Total Synthesis of the Tumour-inhibitory Alkaloids Thalicarpine and Hernandaline[1]

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Summary The tumour-inhibitory alkaloid thalicarpine (**13**) has been synthesized by an approach which proceeds from the diaryl ether (**3**) *via* the alkaloid hernandaline (**9**).

THE alkaloid thalicarpine,[2] which has the aporphine–benzylisoquinoline structure (**13**),[3] has a significant inhibitory activity against the Walker intramuscular carcinosarcoma 256 in rats, over a wide dosage range.[4] The alkaloid has undergone extensive preclinical toxicological studies and has been selected for clinical trial. We report here a total synthesis of thalicarpine, by a route which proceeds *via* the synthesis of hernandaline (**9**),[5] a cytotoxic[6] aporphine alkaloid.

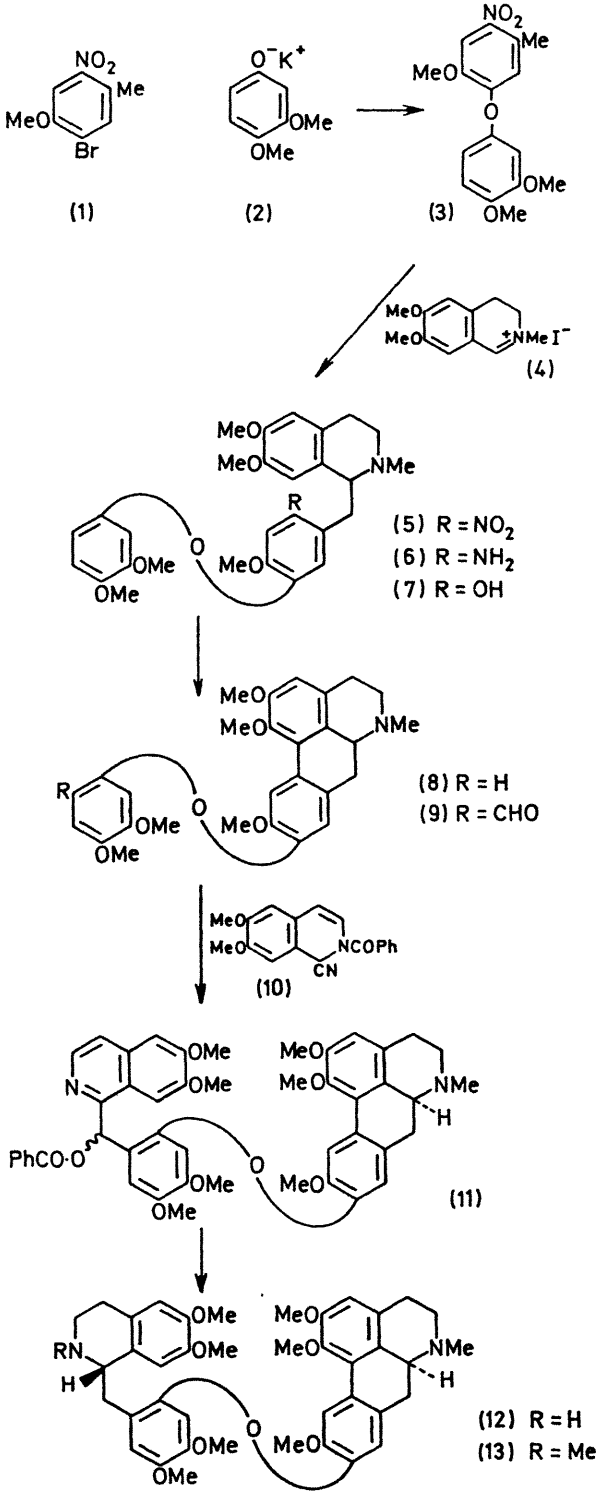
The synthesis of thalicarpine for the structural studies involved an Ullman type ether synthesis[3] with derivatives of alkaloids obtained from natural sources. Drawbacks of this approach are the inaccessibility of the starting materials and the low yield of the final step, the formation of the diaryl ether link.

We therefore devised an alternative sequence beginning with a simple diphenyl ether followed by the construction of an appropriate heterocyclic system on each ring. A suitable diaryl ether (**3**)† (m.p. 127—128°) was prepared in good yield [64% based on unrecovered (**1**)] from the activated aryl halide (**1**) (m.p. 91—92°, obtained in 72% yield by the Sandmeyer reaction) and the phenoxide (**2**)[7] heated under reflux in acetonitrile for 40 h.

