Benzobis(pyrrolopyrimidopiridazines): Molecular Structure and Properties of the First π-Electronic Analogues of Dibenzo[*a*,*o*]picene

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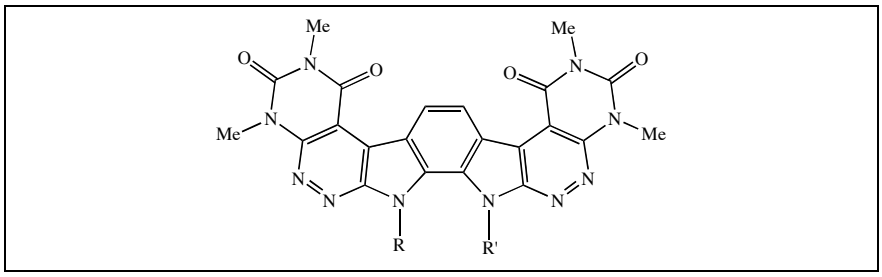

Molecular structure, aromaticity and some spectral properties of benzobis(pyrrolopyrimidopiridazines) **2** that are the first π-electronic analogues of the still unknown dibenzo[*a,o*]picene are discussed.

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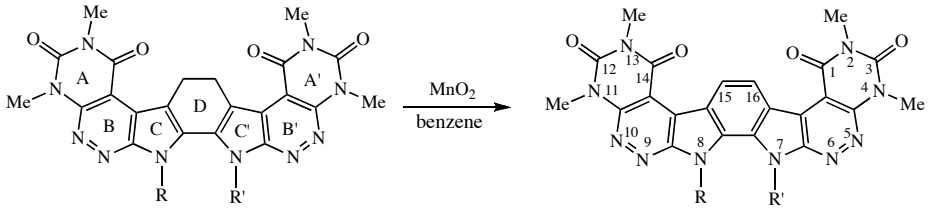
INTRODUCTION

Recently, we have reported on the multi-component, one-pot synthesis of cyclohexabis(pyrrolopyrimidopyridazines) **1** [1]. Oxidation of **1** with MnO_2 affords benzobis(pyrrolopyrimidopyridazines) **2** (Scheme 1). Our ongoing interest to these compounds is caused by two main reasons. Firstly, they are originated from the first iso-30π-electron heterocyclic analogues **3** of hitherto unknown aromatic hydrocarbon dibenzo[*a,o*]picene **4** [2]. Secondly, the arrangement of five central nuclei B, C D, C', and B' in compounds **1** and **2** has remarkable similarity with the skeleton of indolo[2,3-*a*]carbazole alkaloids. The indolo[2,3-*a*]carbazole framework is found in many natural products with antifungal, antimicrobial, antitumor and antihypertensive activities [3]. For example Gö 6976 (**5**) exhibits a selective inhibition of protein kinase C (PKC) and also acts as an antagonist of HIV1 [3]. Taking this into consideration one expects some biological activity from compounds **1** and **2**.

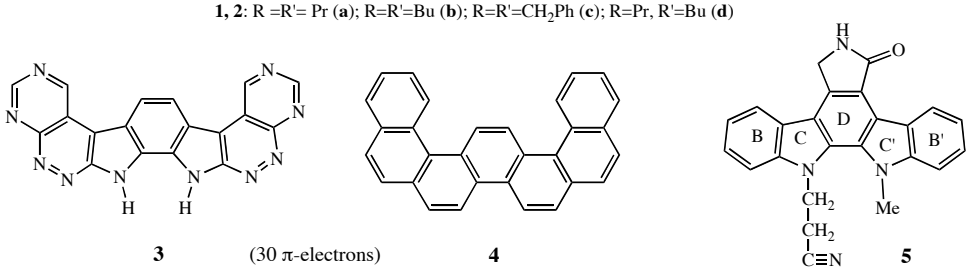
Here, we wish to discuss the molecular structure, aromaticity and some spectral properties of benzobis-(pyrrolopyrimidopyridazines) **2**.

