), 69.00 (t, C-4), 61.46 (t, C-7), 55.61 (d, CHN), 52.10 (d, C-6).

erythro- and threo-5-Hydroxy-6-[1-(4-bromophenyl)-1-aminomethyl]-1,3-dioxepane (VIb, VIIb)

Isoxazoline *Vb* gave colourless oil ($m_e:m_t = 74:26$), yield = 84 %. For $C_{12}H_{16}BrNO_3$ (M_r = 302.24) w_i(calc.): 47.69 % C, 5.34 % H, 4.63 % N; w_i(found): 47.84 % C,

5.62 % H, 4.80 % N. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3350, 3250 (OH, NH_2). ^{1}H NMR spectrum, $\delta(C^2HCl_3)$/ppm: 7.25—7.51 (m, 4H, H_{ar}), 4.76 (m, 1H, H-5), 3.32—4.50 (m, 10H, H_2-1, H_2-4, H_2-6, CHN, OH, NH_2).

erythro- and threo-5-Hydroxy-6-(1-aminoethyl)-1,3-dioxepane (VIc, VIIc)

Isoxazoline *IIb* gave colourless oil, yield = 84 %. For $C_7H_{15}NO_3$ (M_r = 161.20) w_i(calc.): 52.15 % C, 9.38 % H, 8.69 % N; w_i(found): 52.38 % C, 9.57 % H, 9.01 % N. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3340, 3250 (OH, NH_2). ^{1}H NMR spectrum, $\delta(CCl_4)$/ppm: 4.66 (s, 2H, H_2-2), 3.65—3.80 (m, 5H, H-5, H_2-4, H_2-7), 3.13 (m, 1H, CHN), 2.62 (m, 1H, H-6), 1.15 and 1.17 (d, J = 7.0 Hz, 3H, CH_3).

erythro- and threo-3-Hydroxy-4-(1-amino-1-phenylmethyl)tetrahydrofuran (IXa, Xa)

Isoxazoline *VIIIa* gave colourless oil in 86 % yield (m_e : m_t = 7 : 3). For $C_{11}H_{15}NO_2$ (M_r = 193.24) w_i(calc.): 68.37 % C, 7.82 % H, 7.25 % N; w_i(found): 68.43 % C, 8.12 % H, 7.14 % N. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3360, 3290 (OH, NH_2). ^{1}H NMR spectrum, $\delta(C^2HCl_3)$/ppm: 7.30 (s, 5H, H_{ar}), 4.17 (m, 1H, H-3), 3.25—3.93 (m, 9H, H_2-2, H-4, H_2-5, OH, NH_2). ^{13}C NMR spectrum, $\delta(C^2HCl_3)$/ppm: 145.28, 130.07, 128.78, 127.21, 126.30, 125.92 (C_{ar}); *erythro-IXa*: 76.28 (d, C-3), 73.55 (t, C-2), 67.57 (t, C-5), 54.48 (d, CHN), 49.90 (d, C-4); *threo-Xa*: 76.28 (d, C-3), 69.91 (t, C-2), 65.49 (t, C-5), 53.79 (d, CHN), 50.80 (d, C-4).

erythro- and threo-3-Hydroxy-4-[1-amino-1-(4-methylphenyl)methyl]-tetrahydrofuran (IXd, Xd)

Isoxazoline *VIIId* gave colourless oil in 80 % yield (m_e : m_t = 3 : 1). For $C_{12}H_{17}NO_2$ (M_r = 207.26) w_i(calc.): 69.54 % C, 8.27 % H, 6.76 % N; w_i(found): 69.71 % C, 8.37 % H, 6.95 % N. ^{1}H NMR spectrum, $\delta(C^2HCl_3)$/ppm: 7.08 (s, 4H, H_{ar}), 4.35 (m, 1H, H-3), 3.36—4.15 (m, 9H, H_2-2, H-4, H_2-5, CHN, OH, NH_2), 2.26 (s, 3H, CH_3). ^{13}C NMR spectrum, $\delta(C^2HCl_3)$/ppm: 140.34, 137.74, 136.76, 129.62, 129.29, 126.83, 126.17 (C_{ar}); *erythro-IXd*: 77.77 (d, C-3); 74.52 (t, C-2), 64.55 (t, C-5), 55.68 (d, CHN), 50.15 (d, C-4), 20.98 (q, CH_3); *threo-Xd*: 77.77 (d, C-3), 72.31 (t, C-2), 65.55 (t, C-5), 56.20 (d, CHN), 49.64 (d, C-4), 21.89 (q, CH_3).

