An Unexpected Rearrangement of 4-Alkylaminoindoles

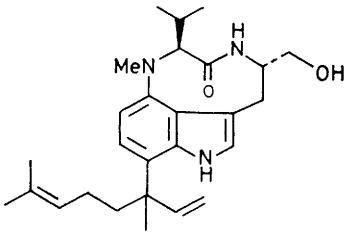
Steven V. Ley* and Roderick A. Porter

Department of Chemistry, Imperial College, London SW7 2AY, U.K.

4-Alkylaminoindoles rearrange in good yield to the corresponding 1-alkyl-4-aminoindoles in the presence of 10 mol% hydrated toluene-*p*-sulphonic acid in boiling toluene.

During studies directed towards the total synthesis of teleocidin[1]A (**1**) (lygnbyatoxin[2]) and related potent tumour promotors,[3] we observed a novel and unexpected rearrangement of 4-alkylaminoindoles, the details of which we report here.

The starting 4-alkylaminoindoles (**2**) used in this work were prepared from 4-aminoindole which in turn can be prepared by the excellent Leimgruber and Batcho method.[4] Compound (**2**, R = Me) was obtained in 78 % yield by lithium aluminium hydride reduction of 4-*N*-formylaminoindole while (**2**, R = CH_2Ph) and (**2**, R = CH_2CO_2Et)† were derived by mono-alklyation of 4-aminoindole using potassium carbonate–potassium iodide and the appropriate bromide, in 47 and 84% yields respectively.

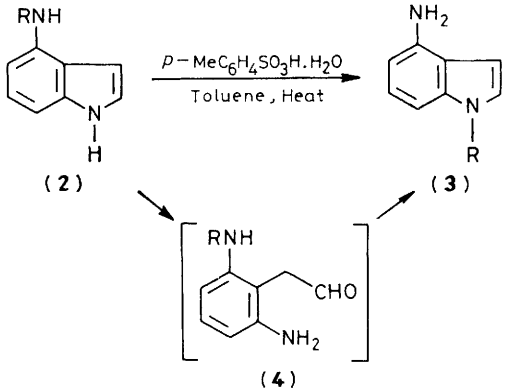


(**1**)

† All new compounds were fully characterised by spectroscopic methods, and accurate mass and/or microanalytical techniques.

Upon heating the indoles (**2**) in toluene containing 10 mol% of monohydrated toluene-*p*-sulphonic acid smooth conversion into the corresponding 1-alkyl-4-aminoindoles (**3**)† was achieved (Table 1). In the absence of water, or using anhydrous camphorsulphonic acid in a similar manner, no rearrangement was observed even after extended periods of time.

We suggest that the mechanism for the rearrangement reaction therefore involves initial ring opening of the 4-alkylaminoindole to produce an intermediate species (**4**) which prefers to undergo ring closure to the more thermodynamically stable 1-alkyl-4-aminoindole system (Scheme 1). This re-



(**2**) (**3**) (**4**)

Scheme 1

Table 1

Starting indole (**2**)	Product (**3**) % yield	Reaction time /h
R = Me	75	23
R = CH_2Ph	90	21
R = CH_2CO_2Et	77[a]	44

[a] Plus 13% recovered starting material.

arrangement has potentially useful synthetic applications for the preparation of specifically substituted indoles.

We thank the S.E.R.C. and Pfizer Central Research, Sandwich, Kent, for a C.A.S.E. research studentship (to R. A. P.), the Royal Society of Chemistry for the Hickinbottom Research Award (to S. V. L.), and Dr. J. C. Ruddock (Pfizer, U.K.) for helpful discussions.

Received, 21st September 1982; Com. 1123

References

1 M. Takashima and H. Sakai, *Bull. Agric. Chem. Soc. Jpn.*, 1960, **24**, 647, 652; M. Takashima, H. Sakai, and K. Arima, *Agric. Biol. Chem.*, 1962, **26**, 660.
2 J. H. Cardellina II, F-J. Marner, and R. E. Moore, *Science*, 1979, **204**, 193.
3 T. Sugimura, F. Hirota, M. Mori, M. Nakayasu, M. Terada, K. Umezawa, and R. E. Moore, *Carcinog. Comp. Serv.*, 1982, **7**, 69 (*Chem. Abs.*, 96, 211 864).
4 A. D. Batcho and W. Leimgruber, U.S. Patent 3,967,639 (1976); L. I. Kruse, *Heterocycles*, 1981, **16**, 1119.