GENERAL STRATEGIES IN THE PREPARATION OF ANTIRHINE-TYPE INDOLE ALKALOIDS

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Abstract - Preparation of dimethyl malonyl-substituted indolo[2,3-a]quinolizidine derivative (9), which is a potential synthon in the antirhine (1) series, has been studied. Routes passing through intermediates (22) or (26) are superior to the route passing via intermediate (7), earlier preconized for that purpose.

Antirhine (1) and its derivatives form a small group of indole alkaloids of Corynanthé-Strychnos type without a C(16) substituent.1,2 In most cases, the C(3)H-C(15)H relationship is trans (biogenetic formation3,4), although some derivatives with the cis relationship are known as well.5

In many synthetic routes to indole alkaloids of indoloquinolizidine type, the most tedious and intellectually least attractive part of the work is the preparation of pyridine derivatives appropriately substituted at β- and γ-positions. Methods that permit direct introduction of substituents into simpler and more easily accessible intermediates are thus an attractive alternative.
Continuing our synthetic efforts towards antirhine analogues\textsuperscript{6,7} we became interested in the application of the above principle to the preparation of indolo[2,3-\textit{n}]quinolizidine derivatives possessing an appropriate substituent [\textit{e.g.} CH\textsubscript{3}-CO-CH-CO\textsubscript{2}Me or -CH(CO\textsubscript{2}Me)\textsubscript{2}] at the C(2) position \textit{[corresponding to the C(15) position in the biogenetic numbering\textsuperscript{2}]}.

About 15 years ago Husson and his research group\textsuperscript{8,9} and Lounasmaa and his research group\textsuperscript{10,11} independently described the use of 2-cyano-3-ethyl-\Delta\textsuperscript{3}-piperideines as synthons in a general synthetic approach to complex alkaloid structures. \textit{N}-Methyl-3-ethyl-5,6-dihydropyridinium salt (3), regenerated \textit{in situ} from \textit{N}-methyl-2-cyano-3-ethyl-\Delta\textsuperscript{3}-piperideine (2), was condensed with sodium dimethyl malonate or sodium methyl acetoacetate (both generating a \(\beta\)-dicarbonyl anion) to yield \textit{N}-methyl-1,2,3,4-tetrahydropyridines (4) and (5) (and/or 6),\textsuperscript{12} respectively (Scheme 1).

A little later Husson and his group replaced the \textit{N}-methyl-2-cyano-3-ethyl-\Delta\textsuperscript{3}-piperideine (2) with \textit{N}\textsubscript{a}-Boc-\textit{N}\textsubscript{b}-tryptophyl-2'-cyano-\Delta\textsuperscript{3}-piperideine (7).\textsuperscript{13} Condensation of (7) with sodium dimethyl malonate was reported to afford \textit{N}\textsubscript{a}-Boc-\textit{N}\textsubscript{b}-tryptophyl-1',2',3',4'-tetrahydropyridine (8) in quantitative yield.\textsuperscript{13,14} Subsequent deprotection at \textit{N}\textsubscript{a} and ring closure, initiated with MeOH/HCl\textsubscript{gas}, was described as leading to compound (9) [C(3)H=C(15)H\textit{trans}, biogenetic numbering\textsuperscript{2}], and the whole procedure [(7)\(\rightarrow\)(8)\(\rightarrow\)(9)] was reported to result in 45% overall yield (Scheme 2).\textsuperscript{13}
As the procedure seemed to be well suited for our present purposes and the reported overall yield (45%) reasonable, we decided to apply it in the preparation of indolo[2,3-al]quinolizidine derivative (10) (vide infra). Thus, the easily obtainable \( N_b \)-tryptophylpyridinium salt (11)\(^{15} \) was reduced with \( \text{NaBH}_4 \) to 1',2',5',6'-tetrahydropyridine (12), which by [(Boc)\(_2\)O] treatment was transformed to the corresponding \( N_B \)-Boc-protected compound (13). Oxidation of compound (13) with mCPBA afforded the corresponding \( N_B \)-oxide (14). Polonovski-Potier reaction\(^ {16-18} \) and subsequent addition of CN\(^{-} \) ions (Fry cyano-trapping method\(^ {19,20} \)) yielded the 2'-cyano-\( \Delta^3' \)-piperideine (7) (Scheme 3).

Reaction of compound (7) with sodium methyl acetoacetate in the presence of AgBF\(_4 \) was expected to yield 1',2',3',4'-tetrahydropyridine (15) (and/or bicyclic compound (16); see Refs. 8 and 10), which would then be transformable to compound (10) with MeOH/HCl treatment. However, we failed to find either 1',2',3',4'-tetrahydropyridine (15) or bicyclic derivative (16) in the reaction mixture (Scheme 4).
These disappointing results incited us to investigate the reliability of the earlier reports, i.e., the reaction of 2'-cyano-Δ³-piperidine (7) with β-dicarbonyl anions (vide supra). For this purpose we decided to utilize exactly the same anion [i.e. \( CH(\text{CO}_2\text{Me})_2 \)] as Husson et al.\(^{13} \) Thus, our above-described 2'-cyano-Δ³-piperidine (7) was reacted with sodium dimethyl malonate in the presence of AgBF₄ or ZnCl₂. Despite our repeated efforts no 1',2',3',4'-tetrahydropyridine (8) was found in the reaction mixture.\(^{13,14} \) Thus, the anticipated acid induced cyclization of compound (8) to compound (9) could not be carried through. Instead, piperidine derivative (17) was isolated in 58% yield. One explanation for the formation of (17) and the absence of compound (8) in the reaction mixture might be that compound (8) was indeed formed but rapidly transformed [e.g. via intermediate (18)] to compound (17) (Scheme 5).
Attempts to transform compound (7) directly to compound (9), without isolation of the hypothetical intermediate (8) [(7)→(8)→(9)], did not give better results.

