Pyrimidine-Annulated Pyrrolobenzodiazepines. A New Ring System Related to *Aspergillus* Alkaloids

Andreas Schmidt,*[a] Abbas Gholipour Shilabin,[a] Jan Christoph Namyslo,[a] Martin Nieger,[b] and Sascha Hemmen[c]

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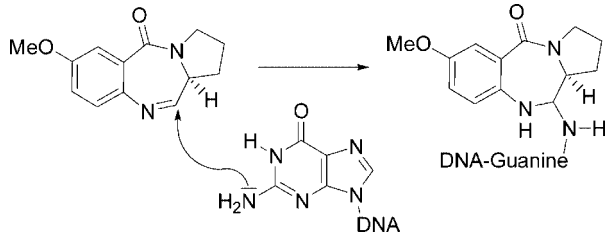
Pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione was converted into the corresponding C-11-monothiolactam and subsequently treated with amines to give cyclic amidines, which racemize due to the formation of tautomers (NMR, X-ray analysis) under basic conditions. We treated these amidines with bis(trichlorophenyl) malonate esters. Formation of neutral tautomers of the 1,3,8-triones of the new 4,7a,12b-triazadibenzo[*e,g*]azulene ring system gave a twisted molecule with both helical and chiral structure elements (NMR, X-ray analysis), which caused a splitting of the NMR signals into two sets. Results of two X-ray single crystal analyses are presented, together with an ab initio calculation.

Introduction

Pyrrolo[2,1-*c*][1,4]benzodiazepines (PBDs) form a class of biologically active compounds. Special interest is currently focused on new derivatives[1,2,3] that can recognize and bind to specific sequences of DNA[4,5,6,7] and cause a wide variety of potential biological responses. In this context, PBDs are one of the most promising types of lead compounds.[8] Some derivatives possess cancerostatic and antiinfective properties[9,10] and can be used as affinity-cleavage reagents in molecular biology.[11] The PBD ring system is also found in natural antitumor antibiotics such as anthramycin,[12,13,14] and many others.[15,16,17,18] All the naturally occurring compounds possess the *S* configuration at the α-carbon atom of the pyrrolidine ring [i.e., C(11a)], which provides them with a right-handed twist and causes isohelicity with the minor groove of the double-stranded B form of DNA. This configuration has been identified as important to the pharmacophore of these compounds. The biological activity of anthramycin, tomaymycin, chicamycin, neothramycin, and other PBDs from *Streptomyces* species is due inter alia to their ability to form aminal bonds on nucleophilic attack of the exocyclic N^2 of a guanine at the electrophilic C(11)-position after sequence-selective insertion in the minor groove (Scheme 1).[19,20,21,22,23]



Scheme 1. Attack of guanine on pyrrolobenzodiazepines after insertion into the minor groove of DNA.

In continuation of our interest in alkaloids,[24,25,26,27] nucleobase betaines,[28,29] and ionic heteroaromatics,[30,31,32] we became interested in this class of compounds because some alkaloids, circumdatin A–G, had been isolated from the fungus *Aspergillus ochraceus* and proposed as suitable chemotaxonomic markers for this species.[33] Total syntheses of circumdatin C and F,[34] and a building block approach to a diverse multi-arrayed library of the circumdatin family by means of aza-Wittig reactions[35] were published recently, demonstrating the interest in derivatives of this ring system. We focused our attention on compounds related to the proposed structures **1** and **2** for circumdatin A and B (Scheme 2), which are heterocyclic mesomeric betaines, in order to study stereochemical and spectroscopic effects of possible tautomerism, in particular in view of the biological relevance of the twisted conformation of the pyrrolobenzodiazepine ring system. Here we report our results concerning the syntheses and surprising spectroscopic properties of structures related to these natural products, diox-

[a] Clausthal University of Technology, Institute of Organic Chemistry,
Leibnizstrasse 6, 38678 Clausthal-Zellerfeld, Germany
Fax: +49-5323-723861
E-mail: schmidt@ioc.tu-clausthal.de
[b] Rheinische Friedrich-Wilhelms-Universität Bonn, Institute of Inorganic Chemistry,
Gerhard-Domagk-Strasse 1, 53121 Bonn, Germany
Fax: +49-228-735327
E-mail: m.nieger@uni-bonn.de
[c] Clausthal University of Technology, Institute of Theoretical Physics, Dept. of Applied Theoretical Physics,
Leibnizstrasse 10, 38678 Clausthal-Zellerfeld, Germany
Fax: +49-5323-723116
E-mail: sascha.hemmen@tu-clausthal.de

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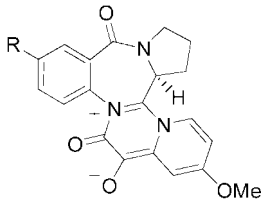
opyrimidine-annulated pyrrolobenzodiazepines, the first representatives of a new ring system.

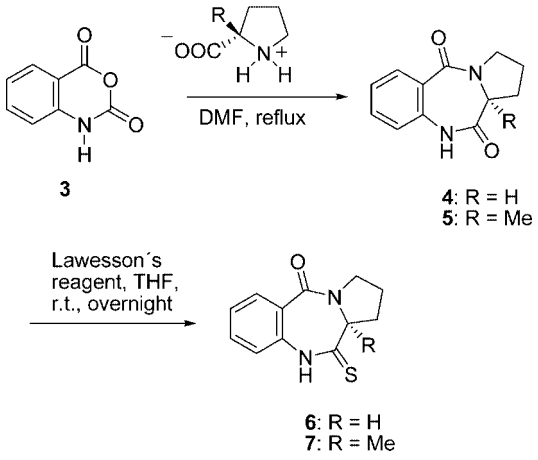


1: R = OMe
2: R = H

Scheme 2. Proposed structures for circumdatin A (**1**) and (B) **2**.

Results and Discussion

We started our investigation from the pyrrolo[2,1-*c*][1,4] benzodiazepine natural product **4** (from *Isatis indigotica*[36]), which is readily available by heating isatoic anhydride **3** at reflux with (*S*)-proline in DMF by literature procedures.[37,38] Its methylated derivative **5** was obtained analogously by starting from (*S*)-α-methylproline. Thionation in THF at room temperature with 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (Lawesson's reagent)[39] resulted in the formation of the monothiolactams **6** and **7** in good yields (Scheme 3).



3
4: R = H
5: R = Me
6: R = H
7: R = Me

Scheme 3.

The monothiolactams **6** and **7** reacted with amines such as aniline, methylamine, and piperidine in the presence of mercury(II) chloride to afford the cyclic amidines **8**–**11** in high yields (Scheme 4). We observed that the neat reaction of **6** and the amines (except for methylamine, which was used as a solution in THF) gave better yields than reactions conducted in THF. We obtained **8** and **10** as optically active compounds, whereas **9** racemized under these conditions. In the ^{1}H NMR spectra of **8**–**10** in $CDCl_3$ at 20 °C only one set of signals is present. In [D_6]DMSO at 20 °C, however, two distinct tautomeric forms of **8**–**10** are detectable. Unambiguous peak assignments through a combination of HSQC and HMBC NMR experiments established the coupling of the more deshielded NH group with the two *ortho*-protons of the aniline moiety and C(11a)-H of **9**, and couplings of the more shielded NH-group with C(9)-H and C(11a)-H, respectively. Thus, the ratios of **8A/8B**, **9A/9B**, and **10A/10B** at 20 °C in [D_6]DMSO were determined to be 10:11, 10:6, and 10:12, respectively, with these ratios changing with temperature. As an example, the **9A/9B** ratio changes to 10:11 at 100 °C in [D_6]DMSO. The tautomeric forms **8C** and **9C**, the bases of racemization of the pyrrolidine moiety, were not detected spectroscopically, and a control experiment with the piperidino derivative **11** confirmed these observations. No traces of **11B** were found in the ^{1}H NMR spectra in [D_6]DMSO; only one set of signals was observable regardless of the solvent used.

