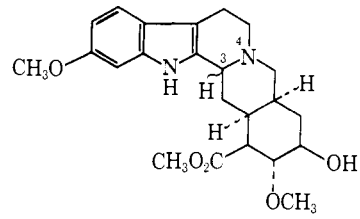
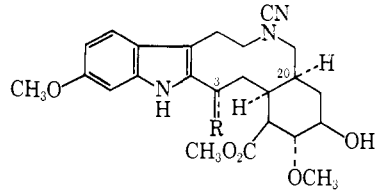
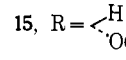
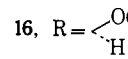


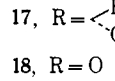
13, 3β-H

14, 3α-H

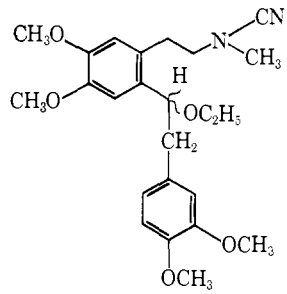


15, R = 

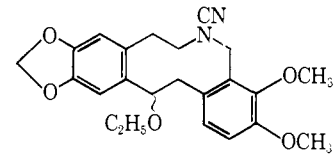
16, R = 

17, R = 

18, R = O



19



20

The above assignments of configuration are based on mechanistic arguments. It is unlikely that a 3-bromo-3-seco derivative is an intermediate in the ring opening, for solvolysis of the bromide should lead, *via* a carbonium ion, to the same epimer or mixture of epimers from both normal (3α-H) and pseudo (3β-H) yohimbanes. The stereoselectivity observed implies that the reaction is mainly an SN2 displacement with nucleophilic attack of alcohol or water on C-3 of the intermediate $N_{(b)}$-cyano quaternary salt, resulting in inversion of configuration at C-3.[10] Formation of a mixture of C-3 epimeric 3-secoyohimbanes,[11] especially in the case of pseudoyohimbanes, is thought to result from simultaneous SN1 and SN2 processes.

With cyanogen bromide in ethanol–chloroform yohimban-17-one (**3**) gives 95% of (3*R*)-ethoxy-3-secocyanamide **9** [$\delta_{TMS}^{DMSO-d_6}$ 4.57 (1 H, m) (C_3–H)] and α-yohimbine (**4**) gives 73% of (3*R*)-ethoxy-3-secocyanamide **10** [$\delta_{TMS}^{CDCl_3}$ 4.40 (1 H, m) (C_3–H)].

(10) High stereospecificity has been observed in the cyclization of (−)-methadone (6-dimethylamino-4,4-diphenylheptan-3-one) to (+)-2-ethylidine-5-methyl-3,3-diphenyltetrahydrofuran with cyanogen bromide, while a lower degree of stereospecificity was obtained with (+)-phenadoxone (6-morpholino-4,4-diphenylheptan-3-one): A. F. Casy and M. M. A. Hassan, *J. Chem. Soc., C*, 683 (1966); see also N. J. Harper, D. Jones, and A. B. Simmonds, *ibid., C*, 438 (1966).

(11) Models strongly suggest that in 3-secocyanamide derivatives the hydroxyl or ethoxyl groups at C-3 will occupy an extraannular position in the ten-membered ring in order to avoid steric crowding (van der Waals compression) with the intraannular hydrogens. Thus 3-seco derivatives with the *R* configuration at C-3 probably exist in a different conformation than those with the *S* configuration at C-3.

The reaction is not limited to 1,2,3,4-tetrahydro-β-carbolines but works well with 1,2,3,4-tetrahydroisoquinolines. For example, (±)-laudanosine and cyanogen bromide in ethanol–chloroform give, in 71% yield, only **19**: mp 84–87°; $\delta_{TMS}^{CDCl_3}$ 1.18 (3 H, t) (CH_3-CH_2O–), 2.73 (3 H, s) (NCH_3), 3.33 (2 H, q) (CH_3CH_2-O–), 4.57 (1 H, t) (>CHO–). Likewise, the tetrahydroisoquinoline ring of (±)-canadine[12] is cleanly cleaved[13] to give 68% of 14-ethoxy-14-secocyanamide **20**: mp 164–166°; $\delta_{TMS}^{CDCl_3}$ 1.13 (3 H, t) (OCH_2CH_3), 3.30 (2 H, q) (OCH_2CH_3), 4.60 (1 H, m) (>CHO–).

