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New 2,3-Dihydro-5*H*-1,4-benzodioxepin Derivatives. Easy Formation and X-ray Structure Determination of a Pentacyclic Acetal Containing a Fourteen-Membered Carbon-Oxygen Ring

Francesco Lucchesini,* Vincenzo Bertini, and Marco Pocci

Istituto di Analisi e Tecnologie Farmaceutiche ed Alimentari, Università di Genova
Via Brigata Salerno, I-16147 Genova

Giovanni De Munno and Alessandra Crispini

Dipartimento di Chimica, Università della Calabria
I-87030 Arcavacata di Rende (Cosenza)

Abstract : The acid catalyzed acetalization of 2,6-bis(2-hydroxyethoxy)benzaldehyde (**4**) is studied under various conditions. New 2,3-dihydro-5*H*-1,4-benzodioxepin derivatives are prepared and a fourteen-membered tetraoxygenated macrocycle is obtained in 81% yield without special synthetic expedients. The solid state molecular structure of the macrocyclic compound is determined by single crystal X-ray analysis.

INTRODUCTION

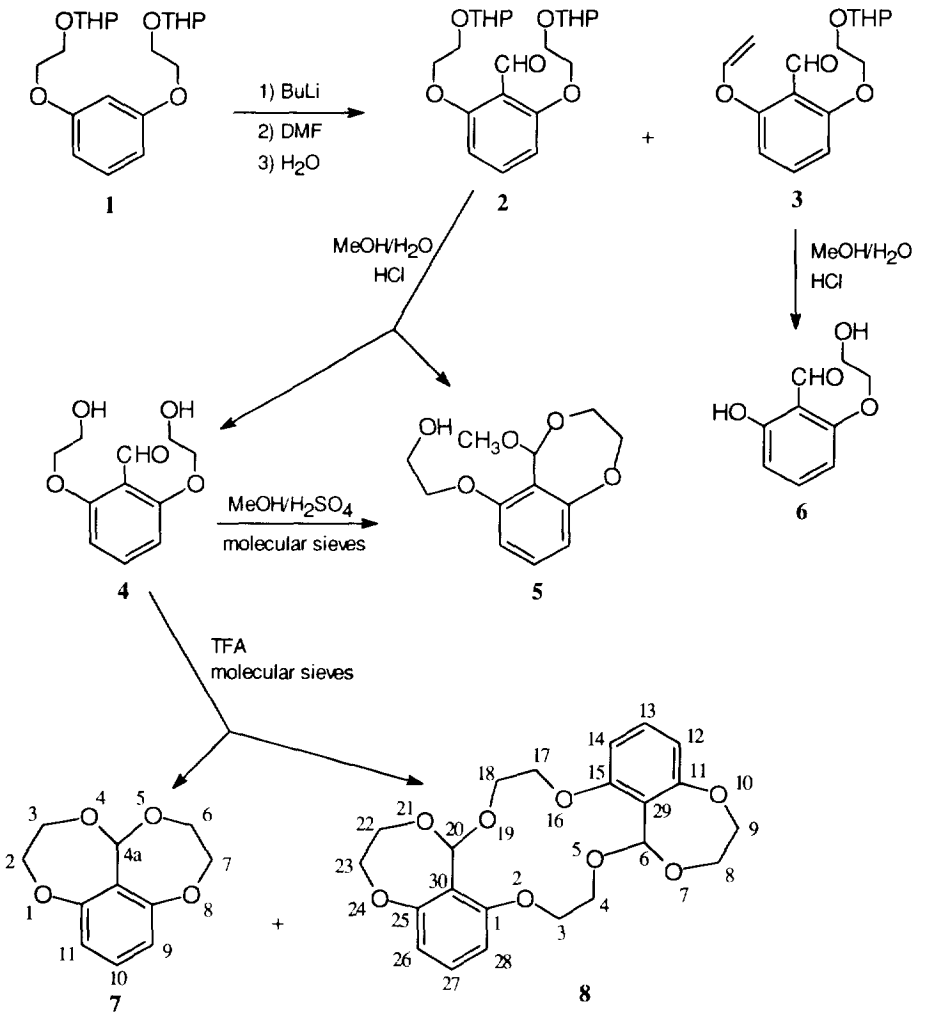
It is known that cyclizations generally take place with good yields when a five to seven-membered ring is formed, whereas the formation of larger rings is disfavoured and over twelve atoms usually requires special conditions such as template effects,[1] high-diluition techniques,[2] cesium ion effect[3] etc.. However, interesting macrocycles are occasionally obtained in good yields even when these conditions do not occur. The inter- or intramolecular acetalization or transacetalization reactions offer some remarkable examples of macro- and polycyclic system formation under simple conditions. Mention may be made of the synthesis in 40% yield, through the transacetalization of a bicyclic dimethylacetal and a bicyclic tetrol, of a very rigid heptacyclic derivative of 18-crown-6 containing an eighteen-membered ring,[4] or the intramolecular acetalization of 7-hydroxy-4-hydroxymethylheptan-2-one to form 1-methyl-2,8-dioxabicyclo[4.2.1]nonane accompanied by a dimerization to the tricyclic 3,10-dimethyl-4,11,16,18-tetraoxatricyclo[8.4.2.2^{3,8}]octadecane containing a fourteen-membered ring,[5] or the highly stereoselective rearrangement of indene ozonide to give in about 20% yield a tetramer containing acetalic carbon atoms and peroxide bridges in a twenty-membered carbon-oxygen ring[6] or the lactonization observed during the preparation of 2-(2-hydroxyethoxy)benzoic acid methyl ester affording in modest yield 2,3-dihydro-5*H*-1,4-benzodioxepin-5-one and dimeric dibenzo[f,m]-2,5,9,12-tetraoxacyclotetradecane-1,8-dione with a fourteen-membered ring.[7] Even if seven-membered carbon-dioxygen

