

Rearrangement of 3-Alkyl-1-allylindoles: a Model Reaction for the Biogenesis of Echinulin-type Compounds

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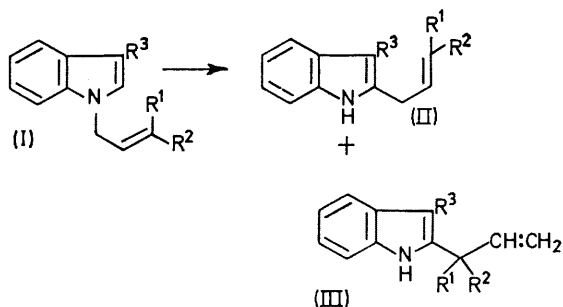
Summary The reactivity of 3-alkyl-1-allylindoles as model systems in the biogenesis and synthesis of the echinulin-type compounds has been studied: in the presence of acids the crotyl and $\gamma\gamma$ -dimethylallyl groups migrate from the 1- to the 2-position of the indole nucleus with a partial allylic rearrangement.

THE problem of the mechanism of insertion of an $\alpha\alpha$ -dimethylallyl chain at the 2-position of the indole nucleus is of interest, especially in regard to the synthesis and biogenesis of echinulin,¹ neoechinulin,² and the brevianamides A and E.³ In the case of echinulin this biogenetic mechanism has been proved to proceed *via* mevalonic acid.⁴

systems, seem to exclude the hypothesis of both a primary attack at the 3-position^{5a} and a direct attack (S_N2' type) at the 2-position.⁶

In order to examine the third possibility (the 1-2-rearrangement of the allylic chain) we have studied the reactivity of 1- $\gamma\gamma$ -dimethylallyl-3-alkylindoles as model systems in the biogenesis and synthesis of the echinulin-type compounds.

An acid-catalysed rearrangement of the isoprene chain from the 1- to the 2-position of the indole nucleus, together with a partial rearrangement of the allyl chain, was observed for the first time. In this way, 1- $\gamma\gamma$ -dimethylallyl-3-methylindole (I) rearranges to 2- $\alpha\alpha$ -dimethylallyl-3-methylindole (III) and to 2- $\gamma\gamma$ -dimethylallyl-3-methylindole (II) (see Table 1).



Different biogenetic mechanisms involving either a direct attack (S_N2' type) of the $\gamma\gamma$ -dimethylallyl group at the 2-position of the indole system or a primary attack at positions 3 or 1, followed by rearrangement, have been suggested.⁵ Several studies, carried out with model

TABLE I.

Acid-catalysed rearrangement of 1- $\gamma\gamma$ -dimethylallyl-3-methylindole

Acid	Time (h)	% (II) ^a	% (III) ^a
CF ₃ CO ₂ H ^c	1	70	30
CF ₃ CO ₂ H ^b	24	50	50
CF ₃ CO ₂ H ^d	144	35	65
BF ₃ in diethyl ether ^b	24	50	50
SnCl ₄ in hexane ^b	72	65	35
AlCl ₃ in hexane ^b	72	75	25

^a R¹ = R² = R³ = Me; Relative weight % composition, excluding unreacted compound. ^b At room temperature. ^c In refluxing CF₃CO₂H. ^d At 0°.

The reaction was further studied with the compounds (Ia, b, c), in CF₃CO₂H at room temperature for 48 h, and a remarkable increase of the yields was observed: allyl << crotyl < $\gamma\gamma$ -dimethylallyl (see Table 2).

In fact compound (Ia) (1-allyl-3-methylindole) does not react at all, while compound (Ib) (1-crotyl-3-methylindole)

TABLE 2

Rearrangement in $\text{CF}_3\text{CO}_2\text{H}$ of 3-alkyl-1-allylindoles							
	R ¹	R ²	R ³	% (I)	% (II)	% (III)	% (II) : % (III)
a	H	H	Me	100	—	—	—
b	Me	H	Me	36	14	36 ^a	27 : 73
c	Me	Me	Me	—	50	50	50 : 50
d	Me	Me	Pr ⁿ	3	52	45	56 : 44

^a Other products: 14%.

reacts more slowly than (Ic) (1- $\gamma\gamma$ -dimethylallyl-3-methylindole). However in the case of (Ib) a higher ratio between the product with the $\alpha\alpha$ -dimethylallyl group (IIIb) and the compound with the $\gamma\gamma$ -dimethylallyl group (IIb) was observed. Generally, whenever the reactions in $\text{CF}_3\text{CO}_2\text{H}$ are carried out under lower-reactivity conditions (low temperature and in the presence of allylic substituents with slower rearrangement rates), an increase of the allylic

rearrangement [*i.e.* formation of compound (III)] is observed.

The influence of the nature of the acid appears to be quite complex. Positive results were obtained with both Lewis (BF_3 , AlCl_3 , SnCl_4) and protic acids ($\text{CF}_3\text{CO}_2\text{H}$), while in sulphuric acid solutions at different concentrations the rearrangement products were obtained in very low yields.

The presence of a bulkier substituent at the 3-position of the indole system [as in compound (Id)] slightly modifies the reaction rate and the ratio between (IIId) and (IID).

Finally, in order to check whether the reaction occurs with an inter- or an intra-molecular mechanism, two experiments with mixtures of (Ic) and skatole and of (Ic) and (Id) were carried out in $\text{CF}_3\text{CO}_2\text{H}$. In neither case was any product from a cross-reaction found. These results seem to be consistent with an intramolecular process, but without excluding completely the possibility of an inter-molecular mechanism.

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¹G. Casnati, A. Quilico, and A. Ricca, *Gazzetta*, 1962, **92**, 128, and refs. therein.

²M. Barbetta, G. Casnati, A. Pochini, and A. Selva, *Tetrahedron Letters*, 1969, 4457.

³A. J. Birch and J. J. Wright, *Tetrahedron*, 1970, **26**, 2329.

⁴A. J. Birch, G. E. Blanche, S. David, and H. Smith, *J. Chem. Soc.*, 1961, 3128.

⁵(a) A. H. Jackson and A. E. Smith, *Tetrahedron*, 1965, **21**, 989; (b) A. J. Birch and K. R. Farrar, *J. Chem. Soc.*, 1963, 4277.

⁶G. Casnati, M. Francioni, A. Guareschi, and A. Pochini, *Tetrahedron Letters*, 1969, 2485.