SYNTHESIS OF NOVEL INDOLO[3,2-c]QUINOLINES; ETHYL 3-CHLORO-9,11-DIMETHOXY INDOLO[3,2-c]QUINOLINE-6-CARBOXYLATE

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ABSTRACT

β-Carboline and its derivatives are significant due to their pharmacological importance. The synthesis of indolo[3,2-c]quinolines as a benzo analog of β-carboline has been carried out via an oxime ether intermediate. Reaction of 2'-glyoxylic ester with hydroxylamine hydrochloride in the presence of sodium acetate afforded the oxime acetate in 82%. It was then treated with natrium and fluoro-2,4-dinitrobenzene in ethanol to give an orange solid of oxime ether acetate which is in subsequent treatment with a base yielded a pale yellow solid of indolo[3,2-c]carboline in 43%.

Keywords: β-carboline, oxime, indolo[3,2-c]quinoline.

INTRODUCTION

β-Carboline as well as its benzo analog, Indolo[3,2-*c*]quinolines, are significant due to their pharmacological importance. β-Carbolines such as harman 1 have been isolated from *Symplocos setchuensis* Brand. Harman shows anti-HIV activity [1], whereas the related indoloquinolinone 2 has been investigated as an inhibiting agent of transplantable tumor growth [2].

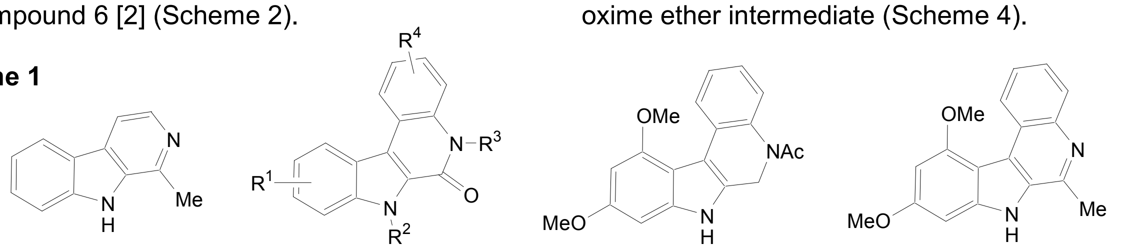
Benzo-β-carbolines can be prepared by a variety of specialized methods. A different approach requiring initial synthesis of an azide intermediate 5, thermal intramolecular cyclization followed by reduction and deprotection has been shown to yield the compound 6 [2] (Scheme 2).

In a low yielding reaction (18%), the benzo-β-carboline 3 was prepared by an intramolecular palladium coupling reaction. However, this method failed if the aryl group had a methyl or methoxy substituent at the para position [3]. It has also been reported that a stepwise Bischler synthesis gives the indolo[3,2-*c*]quinoline 4 [4].

Cyclization reaction via ketoxime ether such as 2,4-dinitrophenyloximes has been reported by Narasaka and co-workers [5-7]. The *O*-2,4-dinitrophenyloxime 7 cyclized at room temperature to give the 2-methyl phenanthridine 8 in 85% yield [6,7] (Scheme 3).

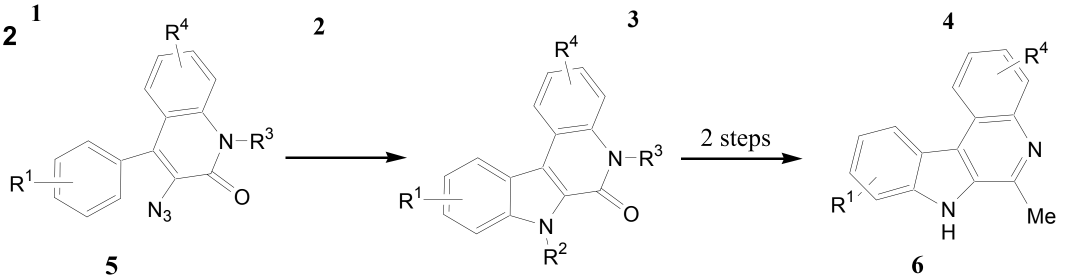
This paper focuses on the synthesis of indolo[3,2-*c*]quinoline from the 2-ketoxime indole via oxime ether intermediate (Scheme 4).

