solution was transferred to Et_2O (150 mL), washed with H_2O (100 mL × 4), and extracted with cold 5% HCl (50 mL × 6). The acid extract was washed with Et_2O (100 mL × 2) and extracted with CH_2Cl_2 (50 mL × 4). The CH_2Cl_2 extract was washed with H_2O and the solvent removed; yield after vacuum drying, 1.07 g (85%). Workup of the ether phases yielded 0.131 g (10.4%) of impure **2.** The major fraction was chromatographed on a silicic acid column (2.5 × 32 cm) with methanol/acetone/CCl_4 1:20:79 and twice crystalized from methylene chloride/pentane. Anal. Calcd for $C_{37}H_{43}O_5N_5$: C, 69.67; H, 6.81; N, 10.98. Found: C, 69.31; H, 6.73; N, 11.11.

To verify the structure of **2** the procedure was modified to employ a quantitative workup. $CHCl_3$ was added directly to the reaction flask, and the organic phase was washed with successive portions of cold water, removing the excess CH_3NH_2 but no chlorin. After solvent removal and vacuum drying, the entire reaction was analyzed by ^1H NMR, demonstrating the presence of only one chlorin.

Determination of the Epimer Ratio. In addition to the C-10 carbomethoxymethyl group used by Katz et al.,[11] the resonances for the β- and δ-methine protons were selected on the basis of minimum signal interference and maximum epimer chemical-shift difference. Either multiple scans were averaged on a Varian A-60 spectrometer and integrated, or in the case of very dilute samples the FT 220-MHz ^1H NMR spectrum was obtained and the peaks were integrated to determine the epimer ratio.

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Registry No.—**1,** 5594-30-9; **2,** 64070-09-3; **3,** 64045-79-0.

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An Improved Chemical Synthesis of Racemic Phycocyanobilin Dimethyl Ester[1]

Albert Gossauer* and Ralf-Peter Hinze

Institut für Organische Chemie der Technischen Universität D-3300 Braunschweig, West Germany

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The title compound, a bile pigment-like product isolated from the photosynthetically active chromoproteins of the blue-green and red algae, has been synthesized chemically in 32% overall yield from readily accessible starting materials. The key reaction of the synthesis consists of the preparation of the 3,4-dihydro-5(1*H*)-pyrromethenone **11a** by condensation of the monothiosuccinimide **8** with the pyrrole derivative **10.** This reaction represents a new type of formation of C=C bonds using resonance-stabilized phosphorus ylides.

Phycocyanobilin is the blue pigment released by boiling methanol from the photosynthetically active chromoproteins R and C phycocyanin and allophycocyanin of the blue-green and red algae.[2,3] The structure of phycocyanobilin has been elucidated by means of spectroscopic[4,5] as well as degradation studies.[6]

Three years ago a convergent chemical synthesis of racemic phycocyanobilin dimethyl ester (***rac*-15**) was achieved for the first time in our laboratory by condensation of methyl 5′-formylisoneoxanthobilirubinate (**13b**) with the 5(1*H*)-pyrromethenone derivative **11b.** The latter was obtained by reaction of the substituted monothiosuccinimide **8** with the brominated pyrrole derivative **9** under the conditions of Eschenmoser's sulfide contraction method.[7] However, the overall yield of this synthesis amounted only to 0.6% when referred to 3-ethylidene-4-methylpyrrolidine-2,5-dione which was used as a precursor of the ring I of the bile pigment. This unsatisfactory result was attributable to the occurence of several critical steps in the synthesis, namely: (i) the nonregiospecific transformation of the 3-ethylidene-4-methylpyrrolidine-2,5-dione into the corresponding 2-monothio derivative **8,** (ii) the moderate yield of the sulfide contraction reaction of **8** with **9** even though it could be improved from 18 to 49% by carrying out the reaction at −78 °C, and (iii) the relatively low reactivity of the *tert*-butyl ester **11b** toward the aldehyde **13b.**

We have now improved considerably the overall yield of the synthesis of phycocyanobilin dimethyl ester by introducing some substantial modifications into our earlier approach. Thus, monothioimide **8** was prepared regiospecifically as follows: alkylation of diethyl cyanomethylphosphonate (**1**)[8]