The 3-hydroxy-3-secocyanamides are readily oxidized to 2-acylindoles.[14] Thus, when (3*R*)-hydroxy-3-secocyanamide **11**, obtained in 94% yield from yohimban-17-one (**3**) and cyanogen bromide in aqueous tetrahydrofuran, is allowed to react with lead tetraacetate in glacial acetic acid,[15] 3-keto-3-secocyanamide **12** [ν_{max}^{KBr} 1715, 1642 cm^{-1}; λ_{max}^{MeOH} 208, 238, 312 mμ (ε 23,300, 13,000, 18,000)] is obtained in 67% yield. (3*S*)-Hydroxy-3-secocyanamide **17** gives **18**, λ_{max}^{MeOH} 215, 232 sh, 260, 336 mμ (ε 25,500, 12,800, 6400, 21,700).

Further details and extensions of this reaction will be reported in our full paper.

Acknowledgment. We wish to thank Mr. L. M. Brancone and staff for elemental analyses, Mr. W. Fulmor and staff for infrared, pmr, and ultraviolet spectral measurements, and Dr. J. Karliner for mass spectral measurements.

(12) Prepared by reduction of berberinium chloride (S. B. Penick and Co.) with sodium borohydride: R. Mirza, *J. Chem. Soc.*, 4400 (1957).

(13) In contrast degradation of (±)-canadine with cyanogen bromide in refluxing benzene gives a complex mixture of products: I. Sallay and R. H. Ayers, *Tetrahedron*, **19**, 1397 (1963).

(14) For a recent review of 2-acylindole alkaloids see J. A. Weisbach and B. Douglas, *Chem. Ind.* (London), 623 (1965); 233 (1966).

(15) Previous workers have used manganese dioxide for this type of transformation: L. J. Dolby and S. Sakai, *J. Am. Chem. Soc.*, **86**, 1890 (1964); G. H. Foster, J. Harley-Mason, and W. R. Waterfield, *Chem. Commun.*, 21 (1967).

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Received April 15, 1969

Total Synthesis of *dl*-Sirenin

Sir:

As a result of the outstanding investigations of Machlis, Rapoport, and collaborators, the powerful sperm attractant produced by the female gametes of the water mold *Allomyces*, termed sirenin, has been isolated and shown to possess structure **1**.[1] This communication describes a synthesis of sirenin which parallels that recently employed[2] for the synthesis of the parent hydrocarbon, sesquicarene (**2**),[3] also a naturally occurring substance.

The hydroxy ester **9** was synthesized by two different routes, one stereoselective and the other stereospecific but less efficient. Treatment of geranyl acetate with 1.6 equiv of ozone in methylene chloride–pyridine[4] at

(1) W. H. Nutting, H. Rapoport, and L. Machlis, *J. Am. Chem. Soc.*, **90**, 6434 (1968), and references cited therein.

(2) E. J. Corey and K. Achiwa, *Tetrahedron Letters*, 1837 (1969).

(3) Y. Ohta and Y. Hirose, *ibid.*, 1251 (1968).

(4) G. Slomp, Jr., and J. L. Johnson, *J. Am. Chem. Soc.*, **80**, 915 (1958).

−78° followed by reduction at −78° to room temperature with excess zinc in acetic acid afforded 57% of the acetoxy aldehyde **3**.[5-7] This aldehyde was allowed to react at 0° with the sodio derivative of diethyl carboxyethylethanephosphonate[8,9] in tetrahydrofuran to give a mixture of the *trans,trans*-acetoxy ester **4** and its *cis,trans* isomer (ratio 88:12), from which the pure *trans,trans* isomer **4**[5-7] was obtained in 73% yield by preparative layer chromatography (plc) on silica gel with 1:6 ether–hexane as solvent (three developments). The nmr spectrum of **4** exhibited two triplets, each due to one olefinic proton, at 5.35 (J = 7 Hz, C-7) and 6.64 ppm (J = 7 Hz, C-3) and peaks due to two olefinic methyl groups at 1.73 (s, C-6) and 1.78 ppm (d, J = 1.5 Hz, C-2); the infrared spectrum showed carbonyl peaks at 5.73 and 5.83 μ. The acetoxy ethyl ester **4** was converted into the hydroxy mesitoate **9** by the following sequence: (1) deacetylation with 0.5 M potassium carbonate in ethanol at 25° for 3.5 hr to form **5**[5,6] (98% yield; molecular ion found at m/e 212.1404; calcd 212.1412); (2) ether formation with 1.5 equiv of dihydropyran in *ca.* six volumes of ether containing 0.06 equiv of *p*-toluenesulfonic acid at 25° for 1 hr to form **6**[5,6] (>98% yield); (3) ester reduction with lithium aluminum hydride–aluminum chloride (3.7:1) in ether at 0° for 20 min to give **7**[5,6] (95% yield); (4) acylation with mesitoyl chloride in pyridine–chloroform at 0° for 14 hr and 23° for 1 hr to from **8**[5-7] isolated in 95% yield after column chromatography using alumina III (neutral); (5) ether cleavage with 2.8 mM *p*-toluenesulfonic acid in methanol at 0° for 1 hr and 23° for 2 hr to give **9**[5-7] (90% yield after plc). The alternative route to **9** proceeded by the sequence: (1) Wittig chloromethylenation of **3** using the ylide from chloromethyltriphenylphosphonium chloride and lithium piperidide in ether[10] followed by deacetylation with sodium methoxide in methanol and dehydrochlorination with butyllithium in ether at 0° for 1 hr to form **10**[5,6] (55% from **3**; molecular ion found at m/e 124.0875; calcd 124.0888); (2) etherification with dihydropyran–*p*-toluenesulfonic acid in ether to give **11**[5,6] (98%); (3) metalation with butyllithium in tetrahydrofuran and hydroxymethylation with dry paraformaldehyde to form **12**[5-7] (68%); (4) reduction with lithium aluminum hydride–aluminum chloride (35:1) in tetrahydrofuran at 45–55° for 3.5 hr, quenching of excess hydride with ethyl acetate, and iodination with excess iodine at −78° to give the iodo ether **13**[5-7,11,12] (49% yield); (5) finally, methylation with dimethylcopperlithium[11,13] led to the diol mono ether **7** (30%) identical with the product obtained by the first sequence.

