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A GENERAL SYNTHESIS OF INDOLO[2,3-a]QUINOLIZINE FROM A SYMMETRICAL STARTING MATERIAL, CIS-Δ^4-TETRAHYDROPHTHALIC ACID ANHYDRIDE

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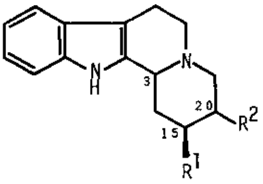
Abstract —— A general synthesis of indolo[2,3-a]quinolizine derivatives (12) and (13) has been achieved by a condensation of tryptamine with the aldehyde (11) derived from a symmetrical starting material, cis-Δ^4-tetrahydrophthalic acid anhydride (2).

In the field of alkaloid chemistry, the indoloquinolizine skeleton (1) is a common structure to a number of indole alkaloids. Change in the geometry of the hydrogen atoms attached to certain vital centers(position 3, 20) completely alters the properties of this family such as corynantheine,[1] hirsuteine,[2] corynantheidine,[3] and speciociliatine.[4]



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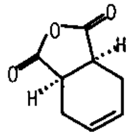
Recently we have shown the anhydride (2) to be an excellent synthon for the construction of the pentacyclic skeleton of yohimbine family.[5] In our continuous efforts for the synthesis of natural products and its related compounds[6] using a symmetrical starting material, we intrigued a synthesis of the corynanthe-type indole alkaloids. Here we wish to report a synthesis of the indolo[2,3-a]quinolizine derivatives which could be potential intermediates leading to indole alkaloids such as dehydrocorynantheol and corynantheine.

The diacetal (5), prepared in 55.7 % yield *via* dialdehyde (4) from the known γ-butyrolactone (3)[7] derived from *cis*-Δ^4-tetrahydrophthalic acid anhydride (2) was heated with potassium cyanide in dimethyl sulfoxide at 190°C to give the cyanated acid (6). Without further purification, the crude carboxylic acid (6) was treated with an ethereal diazomethane to produce the *trans* orientated methyl ester (7)[8] [ir ($CHCl_3$) 2240, 1720 cm^{-1}; δ 3.70 (3H, s, $OC\underline{H}_3$), 3.70 - 4.07 (8H, m, 2 x $\mathrm{CH}{<}\substack{\mathrm{O-CH}\\ \mathrm{O-C\underline{H}_2}}2$), 4.90 (1H, t, J = 4 Hz, $\mathrm{C\underline{H}}{<}\substack{\mathrm{O}\\ \mathrm{O}}$]), 4.92 (1H, t, J = 4 Hz, $\mathrm{C\underline{H}}{<}\substack{\mathrm{O}\\ \mathrm{O}}$]); mass *m/e* 299 ($\underline{M}^+$)] in 74 % yield from the γ-butyrolactone (5). The conformation of 7 was determined by a comparison with an authentic sample derived from 3 *via* known compound (8).[9] The reduction of this ester (7) with 4 equivalents of diisobutylaluminum hydride in toluene at - 60°C afforded, in 80.2 % yield, the alcohol (9)[ir ($CHCl_3$) 3600 - 3200, 2250 cm^{-1}; δ 2.63 - 3.0 (1H, br s, O$\underline{H}$, exchanged with D_2O), 3.50 - 3.77 (2H, br s, $C\underline{H}_2OH$), 3.88, 3.93 (each 4H, each s, 2 x $\mathrm{CH}{<}\substack{\mathrm{O-CH}\\ \mathrm{O-C\underline{H}_2}}2$), 4.9 (2H, t, J = 4 Hz, 2 x $\mathrm{C\underline{H}}{<}\substack{\mathrm{O}\\ \mathrm{O}}$])] which on treatment with *p*-toluenesulfonyl chloride in pyridine at 0°C produced the tosylate (10) in 95 % yield [ir ($CHCl_3$) 2250, 1180 cm^{-1}; δ 2.45 (3H, s, $ArC\underline{H}_3$), 3.67 - 3.97 (8H, m, 2 x $\mathrm{CH}{<}\substack{\mathrm{O-CH}\\ \mathrm{O-C\underline{H}_2}}2$), 3.97 - 4.23 (2H, m, $C\underline{H}_2OSO_2$), 4.80 (2H, t, J = 4 Hz, 2 x $\mathrm{C\underline{H}}{<}\substack{\mathrm{O}\\ \mathrm{O}}$]), 7.30 (2H, d, J = 8 Hz, ArH), 7.73 (2H, d, J = 8 Hz, Ar$\underline{H}$); mass *m/e* 425 ($\underline{M}^+$)]. The conversion of nitrile to aldehyde was also done by use of diisobutylaluminum hydride. Thus, the reduction of the nitrile (10) with 6 equivalents of diisobutylaluminum hydride followed by a treatment of the mixture with saturated ammonium chloride solution produced the desired aldehyde (11) in 82.4 % yield [ir ($CHCl_3$) 2730, 1725, 1180 cm^{-1}; δ 2.43 (3H, s, $ArC\underline{H}_3$), 3.82, 3.85 (each 4H, each s, 2 x $\mathrm{CH}{<}\substack{\mathrm{O-CH}\\ \mathrm{O-C\underline{H}_2}}2$), 3.90 - 4.23 (2H, m, $C\underline{H}_2OSO_2$), 4.63 - 5.0 (2H, m, 2 x $\mathrm{C\underline{H}}{<}\substack{\mathrm{O}\\ \mathrm{O}}$]), 7.28 (2H, d, J = 8 Hz, Ar$\underline{H}$), 7.25 (2H, d, J = 8 Hz, Ar$\underline{H}$), 9.60 (1H, br s, CHO)]. Since this aldehyde is unstable, it was used directly in the next step. Thus, heating the aldehyde (11) with tryptamine in acetic acid at 85°C for 1 hr afforded a separable mixture of indoloquinolizines, 3S,15R,20R-diethylenedioxyethylindoloquinolizine (12) in 27.3 % yield [ir ($CHCl_3$) 3460 cm^{-1}; δ 3.85, 3.89 (each 4H, each s, 2 x $\mathrm{CH}{<}\substack{\mathrm{O-CH}\\ \mathrm{O-C\underline{H}_2}}2$), 4.67 - 5.14 (2H, m, 2 x $\mathrm{C\underline{H}}{<}\substack{\mathrm{O}\\ \mathrm{O}}$]), 6.80 - 7.48 (4H, m, Ar$\underline{H}$), 7.80 - 8.12 (1H, br s, N$\underline{H}$, exchanged with D_2O); mass *m/e* 398.2188 ($\underline{M}^+$)] and 3R,15R,20R-diethylenedioxyethylindoloquinolizine (13) in 28.5 % yield [ir ($CHCl_3$) 3460 cm^{-1}; δ 3.80, 3.85 (each 4 H, each s, 2 x $\mathrm{CH}{<}\substack{\mathrm{O-CH}\\ \mathrm{O-C\underline{H}_2}}2$), 4.67 - 5.08 (2H, m, 2 x $\mathrm{C\underline{H}}{<}\substack{\mathrm{O}\\ \mathrm{O}}$], 6.80 - 7.48 (4H, m, Ar$\underline{H}$), 7.88 - 8.08 (1H, N$\underline{H}$, exchanged with D_2O); mass *m/e* 398.2186 (M^+)], whose configuration at C_3 is not clear at this stage.

