Stereocontrolled Synthesis of theStereoisomers of Perhydropyrido[2,1,6-*de*]-quinolizine: Parent Ring System of the Coccinellid Alkaloids

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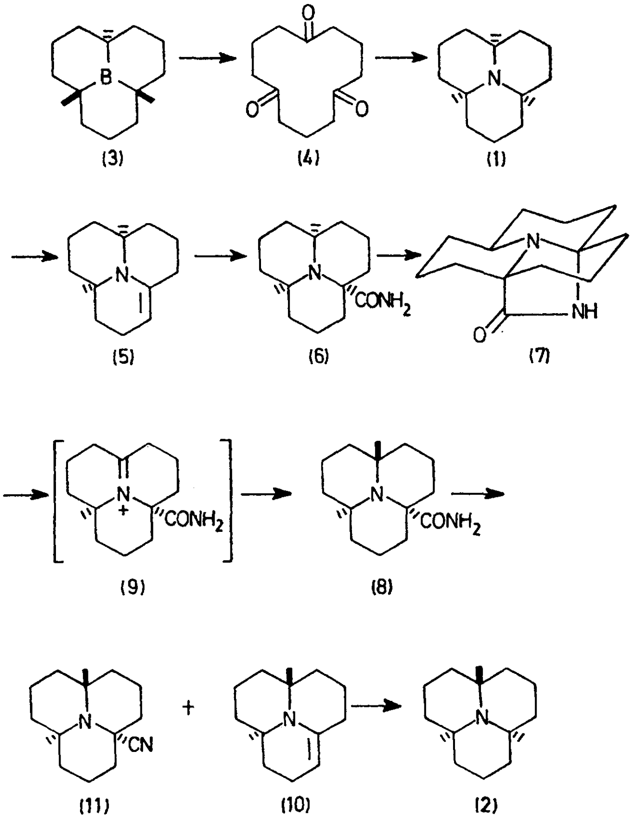
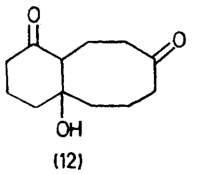
Summary The two possible perhydropyrido[2,1,6-*de*]quinolizine stereoisomers were prepared in a stereocontrolled fashion starting from perhydroboraphenalene.

Recently substituted derivatives of perhydropyrido-[2,1,6-*de*]quinolizine (perhydro-9b-azaphenalene) were found in nature for the first time, occurring in various species of *Coccinellidae*[1] (the ladybugs) and in the Australian plant *Poranthera Corymbosa*.[2] We report the stereocontrolled syntheses of the two possible stereoisomers (**1**) and (**2**) of this ring system. Previous syntheses (with two exceptions[3]) gave the fully unsaturated ring system.[4]

The readily available perhydroboraphenalene (**3**)[5] was oxidized (0·05 equiv. RuO_4, 6 equiv. $NaIO_4$, 0·5 equiv. NaOAc)[6] in aqueous acetone to afford the sensitive† triketone (**4**),‡ m.p. 90—91·5 °C, in 44% isolated yield after crystallization from diethyl ether.[7] Reductive amination (H_2, Pd–C, NH_3, $\mathrm{Pr^{i}OH}$, HOAc)[8] of (**4**) gave the saturated amine (**1**)‡ (picrate:‡ m.p. 191—193 °C) (83%). Compelling evidence for the stereochemistry and threefold symmetry of (**1**) were the Bohlman bands[9] in the i.r. spectrum and the presence of only three absorptions in the proton-decoupled ^{13}C n.m.r. spectrum.

The transformation of the amine (**1**) into the stereoisomer (**2**) required the inversion of stereochemistry at one of the carbon atoms adjacent to the central nitrogen atom. The amine (**1**) was oxidized [$Hg(OAc)_2$, Na_2EDTA; basic workup][10] in aqueous acetic acid to afford the known[3] enamine (**5**) (picrate: m.p.[3] 127—129 °C) in 83% yield after bulb-to-bulb distillation. Reduction of (**5**) under Clemmenson conditions (Zn–Hg, HOAc, aq. HCl) proceeded non-specifically[11] to give a mixture of the saturated amines (**1**) and (**2**), and so a more selective method was sought for the pieparation of (**2**). Conversion of (**5**) into the known[3] aminonitrile (NaCN, HCl, H_2O) followed by hydration (fuming H_2SO_4) gave the aminoamide (**6**), m.p. 195—198 °C (75%). The amide (**6**)‡ was oxidized [as for (**1**)][10] to the lactam (**7**),‡ m.p. 146·5—147 °C (71%), which was then reduced (H_2, Pt–C, EtOH, HOAc) with > 99% stereoselectivity to the amide (**8**),‡ m.p. 155—157 °C (90%), presumably *via* the immonium compound (**9**). The amide group of (**8**) served two functions: to cause reduction from the desired direction[12] and to mask an eventual double bond during the reduction. The amide (**8**) was dehydrated ($POCl_3$, EtOH-free $CHCl_3$) to afford a mixture of the enamine (**10**) and the aminonitrile (**11**). The air-sensitive enamine (**10**)‡ was purified by column chromatography (silica gel, 1% conc. NH_4OH in ether) followed by bulb-to-bulb distillation; the isolated yield was 20% (not optimized). Reduction of (**10**) ($NaBH_3CN$, HCl, THF–MeOH, pH 4·5)[13] gave the amine (**2**) in high yield.§ The proton-decoupled ^{13}C n.m.r. spectrum (7 absorptions) and the absence of Bohlman bands[9] in the i.r. spectrum provided strong