Scheme 1



1 2 3 4

Scheme 2



5 6

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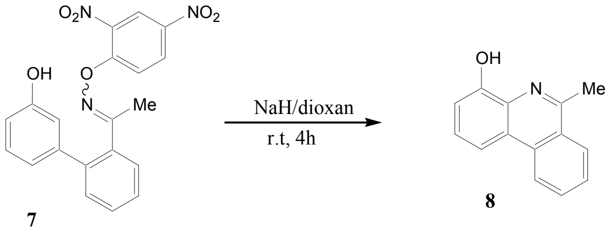
Scheme 3



EXPERIMENTAL SECTION

General

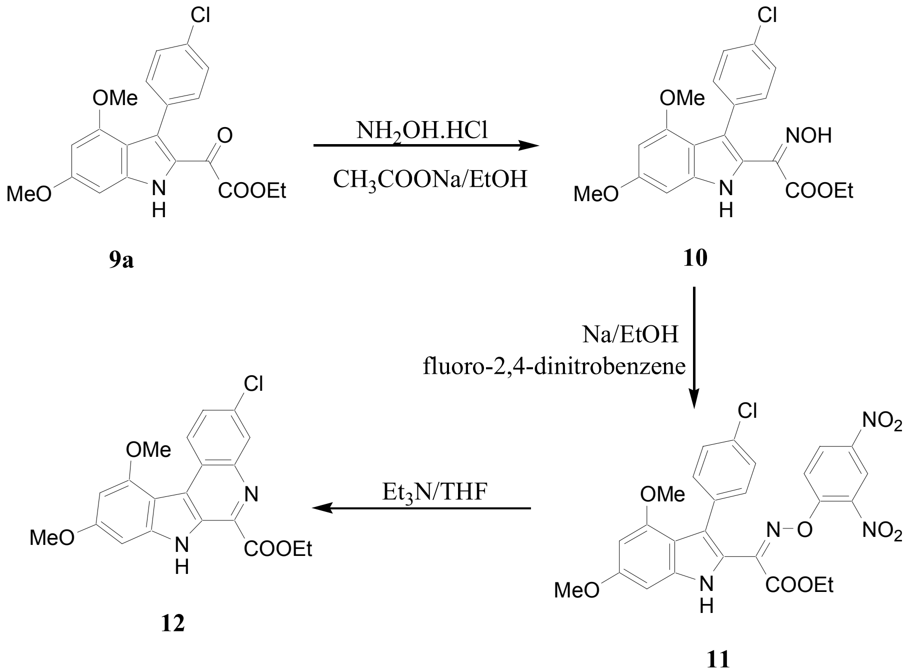
Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Elemental analyses were performed by The Campbell Microanalytical Laboratory, University of Otago, New Zealand. Infrared spectra were obtained on a Mattson Genesis series FTIR spectrometer. Ultraviolet spectra were measured on Carey 100 spectrophotometers and refer to solutions in absolute methanol. ^{1}H NMR spectra were recorded at 300 MHz while ^{13}C NMR spectra were recorded at 75 MHz with a Bruker AC300F spectrometer and the chemical shifts are referenced to internal solvent resonances. The EI mass spectra were measured using a VG Quattro mass spectrometer .

