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REACTION OF METHYLPHEOPHORBIDES *d* AND *b* WITH AMINES

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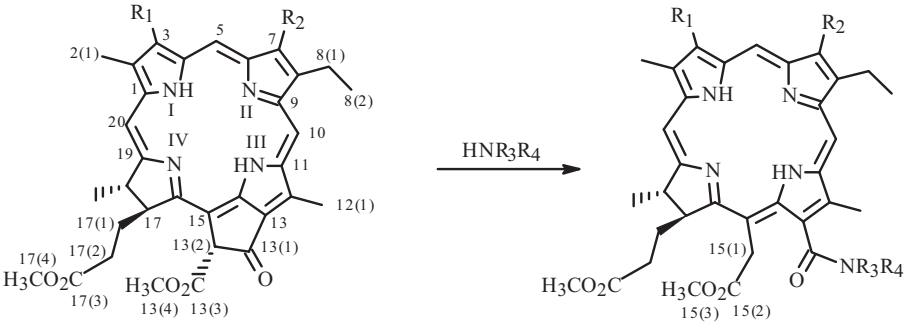
A series of formyl analogs of chlorin e_6 13-amides were synthesized in high yields by reaction under mild conditions of primary and secondary amines with methylpheophorides b and d. In contrast with the secondary 13-amides, tertiary 13-amides were found as two isomers differing in the orientation of the amide plane relative to the plane of the chlorin ring. Methylpheophorbides b and d were more reactive toward the amines than methylpheophorbide a.

Keywords: methylpheophorbides *b* and *d*, amides, rhodin g_7 13-amides, formyl analogs of chlorin e_6 13-amides, atropoisomerism.

Porphyrins are a promising platform for synthesizing antitumor drugs with various mechanisms of action [1–3]. Because the chlorin molecule contains an aldehyde and the possibilities of its further chemical transformations are greatly expanded by the additional reaction center, it seemed interesting to study chemical transformations of chlorophylls *b* and *d* and their derivatives.

The known method for synthesizing chlorin e_6 13-amides consists of the reaction of methylpheophorbide *a* (**1**) with primary and secondary amines [4–7]. We used the reaction of primary and secondary amines with formyl analogs of **1**, methylpheophorbides *b* (**2**) and *d* (**3**), in order to synthesize previously unreported formyl analogs of chlorin e_6 amides.



1 - 3 **4 - 17**

1 → 3 **3 → 4 - 7, 2 → 8 - 12, 1 → 13 - 17**

1, 13 – 17: R_1 = CH=CH_2, R_2 = CH_3; **2, 8 – 12:** R_1 = $CHCH_2$, R_2 = CHO; **3 – 7:** R_1 = CHO, R_2 = CH_3
4, 8, 13: R_3 = H, R_4 = CH_3; **5, 9, 14:** R_3 = R_4 = CH_3; **6, 10, 15:** R_3 = H, R_4 = CH_2Ph
7, 11, 16: R_3 = R_4 = C_2H_5; **12, 17:** R_3–R_4 = $(CH_2)_2O(CH_2)_2$

Scheme 1

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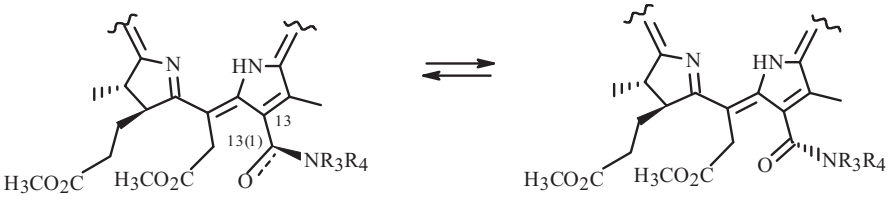
Methylpheophorbide *b* (**2**) was obtained from nettle *Urtica* sp. by the literature method [8]. Methylpheophorbide *d* (**3**) was synthesized from **1** by oxidation of its vinyl group using sodium periodate and OsO_4 [9]. Then, primary and secondary amines were reacted with **3** and **2** to synthesize several analogs of chlorin e_6 (**4**–**7**) for representatives of the *d*-series and rhodin g_7 13-amides (**8**–**12**), respectively (Scheme 1). Formation of products from reaction of the aldehyde (Schiff bases for primary amines and geminal *N*-substituted amino-alcohols for secondary) was not observed. The results can be explained by the reversibility of the reaction of amines with aldehydes and a shift of the equilibrium toward the aldehyde under the synthetic conditions or during work up of the mixture.

Opening of the exocycle and formation of the corresponding 13-amides **4**–**12** was confirmed by IR, PMR, and mass spectral data. Mass spectra of the products contained peaks with *m*/*z* values corresponding to the structures of the 13-amide derivatives **4**–**12** and peaks for fragment ions corresponding to loss of the methylpropionate substituent and methyl, methoxyl, and ester groups. Many spectra showed an $[M - H]^+$ peak characteristic of spectra of aromatic aldehydes [10].