rings are usually prepared without particular difficulties, the synthesis of 2,3-dihydro-5*H*-1,4-benzodioxepins has been poorly studied.[8-11] Acetal derivatives of such benzodioxepin system and a carbon-oxygen macrocycle are the subject of the present paper. Working in the field of selective inhibitors of copper containing amine oxidases[12] we had the occasion to encounter the synthesis of the intermediate 2,6-bis(2-hydroxyethoxy)benzaldehyde (**4**)[13] obtained by a process which also afforded poor yields of a preliminary observed seven membered oxygen containing cyclic compound (**5**), sign of an interesting tendency to give benzodioxepin structures and unordinary acetalizations worthful of further study. The present work reexamines the process of production of **4**, explores some aspects of the acetalization reactions and refers about synthesis and properties of new 2,3-dihydro-5*H*-1,4-benzodioxepin compounds among which the benzodioxepinic tricycle **7** and pentacycle **8** with a fourteen-membered ring obtained in 81% yield and characterized by X-ray structure determination.

RESULTS AND DISCUSSION

The reexamined synthesis of **4** started from compound **1** (Scheme 1) prepared in 85% yields from resorcinol and 1-bromo-2-tetrahydropyranyloxyethane.[12] The ortho metallation and formylation of **1** afforded a crude mixture containing phenolic by-products from which it was possible to obtain the expected **2** as an oil in only 38% yields and a new product (**3**) (4%) probably derived from a base-catalyzed second order elimination of 2-hydroxytetrahydropyran. Compound **2** submitted to deprotection with HCl in methanol-water solution yielded a 65% of **4** and a 4% of **5** probably derived from the hemiacetalization of **4** blocked by methanol in the acetal form. In agreement with such hypothesis the treatment of **4** with methanol and sulphuric acid in presence of molecular sieves to remove water afforded **5** in 70% yields and the reaction of **3** with HCl in methanol-water under the same conditions as for the deprotection of **2** produced the new crystalline compound **6** in 97% yields by cleaving the vinyl ether function and removing the tetrahydropyranyl group. Mass, ^{1}H- and ^{13}C-NMR spectra unequivocally accounted for the structures of the new compounds **2**, **3**, **5** and **6**. To avoid the interference of methanol and water a sample of **4** was dissolved in acetonitrile-d_3 treated with traces of trifluoroacetic acid and examined by ^{1}H-NMR: the initial spectrum rapidly changed owing to the formation of two new compounds while the complete disappearance of signals of **4** needed the addition of 3 Å molecular sieves to remove the produced water. The new products prepared on a greater scale were separable by TLC, and their mass, ^{1}H- and ^{13}C-NMR spectra suggested the structures **7** and **8** for them, confirmed for **8** by X-ray structure determination. The reaction carried out with trifluoracetic acid in other solvents like benzene, tetrahydrofuran, dimethoxyethane and chloroform showed that the most favourable preparation conditions were in refluxing benzene for **7** (**7**: 77%; **8**: 8%) and in acetonitrile at room temperature for **8** (**7**: 15%; **8**: 80%). In all the examined solvents even if with variable selectivity, the sum of **7** and **8** accounted for more than 80% of the reacted **4**, while an appreciable amount of polymeric materials was never observed. In order to cast light on the process affording **7** and **8**, compound **4** was dissolved in various aprotic solvents (Table 1) containing a trace of triethylamine to prevent any formation of **7** and **8** and examined by ^{1}H-NMR spectroscopy. The observed spectrum modification accounted for the appearance of a chemical equilibrium between **4** and its hemiacetal **9** (Scheme 2) and allowed determination of the molar ratio **9**:**4** by integrating the well separated triplet signals of the aromatic proton in para position to the aldehydic group hemiacetalized (**9**) or not (**4**)

