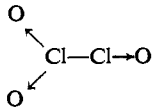
Cl–O–Cl linkage in their structures. ClO_2 is much less stable and decomposes heterogeneously at 40–50°,[2] while Cl_2O_6 is even less stable and decomposes heterogeneously at room temperature.[5] If Cl_2O_3 had a stability-imparting Cl–O–Cl linkage, one would expect to find it a considerably less labile molecule than it is.

A consideration of the relative volatilities of the oxides likewise indicates the structure. Cl_2O_7 is a relatively volatile material with a vapor pressure of 80 torr at 0°,[9] and an estimated 1 torr at −45°. Cl_2O_6 is an oil at 20°, with a vapor pressure of approximately 1 torr, and 0.31 torr at 0°.[5] Since Cl_2O_3 is less volatile than Cl_2O_7, its structure can hardly be of the same type as Cl_2O_7, whereas a structure similar to Cl_2O_6 accounts for its behavior very satisfactorily. Cl_2O_6 is bound in the condensed phase by a Cl–Cl bond which is only 1.7 kcal;[10] it exists almost entirely as ClO_3 in the vapor phase.[5,6] Accordingly, we believe the structure of Cl_2O_3 to be



with a weak Cl–Cl bond of a few kilocalories. The extreme instability is then due to dissociation to yield the reactive ClO radical. The heat of formation of Cl_2O_3 should then be of the order of +45 kcal/mole, since the heats of formation of ClO and ClO_2 are +24 and +25 kcal/mole, respectively.[11]

Acknowledgment. This work was supported by the Air Force Office of Scientific Research, Propulsion Division, under Contract No. AF 49(638)-1645.

(9) C. F. Goodeve and J. Powney, *J. Chem. Soc.*, 2078 (1932).
(10) J. Farquharson, C. F. Goodeve, and F. D. Richardson, *Trans. Faraday Soc.*, 32, 790 (1936).
(11) "JANAF Thermochemical Tables," The Dow Chemical Co., Midland, Mich., 1964.

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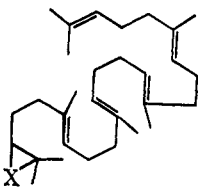
2,3-Iminosqualene, a Potent Inhibitor of the Enzymic Cyclization of 2,3-Oxidosqualene to Sterols

Sir:

Recent studies have demonstrated that the squalene analog 10,11-dihydrosqualene is not readily cyclized under the influence of the sterol-producing enzymes of rat liver homogenate, but instead is converted to a mixture of mono- and dioxido derivatives by addition of oxygen to *either* or *both* of the terminal olefinic groupings,[1] a fact which suggested that 2,3-oxidosqualene (**1a**) might be an intermediate in the biosynthesis of sterols from squalene. This possibility has been fully verified by an appropriate series of experiments.[2,3] More recently, the enzyme which effects anaerobically the conversion of 2,3-oxidosqualene has been separated from hog liver microsomes in water-soluble form and has been partially purified.[4] This note describes the results of an investigation aimed at the development of an effective inhibitor for this enzyme, 2,3-oxidosqualene cyclase.

Experiments to determine inhibition were performed anaerobically with solutions of partially purified 2,3-oxidosqualene cyclase in amounts sufficient to effect *ca.* 30% conversion of 25 μM ^{14}C-labeled 2,3-oxidosqualene to lanosterol in 30 min. Parallel, duplicate runs were made with and without the substance under test. Table I records some of the data which have been obtained from the study of (±)-2,3-iminosqualene (**1b**), (±)-2,3-sulfidosqualene (**1c**), and decahydro-(±)-2,3-iminosqualene as potential inhibitors. The results summarized in the table show strikingly that 2,3-iminosqualene (**1b**) is a powerful inhibitor of 2,3-



1a, X=O
b, X=NH
c, X=S

oxidosqualene cyclase, as might be expected from the greater basicity of **1b** as compared with **1a** and the supposition that the enzyme operates on the oxygen of **1a** as a proton-transfer reagent. Decahydro-**1b**, although a weaker inhibitor than **1b**, is still effective; evidently the high basicity of the imino grouping largely offsets the geometric perturbations in the enzyme–inhibitor complex due to the saturated carbon chain. Relative to these aziranes, 2,3-sulfidosqualene (**1c**) is a weak inhibitor. It is also inert to 2,3-oxidosqualene cyclase, as could be shown by experiments with ^{14}C-labeled **1c** in which essentially all the radioactivity was accounted for in the recovered substrate **1c** after incubation with the cyclizing enzyme. Little, if any, inhibition of lanosterol synthesis from the oxide **1a** and 2,3-oxidosqualene cyclase was observed with 3β-amino-