IR spectra of all products **4**–**12** lacked bands for 13(1)-carbonyl stretching vibrations. This confirmed that the exocycle had opened. Furthermore, spectra of the products exhibited amide bands such as the amide-I and amide-II bands in secondary amides (**4**, **6**, **8**, **10**, **13**, **15**) and the amide-I band in tertiary amides (**5**, **7**, **9**, **11**, **12**, **14**, **16**, **17**). PMR spectra of the products from reaction of **2** and **3** with all amines differed from those of the starting materials by the lack of a resonance for the proton in the 13(2)-position and the presence of multiplets for an AB-system of CH_2-15(1) that was formed by opening of the exocycle [a slight exception was 13-diethylamide (**11**), the protons of this group in its minor atropoisomer (see below) appeared as a singlet].

Furthermore, spectra of the synthesized secondary amides showed resonances for the NH protons of the secondary amide as broad triplets. Resonances of the 13-amide substituent protons appeared in all spectra of the synthesized amides. The study of the products using PMR spectroscopy showed that all synthesized tertiary 13-amides, like analogous amides of chlorin e_6, exist as two atropoisomers (Scheme 2).



5, 7, 9, 11, 12, 14, 16, 17

Scheme 2

PMR spectra of all tertiary amides could be interpreted as the superposition of spectra of two isomers. Each of the overlapping spectra had the same number of resonances of the same multiplicity. They differed only in the values of their chemical shifts. The intensity ratio of the resonances in PMR spectra of the atropoisomers of the tertiary amides was approximately 2:1. According to the literature, an analogous phenomenon was observed for tertiary amides of chlorin e_6. It was thought that the isomers of chlorin e_6 tertiary amides differed from each other by the mutual location of the 13-amide and the chlorin ring. They were able to form owing to hindrance to rotation of the amide group around the C-13–C-13(1) bond [5–7]. Apparently the isomers of the formyl analogs of chlorin e_6 tertiary amides synthesized in the present work appeared for the same reasons. Their molecular structures were analogous to the chlorin e_6 13-amides.

Formyl derivatives **2** and **3** were very reactive in all reactions between **1**, **2**, and **3** and amines. The reactivity was evident in the more complete conversion of the starting materials, the substantially shorter reaction time, and, in certain instances, the increased yields of the target amides **4–12** compared with the analogous chlorin e_6 13-amides **13**–**17** [5–7]. Thus, the reactions of **2** and **3** with benzylamine at room temperature was complete in less than 1 h. The analogous amide of chlorin e_6 (**15**) was obtained under the same conditions in 14 h and its yield was less than 5%. The yields of benzylamide derivatives **6** and **10** that were obtained under the same conditions were 30 and 50%, which were much greater than the yield of the corresponding chlorin e_6 amide. The yield of the chlorin e_6 amide (**15**) could be increased to 47% by carrying out the reaction in refluxing benzene [7]. This enabled the reaction time to be shortened and avoided side processes that reduced the yield of the target compound.

An analogous trend was observed for the diethylamide derivatives. Amides **7** and **11** were obtained in yields of 36 and 48%, respectively, by reacting diethylamine and the corresponding pheophorbide at room temperature (THF solvent).

The analogous chlorin e_6 derivative was synthesized in 27% yield only by refluxing the reaction mixture [7]. The results are in agreement with the literature [11, 12]. The increased reactivity of **2** and **3** compared with **1** is explained by the decrease of electron density on the 13(1)-carbonyl C atom caused by the electron-accepting action of the aldehyde. The reduction of electron density enhances nucleophilic attack at the carbonyl C atom from the amine side and increases the reactivity.

Thus, the reaction of **2** and **3** with primary and secondary amines is a convenient method for synthesizing formyl analogs of chlorin e_6 in high yield under mild conditions.

EXPERIMENTAL

PMR spectra of the synthesized compounds were recorded in $CDCl_3$ on a Bruker DRX-400 instrument (operating frequency 400 MHz). Resonances in spectra of isomeric mixtures are given for tertiary amides with the resonances of each isomer given separately. Mass spectra (EI) were taken in a Thermo DSQ mass spectrometer (direct sample introduction) at ionizing-electron energy 70 eV. MALDI mass spectra were taken in a Vision 2000 spectrometer. IR spectra were recorded on a Shimadzu IR Prestige 21 IR-Fourier spectrometer (diffuse reflection, KBr powder). The course of reactions was monitored by TLC using Sorbfil plates (eluent CCl_4:acetone, 4:1). Column chromatography used silica gel L 100/400 μ (column packed by the wet method). Methylpheophorbide *a* (**1**) was obtained from *Spirulina* sp. of blue-green algae as before [13]. The spectral properties of **1** and amides **13**–**17** were analogous to those published earlier [9 and 5–7, respectively].

