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ON THE C-9 CONFIGURATION OF VERATRAMINE AND JERVINE

Denis M. Bailey, David P. G. Hamon and William S. Johnson
Department of Chemistry, Stanford University,
Stanford, California

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HOUSE and co-workers[1] have shown unequivocally, by equilibration studies, that the benzindanone I is considerably more stable than the epimer II, *i. e.*, the equilibrium lies 85% in favor of the *cis* substance I. We have synthesized the pair of epimers V and VI[2] and have shown (see below) that at equilibrium the ratio of *cis* to *trans* form is about 7 to 3. All of these observations are consistent with the general predilection of hydrindanones for the *cis* configuration.[3] By simple analogy, therefore, it might be presumed that 11-ketoveratramine (11-keto III), which is known in only one stable form,[4] has the

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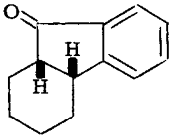
[1] H. O. House, V. Paragamian, R. S. Ro and D. J. Wluka, *J. Amer. Chem. Soc.* **82**, 1457 (1960).

[2] P. W. Schiess, D. M. Bailey and W. S. Johnson, *Tetrahedron Letters* No. 9, 549 (1963).

[3] Cf. *inter alia* J. F. Biellmann, P. Crabbé and G. Ourisson, *Tetrahedron* **3**, 303 (1958); W. S. Johnson and K. V. Yorka, *Tetrahedron Letters*, No. 8, 11 (1960); K. V. Yorka, W. L. Truett and W. S. Johnson, *J. Org. Chem.*, in press.

[4] J. Fried, O. Wintersteiner, A. Klingsberg, M. Moore and B. M. Iselin, *J. Amer. Chem. Soc.* **73**, 2970 (1951); O. Wintersteiner and M. Moore, *ibid.* **75**, 4938 (1953).

B/C cis (9β) configuration. If this is indeed the case, veratramine (III) also must have the B/C cis configuration because we have been able to convert the 11-keto compound into veratramine under conditions (see below) which do not affect the configuration at C-9. Now the B/C configuration of veratramine, on the contrary, has been generally assumed to be trans on the basis of biogenetic considerations.[5] There is good evidence that the B/C configuration of jervine (IV) is trans,[6] but in view of the possibility that the biogenesis of veratramine could well involve 11-ketoveratramine (derived from jervine) as an intermediate, which would thus render C-9 readily epimerizable, the question of the configuration of veratramine at this position still remains open. The fact that jervine appears to be more stable in the B/C trans than the cis form cannot be used as convincing evidence that 11-ketoveratramine prefers this same configuration because, unlike the former substance, the latter has an aromatic ring D (as in substances I, II, V and VI) which increases the rigidity and coplanarity of the 5-membered ring, the effect of which would be expected to stabilize the cis relative to the trans B/C fusion more than in the case without the aromatic ring.



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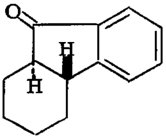

II

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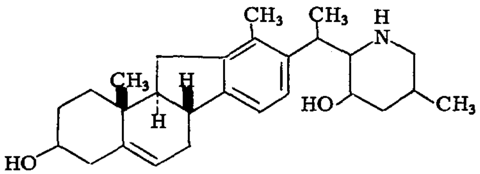
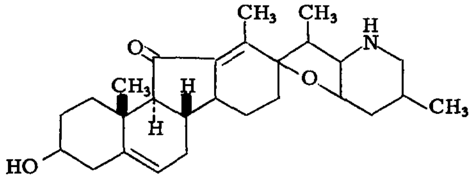
[5] L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 876.

[6] M. Mitsuhashi and Y. Shimizu, Tetrahedron Letters No. 21, 777 (1961).

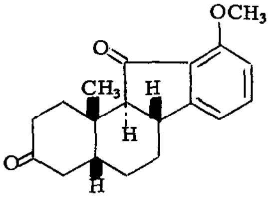


III



IV

In the present communication, evidence is presented which indicates that 11-ketoveratramine and veratramine both have the B/C trans (9α) configuration. Since we have also shown that N-acetyl-3, 11-diketo-5β, 6-dihydroveratramine (VIII), in contrast, is more stable in the B/C cis configuration (see below), the preference of veratramine for the B/C trans configuration must be due to the 5, 6-double bond.[7] This 5, 6-double bond,



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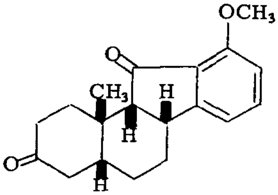

VI

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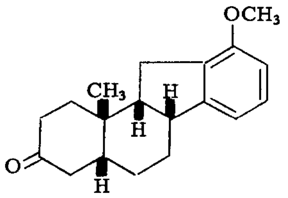
[7] H. O. House and G. H. Rasmusson have shown that introduction of such a double bond in the 1-hydrindanone system results in a stabilizing effect on the trans relative to the cis form (unpublished observations, in press).



VII

therefore, may be responsible also for the preference shown by jervine for the B/C trans configuration.

