Synthesis of Some Naturally-occurring Styrylamides

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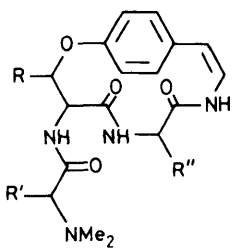
Thermal elimination from *N*-(β-phenyl-β-phenylsulphinylethyl)amides yielded styrylamides (**2**)—(**4**)

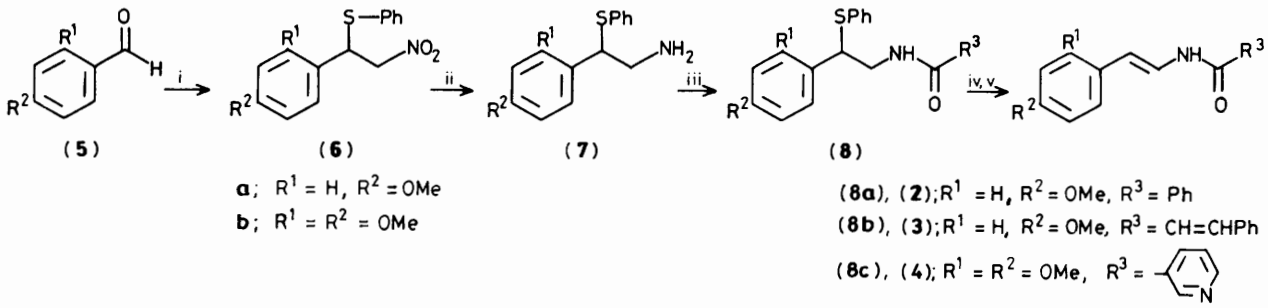
In connection with our programme of synthesis of cyclic peptides based on the route developed by Rapoport,[1] we needed a simple, efficient modification to permit introduction of the styrylamide group in such peptides, (**1**).[2] To explore such a synthetic goal, we selected as targets three naturally-occurring styrylamides (**2**)—(**4**), isolated from *Pleiosperium alatum.* (Wight and Arn) Swingle,[3] *Aegle marmelos* Corr.,[4] and *Amyris plumeri* D.C.,[5a] respectively. Several new styrylamides, including Tunichrome B-1, a V-complexing agent,[6] and Amathamide A and B, from a marine Bryozoa,[7] prompt us to report one successful route to the styrylamide group (Scheme 1).

Beginning with the appropriate aldehyde (**5**), the thiophenol present in the alkaline solution of (**5**) and nitromethane added to the intermediate β-nitrostyrene to give (**6**) in a one-pot sequence. Following reduction of (**6**) to (**7**), acylation with the appropriate acid derivative gave the three amides (**8**). Oxidation of (**8a**—**c**) with *m*-chloroperbenzoic acid (MCPBA) at −50 °C gave sulphoxides that under reflux



(**1**)

Nummularine-M; R = Ph, R′ = R″ = Bu^s (ref. 2a)
Frangulanin; R = Pr^i, R′ = Bu^s, R″ = Bu^i (ref. 2c)
Sativanine-A; R = Ph, R′ = Bu^s, R″ = Pr^i (ref. 2d)



Scheme 1. *Reagents and conditions:* i, $MeNO_2$, $MeNH_3Cl$–Na_2CO_3, PhSH, 25 °C, 3 days [(**6a**) 86%, (**6b**) pure oil, t.l.c. quantitative]; ii, Zn, HCl–HOAc, heat, 2 h (pure oils, t.l.c., 84—90%); iii, CH_2Cl_2, **a**: (**7a**), $PhCOCl$–$NaHCO_3$, 25 °C (83% MeOH), **b**: (**7a**), $(PhCH{=}CHCO)_2O$, $NaHCO_3$, 25 °C (66% MeOH), **c**: (**7b**), 3-pyCOOCOEt (from 3-$pyCO_2H$, $ClCO_2Et$, Et_3N), 0 °C (82% crude, glass solid); iv, MCPBA–CH_2Cl_2–Et_2O, −50 to 0 °C, 6 h (quantitative, pure by t.l.c., solids); v, toluene, $CaCO_3$, reflux, 5 h [(**2**) and (**3**) 65% from $CHCl_3$; (**4**) 29%, recrystallised poorly from C_6H_6].

yielded (**2**)—(**4**) in 20 [for (**4**)]—40% overall yields.†‡ Presumably then, ring closure of appropriate substituents at R^2 and R^3 of (**8**) followed by oxidation–thermal elimination as above would lead to the desired cyclic peptide having the styrylamide function.

