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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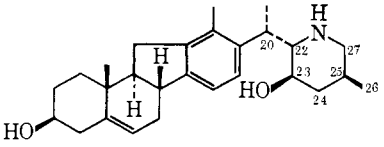
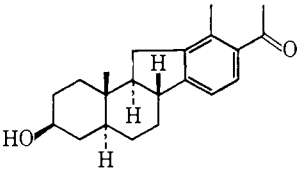
The Synthesis of Veratramine

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.

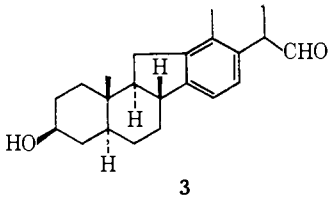


1

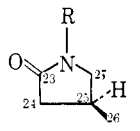


2

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-



3



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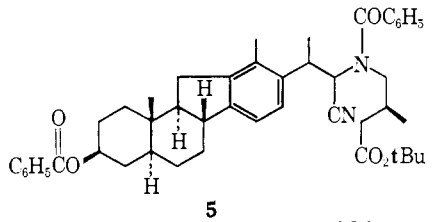

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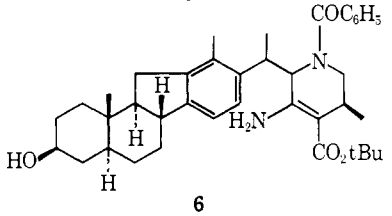
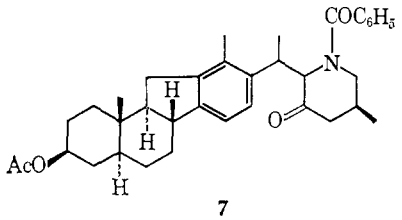


6

(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).

stance was transformed, on treatment with hydrogen chloride in acetic acid, into the ketone **7**, about 14% of which was separated, by crystallization, as a single isomer, mp 252–258.5°. That this isomer belonged to the unnatural (20-iso) series was shown by its transformation, upon saponification and oxidation with Jones reagent,[11] into a diketone, mp 258–261°, which was different from, and therefore stereoisomeric with, either the diketone **8** of natural configuration or 22-iso-**8** described below. The noncrystalline fraction of the ketone **7** was saponified and oxidized[11] to give a mixture the main constituents of which were the diketone **8**, mp 210–212°, and its C-22 epimer, mp 240–242°.



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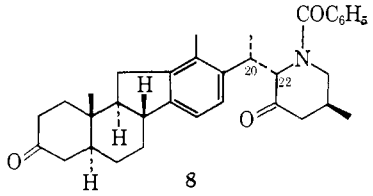
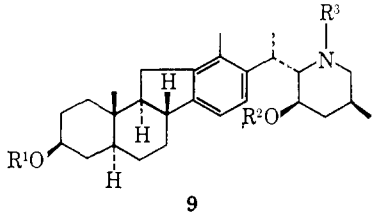


8

These isomers were readily separated by crystallization or by preparative tlc and identified by comparison with authentic specimens produced as follows: 5α,6-dihydroveratramine[12] (**9**, $R^1 = R^2 = R^3 = H$) upon treatment with benzoyl chloride in pyridine followed by selective saponification gave the N-benzoyl compound **9** ($R^1 = R^2 = H$; $R^3 = COC_6H_5$) which on oxidation[11] was converted into the dione **8** of natural configuration, mp 210–212°. This substance on heating with methanolic sodium acetate (or potassium fluoride) was partially isomerized to the 22-iso compound, mp 242–244°. Since the position of the equilibrium is about 1:1, a method was thus available for converting the 22-iso compound partially into the desired diketone **8**. Using this means of increasing the yield, we were able to obtain the synthetic diketone **8** in 6.1% over-all yield from the aldehyde **3**.



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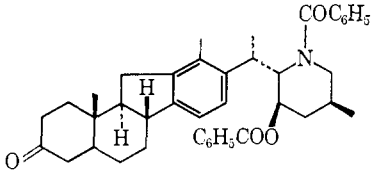

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Reduction of the 210–211° dione with sodium borohydride in isopropyl alcohol gave a mixture of two compounds which were separated by preparative tlc. One of these materials, isolated in 44% yield, was identified as N-benzoyl-5α,6-dihydroveratramine (**9**, $R^1 = R^2 = H$; $R^3 = COC_6H_5$) by comparison with the authentic sample. The second product, isolated in 40% yield, was N-benzoyl-5α,6-dihydro-23-isoveratramine, mp 245–247°. Oxidation of the 23-iso compound with Jones reagent[11] regenerated N-benzoyl-5α,6-dihydroveratramine-3,23-dione, which could be rereduced to produce additional natural isomer. This material on benzoylation followed by selective saponification of the tribenzoyl compound **9** ($R^1 = R^2 = R^3 = COC_6H_5$) was converted into the dibenzoyl derivative **9** ($R^1 = H$; $R^2 = R^3 = COC_6H_5$), mp 254–255.5°. Oxidation[11] of this dibenzoyl derivative afforded the 3-keto compound **10**, mp 233–235°, which was converted, in 51% yield, into the unsaturated ketone (4,5-dehydro-**10**), mp 238–239°, by a known technique.[13] The established method for conversion of a 3-keto-4,5-dehydro steroid into the corresponding 3β-hydroxy-5,6-dehydro steroid[14] was applied to the 239° unsaturated ketone to give, in 52% yield, dibenzoylveratramine. Hydrolysis by heating with potassium hydroxide in ethylene glycol afforded a sample of veratramine which was identical with the natural product.

Acknowledgment. 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.

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

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

(13) R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, A. G. Long, J. F. Oughton, L. Stephensen, T. Walker, and B. M. Wilson, *J. Chem. Soc.*, 4356 (1956).

(14) W. G. Dauben and J. F. Eastham, *J. Am. Chem. Soc.*, 73, 4463 (1951).

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The Total Synthesis of 17-Acetyl-5α-etiojerva-12,14,16-trien-3β-ol

Sir:

We disclose herein the synthesis of the title compound (formula **1**) from simple chemicals. Since we have converted the ketone **1** into veratramine[1] (**2**), the combined achievements constitute a direct, formal total synthesis of veratramine.

Hagemann's ester (**3**) was submitted to the Wilds–Stoutamire annelation sequence,[2] *i.e.*, alkylation with ethyl β-ethoxy-γ-bromocrotonate in the presence of potassium *t*-butoxide to give **4**, followed by hydrolysis with aqueous hydrochloric acid in ethanol, then cyclization of the resulting β-keto ester with piperidine and acetic acid to afford the bicyclic keto diester **5**, mp 56–57°, λ_{max}^{EtOH} 304 (ε 29,500) and 225 mμ (10,600). This last substance, on treatment with 10% palladium on carbon in refluxing *p*-cymene, suffered aromatization

(1) W. S. Johnson, H. A. P. deJongh, C. E. Coverdale, J. W. Scott, and U. Burckhardt, *J. Am. Chem. Soc.*, **89**, 4523 (1967).

(2) A. L. Wilds and D. W. Stoutamire; see the Ph.D. dissertation of D. W. S., University of Wisconsin, 1957. The preliminary experiments in the present application were carried out by J. P. Dickie at the University of Wisconsin.