the thiocyanate ligand allows for the M–N–C bond to be angular rather than linear. This feature would explain the presence of more than one absorption band in the $C\equiv N$ region of the niobium and tantalum complexes. The infrared data imply that the $C\equiv N$ and C—S bonds are weaker and stronger, respectively, than those observed in any previously reported thiocyanato complex. A preliminary examination of the niobium(IV) complex, $[(C_6H_5)_4As]_2Nb(NCS)_6$, has shown the $C\equiv N$ stretching absorption to occur at 2030 cm^{-1}. This leads us to believe that the bonding in the thiocyanate ligand is dependent upon the oxidation state of the central atom, especially for those elements containing few if any available d electrons. In order to examine the effect of oxidation state on the $C\equiv N$ and C—S bonds in isothiocyanato complexes, we are presently preparing and studying similar complexes with molybdenum and tungsten, as these elements are capable of exhibiting an even wider range of oxidation states.[8]

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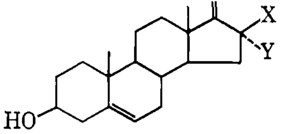
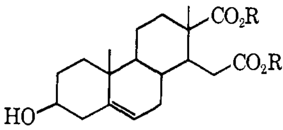
On the Mechanism of Oxidation of Enolizable Nonmethyl Ketones by Base and Iodine. The Role of Atmospheric Oxygen

Sir:

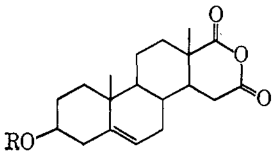
In contrast to the well-studied iodoform reaction of methyl ketones,[1] the reaction of enolizable nonmethyl ketones with alkaline solutions of iodine has received little attention. Cullis and Hashmi[2] subjected 3-pentanone and 3-heptanone to these conditions and isolated a mixture of acids, but only a small amount of organically bound iodine was found among the products. Similarly, cyclic ketones have yielded dibasic acids on treatment with alkaline solutions of iodine.[3]



1a, X = Y = H
b, X = H; Y = I
c, X = Y = I



2a, R = R¹ = H
b, R = H; R¹ = CH$_3$
c, R = CH$_3$; R¹ = H
d, R = R¹ = CH$_3$

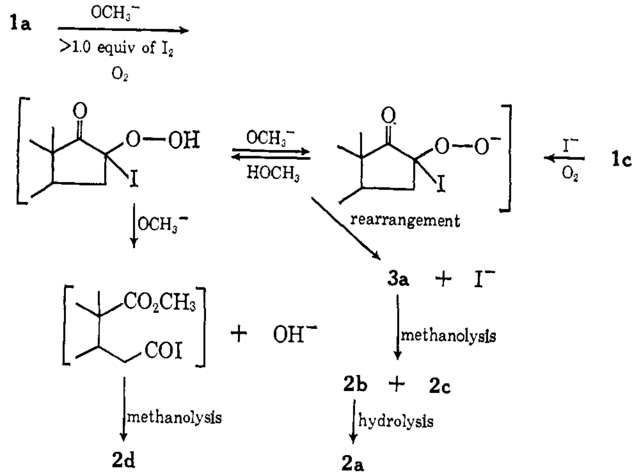


3a, R = H
b, R = Ac

For example, in aqueous methanol 5-androsten-3β-ol-17-one (**1a**) has been reported[3a,e-g] to yield varying amounts of **2a–d** depending on the reaction conditions and method of work-up.

The present work shows that, in methanolic iodine and base, oxidation of **1a** proceeds *via* a novel mechanism requiring the incorporation of molecular oxygen. Furthermore, the accumulated data on stoichiometry, detectable intermediates, and observed products define a probable reaction pathway, as shown in Chart I.

Chart I



The participation of molecular oxygen is demonstrated by the contrasting results obtained on reaction of **1a** in nitrogen-purged and air-saturated solutions. Thus, treating methanolic sodium methoxide (or methanolic potassium hydroxide) solutions of **1a** at 0° *under nitrogen* with 1 equiv of iodine gives the monoiodo ketone **1b** in 58% yield; mp 142–143° dec; $[\alpha]^{24}\text{D}$ +17° (CHCl$_3$) (*Anal.* Calcd for $C_{19}H_{27}O_2I$: I, 30.63. Found: I, 30.32);[4] carbonyl band in the infrared (CHCl$_3$) at 1741 cm^{-1}; ultraviolet (CHCl$_3$) $\lambda_{\max}$ 285 mμ (ϵ 485), λ_{sh} 330 mμ (ϵ 290); nmr peaks (CDCl$_3$) at δ 0.91 (3 H, singlet, C-13 angular methyl) and 4.86 (1 H, multiplet, C-16 β proton).[5,6] Similar treatment of **1a** with 2 equiv of iodine under nitrogen yields the diiodo ketone **1c** (85%) which crystallizes from the solution as pale yellow needles; mp 131–133° dec; $[\alpha]^{24}\text{D}$ −11° (CHCl$_3$) (*Anal.* Calcd for $C_{19}H_{26}O_2I_2$: I, 47.00. Found: I, 46.78); carbonyl band in the infrared (CHCl$_3$) at 1741 cm^{-1}; ultraviolet (CHCl$_3$) $\lambda_{\max}$ 305 mμ (ϵ 1470); nmr peak (CDCl$_3$) at δ 1.13 (3 H, singlet, C-13 angular methyl). Both **1b** and **1c** are stable for several hours under these reaction conditions. However, rapid and complete oxidation of **1a** occurs in *air-saturated* solutions using only 1.25 equiv of iodine. Moreover, a suspension of **1c**, prepared *in situ* under nitrogen, rapidly (10–15 min) produces a reddish brown solution (due to liberated iodine as I_3^-) after saturation with air giving **2a–d** in over 90% yield. Quantitative measure-