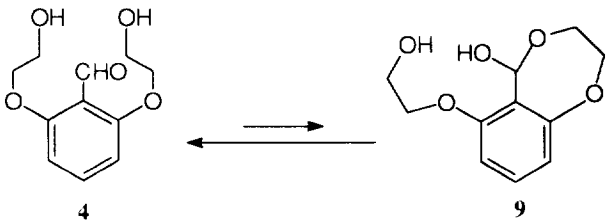
(Table 1). Since 2-(2-hydroxyethoxy)benzaldehyde, in contrast with some of its derivatives substituted in position 3 i.e. ortho to the alkoxy side chain, does not yield cyclic hemiacetal in consequence of a steric effect for seven-membered ring tautomer formation,[14] the observed ring-chain equilibrium **9**:**4** could indicate for the same reaction a similar effect promoted by a substituent ortho to the aldehydic group.



Scheme 1.

The proposed hemiacetal **9** in spontaneous equilibrium with **4** accounts very well for the formation of **7** and **8** under acidic anhydrous conditions. It is remarkable that polymeric acetals, in principle not incompatible

with the bifunctional hemiacetal **9**, were practically not found, indicating the prevalent tendency of an initially formed linear dimer towards the formation of an unordinary cycle with fourteen members.



4 **9**

Scheme 2.

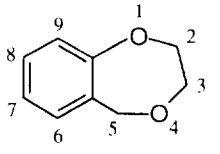
Table 1. Equilibrium composition of the emiacetalization of **4** at 25 °C in various solvent

Molar ratio	$CDCl_3$	Acetonitrile-d_3	DMSO-d_6
9 : **4**	1/28	1/18	1/11

Since **8** contains two asymmetric carbon atoms its reported structure corresponds to three different isomers: two enantiomers corresponding to a racemate and a meso compound. The ^{1}H-NMR spectrum of crude **8** accounted for both racemate and meso form indicating one much prevalent on the other, but not allowing to distinguish between them for the presence in all the stereoisomers of **8** of a symmetry element as an inversion centre (meso form) or a binary axis (racemate) confirmed by the appearance of only eleven signals in the ^{13}C-NMR spectrum. Their separation, unsuccessful by recrystallization from various solvents, was partially attained through column chromatography by obtaining few pure crystals of the more abundant product. Regular crystals of such product obtained from acetonitrile, submitted to X-ray structure determination, showed no large deviations of bond lengths and angles from their standard values and proved that the two asymmetric carbon atoms in the positions 6 and 20 had equal configurations in agreement with the racemate (Figure1).

Table 2 collects the ^{1}H- and ^{13}C-NMR data of the 2,3-dihydro-5*H*-1,4-benzodioxepin derivatives **5**, **7** and **8** whose signals are attributed by comparing the known spectrum of the parent compound (**10**) and carrying out COSY, NOE and HETCOR experiments. Signals in the ^{13}C-NMR spectra at ppm 72.1 for **5**, 73.0 for **7** and 72.2 for **8** are attributed to the carbon atom structurally corresponding in the parent compound to C(2) (74.60 ppm[11]) and those at ppm 63.6 for **5**, 66.3 for **7** and 64.0 for **8** to the carbon atom C(3) (74.66 ppm[11]). The remarkable differences between the observed value in the range 63.6-66.3 and the reported one at 74.66 account for the presence in our products of an alkoxy group substituted at the carbon structurally corresponding to C(5). Such alkoxy group is quite likely to cause a large γ-effect through the oxygen atom shifting upfield the C(3) signal in agreement with the following observations. Comparing 2,3-dihydro-5*H*-1,4-benzodioxepin with 3-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepin the C(5) signal is shifted from 75.41 to 63.61 ppm in CHF_2Cl/CD_2Cl_2 4:1.[11] Analogously, for tetrahydropyran and 2-methoxytetrahydropyran the C(6)

signal is shifted from 68.69 to 61.88 ppm[15] and for tetrahydrofuran and 2-methoxytetrahydrofuran the C(5) signal is shifted from 67.96 to 66.86 ppm[15] both in $CDCl_3$ solution.



