HETEROCYCLES, Vol. 98, No. 2, 2019, pp. 205 - 214. © 2019 The Japan Institute of Heterocyclic Chemistry
Received, 15th November, 2018, Accepted, 15th January, 2019, Published online, 1st February, 2019
DOI: 10.3987/COM-18-14015

BIS-HETEROCYCLES. PART II.[1] TETRAHYDRO-3,3'-BI(1,2,4,5-OXATRIAZINES)

Mustafa M. El-Abadelah,[a] Firas F. Awwadi,[a] Monther S. Zreid,[a] and Mohammed M. Abadleh[b]*

[a] Department of Chemistry, Faculty of Science, The University of Jordan, Amman 11942, Jordan. [b]Department of Pharmaceutical Medicinal Chemistry and Pharmacognosy, Faculty of Pharmacy and Medical Sciences, University of Petra, Amman 11196, Jordan

Abstract – A new set of tetrahydro-3,3'-bi(1,2,4,5-oxatriazines) **3a-e** has been prepared *via* condensation reaction of alkanone- and cycloalkanone *N*-methylhydrazones with bis-nitrile oxide. Structures of the synthesized bis-heterocycles are based on IR, NMR and MS spectral data and further by single-crystal X-ray diffraction analysis for compounds **3a** and **3d**. Compound **3c** exhibited inhibitory activity against butyrylcholinesterase (BChE) with $IC_{50} = 1.75 \times 10^{-5}$ μM.

INTRODUCTION

We previously reported on the synthesis of 5,6-dihydro-1,2,4,5-oxatriazines **I** (Figure 1)[2,3] *via* one-pot reaction of carbonyl-methylhydrazones and nitrile oxides (1,3-dipolar species generated *in situ* from their respective *α*-chloroxime precursors by the action of triethylamine). This route, utilizing *N*-alkylhydrazones of alkanones, cycloalkanones[2] or benzaldehydes,[3] allowed variation of substituents at *N*(4), C(3) and C(6) positions of the oxatriazine ring. Recently, the synthesis of model 4,5-dihydro-1,2,4,5-oxatriazin-6-ones (**II**),[4] tetrahydro-1,2,4,5-oxatriazine-3,6-diones and their 6-thioxo analogs (**III**),[5] has been described. Meanwhile, the construction of the parent tetrahydro-1,2,4,5-oxatriazine, embedded as central ring in the heptacyclic condensed diisoquinoline (**IV**), has been also reported.[6]

It is generally noted that bioactive bis-heterocycles, exemplified by naturally occurring 3,3'- biindoles[7] and 2,2'-bithiophenes,[8] display improved potency compared to their respective parent mono-analogs. Preliminary screening tests of some derivatives of dihydro-1,2,4,5-oxatriazines showed them to act as good inhibitors of acetylcholinestrase (AChE) and/or butyrylcholinesterase (BChE), and the results will

be published once completed. Hence, we envisaged it would be worthwhile to adopt a relevant route towards synthesis and subsequent assessment of the related bis-oxatriazine analogs. Accordingly, and for parallel study, the present work deals with the synthesis of a selected set of 4,4'-tetrahydro-3,3'-bi(1,2,4,5-oxatriazines) (**3a-e**) *via* direct reaction of alkanone- and cycloalkanone-methylhydrazones (**2a-e**) with dichloroglyoxime (**1**) as illustrated in Scheme 1.