Reaction of the hydroxy ester **9** with 0.4 molar equiv of phosphorus tribromide in ether at 0° for 6 hr afforded the bromo ester **14**[5,6] (>95%), which was subjected to ethynylation with the lithio derivative of propargyl tetrahydropyranyl ether in tetrahydrofuran at 25° for 15 hr and subsequent acid-catalyzed methanolysis to give 73% of the acetylenic hydroxy ester **15**,[5,6] molecular ion at m/e 354.2186 (calcd 354.2195). The nmr spectrum of **15** exhibited peaks at 1.61 and 1.70 ppm each due to methyl attached to C=C, triplets at 5.27 (J = 6.5 Hz) and 5.60 (J = 7 Hz) ppm each due to an olefinic proton, peaks at 4.14 and 4.70 ppm each due to a pair of oxymethylene protons, as well as peaks due to the mesitoate group; the infrared spectrum showed bands at 2.83 and 2.92 μ (OH), 4.43 and 4.53 μ (C≡C), and 5.78 μ (mesitoate CO). Selective saturation of the triple bond in **15** was performed using hydrogen and P-1 type nickel boride[14] catalyst in aqueous ethanol to give 80% yield (after plc) of the alcohol **16**,[5-7] which was oxidized by chromium trioxide–pyridine (1:2) complex in methylene chloride to the corresponding aldehyde and thence with alkaline silver oxide to the acid **17**,[5,6] molecular ion found at m/e 375.2300 (calcd 375.2300), in 76% yield. The acid **17** was converted *via* the acid chloride (from oxalyl chloride and the sodium salt in benzene) to the diazo ketone **18** with excess diazomethane, infrared max (cyclohexane) 4.74 (N_2 stretch), 5.76 (mesitoate C=O), and 5.98 μ (diazo ketone C=O).

The diazo ketone **18** was heated at reflux for 2 hr in 10^{-2} M solution in cyclohexane with 2 equiv of anhydrous copper sulfate to give as the only volatile product the bicyclic ketone **19**,[5-7] purified by plc and distillation at 180° (0.008 mm); yield 58%, molecular ion found at m/e 368.2349 (calcd 368.2351), carbonyl absorption at 5.79 and 5.91 μ, purity >99% by vpc analysis using a 3% OV-7 column at 220°.[15] The nmr spectrum of **19** indicated *inter alia* the presence of a single olefinic proton (5.55 ppm, t, J = 7 Hz), one methyl group attached to a quaternary carbon (1.12 ppm, s), and one methyl attached to C=C (1.73 ppm, br s). Ethoxycarbonylation of **19** (sodium hydride, excess ethyl carbonate in dimethoxyethane at 25° for 4 hr) afforded 57% of the β-keto ester **20**, largely in the enolic form,[5,6] molecular ion found at m/e 440.2563 (calcd 440.2563). Reduction of **20** with sodium borohydride in ethanol at −20° for 45 hr gave the corresponding β-hydroxy ester[5,6] which was benzoylated (benzoyl chloride–pyridine) and subsequently subjected to α,β elimination of benzoic acid (1.5 equiv of potassium *t*-butoxide in *t*-butyl alcohol at 25° for 15 min) to afforded the doubly unsaturated diester **21**[5,6] in 42% yield (from **20**) after plc; molecular ion found at m/e 424.2595 (calcd 424.2613); infrared max due to $COOC_2H_5$ at 5.87 μ and mesitoyl at 5.81 μ; nmr absorption due to olefinic protons at 7.18 (d, J = 5 Hz, β to $COOC_2H_5$) and 5.60 ppm (t, J = 7 Hz) and one unsplit methyl at