Scheme 1



1a-d **2a-d**

1, 2: R =R'= Pr (**a**); R=R'=Bu (**b**); R=R'=CH_2Ph (**c**); R=Pr, R'=Bu (**d**)



3 (30 π-electrons) **4** **5**

RESULTS AND DISCUSSION

^{1}H nmr, mass and uv spectra. Benzobis(pyrrolopyrimidopyridazines) **2** are hardly soluble in both polar and nonpolar organic solvents. Nevertheless, their solubility in chloroform is sufficient to record ^{1}H nmr and uv spectra.

The compounds **2** have a deep red colour and in uv spectra display an intensive absorption band with λ_{max} at *ca*. 530 nm and two other bands at 385-400 and 280 nm; the second one is usually split (Figure 1, Table 1).

The chloroform solutions of compounds **2** demonstrate a dark red fluorescence with the Stokes shift value of 75 nm. Their dihydroderivatives **1** are bright red coloured (λ_{max} 512-519 nm) and differ by yellow fluorescence with the Stokes shift ~25 nm.

The mass spectra of compounds **2** show the molecular ions of moderate to low intensity. The character of fragmentation can be exemplified with the spectrum of **2d**, which contains the following selected peaks (Figure 2): 582 (64%) $[M]^+$, 540 (23%) $[M\text{-}C_3H_6]^+$, 526 (23%) $[M\text{-}C_4H_8]^+$. Thus, the loss of N(7)- and N(8)-substituents from the pyrrole rings seems to be the most important process. One more peak with m/z=554 (8%) arises, apparently, from the elimination of N_2 or CO species that is typical for pyridazines and uracils, respectively [4].

^{1}H nmr spectra of compounds **2a-d** (Figure 3) reveal two singlets of N-Me groups of the uracil ring at δ 3.6 and 4.0, the set of signals of the N(7)-substituent and the characteristic singlet at 9.6 ppm of two aromatic protons 15(16)-H. The latter experience a significant deshielding effect due to the proximity of C(1)=O and C(14)=O groups. Notably, the asymmetry of the compound **2d**, caused by different N(7) and N(8)-substituents, does not lead to a differentiation of the aromatic and N-Me protons, which appear as singlets.

Table 1

Uv Spectra of Compounds **2** in $CHCl_3$

Compound	λ_{max} nm (log ε)			
2a	281 (4.45)	384 (4.30)	404 (4.26)	534 (3.35)
2b	281 (4.54)	384 (4.40)		527 (3.54)
2c	279 (4.58)	384 (4.19)		530 (3.52)
2d	282 (4.61)	386 (4.47)	486 (3.90)	520 (3.48)

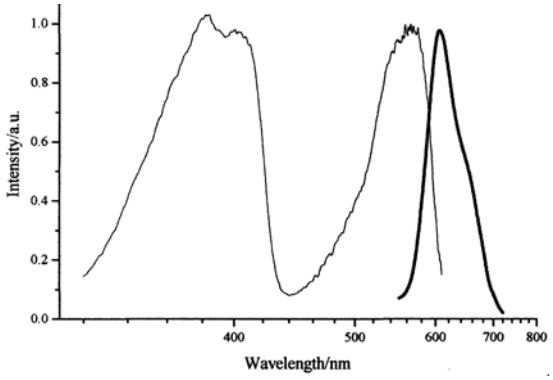


Figure 1. Uv and luminescence spectra (bold) of compound **2a** ($CHCl_3$).

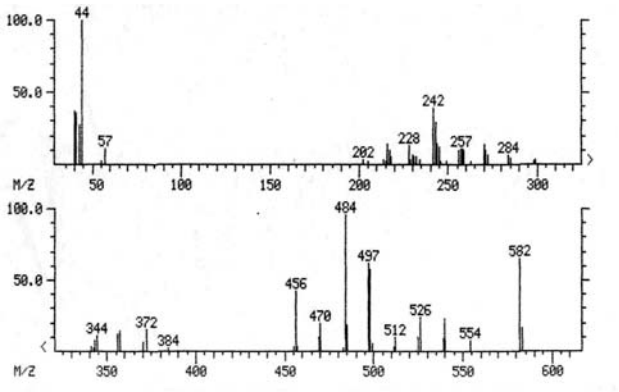


Figure 2. Mass spectrum of compound **2d**.