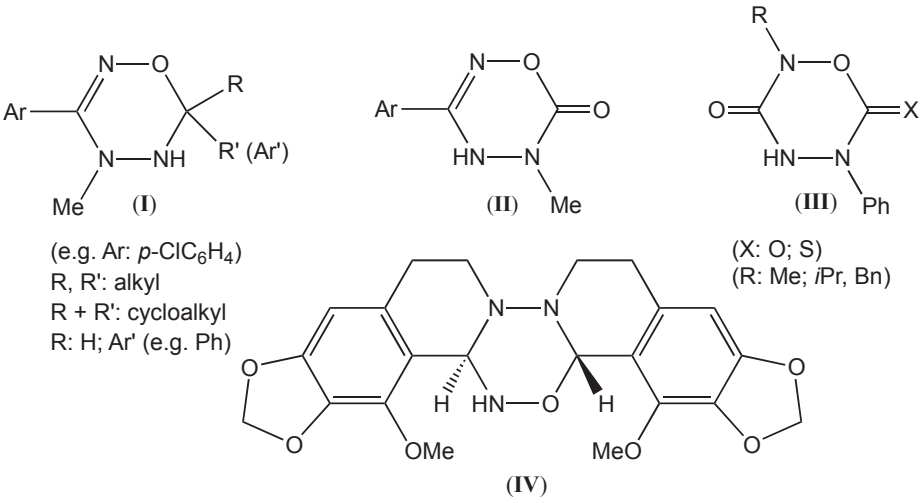
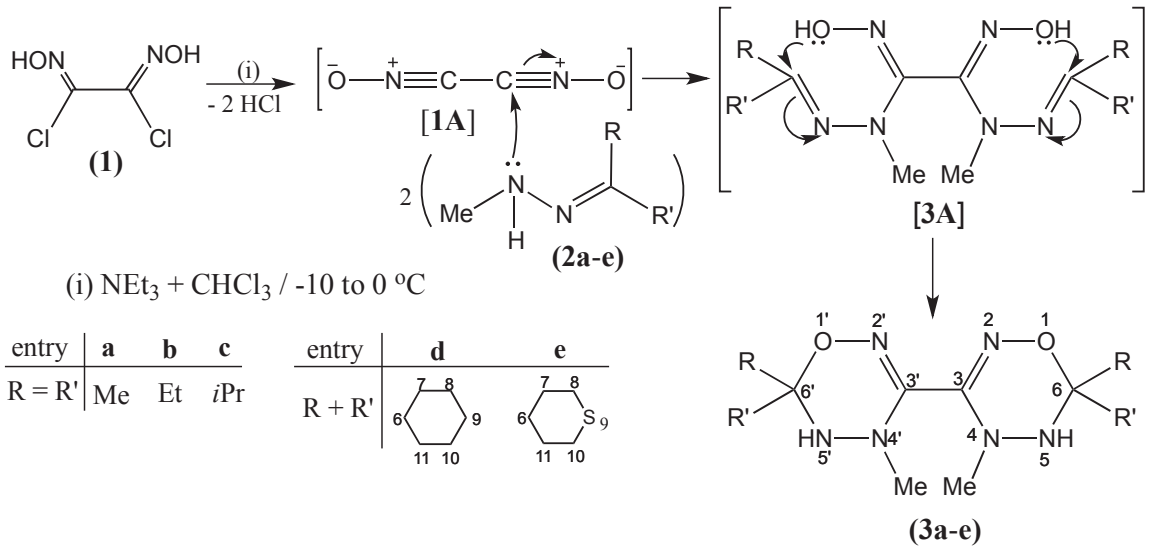


Figure 1. Representatives of dihydro- and tetrahydro-1,2,4,5-oxatriazines



entry	a	b	c
R = R'	Me	Et	*i*Pr

entry	d	e
R + R'		

Scheme 1. Synthesis of tetrahydro-bi(1,2,4,5-oxatriazines) **3a-e**

RESULTS AND DISCUSSION

Primary and secondary amines are known to add readily onto nitrile oxides and yield initially the corresponding (*Z*)-amidoximes as kinetically controlled products.[9] In these nucleophilic 1,3-dipolar addition reactions, the entering nucleophile and the developing lone pair are mutually *trans* thus leading to a stereospecific addition.[10] *N*-Methylhydrazones **2** should similarly add to the bis-nitrile oxide [**1A**] to

give the corresponding (*Z*)-bi(hydrazoxime) adducts [**3A**] in which the terminal nucleophilic OH and the electrophilic C=N moieties are suitably located to undergo cyclization in an allowed "6-Endo-Trig" process[11] to deliver the corresponding tetrahydro-3,3'-bi(1,2,4,5-oxatriazines) **3a-e** (Scheme 1). This one-pot reaction is perhaps the most direct and versatile route towards the preparation of the latter bi(oxatriazines).

The newly prepared compounds **3a-e** were characterized by IR, MS and NMR spectral data. These data, detailed in the experimental section, are consistent with the suggested structures. Thus, the IR spectra exhibit sharp *N*-H stretching bands in the range 3270-3170 cm^{-1} and absorption bands around 1570 cm^{-1} attributed to –C(3)=N- stretching. The mass spectra display the correct molecular ion peaks for which the measured high resolution (HRMS) data are in good agreement with the calculated values. DEPT and 2D (COSY, HMQC) experiments showed correlations that helped in the ^{1}H- and ^{13}C-signal assignments to the different carbons and their attached and/or neighboring hydrogens. The ^{13}C-NMR spectra exhibit two signals at about 147 and 84-90 ppm characteristic of the C-3 and C-6 carbons, respectively, of the dihydro-oxatriazine ring.