Synthesis Ethyl 2-[3-(4-chlorophenyl)-4,6-dimethoxyindol-2-yl]glyoxylate (9a) and Ethyl 2-[3-(4-chlorophenyl)-4,6-dimethoxyindol-7-yl]glyoxylate (9b)

Indole **13** (1.00 g, 3.5 mmol) was partially dissolved in anhydrous diethylether (100 mL). Oxalyl chloride (0.90 mL, 9.46 mmol) was then added in one portion and the mixture was stirred for 3h at room temperature. The resulting red precipitate was filtered off. This red solid was stirred at room temperature in absolute ethanol (15 mL) for 2h. The precipitate was filtered off, washed until neutral and dried to give the *title compound* **9a** (0.56 g, 42%) as an orange solid. m.p. 188^{o}C. (Found : C, 61.9; H, 4.8; N, 3.7. $C_{20}H_{18}ClNO_5$ requires C, 61.9; H, 4.7; N, 3.6%). ν_{max} : 3323, 1741, 1600, 1571, 1236, 1206, 1132, 816 cm^{-1}. λ_{max} : 228 nm (ε 18,350 cm^{-1} M^{-1}), 264 (20,350), 334 (13,850). δ_H (300 MHz, $CDCl_3$) 1.14 (3H, t, *J* 7.2 Hz, CH_3), 3.63, 3.86 (6H, 2s, OCH_3), 3.79 (2H, q, *J* 7.2 Hz, OCH_2), 6.11 (1H, d, *J* 1.5 Hz, H5), 6.41 (1H, d, *J* 1.9 Hz, H7), 7.34 (4H, m, ArH), 9.44 (1H, br, NH). δ_C (75 MHz, $CDCl_3$) 13.5 (CH_3), 55.1, 55.6 (OCH_3), 62.0 (OCH_2), 85.6 (C5), 93.8 (C7), 127.1, 132.2 (ArCH), 113.3, 127.1, 128.6, 131.9, 133.6, 139.8, 156.9, 162.4 (ArC), 163.9, 176.8 (C=O). Mass spectrum (EI) : *m/z* 389 (M+2, ^{37}Cl, 20%), 387 (M, ^{35}Cl, 62), 316 (27), 314 (83), 279 (100), 264 (21).

Absolute ethanol (10 mL) was added to the filtrate and the mixture was refluxed for 2h. Water was then added and the mixture was extracted with dichloromethane. The organic layer was washed until neutral, dried and the solvent was removed under reduced pressure to give the *title compound* **9b** (0.33 g, 24%) as a yellow solid. m.p. 188-189^{o}C. (Found : C, 61.7; H, 4.5; N, 3.7. $C_{20}H_{18}ClNO_5$ requires C, 61.9; H, 4.7; N, 3.6%). ν_{max} : 3426, 1728, 1584, 1309, 1218, 1170, 1058 cm^{-1}. λ_{max} : 232 nm (ε 21,600 cm^{-1} M^{-1}), 256 (20,900), 336 (12,100).

Scheme 4



δ_H (300 MHz, $CDCl_3$) 1.41 (3H, t, *J* 7.2 Hz, CH_3), 3.92, 3.94 (6H, 2s, OCH_3), 4.43 (2H, q, *J* 7.2 Hz, OCH_2), 6.18 (1H, s, H5), 7.09 (1H, d, *J* 2.2 Hz, H2), 7.31-7.48 (4H, m, ArH), 10.56 (1H, br, NH). δ_C (75 MHz, $CDCl_3$) 14.1 (CH_3), 55.4, 56.9 (OCH_3), 61.4 (OCH_2), 87.4 (C5), 121.9 (C7), 127.7, 130.6 (ArCH), 100.8, 110.7, 118.0, 131.9, 133.6, 138.4, 162.0, 162.1 (ArC), 165.9, 185.1 (C=O). Mass spectrum (EI) : *m/z* 389 (M+2, ^{37}Cl, 16%), 387 (M, ^{35}Cl, 47), 316 (58), 314 (100), 299 (7), 284 (9).

