Tetrahedron Letters No.25, pp. 2381-2386, 1967. Pergamon Press Ltd. Printed in Great Britain.

REVISION OF THE CONFIGURATION OF VERATRAMINE AND JERVINE

John W. Scott, Lois J. Durham, Hendrik A. P. deJongh,
Urs Burckhardt and William S. Johnson

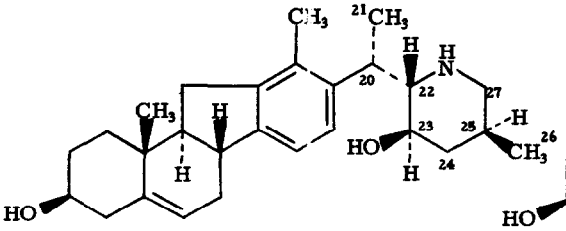
Department of Chemistry, Stanford University,
Stanford, California 94305

(Received 25 February 1967; in revised form 22 April 1967)

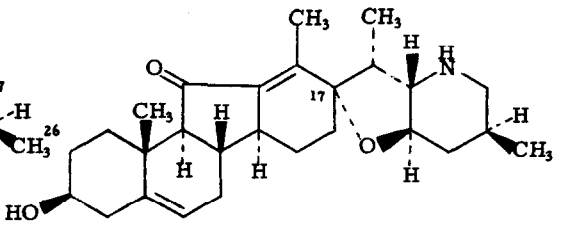
We present herewith proof that the configurations of veratramine and of jervine are correctly represented by formulas I and II,* respectively, rather than by III and IV, as previously postulated (1). It follows that the configuration of verarine, which has been shown (2) to be 23-deoxyveratramine, must be revised accordingly.

The arguments that the C-23 hydroxyl group of veratramine is equatorial (3) and that C-25 has the S configuration (4) appear to be secure. The question at hand involves the matter of the relative configuration of the groups attached to C-22 and C-25. Augustine (1) concluded that they were cis to each other (and hence both β oriented, with the methyl group axial), as in formulas III and IV, because the triketo amide V (5) derived from jervine, on treatment with base, was converted into a diastereoisomer in 75% yield. Since N-acetyl-5α,6,12,13-tetrahydrojervine was unaffected by the same treatment, he assumed that the isomerization had occurred exclusively at C-22 (without affecting the configuration at C-9 or C-12), to give the presumably more stable system with the C-22 and C-25 substituents trans (diequatorial). Masamune and co-workers (2), in a more rigorous experiment, have obtained similar results in that treatment of 23-dehydro-3,N-diacetylveratramine with alkali afforded a 1:10 equilibrium mixture of this compound and its C-22 epimer.

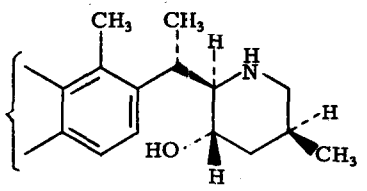
*It is to be noted that there is no definitive proof for the configurations at C-20 and (in the case of jervine) at C-17; the configurations at these centers, as shown in formulas I and II, have been assigned solely on the basis of biogenetic analogy.



