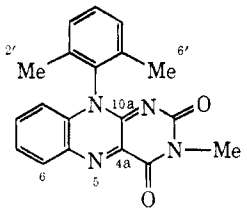
positions of the isoalloxazine ring involved in catalysis remains to be answered. The 10a, 8, 5, and 4a positions have received consideration as those involved in the formation of HFl-Y. Though numerous covalent

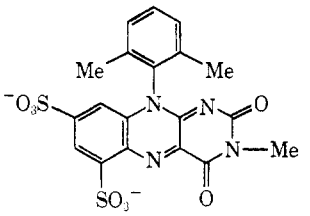
$$Fl + :Y \xrightarrow{+H^+} HFl\text{-}Y \underset{+H^+}{\overset{:Y}{\longrightarrow}} H_2Fl + Y_2 \qquad (1)$$

adducts to isoalloxazines are available through photocatalytic reactions,[3] only one example of a nucleophilic addition (dark) to a flavin has been reported.[4] We wish to report herein that the position of addition of SO_3^{2-} may, dependent upon steric and electrostatic factors, be to either the 5 or 4a positions of an isoalloxazine.

Substrates employed in the present investigation are I[5] and II.[6] In I and II the 2,6-dimethylphenyl



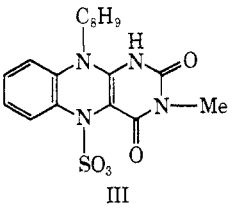
I



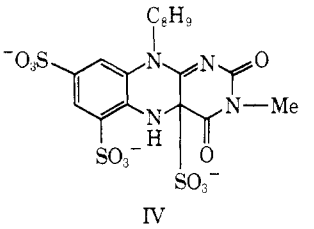
II

substituent at N(10) of the isoalloxazine system provides steric hindrance to nucleophilic attack at the 10a position. By use of I the 10a position has previously been eliminated as a site for catalysis in several flavin mediated reactions.[5] In II, not only is the 10a position hindered but approach of a negatively charged nucleophile (SO_3^{2-}) to the 5 position should be disfavored due to charge and steric repulsion by the SO_3^- substituent at the 6 position.

I was found to react with the SO_3^{2-} component of sulfite buffers to provide a product with λ_{max} 307 nm (ϵ_{max} 8700) at pH 7.1. Under the same conditions, II provides an adduct with λ_{max} 367 nm (ϵ_{max} 3460) and a shoulder at 300 nm. The numerous 4a and 5 adducts previously synthesized by photochemical reactions and indirect routes have invariably been found to be differentiable by their characteristic uv–visible spectra. Thus, for 16 odd 5 adducts, λ_{max} is characteristically[4,7] between 296 and 330 nm and for 15 odd 4a adducts the λ_{max} values are invariably between 360 and 370 nm with shoulders near 300 nm.[7c,8] The spectra of the adducts of I and II are, therefore, as anticipated for III and IV, respectively. Finally, nmr (D_2O) splitting of absorption of the 2′- and 6′-methyl groups (112 and 137 Hz) conclusively establishes IV. In IV a differential magnetic environment is provided for the 2′- and 6′-methyl groups due to an asymmetrically substituted 4a carbon. We conclude that the adduct of I possesses structure III and that of II, structure IV. The reversible formation of 5 ad-



III



IV

ducts in reactions of SO_3^{2-} with flavinium salts has been most conclusively established.[4] The readily reversible formation of the 4a adduct IV establishes that the $\Delta\Delta F°$ for formation of the 5 and 4a adducts is not prohibitive. Our results also establish that 5 and 4a adducts, depending upon the nucleophile, may accompany one another in which case the minor constituent cannot be dismissed as not being along the reaction path (eq 1). One can envision steric and electrostatic hindrance at an enzyme site which could control the direction of nucleophilic addition.

Acknowledgment. This research was supported by a grant from the National Science Foundation.

(9) Postdoctoral fellow, University of California.