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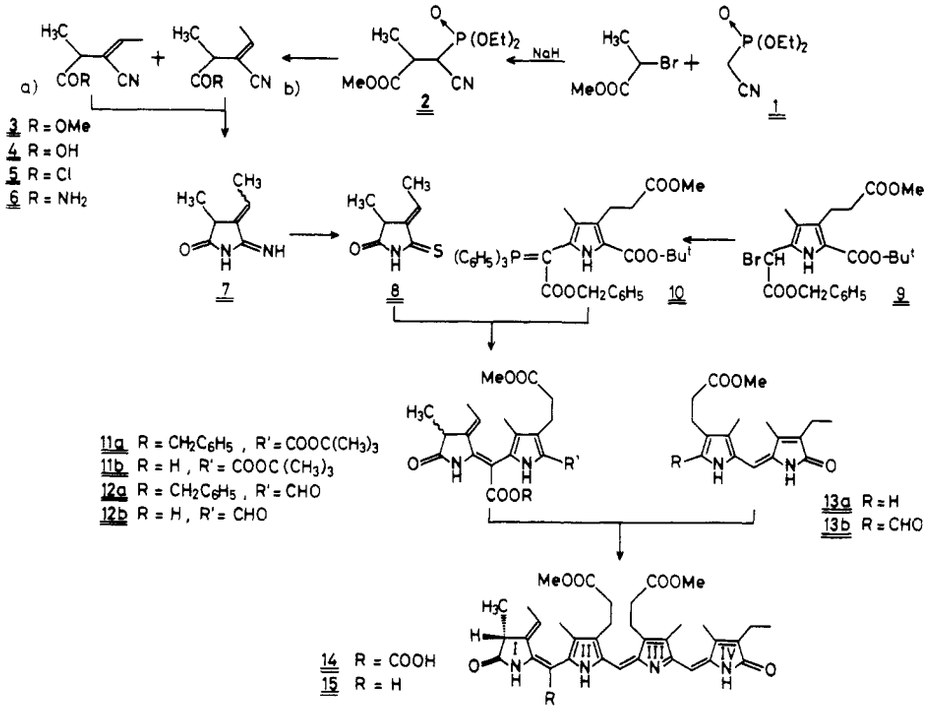

with methyl α-bromopropionate and subsequent Horner reaction of the obtained phosphonic acid ester **2** with acetaldehyde led to the monomethyl ester **3** (as a mixture of *Z* and *E* isomers) which was selectively hydrolyzed to the corresponding carboxylic acids **4** and subsequently transformed into the chlorides **5** and the amides **6**. The latter were cyclized in the presence of sodium ethoxide, yielding the succinimidines **7** which on treatment with hydrogen sulfide in pyridine afforded pure (*E*)-ethylidenemethylmonothiosuccinimide (**8**) in 38% overall yield (referred to **3**). As only the *E* isomer of **8** is obtained from a mixture of *Z*- and *E*-configurated **7**, no attempt was made to separate the stereoisomers of the intermediates **4** to **7**. Reaction of **8** with the phosphorus ylide **10**, which is readily accessible from the brominated pyrrole derivative **9**[7] by treatment with triphenylphosphine, afforded the 3,4-dihydro-5(1*H*)-pyrromethenone derivative **11a** in 79% yield. This kind of reaction, whose mechanism is presumably analogous to that of the Wittig reaction involving the C=S bond, represents a new general method for the synthesis of alkylidene lactams from monothioimides and resonance-stabilized phosphorus ylides.

Formylation of **11a** with triethyl orthoformate in trifluoroacetic acid (see ref 10) afforded the corresponding aldehyde **12a** whose benzylic ester group was cleaved by hydrogenolysis. Acid-catalyzed condensation of **12b** with the already known[11] methyl isoneoxanthobilirubinate **13a** yielded 5-hydroxycarbonylphycocyanobilin dimethyl ester ***rac*-14** which was finally decarboxylated by treatment with trifluoracetic acid at room temperature.