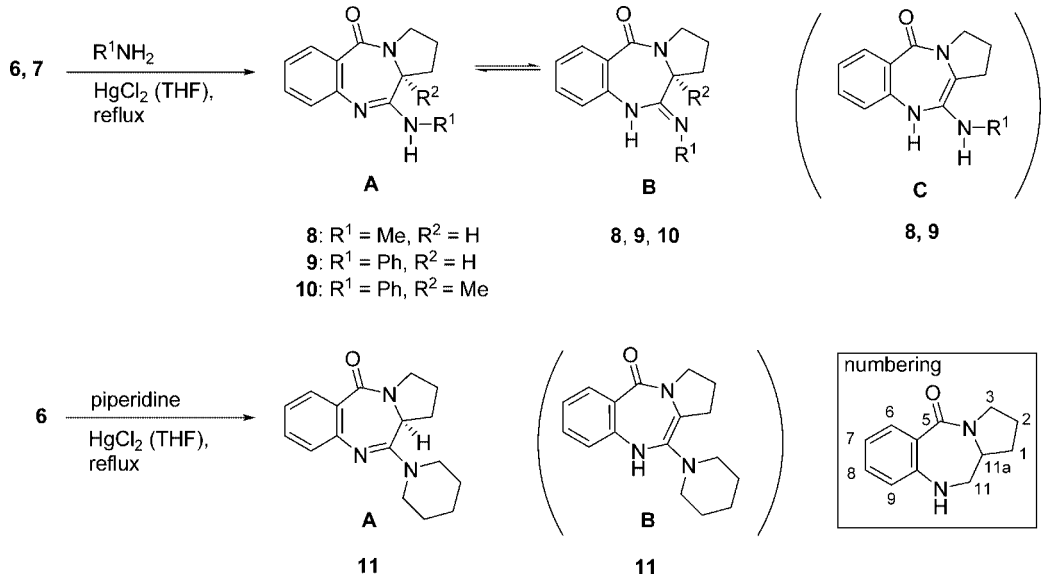
In the solid state, compound **9** exists as the exocyclic imine **9B** in the *Z* configuration, as evidenced by a single-crystal X-ray analysis (Figure 1).[40] The phenylimino group is strongly twisted out of the plane defined by the phenyl ring of the benzodiazepine moiety. The bond length of the C=N bond [crystallographic numbering: C2–N2] was determined to be 128.03(13) pm, whereas the N(10)–C(11) distance [N1–C2] is 138.07(13) pm. The bond length between C(11) and C(11a) [C2–C2A] is 151.61(13) pm.

Methylation of racemic **9** with sodium hydride and methyl iodide gave only product **12** (Scheme 5), as evidenced by couplings of the methyl group to C(9a) and C(11) in HMBC NMR experiments.

We then treated the amidines **8**–**10** with bis(2,4,6-trichlorophenyl) 2-phenylmalonates (Scheme 6) in order to obtain the target pyrimidine-annulated pyrrolobenzodiazepines. Heating of the starting materials in a Zincke apparatus gave 2,4,6-trichlorophenol as expected, and this was distilled off in vacuo. On recrystallization of the residues obtained from **8** and **9** pale yellow solids were obtained in good yields, whereas no isolable compounds were obtained when starting from the methylated species **10**. All NMR spectra taken in $CDCl_3$ are in agreement with tautomers **13B** and **14B**, resulting from elimination of the α-hydrogen atoms of the pyrrolidine ring. The NMR spectra in $CDCl_3$ clearly indicate the existence of only three CH_2 groups and one CH group, joined to the phenyl group. These results corroborate the formation of a 3*H*-2,4-dioxopyrimidine ring and a sp^2-hybridized C-11a in tautomers **13B** and **14B**, instead of the cross-conjugated mesomeric betaines **13A** and **14A** in $CDCl_3$ solution. These findings explain the failure of the reaction of **10** to give **15**, which would be compelled to adopt a clearly unstable betainic structure **15A**.

A striking feature of **13** and **14**, however, is a doubling of the ^{1}H NMR and ^{13}C NMR resonance frequencies in [D_6]DMSO, C_6D_6, [D_7]DMF, and MeOD (Figure 2). Whereas traces of acids and bases do not cause any changes in the spectra taken in $CDCl_3$, splitting of the signals is observable on addition of [D_6]DMSO to this solution, the chemical shift difference depending on the relative concentration of these two solvents.

As evidenced by HSQC, HMBC, and NOESY experiments and by ^{13}C NMR, either form of **14** possesses the C(= O)–CHPh–C(= O) partial structure, so that the formation of tautomers such as the mesomeric betaine **14A** and



Scheme 4. Tautomeric forms of 11-amino-substituted pyrrolobenzodiazepines.

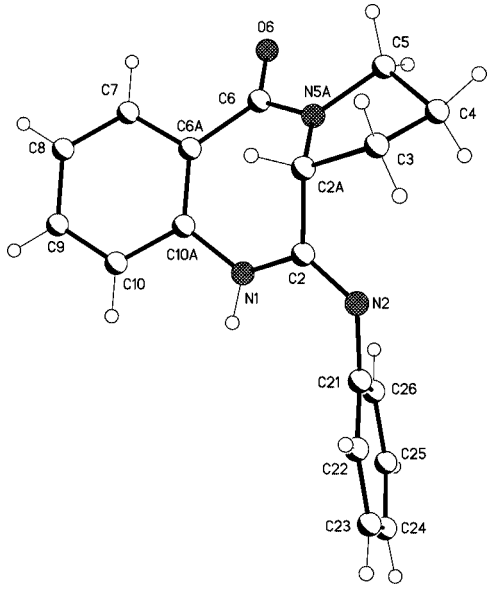
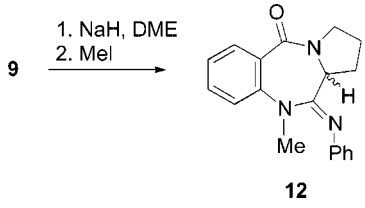
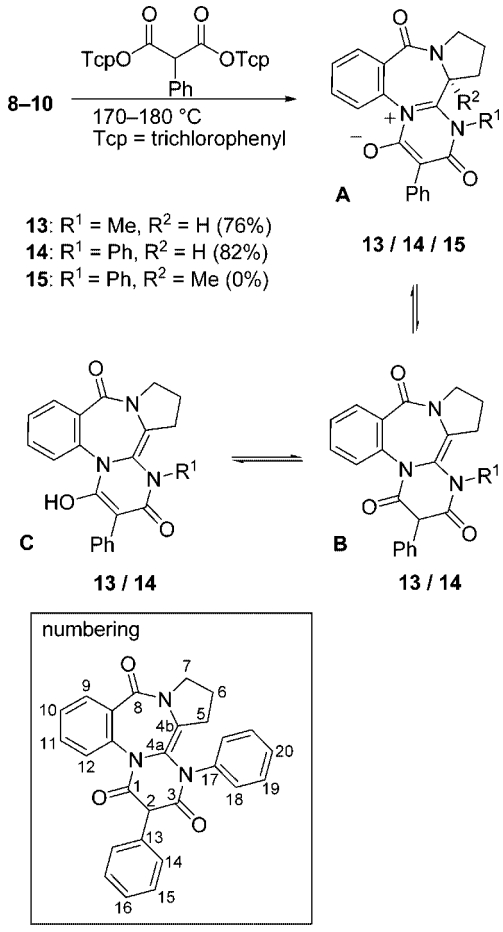


Figure 1. Molecular structure of **9** according to a single-crystal X-ray analysis.



