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THE MECHANISM OF HYDROXYLAMINE ADDITION TO α,β -UNSATURATED ESTERS

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The addition of α-nucleophiles to unsaturated substrates has recently drawn both theoretical[1] and experimental attention.[2] In this report we present data pertaining to the addition of α-nucleophiles to α,β -unsaturated esters, in particular ethyl cinnamate. We assign a key role for the OH group in formation of the transition state because when O-methyl-hydroxylamine is substituted for N-methyl hydroxylamine no reaction occurs.

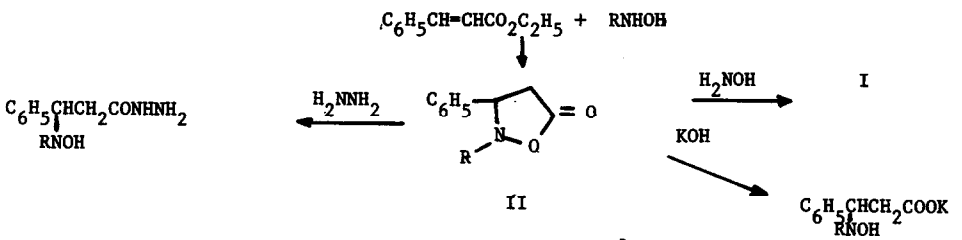
Hydroxamic acids are known to be potent anti-hypertensive compounds,[3] and this fact led us to explore the synthesis of 3-phenyl-3-(N-alkyl hydroxyamino) propanohydroxamic acids (I). The synthesis of the parent compound ($C_6H_5CHCH_2CONHOH$, RNOH) (I,R=H) has been known since at least 1902 when Posner reported the addition of hydroxylamine to ethyl cinnamate and cinnamic acid, but little work has been done since that time.[4]

I

We undertook the synthesis of β-N-methyl I ($R=CH_3$) by the straightforward addition of N-methylhydroxylamine to ethyl cinnamate in methanol in a manner analogous to the synthesis of the parent (I,R=H)[3,4] but obtained instead of the di-N-methyl analog of I an isoxazolone (II $R=CH_3$) in 96% yield. This compound was characterized by the absence of OH or NH bands in the IR, but had high frequency twinned carbonyl bands at 1793 and 1773 $cm.^{-1}$; m/e peak at 177 (M+ 1=12%),[5] and an N M R spectrum displaying a typical A_2B spectrum at 4.18, 2.88 ppm(2H) with a methyl signal at 2.73 (3H); additionally this intermediate could be extensively derivitized as summarized in Scheme I.[6]

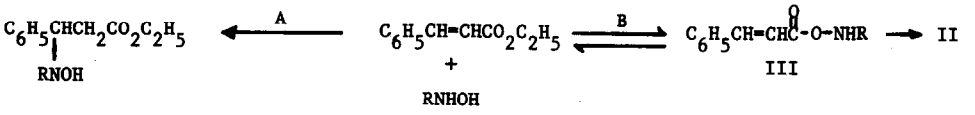
The mechanism for productio. of II has a bearing on both the mechanism of parent (I,R=H) synthesis and operation of the α-effect in hydroxylamine. One might envision a straightforward Michael type of addition of N-alkylhydroxylamine as in scheme II A; however, in testing this possible path with O-methylhydroxylamine we found no reaction after one week under the conditions which caused rapid formation of II (alkaline methanolic solution pH @ 8.5 by hydrion paper.)[7] This indicates a key role for the OH group of the N-alkylated hydroxyl amine.

Scheme 1



Scheme II B thus seems more likely especially since Jencks[9] has reported the production

Scheme II



of O-acylderivatives of hydroxylamine over a pH range of 6.0 to 9.0. Indeed, when we attempted to isolate the N-methyl-O-acyl derivative from ethyl cinnamate and N-methylhydroxylamine by following Jencks procedure, we obtained a mixture of unreacted ethyl cinnamate, II, and a compound producing a shoulder at 1725 cm.$^{-1}$ on the cinnamate band at 1710 cm.$^{-1}$ The ether extracted material was analysed by NMR and the mixture was found to have a signal at δ 2.45 which appears neither in N-methylhydroxylamine nor in II. On standing for 24 hours this signal had decreased by 10% in area and a signal at δ 2.73 appeared as well as the upfield portion of the A_2B spectrum of II. We take this as evidence for formation of II as an intermediate for addition of hydroxylamines to cinnamate esters.[11] Evidence that this type of intermediate is also formed in the synthesis of the parent (I,R=H) was obtained when ethyl cinnamate was reacted with hydroxylamine in methanol and the reaction followed by IR. After 24 hours there was obtained a spectrum showing an extremely weak twinned band at 1770 and 1785 cm.$^{-1}$ and a band at 1730 cm.$^{-1}$ appearing as a shoulder on the ester band[12] at 1710 cm.$^{-1}$ We interpret these facts to indicate III (R=H) to be intermediate in the formation of II (R-H), and that the concentration of II (R=H) does not build to substantial amounts because of facile ring opening. (Indeed when II (R=CH_3) is subjected to hydroxylamine in methanol ring opening is complete in less than one minute.) From the reaction mixture there was obtained I (R=H) as a fine white precipitate. Further evidence for the intermediacy of O-cinnamonylhydroxylamine as an intermediate was obtained by an independent synthesis of O-cinnamonylhydroxylamine by the method of Carpino.[8] This compound has, in concentrated solution or in the pure form, a complex chemistry which will be reported elsewhere.

