The ratio of **10** to **9** increases as the molar amount of $CuCl_2$ increases.

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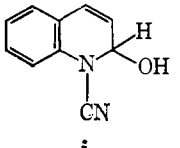
Alkaloid Studies. V.[1] Reaction of Tertiary Amines with Cyanogen Bromide under Solvolytic Conditions

Sir:

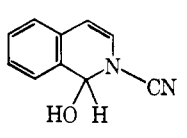
We wish to report the use of water and alcohols as participating solvents in the von Braun reaction. Classically,[2] reactions of tertiary amines with cyanogen bromide are normally carried out in inert solvents such as ether, chloroform, or benzene, and only meager information is available on the course of the reaction in hydroxylic solvents.[3] In addition, configurational changes occurring around the carbon which picks up bromide in the von Braun cyanogen bromide reaction have not been thoroughly studied. We have found that yohimbanes and alloyohimbanes react with cyanogen bromide in ethanol–chloroform or in aqueous tetrahydrofuran to give high yields of 3-substituted 3-secocyanamides. These result from ring opening between $N_{(b)}$ and C-3 with concomitant introduction of hydroxyl or ethoxyl groups at C-3.[4] The reaction is noteworthy in that: (i) it occurs cleanly at benzylic positions, (ii) it allows the introduction of hydroxyl or alkoxyl groups, and (iii) it occurs without formation of troublesome reactive bromides.

Reaction of 2 moles of yohimbine (**1**) with 1 mole of cyanogen bromide in ethanol–chloroform (1:3) for 20 hr at room temperature yields, after removal of precipitated **1**·HBr, 94% of (3*R*)-ethoxy-3-secocyanamide **5**:[5,6] mp 115–125°: $[\alpha]^{25}D$ −27° (*c* 1, pyridine); ν_{max}^{KBr} 2198 (CN), 1718 cm^{-1} (CO); $\delta_{TMS}^{CDCl_3}$ 1.07 (3H, t) (CH_3-CH_2O–), 3.80 (3 H, s) ($COOCH_3$), 4.33 (1 H, m) (C_3–H). Under the same conditions pseudoyohimbine (**2**) gives 59% of (3*S*)-ethoxy-3-secocyanamide **6** [mp 174–176°; $[\alpha]^{25}D$ −97° (*c* 1, pyridine); ν_{max}^{KBr} 2208 (CN), 1704 cm^{-1} (CO); $\delta_{TMS}^{CDCl_3}$ 1.18 (3 H, t) (CH_3CH_2O–), 3.78 (3 H, s) ($COOCH_3$), 4.78 (1 H, m) (C_3–H)] and 9% of (3*R*)-ethoxy compound **5**. In tetrahydrofuran–water (2.5:1) yohimbine (**1**) and cyanogen bromide give 81% of (3*R*)-hydroxy-3-secocyanamide **7** [$\delta_{TMS}^{DMSO-d_6}$ 3.70 (3 H, s) ($COOCH_3$), 4.80 (1 H, d) (C_3–OH), 4.97 (1 H, m) (C_3–H)] whereas pseudoyohimbine (**2**) gives 35% of (3*S*)-hydroxy-3-secocyanamide **8** [$\delta_{TMS}^{DMSO-d_6}$ 3.53 (3 H, s) ($COOCH_3$), 5.07 (1 H, m) (C_3–H), 5.15 (1 H, d) (C_3–OH)] and 10% of (3*R*)-hydroxy compound **7**.

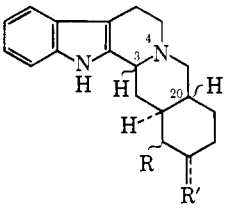
Methyl reserpate (**13**), with cyanogen bromide in ethanol–chloroform, affords 70% of (3*S*)-ethoxy derivative **15** [mp 258–260°; $\delta_{TMS}^{CDCl_3}$ 4.68 (1 H, m) (C_3–H)] whereas methyl 3-isoreserpate (**14**) affords 59% of (3*R*)-ethoxy derivative **16** [mp 270–272°; $\delta_{TMS}^{CDCl_3}$ 4.27 (C_3–H)]. In aqueous tetrahydrofuran, methyl reserpate gives 70% of (3*S*)-hydroxy-3-secocyanamide **17** which, when refluxed with ethanol, is converted exclusively to (3*S*)-ethoxy-3-secocyanamide **15**[7] (stereospecific replacement with retention of configuration).[8,9]



