

## SYNTHESIS AND PROPERTIES OF AZIDOSTYRYLQUINOLINES

M. F. Budyka, N. V. Biktimirova, and T. N. Gavrishova

*Isomeric azidostyrylquinolines with a 4-azidostyryl group in position 2 or 4 of the quinoline ring have been synthesized. In the neutral form the azidostyrylquinolines absorb in the near UV but the protonated species absorb in the short wavelength region of the visible spectrum. In both forms the azides are light-sensitive and decompose under the influence of light with a quantum yield close to 1.*

**Keywords:** aromatic azide, styrylquinoline, light sensitivity, absorption spectrum, photoaffinity probe, photodissociation.

Investigation of a series of heteroaromatic azides including 4-azidopyridine, 4-azidoquinoline, and 9-azidoacridine has shown that these azides are photoactive, i.e. decompose with a quantum yield  $\phi > 0.1$  both as the neutral and protonated forms [1-3]. The absorption bands of the azides studied are found in the UV region of the spectrum and are shifted bathochromically upon protonation of the endocyclic nitrogen atom in the heterocycle, the spectrum of the 9-azidoacridine hydrochloride even entering the visible region.

The latter property is of practical interest, e.g. when using the azides as photoaffinity probes in biochemistry and molecular biology [4, 5]. In order that the photoaffinity modification of the investigated biomacromolecule does not lead to photodestruction it is desirable to irradiate the system with mild, long wavelength UV (300-400 nm) or even better visible light. For this purpose the azide has to possess absorption bands in this region of the spectrum. 9-Azidoacridine is sensitive to UV light in the indicated region and its cation to visible light in the region 400-470 nm. However, the acridine cation is readily hydrolyzed even in the presence of traces of water to give acridone and this hinders the practical application of the 9-azidoacridine.

9-(4-Azidophenyl)acridine is more stable towards hydrolysis with spectroscopic properties for the neutral and protonated forms similar to 9-azidoacridine but, in contrast to the latter, the 9-(4-azidophenyl)-acridine loses photoactivity in the cationic form, the quantum yield of its photodissociation falling to a  $\phi$  value of  $< 0.01$  [6, 7].

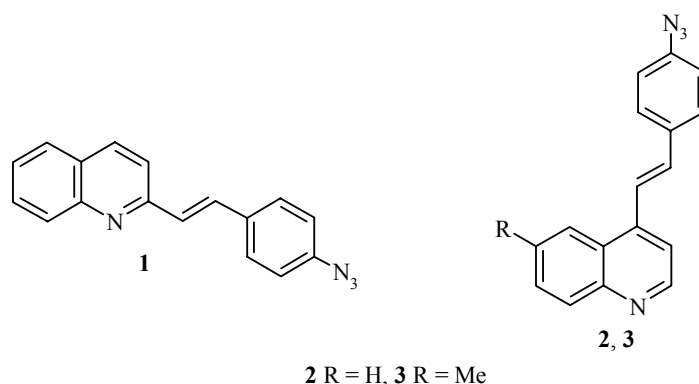
In order to obtain azides sensitive to long wavelength light it seemed promising to use a route based on the bathochromic shift of the absorption spectrum of the heteroaromatic azide on crossing from the neutral form to the cation. Moreover, it was necessary that protonation (or alkylation) at the heterocyclic nitrogen atom of the azide should retain a high quantum yield ( $\phi > 0.1$ ).

Based on a theoretical investigation of the dependence of the photochemical activity of heteroaromatic azides on the size of the heteroaromatic nucleus in a series from pyridine to azahexacene it was proposed that azides with a  $\pi$ -system size up to 18 electrons should give high ( $\phi > 0.1$ ) quantum yields of photodissociation both in the neutral and the cation forms [8]. Styrylquinolines have an overall size of the conjugated  $\pi$ -system of 18 electrons and it is known that the absorption spectrum of the protonated form for these compounds is shifted to the visible region (e.g. the long wavelength absorption maximum of 2-styrylquinoline is shifted from 353 to

