# THE C(7) STEREOCHEMISTRY OF THE CHLOROINDOLENINES OF CLEAVAMINES AND QUEBRACHAMINES[1]

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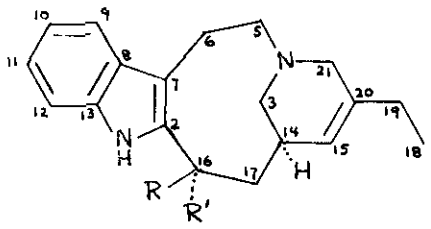
A $^{13}C$ NMR analysis of the 7-chloroindolenine derivatives of representative cleavamines and quebrachamines reveals these products of indole chlorination to possess a 7β-chloro configuration.

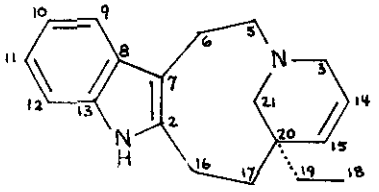
Many indole alkaloids have been known for some time to undergo ready oxidation with t-butyl hypochlorite to yield β-chloroindolenines.[2] The chlorination products of especially cleavamine--like (1) and quebrachamine-like (2) alkaloids have attracted attention recently in view of the ease of their solvolysis and the facility of trapping of the resultant α-indolylcarbonium ion species by activated benzene subunits of natural indolines (e.g. vindoline) having permitted simple access to the biologically important vincaleukoblastine-like substances.[3,4] Whereas most of the stereochemistry of the chloroindolenines is known, the configuration of the chlorocarbon site has remained undetermined. The present communication resolves this residual point of constitution by the $^{13}C$ NMR analysis of four chloroindolenines and two hydroxyindolenines and carbon shift correlation with voaphylline hydroxyindolenine (6a),[5] an alkaloid whose total stereochemistry had been ascertained by x-ray crystallography.[6]

The carbon shift assignment of the indolenines depended on a similar treatment of their indole precursors 1-3. The shift designation of 14,15-dehydroquebrachamine (2)[7] and voaphylline (3)[8] was based on the data of earlier $^{13}C$ NMR and conformational analyses of cleavamine- and quebrachamine--like bases,[4] the δ values of substances 1-3 being listed in Table I. Thus the tetrahedral carbon resonances of 2, except for C(16) and C(17), were identical with those of dehydroepivincadine (16α-carbomethoxy-2)[4,7] to within ±0.4 ppm and the Δδ(C-16) and Δδ(C-17) values for the two substances mimicked those for cleavamine (1a) and its 16α-carbomethoxy derivative (1c).[4] Comparison of the spectra of 2 with those of voaphylline (3) revealed that the change of a double bond into an epoxide altered only the piperidine carbon shifts. Differentiation of the individual resonances of the aminomethylene pair C(3) and C(21) as well as of the oxymethines C(14) and C(15)

was made feasible by one carbon each being positioned next to quaternary C(20), whose β-effects expectedly deshielded C(21) and C(15), respectively.[9]



1a, R = R' = H
b, R = $CO_2Me$, R' = H
c, R = H, R' = $CO_2Me$



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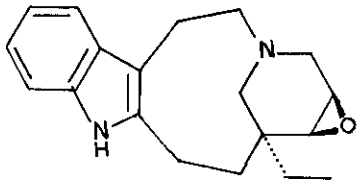

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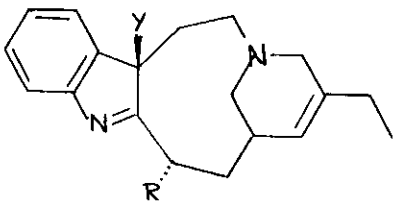
Table I. Carbon Shifts of Compounds 1-3[a]

