SYNTHESIS AND STEREOCHEMISTRY OF 2-METHYL-4*H*-9,12-DIOXA-1,4-DIAZADISPIRO[5.2.5.2]TETRADEC-1-EN-3-ONE AND ITS 2*H*-IMIDAZOLO-2-SPIROCYCLOHEXANE ANALOGUE. AN ANOMALOUS MICHAEL TYPE CYCLOCONDENSATION

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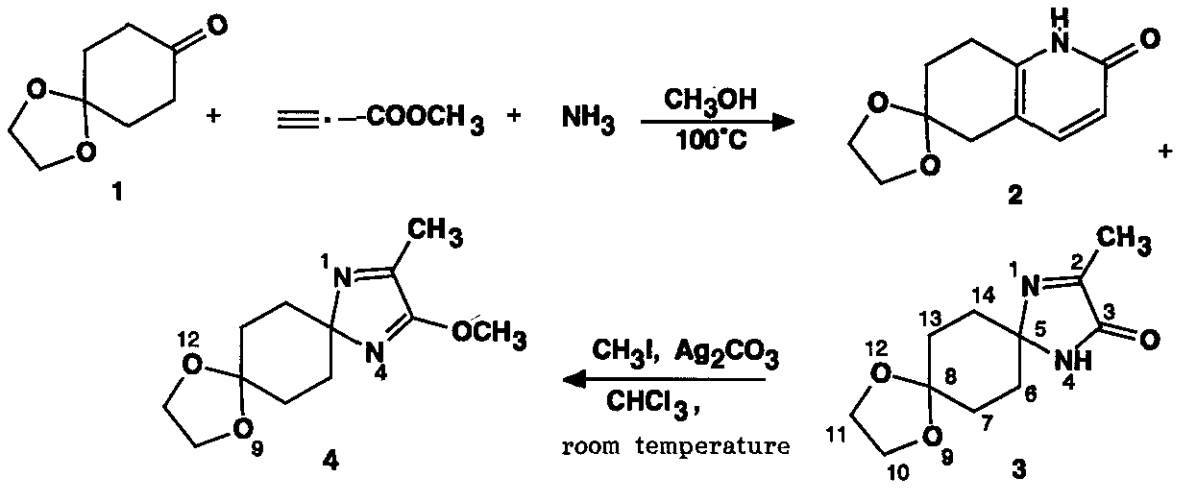
Abstract - Starting from 1,4-cyclohexanedione monoethylene ketal and methyl propiolate in ammonia-saturated methanol at 100°C we obtained 2-methyl-4*H*-9,12-dioxa-1,4-diazadispiro[5.2.5.2]tetradec-1-en-3-one which was subsequently transformed into its *O*-methyl ether - a 2*H*-imidazolo-2-spirocyclohexane derivative. The mechanism of formation of this new heterocyclic system by anomalous Michael type cyclocondensation was proposed.

The 2-pyridone ring annelation between 1,4-cyclohexanedione monoethylene ketal (**1**) and methyl propiolate in ammonia-saturated methanolic solution at 100°C affording 5,6,7,8-tetrahydroquinolin-2-one ethylene ketal (**2**) in 70% yield has been described as the first step of a total synthesis of Huperzine A.[1,2] We repeated this experiment and found the yield was not higher than 51% and several other labile products were formed (especially when dry methanol was used). Thus a crystalline compound (**3**) was obtained in 20 % yield beside the expected tetrahydroquinolinone (**2**) after purification by chromatography (Scheme 1).

The structure of compound (**3**) was examined using different instrumental analysis methods; ^{1}H-, ^{13}C-nuclear magnetic resonance (nmr) and infrared (ir) spectroscopy, electron impact (EI) and chemical ionization (CI) mass spectrometry (ms), elementary analysis as well as X-ray analysis for full confirmation of the proposed structure. Compound (**3**) was also alkylated with methyl iodide in the presence of silver carbonate in chloroform at room temperature affording the *O*-methyl derivative (**4**).[2,3]



Scheme 1

All performed analytical methods let to propose the structure of compound (**3**) as 2–methyl-4*H*–9,12-dioxa–1,4-diazadispiro[5.2.5.2]tetradec–1-en–3-one, (**3**), and its methyl derivative as an *O*–methyl ether, 3–methoxy-2–methyl-9,12–dioxa-1,4–diazadispiro[5.2.5.2]tetradeca-1,3–diene (**4**). This statement was fully confirmed by X-ray analysis of **3** .

