Convenient Total Synthesis of (*dl*)-Quebrachamine

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Racemic quebrachamine (**1**) has been synthesised from 2-hydroxytryptamine and dimethyl 4-ethyl-4-formylpimelate through 1,2-dehydroaspidospermidine (**8**), obtained by selective reduction of the carbonyl function of lactam **3**.

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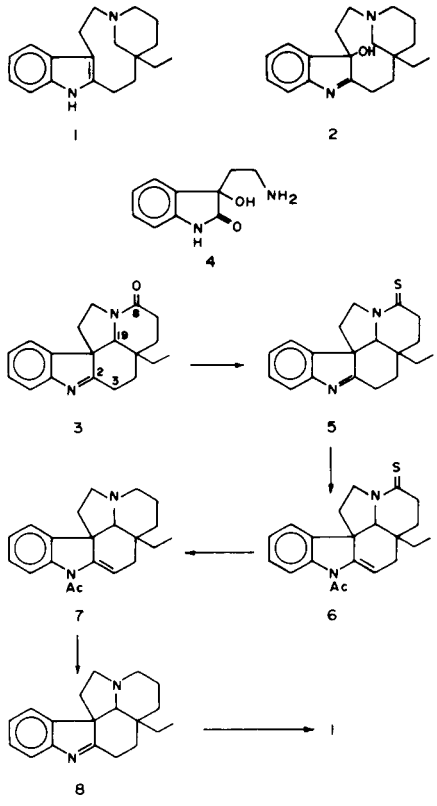
In connection with the pharmacological study of quebrachamine (1) and its oxidation product, rhazidine (2), we required these two physiologically active (3,4) indole alkaloids in sufficient quantities. Though several total syntheses have so far been reported (5) for quebrachamine, none of them appeared to be suitable for its large scale preparation. We, therefore, undertook and accomplished a simpler and more convenient synthesis of (*dl*)-quebrachamine (**1**), and hence of rhazidine (**2**), as described below.

Our method involved the lactam **3**, a key intermediate in the recently reported (6) syntheses of some other *Aspidosperma* alkaloids. The starting materials, 2-hydroxytryptamine (7,8) and dimethyl 4-ethyl-4-formylpimelate (9) were conveniently obtained by direct oxidation of tryptamine with dimethyl sulphoxide/hydrochloric acid (10,11) and one step alkylation of the pyrrolidine enamine of butyraldehyde with methyl acrylate, respectively.



The lactam **3** was smoothly thiolated (12) with phosphorus pentasulphide in acetonitrile in presence of triethylamine to the thiolactam **5**. Attempted desulphurisation of **5** with Raney nickel (13) led to concomitant reduction of the C=N bond. However, acetylation of **5** to **6**, followed by desulphurisation with Raney nickel in tetrahydrofuran afforded 1-acetyl-2,3-dehydroaspidospermidine (**7**).

Hydrolysis of **7** with 6*N* hydrochloric acid under reflux yielded 1,2-dehydroaspidospermidine (**8**), which on reduction by refluxing with potassium borohydride (1) in 1% methanolic potassium hydroxide yielded (*dl*)-quebrachamine (**1**).

The ir (in chloroform), uv and mass spectra of the synthetic quebrachamine (**1**) were superimposable with those of an authentic specimen of natural (*l*)-quebrachamine (14). Since the conversion of quebrachamine to rhazidine by peracid oxidation is known (15), this constitutes a formal synthesis of rhazidine also.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with a Perkin Elmer Model 177 spectrophotometer, uv spectra on a Carl Zeiss Jena Specord spectrophotometer, nmr spectra with Varian EM-390 and Varian A60D spectrometers, and mass spectrs (80 eV) with a Hitachi Model RMU-6L spectrometer.

Materials.

2-Hydroxytryptamine monohydrochloride, m.p. 250-251°, [lit. (8) m.p. 244-246°] was prepared using the method of Savige and Fontana (10); dimethyl 4-ethyl-4-formylpimelate, b.p. 135-137° (0.2 mm) [lit. (9) b.p. 108-109° (0.03 mm)] was prepared as described by Kuehne (9); and 1,2-dehydro-8-oxoaspidospermidine was prepared as described by Le Men, *et al.* (6).

1,2-Dehydro-8-thioaspidospermidine (**5**).

Phosphorus pentasulphide (12.4 g., 0.054 mole) was added to a stirred solution of 1,2-dehydro-8-oxoaspidospermidine (7 g., 0.023 mole) in acetonitrile (75 ml.) under dry nitrogen atmosphere. The reaction mixture was cooled and triethylamine (14.6 ml., 0.116 mole) added to it in portions with stirring. It was then left overnight at ambient temperature. The reaction mixture was cooled and water (25 ml.) added to it with stirring. The mixture was diluted with dichloromethane (150 ml.), washed with sodium bicarbonate solution, dried (sodium sulphate) and the sol-

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vent evaporated under reduced pressure. The residue on crystallisation from methanol-petroleum ether (b.p. 60-80°) afforded **5** (5.1 g., 73%) as colourless needles, m.p. 198-200°; ir (potassium bromide): 1580 (C=N), 755 cm^{-1}; uv (ethanol): λ max nm (log ε) 223 (4.23), 274 (4.30); ms: m/e 310 (M^+), 277, 223, 219, 201, 186, 169, 85.

