REACTION OF ARYL-β-NITROVINYL KETONES WITH HYDROGEN HALIDES. PREPARATION OF ISOXAZOLES

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Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 5, pp. 800–805, 1967

UDC 547.332.384 + 547.78

A study is made of the reactions of aryl-β-nitrovinyl ketones with hydrogen chloride, hydrogen bromide, and hydriodic acid. It is shown that reaction leads to cyclization forming substituted isoxazoles, and that with hydrogen bromide and hydriodic acid, cyclization is accompanied by reduction. The action of hydrogen chloride on phenyl-β-nitrovinyl ketone gives 3,4-dichloro-5-phenylisoxazole, while hydrogen bromide gives 5-phenyl- and 3-bromo-5-phenylisoxazoles, and hydriodic acid 5-phenylisoxazole. Chlorination of 3-chloro-5-phenyl-isoxazole and bromination of 3-bromo-5-phenyl-isoxazole are methods of synthesizing 3,4-dichloro- and 3,4-dibromo-5-phenylisoxazole, respectively. The general equations for the reactions are given.

Continuing a study of the properties of aryl-β-nitrovinyl ketones, their reactions with hydrogen chloride, bromide, and hydriodic acid have been investigated.

Passing hydrogen halides (HCl and HBr) into an ether solution of the aryl-β-nitrovinyl ketone (**Ia** and b) for 1–2 hr gives addition products which are aryl-α-halogeno-β-nitroethyl ketones (**IIa,b** and **IIIa**).

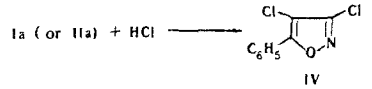
$$RCOCH{=}CHNO_2 + HX \rightarrow \underset{\displaystyle X}{RCOCHCH_2NO_2}$$

Ia,b — IIa,b IIIa

IIa,b X=Cl
IIIa X=Br
a R=C_6H_5; b R=p-BrC_6H_4

Trans-phenyl-β-chlorovinyl ketone was shown, by TLC on alumina, to be among the products of reaction of hydrogen chloride with phenyl-β-nitrovinyl ketone. The formation of phenyl-β-chlorovinyl ketone and phenyl-α-chloro-β-nitroethyl ketone confirms the possibility of a dual orientation of the attacking reagent in reactions of aryl-β-nitrovinyl ketones, as papers of ours [1,2] have already shown.

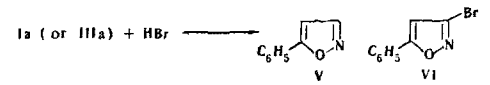
Passing hydrogen chloride for a longer time into a solution of phenyl-β-nitrovinyl ketone (**Ia**) gave the hitherto unknown 3,4-dichloro-5-phenylisoxazole (**IV**) in 40% yield. The latter was also obtained by the action of hydrogen chloride on phenyl-α-chloro-β-nitroethyl ketone (**IIa**).



IV

To prove the structure of the dichloroisoxazole, it was synthesized. The method of Bravo and coworkers [3] was used to prepare 3-chloro-5-phenyl-isoxazole, which was then further chlorinated to 3,4-dichloro-5-phenylisoxazole (**IV**) by treating with hydrochloric acid and hydrogen peroxide.

Prolonged action of hydrogen bromide on phenyl-β-nitrovinyl ketone (**Ia**) or phenyl-α-bromo-β-nitroethyl ketone (**IIIa**) gave mainly 5-phenyl- or 3-bromo-5-phenylisoxazole (**V** and **VI**), while only traces of 3,4-dibromo-5-phenylisoxazole (**VII**) was formed.

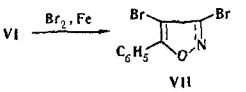


V VI

Thus hydrogen bromide acts as a reducing agent towards compounds such a nitrovinyl ketones, and that is not surprising, since unsaturated systems, where the double bond is conjugated with powerful electron accepting groups are known to have an oxidizing action [4].

As was to be expected, hydriodic acid proves itself to be an even more powerful reducing agent. The sole product isolated from the reaction of phenyl-β-nitrovinyl ketone (**Ia**) with hydriodic acid was 5-phenylisoxazole (**V**).

To confirm the structures of all the bromine-substituted isoxazoles and of 5-phenylisoxazole, they were synthesized, and the physical constants and TLC on alumina R_f values found to be the same for the two lots of preparations. For example, 3,4-dibromo-5-phenylisoxazole (**VI**) was prepared by brominating 3-bromo-5-phenylisoxazole (**VI**) with bromine in the presence of iron powder. It is of interest to note that under those conditions the isomeric 4-bromo-5-phenylisoxazole is not brominated.



