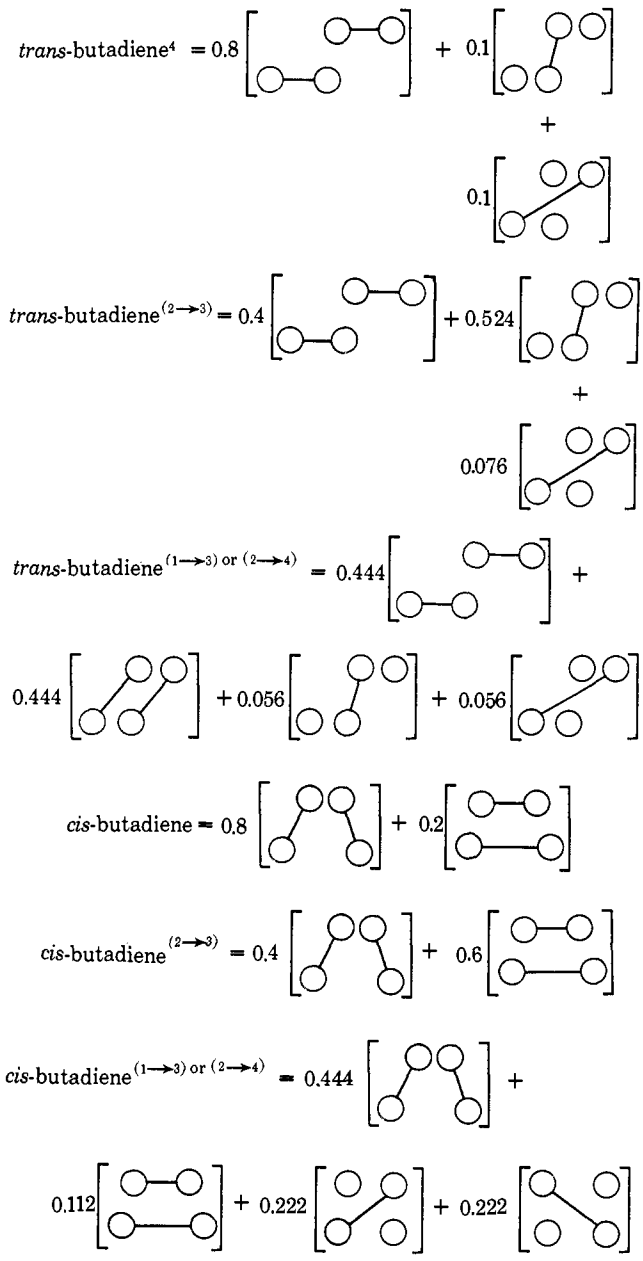
Chart I



spectively,[5] and the corresponding CI wave functions are

$$^1\Psi_{CI}{}^{first} = 0.992\psi_{II} + 0.135\psi_V$$

$$^1\Psi_{CI}{}^{second} = 0.707\psi_{III} + 0.707\psi_{IV}$$

where

$$\psi_{II} = (1/\sqrt{4})(1/\sqrt{2})(\det\{\psi_1\bar{\psi}_1\psi_2\bar{\psi}_3\} - \det\{\psi_1\bar{\psi}_1\bar{\psi}_2\psi_3\})$$

$$\psi_{III} = (1/\sqrt{4})(1/\sqrt{2})(\det\{\psi_1\bar{\psi}_1\psi_2\bar{\psi}_4\} - \det\{\psi_1\bar{\psi}_1\bar{\psi}_2\psi_4\})$$

$$\psi_{IV} = (1/\sqrt{4})(1/\sqrt{2})(\det\{\psi_1\psi_2\bar{\psi}_2\bar{\psi}_3\} - \det\{\bar{\psi}_1\psi_2\bar{\psi}_2\psi_3\})$$

$$\psi_V = (1/\sqrt{4})(1/\sqrt{2})(\det\{\psi_1\psi_2\bar{\psi}_2\bar{\psi}_1\} - \det\{\bar{\psi}_1\psi_2\bar{\psi}_2\psi_4\})$$

CI calculations show us that the first excited state is composed largely of the ψ_{II} configuration and the second excited state of the ψ_{III} and ψ_{IV} configurations. With this analysis and the above assumption, we may say that cyclobutene formation is favored from the first excited state of *cis*-butadiene, and bicyclobutane formation is favored from the second excited state of *trans*-butadiene.