Anal. Calcd. for $C_{19}H_{22}N_2S$: C, 73.51; H, 7.14; N, 9.03. Found: C, 73.60; H, 7.37; N, 9.35.

1-Acetyl-2,3-dehydro-8-thioaspidospermidine (**6**).

A solution of **5** (2 g., 6.45 mmoles) in pyridine (1.2 ml.) and acetic anhydride (0.8 ml.) was heated on a steam bath for 4 hours. The reaction mixture was evaporated under reduced pressure to remove the excess reagents and the residue was crystallized from ether to afford **6** (1.8 g., 80%) as colourless needles, m.p. 91-92°; ir (nujol): 1660 (C=O), 1600, 760 cm^{-1}; uv (ethanol): λ max nm (log ε) 223 (4.19), 272 (4.37); nmr (deuteriochloroform): δ 8.05 (m, 1H, 17-*H*), 7.1-7.25 (m, 3H, Ar-*H*), 5.79 (dd, 1H, J = 4, 7 Hz, 3-*H*), 2.50 (s, 3H, $COCH_3$), 0.87 (m, 3H, CH_2CH_3); ms: m/e 352 (M^+), 319, 211, 180, 169, 114, 43.

Anal. Calcd. for $C_{21}H_{24}N_2OS$: C, 71.56; H, 6.86; N, 7.95. Found: C, 71.38; H, 6.85; N, 8.27.

1-Acetyl-2,3-dehydroaspidospermidine (**7**).

A solution of **6** (1 g., 2.84 mmoles) in tetrahydrofuran (50 ml.) was refluxed for 2 hours with Raney nickel (prewashed with distilled water and tetrahydrofuran, 5 g.). The reaction mixture was filtered and the solvent evaporated under reduced pressure. The residue on crystallisation from petroleum ether (b.p. 60-80°) yielded **7** (0.64 g., 70%) as colourless needles, m.p. 121-122°; ir (nujol): 2775, 2720 (Bohlmann's absorptions), 1660, 1600, 745 cm^{-1}; uv (ethanol): λ max nm (log ε) 223 (3.92), 265 (4.01), 280 sh (3.68); nmr (deuteriochloroform): δ 8.13 (m, 1H, 17-*H*), 7.05-7.30 (m, 3H, Ar-*H*), 5.50 (dd, 1H, J = 4, 7 Hz, 3-*H*), 2.40 (s, 3H, $COCH_3$), 0.62 (m, 3H, CH_2CH_3); ms: m/e 322 (M^+), 219, 141, 125, 124, 57, 43.

Anal. Calcd. for $C_{21}H_{26}N_2O$: C, 78.22; H, 8.13; N, 8.69. Found: C, 78.13; H, 8.40; N, 8.36.

1,2-Dehydroaspidospermidine (**8**).

1-Acetyl-2,3-dehydroaspidospermidine (0.5 g., 1.55 mmoles) in 6*N* hydrochloric acid (25 ml.) was refluxed for 3 hours under nitrogen atmosphere. The reaction mixture was cooled, neutralised with ammonia solution, extracted with dichloromethane, dried (sodium sulphate) and the solvent evaporated under reduced pressure to afford **8** (0.36 g., 85%) as colourless glass homogeneous by tlc; ir (film): 2780, 2720 (Bohlmann's absorptions), 1580, 760 cm^{-1}; uv (ethanol): λ max nm 223, 269; ms: m/e 280 (M^+), 251, 223, 219, 125.

(±)-Quebrachamine (**1**).

A solution of 1,2-dehydroaspidospermidine (0.3 g., 1.07 mmoles) in 1% methanolic potassium hydroxide (50 ml.) and potassium borohydride (0.22 g., 4.10 mmoles) were heated under reflux for 2 hours. The solvent was removed under reduced pressure and the residue was extracted with dichloromethane. The organic layer was washed, dried (sodium sulphate) and the solvent evaporated. Crystallisation of the residue from methanol afforded (±)-quebrachamine (0.164 g., 60%) as colourless needles, m.p. 113-114°, ir (potassium chloride): 3360 (NH), 2780, 2720 (Bohlmann's absorptions), 750 cm^{-1}; uv (ethanol): λ max nm (log ε) 229 (4.11), 290 (3.29); nmr (deuteriochloroform): δ 7.66 (br, 1H, N*H*), 7.0-7.55 (m, 4H, Ar-*H*), 0.80 (m, 3H, CH_2CH_3); ms: m/e 282 (M^+), 253, 157, 138, 125, 110, 96, 70, 58.

Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.65; H, 9.12; N, 9.71.

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(11) Extractive work up of DMSO/hydrochloric acid reaction product led to formation of considerable amount of the so called "dioxindole" (7), **4** [m.p. 258-259°; ms: M^+ m/e 192; ir (nujol): 3300-3100, 1715, 1610 and 760 cm^{-1}; uv (ethanol): λ max nm (log ε) 250 (4.6)]. However, 2-hydroxytryptamine hydrochloride could be precipitated directly from the reaction mixture by addition of excess methylene chloride or diethyl ether and used as such for the next step.

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