erythro-3-Hydroxy-4-[1-amino-1-(4-methoxyphenyl)methyl]tetrahydrofuran (IXe)

Isoxazoline *VIIIe* gave colourless oil in 88 % yield, its ^{13}C NMR spectrum indicates pure *erythro* isomer *IXe*. For $C_{12}H_{17}NO_3$ (M_r = 223.26) w_i(calc.): 64.55 % C, 7.68 % H,

6.27 % N; w_i(found): 64.71 % C, 8.01 % H, 6.31 % N. ^{1}H NMR spectrum, $\delta(C^2HCl_3)$/ppm: 6.77—7.23 (m, 4H, H_{ar}), 4.38 (m, 1H, H-3), 3.40—4.20 (m, 9H, H_2-2, H-4, H_2-5, CHN, OH, NH_2), 3.76 (s, 3H, OCH_3). ^{13}C NMR spectrum, $\delta(C^2HCl_3)$/ppm: 161.26, 128.52, 126.44 (C_{ar}), 77.83 (d, C-3), 71.89 (t, C-2), 65.62 (t, C-5), 55.36 (CHN, OCH_3).

erythro- and threo-3-Hydroxy-4-[1-amino-1-(4-chlorophenyl)-methyl]tetrahydrofuran (IXf, Xf)

Isoxazoline *VIIIf* gave colourless oil in 99 % yield ($m_e : m_t = 80 : 20$). For $C_{11}H_{14}ClNO_2$ ($M_r = 227.66$) w_i(calc.): 58.03 % C, 6.20 % H, 6.15 % N; w_i(found): 57.71 % C, 6.49 % H, 6.38 % N. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3350, 3250 (OH, NH_2). ^{1}H NMR spectrum, $\delta(C^2HCl_3)$/ppm: 7.25 (s, 4H, H_{ar}), 4.19 (m, 1H, H-3), 3.0—3.95 (m, 9H, H_2-2, H-4, H_2-5, CHN, OH, NH_2). ^{13}C NMR spectrum, $\delta(C^2HCl_3)$/ppm: 143.48, 128.86, 128.81, 127.74, 127.33, 126.63 (C_{ar}); *erythro-IXf*: 76.72 (d, C-3), 73.16 (t, C-2), 67.66 (t, C-5), 53.85 (d, CHN), 49.99 (d, C-4); *threo-Xf*: 75.79 (d, C-3), 71.75 (t, C-2), 69.70 (t, C-5), 54.14 (d, CHN), 51.20 (d, C-4).

erythro- and threo-3-Hydroxy-4-[1-amino(2-furyl)methyl]tetrahydrofuran (IXg, Xg)

Isoxazoline *VIIIg* gave colourless oil in 82 % yield. For $C_9H_{13}NO_3$ ($M_r = 183.20$) w_i(calc.): 59.00 % C, 7.15 % H, 7.65 % N; w_i(found): 59.29 % C, 7.14 % H, 8.01 % N. IR spectrum, $\tilde{\nu}$/cm^{-1}: 3370, 3280 (OH, NH_2). ^{1}H NMR spectrum, $\delta(C^2HCl_3)$/ppm: 7.36 (d, d, 1H, H-5′), 6.77 (d, d, 1H, H-4′), 6.13 (d, d, 1H, 1H, H-3′), 3.50—4.32 (m, 10H, H_2-2, H-3, H_2-5, H-4, CHN, OH, NH_2).

9-(4-Nitrophenyl)-11-phenyl-3,5,8-trioxa-10-azabicyclo[5,4,0]undecane (XIa)

To the solution of γ-amino alcohol (a mixture of *VIa*, *VIIa*) (0.38 g; 1.7 mol) in 20 cm^3 of dry ether and 15 cm^3 of chloroform solution of 4-nitrobenzaldehyde (0.3 g; 2 mmol) in 10 cm^3 of dry chloroform was added, followed by the addition of *p*-toluenesulfonic acid (40 mg solved in a mixture of chloroform (2 cm^3) and ether (2 cm^3)). Finally 1 g of molecular sieve (4×10^{-10} m) was added, the reaction mixture was refluxed (48 h), then filtered through a short column filled with sodium carbonate. After concentration *in vacuo* the resulting oil was chromatographed on an aluminium oxide column, eluted by cyclohexane—ethyl acetate mixture ($r_V = 1 : 5$). Yield of the yellow crystalline solid (crystallized from methanol) 0.4 g (66 %), m.p. = 143—145 °C. For $C_{19}H_{20}N_2O_5$ ($M_r = 356.37$) w_i(calc.): 64.03 % C, 5.66 % H, 7.86 % N; w_i(found): 64.21 % C, 5.95 % H, 8.02 % N. Mass spectrum: $m/z = 356$ ($M^{+\bullet}$). ^{1}H NMR spectrum, $\delta(C^2HCl_3)$/ppm: 8.15 (d, 2H, $J_{AB} = J_{A'B'} = 8$ Hz, H-A, H-A′), 7.78 (d, 2H, H-B, H-B′), 7.23 (s, 5H,