According to selection rules,[6] *trans*-butadiene cannot reach the second excited state. However, it is reasonable to consider that *trans*-butadiene reaches this state from the vibrationally excited ground state[7] that is formed by internal conversion from the excited singlet state, since the calculated energy difference between the first and second excited states is very small. The probability of this process, however, should be very small. Therefore, we can explain the experimental results that bicyclobutane is produced in much smaller amount than cyclobutene in spite of the fact that in equilibrium butadiene assumes largely the *s*-trans conformation, and that the yield of bicyclobutane is decreased by an increase in pressure.[8,9]

Correlation diagrams based on orbital and symmetry[10] gave the same results as bond index analyses. In this respect Trindle's method of mapping analysis[11] is considered to be useful for studying open-shell-system reactions. Full details of work on various systems are now in preparation.

Acknowledgment. We wish to thank Dr. R. Hoffmann for reading the manuscript and helpful suggestions.

(5) R. L. Flurry, Jr., "Molecular Orbital Theories of Bonding in Organic Molecules," Marcel Dekker, New York, N. Y., 1968, p 259.

(6) C. Sandorfy, "Electronic Spectra and Quantum Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1964, p 186.

(7) L. Salem, "The Molecular Orbital Theory of Conjugated Systems," W. A. Benjamin, New York, N. Y., 1966, p 402.

(8) R. Srinivasan, *J. Amer. Chem. Soc.*, **85**, 4045 (1963).

(9) A. A. Lamola and N. J. Turro, "Energy Transfer and Organic Photochemistry," Interscience, New York, N. Y., 1969, p 159.

(10) H. C. Longuet-Higgins and E. W. Abrahamson, *J. Amer. Chem. Soc.*, **87**, 2045 (1965).

(11) C. Trindle, *ibid.*, **92**, 3251 (1970).

Myung-Hwan Whangbo, Ikchoon Lee
Department of Applied Chemistry, College of Engineering
Seoul National University, Seoul, Korea
Received January 28, 1971

Selective Oxidation of Unactivated Methylene Groups by Reagent–Substrate Orientation in Mixed Complexes

Sir:

Previous reports from our laboratory have described the development of a new synthetic procedure, remote oxidation, and its application to the functionalization of straight-chain[1] or steroid substrates.[2] The process involves attachment of a rigid ketonic reagent to the substrate, followed by irradiation. This generates an excited carbonyl group in the reagent, which then attacks a substrate C–H bond remote from the point of attachment. In some cases this is followed by abstraction of a second hydrogen from the substrate,[2] with the overall result being direct introduction of a double bond in a selective fashion into a particular position of the substrate. In other cases,[1,2] the intermediate diradical couples to form a new carbon–carbon bond; straightforward chemical processes can be used to convert this to a product with a new carbonyl group selectively introduced into the substrate,[1,2]

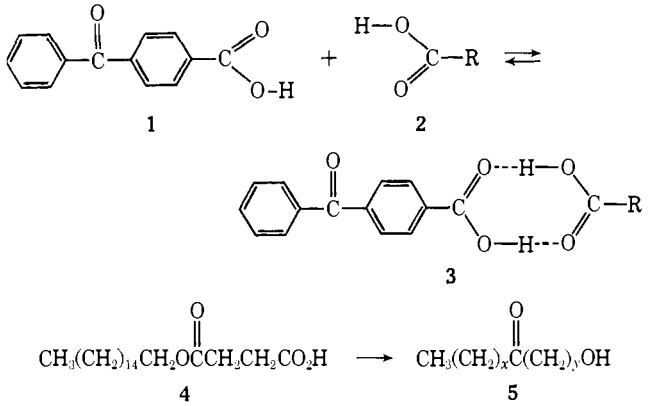
(1) R. Breslow and M. Winnik, *J. Amer. Chem. Soc.*, **91**, 3083 (1969).