It thus turned out that, at least in our hands, the preparation of the 15-substituted compound (9) (and/or 10) by the described route is not the méthode de choix. The desethyl analogue and its derivatives seem to be more unstable than the corresponding ethyl analogue and make the reaction path more unreliable (vide supra). Accordingly, we switched our attention to the alternative route that we recently developed for our hirsutine synthesis.21

The easily obtainable compound (19)22 was oxidized with mCPBA to N₆-oxide (20). Polonovski-Potier reaction, followed by CN⁻ trapping, afforded 4-cyanoindolo[2,3-alquinolizidine (21) (IUPAC numbering23). Treatment of compound (21) with sodium dimethyl malonate in the presence of AgBF₄ yielded, via the corresponding iminium salt, compound (22), albeit in low yield. Catalytic hydrogenation (H₂, PtO₂·H₂O) of compound (22) yielded compound (9) (Scheme 6).

As the total yield of the above procedure was relatively low, mainly due to resinification, compound (19)22 was transformed by (Boc)₂O treatment to the corresponding N₆-Boc protected compound (23), which was oxidized with mCPBA to a mixture of N₅-oxides (24a) and (24b). Polonovski-Potier reaction, followed by CN⁻ trapping, yielded the crude product as a complex mixture containing at least two cyano derivatives, 4-monocyano compound (25) (minor) and 2,4-dicyano compound (25a) (major). The crude product was submitted to TLC purification, which led to the isolation of compound (25b), formed during the purification procedure (Scheme 7).
Scheme 7. Formation of compounds (25) and (25a), and their transformation to compound (25b) during the purification.

To avoid the undesired substitution product (25b), we treated the crude product of the Polonovski-Potier reaction and CN\(^{-}\) trapping directly with sodium dimethyl malonate in the presence of AgBF\(_4\). In this way compound (26) was obtained, after fractionation, in reasonable yield. Catalytic hydrogenation (H\(_2\), PtO\(_2\), H\(_2\)O) of compound (26) afforded compound (27), which was Boc deprotected in acidic conditions, yielding compound (9) (Scheme 8).

Scheme 8. Transformation of the mixture of compounds (25) and (25a) to compound (9) via compounds (26) and (27).
Chart 1. $^{13}$C NMR data of compounds (7, 9, 12-14, 17, 19-27). The values for compound (24a) are taken from the spectrum of the 2:1 mixture of compounds (24a) and (24b) (cf. Experimental). The influence of the endocyclic homoallylic effect is easily identifiable in most of the cases [compounds (7, 12-14, 19-26)].$^{24,25}$
CONCLUSIONS

We have shown that for the preparation of dimethyl malonyl-substituted indolo[2,3-a]quinolizidine derivative (9), a potential synthon in the antirhine (1) series, intermediates (21) and (25) [and eventually intermediate (25a)] are superior to intermediate (7), earlier\textsuperscript{13} preconized for that purpose. However, in all cases examined the total yields are relatively low. Thus, it seems to us recommended that the use of the desethyl derivatives (present case) is much more delicate than that of ethyl derivatives described earlier\textsuperscript{8-10}

EXPERIMENTAL

IR spectra were recorded with a Perkin-Elmer 700 IR spectrophotometer using CHCl\textsubscript{3} as solvent. IR absorption bands are expressed in reciprocal centimetres (cm\textsuperscript{-1}). \textsuperscript{1}H- and \textsuperscript{13}C-NMR spectra were measured with a Varian Gemini-200 NMR spectrometer working at 199.975 MHz (\textsuperscript{1}H-NMR) and at 50.289 MHz (\textsuperscript{13}C-NMR) using CDCl\textsubscript{3} as solvent if not otherwise stated. Chemical shifts are given in ppm by reference to TMS (\textsuperscript{1}H-NMR; \(\delta_{\text{H}}\)=0.00 ppm) and CDCl\textsubscript{3} (\textsuperscript{13}C-NMR; \(\delta_{\text{C}}\)=77.00 ppm). Signal assignments were confirmed by APT and HETCOR (partly) experiments. Abbreviations s, d, t, q, m, def, and br are used to designate singlet, doublet, triplet, quartet, multiplet, deformed, and broad, respectively. For the \textsuperscript{13}C-NMR data, see Chart 1. Mass spectrometry (EI and HRMS) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of \(N_5\)-tryptophylpyridinium salt (11)

For the preparation and analytical data of compound (11), see Ref. 26 [compound (1) in Ref. 26].

