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

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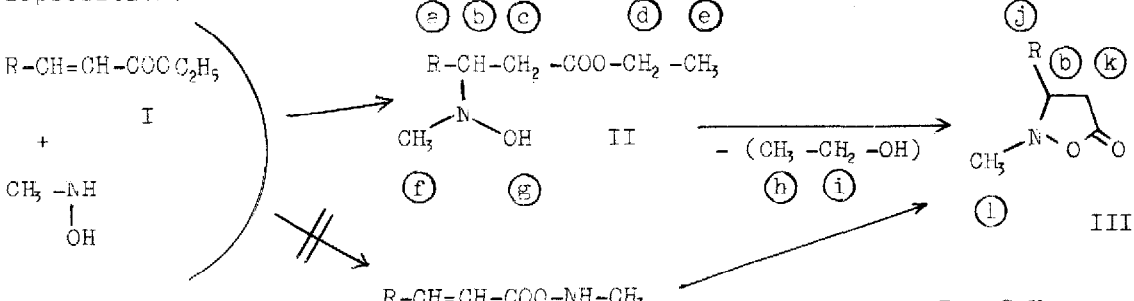
Fountain, Kehl et al.[1] obtained the isoxazolidinone IIIa by reaction of ethyl cinnamate (Ia) with N-methyl hydroxylamine. The authors believe the first step to be not a Michael type addition yielding II but a transesterification yielding IV, and they make theoretical considerations based on this supposition.



a: R = C_6H_5

b: R = CH_3

c: R = 4-Pyridyl

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^{1}H-NMR of IIb, IIIb ($CDCl_3$): ppm, splitting, J in Hz ("J" apparent coupling)

	a	b	c	d	e	f	g	h	i	j	k	l
IIb	1.12	~3.2	2.06-~2.73	4.14	1.25	2.61	7.40	hidden under e + a	3.66	1.28	2.68	2.86
	d	m	m	q	t	s	s		q	d	m	s
	6.0		"14.8" "7.8" "?"	7.1	7.1				7.1	5.9	"11.0" "6.9"	

IR (cm^{-1}): IIb 1730; IIc 1730; IIIb 1788, 1773; IIIc 1796 sh., 1779.

The reported evidence for IV as intermediate is

A) that Jencks[2] found O-acylation of hydroxylamine over a pH range of 6 to 9,

B) that the authors found no reaction of methoxyamine with Ia,

C) IR and ^{1}H-NMR data of their reaction mixture, which were due to IVa,

D) analogous IR data from a reaction of Ia with hydroxylamine, and

E) that the demethyl analogue of IVa (synthesized by another way) on standing in methanol yielded a mixture giving spectroscopic data corresponding to O,N-dicinnamoyl hydroxylamine and to the demethyl analogue of IIIa.

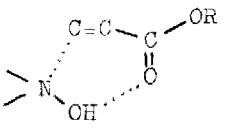
Compound IIIa, which they had obtained as crude material and not analytically pure, has previously been synthesized by us through Reformatzky reaction of the nitrone C_6H_5-CH=N(O)-CH_3 within a series of similar isoxazolidinones[3]. The reported spectroscopic data are exactly ours except some minor differences of the chemical shifts of the ABX proton system (A_2B of Fountain, Kehl et al.).

In the course of our work on isoxazolidinones we have synthesized IIIa (75 % yield, analytically pure) in the same manner (Ia, N-methyl hydroxylammonium chloride, one equivalent of alcoholic sodium ethoxide) as Fountain, Kehl et al. but independently, and we have reasons to regard II and not IV as intermediate. The reported evidence is not conclusive or is misinterpreted:

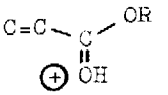
A) Jencks[2] has found O-acylation of hydroxylamine with strong acylating agents only, among esters with aryl esters only. He stated explicitly: "No evidence for O-acyl hydroxylamine formation could be obtained with ethyl acetate, which reacted with hydroxylamine at a slower rate than did O-acetylhydroxylamine". Therefore, attachment of structure IV to a not isolated intermediate cannot lean on Jencks.

B) While "Michael additions" of aliphatic amines to α,ß-unsaturated esters can be performed readily without catalyst, addition of aniline (pK_a 4.6) or p-anisidine (pK_a 5.44) to acrylates requires acid catalysis[4]. So methoxyamine (pK_a 4.6) cannot be expected to react under the reported conditions, particularly since cinnamate esters generally react slower than acrylate esters do[4a]. An α-effect seems to be absent or not strong enough. On the other side, with hydroxylamines (pK_a 5.96) and N-methyl hydroxylamine (pK_a 5.96) one can well imagine an acceleration of the reaction typical for

α-nucleophiles, e. g. through a push pull combination as in V, that finally approaches an acid catalysis as in VI.



V



VI

Further, methoxyamine and N-methyl methoxyamine react slower in nucleophilic reactions than do the corresponding hydroxylamines[5], and one cannot simply take a change of the reacting atom (O for N) for granted, since also N,N-dimethylhydrazine reacts slower than hydrazine (see for instance[5c]). There need not be a single cause for all α-effects, and in particular an acidic hydrogen atom attached to the α-atom may be the crucial factor in some cases.

C) An IR absorption (shoulder) at 1725 cm^{-1} and a proton signal at δ 2.45 ppm (solvent not stated) a priori are compatible equally well with II as with IV.

D) The same holds for the demethyl compounds (shoulder at 1730 cm^{-1}).

E) It can be expected, that IV (or its demethyl analogue) cyclizes to III (or its demethyl analogue) once it has been formed.

Apart from our view of the arguments pro and con we have been able to achieve direct evidence for II as intermediate. From reaction of Ib and Ic (n butyl ester) respectively in ethanol we have obtained (besides IIIb,c) IIb,c in a sufficiently pure form, that allows an unequivocal decision between structures II and IV. IIb,c could be enriched chromatographically up to about 50 % beside the predominant product IIIb,c, the chromatographic separation warranting complete removal of Ib,c as well as of ethanol and N-methyl hydroxylamine. These fractions, consisting of nearly equal parts of II and III, were characterized by the proper spectroscopic data, shown for the case of IIb/IIIb beneath the formula scheme. Structurally decisive are the NMR ester signals of IIb and IIc (mixture of Bu and Et ester).

On standing some days in $CDCl_3$ solution the f signals decreased in favour of the l signals. The simultaneous decrease of the d signal of IIb in favour of the newly appearing i signal (ethanol) seems to us particularly conclusive.

An isoxazolidinone of type III previously had been shown[6] to be converted to a type II-hydrochloride on treatment with CH_3OH/HCl and to reform spontaneously the original isoxazolidinone (readily up to 75 %) on liberation of the free base II.

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