A Novel Synthesis of 1,2,3,4-Tetrahydroisoquinolines and a Note on the Reactivity of a 4-Methoxy-derivative

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Summary *N*-Benzoyl homoveratrylamines react with chloromethyl methyl ether to form 1,2,3,4-tetrahydroisoquinolines.

RECENT interest in 4-oxygenated 1,2,3,4-tetrahydroisoquinolines has been expressed in the publication of a number of synthetic approaches to this class of compound[1] and the report of the isolation of an alkaloid of this type.[2] We report some results of a procedure which affords an acylated 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2**; R = H)† in good yield and an acylated 4,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**2**; R = OMe) in moderate yield.

Treatment of *N*-benzoyl-2-(3′,4′-dimethoxyphenyl)ethylamine (**1**; R = H) with chloromethyl methyl ether in glacial acetic acid at room temperature (18°) for eighteen hours afforded *N*-benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline in 85% yield, m.p. 106—106·5 (lit.[3] 110°). The identity of the product was confirmed by comparison with an authentic sample prepared by benzoylating the tetrahydroisoquinoline.

† Satisfactory elemental analyses have been obtained of compounds named herein.

Other solvents which were examined (yield): acetone (60%); THF (negligible); CS_2 (neg.).

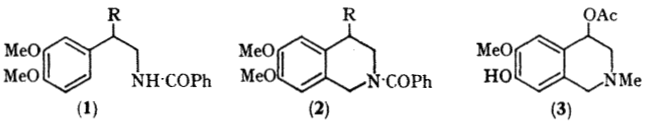
The process of cyclisation may be followed using t.l.c. by the intense fluorescence exhibited by the tetrahydroisoquinoline when sprayed with 4%-$Ce(SO_4)_2$ in 2N-H_2SO_4 and examined in u.v. light.

The reaction of *N*-benzoyl-2(3′,4′-dimethoxyphenyl)-2-methoxyethylamine (**1**; R = OMe) with chloromethyl methyl ether was investigated in a number of solvents; best results were obtained in dry tetrahydrofuran (18°, 5d.) when *N*-Benzoyl-4,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (**2**; R = OMe), m.p. 122—123° (benzene–petroleum), was obtained in up to 30% yield (variable), and identified by i.r. and n.m.r. No cyclisation was detected when the experiment was performed at 5° and a mixture resulted at 35°.

The 4-acetoxytetrahydroisoquinoline (**3**) undergoes nucleophilic substitution of the acetoxy-group by alcohols, amines, and thiols.[4] The 7-methoxy-analogue was not similarly reactive; it was suggested that a quinonoid intermediate was involved in the reactivity of the former compound.

The 4,6,7-trimethoxy-amide (**2**; R = OMe) shows unusual reactivity: crystallisation from ethanol affords the 4-ethoxy-compound (**2**; R = OEt), m.p. 132—133° identified by i.r. and n.m.r.

Treatment of *N*-benzoyl-2-ethoxy-2-(3′,4′-dimethoxyphenyl)ethylamine (**1**; R = OEt) with chloromethyl methyl ether as for the methoxy-analogue afforded the 4-ethoxy-1,2,3,4-tetrahydroisoquinoline, in a less pure form than from the transformation reaction, identified by n.m.r., i.r., and t.l.c.



(1) (2) (3)

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[1] (a) G. Grethe, H. L. Lee, M. Uskokovic, and A. Brossi, *J. Org. Chem.*, 1968, **33**, 491, 494; (b) G. Grethe, V. Toome, H. L. Lee, M. Uskokovic, and A. Brossi, *ibid.*, p. 504; (c) D. N. Harcourt and R. D. Waigh, *Chem. Comm.*, 1968, 692; (d) H. Nakao, Y. Yura, and M. Ito, *Sankyo Kenkyusho Nempo*, 1966, **18**, 48; *Chem. Abs.*, 1967, **66**, 104886x; (e) J. M. Bobbitt and T. E. Moore, *J. Org. Chem.*, 1968, **33**, 2958 and refs. therein; (f) D. W. Brown, S. F. Dyke, and M. Sainsbury, *Tetrahedron*, 1969, **25**, 101; see also O. M. Friedman, K. N. Parameswaran, and S. Burstein, *J. Medicin. Chem.*, 1963, **6**, 227; T. Kondo and S. Tanaka, *J. Pharm. Soc. Japan*, 1930, **50**, 119 (*Org. Reactions*, 1951, **6**, 164).

[2] J. E. Hodgkins, S. D. Brown, and J. L. Massingill, *Tetrahedron Letters*, 1967, 1321; *cf.*, however, G. Grethe, M. Uskokovic, T. Williams, and A. Brossi, *Helv. Chim. Acta*, 1967, **50**, 2397.

[3] G. Hazebroucq, *Ann. Chim.* (*France*), 1966, **1**, 221.

[4] (a) B. Umezawa, O. Hoshino, and Y. Yamanishi, *Tetrahedron Letters*, 1969, 933; (b) O. Hoshino, Y. Yamanishi, and B. Umezawa, *ibid*, p. 937.