Synthesis of the Phosphodiesterase Inhibitors PDE-I and PDE-II

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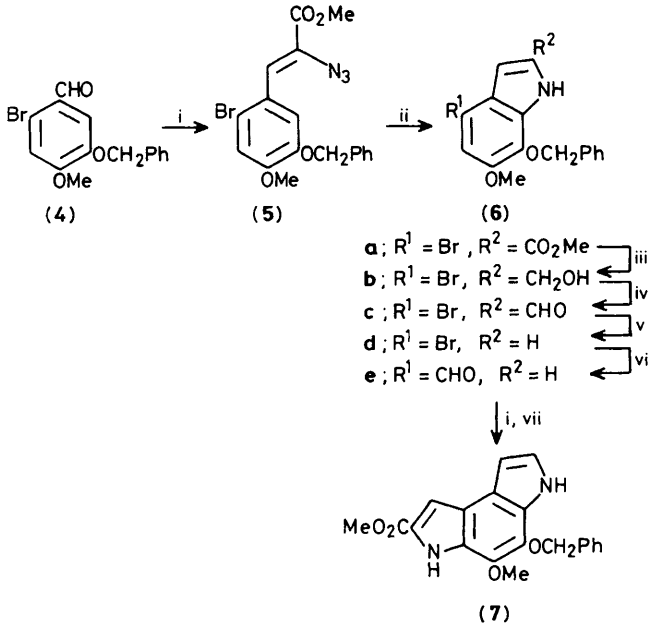
The pyrrolo[3,2-*e*]indole phosphodiesterase inhibitors PDE-I (**1**) and PDE-II (**2**) have been synthesised from isovanillin by a route which involves construction of both pyrrole rings by thermolysis of azidoacrylates readily derived from benzaldehydes.

The naturally occurring pyrrolo[3,2-*e*]indoles (**1**) and (**2**), known respectively as PDE-I and PDE-II, are isolated from *Streptomyces* MD769-C6 and exhibit inhibitory activity towards cyclic adenosine-3′,5′-monophosphate phosphodiesterase.[1] The structures, assigned by n.m.r. spectroscopy, were confirmed by *X*-ray crystallography,[2] and by synthesis by classical routes.[3,4]

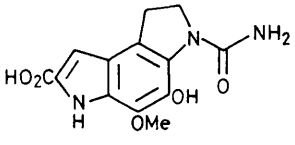
Pyrroloindoles very closely related to PDE-I and PDE-II also make up the B- and C-units of the antibiotic CC-1065 (**3**),[5] which because of its potent antitumour activity has been the subject of considerable synthetic efforts.[6] We now report a new route to pyrrolo[3,2-*e*]indoles, and the synthesis of the natural products PDE-I (**1**) and PDE-II (**2**).

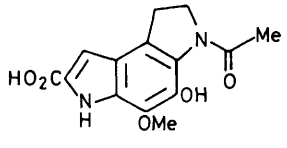
The overall strategy involves, as key steps, the fusion of both the pyrrole rings by decomposition of azidoacrylate derivatives readily prepared from aromatic aldehydes. We have recently used a similar sequence in the total synthesis of the bacterial coenzyme methoxatin.[7] The starting material is the known bromobenzaldehyde (**4**) easily prepared on a large scale from isovanillin in two steps (77% overall, lit.,[8] 20%). Condensation of the aldehyde (**4**) with methyl azidoacetate gave the azide (**5**) (71%) which was thermolysed in xylene to give the indole (**6a**), followed by reduction with lithium aluminium hydride to the alcohol (**6b**) [93% from (**5**)]. Oxidation of (**6b**) with manganese dioxide in refluxing dichloromethane gave the corresponding aldehyde (**6c**) (84%) which was decarbonylated (70%) to the indole (**6d**), m.p. 82—83 °C, by treatment with a catalytic amount of $(Ph_3P)_2Rh(CO)Cl$ and 1,3-bis(diphenylphosphino)propane (dppp) in refluxing mesitylene.[9] Initially it had been intended to remove the unwanted ester substituent by hydrolysis and decarboxylation, but in common with other workers,[9] we found that the decarboxylation of the indole-2-carboxylic acid was unsatisfactory, and hence the alternative decarbonylation approach.