Methylpheophorbide *b* (2) was isolated from a mixture of methylpheophorbides obtained from the lipophilic fraction of compounds extracted from *Serratula coronata* as before [12]. IR spectrum (KBr, ν, cm^{-1}): 2740 (aldehyde C–H), 1750 (ester C=O), 1718 (ketone C=O), 1672 (aldehyde C=O), 1624 (chlorin band).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 10.86 (1H, s, 7-CHO), 10.86 (1H, s, H-5), 9.27 (1H, s, H-10), 8.52 (1H, s, H-20), 7.88 [1H, dd, J = 17.6, 11.6, H-3(1)], 6.31 [1H, dd, J = 17.6, 1.2, H*trans*-3(2)], 6.18 [1H, dd, J = 11.6, 1.2, H*cis*-3(2)], 6.23 [1H, s, H-13(2)], 4.46 (1H, qd, J = 7.2, 2.0, H-18), 4.20 (1H, dt, J = 8.4, 2.4, H-17), 3.93 [3H, s, Me-13(4)], 3.69 [2H, m, CH_2-8(1)], 3.62 [3H, s, Me-17(4)], 3.58 (3H, s, Me-12), 3.35 (3H, s, Me-2), 2.74–2.51 [2H, m, CH_2-17(1)], 2.38–2.26 [2H, m, CH_2-17(2)], 1.87 [3H, d, J = 8.0, Me-18(1)], 1.65 [3H, t, J = 7.6, Me-8(2)], 0.24(1H, br.s, I-NH), –1.80 (1H, br.s, III-NH).

Methylpheophorbide *d* (3) was prepared by oxidation of the vinyl group of **1** as before [8]. IR spectrum (KBr, ν, cm^{-1}): 2741, 1734, 1701 (exocycle C=O), 1678, 1616.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 11.49 (1H, s, 3-CHO), 10.16 (1H, s, H-5), 9.54 (1H, s, H-10), 8.81 (1H, s, H-20), 6.33 [1H, s, H-13(2)], 4.54 (1H, qd, J = 7.2, 2.0, H-18), 4.22 (1H, dt, J = 8.4, 2.4, H-17), 3.91 [3H, s, Me-13(4)], 3.71 (3H, s, Me-2), 3.71 (3H, s, Me-7), 3.58 [3H, s, Me-17(4)], 3.67–3.61 [2H, m, CH_2-8(1)], 3.21 (3H, s, Me-12), 2.73–2.50 [2H, m, CH_2-17(1)], 2.37–2.21 [2H, m, CH_2-17(2)], 1.86 [3H, d, J = 6.8, Me-18(1)], 1.67 [3H, t, J = 8.0, Me-8(2)], –0.14 (1H, br.s, I-NH), –2.10 (1H, br.s, III-NH).

Mass spectrum (EI, *m*/*z*, I_{rel}, %): 609 (73) $[MH]^+$, 608 (100) $[M]^+$, 576 (18) $[M - H - OMe]^+$, 550 (57) $[MH - CO_2Me]^+$, 549 (43) $[M - CO_2Me]^+$, 521 (15) $[M - CH_2CH_2CO_2Me]^+$, 462 (23) $[M - CO_2Me - CH_2CH_2CO_2Me]^+$, 461 (53) $[M - H - CO_2Me - CH_2CH_2CO_2Me]^+$.

General Method for Preparing Amides 4–12 Using the Synthesis of 4 as an Example. Compound **3** (30 mg, 0.048 mmol) was dissolved in THF (3 mL) ($CHCl_3$ for **9** and **11**), treated with aqueous methylamine (33%, 1 mL, ~42 mmol), stirred for 15 min, diluted with $CHCl_3$ (100 mL), and transferred to a separatory funnel. Traces of residual amine were rinsed out with aqueous HCl (1%, 200 mL) and then H_2O until the rinsings were neutral. The resulting solution was dried over anhydrous Na_2SO_4. Solvent was removed at reduced pressure. The resulting mixture of porphyrin compounds was separated by column chromatography (SiO_2, eluent CCl_4:acetone with increasing fraction of the latter).

Chlorin e_6 3-devinyl-3-formyl-13(1)-*N*-(methyl)-amide-15(2),17(3)-dimethyl ester (4) was obtained (16 mg, 60%) as a dark reddish-brown powder. IR spectrum (KBr, ν, cm^{-1}): 2752, 1738, 1664, 1656 (amide-I), 1608, 1507 (amide-II).

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 11.52 (1H, s, 3-CHO), 10.27 (1H, s, H-5), 9.63 (1H, s, H-10), 8.96 (1H, s, H-20), 6.43 (1H, m, NHMe), 5.56 and 5.29 [1H each, both d, J = 20.0, CH_2-15(1)], 4.48 (1H, q, J = 7.0, H-18), 4.38 (1H, br.d, J = 9.2, H-17), 3.84 [3H, s, Me-15(2)], 3.78 (3H, s, Me-2), 3.74 [2H, q, J = 7.5, CH_2-8(1)], 3.64 [3H, s, Me-17(4)], 3.55 (3H, s, Me-12), 3.31 (3H, s, Me-7), 3.29 (3H, d, J = 4.8, NHMe), 2.60-2.00 [4H, m, CH_2-17(1), CH_2-17(2)], 1.72 [3H, d, J = 7.0, Me-18(1)], 1.70 [3H, t, J = 7.7, Me-8(2)], –1.49 (1H, br.s, I-NH), –2.00 (1H, br.s, III-NH).

