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A New Route to Spiropyrrolidinyl-oxindole Alkaloids via Iodide Ion Induced Rearrangement of [(*N*-Aziridinomethylthio)methylene]-2-oxindoles

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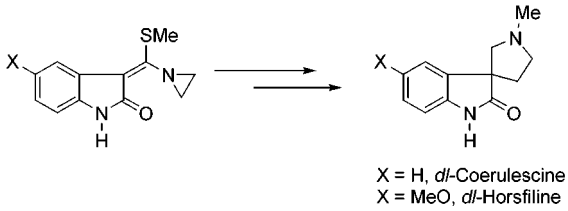
ABSTRACT



A new approach for the synthesis of spiropyrrolidinyloxindole alkaloids, i.e. coerulescine (4) and horsfiline (5) has been developed via iodide ion induced rearrangement of [(*N*-aziridinomethylthio)methylene]oxindoles 2 to the respective spiropyrroline-2-oxindole derivatives 3 and their subsequent one-pot reductive dethiomethylation–*N*-methylation.

The spiro[pyrrolidin-3,3′-oxindole] ring system is a widely distributed structural framework present in a number of cytostatic alkaloids such as spirotryprostatins A, B and strychnophylline.[1,2] Among them, coerulescine (**4**) and horsfiline (**5**) represent the simplest prototype members of this subfamily. The unique structural array and the unusual biological activity displayed by this class of compounds have made them attractive synthetic targets[3,4] as evident in the recent elegant total synthesis of spirotryprostatin A[5] and aspidophytine.[6] Herein we report a novel synthesis of coerulescine and horsfiline which relies upon the constuction of the spiro[pyrrolidin-3,3′-oxindole] ring system via iodide ion induced rearrangement of [(*N*-aziridinomethylthio)-methylene]oxindole intermediates **2** as the key step.

Horsfiline (**5**) was first isolated by Bodo and co-workers from the Malaysian medicinal plant *Horsfildea Superba*[7] whereas coerulescine (**4**) had been already synthesized in pilot studies toward the synthesis of horsfiline[8] and vincadifformine[9] before it was isolated and characterized from the natural resources (i.e. *Phalaris coerulescens*).[10] Several synthetic approaches have been developed for construc-

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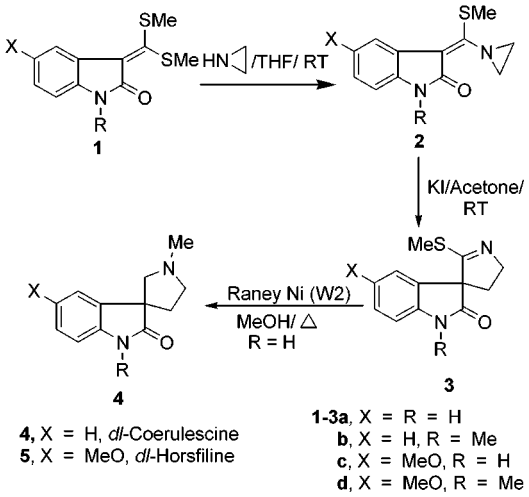
tion of the spiro[pyrrolidin-3,3′-oxindole] framework of both racemic and enantiomeric horsfiline, the most common one involving oxidative rearrangement of tetrahydro-β-carboline derivatives according to the biogenetically patterned approach.[7] Jones and Wilkinson have reported the synthesis of racemic **5** along a radical cyclization strategy.[11] Recently two alternative routes to (±)-**5** have been reported by a French team,[8] one involving skeletal rearrangement of a tetrahydro-γ-carboline derivative and the other involving a spirocyclization between 2-oxo-5-methoxytryptamine and formaldehyde. Recently two groups have disclosed the synthesis of enantiomeric **5** via rearrangement of a tetrahydro-β-carboline derivative[12] and 1,3-dipolar cycloaddition of thermally generated *N*-azomethine ylid,[13] respectively. A highly enantioselective total synthesis of (−)-horsfiline has been reported by Fuji and co-workers[14] via asymmetric nitroolefination using chiral nitroenamine as the key step.

