creased by using a threefold excess of **1**, in which case 90% of **6** was consumed and a 38% yield of **7** was again obtained.

It is thus apparent that it is possible to use simple complexing forces in remote oxidation to align the reagent and substrate and achieve selective functionalization. While we have observed a somewhat greater proportion of side reactions in this case, with resulting lower yields than we achieved in the situation[1,2] in which reagent and substrate were directly attached, the yield of 38% in the conversion of **6** to pure **7** uncontaminated by other isomers is certainly respectable. Furthermore, it may be possible to use complexing forces in situations in which a direct covalent attachment of reagent and substrate is not possible, as in our previously demonstrated selective aromatic substitution[8] in which hydrophobic binding forces orient a reagent and a substrate. Such extensions move us closer to the original inspiration for all such efforts, the highly selective substitutions of unactivated positions in some enzymatic reactions because of the orientation within an enzyme–substrate complex.[9]

(8) R. Breslow and P. Campbell, *J. Amer. Chem. Soc.*, 91, 3085 (1969); *Bioorg. Chem.*, in press.

(9) We wish to acknowledge helpful assistance by Mr. Jerome Groopman, and financial support of the work by the National Institutes of Health.

(10) NIH Postdoctoral Fellow, 1969–1971.

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An Unambiguous Synthesis of *Cypridina* Etioluciferamine. An Application of Titanium Tetrachloride to the Synthesis of Pyrazine *N*-Oxides

Sir:

Cypridina luciferin (**1**) is a bioluminescent compound found in the ostracod *Cypridina hilgendorfii*.[1,2] Due to the relative simplicity of the light emitting reaction, which requires only the enzyme, oxygen, and luciferin,[2,3] this natural product is useful in bioluminescence studies.[4] Aside from firefly luciferin,[5,6] *Cypridina* luciferin is the only complex luciferin for which a structure has been proposed.

Structure **1** was established by Kishi, *et al.*,[7] with the exception that the placement of the indol-3-yl moiety on the 6 position of the imidazo[1,2-a]pyrazine nucleus was not established rigorously; it could also have been located at C-5.[7b] This ambiguity was not solved by a synthesis of *Cypridina* luciferin[8–10]

(1) A. M. Chase, *Ann. N. Y. Acad. Sci.*, 49, 353 (1948).

(2) E. N. Harvey, "Bioluminescence," Academic Press, New York, N. Y., 1952, pp 299–331.

(3) T. Goto and Y. Kishi, *Angew. Chem., Int. Ed. Engl.*, 7 (6), 411 (1968).

(4) T. Goto, *Pure Appl. Chem.*, 17, 421 (1968).

(5) E. H. White, F. McCapra, G. Field, and W. D. McElroy, *J. Amer. Chem. Soc.*, 83, 2402 (1961).

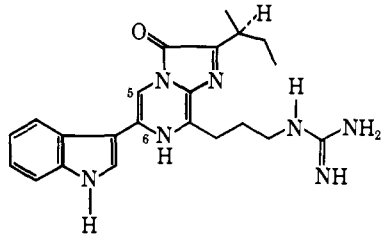
(6) E. H. White, F. McCapra, and G. Field, *ibid.*, 85, 337 (1963).

(7) (a) Y. Kishi, T. Goto, Y. Hirata, O. Shimomura, and F. H. Johnson, *Tetrahedron Lett.*, 3427 (1966); (b) mass spectra and amino acid analyses, the data reported,[7a] are ambiguous on this point.

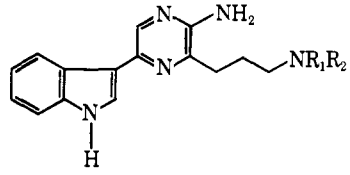
(8) Y. Kishi, T. Goto, S. Inoue, S. Sugiura, and M. Kishimoto, *Tetrahedron Lett.*, 3445 (1966).

