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# A NOVEL SYNTHESIS OF 2-AMINO- AND 2-HYDROXYCARBAZOLES

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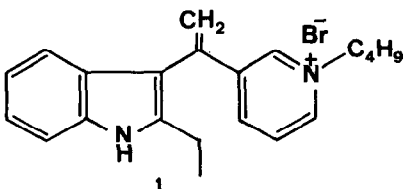
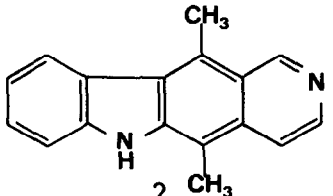
Thermolytic cyclization of the readily available compound 1 gives ellipticine ( 2 ) in good yield and an isomer, assigned structure 3, in various amounts ( cf ref 1 ).



1



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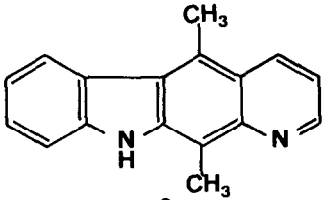

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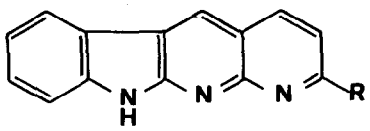

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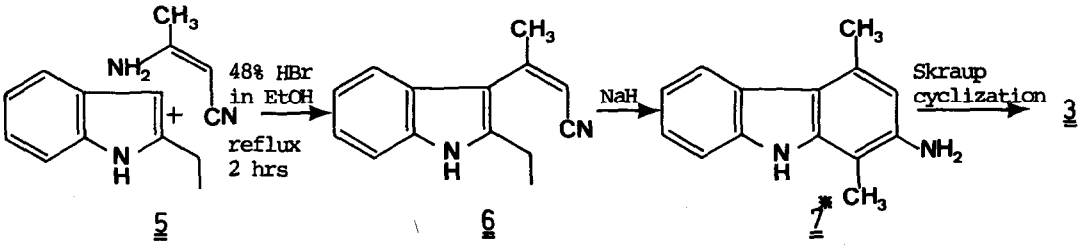
In order to prove the structure of 3 and to establish a more convenient synthesis of this potentially interesting compound ( cf ref 2 where the azaanalogue 4 is described ) the following rapid, high-yield route was developed.

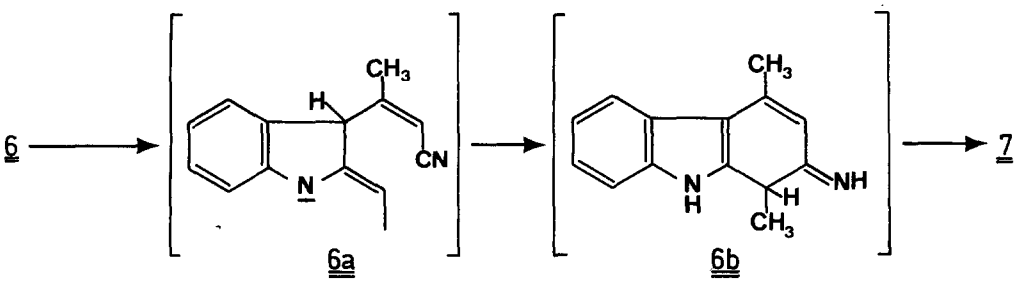



5 6 7 3

* This compound also deserves interest as a desazaanalogue of 3-amino-1,4-dimethyl-5H-pyrido-[4,3-b] indole, which recently has been reported[15,16] to be highly mutagenic.