Ethyl 2-[3-(4-chlorophenyl-4,6-dimethoxyindol-2-yl]-2-(hydroxyimino) acetate (10)

Indole glyoxylic ester **9a** (0.40 g, 1.0 mmol), hydroxylamine hydrochloride (0.36 g, 5.2 mmol), sodium acetate (0.4 g, 2.9 mmol) and absolute ethanol (40 mL) were heated under reflux for 7h. After cooling, the solvent was evaporated off under reduced pressure. The residue was dissolved in dichloromethane, acidified with 1N HCl, washed with water and dried. The solvent was evaporated off and the residue was chromatographed with dichloromethane/ethyl acetate (95:5) as eluent to give the *title compound* **10** (0.34 g, 82%) as a light brown solid. m.p. 183-184^{o}C. (Found : C, 59.6; H, 4.8; N, 7.0. $C_{20}H_{19}ClN_2O_5$ requires C, 59.6; H, 4.8; N, 6.9%). ν_{max} : 3373, 1719, 1624, 1584, 1212, 1151, 1131, 998, 818 cm^{-1}. λ_{max} : 228 nm (ε 23,750 cm^{-1} M^{-1}), 255 (19,850), 337 (7,200). δ_H (300 MHz, d_6-DMSO) 0.97 (6H, m, *syn* & *anti* CH_3), 3.51-3.76 (16H, m, *syn* & *anti* OCH_2 & OCH_3), 6.09, 6.17 (2H, 2s, *syn* & *anti* H5), 6.52, 6.56 (2H, 2d, *J* 1.5 Hz, *syn* & *anti* H7), 7.19, 7.32 (8H, 2d, *J* 8.3 Hz, *syn* & *anti* ArH), 11.17, 11.28 (2H, 2s, *syn* & *anti* NH), 11.64, 12.60 (2H, 2s, *syn* & *anti* OH). δ_C (75 MHz, d_6-DMSO) 13.7, 13.9 (CH_3), 55.3, 55.4, 55.6, 55.6 (OCH_3), 61.1, 61.2 (OCH_2), 87.2, 87.3 (C5), 92.4 (C7), 126.9, 127.3, 132.2, 133.4 (ArCH), 110.2, 112.4, 117.3, 117.6, 121.7, 123.4, 131.1, 131.8, 134.5, 138.3, 138.4, 143.4, 144.7, 154.9, 155.0 (ArC), 158.2, 158.7 (C=N), 162.2, 163.2. (C=O). Mass spectrum (EI) : *m/z* 404 (M+2, ^{37}Cl, 31%), 402 (M, ^{35}Cl, 100), 385 (35), 313 (34), 312 (81), 291 (61), 262 (46).

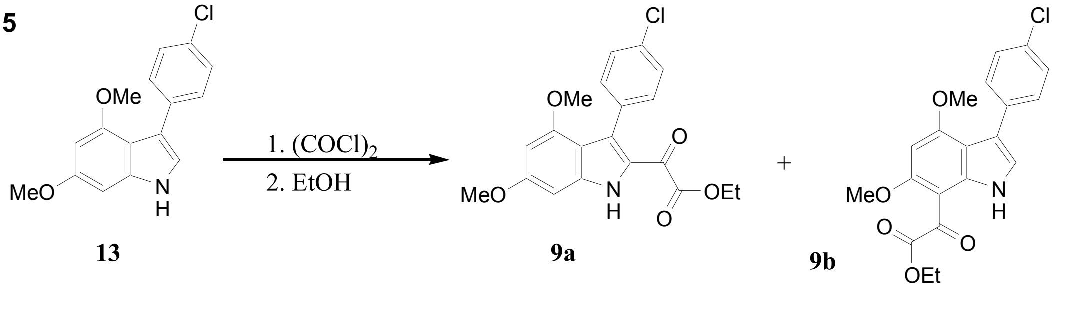
Ethyl 2-[3-(4-chlorophenyl-4,6-dimethoxyindol-2-yl]-2-(*O*-2,4-dinitrophenyloxyimino) acetate (11)

