

## Regioselective Claisen Rearrangements in Indoles

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Heating the 6-allyloxyindoles (**3**), readily prepared from the benzaldehydes (**1**), gives the corresponding 7-allylindoles (**4**) by regioselective Claisen rearrangement; the 7-linalylindole (**10**) is prepared from 4-geranyloxybenzaldehyde by a similar sequence.

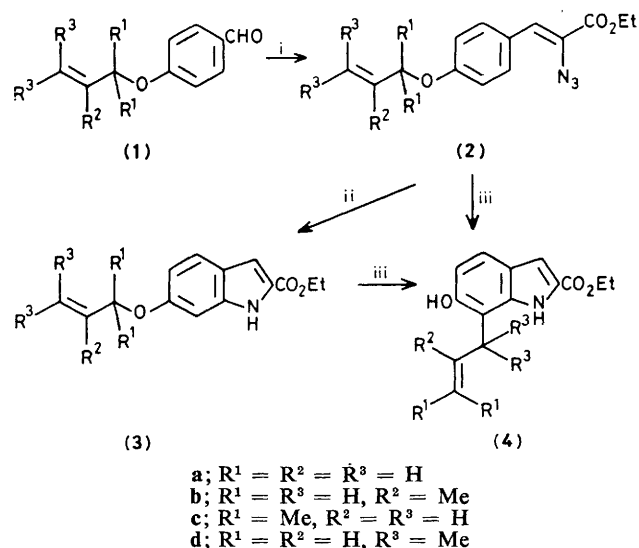
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Regioselectivity in the Claisen rearrangement<sup>1</sup> has been known for many years, although recently it has been the

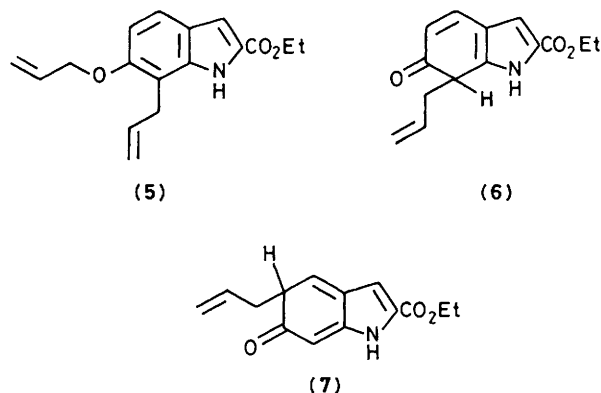
subject of renewed interest.<sup>2,3</sup> Although thermal rearrangements of heteroaromatic allyl ethers are known,<sup>1,4</sup> there is

only one report of Claisen rearrangements in the benzene ring of indoles, in which 5-allyloxyindole and ethyl 5-allyloxyindole-2-carboxylate gave the 4-allyl-5-hydroxyindoles regioselectively on heating.<sup>5</sup> It has now been shown that rearrangement of 6-allyloxyindole-2-carboxylates proceeds selectively to the 7-position, in a reaction which can be extended to the preparation of 7-prenyl- and 7-linalyl-indoles.

The requisite 6-allyloxyindole-2-carboxylates† are easily prepared in two steps (40–60%) from the corresponding known 4-allyloxybenzaldehydes (1) by base condensation with ethyl azidoacetate followed by thermolysis of the resulting azidocinnamates (2) in boiling toluene (Scheme 1).<sup>6</sup> Claisen rearrangement of the indole (3a) occurred readily in boiling bromobenzene (156 °C) to give the 7-allyl-6-hydroxyindole (4a) (71%). No products resulting from rearrangement to the 5-position were isolated. That rearrangement had occurred selectively to the 7-position was immediately clear from the <sup>1</sup>H n.m.r. spectrum which showed the vicinal protons 4-H and 5-H as two doublets (*J* 9 Hz). The fact that rearrangement to the 5-position is strongly disfavoured, by what has been variously described in other systems as aromatic bond fixation, mesomeric, or partial resonance effects,<sup>3</sup> was further demonstrated when the allyl ether (5), prepared from (4a), was recovered unchanged after heating



**Scheme 1.** Reagents: i, N<sub>3</sub>CH<sub>2</sub>CO<sub>2</sub>Et, NaOEt, EtOH, –10 °C; ii, PhMe, reflux; iii, PhBr, reflux, or see text.



