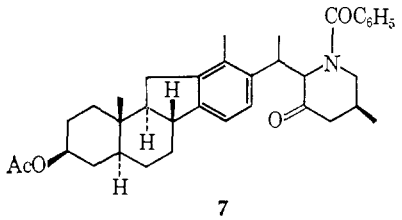
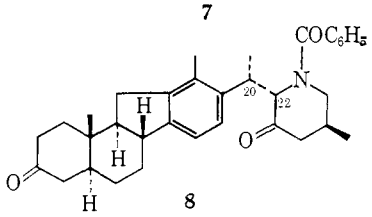
stance was transformed, on treatment with hydrogen chloride in acetic acid, into the ketone **7**, about 14% of which was separated, by crystallization, as a single isomer, mp 252–258.5°. That this isomer belonged to the unnatural (20-iso) series was shown by its transformation, upon saponification and 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°.

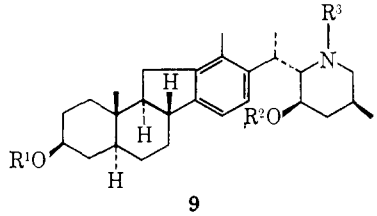


7

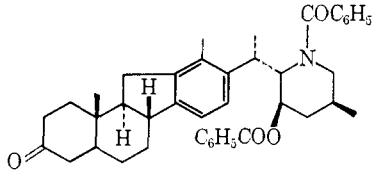


8

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**.



9



10

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).

William S. Johnson, Hendrik A. P. deJongh
Charles E. Coverdale, John W. Scott, Urs Burckhardt
Department of Chemistry, Stanford University
Stanford, California 94305

Received April 24, 1967

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

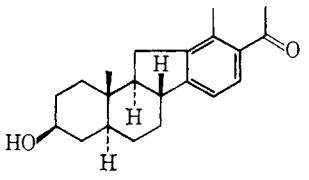
Sir:

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.

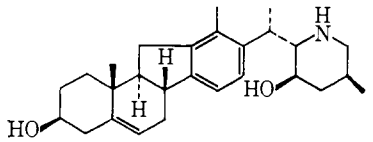
Hagemann's ester (**3**) was submitted to the Wilds–Stoutamire annelation sequence,[2] *i.e.*, alkylation with ethyl β-ethoxy-γ-bromocrotonate in the presence of potassium *t*-butoxide to give **4**, followed by hydrolysis with aqueous hydrochloric acid in ethanol, then cyclization of the resulting β-keto 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.

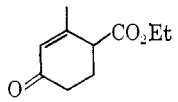


1

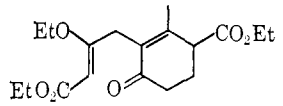


2

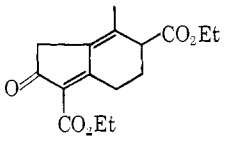
and decarbethoxylation to give the indanone ester **6**, mp 101–103°, λ_{max}^{EtOH} 281 (ϵ 1400) and 241 mμ (12,000). The pyrrolidine enamine, mp 135.5–136°, of the keto ester **6** was treated with ethyl vinyl ketone in dioxane, giving an adduct, mp 94–95°, which on hydrolysis with aqueous acetic acid and sodium acetate afforded the oily diketo ester **7**. This diketo ester, on treatment with 85% phosphoric acid at room temperature, was converted into the tricyclic α,β-unsaturated keto ester **8**, mp 104–105°, λ_{max}^{EtOH} 240 mμ (ϵ 22,300), $\lambda_{max}^{CHCl_3}$ 5.85, 6.05, and 6.24 μ, together with some of its β,γ-unsaturated tautomer, mp 87.5–90°, λ_{max}^{EtOH} 286 mμ (ϵ 18,800), $\lambda_{max}^{CHCl_3}$ 5.84 μ. These structures were confirmed by nmr spectroscopy which clearly showed that the double bond of the β,γ tautomer was in the 8,9 position (steroid numbering).



