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Total Syntheses of the Chlorinated β-Carboline Alkaloids Bauerine A, B, and C

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Total Syntheses of the Chlorinated β-Carboline Alkaloids Bauerine A, B, and C

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Abstract: The first total synthesis of the chlorinated 1-oxo-β-carboline alkaloid bauerine C based on a Japp–Klingemann reaction is reported. An intermediate of this synthesis was converted to the fully aromatic β-carboline bauerine B, and the related alkaloid bauerine A was prepared in an analogous manner.

Keywords: alkaloids, bauerine, cyclizations, dehydrogenations, 1-oxo-β-carbolines

INTRODUCTION

β-Carboline alkaloids are widely distributed in nature (e.g., in plants, fungi, microorganisms, and marine organisms) and have been described as exhibiting significant biological activities.[1,2] In contrast to β-carbolines of terrestrial origin, numerous alkaloids isolated from marine organisms contain halogen substituents on the aromatic rings.[3] Prominent examples are the antimicrobial and antiviral eudistomins isolated from the tunicate *Eudistoma olivaceum*.[4] In contrast to fully aromatic β-carbolines and the corresponding 1,2,3,4-tetrahydro analogues, only very few 1-oxo-β-carbolines have been found in nature.[5] In 1994, Larsen et al. reported on the isolation of three chlorinated β-carbolines from the blue-green alga *Dichothrix baueriana*.[6] Among these, bauerine C (**1**), representing a 1-oxo-β-carboline with a *N*-methyl substitutent at the indole nitrogen and a unique dichlorobenzene ring, was described as exhibiting very high cytotoxicity on tumor cell lines.

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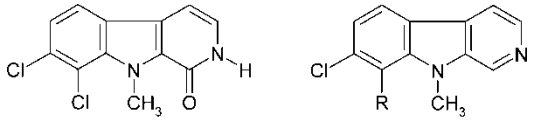
In addition, two chlorinated fully aromatic β-carbolines, bauerine A (**2**) and bauerine B (**3**), were isolated from the same alga (Scheme 1). The three alkaloids were also reported as exhibiting antiviral activity. The first total syntheses of bauerine A[7] and bauerine B,[8] both based on transition metal-based coupling reactions, have been described in the literature.

Here we describe the first total synthesis of bauerine C (**1**) and new approaches to bauerine A and B.

RESULTS AND DISCUSSION

Because among the alkaloids from *Dichothrix baueriana* described previously, bauerine C (**1**) shows highest cytotoxic activity and was the only one that had not been synthesized before, we looked for a synthetic strategy that offered an easy entry to the 1-oxo-β-carboline ring system. The approaches we used earlier for related alkaloids[5,9] were not appropriate here, because the respective chlorinated tryptamines are not readily available. Following the method described by Abramovitch and Shapiro,[10] sodium 2-oxopiperidine-3-carboxylate (**4**) (freshly prepared from the corresponding ethyl ester by alkaline hydrolysis) was reacted with diazotated 2,3-dichloroaniline **5a** in a Japp–Klingemann reaction to give the arylhydrazone **6a** in 71% yield. Subsequent Fischer cyclization with formic acid gave the tetrahydro-1-oxo-β-carboline **7a** in 61% yield. Anhydrous formic acid was found to be superior to 70% formic acid[10] for this reaction, because the substrate **6a** more readily dissolves in this solvent. Selective *N*-methylation at the indolic nitrogen to give **8a** was achieved in 79% yield by deprotonation with potassium *tert.*-butoxide in dimethylsulphoxide (DMSO) followed by treatment with methyl iodide. Comparable results were obtained with ethanolic KOH solution and acetone as a solvent. The regioselectivity of this *N*-alkylation was unambiguously verified by nuclear Overhauser (NOE)-experiments. Alternative attempts with dimethyl sulfate, the methylating reagent originally described to be superior for this purpose,[11] did not give substantial amounts of the desired monomethylated product **8a**. Deprotonation with sodium hydride in toluene, followed by treatment with methyl iodide, gave mainly the N^2,N^9-dimethyl derivative. To complete the total synthesis of bauerine C (**1**), intermediate **8a** had to be dehydrogenated at the C-3/C-4 position. First attempts with palladium on charcoal in high boiling solvents[9,12] were not successful. Finally, dehydrogenation of **8a** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in refluxing THF gave alkaloid **1** in 43% yield (Scheme 2).

