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Chemistry of 1,3-Dioxepins. XI.[1] Bis-(4,7-dihydro-1,3-dioxepin) Approach to Pyridoxine Intermediates 1,5-Dihydro-8-methyl-3*H*-[1,3]dioxepino[5,6-*c*]pyridin-9-ols[†]

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The novel pyridoxine intermediates, bis-dioxepino[5,6-*c*]pyridin-9-ols **3** and **4** have been synthesized starting from bis-(4,7-dihydro-1,3-dioxepins) **1**. Their constitution and configuration has been confirmed by single-crystal X-ray diffractions of bis-dioxepins **1a** and **1b**, dioxepinopyridinol **3a** maleate salt, as well as **3b** and **4b** monohydrates.

INTRODUCTION

Syntheses of 1,5-dihydro-8-methyl-3*H*-[1,3]dioxepino-[5,6-*c*]pyridin-9-ols, pyridoxine (vitamin B_6) intermediates, starting from the different kinds of 4,7-dihydro-1,3-dioxepins are of our current interest.[2–7] Related to the above, we studied the syntheses and/or application of 5-substituted-4,7-dihydro-1,3-dioxepins.[8–12] Now, we would like to report a bis-(4,7-dihydro-1,3-dioxepin) approach to the novel pyridoxine intermediates, 1,5-dihydro-8-methyl-3*H*-[1,3]dioxepino[5,6-*c*]pyridin-9-ols **3** and **4** (Scheme 1).

[†] Dedicated to the memory of the late Professor Stanko Borčić.

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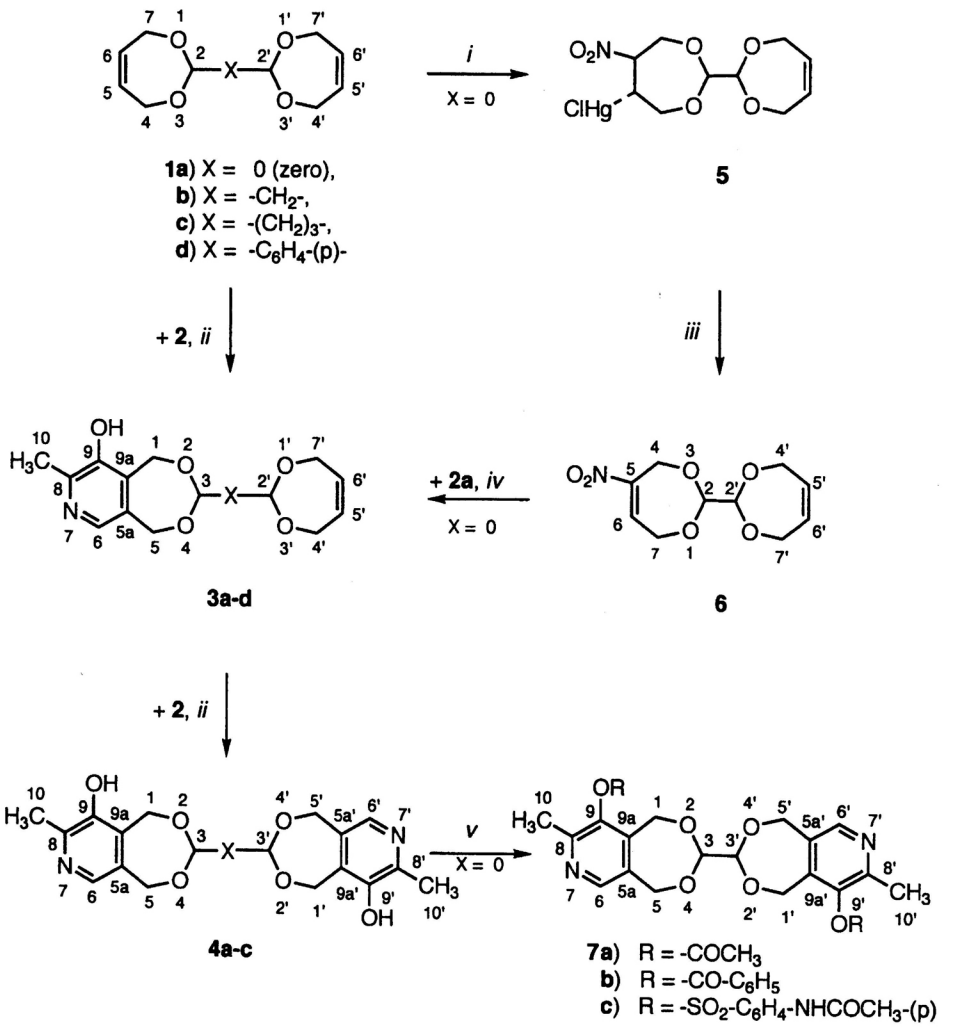
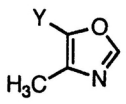


1a) X = 0 (zero),
b) X = $-CH_2-$,
c) X = $-(CH_2)_3-$,
d) X = $-C_6H_4-(p)-$



2 a) Y = -H
b) Y = -OEt
c) Y = -CN

Reagents and conditions:

i, $HgCl_2/NaNO_2/H_2O$, rt, 24 hrs.;
ii, catalyst, antioxidant and reflux in excess of **2b,c** or $C_6H_5NO_2$, antioxidant and heating in excess of **2a** at 180-190 °C;
iii, aq. $NaOH/CH_2Cl_2$, rt,1 hr;
iv, cat. $HClO_4$ and reflux in excess of **2a** as solvent, refl., 4 hrs.;
v, $(CH_3CO)_2O$, C_6H_5COCl or p-$CH_3CONH-C_6H_4-SO_2Cl$, base, THF, rt

Scheme 1.

RESULTS AND DISCUSSION

Despite of the simplicity of their structure, the starting bis-(4,7-dihydro-1,3-dioxepins) **1** have not been hitherto studied in any great detail. The only products synthesized so far, **1b–d**, are covered by patents and their preparative methods and physical constants are not well known.[13–15] Therefore, we prepared **1** by the known acetalization/transacetalization procedures[16] of *cis*-2-butene-1,4-diol with glutardialdehyde, terephtalaldehyde and 1,1,3,3-tetra-methoxypropane, respectively. Otherwise, we prepared the hitherto unknown bis-dioxepin **1a**, accompanied by viscous oligomeric material,[17] in 55.6%, (m.p. 101–102 °C from acetone) according to the Sprung and Guenther procedure,[18] *i.e.* by *p*-toluenesulfonic acid catalyzed reaction of *cis*-2-butene-1,4-diol with glyoxal (mol ratio 2.4 to 1) in toluene, under azeotropic removal of reaction formed water.

