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SYNTHESIS OF THE LADYBUG ALKALOIDS (±)-PROPYLEINE AND (±)-ISOPROPYLEINE. MODIFICATION OF THE PUBLISHED STRUCTURE OF PROPYLEINE

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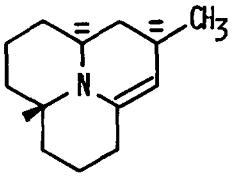
Summary: The total syntheses of the ladybug alkaloids (±)-propyleine and (±)-isopropyleine are described. Evidence that the alkaloid propyleine is actually a rapidly interconverting mixture of propyleine and a previously unknown isomer isopropyleine is presented.

Propyleine (1), isolated from the ladybug Propylaea quattuordecimpunctata, was assigned the depicted enamine structure on the basis of chemical and spectroscopic evidence.[1] Given the method of isolation (acid-base extraction), we found it somewhat curious that the regioisomer 2 (we propose the name isopropyleine) was not reported, as deprotonation of the immonium salt 3 (presumably formed during the isolation procedure) would be expected to give a mixture of 1 and 2. However, since enamines undergo kinetic N-protonation,[2] it was remotely conceivable that the N-protonated species was kinetically stable towards formation of the normally thermodynamically favored C-protonated species because of poor overlap between the nitrogen lone pair and the pi-orbital of the double bond. We report the synthesis of (±)-1 and (±)-2 (as a mixture) and evidence that the alkaloid isolated from P. 14-punctata is actually a rapidly[3] interconverting mixture of 1 and 2 with the previously unknown 2 as the major (75%) component.



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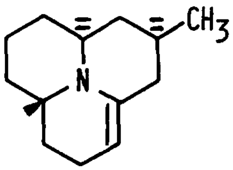

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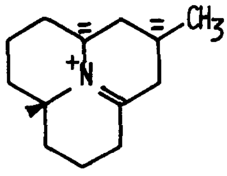