Preparation of \(N_5\)-tryptophyl-1',2',5',6'-tetrahydropyridine (12)

Compound (11) (200.0 mg, 0.662 mmol) was dissolved in MeOH (20 mL), and NaBH\textsubscript{4} (50.1 mg, 1.32 mmol) was added during 10 min to the cooled stirred solution. Stirring was continued for 0.5 h at rt (Ar atm) after which H\textsubscript{2}O was added and MeOH evaporated. The reaction mixture was extracted with CH\textsubscript{2}Cl\textsubscript{2} and the extract was dried with anhydrous Na\textsubscript{2}SO\textsubscript{4} and evaporated to give essentially pure compound (12). Compound (12): 112.2 mg (75%). Amorphous (lit,\textsuperscript{9} colorless solid). \textsuperscript{1}H-NMR (CDCl\textsubscript{3}/CD\textsubscript{3}OD : 70/1): 2.25 (2H, m, H-5'), 2.70 (2H, t, J = 6 Hz, -CH\textsubscript{2}CH\textsubscript{2}N<), 2.79 (2H, m, -CH\textsubscript{2}CH\textsubscript{2}N<), 3.01 (2H, m, H-6'), 3.11 (2H, m, H-2'), 5.76 (2H, m, H-3', H-4'), 7.02 (1H, s, H-2), 7.15 (2H, m, H-5, H-6), 7.36 (1H, d, J = 8 Hz, H-7), 7.62 (1H, d, J = 8 Hz, H-4), 8.35 (1H, br s, NH). MS: 226 (M\textsuperscript{+}, 100%), 144, 143, 130, 96. HRMS: Calcd for C\textsubscript{15}H\textsubscript{18}N\textsubscript{2}: 226.1470. Found: 226.1456. Anal. Calcd for C\textsubscript{15}H\textsubscript{18}N\textsubscript{2}: C, 79.61; H, 8.02; N, 12.38. Found: C, 79.40; H, 7.88; N, 12.26.
Preparation of \( N_{\alpha}\)-Boc-\( N_{\beta}\)-tryptophyl-1',2',5',6'-tetrahydropyridine (13)

Compound (12) (366.3 mg, 1.621 mmol), (Boc)\(_2\)O (97%) (389.1 mg, 1.73 mmol), and DMAP (19.8 mg, 0.162 mmol) were dissolved in \( \text{CH}_2\text{Cl}_2 \) (50 mL). The reaction mixture was stirred for 2.5 h at rt (Ar atm), after which the solvent was evaporated and the crude product was purified by column chromatography (silica gel, \( \text{CH}_2\text{Cl}_2/\text{MeOH} ; 99.8/0.2 \)) to give compound (13).

Compound (13): 386.6 mg (73%). Amorphous (lit., colorless oil). IR: 1735 (C=O). \( ^1\text{H}-\text{NMR} \) (CDCl\(_3\)): 1.67 [9H, s, -C(CH\(_3\))\(_3\)], 2.24 (2H, m, H-5'), 2.68 (2H, t, J = 6 Hz, -CH\(_2\)CH\(_2\)N<), 2.78 (2H, m, -CH\(_2\)CH\(_2\)N<), 2.95 (2H, m, H-6'), 3.10 (2H, m, H-2'), 5.76 (2H, m, H-3', H-4'), 7.26 (2H, m, H-5, H-6), 7.41 (lH, s, H-2), 7.55 (lH, d, J = 8 Hz, H-4), 8.12 (1H, d, J = 8 Hz, H-7). MS: 326 (M\(^+\), 100%), 269, 144, 143, 130, 96. HRMS: Calcd for C\(_{26}\)H\(_{25}\)N\(_2\)O\(_2\): 326.1994. Found: 326.1986. Anal. Calcd for C\(_{26}\)H\(_{25}\)N\(_2\)O\(_2\): C, 73.82; H, 7.74; N, 8.61. Found: C, 73.56; H, 7.82; N, 8.46.

Preparation of \( N_{\alpha}\)-Boc-\( N_{\beta}\)-tryptophyl-1',2',5',6'-tetrahydropyridine \( N_{\beta}\)-oxide (14)

Compound (13) (375.0 mg, 1.15 mmol) was dissolved in \( \text{CH}_2\text{Cl}_2 \) (30 mL), and mCPBA (90%) (238.2 mg, 1.24 mmol) was added to the stirred solution. Stirring was continued for 2 h at rt (Ar atm), after which the solvent was evaporated and the crude product was purified by column chromatography (alumina, \( \text{CH}_2\text{Cl}_2/\text{MeOH} ; 99/1 \)) to give compound (14).

Compound (14): 377.0 mg (96%). Amorphous (lit., colorless foam). IR: 1730 (C=O). \( ^1\text{H}-\text{NMR} \) (CDCl\(_3\)): 1.67 [9H, s, -C(CH\(_3\))\(_3\)], 3.97 (2H, t, def, H-2'), 5.67 (1H, br d, J = 10 Hz, H-4'), 5.93 (1H, br d, J = 10 Hz, H-3'), 7.29 (2H, m, H-5, H-6), 7.46 (1H, s, H-2), 7.61 (1H, d, J = 7 Hz, H-4), 8.13 (1H, d, J = 7 Hz, H-7). MS: 342 (M\(^+\), <1%), 326, 243, 187, 156, 143 (100%). HRMS: Calcd for C\(_{26}\)H\(_{25}\)N\(_2\)O\(_3\): 342.1943. Found: 342.1932. Anal. Calcd for C\(_{26}\)H\(_{25}\)N\(_2\)O\(_3\): C, 73.06; H, 7.38; N, 8.20. Found: C, 70.26; H, 7.26; N, 8.08.

