3 H), 1.60 (q, 2 H), 2.07 (s, 3 H), 2.18 (s, 3 H), 2.2–3.0 (m, 10 H), 10.42 (s, 1 H). Anal. Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 73.04; H, 8.98; N, 11.40.

The isomerization of 8 to 1 was previously described.¹

Registry No. (\pm) -1, 78541-97-6; 2, 63-75-2; 2·HCl, 61-94-9; 2·HBr, 300-08-3; 3, 75690-06-1; 3·HCl, 75690-07-2; 4, 6456-92-4; 5, 55806-53-6; (\pm) -6, 93222-91-4; (\pm) -8, 93222-95-8; (\pm) -9, 93222-94-7; 11, 78685-86-6; (\pm) -12, 93222-92-5; (\pm) -13, 93222-93-6; 2-oximido-3-pentanone, 32818-79-4; 3-(2-methyl-1,3-dioxolan-2yl)pyridine, 55676-25-0; 1-methyl-3-(2-methyl-1,3-dioxolan-2yl)pyridinium iodide, 88599-19-3; diethyl malonate, 105-53-3; methyl acetylacetate, 105-45-3; 3-acetylpyridine, 350-03-8; 3aminopentane, 616-24-0.

Supplementary Material Available: A computer-generated drawing of 9 and tables of crystal data, final atomic parameters, final anisotropic thermal parameters, bond lengths, and bond angles for 9 (5 pages). Ordering information is given on any current masthead page.

Bicyclic Imides with Bridgehead Nitrogen. Synthesis and X-ray Crystal Structure of a Bicyclic 2,4-Oxazolidinedione¹

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The first successful synthesis of bicyclic 2,4-oxazolidinediones with bridgehead nitrogen, examples of anti-Bredt imides, was accomplished. The synthetic approaches involved three homologous bridging sizes, and the smallest product capable of preparation was 1-aza-8,9-dioxo-7-oxa-6-phenylbicyclo[4.2.1]nonane, for which the structure was verified by X-ray diffraction. Also prepared was 1-aza-9,10-dioxo-8-oxa-7-phenylbicyclo[5.2.1]decane. These results were accurately predicted by using anti-Bredt olefins as models, suggesting that resonance effects may be essential for the stability of anti-Bredt imides.

Bicyclic imides with bridghead nitrogen, of the type shown in structures 1-3, were first proposed² by Edward E. Smissman as potential stereoselective anticonvulsants.



Despite numerous attempts by him to prepare examples of these compounds with n = 1, the only reported³ success was for a methoxy-substituted bicyclic barbiturate related to 3. However, we recently demonstrated via ¹H and ¹³C NMR studies⁴ that the structure assignment for this bicyclic barbiturate was incorrect.

The difficulty encountered in preparing imides 1–3 with n = 1 is not surprising since these compounds are examples of anti-Bredt bridgehead nitrogen amides.⁵ Such compounds are destabilized when n is small, possibly because delocalization of the lone pair of electrons on nitrogen into the π orbitals of the carbonyls is minimal. As shown by Hall,^{5–7} such destabilization in related compounds is characterized by a tendency to undergo ring-opening polymerization, which may preclude isolation of monomer.

Here we report the preparation (n = 2 and 3) and X-ray crystal structure (n = 2) of bicyclic 2,4-oxazolidinedione 1, which represents the first successful synthesis of anti-Bredt bicyclic imides of the type proposed by Smissman.

Results and Discussion

If resonance is required for the stability of bicyclic imides 1-3, anti-Bredt olefins might serve as models for predicting their lower size limits. One finds that the



smallest anti-Bredt olefins capable of isolation at present are compounds $4-6.^{8-10}$ If similar restraints apply, model



⁽¹⁾ Dedicated to the memory of Professor Edward E. Smissman. In recognition of his accomplishments in this area, we routinely refer to anti-Bredt bicyclic imides related to 1-3 as "smissmanones".

