Construction of the dihydroisocoumarin derivative **2**, the western fragment of **1**, commenced with transformation of ethyl 6-methylsalicylate[7] to the methoxymethyl (MOM) methyl ester **3** (R = H) in the usual manner. Reaction of (*tert*-butyloxycarbonyl (Boc))-L-leucinal (**4**)[8] with the in situ generated benzylic anion **3** (R = Li), prepared by treatment with lithium diisopropylamide (LDA) in the presence of tetramethylethylenediamine in THF (−78 °C, 1 h), afforded a separable mixture of **5a** and **5b** in 32% yield (61% conversion yield). By use of an excess of LDA (2.6 equiv) and **4** (1.4 equiv), the desired **5a** was obtained as the major product with 81:19 diastereoselectivity.[9] The diastereoselection in this reaction can be explained in terms of Cram's chelation control as shown in Scheme I. The stereochemistry of **5a** was firmly established by its conversion to **2** (mp 206–207 °C, $[\alpha]^{22}_D$ −47.4° (*c* 0.11, MeOH)), which was completely identical with the sample (mp 210 °C, $[\alpha]^{22}_D$ −47.45° (*c* 0.11, MeOH)) derived from natural Al-77-B.[3]

Construction of the hydroxy amino acid moiety **13**, the eastern building block of **1**,[10] started from the *N,O*-benzylidene derivative **6** of D-pyroglutaminol, prepared from D-glutamic acid by the known procedure.[11] Treatment of **6** with LDA in THF followed by phenylselenyl bromide afforded the crude selenide, which was oxidized with ozone in methylene chloride to give the α,β-unsaturated lactam **7** (mp 85–86 °C, $[\alpha]^{26}_D$ −215.6° (*c* 1.05, $CHCl_3$)) in 75% yield. Catalytic osmylation of **7** in aqueous acetone in the presence of *N*-methylmorpholine *N*-oxide (NMO) stereoselectively proceeded on the less hindered convex side with 98.4:1.6 diastereoselectivity, giving after chromatographic purification the desired β-diol **8** (mp 164–166 °C, $[\alpha]^{25}_D$ −221° (*c* 1.14, MeOH)) in 65% yield. After protection of the diol group as the acetal, removal of the benzylidene function of the acetonide **9** was achieved under catalytic hydrogen-transfer conditions using palladium–carbon and hydrazine hydrate in MeOH,[12] providing the lactam alcohol **10** (mp 141–142 °C, $[\alpha]^{24}_D$ +46.7° (*c* 1.03, MeOH)) in 95% yield. Introduction of the C_1 unit to **10** was accomplished by our own method[13] using potassium cyanide, 18-crown-6, tributylphosphine, and carbon tetrachloride to give the nitrile **11** (mp 207–208 °C, $[\alpha]^{24}_D$ +42° (*c* 0.84, MeOH)) in 71% yield. Treatment of **11** with di-*tert*-butyl dicarbonate ($(Boc)_2O$) in the presence of 4-(dimethylamino)pyridine (DMAP) in acetonitrile afforded the *N*-Boc lactam **12**, which was easily ring opened by brief treatment with lithium hydroxide in aqueous THF to give the key Boc amino acid **13**.

Coupling of **13** with **2** was performed by use of diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$)[14] in the presence of triethylamine in DMF to produce the amide **14**, containing the full carbon skeleton of **1**, in 70% yield. Transformation of the nitrile function of **14** to a carboxyl group was achieved by use of the intramolecular Pinner reaction as follows. Treatment of **14** with 5% hydrogen chloride–MeOH in the presence of trimethyl orthoformate under strictly anhydrous conditions generated the imino lactone hydrochloride **15**, which was directly subjected to hydrolysis of the imino function with water. Selective ring opening[5] of the five-membered lactone function with 0.1 N NaOH at pH 9 was followed by neutralization to pH 6.5 with 0.1 N HCl.[3a,c] After purification on ion-exchange resin (Amberlite XAD-2), AI-77-B (**1**) was obtained in 76% yield from **14**. The synthetic sample ($[\alpha]^{22}_D$ −72.2° (*c* 0.07, MeOH)) was identical with the natural one ($[\alpha]^{22}_D$ −78.2° (*c* 0.08, MeOH) in every respect (TLC, NMR, FAB-MS).