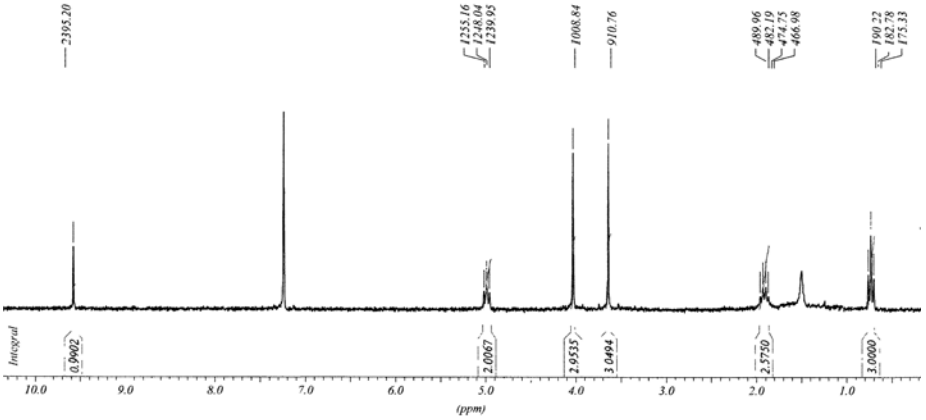


Figure 3. ^{1}H nmr spectrum of **2a** ($CDCl_3$, 250 MHz).

Molecular structure. Detailed crystallographic parameters of **2a** have been deposited at the Cambridge Crystallographic Data Centre (CCDC reference number 277966).

Figure 4 shows the molecular structure with the displacement thermal ellipsoids drawn at the 30% probability level. Compound **2a** crystallizes in a monoclinic crystal system (*C*2/c). Since the molecule is arranged around a two fold axis and contains four independent molecules in the unit it is rather to use Z'=4. The dihedral angle between the terminal uracil rings amounts 4.2° that allows to notice a small spirality of the molecule **2a** (Figure 5). For comparison, the analogous values for heptahelicene, picene and phenanthrene are 32.3° [5], 3.73° and 2.1° respectively [6, 7].

There is no information for indolo[2,3-*a*]carbazole itself, but its 5,6,11,12-substituted derivatives are known to be not strictly planar [8,9].

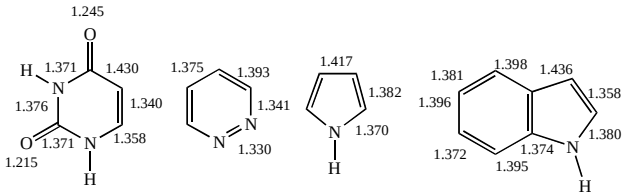
The deviation of the ring atoms of **2a** from the molecule plane does not exceed 0.077 Å with maximum values for N(1) and N(1A). Unlike this, deviation of Cα-atoms of the N-propyl groups from the ring plane amounts 0.637 Å and it is higher for β- and γ-carbons. Both N-propyl groups are directed away from each other and located on the opposite sides of the ring plane (Figure 5).

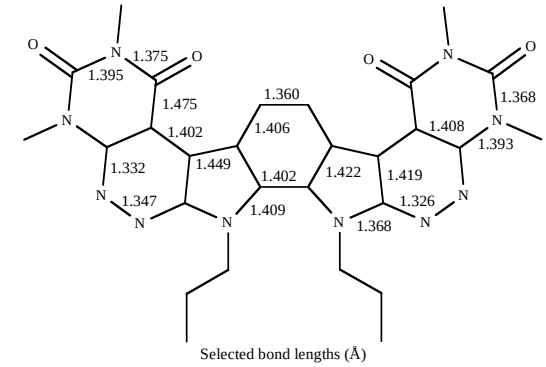
The crystal structure of **2a** is stabilized by weak π-π stacking between related fused six member rings and also by numerous van der Waals interactions (Figure 6). The non-valence contacts between C(1)-H (C(1A)-H) hydrogen atoms and carbonyl oxygens C(9)-O(1) (C(9A)-O(1A)) are rather short (2.24 Å) and lay inside the common range for the hydrogen bond of C-H...O type (2.2-2.3 Å) [10].

