$$\text{enz-biotin-CO}_2 + \text{H}_3\text{O}^+ \rightleftharpoons \text{enz-biotin} + \text{CO}_2 \quad (5)$$

that a similar constant describes the equilibrium for decarboxylation of carboxyimidazolidone,[38] it is possible to calculate the rate constant for the back reaction, k_r, in eq 6 from the equilibrium constant and the rate constant for hydronium ion catalysis ($k_f = k_{H_3O}/$

$$\text{imidazolidone-CO}_2 + \text{H}_3\text{O}^+ \underset{k_r}{\overset{k_f}{\rightleftharpoons}} \text{imidazolidone} + \text{CO}_2 \quad (6)$$

H_3O^+). The value of k_r obtained from this calculation is 1.0×10^{-5} M^{-1} min^{-1}. We have, as yet, been unable to obtain a rate constant for the reaction of imidazolidone with carbon dioxide; however, we have set an upper limit to this constant equal to 5.3×10^{-2} M^{-1} min^{-1} (25°).[30,39] The value of k_r obtained from the equilibrium constant suggests that the reactivity of 55 M water is 2.3×10^5 times that of 1 M imidazolidone. Although previous efforts to observe nucleophilic reactions of imidazolidone with activated acyl compounds were not successful because of the greater reactivity of water,[2] we are dubious that the difference in nucleophilic reactivity is as large as that calculated here. Studies with acetaldehyde indicate that the pseudo-first-order rate constant for reaction of water[40] is approximately 200 times as large as the second-order rate constant for reaction of urea.[41] The apparently abnormally low reactivity calculated for imidazolidone suggests that the decarboxylation of the carboxybiotin intermediate is more exergonic than carboxyimidazolidone. Possible sources of this greater driving force might be a conformational change accompanying decarboxylation or a lesser dissociation constant for the carboxyl group of the biotin carbamic acid.[42]

(38) Knappe has reported that the rate of decarboxylation of carboxybiotin is 1.6 times that of carboxyimidazolidone supporting the assumption that the chemical properties of carbamates of imidazolidone and biotin are similar: J. Knappe, Abstracts of the 6th International Congress of Biochemistry, Vol. V, New York, N. Y., 1964, p 355.

(39) The rate constant for reaction of imidazolidone with carbon dioxide is calculated at 9.6×10^{-1} M^{-1} min^{-1} at 10° from extrapolation of a Brønsted plot for the reaction of amines of pK = 3.6–11.2 with carbon dioxide assuming a pK for imidazolidone of 0 (unpublished results obtained in this laboratory).

(40) R. P. Bell and P. G. Evans, *Proc. Roy. Soc.* (London), **A291**, 297 (1966).

(41) Calculated from the data given in Figure 2 in L. do Amaral, W. A. Sandstrom, and E. H. Cordes, *J. Am. Chem. Soc.*, **88**, 2225 (1966).

(42) Equation 5, which describes the reaction of a proton with carboxybiotin, is actually the sum of two reactions, one forming the neutral carbamic acid and another producing biotin and carbon dioxide. The composite equilibrium constant, K_1 [K_1 = (enz–biotin–COOH) + (CO_2)(enz–biotin)/(enz–biotin–COO^-)(H_3O^+)], is related to the separate reactions for protonation [K_2 = (enz–biotin–COOH)/(enz–biotin–COO^-)(H_3O^+)] and decarboxylation [K_3 = (enz–biotin)(CO_2)/(enz–biotin–COOH)] by the relationship $K_1 = K_2K_3 + K_2$. Since it is very likely that K_2 is large, a significant portion of the driving force for decarboxylation apparently originates from elimination of the negative charge on the carboxyl function.

