results are incompatible with only one (classical) norbornyl intermediate.

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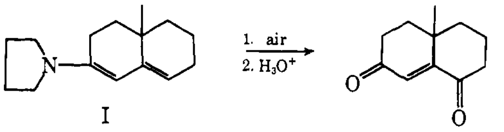
Autoxidation of Enamines and Schiff Bases of α,β-Unsaturated Ketones. A New Synthesis of Unsaturated 1,4-Diones

Sir:

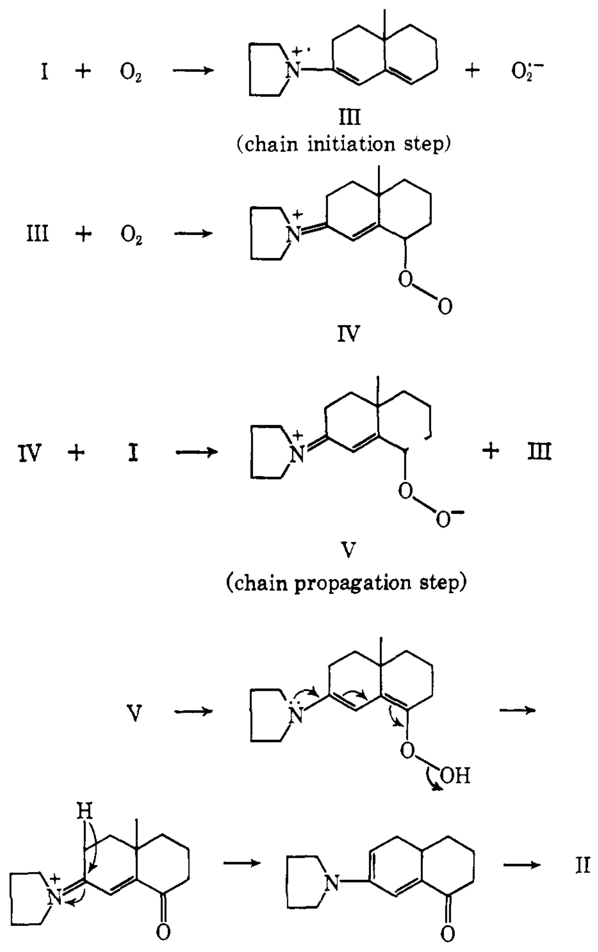
Enamines and enolate anions derived from α,β-unsaturated ketones undergo electrophilic attack at the α-carbon atom.[1] We wish to report that, unlike the autoxidation of enolate anions which leads mainly to the α-keto products,[2] the enamines undergo autoxidation giving mainly the γ-keto products, which on hydrolysis provide the corresponding 1,4-diones. Bubbling a slow stream of air through a 0.01 *M* benzene solution of the pyrrolidine enamine of 10-methyl-$\Delta^{1(9)}$-octalone-2 (I) for 16 hr at room temperature and subsequent hydrolysis with dilute acetic acid gave 10-methyl-$\Delta^{1(9)}$-octalin-2,8-dione (II) [mp 70–72°; $\nu_{\max}$ (film) 1680 cm^{-1}; $\lambda_{\max}^{\mathrm{MeOH}}$ 250 mμ (ε 11,300); δ (CDCl$_3$, Me$_4$Si reference) 6.3 (vinylic H, sharp, 1 H) and 1.26 (angular CH$_3$, 3 H)]. The amount of the dione produced was rather low (20%) but addition of a catalytic amount of ferric chloride, cupric acetate, or cupric chloride caused a pronounced enhancement in the oxidation rate. Addition of a 0.1 molar equiv of these catalysts to the benzene solution of the enamine I to which a minimum amount of a cosolvent[3] such as hexamethylphosphoramide or methanol was added to keep the solution homogeneous led to the dione in 80–85% yield[4] after 1 hr. The reaction proceeds equally well in the dark, thus excluding the possibility of any photosensitized oxidation.[5] Since an ionic reaction between the molecular oxygen and the enamine violates the spin conservation rule and the electrophilic attack on the enamines of α,β-unsaturated ketones occurs at the α-carbon atom,[1] this reaction is most likely a free-radical chain process,[6] and may proceed *via* the radical cation III as outlined in Scheme I.



I

II

Scheme I



The striking catalytic effect of the metal ions such as Cu^{2+} and Fe^{3+} may be attributed to their ability to accept an electron from the enamine in the chain-initiation step.[6] Similar autoxidation of the morpholine enamine of 10-methyl-$\Delta^{1(9)}$-octalone-2 was slightly slower than that of III, the dione being formed in 65% yield after 1 hr.