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Received August 18, 1972

(3) See, for example: (a) W. H. Walker, P. Hemmerich, and V. Massey, *Eur. J. Biochem.*, **13**, 258 (1970); (b) M. Brüstlein, W.-R. Knappe, and P. Hemmerich, *Angew. Chem., Int. Ed. Engl.*, **10**, 804 (1971).

(4) F. Müller and V. Massey, *J. Biol. Chem.*, **59**, 1295 (1970).

(5) T. C. Bruice, L. Main, S. Smith, and P. Y. Bruice, *J. Amer. Chem. Soc.*, **93**, 7327 (1971); (b) L. Main, G. Kasperek, and T. C. Bruice, *Chem. Commun.*, 847 (1972).

(6) II: *Anal.* Calcd for $C_{19}H_{16}N_4O_8S_2 \cdot 4H_2O$: C, 40.42; H, 4.28; N, 9.93; S, 11.36. Found: C, 40.39; H, 4.26; N, 9.93; S, 11.16. Neutral equivalent: calcd, 2.0; found, 2.05. As the dipotassium salt: *Anal.* Calcd for $C_{19}H_{14}O_8N_4S_2K_2 \cdot 4H_2O$: C, 35.62; H, 3.46; N, 8.74; S, 10.01; K, 12.21. Found: C, 34.97; H, 3.62; N, 8.95; S, 10.25; K, 11.66. The nmr spectrum in DMSO-d_6 solution (δ ppm) showed: 1.93 (s, 6 H), 3.28 (s, 3 H), 7.00 (d, 1 H), 7.43 (s, 3 H), 8.33 (d 1 H). The two doublets (J = 2 Hz) arise from the aromatic hydrogens of the isoalloxazine ring in meta position.

(7) (a) K. H. Dudley, A. Ehrenberg, P. Hemmerich, and F. Müller, *Helv. Chim. Acta*, **47**, 1354 (1964); (b) M. Brüstlein and P. Hemmerich, *FEBS (Fed. Eur. Biochem. Soc.) Lett.*, **1**, 335 (1968); (c) P. Hemmerich, S. Ghisla, U. Hartmann, and F. Müller, "Flavins and Flavoproteins," H. Kamin, Ed., University Park Press, Baltimore, Md., 1971, p 83.

(8) (a) W. H. Walker, P. Hemmerich, and V. Massey, *Helv. Chim. Acta*, **50**, 2269 (1967); (b) M. Brüstlein, Ph.D. Thesis, University of Konstanz (Germany), 1971; (c) W.-R. Knappe, Ph.D. Thesis, University of Konstanz (Germany), 1971.

Total Synthesis of *dl*-Dendrobine

Sir:

Dendrobine is the main alkaloid obtained from *Dendrobium nobile* L.[1] with biological activities similar to those of picrotoxin.[2] By chemical and spectral means the structure[3] of dendrobine was determined to be **1** possessing a picrotoxane skeleton.

The result of our synthetic study on dendrobine was published previously,[4] and we are reporting here the total synthesis of (±)-dendrobine. An ingenious method of constructing a *cis*-hydrindan system stereoselectively by intramolecular Michael addition was thoroughly studied by Johnson and his coworkers[5] and was employed in the present work. 3,4-Dihydro-7-

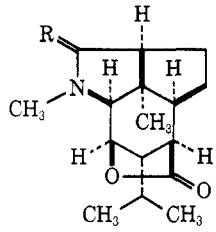
(1) H. Suzuki and I. Keimatsu, *Yakugaku Zasshi*, **52**, 1049 (1932); *Chem. Abstr.*, **27**, 1886 (1933).

(2) L. A. Porter, *Chem. Rev.*, **67**, 441 (1967), and the references cited therein.