Physical data of the thus obtained bis-dioxepins **1** were consistent with literature data,[13–15] and ^{1}H- and ^{13}C-NMR data (Table I) with the prepositional structures. However, the configurations of **1a** and **1b** were confirmed by X-ray diffraction (Figure 1, Table II).[19]

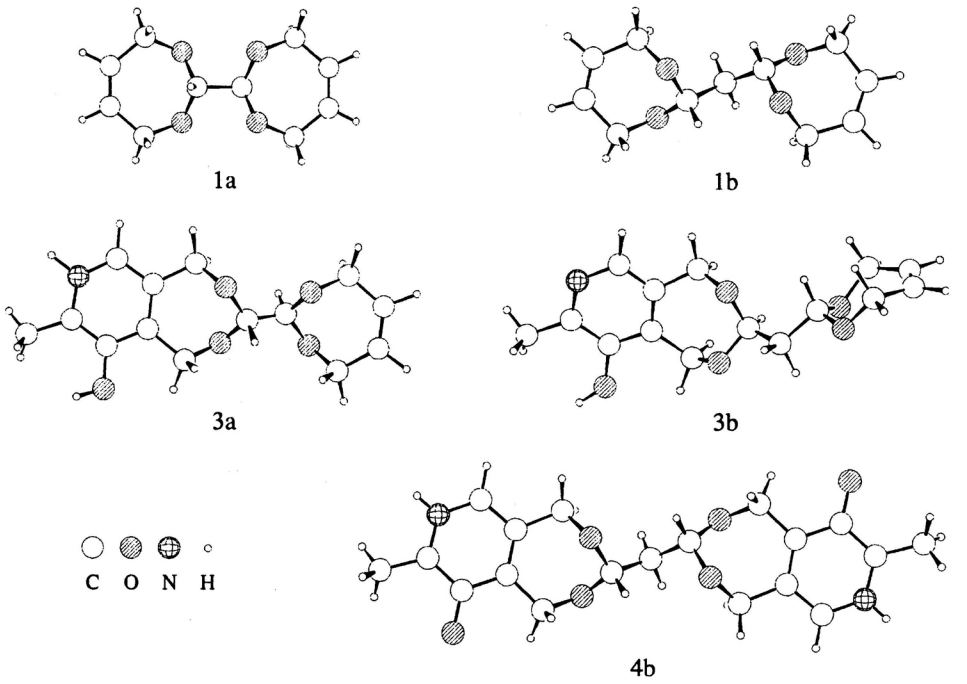


Figure 1. PLUTON plots of some bis-dioxepins **1** and dioxepinopyridinols **3** and **4**.

TABLE I

^{1}H- and ^{13}C-NMR data of bis-(1,3-dioxepin) derivates **1**, **3**, **4** and **7**

Compd. No.	^{1}H-NMR, 300 MHz, δ/ppm (DMSO-d_6, 25 °C, TMS)
1a	5.68 (t, 4H, *J* 1.8, H-C5, 6&5',6'); 4.65 (s, 2H, H-C2&2'); 4.52–4.02 (m, 8H, H-C4, 7&4',7')
1b	5.81 (s, 4H, H-C5, 6&5',6'); 4.91 (t, 2H, *J* 5.8, H-C2&2'); 4.34 & 4.22 (dd, 8H, *J* 14.9, H-C4, 7&4',7'); 2.02 (t, 2H, *J* 5.8, -C*H*$_2$-)
1c	5.61 (s, 4H, H-C5, 6&5',6'); 4.63 (t, 2H, *J* 5.6, H-C2&2'); 4.21 & 4.00 (dd, 8H, *J* 15.4, H-C4, 7&4',7'); 1.53–1.46 (m, 4H, -C*H*$_2$-CH$_2$-C*H*$_2$-); 1.32–1.24 (m, 2H, -CH$_2$-C*H*$_2$-CH$_2$-)
1d*	7.54 (s, 4H, H-arom.); 5.86 (s, 2H, H-C2&2'); 5.80 (s, 4H, H-C5, 6&5',6'); 4.39 & 4.28 (dd, 8H, J 14.9, H-C4, 7&4',7')
3a	8.88 (br, 1H, OH); 7.81 (s, 1H, H-C6); 5.70 (s, 2H, H-C5',6'); 5.25–4.71 (m, 6H, H-C1,3,5&2'), 4.44 & 4.15 (dd, 4H, *J* 15.1, H-C4',7'); 2.36 (s, 3H, H-C10)
3a**	7.50–6.30 (br, 3H, OH & COOH); 7.94 (s, 1H, H-C6); 6.18 (s, 2H, -CH=); 5.70 (s, 2H, H-C5',6'); 5.37–4.68 (m, 6H, H-C1,3,5&2'); 4.44 & 4.15 (dd, 4H, *J* 14.7, H-C4',7'); 2.42 (s, 3H, H-C10)
3b	8.98 (br, 1H, OH); 7.82 (s, 1H, H-C6); 5.71 (s, 2H, H-C5',6'); 5.19–4.70 (m, 6H, H-C1,3,5&2'); 4.33 & 4.12 (dd, 4H, *J* 15.2, H-C4',7'); 2.37 (s, 3H, H-C10); 1.93 (t, 2H, *J* 5.6, -C*H*$_2$-)
3c	8.96 (br, 1H, OH); 7.81 (s, 1H, H-C6); 5.70 (s, 2H, H-C5',6'); 5.17–4.67 (m, 6H, H-C1,3,5&2'); 4.29 & 4.09 (dd, 4H, *J* 14.7, H-C4',7'); 2.37 (s, 3H, H-C10); 1.62–1.55 (m, 4H, -C*H*$_2$-CH$_2$-C*H*$_2$-); 1.55–1.35 (m, 2H, -CH$_2$-C*H*$_2$-CH$_2$-)
3d	9.00 (br, 1H, OH); 7.85 (s, 1H, H-C6); 7.48 (s, 4H, H-arom.); 6.00 & 5.83 (2 s, 2H, H-C3 & 2'); 5.76 (s, 2H, H-C5',6'); 5.11 & 4.88 (dd, 2H, *J* 15.4, H-C1); 4.91 & 4.86 (dd, 2H, *J* 14.2, H-C5); 4.29 & 4.25 (dd, 4H, *J* 15.7, H-C4',7'); 2.38 (s, 3H, H-C10)
4a	8.85 (br, 2H, OH); 7.82 (s, 2H, H-C6&6'); 5.31–4.75 (m, 10H, H-C1,3,5 & 1',3',5'); 2.39 (s, 6H, H-C10 &10')
4b	8.99 (br, 2H, OH); 7.83 (s, 2H, H-C6&6'); 5.17 & 4.76; (dd, 4H, *J* 15.3, H-C1, & 1'); 5.06 (t, 2H, *J* 5.0, H-C3 &3'); 4.85 & 4.79 (dd, 4H, *J* 13.4, H-C5 & 5'); 2.37 (s, 6H, H-C10 &10'); 1.99 (t, 2H, *J* 5.0, -C*H*2-)
4c	8.90 (br, 2H, OH); 7.82 (s, 2H, H-C6&6'); 5.18–4.67 (m, 10H, H-C1,3,5 & 1',3',5'); 2.37 (s, 6H, H-C10 &10'); 1.67–1.56 (m, 4H, -C*H*$_2$-CH$_2$-C*H*$_2$-); 1.55-1.43 (m, 2H, -CH$_2$-C*H*$_2$-CH$_2$-)
7a	8.26 (s, 2H, H-C6&6'); 5.11–4.74 (m, 10H, H-C1,3,5 & 1',3',5'); 2.41 (s, 6H, COCH$_3$); 2.31 (s, 6H, H-C10 &10')
7b	8.31 (s, 2H, H-C6&6'); 8.22–7.63 (m, 10H, H-arom.); 5.16–4.79 (m, 10H, H-C1,3,5 & 1',3',5'); 2.33 (s, 6H, H-C10 &10')
7c	10.58 (s, 2H, NH); 8.31 (s, 2H, H-C6&6'); 7.91 (s, 8H, H-arom.); 5.09–4.70 (m, 10H, H-C1,3,5 & 1',3',5'); 2.15 (s, 6H, H-C10 &10'); 2.10 (s, 6H, COCH$_3$)