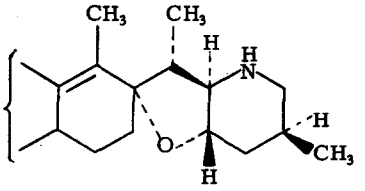
I



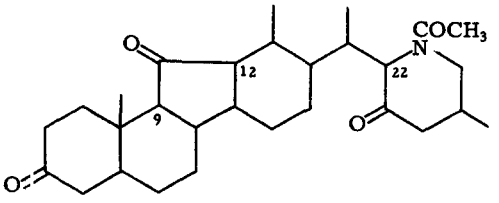
II



III



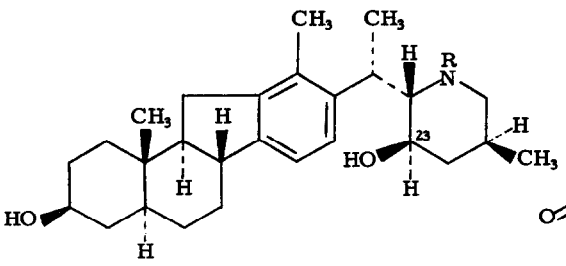
IV



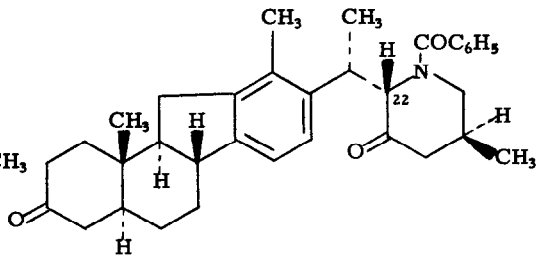
V

In the course of some synthetic studies we had occasion to probe further into the configuration of ring E in the 5α,6-dihydroveratramine series. This substance, VI (R = H) (6), upon treatment with benzoyl chloride in pyridine, followed by selective saponification, gave N-benzoyl-5α,6-dihydroveratramine (VI, R = COC_6H_5), mp 154-157°, $\lambda_{max}^{CHCl_3}$ 3380 and 1610 cm^{-1}, $[\alpha]_D^{26}$ + 40 (c 0.25, $CHCl_3$). Oxidation of this material with Jones reagent (7) afforded the N-benzoyl-3,23-dione VII, mp 210-212°, $\lambda_{max}^{CHCl_3}$ 1710 and 1630 cm^{-1}, $[\alpha]_D^{25.3}$ + 41.3 (c 1.46, $CHCl_3$). Reduction of the dione VII with sodium borohydride in isopropyl alcohol gave a mixture of two compounds which were separated by preparative TLC. One of these materials, isolated in 44% yield, was identified as N-benzoyl-5α,6-dihydroveratramine (VI, R = COC_6H_5) by its melting point, mixture melting point with an authentic sample, and

infrared spectrum. The second product, isolated in 40% yield, was N-benzoyl-5α,6-dihydro-23-iso-veratramine, mp 245-247°. Oxidation of the 23-iso compound with Jones reagent regenerated the dione VII, proving that isomerization at C-22 had not occurred prior to reduction. The 23-iso amide, on treatment with potassium hydroxide in refluxing ethylene glycol, was hydrolyzed to give 5α,6-dihydro-23-iso-veratramine, mp 125-128.5°, $[\alpha]_D^{26.5}$ + 45.5 (c 1.33, $CHCl_3$). A concentration-independent OH band was noted in the infrared spectrum (C_2Cl_4 solution) at 3515 cm^{-1}. This result indicates intramolecular hydrogen bonding, which requires an axial hydroxyl group in the 23-iso compound. This finding provides the corollary evidence to that of Sicher and Tichý (3) for an equatorial 23-hydroxyl in veratramine.