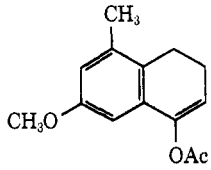
(3) S. Yamamura and Y. Hirata, *Tetrahedron Lett.*, 79 (1964); T. Onaka, S. Kamata, T. Maeda, Y. Kawazoe, M. Natsume, T. Okamoto, F. Uchimaru, and M. Shimizu, *Chem. Pharm. Bull.*, **12**, 506 (1964); Y. Inubushi, Y. Sasaki, Y. Tsuda, B. Yasui, T. Konita, J. Matsumoto, E. Katarao, and J. Nakano, *Tetrahedron*, **20**, 2007 (1964); Y. Inubushi, E. Katarao, Y. Tsuda, and B. Yasui, *Chem. Ind. (London)*, 1689 (1964).

(4) Y. Hayakawa, H. Nakamura, K. Aoki, M. Suzuki, K. Yamada, and Y. Hirata, *Tetrahedron*, **27**, 5157 (1971).

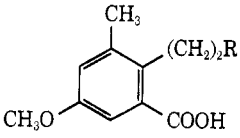
(5) W. S. Johnson, S. Shulman, K. L. Williamson, and R. Pappo, *J. Org. Chem.*, **27**, 2015 (1962).



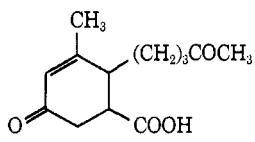
1, R = H_2
2, R = O



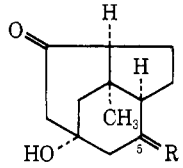
3



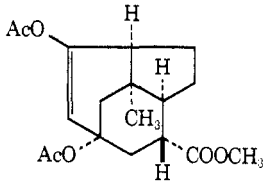
4, R = CHO
5, R = CH_2COCH_3
6, R = CH_2—C(O)(O)—CH_3



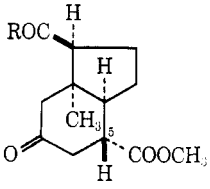
7



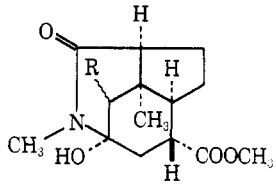
8, R = COOH (H)
9, R = COOH (H)
10, R = $COOCH_3$ (H)



