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BECKMANN REARRANGEMENT OF 3-PHENYL-2-ISOXAZOLINES

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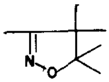
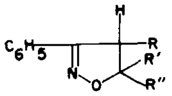
2-Isoxazolines may be regarded as cyclic ethers of β-ketol oximes, although ring I is remarkably stable towards hydrolytic agents. Since it is known that oxime ethers may undergo the Beckmann rearrangement, it was considered probable that under suitable conditions 2-isoxazolines should also give this reaction.

3-Phenyl-2-isoxazolines II, easily available by addition of benzonitrile oxide on ethylenic derivatives[2] were used for this investigation.



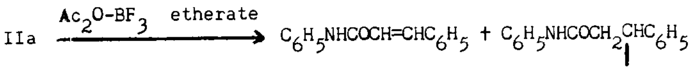
I



II

IIa: $R=R'=H$; $R''=C_6H_5$
IIb: $R=H$; $R'=R''=C_6H_5$
IIc: $R=H$; $R'=CH_3$; $R''=C_6H_5$
IId: $R=R'=H$; $R''=CH_3$
IIe: $R=R'=C_6H_5$; $R''=H$

Preliminary experiments were carried out on 3,5-diphenyl-2-isoxazoline(IIa) for the choice of a suitable catalyst and the proper experimental conditions, with Phosphorus pentachloride in ether, phosphorus oxychloride in pyridine, antimony pentachloride in chloroform, tosyl chloride in pyridine, and boron trifluoride etherate all gave negative results. In every case after decomposition of the complex that was formed in some cases, the starting material was recovered unchanged[3]. The desired results were eventually obtained by using a mixture of acetic anydride-boron trifluoride etherate, a reagent which is only rarely employed as the catalyst for the Beckmann rearrangement and which has recently found interesting applications for the opening of oxygenated rings in steroids. After leaving a solution of IIa in an excess of the reagent for three days at room temperature and decomposing the reaction mixture with ice water, two substances were obtained. The main product, m.p.150-153° was trans-cinnamanilide (III) together with a compound m.p.124°-125° which proved to be identical with 3-acetoxy-3-phenyl-propionanilide (IV)[4]

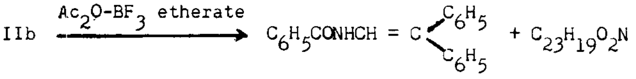


$$\mathrm{IIa} \xrightarrow{Ac_2O\text{-}BF_3\ \text{etherate}} C_6H_5NHCOCH{=}CHC_6H_5 + C_6H_5NHCOCH_2\underset{OAc}{CH}C_6H_5$$

III IV

Since cinnamanilide does not give IV on treatment with the reagent, it may be inferred that III is not the intermediate of IV.

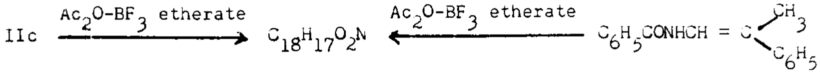
Treatment of 3,5,5-triphenyl-2-isoxazoline (IIb) with Ac20-BF3 etherate under similar conditions afforded a product m.p.130-131° together with lesser amounts of a substance m.p.211-212°. The first product proved to be identical with benzoyl-ββ-diphenylvinylamine V[5]; but the second (VI) was not the expected β-phenylcinnamanilide, and its formula $C_{23}H_{19}O_2N = C_{21}H_{17}ON + C_2H_2O$ indicated that substitution of an hydrogen by a CH_3CO- group had occurred.



$$\mathrm{IIb} \xrightarrow{Ac_2O\text{-}BF_3\ \text{etherate}} C_6H_5CONHCH = C\left\langle\begin{matrix}C_6H_5\\ C_6H_5\end{matrix}\right. + C_{23}H_{19}O_2N$$

V VI

A compound (VII) m.p.170-172° corresponding to VI was isolated on treatment of 3,5-diphenyl-5-methyl-2-isoxazoline (IIc) with the reagent.