Acknowledgment. This work was supported in part by the Ministry of Education, Science and Culture, Japan (a Grant-in-Aid, No. 62570948), the Japan Foundation for Optically Active Compounds, and the Terumo Life Science Foundation. We are grateful to Dr. Y. Shimojima of Asahi Chemical Industry for a generous gift of natural AI-77-B.

Supplementary Material Available: Spectra of **1**, **2**, **5a**, **5b**, and **7–14** (22 pages). Ordering information is given on any current masthead page.

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(9) In this reaction, replacement of the *N*-Boc group with benzylsulfonyl proceeded with complete diastereoselectivity. After removal of the MOM function with hydrogen chloride in methanol, the benzylsulfonyl derivative of 6 with the desired stereochemistry was obtained in 70% yield. However, deprotection of the *N*-benzylsulfonyl group was unsuccessful under various conditions.
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Total Synthesis of "Extended" Biliverdins: The Relation between Their Conformation and Their Spectroscopic Properties

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Received September 7, 1988

Biliverdins are open chain tetrapyrrole compounds widely distributed in nature and are either free or bound to proteins.[1] All the free biliverdins have the energetically favored helical-all-syn conformation (as in **1–3**, 5*Z*-syn, 10*Z*-syn, 15*Z*-syn; Scheme I). Their absorption spectra have a ratio $\epsilon(vis)/\epsilon(UV) = 0.25$,[2] in agreement with MO calculations[3] and similar to the UV–vis absorption ratio observed in a porphyrin spectrum. In the phycobiliproteins from algae (which are light harvesting complexes[4]) the biliverdin chromophore is held in an "extended" conformation by the protein matrix. A similar situation is present in phytochrome, a plant biliprotein which governs plant morphogenesis.[5] In all these biliproteins the $\epsilon(vis)/\epsilon(UV)$ ratio of the biliverdin chromophore spectrum is greatly enhanced (about 16-fold over the ratio found in the helical-shaped conformation) since the extended bilitriene is more similar to a polyene than to a cyclic tetrapyrrole. In solution extended forms of biliverdins could only be detected as short-lived species.[6] Helicoidal (*ZZZ*)-biliverdins could be photoisomerized to their extended *EZZ* or *EZE* conformers,[7] but the latter reconverted back to their helical forms. Free biliverdins are in stable extended conformations only in the neopterobilins,[8] a group of butterfly pigments where an intramolecular addition of vinyl side chains to the pyrrole nitrogens provide rigid structures. The synthesis of a biliverdin held in the extended form by a covalent bound stilbenoparacyclophane was recently described.[9]

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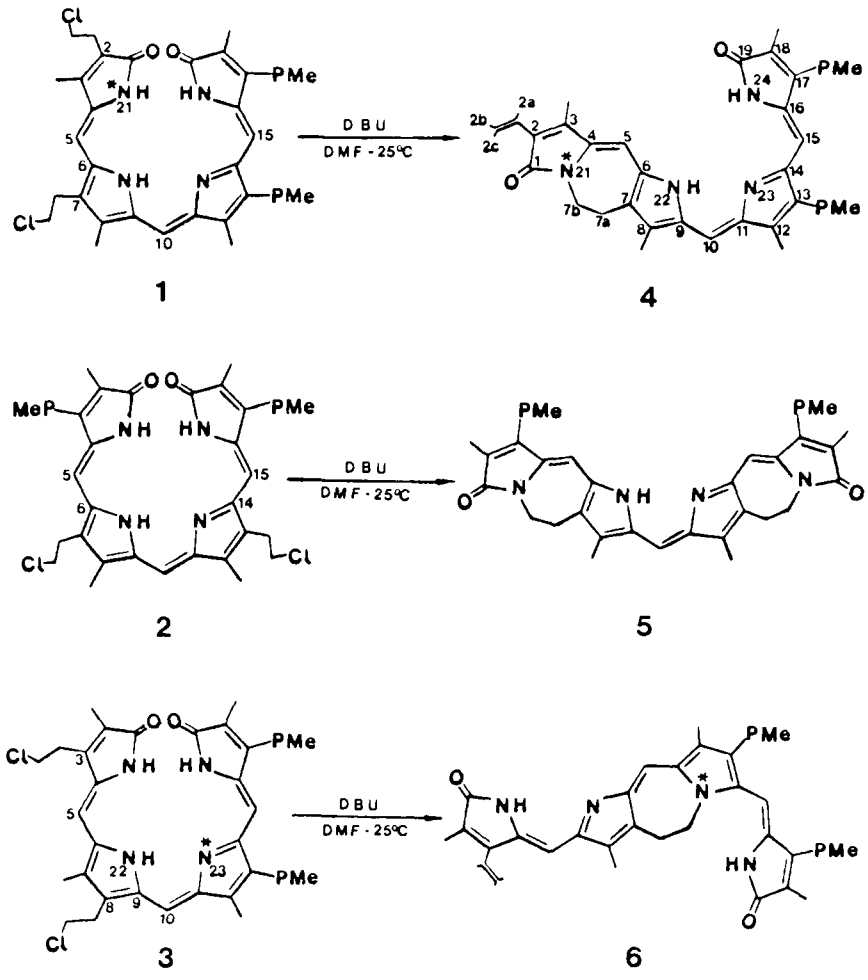
Scheme I