Mass spectrum (EI, *m*/*z*, I_{rel}, %): 639 (100) $[M]^+$, 608 (17) $[M - OMe]^+$, 607 (25) $[M - MeOH]^+$, 580 (20) $[MH - H_2 - CONHMe]^+$, 566 (35) $[MH - Me - CO_2Me]^+$, 550 (7) $[MH - H_2 - CH_2CO_2Me - Me]^+$, 549 (9) $[M - H_2 - CH_2CO_2Me - CH_3]^+$, 521 (7) $[MH - H_2 - CO_2CH_3 - CONHCH_3]^+$, 520 (8) $[M - H_2 - CO_2CH_3 - CONHMe]^+$, 495 (8) $[MH - CH_2CH_2CO_2Me - CONHMe]^+$, 480 (17) $[MH - CH_2CH_2CO_2Me - CH_2CO_2Me]^+$.

Chlorin e_6 3-devinyl-3-formyl-13(1)-*N*,*N*-(dimethyl)-amide-15(2),17(3)-dimethyl ester (5) was obtained (15 mg, 45%) from **3** (30 mg) as a dark reddish-brown powder. IR spectrum (KBr, ν, cm^{-1}): 2754, 1740, 1661, 1662, 1611.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): Major isomer: 11.57 (1H, s, 3-CHO), 10.34 (1H, s, H-5), 9.66 (1H, s, H-10), 9.00 (1H, s, H-20), 5.87 and 5.08 [1H each, both d, J = 18.7, CH_2-15(1)], 4.50 (1H, q, J = 7.0, H-18), 4.40 (1H, br.d, J = 9.6, H-17), 3.82 [3H, s, Me-15(2)], 3.81 (3H, s, Me-2), 3.80 [2H, m, CH_2-8(1)], 3.67 [3H, s, Me-17(4)], 3.50 (3H, s, Me-12), 3.47 and 2.77 (3H each, both s, NMe_2), 3.36 (3H, s, Me-7), 2.60–2.00 [4H, m, CH_2-17(1), CH_2-17(2)], 1.86–1.80 [6H, m, Me-18(1), Me-8(2)], –1.48 (1H, br.s, I-NH), –2.00 (1H, br.s, III-NH). Minor isomer: 11.56 (1H, s, 3-CHO), 10.34 (1H, s, H-5), 9.66 (1H, s, H-10), 8.97 (1H, s, H-20), 5.66 and 5.16 [1H each, both d, J = 19.3, CH_2-15(1)], 4.50 (1H, q, J = 7.0, H-18), 4.45 (1H, br.d, J = 9.4, H-17), 3.81 (3H, s, Me-2), 3.80 [2H, m, CH_2-8(1)], 3.79 [3H, s, Me-15(2)], 3.64 [3H, s, Me-17(4)], 3.51 and 3.14 (3H each, both s, NMe_2), 3.49 (3H, s, Me-12), 3.36 (3H, s, Me-7), 2.60–2.00 [4H, m, CH_2-17(1), CH_2-17(2)], 1.80–1.60 [6H, m, Me-18(1), Me-8(2)], –1.48 (1H, br.s, I-NH), –1.86 (1H, br.s, III-NH).

Mass spectrum (EI, *m*/*z*, I_{rel}, %): 654 (75) $[MH]^+$, 654 (100) $[M]^+$, 609 (16) $[MH - NHMe_2]^+$, 608 (20) $[M - NHMe_2]^+$, 582 (20) $[MH - CONMe_2]^+$, 581 (50) $[M - CONMe_2]^+$, 580 (36) $[MH - H_2 - CONMe_2]^+$, 549 (36) $[MH - H_2 - CONMe_2 - OMe]^+$, 495 (32) $[MH - CONMe_2 - CH_2CH_2CO_2Me]^+$, 494 (20) $[M - CONMe_2 - CH_2CH_2CO_2Me]^+$, 462 (18) $[MH - H_2 - CONMe_2 - CH_2CH_2CO_2Me - OMe]^+$, 461 (58) $[M - H_2 - CONMe_2 - CH_2CH_2CO_2Me - OMe]^+$.