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[1] For the most recent review see M. H. Hashmi, *Pakistan J. Sci.*, 10, 159 (1958).

[2] C. F. Cullis and M. H. Hashmi, *J. Chem. Soc.*, 1548 (1957).

[3] (a) A. Wettstein, H. Fritzsche, F. Hunziker, and K. Miescher, *Helv. Chim. Acta*, **24**, 332 E (1941); (b) C. Djerassi, H. Bendas, and P. Sengupta, *J. Org. Chem.*, **20**, 1046 (1955); (c) J. Heer and K. Miescher, *Helv. Chim. Acta*, **28**, 156 (1945); (d) J. Heer, J. R. Billeter, and K. Miescher, *ibid.*, **28**, 991 (1945); (e) J. Heer and K. Miescher, *ibid.*, **30**, 786 (1947); (f) C. von Seemann and G. A. Grant, *J. Am. Chem. Soc.*, **72**, 4073 (1950); (g) E. B. Hershberg, E. Schwenk, and E. Stahl, *Arch. Biochem.*, **19**, 300 (1948); (h) L. Mamlok, A. Horeau, and J. Jacques, *Bull. Soc. Chim. France*, 2359 (1965).

[4] Satisfactory carbon and hydrogen analyses were obtained for all new compounds.

[5] The chemical shifts are downfield from TMS as internal standard.

[6] The assignment of the 16α-iodo configuration is based on the ultraviolet and pmr spectral data by analogy with the work of R. E. Counsell and G. W. Adelstein, *J. Pharm. Sci.*, **55**, 947 (1966).

ments using a gas buret show that 1 equiv of molecular oxygen is consumed from air (or oxygen) per molar equiv of **1c** reacting;[7] the products isolated are **2a–d**.

The kinetic product distributions obtained on oxidation in aerated methanol have been determined and are reported in Table I. The low and invariant amount of **2c** in the acid fractions suggests that the anhydride **3a** is an intermediate. Basic methanolysis of **3b** (mp 186–189°; $[\alpha]^{24}\text{D}$ −148° ($CHCl_3$))[3a] supports this presumption since the percentage of **2c** in the resulting acid mixture is within experimental error of that observed in the acid fractions from oxidation (Table I). Attempts to isolate this intermediate, by aeration of **1c** in methanolic sodium iodide (with or without added methoxide) and quenching immediately after reaction, gives instead the methanolysis products **2b** and **2c**. However, oxidation (I^-, O_2) of **1c** in acetonitrile provides **3a** in 30% yield: mp 209–212° (ether); $[\alpha]^{24}\text{D}$ −165° ($CHCl_3$); bands in the infrared at 3609 (hydroxyl) and at 1808 and 1761 (anhydride) cm^{-1}; nmr peaks ($CDCl_3$) at δ 1.23 (3 H, singlet, C-13 angular methyl), 1.78 (1 H, singlet, OH), and 3.55 (1 H, broad multiplet, C-3 α proton).[8] Treatment of **3a** with aqueous pyridine yields **2a** which is identified by comparison of physical properties with an authentic sample.

Table I. Effect of Reaction Conditions on Kinetic Product Distributions in Aerated Methanol at 0°[a]

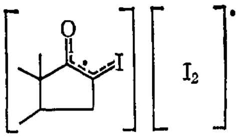
Sub-strate	Reagents, equiv: I_2	Reagents, equiv: $NaOCH_3$	Reagents, equiv: NaI	Yields, %[b]: **2d**[c]	Yields, %[b]: (**2a** + **2b** + **2c**)[d]	Mole % **2c** in acid fraction
1a	2.20	5.0		30	54	9.4
1a	1.25	5.0		37	56	8.7
1a	1.25	5.0	2.0	37	57	8.3
1a	1.25	10.0		76	15	9.7
1a	1.25	15.0		81	*e*	
Ic[f]			2.0	*e*	66	7.0[g]
1c[f]		10.0	2.0	76	16	8.2
3b		5.1		0	92	8.9

[a] The substrate (3.45 × 10^{-2} *M*) and reagents were mixed and equilibrated under nitrogen for 20 min prior to saturating with dry air. The products after initial processing were separated into acidic and neutral fractions by extraction with 2.5% NaOH. The extraction caused partial hydrolysis of **2b**, but **2c** and **2d** were not affected. [b] The yields are per cent of theoretical based on substrate. [c] Calculated from weights of neutral fractions, which contained some **1a** (tlc) not exceeding 5% (nmr). [d] Calculated from weights of acid fractions and the mole fractions of **2a–c** as determined from peak heights of the methoxyl and C-13 angular methyl resonances in the nmr (Varian A-60 and C-1024 computer of average transients, 25 scans) [e] Not determined. [f] Initially as suspensions. [g] HA-100 single scan.