Intermediate **8a** also offered a new entry to the total synthesis of the alkaloid bauerine B (**3**). Lactam **8a** was easily reduced to the tetrahydro-β-carboline **9a** by diborane. In the final step, **9a** had to be dehydrogenated to the fully aromatic alkaloid **3.** A literature search revealed that this reaction might be difficult. Rinehart[4] described a dehydrogenation of 7-bromo-1,2,3,4-tetrahydro-β-carboline with diphenylseleniumbis(trifluoroacetate) in

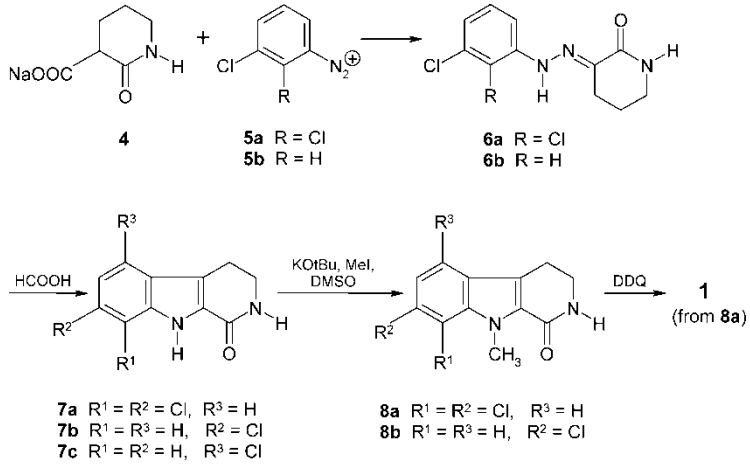


1 **2** R = H
3 R = Cl

Scheme 1.

40% yield, whereas Schumacher[13] reported that this reaction failed to give the desired product. In the latter publication, other dehydrogenation reagents (manganese dioxide, palladium on charcoal, chloranil, and DDQ) were also described to be ineffective, whereas sulphur in refluxing xylene gave the desired β-carboline in 15% yield. Trichloroisocyanuric acid–mediated dehydrogenation of tetrahydro-β-carbolines has been reported to result in mixtures of 3,4-dihydro-β-carbolines and β-carbolines.[14] Dantale and Söderberg[7] used manganese dioxide for dehydrogenation in the first total synthesis of bauerine A. In our hands, reaction of **9a** with DDQ in refluxing dioxane gave the best yield (17%) of bauerine B (**3**). The product was accompanied by large amounts of an insoluble, tarry mass (Scheme 3).

The related alkaloid bauerine A (**2**) was prepared in an analogous manner. Thus, the Japp–Klingemann reaction of diazotated 3-chlorophenylhydrazine (**5b**) with ketoacid **4** gave the hydrazone **6b** in 59% yield. Subsequent cyclization with formic acid gave a poorly separable mixture of the desired 7-chloro-derivative **7b** and the isomeric 5-chloro compound **7c**. N^9-methylation of **7b** to **8b** and reduction of the lactam group gave the tetrahydro-β-carboline **9b**, which was dehydrogenated to bauerine A (**2**) with DDQ in 12% yield (Scheme 3).

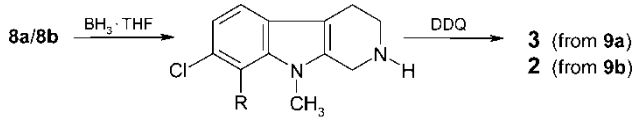


4 **5a** R = Cl **5b** R = H **6a** R = Cl **6b** R = H

7a $R^1 = R^2 = Cl$, $R^3 = H$
7b $R^1 = R^3 = H$, $R^2 = Cl$
7c $R^1 = R^2 = H$, $R^3 = Cl$

8a $R^1 = R^2 = Cl$, $R^3 = H$
8b $R^1 = R^3 = H$, $R^2 = Cl$

Scheme 2.