Indole oxime **10** (0.27 g, 0.66 mmol) was dissolved in absolute ethanol (25 mL) and sodium (22 mg, 0.96 mmol) was added. The solution became clear and was stirred at room temperature for 30 min. The mixture was cooled in an ice-bath, and fluoro-2,4-dinitrobenzene (0.12 mL, 0.66 mmol) was added dropwise. The mixture was stirred for another 2h and the resulting precipitate was filtered off, washed with absolute ethanol and dried to yield the *title compound* **11** (0.34 g, 89%) as an orange solid. m.p. 214-216^{o}C. (Found : C, 54.3; H, 3.7; N, 9.5. $C_{26}H_{21}ClN_4O_9$ 0.3H_2O requires C, 54.4; H, 3.8; N, 9.8%). ν_{max} : 3383, 1736, 1605, 1565, 1536, 1340, 1251, 1137, 1089 cm^{-1}. λ_{max} : 231 nm (ε 34,950 cm^{-1} M^{-1}), 327 (17,150). δ_H (300 MHz, $CDCl_3$) 1.12-1.18 (6H, m, *syn* & *anti* CH_3), 3.59-3.92 (16H, m, *syn* & *anti* OCH_2 & OCH_3), 6.14 (2H, s, *syn* & *anti* H5), 6.47, 6.61 (2H, 2d, *J* 1.5 Hz, *syn* & *anti* H7), 7.33 (8H, s, *syn* & *anti* ArH), 7.89 (1H, d, *J* 9.0 Hz, ArH) 8.23 (1H, d, *J* 9.4, ArH), 8.43-8.56 (2H, m, ArH), 8.88, 9.09 (2H, 2d, ArH), 8.68, 10.77 (2H, 2s, *syn* & *anti* NH). The sample was not soluble enough for ^{13}C NMR measurement. Mass spectrum (EI) : *m/z* 386 (M-OAr $(NO_2)_2$, 23%), 384 (59), 314 (32), 312 (100), 295 (27), 269 (19).

Ethyl 3-chloro-9,11-dimethoxy indolo[3,2-*c*]quinoline-6-carboxylate (12)

A mixture of indole **11** (0.33 g, 0.59 mmol) and triethylamine (1 mL) in dry tetrahydrofuran (25 mL) was heated under reflux overnight. The solvent was evaporated off and the residue dissolved in dichloromethane. The organic layer was washed with 2N NaOH and water, dried and concentrated. Column chromatography with dichloromethane/ methanol (95:5) as eluent yielded the *title compound* **12** (98 mg, 43%) as a pale yellow solid. m.p. 197-198^{o}C. (Found : C, 55.4; H, 4.0; N, 6.1. $C_{20}H_{17}ClN_2O_4$ 0.75CH_2Cl_2 requires C, 55.6; H, 4.2; N, 6.2%). ν_{max} : 3431, 1702, 1621, 1345, 1247, 1190, 1152, 1101 cm^{-1}. δ_H (300 MHz, $CDCl_3$) 1.58

Scheme 5



(3H, t, *J* 7.1 Hz, CH_3), 3.95, 4.12 (6H, 2s, OCH_3), 4.66 (2H, q, *J* 7.1 Hz, OCH_2), 6.42 (1H, d, *J* 1.9 Hz, H5), 6.67 (1H, d, *J* 1.9 Hz, H7), 7.61 (1H, dd, *J* 7.2, 2.3 Hz, ArH), 8.36 (1H, d, *J* 2.3 Hz, ArH), 9.46 (1H, d, *J* 9.4 Hz, ArH), 10.36 (H, br, NH). δ_C (75 MHz, $CDCl_3$) 14.3 (CH_3), 55.4, 55.6 (OCH_3), 62.4 (OCH_2), 86.9 (C5), 92.9 (C7), 128.1, 128.5, 129.7 (ArCH), 106.6, 123.7, 125.6, 129.7, 131.9, 132.6, 142.6, 143.2, 155.9, 162.1 (ArC), 166.7 (C=O).

