

Synthesis of 2,1-benzisoxazol-3(1H)-one by intramolecular photochemical cyclization of 2-azidobenzoic acid.

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Abstract: Peculiarities of 2,1-benzisoxazol-3(1H)-one synthesis by means of the photochemical cycle forming reaction of 2-azidobenzoic acid in ethanol. Based upon HPLC kinetical data we have observed the 2,1-benzisoxazol-3(1H)-one yield decrease in the course of decreasing of the starting azide concentration. It was stated that the 2,1-benzisoxazol-3(1H)-one formation effectiveness depended on the actinic light wavelength. Changing the light wavelength from 365 to 253.7 nm we observed an increase of the cycle formation yield. The decrease of the 2,1-benzisoxazol-3(1H)-one yield in the course of irradiating at 365 nm was explained by the secondary photolysis.

Keywords: aromatic azide photochemistry, photochemical cyclization, 2,1-benzisoxazol-3(1H)-one, 2-azidobenzoic acid, photolysis, nitrenes

Introduction

2,1-benzisoxazol is the most label in the community of N,O-containing 5-membered benzene condensed heterocycles.

In the case of introduction of carbonyl group into a hetero cycle such compound forms two tautomeric moieties, ketone and enone ones. It is possible that because of the tautomerism of 2,1-benzisoxazole or a label character of N – O bond in the hetero cycle he said compounds have pharmacological activity [1-3]. Biological activity of benzisoxazol derivatives and possibility to use them as stating materials for preparing a great majority of biologically active hetero cycle compounds enlarge importance of finding and development new 2,1-benzisoxazol synthesis.

It was described two main methods of 2,1-benzisoxazole synthesis, such as recovering of CO-containing 2-substituted nitro- and nitroso compounds up to corresponding hydroxylamines followed by their dehydration [4-7] and thermal or catalytic decomposition of analogous azides [8-10].

Synthesis of 2,1-benzisoxazole-3(1H)-one is specially difficult. Its yield in the twostep synthesis comprising o recovering of 2-nitrobenzoic acid and subsequent cyclization of 2-hydroxylaminebenzoic acid is not more than 20-25% [7]. Besides, the compound is unstable at room temperature and so it is not possible to use thermolysis of 2-azidobenzoic acid for its synthesis.

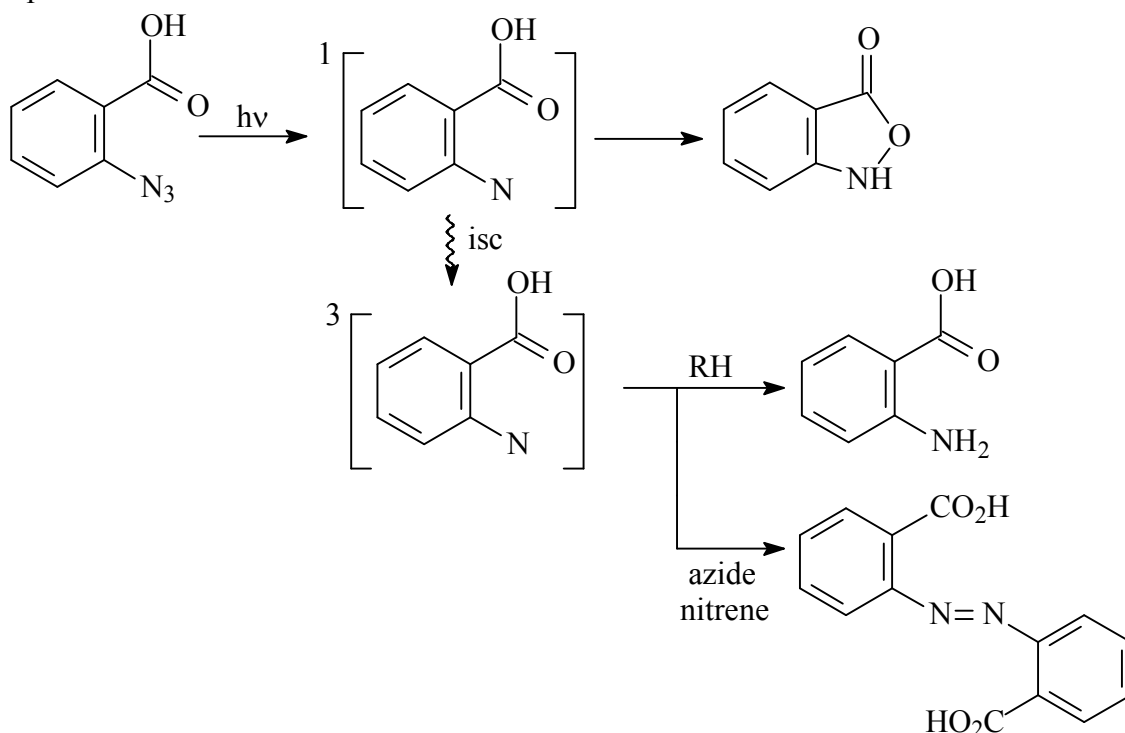
Earlier, it was observed formation of 2,1-benzisoxazole-3(1H)-one, 2-aminobenzoic acid, 2,2'-dicarboxyazobenzene, and some unidentified products in the course of the 2-azidobenzoic acid [11,12].

Thermolysis of 2-substituted phenylazides containing multiple bond in α - or β - position respective to azide group gives products of intramolecular cycle formation with yields close to quantitative. For instance, the main product of the 2-azidobenzene thermolysis is 2-phenylbenzotriazole [8], and the main product of the 2-azidobenzophenone is 3-phenylanthranil [9].

The large yields of heterocyclic products is due to intramolecular 1,3-dipolar addition when cyclization and loss of nitrogen proceeds simultaneously.

A photochemical cycle formation usually follows along other route. Aromatic azides decompose under irradiation to form singlet aryl nitrenes. They inset into C – H and multiple bonds of own molecules giving the cycle formation products. The reason of the said behavior is high reactivities and short lifetimes of the aryl nitrenes.

However, the nitrene ground state is triplet. After the nitrenes transfer into the triplet state their reactivities become slower and the lifetimes become longer. The triplet nitrenes are unable to form the intramolecular cycle formation products, and because of their long lifetimes they react mainly due to bimolecular ways. They abstract H-atoms from solvent molecules to form aromatic amines and insert into double bonds of azido groups of other azide molecules to form azocompounds.



