Pergamon

Tetrahedron Letters, Vol. 35, No. 48, pp. 8995-8998, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01995-9

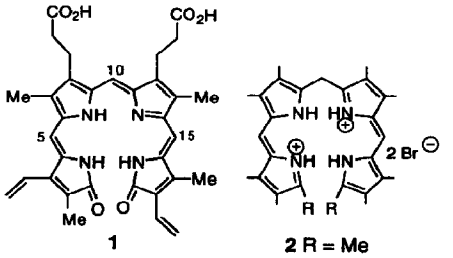
A NOVEL BILIVERDIN WITH AN INVERTED PYRROLE SUBUNIT

Ravindra K. Pandey,[a,b*] Sam H. Leung,[a] Timothy P. Forsyth[a] and Kevin M. Smith[a*]

[a]Department of Chemistry, University of California, Davis, CA 95616, USA, and
[b]Chemistry Division, PDT Center, Department of Radiation Biology
Roswell Park Cancer Institute, Buffalo, NY 14263, USA.

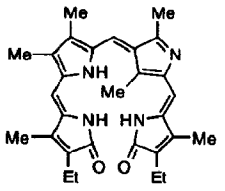
Abstract: The synthesis and spectroscopic properties of a novel biliverdin **4** with one inverted pyrrole ring are described; the dipyrromethane **8** and a,c-biladiene **6** were the key intermediates in the synthesis of **4**.

Biliverdin IXα **1** and related bile pigments, such as bilirubins, phycobilins and phytochromobilin, are widely distributed in animals or plants.[1,2] A number of synthetic approaches to bile pigments have been reported.[2-9] a,c-Biladiene dihydrobromides (e.g. **2**) are commonly used as intermediates in the synthesis of unsymmetrically substituted porphyrins,[10,11] and we recently showed that unsymmetrical 1,19-dibromo-a,c-biladienes (e.g. **3**) can be converted in >70% yield into the corresponding biliverdins upon reaction with dimethyl sulfoxide (DMSO) in the presence of a catalytic amount of p-toluene sulfonic acid[12] or bromine/trifluoroacetic acid.[13,14] Structural isomers of porphyrins are currently attracting great attention,[15] on account of their novel spectroscopic and physical properties. A new class of porphyrin system with an inverted pyrrole ring was recently described,[16,17] and named "N-confused porphyrin".[17] These compounds were obtained serendipitously from routine porphyrin synthetic approaches. Herein we report the results of rationally designed syntheses of a biliverdin **4** possessing an inverted central pyrrole subunit[18] and an attempt to prepare the doubly inverted analogue **5**, using synthetic methodology via intermediate 1,19-dibromo-a,c-biladienes.[12]

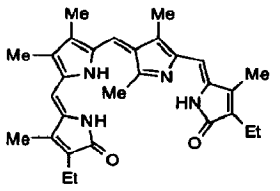


1

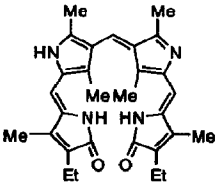
2 R = Me
3 R = Br



4A



4B



5

The key intermediates in our synthetic strategy for the synthesis of mono-inverted and bis-inverted biliverdins **4** and **5**, respectively, were the a,c-biladienes **6** and **7**; we planned to obtain these compounds from dipyrromethanes **8** and **9**. Dipyrromethane **8** was obtained by reacting benzyl 4-hydroxymethyl-3,5-dimethylpyrrole-2-carboxylate **10**, (obtained by $NaBH_4$ reduction of the corresponding formyl analogue **11**)[19] with the α-free pyrrole **12**[20] in >90% yield using Montmorillonite clay as a catalyst.[21] Self-condensation of hydroxymethylpyrrole **10** gave the 3,3'-linked dipyrromethane **9** in almost quantitative yield. Hydrogenolysis of dipyrromethanes **8** and **9** gave dipyromethane dicarboxylic acids **13** and **14**, respectively. Condensation of dipyrromethane **13** with 2-bromo-5-formylpyrrole **15** in the presence of p-toluene sulfonic acid/HBr gas afforded the monopyrrole-inverted 1,19-dibromo-a,c,-biladiene **6** in 80% yield. Bromoformylpyrrole **15** was prepared from pyrrole **16** by following the literature procedure.[12]