Preparation of \( N_{\alpha}\)-Boc-\( N_{\beta}\)-tryptophyl-2'-cyano-\( \Delta^3\)-piperideine (7)

Compound (14) (56.0 mg, 0.16 mmol) was dissolved in \( \text{CH}_2\text{Cl}_2 \) (30 mL), and trifluoroacetic anhydride (TFAA) (40 \( \mu \)L, 0.28 mmol) was added to the solution during 5 min. The reaction mixture was stirred for 2 h at rt (Ar atm), after which KCN (45.6 mg, 0.70 mmol) in \( \text{H}_2\text{O} \) (12 mL) was added, and stirring was continued for 45 min at rt (Ar atm). The reaction mixture was neutralized with saturated NaHCO\(_3\) solution, extracted with \( \text{CH}_2\text{Cl}_2 \), and the extract was dried with anhydrous Na\(_2\)SO\(_4\). The crude product was purified by flash chromatography (silica gel, \( \text{CH}_2\text{Cl}_2/\text{MeOH} ; 99/1 \)) to give compound (7).

Compound (7): 11.5 mg (20%). Amorphous (lit., colorless oil which turned to foam under vacuum). IR: 1730 (C=O). \( ^1\text{H}-\text{NMR} \) (CDCl\(_3\)): 1.67 [9H, s, -C(CH\(_3\))\(_3\)], 4.26 (1H, br s, H-2'), 5.68-5.77 (1H, m, H-4'), 6.00-6.07 (1H, m, H-3'), 7.21-7.37 (2H, m, H-5, H-6), 7.46 (1H, s, H-2), 7.56 (1H, dd, J\(_1\) = 7 Hz, J\(_2\) = 2...
Hz, H-4), 8.13 (1H, br d, J = 7 Hz, H-7). MS: 351 (M'), 251, 144, 143, 130, 121 (100%). HRMS: Calcd for C_{21}H_{25}N_{3}O_{2}: 351.1947. Found: 351.1939. Anal. Calcd for C_{21}H_{25}N_{3}O_{2}: C, 68.64; H, 6.86; N, 11.44. Found: C, 68.52; H, 6.68; N, 11.56.

Attempt to prepare methyl acetoacetyl-substituted N_{5}-Boc-N_{6}-tryptophyl-1',2',3',4'-tetrahydropyridine (15) [and/or bicyclic piperidine derivative (16)]

AgBF_{4} (24.7 mg, 0.127 mmol) was added to the stirred solution of compound (7) (371 mg, 0.106 mmol) in THF (2 mL). Stirring was continued for 5 min at rt (Ar atm). Sodium methyl acetoacetate [NaH (60%, 6.7 mg, 0.167 mmol) and methyl acetoacetate (15 µL, 0.139 mmol) in THF (1 mL)] was added to the solution and the reaction mixture was stirred for 20 h at rt. Saturated NaHCO_{3} solution was added and the reaction mixture was extracted with CH_{2}Cl_{2} and the extract was dried with anhydrous Na_{2}SO_{4}. NMR and mass spectral examination of the crude product did not indicate the presence of any detectable amount of compound 15 (and/or compound 16) in the mixture.

Attempt to prepare dimethyl malonyl-substituted N_{5}-Boc-N_{6}-tryptophyl-1',2',3',4'-tetrahydropyridine (8);
Formation of piperidine derivative (17)

AgBF_{4} (7.0 mg, 0.036 mmol) was added to the stirred solution of compound (7) (11.5 mg, 0.033 mmol) in THF (1 mL). Stirring was continued for 5 min at rt (Ar atm). Sodium dimethyl malonate [NaH (60%, 4.2 mg, 0.105 mmol) and dimethyl malonate (10 µL, 0.088 mmol) in THF (0.5 mL)] was added to the solution and the reaction mixture was stirred for 15 h at rt. Saturated NaHCO_{3} solution was added and the reaction mixture was extracted with CH_{2}Cl_{2} and the extract was dried with anhydrous Na_{2}SO_{4}. The crude product, which did not contain compound (8) in detectable amount (no ^1{H} NMR signals between 4.5 - 7.2 ppm), was purified by CH_{2}Cl_{2}/hexane extraction to give compound (17).

Compound (17): 8.6 mg (58%). Amorphous. IR: 1730 (C=O). ^1{H}-NMR (CDCl_{3}): 1.67 [9H, s, -C(CH_{3})_{3}], 3.69 (6H, s, 2 x -CO_{2}CH_{3}), 7.2-7.6 (3H, m, H-4, H-5, H-6), 8.13 (1H, d, J = 8 Hz, H-7). MS: 456 (M'), 226 (100%), 144, 143, 130. HRMS: Calcd for C_{23}H_{32}N_{3}O_{6}: 456.2260. Found: 456.2246. Anal. Calcd for C_{23}H_{32}N_{3}O_{6}: C, 65.77; H, 7.06; N, 6.14. Found: C, 65.52; H, 7.14; N, 6.04.