Scheme 1. Mechanism of 2,1-benzisoxazole-3(1H)-one and 2-aminobenzoic acid in the course of photolysis of 2-azidobenzoic acid.

Our goal was to find photochemical synthetic methods of 2,1-benzisoxazole-3(1H)-one starting from 2-azidobenzoic acid, and to study effects of the starting azide concentration and spectral range of the actinic irradiation upon the 2,1-benzisoxazole-3(1H)-one yield.

Experimental Part

General information

All solvents were twice distilled. Infrared (IR) spectra were recorded as nujol mull and KBr disk on a Shimadzu IRPrestige-21 FTIR spectrophotometer. UV-Vis spectra were recorded on AnalytikJena Specord 40.

Identification and purity estimation of the synthesized compound was performed by means of Thermo Electron Trace GC Ultra/DSQII (GCMS) chromatograph – mass spectrometer unit.

Analytical thin layer chromatography (TLC) was performed on Silufol UV254 aluminium foil with silica gel starch binder, eluent - chloroform: acetonitrile (2:1, v/v). The spots on TLC plates, products were visualized by fluorescence and ultraviolet radiation. Preparative column chromatography was performed using Silica gel LS 5/40, eluent - chloroform: carbon tetrachloride (1:1, v/v).

The photolysis products were separated and identified by means of HPLC on liquid chromatography Shimadzu LC-20AD equipped with SPD-M20A detector, column Discovery C-18, 5 μ m, d=3mm, l=25cm. Gradient eluent – ethanol : 0,01% phosphonic acid, amount of which was linearly decreasing from 65,5% till 0% in 20 min. Flow rate was 0.15 ml/min.

Concentrations of 2-azidobenzoic acid, 2,1-benzisoxazole-3(1H)-one and 2-aminobenzoic acid in the reaction mixture were determined on the basis of calibration curves by means of the external standard method (Fig. 1, Fig. 2).

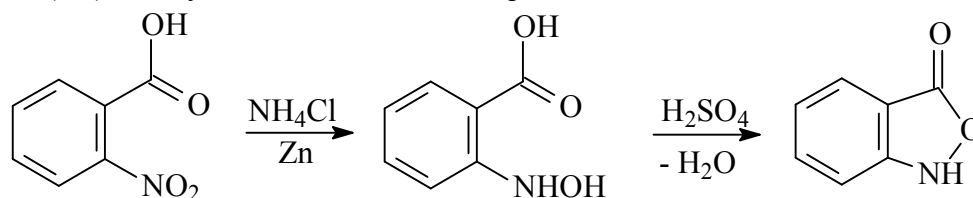
Photolysis

Ethanol solutions of 2-azidobenzoic acid were irradiated in a quartz reactor with u.v. light of Hg-lamps of lower pressure BUF-15 (253.7 nm) and of super high pressure DRK-120 (365 nm).

Synthesis

2-azidobenzoic acid was prepared by diazotization of 2-aminobenzoic acid in HCl solution at 0-5 °C With NaNO₂. NaN₃ was added to the diazonium salt obtained and then reaction mixture was subsequently heated up to room temperature. The azide was separated as white crystalline precipitate by filtration and subsequent washing with cold water. After that it was dried in dark at room temperature and recrystallined from benzene. [11] T_m = 144 °C. IR (nujol mull, cm⁻¹): 2131.34, 2110.12, 2081.19 (ν_{as} N₃); 1691.57 (ν C=O); 1267.23 (ν_s N₃). UV-Vis in acetonitrile (λ, nm / lg(ε), 1 × mol⁻¹ × cm⁻¹): 221/4.29, 255/3.99, 296/3.43.

Preparation of 2,1-benzisoxazol-3(1H)-one was realized as two-stage procedure [11]. At the first stage 2-nitrobenzoic acid was recovered into 2-hydroxylaminebenzoic acid by means of zinc powder in aqueous solution of NH₄Cl in neutral media without oxygen access. After that 2-hydroxylaminebenzoic acid was dehydrated with simultaneous cycle formation into 2,1-benzisoxazol-3(1H)-one by slow addition of it to aqueous solution of H₂SO₄.



Scheme 2. Synthesis of 2,1-benzisoxazol-3(1H)-one by recovering of 2-nitrobenzoic acid.

Obtained 2,1-benzisoxazol-3(1H)-one was extracted with benzene and purified by means of preparative column chromatography. Silica gel was used as an adsorber and 1:1 (v/v) mixture of chloroform and carbon tetrachloride.

Colorless crystals were isolated from yellowish solutions. Obtained 2,1-benzisoxazol-3(1H)-one is thermolabile compound being stored at room temperature, isolated from air 2,1-benzisoxazol-3(1H)-one solution becomes red-brown colored in some hours. Solid 2,1-benzisoxazol-3(1H)-one decomposes too, but with lower rate.

IR (nujol mull, cm⁻¹): 3127.12 (ν NH), 1743.66, 1719.07 (ν C=O), 1068.61 (ν C-O). GCMS m/z: 134.9, 119, 104, 91, 79, 64, 61, 50, 38. UV-Vis in acetonitrile (λ, nm / lg(ε), M⁻¹ × cm⁻¹): 213/4.17, 306/3.31.

Quantitative identification was performed for the 2-azidobenzoic acid and two of the possible products of the photolysis - 2-aminobenzoic acid and 2,1-benzisoxazol-3(1H)-one.

Results and Discussion

The ν_{as} N₃ with peak at 2134 cm⁻¹ diminishes in the IR spectrum of 2-azidobenzoic acid in 96% ethanol (Fig.3, Fig.4). That means that the photolysis has place in the case. Additionally, there has place growth of the carbonyl group peak at 1740 cm⁻¹ corresponding to the 2,1-benzisoxazol-3(1H)-one carbonyl.

Absorption of asymmetrical stretching vibration of azido group is situated in region that is transparent in the case of the great majority of organic compounds and that fact makes it convenient to determine quantitatively the content of azido compound. However, absorptions of the stretching vibration of carbonyl group in the azide and in the 2,1-benzisoxazol-3(1H)-one are overlapping and it seems to be difficult to characterize them precisely and can not be used as an analytical vibration. The said difficulty prohibited any usage of IR spectroscopy of the azide solutions to analyze the photolysis products.

Eluent for HPLC was selected to simultaneous separation of more polar compounds such as 2,1-benzisoxazol-3(1H)-one, and 2-aminobenzoic acid, and less polar 2-azidobenzoic acid. As a

component of the preparation step 2 % aqueous solution of phosphoric acid was added to the irradiated solution of the azide (1:1 v/v ratio).