Table 1. Summary of data collection and refinement parameters for compounds **3a** and **3d**

Crystal	**3a**	**3d**
Molecular formula	$C_{10}H_{20}N_6O_2$	$C_{16}H_{28}N_6O_2$
Formula weight, M_r	256.32	336.44
T (K)	293(2)	293(2)
Crystal system	Monoclinic	Monoclinic
Space group	C*2/c*	C*2/c*
a (Å)	15.2480(16)	22.184(3)
b (Å)	6.2791(16)	9.8922(17)
c (Å)	14.0398(13)	8.4075(11)
β (°)	91.203(8)	97.877(13)
Volume (Å^3)	1342.9(2)	1827.6(5)
Z	4	4
Independent reflections	1360	1581
ρ_{calc} (Mg / m^3)	1.267	1.223
Reflections collected	2712	3237
[R_{int} $(F)^2$]	0.0236	0.0543
Index ranges *hkl*	-18 ≤ *h* ≤ 12, -7 ≤ *k* ≤ 7, -17 ≤ *l* ≤ 14	-27 ≤ *h* ≤ 17, -12 ≤ *k* -10 ≤ *l* ≤ 10
Goodness-of-fit on F^2	1.047	1.016
Final *R* indices [$I > 2\sigma(I)$]	R_1[a] = 0.0483, wR_2[b] = 0.1306	R_1[a] = 0.0705, wR_2[b] = 0.2129
μ, mm^{-1}	0.092	0.084
$\Delta\rho_{min}$ and $_{max}$ (*e* / Å^3)	0.212 and -0.187	0.303 and -0.343

[a] $R_1 = \Sigma||Fo| - |Fc||/| \Sigma |Fo|$ [b] $wR_2 = \{ \Sigma w(Fo^2 - Fc^2)^2/ \Sigma w(Fo^2)^2\}^{1/2}$

The latter signal, assigned to the sp^3-hybridized C-6 carbon, is in agreement with reported data for an sp^3-carbon flanked by two electronegative atoms (oxygen and nitrogen) in related heterocycles.[1,12] The lowest field signal at about δ 147 ppm is assigned to the C-3 sp^2 carbon, by analogy to several related azomethine systems.[1,13] Eventually, structures of these heterocycles were unambiguously confirmed by single-crystal X-ray crystallography (Figure 2 /*vide infra*) of compounds **3a** and **3d** as representatives of the series.

X-Ray Structure

X-Ray crystal structure determination was performed to confirm the structures of **3a** and **3d** (Scheme 1). A summary of data collection and refinement parameters is given in Table 1, while selected bond lengths and angles are provided in Table 2. The molecular structures of **3a** and **3d,** based on crystallographic data, are shown in Figure 2. In each compound, the asymmetric unit is composed of a half molecule, the second half is generated by two-fold rotation around C2-axis perpendicular to the plane of the oxatriazine ring at the middle of C3-C(A) bond. The five atoms (O1, N2, C3, N4 and N5) are coplanar in both compounds; the mean deviations from the corresponding planes are 0.0140 Å and 0.0407 Å for **3a** and **3d**, respectively; the corresponding deviations of C6 from the planes are 0.6515 Å and 0.5858 Å for **3a** and **3d**, respectively. It is worthnoting that the crystal structure of **3a** / **3d** belongs to two different conformers in the solid-state; in **3a** the two oxygen atoms (O1 and O1A) are located on the same side of the molecule, whereas they are located on opposite sides of the molecule in **3d**. This results in that the methyl groups attached to N4 are in *cis*-position in **3a** and *trans*-position in **3d**.

Table 2. Selected distances (Å) and angles (°) for compounds **3a** and **3d**

3a	O(1)-N(2)	1.4321(17)	N(2)-O(1)-C(6)	114.15(12)
3d	O(1) -N(2)	1.417(4)	N(2)-O(1)-C(6)	115.4(3)
3a	N(2)-C(3)	1.288(2)	C(3)-N(2)-O(1)	114.44(13)
3d	N(2)-C(3)	1.278(5)	C(3)-N(2)-O(1)	117.4(3)
3a	N(4)-C(3)	1.363(2)	N(2)-C(3)-N(4)	127.80(14)
3d	N(4)-C(3)	1.365(4)	N(2)-C(3)-N(4)	126.8(3)
3a	N(5)-N(4)	1.4298(17)	N(2)-C(3)-C(3A)[a]	113.66(11)
3d	N(5)-N(4)	1.422(4)	N(2)-C(3)-C(3A)[b]	114.6(4)
3a	N(5)-C(6)	1.445(2)	C(3)-N(4)-N(5)	116.80(12)
3d	N(5)-C(6)	1.442(5)	C(3)-N(4)-N(5)	115.7(3)