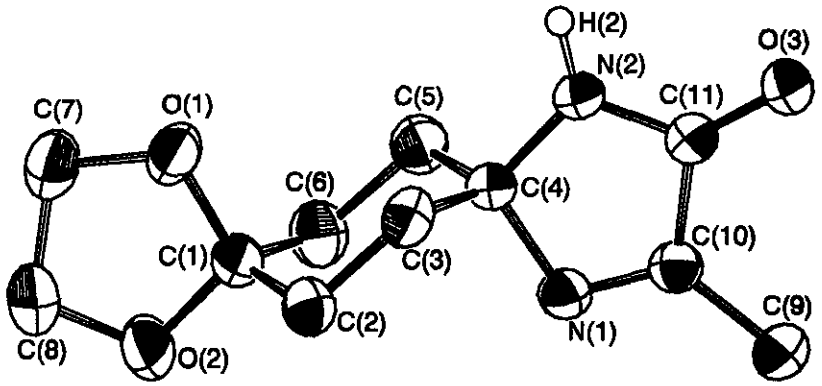


Figure 1. ORTEP drawing of **3** with thermal ellipsoids drawn with 50% probability. The hydrogen atoms, except H(2) were omitted for clarity.

Crystals of **3** suitable for an X-ray diffraction study were grown from methanol. An ORTEP diagram showing the atom numbering scheme and solid-state conformation is presented in Figure 1. Non-hydrogen atom fractional coordinates and equivalent isotropic thermal parameters are listed in Table 1. Selected bond distances are provided in Table 2. They showed that the bond distances were in agreement with those reported in the literature. The interatomic distance N(2)–C(11) 1.331Å is substantially less than those expected for single bond and comparable with observed for N(1)–C(10) double bond (1.278 Å). This can be interpreted

in terms of appreciable p_π–p_π interaction.

Moreover, it was found that in solid state two molecules (related by center of symmetry) form a dimer with two strong intermolecular hydrogen bonds (Figure 2). The distance N(2)···O(3') and bond angle N(2)–H(2)···O(3') were 2.844(2)Å and 172(2)°, respectively. Mentioned distance between nitrogen and oxygen was shorter than the sum of their van der Waals' radii 2.90Å (length of typical N–H···O bonds is in the range of 2.81–3.04Å). Due to the near planarity of the 8-membered OCNHOCNH ring and to the conjugation between N=C and C=O double bonds, the system formed by sequence of three heterocyclic rings is almost planar. The dihedral angle between the least-squares molecular planes (C(4) N(1) C(10) C(11) N(2)) and H-bonded 8-membered ring was 2.9(1)°.