In a similar procedure, where AgBF_{4} was replaced by a small amount (0.1 equiv.) of anhydrous ZnCl_{2}, compound (8) was not detected.

Preparation of 1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine (19)

For the preparation and analytical data of compound (19), see Ref. 22 [compound (3a) in Ref. 22].
Preparation of 1,4,6,7,12,12b-hexahydromindolo[2,3-a]quinolizine N₉-trans-oxide (20)

Compound (19) (331.9 mg, 1.482 mmol) was dissolved in CH₂Cl₂ (20 mL) and mCPBA (90%) (319.5 mg, 1.67 mmol) was added to the stirred solution. Stirring was continued for 3 h at rt (Ar atm), after which the solvent was evaporated and the crude product was purified by column chromatography (alumina, CH₂Cl₂/MeOH, 99/1) to give compound (20).

Compound (20): 211.8 mg (60%). Amorphous. 'H-NMR (CDCl₃/CD₂OD; 13/1): 4.44 (1H, dd, J₁ = 10 Hz, J₂ = 6 Hz, H-12b), 5.65 (1H, br d, J = 12 Hz, H-2), 5.88 (1H, br d, J = 12 Hz, H-3), 7.0-7.2 (2H, m, H-9, H-10), 7.28 (1H, dd, J₁ = 7.5 Hz, J₂ = 2.5 Hz, H-11), 7.49 (1H, dd, J₁ = 7.5 Hz, J₂ = 2.5 Hz, H-8). MS: 240 (M⁺), 239, 224 (100%), 197, 170, 169. HRMS: Calcd for C₁₅H₁₅N₂O: 240.1263. Found: 240.1242. Anal. Calcd for C₁₅H₁₅N₂O: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.06; H, 6.56; N, 11.42.

Preparation of 1,4,6,7,12,12b-hexahydro-4-cyanoindolo[2,3-a]quinolizine (21)

Compound (20) (377.1 mg, 1.57 mmol) was dissolved in CH₂Cl₂ (30 mL) and trifluoroacetic anhydride (TFAA) (310 µL, 2.19 mmol) was added to the solution during 5 min. The reaction mixture was stirred for 2 h at rt (Ar atm), after which KCN (306.9 mg, 4.71 mmol) in H₂O (12 mL) was added, and stirring was continued for 45 min at rt (Ar atm). The reaction mixture was neutralized with saturated NaHCO₃ solution, extracted with CH₂Cl₂, and the extract was dried with anhydrous Na₂SO₄. The crude product was purified by flash chromatography (silica gel, CH₂Cl₂/MeOH; 99/1) to give compound (21).

Compound (21): 20 mg (7.5%). Amorphous. 'H-NMR (CDCl₃): 2.31 (1H, ddd, J₁ = 10.5 Hz, J₂ = 4 Hz, J₃ = 2 Hz, H-1α), 2.54 (1H, ddd, J₁ = 17 Hz, J₂ = 4.5 Hz, J₃ = 4.5 Hz, H-6β), 2.82 (1H, m, H-7α), 3.0-3.1 (2H, m, H-6α, H-7β), 3.98 (1H, dd, J₁ = 11 Hz, J₂ = 3.5 Hz, H-12b), 4.38 (1H, br dd, J = 12 Hz, H-4), 5.79-5.84 (1H, m, H-2), 6.04-6.08 (1H, m, H-3), 7.12 (1H, t, J = 7 Hz, H-9), 7.17 (1H, t, J = 7 Hz, H-10), 7.32 (1H, d, J = 7 Hz, H-11), 7.50 (1H, d, J = 7 Hz, H-8), 7.80 (1H, br s, NH). MS: 249 (M⁺), 221, 170 (100%), 169. HRMS: Calcd for C₁₅H₁₅N₂O₂: 349.1790. Found: 349.1778. Anal. Calcd for C₁₅H₁₅N₂O₂: C, 72.18; H, 6.63; N, 12.03. Found: C, 72.26; H, 6.52; N, 11.84.

Preparation of dimethyl malonyl-substituted indolo[2,3-a]quinolizidine derivative (22)