The overall yield of the thus obtained phycocyanobilin dimethyl ester (***rac*-15**) amounted to 32% (referred to **8**); its analytical and spectroscopic data, including IR, UV/vis, and ^{1}H NMR, agree with those of the pigment isolated from C phycocyanin by treatment with boiling methanol as well as of the synthetic material prepared earlier by us.[7]

Experimental Section

Melting points were determined with a Kofler hot-stage melting-point apparatus (Reichert) and are uncorrected. UV and visible spectra were recorded on a Leitz-Unicam SP 800 B spectrophotometer using methanol solutions unless otherwise specified. Infrared spectra (IR) were run on a Perkin-Elmer Model 157 G spectrometer in KBr disks. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian Associates Models T-60 and XL 100 and a Bruker Model HFX-90 instruments using deuteriochloroform solutions. Chemical shifts (δ) are expressed in parts per million downfield from internal tetramethylsilane and coupling constants (*J* values) in hertz. Spin multiplicities are indicated by symbols s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Mass spectra (MS) data were obtained at an ionizing voltage of 70 eV on AEI MS 9 and MS 30 instruments as well as on a Varian-Mat Model CH 4 mass spectrometer. Metastable peaks are given as m*. Elemental analyses were performed by I. Beetz Microanalytical Laboratories, D-8640 Kronach. Preparative layer chromatography of colorless products or pigments made use of 2-mm-thick plates measuring 100 × 20 cm precoated with silica gel $PF_{254+366}$ or silica gel H (both from E. Merck, Darmstadt), respectively.

(*Z*)- and (*E*)-Methyl 3-Cyano-2-methyl-3-pentenoate (3a and 3b). A cooled suspension of sodium hydride (3 g as 80% dispersion in mineral oil) in ethylene glycol dimethyl ether (250 mL) was treated dropwise with diethyl cyanomethylphosphonate[8] (17.7 g), and the mixture was stirred until the evolution of hydrogen was complete. Thereafter, methyl 2-bromopropionate (16.7 g) was added at once and the mixture was allowed to stand at room temperature overnight. Then, sodium hydride (3 g as 80% dispersion in mineral oil) was added, the suspension was stirred for 5 h at room temperature before it was cooled to 0 °C and acetaldehyde (4.4 g) was added dropwise. The mixture was stirred overnight at room temperature, thereupon water (200 mL) was added and the reaction mixture was extracted repeatedly with ether (4 × 100 mL). The organic phases were dried (Na_2SO_4) and the solvent was removed on the rotary evaporator. The oily residue was then fractionated in a spinning-band column to give 10 g (63%) of the *E* isomer **3b:** $bp_{0.1}$ 48 °C; IR (neat) 2800, 2170, 1710, 1620, 1420, 1190, 1080, 1050, 980, 840 cm^{-1}; ^{1}H NMR δ 1.33 (d, 3, *J* = 7.5 Hz, CH_3), 1.90 (d, 3, *J* = 7 Hz, vinylic CH_3), 3.40 (9, 1, *J* = 7.5 Hz, 2-H), 3.72 (s, 3, OCH_3), 6.53 ppm (q, 1, *J* = 7 Hz, vinylic H); MS *m/e* (rel intensity) 153 (52, M^+), 138 (20), 122 (10), 94 (78), 67 (55), 59 (100); m* 124.4 (153 → 138), 47.7 (94 → 67).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.76; H, 7.90; N, 9.14. Found: C, 62.80; H, 7.95; N, 9.14.

A second fraction ($bp_{0.1}$ 51 °C) contained the *Z*-isomer **3a** (2 g; 15%): IR (neat) 2800, 2170, 1710, 1625, 1420, 1190, 1110, 1050, 980, 840 cm^{-1}; ^{1}H NMR δ 1.33 (d, 3, *J* = 7.5 Hz, CH_3) 2.03 (d, 3, *J* = 7 Hz, vinyl CH_3), 3.41 (q, 1, *J* = 7.5 Hz, H-2), 3.72 (s, 3, OCH_3), 6.54 ppm (q, 1, *J* = 7 Hz, vinylic H); MS *m/e* (rel intensity) 153 (53, M^+), 138 (20), 122 (10), 94 (78), 67 (55), 59 (100); m* 124.4 (153 → 138), 47.7 (94 → 67).