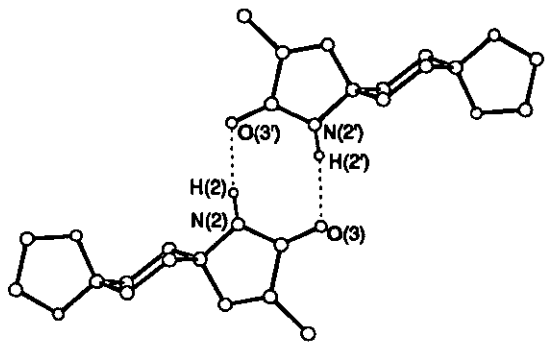
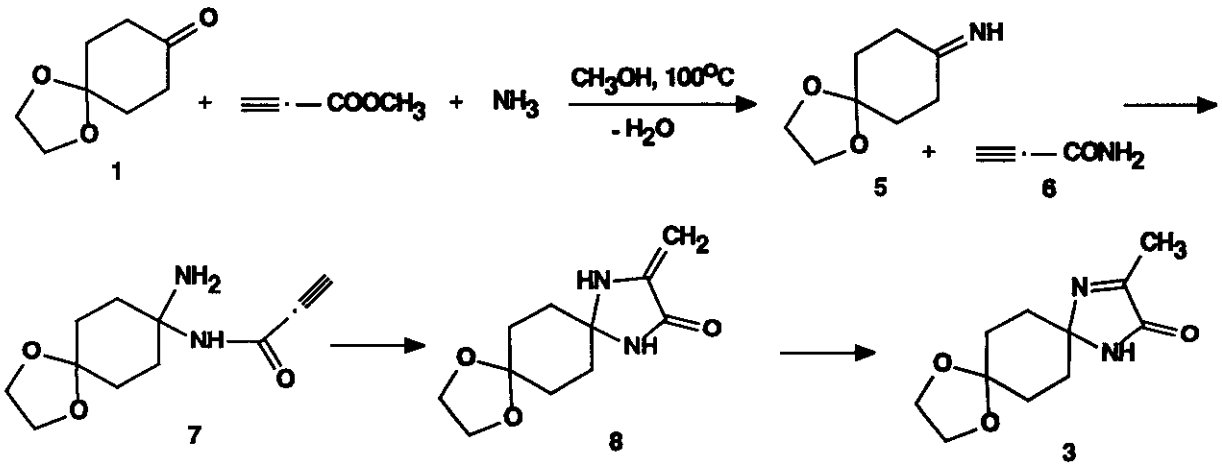
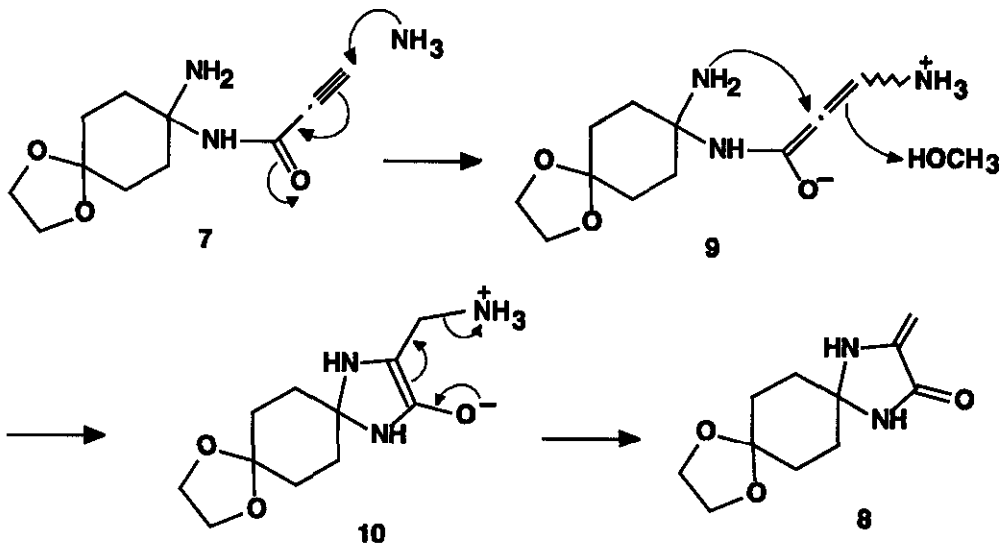


Figure 2. Two molecules of **3** forming a dimer.



Scheme 2

This result let us to propose a mechanism of formation of this new heterocyclic system. In the first step the ketone ketal (**1**) was transformed into corresponding imine (**5**) and methyl propiolate into propiolamide (**6**) according to reported reaction mechanism.[1] In the next step the addition of **6** to imine (**5**) afforded the aminal intermediate (**7**). In the following step, ring closure could proceed with formation of spirointermediate (**8**). Subsequently, this labile methylidene compound rearranges easily into corresponding spiro 2*H*–imidazolone (**3**) with more stable conjugate double bonds system, in the way analogical as decomposition of Methylenomycin B [4] or similar compounds (Scheme 2). The possible mechanism of transformation of **7** into **8** could result from an additions-eliminations sequence as depicted in Scheme 3.