Scheme 5. Methylation of **9** occurs at N(10).

enols such as **14C** in the above solvents were ruled out. NOESY experiments, however, detected closely spaced protons of the pyrrolidine and of the phenyl ring at C-2 (15-*H*↔5-*H*, 15-*H*↔6-*H*, 15-*H*↔7-*H*, 16-*H*↔5-*H*, 16-*H*↔6-*H*)



Scheme 6. Treatment with trichlorophenyl malonates results in the formation of tautomers **13B/14B** instead of cross-conjugated mesomeric betaines **13A/14A** or enols such as **13C/14C**.

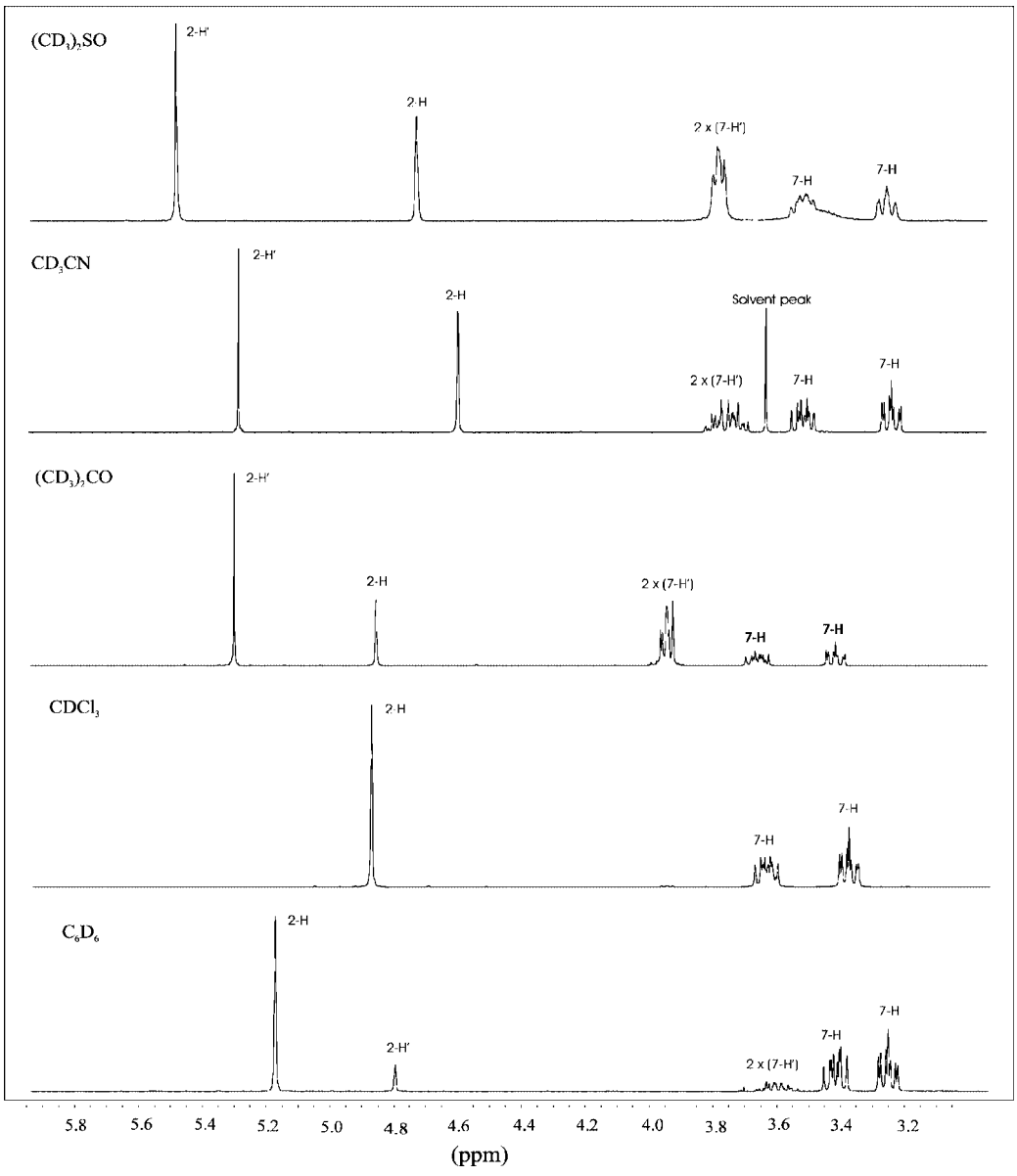


Figure 2. NMR spectra of **14** in various solvents.

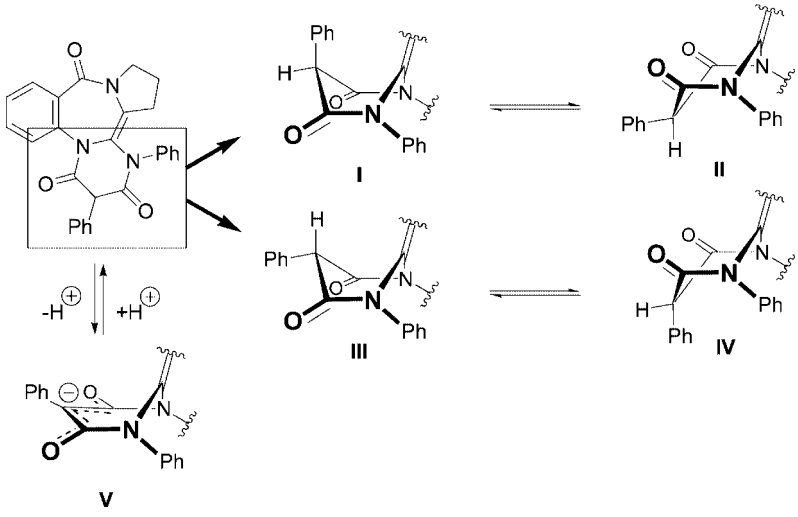
in one of the two conformers observable in the spectra. This finding provides evidence for a conformation of **14** in which these partial structures are situated in close proximity, which causes the more shielded resonance frequencies. A boat conformation of the dioxopyrimidine moiety with an axial phenyl ring at C-2 could explain the proximity of these partial structures, and this assumption was supported by the chemical shift difference of 2-*H*, which is consistent with axial and equatorial positions. Interconversion of the ring system in $CDCl_3$ is obviously fast. As the $CDCl_3$ solutions solidified to glassy materials on cooling, however, we were prevented from taking NMR spectra at low temperatures. We were able to assign the resonance frequencies to the two forms unambiguously from the spectra, and our results are presented in Table 1.