| | 1a | 1b | 1c | 2 | 3 | | 1a | 1b | 1c | 2 | 3 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| C(2) | 139.2 | 138.4 | 134.2 | 139.3 | 139.1 | C(12) | 109.8 | 110.6 | 110.3 | 109.9 | 109.9 |
| C(3) | 53.5[b] | 47.0 | 52.8[b] | 51.8 | 53.2[b] | C(13) | 135.2 | 135.0 | 135.3 | 135.3 | 135.2 |
| C(5) | 53.8[b] | 51.2 | 53.2[b] | 54.0 | 53.5[b] | C(14) | 35.3 | 34.1 | 34.3 | 126.4 | 52.1 |
| C(6) | 26.1 | 21.7 | 26.0 | 25.6 | 25.9 | C(15) | 122.3 | 124.0 | 121.5 | 133.7 | 59.2 |
| C(7) | 109.5 | 109.5 | 110.9 | 109.9 | 109.0 | C(16) | 22.4 | 39.3 | 38.3 | 22.9 | 23.0 |
| C(8) | 128.5 | 127.9 | 127.5 | 128.6 | 128.2 | C(17) | 34.1 | 39.1 | 37.5 | 39.5 | 36.3 |
| C(9) | 117.6 | 117.5 | 117.7 | 117.7 | 117.2 | C(18) | 12.6 | 12.3 | 12.3 | 7.8 | 7.2 |
| C(10) | 118.5 | 118.6 | 118.5 | 118.6 | 118.3 | C(19) | 27.6 | 27.3 | 27.4 | 33.1 | 32.1 |
| C(11) | 120.3 | 120.9 | 121.0 | 120.4 | 120.1 | C(20) | 140.4 | 138.4 | 140.8 | 39.7 | 33.3 |
| | | | | | | C(21) | 55.1 | 57.5 | 54.9 | 58.7 | 58.1 |

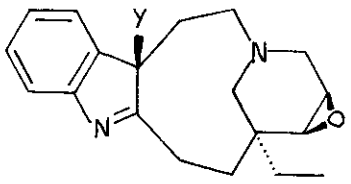
[a] Spectra recorded on a Varian XL-100-15 NMR spectrometer operating at 25.2 MHz in the Fourier transform mode. δ values of $CDCl_3$ solutions in ppm downfield from TMS; δ(TMS) = δ($CDCl_3$) + 76.9 ppm. Those of compounds 1 cited from reference 4. [b]Values in any vertical column may be interchanged.

The indolenines analyzed by the $^{13}C$ NMR spectral method include cleavamine 7-hydroxyindolenine (4a), prepared by peracetic acid oxidation of cleavamine (1a), cleavamine 7-chloroindolenine (4b),[4,10] the 7-chloroindolenine (4c) of methyl cleavamine-16α-carboxylate, prepared by a reaction of 1c with t-butyl hypochlorite[2] at -50°C, 14,15-dehydroquebrachamine 7-chloroindolenine (5), obtained by the same chlorination of 2, voaphylline 7-hydroxyindolenine (6a)[5] and voaphylline 7-chloroindolenine (6b), acquired by the afore-mentioned chlorination of 3, and their carbon shifts are listed in Table II. The chloroindolenines were quite unstable, as

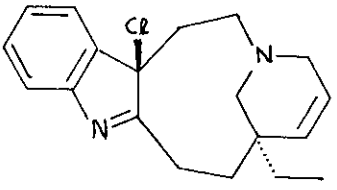
illustrated by the formation of a quaternary ammonium salt from voaphylline 7-chloroindolenine (6b) on short contact with chloroform (presumably in the presence of some hydrogen chloride). On the basis of its $^{13}C$ NMR analysis the salt possessed structure 7,[11] indicating it to be the product of solvolysis of 6b enamine and trapping of the resultant α-indolylcarbonium ion by $N_b$.




4a, R = H, Y = OH
b, R = H, Y = Cl
c, R = $CO_2Me$, Y = Cl




6a, Y = OH
b, Y = Cl

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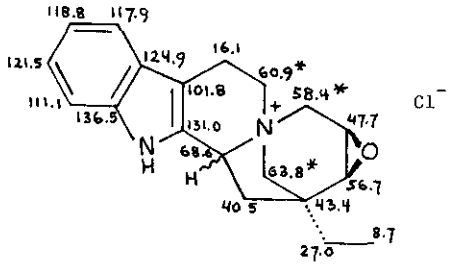


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The iminocarbon signal of the indolenines was at a characteristically low field position and affected not only by a C(16) substituent but also by the nature of the C(7) heteroatom substituent, as illustrated by the magnitude difference of the latter's β-effect exerted on C(2) in the voaphylline indolenines 6a and 6b. The aromatic carbon shifts were reminiscent of those of typical indolines[12,13] but distinctly downfield of the latter. Thus C(12) and C(10), the methines ortho and para to $N_a$, were 13 and 8 ppm, respectively, downfield of their positions in the indoline 1-methyl-2,16-dihydrovincadifformine[12] and C(8), the non-protonated ortho carbon, 7 ppm downfield of that in the indoline model. Whereas the shift correlation between the indolenines and indolines appeared satisfactory, i.e. Δδ(ortho-methine) > Δδ(para-methine), it did not provide a strict enough assignment criterion and hence the aromatic carbon shift designation of the indolenines can be considered only tentative at this time.