In a similar manner, several Δ^4-3-keto steroids have been oxidized *via* their corresponding enamines to 6-keto derivatives in 65–75% yield. For example, Δ^4-cholesten-3-one was oxidized to Δ^4-cholestene-3,6-dione[7] and testosterone to 6-ketotestosterone.[8] Progestrone and Δ^4-androstene-3,17-dione were oxidized to Δ^4-pregnene-3,6-20-trione[9] and Δ^4-androstene-3,6,17-trione,[9] respectively.

We also wish to report that the autoxidation of the Schiff bases of α,β-unsaturated ketones also involves attack at the γ position, the product on hydrolysis in acidic medium giving the corresponding unsaturated 1,4-dione. For example, bubbling a slow stream of air through the 0.01 *M* benzene solutions of benzylamine Schiff bases of testosterone and Δ^4-cholesten-3-one for 24 hr at room temperature followed by hydrolysis with dilute acetic acid led to 6-ketotestosterone[8] and Δ^4-cholestene-3,6-dione,[7] respectively, in 70–75% yield. Benzylamine and cyclohexylamine Schiff bases of 10-

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(1) J. A. Marshall and W. S. Johnson, *J. Org. Chem.*, 28, 421 (1963); G. Stork and G. Birnbaum, *Tetrahedron Lett.*, 313 (1961); S. K. Malhotra and H. J. Ringold, *J. Amer. Chem. Soc.*, 85, 1538 (1963); 86, 1997 (1964); H. J. Ringold and S. K. Malhotra, *ibid.*, 84, 3402 (1962).

(2) B. Camerino, B. Patelli, and R. Sciaky, *Tetrahedron Lett.*, 554 (1961).

(3) Addition of cosolvents alone failed to show any noticeable increase in the yield of the product.

(4) The reported yields are the values obtained from several runs.

(5) For recent references on the photosensitised oxygenation of enamines, see C. S. Foote and J. W. P. Lin, *Tetrahedron Lett.*, 3267 (1968), and J. E. Huber, *ibid.*, 3271 (1968).

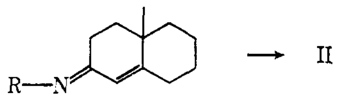
(6) For a review on the autoxidation of carbanions involving free-radical chain processes, see G. A. Russell, E. G. Janzen, A. G. Ames, E. J. Geels, A. J. Moye, S. Mak, and E. T. Strom, "Selective Oxidation Processes," Advances in Chemistry Series, No. 51, American Chemical Society, Washington, D. C., 1965, pp 112–171.

(7) L. F. Fieser, Organic Syntheses, Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1953, p 189.

(8) A. Butenandt and B. Riegel, *Ber.*, 69B, 1163 (1936).

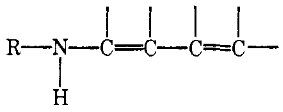
(9) R. D. Barry, F. Kraft, P. K. Besch, D. J. Watson, and M. Pflaumer, *Steroids*, 2, 379 (1963).

methyl-$\Delta^{1(9)}$-octalone-2 (VI) provided the dione II in 50% yield after 15 hr.



VI
R = benzyl, cyclohexyl

Like the autoxidation of enamines this oxidation is most likely a free-radical chain process which may proceed *via* the enamine form VII of the Schiff bases. The slower rate of the uncatalyzed oxidation of the enamine I than that of the similar oxidation of Schiff base VI may be ascribed to steric factors. The methylene groups adjacent to the nitrogen atom in I may tend to prevent the electron transfer in the chain-initiation step.


$\mathrm{R-\underset{H}{\underset{|}{N}}-\overset{|}{C}=\overset{|}{C}-\overset{|}{C}=\overset{|}{C}-}$

VII

Autoxidation of Schiff bases is strongly catalyzed by ferric chloride, which may not only act as an electron acceptor from the enamine form VII of the Schiff bases, but being a good Lewis acid may also promote the Schiff base–enamine tautomerism. On the other hand cupric chloride, a weak Lewis acid, proved to be a rather poor catalyst. For example, the cupric chloride catalyzed oxidation of VI, which contains on the basis of nmr spectral data about 35% of the enamine form,[10] gave the dione II in only 40% yield after 1 hr; the ferric chloride catalyzed oxidation of VI under similar conditions led to the dione II in 75–80% yield. The oxidation of the benzylamine Schiff base of 8,10-dimethyl-$\Delta^{1(9)}$-octalone-2, which on the basis of its nmr spectrum contains about 75% of the enamine form, was equally well catalyzed both by cupric chloride and ferric chloride. The preponderance of the enamine form in this case is undoubtedly due to the hyperconjungative effect of the C-8 methyl group which stabilizes the Δ^8 double bond. The product consisted primarily of a 3:1 mixture of the 8β- and 8α-hydroxy derivatives of the ketone showing that the oxygenation at the γ position is subject largely to stereoelectronic control. Interestingly the uncatalyzed oxidation of the benzylamine Schiff base of ergosterone, which according to its nmr spectrum exists entirely in the trienamine form, gave 6-ketoergosterone (mp 176–177°) in 91% yield after 1 hr.[11]

Further work along these lines is in progress.

