An Efficient Synthesis of Phthalideisoquinoline Alkaloids

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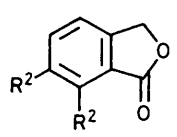
A general synthesis of the phthalide-1,2,3,4-tetrahydroisoquinolines, including the synthesis of the alkaloid cordrastine, is described.

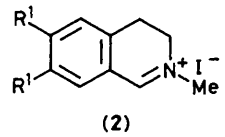
An efficient convergent synthesis of the phthalide-1,2,3,4-tetrahydroisoquinolines would be the direct condensation of phthalides (**1**) with 3,4-dihydroisoquinolinium salts (**2**). However, Prager *et al.*[1] reported recently that this condensation reaction failed under a variety of experimental conditions, although it succeeded with the fully-aromatic isoquinolinium salts.

The failure of the condensation reaction was attributed to the unstable nature of the end products, *i.e.* the phthalide-tetrahydroisoquinolines (**3**), under the basic conditions used for the condensation. In fact (**3a**) was totally destroyed after refluxing for 3 h with methanolic NaOMe. This suggested that if the condensation was effected in such a way that the end product was in contact with the strong base for only the briefest period, the reaction could succeed. This is plausible since the 3,4-dihydroisoquinolinium salts are expected to be highly electrophilic in their reactions.

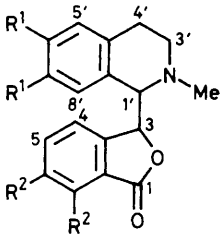
We have now achieved the successful condensation of phthalides with 3,4-dihydroisoquinolinium salts. The procedure involved the generation of the phthalide anion[2] in



(1)

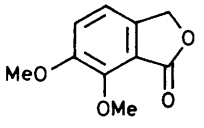


(2)

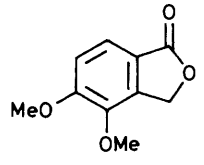


(3)

	R^1	R^2
a;	H	H
b;	OMe	H
c;	—O—CH_2—O—	H
d;	OMe	OMe



(4)



(5)

tetrahydrofuran at −78 °C using lithium di-isopropylamide and subsequent addition of the dihydroisoquinolinium salt. After stirring for only 15—20 min, the reaction mixture was poured into aqueous HCl–ice and extracted with diethyl ether. The acidic extract, after basification with $NaHCO_3$, extraction with diethyl ether, and evaporation of the solvent, gave a residue which, on chromatography over silica gel using MeOH–$CHCl_3$ for elution, gave the *threo* and the *erythro* isomers of the phthalidetetrahydroisoquinolines (**3**).

Compounds (**3b**), (**3c**), and (**3d**) [cordrastine I, *threo* (**3d**); and cordrastine II, *erythro* (**3d**)] were synthesised by the above method in yields (actual yields after chromatography over silica gel) of 30 (*threo* : *erythro* 35 : 65), 50 (*threo* : *erythro* 23 : 77), and 22% (*threo* : *erythro* 42 : 58) respectively. The configurations of the isomers were assigned on the basis of (i) the lower R_f value for the *erythro* isomer as compared to the *threo*[3] and (ii) the higher δ (n.m.r.) value (deshielded) for H-4 (numbering according to Prager[1]) in the *threo* isomer as compared to the *erythro*.[4]†

The synthesis is extremely useful since the starting compounds, *i.e.* phthalides and 3,4-dihydroisoquinolinium salts, can be readily synthesised. Even the phthalides (**4**) and (**5**), which were difficult to synthesise are now readily available through heteroatom directed lithiation reactions.[5]

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References

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† *Spectroscopic data: threo* (**3b**): m.p. 159 °C; n.m.r. ($CDCl_3$) δ 7.20—7.70 (m, 4H, aromatic protons of phthalide ring), 6.65 (s, 1H, H-5′ or H-8′), 6.30 (s, 1H, H-8′ or H-5′), 5.65 (d, *J* 3.0 Hz, 1H, H-3), 4.10 (d, *J* 3.0 Hz, 1H, H-1′). *erythro* (**3b**): methiodide m.p. 232 °C; n.m.r. ($CDCl_3$) δ 7.80 (dd, 1H, H-7), 7.40 (m, 2H, H-5 and H-6), 6.80 (dd, 1H, H-4), 6.55 (s, 1H, H-5′ or H-8′), 6.45 (s, 1H, H-8′ or H-5′), 5.60 (d, *J* 3.5 Hz, 1H, H-3), 4.30 (d, *J* 3.5 Hz, 1H, H-1′). *threo* (**3c**): methiodide m.p. 237 °C; n.m.r. ($CDCl_3$) δ 7.30—7.70 (m, 4H, aromatic protons of phthalide ring), 6.65 (s, 1H, H-5′ or H-8′), 6.25 (s, 1H, H-8′ or H-5′), 5.70 (d, *J* 4.0 Hz, 1H, H-3), 4.10 (d, *J* 4.0 Hz, 1H, H-1′). *erythro* (**3c**): m.p. 105 °C; n.m.r. ($CDCl_3$) δ 7.85 (dd, 1H, H-7), 7.50 (m, 2H, H-5 and H-6), 6.90 (dd, 1H, H-4), 6.60 (s, 1H, H-5′ or H-8′), 6.50 (s, 1H, H-8′ or H-5′), 5.65 (d, *J* 4.5 Hz, 1H, H-3), 4.10 (d, *J* 4.5 Hz, 1H, H-1′). The m.p. and n.m.r. spectra of cordrastine I [*threo* (**3d**)] and cordrastine II [*erythro* (**3d**)] are in agreement with the literature (ref. 1).