* Spectra were taken in $CDCl_3$

** **3a** maleate salt

TABLE I – (continued)

Compd. No.	^{13}C-NMR, 75 MHz, δ/ppm (DMSO-d_6, 25 °C, TMS)
1a	129.12 (C5,6&5',6'); 101.24 (C2&2'); 65.46 (C4,7&4',7')
1b	129.71 (C5,6&5',6'); 100.98 (C2&2'); 64.77 (C4,7&4',7'); 37.57 (-*C*H$_2$-)
1c	129.82 (C5,6&5',6'); 103.63 (C2&2'); 64.56 (C4,7&4',7'); 32.95 (-*C*H$_2$-CH$_2$-*C*H$_2$-); 19.96 (-CH$_2$-*C*H$_2$-CH$_2$-)
1d*	138.88 & 126.16 (C-arom.); 129.77 (C5,6&5',6'); 101.84 (C2&2'); 64.44 (C4,7&4',7')
3a	147.29, 146.51, 138.09, 133.64 & 133.24 (C5a,6,8,9&9a); 129.57 (C5',6'); 103.50 (C3); 101.96 (C2'); 66.48, 65.69 & 64.28 (C1&4',7'&5); 19.75 (C10)
3a**	167.10 (COOH); 148.59, 144.70, 137.70, 134.88 & 132.56 (C5a,6,8,9,9a& -CH=); 129.57 (C5',6'); 103.10 (C3); 100.91 (C2'); 65.86 & 64.34 (C1,5&4',7'); 18.06 (C10)
3b	147.60, 146.90, 138.33, 134.14 & 133.79 (C5a,6,8,9&9a); 129.97 (C5',6'); 104.17 (C3); 100.82 (C2'); 66.69, 64.82 & 63.69 (C1&4',7'&5); 38.07 (-*C*H$_2$-); 19.81 (C10)
3c	147.49, 146.80, 138.31, 134.24 & 133.89 (C5a,6,8,9&9a); 130.05 (C5',6'); 106.73 (C3); 103.75 (C2'); 66.54, 64.68 & 63.45 (C1&4',7'&5); 33.36 & 32.93 (-*C*H$_2$-CH$_2$-*C*H$_2$-); 19.74 (C10); 19.71 (-CH$_2$-*C*H$_2$-CH$_2$-)
3d	147.42, 146.52, 139.41, 133.78 & 133.33 (C5a,6,8,9&9a); 138.78, 138.15, 126.28 & 126.18 (C-arom.); 129.92 (C5',6'); 103.89 (C3); 101.41 (C2'); 66.09, 64.47 & 63.15 (C1&4'7'&5); 19.72 (C10)
4a	147.32, 146.61, 138.05, 133.75 & 133.09 (C5a,6,8,9,9a&5a',6',8',9',9a'); 103.31 (C3&3'); 66.39 (C1&1'); 64.30 (C5&5'); 19.25 (C10&10')
4b	147.33, 146.64, 138.15, 133.90 & 133.52 (C5a,6,8,9,9a&5a',6',8',9',9a'); 103.61 (C3&3'); 66.53 (C1&1'); 63.58 (C5&5'); 38.54 (-*C*H$_2$-);19.79 (C10&10')
4c	147.58, 146.84, 138.31, 134.31 & 133.96 (C5a,6,8,9,9a&5a',6',8',9',9a'); 106.79 (C3&3'); 66.60 (C1&1'); 63.51 (C5&5'); 33.39 (-*C*H$_2$-CH$_2$-*C*H$_2$-); 19.78 (C10&10'); 19.54 (CH$_2$-*C*H$_2$-CH$_2$)
7a	–
7b	163.93 (*C*O); 152.42, 144.68, 141.99, 139.90, 134.94, 133.83, 130.16, 129.28 & 127.66 (C5a,6,8,9,9a&5a',6',8',9',9a'&C-arom.); 102.83 (C3&3'); 66.35 (C1&1'); 63.80 (C5&5'); 19.09 (C10&10')
7c	169.85 (*C*O); 152.07, 145.81, 145.71, 142.01, 141.04, 134.39, 129.98, 127.67 & 119.31 (C5a,6,8,9,9a&5a',6',8',9',9a'&C-arom.); 103.14 (C3&3'); 66.71 (C1&1'); 63.92 (C5&5'); 24.31 (CO*C*H$_3$); 19.59 (C10&10')

* Spectra were taken in $CDCl_3$

** **3a** maleate salt

In our experiment, all of the thus synthesized bis-dioxepins **1** underwent the Diels-Alder cycloaddition with 4-methyloxazole[20] or its 5-ethoxy-[21] and 5-cyano-[22] derivatives **2a–c** at 130–190 °C, furnishing the mixture of bis-di-

TABLE II

Summary of some essential crystallographic data for bis-dioxepin derivates: **1a**, **1b**, **3a** maleate salt, **3b** and **4b** monohydrates[a]

	1a	**1b**	**3a** maleate salt	**3b** × H_2O	**4b** × H_2O
Crystal system	triclinic	triclinic	monoclinic	monoclinic	monoclinic
Space group	$P\bar{1}$	$P\bar{1}$	$P2_1/n$	$P2_1/c$	$P2_1/n$
a/Å	4.348 (2)	6.367 (4)	6.465 (3)	13.096 (3)	6.550 (1)
b/Å	6.014 (2)	9.113 (8)	20.720 (7)	10.050 (3)	8.987 (2)
c/Å	9.552 (6)	10.543 (7)	13.717 (4)	12.306 (3)	16.374 (4)
α/deg	91.50 (4)	67.50 (2)	90	90	90
β/deg	93.64 (3)	73.47 (3)	95.61 (2)	108.27 (2)	98.55 (2)
γ/deg	103.74 (3)	73.54 (5)	90	90	90
Reference	19	24	23	24	24

[a] X-ray diffractions were performed on a Phillips PW1100 diffractometer with Mo-Kα radiation and graphite monochromator. For further details of crystal structure determinations see the above References.

oxepinopiridinols **3** and **4**. Thus, refluxing of **1a** in a twelve molar excess of 5-cyano-4-methyloxazole (**2c**) in the presence of 2,6-di-*tert*-butyl-4-methylphenol as antioxidant and *p*-toluenesulfonic acid as catalyst for 15 hours produced a mixture of products, accompanied by a solid polymeric material which, after separation and purification by column chromatography gave dioxepino[5,6-*c*]pyridin-9-ols **3a** (20.1%) and **4a** (4.4%), respectively.