(9) S. Sugiura, S. Inoue, Y. Kishi, and T. Goto, *Yakugaku Zasshi*, 89 (12), 1652 (1969); *Chem. Abstr.*, 72, 90405z (1970).

(10) Y. Kishi, S. Sugiura, S. Inoue, and T. Goto, *Yakugaku Zasshi*, 89 (12), 1657 (1969); *Chem. Abstr.*, 72, 90406a (1970).



1

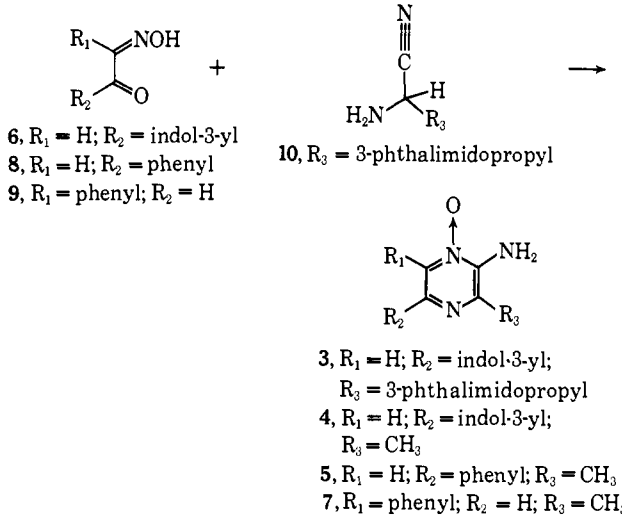


2, $R_1 = R_2 = H$
11, R_1R_2 = phthalimido
12, R_1 = H; R_2 = benzoyl

since the pathway used could have led to either the 5- or 6-indol-3-yl substituted isomers.[11] It was to settle this question that we undertook a synthesis of *Cypridina* etioluciferamine (**2**), a degradation product of *Cypridina* luciferin that has been converted to the luciferin in two steps.[8–10]

The 2-aminopyrazine 1-oxide synthesis of Sharp and Spring[12] shown in Scheme I was used in our synthesis

Scheme I



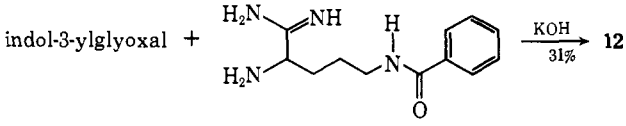
6, R_1 = H; R_2 = indol-3-yl
8, R_1 = H; R_2 = phenyl
9, R_1 = phenyl; R_2 = H

10, R_3 = 3-phthalimidopropyl

3, R_1 = H; R_2 = indol-3-yl; R_3 = 3-phthalimidopropyl
4, R_1 = H; R_2 = indol-3-yl; $R_3 = CH_3$
5, R_1 = H; R_2 = phenyl; $R_3 = CH_3$
7, R_1 = phenyl; R_2 = H; $R_3 = CH_3$

for the preparation of the key intermediate **3**. Work with model compounds showed that the yields of substituted 2-aminopyrazine 1-oxides could be greatly increased by using titanium tetrachloride in this reaction. This reagent may function by complexing with the carbonyl moiety of the α-oximino ketone and therefore increasing that group's susceptibility to attack by the α-aminonitrile in the first step of the ring-forming reaction.[13,14] The yield

(11) The reaction used in the synthesis was a condensation of an α-aminoamidine with a substituted glyoxal



(12) W. Sharp and F. S. Spring, *J. Chem. Soc.*, 932 (1951).

(13) W. A. White and H. Weingarten, *J. Org. Chem.*, 32, 213 (1967).

(14) H. Weingarten, J. P. Chupp, and W. A. White, *ibid.*, 32, 3246 (1967).