Chlorin e_6 3-devinyl-3-formyl-13(1)-*N*-(benzyl)-amide-15(2),17(3)-dimethyl ester (6) was obtained (16 mg, 30%) from **3** (50 mg) as a dark reddish-brown powder. IR spectrum (KBr, ν, cm^{-1}): 2749, 1735, 1659, 1653, 1608, 1501.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 11.52 (1H, s, 3-CHO), 10.27 (1H, s, H-5), 9.62 (1H, s, H-10), 8.96 (1H, s, H-20), 7.58 [2H, d, J = 7.9, $NHCH_2\underline{Ph(o\text{-}H)}$], 7.45 [2H, t, J = 7.5, $NHCH_2\underline{Ph(m\text{-}H)}$], 7.37 [1H, t, J = 7.5, $NHCH_2\underline{Ph(p\text{-}H)}$], 6.80 (1H, br.t, J = 5.3, $N\underline{H}CH_2Ph$), 5.59 and 5.30 [1H each, both d, J = 18.7, CH_2-15(1)], 5.12 and 4.80 (1H each, both dd, J = 14.5, 6.1, $NHC\underline{H}_2Ph$), 4.48 (1H, q, J = 7.5, H-18), 4.40 (1H, br.d, J = 9.6, H-17), 3.78 [3H, s, Me-15(2)], 3.73 (3H, s, Me-2), 3.73 [2H, q, J = 7.5, CH_2-8(1)], 3.63 [3H, s, Me-17(4)], 3.54 (3H, s, Me-12), 3.30 (3H, s, Me-7), 2.00–2.80 [4H, m, CH_2-17(1), CH_2-17(2)], 1.71 [3H, d, J = 7.3, Me-18(1)], 1.68 [3H, t, J = 7.5, Me-8(2)], –1.50 (1H, br.s, I-NH), –1.98 (1H, br.s, III-NH).

Mass spectrum (EI, *m*/*z*, I_{rel}, %): 716 (73) $[MH]^+$, 715 (100) $[M]^+$, 684 (5) $[M - OMe]^+$, 656 (15) $[M - CO_2Me]^+$, 642 (48) $[M - CH_2CO_2Me]^+$, 625 (40) $[MH - CH_2Ph]^+$, 624 (78) $[M - CH_2Ph]^+$, 608 (34) $[MH - H_2 - NHCH_2Ph]^+$, 582 (8) $[MH - CONHCH_2Ph]^+$, 581 (10) $[M - CONHCH_2Ph]^+$, 566 (41) $[MH - CH_2Ph - CO_2Me]^+$, 565 (55) $[M - CH_2Ph - CO_2Me]^+$, 551 (30) $[M - CH_2Ph - CH_2CO_2Me]^+$, 550 (36) $[M - CONHCH_2Ph - OMe]^+$, 549 (27) $[MH - H_2 - CONHCH_2Ph - OMe]^+$.

Chlorin e_6 3-devinyl-3-formyl-13(1)-*N*,*N*-(diethyl)-amide-15(2),17(3)-dimethyl ester (7) was obtained (12 mg, 36%) from **3** (30 mg) as a dark reddish-brown powder. IR spectrum (KBr, ν, cm^{-1}): 2746, 1739, 1667, 1658, 1608.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): Major isomer: 11.58 (1H, s, 3-CHO), 10.37 (1H, s, H-5), 9.68 (1H, s, H-10), 9.03 (1H, s, H-20), 5.74 and 5.12 [1H each, both d, J = 19.0, CH_2-15(1)], 4.70–4.50 [4H, m, $N(C\underline{H}_2Me)_2$], 4.49 (1H, m, H-18), 4.34 (1H, m, H-17), 3.82 [3H, s, Me-15(2)], 3.82 (3H, s, Me-2), 3.80 [2H, m, CH_2-8(1)], 3.65 [3H, s, Me-17(4)], 3.54 (3H, s, Me-12), 3.37 (3H, s, Me-7), 2.60–1.90 [4H, m, CH_2-17(1), CH_2-17(2)], 1.77 [3H, d, J = 8.0, Me-18(1)], 1.73 [3H, t, J = 8.0, Me-8(2)], 1.20 [6H, m, $N(CH_2\underline{Me})_2$], –1.51 (1H, br.s, I-NH), –2.00 (1H, br.s, III-NH). Minor isomer: 11.57 (1H, s, 3-CHO), 10.35 (1H, s, H-5), 9.67 (1H, s, H-10), 9.03 (1H, s, H-20), 5.34 and 5.27 [1H each, both d, J = 19.0, CH_2-15(1)], 4.70–4.50 [4H, m, $N(C\underline{H}_2Me)_2$], 4.49 (1H, m, H-18), 4.34 (1H, m, H-17), 3.82 (3H, s, Me-2), 3.80 [2H, m, CH_2-8(1)], 3.78 [3H, s, Me-15(2)], 3.64 [3H, s, Me-17(4)], 3.51 (3H, s, Me-12), 3.37 (3H, s, Me-7), 2.60–1.90 [4H, m, CH_2-17(1), CH_2-17(2)], 1.77 [3H, d, J = 8.0, Me-18(1)], 1.73 [3H, t, J = 8.0, Me-8(2)], 1.20 [6H, m, $N(CH_2\underline{Me})_2$], –1.51 (1H, br.s, I-NH), –1.90 (1H, br.s, III-NH).

