REACTION OF SOME AMINES WITH UNSATURATED N-ACYLBENZOXAZOLONES

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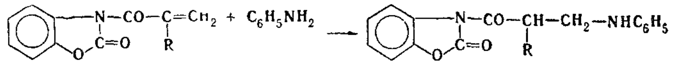
It is shown that the addition of aniline proceeds at the carbon–carbon double bond of N-acryloyl-, N-chloroacryloyl-, and N-methylacryloylbenzoxazolones. The basicity of the amine has a substantial effect on the course of the reaction with various amines. Transamidation of the acryloyl residue occurs with strongly basic amines.

We have previously shown [1] that benzoxazolone (I) adds readily to N-acryloylbenzoxazolone (IIa). The present paper is devoted to a study of the addition of various nucleophilic reagents to unsaturated N-acylbenzoxazolones. The facts available in the literature indicate that nucleophilic addition of the base to the carbonyl group of oxazolone I with ring opening occurs in the reaction of amines [2] and hydrazines [3] with various benzoxazolones.

On the basis of [1, 2], it may be assumed that addition to the carbon–carbon double bond (formation of IVa), to the carbonyl group of the acryloyl residue, or to the C=O group of the oxazole ring with subsequent cleavage of either the carbon–oxygen or carbon–nitrogen bond is possible in the reaction of aniline (III) with IIa.



II III IVa-c

IV a R=H; b R=CH_3; c R=Cl

It was shown on the basis of the spectral data that the first of the addition paths indicated above formation of IVa) is realized.

The signals from the aromatic ring protons in the PMR spectrum of IIa appear as multiplets at 6.86 ppm (5-H, 6-H, 7-H) and 7.64 ppm (4-H). The shift of the 4-H signal to weak field is due to the steric deshielding effect of the C=O group of the acryloyl residue. The equivalence of all of the aromatic protons of I (singlet at 6.83 ppm) may be a confirmation of this. The signals from the protons of the acryloyl residue of IIa are found at 7.21 ppm (–CH=, J_{CH+CH_2}=17.3 and 10.5 Hz) and 6.34 and 5.79 ppm (=CH_2). As one should have expected, on passing from IIa to IVa, one observes that the PMR spectrum of the latter contains, in place of the vanished signals from the vinyl protons, a two-proton triplet at 3.35 ppm and an unresolved multiplet with a chemical shift of 3.66 ppm, which are affiliated, respectively, with the protons of the $COCH_2CH_2$ and CH_2-CH_2-N fragments. Singlets from the C_6H_5 and NH protons are found at 7.16 and 8.67 ppm, respectively. The parameters of the signals of the aromatic protons of the benzoxazolone ring for IVa are the same as those for IIa.

The absence of an OH^- group was confirmed by qualitative reaction with $FeCl_3$.

Compound IVa was also synthesized by alkylation of amine III with N-(β-chloropropionyl)benzoxazolone in the presence of K_2CO_3; the products obtained by the two methods were identical.

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The presumed product of the reaction with opening of the heterorings – 2-(acryloylamino)phenyl N-phenylcarbamate (VI) – was synthesized by acylation of o-aminophenol with acryloyl chloride and subsequent treatment of the resulting N-acryoyl-o-aminophenol (V) with phenyl isocyanate.

The PMR spectrum of carbamate VI contains two broad singlets at 7.78 and 8.49 ppm, which are related to the protons of the NH groups. The signals of equivalent aromatic protons are found at 6.93 ppm. The multiplets from the protons of the $-CH=$and $=CH_2$ groups resonate at 5.61 and 6.11 ppm, respectively.

It should be noted that the use of 2 moles of aniline per mole of IIa does not promote the reaction with opening of the heteroring, i.e., addition product IVa was isolated in quantitative yield in this case also. Thus, nucleophilic addition of aniline to the double bond of the acryloyl residue of IIa occurs in the cases presented above. The double bond in IIa is evidently polarized, and this facilitates the addition of a proton. In addition, it is possible that the acyl group directly bonded to the nitrogen atom sterically hinders attack on the $C=O$ reaction center in the oxazolone ring by the base.

