A Convenient Method for the Preparation of Chlorin e₆ and Rhodin g₇ Trimethyl Esters

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Chlorin e₆ (2a, R¹ = CH₃, R² = R³ = R⁴ = H) and rhodin g₇ (2b, R¹ = CHO, R² = R³ = R⁴ = H) as well as their trimethyl esters (2c, R¹ = CH₃, R² = R³ = R⁴ = CH₃; 2d, R¹ = CHO, R² = R³ = R⁴ = CH₃) are important chlorophyll derivatives which have frequently been used in electrochemical, chiroptical, and (bio)synthetic investigations. Several methods for the preparation of 2c and 2d have been described. These methods are, however, inconvenient in terms of yield (<30%) and/or degree of purity of the products.
In a previous report, it was shown that the methanolation of pheopside a (R1 = CH2, R2 = H) or pheopside b (R1 = CHO, R2 = H) with 0.5% methanolic potassium hydroxide yields almost exclusively a mixture of different methyl esters of 2a or 2b. Under these conditions, the methanolation of ring V proceeds more rapidly than its oxidation. Derivative 2a or 2b was obtained in high yield and high purity by hydrolyzing the ester mixture with 30% (w/w) methanolic potassium hydroxide under an argon atmosphere. In the present publication, we report a simple and high-yield method for the preparation of 2c and 2d by methanolation of methylpheopside a (R1 = CH2, R2 = CH3) and b (R1 = CHO, R2 = CH3), respectively.

It has previously been suggested that ring V cleavage involves the enolate anion of 1 as an intermediate. However, it now appears likely that at least methanolation (hydrolysis)

Derivatives 1c and 1d were prepared from chlorophyll mixture (containing ~80% of chlorophyll a and 20% of chlorophyll b) by the methods described in the accompanying communication. The spectroscopic properties (U.V./VIS, 1H-N.M.R.) of these derivatives were consistent with a high degree of purity. The methanolation of 1c or 1d in 0.5% methanolic potassium hydroxide is complete within 10-20 min and virtually no allomerization (oxidation) products are formed under these conditions, even in the presence of atmospheric oxygen. The principal product from the methanolysis is 2c or 2d, respectively. The small amount of by-products, consisting of lower methyl esters of 2a or 2b, can easily be removed utilizing the conventional hydrochloric acid - diethyl ether fractionation which is based on the different hydrochloric acid numbers (nHCl) of the derivatives. The purities of the products can be rapidly checked employing T.L.C. on cellulose.

