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REACTION OF ALKYLIDENE-PSEUDOXAZOLONES WITH AMINES

Yoshio Iwakura, Fujio Toda, Yoshinori Torii,
and Kozaburo Tomioka
Department of Synthetic Chemistry, Faculty of
Engineering, The University of Tokyo

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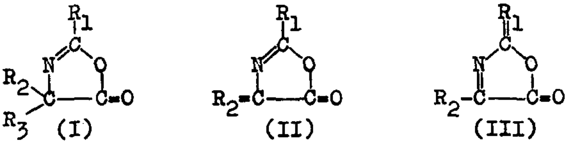
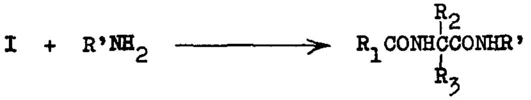
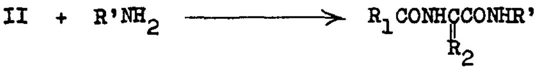
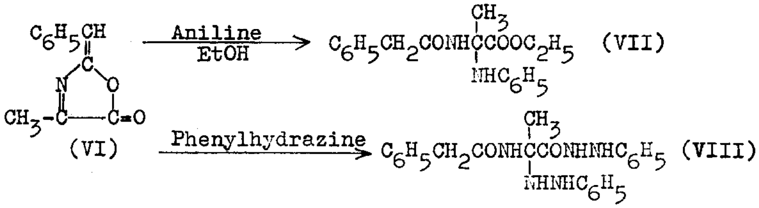
5-Oxazolones are conveniently classified into two groups, saturated (I) and unsaturated ones (II and III)(1). III is called pseudoxazolone. It is well-known that the reaction of I and II (less readily) with primary and secondary amines takes place exclusively at the C-5 position as shown below.


(I) (II) (III)


$$I + R'NH_2 \longrightarrow R_1CONHC(R_2)(R_3)CONHR' \qquad (IV)$$


$$II + R'NH_2 \longrightarrow R_1CONHC(=R_2)CONHR' \qquad (V)$$

Although in recent years much interesting work has been reported in the chemistry of 2-arylidenepseudoxazolones, the reactivity of 2-alkylidenepseudoxazolones towards nucleophilic reagents has not been investigated. It was said that the principal sites attacked by most nucleophilic reagents are C-4 and C-5 positions. For instance, 2-benzylidene-4-methyl-3-oxazolin-5-one (VI) reacted with aniline in ethanol to give a product (VII)(2) and with excess phenylhydrazine to give a product for which the structure VIII was given (3). VI reacted with benzylamine to form a product



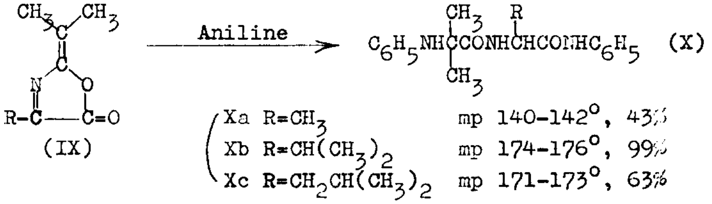
(VI)

$C_6H_5CH_2CONHC(CH_3)(NHC_6H_5)COOC_2H_5$ (VII)

$C_6H_5CH_2CONHC(CH_3)(NHNHC_6H_5)CONHNHC_6H_5$ (VIII)

by addition of two moles of amine, but no experimental data were reported (4). The recent letter on the preparation of 2-alkylidene-pseudoxazolones by Steglich (5) prompts us to report our work on their unusual chemical behaviors.

We have found that 2-isopropylidene-4-alkyl-3-oxazolin-5-ones (IX) prepared by our method (6) reacted quantitatively with two moles of aniline at 60° for 12-24hrs. to give the reaction products (X). By the hydrolysis of X, the reaction sites were confirmed as follows:



(IX)

$C_6H_5NHC(CH_3)_2CONHCH(R)CONHC_6H_5$ (X)

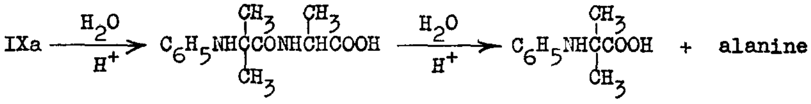
Xa $R=CH_3$ mp 140-142°, 43%

Xb $R=CH(CH_3)_2$ mp 174-176°, 99%

Xc $R=CH_2CH(CH_3)_2$ mp 171-173°, 63%

The NMR spectrum of Xa showed peaks at δ 1.60 (6H, sharp singlet for gem-dimethyl) and at δ 1.44 (3H, J=6.6cps, $>CHC\underline{H}_3$) in pyridine.