Communications to the Editor

The Synthesis of Jervine and Related Alkaloids[1]

Sir:

The title alkaloids are a group of numerous naturally occurring C-nor-D-homosteroid alkaloids,[2] and the structure[2] and configurations[2,3] of all the asymmetric carbons except C-17 and C-20 in jervine (I), a representative member of the group, have been established. We describe herein the conversion of 17-acetyl-5α-etiojerva-12,14,16-trien-3β-ol (VIII) into I.[4] Since compound VIII has been prepared directly[4b] or by degradation[5] of hecogenin, a totally synthesized sapogenin,[6] the present work constitutes, in a formal sense, a total synthesis of jervine. Moreover, in view of the known conversions, this work leads to the related alkaloids, veratramine[7] (II), 11-deoxojervine[7b] (III), and verarine[8] (IV).

N-Chlorination of 3-(*S*)-methylpiperidine[9] (V) with bleaching powder followed by treatment with alkali and then with acetic anhydride[10] afforded a 1:1 mixture of 1-acetyl-3-(*S*)-methyl-Δ^5-piperidine (VI) and its Δ^2 isomer, which could be separated by chromatography. The compound VI,[11] λ_{max}^{EtOH} 235 mμ (ϵ 16,000), ν_{max}^{film} 1670 and 1644 cm^{-1}, nmr ($CDCl_3$) τ 8.93 (Me at C-3), gave, on perbenzoic acid oxidation and pyrolysis, 1-acetyl-3-(*S*)-methyl-5-piperidone (VII), ν_{max}^{film} 1730 and 1634 cm^{-1}, in 9% over-all yield from V.

(1) Part IX of "C-Nor-D-homosteroids and Related Alkaloids"; Part VIII: H. Suginome, N. Sato, and T. Masamune, *Tetrahedron Letters*, 1557 (1967).

(2) C. R. Narayanan, "Progress in the Chemistry of Organic Natural Products," Vol. XX, L. Zechmeister, Ed., Springer-Verlag, Vienna, 1962, p 298.

(3) The configurations of C-17 and C-20 have been assigned solely from the biogenetical ground and those of C-22 and C-23 revised recently as shown in the formula: (a) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **78**, 6193 (1956); (b) J. W. Scott, L. J. Durham, H. A. P. deJongh, U. Burckhardt, and W. S. Johnson, *Tetrahedron Letters*, in press.

(4) After submission of this communication, Professor Johnson informed us that his group has completed both the synthesis of veratramine II from VIII and the total synthesis of VIII: (a) W. S. Johnson, H. A. P. deJongh, C. E. Coverdale, J. W. Scott, and U. Burckhardt, *J. Am. Chem. Soc.*, **89**, 4523 (1967); (b) W. S. Johnson, J. M. Cox, D. W. Graham, and H. W. Whitlock Jr., *ibid.*, **89**, 4524 (1967). We are grateful to Professor Johnson for making available to us prepublication copies of his manuscripts.

(5) (a) H. Mitsuhashi and K. Shibata, *Tetrahedron Letters*, 2281 (1964); b) W. F. Johns and I. Laos, *J. Org. Chem.*, **30**, 4220 (1965).

(6) Y. Mazur, N. Danieli, and F. Sondheimer, *J. Am. Chem. Soc.*, **82**, 5889 (1960).

(7) (a) T. Masamune, Y. Mori, M. Takasugi, and A. Murai, *Tetrahedron Letters*, 913 (1964); (b) T. Masamune, Y. Mori, M. Takasugi, A. Murai, S. Ohuchi, N. Sato, and N. Katsui, *Bull. Chem. Soc. Japan*, **38**, 1374 (1965).

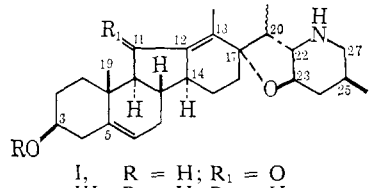
(8) T. Masamune, I. Yamazaki, and M. Takasugi, *ibid.*, **39**, 1090 (1966). N-Acetylverarine was converted into IV by saponification.

(9) A. Ladenburg, *Ber.*, **27**, 75 (1894). The hydrobromide of its N-methyl derivative had $[\alpha]_{589}$ +0.012°, $[\alpha]_{480}$ 0.0°, and $[\alpha]_{350}$ −1.7° (water): S. Okuda, K. Tsuda, and H. Kataoka, *Chem. Ind.* (London), 512 (1961).