3a	N(4)-C(9)	1.447(2)	C(3)-N(4)-C(9)	122.34(14)
3d	N(4)-C(12)	1.443(5)	C(3)-N(4)-C(12)	124.8(3)
3a	O(1)-C(6)	1.450(2)	N(4)-N(5)-C(6)	110.37(12)
3d	O(1)-C(6)	1.450(4)	N(4)-N(5)-C(6)	111.6(3)
3a	C(6)-C(7)	1.511(3)	N(5)-C(6)-O(1)	109.38(13)
3d	C(6)-C(7)	1.521(5)	N(5)-C(6)-O(1)	110.3(3)
3a	C(6)-C(8)	1.515(2)	C(7)-C(6)-C(8)	112.41(15)
3d	C(6)-C(11)	1.518(5)	C(11)-C(6)-C(7)	111.8(3)
3a	C(3)-C(3A)[a]	1.499(3)	N(5)-C(6)-C(7)	110.81(16)
3d	C(3)-C(3A)[b]	1.502(7)	N(5)-C(6)-C(7)	111.0(3)

Symmetry transformations used to generate equivalent atoms: [a] -x,y,-z+3/2 [b] -x+1,y,-z+1/2

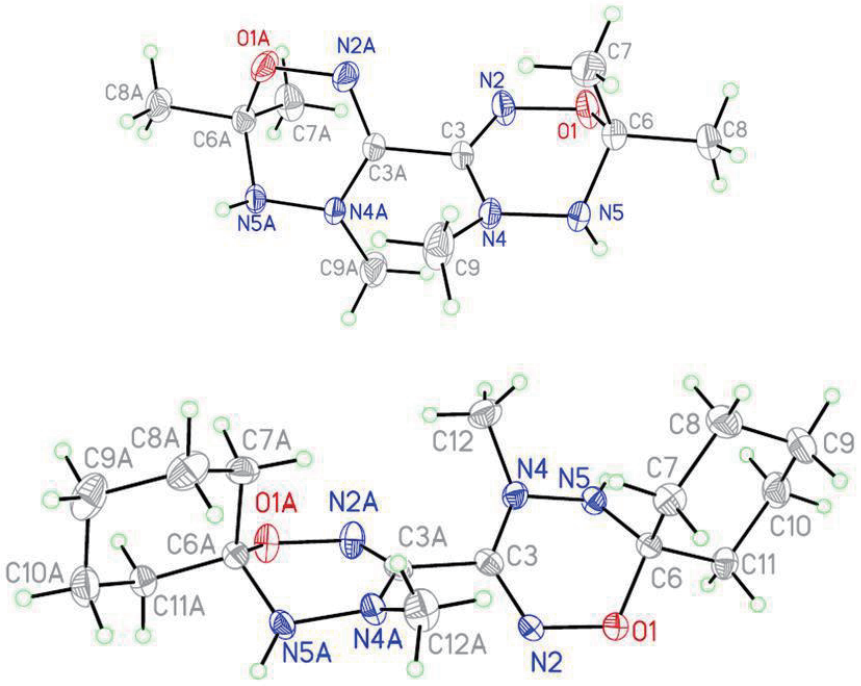


Figure 2. Molecular structures of **3a** (top) and **3d** (bottom). Thermal ellepsoides are shown at 30% probabilty. Atoms with suffix label are generated by 2-fold rotation of the asymmetric uint. Symmetry transformations used to generate equivalent atoms: -x,y,-z+3/2 in **3a** and -x+1,y,-z+1/2 in **3d**.

The supramolecular structure of **3a** is developed based on N-H…O interactions, whereas the supramolecular structure of **3d** is developed based on N-H…N interactions. The N-H…O interactions connect the molecular units of **3a** to form layer structure in the ab plane, while the N-H…N interactions

link the molecular units of **3d** to form chain structures that run parallel to the c-axis (Figure 3). This reflects the competition between the N-H…O and N-H…N interactions.

Cholinesterase Inhibition Assay

The cholinesterase inhibitory activity of compounds **3a-e** were measured *in vitro* by a modified spectrophotometric method previously developed by Ellman *et al.*[14] In brief, compound **3c** exhibited activity against BChE with $IC_{50} = 1.75 \times 10^{-5}$ μM (compared to $IC_{50} = 1.16 \times 10^{-6}$ μM for the reference Tacrine), whilst the rest compounds were inactive at $\leq 0.5 \times 10^{-3}$ μM. However, none of compounds **3a-e** showed inhibitory activity against AChE at $\leq 0.5 \times 10^{-3}$ μM. Currently, structural modifications of **3c** (such as attachment of various substituents at N5 and/or N4) and related congeners, guided by computer-aided molecular modeling are in progress. Such pharmacophore-based virtual screening studies might hopefully lead to optimization of the bioactivity profile of new bi(oxatriazines) as BChE and /or AChE inhibitors.