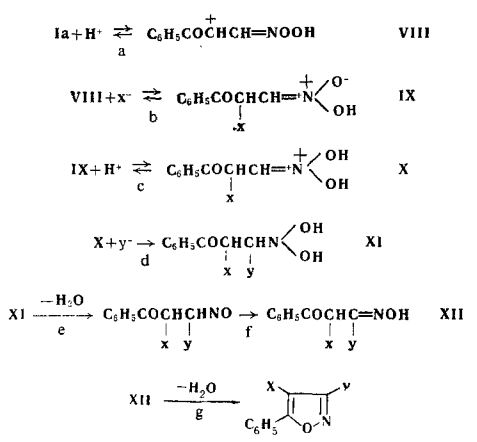
VII

Our observation that β-nitropropiophenone (the saturated isolog of phenyl-β-nitrovinyl ketone) is inert towards hydrogen chloride, hydrogen bromide, and hydriodic acid under the conditions used (ether solution, room temperature), is important in considering the mechanisms of the processes taking place. In all three cases the starting compound is unchanged, and can be recovered quantitatively from the reaction mixture. This shows that obviously saturated β-nitro ketones can hardly be intermediate products of reduction and cyclization, and this is confirmed by the following. Phenyl-α-chloro-β-nitrovinyl ketone (**IIa**), the product of addition of hydrogen chloride to phenyl-β-nitrovinyl ketone, reacts with hydrogen bromide to give 5-phenylisoxazole (**V**) and 3-bromo-5-phenylisoxazole (**VI**), i.e. the same products, and in approximately the same yields, as with phenyl-β-nitrovinyl ketone itself. From these results it can be assumed that there is probably equilibrium between β-nitrovinyl ketone and the hydrogen halide additions prod-

ucts that it forms. At least in the case of hydrogen bromide, formation of isoxazoles proceeds via the unsaturated form, independent of whether one starts with phenyl-β-nitrovinyl ketone or its hydrogen halide addition product.

It must also be mentioned that a special experiment showed that under our conditions, hydrogen bromide does not debrominate 3,4-dibromo-5-phenylisoxazole (**VII**), so that reduction cannot take place in the last stage, after cyclization to dihalogenoisoxazoles.

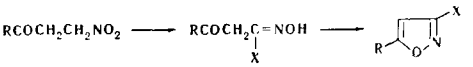
Though there is no doubt that the reaction investigated has a complex mechanism, and that further research is necessary to describe it in detail, all the same it is possible to put forward the following general plan to explain the processes which take place. Obviously the first stage is attack by a proton at the nitro group of the phenyl-β-nitrovinyl ketone **Ia**, giving rise to formation of the corresponding carbonium ion VIII*. In the case of hydrogen chloride, **VIII** can add the chlorine anion (X = Cl at stage b), to give the aci-form of phenyl-α-chloro-β-nitroethyl ketone (**IX**, X = Cl), which, as might be expected, under the further action of hydrogen chloride rearranges (stages c–e) to the acid chloride of the corresponding hydroxamic acid **XII** (X = Y = Cl).



Thus in stages a and b, there is 1,4 addition of hydrogen chloride to the α-nitro-olefin system. Just such a mechanism is usually assumed for the reaction of unsaturated nitro compounds with hydrogen chloride. The literature [5] emphasizes the importance of this, giving the aci-form, via which further conversion to hydroxamic acids occurs. Isomerization of the aci-nitro compound **IX** to the ordinary form gives α-halogeno-β-nitroethyl ketones (**IIa,b, IIIa**), which as has already been recalled, are evidently not intermediate products, at least in the case of hydrogen bromide. This agrees with the results of Heath and Rose [5], who showed that 2-nitroisopropylchloride ($CH_3CHClCH_2NO_2$) is not acted on by an ether solution of hydrogen chloride under conditions where 1-nitropropene ($CH_3CH{=}CHNO_2$) is converted to α-chloropropionic acid and hydroxylamine hydrochloride.

We postulate stages c and d mainly from the results of Hawthorne [6], and Kornblum and Brown [7] regarding the mechanisms of the Nef and Meyer reactions. They showed that a type c equilibrium plays an important part in converting nitroalkanes to the corresponding hydroxamic acids. The conjugated acid of the aci-nitro form (**X** in our scheme), here forming an equilibrium, has an electron-deficient carbon atom, linked to a nitrogen atom, and it readily undergoes nucleophilic attack, e.g. by the chlorine anion, when reacted with hydrogen chloride ($X^- = Cl^-$ at stage d).

The possibility of cyclizing the acid chloride of the hydroxamic acid formed (**XII**) to an isoxazole ring, is confirmed by Fusco and Rossi's results [8], showing that heating β-nitro ketones with halogen hydride acids converts them to substituted 3-halogenoisoxazoles, probably also via derivatives of hydroxamic acids.