### Table. Preparation and Spectroscopic Properties of Chlorin e.- and Rhodin g.-Trimethyl Esters

<table>
<thead>
<tr>
<th>Product</th>
<th>R'</th>
<th>R''</th>
<th>R''</th>
<th>R'</th>
<th>Yield [%]</th>
<th>Molecular Formula (Mol. weight)</th>
<th>U.V./VIS. (THF)</th>
<th>1H-N.M.R. (60 MHz, acetone-d6/TMS)</th>
<th>δ [ppm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2c</td>
<td>CH3</td>
<td>CH3</td>
<td>CH3</td>
<td>CH3</td>
<td>80</td>
<td>C20H22N2O5 (638.8)</td>
<td>665.0 (43.7), 608 (4.53), 558 (1.74), 529 (4.70), 500 (11.24), 401.5 (123.4), 303 (9.58)</td>
<td>9.73 (s, 1H, β-H); 9.53 (s, 1H, α-H); 9.02 (s, 1H, δ-H); 8.09 (dd, 1H, J = 11 Hz, 18 Hz, 2a-H2); 6.30 (dd, 1H, J = 2 Hz, 18 Hz, 2b-H2); 6.05 (dd, 1H, J = 2 Hz, 11 Hz, 2b-Hα); 5.36 (s, 2H, 10-CH2); 4.69 (m, 1H, J = 7 Hz, 8-H2); 4.46 (m, 1H, J = 7 Hz, 7-H2); 5.45 (s, 3H, 9a-CH3); 4.02 (q, 2H, J = 7 Hz, 7a-CH2); 3.77 (s, 3H, 10β-CH3); 3.61 (s, 3H, 7d-CH3); 3.54 (s, 3H, 5a-CH3); 3.44 (s, 3H, 4a-CH3); 3.17 (s, 3H, 3a-CH3); 2.46-2.22 (m, 4H, 7a-CH2); 1.75 (m, 1H, J = 7 Hz, 8α-CH3); 1.64 (s, 3H, J = 8 Hz, 4b-CH3); 1.07 (s, 3H, 3α-CH3); 1.00 (s, 1H, β-CH); 0.94 (s, 1H, α-CH); 0.92 (s, 1H, δ-H); 0.75 (dd, 1H, J = 11 Hz, 18 Hz, 2a-H2); 6.23 (dd, 1H, J = 2 Hz, 18 Hz, 2b-H2); 6.04 (dd, 1H, J = 2 Hz, 11 Hz, 2b-Hα); 5.31 (s, 2H, 10-CH2); 4.56 (m, 1H, J = 7 Hz, 8-H2); 4.43 (m, 1H, J = 8 Hz, 7-H2); 4.23 (s, 3H, 9a-CH3); 3.80 (s, 3H, 10β-CH3); 3.64 (s, 3H, 7d-CH3); 3.59 (q, 2H, J = 7 Hz, 7a-CH2); 3.44 (s, 3H, 5a-CH3); 3.36 (s, 3H, 3a-CH3); 2.52-2.25 (m, 4H, 7a-CH2); 1.77 (d, 3H, J = 7 Hz, 8α-CH3); 1.58 (t, 3H, J = 8 Hz, 4b-CH3)</td>
<td></td>
</tr>
<tr>
<td>2d</td>
<td>CHO</td>
<td>CH3</td>
<td>CH3</td>
<td>CH3</td>
<td>70</td>
<td>C19H16N2O4 (652.8)</td>
<td>562.0 (25.7), 597 (7.54), 558 (7.26), 522 (10.6), 427 (17.6), 359 (21.8), 313 (24.5)</td>
<td>9.73 (s, 1H, β-H); 9.53 (s, 1H, α-H); 9.02 (s, 1H, δ-H); 8.09 (dd, 1H, J = 11 Hz, 18 Hz, 2a-H2); 6.30 (dd, 1H, J = 2 Hz, 18 Hz, 2b-H2); 6.05 (dd, 1H, J = 2 Hz, 11 Hz, 2b-Hα); 5.36 (s, 2H, 10-CH2); 4.69 (m, 1H, J = 7 Hz, 8-H2); 4.46 (m, 1H, J = 7 Hz, 7-H2); 5.45 (s, 3H, 9a-CH3); 4.02 (q, 2H, J = 7 Hz, 7a-CH2); 3.77 (s, 3H, 10β-CH3); 3.61 (s, 3H, 7d-CH3); 3.54 (s, 3H, 5a-CH3); 3.44 (s, 3H, 4a-CH3); 3.17 (s, 3H, 3a-CH3); 2.46-2.22 (m, 4H, 7a-CH2); 1.75 (m, 1H, J = 7 Hz, 8α-CH3); 1.64 (s, 3H, J = 8 Hz, 4b-CH3); 1.07 (s, 3H, 3α-CH3); 1.00 (s, 1H, β-CH); 0.94 (s, 1H, α-CH); 0.92 (s, 1H, δ-H); 0.75 (dd, 1H, J = 11 Hz, 18 Hz, 2a-H2); 6.23 (dd, 1H, J = 2 Hz, 18 Hz, 2b-H2); 6.04 (dd, 1H, J = 2 Hz, 11 Hz, 2b-Hα); 5.31 (s, 2H, 10-CH2); 4.56 (m, 1H, J = 7 Hz, 8-H2); 4.43 (m, 1H, J = 8 Hz, 7-H2); 4.23 (s, 3H, 9a-CH3); 3.80 (s, 3H, 10β-CH3); 3.64 (s, 3H, 7d-CH3); 3.59 (q, 2H, J = 7 Hz, 7a-CH2); 3.44 (s, 3H, 5a-CH3); 3.36 (s, 3H, 3a-CH3); 2.52-2.25 (m, 4H, 7a-CH2); 1.77 (d, 3H, J = 7 Hz, 8α-CH3); 1.58 (t, 3H, J = 8 Hz, 4b-CH3)</td>
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</table>

* The purity was checked by T.L.C. and by comparing the spectroscopic values of the Table with those given in literature.
can occur directly via the nucleophilic attack by methoxyl (hydroxyl) ions at the carbonyl C-9.

The method developed yields 2c and 2d in high yield and a high degree of purity. The method is rapid and easy to perform and requires no special precautions. Combination of this method with those described in the accompanying paper makes possible the preparation of 2c and 2d directly from plant material without chromatographic separations. The method is also amenable to a larger scale than that mentioned in the following examples.

Chlorin e, Trimethyl Ester (2c; \( R^1 = CH_3 \), \( R^2 = R^3 = R^4 = CH_3 \));

Typical Procedure:
0.5% Methanolic potassium hydroxide (100 ml) is added to a solution of compound 1e (76 mg) in pyridine (5 ml) and the mixture is stirred for 20 min. It is then diluted with water (~ 500 ml), neutralized with ammonia, and extracted with ether (2 × 250 ml). The organic extract is shaken with 5% hydrochloric acid (3 × 300 ml) to remove small amounts of by-products which consist mainly of 2a and its monomethyl ester(s). The fraction 30% has a 10 consists of pure 2c. The product can be crystallized from tetrahydrofuran/heptane; yield: 65 mg. The \(^1\)H-N.M.R. spectrum of the product shows no impurities.

Rhodin g, Trimethyl Ester (2d; \( R^1 = CHO \), \( R^2 = R^3 = R^4 = CH_3 \));

Compound 1d (28 mg) is hydrolyzed under the conditions described for 1e. Work-up of the ether extract fraction, gives pure 2d. The product is crystallized from tetrahydrofuran/heptane; yield: 20 mg. The \(^1\)H-N.M.R. spectrum of the product shows no impurities.

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18 P. H. Hyndinen, S. Lötjönen, Synthesis 1980, 539.