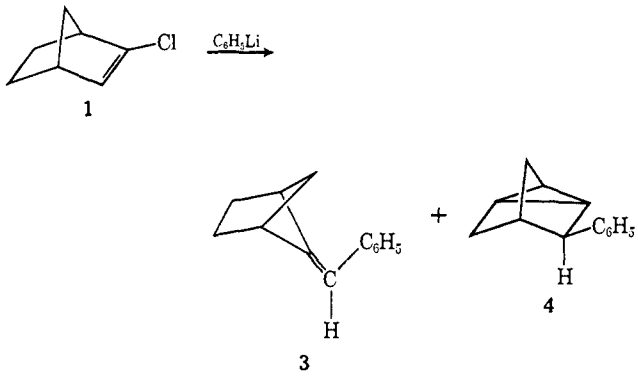
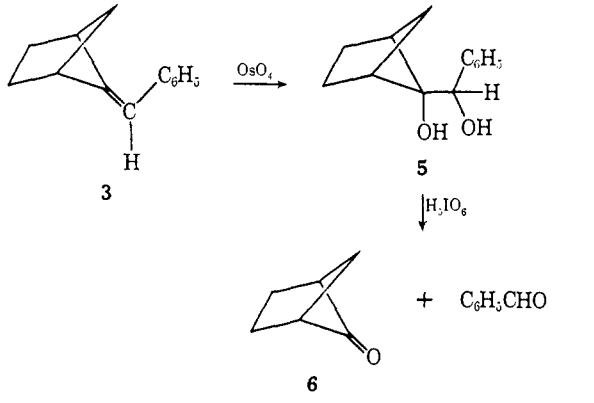


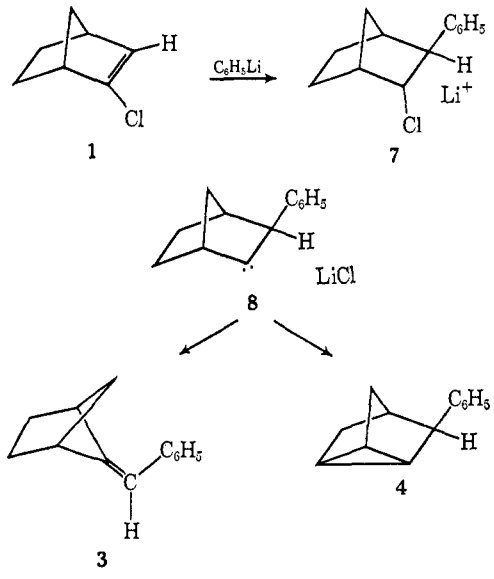
characteristic olefinic stretching vibration at 5.90 μ. The nmr spectrum showed the aromatic hydrogens as a five-proton singlet at τ 2.83. The aliphatic protons appeared at τ 4.22 (singlet, 1 H), 6.60 (multiplet, 1 H), 7.07 (multiplet, 1 H), 8.20 (singlet, 5 H), and 8.78 (doublet, J = 7 Hz, 1 H). Osmium tetroxide in pyridine converted **3** into **5** in 92% yield.[6] Cleavage of **5** with periodic acid[8] gave a 67% yield of **6**[9] and 68% yield of benzaldehyde. The nmr spectrum of **6** was



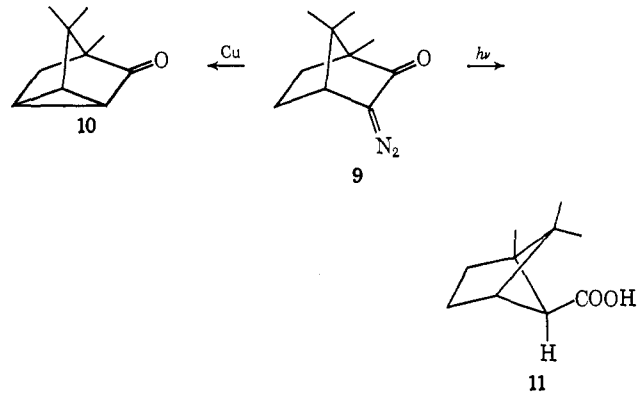
identical with the published spectrum of bicyclo[2.1.1]-hexan-5-one.[7,10]

The structural assignment of **4** was based on its ir, nmr, and near-infrared spectra. This spectroscopic data demonstrated the presence of a monosubstituted benzene ring and of the nortricyclyl skeleton. The single benzylic proton at τ 7.17 showed that the phenyl group was at the 2 position.