The kinetics of the azide photolysis and the 2,1-benzisoxazol-3(1H)-one appearance under the super high pressure Hg-lamp DPK-120 for the azide concentration from 2.5×10^{-3} up to 9.3×10^{-5} M is described by exponential relationship with correlation coefficient of 0.99 (Fig. 5 and 6). In the case of concentration of 9.3×10^{-5} M the kinetics is obeyed with the linear law. The cause of the situation is explained by lower changing of the actinic irradiation intensity in depth of the reactor (Fig. 7). Photolysis was performed up to conversion of 50-90%.

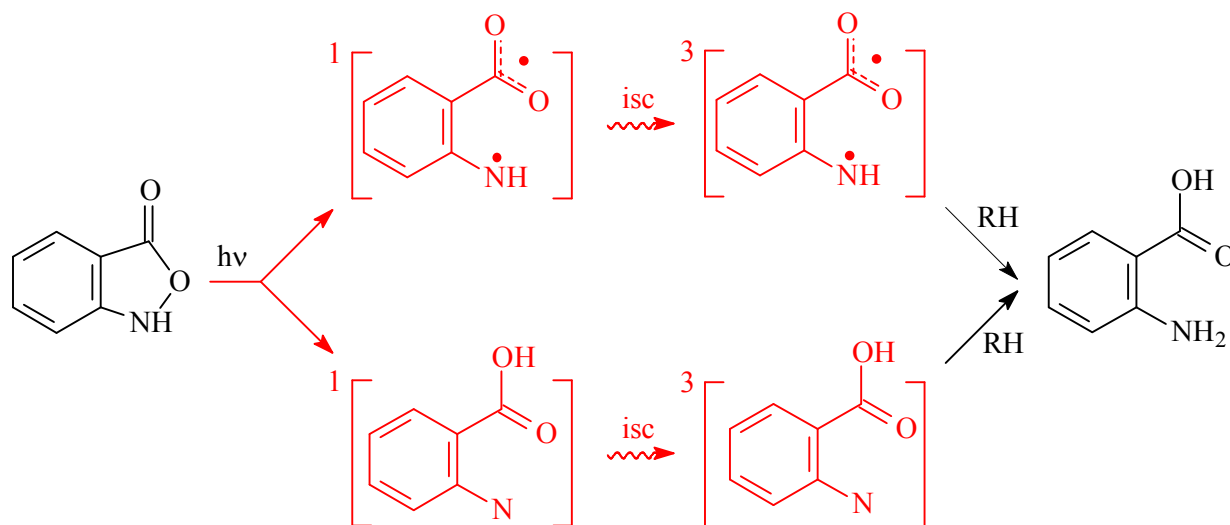
The yield of 2,1-benzisoxazol-3(1H)-one in the photolysis under DPK-120 Hg-lamp slightly increases with increase of the starting azide concentration from 50% at concentration of 9.3×10^{-5} M up to 70% at concentration of 2.5×10^{-3} . In addition to 2,1-benzisoxazol-3(1H)-one there have place traces (ca. 1%) of 2-aminobenzoic acid. The actinic irradiation of the lamp is overlaps with the absorption band of 2,1-benzisoxazol-3(1H)-one and it this gives us an opportunity to propose that the secondary photolysis of 2,1-benzisoxazol-3(1H)-one gives 2-aminobenzoic acid.

We have chose the region of wavelength with strong absorption of 2-azidobenzoic acid and with slight absorption of 2,1-benzisoxazol-3(1H)-one from comparison of US-Vis spectra of the starting azide and 2,1-benzisoxazol-3(1H)-one (Fig. 8). The region coincides with the emission region of the low pressure Hg-lamp BUF-30 centered at 253.7 nm.

The 2-azidobenzoic acid photolysis kinetics under the lamp irradiation at 4.1×10^{-2} - 2.6×10^{-4} M was studied.

Increasing of the 2-aminobenzoic acid concentration in the irradiated under BUF-30 Hg-lamp reaction mixture was not observed that supported our assumption about possibility of the secondary photolysis of 2,1-benzisoxazol-3(1H)-one giving 2-aminobenzoic acid. But the yield of the aimed product slightly increased and was about 60%. Concentration of azide in the course of the photolysis was diminishing in photolysis under both BUF-30 and DRK-120, and concentration of 2,1-benzisoxazol-3(1H)-one was exponentially raising up to high conversions of the azide (Fig.9, 10, 11, and 12). It is worth to note that the yield of the cycle formation product in the case of concentration of 4.1×10^{-2} M was substantially lower (35 %) than at lower concentration. It is possible that the decreasing of the 2,1-benzisoxazol-3(1H)-one yield was caused by too long irradiation times and by complicating of the photolysis mechanism.

The secondary photolysis of 2,1-benzisoxazol-3(1H)-one gives the singlet carboxyaminyl biradicals that itself or after rearrangement into nitrene from the triplet state that abstracts H-atoms from the solvent molecule to form primary amine – 2-aminobenzoic acid.



Scheme 3. Possible mechanism of the secondary photolysis of 2,1-benzisoxazol-3(1H)-one.

Thus, we can conclude that under the reaction conditions studied the cycle product yields were not quantitative that supported the assumption on intermediate formation of nitrene in the

course of the 2-azidobenzoic acid photochemical cyclization. An absence of the relation between the yields and the azide concentrations evidences that there is no substantial contribution from bimolecular processes having the singlet character.

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Appendix:

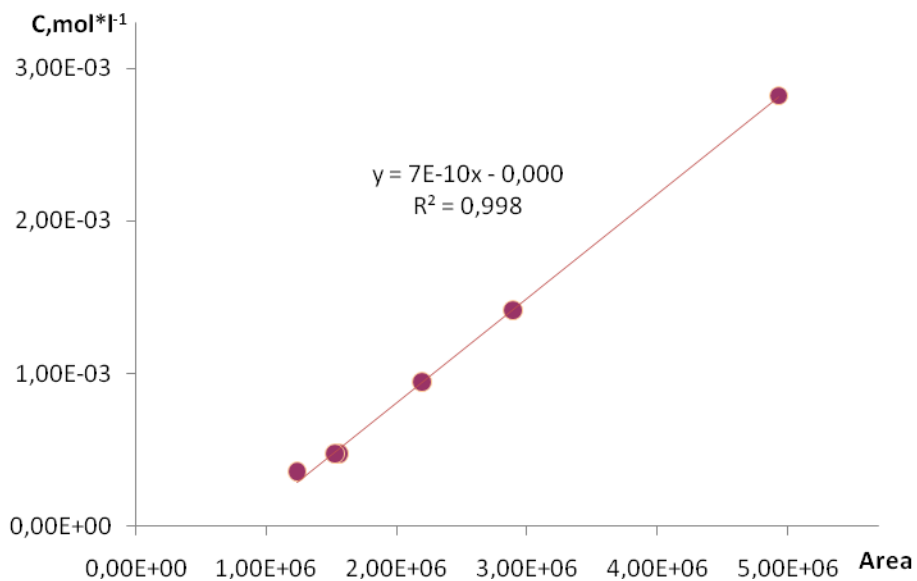


Figure 1. The Calibration curve 2-azidobezoic acid (335nm)