RESULT AND DISCUSSION

Treatment of 3-chlorophenylindole **13** with oxalyl chloride in diethyl ether followed by addition of excess absolute ethanol gave the 2- and 7-glyoxylic esters **9a** and **9b** in 42% and 24% yield respectively.

The 2-glyoxylchloride precipitated and could be separated from the filtrate, which contained the 7-glyoxylchloride. Treatment of the 2-isomer with ethanol at room temperature gave the ester **9a**. The 7-isomer was more stable and reflux in ethanol was required to form the ester **9b**.

The ^{1}H NMR spectrum demonstrated the presence of the ethyl ester groups as a triplet and quartet at 1.13-1.40 ppm and 3.50-4.50 ppm. In the case of compound **9a**, there was no H2 resonance and compound **9b** showed no H7 resonance. The infrared spectrum proved the presence of carbonyl groups and the mass spectrum demonstrated the molecular ion at *m/z* 387.

Reaction of 2-glyoxylic ester **9a** with hydroxylamine hydrochloride in absolute ethanol containing sodium acetate yielded the expected indole oxime **10** in 82%. A mixture of *syn* and *anti* isomers was observed. The ratio of *anti* to *syn* isomer was 10 : 1 for indole oximes **10**. In addition, the mass spectrum of compounds **10** showed molecular ions at *m/z* 402 (100%).

Treatment of indole oximes **10** with fluoro-2,4-dinitrobenzene in the presence of sodium ethoxide at 0°C for 2 hours afforded the corresponding indole oxime-ethers **11** in high yield.

The ^{1}H NMR spectrum of indole **11** showed that the compound exists as a mixture of *syn* and *anti*-isomers, as indicated by two sets of aryl protons from the dinitrophenyl group. The more intense peaks should correspond to the *anti*-isomer, which should be more stable than the *syn*-isomer. The infrared spectrum proved this assignment by the strong intensity of its C=N frequency at 1605 cm^{-1} for the *anti*-isomer and the low intensity at 1628 cm^{-1} for the *syn*-isomer [8].

The indole oxime ethers **11** were treated with triethylamine in tetrahydrofuran to afford a light yellow solid compound. The ^{1}H NMR spectrum showed the presence of two doublets at 8.33 and 9.33 ppm and one doublet of doublets at 7.69 ppm corresponding to the three aryl protons. This indicates that one of the aryl protons has disappeared and the nitrogen of the oxime ether has been linked to one of the aryl carbons to produce the cyclic products **12**. The structures are supported by mass spectra and elemental analysis.

CONCLUSION

In conclusion, I has reported a new and effective method for the preparation of indolo[3,2-c]quinoline from the 2-ketoxime indole via oxime ether intermediate.

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REFFERENCES

1. Ishida, J., Wang, H.K., Oyama, M., Cosentino, M.L., Hu, C.Q. and Lee, H.H., 2001, *J. Nat. Prod., 64*, 958-960.
2. Fryer, R.I., Ning, R.Y.F., Sternbach, L.H. and Walser, A. U.S.patent 1977, 4014883.
3. Jeevanandam, A. and Srinivasan, P.C., 1995, *Synth. Commun., 25*, 3427-3434.
4. Jones, A.W., 2000, *Investigation into indole synthesis, manipulation and macrocyclisation*, Ph.D Thesis, University of New South Wales.
5. Uchiyama, K., Hayashi, Y. and Narasaka, K., 1997, *Synlett,* 445-446.
6. Uchiyama, K., Ono, A., Hayashi, Y. and Narasaka, K., 1998, *Bull. Chem. Soc. Jpn., 71*, 2945-2955.
7. Ono, A. and Narasaka, K., 2001, *Chem. Lett.*, 146-147.
8. Cho, B.R., Park, C.W. and Je, J.T., 1995, *J. Chem. Res. Synop.*, 200-201.