A New Route to the Pavine (5,6,11,12-Tetrahydro-5,11-imino-13-methyldibenzo[*a,e*]cyclo-octene) Skeleton: Synthesis of (±)-Argemonine

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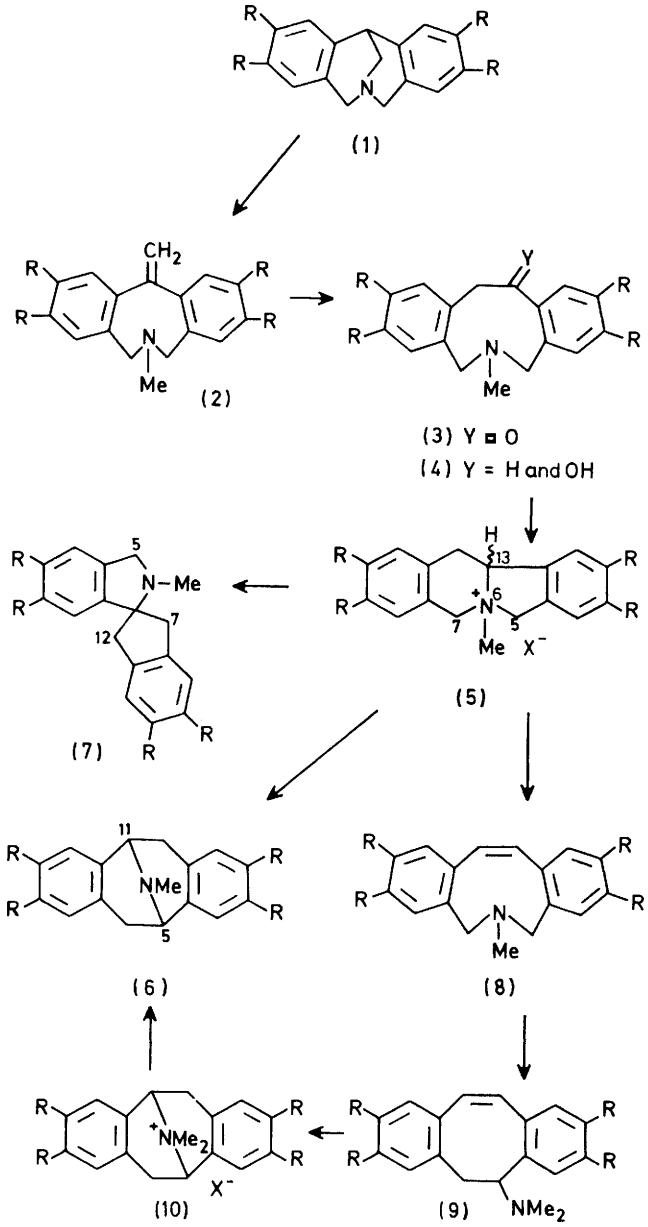
A new route to the pavine skeleton was investigated starting from the readily accessible tetrahydro-6,12-methanodibenz[*c,f*]azocine (**1**, R = H or Me); an efficient synthesis of a typical pavine alkaloid (±)-argemonine (**6**, R = OMe) from (**1**, R = OMe) was accomplished in 53% overall yield.

A number of natural isopavine and pavine alkaloids[1] possess a 10,11-dihydro-5*H*-dibenzo[*a,d*]cycloheptene or 5,6,11,12-tetrahydrodibenzo[*a,e*]cyclo-octene ring system. Recently, we have developed a facile synthesis of tetrahydro-6,12-methano-



dibenz[*c*,*f*]azocines optionally substituted at suitable positions[2] and have successfully transformed them to the isopavine skeleton [10,11-dihydro-10,5-(iminomethano)-5*H*-dibenzo-[*a*,*d*]cycloheptene] by Stevens rearrangement.[3] Most of the syntheses of pavine alkaloids so far reported have involved the acid-catalysed cyclization of *N*-methyl-1-benzyl-1,2-dihydroisoquinolines oxygenated at appropriate positions on aromatic rings.[4]† We now report a convenient and efficient synthesis of pavine alkaloids which could be useful in the study of the pharmacological activity‡ of pavine compounds.

† Conversion of tetrahydroberberine into the pavine alkaloid *O*,*O*-dimethylmunitagine has been reported; K. Ito, H. Furukawa T. Iida, K-H Lee, and T. O. Soine, *J. Chem. Soc., Chem. Commun.* 1974, 1037.

‡ Some isopavine and pavine compounds having appropriate substituents on aromatic rings displayed pharmacological activities (unpublished results).

