Synthetic Approach to Rhoeadine-type Alkaloids

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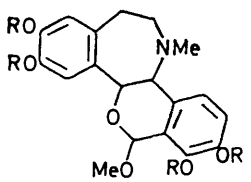
The reaction of 3,4-dihydropapaveraldine [1-(3,4-dimethoxybenzoyl)-3,4-dihydro-6,7-dimethoxyisoquinoline] methiodide (2) with diazomethane gave 5-(3,4-dimethoxybenzoyl)-2,3-dihydro-7,8-dimethoxy-3-methyl-1*H*-3-benzazepine (5), which was converted into 5,6,7,7a-tetrahydro-2,3,9,10-tetramethoxy-7-methylindeno-[2,1-*a*][3]benzazepin-12-ol (3) with hot phosphoryl chloride.

THE rhoeadine (1) type of alkaloid,[1] found only in *Papaveraceae* species, is characterised by structures possessing a benzazepine ring and a six-membered heterocycle containing oxygen in an acetal function. Although many methods for synthesising azepines and benzazepines have been reported,[2] only a few syntheses of the rhoeadine system are available. The first total synthesis of rhoeadine involved an enlargement of the isoquinoline ring in an ochotensine analogue by Wagner–Meerwein rearrangement,[3] and the second the conversion of a phthalide alkaloid into rhoeadine.[4] Recently, Manske and his co-workers reported the novel conversion of a benzindenoazepine into the rhoeadine system.[5] Starting materials for these methods are not easily available, and we have therefore been investigating the synthesis of the rhoeadine system from simple readily available materials.[6] We report here a novel and simple synthesis of the rhoeadine-like compound (3) from 3,4-dihydropapaveraldine methiodide (2).

Previously, we [7] have reported the total synthesis of isopavine-type alkaloids, containing a 3-benzazepine ring, from 3,4-dihydro-2-methyl-3-phenylisoquinolinium



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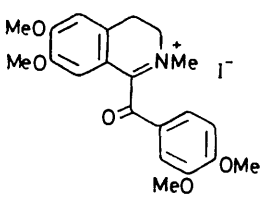

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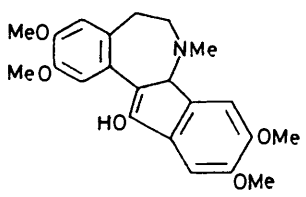
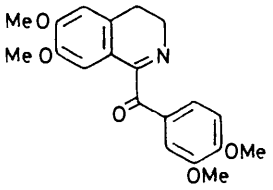


(3)

iodide by a route involving insertion of diazomethane into the imine system. This type of ring expansion [8] has been applied to the present synthesis.

The 3,4-dihydropapaveraldine (4) [9] was treated with methyl iodide to give the methiodide (2), which was methylated with an excess of ethereal diazomethane at 0° in methanol to afford the 3-benzazepine (5) in 82% yield. The structure of this product was confirmed by microanalysis and i.r., n.m.r., and u.v. spectra (see Experimental section). The shift in u.v. spectrum in changing from neutral to acidic medium indicated the presence of a conjugated enamine system,[6] and the n.m.r. spectrum suggested the presence of a veratroyl group at the β-position of the enamine system. Treatment of (5) with 35% hydrochloric acid gave the 3-benzazepine (6) and



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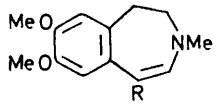

(5) R = 3,4-$(MeO)_2C_6H_3CO$
(6) R = H

veratric acid. Heating the 3-benzazepine (5) with phosphoryl chloride in dry benzene afforded the expected indeno[2,1-*a*][3]benzazepine (3), identified by microanalysis and mass and n.m.r. spectra (Experimental section).

EXPERIMENTAL

N.m.r. spectra were measured with a Hitachi R-20 spectrometer (solutions in deuteriochloroform; tetramethylsilane as internal reference), i.r. spectra with a Hitachi 215 spectrometer, and mass spectra with a Hitachi RMU-7 spectrometer.