It seems likely that a single intermediate may be involved in the formation of both **3** and **4**. Addition of phenyllithium to **1** could give **7** which, *via* α elimination of chloride, would give the carbenoid intermediate **8**. Intramolecular insertion into the C–H bond across the ring would give **4**, while ring contraction would produce **3**. The chemical fate of **7** can be compared to that of diazocamphor (**9**) which on treatment with copper powder gives primarily the insertion product **10**[11] and on irradiation undergoes a



photochemical ring contraction to yield **11** as the major product.[12] This photochemical Wolff rearrangement



has served as a major route to the bicyclo[2.1.1]hexane ring system. In this regard the formation of **3** from **1** provides one of the few nonphotochemical routes to derivatives of bicyclo[2.1.1]hexane.

The formation of **3** observed in the reaction of **1** with phenyllithium provides the first example of a new type of ring contraction. In view of the strained nature of **3**, it is evident that this procedure can be utilized in the synthesis of small rings. We are currently investigating the scope and detailed mechanistic aspects of this unusual ring contraction.

(6) The stereochemistry of **5** was based on a comparison of its nmr spectrum with those of *exo*- and *endo*-5-hydroxybicyclo[2.1.1]hexane.[7]

(7) K. B. Wiberg, B. R. Lowry, and B. J. Nist, *J. Amer. Chem. Soc.*, **84**, 1594 (1962).

(8) A saturated ethereal solution of periodic acid was used, as described in L. Feiser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, N. Y., 1967, p 817.

(9) The preparation of **6** described in this communication provides an improved method for the synthesis of numerous derivatives of the bicyclo[2.1.1]hexyl system, including bicyclo[2.1.1]hexan-5-one.

(10) K. B. Wiberg, B. R. Lowry, and T. H. Colby, *J. Amer. Chem. Soc.*, **83**, 3998 (1961).

(11) J. Bredt and W. Holz, *J. Prakt. Chem.*, 203, 133 (1917); A. Angeli, *Gazz. Chim. Ital.*, **24**, II, 317 (1894).

(12) L. Horner and E. Spietschka, *Chem. Ber.*, **88**, 934 (1955); J. Meinwald, A. Lewis, and P. G. Gassman, *J. Amer. Chem. Soc.*, **82**, 2649 (1960); **84**, 977 (1962).

(13) Alfred P. Sloan Research Fellow, 1967–1969.

(14) National Science Foundation Trainee, 1968–1970.