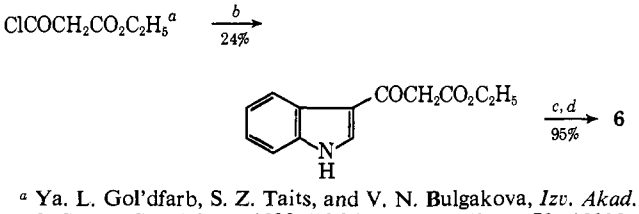
of **5** (mp 188.5–189.5° dec; lit.[12] 188–189°)[15] was raised from 3% (chloroform, reflux 8 hr)[12] to 51% by the use of titanium tetrachloride. Compound **4**, which we were unable to synthesize under a variety of reaction conditions in the absence of titanium tetrachloride, was prepared in 3% yield when that reagent was used in chloroform. Through changing the solvent to pyridine, **4** (mp 229–230° dec) was obtained in 44% yield.

We had now established conditions under which moderate yields of substituted 2-aminopyrazine 1-oxides could be obtained. It was also necessary to verify that titanium tetrachloride does not alter the course of the reaction and lead to undesirable isomers. Accordingly, **7** (mp 172.5–174.5°), the positional isomer of **5**, was prepared in 38% yield from phenylglyoxal 2-oxime (mp 114.5–117.5°, dimeric) and α-aminopropionitrile under conditions similar to those used to form **5**. Although the synthesis of a pair of isomeric 2-amino-3-methyl-5(or 6)-substituted pyrazine 1-oxides had been previously reported, no infrared or nuclear magnetic resonance spectral data were given for these compounds,[12,16] and no general methods were available in the literature for distinguishing isomers of this type. Thus, the fact that **7** can be easily distinguished from **5** by comparison of their nmr spectra represents the first time such isomers have been differentiated on the basis of spectral evidence. The absorption of the lone pyrazine ring proton of **7** appears at τ 2.18, that of **5** at 1.37. This difference in chemical shifts results from the ring proton being ortho (**5**) or meta (**7**) to the electron-withdrawing *N*-oxide linkage. Therefore, in these two cases it is quite certain that the heterocyclic isomer isolated was the one predicted on the basis of Scheme I and the structures of starting materials, *i,e.*, **8** led to **5**, and **9** to **7**.

The chemical shifts of the pyrazine ring protons in **4** and **3** are τ 1.50. This value is close to that of isomer **5** and therefore these compounds are 5-, not 6- substituted 2-aminopyrazine 1-oxides. With the structure of the intermediate **3** established, **2**, having the structure purported to be that of *Cypridina* etioluciferamine, could be unambiguously prepared.

The synthesis of **3** was effected using compounds **6** and **10**. Indol-3-ylglyoxal 1-oxime (**6**) (mp 213.5–214.5° dec)[17] was prepared in 16% overall yield by the sequence shown in Scheme II.

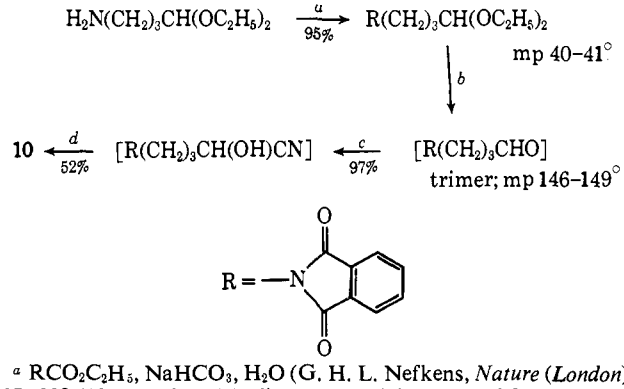
Scheme II



[a] Ya. L. Gol'dfarb, S. Z. Taits, and V. N. Bulgakova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1299 (1963); *Chem. Abstr.*, **59**, 13990g (1963). [b] Indolylmagnesium chloride (J. W. Baker, *J. Chem. Soc.*, 461 (1946)). [c] KOH. [d] $NaNO_2$, aqueous HCl (O. Touster, *Org. React.*, **7**, 336 (1953)).