The elaboration of the aporphine ring system was expected to be more difficult than the preparation of the benzylisoquinoline segment. Hernandaline was selected as the primary synthetic goal since the aporphine portion of this molecule is duplicated in thalicarpine (**13**) and, in addition, hernandaline has a formyl group which allows for the attachment of an isoquinoline moiety at a later stage.

The aporphine precursor (**5**) was obtained from (**3**) by condensation with the 3,4-dihydroisoquinolinium salt (**4**)[8] in a Robinson–Hope type synthesis.[9] Although the usual treatment with sodium ethoxide in ethanol failed to give a significant amount of (**5**), satisfactory results were obtained with sodium hydride in *NN*-dimethylacetamide. The amorphous base [oxalate m.p. 127—129° (decomp.) (ethanol–ethyl acetate)] extracted by aqueous hydrochloric acid was hydrogenated over 5% Pd–C in ethanol to give the diamine (**6**) [m.p. 172—173° (aqueous ethanol); λ_{max} ($CHCl_3$) (log ϵ), 238 (4·32), 291 (4·04) nm; δ ($CDCl_3$), 2·54 (NMe), 3·64, 3·75, 3·83 (3H, 3H, 9H, 5MeO), 6·15—6·71 (7H, aromatic); 35% yield from (**3**)]. Diazotization of (**6**) followed by cyclization in 50% aqueous phosphoric acid at 80° for 1 h gave the aporphine (**8**) [15%, isolated as the HBr salt, m.p. 212—214° (decomp.); λ_{max} (MeOH) (log ϵ), 280 (4·25), 300 (4·18), 316 (infl) (4·04) nm; δ ($CDCl_3$), 3·03 (br s, N⁺Me), 3·59, 3·82, 3·86, 3·90 (3H, 3H, 3H, 6H, 5MeO), 6·51—8·17 (6H, aromatic)] and the phenol (**7**) [13%, isolated as the HBr salt, m.p. 164—166°, free base, m.p. 135·5—137° (ethanol)], separated by preparative t.l.c. on silica.

Introduction of a formyl group into the aporphine (**8**)



† All new crystalline compounds have been characterized by concordant analytical and spectral data.

hydrobromide was achieved in 65% yield by heating with a mixture of phosphorus oxychloride and *NN*-dimethylformamide in nitrobenzene at 85° for 45 min. The product was shown to be (±)-hernandaline (**9**) [m.p. 148—149·5° (aq. ethanol)] by the congruence of i.r., n.m.r., and mass spectra with a sample of hernandaline obtained (33% yield) by oxidation of thalicarpine (**13**) with sodium metavanadate in 10% aqueous sulphuric acid (*cf.* ref. 10). A solution of the (−)-α-bromocamphor-π-sulphonate salt of the racemate in aqueous ethanol seeded with the hernandaline salt [m.p. 158° (decomp.), $[\alpha]_D^{25}$ + 46·5° in methanol] deposited crystals which, when treated with base and the product recrystallized from aqueous ethanol, gave the pure enantiomer (64% yield), m.p. 170—171°, identical (m.p., mixture m.p., $[\alpha]_D$ and spectra) with hernandaline.

The condensation of hernandaline with the Reissert compound (**10**)[11] in the presence of sodium hydride in *NN*-dimethylformamide gave an amorphous product which showed one spot on t.l.c., (silica, alumina) but an n.m.r. spectrum indicative of a mixture of the expected epimers (**11**) [λ_{max} (KBr) 5·87 μm]. While hydrogenation of the product over platinum oxide in ethanol or acetic acid proceeded only very slowly, treatment with zinc powder in aqueous acetic acid at 50° overnight efficiently converted (**11**) into the nor-bases [(**12**) and epimer]. Methylation of the product with formalin–formic acid (**1**:**4**) at 85° for 45 min gave, after neutralization of the mixture, an amorphous material indistinguishable from thalicarpine by t.l.c. Prolonged stirring of a solution of the product in 60% aqueous ethanol led to separation of crystals of (**13**) (25% overall yield from hernandaline), m.p. 108—110°, identical (m.p., mixture m.p., $[\alpha]_D$, and spectra) with an authentic sample of thalicarpine crystallized from aqueous ethanol. Recrystallization from ether yielded the isomorphic form, m.p. 155—157° (*cf.* ref. 12).

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[1] For previous paper in the series "Tumor Inhibitors" see: S. M. Kupchan, J. L. Moniot, C. W. Sigel, and R. J. Hemingway, *J. Org. Chem.*, in the press.
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