Photocyclisation of Haloacetyl Tryptophan Derivatives

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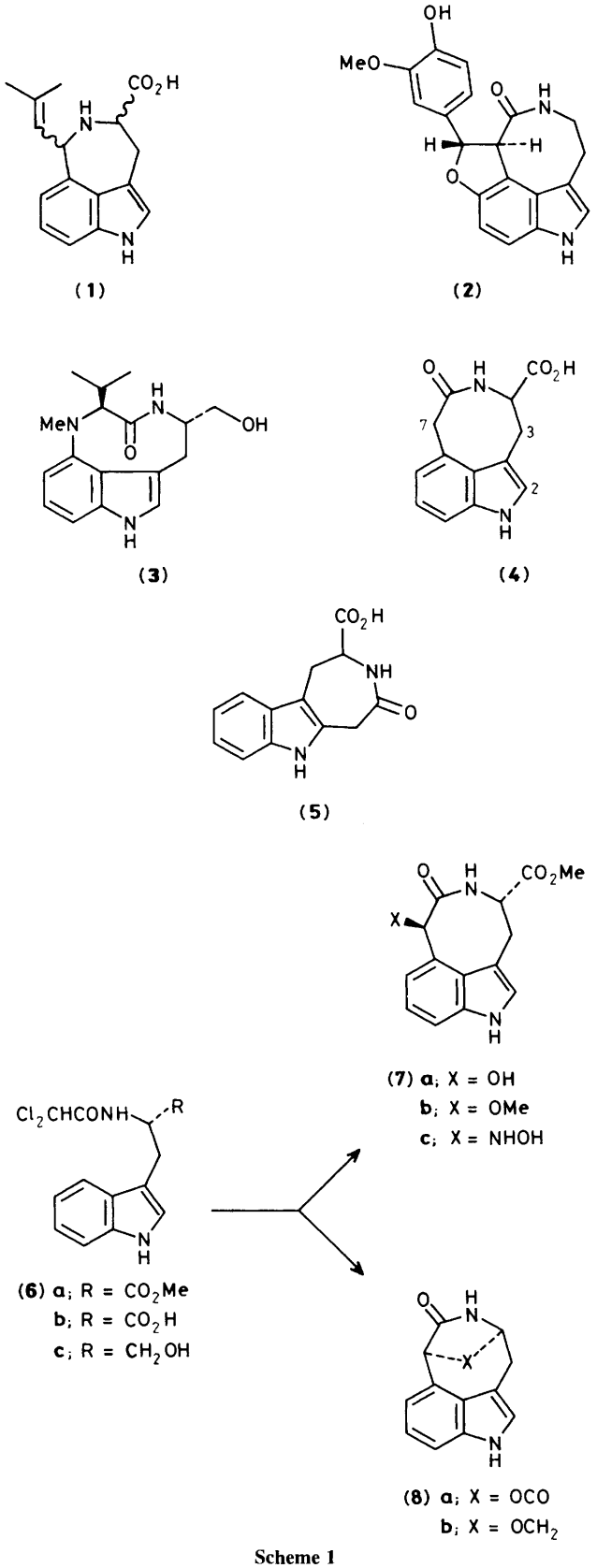
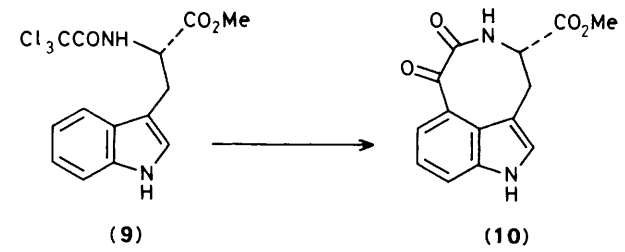
Irradiation of dichloroacetyl tryptophan methyl ester gives, after addition of a nucleophile in work-up, the 7-substituted pyrrolobenzazocines (**7**); similar cyclisation of the tryptophan derivative (**11**) gives the pyrrolobenzazocine (**12**), a compound related to serotobenine.