(*Z*)- and (*E*)-3-Cyano-2-methyl-3-pentenoic Acid Amide (6). Both *Z* and *E* isomers **3a** and **3b** were suspended together in 2 N KOH (100 mL), and the mixture was stirred for 40 min at room temperature. The obtained solution was extracted repeatedly with ether (4 × 50 mL), then acidified with 2 N H_2SO_4, and extracted with ethyl acetate (5 × 100 mL). The organic phases were dried (Na_2SO_4), the solvent was removed on a rotary evaporator, and the oily residue (10 g) was dissolved without further purification in dry benzene (50 mL). The solution was cooled to 0 °C and $SOCl_2$ (10 mL) was added. After the evolution of gas had ceased, the mixture was stirred for 30 min at 40

°C and thereafter the solvent was removed in vacuo. The oily residue was dissolved in dry tetrahydrofuran (20 mL) and the solution was dropped slowly into a chilled (−78 °C) solution of liquid ammonia (20 mL) in tetrahydrofuran (100 mL). The mixture was allowed to warm to room temperature, the solvent was removed in vacuo, the residue was extracted with boiling acetone, and the remaining NH_4Cl was filtered off. The filtrate was concentrated in vacuo, and the oily residue was purified by column chromatography on alumina (activity grade II) eluting successively with ethyl acetate and ethyl acetate/methanol (8:2). The product obtained after evaporation of the solvent (5.5 g, 55%) was further purified by crystallization from ethyl acetate/ether, yielding a white solid which consisted of a mixture of both stereoisomeric amides **6**: MS *m/e* (rel intensity) 138 (20, M^+), 123 (20), 94 (78), 79 (25), 67 (100), 66 (95), 44 (75); m* 47.8 (94 → 67), 32.5 (138 → 66).

Anal. Calcd for $C_7H_{10}N_2O$: C, 60.83; H, 7.29; N, 20.27. Found: C, 60.72; H, 7.15; N, 20.20.

(*Z*)- and (*E*)-2-Ethylidene-5-imino-3-methylpyrrolidine-2-one (7). A solution of the amides **6** (5 g) in dry ethanol (100 mL) was treated with 2 N sodium ethoxide in ethanol (100 mL), and the mixture was allowed to stand for 1 h at room temperature. The solvent was removed on a rotary evaporator and the remaining oily residue was purified by column chromatography on silica gel (300 g) with ethyl acetate as eluent. After removal of the solvent, a white solid (4.8 g; 96%) was obtained: mp 189–190 °C; UV λ_{max} (log ϵ) 218 (3.95), 265 nm (4.10); MS *m/e* (rel intensity) 138 (80, M^+), 123 (30), 111 (60), 96 (35), 68 (45), 44 (100); m* 109.6 (138 → 123), 89.3 (138 → 111), 81.3 (111 → 96).

(*E*)-2-Ethylidene-3-methyl-1-thiosuccinimide (8). Gaseous hydrogen sulfide (dried over Al_2S_3) was bubbled for 1 h into a solution of the iminopyrrolidinones **7** (4 g) in dry pyridine (25 mL). Thereafter a stream of nitrogen was passed for 10 min through the boiling reaction mixture. After evaporation of the solvent, the remaining pyridine was removed by repeated addition of toluene and evaporation to dryness on the rotary evaporator. Recrystallization of the residue from ether/*n*-hexane yielded 3.5 g (78%) of the product as a pale-yellow solid, mp 115 °C (Lit.[7] mp 113–115 °C).

