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ACID-CATALYSED REACTION OF ACTIVATED INDOLES WITH METHYL KETONES

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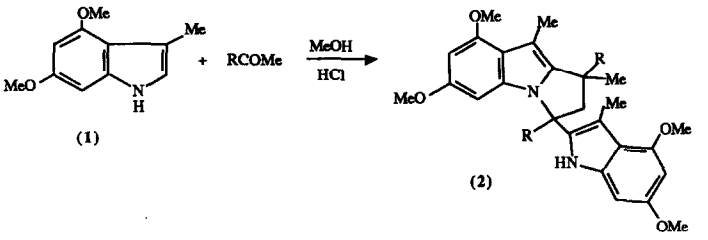
Abstract: *4,6-Dimethoxy-3-methylindole can be converted by treatment with acetone or acetophenones in methanolic hydrochloric acid into ring-fused indoles in good yields.*

4,6-Dimethoxy-3-methylindole (1)[1] has been shown to undergo acid-catalysed reaction with aryl aldehydes to give 2,2'-di-indolylmethanes and macrocyclic tri-indolylmethanes under different conditions[2]. In an attempt to extend this behaviour to ketones, the indole (1) was treated with acetone and a range of acetophenones in methanolic hydrochloric acid. In most cases, only traces of the corresponding 2,2'-di-indolylmethanes were obtained and the major products were the pyrrolo-indole derivatives (2)(**Scheme 1**)[3].

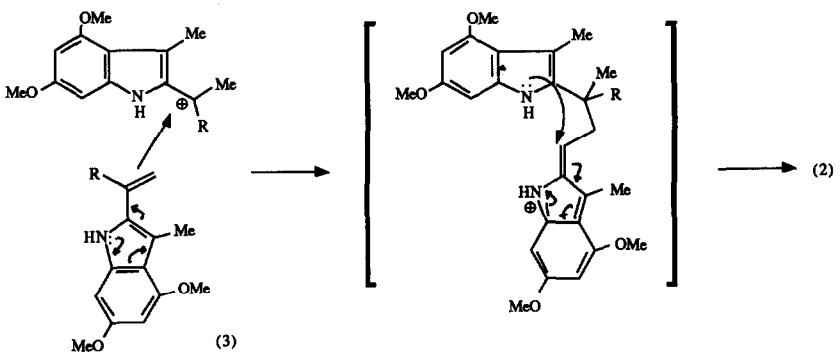


(2)	R	Yield %
a	Me	92
b	Ph	75
c	4-MePh	63
d	4-EtPh	57
e	4-MeOPh	73

Scheme 1

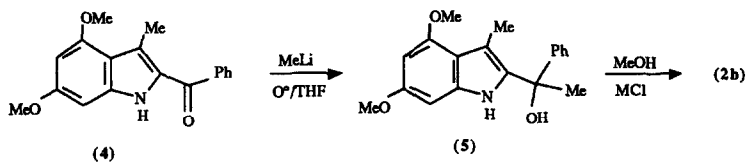
Compounds (2b-e) were formed as mixtures of diastereomers which in the case of the methoxyphenyl compound (2e) could be easily separated by column chromatography. The structure of compound (2b) was confirmed by X-ray crystallographic analysis (**Figure 1**)[4]. In this crystal, the two phenyl groups lie on the same side of the pyrrolidine ring.

Formation of the ring-fused indoles (2) could be envisaged formally by the intermediacy of the alkenyl indole (3), as shown in **Scheme 2.**



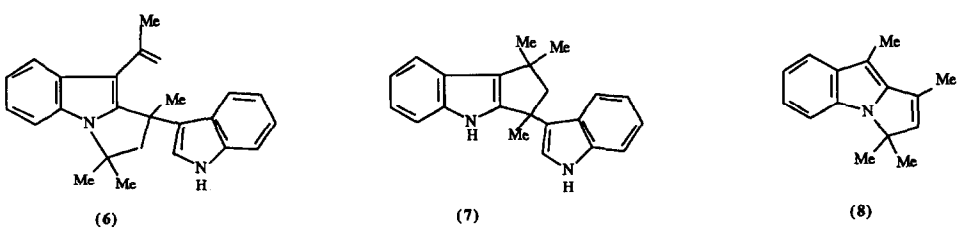
Scheme 2

This mechanistic postulate is strengthened by the observation that the alcohol (5), formed by addition of methyl lithium to the ketone (4)[2], can be converted in methanolic hydrochloric acid into the pyrrolo-indole (2b)(**Scheme 3**).