Scheme 3

EXPERIMENTAL

^1H and ^{13}C nuclear magnetic resonance (nmr) spectra were performed using a Bruker AM 250 unit in $CDCl_3$ at 250 MHz (^1H) or 62 MHz (^{13}C, both proton broadband decoupling and DEPT 135° modes); chemical shifts (δ) were presented. Infrared (ir) spectra were measured with a Perkin–Elmer 1310 spectrophotometer in chloroform solution or using a Zeiss Specord 75 IR spectrophotometer in potassium bromide pellets. Electron impact mass spectra (EI ms) were performed at 70 eV using a Nermag R 10–10 mass spectrometer if the sample was introduced by gas chromatograph (gcms mode), or in direct insertion probe (dip mode) with an AMD–604 unit, resolution 1200, acceleration voltage 8 kV and ion source temperature 220°C, dip temperature of 30°C. The accurate mass measurements were performed by the peak–matching technique on the AMD–604 double focusing instrument with BE geometry at a resolution 9000 using perfluorokerosene (PFK) as an internal reference. The structure of all compounds presented in this paper were confirmed by elementary analysis or exact mass measurements under the mentioned above high–resolution (hr ms) conditions. Chemical ionsation mass spectra (CI ms) were obtained on the Nermag apparatus using ammonia as reagent gas. Gas chromatography (glc) was performed on Carbo Erba 5160 MEGA unit using 25 m CPSiL 5CB fused silica WCOT capillary column, 0.3 mm i.d., injector temp. 200°C, flame ionization detector (fid) temp. 280°C, column temp. programmed from 100°C to 280°C (10°C/min), carrier gas: helium, 2 ml/min. Melting points (mp, non-corrected) were measured using a Reichert microscope apparatus.

2–Methyl–4(*H*)–9,12–dioxa–1,4–diazadispiro[5.2.5.2]tetradec–1–en–3–one (3). To a solution of 1,4–cyclohexanedione monoethylene ketal (**1**) (Janssen, 98%, 450 mg, 2.82 mmol) in 10 ml of ammonia-saturated methanol (Prolabo) in a resealable tube was added 0.50 ml of methyl propiolate (Janssen, 471 mg, 5.60 mmol). After sealing the tube, the reaction mixture was heated for 10 h at 100°C.[1,2] After cooling, the solvent was removed under reduced pressure using a rotary evaporator and the obtained viscous brown sirop was purified by chromatographic filtration on 20 g of silica (Merck Silicagel for flash chromatography). Ethyl acetate (Prolabo, 250 ml) and ethyl acetate–methanol 85:15 *v/v* (300 ml) were subsequently used as eluents. The solvents from this last fraction was removed under reduced pressure and the crude 5,6,7,8–tetrahydroquinolin–2–one ethylene ketal (**2**)[1] was repurified by flash chromatography on silica (Merck Silicagel for flash chromatography with ethyl acetate–methanol 95:5 *v/v* as eluent, R_f = 0.2) (305 mg, 51%). The ethyl acetate fraction from chromatographic filtration was evaporated to dryness affording a white solide which recrystallized from methanol. Yield of spiro compound (**3**) 129 mg (20%), mp 265–266°C (methanol). Anal. Calcd for $C_{11}H_{16}N_2O_3$: C: 58.91, H: 7.19, N: 12.49. Found: C: 58.29, H: 7.17; N: 12.37. ^{1}H Nmr: 8.90 (s, 1H, N**H**), 3.96 (s, 4H, C-10 **H$_2$**, C-11 **H$_2$**), 2.18 (s, 3H, C**H$_3$**), 2.03, 1.80 ppm (2m, 8H, cyclohexane ring protons). ^{13}C Nmr: 166.1 (**C**-2), 165.9 (**C**-3), 107.8 (**C**-8), 82.9 (**C**-5), 64.5, 64,6 (**C**-10,11), 34.3 (**C**-7,13), 32.0 (**C**-6,14), 14.4 ppm (**C**H$_3$). Ir ($CHCl_3$): 3420 sh (N-H), 3200 br (N-H˙˙O), 2920, 2840 (C-H), 1710 vs, 1640m (C=O and C=N), 1440, 1380 (def. CH_3 and CH_2), 1160, 1120, 1090 cm^{-1} (C-O). EI ms (Nermag): *m/z* 196 (26%, $M^{+\cdot}$ - C_2H_4), 99 (63%), 86 (100%, (-O-$CH_2$$CH_2$-O-)>C=$CH_2^{+\cdot}$), 55 (13%), 42 (22%). CI ms (Nermag, NH_3): 242 (8%, M+NH_4^+), 226 (45%, $MH_2^{+\cdot}$), 225 (100%, MH^+), 209 (9%, $M^{+\cdot}$ - ·CH_3), 196 (6%), 181 (3%), 156 (5%), 112 (3%). glc: T_r = 10.4 min.