Benzyl α-Triphenylphosphoranylidene-α-[5-*tert*-butoxycarbonyl-4-(2-methoxycarbonylethyl)-3-methylpyrrol-2-yl)-acetate (10). A solution of triphenylphosphine (262 mg) in ether (10 mL) was added dropwise to a solution of **9**[7] (493 mg) in anhydrous ether (50 mL) and the mixture was allowed to stand overnight at room temperature. The formed phosphonium salt was separated by filtration, washed with ether (200 mL) and suspended in the same solvent (50 mL). The suspension was shaken in a separatory funnel with saturated aqueous Na_2CO_3 solution (50 mL) until two clear layers appeared. The organic phase was separated and the aqueous layer extracted once with ether (50 mL). The organic phases were dried (Na_2SO_4) and evaporated in vacuo to afford the product (641 mg; 95%) as a while solid: mp 65 °C; UV λ_{max} (log ϵ) 267 (4.29), 275 (4,31), 294 nm (4.44); IR 3470, 2980, 2920, 1730, 1640, 1620, 1430, 740, 697 cm^{-1}; ^1H NMR δ 1.50 (s, 9, $C(CH_3)_3$), 1.62 (s, 3, CH_3), 2.3 (m, 2, α-methylene of propionic ester), 2.8 (m, 2, β-methylene of propionic ester), 3.65 (s, 3, OCH_3), 5.10 (br s, 2, benzylic H), 7.3–7.6 (m, 20, phenyl H), 8.2 ppm (br s, 1, NH); MS m/e (rel intensity) 675 (10, M^+), 619 (10), 262 (12), 247 (30), 166 (100), 91 (55).

Anal. Calcd for $C_{41}H_{42}NO_6P$: C, 72.88; H, 6.27; N, 2.07; P, 4.58. Found: C, 73.04. H, 6.40: N, 2.10; P, 4.50.

3-Ethylidene-*ms*-benzyloxycarbonyl-5′-*tert*-butoxycarbonyl-3′,4-dimethyl-3,4-dihydro-5(1*H*)-2,2′-pyrromethenone-4′-propionic Acid Methyl Ester (11a). A solution of **10** (641 mg) and **8** (221 mg) in dry toluene (20 mL) was refluxed for 18 h under argon. After evaporation of the solvent in vacuo, the desired product was separated from the formed triphenylphosphine sulfide by preparative TLC eluting with ether/*n*-hexane (6:4). Besides **11a** (420 mg; 79%), small quantities of the starting materials **8** (55 mg) and **10** (14 mg) were recovered, corresponding to two minor components of the reaction mixture with a higher and a lower R_f value than the main product, respectively. Crystallization of the latter from ether/*n*-hexane yielded yellow prisms, mp 138 °C, (lit.[7] 137–138 °C).

3-Ethylidene-*ms*-benzyloxycarbonyl-5′-formyl-3′,4-dimethyl-3,4-dihydro-5(1*H*)-2,2′-pyrromethenone-4′-propionic Acid Methyl Ester (12a). A solution of **11a** (400 mg) in trifluoroacetic acid (8 mL) was allowed to stand under argon for 5 min at room temperature. Trimethyl orthoformate (4 mL) was added, and after 4 min the mixture was poured into water (50 mL). The obtained solution was extracted several times with CH_2Cl_2, the organic phases were dried (Na_2SO_4), and the solvent was removed on the rotary evaporator. Crystallization of the residue from ether/*n*-hexane yielded **12a** (300 mg; 93%): mp 142–143 °C; UV λ_{max} (log ϵ) 234 (4.57), 309 (4.74), 350 nm (4.22); IR 3480, 3330, 2950, 1780, 1665, 1640, 1250, 1150, 1025, 740 cm^{-1}; ^1H NMR δ 1.35 (d, 3, J = 7 Hz, 4-CH_3), 1.66 (dd, 3, ^3J = 7 Hz, ^5J = 1.5 Hz, ethylidene CH_3), 1.80 (s, 3, 3′-CH_3), 2.55 (m, 2, α-methylene of propionic ester), 3.08 (m, 3, β-methylene of propionic ester overlapped by 4-H), 3.63 (s, 3, OCH_3), 5.16 (s, 2, benzylic H), 5.24 (dq, 1, ^3J = 7 Hz, ^4J = 2 Hz, vinylic H), 7.24 (s, 5, phenyl H), 8.9 (br s, 1, NH), 9.61 (s, 1, CHO), 10.7 ppm (br s, 1, NH); MS *m/e* (rel intensity) 464 (10, M^+), 329 (20), 148 (15), 91 (100).