Mass spectrum (EI, *m*/*z*, I_{rel}, %): 682 (46) $[MH]^+$, 681 (100) $[M]^+$, 653 (12) $[MH - Et]^+$, 609 (26) $[MH - NHEt_2]^+$, 608 (65) $[MH - H_2 - NEt_2]^+$, 582 (12) $[MH - CONEt_2]^+$, 580 (12) $[MH - H_2 - CONEt_2]^+$, 550 (22) $[MH - CO - NHEt_2 - OMe]^+$, 549 (46) $[MH - H_2 - CONEt_2 - OMe]^+$, 522 (41) $[MH - CO - NHEt_2 - CO_2Me]^+$, 463 (14) $[M - CONEt_2 - CH_2CH_2CO_2Me - OMe]^+$, 462 (20) $[MH - H_2 - CONEt_2 - CH_2CH_2CO_2Me - OMe]^+$, 461 (29) $[M - H_2 - CONEt_2 - CH_2CH_2CO_2Me - OMe]^+$.

Rhodin g_7 13-*N*-methylamide-15,17-dimethyl ester (8) was obtained (9 mg, 52%) from **2** (15 mg) as a dark brown powder. IR spectrum (KBr, ν, cm^{-1}): 2750, 1736, 1661, 1650, 1605, 1503.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 10.30 (1H, s, 7-CHO), 10.14 (1H, s, H-5), 8.71 (1H, s, H-10), 8.47 (1H, s, H-20), 8.06 [1H, dd, J = 18.0, 11.3, H-3(1)], 7.24 (1H, q, J = 4.0, NHMe), 6.46 [1H, d, J = 18.0, H*trans*-3(2)], 6.22 [1H, d, J = 11.7, H*cis*-3(2)], 5.48 and 5.32 [1H each, both d, J = 19.6, CH_2-15(1)], 4.45 (1H, q, J = 7.1, H-18), 4.35 (1H, br.d, J = 9.4, H-17), 3.91 [3H, s, Me-15(2)], 3.67 [3H, s, Me-17(4)], 3.47 (3H, s, Me-12), 3.40 (3H, d, J = 4.3, NHMe), 2.66–2.56 [2H, m, CH_2-8(1)], 3.24 (3H, s, Me-2), 2.36–2.18, 1.90–1.80 [4H, all m, CH_2-17(1), CH_2-17(2)], 1.73 [3H, d, J = 6.4, Me-18(1)], 0.98 [3H, t, J = 6.4, Me-8(2)], –1.17 (1H, br.s, I-NH), –1.32 (1H, br.s, III-NH).

Mass spectrum (EI, *m*/*z*, I_{rel}, %): 652 (35) $[MH]^+$, 651 (40) $[M]^+$, 650 (7) $[MH - H_2]^+$ or $[M - H]^+$, 620 (14) $[MH - NHMe]^+$, 592 (15) $[M - H - CONHMe]^+$, 534 (40) $[M - CONHMe - CH_2CH_2CO_2Me]^+$, 533 (75) $[M - H - CONHMe - CH_2CH_2CO_2Me]^+$, 532 (100) $[M - CONHMe - CH_2CH_2CO_2Me - H_2]^+$, 445 (55) $[M - CONHMe - CO_2Me - CH_2CH_2CO_2Me - H_2]^+$.

Rhodin g_7 13-*N*,*N*-dimethylamide-15,17-dimethyl ester (9) was obtained (87 mg, 84%) from **2** (100 mg) as a dark reddish-brown powder. IR spectrum (KBr, ν, cm^{-1}): 2740, 1742, 1666, 1638, 1610.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): Major isomer: 11.17 (1H, s, 7-CHO), 10.45 (1H, s, H-5), 9.71 (1H, s, H-10), 8.71 (1H, s, H-20), 8.02 [1H, dd, J = 17.6, 12.0, H-3(1)], 6.39 [1H, dd, J = 17.6, 1.2, H*trans*-3(2)], 6.15 [1H, dd, J = 12.0, 1.2, H*cis*-3(2)], 5.77 and 5.01 [1H each, both d, J = 19.2, CH_2-15(1)], 4.44 (1H, q, J = 7.0, H-18), 4.31 (1H, br.d, J = 9.4, H-17), 4.11 [2H, q, J = 7.4, CH_2-8(1)], 3.82 [3H, s, Me-15(2)], 3.67 [3H, s, Me-17(4)], 3.45 (3H, s, Me-12), 3.41 (3H, s, Me-2), 3.45 and 2.77 (3H each, both s, NMe_2), 2.65–2.51, 2.34–2.15, 1.77–1.68 [4H, all m, CH_2-17(1), CH_2-17(2)], 1.82 [3H, t, J = 7.4, Me-8(2)], 1.72 [3H, d, J = 6.7, Me-18(1)], –1.19 (1H, br.s, I-NH), –1.23 (1H, br.s, III-NH). Minor isomer: 11.17 (1H, s, 7-CHO), 10.41 (1H, s, H-5), 9.69 (1H, s, H-10), 8.67 (1H, s, H-20), 8.00 [1H, dd, J = 18.4, 11.6, H-3(1)], 6.38 [1H, dd, J = 18.0, 1.2, H*trans*-3(2)], 6.15 [1H, dd, J = 12.0, 1.2, H*cis*-3(2)], 5.61 and 5.06 [1H each, both d, J = 19.1, CH_2-15(1)], 4.42 (1H, q, J = 7.0, H-18), 4.38 (1H, br.d, J = 9.6, H-17), 4.11 [2H, q, J = 7.4, CH_2-8(1)], 3.79 [3H, s, Me-15(2)], 3.64 [3H, s, Me-17(4)], 3.44 (3H, s, Me-12), 3.40 (3H, s, Me-2), 3.49 and 3.14 (3H each, both s, NMe_2), 2.66–2.51, 2.34–2.15, 1.77–1.68 [4H, all m, CH_2-17(1), CH_2-17(2)], 1.82 [3H, t, J = 7.4, Me-8(2)], 1.67 [3H, d, J = 6.7, Me-18(1)], –1.00 (1H, br.s, I-NH), –1.12 (1H, br.s, III-NH).