We report below a general synthetic approach for the synthesis of stable extended biliverdins of the neopterobilin type which has allowed correlation of their structure with their spectroscopic properties. Biliverdins **1**–**3** (Scheme I) were obtained following established procedures.[1b,10,11] Treatment of the turquoise-colored biliverdin **1** with DBU led to the obtention of a blue biliverdin of the neopterobilin type such as **4** in 70% yield. The ^{1}H NMR spectrum of **4**[12] showed the presence of only one vinyl residue and of two new methylene resonances at 2.85[13] and at 3.95 ppm. The downfield shift of the latter signal indicated that the methylene was bound to an electronegative atom. The ^{13}C NMR spectrum[12] of **4** had the new methylene signals at 25.13 and 39.95 ppm, where the latter could be attributed to an *N*-methylene residue. However, when the early assignments of the analogous methylene signals of the seven-membered rings of the neopterobilins were made,[8] the *N*-methylene resonances were assigned either to 2.65 ppm signals (in phorcabilins) or to a 2.60 ppm signal (in neobiliverdin IX-δ). To settle the issue, the synthesis of **1** enriched with ^{15}N at N-21 was carried out and was then converted to **4** (Scheme I). In the latter the resonance at 39.95 ppm was a doublet ($J_{^{13}C-^{15}N}$ = 9.8 Hz),[14] indicating that the downfield shift was due to an N-21 bound methylene. Therefore the 3.93 ppm signal in **4** is due to the 7b methylene and the 2.85 ppm signal to the 7a methylene.[15] The intramolecular alkylation at N-21 arises from the unhindered rotation of the pyrrolinone ring around the C5–C6 bond, where a 5*Z*-syn → 5*Z*-anti conformational change takes place. In the latter conformation the C7 side chain is in the vicinity of N-21. This is not the case with the C2 chain, which therefore undergoes an elimination reaction to the vinyl group.

When the greenish-blue biliverdin **2** was treated with DBU, it afforded the navy blue biliverdin **5** with two seven-membered rings (Scheme I). This is again due to the facile rotation in **2** at the C5–C6 and C14–C15 bonds, which allow the 5*Z*-syn → 5*Z*-anti and the 15*Z*-syn → 15*Z*-anti changes in conformation and therefore favor the intramolecular substitutions at N-21 and N-24. By treatment of **3** with DBU, the deep blue biliverdin **6** (neobiliverdin IX-δ[8]) was obtained. The 8b methylene signal was at 45.75 ppm in the ^{13}C NMR spectrum and at 3.90 ppm in the ^{1}H NMR spectrum. When **6** was obtained from **3** enriched with ^{15}N at N-23, the 45.75 ppm signal was a doublet (J = 9.8 Hz). Rotation at C9–C10 in **3** is sterically unhindered, and, therefore, in the 10*E*-anti conformation the alkylation of N-23 by the vicinal C8 side chain is possible. A 5*Z*-anti conformation will still keep the C3 side chain away from N-22 and thus favors the elimination to a vinyl residue.[16] Only a *E*-anti conformation at C5 could bring