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	method	isolated	Selected Data	elemental	ic intermediates and Froducts	
compd	of prep	yield, %	mp, °C	anal.	¹³ C NMR, (CDCl ₃), δ	cm^{-1}
$1 \ (n=2)^b$	see Exptl Section	44	$\begin{array}{c} 99-100 \\ (Et_2O-hexane) \end{array}$	C, H, N	21.2, 24.4, 41.6, 45.1, 89.6, 125.5, 128.6, 129.1, 132.6, 160.1, 178.8	1810 1750
$1 (n = 3)^b$	see Exptl Section	90	46–47 (hexane)	C, H, N	22.2, 24.5, 32.6, 42.6, 45.9, 87.5, 125.2, 128.6, 128.9, 133.9, 156.2, 178.4	1810 1740
8 (n = 2)	с	85	160-162 (benzene) (lit. ^c 162-163.5)		28.2, 28.4, 42.5, 45.9, 69.6, 168.6	1660
8 (n = 3)	с	77	147-148 (CHCl ₃ -hex- ane) (lit. ^g 147-148)		21.6, 26.8, 31.1, 43.1, 52.7, 68.8, 169.8	1660
8 (n = 4)	С	92	156-158 (CHCl ₃ -hex- ane) (lit. ^g 156-157)		23.3, 24.3, 27.8, 28.4, 41.7, 50.6, 66.9, 166.1	1660
9 ^b	see Exptl Section	60	94-96 (Et ₂ O-hexane)	C, H, N	26.5, 28.0, 29.1, 30.4, 45.1, 110.9, 135.5, 168.6	1655 (1635, C = C)
10 $(n = 2)$	d	75	158-160 (EtOAc) (lit. ^d 156-158)		21.3, 24.2, 25.2, 30.0, 39.1, 50.0, 105.0, 147.3, 171.5	1650 (1600, C _ C)
10 $(n = 3)^b$	d	75	144-145 (Et ₂ O)	C, H, N	24.2, 24.7, 25.3, 25.4, 29.8, 42.0, 49.4, 106.7, 143.3, 170.6	1665 (1630, C _ C)
11 $(n = 2)$	see Exptl Section	92	71-72 (Et ₂ O-hexane) (lit. ^e 71-73)		22.8, 27.4, 39.4, 40.5, 169.7, 203.5	1720 1665
11 $(n = 3)^b$	see Exptl Section	86	69-70 (Et ₂ O-hexane)	C, H, N	22.3, 24.9, 30.7, 40.2, 43.1, 171.7, 205.0	1705 1660
12 $(n = 2)$	f	50	$141-142 (Et_2O) (lit.f 139-140)$		25.1, 28.6, 35.4, 42.3, 78.1, 126.3, 128.1, 129.0, 139.6, 178.7	1655
12 $(n = 3)^b$	f	60	127-128 (Et ₂ O-hexane)	C, H, N	22.5 (2 carbons), 29.7, 39.9, 40.8, 77.2, 125.6, 127.8, 128.7, 142.1, 178.9	1650
13 ^b	see Exptl Section	98	72-74 (Et ₂ O-hexane)	C, H, N	14.1, 24.2, 27.4, 35.4, 45.3, 63.9, 80.1, 125.9, 128.3, 129.1, 140.1, 154.5, 177.3	1730 (sh) 1715
14 ^b	see Exptl Section	59	176–177 (CHCl ₃ -hex- ane)	C, H, N	19.3, 35.1, 48.0, 77.4, 122.3, 125.3, 125.6, 128.5, 128.9, 142.6, 145.7, 151.9, 155.1, 175.9	1735 1720

Table I. Selected Data^a for Synthetic Intermediates and Products

^a See Experimental Section for details. ^b New compound. ^cReference 15. ^dReference 14. ^eReference 13. ^fReference 16. ^gReference 21.

6 predicts that the smallest stable bridging size for bicyclic 2,4-oxazolidinedione 1 should be that with n = 2. This prediction appears, in part, to be supported by our earlier failure to prepare imide 1 with n = 1.¹¹

It was therefore desirable to develop a general synthetic approach to 1 that would allow, in theory, the preparation of several homologous bridging sizes. The procedure used is shown in Scheme I and takes advantage of the commercial availability of lactam 7 (n = 2-4). In this procedure it was envisioned that the 3-hydroxylactam 12 could be cyclized to the bicyclic 2,4-oxazolidinedione 1 in a manner analogous to that reported¹² for the formation of

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monocyclic 2,4-oxazolidinediones from acyclic 3-hydroxyamides.