(5) Nmr spectra were obtained (in CCl_4 at 60 MHz unless otherwise indicated) for each intermediate and were in every instance in accord with the assigned structure. Chemical shifts are expressed in parts per million downfield from tetramethylsilane and coupling constants are given in hertz.

(6) Infrared spectra were obtained for each intermediate (neat or in CCl_4, except for that of **1**, which was determined in $CHCl_3$) and were consistent with the structures indicated.

(7) Satisfactory C, H analyses were obtained.

(8) K. Sasaki, *Bull. Chem. Soc. Japan*, **41**, 1252 (1968).

(9) T. H. Kinstle and B. Y. Mandanas, *Chem. Commun.*, 1699 (1968).

(10) G. Köbrich, H. Trapp, K. Flory, and W. Drischel, *Chem. Ber.*, **99**, 689 (1966).

(11) (a) E. J. Corey, J. A. Katzenellenbogen, and G. H. Posner, *J. Am. Chem. Soc.*, **89**, 4245 (1967); (b) E. J. Corey, J. A. Katzenellenbogen, N. W. Gilman, S. A. Roman, and B. W. Erickson, *ibid.*, **90**, 5618 (1968).

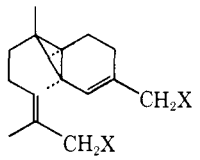
(12) The 2-iodo alcohol **13** was formed stereospecifically, but the 3-iodo isomer was also produced (ratio *ca.* 2:1, respectively) under a variety of conditions. The position isomeric iodo alcohols, each the product of *trans* addition of H and I to the triplet bond, were separated by plc on silica gel using 1:1 hexane–ether with four developments (R_f 0.39 and 0.49 for the 2-iodo (**13**) and 3-iodo alcohols, respectively).

(13) E. J. Corey and G. H. Posner, *J. Am. Chem. Soc.*, **89**, 3911 (1967).

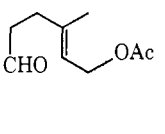
(14) C. A. Brown and H. C. Brown, *ibid.*, **85**, 1003 (1963).

(15) For other examples of intramolecular addition of α-diazo ketones, see G. Stork and J. Ficini, *ibid.*, **83**, 4678 (1961), and E. Piers, W. De Waal, and R. W. Britton, *Chem. Commun.*, 188 (1968).

0.92 ppm. Reduction of **21** using a twofold excess of lithium aluminum hydride–aluminum chloride (3:1) in ether at 0° for 10 min and 25° for 1 hr afforded after plc (on silica gel buffered to pH 10 using ether for development) 76% of pure *dl*-sirenin (**1**)[5,6] as a colorless oil, molecular ion found at *m/e* 236.1775 (calcd 236.1776). Vapor phase chromatographic analysis of the bis(trimethylsilyl) derivative of **1** using a 2.5 ft × 0 125 in. column of 3% OV-7 on neutral silanized support at 180° showed a single peak (retention time 5.0 min at 60 cc/min N_2 flow).



1, X = OH
2, X = H



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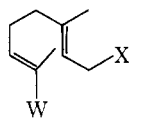
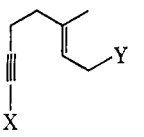
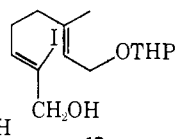


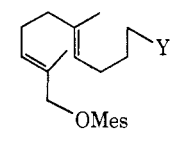
4, W = COOEt; X = OAc
5, W = COOEt; X = OH
6, W = COOEt; X = OTHP
7, W = CH_2OH; X = OTHP
8, W = CH_2OMes; X = OTHP
9, W = CH_2OMes; X = OH
14, W = CH_2OMes; X = Br
15, W = CH_2OMes; X = C≡CCH_2OH



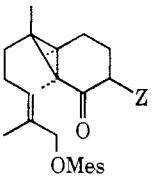
10, X = H; Y = OH
11, X = H; Y = OTHP
12, X = CH_2OH; Y = OTHP