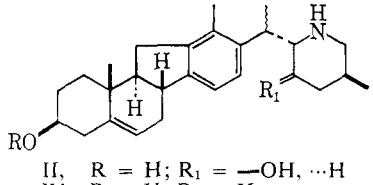
(10) *Cf.* C. Schöpf, A. Komzak, F. Braun, and E. Jacobi, *Ann.*, **559**, 1 (1948).

(11) Satisfactory analyses were obtained for all new compounds described herein.

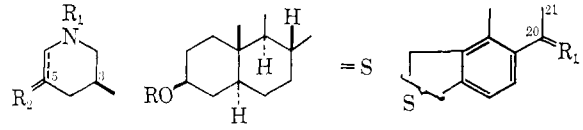
Compound VIII[5,12] gave on sodium borohydride reduction of its 3-acetate, mp 114–115°, a 1:1 mixture of readily separable 20-epimeric alcohols IX, mp 156–158°, and X, mp 122–124°, both τ 8.56 (21-Me), which were converted, with phosphorus tribromide, into the respective 20-bromides (XI), mp 124–126°, and XII, mp 131–133°, both τ 7.85 (21-Me). Treatment of the latter XII with the pyrrolidine enamine, λ_{max}^{EtOH} 267 mμ (ϵ 10,000), of VII in dioxane at 100° produced a mixture,



I, R = H; R_1 = O
III, R = H; R_1 = H_2



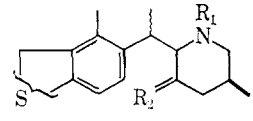
II, R = H; R_1 = —OH, ···H
IV, R = H; R_1 = H_2



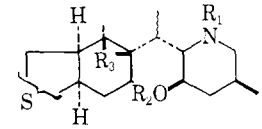
V, R_1 = H; R_2 = H_2
VI, R_1 = Ac; R_2 = H, with Δ^5
VII, R_1 = Ac; R_2 = O

VIII, R = H; R_1 = O
IX, X, R = Ac; R_1 = ~OH, ~H
XI, XII, R = Ac; R_1 = ~Br, ~H

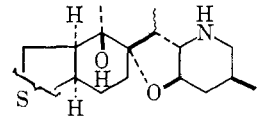
which was separated into three fractions by preparative tlc. The middle fraction (*ca.* 35%) gave on recrystallization a ketone XIII, mp 185–187°, λ_{max}^{EtOH} 302 mμ (ϵ 210), in 5% yield,[13] and the least mobile and practically homogeneous (*ca.* 35%) afforded a ketone[14] XIV, λ_{max}^{EtOH} 302 mμ (ϵ 310), in 20% yield. The ketones XIII and XIV were identified as 3-O,N-diacetyl-23-dehydro-5α,6-dihydroveratramine and its 22 epimer, respectively, by comparison with authentic specimens prepared as follows: successive partial acetylation of 5α,6-dihydroveratramine[15] (XV) to the 3-O,N-diacetyl derivative, mp 233–234°, and Jones oxidation[16] produced XIII, which on refluxing with methanolic sodium methoxide followed by acetylation was partially isomerized to XIV. These ketones gave under the equilibrating conditions a 2:1 mixture of XIV and XIII, which were readily separated. After the repeated epimerizations, we obtained XIII in 16% over-all yield from VIII, as the epimeric 20-bromide XI gave almost the same result as XII. The Birch reduction of XIII and saponification ($KOH-NH_2NH_2$) in refluxing diethylene glycol afforded XV in 70% yield.



