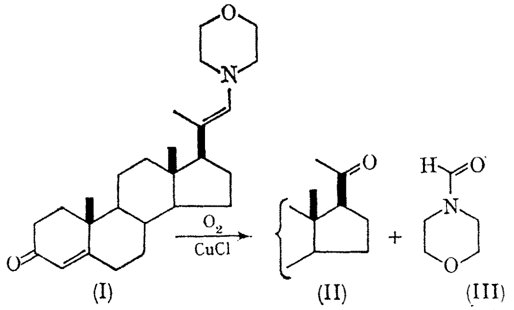
Copper-catalysed Oxygenation of Enamines

By V. VAN RHEENEN
(*The Upjohn Company, Kalamazoo, Michigan* 49001)

Summary Copper salts catalyse oxygenation of enamines under mild conditions, giving ketone and amide in good yields.

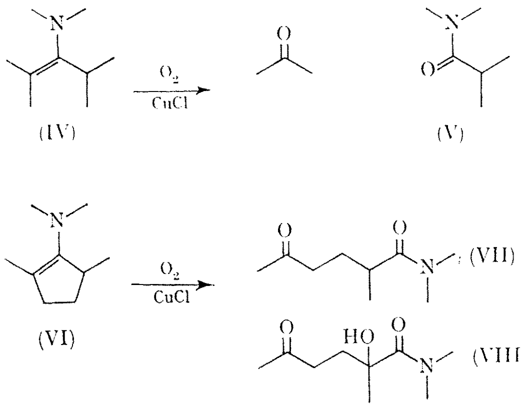
ALDEHYDE ENAMINES such as (I) are stable to molecular oxygen.[1] In the presence of cuprous chloride, however, they rapidly absorb 1 mol. of oxygen, and the enamine double bond is cleaved. When a solution of (I) in chloroform containing cuprous chloride was oxygenated for 4·5 hr. at 0°, progesterone (II) and *N*-formylmorpholine (III)† were formed in quantitative yield. Similarly the morpholine enamine of cyclohexanecarboxaldehyde yielded cyclohexanone and (III), whereas the morpholine enamine of isobutyraldehyde gave acetone and (III). These yields were likewise quantitative, as determined by g.l.c. analysis using an internal standard.



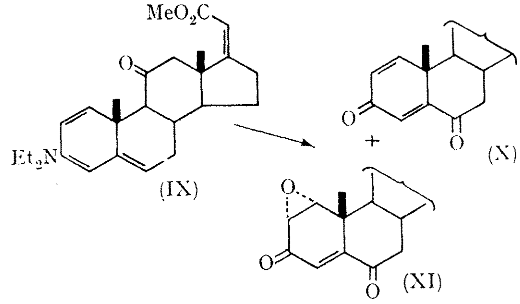
(I) (II) (III)

Sterically hindered enamines derived from α-alkylated ketones could also be cleaved by this procedure. Oxygenation of (IV)[2] at 0° in chloroform with a trace of cuprous chloride gave acetone and *NN*-dimethylisobutyramide (V) in 80% yield. Under the same conditions cyclic enamine (VI) underwent cleavage of the double bond to yield the keto-amide (VII) (*m/e* 171; m.p. of 2,4-dinitrophenylhydrazone 94–96°) along with a small amount of the hydroxyketo-amide (VIII), isolated as the 2,4-dinitrophenylhydrazone (m.p. 107—109°; *m/e* 367).

With an enamine containing a vinyl hydrogen, the oxygenation was complicated by diketone formation becoming competitive with double-bond cleavage. For example, cuprous chloride-catalysed oxygenation of deoxybenzoin pyrrolidine enamine (stable to oxygen without CuCl) gave benzil, benzaldehyde and *N*-benzoylpyrrolidine in the approximate proportion of 4 : 1 : 1. Similarly, the 3-pyrrolidine enamine of 11α-hydroxyprogesterone gave 11α-hydroxy-6-oxoprogesterone,[3] and enamine (IX)[4] yielded the 6-keto-derivative (X) (m.p. 196—198°; *m/e* 368) and its 1,2-epoxide (XI) (m.p. 217—219°; *m/e* 384).



(IV) (V)
(VI) (VII) (VIII)



(IX) (X) (XI)

A study with enamine (I) revealed the oxygenation rate to be first-order in concentration of (I) after an induction

---

† All previously reported products were characterized by spectroscopic and g.l.c. comparison with authentic materials. Satisfactory analytical and spectral data have been obtained for all new products.

period, but also dependent on the amount of cuprous chloride present. 2,6-Di-t-butyl-*p*-cresol did not retard the reaction, but pyridine and trimethyl phosphite, both of which may compete with the enamine for co-ordination with copper, inhibited the oxygenation completely. The rate was also markedly dependent on the anion attached to copper. With dimethylformamide and with either chloroform or methylene chloride as solvent,‡ cupric acetate, cuprous acetate, cupric nitrate, and cupric sulphate were inefficient oxygenation catalysts. Cuprous cyanide and the chlorides and bromides of both oxidation states of copper, however, were active,[5] although cupric chloride and bromide gave traces of halogenated by-products.§

Similar oxidative cleavage of enamines to ketones (or aldehydes) and amides has been accomplished by dye-sensitized photo-oxygenation, as reported recently by Huber[1] and by Foote.[6] Our reaction proceeded in the dark as well as in the light, however, thus excluding the intermediacy of photo-generated singlet oxygen.

Copper salts also catalyse oxidative decarbonylation of branched aldehydes to ketones in the presence of oxygen and a weak base.[7]

We gratefully acknowledge the technical assistance of M. D. Pillai and the analytical work of J. F. Loher.

(*Received, January 16th,* 1969; *Com.* 060.)

---

‡ Upon oxygenation, sufficient solubility was obtained to effect catalysis by all salts studied.

§ Ferrous and ferric chloride were poor oxygenation catalysts.

[1] J. E. Huber, *Tetrahedron Letters*, 1968, 3271.

[2] Enamines (IV) and (VI) were prepared by the titanium tetrachloride procedure reported by W. A. White and H. Weingarten, *J. Org. Chem.*, 1967, **32**, 213.

[3] Autoxidation of enamines of $\alpha\beta$-unsaturated ketones to their γ-keto-derivatives has recently been reported to be facilitated by cupric and ferric ion: S. K. Malhotra, J. J. Hostynek, and A. F. Lundin, *J. Amer. Chem. Soc.*, 1968, **90**, 6565.

[4] The procedure for preparation of the previously elusive enamine (IX) [J. A. Hogg, B. J. Magerlein, and J. Korman, *Steroids*, 1964, **3**, 189] will be the subject of a subsequent communication. The other enamines reported herein were prepared by known procedures.

[5] Similar catalytic requirements were observed for the air oxidation of aniline: K. Kinoshita, *Bull. Chem. Soc. Japan*, 1959, **32**, 780.

[6] C. S. Foote and J. Wei-Ping Lin, *Tetrahedron Letters*, 1968, 3267.

[7] V. Van Rheenen, *Tetrahedron Letters*, in the press.