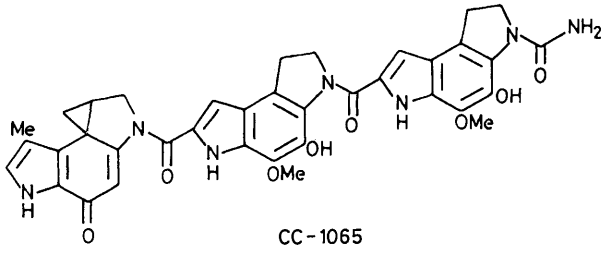
The bromoindole (**6d**) was lithiated with an excess of t-butyl-lithium at −78 °C and the resulting organolithium quenched with dimethylformamide (DMF) to give the aldehyde (**6e**) (57%). Condensation of (**6e**) with methyl

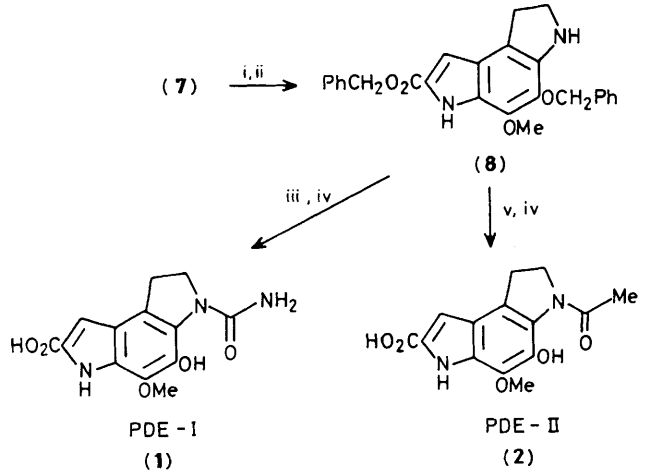


Scheme 1. *Reagents:* i, $MeO_2CCH_2N_3$, NaOMe, MeOH, 4 °C; ii, xylene, reflux; iii, $LiAlH_4$, Et_2O, reflux; iv, MnO_2, CH_2Cl_2, reflux; v, $(Ph_3P)_2Rh(CO)Cl$ (0.06 equiv.), dppp (0.12 equiv.), mesitylene, reflux; vi, Bu^tLi (6.5 equiv.), tetrahydrofuran (THF), −78 °C, then DMF, −78 °C to room temp., aq. NH_4Cl work-up; vii, toluene, reflux.









Scheme 2. *Reagents:* i, $PhCH_2OH$, $PhCH_2ONa$, benzene, reflux; ii, $NaBH_3CN$, AcOH, room temp.; iii, Me_3SiNCO, benzene, room temp.; iv, H_2 (4 atm.), Pd–C, MeOH; v, Ac_2O, pyridine, room temp.

azidoacetate, and thermolysis of the resulting azide in toluene gave the key intermediate, the tricyclic compound (**7**) [59% from (**6e**)] (Scheme 1).

The conversion of the pyrroloindole (**7**) into PDE-I and PDE-II was achieved as shown in Scheme 2. Thus transesterification with benzyl alcohol followed by selective reduction with sodium cyanoborohydride in acetic acid[10] gave the pyrroloindoline (**8**) [65% from (**7**)]. Reaction of (**8**) with trimethylsilyl isocyanate in benzene, followed by hydrogenolysis of the benzyl groups then gave PDE-I (**1**) [65% from (**8**)]. Similarly, PDE-II (**2**) was obtained from (**8**) by acetylation (acetic anhydride–pyridine) and hydrogenolysis [84% from (**8**)]. The spectra of synthetic PDE-I and PDE-II were identical to those reported for the natural products.[1]

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