In an analogous manner, using other bis-dioxepins **1** and oxazoles **2**, dioxepino[5,6-*c*]pyridin-9-ols **3b–d** and **4b–c** were obtained in low to moderate yields (Scheme 1).

We suggest that formation of **4** is the consequence of a consecutive reaction, confirmation of which is done by the parallel preparation of **4** from **3** under the above cited reaction conditions.

In the case of acetic anhydride catalyzed cycloadditions, small quantities of one or two additional, hitherto to us unknown pyridinol derivatives were detected by TLC (red spots by Pauly- and blue by Gibbs reagents), unfortunately, not isolated and characterized so far. Because of their increased presence in the case of [4 + 2]-cycloaddition of **2** to **3**, and the well known reactivity of pyridinol derivatives with acetic anhydride, we supposed that they could be the mono-*O*-acetyl derivatives of **4** and/or the possible nonaromatic cycloadduct-precursor to **4**.

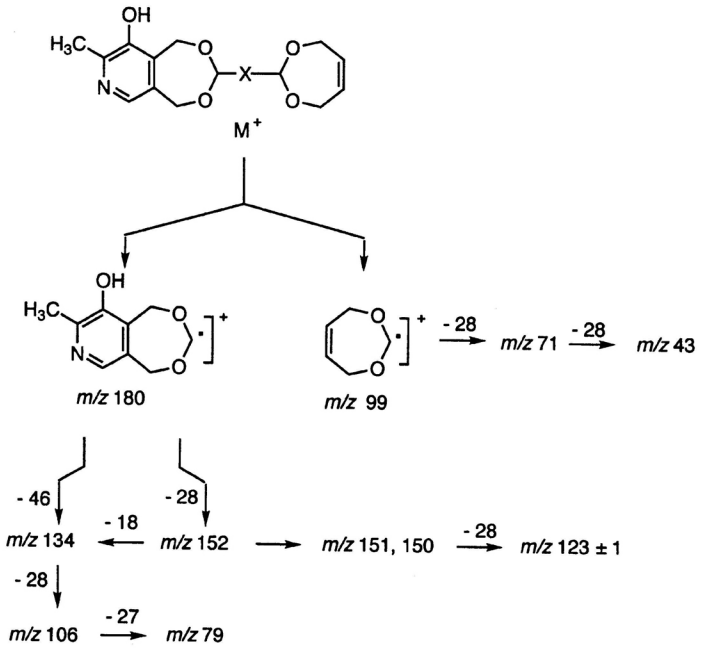


Figure 2. MS fragmentation of dioxepinopyridinols **3** at 70 eV.

The structures of **3** and **4** were assigned from analytical, NMR- (Table I) and MS (Figure 2) spectral data as well as by the parallel three steps synthesis of the **3a** following sequences: **1a→5→6→3a** in an overall yield of 14.4%.[11]

Additionally, the configuration of **3** was confirmed by the single crystal X-ray diffractions of **3a** maleate salt[23] and of **3b** monohydrate (m.p. 112–114 °C), obtained by crystallization of **3b** from wet ethyl acetate (Figure 1).

Despite several attempts, it was not possible to prepare a sample of **4a** of acceptable elemental analysis. Therefore, we turned our attention to the preparation of a good-quality single crystal suitable for X-ray structure analysis. Unfortunately, neither the single crystal of **4a**, nor the single crystals of any, for this purpose specially synthesized new bis-(*O*-acetyl)-(**7a**), bis-(*O*-benzoyl)-(**7b**) and bis-(*O*-4-acetylaminophenylsulfonyl)-(**7c**) derivatives, were obtained. However, the configuration of the prepared bis-(dioxepino[5,6-*c*]pyridin-9-ols) **4** was confirmed by the single crystal X-ray diffraction of bis-(dioxepino[5,6-*c*]pyridin-9-ol) **4b** monohydrate, showing its racemic but not *meso* configuration[24] (Figure 1).

The essential crystallographic data of **1a**, **1b**, **3a** maleate salt, as well as those of **3b** and **4b** monohydrates, are shown in Table II. Full details of their crystal structures are or will be published elsewhere.[19,23,24]

All synthesized bis-dioxepinopyridinols **3** and **4** represent novel pyridoxine intermediates in which they can be easily hydrolyzed in hydrochloric acid.

The significance of this finding is still under investigation.

EXPERIMENTAL

Chemistry. General Information.

Melting points were determined using a Fischer-Johns apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer from a KBr pelleted sample or as film. ^{1}H- (300 and 90 MHz) and ^{13}C- (75 and 25 MHz) NMR spectra were recorded by Varian XL-GEM 300 and Jeol FX 90Q spectrometers, with TMS as internal standard; the values of chemical shifts (δ) are given in ppm and coupling constants (J) in Hz; DMSO-d_6 was used as solvent unless otherwise stated. Mass spectra were scanned on a Hitachi-Perkin-Elmer RMU-6M instrument operating at 70 eV. TLC was performed using the Merck Kieselgel 60 F_{254} silica plates and components were visualized using UV light (UV 254 nm), iodine vapor and spraying by diazotized sulfanilamide (red spots). Compounds were purified by column chromatography using Merck Kieselgel 60 (0.063–0.200 mm, 70–230 mesh), and were homogeneous by TLC. Solvents *p.a.* grade were used without further purification. All chemicals, *i.e. cis*-2-buten-1,4-diol, glyoxal (30% aqueous solution), glutardialdehyde (25% aqueous solution), terephtalaldehyde and 1,1,3,3-tetramethoxypropane for preparing the starting olefins are commercially available and were supplied by Merck. Oxazoles **2a–c** were prepared by known procedures.[20–22] Hydrochinone and 2,6-di-*tert*-butyl-4-methylphenol were used as antioxidants and *p*-toluenesulfonic- and perchloric acid, and acetic anhydride as catalysts. The yields were not optimized.

*4,7-Dihydro-2-(4,7-dihydro-1,3-dioxepin-2-yl)-1,3-dioxepin (**1a**)*

A mixture of *cis*-2-butene-1,4-diol (211.2 g, 2.4 mole), aqueous solution of glyoxal (30%, w/w, 193.0 g, 1.0 mole), toluene (160 mL) and *p*-toluenesulfonic acid (2.7 g) was heated at boiling temperature until complete azeotropic removal of water (about 44 mL). The reaction mixture was cooled and the formed crystals were suction filtered, washed with toluene and dried in vacuo to yield the title compound **1a** (110.0 g, 55.6%, m.p. 93–96 °C). After recrystallization from acetone, the sample showed m.p. 100–102 °C. IR (KBr) ν_{max}/cm^{-1}: 3010m, 2960w, 2940m, 2850m, 1455s, 1395m, 1380s, 1330s, 1270s, 1230s, 1120vs, 1000vs, 950vs, 905w, 830m and 720s.

Anal. Calc. for C_{10} $H_{14}O_4$ (M_r = 198.22): C 60.59, H 7.12%; found: C 60.77, H 7.33%.