In dilute methanol solution at a pH of 8-9 (by Hydrion paper) we obtained, after 24 hrs., infrared spectra showing weak but distinct bands at 1785 $cm.^{-1}$ and at 1770 $cm.^{-1}$. In addition bands due to the O,N-diacylderivative[8] at 1705 and 1660 $cm.^{-1}$ were observed. The N.M.R. spectrum in methanol showed bands at δ 4.35, the B portion of an A_2B spectrum and slightly broadened lines at 2.65 and 2.55, the upfield A_2 portion of an A_2B spectrum. These data were interpreted as indicating cyclization of III (R=H).

A key point in the mechanism is the nature of the attacking nucleophile. Jencks[9] has shown that the hydroxylamine species carries no net charge over the pH range 6.0 to 9. Aubort and Hudson[10] have presented evidence that reactions of this type involve the neutral nonpolar, H_2NOH, form of hydroxylamine with general base catalysis.

Apparently the spearhead for hydroxylamine attack is the O atom and attack at the carbonyl group is more important than attack in a conjugate manner. It is interesting to compare this result with that found in the addition of hydroxylamine to mesityloxide where conjugate addition of the O atom predominates.[14] Apparently the presence of the ethoxide leaving group allows rapid reversible O-Acylhydroxylamine formation to occur (as in Scheme II B) faster than Michael type addition. In terms of a recent formulation shown below in Figure 1 for the transition state for α-nucleophiles and carbonyls[13] this would mean attack of the oxygen lone pair is probably well underway before the development of any overlap or aromatic character involving the N atom, as in Figure 2. If aromatic character such as that postulated in reference 1d and shown in Figure 1 is truely important in the α-effect, it is hard to see how the presence of an ethoxide

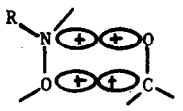


Figure 1

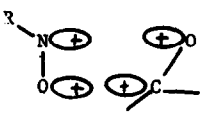


Figure 2

leaving group in the present case makes the transition state for attack at the carbonyl more aromatic than for attack at the C=C bond. Yet the position of nucleophilic attack changes from the quite hindered B position in mesityloxide to the carbonyl group in ethyl cinnamate (even though the β position in the ester is less hindered than the β position in the ketone). We, therefore, favor formation of a transition state by attack of either H_2NOH or the oxyanion as in Figure 2, at least for this case, without involking any special aromatic type transition state for the α-effect. In our mechanism the reversal of 1,4 addition of hydroxylamine in

mesityloxide to 1,2 addition in ethyl cinnamate could be accomodated by classical means, i.e., the ester carbonyl is a better target for nucleophilic attack by the α-nucleophile. Other factors may be responsible for this reversal also, but they are likely to be factors of this type rather than perturbations of an aromatic transition state.

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References

[1] J.D. Aubort, R.F. Hudson and R.C. Woodcock, Tetrahedron Letters, 2229 (1973); b) J.D. Aubort and R.F. Hudson, Chemical Communications, 1342 (1969); 937 (1970); c) R.F. Hudson and F. Filippini, Chemical Communications, 726 (1972); c) G. Klopman and R.F. Hudson, Theor. Chem. Acta., 7, 165 (1967); d) J.F. Liebman and R.M. Pollack, J. Org. Chem., 38, 3444 (1973).

[2] E.G. Sandes and W.P. Jencks, J. Am. Chem. Soc., 90 6162 (1968); W.P. Jencks and J. Carriuolo, ibid, 82, 1778 (1960); J.D. Edwards and R.M. Pearson, 84, 16 (1962); A.L. Green, G.L. Sainsbury, B. Saville, and M. Stanfield, J. Chem. Soc., 1583 (1950).

[3] Horst Kehl, J. Pharm. Sci., 60, 839 (1971); J. Am. Osteopathic Assoc., 68, 1070 (1969); ibid., 63, 872 (1964); ibid, 60, 1038 (1967).

[4] T. Posner, Ber. der. Deutsch. Chem. Gesellshaft, 35, 2344 (1902).

[5] We thank Dr. P.T. Lansbury, State University of New York at Buffalo for these data.

[6] All new compounds were derived from II in high yield (78%) and gave acceptable ($\pm$0.3%) microanalysis. Compound II itself was not analysed because an attempted distillation extensive decomposition invariably occurred.

[7] These conditions were standard for all reactions reported in this paper.

[8] L.A. Carpino, C.A. Giza and B.A. Carpino, J. Amer. Chem. Soc., 81, 955 (1959).

[9] W.P. Jencks, J. Amer. Chem. Soc., 80, 4581 (1958), ibid, 80, 4585 (1958).

[10] J.D. Aubort and R.F. Hudson, Chem. Communications, 1378 (1970).

[11] We have also obtained oils having high frequency IR bands at 1780 $cm.^{-1}$ from R=ET and C_7H_{15} - hydroxyl amines.

[12] Ref. 7 indicates the position of absorption for a conjugated carbonyl in the -C-O-N situation to be 1730 $cm.^{-1}$

[13] Ref. 1 d.

[14] A. Belly, R. Petrus and J. Verducci, Bull. Soc. Chim. France, 1395 (1973).