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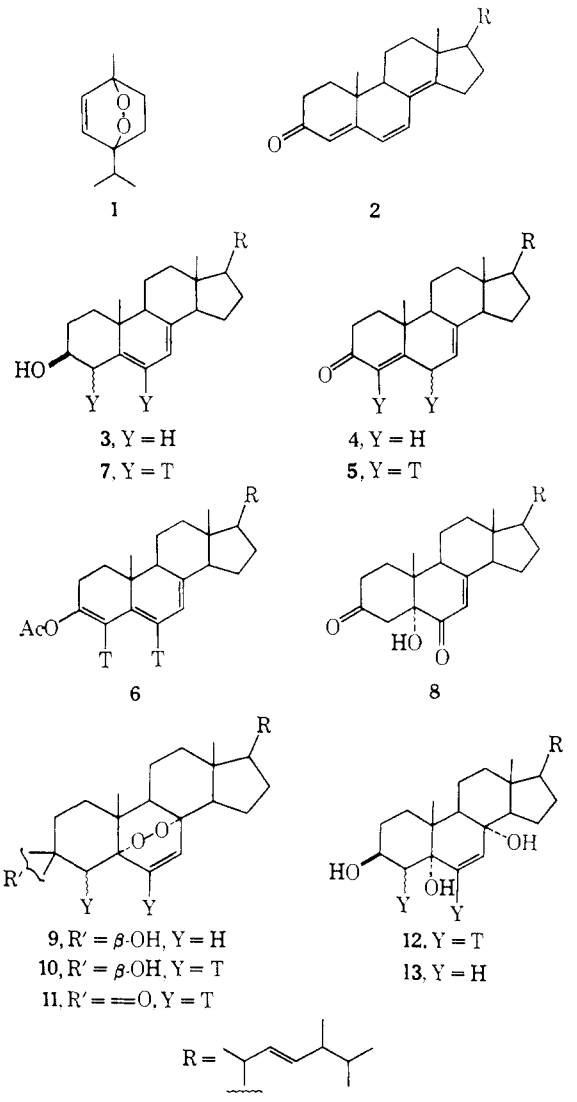
Biosynthesis of Ergosta-4,6,8(14),22-tetraen-3-one. *In Vivo* Incorporation of a 1,4-Dioxide

Sir:

The participation of dioxides in biological oxygenation has been suggested by Hayaishi[1] and, more re-

cently, others have given consideration to this idea.[2] As judged from *in vitro* experiments,[3] 1,4-dioxides seem particularly attractive biosynthetic intermediates in certain enzymatic processes involving dioxygenases. Although the transannular 1,4-dioxides ascaridole (**1**)[4] and ergosterol peroxide (**9**)[5] appear to be authentic products of secondary metabolism, it has yet to be established whether these serve any function *in vivo*. We report the results of incorporation studies with *Penicillium rubrum* which reveal that **9** is further metabolized, leading ultimately to ergosta-4,6,8(14),22-tetraen-3-one (**2**).

Isolation of **2** from *P. rubrum* and its characterization had been completed earlier,[6] and it was surmised that biosynthesis of **2** involved either direct dehydrogenation of ergosterol (**3**) or an oxidation–elimination route from **3**.[7] Specifically ^{3}H-labeled precursors, including ergosterol peroxide, designed to test this latter alternative were prepared for feeding experiments. Oppenauer oxidation of **3** gave $\Delta^{4,7}$-ergosterone (**4**),[8] into which tritium was introduced *via* base-catalyzed exchange ($NaOCH_3$–THF). Parallel deuteration experiments indicated that label was incorporated at both C-4 and C-6 of **4**, as measured from decriments in area under nmr signals at δ 5.77 (singlet) and 2.62, 3.16 (AB quartet, J = 19 Hz); quantitative estimation of radioactive label was obtained as indicated below. Treatment of **5** with Ac_2O–pyridine gave enol acetate **6**[9] which had retained all of the label originally present in **5**.[10] Reduction of **5** to [*4,6-*^{3}*H*]ergosterol (**7**) was effected with sodium borohydride in aqueous dioxane.[11] It has previously been shown that oxidation of ergosterol with CrO_3–AcOH yields **8**[12] and, when this procedure was applied



to **7**, the product isolated had retained 38% of the label. Thus, 62% of the tritium was originally introduced at C-6 of ergosterone. Photosensitized oxygenation (methylene blue) of **7** gave **10**[13] which was oxidized with Jones' reagent to keto peroxide **11**.[14] Reduction of **10** with zinc in ethanolic KOH gave labeled triol **12**.[15]

Incubation of ^{3}H-labeled precursors with *P. rubrum* was carried out in liquid culture on the basic growth medium previously described,[16] to which Dow Antifoam B had been added. The medium contained in Fernbach flasks shielded from light was innoculated from a suspension of conidia in phosphate buffer. Production of **2** was followed qualitatively by tlc, using the characteristic blue-green fluorescence visible under

(1) O. Hayaishi, M. Katagiri, and S. Rothberg, *J. Biol. Chem.*, **229**, 905 (1957).

