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SYNTHESIS OF THE LADYBUG DEFENSIVE AGENTS (±)-HIPPODAMINE, (±)-CONVERGINE, (±)-HIPPOCASINE AND (±)-HIPPOCASINE OXIDE

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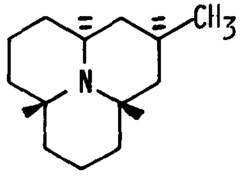
Summary: The total syntheses of the ladybug defensive agents (±)-hippodamine, (±)-convergine, (±)-hippocasine, and (±)-hippocasine oxide are described starting from perhydroboraphenalene.

A number of tricyclic alkaloids have been isolated from various ladybug species.[1] Among these compounds are hippodamine (1) and its hydrated N-oxide convergine (2), present in *Hippodamia convergens*,[2] *Anisosticta 19-punctata*,[3] and *H. caseyi*.[4] Also occurring in *H. caseyi* are hippocasine (3) and hippocasine N-oxide (4).[4] These compounds apparently serve the insects as defensive agents, protecting the beetles from consumption by potential predators such as ants and quail.[3] Ayer has reported the synthesis of (±)-1 and (±)-2 starting from collidine.[5] We report an alternative synthesis of (±)-1 and (±)-2 and the first synthesis of (±)-3 and (±)-4 starting from the readily available perhydroboraphenalene 5.[6]



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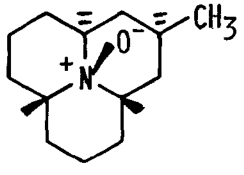

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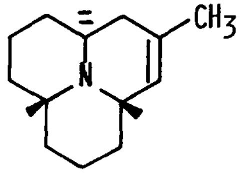

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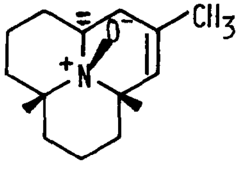

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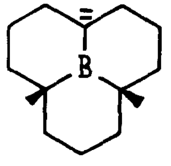

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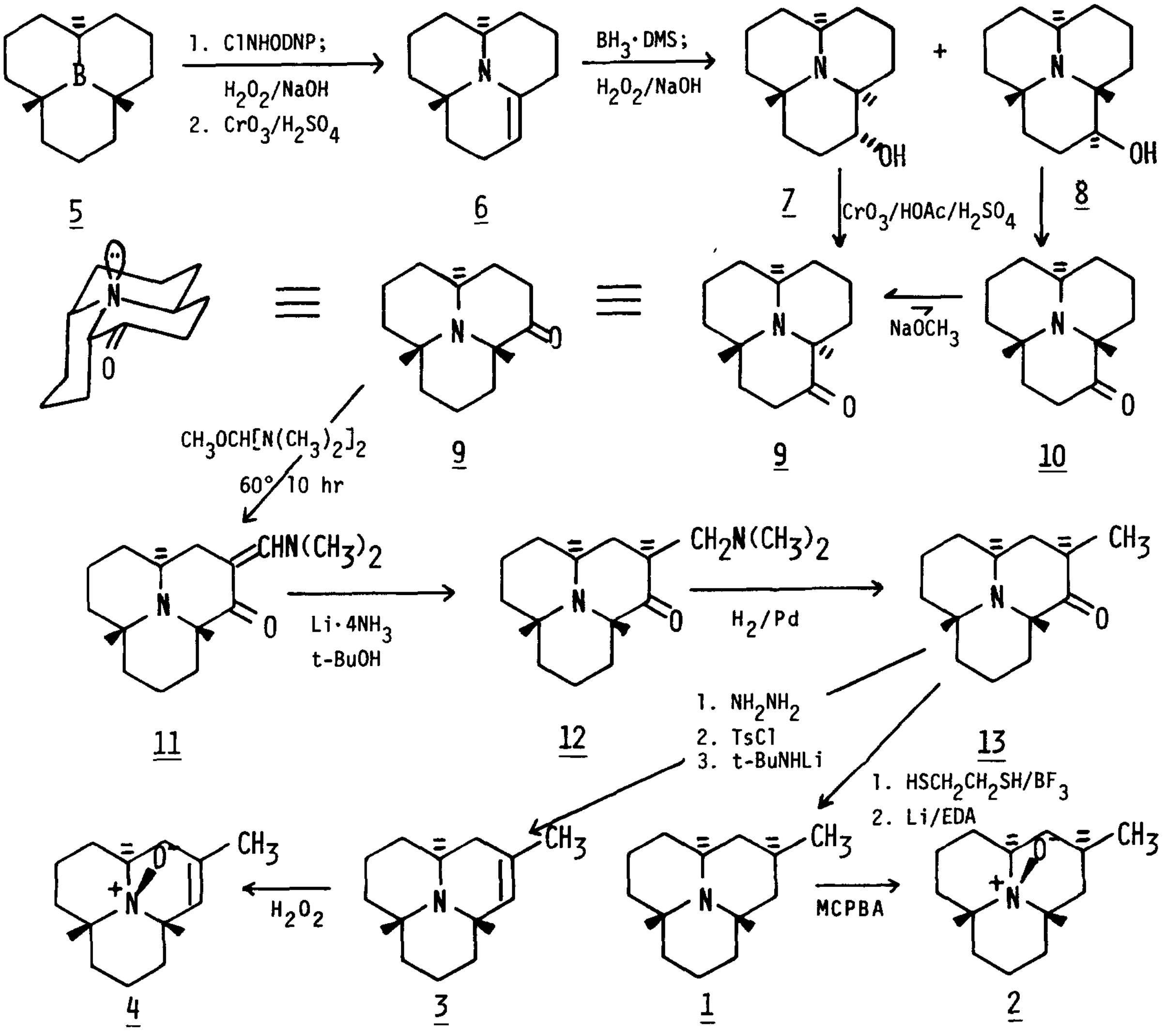
Hydroboration-oxidation of the *trans*-enamine 6, prepared stereoselectively in two steps as described previously[7] from perhydroboraphenalene 5,[6] gave in 95% yield a 3:1 mixture of the alcohols 7,[8] mp 66.5-67.5°, and 8,[8] mp 178-178.5°, respectively. The alcohols were separated by continuous extractive steam distillation[9] (the axial hydroxyl group of 7 is intramolecularly hydrogen-bonded to the nitrogen lone pair; the hydroxyl group in 8 is equatorial) followed by crystallization (pure 7 was obtained in 52% yield). Oxidation of 7 gave the corresponding ketone 9[8] (76% yield) without epimerization *alpha* to the nitrogen atom. Alternatively, the mixture of alcohols could be oxidized to a mixture of ketones 9 and 10 (72% yield), which on treatment with mild base gave the thermodynamic 9:1 mixture of ketones,[10] 9 predominating, presumably due to destabilization of 10 by a steric interaction between the carbonyl oxygen atom and an axial hydrogen atom.[11]