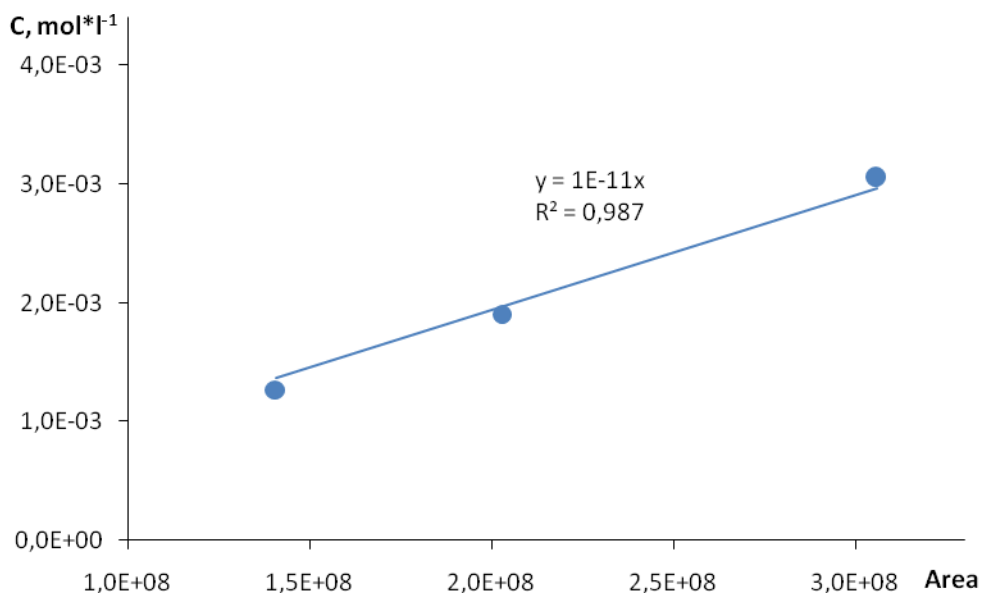


Figure 2. The Calibration curve 2,1-benzisoxazol-3(1H)-one_(220nm)

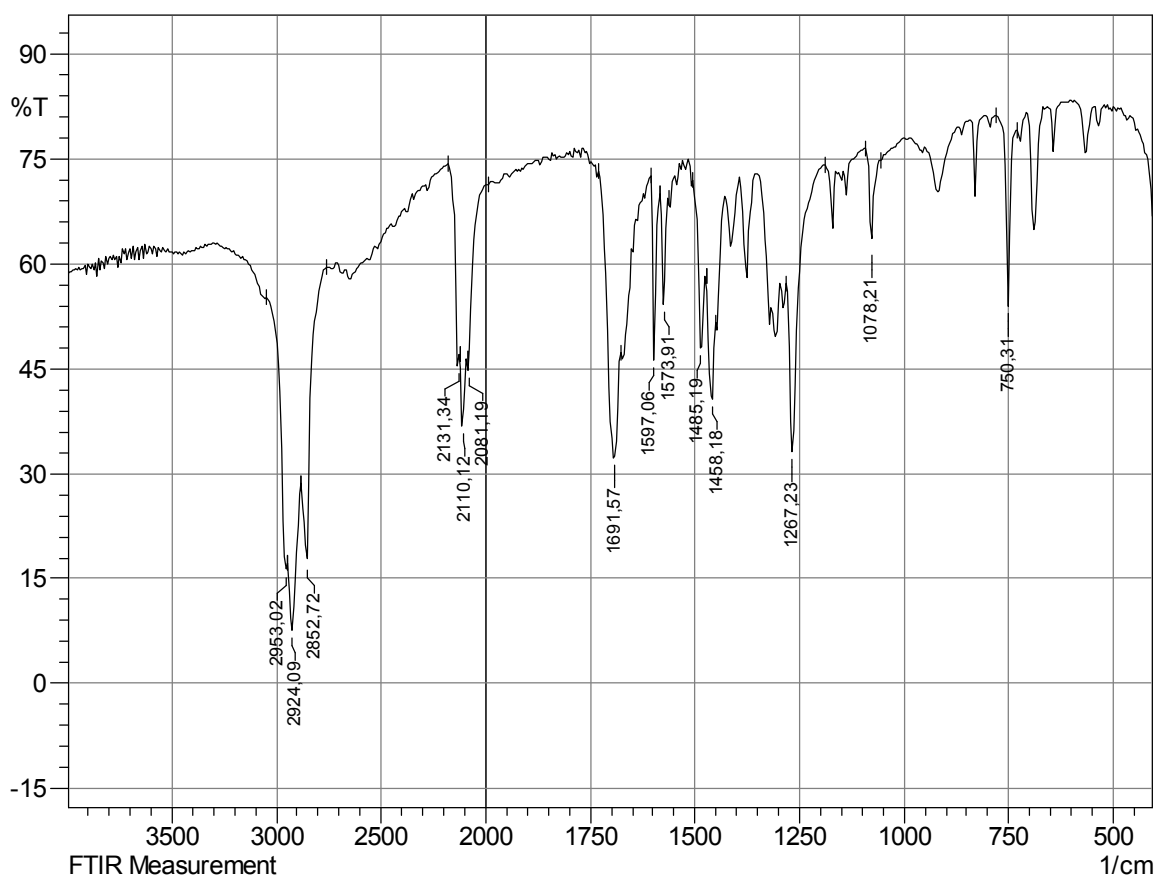


Figure 3. Infrared spectra of 2-azidobezoic acid in nujol mull.