In order to compare the reactivities, we carried out reactions of benzoxazolone I with acrylamide and acrylanilide. We were unable to accomplish these reactions under the conditions developed for the addition of I to various N-acryloylbenzoxazolones. More severe conditions and the use of a catalyst were required for the synthesis of N-(β-carboxyethyl)benzoxazolone amide (VII) and N-(β-carboxyethyl)benzoxazolone anilide (VIII). The structure of amide VIII was confirmed by alternative synthesis, for which N-benzoxazolonyl-β-propionyl chloride was used.

Various bases did not add to N-α-methacryloylbenzoxazolone (IIb) under the above reaction conditions, and starting I and IIa were recovered. A CH_3 group introduced into the 3-position, in addition to its + I effect, also markedly shields the double bond, i.e., additional steric interactions of the CH_3 group with the reacting molecule of I are apparently possible in the transition state.

When we carried out the reaction of IIb with aniline, we were able to obtain N-(α-methyl-β-phenylaminopropionyl)benzoxazolone (IVb, $R=CH_3$).

Singlets from the protons of CH_3 and $=CH_2$ groups are found at 1.73 and 5.37 ppm, respectively, in the PMR spectrum of IIb. Multiplets with a signal intensity ratio of 3 : 1, which are found at 6.90 and 7.62 ppm, are affiliated with the 5-H, 6-H, 7-H, and 4-H protons. However, in the case of IVb the signal of the methyl group at 1.13 ppm is a doublet, and, in addition, signals related to the following groups appeared in place of the absent singlet from the CH_2 group (in the spectrum of IIb): $-C-CH_2-N-$ (3.59 ppm), $-CO-CH-$ (4.06 ppm), NH (8.60 ppm), and C_6H_5 (7.12 ppm). Signals from 4-H and the remaining aromatic protons are found at 7.62 and 6.90 ppm, respectively.

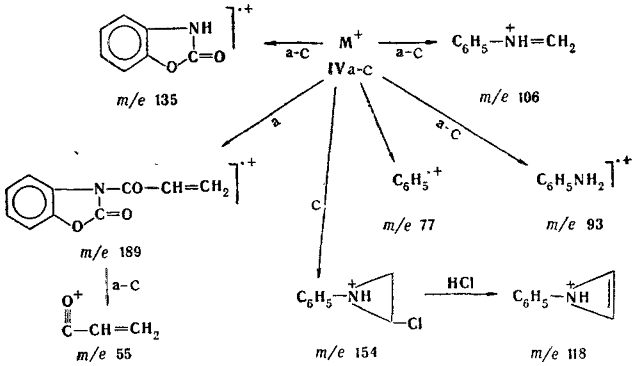
The mass spectrum of IVb ($R=CH_3$) completely confirms the assumed structure and is analogous to the mass spectrum of IVa.

It was assumed that, in contrast to the addition reaction presented above, the addition of aniline to N-(α-chloroacryloyl)benzoxazolone (IIc) should proceed more readily, i.e., the electron-acceptor chlorine substituent additionally intensifies the polarization of the carbon–carbon bond. In addition to this, the introduced group could promote the addition of base also to the $C=O$ group of the five-membered ring of IIc, inasmuch as the nitrogen–carbon bond in the oxazolone ring is weakened in this case. A product of addition to the double bond – N-(α-chloro-β-phenylaminopropionyl)benzoxazolone (IVc)– was obtained in quantitative yield as a result of reaction of unsaturated IIc with aniline. This is in good agreement with the results [1] that we obtained for the addition of I to IIc.