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(12) ^{1}H NMR (500 MHz) **4** ($CDCl_3$ at 294 K, 10^{-2} M) δ 6.70 (H-10), 6.55 (H-2a), 6.34 (H-2b), 6.33 (H-5), 5.99 (H-15), 5.47 (H-2c), 3.93 (H-7b), 2.85 (H-7a), 2.27 (CH_3-3), 2.17, 2.16 (CH_3-8, CH_3-12), 1.96 (CH_3-18); **4** $CDCl_3$ at 294 K, 10^{-4} M) δ 7.06 (H-5), 6.98 (H-10), 6.10 (H-15), 4.99 (H-2a), 4.36 (H-2b), 3.99 (H-2c), 3.75 (H-7b), 2.88 (H-7a); ^{13}C NMR (20 MHz) **4** ($CDCl_3$ at 294 K, 10^{-2} M) δ 114.73, 98.96, 97.00 (C-10, C-5, C-15), 39.95 (C-7b), 34.41, 33.56 (C-13a, C-17a), 25.13 (C-7a).
(13) The 2.85 ppm signal is obscured by overlapping with the methylene resonances of the propionate side chains in the 2.53–2.92 ppm range and can only be located by the COSY and NOESY correlations at 500 MHz.
(14) A similar shift and coupling constant was observed for the ^{15}N-CH_2 resonance of an *N*-alkyl macrocyclic tetrapyrrole, see: Gossauer, A.; Neidhart, W.; Scott, A. I. *J. Chem. Soc., Chem. Commun.* **1983**, 883.
(15) The 3.90 ppm signals are present in the spectra of the natural pterobilins[8] but went unassigned.

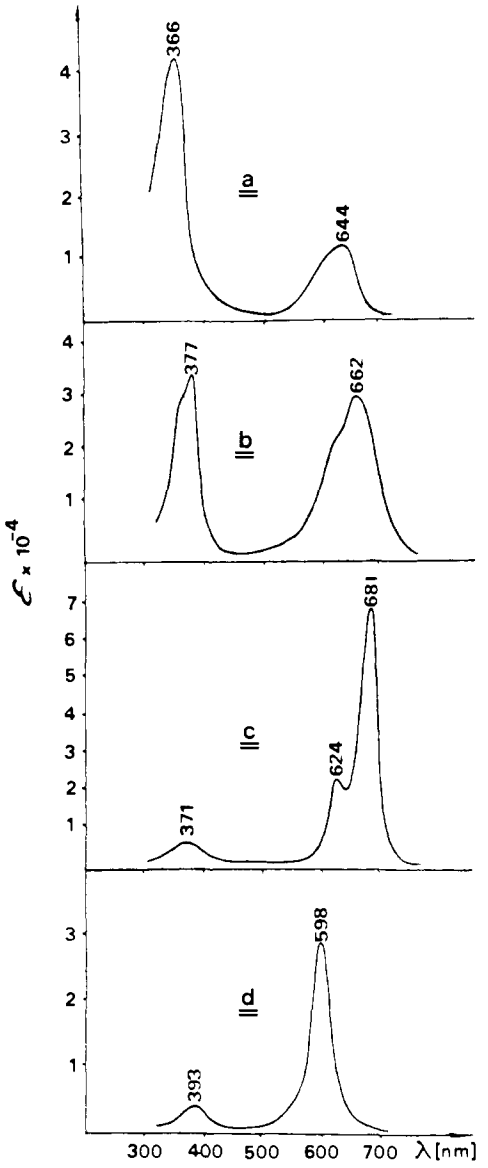

Figure 1. UV-vis spectra in CH_2Cl_2: (a) biliverdin **1**; (b) biliverdin **4**; (c) biliverdin **5**; (d) biliverdin **6**. The inflexions in the spectra of **4** and **5** are due to the presence of several conformers (see text).

the C3 side chain into the vicinity of N-22, but this requires a light-driven isomerization.