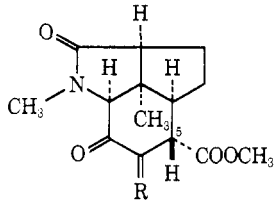
11



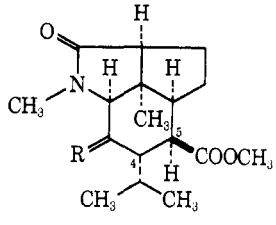
12, R = OH
13, R = imidazolyl



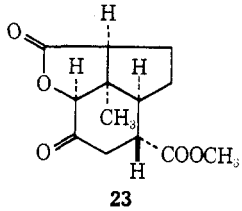
14, R = H
15, R = Br



16, R = H_2
17, R = CHOH
18, R = $CHOCH_3$
19, R = $CHS(CH_2)_3CH_3$
20, R = H, $CH(CH_3)_2$



21, R = O
22, R = H, OH



23

methoxy-5-methyl-1(2*H*)-naphthalenone[6] was converted (Ac$_2$O–*p*-TsOH reflux) to the enol acetate **3**,[7,8a] mp 88–90° (85%). Ozonolysis of **3** (MeOH–Me_2S,[9] −75°) followed by hydrolysis of the anhydride afforded the acid **4**,[7,8a] mp 119–121° (75%). The Wittig reaction of **4** with α-methoxyethyltriphenylphosphonium chloride[10] and methylsulfinyl carbanion[11] (DMSO–glyme, −40°) followed by treatment with aqueous oxalic acid afforded the keto acid **5**,[7,8a] mp 101–102° (77%), which was converted to the oily diketo acid **7**[7,12] [nmr ($CDCl_3$) δ 2.02 (3 H, d, J = 1.5 Hz), 2.19 (3 H, s, $COCH_3$)] in 80% overall yield by the sequence: (1) ketalization to afford the ketal acid **6**,[7,8a] mp 98–100°; (2) reduction of **6** [Li (20 atom equiv) in liquid NH_3–*tert*-BuOH–THF (9:3:1), −33°, 30 min] to give the dihydro derivative; (3) hydrolysis of the enol ether group and deketalization (aqueous oxalic acid); (4) formation of the conjugated keto group (1:1 EtOH–0.4 *N* HCl reflux, 1 hr); and (5) chromatographic purification (silica gel). Cyclization of **7** [*tert*-BuOK (1.2 equiv)–*tert*-BuOH, 30°, 50 hr under nitrogen] gave a crystalline mixture of two products epimeric at C-5,[13] ketol acids **8** and **9** (ratio *ca.* 8:1),[14] mp 144–147° (97%), which was separated by fractional recrystallization (*n*-hexane–EtOAc): **8**,[7,8a] mp 146.5–147.5°; **9**,[7,8a] mp 160–163°. The ketol acid **8** was methylated (diazomethane) and the ester **10** [ir ($CHCl_3$) 1735, 1720 cm^{-1}; nmr ($CDCl_3$) δ 1.13 (3 H, s), 2.45 (1 H, br s, OH), 3.67 (3 H, s); mass 252 (M^+)] was converted (Ac$_2$O–10-camphorsulfonic acid, 105°, 24 hr) to **11**[7] as an oil [97% from **8** after chromatographic purification (silica gel)]. Ozonolysis of **11** (9:1 EtOAc–AcOH, 0°) followed by treatment with water afforded **12**,[7,8a] mp 113–114° [mass 254 (M^+); 60% after chromatographic purification (silica gel)]. A mixture of **12** and *N*,*N*′-carbonyldiimidazole was heated at 80° for 5 min without solvent,[15] and the crude imidazolide **13** was converted (1:1 40% aqueous $MeNH_2$–glyme) to the lactam **14**,[7,8a] mp 180–181° [ir ($CHCl_3$) ~3400, 1730, 1615 cm^{-1}; 75% from **12**], which was then converted (pyridinium bromide perbromide in THF) to the bromo derivative **15**,[7,8a,16,17] mp 145–148° [ir ($CHCl_3$) ~3400, 1740, 1630 cm^{-1}; nmr ($CDCl_3$) δ 4.22 (1 H, s, CHBr); 51%]. Treatment of **15** with sodium hydride in glyme (reflux, 3 hr under nitrogen) followed by acidification with anhydrous oxalic acid[18] yielded the oily pyrrolidone **16**[7,8b] [ir ($CHCl_3$) 1730, 1683 cm^{-1} (γ lactam); nmr

(6) L. Ruzicka and L. Sternbach, *Helv. Chim. Acta*, **23**, 355 (1940).

(7) This compound has been fully characterized by infrared, nmr, and mass spectra, confirmatory of the structure presented.

(8) (a) Elemental analysis for this compound was in accord with theory. (b) Elemental composition of this compound was verified by high-resolution mass spectral determination on the molecular ion.

(9) J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, 4273 (1966).

(10) D. R. Coulson, *ibid.*, 3323 (1964).

(11) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

(12) The glpc analysis (SE-30) of the methyl ester showed the formation of the single isomer.

(13) For the numbering system see ref 2. Assignment of the stereochemistry at C-5 on both stereoisomers was made by chemical and spectral means (K. Yamada, M. Suzuki, Y. Hayakawa, and Y. Hirata, *Tetrahedron Lett.*, in press).

(14) Estimated by glpc analysis (SE-30), after methylation.

(15) The acid **12** failed to react with *N*,*N*′-carbonyldiimidazole in solution (*e.g.*, $CHCl_3$, glyme) at reflux.

(16) Significant difference of reactivities on **12** and its C-5 epimer was observed in the sequence of reactions **12** → **15**.