Anal. Calcd for $C_{26}H_{28}N_2O_6$: C, 67.24; H, 6.08; N, 6.03. Found: C, 67.24; H, 6.21; N, 6.06.

3-Ethylidene-4′-(2-methoxycarbonylethyl)-5′-formyl-3′,4-dimethyl-3,4-dihydro-5(1*H*)-2,2′-pyrromethenone-*ms*-carboxylic Acid (12b). A solution of **12a** (300 mg) in tetrahydrofuran (30 mL) was hydrogenated on 10% palladized charcoal (100 mg) at atmospheric pressure for 10 min. The catalyst was removed by filtration and the solvent evaporated in vacuo. Crystallization of the residue from ether/*n*-hexane yielded the product (215 mg; 89%): mp 163 °C; UV λ_{max} (log ϵ) 234 (4.61), 311 (4.77), 349 nm (4.36); IR 3480, 3260, 2980, 1760, 1660, 1590, 1248 cm^{-1}; ^1H NMR δ 1.36 (d, 3, J = 7 Hz, 4-CH_3), 1.68 (d, 3, J = 7 Hz, ethylidene CH_3), 1.92 (s, 3, 3′-CH_3), 2.6 (m, 2, α-methylene of propionic ester), 3.1 (m, 3, β-methylene of propionic ester overlapped by 4-H), 3.73 (s, 3, OCH_3), 5.33 (q, 1, J = 7 Hz, vinylic H), 9.46 (s, 1, CHO), 10.3 (br s, 1, NH), 10.7 ppm (br s, 1, NH); MS *m/e* (rel intensity) 374 (<1, M^+), 330 (100), 315 (10); m* 291.2 (374 → 330).

18-Ethyl-3-ethylidene-2,7,13,17-tetramethyl-1,2,3,19,21,24-hexahydro-1,19-dioxo-22*H*-biline-8,12-dipropionic Acid Dimethyl Ester (Racemic Phycocyanobilin Dimethyl Ester) (*rac*-15). A solution of the aldehyde **12b** (33 mg) and methyl isoneoxanthobilirubinate (**13a**)[11] (33 mg) in methanol (10 mL) to which 2 drops of 40% HBr in glacial acetic acid had been added was refluxed under nitrogen for 30 min. The deep-blue reaction mixture was evaporated to dryness in vacuo and the residue was dissolved in CH_2Cl_2 and shaken with dilute aqueous $NaHCO_3$. The organic phase was evaporated to dryness, and the residue was purified by preparative TLC on silica gel eluting with CH_2Cl_2/methanol (98:2). The obtained 5-hydroxycarbonylphycocyanobilin dimethyl ester (***rac*-14**) was dissolved in trifluoroacetic acid (2 mL) and the mixture was allowed to stand at room temperature for 5 min. The solvent was evaporated in a stream of dry nitrogen, and the residue was dissolved in CH_2Cl_2 and shaken with dilute aqueous $NaHCO_3$ solution. The organic phase was evaporated and the residue purified by preparative TLC on silica gel eluting with CH_2Cl_2/methanol (98:2). Recrystallization from CH_2Cl_2/*n*-hexane yielded 28 mg (46%) of phycocyanobilin dimethyl ester (***rac*-15**), mp 194 °C (Lit.[7] mp 194–195 °C), whose UV/vis, IR, and ^1H NMR spectra were identical with those reported earlier.[7]

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Registry No.—**1**, 2537-48-6; **3a**, 64056-66-2; **3b**, 64056-67-3; (*Z*)-**6**, 64056-70-8; (*E*)-**6**, 64056-71-9; (*E*)-**7**, 64056-68-4; (*Z*)-**7**, 64056-69-5; **8**, 64056-72-0; **9**, 43155-00-6; **10**, 64056-73-1; **11a**, 64091-58-3; **12a**, 64056-74-2; **12b**, 64056-75-3; **13a**, 64056-76-4; **14**, 64056-77-5; **15**, 43155-04-0; methyl 2-homopropionate, 5445-17-0; triphenyl phosphine, 603-35-0; trimethyl orthoformate, 149-73-5.

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