Acknowledgment. The authors thank Drs. Francis Johnson and Laurence I. Peterson for helpful discussions.

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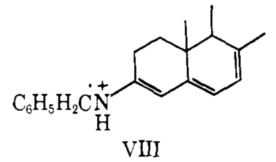
(10) The Schiff base:enamine ratio did not alter significantly when treated with a catalytic amount of *p*-toluenesulfonic acid in refluxing benzene overnight.

(11) This facile oxidation is most probably due to the intermediacy of a highly resonance-stabilized radical cation VIII.



VIII

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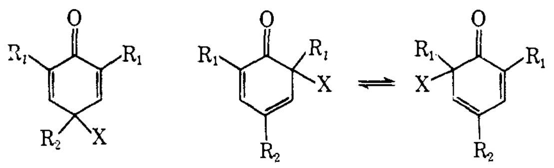
Nonhydrogen Tautomerism and Other Chemical Rate Processes in Cyclohexadienones[1,2]

Sir:

Cyclohexadien-2,5-ones (**1**) and cyclohexadien-2,4-ones (**2** and **2′**) formally are nonhydrogen tautomers where X is the migrating group. Some chemical reactions of quinol ethers (X = OAr)[3] and quinol halogenides (X = Br)[4] show that true equilibria between **1** and **2** should be possible. We have investigated several sterically hindered cyclohexadienones by nmr spectroscopy in the range from 0° to the temperature of decomposition (100–200°) and have found either the *para* form (**1**) or the *ortho* form (**2**). Compounds **1** give one signal for olefinic protons at τ 2.7–4.0 and one signal for R_1, whereas compounds **2** give an AB spectrum (J_{AB} = 2.0–2.8 cps) at τ 2.2–3.5 and two signals for R_1.



1 **2** **2′**

The *o*-quinol halogenides **2a** [$R_1 = C(CH_3)_3$; R_2 = CN; X = Br][5] and **2b** [$R_1 = C(CH_3)_3$; $R_2 = NO_2$; X = Br][4] show temperature-dependent spectra. At 0° **2a** and **2b** give the expected AB spectrum (**2a**: τ_A 2.72, τ_B 3.26, J_{AB} = 2.0 cps; **2b**: τ_A 2.24, τ_B 2.55, J_{AB} = 2.5 cps; olefinic protons) and two singlets (**2a**: τ 8.71, 8.79; **2b**: τ 8.70, 8.78; *t*-butyl groups). On warming, the signals of H_A and H_B as well as those of the *t*-butyl groups first collapse, then sharpen again on further heating. By using the Eyring equation the free enthalpy of activation can be calculated[6] (Table I).

An explanation for this phenomenon can be given if one assumes a reversible transition **2** $\rightleftharpoons$ **2′**. At sufficiently high temperatures this equilibrium is fast with respect to the nmr time scale. Thus we are able to show that bromine tautomerism indeed takes place in cyclohexadien-2,4-ones.[7]

From our nmr data alone we cannot draw any conclusion as to whether the rearrangement of the

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(1) Innermolecular Motion by Nmr Spectroscopy. VII; VI: H. Kessler and W. Rundel, *Ber.*, **101**, 3350 (1968).

(2) The quinonoid state XI; X: A. Rieker and G. Henes, *Tetrahedron Lett.*, 3775 (1968).

(3) N. Zeller, doctoral thesis, 1968, University of Tuebingen.

(4) V. V. Ershov and A. A. Volod'kin, *Izv. Akad. Nauk SSSR, Ser. Chim.*, 336 (1965); *Chem. Abstr.*, **62**, 14520*h* (1965).

(5) E. Mueller, A. Rieker, K. Ley, R. Mayer, and K. Scheffler, *Ber.*, **92**, 2278 (1959).

(6) H. G. Schmid, H. Friebolin, S. Kabuss, and R. Mecke, *Spectrochim. Acta*, **22**, 623 (1966); A. Rieker and H. Kessler, *Tetrahedron*, **23**, 3723 (1967).