*4,7-Dihydro-2-(4,7-dihydro-1,3-dioxepin-2-yl-methyl)-1,3-dioxepin (**1b**)*

A mixture of 1,1,3,3-tetramethoxypropane (82.0 g, 0.5 mole), 88.0 g (1.0 mole) of *cis*-2-butene-1,4-diol and two drops of concentrated sulfuric acid was slowly warmed up to 115 °C along with simultaneous distillation of the reaction formed methanol. Following the cooling and neutralization by solid sodium carbonate, the reaction mixture was distilled in vacuo to yield the title compound **1b** (61.5 g, 58.0%, b.p. 85 °C/ 53.3 Pa). After recrystallization from *n*-hexane or light petroleum, the samples

showed m.p. 58–59 °C, and 60–61 °C respectively (Ref. 13: Y. = 92.0%, b.p. 100 °C/ 240 Pa, m.p. 58–59 °C). IR (KBr) ν_{max}/cm^{-1}: 3040w, 2950m, 2910m, 2870m, 1450s, 1400s, 1370m, 1290m, 1250m, 1205s, 1120vs, 1080vs, 1060s, 1030s, 1010s, 965s, 900s, 870s and 780s.

*4,7-Dihydro-2-[3-(4,7-dihydro-1,3-dioxepin-2-yl)-propyl]-1,3-dioxepin (**1c**)*

A mixture of *cis*-2-butene-1,4-diol (44.0 g, 0.5 mol), 100.0 g (0.25 mol) aqueous solution of glutardialdehyde (25%, w/w), 100 mL toluene and 0.8 g of *p*-toluenesulfonic acid was heated at boiling temperature until complete azeotropic removal of water. Following the cooling, neutralization by solid sodium carbonate and evaporation of the excess of toluene, the reaction mixture was distilled *in vacuo* to yield the title compound **1c** (50.5 g, 84.1%, b.p. 129–134 °C/ 26.7 Pa). After recrystallization from *n*-hexane or light petroleum, the sample showed m.p. 38 °C and 33–34 °C, respectively (Ref. 15: Y. = 80.0%, b.p. 130–133 °C/ 200 Pa, m.p. 34 °C from pentane; Ref. 14: b.p. 144–146 °C/ 53.3 Pa, m.p. 37–38 °C). IR (film) ν_{max}/cm^{-1}: 3040m, 2950s, 2870s, 1485s, 1395s, 1275s, 1205s, 1135vs, 1090s, 1015s, 985s, 920m and 845m.

*4,7-Dihydro-2-[4-(4,7-dihydro-1,3-dioxepin-2-yl)-phenyl]-1,3-dioxepin (**1d**)*

A mixture of *cis*-2-butene-1,4-diol (105.6 g, 1.2 mole), 67.1 g (0.5 mole) terephtalaldehyde, 100 mL toluene and 1.4 g of *p*-toluenesulfonic acid was heated at boiling temperature until complete azeotropic removal of water. The reaction mixture was concentrated under reduced pressure to half volume, cooled and the formed crystals were suction filtered, washed with acetone and dried in vacuo to yield the title compouns **1d** (59.6 g, 43.5%, m.p. 119–122 °C). After recrystallization from acetone, the sample showed m.p. 132–133 °C (Ref. 13: m.p. 134–136 °C from benzene). IR (KBr) $\nu_{max}/cm.^{-1}$: 3020m, 2930m, 2900w, 2860m, 1450m, 1425s, 1350vs, 1265s, 1225s, 1115vs, 1085vs, 1040s, 1020s, 1010s, 985m, 945w, 925s, 900s, 800s and 780vs.

*General Procedure for the Preparation of 1,5-Dihydro-9-hydroxy-8-methyl-3*H*-[1,3]-dioxepino[5,6-c]pyridines **3** and **4***

This procedure is illustrated by the preparation of 1,5-dihydro-3-(4,7-dihydro-1,3-dioxepin-2-yl)-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino[5,6-*c*]pyridine (**3a**) and 3-(1,5-dihydro-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino[5,6-*c*]pyridin-3-yl)-1,5-dihydro-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino[5,6-*c*]pyridine (**4a**). A mixture of bis-dioxepin **1a** (1.98 g, 0.01 mol), oxazole **2c** (12.96 g, 0.12 mol), *p*-toluenesulfonic acid (0.03 g) and 2,6-di-*tert*-butyl-4-methylphenol (0.1 g) was refluxed for 15 hours. The excess of oxazole **2c** was removed by distillation under reduced pressure, and purification of the residue by column chromatography using ethyl acetate-methanol mixture under gradient mode as eluent furnished the title compounds **3a** and **4a.** Mono-aduct **3a** (0.56 g, 20.1%, m.p. 165–170 °C) was eluted as the first. After recrystallization from ethyl acetate the sample displayed m.p. 177–179 °C. R_f = 0.57 & 0.68 [TLC; Eluents: ethyl acetate-methanol-aq. ammonia (25%) = 20 : 5 : 1 and ethyl acetate-methanol = 4 : 1, respectively; Visualization: UV 254 nm and spraying by diazotized sulfanilamide (red spots)]. IR (KBr) ν_{max}/cm^{-1}: 3500–2300 broad, assoc., 1605w, 1450m, 1420m, 1380m, 1330m, 1260s, 1245s, 1210m, 1130vs, 1060m, 1040m, 1000m, 990m, 945s, 900w, 840w, 810w, 750 w and 710w; MS *m/z* 279 (4.3%) $[M]^+$, 180 (53.0%), 152

(19.0%), 151 (14.9%), 150 (10.0%), 135 (5.8%), 134 (23.0%), 124 (7.2%), 123 (5.5%), 122 (9.7%), 106 (65.2%), 99 (38.7%), 79 (7.6%), 71 (48.9%) and 43 (100.0%).

Anal. Calcd. for $C_{14}H_{17}NO_5$ (M_r = 279.29): C 60.21, H 6.14, N 5.02%; found: C 60.36, H 6.42, N 5.08%.

Continued elution gave the bis-adduct **4a** (0.16 g, 4.4%, m.p. 210–213 °C). After recrystallization from absolute ethanol, the sample displayed m.p. 215–217 °C. R_f = 0.09 & 0.16 [for TLC conditions see above]. IR (KBr) ν_{max}/cm^{-1}: 3600–2000 broad, assoc., 1590m, 1510m, 1435s, 1410s, 1370s, 1330s, 1280s, 1240vs, 1130vs, 1060s, 990m, 940m, 890m and 700m.

Anal. Calcd. for $C_{18}H_{20}N_2O_6$(M_r = 360.37): C 59.99, H 5.59, N 7.77%; found: C 60.36, H 5.86, N 7.42%.