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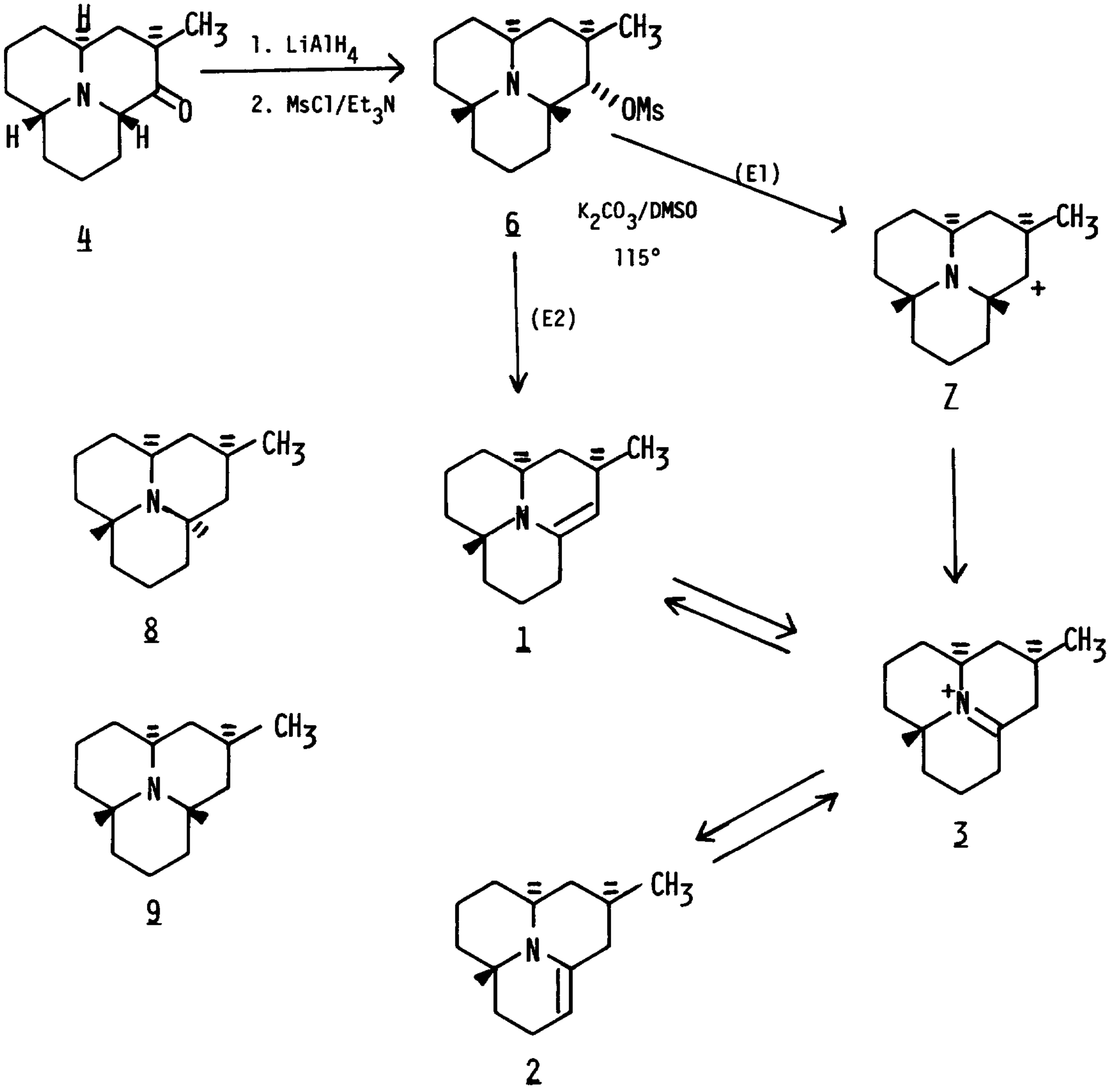
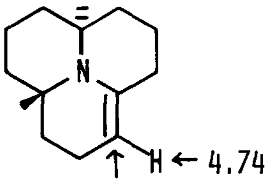
Our synthesis proceeds from the methyl ketone 4, prepared and utilized in the preceding communication.[4] Reduction to the alcohol 5,[5] mp 172-172.5°, followed by treatment with methanesulfonyl chloride in the presence of triethylamine gave the mesylate 6,[5] mp 138-140° (90% from 4). Treatment of either 6 or the corresponding benzenesulfonate under E2 conditions (*t*-BuOK, DMSO, 50°) gave primarily the cleavage product, alcohol 5 (*anti* elimination would have to proceed via a boat conformation). However, under what are presumably E1 conditions (K_2CO_3, DMSO, 115°) elimination occurred to give a mixture of two enamines (±)-1 and (±)-2 (76% yield, picrate[5] mp 141-143°) in the ratio of 1:3, as evidenced by the presence of two methyl doublets and two olefinic singlets in the 270 MHz PMR spectrum. The IR and 60 MHz PMR spectra of the synthetic and natural material were virtually identical, establishing that the isolated natural material actually was a mixture of two compounds. At 270 MHz, the minor isomer showed absorptions at δ4.60 and 0.97 ppm, the major isomer at δ4.75 and 0.90 ppm. Treatment of our synthetic mixture with trifluoroacetic acid in $CDCl_3$ in an NMR tube resulted in the disappearance of the downfield olefinic protons and collapse of the two methyl doublets into a single doublet, indicating formation of the same immonium salt 3 from the two regioisomeric enamines 1 and 2. Also, the CMR indicated two pairs of olefinic carbon atoms, the major pair at δ147.1 and 103.9 ppm, the minor at δ147.0 and 111.4 ppm. Again, treatment with TFA in an NMR tube resulted in collapse of the four olefinic carbon absorptions into a single downfield immonium carbon resonance at δ186.9 ppm; also, a number of weak absorptions in the upfield region disappeared to give a clean eleven line pattern (two absorptions apparently overlapping), again indicating formation of the same immonium salt 3.