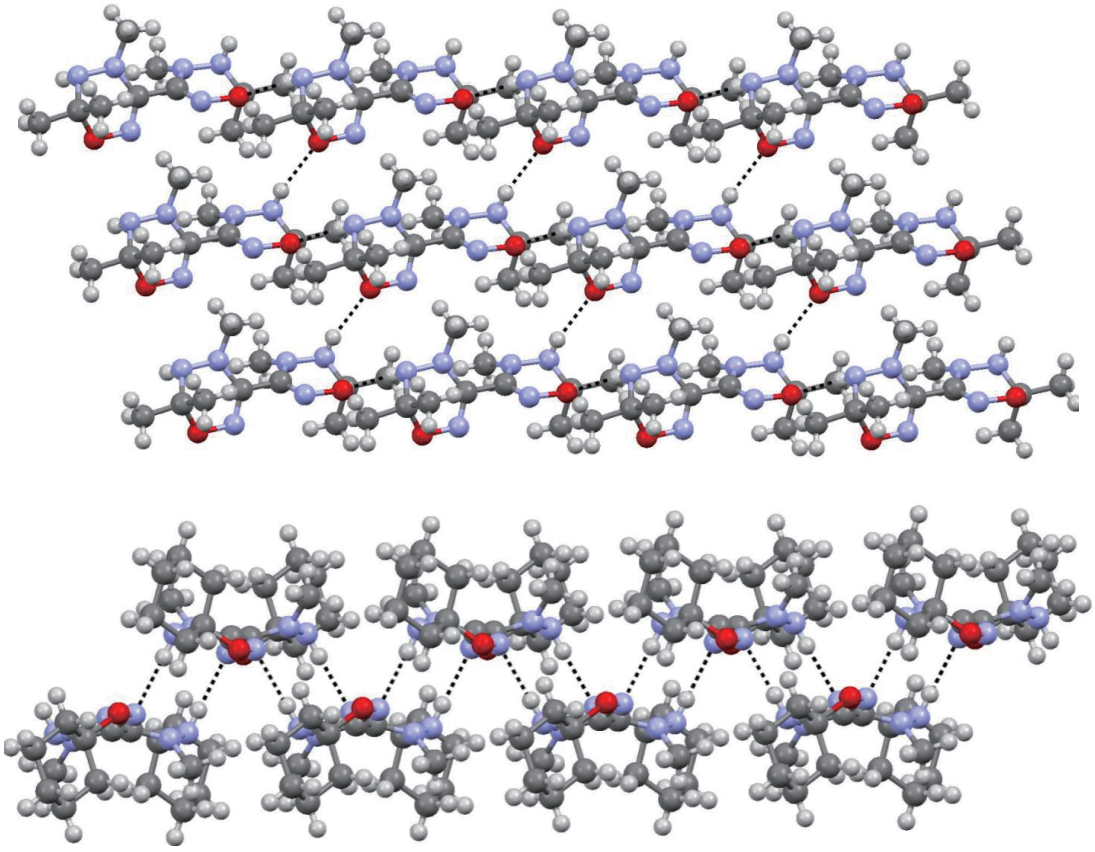


Figure 3. Layer structure of **3a** (top) and chain structure of **3d** (bottom). N-H…O (in **3a**) and N-H…N (in **3d**) hydrogen bonding interactions are shown in black dotted lines

EXPERIMENTAL

Glyoxal, hydroxylamine hydrochloride, *N*-chlorosuccinimide (NCS), triethylamine, methylhydrazine,

tetrahydro-4*H*-thiopyran-4-one, alkanones and cycloalkanones, used in this study, were purchased from Acros and used as received. Melting points (uncorrected) were determined on a Gallenkamp melting temperature apparatus in open capillary tubes. IR spectra were measured as neat films on a Thermo Nicolet Nexus 670 ATR FT-IR instrument. ^{1}H-, ^{13}C-, and 2D (COSY, HMQC, HMBC) NMR spectra were recorded on a 500 MHz spectrometer (Bruker Avance-III) with TMS as internal standard. Chemical shifts are expressed in δ units; J values for ^{1}H-^{1}H, coupling constants are given in Hertz. High-resolution mass spectra (HRMS) were measured using the electrospray ion trap (ESI) technique by collision-induced dissociation on a Bruker APEX-IV (7 Tesla) instrument.

***N*-Methylhydrazones (2a-e).** These compounds were obtained by direct interaction between methylhydrazine and the corresponding alkanone or cycloalkanone following literature procedures,[15,16] and used directly without further purification.

Dichloroglyoxime (1). This compound was prepared *via* reaction of glyoxime with NCS, following a reported procedure.[17] Mp 201-202 ºC (Lit.[17] mp 202-203 ºC). HRMS ((-)-ESI): *m/z* = 154.94121 (calcd. 154.94206 for $C_2H\ ^{35}Cl_2N_2O_2$, $[M - H]^-$); *m/z* = 156.93812 (calcd. 156.93911 for $C_2H\ ^{35}Cl\ ^{37}ClN_2O_2$, $[M + 2 - H]^-$); *m/z* = 158.93516 (calcd. 158.93616 for $C_2H\ ^{37}Cl_2N_2O_2$, $[M + 4 - H]^-$).