i



ii

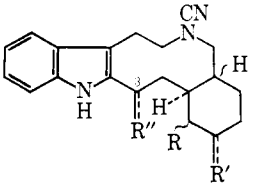


1, 3α-H, 20β-H, R = ---CO_2CH_3; R′ =

2, 3β-H, 20β-H, R = ---CO_2CH_3; R′ =

3, 3α-H, 20β-H, R = H; R′ = O

4, 3α-H, 20α-H, R = —CO_2CH_3; R′ =



5, 20β-H, R = ---CO_2CH_3; R′ =  ; R″ =

6, 20β-H, R = ---CO_2CH_3; R′ =  ; R″ =

7, 20β-H, R = ---CO_2CH_3; R′ =  ; R″ =

8, 20β-H, R = ---CO_2CH_3; R′ =  ; R″ =

9, 20β-H, R = H; R′ = O; R″ =

10, 20α-H, R = —CO_2CH_3; R′ =  ; R″ =

11, 20β-H, R = H; R′ = O; R″ =

12, 20β-H, R = H; R′ = R″ = O

(1) Alkaloid Studies. IV: J. D. Albright, J. C. Van Meter, and L. Goldman, *Lloydia*, **28**, 212 (1965).

(2) H. A. Hageman, *Org. Reactions*, **7**, 198 (1953).

(3) Quinolines and isoquinolines are reported to give hydroxy-substituted derivatives such as i and ii in the presence of moisture;[2] however, it has not been established that these derivatives are formed through bromo intermediates.

(4) A. F. Casy and M. M. A. Hassan [*Tetrahedron*, **23**, 2075 (1967)] have reported the cyclization of 6-dimethylamino-4,4-diphenyl-3-heptanol with cyanogen bromide to give 2-ethyl-3,3-diphenyl-5-methyltetrahydrofuran—an example of an internal alcohol function reacting with the initially formed quaternary cyanodimethylammonium bromide.

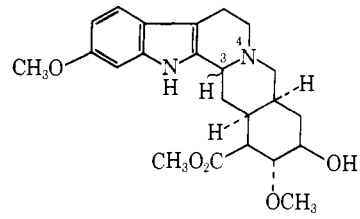
(5) All products reported here are new compounds; elemental analyses and infrared, ultraviolet, pmr, and mass spectra support the assigned structures.

(6) *R,S* configurational nomenclature is used to denote configuration at the asymmetric C-3 center.

(7) A closely related reaction is conversion of 18-hydroxyibogaine to 18-methoxyibogaine with acidic methanol: G. Büchi and R. E. Manning, *J. Am. Chem. Soc.*, **88**, 2532 (1966).

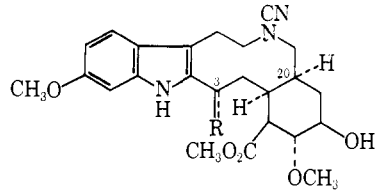
(8) Replacement of a C-3 hydroxyl group in 3-secocyanamides must depend on the stereochemistry of the ring fusion between the ten- and six-membered rings because the C-3 hydroxyl in **8** and **11** is not replaced by refluxing in ethanol. Ease of replacement and retention of configuration may result from participation of the C-16 ethoxycarbonyl function in **17**.

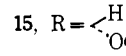
(9) See P. B. D. de la Mare in "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, pp 30–51, for a discussion on retention of configuration in allylic cationic intermediates.

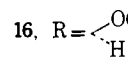


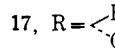
13, 3β-H

14, 3α-H

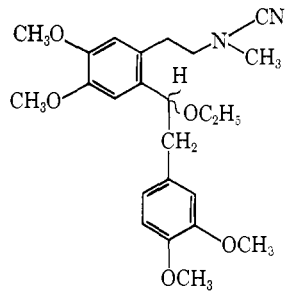


15, R = 

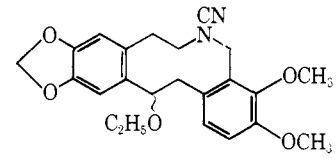
16, R = 

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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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).