Mass spectrum (EI, *m*/*z*, I_{rel}, %): 666 (100) $[MH]^+$, 665 (95) $[M]^+$, 634 (7) $[M - OMe]^+$, 621 (24) $[MH - HNMe_2]^+$, 593 (29) $[MH - NHMe_2 - CO]^+$, 592 (34) $[MH - HNMe_2 - H - CO]^+$, 561 (55) $[MH - NHMe_2 - H - CO_2Me]^+$ or $[MH - NHMe_2 - H - CO - OMe]^+$, 546 (17) $[M - H - CO - OMe]^+$ or $[M - H - OMe - CH_2CH_2CO_2Me]^+$, 533 (15) $[MH - NHMe_2 - H - CO - CO_2Me]^+$, 506 (60) $[MH - HNMe_2 - CO - CH_2CH_2CO_2Me]^+$, 474 (16) $[MH - HNMe_2 - H - CH_2CH_2CO_2Me - CO_2Me]^+$.

Rhodin g_7 13-*N*-benzylamide-15,17-dimethyl ester (10) was obtained (11 mg, 50%) from **2** (15 mg) as a dark brown powder. IR spectrum (KBr, ν, cm^{-1}): 2750, 1736, 1653, 1650, 1605, 1522.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 10.31 (1H, s, 7-CHO), 10.16 (1H, s, H-5), 8.70 (1H, s, H-10), 8.59 (1H, s, H-20), 8.01 [1H, dd, J = 18.0, 11.6, H-3(1)], 7.61 (1H, m, NHCH$_2$Ph), 7.73 [2H, d, J = 7.8, NHCH$_2$Ph(*o*-H)], 7.54 [2H, t, J = 7.4, NHCH$_2$Ph(*m*-H)], 7.44 [1H, t, J = 7.4, NHCH$_2$Ph(*p*-H)], 6.42 [1H, d, J = 18.0, H*trans*-3(2)], 6.14 [1H, d, J = 11.2, H*cis*-3(2)], 5.52 and 5.33 [1H each, both d, J = 19.2, CH_2-15(1)], 5.13 and 4.93 (1H each, both dd, J = 15.1, 5.8, NHCH_2Ph), 4.59 (1H, m, H-18), 4.44 [2H, q, J = 6.8, CH_2-8(1)], 4.36 (1H, br.d, J = 9.4, H-17), 3.80 [3H, s, Me-15(2)], 3.66 [3H, s, Me-17(4)], 3.47 (3H, s, Me-12), 3.28 (3H, s, Me-2), 2.66–2.54, 2.38–2.18, 1.90–1.80 [4H, all m, CH_2-17(1), CH_2-17(2)], 1.71 [3H, d, J = 6.8, Me-18(1)], 1.01 [3H, t, J = 6.4, Me-8(2)], –1.16 (1H, br.s, I-NH), –1.28 (1H, br.s, III-NH).

Mass spectrum (MALDI, *m*/*z*): 728.521 $[MH]^+$.

Rhodin g_7 13-*N*,*N*-diethylamide-15,17-dimethyl ester (11) was obtained (11 mg, 48%) from **2** (15 mg) as a dark brown powder. IR spectrum (KBr, ν, cm^{-1}): 2740, 1740, 1661, 1636, 1608.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): Major isomer: 11.22 (1H, s, 7-CHO), 10.50 (1H, s, H-5), 9.74 (1H, s, H-10), 8.72 (1H, s, H-20), 8.06 [1H, dd, J = 18.0, 12.0, H-3(1)], 6.42 [1H, d, J = 18.0, H*trans*-3(2)], 6.18 [1H, d, J = 11.6, H*cis*-3(2)], 5.63 and 5.03 [1H each, both d, J = 19.0, CH_2-15(1)], 4.41 (1H, q, J = 8.0, H-18), 4.26 (1H, br.d, J = 10.6, H-17), 4.16 [2H, q, J = 7.8, CH_2-8(1)], 4.05–3.80 (4H, m, NCH_2Me), 3.82 [3H, s, Me-15(2)], 3.65 [3H, s, Me-17(4)], 3.50 (3H, s, Me-12), 3.44 (3H, s, Me-2), 2.66–2.51, 2.34–2.15, 1.77–1.68 [4H, all m, CH_2-17(1), CH_2-17(2)], 1.84 [3H, t, J = 7.6, Me-8(2)], 1.74 [3H, d, J = 7.6, Me-18(1)], 0.92 (6H, t, J = 7.4, NCH$_2$Me), –1.17 (1H, br.s, I-NH), – 1.23 (1H, br.s, III-NH). Minor isomer: 11.22 (1H, s, 7-CHO), 10.48 (1H, s, H-5), 9.72 (1H, s, H-10), 8.70 (1H, s, H-20), 8.05 [1H, dd, J = 18.4, 12.0, H-3(1)], 6.42 [1H, d, J = 18.0, H*trans*-3(2)], 6.18 [1H, d, J = 11.6, H*cis*-3(2)], 5.21 [2H, s, CH_2-15(1)], 4.43 (1H, q, J = 6.8, H-18), 4.28 (1H, br.d, J = 10.6, H-17), 4.16 [2H, q, J = 7.8, CH_2-8(1)], 3.78 [3H, s, Me-15(2)], 3.64 [3H, s, Me-17(4)], 3.47 (3H, s, Me-12), 3.43 (3H, s, Me-2), 3.21–2.93 (4H, m, NCH_2Me), 2.66–2.51, 2.34–2.15, 1.77–1.68 [4H, all m, CH_2-17(1),