General Procedure for the preparation of tetrahydro-3,3'-bi(-1,2,4,5-oxatriazines) and related congeners 3a-e. To a stirred and cooled (-10 ºC) solution of the appropriate methylhydrazone (25 mmol) and triethylamine (6 mL) in $CHCl_3$ (100 mL), was added dichloroxime (12 mmol) in portions over 15 min. Following the addition, the temperature of the reaction mixture was allowed to rise slowly to rt, and stirring was continued for 1 h. The solvent was then removed in vacuo, the resulting solid product was washed with diethyl Et_2O (2 × 30 mL) and recrystallized from 50% aqueous MeOH.

4,4',6,6,6',6'-Hexamethyl-5,5',6,6'-tetrahydro-4*H*,4'*H*-3,3'-bi(1,2,4,5-oxatriazine) (3a): Yield: 66%, mp 162-163 ºC. IR (ν_{max}): 3272, 3175, 2977, 2942, 2878, 1579, 1490, 1407, 1377, 1259, 1144, 1079, 1038, 1001, 913 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.39 (s, 6H, C6-(CH_3)$_2$), 3.09 (s, 3H, N4-CH_3), 4.26 (s, 1H, N6-H, exchangeable with D_2O). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 22.6 (C6-(*C*H_3)$_2$), 42.4 (N4-CH_3), 84.4 (C-6), 147.3 (C-3). HRMS ((+)-ESI): *m/z* = 257.17273 (calcd. 257.17205 for $C_{10}H_{21}N_6O_2$, $[M + H]^+$); *m/z* = 279.15381 (calcd. 279.15400 for $C_{10}H_{20}N_6O_2Na$, $[M + Na]^+$); *m/z* = 535.31805 (calcd. 535.31877 for $C_{20}H_{40}N_{12}O_4Na$, $[2M + Na]^+$).

Prismatic crystals of **3a**, suitable for X-ray crystallography, were obtained by allowing a hot aqueous methanolic solution to cool down slowly and left to stand at rt for 2-3 days.

6,6,6',6'-Tetraethyl-4,4'-dimethyl-5,5',6,6'-tetrahydro-4*H*,4'*H*-3,3'-bi(1,2,4,5-oxatriazine) (3b): Yield: 68%, mp 141-142 ºC. IR (ν_{max}): 3174, 2967, 2941, 2878, 1578, 1462, 1352, 1283, 1237, 1186, 1119, 1080, 1052, 1021, 998 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.92 (t, J = 7.5 Hz, 6H, C6-(CH_2C*H*$_3$)$_2$), 1.63 (m, 4H, C6-(C*H*$_2$$CH_3$)$_2$), 3.02 (s, 3H, N4-$CH_3$), 4.11 (s, 1H, N6-H, exchangeable

with D_2O). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 7.5 (C6-(CH_2CH_3)$_2$), 24.7 (C6-(CH_2CH_3)$_2$), 42.3 (N4-CH_3), 88.5 (C-6), 147.4 (C-3). HRMS ((+)-ESI): *m/z* = 313.23477 (calcd. 313.23465 for $C_{14}H_{29}N_6O_2$, $[M + H]^+$); *m/z* = 335.21713 (calcd. 335.21660 for $C_{14}H_{28}N_6O_2Na$, $[M + Na]^+$); *m/z* = 647.44274 (calcd. 647.44397 for $C_{28}H_{56}N_{12}O_4Na$, $[2M + Na]^+$).

6,6,6',6'-Tetraisopropyl-4,4'-dimethyl-5,5',6,6'-tetrahydro-4*H*,4'*H*-3,3'-bi(1,2,4,5-oxatriazine) (3c): Yield: 62%, mp 122-123 °C. IR (ν_{max}): 3188, 2969, 2876, 1569, 1461, 1389, 1363, 1318, 1228, 1157, 1130, 1081, 1059, 1028, 964 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.00, 1.03 (2d, *J* = 7.0 Hz, 12H, C6-CH(C*H*$_3$)$_2$), 2.15 (m, 2H, C6-C*H*(Me)$_2$), 3.05 (s, 3H, N4-CH_3), 4.17 (s, 1H, N5-H, exchangeable with D_2O). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 17.3, 18.3 (CH(*C*H$_3$)$_2$), 29.9 (*C*H(Me)$_2$), 41.8 (N4-*C*H$_3$), 90.7 (C-6), 146.7 (C-3). HRMS ((+)-ESI): *m/z* = 391.27924 (calcd. 391.27920 for $C_{18}H_{36}N_6O_2Na$, $[M + Na]^+$).