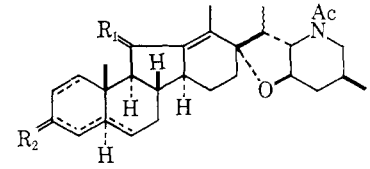
XIII, R = R_1 = Ac; R_2 = O; β-22H
XIV, R = R_1 = Ac; R_2 = O; α-22H
XV, R = R_1 = H; R_2 = OH, ···H; β-22H



XVI, R = R_1 = R_3 = H; R_3 = $\Delta^{13(17)}$
XVII, R = R_1 = R_2 = Ac; R_3 = -O-
XVIII, R = R_2 = H; R_1 = Ac; R_3 = -O-



XIX, R = H



XX, R_1 = H_2; R_2 = —OAc, ··H
XXI, R_1 = O; R_2 = —OAc, ··H
XXII, R_1, R_2 = O
XXIII, R_1, R_2 = O, with Δ^1, Δ^4
XXV, R_1 = O; R_2 = OAc, with Δ^3, Δ^5

Reduction of XV with lithium in ethylamine containing isopropyl alcohol[17] produced a mixture of the dihydro derivatives which, without further purification, was hydrogenated over platinum in acetic acid. Preparative tlc of the product effected the isolation of a single compound XVI (10%), mp 152–154°, which was identified as 22,27-iminojervan-13(17)-ene-3β,23β-diol by comparison with material[18] prepared from III. Acetylation[18] of XVI and perbenzoic acid oxidation produced the 13β,17β-epoxide XVII (90%), mp 203–204°, τ 9.14 (19-Me),[19] which was hydrolyzed to the N-acetyl derivative XVIII, mp 251–253°, along with the α-epoxide (2%), mp 217–219°, τ 9.21 (19-Me).[19] Refluxing XVIII with potassium hydroxide in aqueous dimethyl sulfoxide (KOH–DMSO) resulted in the formation of a 17α,23β-oxido linkage with concomitant hydrolysis of the N-acetyl group, producing 22,27-imino-17α,23β-oxidojervane-3β,13β-diol (XIX), mp 222–223°, ν_{max}^{Nujol} 1106 cm^{-1}, in 8% over-all yield from XV. The 3-O,N-diacetyl compound, mp 187–189°, underwent dehydration with thionyl chloride and pyridine at −18° for 10 min to give 3-O,N-diacetyl-11-deoxo-5α,6-dihydrojervine (XX), mp 186–187°, in 30% yield along with the $\Delta^{13(18)}$ isomer (40%), $\nu_{max}^{CHCl_3}$ 904 cm^{-1}. Since XX has been prepared in an unambiguous way from III,[20] these results not only establish the structures and stereochemistry of XVI to XX but also the configuration of C-17[3a] in I and III.

Oxidation of XX with chromic anhydride and pyridine gave, as a main product, the 14-hydroxy compound, mp 163–164°, ν_{max}^{Nujol} 3500 cm^{-1}, which resisted mild oxidation. However, after careful chromatography, we could isolate an α,β-unsaturated ketone XXI (mp 150–151°, λ_{max}^{EtOH} 248 mμ (ϵ 22,000), ν 7.72 (18-Me), although in low yield (1%)) which was derived, by successive hydrolysis to the N-acetyl derivative, mp 222–224°, and oxidation with chromic anhydride in dimethylformamide,[21] to the known compound, N-

(12) (a) R. W. Franck, G. F. Rizzi, and W. S. Johnson, *Steroids*, **4**, 463 (1964); (b) T. Masamune, M. Takasugi, and Y. Mori, *Tetrahedron Letters*, 489 (1965).

(13) The remaining part of this fraction, mp 201–213°, λ_{max}^{EtOH} 303 mμ (ϵ 320), would probably be a mixture of the 20 epimers of XIII and XIV. The most mobile fraction (*ca.* 30%) consisted mainly of the styrene derivative.

(14) The ketone XIV crystallized in two forms: needles, mp 222–224°, and plates, mp 229–231°.

(15) K. Saito, *Bull. Chem. Soc. Japan*, **15**, 22 (1940).

(16) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(17) *Cf.* A. W. Burgstahler and L. R. Worden, *J. Am. Chem. Soc.*, **83**, 2587 (1961).