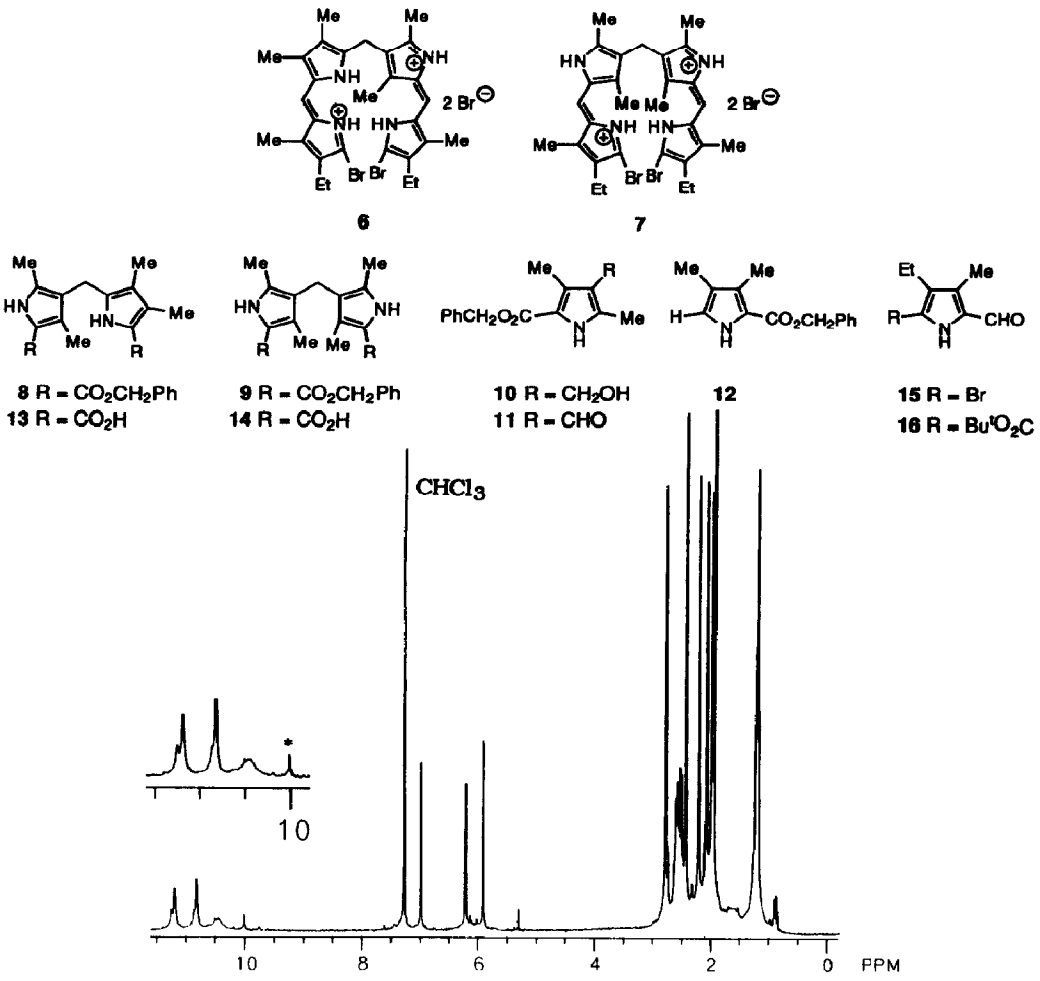


Figure 1: Proton NMR Spectrum, in $CDCl_3$, of Mono-inverted Biliverdin **4**; (* = impurity)