In order to confirm these assumptions, we performed ab initio calculations on boat and chair conformations of the dioxopyrimidine ring of **14** with equatorial (**II**, **III**) and axial (**I**, **IV**) substituents at C-2, respectively (Scheme 7). All calculations were carried out with the projector-augmented wave method[41] as implemented in the PAW program.[41–45] The calculations show that the boat conformation with axial phenyl ring (**I**) indeed has the lowest total energy. The difference with the boat conformation with equatorial phenyl ring (**III**) is ΔE = 8.9 kJ mol^{-1}. Both axial (**IV**) and equatorial phenyl rings (**II**) in chair conformations have higher energies, of ΔE = 78.0 kJ mol^{-1} and ΔE = 58.2 kJ mol^{-1}, respectively. In addition, the calculations show twisted conformations of the pyrrolobenzodiazepine partial structure.

Table 1. Chemical shifts of **14** in $CDCl_3$ and $[D_6]$DMSO.

Atom no.	^{13}C NMR ($CDCl_3$)	^{1}H NMR ($CDCl_3$)	^{13}C NMR ($[D_6]$DMSO)	^{1}H NMR ($[D_6]$DMSO)
1	166.7	–	166.2/166.7	–
2	62.3	4.94 (s)	59.3/62.0	4.79 (s)/5.54 (s)
3	166.7	–	166.5/166.8	–
4a[a]	128.6	–	128.9	–
4b	119.3	–	118.7/118.1	–
5	29.3	1.61–1.65 (m) 1.73–1.80 (m)	29.3/29.8	1.63–1.68 (m)/1.87–2.01 (m) 1.79–1.84 (m)/1.87–2.01 (m)
6	19.8	0.88–1.00 (m) 1.54–1.60 (m)	19.9/20.3	0.83–0.94 (m)/1.77–1.85 (m) 1.58–1.62 (m)/1.77–1.85 (m)
7	49.5	3.41–3.47 (m) 3.66–3.73 (m)	49.8/50.4	3.29–3.35 (m)/3.82–3.86 (m) 3.55–3.62 (m)/3.82–3.86 (m)
8	165.2	–	164.8/165.3	–
8a	139.5	–	139.9	–
9	132.9	8.08 (dd)	132.5	7.92 (dd)/7.93–7.96 (m)
10	134.1	7.70 (ddd)	134.2/134.4	7.76–7.77 (m)/7.72–7.74 (m)
11	128.4	7.48 (ddd)	128.7	7.51–7.55 (m)/7.48–7.52 (m)
12	126.2	7.53 (dd)	127.3/127.4	7.75 (d)/7.71–7.72 (m)
12a	139.5	–	140.4	–
13[a]	133.2	–	133.4	–
14	126.3	7.40–7.44 (m)	126.5	7.45–7.48 (m)
15	129.5	7.37–7.40 (m)	129.9	7.37–7.39 (m)
16	132.1	7.35–7.37 (m)	128.9	7.41–7.42 (m)
17	139.0	–	139.5	–
18	124.2	7.18–7.20 (m)	124.9/125.1	7.18–7.21 (m)
19	129.7	7.29–7.33 (m)	130.1	7.33–7.35 (m)
20	126.8	7.15–7.18 (m)	127.1	7.22–7.23 (m)

[a]: Peak assignments exchangeable.



Scheme 7. Boat-chair isomerizations **I/II** and **III/IV** (above), and racemizations via anionic species **V** (below) of the dioxopyridimidine moiety of **14**.

These results are in qualitative agreement with an X-ray single crystal analysis of **14**, which shows tautomer **14B** in the solid state (Figure 3): The 6:7:5 pyrrolobenzodiazepine ring system adopts a twisted conformation. The C6–C7 bond length is 132.71(16) pm (calcd. 135.2 pm), which corresponds to a $C(sp^2) = C(sp^2)$ double bond. This C=C bond is twisted due to the helicity of the 6:7:5 ring system, so that the dihedral angles N1–C6–C7–N11 and N5–C6–C7–C8 are 4.77(18)° and 6.37(19)°, respectively [calcd. 4.9° and 4.7°, respectively]. In the elemental cell, the 3*H*-2,4-dioxopyrimidine ring adopts a boat-like conformation with C6 and C3 above the plane formed by N1, N5, C4, and C2, and the phenyl ring at C3 in axial position (Figure 4). The phenyl ring is twisted by –30.16(12)° [C4–C3–C31–C32, calcd. –34.2°].

The ab initio calculation gave a bond length of 135.3 pm between C-4a and C-4b [crystallographic numbering: C6–C7] in conformer **III** (Scheme 7) in which the phenyl ring is in an equatorial position in the boat conformation of the dioxopyrimidine moiety. Again, this double bond is twisted by –3.5° (C6–N1–C2–C3).

Conversion of the configuration at C-2 of **14** must proceed via an anionic species **V** as represented in Scheme 7. On isomerization, the phenyl ring changes from an axial

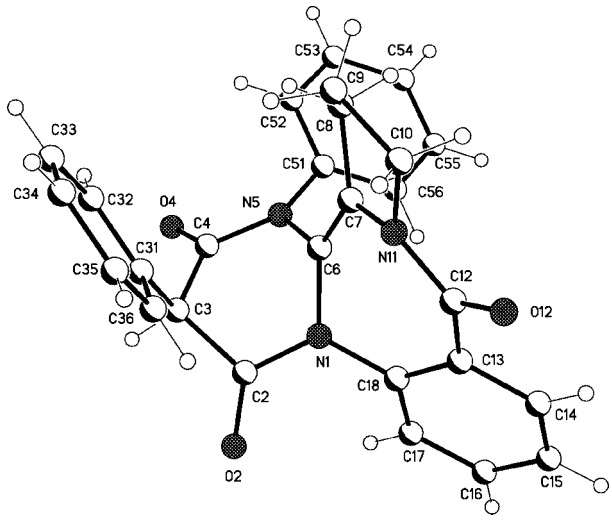


Figure 3. Results of an X-ray analysis of **14**. The drawing shows the helicity of the benzopyrrolodiazepine moiety of **14**.

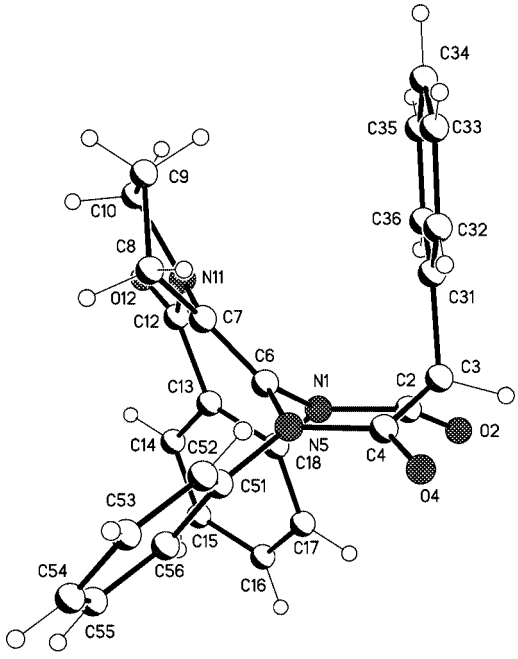
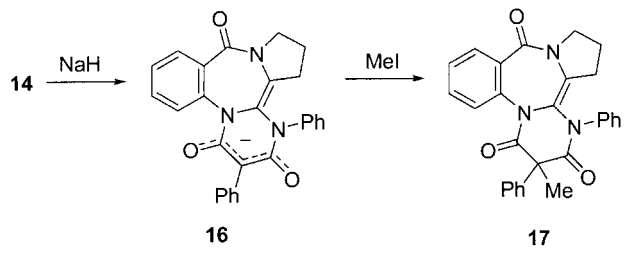


Figure 4. X-ray analysis of **14**. In the single crystal, the dioxopyrimidine fragment of **14** adopts a boat-like conformation with the phenyl ring at C3 in axial position.

into an equatorial position, which must be accompanied by a considerable change of the NMR signals. In order to confirm these assumptions, we deprotonated **14** with NaH in dimethoxyethane and indeed obtained the anionic molecule **16**, which is a stable yellow solid (Scheme 8). The anion displays a single set of signals in the ^{1}H NMR spectra, regardless of the solvent used. In electrospray ionization mass spectrometry in methanol in the negative ion detection mode, the molecular peaks appear at *m*/*z* = 434.0 u as base peak. Methylation of the salt **16** with methyl iodide gave **17** in good yield.