Partitioning between the anhydride **3a** and the diester **2d** is dependent only on the concentration of base employed. In view of the incorporation of molecular oxygen, an initial hydroperoxide intermediate is presumed (Chart I) which may either rearrange to anhydride or undergo specific nucleophilic attack by methoxide to yield the diester. Under neutral or basic conditions, cleavages like these occur with α-hydroperoxy ketones[9] and in reactions that proceed through α-hydroperoxy ketone intermediates.[10]

The conditions under which oxidation occurs appear to eliminate both base-catalyzed[11] and light- or thermal-initiated free-radical mechanisms. Thus, **1b**, prepared *in situ* with 1 equiv of iodine and excess base, is recovered in 67% yield after aeration for 6 hr. Suspensions of **1c** in aerated methanolic sodium methoxide are stable in the absence of iodide ion (86% recovery of **1c** after 3 hr). Also, the reaction proceeds as rapidly to give the same products in both the presence or absence of light and is not inhibited by added iodoform which is recovered in 70% yield.

The unusual reactivity toward oxygen presently observed may involve a molecular complex (π complex) in equilibrium with both the enolate of **1b** and iodine and with **1c** and iodide ion.[12] Complete electron transfer from the donor to iodine may take place in the ground state to give a charge-transfer complex such as **4**.[13] Such complexes are expected to show free-radical behavior.[14]



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Acknowledgment. We thank Drs. J. S. Tadanier and H. E. Zaugg of this department and Dr. P. Beak of the University of Illinois for helpful discussions.

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[7] Two other enolizable ketones have been briefly studied. They are 5α-androstan-17β-ol-3-one and propiophenone. Quantitative measurements show that in methanol each consumes molecular oxygen (0.75 equiv) under conditions of base-catalyzed iodination (4.5 and 2.5 equiv of iodine, respectively).

[8] For comparison **3b** shows carbonyl bands in the infrared ($CHCl_3$) at 1808, 1760 (anhydride), and 1728 (acetate) cm^{-1}, while in the nmr ($CDCl_3$) peaks are observed at δ 1.22 (3 H, singlet, C-13 angular methyl), 2.02 (3 H singlet, acetate), and 4.57 (1 H, broad multiplet, C-3α proton). The C-15 methylene protons of **3a** and **3b** gave superimposable patterns of the ABX type with $|J_{AB}|$ = 18 Hz but only the A proton was completely separated from the resonance envelope of the steroid nucleus.

(9) P. S. Bailey and S. S. Bath, *J. Am. Chem. Soc.* 79, 3120 (1957).

(10) (a) E. Elkik, *Bull. Soc. Chim. France*, 933 (1959); (b) H. Kwart and N. J. Wegemer, *J. Am. Chem. Soc.*, **83**, 2746 (1961), and references cited therein.

(11) (a) W. von E. Doering and R. M. Haines, *J. Am. Chem. Soc.*, **76**, 482 (1954); (b) G. A. Russell, E. R. Talaty, and R. H. Horrocks, *J. Org. Chem.*, **32**, 353 (1967).

(12) The failure of oxidation with 1 equiv of iodine could be the result of one of the following situations. If the rate-determining step precedes the step involving oxygen, then the rate of deiodination of **1b** with iodide ion must be very slow compared to the rate of deiodination of **1c** with iodide ion. Other wiseiodine would accumulate in the presence of **1b** and base, allowing oxidation to take place. However, if the oxygenation step is rate determining, then the equilibrium between **1b** and a mixture of **1a** and **1c** must favor **1b**. Otherwise **1c** would accumulate in the presence of iodide ion and allow oxidation to take place. We thank a referee for suggesting the former possibility.

(13) A referee has pointed out that the donor system is isoelectronic with the stable radicals derived from reduction of 1,2-diones.[11b]

(14) D. N. Stamires and J. Turkevich, *J. Am. Chem. Soc.*, **85**, 2557 (1963).

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Received May 5, 1967

Studies on Polypeptides. XXXVII. Competitive Inhibition in the S-Peptide–S-Protein System[1,2]

Sir:

Structure-function studies carried out in our laboratories have shown that the six C-terminal amino acid

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(1) The authors wish to express their appreciation to the U. S. Public Health Service for generous support of this investigation.

(2) The peptides and peptide derivatives mentioned are of the L configuration.