A preparation for the key intermediate 12 (n = 2 only)from the dichlorolactam analogous to 8 has been previously reported.^{13,14} We repeated this general approach for n =2-4 but, as shown in Scheme I, employed several modifications. Lactam 7 was more conveniently converted to the dibromolactam 8 according to a published method (reported for n = 2 only,¹⁵ although the analogues with n= 3 and n = 4 have been subsequently reported).²¹ The reaction of lactam 8 with piperidine resulted in the formation of enamine 10 for n = 2 and 3; however, when n= 4 the major product was the bromoalkene 9. Also, instead of the reported¹³ method using aqueous acid (n =2 only), the hydrolysis of enamine 10 was more conveniently accomplished on a silica gel column to provide pure oxolactam 11 (n = 2, 3) in high yield. As previously reported¹⁶ for n = 2, the reaction of 11 (n = 2, 3) with PhMgBr resulted in regioselective addition at the ketone carbonyl to provide hydroxylactam 12 (n = 2, 3).

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Figure 1. Molecular structure of 1-aza-8,9-dioxo-7-oxa-6phenylbicyclo[4.2.1]nonane (1, n = 2). Atoms are represented by ellipsoids defined by the principal axes of thermal vibration and scaled to the 33% probability level.

Scheme I also gives the methods employed for the cyclization of 12 to 1. As was previously observed with 12 (n = 1),¹¹ the reaction of 12 (n = 2) with ethyl chloroformate provided only the N-acylated product 13. However, the reaction of 12 (n = 3) with ethyl chloroformate gave a 45% yield of the bicyclic 2,4-oxazolidinedione 1 (n = 3).

A more reactive cyclization reagent, *p*-nitrophenyl chloroformate, was then employed in a series of reactions with 12. Where n = 1, the major product was the N-acylated derivative 14. For n = 2 and 3 the desired bicyclic 2,4-oxazolidinediones 1 were formed in yields of 44% and 90%, respectively.

As shown in Table I and given in the Experimental Section, the structural assignments for compounds 1 (n = 2 and 3) are completely consistent with spectral data, which includes IR, ¹H and ¹³C NMR, and mass spectra, as well as elemental analyses. Also given in Table I are selected data for the synthetic intermediates found in Scheme I.

In order to unambiguously establish the structural assignments for these unique bicyclic imides, a single-crystal X-ray diffraction study of 1 (n = 2) was undertaken. The resulting structure is shown in Figure 1.

In an effort to determine if resonance effects are diminished in 1 (n = 2) as compared to monocyclic 2,4-oxazolidinediones, the observed N–C and carbonyl C–O bond distances of 1 (n = 2) were compared to those reported¹⁷ for the crystal structure of 3,5,5-trimethyl-2,4-oxazolidinedione. It is of interest that the N3–C2 and C2–O10 bond distances are identical within 1 e.s.d. of corresponding distances in the model, while the N3–C4 bond distance for 1 (n = 2) is longer by 0.038 (3) Å and that for C4–O11 is shorter by 0.014 (2) Å. This is consistent with a slight decrease in resonance effects between nitrogen and the C4 carbonyl while such effects with the C2 carbonyl appear to be undiminished.

In summary, the first examples of anti-Bredt bicyclic imides, 2,4-oxazolidinediones 1 (n = 2 and 3), have been synthesized and their structures unambiguously established. The smallest accessible bridging size by the methods employed was found to be n = 2, as predicted by the smallest accessible anti-Bredt olefin 6. These results suggest that resonance effects may be essential for the stability of anti-Bredt bridgehead nitrogen imides.

Experimental Section

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. IR spectra were recorded on a Beckmann Acculab 6 spectrophotometer. ¹H NMR spectra were obtained on a Varian Associates EM 360 spectrometer with 1% Me₄Si as internal standard, and ¹H-decoupled ¹³C NMR spectra were obtained at 25 °C on a Nicolet 300 (NT series) spectrometer operating at 75.5 MHz and equipped with a Nicolet 1280 computer and 293C pulse programmer. For ¹³C NMR spectra, chemical shifts from Me₄Si were referenced internally to CDCl₃ (77.0 ppm). Mass spectra were obtained on a Hewlett-Packard 5885 GC/MS. Elemental analyses, when indicated only by the symbol for the element tested, were within $\pm 0.3\%$ of the calculated values and were performed at Atlantic Microlab of Atlanta, GA. R_f values were determined by using Analtech precoated silica gel plates (silica gel GF, 5 × 10 cm, 0.25 mm layer). (Much of the above data appears in Table I).