Scheme 8. Deprotonation and methylation.

In summary, we present the first representatives of a new ring system, 4,5,6,7-tetrahydro-4,7a,12b-triaza-dibenzo[*e,g*] azulene and its precursors, which are related to biologically interesting natural products and display a priori unexpected spectroscopic features.

Experimental Section

General Remarks: The ^{1}H and ^{13}C NMR spectra were recorded on Bruker ARX 400 and DPX 200 spectrometers and were taken in [D$_6$]DMSO and $CDCl_3$ at 200 and 400 MHz. The chemical shifts are reported in ppm relative to internal tetramethylsilane (δ = 0.00 ppm). Multiplicities are described by the following abbreviations: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad. FT-IR spectra were obtained on a Bruker Vektor 22 instrument in the 400 to 4000 cm^{-1} range (2.5% pellets in KBr). The GC-MS spectra (EI) were recorded variously on a GC Hewlett Packard 5980, Serie II/MS Hewlett Packard 5989 B, or on a Varian GC3900 with SAT2100T. The ESI mass spectra were measured with an Agilent LCMSD Series HP1100 with APIES. Samples were sprayed from methanol at 0 V fragmentor voltage unless otherwise noted. All reactions were monitored by analytical thin layer chromatography on precoated plates (silica gel 60 F^{254}) and spots were detected either by UV absorption or by treatment with iodine. All commercially available chemicals were purchased from Fluka, Aldrich, and Lancaster Chemical Co. and were used as received without further purification.

1,2,5,10,11,11a-Hexahydro-11a-methyl-3*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (5): Isatoic anhydride (1.84 g, 11.3 mmol) and (*S*)-α-methylproline (1.47 g, 11.3 mmol) were dissolved in DMF (10 mL) and were then heated under reflux for 3 h. After cooling, the solvent was removed under reduced pressure to yield an oily residue. Purification by flash column chromatography on silica gel (petroleum ether/ethyl acetate, 5:1) afforded **5** as a colorless solid (2.0 g, 8.7 mmol, 77%). m.p. 203–204 °C. $[a]_D^{20}$ = +385.9 (*c* = 1.0 in $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.23 (s, 3 H, CH_3), 1.74–1.96 (m, 3 H, 1-H, 2-H), 3.06–3.22 (m, 1 H, 1-H), 3.64–3.78 (m, 1 H, 3-H), 3.92–4.02 (m, 1 H, 3-H), 6.99 (dd, $J_{8,9}$ = 8.02, $J_{7,9}$ = 0.95 Hz, 1 H, 9-H), 7.20–7.28 (m, 1 H, 8-H), 7.43–7.51 (m, 1 H, 7-H), 8.02 (dd, $J_{6,7}$ = 7.89, $J_{6,8}$ = 1.58 Hz, 1 H, 6-H), 8.66 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.7 (C-2), 22.1 (CH_3), 38.7 (C-1), 49.8 (C-3), 66.28 (C-11a), 119.7/124.6/126.0/131.4/132.6/135.3 (Ph), 165.1 (CO), 173.3 (CO) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3227 (N–H), 3069, 2997, 1677 (C=O), 1630 (C=O), 1483, 1435, 1404, 1361, 1256, 1180 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 230 (99) [M]$^+$, 187 (100), 119 (16), 84 (54), 63 (17). $C_{13}H_{14}N_2O_2$ (230.26): calcd. C 67.81, H 6.13, N 12.17; found C 67.49, H 6.07, N 12.06.

1,2,5,10,11,11a-Hexahydro-11a-methyl-11-thioxo-3*H*-pyrrolo[2,1-*c*]-[1,4]benzodiazepin-5-one (7): A mixture of dilactam **5** (2.30 g,

10.0 mmol) and Lawesson's reagent (2.02 g, 5.0 mmol) in THF (40 mL) was stirred overnight at room temperature. Evaporation of the solvent in vacuo gave a solid residue, which was purified by flash column chromatography on silica gel (dichloromethane/acetone, 100:1) to give monothiolactam **7** as a yellow solid (1.77 g, 7.20 mmol, 72%). m.p. 258–260 °C. $[\alpha]_D^{20}$ = +113.1 (*c* = 0.2 in $CHCl_3$). ^1H NMR (200 MHz, [D$_6$]DMSO): δ = 1.14 (s, 3 H, CH_3), 1.71–1.86 (m, 2 H, 2-H), 1.90–2.09 (m, 1 H, 1-H), 3.40–3.61 (m, 2 H, 1-H, 3-H), 3.71–3.81 (m, 1 H, 3-H), 7.29–7.37 (m, 2 H, 8-H, 9-H), 7.53–7.62 (m, 1 H, 7-H), 7.83 (dd, $J_{6,7}$ = 8.08, $J_{6,8}$ = 1.64 Hz, 1 H, 6-H), 12.47 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, [D$_6$]-DMSO): δ = 20.6 (C-2), 22.2 (CH_3), 42.4 (C-1), 49.4 (C-3), 66.3 (C-11a), 120.7/125.4/126.4/130.4/132.4/136.6 (Ph), 163.6 (CO), 205.0 (CS) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3178 (N–H), 2968, 1605 (C=O), 1582, 1519, 1479, 1419, 1352, 1270, 1146, 1108, 1076 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 247 (24) $[M + 1]^+$, 162 (8), 84 (100). $C_{13}H_{14}N_2OS$ (246.33): calcd. C 63.39, H 5.73, N 11.37; found C 63.16, H 5.62, N 11.29.