During the course of our studies aimed at development of new and efficient synthetic methods for various heterocycles using α-oxoketene dithioacetals,[15] we have previously reported in a preliminary communication,[16] an efficient synthesis of novel hitherto unknown *N*-(thiomethylvinyl)-aziridines involving nucleophilic displacement on a wide range of polarized ketene dithioacetals by aziridine. These *N*-vinylaziridines were shown to undergo facile iodide ion induced rearrangement to 2-methylthio-3,3-substituted pyrrolines in high yields. The methodology was also extended for the synthesis of some spiropyrrolines from cyclic and heterocyclic oxoketene dithioacetal precursors.[16,17] This transformation is significant in view of the labile nature of *N*-vinylaziridines and difficulty involved in their preparation[18] which has probably restricted their investigation as potentially valuable synthetic intermediates. The ready accessibility accompanied with the reasonable stability of these *N*-(thiomethylvinyl)aziridines and their facile ring expansion to pyrroline derivatives under mild conditions prompted us to elaborate this transformation along with a one-pot reductive dethiomethylation−*N*-methylation sequence [**1**, **2**, **3** to **4**] for fashioning the spiro[pyrrolidin-3,3′-oxindole] moiety, leading to a short three-step synthesis of both coerulescine (**4**) and horsfiline (**5**) as described in the following section.

The α-oxoketene dithioacetals **1a**−**d** required for the present study were prepared from the respective 2-oxindoles according to the earlier reported procedure.[19] In a typical experiment, **1a** was reacted with an equimolar quantity of aziridine in THF at room temperature (10 h) to afford the corresponding 3-[(*N*-aziridinomethylthio)methylene]oxindole **2a** as light yellow solid (mp 109−110 °C) in 65% yield. Similarly, the other substituted vinylaziridine derivatives **2b**−**d** were obtained in 65−69% overall yields as light yellow crystalline solids under identical conditions. Although the vinylaziridines **2a**−**d** were found to be stable at room temperature for 20−24 h, their attempted purification on silica gel column or via crystallization resulted in decomposition. In the next experiment, the iodide ion induced rearrangement of these newly synthesized vinylaziridines **2** was studied. Thus when **2a** was reacted with potassium iodide in acetone at room temperature under nitrogen atmosphere, workup of the reaction mixture furnished a yellow crystalline solid characterized as 2′-methylthio-2-oxospiro-(3*H*-indole-3,3′-1′-pyrroline) (**3a**) (70%) on the basis of its spectral and analytical data.[20] The other substituted spiro[pyrrolin-3,3′-oxindole] derivatives **3b**−**d** were similarly prepared in overall high yields (66−70%) from the respective vinyl aziridines **2b**−**d** (Scheme 1). With crucial

Scheme 1



assembly of the spiro[pyrrolin-3,3′-oxindole] subunit accomplished, the stage was set for the reductive dethiomethylation of **3** to provide the desired spiro[pyrrolidin-3,3′-oxindole] framework of **4** and **5**. However ,our initial attempts of pilot studies on either **3a** or **3b** with various

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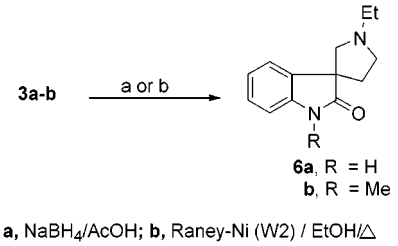
reducing agents ($NaBH_4$, $NaCNBH_3$, $BH_3{\cdot}Et_3N$) did not meet with much success and yielded only intractable reaction mixtures from which the desired NH-spiropyrrolidinyloxindole could not be isolated. Interestingly, **3a** underwent smooth reduction with sodium borohydride in acetic acid to afford a single product (65%) which was characterized as *N*′-ethyspiropyrrolidinyoxindole **6a** on the basis of its spectral data (Scheme 2).[20] Similarly the *N*-methylspiropyrrolinyloxindole **3b** also gave the corresponding *N*′-ethyl derivative **6b** in 63% yield under identical conditions. The products **6a**−**b** are apparently formed by further reduction of the initially formed *N*′-acetylated intermediates under these reaction conditions.[21] These observations led us to the idea of accomplishing with reductive dethiomethylation−*N*-methylation of **3** to either **4** or **5** in one-pot operation. After much experimentation, these two objectives were readily