The lengths of the C-C bonds of the central benzene ring in **2a** are near the standard aromatic value (1.40 Å), except for the somewhat shortened C(1)-C(1A) bond (1.360 Å). The latter value seems to be favorable for participation of **2** in [4+2]-cycloaddition with dienes. All C-C bonds in the pyrrole and pyridazine rings of **2a** are also lengthened (1.409-1.449 Å) relatively to the parent monocyclic systems. Several C-N bonds are an exception, in particular C(4)-N(1) and C(4A)-N(1A) (1.368 Å) in pyrrole rings and both C-N bonds in pyridazine rings (Scheme 2).

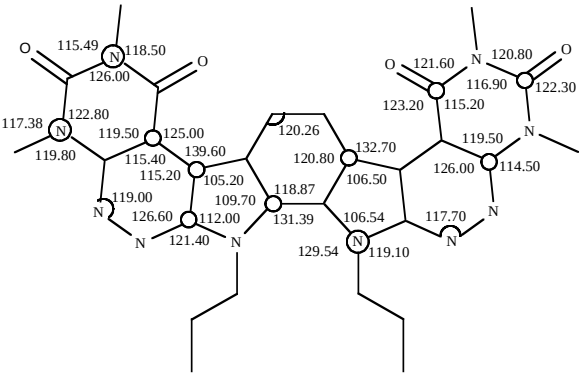
Scheme 2

Bond lengths (Å) in some parent heterocyclic systems [11, 12]





Selected bond lengths (Å)



Selected bond angles (degree)

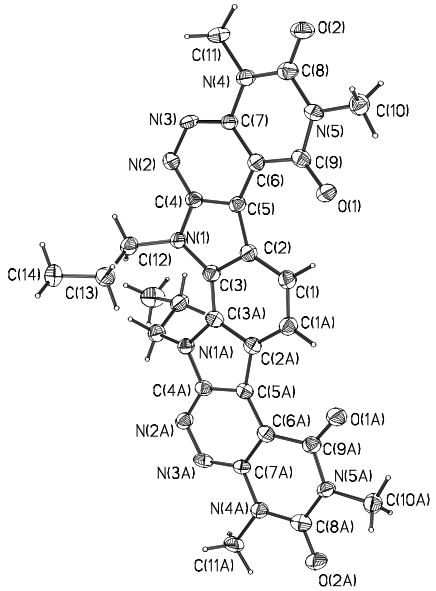


Figure 4. The molecular structure of **2a** with crystallographic numbering scheme.

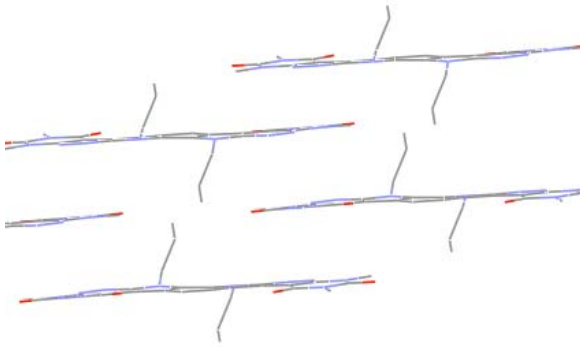


Figure 5. Fragment of the crystal packing of **2a, i**llustrating a small spirality of this molecule (hydrogens are omitted for clarity).

