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RAUWOLFIA ALKALOIDS - XLII

METHYL NEORESERPATE, AN ISOMER OF METHYL RESERPATE. PART 4. INFRARED SPECTRA AND CONFIGURATION AT C-3

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IN connection with our studies of the structure[1] and mechanism of formation[2] of methyl *neo*reserpate, an isomer of methyl reserpate, we have examined the infrared spectra of a number of 16α-carbomethoxyl derivatives. We have found that these compounds are not in agreement with Wenkert's correlation[3] of infrared spectra with configuration at C-3, and propose that observed differences in the 2800 cm^{-1} region of the infrared spectrum reflect not changes in configuration, but changes in conformation at C-3. Our assignments of specific conformations to C-3 hydrogens are strongly supported by our studies of the NMR spectra of methyl reserpate, methyl *neo*reserpate, and methyl 3-isoreserpate.[4]

In the quinolizidine series, infrared bands in the 2700-2800 cm^{-1} region have been correlated with the presence of at least two α-hydrogen atoms *trans* coplanar (diaxial) to the electron pair on the bridgehead nitrogen.[5] This

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[1] W.E. Rosen and J.M. O'Connor, *J.Org.Chem.* In press.

[2] W.E. Rosen and H. Sheppard, *J.Amer.Chem.Soc.* In press.

[3] E. Wenkert and D. Roychaudhuri, *J.Amer.Chem.Soc.* *78*, 6417 (1956).

[4] W.E. Rosen and J.N. Shoolery, *J.Amer.Chem.Soc.* In press. The conformations are also consistent with infrared spectra, pKa measurements, and optical rotatory dispersion curves obtained by K. Nakanishi and F. Yamasaki [private communication; see F. Yamasaki, *Nippon Kagaku Zasshi* *82*, 72 (1961)].

[5] F. Bohlmann, *Angew.Chem.* *69*, 641 (1957); *Chem.Ber.* *91*, 2157 (1958).

correlation has been applied successfully to similar systems,[6,7] including various alkaloids.[8,9,10] Prior to this correlation, Wenkert had suggested[3] that infrared bands in the 2800 cm^{-1} region could be used with indole alkaloids containing the ring system of yohimbine, ajmalicine, or corynantheine to distinguish between normal or allo derivatives (those possessing a 3α- hydrogen) and pseudo or epiallo derivatives (those possessing a 3β-hydrogen). The appearance of two characteristic infrared bands in chloroform spectra of all those alkaloids known to have a 3α- hydrogen, and its absence in spectra of those alkaloids known to have a 3β- hydrogen, suggested its use as an analytical method for assigning configuration at C-3 for new alkaloids. The application of this analytical method has proved useful,[11] although two exceptions (3-epialloyohimbone and 3-epialloyohimbine) have been reported.[12]

We feel that Wenkert's rule[3] for the chloroform spectra of indole alkaloids should be modified to: "All compounds possessing in their stable conformations axial hydrogens at C-3 exhibit two or more peaks or distinct shoulders between 2700-2900 cm^{-1} (at least one of which absorbs below 2800 cm^{-1}) on the low wave number side of the major (ca. 2900 cm^{-1}) band, whereas those containing equatorial hydrogens at C-3 do not". This modified rule does not explain differences in the position or the appearance of these extra peaks, but it points out that secure assignment of configuration at C-3 by infrared spectroscopy requires that the compound be fairly pure

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[6] S. Ohki and Y. Noike, Chem.Pharm.Bull.Japan 7, 708 (1959).

[7] N.J. Leonard and W.K. Musker, J.Amer.Chem.Soc. 82, 5148 (1960).

[8] A.R. Battersby, R. Binks and G.C. Davidson, J.Chem.Soc. 2704 (1959).

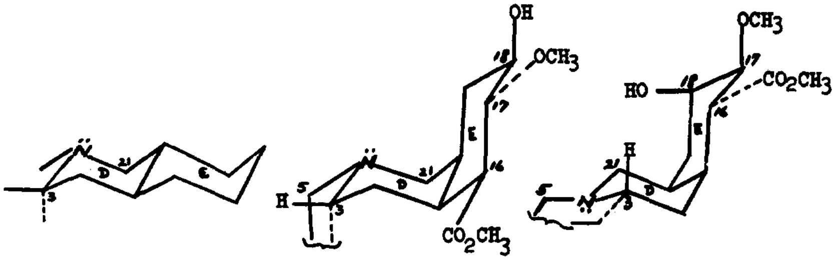
[9] M. Terashima, Chem.Pharm.Bull.Japan 8, 517 (1960).

[10] F. Bohlmann et al., Chem.Ber. 91, 2167, 2176, 2189, 2194 (1958).

[11] N. Neuss and H.E. Boaz, J.Org.Chem. 22, 1001 (1957).

[12] M.-M. Janot, R. Goutarel, E.W. Warnhoff and A. LeHir, Bull.Soc.Chim.Fr. 637 (1961).

conformationally, and that the relation between conformation and configuration be known. Application of the modified rule and recognition of its limitations will prevent the errors of assignment which might follow strict application of the original rule.



I II III

With D/E <u>trans</u>-locked alkaloids (partial formula I), the ring system requires that the 3α- substituent be axial and the 3β- substituent be equatorial, so that the modified rule leads to the same conclusion as the original rule. With D/E <u>cis</u>-locked alkaloids, however, <u>two</u> stable chair conformations (II and III) are possible. Methyl reserpate (partial formula II) and its derivatives (including 3-iso-derivatives) are stable in the conformation which has the 3α- substituent axial and the 3β- substituent equatorial with respect to ring D.[4] With methyl <u>neo</u>reserpate (partial formula III) and its derivatives, however, the 3α- substituent is equatorial and the 3β- substituent is axial in the stable conformation.[4] The derivatives of methyl <u>neo</u>reserpate show, as expected, characteristic extra peaks in the 2700-2900 cm^{-1} region. The so-called exceptions[12] to Wenkert's rule, 3-epialloyohimbone and 3-epialloyohimbine, are probably structurally similar to III. We have found, analogous to the 3-epialloyohimbone exception, that both alloreserpone and 3-epialloreserpone[1] show extra peaks in the 2700-2900 cm^{-1} region.

The modified rule proposed here is actually an application of the correlation described by Bohlmann.[5] With I and II, the ring system does not permit the hydrogen on C-5 to be trans diaxial to the nitrogen electrons unless the hydrogen on C-3 is axial; since systems I and II have either one axial hydrogen (on C-21) or three axial hydrogens (C-3, C-5, and C-21) trans to the nitrogen electrons, the infrared bands for two or more can be correlated with the C-3 hydrogen alone. With the ring system III, trans diaxial hydrogens at C-5 and C-21 are necessarily present when the 3β-hydrogen is present. The hypothetical 3α- hydrogen (equatorial) epimer of ring system III would have only one trans axial hydrogen (at C-21) and therefore would not show the characteristic infrared peaks.

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