(2) R. Breslow and S. W. Baldwin, *ibid.*, **92**, 732 (1970); *cf.* also J. E. Baldwin, A. K. Bhatnagar, and R. W. Harper, *Chem. Commun.*, 659 (1970). Further investigation in our laboratory shows that attack at C-7 accompanies the functionalizations reported.

or a new double bond.[2] It is also possible to intercept the intermediate diradical before coupling or hydrogen transfer and divert the substrate to yet other kinds of functional derivatives.[3]

In a sense, the method which has been used can be considered to involve the orientation of a reagent and a substrate, but in this case the orientation occurs because of the presence of a full bond between them. Of course, this should in principle not be necessary, since even a 3 kcal/mol stabilizing interaction in a transition state would be enough to give a 100:1 preference for that transition state over some arrangements lacking that stabilization. Thus, it seemed clear that it should be possible to extend the process we have developed to a situation in which simple complexing forces align the substrate and the reagent. In this communication we wish to report that this is indeed possible, and that using oriented substrate–reagent complexes it is possible to achieve selective functionalization of unactivated methylene groups.

The mode of complexing which we have examined is hydrogen bonding in a carboxylic acid mixed dimer. Thus, in a nonpolar solvent a reagent carboxylic acid, such as benzophenone-4-carboxylic acid (**1**), and a substrate carboxylic acid (**2**) form a mixed complex **3** in equilibrium with the dimers of **1** and **2**. These latter dimers play no role in the subsequent reactions. For ease of analysis we selected as substrates the hemisuccinates of substrate alcohols, and our preliminary investigation concerned long flexible alcohols of the type first examined in our previous studies[1] on remote oxidation. Thus, 500 ml of a CCl_4 solution 1.0 m*M* in **1** and 1.0 m*M* in *n*-hexadecanol hemisuccinate (**4**) was degassed and irradiated with a 450-W medium-pressure lamp using a uranium glass filter for 8 hr. At the end of this time the material was saponified and the acidic fraction was dehydrated in refluxing acetic acid. Ozonolysis, with dimethyl sulfide work-up, afforded a mixture of ketohexadecanols (**5**) in 24% overall yield.



1 **2** **3**

$CH_3(CH_2)_{14}CH_2OCCH_2CH_2CO_2H \longrightarrow CH_3(CH_2)_xC(CH_2)_yOH$

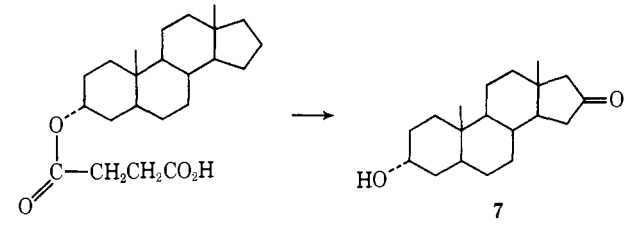
4 **5**

The ketone distribution (Table I) was determined by quantitative conversion to the ethylene thioketal with ethanedithiol, followed by mass spectral analysis.[4] There is a preference for functionalization at C-11 of the alcohol (Table I), which is the position predicted from an examination of molecular models of the mixed complex. However, there is also a distribution around this position of maximum attack because of the flexibility of the substrate. Such a distribution around the maximum had been observed previously[1] for reaction within the covalently attached system, although the present reaction gives a somewhat wider dispersion. Furthermore, in the covalent case we had achieved[1] essentially a quantitative conversion of the alcohol to the mixture of keto alcohols, while in this case there was only a 24% conversion, along with a number of other side products.

Table I. Ketohexadecanol Distribution (**5**)

Carbon	%
6	0
7	0.7
8	2.7
9	6.2
10	13.6
11	19.3
12	16.0
13	14.8
14	12.8
15	11.0
16	3.1

We next applied the current technique to a steroid substrate, 3α,5α-androstanyl hemisuccinate (**6**). This is a system of greater synthetic interest than the straight-chain alcohol, and because of its rigidity we have found that functionalizations can be much more selective on the steroid nucleus. Irradiation of **6** with **1** as described above, with the same subsequent processing, led to 21% of keto steroid, mp 153.5–154.5°, which proved to be a single compound. It was identified as 16-keto-3α,5α-androstanol (**7**) by conversion to the known[5] 5α-androstane-3,16-dione, mp 162–163.5°, and comparison with a synthesized sample.[6] Molecular models of the mixed complex of **6** and **1** indicate that



6 **7**

C-16 is the most likely point of attack within this complex.[7] The other products consisted of recovered starting androstanol (30%), olefins derived from chloro steroids (22%), and material still carrying the benzophenone residue (14%). When the photolysis of **6** and **1** was performed in benzene solution, again the only ketone product was **7** (19%) and 50% of the starting material was recovered. The conversion was in-

(3) W. Washburn, unpublished work.