The following were prepared in the same manner:

*1,5-Dihydro-3-(4,7-dihydro-1,3-dioxepin-2-yl-methyl-)-9-hydroxy-8-methyl-3*H*-[1,3]-dioxepino[5,6-c]pyridine (**3b**) and 3-(1,5-Dihydro-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino-[5,6-c]pyridin-3-yl-methyl)-1,5-dihydro-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino [5,6-c]-pyridine (**4b**)*

Starting from bis-dioxepine **1b** (2.12g, 0.01mol), oxazole **2c** (12.96 g, 0.12 mol), acetic anhydride (0.06 g) and hydrochinone (0.03 g) according to the general procedure, bis-dioxepin **3b** (1.13 g, 38.5%, m.p. 127–130 °C) was obtained first. After recrystallization from ethyl acetate, the sample showed m.p. 131–133 °C. R_f = 0.70 & 0.74 [for TLC conditions see above]. IR (KBr) ν_{max}/cm^{-1}: 3500m, 3400–2000 broad, assoc., 1600m, 1550m, 1490m, 1440s, 1400s, 1370vs, 1350s, 1295s, 1285s, 1260s, 1245s, 1215vs, 1130vs, 1100vs, 1080vs, 1050vs, 1035s, 1015s, 995s, 950m, 920m, 910m, 860m, 800m, 770m, 705m, 695m, and 635m; MS *m/z* 293 (4.7%) $[M]^+$, 180 (7.5%), 152 (42.3%), 151 (100.0%), 135 (19.3%), 134 (14.9%), 124 (9.3%), 123 (29.8%), 122 (27.3%), 106 (47.2%), 99 (6.9%), 79 (6.7%), 71 (42.9%) and 43 (46.0%).

Anal. Calcd. for $C_{15}H_{19}NO_5$ (M_r = 293.32): C 61.42, H 6.53, N 4.78%; found: C 61.64, H 6.41, N 4.51%.

Continued elution gave the bis-adduct **4b** (0.73 g, 19.5%, m.p. 226–229 °C). After recrystallization from the ethyl acetate-ethanol (4 : 1, v/v) mixture, the sample showed m.p. 231–233 °C. R_f = 0.21 & 0.22 [for TLC conditions see above]. IR (KBr) ν_{max}/cm^{-1}: 3500–2500 broad, assoc., 1590s, 1555m, 1520s, 1440s, 1420vs, 1390vs, 1370vs, 1310vs, 1290vs, 1240s, 1215vs, 1130vs, 1080vs, 1060vs, 1020s, 990m, 940w, 900m, 875m, 790m and 705m.

Anal. Calcd. for $C_{19}H_{22}N_2O_6$ (M_r = 374.39): C 60.95, H 5.92, N 7.48%; found: C 60.72, H 5.82, N 7.61%.

*1,5-Dihydro-3-[3-(4,7-dihydro-1,3-dioxepin-2-yl)-propyl]-9-hydroxy-8-methyl-3*H*-[1,3]-dioxepino[5,6-c]pyridine (**3c**) and 3-[3-(1,5-Dihydro-9-hydroxy-8-methyl-3*H*-[1,3]di-oxepino[5,6-c]pyridin-3-yl)-propyl]-1,5-dihydro-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino-[5,6-c]pyridine (**4c**)*

Method A

Starting from bis-dioxepine **1c** (2.40 g, 0.01 mol), oxazole **2c** (12.96 g, 0.12 mol), acetic anhydride (0.30 g) and hydrochinone (0.1 g) according to the general procedure, bis-dioxepin **3c** (0.51 g, 15.9%, m.p. 110–114 °C) was obtained first. After re-

crystallization from ethyl acetate, the sample displayed m.p. 116–118 °C. R_f = 0.74 & 0.77 [for TLC conditions see above]. IR (KBr) ν_{max}/cm^{-1}: 3020w, 2920s, 2860s, 1595s, 1445s, 1375s, 1285s, 1270s, 1185s, 1150sh, 1130vs, 1120vs, 1090s, 1070s, 1010m, 990s and 910m; MS *m/z* 321 (11.1%) $[M]^+$, 180 (30.0%), 152 (98.6%), 151 (100.0%), 150 (37.8%), 135 (40.6%), 134 (36.2%), 124 (14.9%), 123 (34.9%), 122 (33.9%), 106 (98.4%), 99 (52.6%), 79 (10.0%), 71 (61.0%) and 43 (85.5%).

Anal. Calcd. for $C_{17}H_{23}NO_5$ (M_r = 321.37): C 63.54, H 7.21, N 4.36%; found: C 63.71, H 7.04, N 4.59%.

Continued elution gave the bis-adduct **4c** (0.21 g, 5.2%, m.p. 157–161 °C). After recrystallization from the ethyl acetate-ethanol (4 : 1, v/v) mixture, the sample showed m.p. 165–168 °C. R_f = 0.27 & 0.23 [for TLC conditions see above]. IR (KBr) ν_{max}/cm^{-1}: 3600–2500 broad, assoc., 1600s, 1435m, 1415m, 1335m, 1310s, 1280s, 1230s, 1210s, 1140vs, 1120s, 1080m, 1040m, 935m and 860m.

Anal. Calcd. for $C_{21}H_{26}N_2O_6$ (M_r = 403.44): C 62.51, H 6.75, N 6.94%; found: C 62.28, H 6.98, N 6.78%.

Method B

A mixture of bis-dioxepine **1c** (2.40g, 0.01 mol), oxazole **2a** (10.0 g, 0.12 mol), nitrobenzene (1.23 g, 0.01 mol), acetic anhydride (0.06 g) and hydrochinone (0.04 g) was heated in a sealed tube at 180–190 °C for 2 hours. After the workup of the reaction mixture according to the general procedure, bis-dioxepin **3c** (0.76 g, 23.6%, m.p. 111–115 °C) was obtained first. After recrystallization from ethyl acetate, the sample displayed m.p. 116–118 °C. Its IR spectrum was identical to the spectrum of an authentic sample from procedure A (see above). Continued elution gave the bis-adduct **4c** (0.48 g, 11.9%, m.p. 158–161 °C). After recrystallization from the ethyl acetate-ethanol (4 : 1, v/v) mixture, the sample showed m.p. 165–168 °C. Its IR spectrum was identical to the spectrum of an authentic sample from procedure A (see above).

*1,5-Dihydro-3-[4-(4,7-dihydro-1,3-dioxepin-2-yl)-phenyl]-9-hydroxy-8-methyl-3*H*-[1,3]-dioxepino[5,6-c]pyridine (**3d**)*

Starting from bis-dioxepine **1d** (2.74 g, 0.01 mol), oxazole **2b** (11.0 g, 0.0865 mol), and hydrochinone (0.1 g) according to the general procedure, only the bis-dioxepin **3d** (0.70 g, 19.7%, m.p. 156–160 °C) was obtained. After recrystallization from ethyl acetate, the sample showed m.p. 165–167 °C. R_f = 0.77 & 0.81 [for TLC conditions see above]. IR (KBr) ν_{max}/cm^{-1}: 3400m, 3400–2500 broad, assoc., 1445m, 1420s, 1410s, 1370m, 1360s, 1340vs, 1300m, 1280s, 1260vs, 1240vs, 1220s, 1120vs, 1110vs, 1080vs, 1060s, 1035s, 1010s, 1005s, 955m, 920w, 890s, 790s, 775vs, 700w and 625s; MS *m/z* 355 (100.0%) $[M]^+$, 180 (2.0%), 152 (9.9%), 151 (45.5%), 150 (20.4%), 135 (100.0%), 134 (6.5%), 124 (4.1%), 123 (26.7%), 122 (17.4%), 106 (19.1%), 99 (3.0%), 79 (10.9%), 71 (6.8%) and 43 (9.0%).