In the accompanying communication,[2] we have described the total synthesis of the two diketones V and VI which differ only in configuration at C-9. Of particular note are the NMR spectra of these epimers[8] which showed a signal for the C-19 methyl group at δ = 1.19 p.p.m. for V and 1.55 for VI. With the aid of these signals, it was possible to show that, on treatment of these C-9 epimers under alkaline conditions, an equilibrium mixture was produced consisting of approximately 30% of the trans form V and 70% of the cis form VI. The configurations of these substances were proved by hydrogenolysis of the oxygen at C-11 and comparison with the authentic cis-syn-cis ketone VII[2] as follows. Reduction of the less stable (trans) diketone with lithium aluminum hydride gave a mixture of diols which could be reoxidized in high yield to the starting diketone. Therefore there was no significant isomerization at C-9 during the reduction step. The diol mixture was converted to the diacetate, and treated with potassium in liquid ammonia which effected hydrogenolysis of the acetoxy group at C-11. The

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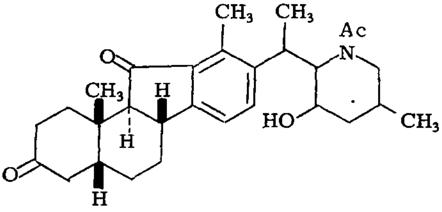
[8] Spectra were obtained at 60 megacyles. Deuterochloroform was employed as solvent and tetramethylsilane as an internal standard.

product was then oxidized to give the 3-keto compound, m.p. 100-103°, depressed on admixture with the ketone VII prepared from the $\Delta^{9,11}$-compound.[2] When the same sequence of reactions was performed with the more stable (cis) diketone, the mono-ketone thus prepared was identical with the authentic cis-syn-cis VII material as shown by mixture melting point and infrared spectroscopic comparison.



VIII

In order to obtain evidence for the configuration of 11-ketoveratramine, we have observed the effect of eliminating the 5,6-double bond. Thus N-acetyl-11-ketoveratramine[4] was oxidized by the Oppenauer method to the 3-keto-Δ^4-unsaturated compound.[4,9] Catalytic hydrogenation afforded a diketone, m.p. 229-233° (Found: C, 74.9; H, 8.7; N, 2.95), which probably, but not certainly, has the 5β configuration.[10] Of particular note is the NMR spectrum in which the absorption for the C-19 methyl group occurred, albeit

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[9] This product, which is obtained in poor yield, is evidently that isomer with the same B/C configuration as N-acetyl-11-ketoveratramine because the signal for the C-19 methyl group in the NMR spectra of these two compounds lie at 1.38 and 1.19 p.p.m. respectively. The magnitude of this difference is in agreement with the shift expected according to the rules of J. N. Shoolery and M. T. Rogers, J. Amer. Chem. Soc. 80, 5121 (1958).

[10] We expect to examine the C-5 configuration of this substance, but this point is not important to the argument advanced in the present work.

in the same region as that of the C-21 and C-26 methyl groups, at exactly the same position (1.19 p.p.m.) as for the C-19 methyl group in the synthetic B/C trans epimer V (as well as in N-acetyl-11-ketoveratramine[11]). On treatment of the diketone with methanolic potassium hydroxide, it readily underwent partial conversion into a new substance with a smaller R_f value as shown by thin layer chromatography. This new substance has not yet been obtained crystalline, but it has been shown to be readily reconvertible, by base, into the 233° diketone by an equilibration process. The non-crystalline substance, therefore, is surely the C-9 epimer of the 233° ketone. At equilibrium the former epimer is predominant. Of particular note is the NMR spectrum of the equilibrated mixture of diketones which exhibited a new sharp maximum at 1.55 p.p.m. superimposable on that for the C-19 methyl group in the synthetic cis compound VI. The diketone, therefore, has the configuration VIII (or possibly the 5α-epimer of VIII[10]) which, by analogy to the synthetic series, is rendered unstable relative to the B/C cis epimer by virtue of the absence of the 5,6-double bond.

Having thus established the B/C trans configuration of 11-ketoveratramine, i.e. 11-keto III, we undertook the problem of relating this substance to veratramine itself by removal of the carbonyl group under conditions which preclude inversion at C-9. This transformation was effected by reducing triacetyl 11-ketoveratramine[4] with lithium aluminum hydride, then acetylating and reducing the product with sodium in anhydrous liquid

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[11] This coincidence of absorption for the C-19 methyl group in the NMR spectra of the diketone VIII and N-acetyl-11-ketoveratramine indicates that both substances have the same B/C configuration (cf. ref. 9).

ammonia (as in the synthetic series described above). The major and only isolable product was identified as N-ethylveratramine.[12] Veratramine, therefore, has the B/C *trans* configuration III.

Acknowledgements. We thank Dr. L. J. Durham for determining the NMR spectra, and the U. S. Public Health Service as well as the National Science Foundation for supporting this study.

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[12] F. C. Uhle, J. E. Kreuger and F. Sallmann, *J. Amer. Chem. Soc.* **82**, 489 (1960).