1-Aza-8,9-dioxo-7-oxa-6-phenylbicyclo[4.2.1]nonane (1, n = 2). A solution of 0.10 g (0.49 mmol) of 12 (n = 2) and 0.22 g (1.1 mmol) of p-nitrophenyl chloroformate in 20 mL of toluene was heated at reflux for 8 h. The reaction mixture was concentrated to dryness and the residue chromatographed on a preparative silica gel plate ($20 \times 20 \times 0.2$ cm, 20% Et₂O-CHCl₃ eluent). Two overlapping bands at R_f 0.49 and R_f 0.59 were combined and washed from the silica with EtOAc and the washings concentrated to give a yellow oil. The oil was taken up in Et₂O-hexane and cooled to provide 0.050 g (44%) of 1 (n = 2) as a white solid: mp 99–100 °C (Et₂O-hexane); ¹H NMR (CDCl₃) δ 1.4–2.2 (m, 4 H, CH₂CH₂), 2.2–2.5 (m, 2 H, PhCCH₂), 3.4–4.0 (m, 2 H, CH₂N), 7.3–7.7 (m, 5 H, aromatic); MS (70 eV), m/e 231 (M⁺).

1-Aza-9,10-dioxo-8-oxa-7-phenylbicyclo[5.2.1]decane (1, *n* = 3). A solution of 0.20 g (0.91 mmol) of 12 (n = 3) and 0.40 g (2.0 mmol) of p-nitrophenyl chloroformate in 25 mL of toluene was heated at gentle reflux for 24 h. The solution was concentrated to dryness and the residue chromatographed on two preparative silica gel plates ($20 \times 20 \times 0.2$ cm, 20% Et₂O-CHCl₃ eluent). The band at $R_f 0.75$ was extracted with EtOAc and the solvent removed to yield 0.40 g of yellow oil. This was triturated with 50% Et₂O-hexane, cooled, and filtered to provide 0.20 g of a white solid, mp 127-130 °C, which appeared by NMR and IR to be p-nitrophenyl carbonate. The filtrate was concentrated to provide 0.20 g (90%) of 1 (n = 3) as a pale yellow oil. The oil was crystallized from hexane to give a white solid: mp 46-47 °C; ¹H NMR (CDCl₃) δ 1.1–2.6 (m, 8 H, PhCCH₂CH₂CH₂CH₂), 3.6–4.3 (m, 2 H, CH₂N), 7.1-7.7 (m, 5 H, aromatic); MS (70 eV), m/e 245 (M^{+})

3-Bromo-5,6,7,8,9,10-hexahydro-2H-azonin-2-one (9). A solution of 2.5 g (0.0084 mol) of 8 (n = 4) in 15 mL of piperidine was heated at reflux for 4.5 h. After being cooled 10 mL of 5% NaHCO₃ was added and the mixture extracted with 3×25 mL of CHCl₃. The combined extracts were dried (MgSO₄) and concentrated to give 1.9 g of an oily residue. This was placed on a silica gel column (2×30 cm) and eluted with EtOAc. The fractions containing material with R_f 0.69 were combined and concentrated to give 1.1 g (60%) of an oil which crystallized on standing: mp 94–96 °C (Et₂O-hexane); ¹H NMR (CDCl₃) δ 1.7 (m, 6 H, CH₂CH₂CH₂), 2.3 (m, 2 H, allylic CH₂), 3.3 (m, 2 H, NCH₂), 6.2 (t, 1 H, vinyl CH), 7.4 (b s, 1 H, NH); MS (70 eV), m/e 219 (M⁺).