(2) N. Itada, *Biochem. Biophys. Res. Commun.*, 20, 149 (1965); J. W. Cornforth, B. V. Milborrow, and G. Ryback, *Nature (London)*, 206, 715 (1965); B. Samuelsson, *J. Amer. Chem. Soc.*, **87**, 3011 (1965); G. A. Blondin, B. D. Kulkarni, and W. R. Nes, *ibid.*, **86**, 2528 (1964); M. Biollaz, G. Büchi, and G. Milne, *ibid.*, **90**, 5019 (1968); J. E. Baldwin, H. H. Basson, and H. Krauss, *Chem. Commun.*, 984 (1968).

(3) R. A. LeMahieu, M. Carson, and R. W. Kierstead, *J. Org. Chem.*, **33**, 3660 (1968); J. Boche and O. Runquist, *ibid.*, **33**, 4285 (1968); J. Rigaudy, *Pure Appl. Chem.*, **16**, 169 (1968); J. Rigaudy, C. Deletang, D. Sparfel, and N. K. Cuong, *C. R. Acad. Sci., Ser. C*, **267**, 1714 (1968); S. Isoe, S. B. Hyeon, H. Ichikawa, S. Katsumura, and T. Sakau, *Tetrahedron Lett.*, 5561 (1968); M. Mousseron-Canet, J. P. Dalle, and J. C. Mani, *ibid.*, 6037 (1968); I. Saito, S. Kato, and T. Matsuura, *ibid.*, 239 (1970); T. Wilson, *Photochem. Photobiol.*, 10, 441 (1969); E. McKeown and W. A. Waters, *J. Chem. Soc. B*, 1040 (1966).

(4) E. K. Nelson, *J. Amer. Chem. Soc.*, **33**, 1404 (1911); G. O. Schenck and K. Ziegler, *Naturwissenschaften*, **32**, 157 (1944); G. O. Schenck, *Angew. Chem.*, **64**, 12 (1952). The related α-phellandrene peroxide has also been reported to occur naturally [G. O. Schenck, *Naturwissenschaften*, **35**, 28 (1948)].

(5) (a) P. Wieland and V. Prelog, *Helv. Chim. Acta*, 30, 1028 (1947); G. Bauslaugh, G. Just, and F. Blank, *Nature (London)*, 202, 1218 (1964); S. M. Clarke and M. McKenzie, *ibid.*, **213**, 504 (1967); Y. Tanahashi and T. Takahashi, *Bull. Chem. Soc. Jap.*, **39**, 848 (1966). However, see H. K. Adam, I. M. Campbell, and N. J. McCorkindale, *Nature (London)*, **216**, 397 (1967), for a dissenting opinion on the authenticity of **9** as a natural product. (b) M. Endo, M. Kajiwara, and K. Nakanishi, *Chem. Commun.*, 309 (1970).

(6) (a) Identity was established by comparison with a sample kindly provided by Professor D. H. R. Barton [D. H. R. Barton and T. Bruun, *J. Chem. Soc.*, 2728 (1941)] and by synthesis [J. Elks, *ibid.*, 468 (1954)]; (b) **2** has also been isolated from *Candida utilis* [H. Morimoto, I. Imada, T. Murata, and N. Matsumoto, *Justus Liebigs Ann. Chem.*, 708, 230 (1967)], from *Fomes officinalis* [K. E. Schulte, G. Rücker, and H. Fachmann, *Tetrahedron Lett.*, 4763 (1968)], and from the bioluminescent mushroom *Lampteromyces japonicus*.[5b]

(7) S. Kaufman, *Advan. Chem. Ser.*, **No. 77**, 170 (1968).

(8) D. A. Shepherd, R. A. Donia, J. A. Campbell, B. A. Johnson, R. P. Holysz, G. Slomp, J. E. Stafford, R. L. Pederson, and A. C. Ott, *J. Amer. Chem. Soc.*, 77, 1212 (1955).

(9) I. M. Heilbron, T. Kennedy, F. Spring, and G. Swain, *J. Chem. Soc.*, 869 (1963).

