Cycloaddition Reactions of 2-(Indol-2-yl)acrylates and *N*-Alkoxycarbonyl-1,2-dihydropyridine; New Synthesis of Desethylcatharanthine

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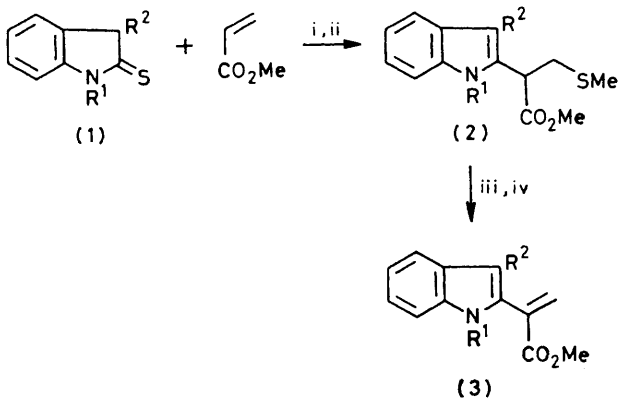
Summary A new synthesis of desethylcatharanthine (**7b**) by utilising a cycloaddition reaction between the 2-(indol-2-yl)acrylate (**10**) and the *N*-alkoxycarbonyl-1,2-dihydropyridine (**4b**) is described.

THE photoaddition reactions between the indoline-2-thiones (**1**) and methyl acrylate provide[1] a facile access to the methyl 2-(indol-2-yl)acrylate derivatives (**3**). Unlike other methods,[2,3] this procedure[1] offers the possibility of using an indoline-2-thione (**1**) with or without a substituent

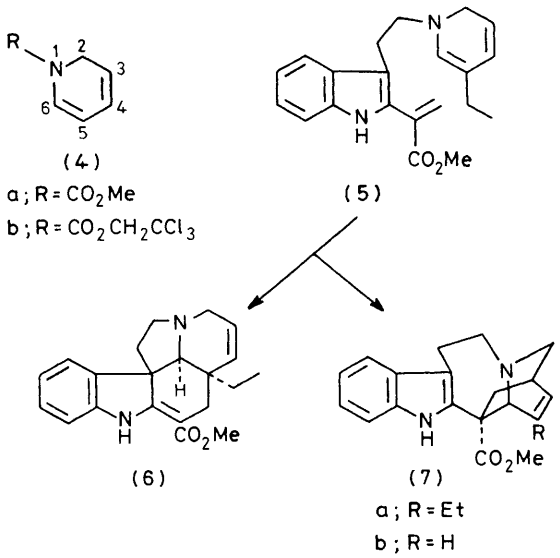
on the nitrogen or the 3-position of the indole, thereby enabling us to obtain indoleacrylates, such as (**3a**) and (**3b**), by way of their stable precursors (**2a**) and (**2b**). (Scheme 1).



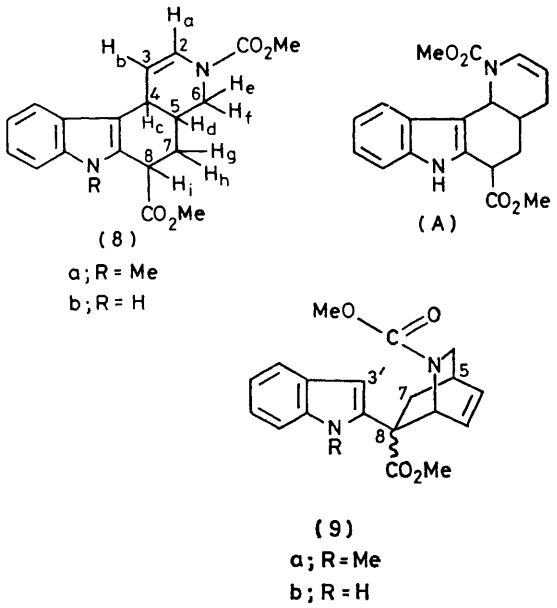
a; R^1 = Me, R^2 = H
b; R^1 = R^2 = H
c; R^1 = H, R^2 = CH_2CH_2OH

SCHEME 1. *Reagents:* i, *hν*; ii, CH_2N_2; iii, *m*-$ClC_6H_4CO_3H$; iv, toluene, heat for 5 min at 110 °C.

We have investigated the reactivity of the acrylates (**3a**) and (**3b**) toward the dihydropyridine (**4a**) to determine the cycloaddition reaction conditions that could, ultimately, lead to Aspidosperma- and/or Iboga-type alkaloids *via* a biomimetic pathway resembling the proposed[5] intramolecular Diels–Alder type cyclisation of the hypothetical intermediate dehydrosecodine (**5**) into tabersonine (**6**) and catharanthine (**7a**). The scope of the method has been tested by effecting a short synthesis of desethylcatharanthine (**7b**).[6]