(17) The bromine position in **15** was deduced from the fact that bromination of **12** afforded the γ lactone **23**[7,8b] [ir ($CHCl_3$) 1783, 1725 cm^{-1}] and from the nmr spectrum (a singlet at δ 4.22) of **15**.

(18) Acidification with *aqueous* oxalic acid gave **16** and its C-5 epimer, the latter being predominant. Both **16** and the C-5 epimer gave the same compound **17** on hydroxymethylenation.

($CDCl_3$) δ 3.52 (1 H, s, $COCHN(CH_3)CO$); 87% after purification[19a]], which was transformed (HCOOMe–NaOMe–benzene) into a mixture of **17**[7] and **18**,[7] the former being readily converted to the latter (diazomethane). The oily compound **18** (80% from **16** after purification[19a]) was treated with *n*-butyl mercaptan and 10-camphorsulfonic acid in benzene giving oily **19**[7] (93% after purification[19a]), which on treatment with lithium dimethylcopper[20] in ether (−25°, 3 hr) gave **20**[7,8b,21] as an oil [ir ($CHCl_3$) 1730 (br), 1680 cm^{-1}; nmr ($CDCl_3$) δ 0.92 (6 H, d, J = 6.0 Hz, $CH(CH_3)_2$); 94% after purification[19b]]. Isomerization of **20** was effected by sodium hydride in glyme (reflux, 3 hr under nitrogen) affording a mixture of **20** and **21** (ratio 1:1), which was separated[22a] to give **21**,[7,8a,b,23,24] mp 146–147.5° [ir ($CHCl_3$) 1735, 1717, 1678 cm^{-1}; 50% based on reacted **20**]. Reduction of **21** with ethanolic sodium borohydride followed by acidification and subsequent purification[22b] afforded (±)-oxodendrobine (**2**),[7,8a,b,23] mp 182.5–183.5° (71%). Treatment of **2** with triethyloxonium fluoroborate in methylene chloride followed by reduction[25] of the resulting imino ether ($NaBH_4$–glyme) yielded an oily product forming a complex with boron; purification[19c] followed by passing the pyridine solution through a column of the anion exchange resin Amberlite IR-4B afforded (±)-dendrobine (**1**),[7,8a,b] mp 128–130° (61%), spectroscopically (ir, nmr, mass spectrum) and chromatographically identical with natural dendrobine.

(19) By preparative tlc on silica gel with $CHCl_3$–MeOH: (a) 95:5; (b) 97:3; (c) 90:10.

(20) R. M. Coates and R. L. Sowerby, *J. Amer. Chem. Soc.*, **93**, 1028 (1971).

(21) The stereochemistry at C-5 was secured to be retained in the derivatives **10**–**20** by chemical and/or nmr spectral evidence.

(22) By preparative tlc on aluminum oxide with (a) 1:1 EtOAc–C_6H_6; (b) 1:1 EtOAc–$CHCl_3$.

(23) Proved to be identical with the corresponding compound[3] prepared from natural **1** by spectral (ir, nmr, mass spectrum) and tlc comparison.

(24) Stereochemistry at C-4 and C-5 of **21**, a derivative of dendrobine, was rigorously established in the structural studies[3] of dendrobine, in connection with the stereochemistry of methyl oxodendrobinate **22** secured by extensive nmr spectral analysis.

(25) R. F. Borch, *Tetrahedron Lett.*, 61 (1968).