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† The alkene of the styrylamide in Zizyphin-A, a cyclic peptide, was introduced *via* oxidative elimination on a selenide formed by substitution; U. Schmidt, A. Lieferknecht, H. Bokens, and H. Griesser, *Angew. Chem.*, 1981, **93**, 1121.

‡ Satisfactory C, H analysis were obtained for (**2**)—(**4**).

(**2**) M.p. 192—193 °C (lit.[3] m.p. 178—180 °C); i.r. (KBr) 3325, 1655 cm^{-1}; u.v. (EtOH) 221 (log ε 4.21), 311 (4.39), 317 (4.39) nm; *m/z* 253 (M^+); ^1H n.m.r. (200 MHz) [$(CD_3)_2CO$] δ 3.79 (3H, s, OMe), 6.42 (1H, d, *J* 15 Hz, =CH), 6.89 (2H, d, *J* 8.8 Hz, *o*-*H*ArOMe), 7.35 (2H, d, *J* 8.8 Hz, *m*-*H*ArOMe), 7.52 (3H, m, ArH), 7.58 (1H, d, *J* 15 Hz, =CHN), 8.00 (2H, dd, *J* 7.7, 1.8 Hz, *o*-HArCO).

(**3**) M.p. 206.5—207.5 °C (lit.[4] m.p. 191 °C); i.r. 3462, 1640 cm^{-1}; u.v. 284 (log ε 4.47), 300 (4.49), 338 (4.52) nm; *m/z* 279 (M^+); ^1H n.m.r. [$(CD_3)_2CO$)] δ 3.78 (3H, s, OMe), 6.25 (1H, d, *J* 14.7 Hz, =C*H*ArOMe), 6.74 (1H, d, *J* 15.4 Hz, =CHCO–), 6.88 (2H, d, *J* 8.8 Hz, *o*-*H*ArOMe), 7.32 (2H, d, *J* 8.8 Hz, *m*-*H*ArOMe), 7.45 (3H, m, ArH), 7.55 (1H, d, *J* 14.7 Hz, =CHN), 7.61 (2H, m, ArH), 7.65 (1H, d, *J* 15.4 Hz, =C*H*Ar).

(**4**) M.p. 160—161.5 °C (lit.[5] m.p. 159—160 °C); i.r. 3250, 1655 cm^{-1}; u.v. 220 (log ε 4.40), 262 (4.20) 331 (4.38) nm; *m/z* 284 (M^+); ^1H n.m.r. ($CDCl_3$) δ 3.82 (3H, s, OMe), 3.85 (3H, s, OMe), 6.46 [1H, m, 3-*H*Ar$(OMe)_2$], 6.49 [1H, dd, *J* 8, 2 Hz, 5-*H*Ar$(OMe)_2$], 6.51 [1H, d, *J* 14.7 Hz, =C*H*Ar$(OMe)_2$], 7.33 [1H, d, *J* 8 Hz, 6-*H*Ar$(OMe)_2$], 7.43 [1H, dd, *J* 8, 7.8 Hz, 5H-3 pyridyl (py)], 7.67 (1H, dd, *J* 14.7, 14.3 Hz, =CHN–), 8.06 (1H, br. d, NH), 8.19 (1H, dt, *J* 7.8 Hz, 4H-3 py), 8.76 (1H, d, *J* 4.3 Hz, 6H-3 py), 9.06 (1H, br. s, 2H-3 py); shaking with D_2O removes the signal at δ 8.06 and reduces δ 7.67 to a doublet.

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