In refluxing toluene, the reaction of (**3a**) with (**4a**) gave, in addition to the dimers (*M* 430, yield 25%) of (**3a**), a mixture of two types of adduct (**8a**) and (**9a**) in 6 and 30% isolated yields, respectively. The isomeric cycloaddition products could be differentiated by their mass spectra. The major products (**9a**) ($M^{+\cdot}$ 354) gave the base peak at *m/z* 215 [corresponding to (**3a**)], resulting from retro-Diels–Alder fragmentation. This peak at *m/z* 215 is of low intensity in the mass spectrum of (**8a**), which showed the most abundant fragment ions at *m/z* 339 (*M* − 15). The ^{1}H n.m.r. spectrum of (**8a**) revealed only two olefinic protons which were mutually coupled. Their chemical shift values (δ 6·70 and 5·02) were different from those observed for the olefinic protons[7] of the Aspidosperma alkaloid tabersonine (**6**). The proposed structure of (**8a**) was reached principally on the basis of double-resonance ^{1}H n.m.r. experiments with the related isomeric compound (**8b**) (see below). The two isomers of (**9a**), with α- and β-CO_2Me, were isolated in the ratio α/β 3/2. Unlike compound (**8a**) they could be characterised by the presence of the indole 3′-H proton signals at δ 6·30 and 6·89. The major isomer of (**9a**) was assigned the α-configuration by analogy with the results previously reported by Sundberg and Bloom.[6]



Similarly, heating (**3b**) [generated *in situ* from (**2b**) in refluxing toluene] with (**4a**) gave (**8b**) (two isomers which could be separated) and (**9b**) in 45 and 7% yields, respectively, in addition to the dimers (*M* 402, yield 25%) of (**3b**). The spectral data were consistent with the proposed structures (**8b**) and (**9b**). Thus, the ^{1}H n.m.r. spectrum (250 MHz, $CDCl_3$, recorded at 60 °C because of the slow rotation of the carbamate group at room temperature[6]) of the major isomer of (**8b**) showed δ 8·12 (s, >NH), 7·6—7·1 (m, 4 H, aromatic), 6·75 (broad signal at 60 °C, H_a; at 20 °C appeared as a pair of doublets at 6·83 and 6·68, J_{ab} 8 Hz each), 5·1 (dd, J_{ab} 8 Hz, J_{bc} *ca.* 1·5 Hz,† H_b),

† The signal due to 4-H_c could not be detected as it remained obscured by the *O*-methyl signals.

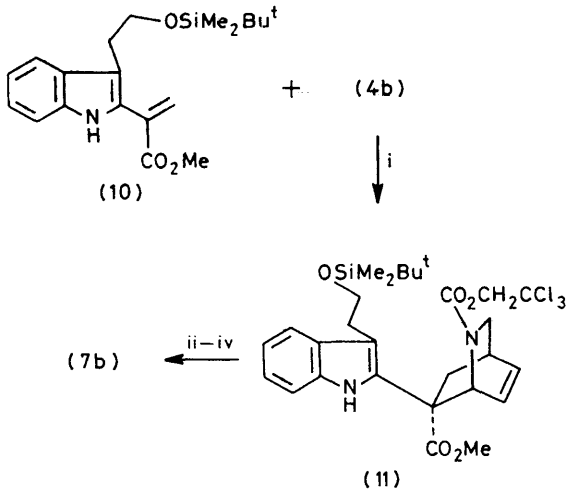
4·02 (dd, J_{ef} 13 Hz, J_{de} 5 Hz, H_e), 3·84 (dd, J_{hi} 6 Hz, J_{gi} 4 Hz, H_i), 3·72 (s, 3 H, CO_2Me), 3·70 (s, 3 H, CO_2Me), 3·56 (dd, J_{ef} 13 Hz, J_{df} 4 Hz; H_f), 2·56 (broad m, H_d), 2·23 (broad d, appeared as dd on irradiating H_d, J_{gh} 13 Hz, J_{gi} 4 Hz, H_g), and 2·10 (ddd, J_{gh} 13 Hz, J_{hi} 6 Hz, J_{dh} 11 Hz, H_h).

The interpretation of the ^1H n.m.r. data followed from appropriate decoupling experiments. In particular, the irradiation of the 6-C methylene protons (H_e and H_f) did not modify the splitting pattern of 3-H_b thus ruling out the alternative structure (A). Similar results were also observed with the minor isomer of (**8b**).

Finally, we have examined the behaviour of the 3-substituted indoleacrylate (**10**)‡ toward the dihydropyridine (**4b**).[8] The only adduct which could be isolated (30% yield) besides the dimers of (**10**) was assigned the structure (**11**) on the basis of its facile conversion into desethylcatharanthine (**7b**) (Scheme 2), an independent synthesis of which has been recently reported.[6]

Surprisingly, we could not detect any Aspidosperma-type cycloaddition product in the reaction mixture. It is very likely that an initial bond formation between C-5 and C-7 occurs giving, ultimately, compounds of type (**8**) or (**9**). Also, it is noteworthy that a substituent on the nitrogen or at the 3-position of indole favours the formation of the Iboga-type addition products.

The synthesis of desethylcatharanthine (**7b**) described here is simple and straightforward. We are currently investigating the application of a similar approach to the synthesis of catharanthine (**7a**).



SCHEME 2. *Reagents and conditions:* i, toluene, 110 °C for 18 h, 30% yield; ii, AcOH, H_2O, tetrahydrofuran, overnight, 65%; iii, $MeSO_2Cl$, NEt_3, CH_2Cl_2, 98%; iv, Zn–MeCN, 60 °C for 1 h, 35%.

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‡ This compound was obtained from (**2c**) in 76% yield by successive treatment with chlorodimethyl-t-butylsilane–CH_2Cl_2–NEt_3–4-dimethylaminopyridine (E. J. Corey and A. Wenkateswarlu, *J. Am. Chem. Soc.*, 1972, **94**, 6190; S. K. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 1979, 99) and *m*-chloroperbenzoic acid followed by heating in toluene at 110 °C.

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