AgBF₄ (18.8 mg, 0.096 mmol) was added to the stirred solution of compound (21) (20.0 mg, 0.080 mmol) in THF (2 mL). Stirring was continued for 5 min at rt (Ar atm). Sodium dimethyl malonate [NaH (60%, 7.7 mg, 0.19 mmol) and dimethyl malonate (20 µL, 0.175 mmol) in THF (1 mL)] was added to the solution and the reaction mixture was stirred for 16 h at rt. Saturated NaHCO₃ solution was added and the reaction mixture was extracted with CH₂Cl₂, and the extract was dried with anhydrous Na₂SO₄. The crude product was purified by flash chromatography (silica gel, CH₂Cl₂/MeOH; 99.8/0.2) to give compound (22).
Compound (22): 14.8 mg (52%). Amorphous. IR: 1730 (C=O). \textsuperscript{1}H-NMR (CDCl\textsubscript{3}): 3.75 (3H, s, -CO,CH\textsubscript{2}), 3.80 (3H, s, -CO\textsubscript{2}CH\textsubscript{2}), 4.26 (1H, br d, J = 8 Hz, H-3), 4.34 (1H, br dd, J\textsubscript{1} = 8 Hz, J\textsubscript{2} = 4 Hz, H-16), 6.08 (1H, dd, J\textsubscript{1} = 8 Hz, J\textsubscript{2} = 1.5 Hz, H-17), 7.10 (1H, t-like, J = 8 Hz, H-10), 7.15 (1H, t-like, J = 8 Hz, H-11), 7.34 (1H, d, J = 8 Hz, H-12), 7.47 (1H, d, J = 8 Hz, H-9), 7.92 (1H, br s, NH). MS: 354 (M\textsuperscript{+}), 223 (100%) 170, 169. HRMS: Calcd for C\textsubscript{22}H\textsubscript{22}N\textsubscript{2}O\textsubscript{4}: 354.1580. Found: 354.1558. Anal. Calcd for C\textsubscript{22}H\textsubscript{22}N\textsubscript{2}O\textsubscript{4}: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.62; H, 6.38; N, 7.72.

Preparation of dimethyl malonyl-substituted indolo[2,3-a]quinolizidine derivative (9) from compound (22)

Catalytic hydrogenation (H\textsubscript{2}, PtO\textsubscript{2} H\textsubscript{2}O, 15 mg, 1 atm, 1 h) of compound (22) (8.9 mg, 0.025 mmol) in MeOH (3 mL) afforded the crude product, which was purified by TLC (silica gel, CH\textsubscript{2}Cl\textsubscript{2}/MeOH; 95/5) to give compound (9).

Compound (9): 3.1 mg (35%). Amorphous. For the analytical data, see below.

Preparation of \textit{N\textsubscript{4}}-\textit{Boc}-1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine (23)

Compound (19) (184.7 mg, 0.825 mmol), (Boc\textsubscript{2}O (97%) (265.5 mg, 1.18 mmol), and DMAP (10.2 mg, 0.0835 mmol) were dissolved in CH\textsubscript{2}Cl\textsubscript{2} (10 mL). The reaction mixture was stirred for 1 h at rt (Ar atm), after which the solvent was evaporated and the crude product was purified by column chromatography (silica gel, CH\textsubscript{2}Cl\textsubscript{2}/MeOH; 99/1) to give compound (23).

Compound (23): 248.6 mg (93%). Amorphous. IR: 1730 (C=O). \textsuperscript{1}H-NMR (CDCl\textsubscript{3}): 1.66 [9H, s, -C(CH\textsubscript{3})\textsubscript{3}], 4.14 (1H, dd, J\textsubscript{1} = 10 Hz, J\textsubscript{2} = 3 Hz, H-12b), 5.79 (2H, m, H-2, H-3), 7.2-7.3 (2H, m, H-9, H-10), 7.43 (1H, dd, J\textsubscript{1} = 7 Hz, J\textsubscript{2} = 2 Hz, H-8), 8.07 (1H, dd, J\textsubscript{1} = 7 Hz, J\textsubscript{2} = 2 Hz, H-11). MS: 324 (M\textsuperscript{+}), 268, 267, 214, 170, 169 (100%). HRMS: Calcd for C\textsubscript{20}H\textsubscript{24}N\textsubscript{2}O\textsubscript{2}: 324.1838. Found: 324.1826. Anal. Calcd for C\textsubscript{20}H\textsubscript{24}N\textsubscript{2}O\textsubscript{2}: C, 74.05; H, 7.46; N, 8.63. Found: C, 74.16; H, 7.32; N, 8.46.

Preparation of \textit{N\textsubscript{4}}-\textit{Boc}-1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine \textit{N\textsubscript{1}}-cis-oxide (24a) and \textit{N\textsubscript{4}}-\textit{Boc}-1,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine \textit{N\textsubscript{1}}-trans-oxide (24b)

Compound (23) (216.3 mg, 0.668 mmol) was dissolved in CH\textsubscript{2}Cl\textsubscript{2} (15 mL) and mCPBA (90%) (172.4 mg, 0.899 mmol) was added to the stirred solution. Stirring was continued for 3 h at rt (Ar atm), after which the solvent was evaporated and the crude product was purified by column chromatography (alumina, CH\textsubscript{2}Cl\textsubscript{2}/MeOH; 99/1) to give compounds (24a) (cis) and (24b) (trans) as ~2:1 mixture.