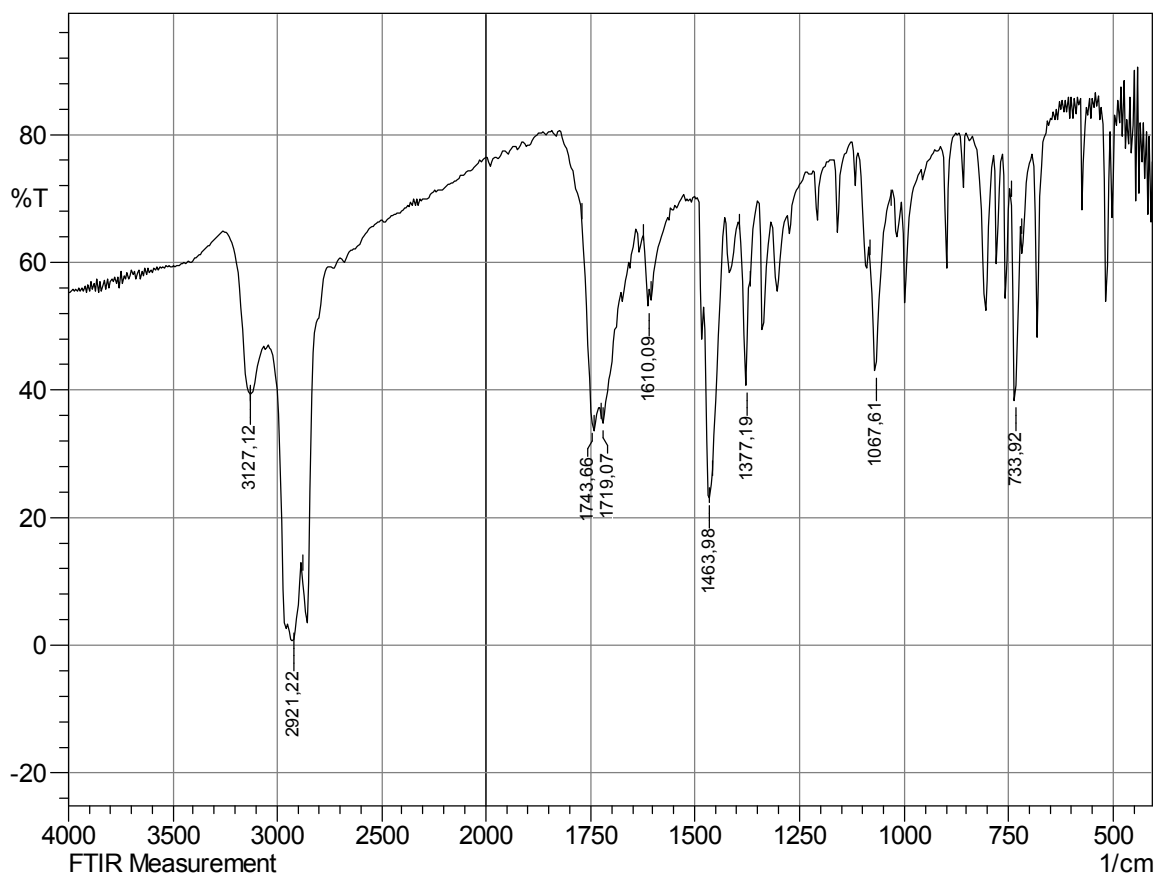


Figure 4. Infrared spectra of 2,1-benzisoxazol-3(1H)-one in nujol mull.

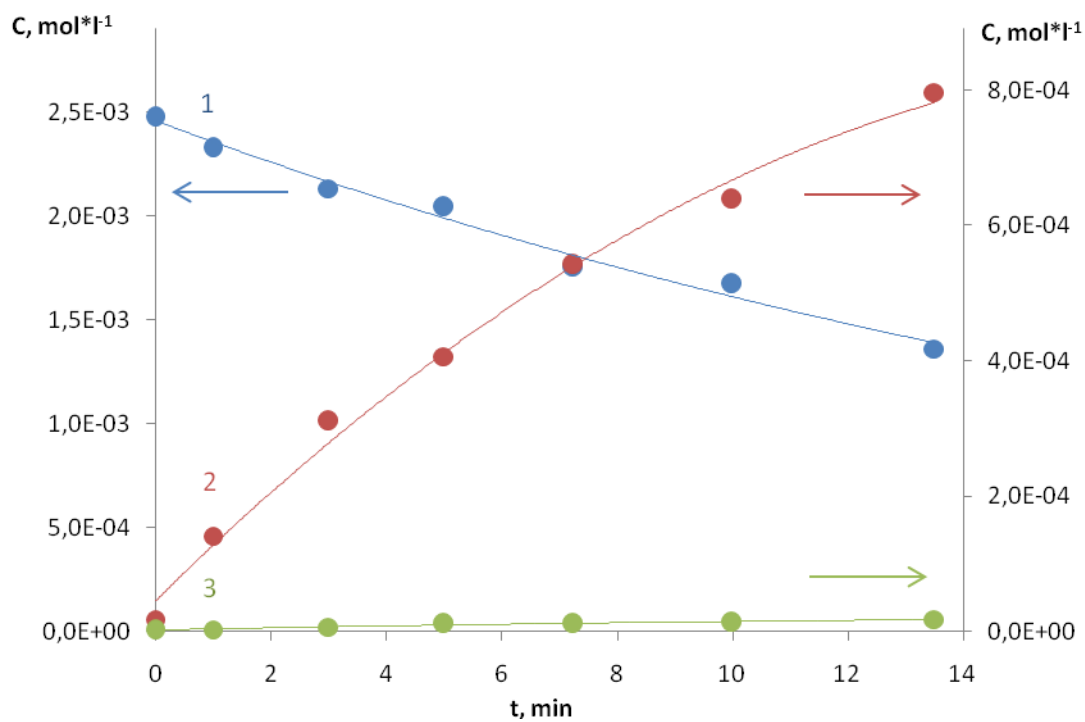


Рис. 5. The kinetics of the photolysis (DRK-120) 2-azidobenzoic acid (1) $C=2.5 \times 10^{-3} \text{ mol} \times \text{l}^{-1}$ and formation 2,1-benzisoxazol-3(1H)-one (2) and 2-aminobenzoic acid (3).

