A SHORT AND NOVEL SYNTHESIS OF THE PYRROLIZIDINE ALKALOIDS, (±)-SUPINIDINE AND (±)-TRACHELANTHAMIDINE

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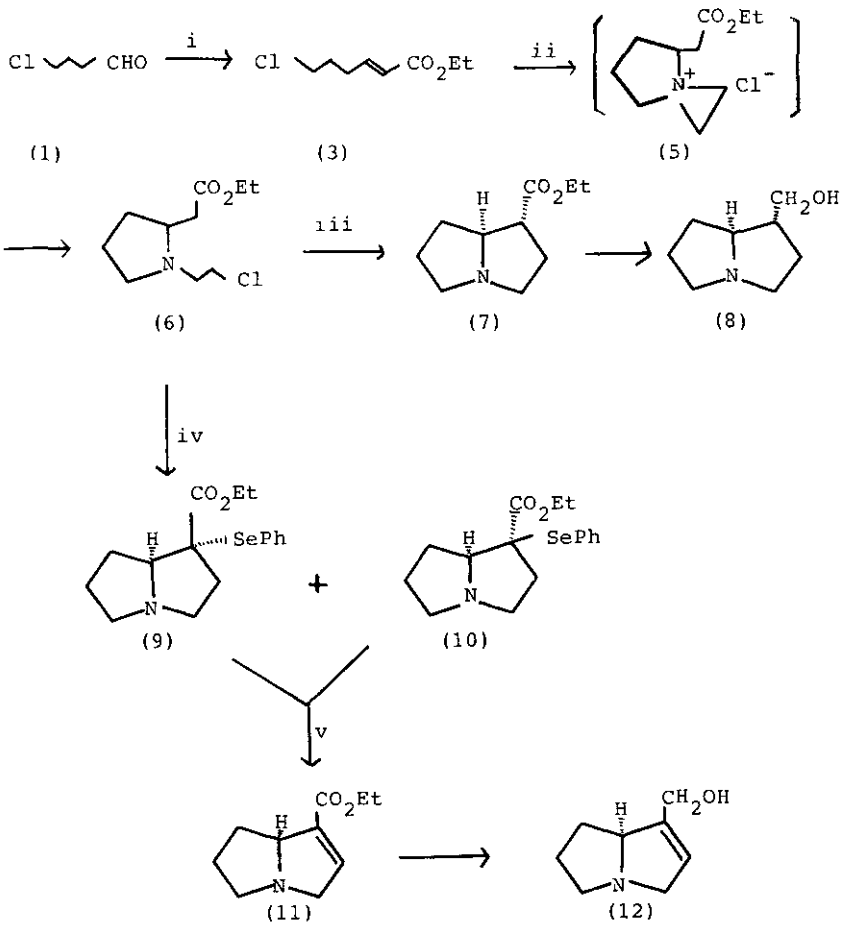
Abstract —— The effective and short syntheses of the pyrrolizidine alkaloids, (±)-trachelanthamidine (8) and (±)-supinidine (12) were described.

Pyrrolizidine alkaloids[1], widely distributed in nature, have received a considerable attention directed to evaluating their physiological activities and to devising the synthetic methodologies. These alkaloids usually consist of a necine base linked to a necic acid, and it is known that necine bases must contain a 1,2-didehydro system in their molecules in order to exhibit the physiological activities. We here wish to report an efficient and novel syntheses of necine bases, (±)-trachelanthamidine (8) and (±)-supinidine (12). Our design for the synthesis of a necine base was based on the facile ring opening reaction of an aziridinium salt, and a subsequent intramolecular alkylation reaction.

The treatment of γ-chlorobutyraldehyde (1)[2] with ethyl diethyl phosphonoacetate (2) in benzene in the presence of sodium hydride afforded the α,β-unsaturated ester (3) (bp 91 - 92 °C / 3 mmHg), in 89.7 % yield, whose treatment with an excess of aziridine (4) brought about the formation of the pyrrolidine derivative (6) (bp 113 - 115 °C / 3 mmHg), probably *via* the aziridinium salt (5), in 72.5 % yield. The intramolecular alkylation of (6) with lithium diisopropylamide furnished the thermodynamically more stable ester (7) [bp 80 - 82 °C / 3 mmHg (lit.[3], 80 - 82 °C / 3 mmHg)] as the sole cyclised product in 85.9 % yield, physicochemical properties of which were identical with those reported[3]. Since the conversion of the ester (7) into the alcohol (8) has already been achieved by Borch[3], this synthesis constitutes a formal synthesis of (±)-trachelanthamidine (8).

Next, our attention was focused on a synthesis of (±)-supinidine (12) from (6). Robins[4] already reported the effective method to introduce a 1,2-didehydro system into the ester by the introduction of a phenylselenenyl group to give the selenide (9 or 10) as the sole product, followed by its oxidative elimination, which leads to the synthesis of (±)-supinidine. However, when the pyrrolidine (6) was treated with lithium diisopropylamide (LDA) (2.4 equiv.), followed by the addition of phenylselenenyl chloride (1.2 equiv.), the formation of two selenides (9 and 10) was observed in 19.4 % and 16.4 % yields, respectively.



Scheme 1. Reagents : i, NaH, $(EtO)_2POCH_2CO_2Et$ (2), benzene, r.t.; ii, HN (4), neat, 0°; iii, LDA (1.2 equiv.), THF, -78 ∿ -40°C; iv. LDA (2.4 equiv.), -78 ∿ -40°C, then PhSeCl (1.2 equiv.), -78°C; v, MCPBA (1.1 equiv.), CH_2Cl_2, -78°C, then r.t.

The spectroscopic data of the less polar compound (9) and the melting point of its picrate [mp 159 - 162 °C (lit.[4], 155 - 157 °C)] were in accord with reported values[4]. Whereas the structure of the more polar compound (10) was assumed to be the diastereoisomer based on its spectral data and microanalysis [picrate of (10), mp 132 - 136 °C]. These structures were unambiguously confirmed to be diastereoisomers by the oxidative elimination to give the same α,β-unsaturated ester (11), which was identical with an authentic sample in all respects. Since the selenide (9) and the ester (11) had been converted to (±)-supinidine by Robins[4], this synthesis also constitutes a formal total synthesis of (±)-supinidine (12).

Thus, we have achieved the short and novel synthesis of pyrrolizidine alkaloids, (±)-trachelanthamidine and (±)-supinidine, and this method should be applicable to the synthesis of other naturally occurring pyrrolizidine alkaloids.

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