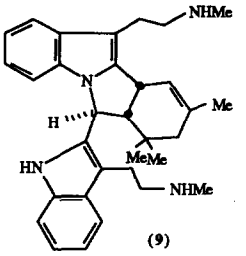
Scheme 3

Reactions of indole and 2-methylindole with acetophenones under acidic conditions have previously been reported to give only 3,3'-di-indolylmethanes[5]. There is no report of a similar reaction with 3-methylindole and we have confirmed that no reaction occurs under the above conditions. However, the acid-catalysed reaction of indoles with acetone has been widely studied. Indole itself gives a poor yield of the pyrrolo[a]indole (6) with boron trifluoride[6,7] or a good yield of the cyclopentano[b]indole (7) with trifluoroacetic acid[8]. The aluminium chloride catalysed reaction of 3-methylindole gives the pyrrolo[a]indole (8)[9,10].

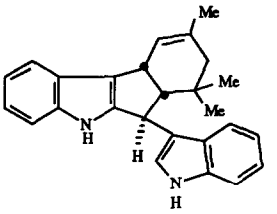


Vinyl indoles are implicated in these reactions and a 2-butadienyl indole derived from the alkaloid borrerine gave a mixture of borrevine and the minor alkaloid isoborreverine (9), all of which are constituents of *Borreria verticillata* and *Flindersia fournieri* [11]. However, the important alkaloid yuehchukene (10), isolated from

Murraya paniculata and shown to possess potent anti-implantation activity[12], has been synthesised in poor yield by the dimerisation of a 3-butadienyl indole[13,14].

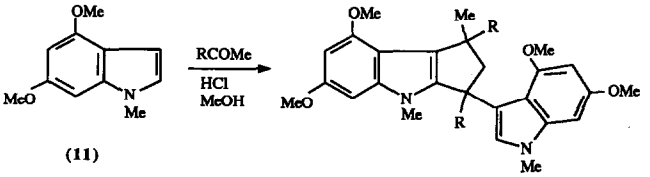


(9)



(10)

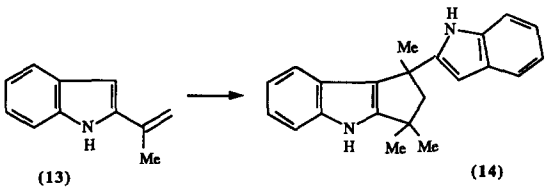
Significantly, 4,6-dimethoxy-1-methylindole (11) undergoes acid-catalysed reaction with acetone and acetophenone to give the cyclopentano[b]indoles (12a,b) respectively, presumably via a 3-alkenyl indole intermediate[15].



(11)

(12)	R	Yield %
a	Me	84
b	Ph	76

1-Methylindole itself, under similar conditions, gives only 3,3'-di-indolyl methanes. However, the independently-formed 2-propenylindole (13) has very recently been shown to give a low yield of the cyclopentano[b]indole (14)[16].



(13) (14)

In summary, reactions of the activated 3-methylindole (1) or 1-methylindole (11) provide very effective synthetic entry into the isoborreverine or yuehchukene structural types.

Acknowledgement *:* We thank the Australian Research Council for financial support.

References and Notes

1. D. St. C. Black, N.E. Rothnie and L.C.H. Wong, *Aust.J.Chem.*, 1983, **36**, 2407.
2. D. St. C. Black, D.C. Craig and N. Kumar, *J.Chem.Soc., Chem.Commun.*, 1989, 425.
3. All new compounds gave spectroscopic and micro-analytical data in accord with assigned structures. For (2a); m.p. 179-80°; ^{1}H n.m.r. δ ($CDCl_3$) 1.14, 1.51, 2.05 (each 3H, s, CH_3), 2.47, 2.49 (each 3H, s,

