Synthesis of the Pyrrolizidine Base, (±)-Supinidine

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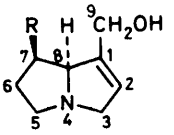
A novel method for the conversion of saturated pyrrolizidine esters into their 1,2-didehydro-derivatives has been established. The unsaturation is introduced by phenylselenenylation α to an ester function, followed by fragmentation of the derived seleno-derivative. Using this technique, (±)-supinidine (1) has been synthesized.

THERE is much interest in 1-substituted pyrrolizidine derivatives because of their toxicity and wide distribution in a number of plant families.[1] The alkaloids usually consist of a ' necine ' base linked to a carboxylic (' necic ') acid. Alkaloids must contain a 1,2-unsaturated necine base in order to exhibit physiological activity. Only two syntheses have been reported leading to these naturally occurring 1,2-didehydronecines. (±)-Retronecine (2) was synthesized by Geissman and Waiss [2] using a lengthy procedure with a very low overall yield (<1%). Tufariello and Tette [3] prepared (±)-supinidine (1), again in very low overall yield (*ca.* 3%), and the final step necessitated separation of a mixture of products by preparative g.l.c.

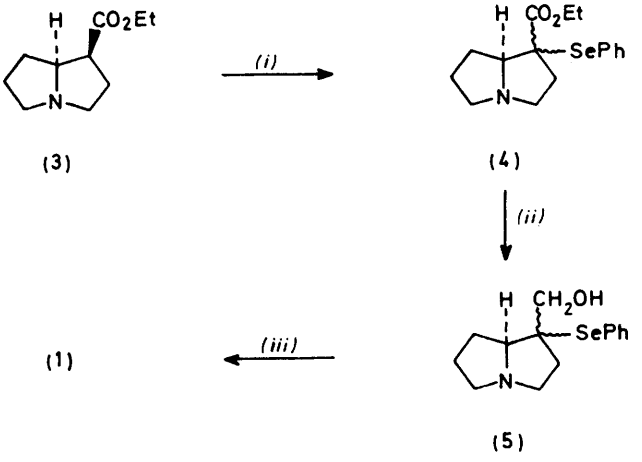
Since many syntheses have been reported leading to fully saturated 1-substituted pyrrolizidines,[4] we have investigated the possibility of converting 1-substituted pyrrolizidines into their 1,2-didehydro-analogues. Thermal elimination of a phenylseleno-group [5] was selected for the introduction of the olefinic double-bond. This approach is illustrated by the synthesis of (±)-supinidine (1).



(1) R = H
(2) R = OH

RESULTS AND DISCUSSION

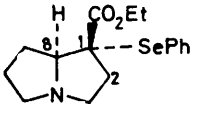
The thermodynamically less-stable racemate of ethyl pyrrolizidine-1-*endo*-carboxylate (3) was prepared in good yield (80%) by the two-step stereospecific route of Pizzorno and Albonico,[6] involving cycloaddition of ethyl propiolate to *N*-formyl-L-proline, followed by catalytic hydrogenation. Selenenylation of the lithium enolate derived from the ester (3) was readily accomplished (Scheme 1) with phenylselenium chloride. Reduction of the ester (4) gave (5), which upon oxidation yielded (±)-supinidine. N.m.r.[7] and mass [3] spectra were in accord with those reported for supinidine. Furthermore, the i.r., n.m.r., and mass spectra of (±)-supinidine picrate were identical with those of a sample of the picrate of natural (−)-supinidine. Each of the three reaction steps proceeded in *ca.* 60% yield, and higher overall yields were achieved when isolation and purification of the selenide (5) were omitted.



(3) (4) (5) (1)

SCHEME 1 (*i*) Pr^i_2NH–Bu^nLi, PhSeCl; (*ii*) $LiAlH_4$; (*iii*) H_2O_2

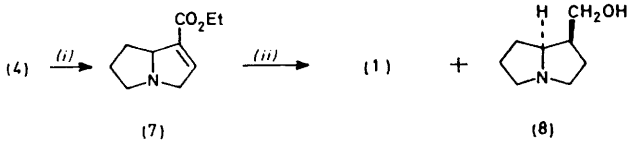
The stereochemistry of the intermediate selenides (Scheme 1) is uncertain. Addition of the phenylselenium chloride to the less-hindered *exo*-face of the intermediate lithium enolate would produce a 1β-ester (6). Elimination of the derived phenylseleno-group is known to proceed in a *syn*-fashion and would be expected to yield both 1,2- and 1,8-didehydropyrrolizidine.