9a R = Cl
9b R = H

Scheme 3.

CONCLUSION

A convenient first total synthesis (four steps, 14% overall yield) of the 1-oxo-β-carboline alkaloid bauerine C (**1**) has been developed starting from commercially available materials using the Japp–Klingemann reaction as the key step. New approaches to the fully aromatic analogues bauerine A (**2**) and bauerine B (**3**), albeit in poor yields, were worked out using the same approach, followed by reduction of the corresponding 1-oxo-tetrahydro-β-carbolines and subsequent dehydrogenation.

EXPERIMENTAL

General Data

Elemental analyses: Analysator CHN-O Rapid (Heraeus). Mass spectra: CH 7 (Varian MAT). IR spectra: Perkin-Elmer 881 IR-1600 FT-IR and FT-IR-Paragon 1000. Melting points (uncorrected): Büchi B 50 apparatus. NMR: Jeol GSX 400 (400 MHz for ^{1}H, 100 MHz for ^{13}C); TMS as internal standard. Solvents were dried using standard methods and freshly destilled prior to use. Flash-column chromatography (FCC) was performed on Kieselgel 60 (0.040–0.063 mm; Merck).

3-(2,3-Piperidinedione)-(2,3-dichlorophenyl)hydrazone (6a)

2,3-Dichloroaniline (6.6 g, 41 mmol) was suspended in 60 ml of water containing 11 ml of conc. hydrochloric acid and cooled to 0–5°C. After addition of 3.6 g (52 mmol) of sodium nitrite in water (10 ml), the solution was kept at this temperature for 10 min. Then 2.0 g of urea were added; the mixture was neutralized with satd. $NaHCO_3$ solution and stirred until the evolution of gas ceased. This mixture was added to an ice-cooled solution of 6.8 g (40 mmol) of 3-ethoxycarbonyl-2-oxopiperidine, which had been kept at 30°C for 2.5 h with 2.4 g (43 mmol) of potassium hydroxide in 80 ml of water. The mixture was adjusted to pH 4 by addition of acetic acid and then stirred for an additional 8 h at room temperature. The precipitate

was separated, washed with water and toluene, and recrystallized from methanol to give 7.8 g (71%) of **6a** as a red solid, mp 226°C. IR (KBr): 3221, 2960, 1689, 1662, 1589, 1451, 1327, 1302, 1196, 1142, 1106, 1042, 767 cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.55 (s, 1H, NH), 8.08 (s, 1H, NH), 7.54 (d, $J = 8.1$ Hz, 1H, CH), 7.33 (dd, $J = 8.1$ Hz, 8.1 Hz, 1H, CH), 7.15 (d, $J = 8.1$ Hz, 1H, CH), 3.22 (m, 2H, CH_2), 2.70 (t, $J = 6.5$ Hz, 2H, CH_2), 1.86 (m, 2H, CH_2). MS (70 eV) m/z (%): 275 (12) [M^+], 273 (60) [M^+], 271 (90) [M^+], 236 (100). Anal. calcd. for $C_{11}H_{11}Cl_2N_3O$ (272.13): C, 48.55; H, 4.07; N, 15.44. Found C, 48.45; H, 4.02; N, 15.24.

3-(2,3-Piperidinedione)-(3-chlorophenyl)hydrazone (6b)

Prepared in the same manner as described previously from 3-chloroaniline in 59% yield. Red crystals, mp 240°C. IR (KBr): 3217, 3168, 3036, 2952, 1661, 1597, 1566, 1474, 1463, 1433, 1329, 1299, 1193 cm^{-1}. ^1H NMR (DMSO-d_6) δ 9.75 (s, 1H, NH), 7.91 (s, 1H, NH), 7.30 (d, $J = 2.1$ Hz, 1H, CH), 7.25 (dd, $J = 8.0$ Hz, 8.0 Hz, 1H, CH), 7.17 (m, 1H, CH), 6.85 (m, 1H, CH), 3.20 (m, 2H, CH_2), 2.67 (t, $J = 6.6$ Hz, 2H, CH_2), 1.86 (m, 2H, CH_2). Anal. calcd. for $C_{11}H_{12}ClN_3O$ (237.69): C, 55.59; H, 5.05; N, 17.68. Found C, 55.32; H, 5.14; N, 17.41.