1,2,3,11a-Tetrahydro-11-(methylamino)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (8): A solution of monomethylamine in THF (2 *m*, 20 mL, 40 mmol) was added at room temperature to a suspension of monothiolactam **6** (2.32 g, 10 mmol) and $HgCl_2$ (3.26 g, 12 mmol) in THF (100 mL) and the mixture was stirred for 30 min at the same temperature. The mixture was then heated at reflux for 15 min. After cooling, the mixture was filtered off through a plug of Celite and dried over $MgSO_4$. Evaporation of the solvent in vacuo gave a white, solid residue, which was recrystallized from acetonitrile to afford **8** as colorless crystals (1.90 g, 8.30 mmol, 83%). m.p. 204–206 °C. $[\alpha]_D^{20}$ = +1190.4 (*c* = 1.0 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.99–2.14 (m, 2 H, 2-H), 2.18–2.27 (m, 2 H, 1-H), 3.00 (s, 3 H, CH_3), 3.56–3.63 (m, 1 H, 3-H), 3.85–3.91 (m, 1 H, 3-H), 4.03 (dd, $J_{1,11a}$ = 7.72, $J_{1,11a}$ = 1.95 Hz, 1 H, 11a-H), 5.18 (br. s, 1 H, NH), 7.08–7.12 (m, 1 H, 8-H), 7.14 (d, $J_{8,9}$ = 8.06 Hz, 1 H, 9-H), 7.40 (ddd, $J_{6,7}$ = 8.03, $J_{7,8}$ = 7.12, $J_{7,9}$ = 1.68 Hz, 1 H, 7-H), 7.96 (dd, $J_{6,7}$ = 8.03, $J_{6,8}$ = 1.34 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2 (C-2), 27.1 (C-1), 29.0 (CH_3), 46.9 (C-3), 54.8 (C-11a), 122.6 (Ph), 126.9 (C-11), 127.3/130.4/132.1/147.9/157.6 (Ph), 167.1 (CO) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3304 (N–H), 3061, 2887, 1620 (C=O), 1603 (C=N), 1536, 1453, 1406, 1226, 1149 cm^{-1}. MS (EI, 70 ev): *m*/*z* (%) = 230 (100) $[M + 1]^+$. $C_{13}H_{15}N_3O$ (229.28): calcd. C 68.10, H 6.59, N 18.33; found C 68.22, H 6.67, N 18.45.

Preparation of the 11-Substituted Pyrrolobenzo[1,4]diazepin-5-ones 9–11. General Procedure: $HgCl_2$ (1.75 g, 6.5 mmol) was added at 80–90 °C to a stirred suspension of the monothiolactams **6** or **7** (1.16 g and 1.23 g, 5.0 mmol) and the corresponding amine (5.0 mL), and the mixture was stirred for a further 30 min at this temperature. After the system had cooled to room temperature, chloroform (100 mL) was added and the mixture was filtered through a plug of Celite. The filtrate was then dried over $MgSO_4$ and filtered, and the solvent and excess amine were evaporated under reduced pressure. The resulting solid was purified by recrystallization in an appropriate solvent to afford pure colorless crystals in very good yields.

1,2,3,11a-Tetrahydro-11-(phenylamino)-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (9): Starting materials **6** and aniline afforded a crude product, which was purified by crystallization from propan-2-ol to yield **9** as colorless crystals (1.32 g, 4.54 mmol, 91%). m.p. 150–152 °C. $[\alpha]_D^{20}$ = 0 (*c* = 1.0 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.05–2.24 (m, 3 H, 1-H, 2-H), 3.03–3.05 (m, 1 H, 1-H), 3.67–3.74 (m, 1 H, 3-H), 3.86–3.92 (m, 1 H, 3-H), 4.32 (d, $J_{1,11a}$ = 7.0 Hz, 1 H, 11a-H), 6.63 (s, 1 H, NH), 6.66 (d, $J_{8,9}$ = 8.0 Hz, 1 H, 9-H), 6.91 (d, *J* = 7.5 Hz, 2 H, Ph), 7.10–7.17 (m, 2 H, Ph), 7.32–7.41 (m, 3 H, Ph), 7.95 (dd, $J_{6,7}$ = 7.9, $J_{6,8}$ = 1.5 Hz, 1 H, 6-H) ppm. ^1H NMR (400 MHz, [D$_6$]DMSO) of **9A**: δ = 1.90–2.22 (m, 3 H, 1-H, 2-H), 2.80–2.84 (m, 1 H, 1-H), 3.50–3.57 (m, 1 H, 3-H), 3.63–3.72 (m, 1 H, 3-H), 4.31 (d, $J_{1,11a}$ = 5.6 Hz, 1 H, 11a-H), 6.75 (d, *J* = 7.3 Hz, 2 H, Ph), 7.01–7.13 (m, 3 H, Ph), 7.29–7.34 (m, 2 H, Ph), 7.36–7.40 (m, 1 H, 7-H), 7.73 (dd, $J_{6,7}$ = 8.0, $J_{6,8}$ = 1.5 Hz, 1 H, 6-H), 7.84 (d, *J* = 7.6 Hz, 2 H, Ph), 8.36 (s, 1 H, NH) ppm. ^1H NMR (400 MHz, [D$_6$]DMSO) of **9B**: δ = 1.90–2.22 (m, 3 H, 1-H, 2-H), 2.80–2.84 (m, 1 H, 1-H), 3.33–3.44 (m, 1 H, 3-H), 3.63–3.72 (m, 1 H, 3-H), 4.07 (d, $J_{1,11a}$ = 7.2 Hz, 1 H, 11a-H), 7.01–7.13 (m, 3 H, Ph), 7.29–7.34 (m, 2 H, Ph), 7.40–7.41 (m, 1 H, 7-H), 7.78 (dd, $J_{6,7}$ = 7.9, $J_{6,8}$ = 1.7 Hz, 1 H, 6-H), 7.84 (d, *J* = 7.6 Hz, 2 H, Ph), 8.42 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.8 (C-2), 27.2 (C-1), 47.8 (C-3), 57.1 (C-11a), 120.7/121.6/124.2/124.3 (Ph), 126.9 (C-11), 130.4/131.6/132.6/137.1/148.1/154.0 (Ph), 166.4 (CO) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO) of **9A**: δ = 23.8 (C-2), 27.4 (C-1), 47.6 (C-3), 57.3 (C-11a), 122.1/122.7/123.5/123.7 (Ph), 127.4 (C-11), 130.2/130.9/132.5/138.7/149.2/153.7 (Ph), 165.8 (CO) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO) of **9B**: δ = 24.50 (C-2), 26.8 (C-1), 47.1 (C-3), 55.9 (C-11a), 122.3/122.9/123.4/124.1 (Ph), 127.3 (C-11), 129.1, 130.4, 132.1, 140.5, 147.6, 155.8 (Ph), 166.0 (CO) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3273 (N–H), 3246, 2945, 2876, 1649 (C=O), 1624, 1593, 1475, 1416, 1377, 1264, 1223 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 291 (100) $[M]^+$, 251 (6), 221 (37), 187 (14), 160 (18), 119 (28), 92 (25), 77 (40), 51 (28). $C_{18}H_{17}N_3$ (275.35): calcd. C 74.20, H 5.88, N 14.42; found C 74.16, H 5.94, N 14.29.

1,2,3,11a-Tetrahydro-11a-methyl-11-(phenylamino)-5*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepin-5-one (10): Starting materials **7** and aniline gave **10** as colorless crystals (1.31 g, 4.30 mmol, 86%). m.p. 182–184 °C) after crystallization from nitromethane. $[\alpha]_D^{20}$ = +530.5 (*c* = 1.0 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 3 H, CH_3), 1.89–2.01 (m, 3 H, 1-H, 2-H), 3.40–3.46 (m, 1 H, 1-H), 3.74–3.81 (m, 1 H, 3-H), 4.00–4.06 (m, 1 H, 3-H), 6.57 (d, *J* = 7.9 Hz, 1 H, Ph), 6.60 (br. s, 1 H, NH), 6.89 (d, *J* = 7.5 Hz, 2 H, Ph), 7.09–7.14 (m, 2 H, 8-H, 9-H), 7.30–7.34 (m, 1 H, 7-H), 7.48–7.42 (m, 2 H, Ph), 7.96 (dd, $J_{6,7}$ = 7.83, $J_{6,8}$ = 1.59 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9 (C-2), 24.4 (CH_3), 39.8 (C-1), 50.4 (C-3), 63.7 (C-11a), 119.3/121.5/123.8/124.2 (Ph), 125.7 (C-11), 130.5/131.9/132.7/137.4/148.2/156.3 (Ph), 166.0 (CO) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3376 (N–H), 3218, 3055, 2968, 1651 (C=O), 1616 (C=N), 1597, 1536, 1437, 1354, 1222, 759, 699 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 306 (100) $[M + 1]^+$. $C_{19}H_{19}N_3O$ (305.38): calcd. C 74.73, H 6.27, N 13.76; found C 74.35, H 6.19, N 13.71.