Tetrahydro-1*H*-azepine-2,3-dione (11, n = 2) and Tetrahydro-1*H*,4*H*-azocine-2,3-dione (11, n = 3). A solution of 10 (0.050 mol) in CHCl₃ was placed on a silica gel column (4 × 75 cm) and eluted with EtOAc. Those fractions containing material with R_f 0.33 (11, n = 2) or R_f 0.51 (11, n = 3) were combined and concentrated to provide 0.046 mol (92%) of 11 (n = 2), mp 71–72 °C (Et₂O-hexane, lit.¹⁴ mp 71–73 °C), or 0.043 mol (86%) of 11 (n = 3), mp 69–70 °C (Et₂O-hexane). For 11 (n = 2): ¹H NMR (CDCl₃) δ 2.0 (m, 4 H, CH₂CH₂), 2.7 (m, 2 H, CH₂CO), 3.4 (m, 2 H, NCH₂), 7.7 (b s, 1 H, NH); MS (70 eV), m/e 127 (M⁺). For 11 (n = 3): ¹H NMR (CDCl₃) δ 1.7 (m, 6 H, CH₂CH₂CH₂), 2.6 (m, 2 H, CH₂CO), 3.2 (m, 2 H, NCH₂), 7.0 (b s, 1 H, NH); MS (70 eV), m/e 141 (M⁺).

1-(Ethoxycarbonyl)-3-hydroxy-3-phenylhexahydro-2Hazepin-2-one (13). A solution of 0.50 g (0.0024 mol) of 12 (n = 2) and 0.52 g (0.0048 mol) of ethyl chloroformate in 50 mL of toluene was heated at reflux for 3 h. Since TLC indicated remaining starting material, an additional 0.26 g (0.0024 mol) of ethyl chloroformate was added and heating continued for 33 h. At this time TLC (20% Et₂O/CHCl₃ eluent) showed only one spot, R_f 0.58. The reaction mixture was concentrated to provide 0.65 g (98%) of 13 as a pale yellow oil, which was crystallized from

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50% Et₂O-hexane to give a white solid: mp 72-74 °C; ¹H NMR (CDCl₃) δ 1.4 (t, 3 H, CH₂CH₃), 1.8 (m, 4 H, CH₂CH₂), 2.0-3.3 (m, 4 H, NCH₂ and PhCCH₂), 4.3 (q, 2 H, CH₂CH₃), 4.7 (b s, 1 H, OH), 7.3 (s, 5 H, aromatic).

3-Hydroxy-1-[[(4-nitrophenyl)oxy]carbonyl]-3-phenyl-2**piperidinone** (14). A solution of 1.0 g (0.0052 mol) of 12 (n = $1)^{11}$ and 1.1 g (0.0055 mol) p-nitrophenyl chloroformate in 100 mL of toluene was heated at reflux for 18 h. The solvent was removed, the residue triturated with Et_2O , and the mixture filtered to provide 1.1 g (61%) of 14 as a white solid: mp 176-177 °C (CHCl₃-hexane); ¹H NMR (CDCl₃) δ 1.5-2.8 (m, 4 H, CH₂CH₂), 3.7-4.0 (m, 3 H, CH₂N and OH), 7.2-8.4 (m, 9 H, aromatic); MS (70 eV), m/e 356 (M⁺).

Crystallography of 1-Aza-8,9-dioxo-7-oxa-6-phenyl**bicyclo**[4.2.1]**nonane** (1, n = 2). A crystal of 1 (n = 2) suitable for X-ray diffraction analysis was selected from a sample that had been crystallized by evaporation from an ether-hexane mixture. A $0.08 \times 0.12 \times 0.58$ mm specimen was used for all X-ray measurements. Crystals of 1 (n = 2) are colorless and acicular. The cell constants a = 25.383 (3) Å, b = 6.523 (1) Å, c = 18.945(2) Å, and $\beta = 133.63$ (1)° ($d_{calcd} = 1.35 \text{ g cm}^{-3}$ for Z = 8) were determined by a least-squares fit to the 2θ values of 15 reflections that had been manually centered on the diffractometer. Systematic absences permit either of two space groups, Cc or C2/c; the choice of the centrosymmetric C2/c is confirmed by successful structure solution and refinement.