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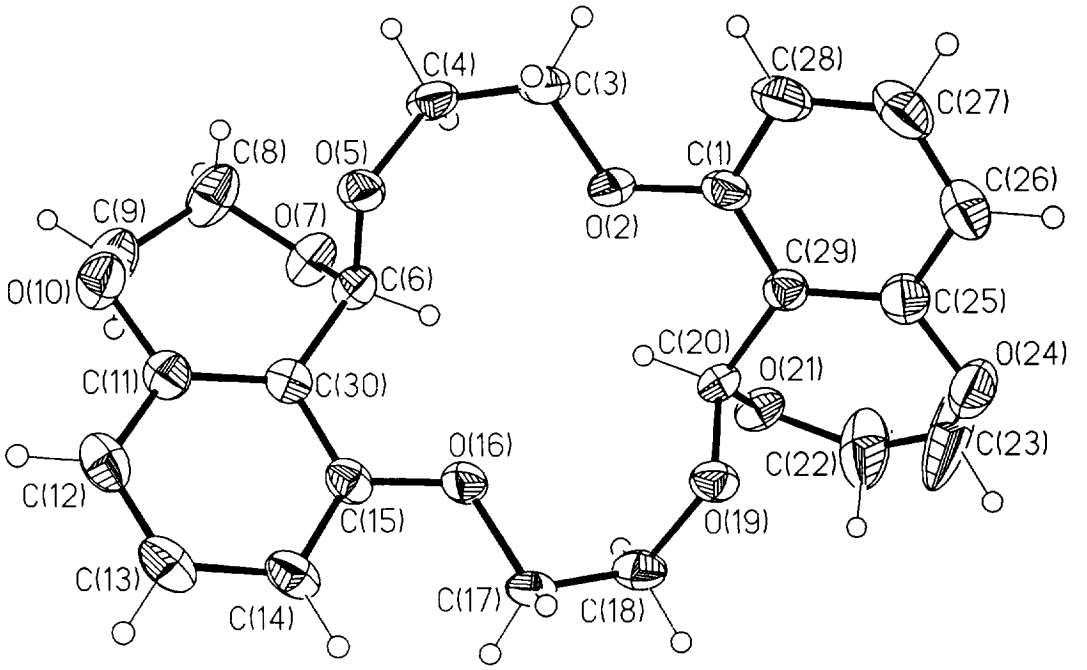

Figure 1. The structure and the atomic labeling of the compound **8** (ellipsoids at the 30% probability level). Selected distances [Å] and angles [°] with standard deviations in parentheses : C(1)-O(2) 1.373(5), O(2)-C(3) 1.427(6), C(3)-C(4) 1.485(8), C(4)-O(5) 1.440(6), O(5)-C(6) 1.403(5), C(6)-O(7) 1.416(6), O(7)-C(8) 1.427(7), C(8)-C(9) 1.493(9), C(9)-O(10) 1.433(7), O(10)-C(11) 1.393(6), C(11)-C(30) 1.397(7), C(30)-C(15) 1.396(6), C(15)-O(16) 1.371(6), O(16)-C(17) 1.438(5), C(17)-C(18) 1.479(7), C(18)-O(19) 1.435(6), O(19)-C(20) 1.407(4), C(20)-O(21) 1.408(4), O(21)-C(22) 1.388(9), C(22)-C(23) 1.253(12), C(23)-O(24) 1.372(9), O(24)C(25) 1.355(6), C(25)-C(29) 1.399(8), C(29)-C(1) 1.398(6), C(1)-O(2)-C(3) 117.7(3), C(4)-O(5)-C(6) 114.5(3), C(15)-O(16)-C(17) 118.9(3), C(18)-O(19)-C(20) 114.6(3).