Anal. Calcd. for $C_{20}H_{21}NO_5$ (M_r = 355.39): C 67.59, H 5.96, N 3.94%; found: C 67.31, H 6.12, N 4.22%.

Their structures were consistent with analytical and spectral data (Table I) and were confirmed by the X-ray analysis data (Table II and Figure 1).

General Procedure for the Preparation of 1,5-Dihydro-9-hydroxy-8-methyl-3H-[1,3] dioxepino[5,6-c]pyridines ***4a–c*** *from Dioxepino[5,6-c]pyridin-9-ols* ***3***

This procedure is illustrated by the preparation of 3-(1,5-dihydro-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino[5,6-*c*]pyridin-3-yl)-1,5-dihydro-9-hydroxy-8-methyl-3*H*-[1,3] dioxepino[5,6-*c*]pyridine (**4a**). A mixture of 1,5-dihydro-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino[5,6-*c*]pyridine **3a** (2.97 g, 0.01 mol), oxazole **2c** (38.5 g, 0.356 mol), *p*-toluenesulfonic acid (0.05 g) and 2,6-di-*tert*-butyl-4-methylphenol (0.1 g) was refluxed for 48 hours. The excess of oxazole **2c** was removed by distillation under reduced pressure, and purification of the residue by column chromatography using the ethyl acetate-methanol mixture under gradient mode as eluent furnished the unreacted **3a** (0.55 g, 18.5%, m.p. 172–176 °C) and the title compound **4a** (1.20 g, 33.3%, m.p. 208–212 °C). After recrystallization from absolute ethanol, the sample showed m.p. 215–217 °C. Its IR spectrum was identical to the spectrum of an authentic sample prepared as above.

The following were prepared in the same manner:

*3-(1,5-Dihydro-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino[5,6-c]pyridin-3-yl-methyl)-1,5-dihydro-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino[5,6-c]pyridine (**4b**)*

A mixture of bis-dioxepine **3b** (2.93 g, 0.01 mol), oxazole **2c** (19.44 g, 0.18 mol), acetic anhydride (0.20 g) and hydrochinone (0.1 g) was refluxed for 8 hours and after the workup of the reaction mixture according to the general procedure, unreacted **3b** (1.38 g, 47.1%, m.p. 126–129 °C) and the title compound **4b** (0.57 g, 15.2%, m.p. 225–229 °C) were obtained. After recrystallization from the ethyl acetate absolute ethanol mixture (4/1), the **4b** sample showed m.p. 231–233 °C. Its IR spectrum was identical to the spectrum of an authentic sample prepared as above.

*3-[3-(1,5-Dihydro-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino[5,6-c]pyridin-3-yl)-propyl]-1,5-dihydro-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino[5,6-c]pyridine (**4c**)*

A mixture of bis-dioxepine **3c** (3.21 g, 0.01 mol), oxazole **2c** (43.3 g, 0.40 mol), acetic anhydride (0.30 g) and hydrochinone (0.1 g) was refluxed for 18 hours. After the workup of the reaction mixture according to the general procedure, unreacted **3c** (0.32 g, 10.0%, m.p. 112–115 °C) and the title compound **4c** (0.64 g, 15.8%, m.p. 159–162 °C) were obtained. After recrystallization from the ethyl acetate absolute ethanol mixture (4/1), the **4c** sample showed m.p. 165–168 °C. Its IR spectrum was identical to the spectrum of an authentic sample prepared as above.

*5-Chloromercury-2-(4,7-dihydro-1,3-dioxepin-2-yl)-6-nitro-1,3-dioxepane (**5**)*

To the solution of mercury(II) chloride (6.9 g, 0.025 mol) and sodium nitrite (3.5 g, 0.050 mol) in 75 mL water, the bis-dioxepin **1a** (5.0 g, 0.025 mol) was added in small portions for 1 hour. The mixture was stirred at room temperature for 24 hours and the formed precipitate was filtered, washed with water and dried under *vacuo* at room temperature to give the nitromercurial **5** (10.0 g, 82.8%, m.p. 160 °C decompn.). IR (KBr) ν_{max}/cm^{-1}: 3050w, 2940m, 2895m, 2860m, 1625w, 1550vs, 1460s, 1395s, 1360s, 1330s, 1285s, 1205m, 1120vs, 1020vs, 930, 820s, 785s,720m and 640s.

*4,7-Dihydro-2-(4,7-dihydro-1,3-dioxepin-2-yl)-5-nitro-1,3-dioxepin (**6**)*

To the suspension of nitromercurial **5** (5.0 g, 0.010 mol) in 50 mL of dichloromethane, aqueous sodium hydroxide solution (4.2 mL, $c = 2.5$ mol L^{-1}) was added dropwise under vigorous stirring at room temperature for 1 hour. The reaction mixture was stirred at the same temperature for further 30 minutes. After addition of diatomaceous earth (2.0 g), the precipitated elementary mercury was filtered off. The dichloromethane layer was washed with water, dried over anhydrous sodium sulfate and concentrated furnishing the crude **6** (1.6 g, 62.9%, m.p. 109–111 °C). After recrystallization from ethylacetate the sample showed m.p. 113–114 °C. IR (KBr) ν_{max}/cm^{-1}: 3090w, 3035w, 2950m, 2850m, 1680m, 1525vs, 1445m, 1390m, 1345vs, 1285m, 1275m, 1260m, 1250m, 1120vs, 1015s, 985m, 965m, 870w, 820w, 800m, 705m and 690m; ^{1}H-NMR (DMSO-d_6) δ: 7.37 (t, 1H, $J = 3.4$, H-C6); 5.70 (s, 2H, H-C5',6'); 4.99–4.67 (m, 6H, H-C4,7 & 2,2'); 4.43 & 4.17 (dd, 4H, $J = 15.3$, H-C4',7'); ^{13}C-NMR δ: 149.88 (C5), 138.04 (C6), 129.44 (C5',6'), 100.59 & 100.54 (C2 & 2'), 65.84 (C4',7'), 62.46 & 61.83 (C7&4).

Anal. calcd. for $C_{10}H_{13}NO_6$ ($M_r = 243.22$): C 49.38, H 5.39, N 5.76%; found: C 49.50, H 5.69, N 5.66%.

*1,5-Dihydro-3-(4,7-dihydro-1,3-dioxepin-2-yl)-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino-[5,6-c]pyridine (**3a**) from **6***

A mixture of nitro-bis-dioxepin **6** (1.00 g, 0.004 mol), oxaxole **2a** (7.00 g, 0.084 mol) and catalytic amount of perchloric acid was refluxed for 4 hours. The excess of oxazole **2a** was removed by distillation under reduced pressure, and purification of the residue by column chromatography using the ethyl acetate-acetone (1 : 1) mixture as eluent furnished **3a** (0.31 g, 27.7%, m.p. 164–165 °C) and some other products. After recrystallization from ethylacetate the sample showed m.p. 177–179 °C. Its IR spectrum was identical to the spectrum of an authentic sample prepared as above.