7,8-Dichloro-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-one (7a)

A solution of 7.7 g (28 mmol) of **6a** in 200 ml of formic acid was stirred at 80°C for 24 h, and then the formic acid was removed by distillation. The residue was dissolved in ethyl acetate, and the mixture was washed with satd. $NaHCO_3$ solution and water. After evaporation, the residue was crystallized from acetone to give 4.4 g (61%) of **7a** as a pale yellow powder, mp 212°C. IR (KBr): 3234, 1651, 1503, 1318, 767 cm^{-1}. ^1H NMR (DMSO-d_6) δ 11.21 (s, 1H, NH), 7.75 (s, 1H, NH), 7.60 (d, $J = 8.5$ Hz, 1H, CH), 7.26 (d, $J = 8.5$ Hz, 1H, CH), 3.53 (m, 2H, CH_2), 2.94 (t, $J = 6.9$ Hz, 2H, CH_2). MS (70 eV) m/z (%): 258 (12) [M^+], 256 (61) [M^+], 254 (95) [M^+], 197 (100). Anal. calcd. for $C_{11}H_8Cl_2N_2O$ (255.10): C, 51.79; H, 3.16; N, 10.98. Found C, 52.18; H, 3.46, N; 10.92.

7-Chloro-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-one (7b) and 5-Chloro-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-one (7c)

Prepared in the same manner as described previously from **6b** as a poorly separable mixture in 59% overall yield. FCC separation (eluent: ethyl acetate) gave, in the order of elution, 13% of **7c**, 28% of a mixture of both compounds, and 12% of **7b**.

7b: White solid, mp 211°C. IR (KBr): 3228, 1659, 1616, 1543, 1322, 1264, 1195, 1061, 850, 778 cm^{-1}. ^1H NMR (DMSO-d_6) δ 11.75 (s, 1H, NH,), 7.63 (s, 1H, NH), 7.62 (d, $J = 8.2$ Hz, 1H, CH), 7.38 (d, $J = 1.5$ Hz, 1H, CH), 7.07 (dd, $J = 8.2$ Hz, 1.5 Hz, 1H, CH), 3.51 (m, 2H, CH_2), 2.92 (t, $J = 7.0$ Hz, 2H, CH_2). Anal. calcd. for $C_{11}H_9ClN_2O$ (220.66): C, 59.88; H, 4.11; N, 12.70. Found C, 60.02; H, 4.03; N, 12.17.

7c: White solid, mp 208°C. IR (KBr): 3215, 1660, 1615, 1544, 1510, 1490, 1415, 1331, 1307, 948, 776. ^1H NMR (DMSO-d_6) δ 11.97 (s, 1H, NH), 7.72 (s, 1H, NH), 7.35 (d, $J = 8.2$ Hz, 1H, CH), 7.17 (dd, $J = 7.5$ Hz, 8.2 Hz, 1H, CH), 7.09 (d, $J = 7.5$ Hz, 1H, CH), 3.51 (m, 2H, CH_2), 3.19 (t, $J = 7.0$ Hz, 2H, CH_2).

7,8-Dichloro-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-one (8a)