In order to certify the configuration at C_3 of these indoloquinolizines, the compound (13) was dehydrogenated with mercuric acetate[10] to give the iminium base (14) which on reduction with sodium borohydride produced 11 in 80.8 % yield. On the other hand, treatment of 12 under the same conditions resulted in recovered starting material. These conversions indicated that the compounds (12) and (13) were the C(3)-epimers of each other.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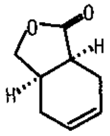
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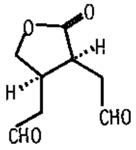
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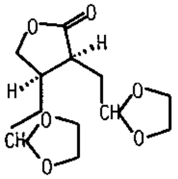
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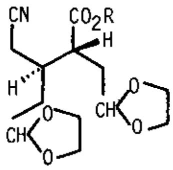
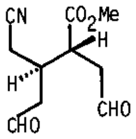

6 : R=H
7 : $R=CH_3$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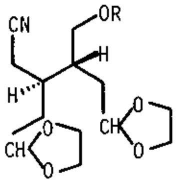
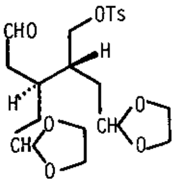

9 : R=H
10 : R=Ts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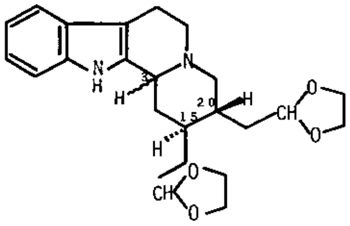
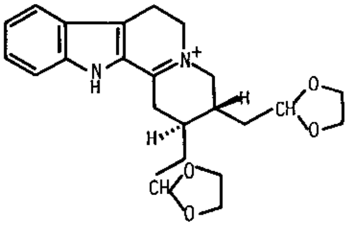

12 : 3αH
13 : 3βH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Thus, we achieved a general synthesis of the indolo[2,3-a]quinolizine derivatives by a condensation of tryptamine with the aldehyde (11) derived from a symmetrical starting material, cis-Δ^4-tetrahydrophthalic acid anhydride (2) and these compounds would be potential intermediates leading to corynan, dihydrocorynantheol and corynantheidol. According to this methodology, a synthesis of corynanthe-type indole alkaloids is under investigation in our laboratory.

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