*1,5-Dihydro-3-(4,7-dihydro-1,3-dioxepin-2-yl)-9-hydroxy-8-methyl-3*H*-[1,3]dioxepino-[5,6-c]pyridine Maleate Salt (**3a** × maleic acid)*

To the solution of bis-dioxepine **3a** (0.60 g, 2.15 mmol) in 10 mL of methanol, a solution of maleic acid (0.20 g, 1.72 mmol) in 3.5 mL of methanol was added, furnishing after two days standing at room temperature the **3a** mono maleate salt (0.52 g, 61.2%, m.p. 193–197 °C). After recrystallization from methanol-water mixture, the sample showed m.p. 198–200 °C. IR (KBr) ν_{max}/cm^{-1}: 3600–1900 broad, assoc., 1580s, 1470vs, 1395s, 1340vs, 1280s, 1265vs, 1245m, 1210m, 1180s, 1140vs, 1090vs, 1020vs, 980s, 930m, 910s, 895s, 880s, 800s 750s and 710s.

Anal. Calcd. for $C_{18}H_{21}NO_9$ ($M_r = 395.37$): C 54.68, H 5.35, N 3.55%; found: C 54.41, H 5.60, N 3.51%.

*3-(9-Acetoxy-1,5-dihydro-8-methyl-3*H*-[1,3]dioxepino[5,6-c]pyridin-3-yl)-9-acetoxy-1,5-dihydro-8-methyl-3*H*-[1,3]dioxepino[5,6-c]pyridine (**7a**)*

A mixture of bis-dioxepinopyridinol **4a** (0.36 g, 0.001 mol), acetic anhydride (7.0 g, 0.0686 mol) and pyridine (7.0 g, 0.0885 mol) was stirred at room temperature for 22 hours. Methanol (10 mL) was carefully added to the reaction mixture under cooling, and the mixture was concentrated under reduced pressure to dryness. The procedure was repeated two more times furnishing the crude **7a** (0.38 g, 86.4%, m.p.

>250 °C). After two recrystallizations from methyl-ethyl-ketone the sample showed m.p. 260–262 °C. IR (KBr) ν_{max}/cm^{-1}: 2970w, 2880w, 2850w, 1740vs, 1590m, 1440s, 1400s, 1370s, 1275s, 1220s, 1200vs, 1160s, 1070s, 1110s, 985s, 980s, 885m, 800w, 760w and 710w.

Anal. Calcd. for $C_{22}H_{24}N_2O_8$ (M_r = 444.44): C 59.45, H 5.44, N 6.30%; found: C 59.21, H 5.59, N 6.18%.

*3-(9-Benzoyloxy-1,5-dihydro-8-methyl-3*H*-[1,3]dioxepino[5,6-*c*]pyridin-3-yl)-9-benzoyloxy-1,5-dihydro-8-methyl-3*H*-[1,3]dioxepino[5,6-*c*]pyridine (**7b**)*

To the refluxed mixture of bis-dioxepinopyridinol **4a** (0.36 g, 0.001 mol) and potassium *tert*-butoxide (0.22 g, 0.002 mol) in tetrahydrofurane (20 mL), the solution of benzoyl-chloride (0.28 g, 0.002 mol) in tetrahydrofurane (5 mL) was added dropwise for 30 minutes, and the mixture was refluxed for further 30 minutes. The reaction mixture was cooled to room temperature, pH was adjusted to 7 by addition of small quantities of powdered potassium *tert*-butoxide and the mixture was concentrated under reduced pressure. Purification of the residue by column chromatography using ethyl acetate methanol mixture under gradient mode as eluent furnished the title compound **7b** (0.28 g, 49.3%, m.p. 240–245 °C). After recrystallization from ethyl acetate the sample showed m.p. 249–251 °C. IR (KBr) ν_{max}/cm^{-1}: 3050w, 2860m, 1740vs, 1590s, 1440s, 1400m, 1360s, 1310m, 1260vs, 1200vs, 1175s, 1120vs, 1085vs, 1070vs, 1020s, 1000m, 930s, 880m, 800w and 755s.

Anal. Calcd. for $C_{32}H_{28}N_2O_8$ (M_r = 568.58): C 67.60, H 4.96, N 4.93%; found: C 67.38, H 5.13, N 5.17%.

*3-{9-(4-Acetylaminophenylsulfonyloxy)-1,5-dihydro-8-methyl-3*H*-[1,3]dioxepino[5,6-*c*]-pyridin-3-yl}-9-(4-acetylaminophenylsulfonyloxy)-1,5-dihydro-8-methyl-3*H*-[1,3]dioxepino[5,6-*c*]pyridine (**7c**)*

To the refluxed mixture of bis-dioxepinopyridinol **4a** (0.36 g, 0.001 mol) and potassium *tert*-butoxide (0.22 g, 0.002 mol) in tetrahydrofurane (20 mL), the solution of 4-acetylaminobenzenesulfonyl-chloride (0.47 g, 0.002 mol) in tetrahydrofurane (5 mL) was added dropwise for 30 minutes, and the mixture was refluxed for further 30 minutes. The reaction mixture was cooled to room temperature, pH was adjusted to 7 by addition of small quantities of powdered potassium *tert*-butoxide and the mixture was concentrated under reduced pressure. Purification of the residue by column chromatography using ethyl acetate methanol mixture under gradient mode as eluent furnished the title compound **7c** (0.40 g, 53.1%, m.p. 178–183 °C). After recrystallization from ethyl acetate, the sample showed m.p. 184–186 °C. IR (KBr) ν_{max}/cm^{-1}: 3500m, 3320–2860 assoc., 1690s, 1590vs, 1530s, 1500sh, 1400s, 1360vs, 1320s, 1270s, 1210vs, 1180vs, 1130s, 1110s, 985m, 940m, 900m, 850m, 820m, 780sh and 770vs.

Anal. Calcd. for $C_{34}H_{34}N_4O_{12}S_2$(M_r = 754.78): C 54.10, H 4.54, N 7.42%; found: C 53.91, H 4.28, N 7.55%.

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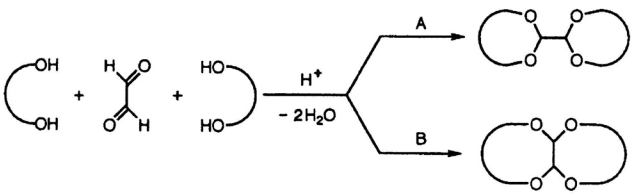

Scheme 2.

The obtained spectral analyses speak well for both of the proposed structures. X-ray diffraction of **1a** sample solved the dilemma and showed that the A direction was right.

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SAŽETAK

Kemija 1,3-dioksepina. XI. Bis-(4,7-dihidro-1,3-dioksepin)-pristup do 1,5-dihidro-8-metil-3*H*-[1,3]dioksepino[5,6-*c*]piridin-9-ola, međuprodukata u sintezi piridoksina

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Novi bis-dioksepino[5,6-*c*]piridin-9-oli **3** i **4**, međuprodukti u sintezi piridoksina, sintetizirani su iz bis-(4,7-dihidro-1,3-dioksepina) **1**. Njihova konstitucija i konfiguracija povrđena je rentgenskom strukturnom analizom monokristala bis-dioksepina **1a** i **1b**, maleata dioksepinopiridinola **3a** te monohidrata dioksepinopiridinola **3b** i **4b**.