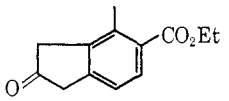
3



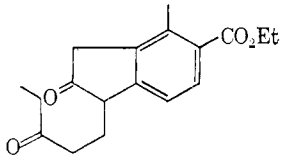
4



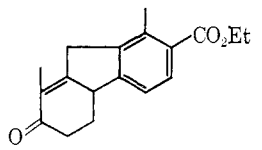
5



6

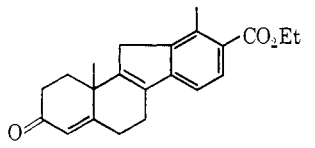


7

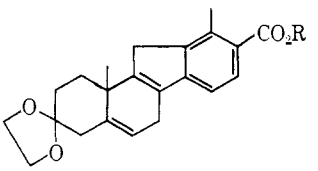


8

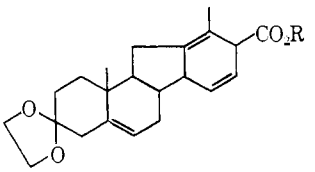
The aforementioned tricyclic ketones, on treatment with methyl vinyl ketone in the presence of ethanolic sodium ethoxide, underwent annelation to give the tetracyclic keto ester **9**, λ_{max}^{EtOH} 231 (ϵ 23,000) and 287 mμ (20,200), $\lambda_{max}^{CCl_4}$ 5.83 and 5.97 μ. Although this substance could not be induced to crystallize, the combustion analysis and the nmr and mass spectra were all in accord with structure **9**. The ethylene ketal **10** (R = Et), produced by acid-catalyzed reaction of the keto ester **9** with ethylene glycol, was saponified to yield the amorphous ketal acid **10** (R = H). A solution of the sodium salt **10** (R = Na) in glyme was prepared by reaction of the acid with sodium hydride, and this was treated with excess potassium in liquid ammonia to give material, probably mainly the substance **11** (R = Na), in which the aromatic nucleus was reduced to the dihydro stage (only end absorption in the ultraviolet spectrum). The acid **11** (R = H) was esterified with diazomethane, giving **11** (R = CH_3) which was treated with dichlorodicyanoquinone in benzene to effect rearomatization of ring D. Preparative thin layer chromatography (tlc) gave a 50% over-all yield (from **10** (R = H)) of crystalline ketal ester **12** (R = CH_3), pure material mp 181–182°. This product was shown to be the racemic form of the naturally derived (see below) ketal ester by nmr, ultraviolet, infrared, mass spectral, tlc, and vpc comparison. The racemic material was saponified and the acid was resolved as the *l*-α-[1-naphthyl]-ethylamine salt. Reconversion to the methyl ester afforded material, mp 200–201°, $[\alpha]^{21}_{589}$ −74° and $[\alpha]^{21}_{320}$ −344° (dioxane) by ORD. The melting point of a mixture of this material with the substance obtained by degradation of veratramine (see below) was also 200–201°.



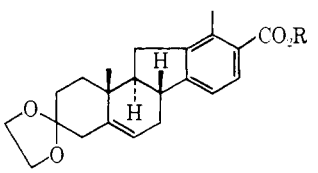
9



10



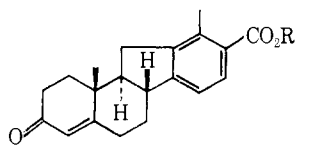
11



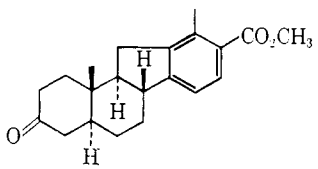
12

The conversion of the optically active ketal ester **12** (R = CH_3) into the ketone **1** was effected by the following transformations which were carried out with the naturally derived substances described below. Base-followed by acid-catalyzed hydrolysis of **12** (R = CH_3) gave the keto acid **13** (R = H) which, as its salt **13** (R = Na), was reduced with lithium in ammonia. The reduction product was converted to the methyl ester and rearomatized as described above to give the 5α,6-dihydro keto ester **14** which, on reduction with sodium borohydride in isopropyl alcohol, was converted into the hydroxy ester **15** (R = CH_3). Saponification, followed by reaction of the resulting acid **15** (R = H) with excess methyllithium, afforded the hydroxy ketone **1**. Thus the synthesis was completed.

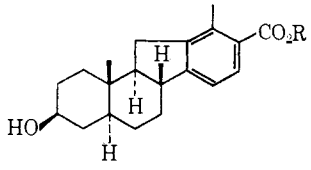
Authentic materials for use in the work described above were prepared as follows. Hypobromite oxidation of the hydroxy ketone **1**[3] afforded the hydroxy



13



14



15

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

acid **15** (R = H), mp 273–276°; treatment with diazomethane gave the ester **15** (R = CH_3), mp 167–168°; oxidation with Jones reagent[4] afforded the keto ester **14**, mp 120–122.5°. The substance **14** was converted, by a known method,[5] into the unsaturated keto ester **13** (R = CH_3), mp 136.5–138°. Treatment with ethylene glycol and *p*-toluenesulfonic acid gave the ketal ester **12** (R = CH_3), mp 200–200.5°, $[\alpha]^{21}_{589}$ −80° and $[\alpha]^{21}_{320}$ −352° (dioxane) by ORD.

Acknowledgment. We wish to express our thanks to the U. S. Public Health Service and the National Science Foundation for supporting this study. We also acknowledge with pleasure the efforts of E. R. Habicht, Jr., and E. T. Jones, who helped to develop the procedures for preparing the tetracyclic material **9**, and of J. W. Scott, who performed some of the transformations involving the naturally derived intermediates. Finally we wish to thank Professor H. S. Mosher for helpful suggestions regarding the resolution experiments.

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

(5) 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, *ibid.*, 4356 (1956).

(6) The preparation of the tricyclic ketone **8** was first performed by W. S. J. and H. W. W. at the University of Wisconsin; H. W. Whitlock, Jr., Ph.D. dissertation, University of Wisconsin, 1960.