(6)

However, no 1,8-didehydropyrrolizidine was detected. It is known that elimination towards an electron-withdrawing substituent (N) is moderately disfavoured.[8] On the other hand, if the 1α-ester is formed, the regioselectivity of the fragmentation is readily understood.

In an alternative route to (±)-supinidine (1) from the selenide (4), elimination of the phenylseleno-group was carried out before the reduction step (Scheme 2). This resulted in a mixture of the fully saturated pyrrolizidine (8), and (±)-supinidine (1), as noted previously.[3]



(4) (7) (1) + (8)

SCHEME 2 (*i*) H_2O_2; (*ii*) $LiAlH_4$

EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage apparatus. N.m.r. spectra were run for solutions in deuteriochloroform with tetramethylsilane as internal standard. Mass spectra were obtained with an A.E.I. MS12 spectrometer. T.l.c. was carried out on Kieselgel G with chloroform–methanol–concentrated ammonia [either 85 : 14 : 1 (solvent system A) or 5 : 4 : 1 (solvent system B)]. The bases were located with the modified Dragondorff reagent.[9]

Ethyl (±)-*Pyrrolizidine*-1-endo-*carboxylate* (3).—This ester was prepared according to the method of Pizzorno and Albonico [6] (overall yield 80%). The picrate derivative (EtOH) had m.p. 119—121 °C (lit.,[6] 119—121 °C; lit.,[10] 119.5—120 °C).

Phenylselenenylation of the Ester (3).—A solution of lithium di-isopropylamide [prepared from di-isopropylamine (1.24 ml, 11.52 mmol) and 1.7M-n-butyl-lithium in hexane (6.8 ml, 11.52 mmol)] in dry tetrahydrofuran (10 ml) at −78 °C was added dropwise during 1 h to a stirred solution of the ester (3) (1.464 g, 8 mmol) in dry tetrahydrofuran (4 ml) under N_2. Phenylselenium chloride (1.728 g, 9 mmol) in dry tetrahydrofuran (4 ml) was added rapidly, and the solution was stirred for 3 h at −78 °C, and then poured into water (50 ml). The mixture was extracted with ether (1 × 80 ml), and chloroform (3 × 80 ml). After drying (Na_2SO_4), filtering, and concentrating, the organic layers yielded a brown oil containing one major component, R_F 0.55 (solvent system A). Preparative t.l.c. afforded *ethyl* 1-*phenylselenopyrrolizidine*-1-*carboxylate* (4) as a pale yellow oil, 1.55 g (57%); $\nu_{max.}$ (CCl_4) 1 720 and 1 580 cm^{-1}; τ 8.80 (3 H, t, *J* 7 Hz), 6.2—8.0 (11 H, complex, 5.80 (2 H, q, *J* 7 Hz), and 2.50 (5 H, m); *m/e* 339 (43), 337 (20), 182 (100), 181 (50), 158 (23), 154 (26), 136 (29), 110 (20), 108 (26), and 83 (50%). The *picrate* had m.p. 155—157 °C (EtOH) (Found: C, 46.3; H, 4.1; N, 9.8. $C_{22}H_{24}N_4O_9Se$ requires C, 46.6; H, 4.2; N, 9.9%).

Reduction of the Phenylseleno-ester [11] (4).—A solution of the ester (4) (339 mg, 1 mmol) in dry ether (4 ml) was slowly added to a cooled (−15 °C) suspension of lithium aluminium hydride (76 mg, 2 mmol) in dry ether (4 ml) under N_2. The mixture was stirred for 2 h at −15 °C and 1 h at room temperature. Excess of lithium aluminium hydride was destroyed by the slow addition of wet ether followed by 20% NaOH (0.5 ml). The resulting suspension was filtered through Celite, dried (Na_2SO_4), filtered, and concentrated to yield a yellow oil. Preparative t.l.c. (solvent system A) gave the major component, 1-*hydroxymethyl*-1-*phenylselenopyrrolizidine* (5) at R_F 0.25 as a pale yellow oil, yield 183.4 mg (62%), which afforded colourless crystals (from ethyl acetate), m.p. 125—127 °C; $\nu_{max.}$ (KBr) 3 400 and 1 580 cm^{-1}; τ 6.4—8.0 (13 H, complex), 6.50 (1 H, s, OH), and 2.60 (5 H, m); *m/e* 297 (8), 158 (40), 139 (60), 130 (40), 122 (45), 120 (60), 108 (30), 83 (100), and 78 (100%) (Found: C, 56.6; H, 6.4; N, 4.5. $C_{14}H_{19}NOSe$ requires C, 56.7; H, 6.4; N, 4.7%).

