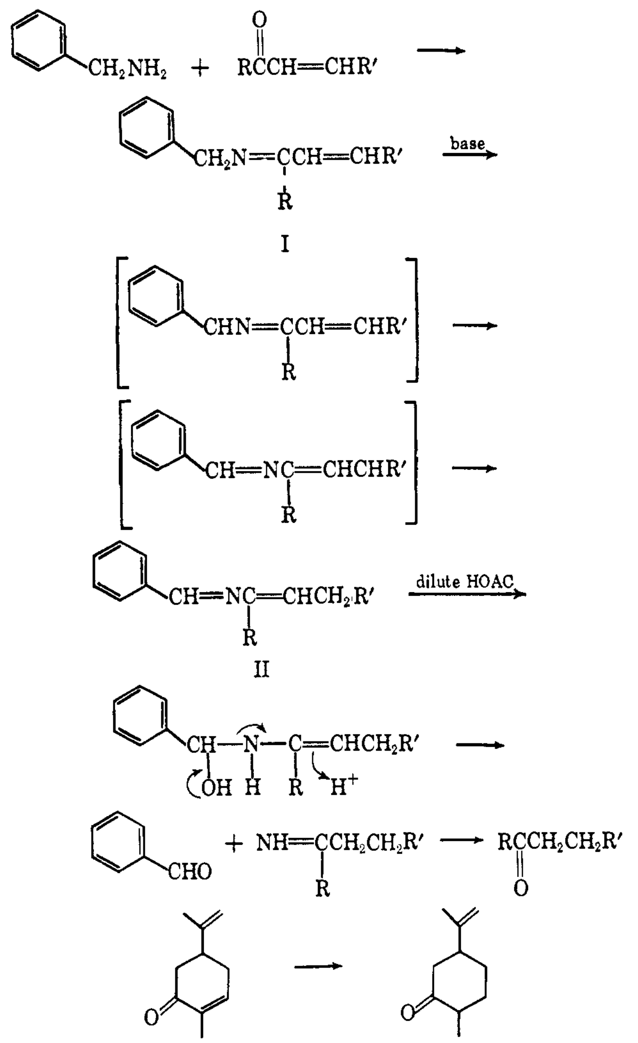
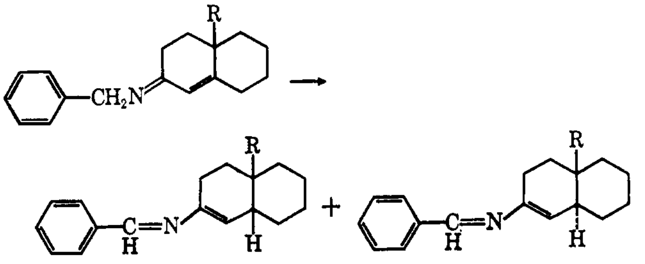
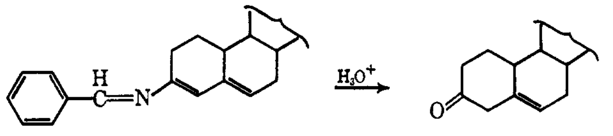


room temperature rearrangement of the Schiff base of 3,5-dimethyl-Δ^{2}-cyclohexenone with 0.1 mole of potassium t-butoxide in hexamethylphosphoramide solution proceeded to the extent of only 56.7% in 1 hr.[2] On the other hand, under similar conditions the rearrangement of the Schiff bases of 2,4-dimethyl-Δ^{2}-cyclohexenone and d-carvone was complete within 5 min. The slowness is most likely due to (a) the intermediacy of a tertiary carbanion in contrast to the secondary carbanion arising from the Schiff's bases of ketones lacking substitution at the β position, and (b) hyperconjugative and inductive effects of the alkyl groups enhancing the ground-state stability of the Schiff bases of the β-substituted ketones. The rate of the rearrangement could, however, be accelerated by increasing the amount of base and the reaction temperature. For instance, the rearrangement of the Schiff base of 3,5-dimethyl-Δ^{2}-cyclohexenone with 1 equiv of KO-t-Bu was complete within 40 min at 100°.

Reduction of bicyclic ketones, *e.g.*, $\Delta^{1(9)}$-2-octalone and 10-methyl-$\Delta^{1(9)}$-2-octalone, when the rearrangement of their Schiff bases was stopped after 30–40% completion, led to the corresponding *trans*-decalones. These results indicate that, in this mode of reduction, the transition state for the kinetic protonation at the β-carbon atom is analogous to that involved in the metal–ammonia reduction of these ketones.[3] It is, however, obvious that under equilibrating conditions the rearrangement of these Schiff bases would lead to a thermodynamic mixture of the *cis* and *trans* isomers and thus provide a direct method for the determination of the thermodynamic stabilities of various substituted Δ^{1}-octalins.[4] Further work along these lines is in progress.