Table 2. ^{1}H- and ^{13}C-NMR data in $CDCl_3$ of 2,3-dihydro-5*H*-1,4-benzodioxepin derivatives

Compound	^{1}H-NMR δ (ppm)	^{13}C-NMR δ (ppm)
5	7.11 (t, 1H, J=8.2 Hz, H(8)), 6.61 (ddd, 1H, $J_{9,8}$=8.2 Hz, $J_{9,7}$=1.0 Hz, $J_{9,5}$=0.3 Hz, H(9)), 6.52 (dd, 1H, $J_{7,8}$=8.2 Hz, $J_{7,9}$=1.0 Hz, H(7)), 6.03 (broad s, 1H, H(5)), 4.52-4.43 (m, 1H, H(2)), 4.13-4.07 (m, 4H), 4.03-3.93 (m, 1H), 3.91 (t, 2H, J=4.5 Hz, H(2')), 3.56 (s, 3H OCH_3), 2.90 (very broad s, 1H, OH)	159.5 (C(6) or C(9a)), 157.2 (C(9a) or C(6)), 129.6 (C(8)), 118.8 (C(5a)), 113.4 (C(9)), 106.8 (C(7)), 97.9 (C(5)), 72.1 (C(2)), 70.7 (C(1')), 63.6 (C(3)), 61.3 (C(2')), 56.0 ($C(OCH_3)$)
7	7.07 (t, 1H, J=8.1 Hz, H(10)), 6.70 (d, 2H, J=8.1 Hz, H(11) + H(9)), 5.93 (s, 1H, H(4a)), 4.39-4.29 (m, 2H), 4.19-4.05 (m, 6H)	159.7 (C(8a) + C(11a)), 128.8 (C(10)), 123.1(C(11b)), 114.2 (C(11) + C(9)), 98.2 (C(4a)), 73.0 (C(7) + C(2)), 66.3 (C(6) + C(3))
8 (racemate)	7.10 (t, 2H, J=8.2 Hz, H(13) + H(27)), 6.59 (ddd, 2H, $J_{12,13}$=8.2 Hz, $J_{12,14}$=1.0 Hz, $J_{12,6}$=0.4 Hz, H(12) + H(26)), 6.48 (dd, 2H, $J_{14,13}$=8.2 Hz, $J_{14,12}$=1.0 Hz, H(14) + H(28)), 6.31 (s, 2H, H(6) + H(20)), 4.58-4.51 (m, 2H, H(9) + H(23)), 4.36-4.28 (m, 2H, H(3) + H(17)), 4.21-3.97 (m, 10H), 3.93 (m, 2H, H(3) + H(17))	159.7 (C(1) + C(15) or C(11) + C(25)), 157.5 (C(11) + C(25) or C(1) + C(15)), 129.6 (C(13) + C(27)), 117.7 (C(29) + C(30)), 112.8 (C(12) + C(26)), 104.9 (C(14) + C(28)), 98.4 (C(6) + C(20)), 72.2 (C(9) + C(23)), 68.1 (C(17) + C(3)), 68.0 (C(4) + C(18)), 64.0 (C(8) + C(22))

EXPERIMENTAL PROCEDURE

Melting points were determined on a Kofler hot-stage and are uncorrected. ^{1}H and ^{13}C-NMR spectra were acquired on a Bruker AC-P instrument at 300 MHz and 75.4 MHz respectively and referred to TMS. Mass spectra were run on a Varian Mat 311-A instrument at 70 eV.[16] Flash-chromatography was performed with Merck 9385 silica gel (230-400 mesh). Preparative-layer chromatography was carried out with Merck 60 $F_{254+366}$ silica gel plates (20x20x0.2 cm) using acetone/hexane 1:1 as eluent.

Metallation and formylation of 1,3-bis [2-(2-tetrahydropyranyloxy)ethoxy]benzene (1)

A solution of **1** (13.30 g; 36.29 mmol) in dry ether (50 ml) was treated during 25 min at 0 °C under nitrogen and efficient stirring with n-BuLi (1.64 M) in hexane (25.7 ml), then it was refluxed 4h, cooled to 0 °C, added with dry DMF (4.1 ml; 52.69 mmol) during 5 min, stirred overnight at room temperature, added with water (50 ml) and further stirred for 20 min. The mixture forming two layers was separated, extracted with ether (2 x 50 ml), washed two times with 2% NaOH and two times with water, then dried over Na_2SO_4. After