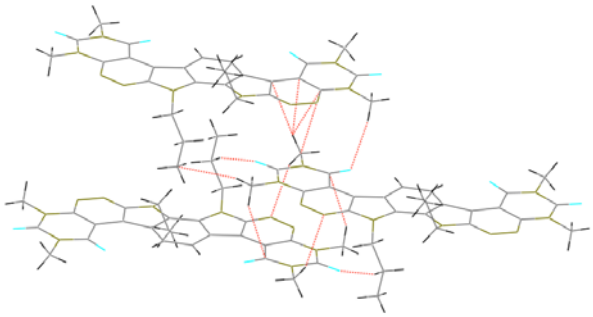


Figure 6. Fragment of the crystal packing of **2a**, illustrating the close contacts between atoms.

Aromaticity. We used X-ray analysis data for calculations of the structural aromaticity indices $\Delta \overline{N}$ for molecule **2a** and its separate rings. This index is determined by the value differences of all bond orders and is expressed as percentage of the aromaticity of benzene (evidently, benzene has equal bond orders and its aromaticity is taken as 100%) [13].

Table 2

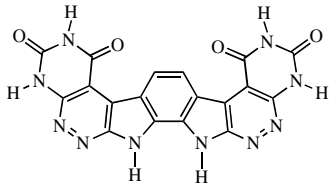
Structural indices of aromaticity

Reference compounds	$\Delta \overline{N}$ (%)	Compound **2a**	$\Delta \overline{N}$ (%)
benzene	100	benzene ring	75
pyrrole	37	pyrrole ring	59
pyridazine	79	pyridazine ring	65
uracil	45	uracil ring	68
-	-	whole molecule	59

Results of these calculations are presented in Table 2. It is easy to see that aromaticity of the benzene ring of **2a** remains significant, though somewhat lower than that of benzene itself. In contrast, aromaticity of the π-excessive pyrrole and uracil moieties of **2a** is notably increased in comparison to the parent molecules. In turn, bond alternation in the pyridazine fragment of **2a** is more pronounced than in the π-deficient pyridazine. Such averaging of properties is typical for condensed systems, consisting of π-excessive and π-deficient rings [13]. The interplay of all these tendencies gives index $\Delta \overline{N}$ = 59 % for molecule **2a** as a whole, that is surprisingly high value for conjugated system with such number of π-electrons.

Thermal stability, calculated dipole moment and ionization potential. Benzobis(pyrrolopyrimidopyridazines) **2** demonstrate a remarkable thermal stability decomposing without melting above 340 °C. We suppose that this originated from the enhanced polarity of these molecules. Owing to this, we have estimated the dipole moment and the first ionization potential, IP_1, of the parent compound **2e** using B3LYP method in 6-311G** basis (Gaussian 98). Analogous parameters for benzene, indole, pyridazine and uracil molecules, which are constituents of skeleton **2**, were also calculated.

As it follows from Table 3, the polarity of the benzobis(pyrrolopyrimidopyridazine) system **2** is rather modest (μ ~3 D) and could not be the only reason for high melting points. Evidently, strong stacking interactions, which are typical for polynuclear aromatic compounds and, in particular, for **2** (see Figure 6), may also be the reason.



2e

Table 3

Dipole moments and IP_1 values

Compound	Dipole moment **μ**, D		IP_1, eV	
	Calculated data	Experimental data [14]	Calculated data	Experimental data [15-17]
2e	2.96	-	7.55	-
benzene	0	0	9.08	9.24
indole	2.20	2.38	7.50	7.76
pyridazine	4.16	4.14	8.46	9.31
uracil	4.28	5.19	9.14	9.34

It should be noted that the calculated IP_1 value for **2e** is very similar to that of indole and is substantially lower than those of its other constituents (Table 3). This fact definitely reflects the presence of a fully conjugated π-electron assemble in **2e** that raises all energetic levels including HOMO.

In conclusion, for the first time we have described molecular structure and spectral characteristics of benzobis(pyrrolopyrimidopiridazines), which are heterocyclic analogues of the still unknown 30π-electronic aromatic hydrocarbon dibenzo[*a,o*]picene. We also estimated aromaticity, dipole moment and ionization potential of these compounds.