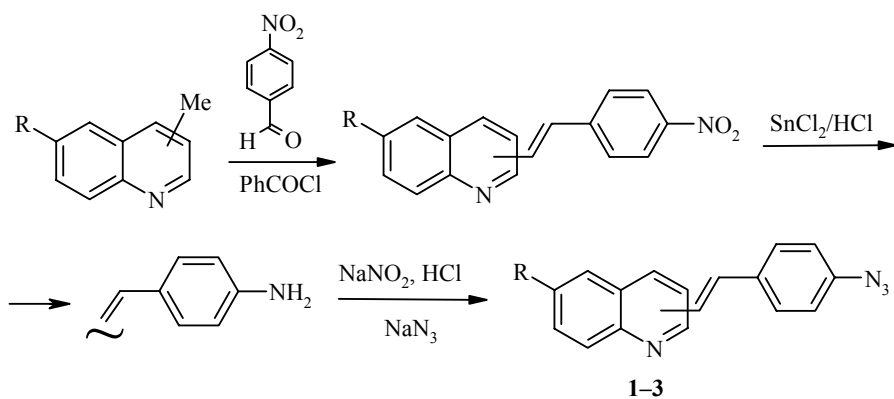
---

Institute of Problems of Chemical Physics, Russian Academy of Sciences, Chernogolovka 142432, Moscow Region; e-mail: budyka@icp.ac.ru. Translated from *Khimiya Geterotsiklicheskikh Soedinenii*, No. 4, pp. 555-561, April, 2007. Original article submitted September 12, 2006.

380 nm and 4-styrylquinoline from 330 to 383 nm [9]). In this connection it was interesting to study the spectroscopic and photochemical properties of azidostyrylquinolines in the neutral and the cation forms. With this in mind we have now synthesized 2-(4-azidostyryl)quinoline (**1**) and 4-(4-azidostyryl)quinoline (**2**) together with its 6-methyl derivative **3**.



Attempts to synthesize the indicated compound by condensation of methylquinolines with 4-azidobenzaldehyde gave the corresponding amines, evidently as a result of a thermal decomposition of the azide at the temperature needed for the condensation reaction. Hence the synthesis was carried out in several stages with the introduction of the azido group at the final stage. Initial condensation of the corresponding methylquinoline with 4-nitrobenzaldehyde gave the nitrostyrylquinoline which was reduced by stannous chloride to the amine. Diazotization of the amine with subsequent work up using sodium azide gave the azidostyrylquinoline.



The condensation method used in the first stage of the synthesis gives a mixture of *cis* and *trans* isomers with the latter predominating. By TLC the admixture of the *cis* isomer appears as a small spot appearing beyond the main *trans* isomer. The isomers were separated by crystallization. In subsequent reactions the *trans* isomer of the nitrostyrylquinolines was introduced hence the final azides have a *trans* configured styryl fragment. This is shown by the <sup>1</sup>H NMR spectra in which the olefin proton doublets for the styryl fragment appear at 7.7 and 7.3 ppm with a vicinal coupling of 16.5 Hz.

The appearance of out of plane deformation vibrations for the olefin group in the range 960-970 cm<sup>-1</sup> in the IR spectra confirms the *trans* configuration of the double bond. In addition the IR spectra also show strong bands for the asymmetrical stretching vibration of the azide group at 2120 and symmetrical vibration at 1290 cm<sup>-1</sup>.

Azides **1-3** have a strong absorption band in the UV region at 320-390 nm which are a superposition of bands for the  $\pi$ - $\pi^*$ - and  $n$ - $\pi^*$ -transitions. Comparison with the spectra of the unsubstituted styrylquinolines shows that the introduction of an azide group leads to a small bathochromic shift in the spectra and for the long wavelength absorption of azide **2** this shift is 19 nm. The shift in the long wavelength absorption band is an indirect pointer to the participation of the azido group electrons into the electron transition involving the long wavelength absorption band and the presence of such a shift can be viewed as the reason for the photodissociation of the azide when irradiated at this band. None the less the presence of the shift is not an essential condition for photoactivity in the azide. This effect (the shift of the long wavelength absorption) is observed for heterocyclic azidochalcones [10] but is absent in 9-(4-azidophenyl)acridine. Despite this difference both the former and the latter are efficiently decomposed upon irradiation at the long wavelength absorption band region with a quantum yield close to 1.