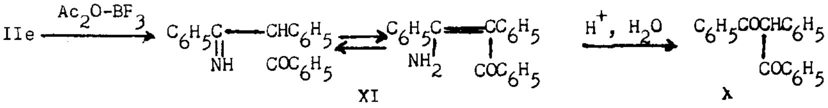


$$\mathrm{IIc} \xrightarrow{Ac_2O\text{-}BF_3\ \text{etherate}} C_{18}H_{17}O_2N \xleftarrow{Ac_2O\text{-}BF_3\ \text{etherate}} C_6H_5CONHCH = C\left\langle\begin{matrix}CH_3\\ C_6H_5\end{matrix}\right.$$

VII VIII

The same compound, $C_{18}H_{17}O_2N = C_{16}H_{15}ON$ was also obtained by treatment of benzoyl-β-methyl-β-phenylvinylamine (VIII)[6] with $Ac_2O\text{-}BF_3$ etherate under similar conditions; and therefore, VIII may be considered as the precursor of VII in this reaction. Although the constitutions of VI and VII have not been established, it may be affirmed that they possess similar structures and result from a further action of the reagent on the amides V and VIII respectively.

In experiments carried out with 3-phenyl-5-methyl-2-isoxazoline (IId) the starting material was recovered unchanged. In the case of trans-3,4,5-triphenyl-2-isoxazoline (IIe), under normal conditions, two yellow crystalline products, m.p.117° and 160-162° respectively, and isomeric with triphenylisoxazoline, were formed. Both gave, on treatment with 20% hydrochloric acid, ammonium chloride and dibenzoylphenylmethane (X). This fact would indicate that the two substances are iminoderivatives of diketone X; actually, the product m.p. 160°-162° was identical with the low-melting form of the known monoiminodibenzoylphenylmethane (IX)[7].

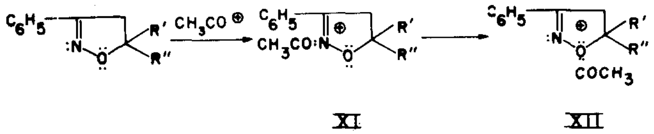


$$\mathrm{IIe} \xrightarrow{\mathrm{Ac_2O\text{-}BF_3}} \underset{\mathrm{NH}}{\underset{\|}{\mathrm{C_6H_5C}}}-\underset{\mathrm{COC_6H_5}}{\mathrm{CHC_6H_5}} \rightleftharpoons \underset{\mathrm{NH_2}}{\mathrm{C_6H_5C}}=\underset{\mathrm{COC_6H_5}}{\mathrm{CC_6H_5}} \xrightarrow{\mathrm{H^+,\ H_2O}} \mathrm{C_6H_5CO}\underset{\mathrm{COC_6H_5}}{\mathrm{CHC_6H_5}}$$

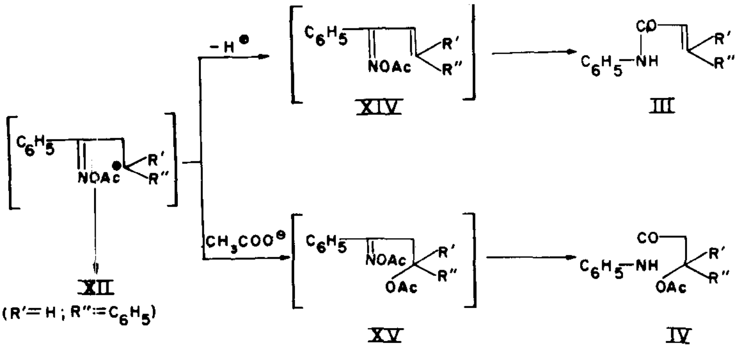
XI X

These results show that the behaviour of 3-phenyl-2-isoxazolines towards $Ac_2O\text{-}BF_3$ etherate is strongly influenced by substitution in the isoxazoline ring. Depending on the nature and position of the substituents, the Beckmann rearrangement may occur with migration of the one or the other of the groups linked to carbon atom 3 or, as in the case of 3,4,5-triphenyl-2-isoxazoline, opening of the ring between the two heteroatoms may accur without any group migration.