removal of the solvent the oily residue was collected with little eluent and flash-chromatographed (silica gel 194.7 g, column diameter 35 mm, eluent acetone/hexane = 1/4) to give 6-ethenyloxy-2-((2-tetrahydro-2*H*-pyran-2-yloxy)ethoxy)benzaldehyde (**3**) as an oil. (0.38 g; 4%). ^{1}H-NMR ($CDCl_3$) δ 10.51 (s, 1H, CHO), 7.43 (t, 1H, J= 8.4 Hz, H(4)), 6.74 (d, 1H, J= 8.4 Hz, H(3)), 6.65 (d, 1H, J= 8.4 Hz, H(5)), 6.62 (dd, 1H, J_1= 6.0 Hz, J_2= 13.7 Hz, H(1")), 4.84 (dd, 1H, J_1= 1.9 Hz, J_2= 13.7 Hz, H(2" trans)), 4.73 (m , 1H, H(2"') THP-ring), 4.54 (dd, 1H, J_1= 1.9 Hz, J_2= 6.0 Hz, H(2" cis), 4.25 (m, 2H, H(1')), 4.09 (m, 1H), 3.87 (m, 2H, H(2')), 3.54 (m, 1H), 1.82-1.53 (m, 6H). ^{13}C-NMR ($CDCl_3$) δ 188.5, 161.6, 158.3, 147.7, 135.3, 116.3, 109.7, 107.8, 99.3, 96.7, 68.8, 65.6, 62.3, 30.5, 25.4, 19.4. Further elution with the same eluent gave 2,6-bis(2-((tetrahydro-2*H*-pyran-2-yloxy)ethoxy)benzaldehyde **2** as an oil (5.38 g; 38%). ^{1}H-NMR ($CDCl_3$) δ 10.54 (s, 1H, CHO), 7.40 (t, 1H, J= 8.4 Hz, H(4)), 6.60 (d, 2H, J= 8.4 Hz, H(3) + H(5)), 4.75 (m, 2H, H(2"), THP-ring), 4.22 (m, 4H, H(1')), 4.08 (m, 2H), 3.86 (m, 4H, H(2')), 3.54 (m, 2H), 1.84-1.51 (m , 12H). ^{13}C-NMR ($CDCl_3$) δ 189.1, 161.4, 135.4, 115.5, 105.6, 99.2, 68.7, 65.7, 62.3, 30.6, 25.4, 19.4.

Deprotection of 2

A solution of **2** (5.82 g; 14.75 mmol) in methanol (40 ml) was treated with 4N hydrochloric acid (30 ml), left 3h at room temperature, brought to pH= 8 with 10% K_2CO_3, extracted with ethyl acetate (10 x 30 ml), anhydrified with Na_2SO_4 and evaporated to dryness. The residue, taken up with hot ethyl acetate (25 ml) and left some hours at 4 °C, after filtration, washing with ether and drying in vacuo, gave crystalline 2,6-bis(2-hydroxyethoxy)benzaldehyde (**4**)[13] (2.04 g; 9.02 mmol). The mother liquor, after evaporation and flash-chromatography (silica gel 100.0 g, column diameter 30 mm, eluent acetone/hexane = 1/1.5) afforded 6-(2-hydroxyethoxy)-5-methoxy-2,3-dihydro-5*H*-1,4-benzodioxepin (**5**) as an oil (0.14 g; 4%). MS (m/z, relative intensity): 240 (m^+, 20), 209 (m^+ -CH_3O, 100)). Further eluition with the same solvent afforded an ulterior amount of **4** (0.126 g; 0.56 mmol). Overall yield 65%. M.p. 101-103 °C (ethyl acetate). ^{13}C-NMR (acetonitrile-d_3) δ 190.8, 162.5, 137.2, 116.3, 107.4, 72.1, 61.2.

Acidic hydrolysis of 3

A solution of **3** (0.381 g; 1.30 mmol) in methanol (4 ml) was treated with 4N hydrochloric acid (3 ml) and left at room temperature for 3h. The mixture was brought to pH= 6 with solid $NaHCO_3$, extracted with ether (5 x 10 ml) dried (Na_2SO_4) and evaporated to afford crystalline 6-hydroxy-2-(2-hydroxyethoxy)benzaldehyde (**6**) (0.231 g; 97%), which was sublimed at 130 °C /0.01 torr and crystallized from acetone/ether. M.p. 101-102 °C. ^{1}H-NMR ($CDCl_3$) δ 11.92 (s, 1H, phenolic OH), 10.37 (d, 1H, J= 0.6 Hz, CHO), 7.39 (t, 1H, J= 8.4 Hz, H(4)), 6.52 (ddd, 1H, J_1= 8.4 Hz, J_2= 0.8 Hz, J_3= 0.6 Hz, H(5)), 6.37 (dd, 1H, J_1= 8.4 Hz, J_2= 0.8 Hz, H(3)), 4.17 (m, 2H, H(1')), 4.02 (m, 2H, H(2')), 2.42 (very broad s, 1H, alcoholic OH). ^{13}C-NMR δ 194.1, 163.7, 161.6, 138.4, 111.0, 110.3, 102.0, 70.1, 61.2. Anal. calcd. for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found : C, 59.20; H, 5.80.