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Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya, Japan

Received August 8, 1972

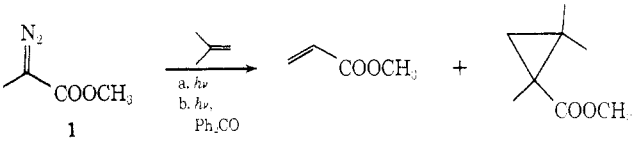
Suppression of Intramolecular Rearrangements of Carbenes. Methylcarbomethoxycarbene and Cyclopropylcarbomethoxycarbene[1]

Sir:

Although the most general synthesis of cyclopropanes utilizes the intermolecular addition of carbenes to olefins,[2] alkylcarbenes are virtually useless as cyclopropane precursors. Typically, intramolecular reactions, and especially insertions into carbon–hydrogen bonds, prevail over all intermolecular reactions. It seemed to us that triplet carbenes might avoid this problem. The suppression of the Wolff rearrangement in aliphatic diazo ketones had been previously noted,[3] and it had been pointed out by Moritani, Yamamoto, and Murahashi[4] that hydrogen or alkyl migrations to triplet carbenes must mimic the unknown[5] 1,2 shift in free radicals.

Accordingly, we have examined the direct and photosensitized photolyses of methyl diazopropionate (**1**).[6] As expected, the direct irradiation of **1** in isobutylene gave only 4% of adduct **2**, the major product being methyl acrylate.[7] By contrast, the benzophenone-sensitized decomposition of **1** led to **2** in 72% yield, with only 3% of the acrylate being formed.

cis- and *trans*-2-butene gave 10 and 6% adducts on direct irradiation.[8] These yields could be increased to 50 and 46%, respectively, by photosensitized decomposition of **1**.[8a] Methyl acrylate was decreased from *ca.* 27 to 3%. Products of abstraction of hydrogen were unimportant in the reactions with isobutylene and the 2-butenes.



a, 14%
b, 3%

a, 4%
b, 72%

In 1968, workers in Japan,[4] elaborating on the previous work of Overberger and Anselme,[9] studied the irradiation of phenylmethyldiazomethane. Here, sensitized decomposition was found to decrease the amount of hydrogen shift to give styrene from 7 to 1.7%, but no significant change could be found in the amount of intermolecular reaction to give cyclopropanes. The major change noted was the increased formation of acetophenone. We see no conflict between our work, in which we see dramatic increases in cyclopropane formation, and the previous. There is a growing conviction that a facile equilibrium exists between singlet and triplet phenylcarbenes.[10] In the case of phenylmethylcarbene, the major reaction of the triplet is apparently with adventitious oxygen, with the singlet forming most of the styrene and cyclopropanes.

In contrast to the 1,2-hydrogen migration, rearrangements of the cyclopropylcarbinyl radical are well known.[11] If it is the reluctance to undergo radical-like rearrangements that deters intramolecular reactions of triplet carbenes, a change of alkyl group from methyl to cyclopropyl should result in decreased deterrence. Ac-

(1) Support for this work from the National Science Foundation through Grants GP-12759 and GP-30797X is warmly acknowledged.

(2) W. Kirmse, "Carbene Chemistry," 2nd ed, Academic Press, New York, N. Y., 1971.

(3) M. Jones, Jr., and W. Ando, *J. Amer. Chem. Soc.*, **90**, 2200 (1968).

(4) I. Moritani, Y. Yamamoto, and S.-I. Murahashi, *Tetrahedron Lett.*, 5697 (1968).

(5) W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966.

(6) M. B. Sohn, M. Jones, Jr., M. E. Hendrick, R. R. Rando, and W. von E. Doering, *Tetrahedron Lett.*, 53 (1972).

(7) All new compounds gave appropriate nmr and ir spectra and consistent elemental analyses.

(8) A report of the direct decomposition of **1** in the 2-butenes can also be found in the thesis of R. R. Rando, Yale University, New Haven, Conn., 1967.

(8a) NOTE ADDED IN PROOF. A determination of the degree of nonstereospecificity was precluded by the apparent photoisomerization of the adducts.

(9) C. C. Overberger and J.-P. Anselme, *J. Org. Chem.*, **29**, 1188 (1964).

(10) G. L. Closs, *Top. Stereochem.*, **3**, 193 (1968).

(11) C. Walling, "Molecular Rearrangements," P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 407.