CH_2-17(2)], 1.84 [3H, t, J = 7.6, Me-8(2)], 1.74 [3H, d, J = 7.6, Me-18(1)], 1.12 (6H, t, J = 7.0, $NCH_2\underline{Me}$), –1.17 (1H, br.s, I-NH), –1.23 (1H, br.s, III-NH).

Rhodin g_7 13-morpholinylamide-15,17-dimethyl ester (12) was obtained (7 mg, 46%) from **2** (10 mg) as a dark brown powder. IR spectrum (KBr, ν, cm^{-1}): 2741, 1736, 1661, 1632, 1605.

PMR spectrum (400 MHz, $CDCl_3$, δ, ppm, J/Hz): Major isomer: 11.23 (1H, s, 7-CHO), 10.51 (1H, s, H-5), 9.76 (1H, s, H-10), 8.72 (1H, s, H-20), 8.06 [1H, dd, J = 18.0, 12.0, H-3(1)], 6.43 [1H, dd, J = 17.6, 1.0, H*trans*-3(2)], 6.19 [1H, dd, J = 11.2, 1.0, H*cis*-3(2)], 5.71 and 5.03 [1H each, both d, J = 19.0, CH_2-15(1)], 4.57 (1H, dt, J = 10.6, 2.4, H-17), 4.42 (1H, q, J = 8.0, H-18), 4.23–4.14 [2H, m, CH_2-8(1)], 4.40–4.31, 4.12–3.98, 3.96–3.87, 3.81–3.73 [6H, all m, $N(CH_2)_2O(CH_2)_2$], 3.14 [2H, t, J = 4.7, $N(CH_2)_2O(CH_2)_2$], 3.87 [3H, s, Me-15(2)], 3.67 [3H, s, Me-17(4)], 3.53 (3H, s, Me-12), 3.44 (3H, s, Me-2), 2.64–2.15 [4H, m, CH_2-17(1), CH_2-17(2)], 1.86 [3H, t, J = 8.0, Me-8(2)], 1.73 [3H, d, J = 7.1, Me-18(1)], –1.14 (1H, br.s, I-NH), –1.18 (1H, br.s, III-NH). Minor isomer: 11.22 (1H, s, 7-CHO), 10.47 (1H, s, H-5), 9.73 (1H, s, H-10), 8.67 (1H, s, H-20), 8.05 [1H, dd, J = 18.0, 12.0, H-3(1)], 6.42 [1H, dd, J = 17.6, 1.0, H*trans*-3(2)], 6.19 [1H, dd, J = 11.2, 1.0, H*cis*-3(2)], 5.42 and 5.12 [1H each, both d, J = 19.0, CH_2-15(1)], 4.35 (1H, t, J = 8.0, H-17), 4.42 (1H, q, J = 8.0, H-18), 4.23–4.14 [2H, m, CH_2-8(1)], 4.40–4.31, 4.12–3.98, 3.96–3.87, 3.81–3.73, 3.58–3.53 [8H, all m, $N(CH_2)_2O(CH_2)_2$], 3.83 [3H, s, Me-15(2)], 3.63 [3H, s, Me-17(4)], 3.49 (3H, s, Me-12), 3.43 (3H, s, Me-2), 2.64–2.15 [4H, m, CH_2-17(1), CH_2-17(2)], 1.86 [3H, t, J = 8.0, Me-8(2)], 1.73 [3H, d, J = 7.1, Me-18(1)], –0.97 (1H, br.s, I-NH), –1.06 (1H, br.s, III-NH).

Mass spectrum (EI, *m*/*z*, I_{rel} %): 706 (100) $[MH]^+$, 707 (80) $[M]^+$, 648 (20) $[M - CO_2Me]^+$, 620 (40) $[MH - NH(CH_2CH_2)_2O - H]^+$ or $[M - CH_2CH_2CO_2Me]^+$.

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