3-Methoxy-2-methyl-9,12-dioxa-1,4-diazadispiro[5.2.5.2]tetradeca-1,3-diene (4). 2-Methyl-4(*H*)-9,12-dioxa-1,4-diazadispiro[5.2.5.2]tetradec-1-en-3-one (**3**) (51 mg, 0.228 mmol) was strirred in 3 ml of chloroform (Prolabo) with methyl iodide (Prolabo, 323 mg, 0.15 ml, 2.28 mol) and silver carbonate (>99%, Fluka, 200 mg, 0.725 mmol) in the dark at room temperature for 7 days (conditions analogical to[2,3]). After filtration through Celite and solvent evaporation, the solid residue was purified by flash chromatography on silica gel (Merck) using ethyl acetate as a mobile phase. 17 mg (33%) of the substrate (**3**) (R_f = 0.37) was recovered and 27.5 mg (51%) of *O*-methylated product (**4**) (R_f = 0.37) was obtained. Recrystallisation from hexane afforded a white solide, mp 87-89°C.

^{1}H Nmr: 3.99 (s, 4H, C-10 **H$_2$**, C-11 **H$_2$**), 3.93 (s, 3H, OC**H$_3$**), 2.19 (s, 3H, C**H$_3$**), 1.98, 1.74 ppm (2m, 8H, cyclohexane ring protons). ^{13}C Nmr: 165.5 (**C**-2), 159.9 (**C**-3), 108.6 (**C**-8), 95.6 (**C**-5), 64.4, 64.3 (**C**-10,11), 56.3 (OCH_3), 32.9 (**C**-7,13), 32.7 (**C**-6,14), 14.3 ppm (**C**H$_3$). Ir (KBr): 2950, 2920, 2870, (C-H), 1640m, 1590vs (N=C-C=N), 1435, 1380, 1350 (def. sciss. OCH_3, def. CH_3 and CH_2), 1145, 1110, 1090 cm^{-1} (C-O). EI ms (AMD): *m/z* 239 (0.5%, MH^+), 223 (0.6%, $M^{+\cdot}$ - ·CH_3), 210 (100%, $M^{+\cdot}$ - C_2H_4), 99 (77%), 86 (84%, (-O-$CH_2$$CH_2$-O-)>C=$CH_2^{+\cdot}$). HR ms (AMD): exact mass: 239.1399 (calcd for $C_{12}H_{19}N_2O_3$: 239.1396),

210.1002 (calcd for $C_{10}H_{14}N_2O_3$: 210.1004), 86.0366 (calcd for $C_4H_6O_2$: 86.0368).

X-ray crystallographic analysis of 3

Crystal data: $C_{11}H_{16}N_2O_3$, M_r=224.26, monoclinic, space group $P2_1/n$, a = 5.6769(9)Å, b = 30.306(5)Å, c = 6.5774(11)Å, β = 98.164(13)°, V = 1120.1(3)Å^3, Z = 4, D_c = 1.330Mg·m^{-3}, F(000) = 480, μ(MoK$_\alpha$)= 0.098 mm^{-1}.

