Novel chlorins with a δ-lactone ring

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The synthesis of chlorins possessing an additional δ-lactone ring *via* reduction of the anhydride ring in purpurins with sodium borohydride has been performed.

Recently, purpurin 18 **1a** and bacteriopurpurin **2b** have attracted attention as second generation sensitizers for the photodynamic therapy of cancer.[1,2] Particular interest centres on the six-membered anhydride ring conjugated with the macrocyclic system, which plays a significant role in the spectral characteristics of purpurins[3] and is widely used in various chemical modifications.[4] However, this ring is stable only in acid and neutral media, while in the presence of a base it undergoes opening to give the corresponding dicarboxylic acids. This restricts the application of purpurins for biological purposes.

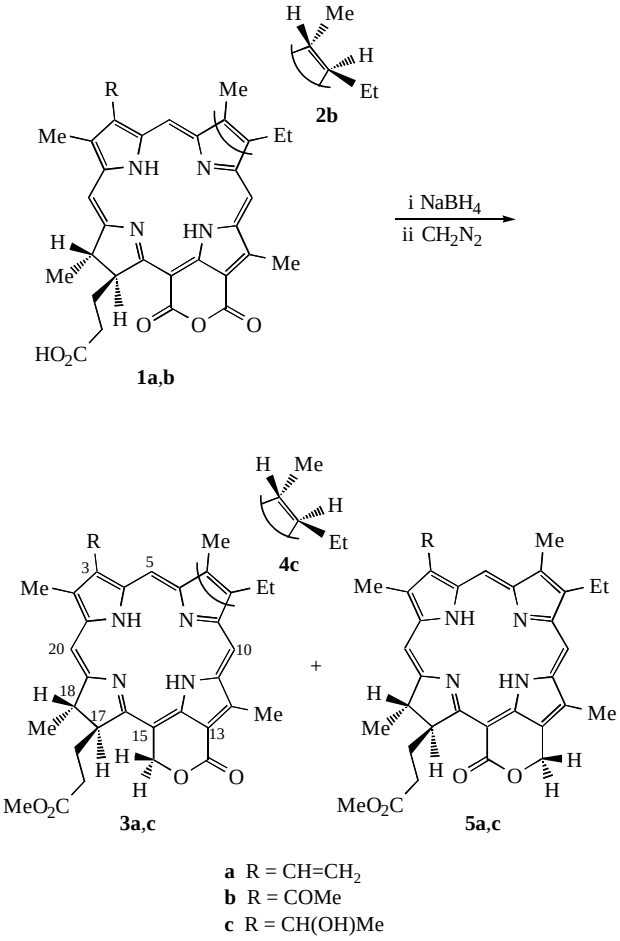
In the present communication we report the chemical modification of the anhydride ring in purpurins with sodium borohydride, which leads to the formation of the more stable δ-lactones. To our knowledge, such transformation of chlorins and bacteriochlorins has not previously been observed.

The reaction was carried out at room temperature with $NaBH_4$ in a pyridine–isopropyl alcohol mixture. The excess of sodium borohydride was quenched with acetone and the final products were isolated as the methyl esters (treatment with CH_2N_2).

In the case of bacteriopurpurin **2b**, the lactone **4c** was obtained in 45% yield (purification was performed by TLC on silica). The structure of this compound was proved by mass spectrometry and ^{1}H NMR. The mass spectrum† contained a molecular ion at *m*/*z* 584 and an intense cleavage peak at *m*/*z* 566, which corresponded to elimination of H_2O. The FAB mass spectrum‡ showed a molecular ion at *m*/*z* 584.2987 ($C_{34}H_{40}N_4O_5$ requires *m*/*z* 584.2999). The electronic absorption spectrum showed λ_{max} 727 nm. This unexpectedly large hypsochromic shift (91 nm) is attributed to the removal of conjugation on reduction of the carbonyl groups at C-13 and C-15 and to the increased flexibility of the exocyclic ring.