Table I. Inhibition of 2,3-Oxidosqualene Cyclase[a]

Inhibitor	Inhibitor concn, μM	% conversion of **1a** to lanosterol
None	....	30
1b	1.4	3
1c	1.4	26
Decahydro-**1b**	1.4	25
1b	4.4	0[b]
1c	4.4	26
Decahydro-**1b**	4.4	18
1c	*Ca.* 1000	15
Decahydro-**1b**	*Ca.* 100	15

[a] Substrate concentration 25 μM; anaerobic incubation at 37° for 30 min. [b] In addition, no conversion of **1a** to lanosterol occurs after 3 hr of incubation.

(1) E. J. Corey and W. E. Russey, *J. Am. Chem. Soc.*, **88**, 4751 (1966).
(2) E. J. Corey, W. E. Russey, and P. R. O. de Montellano, *ibid.*, **88**, 4750 (1966).
(3) E. E. van Tamelen, J. D. Willet, R. B. Clayton, and K. E. Lord, *ibid.*, **88**, 4752 (1966).
(4) P. D. G. Dean, P. R. O. de Montellano, K. Bloch, and E. J. Corey, *J. Biol. Chem.*, in press.

lanosta-8,25-diene, 3β-aminolanost-8-ene, or squalane at concentrations approximating those of substrate **1a**.

The inhibitory effect of 2,3-iminosqualene on the enzymic conversion of **1a** to lanosterol has been utilized to permit the accumulation of 2,3-oxidosqualene using squalene as substrate with rat liver homogenate.[2] Equilibration of 0.12 μmole of (±)-2,3-iminosqualene with 2 ml of rat liver homogenate for 5 min at 37° followed by addition of ^{14}C-labeled squalene (0.075 μmole) and *ca.* 5 mg of reduced triphosphopyridine nucleotide and aerobic incubation for 3 hr led after chromatographic isolation to 2,3-oxidosqualene in 25–30% yield.[5] The isolated labeled oxide **1a** was further identified by its transformation to labeled lanosterol by anaerobic incubation with 2,3-oxidosqualene cyclase for 1 hr (80% conversion).

The synthesis of (±)-2,3-iminosqualene was accomplished by the sequence: all-*trans*-(±)-2,3-oxidosqualene (**1a**)[2] → 2-azido-3-hydroxysqualene (HN_3) → 2-azido-3-*p*-toluenesulfonoxysqualene (*p*-toluenesulfonyl chloride–pyridine) → (±)-2,3-iminosqualene (**1b**) ($LiAlH_4$).[6] The structure of **1b** was confirmed chemically by its conversion using N-nitroso-4-nitrocarbazole to squalene and nitrous oxide.[7] Decahydro-2,3-iminosqualene was synthesized by hydrogenation of **1b** with palladium-on-charcoal catalyst in ethanol; the mass spectrum showed a peak due to the molecular ion at *m/e* 435, as expected for a decahydro derivative of **1b**, and no peak at *m/e* 425, indicating the absence of unreduced **1b**. (±)-2,3-Sulfidosqualene was obtained from the reaction of (±)-**1a** with potassium thiocyanate in ethanol;[8] independent chemical evidence for the formulation of this product as **1c** was obtained from the reaction with *n*-butyllithium which produced squalene cleanly.[9,10]

Work on various aspects of the enzymic cyclization of 2,3-oxidosqualene and its analogs is continuing.

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(5) 2,3,22,23-Dioxidosqualene was also isolated in 3–10% yield. The absence of sterol formation in this experiment was indicated by the lack of radioactivity in the sterol fraction obtained after precipitation with digitonin.

(6) New substances were characterized by infrared, nuclear magnetic resonance, and mass spectroscopy. Homogeneity was indicated by thin-layer chromatographic techniques.

(7) C. L. Bumgardner, K. S. McCallum, and J. P. Freeman, *J. Am. Chem. Soc.*, 83, 4417 (1961).

(8) C. C. J. Culvenor, W. Davis, and N. S. Heath, *J. Chem. Soc.*, 282 (1949).

(9) F. G. Bordwell, H. M. Anderson, and B. M. Pitt, *J. Am. Chem. Soc.*, 76, 1082 (1954).

