Photochemical Approach to the Rhoeadine Alkaloid Skeleton: Synthesis of (±)-*cis*-Alpinigenine

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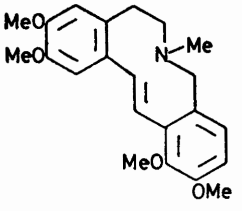
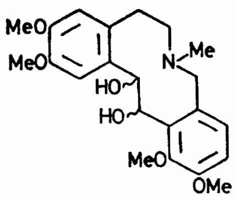
Summary Photolysis of the bis-benzaldehyde (**6**) results in simultaneous formation of rings B and D of the rhoeadine skeleton and leads directly to (±)-*cis*-alpinigenine (**1a**).

THE rhoeadine alkaloids[1] which occur widely in the genus *Papaver* are comprised of about twenty bases, all possessing tetracyclic structures and characterised by the presence of a 3-benzazepine unit *cis* or *trans* fused to a six-membered acetal or hemiacetal.

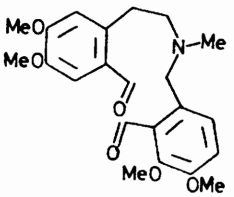
We report here a simple and novel synthesis[2] of the alkaloid $(\pm)$-*cis*-alpinigenine (**1a**) involving the *trans*-azocine intermediate (**4**). The known tetracyclic base[3] (**2**), m.p. 160—162 °C, obtained in good overall yield from homoveratrylamine and *o*-homoveratric acid in four steps, quantitatively formed the methiodides (**3a**) (a mixture of two diastereoisomers†). Conversion into the methochlorides[4] (**3b**) followed by Hofmann elimination of the derived methohydroxides[5,6] (**3c**) by the procedure of Pyman[5] afforded a 51% yield of the *trans*-azocine‡ (**4**), m.p. 142—143 °C, λ_{max} (cyclohexane) 286 nm (ϵ 11,900); δ ($CDCl_3$) 6·92 (2H, q, J 16 Hz, *trans*-stilbene). Treatment of (**4**) (in excess 1N HCl) with *N*-bromosuccinimide and *in situ* solvolysis§ of the halogenohydrin (24 h, room temp.) produced the 1,2-diol (**5**), m.p. 139—141 °C, ν_{max} (Nujol) 3490 cm^{-1}; δ ($CDCl_3$) 5·17 (1H, d, J 2 Hz) and 5·40 (1H, d, J 2 Hz). The diol (in 1N H_2SO_4) was rapidly (10 min, 0 °C) and quantitatively cleaved by periodic acid[6] to the dialdehyde (**6**) (oil) ν_{max} (neat) 2800 and 1690 cm^{-1}; δ ($CDCl_3$) 10·10 (1H, s) and 10·40 (1H, s); MeI salt m.p. 196—198 °C (decomp.). Photolysis[7] of the *o*-aminomethylbenzaldehyde (**6**) in Bu^{t}OH (7×10^{-3}M) (Pyrex filter, 2—3 h, N_2, 34 °C) afforded directly $(\pm)$-*cis*-alpinigenine (**1a**), m.p. 180—182 °C (lit.[8] 183—184 °C), in 28% yield. The t.l.c. properties and the i.r. spectrum ($CHCl_3$) were identical with those of the $(+)$-alkaloid and the ^{1}H n.m.r. spectrum with that of $(\pm)$-*cis*-alpinigenine.[8] Since (**1a**) has been converted[8] into $(\pm)$-*cis*-alpinine (**1b**) this work also formally represents the synthesis of the latter.



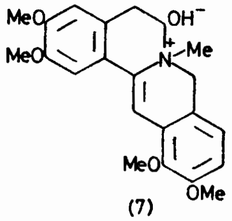
(4)



(5)



(6)



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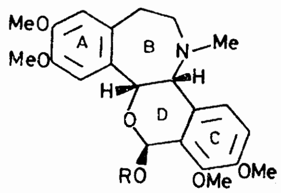
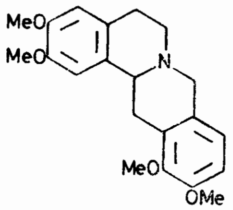


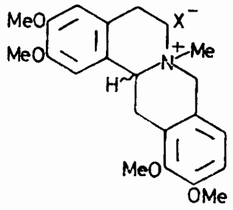
(1)

a; R = H

b; R = Me



(2)



(3)

a, X = I

b, X = Cl

c, X = OH

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† The methiodides can be separated into the less soluble *trans-isomer*, m.p. 254 °C (decomp.) and the *cis*-isomer, m.p. 248—249 °C (decomp.), by fractional crystallisation from aqueous ethanol.

‡ Compounds of the type (**4**) have played a central role in the synthesis of protopine alkaloids (D. Giacopello and V. Deulofeu, *Tetrahedron*, 1967, **23**, 3265; R. D. Haworth and W. H. Perkin Jr., *J. Chem. Soc.*, 1926, 1769) and in the biosynthetic studies of ophiocarpine (P. W. Jeffs and J. D. Scharver, *J. Amer. Chem. Soc.*, 1976, **98**, 4301.)

§ The procedure of Russel (ref. 6) led only to traces of (**5**) and the major product was a highly polar substance, presumably (**7**).

[1] M. Shamma, 'The Isoquinoline Alkaloids, Chemistry and Pharmacology,' Academic Press, New York, 1972, p. 399.
[2] For a review of other syntheses of rhoeadine alkaloids see: T. Kametani and K. Fukomoto, *Heterocycles*, 1975, **3**, 931.
[3] E. Späth and E. Mosettig, *Annalen*, 1923, **433**, 138; S. Chakravarti and M. Swaminathan, *J. Indian Chem. Soc.*, 1934, **11**, 107.
[4] Prepared by the method of A. P. Phillips and R. Baltzly, *J. Amer. Chem. Soc.*, 1952, **74**, 5231.
[5] F. L. Pyman, *J. Chem. Soc.*, 1913, **103**, 817.
[6] P. B. Russel, *J. Amer. Chem. Soc.*, 1956, **78**, 3115.
[7] For a review of photolysis of *o*-alkyl aromatic carbonyl compounds see: P. G. Sammes, *Tetrahedron*, 1976, **32**, 405; for complex photochemical processes that occur in γ-aminoaromatic ketones see: P. J. Wagner, A. E. Kemppainen, and T. Jellink, *J. Amer. Chem. Soc.*, 1972, **94**, 7512; P. J. Wagner and D. A. Ersfeld, *ibid.*, 1976, **98**, 4515; for a recent attempted photochemical conversion of the phthalidylisoquinoline alkaloids into rhoeodine alkaloids see: T. Kemetani, H. Inoue, T. Honda, T. Sugahara, and K. Fukumoto, *J.C.S. Perkin I*, 1977, 374.
[8] K. Orito, R. H. Manske, and R. Rodrigo, *J. Amer. Chem. Soc.*, 1974, **96**, 1944.

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