The α-aminonitrile **10** was synthesized in four steps in 49% overall yield by the conversions shown in Scheme III. This compound was stabilized as its non-

Scheme III



[a] $RCO_2C_2H_5$, $NaHCO_3$, H_2O (G. H. L. Nefkens, *Nature (London)*, **185**, 309 (1960)). [b] H_3O^+, dioxane (S. Keimatsu and S. Sugasawa, *J. Pharm. Soc. Jap.*, **48**, 24 (1928); *Chem. Abstr.*, **22**, 1758 (1928); S. Sugasawa, *J. Pharm. Soc. Jap.*, No. **550**, 1044 (1927); *Chem. Abstr.*, **22**, 1572 (1928)). [c] Liquid HCN, pyridine (H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **27**, 798 (1962)). [d] NH_3, *tert*-butyl alcohol (see Keimatsu and Sugasawa, footnote *b*).

hygroscopic, purifiable *p*-toluenesulfonic acid salt (mp 169.5–170.5° dec). The reaction of **6** and **10** with titanium tetrachloride in pyridine led to **3** (mp 225–228° dec) in 11% yield. This intermediate was deoxygenated under oxygen-free conditions using Raney nickel and hydrogen gas[18] to give, in 82% yield, **11** (mp 245–248° dec). Finally, the phthalimido protecting group was removed using 100% hydrazine hydrate[19] to give **2** in 82% yield. The melting point (sealed, evacuated tube) of **2** dihydrochloride is 263–266.5° dec, while that reported (sealed tube) for *Cypridina* etioluciferamine dihydrochloride is 238–240° dec[9] or 251–252.[20] *Cypridina* etioluciferamine has[7,21] uv max (MeOH–0.1 *N* HCl) 223 nm (log ε 4.41), 306 (4.30), and 410 (3.70); (MeOH–0.1 *N* NaOH) 227 (4.38), 273 (4.26), and 365 (3.88). In comparison, **2** dihydrochloride has uv max (MeOH–0.1 *N* HCl) 221 (4.37), 275 (4.17), 305 (4.28), and 403.5 (3.63); (MeOH–0.1 *N* NaOH) 226.5 (4.35), 272.5 (4.28), 288 (4.19), and 361.5 (3.90). There was a peak for peak correlation in the infrared spectra (KBr) of these two compounds in spite of the fact that they were run on different machines. Finally, comparison of *Cypridina* etioluciferamine dihydrochloride with **2** dihydrochloride by thin-layer chromatography using four different combinations of adsorbant and eluent showed the two compounds to be identical.[22]

These results therefore show that the previously published structures of *Cypridina* etioluciferamine and luciferin are correct.[7,20] Our synthesis of *Cypridina* etioluciferamine in ten steps constitutes the second total synthesis of *Cypridina* luciferin, since this natural

(15) The elemental analyses of this and other compounds with melting points given are in agreement with the proposed formula.

(16) G. T. Newbold, W. Sharp, and F. S. Spring, *J. Chem. Soc.*, 2679 (1951). The ultraviolet spectra of the isomeric pair reported were not diagnostic because of the similarity of the spectra.

(17) A synthesis from 3-acetylindole (26%; mp 206° dec) appeared after the completion of our work (S. Sugiura, S. Inoue, Y. Kishi, and T. Goto, *Yakugaku Zasshi*, **89** (12), 1646 (1969); *Chem. Abstr.*, 72, 90404y (1970)).

(18) E. Ochiai, "Aromatic Amine Oxides," Elsevier, New York, N. Y., 1967, pp 184–190.

(19) F. E. King, J. W. Clark-Lewis, D. A. A. Kidd, and G. R. Smith, *J. Chem. Soc.*, 1039, 1044 (1954).

(20) Y. Kishi, T. Goto, S. Eguchi, Y. Hirata, E. Watanabe, and T. Aoyama, *Tetrahedron Lett.*, 3437 (1966).