Scheme 2

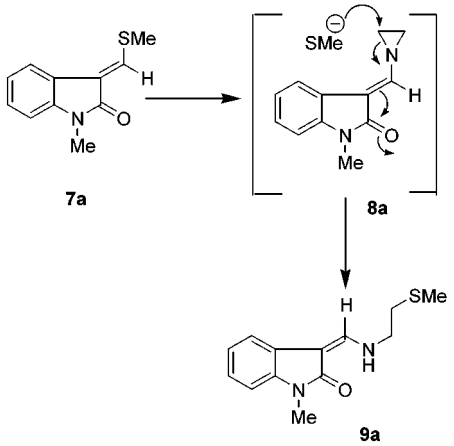


a, $NaBH_4$/AcOH; **b,** Raney-Ni (W2) / EtOH/△

achieved by treatment of **3a** with Raney Nickel (W2) in refluxing methanol (8 h) yielding a single product which surprisingly was found to be the desired *dl*-coerulescine **4** obtained in 80% yield. The ^1H and ^{13}C NMR data and the mp (113−115 °C, lit.[9] 112−113 °C) of the synthetic coerulescine was found to be identical with the reported data.[10] A similar reductive dethiomethylation−*N*-alkylation when performed on the corresponding 5-methoxyspiropyrrolinyloxindole **3c** by subjecting it to Raney Ni (W2) treatment in refluxing methanol afforded the (±)-horsfiline **5** as a single product (75%), mp 151−152 °C (lit.[7] 151−153 °C), with superimposable ^1H and ^{13}C NMR spectra.[7] This concomitant reductive dethiomethylation−*N*-methylation of 2-methylthiopyrroline under Raney Ni/methanol condition is quite unexpected, although examples of the formation of *N*-ethyl products during the reduction of imines and nitriles with Raney Ni in ethanol are known in the literature.[22] Thus, in an another experiment, when **3a** was reduced with W2 Raney Ni in refluxing ethanol, workup of the reaction mixture yielded the *N*′-ethyl product **6a**, which was found to be identical with the product obtained earlier by $NaBH_4$/AcOH reduction of **3a**. Reductive methylation of **3c** with either sodium cyanoborohydride/HCHO or with $HCHO/HCO_2H$ also afforded the (±)-horsfiline **5** in 55% and 30% yields, respectively.

It was of interest to examine the synthesis of *dl*-coerulescine from 2-methylthiomethyleneoxindole **7a**, which should afford the sulfur-free vinylaziridine intermediate **8a** on displacement with aziridine. However, treatment of **7a**