CH_3), 2.63 (1H, d, J 12.6Hz, CH_2), 2.88 (1H, d, J 12.6Hz, CH_2), 3.70, 3.74, 3.87, 3.91 (each 3H, s, OCH_3), 6.14, 6.20, 6.22, 6.27 (1H each, d, J 2.0Hz, ArH), 7.31 (1H, bs, NH); m.s., *m/z* 462 (M^+, 76%). For (**2e**): m.p. 216-18°, ^1H n.m.r. δ ($(CD_3)_2SO$) δ 1.61, 1.79, 2.16 (each 3H, s, CH_3), 3.46 (2H, ABq, J 12.8 Hz, CH_2, 3.32, 3.66, 3.67, 3.68, 3.75, 3.80 (each 3H, s, OCH_3), 5.39, 6.07, 6.09, 6.45 (each 1H, d, J 2.1 Hz, ArH), 6.71, 6.73, 6.93, 7.13 (each 2H, d, J 8.7 Hz, ArH); m.s. *m/z* 646 (M^+, 41%).

4. Crystal data for compound (2b): $C_{38}H_{38}N_2O_4$, M586.7, monoclinic, space group C2/c, a 19.912(7), b 19.157(4), c 17.111(7)Å, β 103.31(2)°, Z 8, 5587 unique reflexions (MoK_α), 2842 observed ($I>3\sigma(I)$), R 0.044, R_w 0.057.
5. W.E. Noland and M.R. Venkiteswaran, *J.Org.Chem.*, 1961, **26**, 4263.
6. A. Chatterjee, S. Manna, J. Banerji, C. Pascard, T. Prangé and J.N. Shoolery, *J.Chem.Soc., Perkin Trans. I*, 1980, 553.
7. J. Banerji, A. Chatterjee, S. Manna, C. Pascard, T. Prangé and J.N. Shoolery, *Heterocycles*, 1981, **15**, 325.
8. J. Bergman, P.O. Norrby, U. Tilstam and L. Vennemalm, *Tetrahedron*, 1989, **45**, 5549.
9. E. Röder, *Arch.Pham.*, 1972, **305**, 96.
10. E. Röder, *Arch.Pham.*, 1972, **305**, 117.
11. F. Tillequin, M. Koch, J.L. Pousset and A. Cavé, *J.Chem.Soc., Chem.Commun.*, 1978, 826.
12. Y.C. Kong, K.F. Cheng, R.C. Cambie and P.G. Waterman, *J.Chem.Soc., Chem Commun.*, 1985, 47.
13. K.F. Cheng, Y.C. Kong and T.Y. Chan, *J.Chem.Soc., Chem.Commun.*, 1985, 48.
14. E. Wenkert, P.D.R. Moeller, S.R. Piettre and A.T. McPhail, *J.Org.Chem.*, 1988, **53**, 3170.
15. (**12a**); m.p. 216-18°; ^1H n.m.r. δ ($CDCl_3$) 1.16, 1.46, 1.91 (each 3H, s, CH_3), 2.50 (1H, d, J 13.0Hz, CH_2), 2.84 (1H, d, J 13.0Hz, CH_2), 3.53, 3.63 (each 3H, s, N-CH_3), 3.87 (6H, s, OCH_3), 3.89, 3.91 (each 3H, s, OCH_3), 6.23 (1H, s, ArH), 6.22, 6.25, 6.32, 6.42 (each 1H, d, J 1.8 - 2.0Hz, ArH); m.s., *m/z* 462 ((M^+, 44%).
16. M. Eitel and U. Pindur, *J.Org.Chem.*, 1990, **55**, 5368.

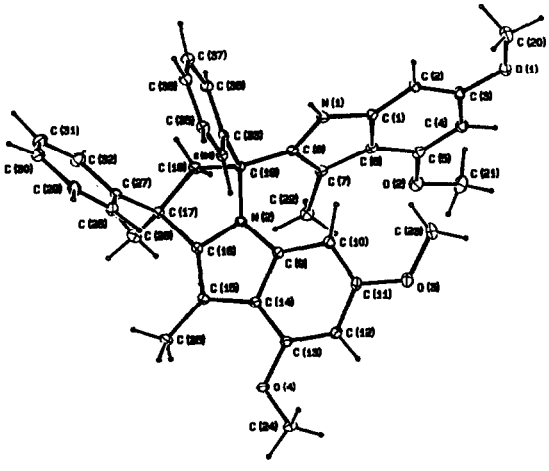


Figure 1: ORTEP plot of compound (2b)

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