Compound **7a** (2.29 g, 8.98 mmol) was dissolved in 10 ml of DMSO, treated with 1.05 g (9.38 mmol) of potassium *tert.*-butylate, and stirred at 80°C for 30 min. After cooling to 20°C, 2 ml of methyl iodide were added; the mixture was stirred at 80°C for 30 min and then poured into ice-cooled 2M ammonia. Extraction with ethyl acetate, evaporation, and crystallization from acetone gave 1.9 g (79%) of **8a** as a off-white powder, mp 213°C. IR (KBr): 3208, 2919, 1671, 1489, 1300, 1158, 1042, 901, 797 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.38 (d, $J = 8.4$ Hz, 1H, 5-H), 7.20 (d, $J = 8.6$ Hz, 1H, 6-H), 5.70 (br. s, NH), 4.53 (s, 3H, N-CH_3), 3.64 (dt, $J = 6.8$ Hz, 2.8 Hz, 2H, CH_2), 2.99 (t, $J = 6.8$ Hz, 2H, CH_2). NOE experiment: saturation at 3.64 ppm (3-H) led to an effect at 5.70 ppm (N^2-H). MS (70 eV) m/z (%): 272 (12) [M^+], 270 (67) [M^+], 268 (100) [M^+], 239 (39), 211 (96). Anal. calcd. for $C_{12}H_{10}Cl_2N_2O$ (269.13): C, 53.55; H, 3.75; N, 10.41. Found C, 53.59; H, 3.89; N, 10.43.

7-Chloro-9-methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-b]indol-1-one (8b)

Prepared in the same manner as described previously from **7b** in 81% yield. White crystals, mp 168°C (from methanol). IR (KBr): 3228, 1659, 1616, 1543, 1322, 1264, 1195, 1061, 850, 778 cm^{-1}. ^1H NMR (DMSO-d_6) δ 7.71 (s, 1H, NH), 7.66 (m, 2H, 2 CH), 7.12 (dd, 1H, $J = 8.6$ Hz, 1.7 Hz, 1H, CH), 4.02 (s, 3H, CH_3), 3.46 (m, 2H, CH_2), 2.92 (t, 2H, $J = 7.0$ Hz, 2H, CH_2). Anal. calcd. for $C_{12}H_{11}ClN_2O \times CH_3OH$ (266.73): C, 58.54; H, 5.67; N, 10.50. Found: C, 58.03; H, 5.09; N: 10.44.

Bauerine C (1)

Compound **8a** (0.27 g, 1.0 mmol) and 0.45 g (2.0 mmol) of DDQ were refluxed in 20 ml of anhydrous THF for 12 h. After cooling to room

temperature, the solution was diluted with ethyl acetate and washed with 1 N sodium hydroxide solution until the aqueous layer was only slightly yellow. Evaporation of the organic layer and crystallization from ethyl acetate gave 0.115 g (43%) of **1** as a pale yellow solid, mp 254–258°C (decomp.; lit.:[6] mp > 220°C). ^{1}H NMR (DMSO-d_6) δ 11.58 (br. s, 1H, NH), 8.08 (d, $J = 8.5$ Hz, 1H, 5-H), 7.41 (d, $J = 8.5$ Hz, 1H, 6-H), 7.16 (m, 1H, 3-H), 7.02 (d, $J = 6.8$ Hz, 1H, 4-H), 4.63 (s, 3H, N-CH_3). ^{13}C NMR (DMSO-d_6) δ 156.0 (C═O), 136.3 (aromat., quart.), 130.6 (aromat., quart.), 128.0 (aromat., quart.), 126.3 (aromat., CH), 124.9 (aromat., quart.), 122.9 (aromat., quart.), 121.8 (aromat., CH), 121.3 (aromat., CH), 115.1 (aromat., quart.), 99.0 (aromat., CH), 34.1 (CH_3).

7,8-Dichloro-9-methyl-1,2,3,4-tetrahydro-1*H*-pyrido-[3,4-b]indole (9a)

Compound **8a** (0.22 g, 0.82 mmol) was dissolved in 15 ml of THF, 10 ml of 1 M borane–THF were added under nitrogen, and the mixture was refluxed for 14 h. After cooling, conc. hydrochloric acid was added carefully until gas evolution ceased, then 100 ml water was added, and the mixture was refluxed for 2 h. After cooling, the mixture was brought to pH 9 with potassium hydroxide and extracted with ethyl acetate (3 × 50 ml). The extract was dried, evaporated, and purified by FCC (eluent: ethyl acetate) to give 134 mg (65%) of **9a** as a white solid, mp 141°C. IR (KBr): 3304, 2931, 1558, 1448, 1410, 798 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 7.33 (d, $J = 8.4$ Hz, 1H, CH), 7.14 (d, $J = 8.4$ Hz, 1H, CH), 3.88 (s, 3H, CH_3), 3.87 (s, 2H, CH_2), 2.94 (t, $J = 7.0$ Hz, 2H, CH_2), 2.56 (m, 2H, CH_2), 1.88 (s, 1H, NH). Anal. calcd. for $C_{12}H_{12}Cl_2N_2$ (255.15): C, 56.49; H, 4.74; N, 10.98. Found: C, 56.20; H, 4.83; N, 9.79.