Scheme 3



(20) The structures of all new compounds was confirmed with the help of spectral and analytical data. **3-[(1-Aziridino)(methylthio)methylene]-2-oxindole 2a**. Light yellow crystals (chloroform−hexane); mp 109−110 °C; yield 65%. IR (KBr): 3051, 2928, 1675, 1606 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.58 (brs, 3H), 2.67 (brs, 2H), 2.68 (brs, 2H), 6.91 (d, J = 7.6 Hz, 1H), 7.03 (dt, J = 1, 7.6 Hz, 1H), 7.15 (dt, J = 1, 7.6 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 8.50 (brs, 1H, exchangeable with D_2O). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.61, 34.67, 35.75, 109.02, 121.08, 122.33, 122.75, 122.92, 125.67, 137.65, 167.77, 169.23. **5-Methoxy-3-[(1-aziridino)-(methylthio)methylene]-2-oxindole 2c**. Light yellow crystalline solids (chloroform−hexane); mp 85−86 °C; yield 66%. IR (KBr): 3169, 2932, 1701, 1600 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.56 (brs, 4H), 2.59 (s, 3H), 3.81 (s, 3H), 6.66 (dd, J = 2.4, 8.6 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 8.79 (brs, 1H, exchangeable with D_2O). **1-Methylthio-2-oxospiro(3*H*-indole-3,3′-1-pyrroline) 3a**. Yellow crystals (chloroform−hexane); mp 145 °C; yield 70%. IR (KBr): 2213, 1616, 1436, 1383 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (ddd, J = 4.9, 7.9, 14.0 Hz, 1H), 2.35 (s, 3H), 2.69 (ddd, J = 4.9, 7.9, 14.0 Hz, 1H), 4.11 (ddd, J = 4.9, 7.9, 14.0 Hz, 1H), 4.20 (ddd, J = 4.9, 7.9, 14.0 Hz, 1H), 6.89 (d, J = 7.8 Hz, 1H), 6.99 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 7.19 (t, J = 7.8 Hz, 1H), 8.75 (brs 1H, exchangeable with D_2O). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.76, 37.37, 60.54, 66.81, 110.29, 123.14, 123.55, 129.08, 130.08, 141.14, 171.14, 178.12. MS (*m*/*z*, %): 232 (M^+, 11.5), 231 (80.5), 158 (100). Anal. Calcd for $C_{12}H_{12}N_2OS$ (232.17): C, 62.07; H, 5.16; N, 12.06. Found: C, 62.15; H, 5.47; N, 12.21. **5-Methoxy-1′-methylthio-2-oxospiro(3*H*-indole-3,3′-1-pyrroline) 3c.** Light yellow crystals (chloroform−hexane); mp 120−121 °C; yield 68%. IR (KBr): 2993, 1795, 1540 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.26−2.41 (m, 1H), 2.42 (s, 3H), 2.74−2.80 (m, 1H), 3.77 (s, 3H), 4.22−4.31 (m, 2H), 6.72 (s, 1H), 6.79 (dd, J = 2.0, 8.3 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 9.42 (brs, 1H, exchangeable with D_2O). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.80, 37.48, 55.77, 60.63, 67.41, 110.42, 110.87, 113.72, 131.44, 134.71, 156.24, 171.29, 178.39. MS (*m*/*z*, %): 262 (M^+, 45), 189 (100.0), 174 (76.4). Anal. Calcd for $C_{12}H_{12}N_2OS$ (232.17): C, 62.07; H, 5.16; N, 12.06. Found: C, 62.22; H, 5.11; N, 12.12. **2′-Ethyl-2-oxospiro(3*H*-indole-3,3′-pyrrolidine) 6a.** Light yellow viscous liquid; yield 65%. IR (Nujol): 2968, 1700, 1612, 1422 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.08 (t, J = 7.3 Hz, 3H), 2.02 (ddd, J = 4.6, 8.0, 12.5 Hz, 1H), 2.32 (ddd, J = 4.6, 8.0, 12.5 Hz, 1H), 2.56 (q, J = 7.3 Hz, 2H), 2.71 (ddd, J = 4.6, 8.0, 12.5 Hz, 1H), 2.8 (d, J = 9.5 Hz, 1H), 2.87 (d, J = 9.5 Hz, 1H), 3.03 (ddd, J = 4.6, 8.0, 12.5 Hz, 1H) 6.80 (d, J = 7.6 Hz, 1H), 6.97 (dt, J = 1.2, 7.6 Hz, 1H), 7.12 (dt, J = 1.2, 7.6 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 8.15 (brs, 1H, exchangeable with D_2O). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.91, 37.33, 49.68, 52.94, 54.28, 65.85, 109.31, 122.81, 123.41, 127.65, 139.89, 141.70, 182.64. MS (*m*/*z*, %): 216 (M^+, 28), 71 (100). Anal. Calcd for $C_{13}H_{16}N_2O$ (216.12): C, 72.22; H, 7.40; N, 12.95. Found: C, 72.04; H, 7.35; N, 12.86. **3-[(2-Methylthio)-ethylaminomethylene]-1-methyl-2-oxindole 9a.** Light yellow crystals (chloroform−hexane); mp 49−50 °C; yield 80%. IR (KBr): 2175, 1657, 1489, 1383 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.15 (s, 3H), 2.74 (t, J = 6.8 Hz, 2H), 3.33 (s, 3H), 3.75 (dt, J = 6.8, 10.0 Hz, 2H), 6.87 (d, J = 7.2 Hz, 1H), 6.99 (t, J = 7.2 Hz, 1H), 7.09 (t, J = 7.2 Hz, 1H), 7.26 (d, J = 7.2 Hz, 1H), 7.48 (d, J = 12.4 Hz, 1H), 8.88 (brs, 1H, exchangeable with D_2O). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.19, 25.51, 35.54, 48.63, 95.95, 107.58, 114.98, 120.86, 123.09, 124.05, 137.87, 147.92, 169.19. MS (*m*/*z*, %): 248 (M^+, 81.6), 187 (100.0). Anal. Calcd for $C_{13}H_{16}N_2OS$ (248.18): C, 62.90; H, 6.44; N, 11.28. Found: C, 62.95; H, 6.28; N, 11.17.

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with aziridine in THF at room temperature furnished only one product, which did not show the spectroscopic data characteristic of **8a** but was identified as open-chain enaminone **9a**. Apparently, the initially formed *N*-vinylaziridine intermediate **8a** undergoes in situ ring opening by a thiomethyl group, resulting in the formation of open-chain product **9a**.

In summary, a highly convergent three-step synthesis of both (±)-coerulescine and (±)-horsfiline has been described which involves new approach for assembling a spiro-[pyrrolidin-3,3′-oxindole], a unique ring system present in several natural products with intriguing biological activity. This new approach via iodide ion induced rearrangement of [(*N*-aziridinomethylthio)methylene]oxindole derivatives employs readily available starting materials and appears to be well suited for preparation of simple congeners and several analogues that may prove useful in defining a pharmacological profile of this class of spirooxindole alkaloids. We are further exploring the application of this rearrangement for the synthesis of other naturally occurring compounds having spiropyrrolidinooxindole or related structural features which will be published in due course.

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Supporting Information Available: Characterization data for products **2b**, **3b**, **3d**, **4**, **5**, **6b**, and **7a**. This material is available free of charge via the Internet at http://www.pubs.acs.org.

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