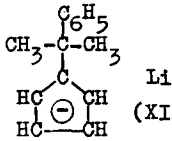
Xa was partially hydrolyzed to XIa (mp 187-188°, 63%) with conc. HCl at 100-120° for 2hrs. and perfectly hydrolyzed to 1-anilino-isobutyric acid (XII, mp 180-182°, 59%)(7) and alanine with conc. HCl at 160° for 16hrs. Alanine was detected by paper-chromatography and isolated in the form of N-benzoyl derivative (mp 159-161°). By perfect hydrolysis of Xb and Xc, XII and the corresponding α-amino acids, valine and leucine, were isolated.



$$\mathrm{IXa} \xrightarrow[H^+]{H_2O} C_6H_5NH\overset{CH_3}{\underset{CH_3}{C}}CONH\overset{CH_3}{C}HCOOH \xrightarrow[H^+]{H_2O} C_6H_5NH\overset{CH_3}{\underset{CH_3}{C}}COOH + \text{alanine}$$

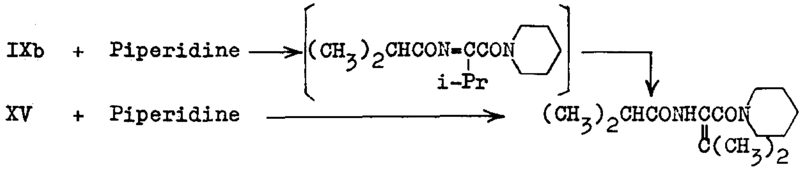
(XIa) (XII)

Dimethylfulvene adds phenyllithium to form a product (XIII)(8) believed to have the following structure. The various molecular orbital calculations on fulvene and its derivatives suggested that there is an appreciable drift of electrons from the exo double bond into the ring (9). The exo double bond of IX would become a reaction center of nucleophilic reagents presumably by an electron drift to the heterocyclic ring in the same fashion with dimethylfulvene. As a probable mechanism of the reaction, it was reasonable to postulate the 1-4 conjugate addition of aniline to $\genfrac{}{}{0pt}{}{Me}{Me}\!>\!C{=}C{-}N{=}C\!<_{R}$ chain, followed by the ring opening of the resulting saturated 5-oxazolones which were known to react with amines far more rapidly. Primary amines such as benzylamine, phenethylamine, and cyclohexylamine afforded 1:2 adducts (mp 89-92°, 91%; mp 120-122°, 20%; mp 127-129°, 33%) with IXb. When piperidine was used to the reaction with IXb instead of primary amines, 1:1 adduct (XIV, mp 129-131°, 73%) was mainly



(XIII)

obtained. XIV was identical to a compound (mp 128-131°, 73%) obtained from 2-isopropyl-4-isopropylidene-2-oxazolin-5-one (XV)



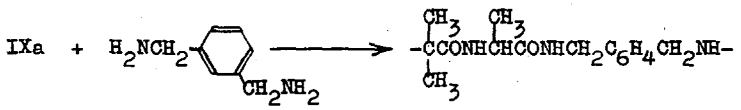
(XIV)

and piperidine. XV was prepared by Erlenmeyer's method (10) from N-isobutyrylglycine in 11% yield. The reaction at the exo double bond was preceeded by the ring opening reaction at C-5 position probably because of steric hindrance. XIV was accompanied with a small amount of 1:2 adduct (mp 95-96°, 17%), the structure of which was thought to be analogous to X. 1:2 Adduct (mp 119-122°, 77%) was isolated from morpholine and IXb as a main product, but from N-methylbenzylamine and pyrrolidine and IXb, only 1:1 adducts (mp 117-118°, 22%; mp 154-156°, 68%, respectively) were obtained. These phenomena might be explained by the differences of nuclophilicity and steric factor of each amine. It was suggested that a tautomeric equilibrium between II and III is easily established, so that each preparative reaction of II and III will produce whichever form happens to be the more stable. However the products obtained by Erlenmeyer's and our method were found to be XV and IXb, respectively, by NMR and UV spectra. They did not interconvert in boiling pyridine as far as we examined. When 2-ethylidene-4-alkyl-3-oxazolin-5-ones (XVI) prepared by Bergmann's method (11) and purified by the fractional distillation reacted with aniline, the mixture of 1:2 and 1:1 adducts were isolated as summarized in TABLE I. But it was not certain which was a possible reason of this reaction giving 1:1 adducts: 1) the preferential attack on C-5 position of XVI; 2) the rearrangement of XVI to the II type compounds in the presence of aniline (12), followed by C-5 attack of the resulting 5-oxazolones to 1:1 adducts.

TABLE I The Reaction Products of XVI with Aniline

		1:1 Adducts	1:2 Adducts
XVIa	$R=CH_3$	mp 172-175°	mp 147-151°
XVIb	$R=CH(CH_3)_2$	-	mp 150-151°
XVIc	$R=CH_2CH(CH_3)_2$	mp 200°	mp 145°
XV		mp 242-243°,43%	-
2-Ethyl-4-isopropylidene-2-oxazolin-5-one		mp 205-207°	-

Using this character of IX, it was possible to prepare new type poly-amide-amines from IX and diamines. A polymer which had the following structure was obtained (η_{sp}/C, C=0.5, 0.18 in DMF) from m-xylylenediamine and IXa. Thiophenol also gave a 1:2 adduct (mp 120-122°, 17%) with IXb.



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