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Octaethyl-1,3-oxazinochlorin: A β-Octaethylchlorin Analogue Made by Pyrrole Expansion

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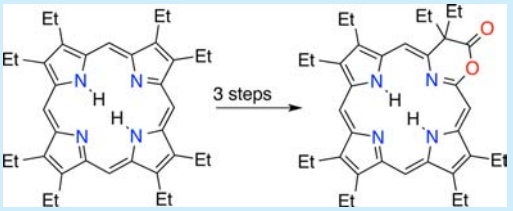
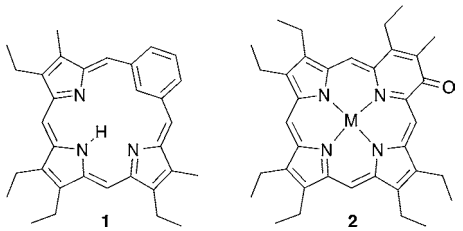
Supporting Information

ABSTRACT: Treatment of the oxime of octaethyloxochlorin **4**, available from octaethylporphyrin **3**, under Beckmann conditions provided not the expected lactam, but octaethyl-1,3-oxazinochlorin **8**, in which a pyrrole moiety of the parent oxochlorin was expanded by an oxygen atom to an 1,3-oxazinone moiety. Its mechanism of formation was demonstrated to occur along an "abnormal Beckmann" pathway, followed by intramolecular ring closure and hydrolysis. The work expands the methodologies known to convert octaethylporphyrin to pyrrole-modified porphyrin analogues.



Few examples of β-alkylporphyrin analogues containing six-membered rings in place of a pyrrole have been reported, among them nonmacrocycle-aromatic benziporphyrin **1**,[1] its pyridine analogue,[2] and the aromatic pyridinone derivative **2**.[3] No analogue was reported in which a pyrrole was formally expanded by a heteroatom.[4] However, multiple such heterocycle-expanded pyrrole-modified porphyrins are known among their *meso*-arylporphyrin-derived congeners, containing morpholine,[5] thiamorpholine,[6] and pyrazine[7] moieties. Most examples of β-alkylporphyrin-derived pyrrole-modified porphyrins were synthesized by total synthesis, notably along the 3 + 1-strategy perfected by the group of Lash.[4,8]



Fundamental research and applications drive the study of these porphyrin analogues. On one hand, the work defines the scopes and limits to which extent porphyrinic macrocycles can be perturbed without losing their porphyrinic characteristics, thus refining our understanding of the concept of aromaticity.[9] On the other hand, some derivatives exhibit widely tunable optical spectra,[10] possess helimeric conformations,[5,11] carry functionalities at their periphery that can be used for chemosensing applications,[12] or have other properties that suggest their use in a number of technical and biological applications.[4]

The Beckmann reaction is a versatile reaction to ring-expand a cyclic ketone via its ketoxime by a nitrogen atom, generating a lactam.[13] We used this reaction to expand a β,β′-diketone moiety in *meso*-tetraphenylporphyrin to an imide functionality.[14]

Known oxochlorin **4**, accessible from octaethylporphyrin (OEP) **3** along two different routes,[15] possesses regular ketone reactivity.[15c,16] Thus, we set out to test if a Beckmann rearrangement of oxochlorin oxime **5** was possible, forming one or both of the lactam isomers **6A** or **6B** (Scheme 1). However, a host of steric and electronic effects control the migratory aptitude of the two different moieties that may migrate in a nonsymmetric oxime.[13] We also showed the strong influence of the presence of a central metal on the outcome of a Beckmann reaction of *meso*-tetraphenylporphyrin-β-oxime.[14,17] Taken together, this makes a prediction of the outcome of a Beckmann reaction of oxime **5** difficult—and the experiments all the more interesting. We report here on the unexpected outcome of the reaction of oxime **5** under Beckmann conditions.

The reaction of red-purple ketone **4** with an excess of hydroxylamine in pyridine at reflux temperature generated the expected brown-colored oxime **5** in good yield. The oxime possesses all the expected spectroscopic properties.[18] Its chlorin-type UV−vis spectrum is similar to that of the parent ketone **4**, albeit slightly shifted (Figure 1).