The 2:1 mixture of compounds (24a) and (24b): 219.8 mg (97%). Amorphous. IR: 1730 (C=O). MS: 340 (M\textsuperscript{+}, <1%), 324, 268, 267, 252, 221, 170, 169 (100%). HRMS: Calcd for C\textsubscript{20}H\textsubscript{24}N\textsubscript{2}O\textsubscript{2} (C\textsubscript{20}H\textsubscript{24}N\textsubscript{2}O\textsubscript{3} - O) = 324.1838. Found: 324.1828. For the \textsuperscript{1}H-NMR spectrum and elemental analysis of compound (24b), see below.
Attempt to prepare N$_2$-Boc-1,4,6,7,12,12b-hexahydro-4$_6$-cyanoindolo[2,3-a]quinolizine (25); Formation of N$_2$-Boc-1,4,6,7,12,12b-hexahydro-2$_2$-methoxy-4$_6$-cyanoindolo[2,3-a]quinolizine (25b)

The mixture of compounds (24a) and (24b) (135.8 mg, 0.400 mmol) was dissolved in CH$_2$Cl$_2$ (2 mL), and trifluoroacetic anhydride (TFAA) (140 µL, 0.991 mmol) was added to the solution during 5 min. The reaction mixture was stirred for 1 h at rt (Ar atm), after which KCN (52.7 mg, 0.809 mmol) in H$_2$O (2 mL) was added, the pH was adjusted to pH 4 (NaOAc), and stirring was continued for 1 h at rt (Ar atm). The reaction mixture was neutralized with saturated NaHCO$_3$ solution, extracted with CH$_2$Cl$_2$, and the extract was dried with anhydrous Na$_2$SO$_4$. The complex crude product mixture, containing (according to MS) two cyano derivatives [monocyano derivative (25) (minor) (M$^+$ at m/z 349) and dicyano compound (25a) (major) (M$^+$ at m/z 376)], was submitted to TLC purification (silica gel, CH$_2$Cl$_2$/MeOH; 99/1). This led to the isolation of compound (25b), formed by substitution during purification.

Compound (25b): 19.2 mg (13%). Amorphous. IR: 1730 (C=O). $^1$H-NMR (CDCl$_3$): 1.47 (1H, ddd, $J_1 = 13$ Hz, $J_2 = 12.5$ Hz, H-1β), 1.69 [9H, s, -C(CH$_3$)$_3$], 3.49 (3H, s, -OCH$_3$), 4.61 (1H, br d, $J = 12.5$ Hz, H-12b), 7.2-7.3 (2H, m, H-9, H-10), 7.42 (1H, dd, $J_1 = 6$ Hz, $J_2 = 2$ Hz, H-8), 8.05 (1H, dd, $J_1 = 6$ Hz, $J_2 = 2$ Hz, H-11). MS: 381 (M$^+$), 324, 281, 241, 221 (100%), 197, 169. HRMS: Calcd for C$_{22}$H$_{27}$N$_3$O$_3$: 381.2052. Found: 381.2038. Anal. Calcd for C$_{22}$H$_{27}$N$_3$O$_3$: C, 69.27; H, 7.13; N, 11.02. Found: C, 69.08; H, 7.02; N, 10.86.

Preparation of dimethyl malonyl-substituted N$_2$-Boc-indolo[2,3-a]quinolizidine derivative (26)

The mixture of compounds (24a) and (24b) (178.6 mg, 0.525 mmol) was dissolved in CH$_2$Cl$_2$ (4 mL), and trifluoroacetic anhydride (TFAA) (110 µL, 0.779 mmol) was added during 5 min. The reaction mixture was stirred for 1 h at rt (Ar atm), after which KCN (39.1 mg, 0.600 mmol) in H$_2$O (4 mL) was added, the pH was adjusted to pH 4 (NaOAc), and stirring was continued for 0.5 h at rt (Ar atm). The reaction mixture was neutralized with saturated NaHCO$_3$ solution, extracted with CH$_2$Cl$_2$, and the extract was dried with anhydrous Na$_2$SO$_4$. AgBF$_4$ (102.3 mg, 0.525 mmol) was added to the stirred solution of crude product (165.6 mg) in THF (4 mL). Stirring was continued for 5 min at rt (Ar atm). Sodium dimethyl malonate [NaH (60%, 47.2 mg, 1.181 mmol) and dimethyl malonate (90 µL, 0.787 mmol) in THF (3 mL)] was added to the solution and the reaction mixture was stirred for 17 h at rt. Saturated NaHCO$_3$ solution was added and the reaction mixture was extracted with CH$_2$Cl$_2$ and the extract was dried with anhydrous Na$_2$SO$_4$. The crude product was purified by column chromatography (alumina, CH$_2$Cl$_2$/MeOH; 99.9/0.1, 99.5/0.5, 99/1) to give compounds (23, 26, and 24b).

Compound (23): 14.5 mg (9%). For the spectral data, see above.

Compound (26): 28.6 mg (12%). Amorphous. IR: 1730 (C=O). $^1$H-NMR (CDCl$_3$): 1.66 [9H, s, -C(CH$_3$)$_3$], 3.75 (6H, s, 2 x -CO$_2$CH$_3$), 4.29 (1H, br dd, $J_1 = 8$ Hz, $J_2 = 4$ Hz, H-16), 4.57 (1H, dd, $J_1 = 10$ Hz, $J_2 = 4$ Hz).
2.5 Hz, H-3), 6.17 (1H, dd, J₁ = 8 Hz, J₂ = 1.5 Hz, H-17), 7.20-7.29 (2H, m, H-10, H-11), 7.41 (1H, dd, J₁ = 8 Hz, J₂ = 2 Hz, H-9), 7.93 (1H, dd, J₁ = 8 Hz, J₂ = 2 Hz, H-12). MS: 454 (M⁺), 398, 340, 324, 284, 267 (100%), 214, 170, 169. HRMS: Calcd for C₂₃H₂₈N₂O₆: 454.2104. Found: 454.2092. Anal. Calcd for C₂₃H₂₈N₂O₆: C, 66.06; H, 6.65; N, 6.16. Found: C, 65.88; H, 6.42; N, 6.02.

