Convenient Route to the Rhoeadanes

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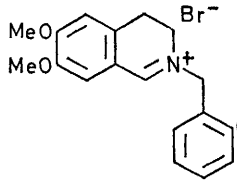
Summary Treatment of the quaternary ammonium salt (**1**) with base and benzoyl chloride afforded the aldehydo-amide (**3**) which was cyclized to the *trans* B/D rhoeadane derivative (**4**); a new route to the benzazepines has thus been developed.

THE rhoeadines are a large group of alkaloids found only in the genus *Papaver* (Papaveraceae).[1] We describe a three-step sequence to the rhoeadanes† which starts from readily available starting materials, and affords synthetically for the first time the thermodynamically less stable *trans* B/D fused series. Additionally, the sequence uses a new method of ring expansion for the formation of the benzazepine system.[2]

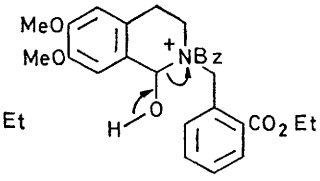
Condensation of 3,4-dihydro-6,7-dimethoxyisoquinoline with ethyl 2-bromomethylbenzoate (obtained from dry EtOH–HBr treatment of phthalide) in ether at room temperature afforded an 80% yield of compound (**1**), m.p. 165° (acetonitrile).

Next, treatment of the salt (**1**) with excess of aq. NaOH and benzoyl chloride with cooling gave rise to compound (**3**), m.p. 101° (ethanol), in 98% yield [λ_{max} (MeOH) 235, 283, and 315 nm (log ϵ 4·56, 4·09, and 3·84] through the probable intermediacy of the *N*-benzyolated pseudo-base (**2**) which was not isolated.[3]

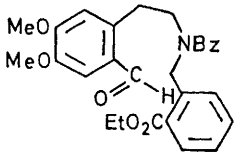
In order to obtain the tetracyclic lactone (**4**) which possesses a *trans* B/D rhoeadane nucleus, the aldehydo-ester (**3**) was subjected to an intramolecular aldol-like cyclization followed by lactonization using potassium t-butoxide in Me_2SO at room temperature. Work-up of this third step gave the rhoeadane (**4**), m.p. 236–237° (Me_2SO), in 56% yield [ν_{max} ($CHCl_3$) 1740 and 1645 cm^{-1}; n.m.r. ($CDCl_3$),



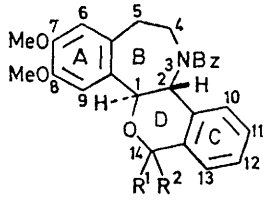
(1)



(2)



(3)



(4) R^1, R^2 = O
(5) R^1 = H, R^2 = OH
(6) R^1 = H, R^2 = OMe

† C,H analyses as well as high resolution mass spectra were obtained for all new compounds. Spectral data (i.r., u.v., n.m.r.) were consistent with the structures assigned.

two rotamers about the amide linkage were present in a ratio of *ca.* 2:1; major isomer δ4·81 (1H, *d*, $J_{1,2}$ 10 Hz, 2-H) and 5·55 (1H, d, $J_{1,2}$ 10 Hz, 1-H); minor isomer δ5·56 (1H, d, $J_{1,2}$ 9 Hz, 2-H), and 5·71 (1H, d, $J_{1,2}$ 9 Hz, 1-H)].

Lactonic rhoeadanes can be reduced to the hemiacetal using sodium bis-(2-methoxyethoxyaluminium) hydride in pyridine,[2a] and addition of this reagent to the lactone (**4**) furnished in essentially quantitative yield the rhoeadane (**5**), m.p. 223° (methanol) [λ_{max} (MeOH) 215, 234, and 284 nm (log ε 4·62, 4·19, and 3·63)].

The corresponding methyl acetal (**6**), m.p. 201° (methanol) was readily obtained by treatment of (**5**) with methyl orthoformate.

The pair of non-bonded electrons at N-3 must be involved in the mechanism of the change from *cis* to *trans* B/D ring fusion in the rhoeadine alkaloids, since no such isomerization was observed in the amidic series.[1]

This work was supported by a NIH grant.

(*Received*, 11*th June* 1973; *Com.* 830.)

[1] For a recent review of the rhoeadine alkaloids see M. Shamma, 'The Isoquinoline Alkaloids,' Academic Press, New York, and Verlag Chemie, Weinheim, 1972, p. 399.

[2] Two synthetic routes to the rhoeadines have recently been described: (a) W. Klötzer, S. Teitel, J. F. Blount, and A. Brossi, *J. Amer. Chem. Soc.*, 1971, **93**, 4321; (b) H. Irie, S. Tani, and H. Yamane, *Chem. Comm.*, 1970, **1713**. Both routes start with alkaloidal compounds and lead to the thermodynamically more stable *cis* B/D series.

[3] The chemistry of pseudo-bases has been reviewed: D. Beke, *Adv. Heterocyclic Chem.*, 1963, **1**, 167.