Cyclization of 4 in various solvents

A solution of **4** in dry solvent was added with 3Å molecular sieves (1.5 g per mmol of **4**), treated with the appropriate acid and allowed to react as specified below. The mixture was quenched with triethylamine (1 ml per mmol of **4**), filtered washing the removed sieves, evaporated, dissolved in ether, washed with saturated

aqueous K_2CO_3, dried (Na_2SO_4), evaporated and worked-up by preparative layer or flash-chromatography as follows.

In methanol.

4 (0.339 g; 1.50 mmol), solvent (10 ml), concentrated sulfuric acid (0.16 ml), room temperature (24h), preparative layer chromatography with eluent acetone/hexane = 1:1. Product obtained : unreacted **4** (0.018 g, 0.08 mmol) and **5** as an oil (0.240 g; 70%).

In benzene.

4 (0.0751 g; 0.33 mmol), solvent (15 ml) trifluoroacetic acid (1 drop), reflux (8h), preparative layer chromatography with eluent acetone/hexane=1:1. Product obtained: 4a*H*-5,6,9,10-Tetrahydro-[1,4]-dioxepino[5,6,7-e,f][1,4]benzodioxepin (**7**) (0.0529 g; 77%). M.p. 87.0-88.5 °C (ether/hexane). MS (m/z, relative intensity) 208 (m^+, 70). Anal. calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found : C, 63.18; H, 5.90. 2,5,7,10,16,19,21,24-Octaoxapentacyclo[8.8.1.1^{6,5}.0^{11,30}.0^{25,29}]triaconta-1(29),11,13,15(30),25,27-hexaene (**8**) (0.0055 g; 8%). M.p. 228-236 °C (dec., acetonitrile). MS: 416 (m^+, 24). Anal. calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81. Found : C, 63.49: H, 6.06.

In acetonitrile

4 (0.803 g; 3.55 mmol), solvent (15 ml), trifluoroacetic acid (1 drop), room temperature (24h), flash chromatography (silica gel 197.6 g, column diameter 35 mm, eluent petroleum ether 40-60/acetone = 2.5/1). Product obtained: **7** (0.1120 g; 15%). **8** in numerous not unified fractions (0.5971 g; 81%). The head fractions resulted at the ^{1}H-NMR spectra to be composed of two diastereoisomers of **8** the minor of which (overall yield about 4%) showed peculiar ^{1}H-NMR signals in $CDCl_3$ at δ= 6.26 (s, 2H, H(6) + H(20)), 6.54 (dd, 2H, J_1=8.2 Hz, J_2=1.0 Hz, H(12) + H(26) or H(14) + H(28)), and 6.61 (dd, 2H, J_1=8.2 Hz J_2=1.0 Hz H(14) + H(28) or H(12) + H(26)). The tail fractions, free from the minor diastereoisomer, allowed to obtain 0.03 g of the pure major one which after slow growing from acetonitrile gave suitable crystals for X-ray investigations.

Hemiacetalization of 4

Solutions in the range 0.14-0.04 M prepared dissolving **4** in various solvents as $CDCl_3$, acetonitrile-d_3 and DMSO-d_6 previously treated with a trace of triethylamine, gave rise to the formation at the equilibrium of 5-hydroxy-6-(2-hydroxyethoxy)-2,3-dihydro-5*H*-1,4-benzodioxepin (**9**). ^{1}H-NMR (acetonitrile-d_3): δ= 7.13 (t, 1H, J= 8.2 Hz, H(8)), 6.64 (dd, 1H, $J_{7,9}$= 1.0 Hz, $J_{7,8}$= 8.2 Hz, H(7)), 6.56 (ddd, 1H, $J_{9,5}$= 0.3 Hz, $J_{9,7}$= 1.0 Hz, $J_{9,8}$= 8.2 Hz, H(9)), 6.47 (broad s, 1H, H(5)), 4.42-4.35 (m, 1H), 4.31-4.23 (m, 1H), 4.07-3.96 (m, 4H). The signals from H(2') and OH are hidden.