Table 1. Atomic coordinates (×10^4) and equivalent isotropic displacement parameters (×Å^{2}10^3) for (**3**).

	x	y	z	U_{eq}
O(1)	466(2)	1619(1)	4895(2)	57(1)
O(2)	-2348(3)	2152(1)	4117(2)	57(1)
O(3)	-2829(2)	-51(1)	-1925(2)	49(1)
N(1)	-4482(2)	998(1)	-505(2)	37(1)
N(2)	-1454(3)	499(1)	372(2)	41(1)
C(1)	-1645(3)	1723(1)	3542(3)	42(1)
C(2)	-3510(4)	1385(1)	3811(3)	43(1)
C(3)	-2828(3)	930(1)	3123(3)	40(1)
C(4)	-2276(3)	931(1)	911(3)	35(1)
C(5)	-456(4)	1286(1)	600(3)	45(1)
C(6)	-1162(4)	1737(1)	1337(3)	48(1)
C(7)	1307(4)	2010(1)	5931(4)	57(1)
C(8)	-910(9)	2274(2)	5937(10)	60(1)[a]
C(81)	-362(44)	2358(8)	5067(65)	59(7)[b]
C(9)	-6977(3)	578(1)	-3189(3)	44(1)
C(10)	-4883(3)	652(1)	-1604(2)	35(1)
C(11)	-2966(3)	312(1)	-1112(3)	36(1)

[a] s.o.f. = 0.87(2), [b] s.o.f. = 0.13(2)

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Data collection and structure solution.

Diffraction data were measured for a single crystal of size 0.20×0.46×0.90 mm at 293K on a Siemens P3 diffractometer. Graphite-monochromated MoKα radiation (λ=0.71073Å) was used. The unit-cell parameters were obtained from the least-squares refinement of the setting angles of 32 reflections (14≤2θ≤29°). A total 2159 intensities within a range 2.7°≤2θ≤50° were measured in θ–2θ scan mode with a variable scan speed. The intensities were corrected for Lorentz and polarization factors. Merging equivalents gave 1940 independent reflections (R_{int}=0.0095). The structure was solved with SHELXS-86[5] program by direct methods and refined with full–matrix least–squares refinement on F^2 (SHELXL-93)[6] for all reflections except for 9 with very negative F^2. Anisotropic temperature factors were used for all non-hydrogen atoms, and H-atoms were

refined with isotropic thermal parameters in positions determined from the succesive Fourier-difference syntheses. One of the methylidene group in a five-membered COCCO ring showed disordering over two sites and was modeled in terms of two carbon atoms: C(8) and C(81) (with H-atoms in calculated positions) with the sum of their occupation factors equal 1. An isotropic extinction coefficient x was refined to a value 0.020(3). Refinement proceeded to wR_2=0.0926 (R_1=0.0385 for I>2σ(I)) for 1931 reflections, 8 restraints and 214 parameters. The final weighting scheme was $w^{-1}= [\sigma^2(F_o^2)+(0.0416P)^2+0.434P]$ where $P=(F_o^2+2F_c^2)/3$;. The largest positive and negative peaks on a final difference Fourier synthesis were of height +0.18/−0.15e/Å^3 and have no signifcant chemical meaning. Maximum shift/error ratio in final cycles of refinement was less than 0.001.

Table 2. Selected bond lenghts [Å] for **(3)**.

O(1)-C(1)	1.422(2)	O(1)-C(7)	1.415(2)
O(2)-C(1)	1.427(2)	O(2)-C(8)	1.400(4)
O(3)-C(11)	1.230(2)	N(2)-H(2)	0.89(2)
N(1)-C(4)	1.465(2)	N(1)-C(10)	1.278(2)
N(2)-C(4)	1.451(2)	N(2)-C(11)	1.331(2)
C(1)-C(2)	1.500(3)	C(1)-C(6)	1.515(3)
C(2)-C(3)	1.521(3)	C(3)-C(4)	1.531(3)
C(4)-C(5)	1.526(3)	C(5)-C(6)	1.523(3)
C(7)-C(8)	1.493(4)	C(9)-C(10)	1.483(2)
C(10)-C(11)	1.499(2)		

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