William S. Johnson, John M. Cox
Donald W. Graham, Howard W. Whitlock, Jr.[6]
Department of Chemistry, Stanford University, Stanford, California 94305
Received May 4, 1967

Base-Promoted Reactions of Epoxides. III. Carbenoid Decomposition in Acyclic Derivatives

Sir:

Several medium-ring epoxides have been shown to give bicyclic alcohols in transannular reactions induced by strong, nonnucleophilic bases.[1] The rearrangement of cyclooctene oxide shown below is an example of this process. This transformation was demonstrated by Cope and co-workers[2] to proceed by an α elimination–carbenoid insertion mechanism. We have recently examined a number of additional epoxides under similar reaction conditions and have provided several more examples of this type of behavior.[3] However, all of the known instances of carbenoid insertion resulting from base treatment of epoxides have involved a transannular C–H bond in a medium ring,[4] and it was consequently of interest to determine if such reactions are unique to this class of compounds. We are now able to describe two cases of typical carbenoid behavior in noncarbocyclic molecules.

(1) A. C. Cope, H. H. Lee, and H. E. Petree, *J. Am. Chem. Soc.*, **80**, 2849 (1958); A. C. Cope, M. Brown, and H. H. Lee, *ibid.*, **80**, 2855 (1958).

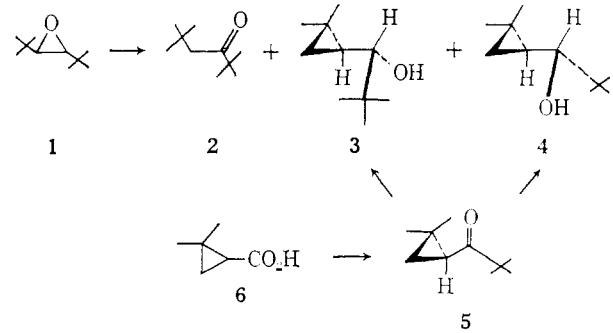
(2) A. C. Cope, G. A. Berchtold, P. E. Peterson, and S. H. Sharman, *ibid.*, **82**, 6370 (1960).

(3) J. K. Crandall and L. H. Chang, *J. Org. Chem.*, **32**, 435, 532 (1967).

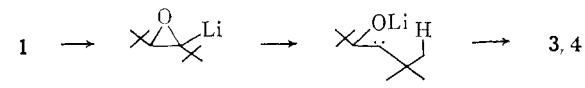
(4) The rearrangement of norbornene oxide to nortricyclanol[5] is an exception, but this carbon skeleton is also particularly prone to transannular reactions.

(5) J. K. Crandall, *J. Org. Chem.*, **29**, 2830 (1964).

trans-Di-*t*-butylethylene oxide[6] (**1**) was selected for examination since competing β elimination[7] is not possible for this species. Treatment of **1** with commercial *t*-butyllithium in hydrocarbon solvent generated three products in the ratio of 28:56:16. The first material was readily recognized as *t*-butyl neopentyl ketone (**2**). The two remaining compounds were deduced to be alcohols from their infrared spectra and are assigned as the diastereomeric cyclopropylcarbinols **3** and **4**. The nmr spectra of the two compounds are very similar; **3** displays a one-proton doublet at δ 2.74 (*CH*OH, J = 9 cps), a one-proton absorption at 1.4 (*OH*), three-proton singlets at 1.17 and 1.07 (CH_3), a nine-proton singlet at 0.92 (*t*-Bu), and a three-proton complex absorption below 0.8 (cyclopropyl protons), while similar absorption for **4** at δ 2.76 (J = 9 cps), 1.05, 1.03, 0.91, and below 0.8 is given a parallel interpretation (the OH proton was obscured in this spectrum). Confirmation of these structures was obtained by the lithium aluminum hydride reduction of cyclopropyl ketone **5** which was in turn prepared by the reaction of *t*-butyllithium with the known acid **6**.[8] The observation of a 91:9 ratio of **3**:**4** in the reduction allows for differentiation between the diastereomeric alcohols on the assumption that steric features determine the course of hydride attack.



The formation of **2** is doubtless similar to several other base rearrangements of epoxides to ketones.[3] Conceivably either an α- or β-elimination mechanism may be operative here, but experimental distinction is lacking. The formation of the diastereomeric cyclopropyl alcohols is rationalized by the sequence of metalation, α elimination, and carbene insertion into a C–H bond of the adjacent *t*-butyl substituent, and this process is depicted below. It is of interest to note that, in contrast to the medium-ring epoxide rearrangements, the insertion products are formed *nonstereospecifically*. The mechanistic implications of this observation will be discussed in the full paper describing this work.



The second example of a carbenoid reaction involves the characteristic addition to an olefinic bond. Attempts to trap a reactive intermediate from various base-induced epoxide decompositions in the presence

(6) All new compounds have spectroscopic and microanalytical data in full agreement with the proposed structures. Known materials have been identified by comparison with authentic samples.

(7) A. C. Cope and J. K. Heeren, *J. Am. Chem. Soc.*, **87**, 3125 (1965).

(8) E. R. Nelson, M. Maienthal, L. A. Lane, and A. A. Benderly, *ibid.*, **79**, 3467 (1957).