(4) Controls show that at 15 eV the only peaks of any significance in the mass spectrum of the ethylene thioketal of an authentic ketotridecanol are the two peaks from α cleavage at the carbon carrying the thioketal group, and indeed the parent peak is only 3% of the sum of these α-cleavage peaks in the mass spectrum. This is a better analytical technique than the one we used previously[1] to determine the position of functionalization in a straight-chain substrate.

(5) D. Varech and J. Jacques, *Bull. Soc. Chim. Fr.*, 67 (1965).

(6) A procedure based on that of C. Djerassi and D. Herbst, (*J. Org. Chem.*, **26**, 4675 (1961)) was used, rather than that of ref 5. Spectroscopic data, in particular the characteristic nmr shifts of the steroid methyl groups, are fully consistent with the assigned structures.

(7) Intermolecular controls were performed using 1.0 m*M* **1** and 1.0 m*M* 3α,5α-androstanyl acetate. After 24-hr irradiation no appreciable coupling could be detected. Thus our reaction indeed occurs within the complex.

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.

Ronald Breslow,* Philip C. Scholl[10]
Department of Chemistry, Columbia University
New York, New York 10027
Received March 1, 1971

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).

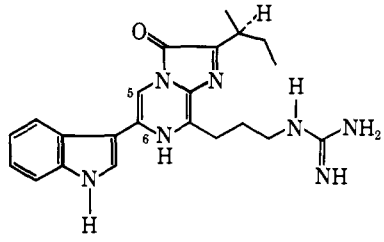
(6) E. H. White, F. McCapra, and G. Field, *ibid.*, **85**, 337 (1963).

(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.

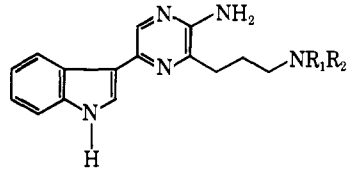
(8) Y. Kishi, T. Goto, S. Inoue, S. Sugiura, and M. Kishimoto, *Tetrahedron Lett.*, 3445 (1966).

(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

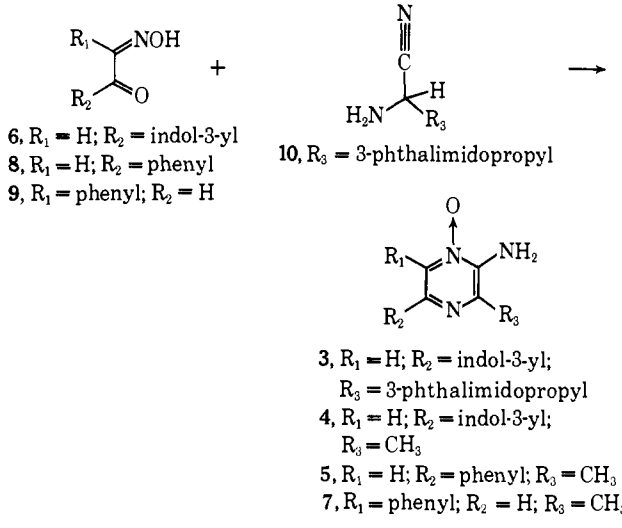


2, $R_1 = R_2 = H$
11, R_1R_2 = phthalimido
12, R_1 = H; R_2 = benzoyl

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



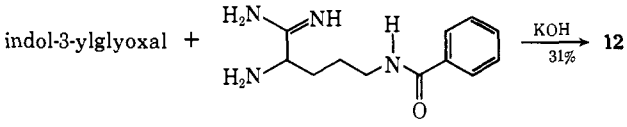
6, R_1 = H; R_2 = indol-3-yl
8, R_1 = H; R_2 = phenyl
9, R_1 = phenyl; R_2 = H

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).