

Synthesis of 1-Methoxyindoles

By R. MORRIN ACHESON,* DAVID M. LITTLEWOOD, and HOWARD E. ROSENBERG

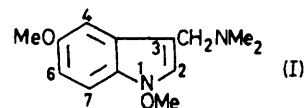
(Department of Biochemistry, South Parks Road, Oxford OX1 3QU)

Summary Reductive cyclization of 2-nitrophenylacetaldehydes, followed by acetylation, hydrolysis, and methylation gave the corresponding 1-methoxyindoles which undergo the Mannich reaction at position 3.

FOUR 1-methoxyindoles have now been isolated from plants: 1,5-dimethoxygramine,¹ 1-methoxy-*NN*-dimethyltryptamine,² 1-methoxyindoleacetonitrile,³ and a derivative of 1-methoxyindole-3-acetic acid called neoglucobrassicin;⁴ their structures have been deduced from their spectra and degradative studies. The only 1-alkoxyindole unsubstituted at position 2 hitherto synthesised is 1-ethoxyindole obtained⁵ in 5% yield along with 2-acylindoles from the reaction of 2-substituted 2-[2-(*o*-nitrophenyl)viny]-1,3-dioxolans with triethyl phosphite. The first synthesis of 1-methoxyindole and the gramine (I) is now described.

2-Nitrophenylacetaldehyde, from the osmium tetroxide-periodate oxidation of 1-chloro-4-(2-nitrophenyl) but-2-ene,⁶ was reductively cyclized to 1-hydroxyindole by Zn-NH₄Cl;⁷ acetylation *in situ* gave 1-acetoxyindole (b.p. 90—93° at 0.3 Torr). In contrast to 1-hydroxyindole, which polymerizes on attempted isolation, the 1-acetoxy-compound is

reasonably stable, and with NaOMe and MeOH gave 1-methoxyindole in 40% yield from the aldehyde. 1-Methoxyindole⁸ on reduction with LiAlH₄ also gave 1-methoxyindole in 60% yield. The methoxy-group was removed by hydrogen over Pd-C giving indole quantitatively.



1-Methoxyindole and 1,5-dimethoxyindole, obtained *via* the aldehyde route, with formaldehyde and dimethylamine in acetic acid as described for indole⁹ gave the corresponding gramines in excellent yield. Synthetic 1,5-dimethoxygramine (I) and its picrate had all the reported properties of material obtained from *Gymnocrantheria paniculata*.¹ 1-Methoxyindole is substituted in the 3-position by a variety of other electrophilic reagents.

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¹ S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, *Austral. J. Chem.*, 1967, **20**, 1737.

² H. Morimoto and H. Oshio, *Annalen*, 1965, **682**, 212.

³ M. Namoto and S. Tamura, *Agric. Biol. Chem.*, 1970, **34**(10), 1590.

⁴ R. Gmelin and A. I. Virtanen, *Acta Chem. Scand.*, 1962, **16**, 1378.

⁵ R. J. Sundberg, *J. Org. Chem.*, 1968, **33**, 487.

⁶ W. E. Noland and J. H. Sellstedt, *J. Org. Chem.*, 1966, **31**, 345.

⁷ M. Mousseron-Canet and J.-P. Boca, *Bull. Soc. chim. France*, 1967, 1296.

⁸ W. B. Wright and K. H. Collins, *J. Amer. Chem. Soc.*, 1956, **78**, 221.

⁹ H. Kuhn and O. Stein, *Ber.*, 1937, **70**, 567.