Hofmann elimination of the methiodide [m.p. 234—238 °C (decomp.)] of the tetrahydro-6,12-methanodibenzazocine (**1**),[5] prepared by the acid-catalysed double-cyclization of *N*,*N*-bis(3,4-dimethoxybenzyl)aminoacetaldehyde dimethyl acetal, with Bu^{t}OK in hot Bu^{t}OH gave the exo-methylene compound (**2**) [83% yield; *m/z* 355 (M^+); ^{1}H n.m.r. δ($CDCl_3$) 5.42 (2H, s, C=CH_2)] as the sole product. Ring expansion reactions of (**2**) with thallium salts[6] under various conditions were investigated. Using thallium perchlorate in methanol in the presence of perchloric acid to protect the lone pair of electrons on the basic nitrogen, (**2**) was converted into the key intermediate ketone (**3**) [*m/z* 371 (M^+), ν($CHCl_3$) 1608 cm^{-1} (C=O)] in 87% yield. Hydride reduction [$LiAlH_4$ in tetrahydrofuran (THF)] of (**3**) afforded the corresponding alcohol (**4**) (m.p. 179—180 °C) [overall yield of (**4**) from (**1**); 75%]. Transannular reaction of (**4**) with refluxing acetic acid–acetic anhydride provided, quantitatively, the tetracyclic quaternary salt (**5**, X = OAc) (*cis*:*trans* ratio of 6-*Me* and 13-*H* was 6:1). On treatment of (**5**, X = Cl) with Bu^{n}Li in dioxan containing hexamethylphosphoramide followed by silica gel chromatographic separation, (±)-argemonine (**6**) (yield 13%; m.p. 140—141 °C)[7] and the spiro-indoline derivative (**7**) (yield, 24%; m.p. 167—168 °C) were isolated.§ The structures of (**6**) and (**7**) were established on the basis of their spectroscopic data.¶ The reactions described above were efficient except for the last step which was less satisfactory than expected [overall yield of (**6**) from (**1**); 10%]. Therefore an alternative route was examined. When the quaternary salt (**5**, X = ClO_4) was allowed to react with Bu^{t}OK in refluxing Bu^{t}OH, Hofmann elimination proceeded smoothly to give (**8**) (yield, 91%; m.p. 138—139 °C). Conversion of the methiodide of (**8**) [m.p. 253—257 °C (decomp.)] into the dimethylamino-derivative (**9**) [*m/z* 369 (M^+); ^{1}H n.m.r. δ ($CDCl_3$) 2.92 (1H, dd, *J* 12.0 and 6.0 Hz), 3.39 (1H, t, *J* 12.0 Hz), and 3.97 (1H, dd, *J* 12.0 and 6.0 Hz)] was accomplished in 97% yield by refluxing with Bu^{t}OK in dioxan. Several intramolecular rections of the amino-group with the olefinic double bond of (**9**) were investigated. The conversion of (**9**) into (**6**) by heating in acetic acid followed by demethylation of the resulting quaternary acetate (**10**, X = OAc) with triethylenediamine (TEDA)[8] was not very much more successful.** However, on employing the internal dimethylaminomercuration–demercuration procedure[9] [Hg(OAc)$_2$ in THF at room temp. for 7 days; $NaBH_4$] followed by demethylation with TEDA (in *N*,*N*-dimethylformamide for 3 h), (**9**) was transformed into (±)-argemonine in 51% yield [as 35% of (**9**) was cleanly recovered, the yield of (**6**) was 81% based on the consumed (**9**)] [overall yield of (**6**) from (**1**) was 53%]. The melting point and ^{1}H n.m.r. spectrum of (±)-

§ The formation of (**6**) and (**7**) can be explained by Stevens rearrangement. Proton abstraction at C(7) and subsequent C(5)-migration from N onto the C(7)-carbanion gives (**6**), whereas proton abstraction at C(13) followed by C(7)-migration from N onto the C(13)-carbanion affords (**7**).

¶ (**6**): *m/z* 355 (M^+); ^{1}H n.m.r. ($CDCl_3$) δ 2.53 (3H, s), 2.64 (2H, d, *J* 16.0 Hz), 3.42 (2H, dd, *J* 16.0 and 6.0 Hz), 3.77 (6H, s), 3.84 (6H, s), and 4.02 (2H, d, *J* 6.0 Hz). (**7**): *m/z* 355 (M^+); ^{1}H n.m.r. ($CDCl_3$) δ 2.40 (3H, s), 2.94 (2H, d, *J* 17.0 Hz), 3.34 (2H, d, *J* 17.0 Hz), 3.72, 3.84, 3.85, and 3.87 (each 3H, s), and 3.93 (2H, s); ^{13}C n.m.r. ($CDCl_3$) δ 34.73 (q, N–Me), 40.64 (t, C-7 and C-12), 55.99 (q, O-Me), 58.44 (t, C-5), and 76.41 p.p.m. (s, spiro-C).

** On heating in acetic acid in a sealed tube at 180 °C for 5 h and subsequent treatment with TEDA in *N*,*N*-dimethylformamide, (**9**, R = H) was transformed *via* (**10**; R = H, X = OAc) into (**6**, R = H) in 62% overall yield. (**9**, R = H) was synthesized from (**1**, R = H) *via* the same route as that of (**9**, R = OMe); (R = H) (**1**) → (**2**) (90%) → (**3**) (88%) → (**4**) (100%) → (**5**, X = OAc) (100%) → (**8**) (80%) → (**9**) (91%) → (**10**, X = OAc) (83%) → (**6**) (75%); overall yield of (**6**, R = H) from (**1**, R = H) was 36%.

argemonine thus synthesised were identical with those reported.[7]

Received, 29th June 1982; *Com. 754*

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