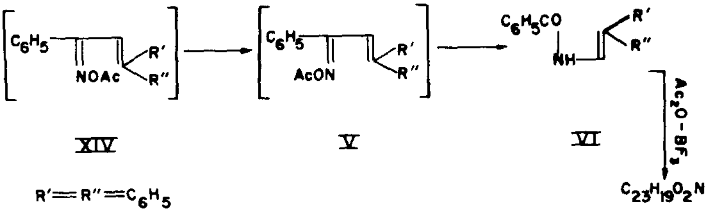
Taking into account the nature of the reagent employed, which probably possesses structure $CH_3CO\text{-}\underset{^{-}BF_3}{\overset{+}{O}}\text{-}COCH_3$,[8] it may be admitted that the attack of the heteroatoms of the isoxazoline ring by the strongly electrophilic ion $CH_3CO^{\oplus}$ first takes place. From what is known of the behaviour of the oximes, it appears probable that the N-adduct(XI) formed eventually rearranges to the O-adduct(XII):



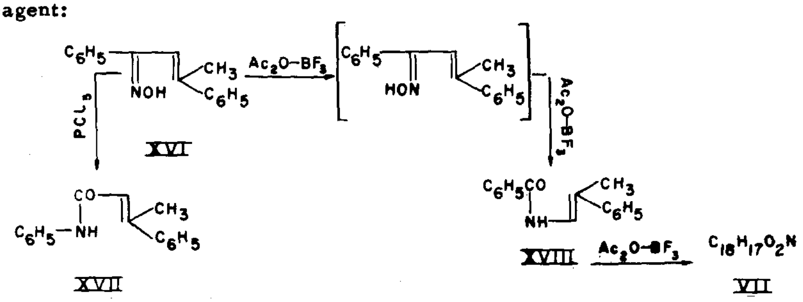
With the possible exception of 3,4,5-triphenyl-2-isoxazoline, the O-adduct is involved in the subsequent transformations. In the case of 3,5-diphenyl-2-isoxazoline(IIa) the experimental evidence is in favour of the cleavage of the C-0 bond of XII with formation of the carbonium ion(XIII), which, in turn, can stabilize: (a) by loss of a proton in 4 giving the acetate(XIV) of the unsaturated oxime; (b) by capture of an anion $CH_3COO^{\ominus}$ present in the solution forming the saturated diacetate(XV). By normal Beckmann rearrangement of these acetylderivatives (migration of the trans phenyl group) III and IV which are the products isolated, would be formed.



The lack of reactivity of IId towards Ac_2O-BF_3 etherate supports this mechanism; since $CH_3CH^{\oplus}$ is far less stable than $C_6H_5CH^{\oplus}$, there is, in this case, no tendency of the C-O bond of XII to rupture with formation of the carbonium ion(XIII). The same mechanism is probably true of the reaction of Ac_2O-BF_3 etherate with 3,5,5-triphenyl- and 3,5-diphenyl-5-methyl-2-isoxazoline(IIb and IIc); however in these cases a change of configuration of the intermediate oxime derivative(XIV) is required prior to the Beckmann rearrangement:



Examples of isomerization of oximes under the influence of Beckmann rearrangement catalysts (boron trifluoride included) are numerous in the literature.[9] Experimental results have shown that dypnone oxime (XVI) yields with PCl_5[10] the expected 3-methylcinnamanilide (XVII), but when treated with Ac_2O-BF_3 etherate an almost quantitative yield of compound VII m.p.172° is obtained, and this, as already stated, is formed from benzoyl-β-methyl-β-phenylvinylamine (XVIII) by action of the same reagent:



The fact that only some of the oximes undergo a change of configuration under the influence of Ac_2O-BF_3 can be attributed to factors which determine the stability of the two forms.

The determination of the structure of products VI and VII and the study of the behaviour of other members of the isoxazoline series are in progress.

Acknowledgement We are indebted to the Consiglio Nazionale delle Ricerche for financial support for this research.

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The reagents used were: HCl in EtOH or AcOH (a,d,f) ; conc. H_2SO_4 (b,c); BF_3 (e).

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