Initially, exposure of oxime **5** to a range of acidic conditions typically used to induce Beckmann rearrangements merely led to the hydrolysis of oxime **5**. Eventually, we found that a mixture of PCl_5 and $BF_3{\cdot}Et_2O$ rapidly induced the formation of a single new sky-blue compound $\mathbf{7}^{OH}$ of higher polarity than oxime **5**.[19] The new product possesses the same composition as oxime **5** ($C_{36}H_{48}N_5O$ for MH^+, as per HR-ESI$^+$). We cautiously interpreted this finding as supportive of the notion that the rearrangement of oxime **5** to a lactam **6** had taken place.

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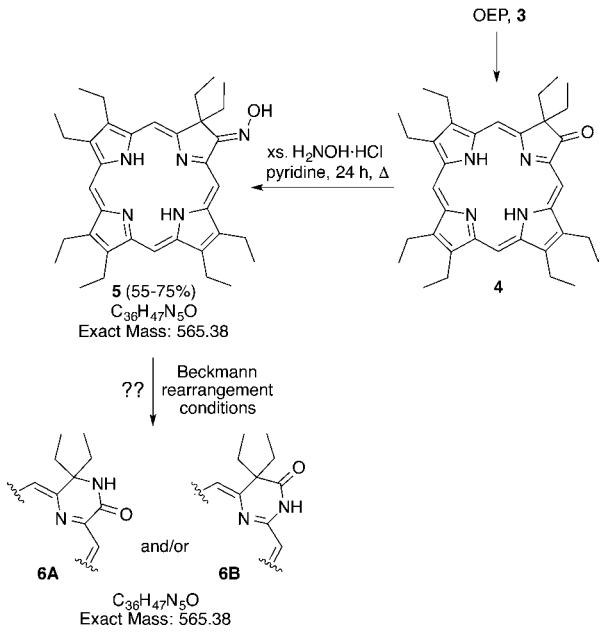
Scheme 1. Planned Reaction Sequence toward the Target Lactams 6A and/or 6B[a]



[a]Oxime stereochemistry not known.

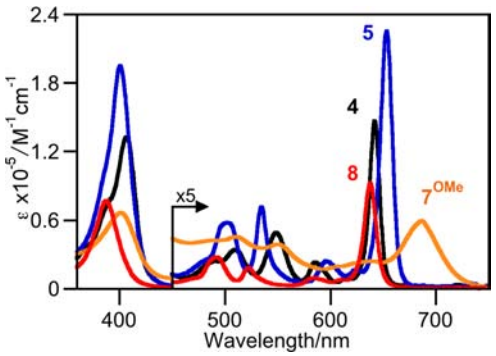


Figure 1. UV−vis spectra (CH_2Cl_2) of the compounds indicated.

Surprisingly, the supposed "lactam" was chemically very sensitive and converted in solution in high yields to a stable green compound (blue on TLC), **8**, upon handling, isolation, or storage, within minutes to hours. The newly formed product **8** possessed a regular chlorin-like UV−vis spectrum with a slightly blue-shifted longest wavelength of absorbance band compared to the parent ketone **4** and oxime **5** (Figure 1). A comparison of the ^{1}H NMR spectral data of product **8** and its direct precursor 7^{OH} revealed some substantial shifts that suggested that a chemical framework change had taken place during the conversion. Compared to the composition of 7^{OH}, the composition of **8** ($C_{36}H_{47}N_4O_2$ for MH+, as per HR-ESI$^+$) reflected the replacement of an NH group by an O atom. Such a replacement corresponds to, for instance, a hydrolysis of a lactam to a lactone, or an imine to a ketone. Indeed, product **8** revealed a strong lactone $\nu_{C=O}$ signal at 1754 cm^{-1} in its IR spectrum (neat) and a signal in the ^{13}C NMR spectrum in the lactone range (at δ 172.8 ppm).[20]

A single X-ray crystal structure analysis of product **8** unambiguously confirmed the lactone connectivity of the product (Figure 2). A ring expansion of ketone **4** by an oxygen had taken place, with the oxygen inserted between the carbonyl and the α-position of the ring. Thus, overall, a pyrrole moiety in the ultimate starting material octaethylporphyrin **3** was replaced by a 1,3-oxazinane-4-one moiety. The nonplanarity of the partially saturated 1,4-oxazinane moiety translates only little into the remainder of the macrocycle. The absence of any major distortion from planarity likely rationalizes why lactone **8** possesses a regular chlorin spectrum.