7-Chloro-9-methyl-1,2,3,4-tetrahydro-9*H*-pyrido-[3,4-b]indole (9b)

Prepared in the same manner as described previously from **8b** in 63% yield. White solid, mp 59°C. ^{1}H NMR ($CDCl_3$) δ 7.37 (d, $J = 8.4$ Hz, 1H, CH), 7.25 (d, $J = 1.6$ Hz, 1H, CH), 7.04 (dd, $J = 8.4$ Hz, 1.6 Hz, 1H, CH), 4.03 (s, 2H, CH_2), 3.54 (s, 3H, CH_3), 3.17 (t, $J = 5.6$ Hz, 2H, CH_2), 2.74 (t, $J = 5.6$ Hz, 2H, CH_2).

Bauerine A (2)

Compound **9b** (90 mg, 0.4 mmol) and 180 mg (0.79 mmol) of DDQ in 15 ml of dioxane were refluxed for 24 h. The mixture was concentrated; the residue was treated with 100 ml of 0.5 M sodium hydroxide and extracted with ethyl acetate (3 × 50 ml). The extract was concentrated and purified by FCC

(eluent: ethyl acetate) to give 13 mg (12%) of **2** as a pale yellow solid, mp 107°C (decomp.; lit.:[6] mp 109–110°C). ^{1}H NMR (acetone-d_6) δ 9.02 (d, $J = 0.5$ Hz, 1H, 1-H), 8.44 (d, $J = 5.1$ Hz, 1H, 3-H), 8.25 (dd, $J = 8.4$ Hz, 0.5 Hz, 1H, 5-H), 8.08 (dd, $J = 5.1$ Hz, 1.1 Hz, 1H, 4-H), 7.73 (d, $J = 1.7$ Hz, 1H, 8-H), 7.29 (dd, $J = 8.4$ Hz, 1.7 Hz, 1H, 6-H), 4.04 (s, 3H, CH_3). ^{13}C NMR (acetone-d_6): δ 143.3 (aromat., quart.), 140.2 (aromat., CH), 138.3 (aromat., quart.), 134.4 (aromat., quart.), 133.6 (aromat., CH), 128.0 (aromat., quart.), 123.8 (aromat., CH), 120.7 (aromat., CH), 120.6 (aromat., quart.), 115.0 (aromat., CH), 110.6 (aromat., CH), 29.6 (CH_3).

Bauerine B (3)

Prepared in the same manner as described previously from **9a** in 17% yield. Pale yellow solid, mp 148°C (decomp.; lit.:[6] mp 164–164°C, lit.:[8] 147–148°C). ^{1}H NMR (acetone-d_6): δ (ppm) 9.08 (s, 1H, 1-H), 8.48 (d, $J = 5.3$ Hz, 1H, 3-H), 8.23 (d, $J = 8.4$ Hz, 1H, 5-H), 8.10 (dd, $J = 5.3$ Hz, 1.1 Hz, 1H, 4-H), 7.46 (d, $J = 8.4$ Hz, 1H, 6-H), 4.41 (s, 3H, CH_3). ^{13}C NMR (acetone-d_6): δ 140.8 (aromat., CH), 139.2 (aromat., quart.), 138.8 (aromat., quart.), 134.2 (aromat., CH), 133.5 (aromat., quart.), 127.8 (aromat., quart.), 123.7 (aromat., quart.), 122.5 (aromat., CH), 121.9 (aromat., CH), 116.2 (aromat., quart.), 114.8 (aromat., CH), 33.2 (CH_3).

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