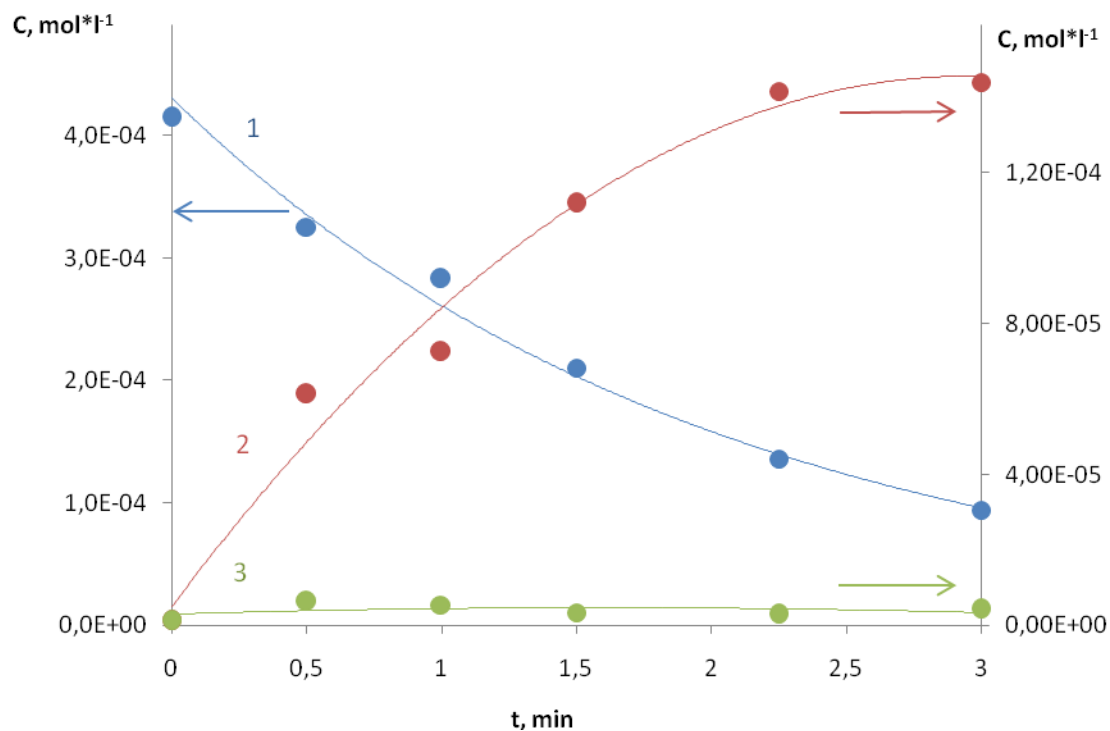


Рис. 6. The kinetics of the photolysis (DRK-120) 2-azidobenzoic acid (1) $C=4.2 \times 10^{-4} \text{ mol} \times \text{l}^{-1}$ and formation 2,1-benzisoxazol-3(1H)-one (2) and 2-aminobenzoic acid (3).

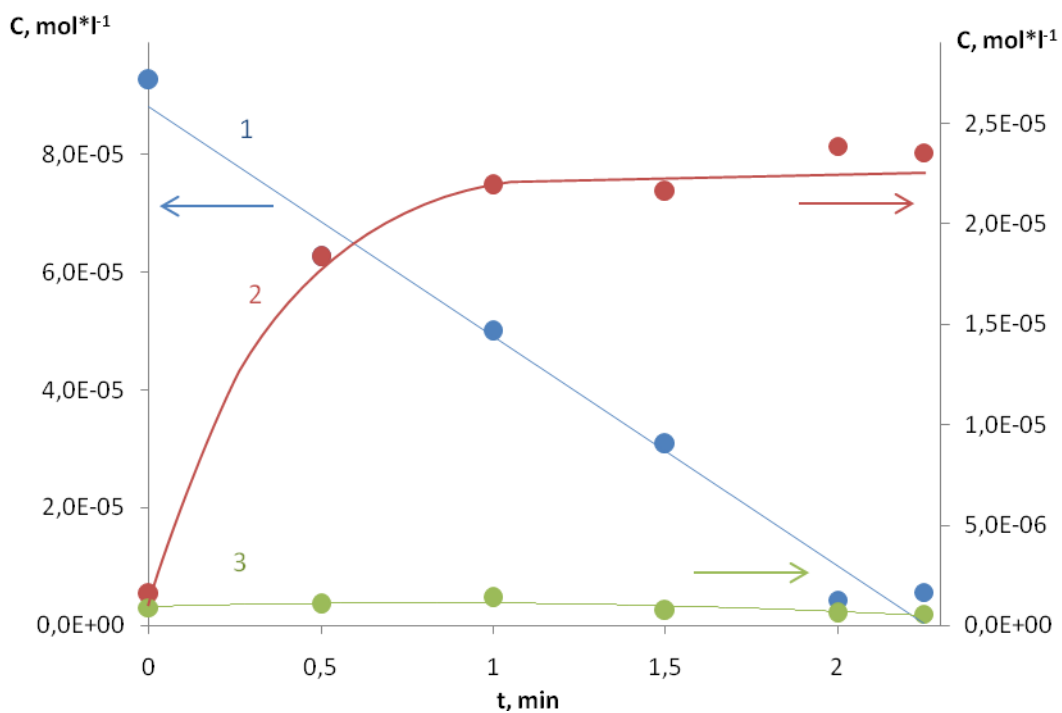


Рис. 7. The kinetics of the photolysis (DRK-120) 2-azidobenzoic acid (1) $C=9.3 \times 10^{-5} \text{ mol} \cdot \text{l}^{-1}$ and formation 2,1-benzisoxazol-3(1H)-one (2) and 2-aminobenzoic acid (3).