Comparison of the spectra of the indolenines with those of their indole precursors showed the chemical shifts of the ethyl and piperidine carbons to be constant to within ±1 ppm for each indolenine-indole pair. The constancy of the 50.5 ± 0.4, 41.8 ± 1.1 and 26.8 ± 0.5 ppm methylene signals among the 16-unsubstituted indolenines permitted their allocation to C(5), C(6) and C(16), respectively. The variable shift of the remaining methylene reflected the proximity of C(17) to the structurally changing piperidine nucleus.

Table II. Carbon Shifts of Compounds 4-6[a]

| | 4a | 4b | 4c[b] | 5 | 6a | 6b |
|---|---|---|---|---|---|---|
| C(2) | c | 186.8 | 181.5 | 186.1 | 192.2 | 187.2 |
| C(3) | 53.7[d] | 53.4[d] | 53.3[d] | 50.8 | 52.0 | 51.5 |
| C(5) | 50.2 | 50.9 | 50.9 | 50.1 | 50.1 | 50.8 |
| C(6) | 40.9 | 42.9 | 43.7 | 42.2 | 40.7 | 42.4 |
| C(7) | 87.2 | 73.5 | 73.8 | 74.0 | 87.1 | 74.1 |
| C(8) | 141.1 | 139.1 | 140.0 | 139.8 | 140.7 | 139.4 |
| C(9) | 122.1[e] | 122.0[e] | 122.2[e] | 122.8 | 122.1 | 122.8 |
| C(10) | 125.2[f] | 125.6[f] | 126.4[f] | 125.7[d,e] | 125.4[d] | 126.1[d] |
| C(11) | 129.1[f] | 129.4[f] | 129.7[f] | 130.0[e] | 129.2[d] | 130.1[d] |
| C(12) | 119.1 | 119.4 | 120.6 | 119.6 | 119.3 | 119.6 |
| C(13) | 153.0 | 152.3 | 152.2 | 152.4 | 152.9 | 152.4 |
| C(14) | 122.0[e] | 121.8[e] | 121.3[e] | 126.1[d] | 51.5 | 51.2 |
| C(15) | 33.9 | 33.7 | 33.8 | 132.8 | 59.4 | 58.7 |
| C(16) | 26.4 | 26.3 | 44.2 | 26.8 | 27.3 | 27.0 |
| C(17) | 29.6 | 29.7 | 35.5 | 34.8 | 33.2 | 33.0 |
| C(18) | 12.5 | 12.3 | 12.4 | 7.8 | 7.4 | 7.3 |
| C(19) | 27.3 | 27.0 | 27.2 | 32.0 | 31.7 | 31.4 |
| C(20) | 139.5 | 139.7 | 140.0 | 38.4 | 32.8 | 32.3 |
| C(21) | 53.9[d] | 53.5[d] | 54.1[d] | 58.0 | 58.7 | 58.7 |

[a]Spectra recorded on a Varian XL-100-15 NMR spectrometer operating at 25.2 MHz in the Fourier transform mode. δ values for $CDCl_3$ solutions of compounds 4 and 6a and for $d_6$-DMSO solutions of 5 and 6b in ppm downfield from TMS; δ(TMS) = δ($CDCl_3$) + 76.9 ppm = δ($d_6$-DMSO) + 39.5 ppm. [b]δ(CO) = 172.6 ppm; δ(Me) = 52.2 ppm. [c]Signal lost because of low sample size. [d,e,f]Values in any vertical column may be interchanged.

The known shift sensitivity of the azacyclononane methylenes in cleavamine- and quebrachamine-like substances to conformational change,[4] e.g. 1a, 1c, 2 and 3 vs. 1b, would be expected to be present also among the indolenines. Thus the invariance of their C(5) and C(6) shifts and the constancy of the C(16) resonance of all indolenines except 4c supports strongly a unique equilibrium conformation for substances 4-6. Since a necessary prerequisite for this condition is a common C(7) stereochemistry and since the hydroxy group of the voaphylline derivative 6a has been shown to be of 7β configuration, all compounds 4-6 have their C(7) substituent in a β orientation.

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