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† Mild acid or base caused intramolecular aldol condensation to form (**12**),‡ m.p. 187—189 °C.

‡ All new compounds gave satisfactory combustion analyses (±0·1%) and spectral data (i.r., ^{1}H n.m.r.).

§ Preliminary work indicates (**11**) can also be reduced under these conditions, thus significantly improving the yield of (**2**).

evidence for the stereochemistry and twofold symmetry of (**2**).

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[1] (a) B. Tursch, D. Daloze, and C. Hootele, *Chimia (Switz.)* 1972, **26**, 74. Structures I and II in this article appear to be indicated incorrectly [*cf.* refs. 1(b) and 1(c)]; (b) R. Karlsson and D. Losman, *J.C.S. Chem. Comm.*, 1972, 626; (c) B. Tursch, D. Daloze, J. M. Pasteels, A. Cravador, J. C. Braekman, C. Hootele, and D. Zimmermann, *Bull. Soc. chim. Belges*, 1972, **81**, 649; (d) B. Tursch, D. Daloze, J. C. Braekman, C. Hootele, A. Cravador, D. Losman, and R. Karlsson, *Tetrahedron Letters*, 1974, 409.

[2] W. A. Denne, S. R. Johns, J. A. Lamberton, A. McL. Mathieson, and H. Suares, *Tetrahedron Letters*, 1972, 1767; W. A. Denne and A. McL. Mathieson, *J. Cryst. Mol. Struct.*, 1973, **3**, 139; see W. A. Denne, S. R. Johns, J. A. Lamberton, and A. McL. Mathieson, *Tetrahedron Letters*, 1971, 3107; 1973, 794 for a somewhat more complex system containing the pyridoquinolizine skeleton.

[3] I. Murakoshi, A. Kubo, J. Saito, and J. Haginiwa, *Chem. Pharm. Bull. (Japan)*, 1964, **12**, 747 have described the preparation of (**5**) by an entirely different route. E. J. Corey and R. D. Balanson, *J. Amer. Chem. Soc.*, 1974, **96**, 6516 have synthesized porantherine, an alkaloid containing the pyridoquinolizine skeleton as part of a more complex system.

[4] D. Farquhar and D. Leaver, *Chem. Comm.*, 1969, 24 and refs. therein.

[5] G. W. Rotermund and R. Koster, *Annalen*, 1965, **686**, 153; see also H. C. Brown and E. Negishi, *J. Amer. Chem. Soc.*, 1967, **89**, 5478 and H. C. Brown and W. C. Dickason, *ibid.*, 1969, **91**, 1226.

[6] Review: D. G. Lee and M. van den Engh in 'Oxidation in Organic Chemistry,' Part B, ed., W. S. Trahanovsky, Academic Press, New York, 1973, pp. 197—225.

[7] Oxidation of (**3**) or of the corresponding triol with Cr^{VI} under a variety of conditions was invariably incomplete (*cf.* S. Fujita and H. Nozaki, *Bull. Chem. Soc. Japan*, 1970, **43**, 2995).

[8] W. S. Emerson, *Organic Reactions*, 1948, **4**, 174.

[9] F. Bohlmann, *Angew. Chem.*, 1957, **69**, 641; T. A. Crabb, R. F. Newton, and D. Jackson, *Chem. Rev.*, 1971, **71**, 109.

[10] N. J. Leonard A. S. Hay, R. W. Fulmer, and V. W. Gash, *J. Amer. Chem. Soc.*, 1955, **77**, 439; J. Knabe and H. Roloff, *Chem. Ber.*, 1964, **97**, 3452 and earlier papers in this series.

[11] Some other systems give opposite stereochemical results with catalytic hydrogenation and zinc metal reduction: F. L. Weisenborn and P. A. Diassi, *J. Amer. Chem. Soc.*, 1956, **78**, 2022; R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *ibid.*, p. 2023.

[12] *Cf.* H. W. Thompson and R. E. Naipawer, *J. Amer. Chem. Soc.*, 1973, **95**, 6379.

[13] R. F. Borch, M. D. Bernstein, and H. DuPont Durst, *J. Amer. Chem. Soc.*, 1971, **93**, 2897.