Obviously in our case, with hydrogen bromide and particularly hydriodic acid, there is mainly reduction of carbonium ion **VIII**, possibly by a hydride mechanism (X = H^- at stage b, and Y^- = Br^- at stage d). The result is formation of 3-bromo-5-phenylisoxazole. Similar reduction of the conjugated acid of the aci-form X ($X^- = Y^- = H^-$ at stages b and c), can give 5-phenylisoxazole via benzoylacetoxime (**XII**, X = Y = H)*.

Undoubtedly the indicated route is not the only one, and it is quite possible that reduction is, for example, connected with the positive character of the halogen in compounds of the type $R_1R_2CXNO_2$ and $R_1R_2CXCOR_3$ [11], or with the powerful electron-accepting properties of systems with negative groups, for which ion-radical reduction is characteristic [4].

The IR and UV spectra of 5-phenylisoxazole and its dichloro and dibromo derivatives were observed. Although analysis of the spectra is made somewhat difficult by the presence of substituents, still it is possible to draw some conclusions. The IR spectra of all the compounds have bands at 1617—1607 cm^{-1}, assigned to the ordinary vibrations of the isoxazole ring [12]. In addition, absorption is found in the 1500—1400 cm^{-1} region, which is also characteristic of this heterocyclic system. However in this case it is impossible to observe three groups of bands, usually separated for substituted isoxazoles [12]. From the literature it is known that the frequency of the band of the phenyl group directly linked to the isoxa-

*It is to be mentioned that proton addition to the carbonyl group will probably give rise to 1,4 addition in the reverse direction, giving in the case of hydrogen chloride, phenyl-β-chlorovinyl ketone.

*Regarding the possibility of using HBr, and particularly HI, as a hydride hydrogen donor, see for example [9,10].

zole ring, is somewhat lower than that of mono-substituted benzenes [12]. A similar lowering was found by us both for 5-phenylisoxazole (1570 cm^{-1}), and for its dihalogeno derivatives (1576 and 1567 cm^{-1}).

The UV spectra of the compounds investigated have λ_{max} and ε values which are close together (see Experimental).

EXPERIMENTAL

The IR spectra* of 3,4-dibromo- and 3,4-dichloro-5-phenylisoxazoles were measured in vaseline mulls, and 5-phenylisoxazole in the form of a film. UV spectra were observed in glacial acetic acid.

Phenyl-α-chloro-β-nitroethyl ketone (IIa). HCl gas was passed for 1.5 hr into a stirred suspension of 8.85 g phenyl-β-nitrovinyl ketone (Ia) in 50 ml dry ether. The resultant solution was washed with water, dried over Na_2SO_4, the solvent evaporated off, and the residue vacuum distilled (0.05 mm, bath 80-100°), to give 9.32 g liquid which crystallized on standing. Recrystallization from petrol ether gave 6.85 g (64%) phenyl-α-chloro-β-nitroethyl ketone (IIa); mp 48-48.5°. Found: C 50.61; H 3.88; Cl 16.69; N 6.79%, calculated for $C_9H_8ClNO_3$: C 50.60; H 3.78; Cl 16.60; N 6.56%.

p-Bromophenyl-α-chloro-β-nitroethyl ketone (IIb). Prepared similarly from 2.56 g p-bromophenyl-β-nitrovinylketone (Ib) in 25 ml dry ether, yield 1.70 g (58%) p-bromophenyl-α-chloro-β-nitroethyl ketone (IIb), mp 99-100° (ex n-heptane). Found: C 36.71; H 2.18; N 4.76%, calculated for $C_9H_7BrClNO_3$: C 36.95; H 2.40; N 4.80%.

3,4-Dichloro-5-phenylisoxazole (IV). a) HCl gas was passed for 32 hr into a stirred suspension of 3.78 g phenyl-β-nitrovinyl ketone in 40 ml dry ether. TLC on aluminum oxide (2 spots) showed the reaction products to contain along with 3,4-dichloro-5-phenylisoxazole, either 3-chloro-5-phenylisoxazole, or phenyl-β-chlorovinyl ketone, or both together. These last two compounds have the same R_f values, and the same value as that of the 2nd spot on the chromatogram (eluant 5% solution of acetone in n-hexane). The ether solution was washed with water, dried over Na_2SO_4, cooled in solid CO_2-acetone, and 2-3 ml Et_3N (liquid) added. After standing for 30 min, the resultant viscous precipitate was filtered off, the ethereal filtrate washed with dilute HCl and then with water. Chromatography of this solution gave only 1 spot, corresponding to 3,4-dichloro-5-phenylisoxazole, and a 2nd spot, which might belong only to phenyl-β-chlorovinyl ketone, was lacking. After drying over Na_2SO_4 the ether was evaporated off, and the residue recrystallized from petrol ether, to give 1.63 g (38%) 3,4-dichloro-5-phenylisoxazole (IV), mp 33-34° (ex aqueous MeOH); λ_{max} 268 nm, lg ε 442 [13]. A run omitting the Et_3N gave an approximately 40% yield. Found: C 50.65; H 2.37; Cl 33.24; N 6.64% calculated for $C_9H_5Cl_2NO$: C 50.50; H 2.35; Cl 33.13; N 6.54%.