The ^1H NMR spectra of **4-6** revealed new features about extended biliverdins. The COSY and NOESY correlations (at 500 MHz) showed that the meso bridges which are not kept in the anti conformations by the rigid seven-membered rings retain their energetically favored *Z*-syn conformations (see Scheme I). While the ^1H NMR spectra of the helical-shaped biliverdins **1-3** are concentration independent, strong shifts were observed in the meso and vinyl signals of **4** when going from a concentrated (10^{-2} M) to a dilute solution (10^{-4} M).[12] This effect can be attributed to the presence in solution of associated (or stacked) forms, a fact which is well known in porphyrin chemistry.[17] A second feature of the ^1H NMR spectra of the extended biliverdins **4-6** is their temperature dependence, a property which is absent in the helical-shaped biliverdins **1-3**. In $CDCl_3$ at 21 °C, the ^1H NMR spectra of **4** showed broad signals, especially at the meso-H. At −80 °C a well-resolved ^1H NMR spectrum corresponding to a mixture of different conformers was obtained, where six meso-H and five methyl residues were detected.[18] The presence of different conformers in a rigidly held extended biliverdin was also recently reported.[9]

The UV-vis spectrum of **1** (Figure 1a) shows the expected strong UV absorption of a helical-shaped biliverdin (ϵ(vis)/ϵ(UV) = 0.27). The partially extended chromophore **4** (Figure 1b) shows the expected[3] increase in vis absorption (ϵ(vis)/ϵ(UV) = 0.90). In the more rigid biliverdin **5** (5*Z*-anti, 10*Z*-syn, 15*Z*-anti) the Soret band almost disappeared (ϵ(vis)/ϵ(UV) = 11.0, Figure 1c). In biliverdin **6** (5*Z*-syn, 10*E*-anti, 15*Z*-syn) only a very weak UV absorption remained (ϵ(vis)/ϵ(UV) = 8.0, Figure 1d). The "extention effect" is therefore more pronounced when a conformation change takes place at the C10 meso bridge than at the C5 or C15 bridges. When the (*ZZZ*)-ethiobiliverdin IV-γ (ϵ-(vis)/ϵ(UV) = 0.27) was photoisomerized to the diasteroisomeric forms *EZZ* and *EZE*,[7a] their ϵ(vis)/ϵ(UV) ratios were found to increase to approximately 0.43 and 0.33. These ratios are much lower than those obtained for **5** and **6** (see above). It is therefore evident that a conformational change at the meso bridges has a more pronounced effect on the vis spectra of the biliverdins than a configurational change, a fact which allows us to further probe into the optical properties of the biliproteins.

Acknowledgment. This work was made possible by a grant (GM-11973) from NIH (PHS). Support from CONICET (Argentina) is also gratefully acknowledged. J.B.I. is grateful to CONICET for a fellowship. We thank Professor Kevin M. Smith (Davis, California) for calling our attention to this problem.

(16) This also explains why base treatment of a 2,17-bis(2-chloroethyl)-biliverdin gave the expected biliverdin IX-α (ref 11) and not a neopterobilin analogue.

(17) Scheer, H.; Katz, J. J. In *Porphyrins and Metalloporphyrins*; Smith, K. M. Ed.; Elsevier: Amsterdam, 1975; p 399 and references therein. It is conceivable that, as is the case for hemoproteins, the binding of extended biliverdins to proteins is a mechanism used by nature to prevent their aggregation.

(18) ^1H NMR (500 MHz) **4** ($CDCl_3$ at 193 K, 10^{-2} M) δ 6.90, 6.55 (H-10), 6.70, 6.09 (H-5), 6.26, 5.90 (H-15), 2.22, 2.16, 2.09, 2.08, 1.87 (CH_3). Compare with spectrum of **4** at 294 K (ref 12).

Structure of the 2-Norbornyl Cation

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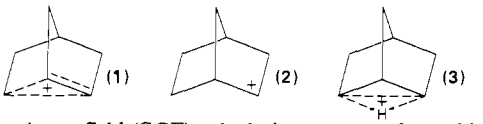
Received June 23, 1988

The structure of the 2-norbornyl cation is possibly the most widely debated issue in physical and organic chemistry. A review of the extensive experimental and theoretical work on this subject can be found in the December 1983 issue of *Acc. Chem. Res.*[1-4] Our ab initio force constant calculations using a range of basis sets show that the nonclassical structure of 2-norbornyl cation (**1**) corresponds to a minimum in the potential energy surface. This finding, combined with previous theoretical results, necessitates the conclusion that the gas-phase structure of the 2-norbornyl cation is nonclassical.



Self-consistent field (SCF) calculations were performed by using a vectorized IBM version of the GAUSSIAN 86 program.[5] The basis

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0002-7863/89/1511-1527$01.50/0