H_{ar}), 5.43 (s, 1H, H-9), 4.70 (s, 2H, H_2-4), 4.48 (d, 2H, H-7), 3.18—4.13 (m, 7H, H-1, H_2-2, H-11, NH).

3-(4-Nitrophenyl)-5-phenyl-2,8-dioxa-4-azabicyclo[4,3,0]nonane (XIIa)

Prepared from the mixture of *IXa*, *Xa* using the procedure for *XIa*, yield of yellow oily compound 51 %. For $C_{18}H_{18}N_2O_4$ (M_r = 326.34) w_i(calc.): 66.24 % C, 5.56 % H, 8.58 % N; w_i(found): 66.37 % C, 5.81 % H, 8.21 % N. ^{1}H NMR spectrum, $\delta(C^2HCl_3)$/ppm: 8.31 (d, 2H, $J_{AB} = J_{A'B'}$ = 9 Hz, H-A, H-A′), 7.84 (d, 2H, H-8, H-8′), 7.25 (s, 5H, H_{ar}), 5.33 (s, 1H, H-3), 4.70 (m, 1H, H-1), 3.45—4.30 (m, 7H, H_2-7, H_2-9, H-6, H-5, NH).

3-(4-Nitrophenyl)-5-(4-chlorophenyl)-2,8-dioxa-4-azabicyclo[4,3,0]nonane (XIIf)

Prepared from a mixture of *IXf*, *Xf* by the procedure for *XIa*, light yellow oil, yield = 99 %. For $C_{18}H_{17}ClN_2O_4$ (M_r = 360.76) w_i(calc.): 59.93 % C, 4.75 % H, 7.82 % N; w_i(found): 60.21 % C, 4.99 % H, 8.01 % N. ^{1}H NMR spectrum, $\delta(C^2HCl_3)$/ppm: 8.24 (d, $J_{AB} = J_{A'B'}$ = 9 Hz, 2H, H-A, H-A′), 7.81 (d, 2H, H-B, H-B′), 7.28 (m, 4H, H_{ar}), 5.43 (s, 1H, H-3), 3.55—4.87 (m, 7H, H-1, H-5, H-6, H_2-7, H_2-9), 2.78 (s, 1H, NH).

11-Phenyl-3,5,8-trioxa-10-azabicyclo[5,4,0]undecane-9-one (XIIIa)

To the solution of γ-amino alcohol (a mixture of *VIa*, *VIIa*) (1 g; 0.45 mmol) and triethylamine (0.08 cm^3) in 20 cm^3 of dry ether was during 1 h added dropwise a solution of 10 cm^3 of ethylchloroformate in dry ether. After the addition of 0.2 cm^3 of triethylamine the reaction mixture was refluxed for 4 h, stirred at laboratory temperature another 2 days, ammonium salt was filtered off and the filtrate dried with sodium sulfate. After the solvent was evaporated *in vacuo* the residue was redissolved in 30 cm^3 of chloroform and heated in autoclave with 3 cm^3 of sodium methoxide (prepared from 216 mg of Na) at 80 °C for two days. Filtration and concentration gave crude *XIIIa*, which was further chromatographed on a silica gel column, eluted with chloroform—methanol mixture (r_V = 20 : 1). Yield of colourless oil 0.6 g (54 %). For $C_{13}H_{15}NO_4$ (M_r = 249.26) w_i(calc.): 62.64 % C, 6.07 % H, 5.62 % N; w_i(found): 62.81 % C, 6.34 % H, 5.59 % N. IR spectrum, $\tilde{\nu}$/cm^{-1}: 1080 (C—O—C), 1680 (C=O), 3450 (NH). ^{1}H NMR spectrum, $\delta(C^2HCl_3)$/ppm: 7.28 (s, 5H, H_{ar}), 5.12 (m, 1H, H-7), 3.28—4.93 (m, 9H, H-1, H_2-2, H_2-4, H_2-6, H-11, NH).

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