Synthesis of Indole Alkaloids and Alkaloidal Precursors: an Improved Synthesis of Flavopereirine

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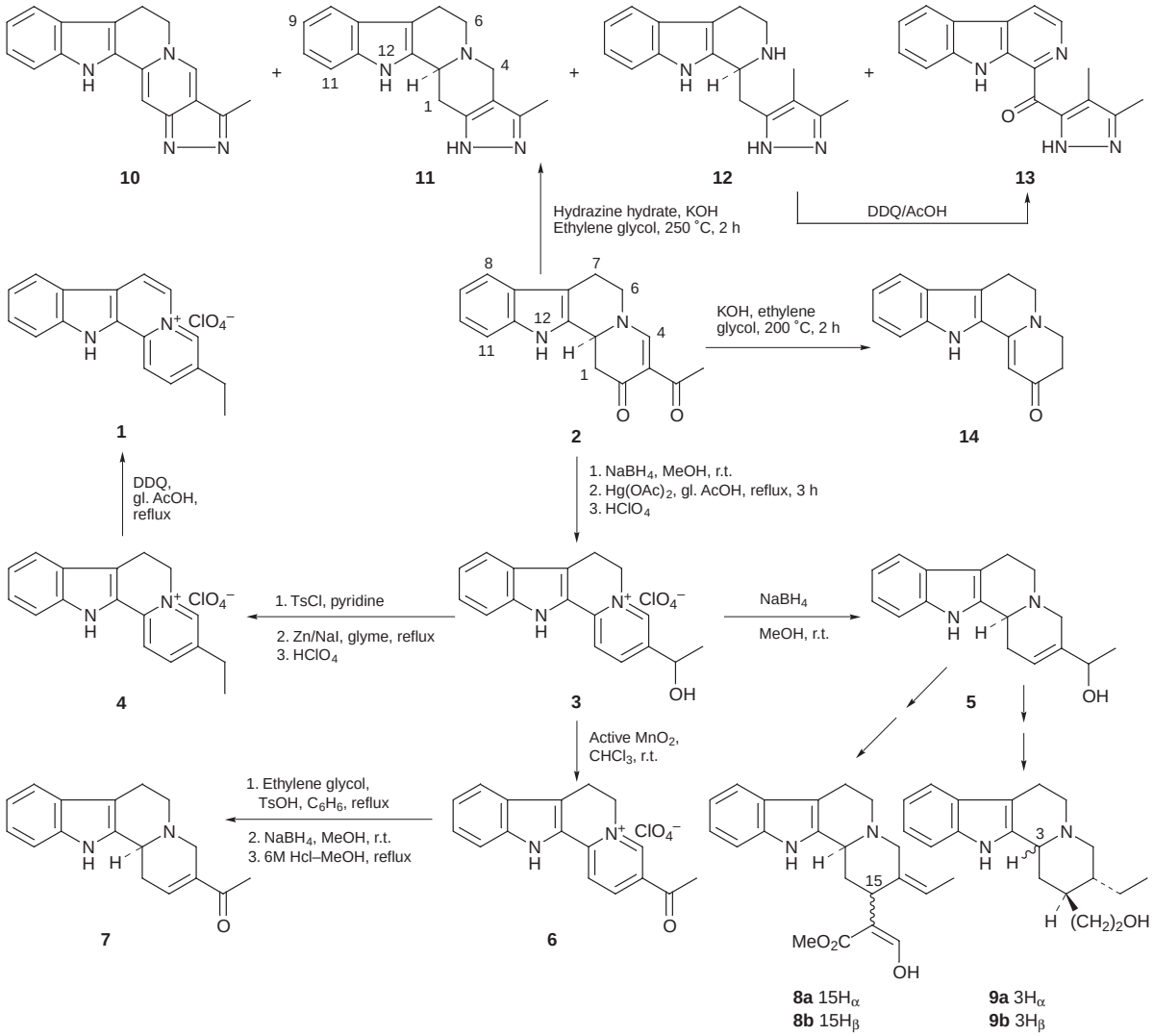
Synthesis of flavopereirine **1**, formal synthesis of isogeissoschizines **8** and dihydrocorynantheols **9** through the intermediacy of 3-(2-hydroxyethyl)-6,7-dihydroindolo[2,3-*a*]quinolizine **3** and also the unexpected formation of the β-carbolines **12** and **13** on Huang–Minlon reaction of **2** are described.

Polycyclic indole alkaloids have continued to attract the attention of synthetic organic chemists because of their physiological importance and structural diversity. We have earlier reported[1] the synthesis of a number of indole alkaloids from 3-acetyl-1,2,6,7,12,12b-hexahydroindolo-[2,3-*a*]quinolizin-2-one **2**. Herein, we report a short synthesis of flavopereirine **1**, which inhibits[2] cancer producing cells, and a convenient synthesis of 3-(2-hydroxyethyl)-1,4,6,7,12,12b-hexahydroindolo-[2,3-*a*]-quinolizine **5**, which has been utilised[3,4] for the synthesis of the alkaloids isogeissoschizines **8**, dihydrocorynantheols **9**, and also an interesting Huang–Minlon reaction of **2** resulting in the unexpected β-carbolines **12** and **13** along with the pyrazoles **10** and **11**. In the last couple of decades, it has been observed that some of the physiologically active compounds obtained[5,6] from marine sources are substituted β-carbolines either in the benzene nucleus or 1-position. Reduction of **2** with $NaBH_4$ in MeOH followed by refluxing with $Hg(OAc)_2$ in glacial AcOH afforded the quaternary salt 3-(2-hydroxyethyl)-6,7-dihydroindolo[2,3-*a*]quinolizine