(18) T. Masamune, K. Orito, and A. Murai, *Bull. Chem. Soc. Japan*, **39**, 2503 (1966).

(19) *Cf.* K. Tori, K. Kitahonoki, Y. Takano, H. Tanida, and T. Tsuji, *Tetrahedron Letters*, 559 (1964); H. C. Brown and A. Suzuki, *J. Am. Chem. Soc.*, **89**, 1933 (1967).

(20) T. Masamune, N. Sato, K. Kobayashi, I. Yamazaki, and Y. Mori, *Tetrahedron*, **23**, 1591 (1967).

(21) *Cf.* G. Snatzke, *Ber.*, **94**, 729 (1961).

acetyl-3-dehydro-5α,6-dihydrojervine[20] (XXII), mp 239–241°. The 3-ketone XXII was transformed, through the dienone XXIII, mp 113–115°, τ 3.82 (4-H), 3.76 (2-H), and 2.10 (1-H), into "N-acetyl-Δ⁴-jervone" (XXIV), mp 123–125°, when treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[22] and then hydrogenated over palladium. The α,β-unsaturated ketone XXIV was converted into the enol acetate XXV, mp 218–221°, τ 4.57 (6-H) and 4.24 (4-H), by a known technique,[23] and then reduced with sodium borohydride, giving N-acetyljervine,[24] mp 225–227°, which on saponification (KOH–DMSO) produced, in 2% over-all yield from XXI, jervine, mp 238–240°, identical with the natural product.

Acknowledgment. We wish to express our sincere thanks to Professor S. Okuda, University of Tokyo, and to Dr. I. Iwai, Sankyo Co. Ltd., for providing us with crude jervine.

(22) *Cf.* R. Owyang, "Steroid Reactions," C. Djerassi, Ed., Holden-Day Inc., San Francisco, Calif., 1963, p 227.

(23) *Cf.* J. Iriarte, C. Djerassi, and H. J. Ringold, *J. Am. Chem. Soc.*, **81**, 436 (1959).

(24) K. Saito, H. Suginome, and M. Takaoka, *Bull. Chem. Soc. Japan*, **11**, 172 (1936).

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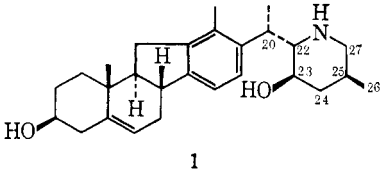
Received April 12, 1967

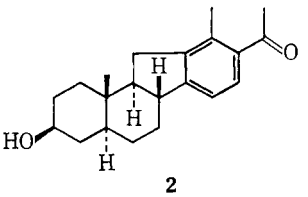
The Synthesis of Veratramine

Sir:

As part of a study directed toward the total synthesis of veratramine (**1**),[1] we have synthesized this substance from 17-acetyl-5α-etiojerva-12,14,16-trien-3β-ol (**2**). The steps for this transformation are described in the present communication.[2] Another route to veratramine, *via* jervine, is described by Masamune and his co-workers.[3] It is noteworthy that the ketone **2** has been obtained[4] by degradation of hecogenin, which has, in turn, been synthesized[5] from isoandrosterone. Since isoandrosterone has been produced by direct total synthesis, the present partial synthesis completes the establishment, in a formal sense, of a totally synthetic pathway to veratramine.