With the protonation of the azidostyrylquinolines a bathochromic shift of the absorption bands is observed, particularly marked for the long wavelength absorption bands (e.g. for azide **2** it is shifted by 58 nm). As a result the maximum of this band of the hydrochlorides is already found in the violet region of the spectrum and the long wavelength taper of the band extends to 500 nm, i.e. into a significant part of the visible spectrum which is a necessary prerequisite for the light sensitivity of the azide in this region.

It was interesting to compare the absorption spectra of the azidostyrylquinolines with the spectra of the corresponding nitro- and aminostyrylquinolines since the latter are possible photolysis products of the azides and the relationship of the absorption bands for these compounds determines the spectroscopic changes observed when carrying out the photolysis reactions. Figure 1 shows the dependence of the long wavelength band maximum position for the styrylquinolines and their hydrochlorides on resonance  $\sigma^+$ -constant [11] for the substituent in the *para*-position of the styryl fragment and it was evident that, for the neutral form, the introduction of both acceptor ( $\text{NO}_2$ ) and donor ( $\text{N}_3$ ,  $\text{NH}_2$ ) substituents into the styrylquinoline molecule leads to a bathochromic shift of the long wavelength absorption (curves 1 and 3). Both types of substituent prove equal in the strength of their effect as indicated by the virtually identical graphical slopes from the null point.

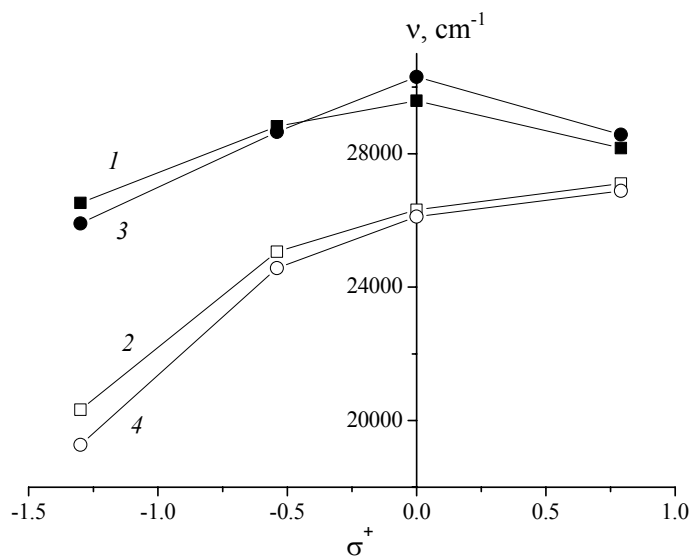


Fig 1. Correlation of the long wavelength absorption band with the substituent  $\sigma^+$ -constants: 1 – 2-styrylquinolines and 2 – their hydrochlorides, 3 – 4-styrylquinolines and 4 – their hydrochlorides. Data for the unsubstituted styrylquinolines is taken from [9].

In the cationic form acceptor substituents show a weak hypsochromic effect and donors a fairly strong bathochromic effect (curves 2 and 4). Hence in the 4-styrylquinoline hydrochloride the introduction of a nitro group into the *para* position of the styryl fragment causes a hypsochromic shift of 11 nm but an amino group to an order greater bathochromic shift of 136 nm. The protonated aminostyrylquinolines are practically hemicyanine dyes [12], their solutions being crimson colored.

The difference in effect of the substituents on the position of the long wavelength absorption can be explained as follows. In the unsymmetrical diarylethylenes of general formula A-CH=CH-D to which the investigated compounds belong this band is associated with an intramolecular charge transfer between the two aromatic rings. In the unsubstituted styrylquinoline the quinoline ring is evidently the acceptor of electrons and the benzene is the donor and the introduction into the latter of  $\pi$ -donor substituents increases the intramolecular charge transfer leading to the bathochromic shift in the long wavelength absorption band. The nitro group is a more powerful acceptor than the quinoline ring and its behavior changes the direction of charge transfer between the two aromatic substituents on the double bond and this also leads to a bathochromic shift in the long wavelength absorption band.

Protonation markedly increases the acceptor property of the quinoline ring and this remains the acceptor group and the benzene ring the donor for all of the styrylquinolines studied. Hence  $\pi$ -donor substituents in the benzene ring increase the intramolecular charge transfer leading to a bathochromic shift of the band but a nitro group in the donor fragment affects the charge transfer oppositely leading to a hypsochromic shift in the long wavelength absorption band.