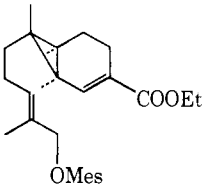
13



16, Y = CH_2OH
17, Y = COOH
18, Y = $COCHN_2$



19, Z = H
20, Z = COOEt



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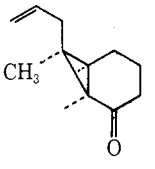

22

The nmr and infrared spectra of synthetic **1** were in complete agreement with reference spectra of natural sirenin kindly provided by Professor H. Rapoport. The nmr spectrum of synthetic **1** (obtained at 100 MHz in chloroform solution) displayed a sharp singlet due to cyclopropyl CH_3 at 0.88 ppm, a broadened peak due to C=CCH_3 at 1.67 ppm, a peak (4 H) due to two carbinyl methylenes at 3.98 ppm, and two olefinic protons at 5.39 (broadened triplet) and 5.82 (broad) ppm, in addition to a complex series of peaks in the region 1–2.2 ppm due to the remaining protons.

Bioassays of synthetic and natural sirenin, kindly performed by Prof. L. Machlis using an approximate (order of magnitude precision) method, indicated comparable biological activity.

A particularly interesting feature of this synthesis of *dl*-sirenin is the efficiency and stereospecificity of the cyclization of the acyclic diazo ketone **18** to the bicyclic ketone **19**. In this connection mention should be made of unpublished work in this laboratory concerning an alternative synthesis of the bicyclo[4.1.1]heptan-2-one system which leads predominantly to the oppostie arrangement of the groups at C-7. Reaction of diphenylsulfonium (1-allyl)ethylide with 2-cyclohexenone[16] produces **22** as the major product.[17]

(16) E. J. Corey and M. Jautelat, *J. Am. Chem. Soc.*, **89**, 3912 (1967).
(17) This work was supported by the National Institutes of Health and the National Science Foundation.

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Received May 16, 1969

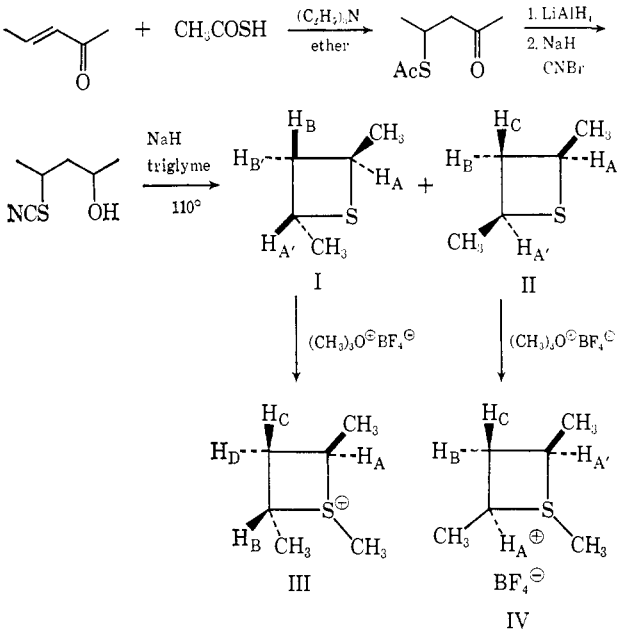
Stereochemistry of Fragmentation of Thietanonium Salts

Sir:

We wish to report the stereochemistry of an unusual fragmentation reaction of thietanonium salts. Such a study provides insight into the effect of d orbitals on the course of reactions in organosulfur compounds.[1]

We have found that treatment of S-methylthietanonium salts with *n*-butyllithium produces cyclopropanes and *n*-butylmethyl sulfide.[2] To elucidate the nature of this process we examined the behavior of the salts derived from *cis*- and *trans*-2,4-dimethylthietane. Scheme I summarizes the syntheses of the requisite materials.[3]

Scheme I



The stereochemistry of the thietanes was assigned utilizing nmr. The *cis* isomer shows the ring protons as

(1) For our previous paper in this series, see B. M. Trost, R. W. LaRochelle, and R. C. Atkins, *J. Am. Chem. Soc.*, **91**, 2175 (1969).
(2) A report of the treatment of thietane with *n*-butyllithium has appeared. A 11% yield of lithium *n*-butylmercaptide was detected and cyclopropane was assumed to be the second product; see F. G. Bordwell, H. M. Andersen, and B. M. Pitt, *ibid.*, **76**, 1082 (1954). Reaction of our thietanes with *n*-butyllithium did not produce any detectable amounts of cyclopropanes.
(3) This mode of synthesis represents a modification of the scheme of S. Searles, Jr., H. R. Hays, and E. F. Lutz, *J. Org. Chem.*, **27**, 2828 (1962).