The doubly inverted 1,19-dibromo-a,c-biladiene **7** was prepared in almost the same yield by reacting the 3,3'-linked dipyrromethane dicarboxylic acid **14** with two equiv. of the 2-bromo-5-formylpyrrole **15** under similar reaction conditions. The a,c-biladiene **6** upon reaction with DMSO/p-toluene sulfonic acid gave the monopyrrole-inverted biliverdin **4** in 25% yield (Found: 470.2700; Calcd for $C_{29}H_{34}N_4O_2$: 470.2682). Interestingly, under similar reaction conditions, reaction of 1,19-dibromo-a,c-biladienes with no inverted pyrrole rings produced normal biliverdins in more than 70% yield.[12] Figure 1 shows the ^1H NMR spectrum of the mono-inverted biliverdin **4**; multiplicity of peaks, particularly in the NH region (inset), suggests the presence of two double-bond isomers, **4A** and **4B**. The chemical shifts of the NH protons are temperature dependent, but do not pass through coalescence. The ^1H NMR data for the monopyrrole inverted dipyrromethanes **8**, **9**,[22] a,c-biladienes **6**, **7**[23] and for biliverdin **4** were similar to those of the related "normal" biliverdin analogues and intermediates. The electronic absorption spectrum of **4** (Figure 2), was also similar to the typical biliverdin type, except the main short wavelength band was red shifted to 394 nm. The longer wavelength transition (a broad band at 526 nm) was also shifted 112 nm to shorter wavelength compared with normal biliverdins (at 638 nm), these changes presumably reflecting the distortion in the linear planarity of the pyrrole subunits.

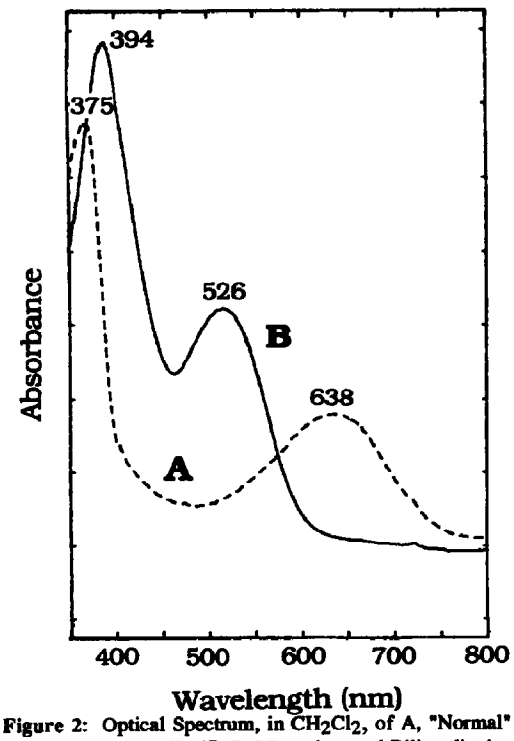


Figure 2: Optical Spectrum, in CH_2Cl_2, of A, "Normal" Biliverdin 17; B, Mono-inverted Biliverdin 4