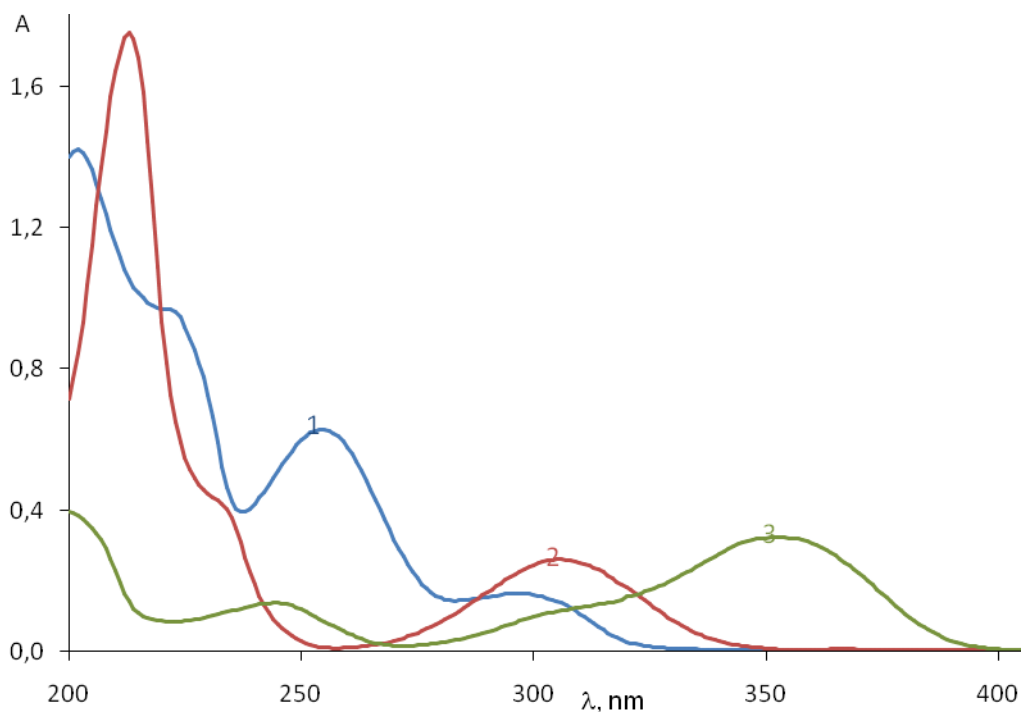


Рис. 8. UV-Vis Absorption Spectra of 2-azidobenzoic acid (1), 2,1-benzisoxazol-3(1H)-one (2) and 2-aminobenzoic acid (3) in acetonitrile.

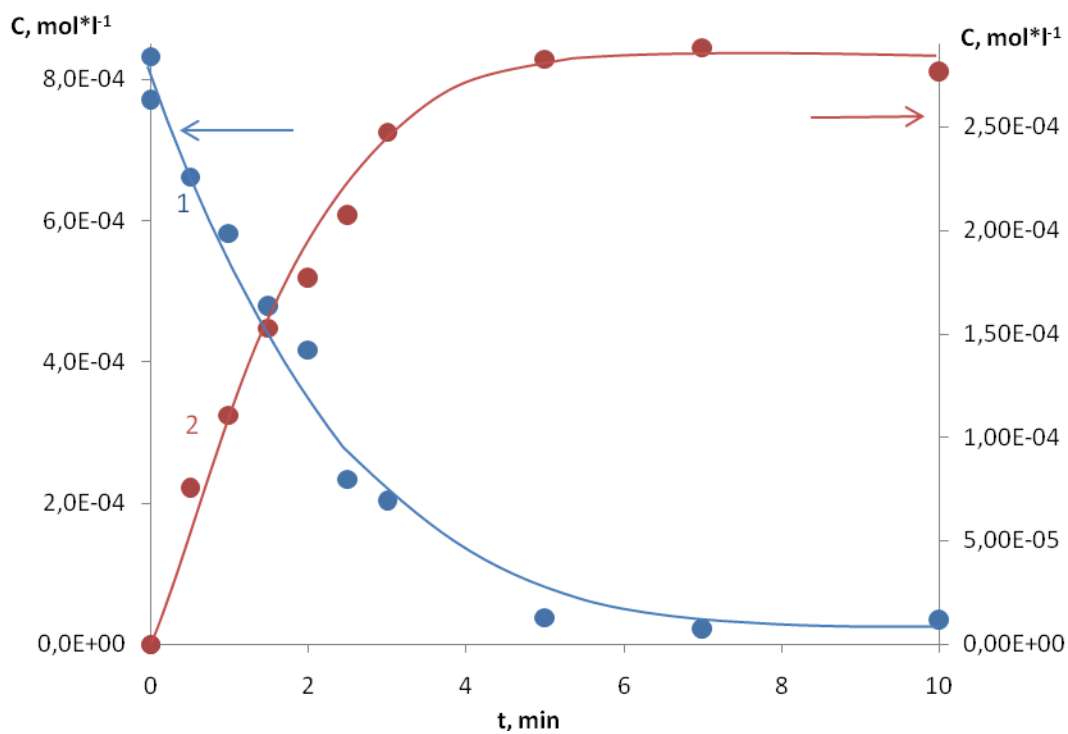


Рис. 9. The kinetics of the photolysis (BUF-30) 2-azidobezoic acid (1) $C=7.7 \times 10^{-4} \text{ mol} \times \text{l}^{-1}$ and formation 2,1-benzisoxazol-3(1H)-one (2)

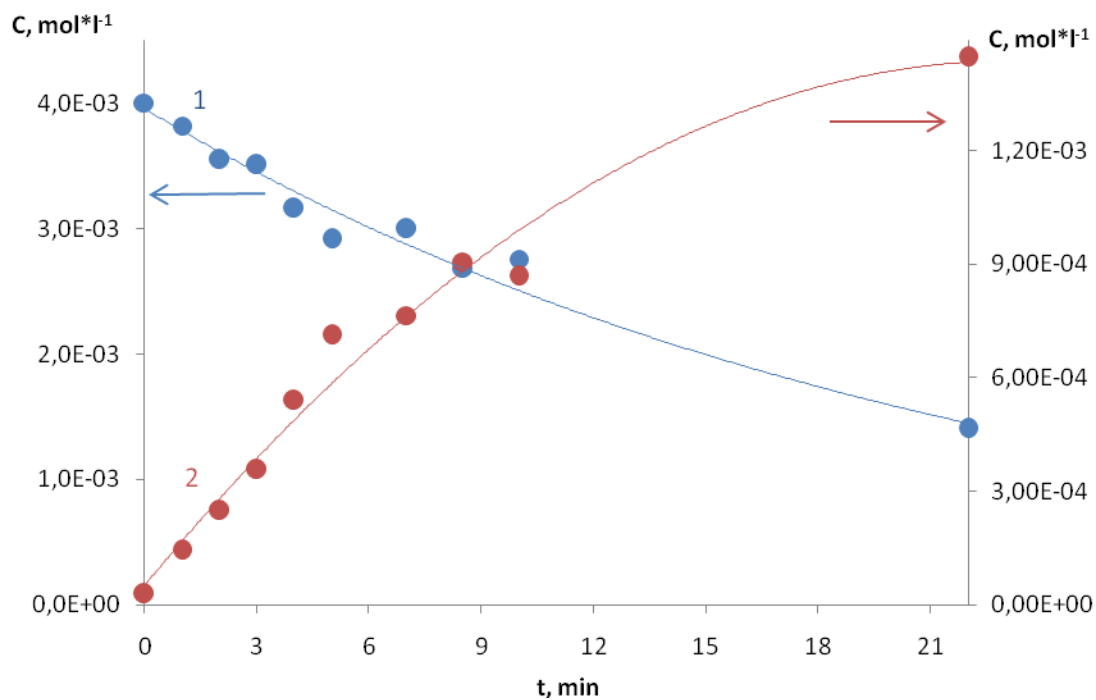


Рис. 10. The kinetics of the photolysis (BUF-30) 2-azidobezoic acid (1) $C=4.0 \times 10^{-3} \text{ mol} \times \text{l}^{-1}$ and formation 2,1-benzisoxazol-3(1H)-one (2)