6,6'-Dicyclohexyl-4,4'-dimethyl-5,5',6,6'-tetrahydro-4*H*,4'*H*-3,3'-bi(1,2,4,5-oxatriazine)[18] (3d): Yield: 71%, mp 163-164 °C. IR (ν_{max}): 3203, 3169, 2968, 2937, 2857, 1570, 1439, 1335, 1179, 1121, 1078, 1056, 1027, 1001, 937 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.50 (m, 2H, CH_2-9), 1.59 (m, 4H, CH_2-8/CH_2-10), 1.73 (m, 4H, CH_2-7/ CH_2-11), 3.08 (s, 3H, N4-CH_3), 4.10 (s, 1H, N-H, exchangeable with D_2O). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 22.1 (C-9), 25.7 (C-8/C-10), 31.4 (C-7/C-11), 42.5 (N4-CH_3), 85.3 (C-6), 147.8 (C-3). HRMS ((+)-ESI): *m/z* = 337.23454 (calcd. 337.23465 for $C_{16}H_{29}N_6O_2$, $[M + H]^+$); *m/z* = 359.21562 (cacld. 359.21660 for $C_{16}H_{28}N_6O_2Na$, $[M + Na]^+$); *m/z* = 695.42392 (calcd. 695.42348 for $C_{32}H_{56}N_{12}O_4Na$, $[2M + Na]^+$).

Parallelepiped crystals of **3d**, suitable for X-ray crystallography, were obtained by allowing a hot aqueous methanolic solution to cool down slowly and left to stand at rt for 2-3 days.

6,6'-Di(4-thiopyranyl)-4,4'-dimethyl-5,5',6,6'-tetrahydro-4*H*,4'*H*-3,3'-bi(1,2,4,5-oxatriazine)[19] (3e): Yield: 53%, mp 172-173 °C. IR (ν_{max}): 3190, 2944, 2917, 1568, 1422, 1327, 1268, 1204, 1147, 1081, 1025, 967 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.89, 2.03 (2m, 4H, CH_2-8/CH_2-10), 2.64, 2.82 (2m, 4H, CH_2-7/CH_2-11), 3.03 (s, 3H, N4-CH_3), 4.10 (s, 1H, N-H, exchangeable with D_2O). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 24.5 (C-7/C-11), 32.7 (C-8/C-10), 42.6 (N4-CH_3), 83.9 (C-6), 147.6 (C-3). HRMS ((+)-ESI): *m/z* = 373.14697 (calcd. 373.14749 for $C_{14}H_{25}N_6O_2S_2$, $[M + H]^+$); *m/z* = 395.12918 (cacld. 395.12944 for $C_{14}H_{24}N_6O_2S_2Na$, $[M + Na]^+$).

Collection of X-ray diffraction data and structure analysis of complexes 3a and 3d

Suitable single crystal of **3a** (approximate dimensions of 0.4 × 0.3 × 0.3 mm^3) and **3d** with approximate dimensions of 0.4 × 0.3 × 0.1 mm^3 were epoxy-mounted on glass fibers. Data for **3a** and **3d** were then collected at room temperature (*T* = 293 K) using an Oxford Xcalibur Diffractometer. Data were acquired and processed to give Shelx-format-*hkl* files using CrysAlisPro software.[20] Cell parameters were determined and refined using CrysAlisPro.[20] A multiscan absorption collection was applied with

maximum and minimum transmission factors of 1.0000 and 0.77392, and 1.00000 and 0.94650 for **3a** and **3d**, respectively. The structures were solved by Direct Methods and refined by full-matrix least-squares on F^2 using all unique data.[21] All non-hydrogen atoms were refined anisotropically with the hydrogen atoms placed on the calculated positions using a riding model.

Crystallographic data for the structural analysis of **3a** and **3d** have been deposited with the Cambridge Crystallographic Data Center (CCDC) under the depository Nos.1873651 and 1873652, respectively. Copies of these data can be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge CB2 IEZ, UK (Fax: +44-1223-336033; e-mail: (deposit@ccdc.com.ac.uk or http://www.ccdc.ac.uk).

ACKNOWLEDGEMENTS

We wish to thank the Deanship of Scientific Research at The University of Jordan, Amman, Jordan for financial support; we also thank the Deanship of Scientific Research at The University of Petra for facilities.