(10) This result is ascribed to an isotope effect since deuteration experiments with **4** indicated that label is incorporated into both 6α and 6β positions.

(11) R. K. Callow, E. Kodicek, and G. A. Thompson, *Proc. Roy. Soc., Ser. B*, **164**, 1 (1966).

(12) A. Burawoy, *J. Chem. Soc.*, 409 (1937).

(13) A. Windaus and J. Brunken, *Justus Liebigs Ann. Chem.*, **460**, 225 (1928).

(14) P. Bladon and T. Sleigh, *J. Chem. Soc.*, 6991 (1965).

(15) A. Windaus and O. Linsert, *Justus Liebigs Ann. Chem.*, **465**, 148 (1928).

(16) G. N. Wogan and R. I. Mateles, *Progr. Ind. Microbiol.*, 7, 149 (1968).

Table I. Incorporation of Precursors into Ergosta-4,6,8(14),22-tetraen-3-one in *Penicillium rubrum*

Precursor	Spec act., counts sec^{-1} $mmol^{-1}$	Spec act. of **2**,[a] counts sec^{-1} $mmol^{-1}$	Incorporation, %
7	2.52×10^5	8.29×10^3	3.3
10	2.75×10^5	1.70×10^3	0.7
11	6.37×10^4	3.27×10^2	0.5
12	2.53×10^4	1.70×10^3	6.7

[a] These data include a correction for quenching of the fluorescer (PPO) by **2**.

shortwave uv light. Cultures were generally harvested after 13–18 days, and pure **2** was isolated by extraction with $CHCl_3$, followed by chromatography on alumina, eluting with heptane–ether (3:1). Quantitative assay of **2** was obtained from its absorption band at 348 nm (ϵ 26,500). Results of feeding experiments are presented in Table I. It was verified that precursors were incorporated into **2** without significant metabolic degradation by isolation of **2** from a feeding experiment with [^3H]ergosterol and reduction with Li–NH_3 to ergosterone (**4**). Base-catalyzed exchange of **4** removed >97% of label, affirming that tritium had been confined to C-4 and C-6 throughout biosynthesis.

Incorporation data support ergosterol as a precursor of **2** and provide evidence for a pathway involving oxygenation and dehydration. The relatively efficient incorporation of triol **12** could be accommodated by a sequence in which oxidation to the 3-keto-5α,8α-diol is followed by double elimination and, in this connection, it is noteworthy that a formal cis removal of water takes place at C-8,14.[17] As an *in vitro* model for this process, it was found that treatment of **13** with CrO_3–pyridine afforded **2** (and **8**) directly, by a route which probably involves allylic rearrangement of the intermediate chromate ester. Ergosterol peroxide (**10**) is also incorporated into **2**, though less efficiently than either **12** or ergosterol itself. In duplicate runs, the ratio of incorporation **10**:**7** remained constant at 0.2. Equivalent incorporation of **10** and **11** implies that **10** is not a *direct* precursor of **12**, and it is expected that experiments in progress will define more precisely the roles of these peroxides in the biosynthetic scheme. The acceptance by *P. rubrum* of 3-keto and 3β-ol functionality in this system is in accord with the demonstrated capacity of certain organisms for assimilation of unnatural substrates of the sterol type.[18] A search of the growth medium for likely biosynthetic intermediates, which has been carried on concurrently, has indicated the presence of **9** in *P. rubrum* cultures, and we also believe it significant that ergosterol and its peroxide have been found along with **2** in cultures of *Lampteromyces japonicus*.[5b]

Acknowledgments. We are indebted to Dr. J. Wang, Massachusetts Institute of Technology, for a soil culture of *P. rubrum* and to Mr. Dennis Perkins for experimental assistance. Financial support was provided by the Research Corporation through a grant from the Brown–Hazen fund and by the Clark fund of the Harvard Graduate Society.

(17) A recent study of ergosterol biosynthesis has revealed that a 5α-hydroxy-Δ^7-sterol precursor [R. W. Topham and J. L. Gaylor, *Biochem. Biophys. Res. Commun.*, 27, 644 (1967)] yields **3** by cis elimination of the 6α hydrogen (personal communication from Professor J. L. Gaylor).