The protons of the $COCH(Cl)CH_2N$ fragment in the PMR spectrum of IVc form an A_2X system with the following chemical shifts: doublet at 3.92 ppm (CH_2) and triplet at 5.70 ppm (CO–CH). Multiplets from the (5-7)-H and 4-H protons are found at 6.93 and 7.63 ppm. The singlet at 7.22 ppm is affiliated with the equivalent protons of the phenyl group.

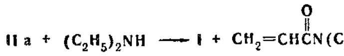
The mass spectrum of IVc contains peaks of chlorine-containing ions with m/e 316 (M^+, 15%), 154 (6%) and of chlorine-free ions with m/e 146 (12%), 135 (15%), 118 (7%), 106 (100%), 79 (9%), and 77 (10%). A characteristic feature of the mass spectra of IVa-c is the maximum intensity of the peak of the ammonium ion with m/e 106 and the presence in them of the peak of a benzoxazolone (I) ion radical.

However, the formation of ions with m/e 106 and 135 is excluded in the case of the alternative structures with opening of the oxazolone ring. The structures and pathways for the formation of the most characteristic fragments in the mass spectra of IVa-c are presented in the scheme below:



The nature of substituent R introduces its own specifics into the mass spectrum. For example, an analog of the ion with m/e 189 that is observed for IVa is absent in the spectra of IVb, c, and this is possibly associated with steric factors. An ion peak with m/e 154, the analog of which is absent in the spectra of products IVa, b, appears in the spectrum of IVc.

Reaction of IIa with diethylamine under various conditions gives benzoxazolone I in high yields. The transamidation reaction below apparently occurs in this case



$$\text{IIa} + (C_2H_5)_2NH \longrightarrow \text{I} + CH_2{=}CH\overset{O}{\overset{\|}{C}}N(C_2H_5)_2$$

It seemed that the basicity of the amine plays the deciding role. For this reason, we carried out the reaction of IIa with the bulky but weakly basic diphenylamine. In fact, we found that diphenylamine does not add to IIa, and starting IIa is recovered from the reaction mixture.

EXPERIMENTAL

The mass spectra were recorded with an MKh-1303 spectrometer at 100° and an ionizing electron energy of 40 eV; the m/e values of the chlorine-containing fragments were taken with respect to Cl^{35}. The PMR spectra of trifluoroacetic acid solutions of the compounds were recorded with a JEOL 4H-100 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The chemical shifts are presented on the δ scale. The IR spectra were recorded with a UR-20 spectrometer. Thin-layer chromatography (TLC) was carried out on a fixed layer of silica gel (Silufol) in benzene–alcohol (21:2).

N-(β-Phenylaminopropionyl)benzoxazolone (IVa). A) An alcohol solution of 0.95 g of freshly distilled aniline was added slowly with stirring and cooling to 0 deg to a solution of 1.9 g (0.01 mole) of IIa in absolute alcohol. Stirring was continued at 0 deg for 30 min and subsequently at room temperature for 30 min. The precipitated crystals were removed by filtration, and an additional amount of IVa was isolated from the filtrate to give a total of 2.56 g (91.4%) of a product with mp 138° (from alcohol). Mass spectrum: M^+ with m/e 283 (30%); peaks of fragments with m/e 189 (7%), 147 (8%), 135 (10%), 106 (100%), 93 (15%), 77 (8%), and 55 (60%). Found: N 9.4%. $C_{16}H_{14}N_2O_3$. Calculated: N 9.9%. Compound IVa reacted with hydrochloric acid (1:1) to give a hydrochloride with mp 197-200°.

B) An acetone solution of 1.12 g (0.005 mole) of N-(β-chloropropionyl)benzoxazolone was added slowly to an aqueous acetone solution of 0.47 g (0.005 mole) of freshly distilled aniline and 0.42 g of Na_2CO_3. Stirring was continued at room temperature for 30 min, after which the mixture was stirred on a boiling-water bath for 1 h. The solvent was evaporated, and the resulting precipitate was washed with 100 ml of water, dried, and recrystallized from alcohol to give 0.98 g (70%) of a product with mp 137-138° (alcohol) and R_f 0.9. No melting-point depression was observed for a mixture of this product with the product obtained by method A.