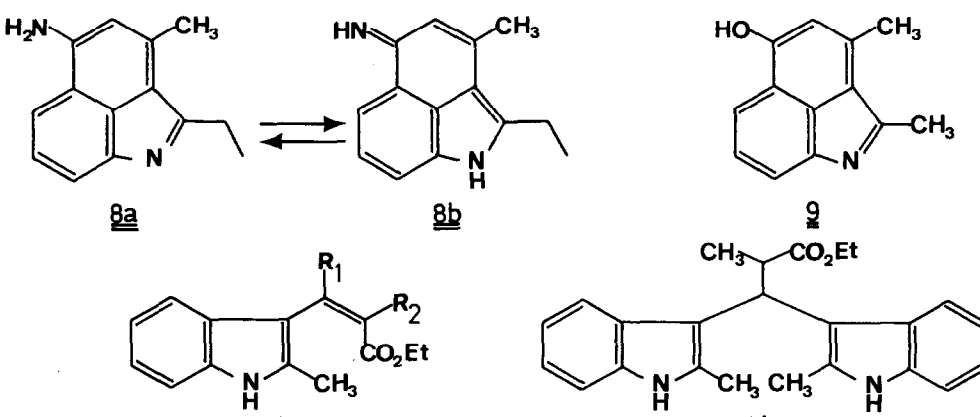
The condensation ( 5 → 6 ) could also be effected with $CH_3COCH_2CN$ ( for similar condensations see ref 3 ). Other 2-alkylindoles gave analogues to 6, whereas indole itself, not unexpectedly[4] gave the 2:1 condensation product 12.

The cyclization[5] ( 6 → 7 ) was carried out with NaH in diphenyl ether at 220° ( 24 hrs ) whereby the anion of the exocyclic tautomer of 6 ( 6a ) cyclized to 6b, which subsequently aromatized into 7[6] through a hydrogen shift.

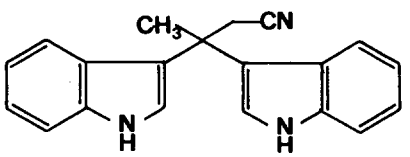



The Skraup cyclization ( 7 → 3[7], yield ∿ 70 % ) was carried out with glycerol, nitrobenzene, sulfuric acid and acetic acid ( the latter as a moderating agent ).

Attempts to cyclize 6 to 7 with HBr in chloroform resulted in a cyclization to the 4-position in the indole ring yielding compound 8a[8] which was stable towards $KOH/H_2O$ ( 100°, 24 hrs. ) indicating that the tautomeric equilibrium 8a ⇄ 8b is greatly shifted to the left. The hydroxy analogue to 8a, 9, could similarly be obtained from the ester 10a by cyclization promoted by hot ( 100° ) polyphosphoric acid.



The condensation product 10a, readily prepared[3] from 2-methylindole and ethyl acetoacetate, could be cyclized ( NaH, 220° ) to 13[9]. This route to 2-hydroxycarbazoles appears to be general and e.g. 2-hydroxy-3-methylcarbazole ( 14 ), precursor of girinimbine ( 15 ) and several related carbazole alkaloids[10], is formed when OHC-CH($CH_3$)-$CO_2$Et is condensed with 2-methylindole followed by cyclization. It is necessary to work at low temperatures ( 0° ) to obtain the ester 10b. At higher temperatures the 2:1 product 11[14] is formed.

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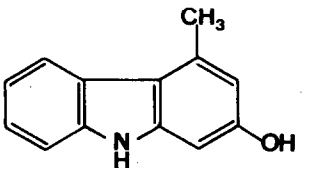


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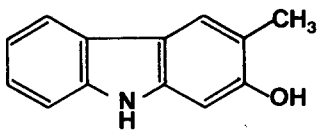


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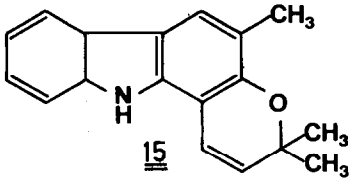


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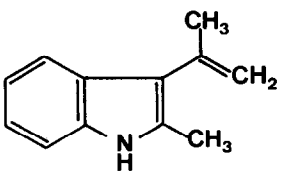
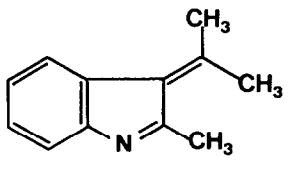
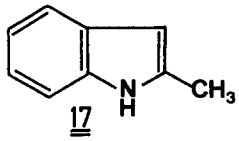
Interestingly, bis( 2-methyl-3-indolyl )-dimethylmethane ( 18 ) appeared as a sideproduct in the cyclization ( 10 → 13 ). This can be explained in terms of decarbethoxylation and dealkenylation of 10 followed by an addition of 17 to 16b ( cf refs 11 and 12 ).