1,2,3,11a-Tetrahydro-11-(piperidin-1-yl)pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (11): Starting materials **6** and piperidine afforded a crude product, which was purified by crystallization from diethyl ether to give **11** as colorless crystals (1.26 g, 4.45 mmol, 89%). m.p. 105–107 °C. $[\alpha]_D^{20}$ = 0 (*c* = 1.0 in $CHCl_3$). ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 1.64 (s, 6 H, 3×CH_2), 1.80–1.89 (m, 1 H, 2-H), 1.98–2.07 (m, 1 H, 2-H), 2.22–2.43 (m, 2 H, 1-H), 3.03–3.08 (m, 2 H, CH_2), 3.26–3.35 (m, 3 H, CH_2, 3-H), 3.83–3.89 (m, 1 H, 3-H), 3.95 (dd, $J_{1,11a}$ = 7.70, $J_{1,11a}$ = 6.24 Hz, 1 H, 11a-H), 7.05 (dd, $J_{8,9}$ = 8.07, $J_{7,9}$ = 1.25 Hz, 1 H, 9-H), 7.10–7.14 (m, 1 H, 8-H), 7.45 (ddd, $J_{6,7}$ = 8.00, $J_{7,8}$ = 7.19, $J_{7,9}$ = 1.25 Hz, 1 H, 7-H), 7.76 (dd, $J_{6,7}$ = 8.00, $J_{6,8}$ = 1.47 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 24.4 (C-2), 24.8 (CH_2), 26.1 (C-1), 29.2 (2×CH_2), 47.2 (C-3), 50.6 (2×CH_2), 56.7 (C-11a), 123.6 (Ph), 126.2 (C-11), 127.0/130.2/132.1/147.2/164.5 (Ph), 166.1 (CO) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3141, 2935, 2857, 2833, 1629 (C=O), 1605, 1593, 1452, 1405, 1375, 1240 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 283 (100) $[M]^+$. $C_{17}H_{21}N_3O$ (283.37): calcd. C 72.06, H 7.47, N 14.83; found C 72.05, H 7.51, N 14.89.

1,2,3,10,11,11a-Hexahydro-10-methyl-11-(phenylimino)-5*H*-pyrrolo-[2,1-*c*][1,4]benzodiazepin-5-one (12): Cycloamidine **9** (146 mg, 0.5 mmol) was added portionwise at room temperature under nitrogen to a suspension of NaH (60% in mineral oil, 20 mg, 0.5 mmol, previously washed with *n*-hexane (2×10 mL)) in anhydrous dimethoxyethane (20 mL). A reaction occurred, whereupon the color changed to yellow. CH_3I (0.5 mL) was added to the resulting solution and the mixture was then stirred for a further 30 min at room temperature. Evaporation of the solvent and excess CH_3I yielded the *N*-methylated cycloamidine **12** as a colorless solid (0.15 g, 0.49 mmol, 98%). m.p. 65–68 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88–1.96 (m, 2 H, 2-H), 2.10–2.20 (m, 1 H, 1-H), 2.77–2.83 (m, 1 H, 1-H), 2.93 (s, 3 H, CH_3), 3.60–3.67 (m, 1 H, 3-H), 3.80–3.85 (m, 1 H, 3-H), 4.28 (d, $J_{1,11a}$ = 6.72 Hz, 1 H, 11a-H), 6.82 (d, J = 7.58 Hz, 2 H, Ph), 6.95 (t, J = 7.27 Hz, 1 H, 8-H), 7.13 (d, $J_{8,9}$ = 8.19 Hz, 1 H, 9-H), 7.23–7.27 (m, 4 H, Ph), 7.48 (t, J = 7.82 Hz, 1 H, 7-H), 7.86 (d, $J_{6,7}$ = 7.82 Hz, 1 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0 (C-2), 28.3 (C-1), 42.4 (CH_3), 46.9 (C-3), 60.2 (C-11a), 120.8/122.0/123.5/125.7/129.0/130.0 (Ph) 131.5 (C-11), 132.4/144.4/149.9/153.3 (Ph), 166.5 (CO) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3347, 2968, 2875, 1637 (C=O), 1591, 1457, 1412, 1359 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 306 (100) $[M + 1]^+$. $C_{19}H_{19}N_3O$ (305.38): calcd. C 74.73, H 6.27, N 13.76; found C 74.43, H 6.21, N 13.56.

Preparation of the 3*H*-2,4-Dioxopyrimidines 13, 14. General Procedure: A mixture of the cycloamidines **8** or **9** (1.145 g and 1.455 g, respectively, 5.0 mmol) and bis(2,4,6-trichlorophenyl) phenylmalonate (5.0 mmol) was heated at 170–180 °C for 10 min in a Zincke apparatus under high vacuum. The residue was treated with diethyl ether (20 mL) to give a precipitate, which was collected by filtration and washed with diethyl ether. The crude solids were purified by crystallization in an appropriate solvent.

4,5,6,7-Tetrahydro-4-methyl-2-phenyl-4,7a,12b-triazadibenzo[*e*,*g*]azulene-1,3,8-trione (13): Starting materials cycloamidine **8** and bis(2,4,6-trichlorophenyl) phenylmalonate (2.695 g, 5.0 mmol) yielded a crude product, which was purified by crystallization from propan-2-ol to give **13** as pale yellow crystals (1.417 g, 3.80 mmol, 76%). m.p. 225–227 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94–1.07 (m, 1 H, 6-H), 1.67–1.85 (m, 1 H, 6-H), 2.04–2.10 (m, 1 H, 5-H), 2.35–2.44 (m, 1 H, 5-H), 3.20 (s, 3 H, NCH_3), 3.54–3.60 (m, 1 H, 7-H), 3.69–3.75 (m, 1 H, 7-H), 4.82 (s, 1 H, 2-H), 7.27–7.33 (m, 5 H, Ph), 7.38–7.45 (m, 2 H, 11-H, 12-H), 7.62 (ddd, $J_{9,10}$ = 8.04, $J_{10,11}$ = 7.27, $J_{9,12}$ = 1.65 Hz, 1 H, 10-H), 8.03 (dd, $J_{9,10}$ = 8.04, $J_{9,11}$ = 1.34, 1 H, 9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3 (C-6), 29.3 (C-5), 35.6 (CH_3), 49.3 (C-7), 61.5 (C-2), 120.6 (C-4b), 126.0/126.4/128.1/128.5 (Ph), 129.0 (C-4a), 129.3/131.0/132.2/132.7/133.8/140.1 (Ph), 165.3 (CO), 166.7 (CO), 168.4 (CO). IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3082, 2972, 1724 (C=O), 1697 (C=O), 1682 (C=O), 1632, 1493, 1452, 1380, 1354, 1258, 1155 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 373 (100) $[M]^+$, 344 (27), 305 (7), 256 (8), 187 (22), 118 (18), 89 (17), 63 (12). $C_{22}H_{19}N_3O_3$ (373.41): calcd. C 70.76, H 5.1, N 11.25; found C 70.51, H 5.22, N 10.96.