X-ray structural analysis of 8

Data were acquired with a Siemens R3m/V automatic diffractometer, MoKα, λ= 0.71073 Å, graphite monochromator. $C_{22}H_{24}O_8$ (416.4), crystal size 0.42x0.36x0.38 mm, orthorombic, space group $Pca2_1$, 298K, *a*= 8.511 (2), *b*= 9.244 (2), *c*= 24.913 (4) Å, *V*= 1960.0 (6) Å^3, *Dc*= 1.411 g cm^{-3}, *F*(000)= 880, *Z*= 4, μ= 1.08 cm^{-1}. A total of 2487 reflections were collected in the 3°≤ 2θ ≤ 54° range by ω scan. 2198 reflections were unique and, from these, 1794 were assumed as observed ($I > 1.5\ \sigma(I)$). Lorentz polarization corrections

were applied to the intensity data. The structures were solved by direct methods and subsequently completed by Fourier recycling. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were set in calculated positions and refined as riding atoms. The final R value was 0.052, R_w= 0.054, S= 1.388. The weighing scheme used in the last refinement cycles was $w^{-1} = [\sigma^2(F_O) + 0.0010(F_O)^2]$. Final geometrical calculations and graphical manipulations were performed with the PARST program[17] and the XP utility of the SHELXTL PLUS system[18] respectively. Positional parameters, molecular dimensions and anisotropic thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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This work is dedicated to Professor Richard Neidlein, University of Heidelberg, on the occasion of his 65th birthday

REFERENCES

1. Hoss, R.; Vögtle, F. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 375-384.
2. Ostrowicki, A.; Koepp, E.; Vögtle, F. *Top. Curr. Chem.* **1992**, *161*, 37-67.
3. Knops, P.; Sendhoff, N.; Mekelburger, H. P.; Vögtle, F. *Top. Curr. Chem.* **1992**, *161*, 1-36.
4. Ge, Li; Clark Still, W. *J. Am. Chem. Soc.* **1993**, *115*, 3804-3805.
5. Liska, F.; Fikar, J.; Trska, P.; Valenta, M. *Collect. Czech. Chem. Commun.* **1989**, *54*, 3278-3283. (*Chem Abstr.*, 1990, 113 : 23886j).
6. McCullough, K. J.; Teshima, K.; Nojima, M. *J. Chem. Soc. Chem. Commun.* **1993**, 931-933.
7. Jones, P. R.; Rothenberger, S. D. *J. Org. Chem.* **1986**, *51*, 3016-3023.
8. Pawlosky, C. E. Dioxepins and Trioxepins. In *Seven-Membered Heterocyclic Compounds Containing Oxygen and Sulfur;* Rosowsky, A. Ed. of the Series *The Chemistry of Heterocyclic Compounds*: Weissberger, A.; Taylor, E. C. Eds.; John Wiley & Sons Inc.: New York 1972; vol. 26, pp 339-343.
9. Tahara, T.; Fujii, T.; Gonjo, T. Jpn. Kokai Koho 78 77,081 (*Chem. Abstr.* 1979, 90:21132s).
10. Sharp, J. T. Seven-Membered Rings with Two or More Heteroatoms. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W. Eds.; Pergamon Press Ltd.: Oxford, 1984; vol.7, pp 620-622.
11. Lachapelle, A.; St-Jacques, M. *Tetrahedron* **1988**, *44*, 5033-5044.
12. Bertini, V.; De Munno, A.; Lucchesini, F.; Buffoni, F.; Bertocci, B. Ital. Patent Appl. 47906-A/85 extended to Europe, U.S.A., Canada and Japan (*Chem. Abstr.*, 1987, 106 : 156038m).
13. to be published
14. Jones, P. R.; Jaglowski, J. A. *J. Org. Chem.* **1990**, 55, 3891-3896.

15. The Aldrich Library of ^{13}C and ^{1}H-FTNMR Spectra, Pouchert, C. J. and Behnke J. eds. 1993, vol. I, 381A, 385C, 389C and 391A.
16. Thanks are due to Mr. Heyko Rudy and Mr. Peter Weyrich, Pharmazeutisch-chemisches Institut, University of Heidelberg, for MS measurements.
17. Nardelli, M. *Comput. Chem.* **1983**, *7*, 95.
18. SHELXTL PLUS, version 4.21/V, Siemens Analytical X-Ray Instruments Inc., Madison WI, 1990.

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