Reduction of steroidal Δ^{4}-3-ketones, *e.g.*, testosterone and cholestenone, proceeded in relatively poor yields in our hands, due to the formation of side products. Pregna-$\Delta^{5,16}$-dien-3β-ol-20-one was reduced to pregnenolone in 40% yield. Reduction of cholest-$\Delta^{4,6}$-dien-3-one led to a mixture of cholest-Δ^{4}- and Δ^{5}-en-3-ones in 50% yields.[5]



IV

---

(2) The extent of the rearrangement of the Schiff base was followed by the disappearance of bands due to benzylic protons in the nmr spectrum and by the determination of saturated and unsaturated ketones in the hydrolyzed product by glpc.

(3) G. Stork and S. D. Darling, *J. Am. Chem. Soc.*, **86**, 1761 (1964); M. J. T. Robinson, *Tetrahedron*, **21**, 2475 (1965).

(4) The Schiff base of $\Delta^{(9)}$-2-octalone on heating with 0.1 mole of potassium t-butoxide at 130° for 19 hr gave a 1:4 mixture of *cis*- and *trans*-decalones.

(5) The formation of Δ^{5}-3-one is due to the protonation of IV at C-4 which is analogous to the protonation of $\Delta^{3,5}$-enolate. Also see S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **87**, 3228 (1965), and references cited therein.

Sudarshan K. Malhotra, Douglas F. Moakley, Francis Johnson
The Dow Chemical Company, Eastern Research Laboratory
Wayland, Massachusetts 01778

Received April 1, 1967

Chlorine(III) Oxide, a New Chlorine Oxide

Sir:

There are four known stable oxides of chlorine: Cl_2O, ClO_2, Cl_2O_6 (which dissociates to ClO_3 in the vapor), and Cl_2O_7. These compounds have been known and characterized for a long time and they are discussed in inorganic textbooks. In the course of a study of the decomposition of chlorine dioxide[1] we have discovered a new oxide of empirical formula $ClO_{1.5}$. We believe this chlorine(III) oxide to be Cl_2O_3, and we wish to report its synthesis and behavior in this communication.

When gaseous ClO_2 is admitted from a Pyrex storage vessel at room temperature to another Pyrex vessel at a temperature above about 50°, it explodes after an induction period. We found that the induction period

---

(1) E. T. McHale and G. von Elbe, to be published.

is reduced or even eliminated by exposure of the storage vessel to light, and the effect of such illumination persists for many hours. Obviously, a photochemical reaction occurs which produces a fairly stable compound that acts as a promoter of the explosive decomposition of ClO_2. The existence of such promoter has already been noted in an earlier study of the chain mechanism of ClO_2 decomposition,[2] but the substance has hitherto not been identified.

Several workers have reported the photolysis of ClO_2,[3,4] where the lowest temperature was 15°. The identified products comprise Cl_2, O_2, and Cl_2O_6. The last is described[5] as a red liquid at room temperature, which freezes at +3.5° to an orange solid. The vapor pressure as a function of temperature has been carefully measured from −30 to +15°, it being 0.31 torr at 0°. In the vapor phase this oxide is almost completely dissociated into ClO_3.[5,6] Prolonged irradiation of Cl_2O_6 produces the heptoxide, Cl_2O_7.[3] We have prepared both Cl_2O_6 and Cl_2O_7 by the procedures described in the literature and have tested the effect of these and other compounds on the ClO_2 induction period. The results were substantially negative for Cl_2O_7, Cl_2, and O_2; this also applies to Cl_2O,[2] whereas Cl_2O_6 (or ClO_3) was found to be an inhibitor rather than a promoter. The promoting agent is thus another, hitherto unknown photolysis product.

We used the following method for isolating this product. One millimole of ClO_2 (see ref 1 for preparation and purification) was admitted to a 500-cc spherical Pyrex flask. A U-tube manometer was connected directly to the top of the vessel, the mercury being protected with a layer of Kel-F oil. The lower half of the reactor was immersed in a −45° bath, and ultraviolet light from a 100-w lamp was directed at the upper half. Under these conditions ClO_2 remains a gas (vapor pressure, 37 torr at −45°); no detectable Cl_2O_7 is formed, and the condensable products, Cl_2O_6 and the unknown agent, collect at the vessel bottom as a dark brown crystalline solid. Within 20–30 min the ClO_2 is completely consumed. The Cl_2 and O_2 products are pumped away and the bulb evacuated to <0.1 torr with no indication of loss of any of the dark brown solid.