The structure of the compound **4c** was confirmed by two-dimensional ^{1}H NMR.§ The NOESY spectra were used to obtain spatial relationships in the usual way. The final assignments were made on the basis of NOE correlations which revealed spatial proximity between proton groups. In contrast to bacteriopurpurin **2b**, the spectrum of compound **4c** had new signals at δ 6.54 and 6.59 ppm. Another difference was that the signal of 17-H was shifted upfield 1.4 ppm. The spectrum of compound **4c** had a characteristic spin system, which corresponded to the $CH_3CH(OH)$ group. The signals of this group were used as the starting point for assignment. The quartet of $CH_3CH(OH)$ had strong NOE cross peaks with a doublet at δ 2.06 ppm (CH_3), a singlet at δ 3.27 ppm and with two closely positioned signals (7 Hz apart) of almost equal intensities of 0.5H each at δ 8.70 and 8.71 ppm for one of the meso-protons. From this it was concluded that these signals (presumably of two diastereoisomers arising due to the formation of a chiral centre at C-3) corresponded to the 5-meso-proton, and the resonance at δ 3.27 ppm was assigned to the 2-CH_3. The signal of the 5-meso-proton showed NOE interactions with signals at δ 1.79 and 4.22 ppm, which were assigned to 7-CH_3 and 7-H, respectively. The resonance of 7-H correlated with the signal of 8^2-CH_3 at δ 1.11 ppm. The presence of an NOE cross peak between 8^2-CH_3 and the meso-proton at δ 8.48 ppm indicated spatial proximity between these two groups. The signal at δ 8.48 ppm was thus assigned as the 10-meso-proton. Following this procedure, all the proton resonances in compound **4c** were assigned. The signal of the 17-H group had NOE cross peaks with 18-CH_3 and the CH_2 of the lactone. Moreover, the resonance of the lactone CH_2-group had an NOE cross peak only with 17-H and CH_2 protons on the propionate chain. This provides strong evidence that the CH_2 of the lactone is located at position 15, as shown in structure **4c**. Formation of the second isomer during the reduction of bacteriopurpurin was not observed.

In contrast to bacteriopurpurin, reduction of purpurins **1a** and **1b** proceeded less regioselectively. In the case of



Scheme 1 Transformation of purpurins into ring *E* δ-lactones.

† Mass spectra were measured on a MSBKh instrument (SELMI, Sumy, Ukraine). Ionisation was caused by ^{252}Cf fission products, and a time-of-flight monitoring ion analyser was employed.

‡ FAB mass spectra were measured on a VG Autospec using caesium ion bombardment at 25 kV, a 3-nitrobenzyl alcohol matrix, and polyethyleneglycol as reference.

§ ^{1}H NMR spectra were recorded on a Bruker MSL 200 in $CDCl_3$; NOESY spectra were obtained on a Varian XR 400 in $CDCl_3$ (SW = SW^2 = 4545.5; NP 1024; NI 256, mix 0.5 s) and on a Bruker AMX600 in $CDCl_3$.

purpurin 18 **1a**, two compounds **3a** and **5a** with similar R_f values were observed in a 3:1 ratio. After repeated TLC on silica (Merck 60 H) and reverse phase HPLC we isolated the major compound (36%) and a small amount of the minor one (6%). The minor component was more mobile on silica gel; on the reverse phase the major component appeared first. Both compounds showed molecular ion peaks [M + H] with *m*/*z* 565.3 in their ^{252}Cf-mass spectra. High precision FAB mass spectrometry of the major isomer **3a** gave *m*/*z* 565.2802 ($C_{34}H_{36}N_4O_4$ + H requires *m*/*z* 565.2815).

However, the electronic absorption spectra of these two compounds, although similar in appearance, showed some differences: the major isomer had λ_{max} 666 nm (the main peak) and the Soret band was at 403 nm, while the minor product had λ_{max} 674.5 and 397 nm, respectively. The ^{1}H NMR spectrum of the major isomer showed a signal of the lactone CH_2 group at δ 6.80 ppm and a double doublet at δ 4.33 ppm from 17-H, shifted upfield compared to the positions in the starting purpurin 18. A similar lactone signal and shifting of the 17-H resonance had already been observed for the bacteriolactone **4c**. Based on the analysis of the ^{1}H NMR spectrum, the structure **3a**, in which a methylene group is at position 15, was assigned to the major of two products obtained on the reduction of purpurin 18 **1a**. Hence, the second isomer has structure **5a** [δ/ppm: 6.46 (CH_2-lactone), 5.42 (17-H), and 3.47 (12-CH_3)].

Reduction of 3-devinyl-3-acetylpurpurin 18 **1b** proceeded similarly. ^{252}Cf-Mass spectra showed that both isomers obtained had molecular ion peaks with *m*/*z* 582. Unfortunately, the isomers had very similar R_f values, which made it difficult to obtain the separated isomers in sufficient amounts for NMR studies. The purified fraction of the product mixture (34%) contained isomers in a ratio of 3:2 as judged from the ^{1}H NMR spectrum. The more abundant isomer had the following resonances (δ/ppm): 6.73 and 6.76 (CH_2-lactone), 4.29 (17-H), and 3.81 (12-CH_3), and we therefore assume its structure to be **3c**. The second isomer **5c** showed these resonances at δ 6.36 and 6.39, 5.42 and 3.30 ppm, respectively.

It is known that simple cyclic anhydrides can be reduced with sodium borohydride at the carbonyl group adjacent to the most highly substituted carbon atom.[5] It seems possible that in our example a similar effect is caused by the bulk of the reduced ring D.

The δ-lactone ring in the chlorins obtained is considerably more stable than the anhydride ring in the starting compounds in both acid and alkali media. This makes it possible to selectively saponify the propionic acid esters, which is unrealisable in the case of purpurin 18 and its analogues, and opens up methods for reactions which should be carried out in the presence of a base.

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