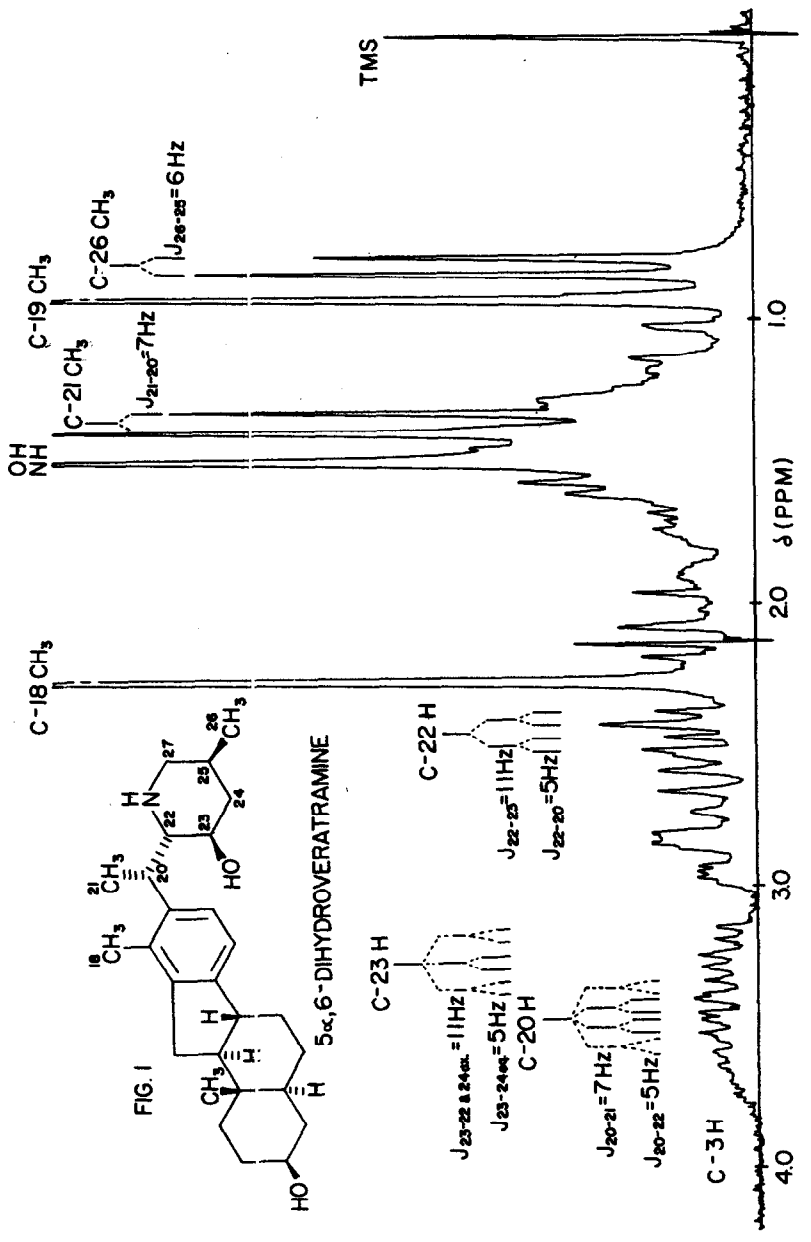
VI



VII

A portion of the 100 MHz NMR spectrum of 5α,6-dihydroveratramine in $CDCl_3$ is reproduced in Figure 1.* It is to be noted that the analysis of the spectrum of veratramine itself promised to be much more complicated because of the extra vinyl and allylic protons. The resonance assignments for the protons on carbons 20, 21, 22, 23, and 26 were verified by the appropriate (field-swept) spin decoupling experiments. The spectrum confirms the assignment of equatorial positions to the C-23 hydroxyl group and to the large substituent on C-22: the C-23 proton signal approximates a doublet of triplets for which the coupling constants are consistent with an axial proton coupled to two adjacent axial protons (10-11 Hz) and to one equatorial proton (5 Hz). The corresponding signal in the spectrum of 5α,6-dihydro-23-iso-veratramine appears at 0.79 ppm lower field as a relatively sharp unresolved multiplet,

*The remainder of the spectrum consisted of an AB quartet, centered at δ = 7.08 ppm, for the ring D aromatic protons.


TMS
C-18 CH3
C-19 CH3
C-21 CH3
C-26 CH3
J21-20=7Hz
J26-25=6Hz
OH
NH
C-23 H
C-22 H
C-20 H
C-3 H
J23-22 & 24eq. =11Hz
J23-24eq=5Hz
J22-23=11Hz
J22-20=5Hz
J20-21=7Hz
J20-22=5Hz
1.0
2.0
3.0
4.0
δ(PPM)
5α,6-DIHYDROVERATRAMINE
FIG. 1

corresponding to an equatorial proton and an axial hydroxyl group.