4,5,6,7-Tetrahydro-2,4-diphenyl-4,7a,12b-triazadibenzo[*e*,*g*]azulene-1,3,8-trione (14): The starting materials cycloamidine **9** and bis(2,4,6-trichlorophenyl) phenylmalonate (2.695 g, 5.0 mmol) gave **14** as pale yellow crystals after recrystallization from butan-2-ol (1.78 g, 4.09 mmol, 82%). m.p. 207–208 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90–0.98 (m, 1 H, 6-H), 1.56–1.65 (m, 2 H, 5-H, 6-H), 1.73–1.80 (m, 1 H, 5-H), 3.41–3.47 (m, 1 H, 7-H), 3.67–3.74 (m, 1 H, 7-H), 4.94 (s, 1 H, 2-H), 7.13–7.20 (m, 3 H, Ph), 7.28–7.43 (m, 7 H, Ph), 7.47–7.51 (m, 1 H, 11-H), 7.53 (dd, $J_{11,12}$ = 8.07, $J_{10,12}$ = 1.22 Hz, 1 H, 12-H), 7.70 (ddd, $J_{9,10}$ = 7.98, $J_{10,11}$ = 7.34, $J_{10,12}$ = 1.22 Hz, 1 H, 10-H), 8.08 (dd, $J_{9,10}$ = 7.98, $J_{9,11}$ = 1.53 Hz, 1 H, 9-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8 (C-6), 29.2 (C-5), 49.5 (C-7), 62.3 (C-2), 119.3 (C-4b), 124.2/126.2/126.3/126.9/128.3/128.6 (Ph), 129.3 (C-4a), 129.5/129.7/132.1/132.9/133.1/134.1/138.9/139.5 (Ph), 165.2 (CO), 166.6 (CO), 166.7(CO) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3057, 2967, 1732 (CO), 1709 (CO), 1694 (CO), 1632, 1597, 1495, 1454, 1256 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 435 (100) $[M]^+$, 407 (6), 317 (10), 260 (6), 172 (7), 90 (14). $C_{27}H_{21}N_3O_3$ (435.48): calcd. C 74.47, H 4.86, N 9.65; found C 74.38, H 4.84, N 9.42.

Sodium 4,5,6,7-Tetrahydro-3,8-dioxo-2,4-diphenyl-3*H*,8*H*-4,7a,12b-triazadibenzo[*e*,*g*]azulen-1-olate (16): NaH (60% in mineral oil, 20 mg, 0.5 mmol, previously washed with *n*-hexane (2×10 mL)) was added to a solution of dioxopyrimidine **14** (0.435 g, 1.0 mmol) in anhydrous dimethoxyethane (20 mL), and the mixture was stirred at room temperature for a further 30 min. The solvent was then removed under reduced pressure to afford the product **16** as a yellow solid (0.444 g, 0.972 mmol, 97%). m.p. > 250 °C (dec). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.46–1.54 (m, 1 H, 6-H), 1.69–1.79 (m, 2 H, 5-H, 6-H), 2.10–2.16 (m, 1 H, 5-H), 3.57–3.63 (m, 1 H, 7-H), 3.67–3.77 (m, 1 H, 7-H), 6.76–6.80 (m, 1 H, Ph), 6.91–6.95 (m, 1 H, Ph), 7.03–7.07 (m, 2 H, Ph), 7.11–7.22 (m, 6 H, Ph), 7.47–7.51 (m, 1 H, 10-H), 7.75 (dd, $J_{9,10}$ = 7.85, $J_{9,11}$ = 1.54 Hz, 1 H, 9-H), 7.85–7.87 (m, 2 H, Ph) ppm. ^{13}C NMR (100 MHz [D$_6$]DMSO): δ = 20.6 (C-6), 28.3 (C-5), 48.8 (C-7), 87.9 (C-2), 121.6 (Ph), 122.4 (C-4b), 123.6/124.7/125.8/126.4 (Ph), 126.5 (C-4a), 126.8/128.7/130.2/130.5/131.7/132.9/141.7/143.9/147.2 (Ph), 164.7 (CO), 166.4 (2CO) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3057, 2934, 1634 (C=O), 1575, 1550, 1488, 1404, 1068 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 435 (4) $[M]^+$, 390 (12), 185 (100), 119 (9), 93 (34), 66 (13). $C_{27}H_{20}N_3NaO_3$ (457.47): calcd. C 70.89, H 4.41, N 9.19; found C 70.53, H 4.68, N 9.36.

4,5,6,7-Tetrahydro-2-methyl-2,4-diphenyl-4,7a,12b-triazadibenzo[*e*,*g*]-azulene-1,3,8-trione (17): A suspension of pyrimidine-olate **16** (0.457 g, 1.0 mmol) in anhydrous dimethoxyethane (20 mL) was treated with CH_3I (1.0 mL) at room temperature and the mixture was then heated at 60 °C for 3 h. Evaporation of the solvent and excess CH_3I under reduced pressure gave a residue, which was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether, 2:1) to afford the dioxopyrimidine **17** as a colorless solid (0.40 g, 0.89 mmol, 89%). m.p. 112–114 °C. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.58–0.66 (m, 1 H, 6-H), 0.79–0.89 (m, 1 H, 6-H), 1.49–1.62 (m, 2 H, 5-H), 1.56 (s, 3 H, CH_3), 3.06–3.12 (m, 1 H, 7-H), 3.48–3.55 (m, 1 H, 7-H), 7.16–7.22 (m, 3 H, Ph), 7.26–7.29 (m, 2 H, Ph), 7.35–7.44 (m, 5 H, Ph), 7.52 (ddd, $J_{11,12}$ = 7.98, $J_{10,11}$ = 7.09, $J_{9,11}$ = 1.32 Hz, 1 H, 11-H), 7.70 (dd, $J_{11,12}$ = 7.98, $J_{10,12}$ = 1.07 Hz, 1 H, 12-H), 7.73–7.77 (m, 1 H, 10-H), 7.89 (dd, $J_{9,10}$ = 7.92, $J_{9,11}$ = 1.32 Hz, 1 H, 9-H) ppm. ^{13}C NMR (100 MHz [D$_6$]DMSO): δ = 19.6 (C-6), 23.4 (CH_3), 28.9 (C-5), 49.6 (C-7), 61.5 (C-2), 118.8 (C-4b), 125.1/125.2/127.0/127.4/128.5/128.6 (Ph), 129.6 (C-4a), 129.9/130.0/132.4/132.8/134.3/139.6/140.0/140.7 (Ph), 164.8 (CO), 168.9 (CO), 169.0 (CO) ppm. IR (KBr, cm^{-1}): $\tilde{\nu}$ = 3069, 2989, 1720 (C=O), 1685 (C=O), 1640 (C=O), 1598, 1490, 1454, 1356, 1259 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 450 (100) $[M + 1]^+$, 289 (6), 261 (8), 172 (16), 132 (20), 104 (15), 77 (14). $C_{28}H_{23}N_3O_3$ (449.51): calcd. C 74.82, H 5.16, N 9.35; found C 74.58, H 5.18, N 9.08.

Supporting Information: VT ^{1}H NMR spectra, and HSQC and HMBC NMR correlations of **9**, and ^{1}H NMR and ^{13}C NMR spectra in $CDCl_3$ and [D$_6$]DMSO as well as the HMBC spectra of **14** are presented in the Supporting Information.

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