EXPERIMENTAL

Proton (^{1}H) nuclear magnetic resonance (nmr) spectra were recorded on a Bruker-250 (250 MHz) and Unity-300 (300 MHz) spectrometers with $CDCl_3$ as a solvent. Infrared (ir) spectra were recorded on a Specord IR-71 spectrometer using nujol. Ultraviolet absorption (uv) spectra were registered on a Specord M-40 spectrophotometer with $CHCl_3$ as a solvent. Mass spectra were measured on a Varian MAT-311A spectrometer. Melting points were determined in glass capillaries and are uncorrected. Al_2O_3 (III-IV activity of Brockman) was used for chromatographic separations.

Crystallographic data for **2a**: at 120 K crystals of $C_{28}H_{28}N_{10}O_4$ are monoclinic, space group *C*2/*c*, *a*=21.589(3) Å, *b*=9.1077(14) Å, *c*=13.032(2) Å, α=90°, β=102.392(4)°, γ=90°, *V*=2502.8(7) Å^3, *Z*'=4, *M*=568.60, d_{calk}=1.509 mg m^{-3}, μ(Mo K_α)=0.106 mm^{-1}, *F*(000)=1192. Intensities of 14157 reflections were measured with a SMART diffractometer at 120 K and 3600 independent reflections (R_{int}=0.1295) were used in further refinement. The structures were solved by direct method and refined by the full-matrix least squares against F^2 in the anisotropic-isotropic approximation. Hydrogen atoms were located from the Fourier synthesis and refined in the isotropic approximation. The refinement converged to *wR*2=0.0991 and GOF=0.812 for all independent reflections [R^1=0.0591 was calculated against *F* for observed 1299 reflections with $I>2\sigma(I)$]. All calculations were performed using SHELXTL-97 on an IBM PC AT. Atomic coordinates, bond lengths, bond angles and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC) and allocated the deposition number CCDC 277966.

Compounds **1a-c** were obtained according to the known procedure [1].

General procedure for synthesis of 2a-d. A stirred suspension of **1b** (0.020 g, 0.033 mmol) and MnO_2 (0.0052 g, 0.06 mmol) was refluxed in benzene (30 mL). After one week of refluxing the reaction mixture was concentrated to dryness. The residue was extracted with boiling $CHCl_3$ (50 mL). The extract was chromatographed on a column with Al_2O_3 (1 x 5 cm) (eluent - $CHCl_3$). 0.019 g (97%) red crystals of **2b** were obtained.

2,4,11,13-Tetramethyl-7,8-dipropyl-7,8-dihydrobenzo[1′′, 2′′:4,5;4′′,3′′:4′,5′]bis(pyrrolo[2,3-*c*]pyrimido[5,4-*e*]pyridazine)-1,3,12,14(2*H*,4*H*,11*H*,13*H*)-tetraone (2a). Compound **2a** was obtained as red crystals in 98% yield, mp >340°C (decomp.); uv ($CHCl_3$): λ_{max} (log ε) 281 (4.45), 384 (4.30), 404 sh (4.26), 534 nm (3.35); ir (Nujol): 1653, 1706 cm^{-1} (C=O); ^{1}H nmr ($CDCl_3$): δ 0.73 (t, J=7.4 Hz, 3H, CH_2CH_2*Me*), 1.92 (m, 2H, CH_2*CH*$_2$Me), 3.64 (s, 3H, 2(13)-Me), 4.04 (s, 3H, 4(11)-Me), 4.99 (t, J=7.3 Hz, 2H, *CH*$_2$CH$_2$Me), 9.58 (s, 1H, 15(16)-H); ms: m/z 568 (M$^+$). *Anal*. Calcd for $C_{28}H_{28}N_{10}O_4$: C, 59.15; H, 4.93; N, 24.65. Found: C, 58.96; H, 5.12; N, 24.51.