Compound (24b): 36.2 mg (20%). ¹H-NMR (CDCl₃): 1.66 [9H, s, -C(CH₃)₃], 3.94 (1H, br d, J = 15.5 Hz, H-4a), 4.20 (1H, dd, J₁ = 15.5 Hz, J₂ = 2 Hz, H-4b). For the other spectral data, see above. Anal. Calcd for C₂₅H₃₂N₂O₆: C, 65.77; H, 7.06; N, 6.14. Found: C, 65.82; H, 6.18; N, 6.02.

Preparation of indolo[2,3-α]quinolizidine derivative (27)
Catalytic hydrogenation (H₂, PtO₂·H₂O, 30 mg, 1 atm, 1 h) of compound (26) (22.4 mg, 0.049 mmol) in MeOH (5 mL) afforded the crude product, which was purified by TLC (silica gel, CH₂Cl₂/MeOH; 95/5) to give compound (27).

Compound (27): 10.1 mg (45%). Amorphous. IR: 1730 (C=O). ¹H-NMR (CDCl₃): 1.65 [9H, s, -C(CH₃)₃], 2.17 (1H, br d, J = 15 Hz, H-14α), 3.75 (3H, s, -CO₂CH₃), 3.81 (3H, s, -CO₂CH₃), 3.98 (1H, d, J = 11.5 Hz, H-20), 4.27 (1H, br d, J = 9 Hz, H-3), 7.17-7.28 (2H, m, H-10, H-11), 7.41 (1H, dd, J₁ = 7 Hz, J₂ = 3 Hz, H-9), 7.92 (1H, dd, J₁ = 7 Hz, J₂ = 2 Hz, H-12). MS: 456 (M⁺), 399 (100%), 355, 283, 269, 223, 170, 169. HRMS: Calcd for C₂₅H₃₂N₂O₆: 456.2260. Found: 456.2252. Anal. Calcd for C₂₅H₃₂N₂O₆: C, 70.57; H, 7.11; N, 8.23. Found: C, 70.72; H, 7.20; N, 8.36.

Preparation of indolo[2,3-α]quinolizidine derivative (9) from compound (27)
Compound (27) (9.2 mg, 0.020 mmol) was dissolved in HCOOH (3 mL) and the reaction mixture was stirred at rt for 20 h (Ar atm). HCOOH was evaporated, the residue was evaporated in CH₂Cl₂, neutralized with NaHCO₃, and the extract was dried with anhydrous Na₂SO₄. The solution was evaporated to yield crude compound (9), which was purified by flash chromatography (alumina, CH₂Cl₂/MeOH; 99/1).

Compound (9): 6.8 mg (95%). Amorphous (lit., ⁹ pale yellow oil). IR: 1730 (C=O). ¹H-NMR (CDCl₃): 3.39 (1H, d, J = 10 Hz, H-20), 3.71 (3H, s, -CO₂CH₃), 3.80 (3H, s, -CO₂CH₃), 4.30 (1H, br, H-3), 7.11 (1H, ddd, J₁ = 7 Hz, J₂ = 7 Hz, J₃ = 1.5 Hz, H-10), 7.18 (1H, ddd, J₁ = 7 Hz, J₂ = 7 Hz, J₃ = 1.5 Hz, H-11), 7.41 (1H, ddd, J₁ = 7 Hz, J₂ = 1.5 Hz, H-12), 7.49 (1H, dd, J₁ = 7 Hz, J₂ = 1.5 Hz, H-9), 8.05 (1H, br s, NH). MS: 356 (M⁺, 100%), 355, 341, 325, 297, 225, 223, 197, 169. HRMS: Calcd for C₂₀H₂₄N₂O₄: 356.1736. Found: 356.1728. Anal. Calcd for C₂₀H₂₄N₂O₄: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.32; H, 6.58; N, 7.66.
REFERENCES AND NOTES


14. The $^1$H-NMR data, few in number, given in Ref. 13 for compound (8) (compound (24) in Ref. 13) are confusing: $\delta$ 2.52 [9H, s, -C(CH$_3$)$_3$], 4.15 (1H, dd, $J_1 \approx 10$ Hz, $J_2 \approx 4$ Hz, H-3; corresponding to H-6' in our numbering), no chemical shift value is given (1H, dd, $J_1 = 10$ Hz, $J_2 \approx 1.5$ Hz, H-14; corresponding to H-5' in our numbering).


25. *N.B.* After reconsideration of the $^{13}$C-NMR data of compound (5) in Ref. 21 we have interchanged the assignments of the C(3) and C(16) signals (biogenetic numbering applied to the corynantheine series) (see compound i below).


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