Intensity data were collected on a Picker FACS-1 diffractometer (Cu K α radiation, Ni filtered) in the θ -2 θ scan mode. Three reference reflections, sampled periodically throughout data collection, varied by no more than 3% from average structure factor values. Intensities were assigned variances according to counting statistics plus an additional term, $(0.02S)^2$, where S is the scan count. Intensities and variances were corrected for Lorentz, polarization, and absorption effects.

Calculations were carried out with the SDP system of programs.¹⁸ Scattering factors and anomalous dispersion corrections were from ref 19. The structure was solved with the aid of the

direct-methods program MULTAN 78.²⁰ All H atoms were located in a difference Fourier map calculated after four cycles of least-squares refinement of the C, N, and O positional and anisotropic temperature parameters. The parameter list in the final cycles of least-squares refinement was augmented by inclusion of an extinction parameter and positional and isotropic thermal parameters for the H atoms. Weights were based on variances of observed intensities. Convergence was achieved in an additional seven cycles; no parameter shift in the final cycle was greater than 0.03 times the corresponding standard deviation. A final difference Fourier map showed no feature greater than $0.1 \text{ e}/\text{Å}^3$. For 1823 reflections, GOF = 2.643 and R = 0.050. The molecule is illustrated in Figure 1. Tables of data collection parameters, positional parameters, bond distances and angles, anisotropic thermal parameters, and structural factors are available as supplementary material.

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Registry No. 1 (n = 2), 93350-08-4; 1 (n = 3), 93350-09-5; 7 (n = 2), 105-60-2; 7 (n = 3), 673-66-5; 7 (n = 4), 935-30-8; 8 (n = 4)= 2), 56987-35-0; 8 (n = 3), 32566-59-9; 8 (n = 4), 32566-63-5; 9, 93350-10-8; 10 (n = 2), 23996-62-5; 10 (n = 3), 93350-11-9; 11 (n= 2), 37840-08-7; 11 (n = 3), 93350-12-0; 12 (n = 1), 65379-06-8; 12 (n = 2), 51129-01-2; 12 (n = 3), 93350-13-1; 13, 93350-14-2; 14 $(Ar = 4 - NO_2C_6H_4), 93350 - 15 - 3; ClC(O)O - p - C_6H_4NO_2, 7693 - 46 - 1;$ p-NO₂C₆H₄OC(O)O-p-C₆H₄NO₂, 5070-13-3; ClC(O)OEt, 541-41-3; PhBr, 108-86-1.

Supplementary Material Available: X-ray analytical data (Tables II-VI) for 1 (n = 2) (22 pages). Ordering information is given on any current masthead page.

Med. Chem. 1971, 14, 501.

Synthesis of Tetrahydrobenzo[b]phenazines as Anthracyclinone **N-Isosteres**

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The anthracycline p-quinone unit has been replaced by a 1,4-di-N-oxide function in the first synthesis of a 7.9-dideoxyanthracyclinone hetero isostere. 4.11-Dimethoxy-9-(methoxycarbonyl)-7.8,9,10-tetrahydrobenzo-[b]phenazine was synthesized and converted to the 5,12-di-N-oxide, which is isosteric with the 6-deoxycarminomycinone or α -citromycinone types. The heterocyclic C ring of tetrahydrobenzo[b]phenazine was formed by coupling 3-methoxy-1,2-benzoquinone as the D-ring moiety with an o-diamine that provided the A,B-ring moiety. The o-diamine was synthesized from 2-carboxy-8-methoxy-1,2,3,4-tetrahydronaphthalene by blocking the 5-position temporarily with a bromo substituent, conducting ortho dinitration in one step at positions 6 and 7, and reducing the nitro groups simultaneously with hydrogenolysis of the Br. A byproduct of the condensation was the regioisomer 1,11-dimethoxy-9-(methoxycarbonyl)-7,8,9,10-tetrahydrobenzo[b]phenazine, which was oxidized to the 5-N-oxide.

Introduction

1,4-Di-N-oxide functions (1) in nitrogen heterocycles can provide useful isosteric replacement¹ of the p-quinone unit (2) that occurs²⁻⁵ in the structure of many antitumor agents. We now report synthesis of the substituted 7,8,9,10-tetrahydrobenzo[b]phenazine⁶ di-N-oxide 3 and

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