16a




16b

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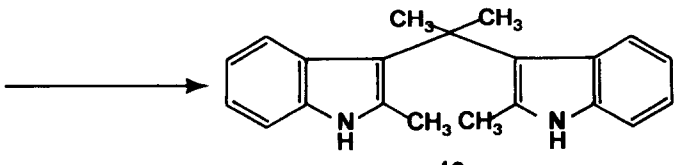


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## REFERENCES AND NOTES


1. J. Bergman and R. Carlsson, Tetrahedron Letters, 4663 ( 1977 ).
2. A. Da Settimo, G. Primofiore, V. Santerini, G. Biagi and L. D'Amico, J. Org. Chem., 42, 1725 ( 1977 ).
3. (a) D. N. Robinson, Ph. D. Thesis, Univ. of Minnesota, Minneapolis ( 1959 ).
   (b) W. E. Noland and D. N. Robinson, J. Org. Chem., 22, 1134 ( 1957 ).
4. This is another example showing that 2-substituted indoles give normal 3-vinylindoles, whereas indole itself condenses further yielding a 2:1 adduct, in this case 1,1-bis(3-indolyl)-1-cyanomethyl ethane ( 12 ), m.p. 180°. MS: 300(13), 299(21), 260(13), 259(100), 182 (14), 142(17), 129(22), 117(14), 115(15), and 40(37). Only peaks greater than 10 % of the base peak are listed. Cf J. Bergman and R. Carlsson, J. Het. Chem., 9, 833 ( 1972 ).
5. (a) For related enamine-nitrile cyclizations see ref. 5b, and earlier papers in this series
   (b) A. I. Meyers, A. H. Reine, and R. Gault, J. Org. Chem., 34, 698 ( 1968 ).
6. M.p. 161-163°. MS: 211(15), 210(100), 209(31), 208(6), 195(13), 180(6), 167(10), and 105 (10). Only peaks greater than 5 % of the base peak are listed.
7. M.p. 212-213°. MS: 247(17), 246(100), 245(35), 233(26), 232(29), and 123(13). Only peaks greater than 10 % of the base peak are listed.
8. M.p. 93-95°. The structure is consistent with the $^1$H-NMR, IR and MS data. ( cf ref 13 where similar compounds are discussed ).
9. M.p. 192-194°. MS: 198(10), 197(67), 196(24), 173(39), 168(10), 167(12), 159(13), 158(100), 130(17), and 103(12). Only peaks greater than 10 % of the base peak are listed.
10. Y. Oikawa and O. Yonemitsu, Heterocycles, 5, 233 ( 1976 ) and refs. therein.
11. J. Bergman, Acta Chem Scand., 26, 970 ( 1972 ).
12. J. Bergman and J.-E. Bäckvall, Tetrahedron, 31, 2063 ( 1975 ).
13. G. M. Buchan and A. B. Turner, J. Chem. Soc., Perkin I, 2257 ( 1975 ).
14. M.p. 158-160°. MS: 274(23), 273(100), 257(10), 243(24), 229(16), 198(13), 170(18), 168(13), 144(10), 131(36), 130(49), 129(12), and 128(10). Only peaks greater than 10 % of the base peak are listed.
15. J. L. Fox, Chem. & Eng. News, Dec 12, 34 ( 1977 ).
16. H. Akimoto, A. Kawai, H. Nomura, M. Nagao, T. Kawachi, and T. Sugimura, Chemistry Letters, 1061 ( 1977 ).


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