The C-26 methyl resonances for both 5α,6-dihydroveratramine and the 23-iso epimer appear at δ = 0.82 ppm as a doublet (J_{26-25} = 5-6 Hz) indicating that this group is equatorial. If it were axial, its resonance would have appeared at 12-15 Hz lower field in the spectrum of the 23-iso compound, because of the 1,3-diaxial interaction with the C-23 hydroxyl group (8). This assignment was confirmed by the determination of the field position at which it was necessary to irradiate in order to collapse the C-26 methyl resonance to a singlet. In this way the C-25 proton resonance position, which was obscured from direct observation because it fell within the methylene envelope, was determined to be at about δ = 1.5 ppm for 5α,6-dihydroveratramine and at about δ = 1.8 ppm for the 23-iso epimer. The lower field position in the latter case indicates that the proton has a 1,3-diaxial interaction (9) with the C-23 hydroxyl group. Thus the equatorial conformation of the C-26 methyl is confirmed, and the trans relationship of the C-22/C-25 substituents is established.

Attention is now turned to the matter of reconciling the results of the aforementioned equilibration experiments of Augustine (1) and Masamune (2) with these revised configurations. A clue was provided by the fact that acylation of 2-methylpiperidine is accompanied by a conformational inversion of the ring (methyl group axial) to relieve steric crowding between the equatorial methyl and amide carbonyl groups (10). Evidently this vicinal alkyl-amide effect is quite powerful, for we have found that the piperidino ring of N-benzoyl-5α,6-dihydroveratramine (VI, R = COC_6H_5) also exists preferentially in that conformation with all of its substituents axial. The 1,3 diaxial relationship of the C-23 OH and the C-26 CH_3 was detected in the NMR spectrum which showed a downfield (8) C-26 methyl signal as a doublet (J = 6 Hz) centered at 1.03 ppm, in comparison with the corresponding signal for the 23-iso epimer, which was found at δ = 0.82 ppm (J_{26-25} = 6 Hz). Moreover, the signal for the C-23 proton in N-benzoyl-5α,6-dihydroveratramine appeared as a relatively sharp unresolved multiplet at δ = 4.31 ppm, indicative of an equatorial proton (axial hydroxyl).

In view of the foregoing considerations it seems probable that the keto amides of Augustine (1) and Masamune (2) exist preferentially in that conformation with the C-22 and

C-25 substituents both axial. In the equilibration experiments these substances were presumably converted into the C-22 epimers, which can exist with the substituents at C-22 and at C-25 axial and equatorial respectively. It is not evident, however, that there should be very great difference in energy between the pairs of epimers, because there are no 1,3 diaxial H/CH_3 interactions in that isomer with the methyl group axial. *

Acknowledgments. - We wish to express our thanks to Dr. Yoko Kanazawa for determining the NMR spectra and performing the spin decoupling experiments. In addition, we are indebted to the U.S. Public Health Service and the National Science Foundation for supporting this study. We also thank the Netherlands Organization for the Advancement of Pure Research for awarding a NATO travel grant to H. A. P. deJ.

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9. Ref. 8, Chapter 8.
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* We have investigated the equilibration of the N-benzoyl dione VII. Upon heating with methanolic sodium acetate (or potassium fluoride), this material was partially converted into an isomer, separable by crystallization or by TLC, which must be the 22-iso compound, mp 242-244°, $[\alpha]_D^{27.5}$ + 62.8 (c 1.31, $CHCl_3$). Equilibration experiments were performed with both epimeric diones and followed by ORD. After heating for 18 hr with methanolic potassium fluoride, equilibrium was reached in which the epimer ratio, natural:22-iso, was 52:48 with an experimental error of <3%. It is not obvious why this compound fails to show the preference for a cis relationship of the C-22 and C-25 substituents observed with the N-acetyl derivatives.