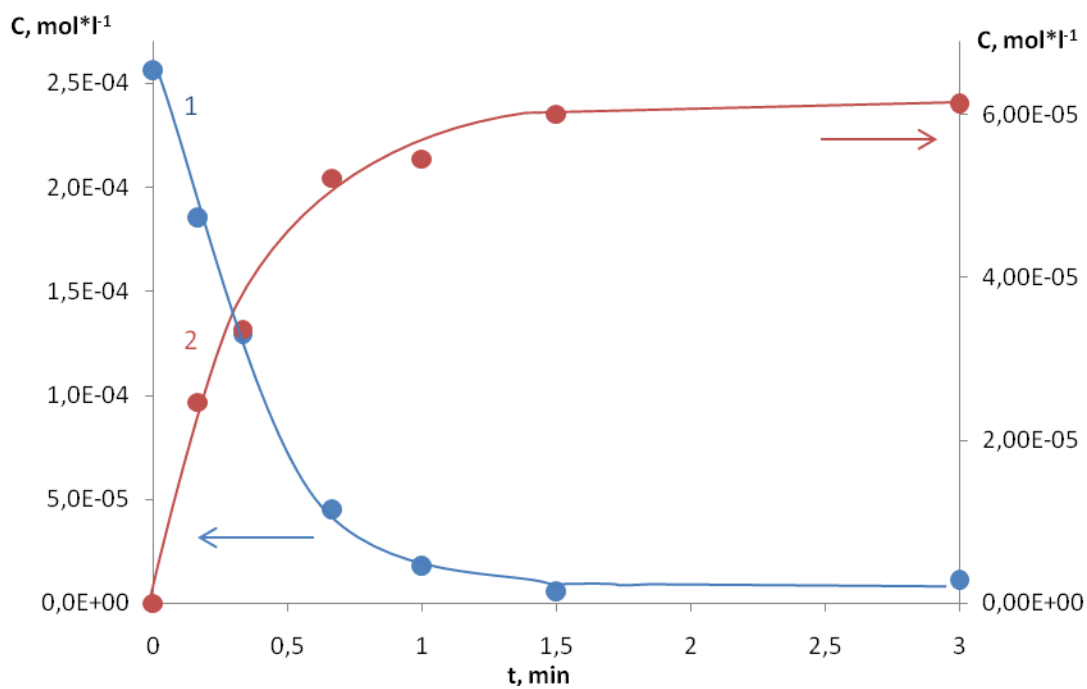


Рис. 11. The kinetics of the photolysis (BUF-30) 2-azidobezoic acid (1) $C=2.6 \times 10^{-4} \text{ mol} \times \text{l}^{-1}$ and formation 2,1-benzisoxazol-3(1H)-one (2)

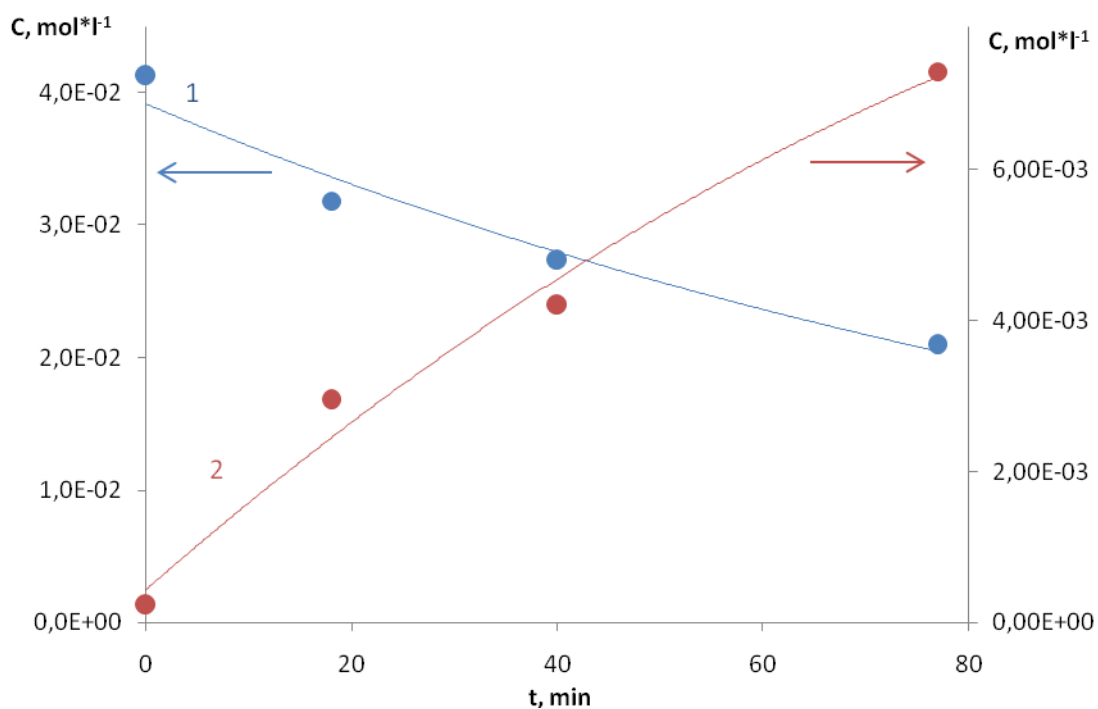


Рис. 12. The kinetics of the photolysis (BUF-30) 2-azidobezoic acid (1) $C=4.1 \times 10^{-2} \text{ mol} \times \text{l}^{-1}$ and formation 2,1-benzisoxazol-3(1H)-one (2)