Figure 2. Stick representation of the molecular structure of lactone **8** as determined by single crystal diffractometry. All disorder, solvents, and hydrogen atoms attached to sp^3-carbons were omitted for clarity. For details, see Supporting Information.

A number of 1,4-oxazinane- (morpholine-) containing pyrrole-modified porphyrins have become known,[5,21,22] but no porphyrinoid incorporating an 1,3-oxazinane moiety. *meso*-Aryl-based lactones,[20,22a,23] lactams,[24] or their carba-analogues[25] also carry carbonyl moieties at their β-positions, albeit within five-membered heterocycles.

With the structure of lactone **8** confirmed, we focused our attention on the connectivity of its precursor 7^{OH} for which a lactam structure seemed unlikely (*vide infra*). In addition to the spectroscopic indications listed above, a facile lactam-to-lactone conversion of 7^{OH} to derive lactone **8** also would have been unexpected since this transformation takes place only in highly ring-strained lactams,[26] a circumstance that could not be recognized here.

Considering the connectivities of the precursor oxime **5** and product **8**, not many options for the structure of 7^{OH} are reasonable. One is imine **9**, the imine of lactone **8** (Scheme 2). This would certainly be susceptible to hydrolysis to the lactone, but we could not find any spectroscopic data supporting this structure. We found in the collision-induced fragmentation ESI$^+$ MS spectrum of 7^{OH} a strong peak corresponding to the loss of HCN, a fragment that cannot be readily rationalized by the imine structure **9**, but this finding provided a first strong clue as to the connectivity of 7^{OH}.

The literature reveals a few examples of "abnormal Beckmann" rearrangements of cyclic oximes that produced a ring-opened nitrile alcohol.[27] This product is formed when the migrating fragment departs from the intermediate because of, for instance, ring strain. Applied to oxime **5**, this would generate, following protonation (or Lewis-adduct formation with PCl_5 or $BF_3{\cdot}Et_2O$), nitrile alcohol 7^{OH} via the resonance-stabilized cation **11**.

Indeed, the nitrile alcohol structure 7^{OH} fits the spectroscopic data for the intermediate described above. Importantly, the much different ^{1}H NMR spectra of 7^{OH} and **8** find an explanation by the open-ring secochlorin versus closed-ring lactone architectures. Several examples of β-alkylsecochlorins, chlorin analogues containing a cleaved β,β'-bond, are known,

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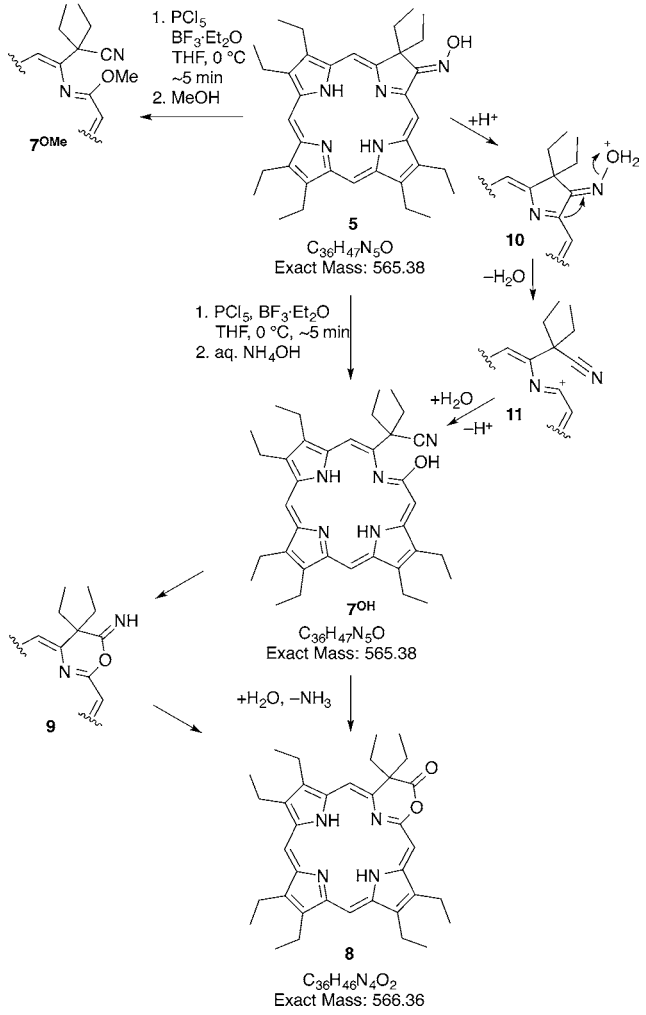
Scheme 2. Mechanism of Conversion of Oxime 5 under Beckmann Conditions To Form Lactone 8 *via* Nitrile 7^{OH}