M-(α-Methyl-β-phenylaminopropionyl)benoxazolone (IVb). Reaction of 1 g (0.005 mole) of IIb via method A gave 0.6 (40%) of a product with mp 124-126° (from ethyl acetate). Mass spectrum: M^+ 296 (70%), 161 (6%), 135 (10%), 106 (100%), 93 (10%), 77 (10%), and 69 (15%).

N-(α-Chloro-β-phenylaminopropionyl)benzoxazolone (IVc). Similarly, 1.15 g (0.005 mole) of IIc gave a quantitative yield of IVc with mp 140° (from alcohol).

Reaction of IIa with Diethylamine. Under the conditions of method A, 1.9 g (0.01 mole) of IIa and 0.75 g (0.01 mole) of diethylamine gave 0.72 g (53%) of benzoxazolone I with mp 130-133° (mp 135-137° [1]) and R_f 0.32.

Benzoxazolone I was also obtained in high yield when the reaction was carried out in n-butanol-ethanol or when the components were refluxed in isopropyl alcohol.

Starting IIa (R_f 0.76) was recovered from the reaction of IIa with diphenylamine under the conditions of method A or at 45-50°; the formation of I was not observed.

N-Acryloyl-o-aminophenol (V). A solution of 2 g (0.02 mole) of Na_2CO_3 in 10 ml of water and 20 ml of acetone was added to an acetone solution of 4.36 g (0.04 mole) of o-aminophenol, after which 3.7 g (0.04 mole) of acryloyl chloride was added with vigorous stirring and cooling. Stirring was continued at room temperature, after which the mixture was heated on a boiling-water bath for 30 min and allowed to stand overnight. It was then acidified slightly with HCl (1 : 1), and the precipitated product was removed by filtration and recrystallized from water with decolorization by activated charcoal. The yield of V with mp 118-119° (from benzene) was 2.4 g (32.3%). The product was quite soluble in acetone and alcohols, but only slightly soluble in n-hexane and petroleum ether. Found: N 8.5%. C_9H_9NO. Calculated: N 8.6%.

2-(Acryloylamino)phenyl N-Phenylcarbamate (VI). A mixture of 0.8 g (0.005 mole) of V, 0.5 g (0.004 mole) of phenyl isocyanate, and a very small amount of hydroquinone was refluxed in 8 ml of m-xylene for 12 h, after which the mixture was allowed to stand overnight. The resulting precipitate was removed by filtration and recrystallized from ethyl acetate to give 0.34 g (24.2%) of a product with mp 152-154°. Found: N 10.1%. $C_{16}H_{14}N_2O_3$. Calculated: N 9.9%.

IR spectrum of V: 3410 (OH^-), 3130-3170 (NH), 1660 (amide C=O), and 980 cm^{-1} (terminal double bond). A split absorption band was observed in the spectrum of VI in the region of the NH stretching vibrations at 3300-3400 cm^{-1}.

N-(β-Carboxyethyl)benzoxazolone Amide (VII). A mixture of 6.75 g (0.05 mole) of I and 7.1 g (0.1 mole) of acrylamide in 50 ml of dry dioxane and 0.6 g of finely ground KOH was heated at 80° for 2 h, after which it was cooled to room temperature, and the solvent was partially removed. The residue was treated with 2% aqueous KOH (300 ml), and the insoluble material was removed by filtration and dried to give 2.4 g (23.3%) of a product with mp 170-171° (from alcohol).

N-(β-Carboxyethyl)benzoxazolone Anilide (VIII). A method similar to the preceding method was used to obtain 0.6 (42.5%) of a product with mp 157-159°. Found: N 9.9%. $C_{16}H_{14}N_2O_3$. Calculated: N 9.9%.

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