b) Similarly 5.3 g phenyl-α-chloro-β-nitroethyl ketone (IIa) gave 1.75 g (33%) 3,4-dichloro-5-phenylisoxazole (IV).

c) 4.8 ml 2% H_2O_2 and 3.6 ml conc HCl were added in portions to a boiling solution of 0.7 g 3-chloro-5-phenylisoxazole [3] in 20 ml AcOH. After 2 hr the mixture was cooled, diluted with water, neutralized with Na_2CO_3, and extracted with $CHCl_3$. After drying over $CaCl_2$, the $CHCl_3$ was evaporated off, the residue dissolved in ether, and the solution filtered through aluminum oxide. The filtrate was evaporated, and the residue recrystallized from MeOH, to give 0.38 g (45%) 3,4-dichloro-5-phenylisoxazole (IV), mp 33°, mixed mp with specimens prepared by methods a) and b) above, undepressed.

Phenyl-α-bromo-β-nitroethyl ketone (IIIa). HBr gas was passed for 1 hr 40 min into a suspension of 8.85 g phenyl-β-nitrovinyl ketone in 100 ml dry ether. The ether solution was washed with water, dried over Na_2SO_4, and the ether evaporated off. The residue was carefully recrystallized from n-heptane, to give 7.36 g (57%) phenyl-α-bromo-β-nitroethyl ketone (IIIa), mp 67-68°. Found: C 41.99; H 3.24; Br 30.83; N 5.34%, calculated for $C_9H_8BrNO_3$: C 41.88; H 3.12; Br 30.97; N 5.43%.

Reaction of phenyl-β-nitrovinyl ketone (Ia) with hydrogen bromide. HBr gas was passed for 14 hr into a stirred suspension of 1.78 g phenyl-β-nitrovinyl ketone in 25 ml dry ether. TLC on Al_2O_3 showed the reaction products to contain 5-phenylisoxazole (V) and 3-bromo-5-phenylisoxazole (VI). The ether solution was washed with water, dried over Na_2SO_4, and the ether distilled off. The residue (2.17 g, oil) was chromatographed on alumina (eluant 5% solution of acetone in n-hexane), to give 0.434 g (20%) 3-bromo-5-phenylisoxazole (VI) and 0.536 g (35%) 5-phenylisoxazole (V). 3-Bromo-5-phenylisoxazole mp 70°, undepressed mixed mp with a known specimen [14]. 5-Phenylisoxazole was identified by decomposing it with sodium methoxide to ω-cyanoacetophenone [15]. Under similar conditions phenyl-α-bromo-β-nitroethyl ketone (IIIa) gave a mixture of isoxazole of approximately the same composition: 5-phenylisoxazole (yield 37% theoretical) and 3-bromo-5-phenylisoxazole (yield 19%).

Reaction of phenyl-α-chloro-β-nitroethylketone (IIa) with hydrogen bromide. HBr gas was passed for 10 hr into a solution of 1.07 g phenyl-α-chloro-β-nitroethylketone (IIa) in 30 ml dry ether. The ether solution was then washed with water, dried over Na_2SO_4, and the ether evaporated. The residue was chromatographed on alumina, to give 0.28 g (25%) 3-bromo-5-phenylisoxazole (VI), and 0.28 g (38%) 5-phenylisoxazole (V).

3,4-Dibromo-5-phenylisoxazole (VII). 1.09 g 3-bromo-5-phenylisoxazole [14] and 0.93 g bromine were heated together at 100° for 16 hr in the presence of Fe powder. The reaction products were dissolved in benzene, and filtered through a layer of alumina. Removal of the solvent then gave 1.06 g (72%) 3,4-dibromo-5-phenylisoxazole, mp 64-65° (ex n-heptane); λ_{max} 272 nm, lg ε 4.21. Found: C 36.10; H 1.59; Br 53.09%, calculated for $C_9H_5Br_2NO$: C 35.65; H 1.66; Br 52.76%.

Reaction of phenyl-β-nitrovinyl ketone (Ia) with hydriodic acid. Hydriodic acid was distilled over red P, and kept over it. 25 ml of this acid was added, in a current of nitrogen to 1.77 g phenyl-β-nitrovinyl ketone. After 10 hr the reaction products were extracted with benzene, the benzene solution dried over Na_2SO_4, and run through alumina. Removal of the solvent gave 0.6 g (41%) 5-phenylisoxazole (V).

*The authors thank L. V. Senyavina for measuring the IR spectra (Institute of Chemistry of Natural Compounds, AS USSR).

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29 November 1965

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