If the elimination mechanism were E2, then 1 must have been the immediate product and 2 formed subsequently by rapid equilibration via 3. On the other hand, an E1 process could have generated 3 directly by a 1,2-hydride shift in 7; thus a mixture of 1 and 2 would necessarily have been obtained, even if 1 and 2 were not rapidly interconverting. In order to establish whether or not 1 and 2 in fact were in equilibrium, a solution of the mixture of 1 and 2 in d_4-methanol was examined by PMR. Disappearance of the two olefinic absorptions was complete well within five minutes, demonstrating the rapid (on the laboratory time scale) interconversion of 1 and 2 in protic media via the immonium salt 3.

The question now arises as to which isomer, 1 or 2, is the major component of the 1:3 equilibrium mixture. In the original structural assignment,[1] catalytic hydrogenation of natural material was found to give precoccinellin (8), the product expected from *cis* addition of hydrogen



to the less hindered face of 1. Hydrogenation of 2 from the less hindered face would have been expected to give hippodamine (9). We repeated the hydrogenation using our synthetic mixture and obtained both precoccinellin and hippodamine, 2:1 respectively. However, if the actual intermediate undergoing reduction is the reactive immonium salt 3, as seems very likely, then the product distribution does not in any way reflect the original enamine regioisomer distribution between 1 and 2. Spectroscopic evidence, however, does allow distinction between 1 and 2. Turning to PMR data first, we would expect the olefinic proton of 2 to show more coupling to the adjacent methylene hydrogen atoms than that of 1; the olefinic proton resonance of the major isomer, although a singlet, is in fact slightly broader than that of the minor isomer. The olefinic proton of 1 might be expected to be slightly shielded by the proximate methyl group relative to that of 2; the olefinic proton absorbs at δ4.60 ppm in the minor isomer, at 4.75 ppm in the major. We might expect the methyl group of 1 to be slightly deshielded by the proximate double bond with respect to that of 2; the major methyl absorption occurs at δ0.90 ppm, the minor at δ0.97 ppm. In the CMR spectrum, we would expect the absorption of the protonated olefinic carbon atom of 1 to be at lower field than that of 2 due to the methyl group; in the major isomer this absorption occurs at δ103.9 ppm, in the minor at δ111.4 ppm. More compelling is to compare values for the enamine lacking the methyl group, i.e., nor-methylpropyleine (10), clearly a better model for 2 than for 1, with those of the major and minor isomers. In 10 the olefinic proton absorption occurs at δ4.74 ppm (major: 4.75; minor: 4.60) and the protonated olefinic carbon atom at δ103.6 ppm (major: 103.9; minor: 111.4). *In toto*, the evidence clearly points to 2 as the major component of the equilibrium mixture. That 2 should be more stable than 1 can be explained on the basis of $A^{1,2}$ strain[6] and/or increased torsional strain when the methyl group is in a quasi-equatorial position (as in 1) rather than an equatorial position (as in 2).[7]



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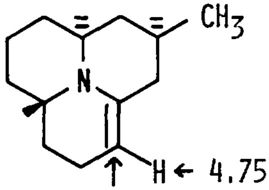

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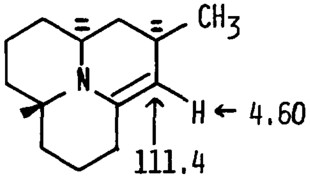

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References and Footnotes

1. B. Tursch, D. Daloze and C. Hootele, *Chimia*, *26*, 74 (1972).
2. G. Opitz and A. Griesinger, *Ann.*, *665*, 101 (1963).
3. Although interconversion is "slow" on the NMR time scale, it is "rapid" on the laboratory time scale.
4. R. H. Mueller and M. E. Thompson, preceding article in this issue.
5. Spectroscopic data and combustion analysis are in accord with this structure. Melting points are corrected.
6. S. K. Malhotra, D. F. Moakley and F. Johnson, *Chem. Commun.*, 448 (1967).
7. E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, *77*, 2505 (1955).

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