(18) D. H. R. Barton, D. M. Harrison, G. P. Moss, and D. A. Widdowson, *J. Chem. Soc. C*, 775 (1970).

(19) National Science Foundation Undergraduate Research Participant, 1968–1969.

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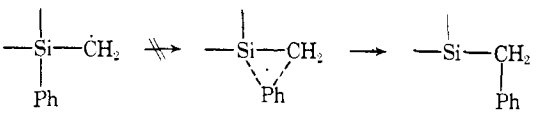
The Search for Radical Rearrangement in Organosilicon Systems. II. Silicon to Carbon Ar_1-5 and Ar_1-6 Phenyl Shifts

Sir:

In contrast to their all-carbon congeners, silaneophyl radicals **1** fail to rearrange.[1,2] It was suggested[1] that this lack of rearrangement of α-silyl radicals may be a consequence of their stabilization *via* d_π–p_π "back-bonding"[3] and the destabilization of the requisite state for such rearrangement (**2**) because of the strain predicted[1] for the (unknown) silacyclopropane ring.



1 **2** **3**

We were therefore prompted to remove both the anti-rearrangement factors associated with **1** and to study *farther* rearrangements in homologs of the silaneophyl type. We report here the first rearrangements of this type in organosilicon systems.[4]

Sequential treatment of 3-chloropropyltrichlorosilane with 1 equiv of phenyl Grignard reagent and 2 equiv of methyl Grignard reagent produced γ-(phenyldimethylsilyl)propyl chloride (**4**; 45.5%; bp 87–89° (1 mm); λ_{neat} 7.0, 9.0 (Ph–Si), 8.0 (CH_3–Si–CH_3); $\delta_{CCl_4}^{TMS}$ 3.28 t (–CH_2Cl)).[5,6] Addition of phenyldimethylsilane to 4-chloro-1-butene in the presence of chloroplatinic acid[7]

$$Cl_3SiCH_2CH_2CH_2Cl \xrightarrow[2.\ CH_3MgI]{1.\ PhMgBr} PhSi(CH_3)_2CH_2CH_2CH_2Cl$$

4

yielded δ-(phenyldimethylsilyl)butyl chloride (**5**; 50%; bp 79–80° (0.1 mm); λ_{neat} 7.0, 9.0 (Ph–Si), 8.0 (CH_3–Si–CH_3); $\delta_{CCl_4}^{TMS}$ 3.37 t (–CH_2Cl)).[6]

$$Ph(CH_3)_2SiH + CH_2{=}CHCH_2CH_2Cl \xrightarrow{H_2PtCl_6} PhSi(CH_3)_2CH_2CH_2CH_2CH_2Cl$$

5

(1) Paper I: J. W. Wilt, O. Kolewe, and J. F. Kraemer, *J. Amer. Chem. Soc.*, **91**, 2624 (1969). For the preliminary account, see J. W. Wilt and O. Kolewe, *ibid.*, **87**, 2071 (1965).

(2) K. Yamamoto, K. Nakamishi, and M. Kumada, *J. Organometal. Chem.*, 7, 197 (1967).

(3) Because α-silyl radicals (and other group IV analogs) are formed in an esr study under conditions where all-carbon radicals are not, P. J. Krusic and J. K. Kochi (*J. Amer. Chem. Soc.*, **91**, 6161 (1969)) deduce a special stability for the former attributable to d_π–p_π delocalization.

(4) For other types of radical rearrangement in silicon-containing species, see ref 1.

(5) This chloride is a minor product observed in the catalyzed addition of phenyldimethylsilane to allyl chloride: Z. V. Belyakova, M. G. Pomerantseva, and S. A. Golubstov, *Zh. Obshch. Khim.*, **36**, 1048 (1965).

(6) The compound gave an acceptable combustion analysis and its ir and nmr spectra were in accord with the structure given.

(7) N. M. Tomiuk, M.Sc. Thseis, Loyola University of Chicago, 1968.