(21) Y. Kishi, T. Goto, Y. Hirata, O. Shimomura, and F. H. Johnson, *Biolumin. Progr., Proc. Conf. 1965*, 89 (1966).

(22) We are indebted to Professor Toshio Goto, Faculty of Agriculture, Nagoya University, Chikusa, Nagoya, Japan for a sample of *Cypridina* etioluciferamine dihydrochloride.

product has been obtained from etioluciferamine (**2**) in two steps.[8-10]

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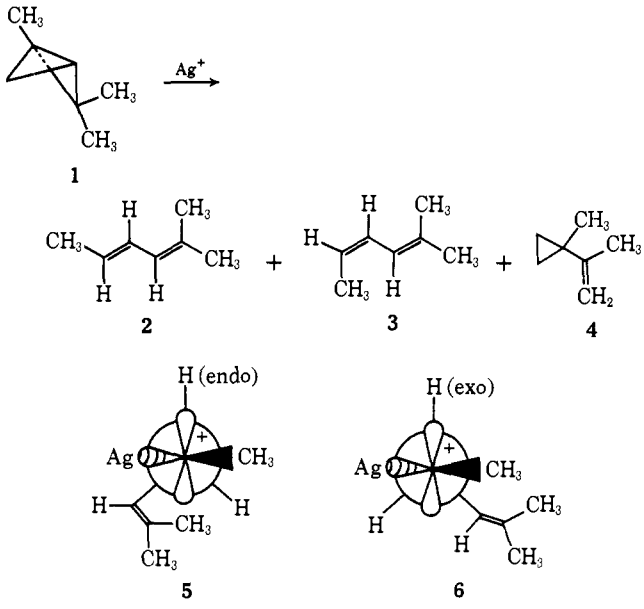
Silver(I) Ion Catalyzed Rearrangements of Strained σ Bonds. VII. Evidence for the Intervention of Argento Carbonium Ions in Bicyclo[1.1.0]butane Isomerizations[1]

Sir:

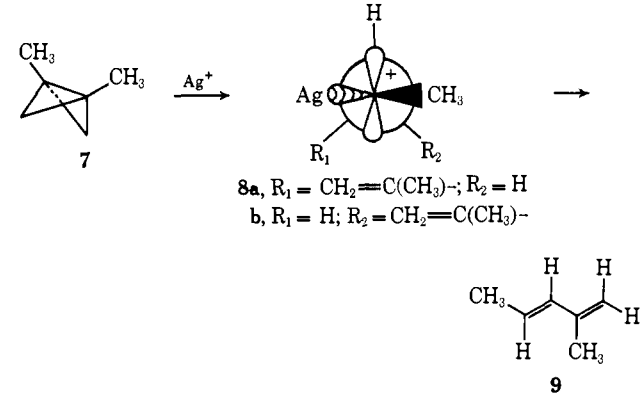
A vexatious problem in the Ag^+-catalyzed rearrangement of bicyclo[1.1.0]butanes has been elucidation of the precise mechanism by which the highly stereoselective isomerization[2,3] to dienes occurs. Earlier, we presented kinetic data which demonstrated the establishment of a rapid preequilibrium with a 1:1 complex and subsequent rate-determining rearrangement of this species.[2] The skeletal reorganizations examined to the present time seemingly involved C_1C_2 and C_3C_4 bond rupture and the stereochemistry of the products hinted at the operation of symmetry-disallowed rotations about the remaining σ bonds. However, reservations can be expressed about the concertedness of these processes because of the improbability that a lone silver(I) ion can coordinate simultaneously in the appropriate manner with the two indicated bicyclobutane bonds. Furthermore, Ag^+ is certain to operate as an electrophilic species and bicyclobutanes are now recognized to interact with such entities by initial cleavage of the central (C_1C_3) bond.[4] We have now secured evidence showing that discrete intermediates intervene after complexation of bicyclobutanes to Ag^+; additionally, the selectivity observed in the generation of these intermediates and their chemical reactivity implicate them to be argento carbonium ions.

