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Ground State Conformational Control of Stereochemistry of a Photochemical Synthesis of the Quebrachamine-Dihydrocleavamine Skeleton

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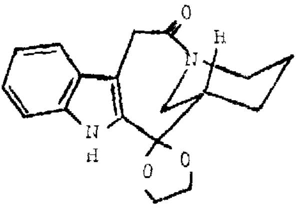
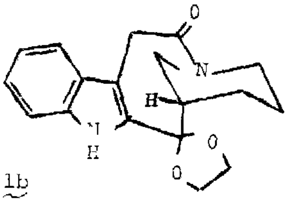
The Witkop photocyclization(1) of 2-(N-chloroacetylpiperidylalkyl)indoles has been recognized as a potentially direct route for synthesis of indole derivatives,(2,3) including alkaloid skeletons,(4) with medium-sized rings fused to the indole nucleus. In an earlier study it was noted that photocyclization of derivatives of 1-chloroacetyl-3-(indol-2-ylmethyl)piperidine gave a mixture of two isomeric photocyclization products (1a, 2a).(3) This was attributed to formation of two conformers of the bicyclic skeleton, one of which is locked in a highly strained "inside-outside"(5) topology by steric factors. The present report describes the stereochemistry of the photocyclization as applied to the molecular skeleton (desethyl) common to quebrachamine and dihydrocleavamine.

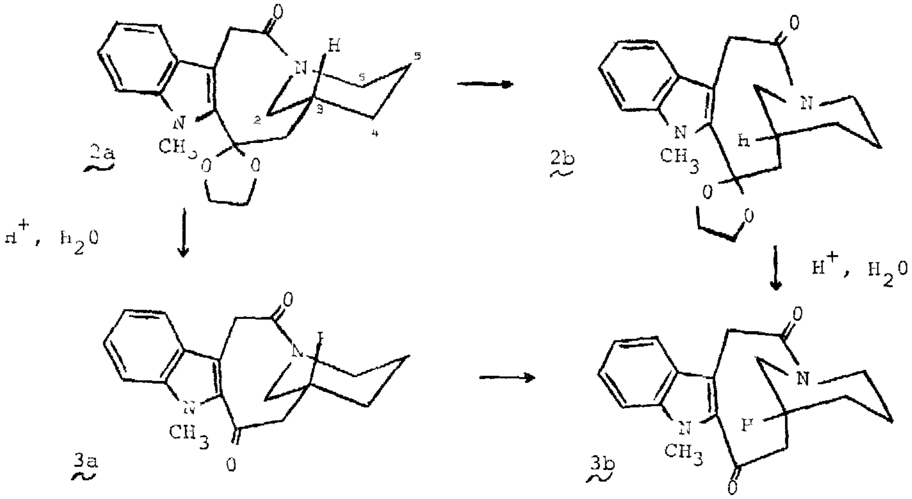
The compound studied was the ethylene glycol ketal of 1-methylindol-2-yl 1-chloroacetyl-3-piperidylmethyl ketone. This compound was prepared by condensation of methyl 1-methylindole-2-carboxylate and 3-pyridylmethyllithium followed by ketalization, catalytic reduction and chloroacetylation following procedures similar to those used previously.(3) Irradiation in 50.50 aqueous methanol containing sodium carbonate gave a photocyclization product, 2a, in 35-40% yield. That the expected photocyclization had occurred was indicated by the mass spectrum and the nmr spectrum which showed the absence of the characteristic indole-3H signal. The N-acetyl analog of the starting material, which arises by dechlorination,(6) was formed in 15% yield. Hydrolysis of the photocyclization product gave the corresponding ketone 3a. Both 2a and 3a were converted to isomeric substances, 2b and 3b, respectively, on heating in refluxing xylene. Hydrolysis of 2b gave 3b.



1a



1b



2a 2b 3a 3b

The 250 MHz nmr spectra of the isomeric ketals 2a and 2b permit assignment of the conformational structures shown above. In 2a the equatorial protons at C-2 and C-6 of the piperidine ring occur as a doublet at 5.25 ppm, J = 14 Hz and a doublet of doublets at 4.25 ppm, J = 14, 4 Hz. The former signal is coupled to a doublet of doublets at 2.52 ppm, J = 14, 10 Hz. The latter is coupled to a triplet of doublets at 2.80 ppm, J = 14, 4 Hz. The downfield doublets can be assigned on the basis of the coupling (confirmed by decoupling) pattern and chemical shift to the equatorial protons on the piperidine C-2 (5.25 ppm) and C-6 (4.65 ppm) carbons. The triplet of doublets (2.80 ppm) is characteristic of protons on piperidine rings having geminal, a-a and a-e couplings and is assigned to the axial proton at C-6. The doublet of doublets at 5.52 ppm is somewhat uncharacteristic. The coupling of 10 Hz is assigned to a distorted aa coupling to an axial proton at C-3. This assignment requires that the carbon-carbon bond at C-3 occupy an equatorial position.

In the more stable isomer the equatorial protons at C-2 and C-6 occur at

5.14 and 4.66 ppm, respectively. The latter is coupled to a multiplet near 2.65 ppm which overlaps another signal, preventing complete analysis. The doublet at 5.14 ppm is coupled, J = 14 Hz, to a doublet at 3.08 ppm. These two signals must be the equatorial and axial protons, respectively at C-2. The absence of additional resolved coupling in these signals requires that the proton at C-3 be equatorial and the C-C bond axial as shown in the structure.

The nmr spectra of the ketones 3a and 3b can be interpreted in an analogous manner. The strained ketone 3a shows a signal at 2.84 ppm which is coupled to a doublet at 3.90 (J = 14 Hz) and a multiplet at 2.12 (J = 10 Hz). These couplings constants correspond to those observed for the axial proton at C-2 in 2a. Ketone 3b shows a doublet at 2.3 ppm which can be assigned to the axial proton at C-2. The lack of a significant coupling to any proton other than the geminal one implies an equatorial position for the proton at C-3.

The thermal isomerization of the ketal 2a to 2b in bis-ethoxyethyl ether followed clean first order kinetics, $t_{1/2}$ = 4.0 ± 0.2 hr at 144°. The ketone 3a is converted to 3b with $t_{1/2}$ = 1.0 ± 0.05 hr at 144°. The much more facile thermal isomerisms of 2a and 3a relative to the previously studied system 1a is consistent with attribution of the stereoisomerism to "locked conformation" since the larger nine-membered ring in 2 and 3 will reduce the barrier to the conformational change which accomplishes the isomerization.(3)

The apparently exclusive formation of 2a also contrasts with the previously studied systems where both stereoisomers were found on photocyclization. The difference in strain energy between 1a and 1b is much larger than 2a and 2b. Apparently, 2a is formed exclusively because it corresponds to the dominant ground state conformation of the starting material, while the strain energy associated with formation of 1a is sufficiently large that some cyclization occurs via a less stable reactant conformation.

It is interesting to note that the alkaloid capuronine adopts the geometry of the bicyclic ring system found in the more strained stereoisomers 2a and 3a.(7)

Acknowledgment

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