With ketone 9 in hand, completion of the synthesis of hippodamine (1) required the stereo- and regiospecific introduction of a methyl group *alpha* to the carbonyl group followed by the reductive removal of the carbonyl group. Treatment of 9 with lithium diisopropylamide followed by acetic anhydride produced the enol acetate derived from deprotonation in the desired direction;[12] however, addition of methyl iodide to the enolate resulted in N-alkylation. Apparently, C-alkylation was sufficiently slow (axial alkylation of the enolate to give a chair product directly must occur from the hindered, bottom face of the molecule; axial alkylation from the unhindered top face would give a boat conformation as the immediate product) that N-alkylation occurred preferentially. A more indirect method was required for introduction of the methyl group. Treatment of 9 with the Bredereck reagent[13] resulted in formation of the vinylogous amide 11,[8] (mp 97-99°, 85% yield) which was reduced to the unstable *beta*-aminoketone 12 using lithium bronze.[14] Catalytic hydrogenation of 12 gave the methyl ketone 13 (75% yield from 11, mp picrate[8] 181-183° dec), the methyl group in the desired more stable equatorial position (epimerization of the presumably kinetically preferred axial product occurring under the hydrogenation conditions). Wolff-Kischner reduction of 13 gave a 2:1 mixture of hippodamine and its axial methyl isomer (significant epimerization occurred during hydrazone formation). However, reduction of the derived thioketal[8] with lithium in ethylenediamine[15] (H_2/RaNi was slow and incomplete) gave (±)-hippodamine (1)[8] cleanly, (67% yield from 13, mp picrate[8] 149-150°) identified by comparison of MS, IR, and PMR spectra with those of authentic material. Reaction of 1 with peracid gave the hydrated form of the N-oxide of 1, (±)-convergine (2). Both 2 and its hydrochloride salt (chars >210° without melting) were identified by comparison of IR and PMR spectra with those of natural material.

Conversion of ketone 13 to hippocasine (3) was accomplished by Bamford-Stevens[16] reaction of the derived tosylhydrazone 14 with lithium *tert*-butylamide.[17] That reaction occurred exclusively in the desired direction to give (±)-hippocasine (3), (40% yield from 13, mp picrate[8] 137.5-139°) presumably is due to the selective removal of the axial, although hindered, proton *alpha* to the methyl group rather than the less hindered, but equatorial, proton *alpha* to the nitrogen atom. Treatment of 3 with methanolic hydrogen peroxide gave 4, (±)-hippocasine oxide. Comparison of IR and PMR spectra of 3, 4, and the hydrochloride of 4 (chars >210° without melting) with those of natural material confirmed their identity.



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References and Footnotes

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8. (a) Satisfactory spectral data (IR, PMR, MS) were obtained for this compound; (b) C,H,N combustion analysis was within 0.3%; (c) melting points are corrected.
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10. When the mixture of alcohols 7 and 8 was oxidized directly, the resulting mixture of ketones was treated with the Bredereck reagent. Crystallization of the mixture of vinylogous amides gave pure 11.
11. Examination of Dreiding models indicates these atoms are closer than the sum of their Van der Waals radii. This could be considered a 2-alkyl ketone effect (N. L. Allinger and H. M. Blatter, J. Am. Chem. Soc., 83, 994 (1961)), although the magnitude of the effect is difficult to judge due to the rigid nature of 9; it presumably lies somewhere in between that for 2-ethylcyclohexanone (0.7 kcal) and 2-isopropylcyclohexanone (1.7 kcal). Stabilization of 9 by a homoconjugative interaction of the nitrogen lone pair with the pi-orbital of the carbonyl group might also be a contributory factor.
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