At −45° the solid decomposes very slowly, an estimated 10% in 20 min. At −78° it is stable indefinitely. When the −45° bath is replaced with a 0° bath, the pressure rises from zero to some constant value of the order of 15 torr depending on the amount of brown solid originally formed, and no further increase takes place. A solid orange residue remains after the pressure rise which has a vapor pressure of *ca.* 0.3 torr at 0° and a melting point of +3°, in near-perfect agreement with the data reported for Cl_2O_6. If the warm-up from −45 to 0° is conducted in darkness, one observes a series of flashes of orange light throughout the vessel, indicating that the brown material explodes as it gasifies. The flashes continue until all the brown solid is gone, leaving the orange Cl_2O_6 residue plus the gaseous explosion products of the other photolysis product.

The brown solid then is a mixture of Cl_2O_6 and the unidentified photolysis product. We have determined the composition of this unknown product by measuring the O_2/Cl_2 ratio of the decomposition products. The results of duplicate measurements on three separate preparations were: 1.42, 1.43; 1.59, 1.59; 1.50, 1.48. The average of these measurements is 1.50 ± 0.1.

The analytical technique consisted of measuring the total pressure of the explosion products, O_2 and Cl_2, in the reactor of 0°, allowing for a vapor pressure of 0.3 torr of Cl_2O_6, and then measuring the O_2 pressure after Cl_2 had been condensed on a cold spot at the bottom of the bulb at −196°. Numerous tests on synthetic mixtures of known O_2/Cl_2 ratios confirmed the validity of the technique. The temperature of −196° ensured that only O_2 remained in the gas phase, and no O_2 itself condensed since the vapor pressure is *ca.* 160 torr at −196°, and in all experiments the O_2 pressure in the 500-cc reactor after cooling ranged from 6.0 to 8.5 torr. Furthermore, we took care to satisfy ourselves that only O_2 and Cl_2 were formed in the explosive decomposition.

Parenthetically it should be noted that this new oxide was probably previously prepared in small quantities by Goodeve and Richardson.[5] They report that the color of Cl_2O_6, prepared photolytically, can be taken as an indication of purity, and that at low temperature an "impurity" colored the hexoxide dark brown.

To summarize, this new chlorine oxide is a dark brown solid at −45° and below when condensed with Cl_2O_6. It has a vapor pressure <0.1 torr and decomposes slowly at −45°, but not at all at −78°. Since its vapor explodes at approximately 1–2 torr pressure and temperatures well below 0°, it does not lend itself to a determination of physical properties such as boiling point, melting point, and vapor pressure. The empirical formula is $ClO_{1.5}$, and we believe it to be the unknown chlorine sesquioxide, Cl_2O_3. This last formula is the most reasonable, but it would be desirable to determine the molecular weight since theoretically the molecular formula could be $(ClO_{1.5})_n$ with n any even integer. Again, however, such measurements as vapor density or freezing point depression are not feasible with this compound.

The new oxide is very likely formed in the reactions

$$ClO_2 + h\nu \longrightarrow ClO + O \qquad (1)$$

$$ClO + ClO_2 \longrightarrow Cl_2O_3 \qquad (2)$$

These are just two of many reactions in the mechanism, since we find Cl_2O_6, O_2, and Cl_2 as primary products. The actual over-all stoichiometry at −45° which we have measured by mass balance is

$$30ClO_2 \longrightarrow 4Cl_2O_6 + 6Cl_2O_3 + 9O_2 + 5Cl_2$$

but this equation is probably unique to our reaction conditions.

Assuming that $n = 2$, it is possible to infer the structure of Cl_2O_3 from this study and what is known of the other chlorine oxides. The most stable of the chlorine oxides are Cl_2O[7] and Cl_2O_7,[8] which decompose homogeneously and must be heated to 100° or above to decompose at measurable rates. These both contain the

---

[2] H.-J. Schumacher and G. Steiger, *Z. Physik. Chem.*, **B7**, 363 (1930).

[3] H. Booth and E. J. Bowen, *J. Chem. Soc.*, **127**, 510 (1925).

[4] J. W. T. Spinks and J. M. Porter, *J. Am. Chem. Soc.*, **56**, 264 (1934).

[5] C. F. Goodeve and F. D. Richardson, *J. Chem. Soc.*, 294 (1937).

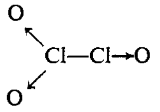
[6] C. F. Goodeve and F. A. Todd, *Nature*, **132**, 514 (1933).

[7] C. N. Hinshelwood and C. R. Prichard, *J. Chem. Soc.*, **123**, 2730 (1928).

[8] R. V. Figini, E. Coloccia, and H.-J. Schumacher, *Z. Physik. Chem.* (Frankfurt), **14**, 32 (1958).

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.

Edward T. McHale, Guenther von Elbe
Kinetics and Combustion Group, Atlantic Research Corporation
Alexandria, Virginia 22314

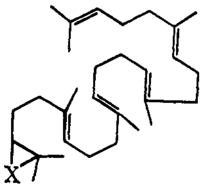
Received August 8, 1966

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-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-



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

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.