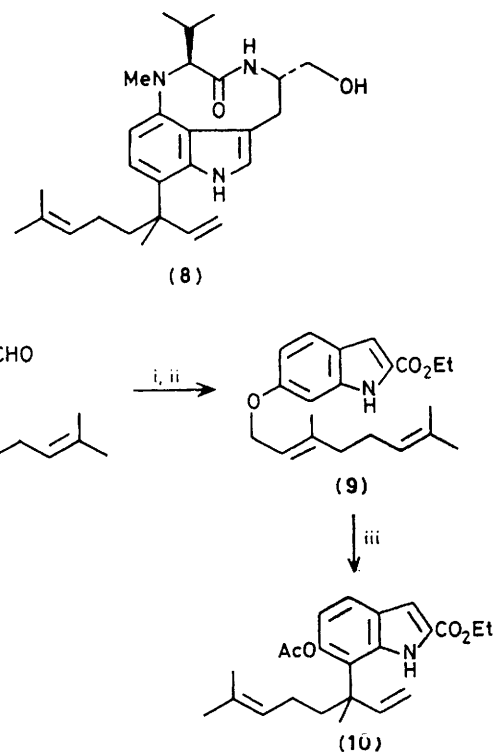
† The structure of all new compounds was supported by spectroscopic methods, and with the exception of azides, by elemental microanalysis.

in bromobenzene. Prolonged heating caused a slow decomposition, from which no recognisable products were obtained. Thus, in exact parallel to the well known regioselective Claisen rearrangement of 2-allyloxynaphthalene, the transition state leading to the intermediate (6) which retains some aromatic stabilisation must be substantially favoured over that leading to (7).

When the azide (2a) was heated in boiling bromobenzene, concomitant indole formation and Claisen rearrangement occurred to give the indole (4a) (78%). Similarly, thermolysis of the azides (2b) and (2c) in bromobenzene resulted in concomitant indolisation and rearrangement to give the corresponding 7-methyl- and 7-prenyl-indoles (4b) (65%) and (4c) (61%) respectively. Subsequently it was found that Claisen rearrangement of the isoprenyl ether occurred at lower temperature, and the unrearranged indole (3c) could not be isolated even after short refluxing of the azide (2c) in toluene.

Since Claisen rearrangements of ethers which bear  $\gamma$ -alkyl substituents on the allyl group are often complicated by further rearrangements of the initial product (the so-called abnormal Claisen rearrangement<sup>1</sup>), the rearrangement of the 6-prenyloxyindole (3d) was carried out differently. Thus, heating the indole (3d) in a mixture of acetic anhydride† and *N,N*-dimethylaniline (1:1 v/v) gave only the normal Claisen product, the 7-isoprenyl-6-hydroxyindole (4d) (89% as its *O*-acetate).

To extend the scope of the indolisation–Claisen rearrangement sequence, and in connection with synthetic studies on lyngbyatoxin A (8), a highly toxic marine indole alkaloid,<sup>10</sup>



**Scheme 2.** Reagents: i, N<sub>3</sub>CH<sub>2</sub>CO<sub>2</sub>Et, NaOEt, EtOH, –10 °C; ii, PhMe, reflux; iii, Ac<sub>2</sub>O, PhNMe<sub>2</sub>, reflux.

† The use of acetic anhydride to intercept the initial phenolic Claisen rearrangement product was first reported by Fieser *et al.* (ref. 7). Various modifications have subsequently been used (*e.g.* refs. 8 and 9).

the conversion of 4-geranyloxybenzaldehyde<sup>11</sup> into the indole (10) was investigated (Scheme 2). Condensation of the aldehyde with ethyl azidoacetate, followed by thermolysis of the resulting azide gave the indole (9) which, without further purification, was heated in acetic anhydride-*N,N*-dimethylaniline to give the indole (10) (32% from 4-geranyloxybenzaldehyde) containing the required 7-linalyl substituent, the introduction of which forms a key step in any approach to (8). Since, in principle, the additional 2- and 6-substituents may be removed if necessary, although the corresponding aza- and thia-Claisen rearrangements might lead to more useful compounds for this latter transformation, the regioselective Claisen rearrangement provides a useful route to a range of 7-allylindoles.

I thank Professor C. W. Rees for helpful discussion.

Received, 12th July 1983; Com. 934

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