Of the naturally occurring indoles, those in which the indole 3-position is bridged to the 4-position ([*c*,*d*]-fused indoles) are among the most interesting in terms of biological activity. Examples include the well known ergot alkaloids, as well as clavicipitic acid (**1**),[1] serotobenine (**2**),[2] and indolactam V (**3**),[3] where the indole is bridged by 6-, 7-, 8-, and 9-membered rings, respectively. Whilst in nature this class of compound can be synthesised from tryptophan, with few exceptions,[4] the usual laboratory approach involves the linking together of existing functionality in both the 3- and 4-positions of the indole ring. However, we have adapted a photochemically-induced ring closure of simple tryptophan derivatives to the synthesis of [*c*,*d*]-fused indoles. The results described herein constitute a useful extension of classic tryptophan chemistry, which has long been used to prepare the well known [*b*]-fused indoles, to the much more difficult [*c*,*d*]-fused systems.

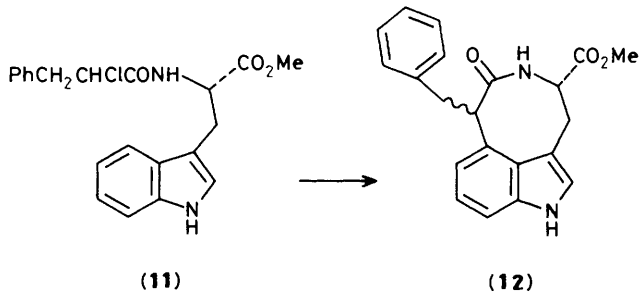
Our photochemical approach is based on an attempted photoreduction of chloroacetyl tryptophan,[5] which resulted in an unusual cyclisation to the indole 4-position to give compound (**4**);[6] such cyclisations are also relevant to the photochemistry of some tryptophan-containing peptides.[7] However, in our hands the yield of the bridged indole (**4**) was low (*ca.* 25%), owing to competing formation of the [*b*]-fused isomer (**5**), and attempts to functionalise the 7-position in (**4**) for further elaboration (*e.g.* ring expansion) were unsuccessful. We have now overcome these limitations by using dichloroacetyl tryptophan derivatives (**6**) as the precursors, the additional halogen providing built-in functionality for the new ring. Thus irradiation of (−)-dichloroacetyl tryptophan methyl ester (**6a**) at 254 nm in acetonitrile gave, after chromatography, the 7-hydroxypyrrolo[4,3,2-*f*,*g*][3]benzazocine (**7a**) (Scheme 1) (58% yield), $[\alpha]_D$ −96.4° (*c* 0.44, MeOH), presumably by displacement of the initially formed 7-chloro derivative. Indeed, when the photolysis reaction was worked up in the presence of other nucleophiles such as methanol or hydroxylamine, the corresponding derivatives (**7b**) {m.p. 190—191 °C (decomp.), $[\alpha]_D$ −59.5° (*c* 0.37, MeOH)} and (**7c**) were isolated in 63 and 51% yield, respectively. In all cases the yields are better than that obtained from the monochloro derivative and no competing cyclisation to the indole 2-position was observed. The reaction also exhibits a remarkable degree of asymmetric induction, in



Scheme 1



Scheme 2



Scheme 3

that the 7-substituent is exclusively *trans* to the ester group, although internal displacement from the *cis* face occurs in the case of the acid (**6b**) and the alcohol (**6c**) to give the novel bridged lactone (**8a**) and ether (**8b**), respectively (Scheme 1). Irradiation of the trichloroacetyl tryptophan ester (**9**) gives, after aqueous work-up, the cyclic keto amide (**10**) (Scheme 2) [75% yield; m.p. 256—258 °C (decomp.)].

Thus these [*c,d*]-fused indoles can be prepared in two steps (acylation and photocyclisation with nucleophilic work-up) from tryptophan methyl ester. The cyclisation method is extended to the preparation of a compound related to serotobenine (**2**) *via* the chlorohydrocinnamoyl tryptophan derivative (**11**), the irradiation of which in acetonitrile gives the serotobenine analogue (**12**) (Scheme 3) (55% yield). The application of a dichloroacetyl tryptophan photocyclisation to the total synthesis of (−)-indolactam V (**3**) is reported in the following communication.

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