*5-(3,4-Dimethoxybenzoyl)-2,3-dihydro-7,8-dimethoxy-3-methyl-*1H*-3-benzazepine* (5).—To a solution of the methiodide (2) (1·5 g) in methanol (100 ml), an excess of ethereal diazomethane was added at 0°. Next day the solvent was evaporated off to leave a syrup, which was dissolved in chloroform. The solution was washed with 10% ammonia and water, dried (Na_2SO_4), and evaporated. The resulting syrup was chromatographed on silica gel (20 g). Elution with chloroform afforded the *dihydrobenzazepine* (5) (900 mg) as yellow prisms, m.p. 95—96° (from chloroform–hexane) (Found: C, 55·25; H, 5·2; N, 3·05. $C_{22}H_{25}NO_5$,-$CHCl_3$ requires C, 55·05; H, 5·2; N, 2·8%), $\nu_{max.}$ ($CHCl_3$) 1635 cm^{-1} (CO), τ ($CDCl_3$) 6·95 (3H, s, N·CH_3), 6·46 (3H, s, O·CH_3), 6·20 (6H, s, 2 × O·CH_3), 6·17 (3H, s, O·CH_3), 3·50

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and 3·38 (1H and 2H, each s, =CH– and 2 × ArH), and 3·35—2·83 (3H, m, 3 × ArH), *m/e* 383 (M^+), $\lambda_{max.}$ (MeOH) 297 and 357 nm, $\lambda_{max.}$ (MeOH–HCl) 286 and 368 nm.

Treatment of the Dihydrobenzazepine (5) *with* 35% *Hydrochloric Acid.*—The dihydrobenzazepine (5) (100 mg) and 35% hydrochloric acid (10 ml) were heated at 100° for 1 h. The mixture was diluted with cold water (30 ml) to give a precipitate (30 mg), which was identical with authentic 3,4-dimethoxybenzoic acid. The diluted solution was basified with 28% ammonia and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to afford 2,3-dihydro-7,8-dimethoxy-3-methyl-1*H*-3-benzazepine (6) as an unstable reddish syrup (40 mg), $\nu_{max.}$ ($CHCl_3$) 1625 cm^{-1} (C=C), τ ($CDCl_3$) 7·19 (3H, s, N·CH_3), 6·20 (6H, s, 2 × O·CH_3), 5·06 (1H, d, *J* 10 Hz, 5-H), and 4·15 (1H, d, *J* 10 Hz, 4-H).

5,6,7,7a-*Tetrahydro*-2,3,9,10-*tetramethoxy*-7-*methylindeno*-[2,1-a][3]*benzazepin*-12-*ol* (3).—A mixture of the dihydrobenzazepine (5) (300 mg), phosphoryl chloride (1·0 g), and dry benzene (80 ml) was refluxed for 30 min, then washed with 10% ammonia and water, dried (Na_2SO_4), and evaporated to afford a syrup. This was chromatographed on silica gel (9 g). Elution with methanol–chloroform (2·5 : 97·5 v/v) gave the *indenobenzazepine* (3) (45 mg) as plates, m.p. 190—191° (from methanol) (Found: C, 57·95; H, 5·4; N, 3·0. $C_{22}H_{25}NO_5$,0·75$CHCl_3$ requires C, 57·85; H, 5·5; N, 2·95%), $\nu_{max.}$ ($CHCl_3$) 2250 cm^{-1} (OH), τ ($CDCl_3$) 7·57 (3H, s, N·CH_3), 5·12 (1H, s, 7a-H), and 3·31, 3·06, 2·74, and 1·79 (4H, each s, 4 × ArH), *m/e* 383 (M^+).

We thank Mrs. A. Satoh, Mrs. C. Koyanagi, Miss A. Ujie, Mrs. H. Hori, Mr. T. Ouchi, Miss R. Kato, Miss C. Satoh, and Miss R. Suenaga for spectral measurements and microanalyses.

[4/1452 *Received*, 16*th July*, 1974]