(10) The racemic compounds **1a–c** are all liquid at room temperature. The nmr spectra of the oxide **1a** and the imine **1b** each show two sharp peaks due to the geminal methyl substituents on the three-membered ring (for **1a** at 1.25 and 1.30 ppm and for **1b** at 1.09 and 1.17 ppm, downfield from tetramethylsilane), whereas on the spectrum of the sulfide **1c** all the peaks due to methyl groups fall together at *ca.* 1.61 ppm.

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Synthesis of a Medium Ring Containing Bridge Biphenyl by Photochemically Induced Intramolecular Arylation

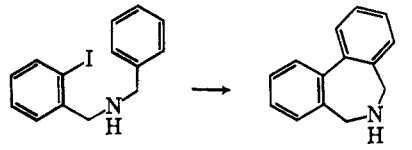
Sir:

Recent interest in intramolecular radical cyclization reactions,[1] particularly those involving aryl radicals,[2] prompts us to present details of a photochemical route to a bridged biphenyl containing a medium ring.

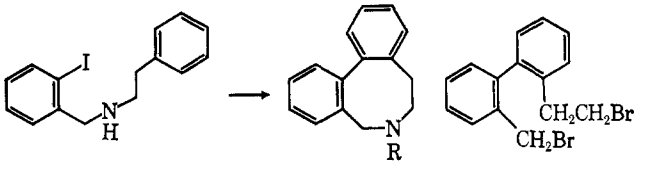
Photolysis of aryl iodides in benzene provides a useful method for the synthesis of substituted biphenyls.[3] An extension of this reaction has been employed for effecting intramolecular arylations leading to phenanthrenes,[4] and more recently to the synthesis of aporphines.[5]

The results presented in this communication demonstrate that photochemically induced intramolecular arylation may be employed not only in the formation of six-membered rings but also for constructing seven- and eight-membered cycles.

Irradiation[6] of a dilute aqueous solution of the iodoaromatic compound **I**, as the hydrochloride, gave after 200 hr the photocyclized product, 6,7-dihydro-5H-dibenz[*c*,*e*]azepine (**2**),[7] mp 74–76°, in 57% yield, together with 13% of starting material. Similarly, irradiation of N-(β-phenethyl)-2-iodobenzylamine (**3**) as the hydrochloride in water for 113 hr, under the same conditions as described above, afforded the photocyclized product **4** (R = H) in 25% yield, mp 119–120°[8] [hydrochloride mp 321–322° dec], λ_{max} 276



1 **2**



3 **4** **5**

mμ (log ε 2.89), λ_{sh} 231 mμ (log ε 4.15), pmr: eight-proton multiplet, δ 7.38–6.95 (aromatic hydrogens), one-proton broad doublets, 3.83 (*J* = 15 Hz), 3.10 (*J* = 15 Hz) ($C_6H_5CH_2N$),[9] five-proton multiplet, 3.20–2.10 ($-HNCH_2CH_2$), mol wt (mass spectrum), 209, together with N-(β-phenethyl)benzylamine (10%). The

(1) C. Walling, J. H. Cooley, A. A. Ponaras, and E. J. Racah, *J. Am. Chem. Soc.*, 88, 5361 (1966); N. C. Yang, A. Shani, and G. R. Lenz, *ibid.*, 88, 5369 (1966).

(2) M. Tiecco, *Chem. Commun.*, 555 (1965); M. P. Cava, S. C. Havlicek, A. Lindert, and R. J. Spangler, *Tetrahedron Letters*, 2937 (1966); N. C. Yang, G. R. Lenz, and A. Shani, *ibid.*, 2941 (1966).

(3) W. Wolf and N. Kharasch, *J. Org. Chem.*, 30, 2493 (1965).

(4) S. M. Kupchan and H. C. Wormser, *Tetrahedron Letters*, 359 (1965); *J. Org. Chem.*, 30, 3792 (1965).

(5) S. M. Kupchan and R. M. Kanojia, *Tetrahedron Letters*, 5353 (1966).

(6) Photolyses were carried out using a 450-w Hanovia high-pressure lamp fitted with a Pyrex sleeve.

(7) W. Wenner, *J. Org. Chem.*, 16, 1475 (1951). We are indebted to Dr. W. E. Scott, Hoffmann-LaRoche, Nutley, N. J., for providing an authentic sample for comparison.

(8) All new compounds gave satisfactory analyses.

(9) The nonequivalence of the benzylic hydrogens indicates the eight-membered ring exists predominantly in one conformation at room temperature. Studies on the temperature dependence of the spectrum of this compound are under investigation.