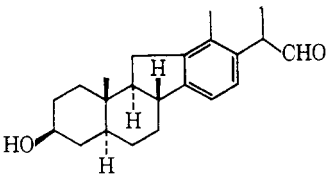


1



2

The ketone **2**,[6] on treatment with dimethylsulfonium methylide (to give the oxirane)[7] followed by boron trifluoride, was converted, in 56% yield, into the aldehyde **3** (mixture of C-20 epimers) which was identified by rigorous comparison with material prepared by degradation of 5α,6-dihydroveratramine.[6,8] A by-product in this degradation, arising from the fragment including carbon atoms 23–27, is β-methyl-γ-aminobutyraldehyde, which on treatment with buffered[9] sodium metaperiodate was converted to 4-methyl-2-pyrrolidone (**4**, R = H); N-*p*-nitrobenzoyl derivative **4** (R = $COC_6H_4NO_2$), mp 107–108°, $[\alpha]^{25}D$ −66.4° (*c* 1.3, EtOH). The aldehyde **3**, as the bisulfite adduct, was submitted to a Strecker reaction with *l*-*t*-butyl 3-methyl-4-aminobutyrate, $[\alpha]^{27}D$ −6.05° (*c* 15, $CHCl_3$), and potassium cyanide to give, after benzoylation, the cyano ester **5** as a mixture of stereoisomers. The amino ester used in this Strecker reaction was produced from racemic material by crystallization of the *l*-tartrate; it was shown to have an optical purity of 93% and also to have the desired (*S*) configuration at the carbon corresponding to C-25 of veratramine by its conversion, upon pyrolysis followed by *p*-nitrobenzoylation, into the aforementioned *l*-amide **4** (R = $COC_6H_4NO_2$). The cyano ester mixture **5**, on treatment with excess methylsulfinylcarbanion in dimethyl sulfoxide,[10] underwent cyclization and cleavage of the 3-benzoate to give the enamino ester **6** (mixture of isomers). This last sub-



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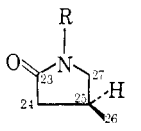

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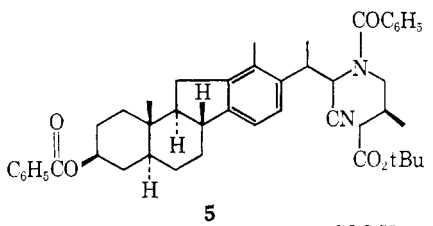

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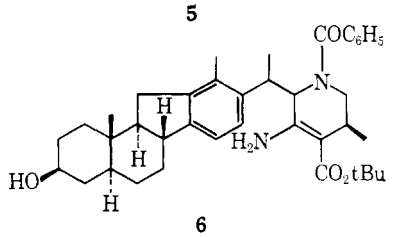

6

(1) Formula **1** respresents the recently revised configuration of veratramine: J. W. Scott, L. J. Durham, H. A. P. deJongh, U. Burckhardt, and W. S. Johnson, *Tetrahedron Letters*, 2381 (1967).

(2) Except for one step, all of this work was disclosed in a lecture delivered on Jan 6, 1966, at the Natural Products Symposium in Kingston, Jamaica. The missing step (**2** → **3**) is described in detail in the Ph.D. dissertation of J. W. Scott, Stanford University, 1966.

(3) T. Masamune, M. Takasugi, A. Murai, and K. Kobayashi, *J. Am. Chem. Soc.*, **89**, 4521 (1967). We gratefully acknowledge Professor Masamune's cooperation in exchanging information.

(4) H. Mitsuhashi and K. Shibata, *Tetrahedron Letters*, 2281 (1964).

(5) Y. Mazur, N. Danieli, and F. Sondheimer, *J. Am. Chem. Soc.*, **82**, 5889 (1960).

(6) R. W. Franck, G. P. Rizzi, and W. S. Johnson, *Steroids*, 463 (1964).

(7) *Cf.* E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, **87**, 1345 (1965).

(8) The previously described (ref 6) specimen of the aldehyde has since been shown to contain a considerable amount of its dimethyl acetal. This contaminant has been eliminated by the use of potassium *t*-butoxide in *t*-butyl alcohol for the fragmentation reaction which afforded aldehyde of good quality, mp 137–150°, in 72% yield.

(9) *Cf.* P. D. Bragg and L. Hough, *J. Chem. Soc.*, 4050 (1958).

(10) *Cf.* J. J. Bloomfield and P. V. Fennessey, *Tetrahedron Letters*, 2273 (1964); E. J. Corey, R. B. Mitra, and H. Uda, *J. Am. Chem. Soc.*, **86**, 485 (1964).