(±)-*Supinidine* (1).—The phenylseleno-alcohol (5) (183.4 mg, 0.61 mmol) in acetic acid (5 ml), was mixed with 27% H_2O_2 (1 ml) and stirred at 0 °C for 1 h, and at room temperature for 12 h. After basification (pH 10), the mixture was extracted with chloroform (4 × 25 ml), and the extracts were dried (K_2CO_3), filtered, and concentrated to a pale yellow oil. Preparative t.l.c. (solvent system B) gave the major component, (±)-supinidine (1), R_F 0.55, as a colourless oil, yield 50 mg (59%); $\nu_{max.}$ ($CHCl_3$) 3 320 and 1 600 cm^{-1}; τ 7.8—8.5 (4 H, complex, H-6 and H-7), 6.9 and 7.5 (2 H, m, H-5), 6.2 and 6.65 (2 H, m, H-3), *ca.* 6 (1 H, m, H-8), 5.87 (2 H, s, H-9), 5.49 (1 H, m, H-2), and 4.88 (1 H, br s, OH); *m/e* 139 (55), 138 (15), 122 (50), 121 (35), 120 (73), 108 (42), 106 (40), 94 (18), and 80 (100%). The picrate had m.p. 125—126 °C (EtOH) (lit.,[3] 124—126 °C) (Found: C, 45.5; H, 4.4; N, 15.0. Calc. for $C_{14}H_{16}N_4O_8$: C, 45.6; H, 4.4; N, 15.2%).

Oxidation of the Phenylseleno-ester (4).—The same procedure was employed as in the oxidation of the alcohol (5). Preparative t.l.c. of the yellow oil (solvent system A) yielded the major component *ethyl* 5,6,7,8-*tetrahydro*-3H-*pyrrolizine*-1-*carboxylate* (7) (60%) as an oil; $\nu_{max.}$ (CCl_4) 1 720 and 1 640 cm^{-1}; τ 8.75 (3 H, t, *J* 7 Hz), 6.1—8.3 (9 H, complex), 5.85 (2 H, q, *J* 7 Hz), and 3.42 (1 H, m, H-2); *m/e* 181 (52), 179 (28), 153 (38), 150 (38), 136 (100), 134 (48), 108 (50), and 80 (76%). The *picrate* had m.p. 156—158 °C (EtOH) (Found: C, 46.5; H, 4.3; N, 13.7. $C_{16}H_{18}N_4O_9$ requires C, 46.8; H, 4.4; N, 13.7%).

(±)-*Supinidine* (1) *and* (±)-*Isoretronecanol* (8).—The procedure was analogous to that used for the reduction of the phenylseleno-ester (4). Preparative t.l.c. (solvent system B) of the pale yellow oil gave two major components. (±)-Supinidine was isolated as a colourless oil (45%); the picrate had m.p. 125—126 °C (lit.,[3] 124—126 °C). The second component, a colourless oil (31%), was (±)-1-hydroxymethylpyrrolizidine [(±)-isoretronecanol] (8); $\nu_{max.}$ ($CHCl_3$) 3 300 cm^{-1}; τ 6.3—8.2 (14 H, complex), 4.8 (1 H, br s, OH); *m/e* 141 (42), 140 (29), 124 (29), 110 (27), 108 (27), 97 (76), 84 (29), 83 (100), and 82 (78%). I.r., n.m.r., and mass spectra were in accord with reported values for (±)-isoretronecanol.[12] The picrate had m.p. 187—189 °C (EtOH) (lit.,[6] 187—189 °C; lit.,[12] 188—190 °C) (Found: C, 45.3; H, 5.2; N, 15.1. Calc. for $C_{14}H_{18}N_4O_8$: C, 45.4; H, 4.9; N, 15.1%). The isomeric (±)-1-hydroxymethylpyrrolizidine [(±)-trachelanthamidine] was not detected.[3]

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