Scheme 1

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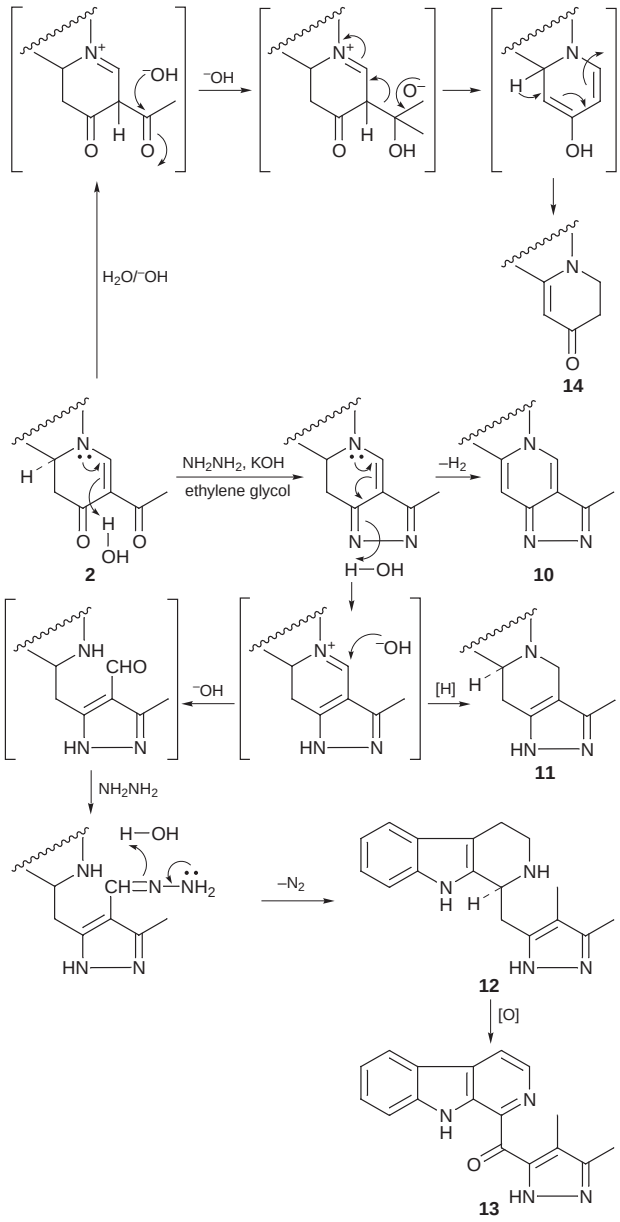
3 as the major product characterised as its perchlorate. Tosylation of **3**, followed by Zn/NaI reduction, gave



Scheme 2

dihydroflavopereirine **4** in 70% yield. Oxidation of **4** with DDQ afforded flavopereirine **1**. Again reduction of **3** with $NaBH_4$ in MeOH gave the diastereomeric alcohols **5** in excellent yield. Compound **5** has been used by different groups[3,4] for the synthesis of the alkaloids isogeissoschizine **8a**, epiisogeissoschizine **8b**, dihydrocorynantheol **9a** and epidihydrocorynantheol **9b**. On the other hand, 3-acetyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine **7**, the building block for heteroyohimbine type alkaloids[7] could be obtained by oxidation of **3** with active MnO_2 followed by ketalisation, $NaBH_4$ reduction and deketalisation (Scheme 1).

Huang–Minlon reaction of **2** with hydrazine hydrate in ethylene glycol yielded the pyrazoles **10** and **11** along with the C/D ring cleaved products 1-(3,4-dimethyl-5-pyrazolyl)-methyl-1,2,3,4-tetrahydro-β-carboline **12** and 1-(3,4-dimethyl-5-pyrazolyl)formyl-β-carboline **13** in 30, 35, 20 and 10% yields respectively. Compound **10** is a straightforward hydrazine condensation product of **2** with an additional double bond between C12b–C1 whereas compound **11** is a rearranged product obtained plausibly *via* an intermediate imminium compound followed by reduction. On the other hand, the formation of compounds **12** and **13** could be rationalised on the basis of cleavage of C/D ring of the pyrazole formed under strong alkaline condition resulting initially in the formation of **12** which then undergoes further oxidation to afford **13**. As expected, oxidation of **12** with DDQ in HOAc resulted in compound **13** corroborating the plausible mechanism (Scheme 2). Interestingly, compound **2** when heated with solid KOH in higher boiling alcohols like Bu^nOH or ethylene glycol underwent deacylation followed by rearrangement to yield 2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizin-2-one **14** probably formed as shown in Scheme 2. All the compounds have been characterised mainly on the basis of their 1D and 2D NMR spectral data.

Techniques used: Elemental analysis, IR, ^1H and ^{13}C NMR, mass spectrometry.

Schemes: 2

References: 11

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