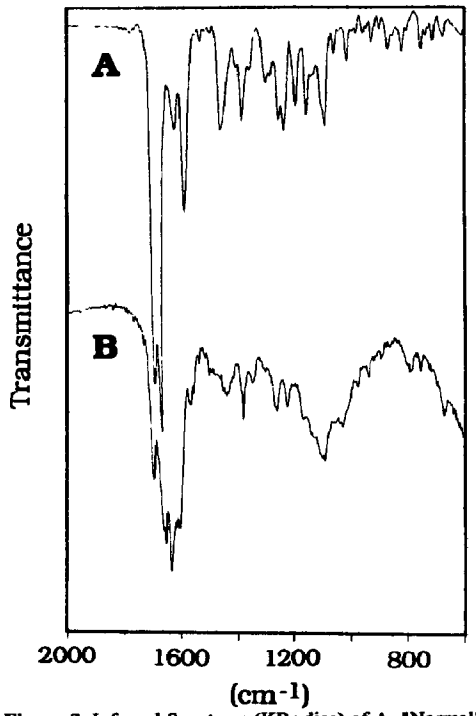
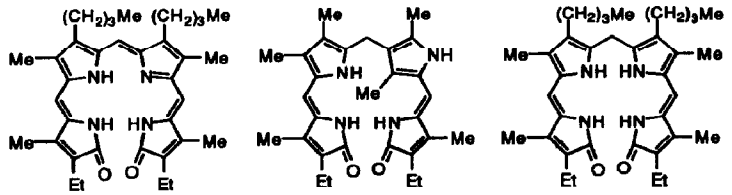


Figure 3: Infrared Spectrum (KBr disc) of A, "Normal" Biliverdin 17; B, Mono-inverted Biliverdin 4



As shown in Figure 3B, the infrared spectrum of the monopyrrole-inverted biliverdin **4** is similar to that of a normal biliverdins (e.g. **17**, Figure 3A). For **4** the lactam carbonyl absorptions appear between 1600-1700 cm^{-1}. It is reported[24] that verdins occasionally show only a single lactam C=O peak, but usually have two peaks separated by up to 26 cm^{-1} (e.g. Figure 3A: 1700, 1677 cm^{-1}). Reduction of the biliverdin **4** with sodium borohydride afforded the corresponding monopyrrole inverted bilirubin **18** which possessed an optical spectrum [λ_{max} (CH_2Cl_2) 408 nm] very similar to that of the bilirubin **19** [λ_{max} (CH_2Cl_2) 381 nm] obtained by reduction of the "normal" octaalkylbiliverdin, **17**.

So far, attempts to convert the a,c-biladiene **7** into bis-inverted biliverdin type **5** have failed; this molecule would possess a cross-conjugated chromophore, and only decomposition products have been observed so far. Other synthetic methodologies are currently being explored to prepare such double-inverted systems.

Acknowledgements: This work was supported by grants from the National Institutes of Health (HL 22252) and Oncologic Foundation of Buffalo. Mass spectrometric analyses were performed by the UCSF Mass Spectrometry Facility

(A. L. Burlingame, Director) supported by the Biomedical Research Technology Program of the National Center for Research Resources, NIH NCRR BRTP 01614.

References and Notes:

1. McDonagh, A. F. In *Jaundice*, C. A. Goresky and M. M. Fisher, eds.; Plenum: New York; **1974**, p. 1.
2. O'Carra, P. In *Porphyrins and Metalloporphyrins*, K. M. Smith, ed.; Elsevier: Amsterdam; **1975**, p. 123.
3. Fischer, H.; Orth, H. *Die Chemie des Pyrrols*, vol II, part 1; Akademische Verlag: Leipzig; **1937**, pp. 619-733.
4. McDonagh, A. F. In *The Porphyrins*, vol VI, Dolphin, D. ed.; Academic Press: New York; **1979**.
5. Gossauer, A. In *Bio-organic Heterocycles*, Plas, H. C.; Simonyi, M. eds.; Elsevier: Amsterdam; **1983**, p. 191.
6. Falk, H. *The Chemistry of Linear Oligopyrroles and Bile Pigments*, Springer Verlag: Vienna; **1989**.
7. Smith, K. M. *J. Chem. Soc., Perkin Trans. 1*, **1972**, 1471; Hudson, M. F.; Smith, K. M. *Chem. Soc. Rev.*, **1975**, *4*, 363..
8. Bonnett, R.; Buckley, D. G.; Hamzetash, D. *J. Chem. Soc., Perkin Trans. 1*, **1981**, 322.
9. Nogales, D. F.; Anstine, D. T.; Lightner, D. A. *Tetrahedron*, **1994**, *50*, 8579; Hwang, K. O.; Lightner, D. A. *Heterocycles*, **1994**, *37*, 807; Trull, F. R.; Rodriguez, M.; Lightner, D A. *Synth. Commun.*, **1993**, *23*, 2771.
10. de Almeida, J. A. P. B.; Kenner, G. W.; Rimmer, J.; Smith, K. M. *Tetrahedron*, **1976**, *32*, 1793. Smith, K. M.; Craig, G. W. *J. Org. Chem.*, **1983**, *48*, 4302.
11. Clezy, P. S. *Aust. J. Chem.*, **1991**, *44*, 1163.
12. Pandey, R. K.; Gerzevske, K. R.; Zhou, H.; Smith, K. M. *J. Chem. Soc., Perkin Trans. 1*, **1994**, 971.
13. Smith, K. M.; Kishore, D. *Tetrahedron*, **1983**, *39*, 1841.
14. Smith, K. M.; Pandey, R. K. *Tetrahedron*, **1984**, *40*, 1754.
15. E.g. Vogel, E.; Balci, M.; Pramod, K.; Koch, P.; Lex, J.; Ermer, O. *Angew. Chem.*, **1987**, *99*, 909.
16. Chmielewski, P. J.; Latos-Grazynski, L.; Rachlewicz, K.; Glowiak, T. *Angew. Chem. Int. Edn. Engl.*, **1994**, *33*, 779.
17. Furuta, H.; Asano, T.; Ogawa,T. *J. Am. Chem. Soc.*, **1994**, *116*, 767.
18. Rational syntheses of pyrrole-inverted porphyrins will be reported elsewhere.
19. Smith, K. M.; Bisset, G. M. F.*J. Org. Chem.*, **1979**, *44*, 2077.
20. Smith, K. M.; Kehres, L. A. *J. Chem. Soc., Perkin Trans. 1*, **1983**, *10*, 2329.
21. Jackson, A. H.; Pandey, R. K.; Roberts, E.; Rao, K. R. N. *Tetrahedron Lett.*, **1985**, *26*, 793.
22. Dipyrromethane 8: NMR (δ ppm, $CDCl_3$): 8.63, 8.15 (each s, 1H, 2NH), 7.26-7.36 (m, 10H, 2Ph), 5.30 and 5.25 (each s, 2H, CH_2Ph), 3.63 (s, 2H, 5-CH_2), 2.57, 2.18, 2.12 and 1.97 (each s, 3H, 4Me).
Dipyrromethane 9: NMR (δ ppm, $CDCl_3$): 8.42 (s, 2H, 2NH), 7.36 (m, 10H, 2Ph), 5.27 (s, 4H, $2CH_2Ph$), 3.45 (s, 2H, 5-CH_2), 2.19, 2.03 (each s, 6H, 4Me).
23 a, c-Biladiene Dihydrobromide 6: NMR (δ ppm, $CDCl_3$): 13.83 (s, 1H, NH), 13.59 (s, 3H, 3NH), 7.10 and 7.06 (each s, 1H, CH), 4.37 (s, 2H, 5-CH_2), 2.74 (q, 4H, $2CH_2CH_3$), 2.62, 2.34, 2.48, 2.03, 2.02 and 1.72 (each s, 3H, Me), 1.20 (t, 6H, $2CH_2CH_3$).
a,c-Biladiene Dihydrobromide 7: NMR (δ ppm, $CDCl_3$): 13.66, 13.70 (each s, 2H, 4NH), 7.04 (s, 2H, 2CH), 3.59 (s, 2H, 5-CH_2), 2.69 (q, 4H, $2CH_2CH_3$), 2.61, 2.16, 2.04 (each s, 6H, 6Me), 1.19 (t, 6H, $2CH_2CH_3$).
24. Reference 4, page 401.

(*Received in USA* 31 *August* 1994; *revised* 4 *October* 1994; *accepted* 7 *October* 1994)