The behavior of 1,2,2-trimethylbicyclobutane (**1**)[5] is illustrative. Exposure of dilute $CDCl_3$ solutions of **1** to catalytic amounts of $AgBF_4$ (added at −70°, followed by warming to 40°) results in essentially quantitative isomerization to dienes **2**[6a] and **3**[6b] (90% yield, ratio 4.5:1), together with **4**[5] (8%) and four very minor products. This isomerization is most simply viewed



as the result of C_1C_2 and C_1C_3 bond cleavage to afford the more highly substituted argento carbonium ion and hydrogen migration from either or both of two possible conformations (**5** and **6**).[7,11] The formation of the second double bond will in all likelihood be thermodynamically controlled, in agreement with the predominance of **2**.

Similar treatment of **7**[12] (to 25% conversion[13]) gives rise to 2-methyl-*trans*-1,3-pentadiene (**9**).[14] In this instance, the rehybridization which occurs subsequent



(1) For paper VI of this series, see L. A. Paquette, R. S. Beckley, and T. McCreadie, *Tetrahedron Lett.*, in press.
(2) L. A. Paquette, S. E. Wilson, and R. P. Henzel, *J. Amer. Chem. Soc.*, **93**, 1288 (1971).
(3) L. A. Paquette, G. R. Allen, Jr., and R. P. Henzel, *ibid.*, **92**, 7002 (1970).
(4) L. A. Paquette, G. R. Allen, Jr., and M. J. Broadhurst, *ibid.*, in press, and references therein.
(5) L. Skattebol, *Tetrahedron Lett.*, 2361 (1970); W. R. Moore, K. G. Taylor, P. Muller, S. S. Hall, and Z. L. F. Geibel, *ibid.*, 2365 (1970).
(6) (a) The structure was established on the basis of its spin-decoupled 100-MHz nmr spectrum, catalytic hydrogenation to 2-methylhexane, and independent synthesis from *trans*-crotonaldehyde and isopropylidenetriphenylphosphorane. (b) The first two criteria in part a were utilized for structure proof of **3**.
(7) Existing theoretical calculations pertaining to hydrogen migration in ethylidene do not permit differentiation between rearrangement to the filled or unfilled orbital.[8] However, the recently established parallelism between migratory aptitudes to carbonium[9] and carbenoid[10] centers is most consistent with stereoelectronically controlled shifts to the unfilled orbital on the sp^2-hybridized carbon in the two systems. Accordingly, we assign analogous behavior to argento carbonium ions.
(8) R. Hoffmann, G. D. Zeiss, and G. W. Van Dine, *J. Amer. Chem. Soc.*, **90**, 1485 (1968); see also R. Hoffmann, R. Gleiter, and F. B. Mallory, *ibid.*, **92**, 1460 (1970).
(9) Y. E. Rhodes and T. Takino, *ibid.*, **92**, 5270 (1970), and references therein.
(10) A. R. Kraska, L. I. Cherney, C. G. Moseley, G. M. Kaufman, and H. Shechter, submitted for publication.
(11) The question of the relative reactivities of conformers **5** and **6** is potentially resolvable since exo and endo hydrogen migration should be specific for a given intermediate. This aspect of the problem is currently receiving attention.
(12) W. von E. Doering and J. F. Coburn, Jr., *Tetrahedron Lett.*, 991 (1965); M. R. Rifi, *J. Amer. Chem. Soc.*, **89**, 4442 (1967); K. Griesbaum and P. E. Butler, *Angew. Chem., Int. Ed. Engl.*, 6, 444 (1967).
(13) Longer reaction times were observed to lead gradually to a complex mixture which included a substantial amount of higher boiling products.
(14) Identical with authentic sample procured from Chemical Samples Co., Columbus, Ohio.