though none containing an OH-functionality directly bound to the porphyrinic π-system.[4,28] Importantly, the steps leading from 7^{OH} to lactone **8** are readily understood: fast intramolecular nitrile alcoholysis by the phenolic hydroxyl group with concomitant ring closure to form imine **9** that subsequently is rapidly hydrolyzed to form final lactone **8**. Consequently, we devised a direct—albeit with 20% isolated yield still unsatisfactorily low yielding—synthesis of **8** that does not require the isolation of 7^{OH}, involving the quenching of the crude reaction mixture of oxime **5** and PCl_5 (with or without the addition of $BF_3{\cdot}Et_2O$) with water.

The chemical instability of intermediate 7^{OH} did not allow its full characterization as a pure compound or even the recording of a reliable UV−vis spectrum, but intermediate **11** could be trapped with MeOH. Thus, quenching the reaction mixture resulting from the treatment of oxime **5** with PCl_5 and $BF_3{\cdot}Et_2O$, using MeOH instead of aqueous ammonia or water, formed secochlorin nitrile 7^{OMe} in low yields. Importantly, however, this compound is hydrolytically stable and allowed its purification and full spectroscopic characterization. It possessed the expected composition ($C_{37}H_{50}N_5O$ for MH^+, as per ESI^+ HR-MS), a broadened and red-shifted UV−vis spectrum seen also in other secochlorins,[4,28] and a ^1H NMR spectrum closely resembling that of 7^{OH} (with the additional OMe signal at δ 4.22 ppm). Its ^{13}C NMR spectrum showed the presence of a signal at δ 122.5 ppm diagnostic of a nitrile group, and its IR (neat) exhibited a weak ν_{CN} stretch at 2232 cm^{-1}.

The connectivity of this secochlorin was confirmed by single crystal X-ray structure analysis (Figure 3). A steric clash between the cyano and methoxy groups causes a significant distortion of the chromophore mean plane from planarity (see Supporting Information for details). It also shows the close proximity of the oxygen to the cyanogroup carbon (2.58 Å) that leads to the facile intramolecular ring closure reaction in 7^{OH}. This structure adds another example to the small number of known free base secochlorins.[4]

Figure 3. Stick representation of the molecular structure of secochlorin 7^{OMe}, as determined by single crystal diffractometry. All disorder, solvents, and hydrogen atoms attached to sp^3-carbons were omitted for clarity. For details, see Supporting Information.

Curiously, product **8** is the product expected from a Baeyer−Villiger oxidation of ketone **4**,[27c] not a Beckmann reaction of oxime **5**. Alas, the Baeyer−Villiger oxidation of ketone **4** results in multiple as yet to be identified products, but lactone **8** was never found in the product mixtures.

In conclusion, we demonstrated a novel methodology to replace a pyrrole in OEP **3** by an 1,3-oxazinone in three steps (1. oxochlorin formation; 2. oxime formation; 3. anomalous Beckmann rearrangement with subsequent intramolecular ring closure and hydrolysis) and delineated the unusual mechanism of the final step. The thus generated first member of a new class of pyrrole-modified porphyrins, octaethyl-1,3-oxazinochlorin **8**, is a chlorin analogue.

■ ASSOCIATED CONTENT

Supporting Information

Procedures and spectroscopic data of the novel compounds reported, a reproduction of key spectra, and details to the structural analyses of **8** and 7^{OMe} (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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