2,4,11,13-Tetramethyl-7,8-dibutyl-7,8-dihydrobenzo[1′′,2′′: 4,5;4′′,3′′:4′,5′]bis(pyrrolo[2,3-*c*]pyrimido[5,4-*e*]pyridazine)-1,3,12,14(2*H*,4*H*,11*H*,13*H*)-tetraone (2b). Compound **2b** was obtained as red crystals in 97% yield, mp >340°C (decomp.); uv ($CHCl_3$): λ_{max} (log ε) 281 (4.54), 384 (4.40), 527 nm (3.54); ir (Nujol): 1660, 1713 cm^{-1} (C=O); ^{1}H nmr ($CDCl_3$): δ 0.78 (t, J=7.3 Hz, 3H, $CH_2CH_2CH_2$*Me*), 1.11 (m, 2H, CH_2CH_2*CH*$_2$Me), 1.81 (m, 2H, CH_2*CH*$_2$CH$_2$Me), 3.64 (s, 3H, 2(13)-Me), 4.04 (s, 3H, 4(11)-Me), 5.04 (t, J=7.5 Hz, 2H, *CH*$_2$CH$_2$CH$_2$Me), 9.57 (s, 1H, 15(16)-H); ms: m/z 596 (M$^+$). *Anal*. calcd for $C_{30}H_{32}N_{10}O_4$: C, 60.40; H, 5.37; N, 23.49. Found: C, 60.52; H, 5.25; N, 23.58.

2,4,11,13-Tetramethyl-7,8-dibenzyl-7,8-dihydrobenzo[1′′, 2′′:4,5;4′′,3′′:4′,5′]bis(pyrrolo[2,3-*c*]pyrimido[5,4-*e*]pyridazine)-1,3,12,14(2*H*,4*H*,11*H*,13*H*)-tetraone (2c). Compound **2c** was obtained as red crystals in 93% yield, mp >340°C (decomp.); uv ($CHCl_3$): λ_{max} (log ε) 279 (4.58), 384 (4.19), 530 nm (3.52); ir (Nujol): 1667, 1713 cm^{-1} (C=O); ^{1}H nmr ($CDCl_3$): δ 3.62 (s, 3H, 2(13)-Me), 3.95 (s, 3H, 4(11)-Me), 5.96 (s, 2H, *CH*$_2$Ph), 6.87 (m, 2H, Ph), 7.19 (m, 3H, Ph), 9.60 (s, 1H, 15(16)-H); ms: m/z 664 (M$^+$). *Anal*. calcd for $C_{36}H_{28}N_{10}O_4$: C, 65.06; H, 4.22; N, 21.08. Found: C, 64.89; H, 4.03; N, 21.26.

2,4,11,13-Tetramethyl-7-propyl-8-butyl-7,8-dihydrobenzo-[1′′,2′′:4,5;4′′,3′′:4′,5′]bis(pyrrolo[2,3-*c*]pyrimido[5,4-*e*]pyridazine)-1,3,12,14(2*H*,4*H*,11*H*,13*H*)-tetraone (2d). Compound **2d** was obtained as red crystals in 95% yield, mp >340°C (decomp.); uv ($CHCl_3$): λ_{max} (log ε) 282 (4.61), 386 (4.47), 486 (3.90), 520 (3.48); ir (Nujol): 1658, 1710 cm^{-1} (C=O); ^{1}H nmr ($CDCl_3$): δ 0.75 (t, J=7.5 Hz, 3H, $CH_2CH_2CH_2$*Me*), 0.78 (t, J=7.0 Hz, 3H, CH_2CH_2*Me*), 1.09 (m, 2H, CH_2CH_2*CH*$_2$Me), 1.84 (m, 4H, CH_2*CH*$_2$Me and CH_2*CH*$_2$CH$_2$Me), 3.65 (s, 6H, 2(13)-Me), 4.04 (s, 3H, 4(11)-Me), 4.99 (t, J=7.3 Hz, 2H, *CH*$_2$CH$_2$Me), 5.02 (t, J=7.5 Hz, 2H, *CH*$_2$CH$_2$CH$_2$Me), 9.57 (s, 2H, 15(16)-H); ms: m/z 582 (M$^+$). *Anal*. calcd for $C_{29}H_{30}N_{10}O_4$: C, 59.79; H, 5.15; N, 24.05. Found: C, 59.93; H, 5.01; N, 23.88.

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