REFERENCES AND NOTES

1. Part I: H. H. Mohammad, M. M. EL-Abadelah, S. S. Sabri, F. F. Awwadi, and W. Voelter, *Z. Naturforsch*., 2018, **73b**, 965.
2. A. Q. Hussein, M. M. El-Abadelah, H. A. Hodali, M. R. Kamal, and M. M. Aouf, *Heterocycles*, 1987, **26**, 2199.
3. M. M. El-Abadelah, A. Q. Hussein, M. Z. Nazer, O. M. Musa, P. Rademacher, and H. Bandmann, *Heterocycles*, 1993, **36**, 455.
4. A. R. S. Ferwanah and A. M. Awadallah, *Asian J. Chem*., 1998, **10**, 180.
5. D. Geffken and S. Zilz, *Heterocycl. Commun*., 2002, **8**, 321.
6. D. Korbonits, B. Podanyi, A. Illar, K. Simon, M. Hanusz, and I. Hermecz, *Heterocycles*, 2009, **78**, 389.
7. (a) B. V. Bertinetti, M. A. Rodroguez, A. M. Godeas, and G. M. Cabrera, *J. Antibiot.*, 2010, **63**, 681; (b) R. S. Norton and R. J. Wells, *J. Am. Chem. Soc*., 1982, **104**, 3628; (c) A. R. Hodder and R. J. Capon, *J. Nat. Prod*., 1991, **54**, 1661; (d) H. Su, Z. H. Yuan, J. Li, S. J. Guo, L. P. Deng, L. J. Han, X. B. Zhu, and D. Y. Shi, *Chin. Chem. Lett.*, 2009, **20**, 456; (e) D. Y. Shi, L. J. Han, J. Sun, S. Li, S. J. Wang, Y. C. Yang, X. Fan, and J. G. Shi, *Chin. Chem. Lett.*, 2005, **16**, 777.
8. (a) F. Bohlmann and C. Zdero, Naturally occurring thiophenes in "thiophene and its derivatives", ed. by A. Weissberger and E. C. Taylor, John Wily, New York, 1985, p 1; (b) J. Kagan, *Prog. Chem. Org. Nat. Prod*., 1991, **56**, 87.
9. (a) K. J. Dignam and A. F. Hegarty, *J. Chem. Soc.*, *Perkin Trans. 2*, 1979, 1437; (b) H. Gozlan, R.

Micheot, C. Riche, and R. Rips, *Tetrahedron*, 1977, **33**, 2535; (c) K. J. Dignam and A. F. Hegarty, *Chem. Commun*., 1976, 862; (d) A. Dondoni, H. Gill, and M. Sacerdoti, *J. Chem. Soc*., *Perkin Trans. 2*, 1976, 1036.

10. (a) G. Leroy, M. T. Nguyen, M. Sana, K. J. Dignam, and A. F. Hegarty, *J. Am. Chem. Soc*., 1979, **101**, 1988; (b) O. Exner, V. Jehlicka, A. Dondoni, and A. C. Biocelli, *J. Chem. Soc.*, *Perkin Trans. 2*, 1974, 567.
11. J. E. Baldwin, *J. Chem. Soc.*, *Chem. Commun.*, 1976, 734.
12. (a) A. R. Katritzky, V. J. Baker, and F. M. S. Brito-Palma, *J. Chem. Soc.*, *Perkin Trans. 2*, 1980, 1739; (b) M. Baudet and M. Gelbcke, *Anal. Lett*., 1979, **12(B)**, 641.
13. E. Breitmaier and W. Voelter, ^{13}C-NMR Spectroscopy, Verlag Chemie, Weinheim, 2nd Ed., 1978, p 196.
14. G. L. Ellman, K. D. Courtney, V. Andres Jr., and R. M. Featherstone, *Biochem. Pharmacol*., 1961, **7**, 88.
15. (a) R. H. Wiley and G. Irick, *J. Org. Chem.*, 1959, **24**, 1925; (b) G. J. Durant, *J. Chem. Soc*. *C*, 1967, 952; (c) D. Todd, *J. Am. Chem. Soc.*, 1949, **71**, 1353.
16. (a) W. Sucrow, M. Slopianka, and A. Neophytou, *Chem. Ber*., 1972, **105**, 2143; (b) K. Bast, M. Christ, R. Huisgen, and W. Mack, *Chem. Ber*., 1972, **105**, 2825.
17. P. L. van der Peet, T. U. Connell, C. Gunawan, J. M. White, P. S. Donnelly, and S. J. Williams, *J. Org. Chem.*, 2013, **78**, 7298.
18. Replacement name: 4,4'-Dimethyl-1,1'-dioxa-2,2',4,4',5,5'-hexaaza-3,3'-bispiro[5.5]undecane-2,2'-diene.
19. Replacement name: 4,4'-Dimethyl-1,1'-dioxa-9,9'-dithia-2,2',4,4',5,5'-hexaaza-3,3'-bispiro[5.5] undecane-2,2'-diene.
20. CrysAlis PRO, Version 1.171.35.11 (2011) Agilent Technologies, Yarnton, England.
21. SHELXTL (XPREP, XS, XL, XP, XCIF), Version 6.10 (2002) Bruker AXS Inc., Madison, WI (USA).