Study of the photochemical properties of the azidostyrylquinolines has shown that they are photoactive both in the neutral and protonated forms. The quantum yields of photodissociation of the azides **1-3** when irradiated with 365 nm wavelength light were 0.88, 0.91, and 0.96 for the neutral forms and 0.78, 0.65, and 0.80 for the corresponding hydrochlorides. In contrast to the photolysis of simple heterocyclic azides a more complex kinetic dependence is seen for the photolysis of the azidostyrylquinolines and this is evidently linked to the presence in the styryl fragment of their molecules of a second photoactive group (the central double bond) which can undergo a photoisomerization reaction. As a result the products of photodissociation of the azido group take part in a further photochemical reaction. More detailed features of the kinetics of the photochemical reactions of the azidostyrylquinolines will be discussed in a later publication.

Hence the synthesized isomeric azidostyrylquinolines have spectroscopic properties close to those of 9-azidoacridine and 9-(4-azidophenyl)acridine: the neutral forms of the compounds absorb light in the near UV region and the protonated in the blue-violet part of the spectrum. However, in the protonated form the newly synthesized azides are stable to hydrolysis (in contrast to 9-azidoacridine) and decompose under the action of light with high quantum yield (in contrast to 9-(4-azidophenyl)acridine). With respect to the size of the aromatic  $\pi$ -system (18 electrons) the azidostyrylquinolines occupy a position intermediate between 9-azidoacridine (14 electrons) and 9-(4-azidophenyl)acridine (20 electrons). The experimental results obtained confirm the theoretical conclusions concerning the photochemical activity of heteroaromatic azides with an 18 electron size  $\pi$ -system in both the neutral and cationic forms.

## EXPERIMENTAL

Electronic absorption spectra were measured on a Specord M-40 spectrophotometer. IR spectra were taken on a Spectrum BX-2 Fourier transform spectrometer for KBr tablets.  $^1\text{H}$  NMR spectra were recorded on Varian VXR-400 and Bruker DPX 200 (400 and 200 MHz respectively) spectrometers in  $\text{CDCl}_3$ ,  $(\text{CD}_3)_2\text{CO}$ , or  $\text{DMSO-d}_6$  with TMS as internal standard. Chromatomass spectra were obtained on an HP5890 instrument (electron impact, 70 eV ionization) using a 5989x-G detector. Electrospray (ES) mass spectra were obtained using an original time of flight mass spectrometer with orthogonal introduction of ions [13] with recording of

the positive ions which represent the protonated molecules of the analyzed compounds. Monitoring of the course of the reaction and the purity of the compounds obtained was carried out by TLC (ALUGRAM SIL G/UV<sub>254</sub>, acetone-hexane, spots revealed using UV light or iodine vapor). Preparative chromatography was carried out on Silpearl silica gel columns. The solvents were purified by standard methods [14]. Commercial aromatic aldehydes and methylquinolines were used without further purification. The azidostyrylquinoline hydrochlorides were prepared *in situ* by the addition of conc. HCl to a solution of the azide. A DRS-500 mercury lamp was used as the UV source and the spectroscopic line 365 nm was separated using UFS-6 and BS-7 filters. The photochemical study was carried out at room temperature in air saturated solvents, concentration of azide  $(2-20) \times 10^{-5}$  molar, quartz cuvet with optical length  $l = 1$  cm, and activating light intensity  $(5-50) \times 10^{-10}$  Es·cm<sup>-2</sup>·s<sup>-1</sup> (using a PP-1 detector cavity or ferroxalate actinometer).

**Nitrostyrylquinolines (General Method).** Benzoyl chloride (1.45 g, 0.01 mol) was added to a solution of the corresponding methylquinoline (0.01 mol) in anhydrous DMF (22 ml), stirred for 20 min at 20°C, 4-nitrobenzaldehyde (0.01 mol) was added, and the product refluxed for 5 h. The precipitate formed after cooling the reaction mixture was filtered, washed with water (2×5 ml) and then aqueous acetone (2×2 ml), and recrystallized from a mixture of chloroform and ethanol. The spectroscopic features and physicochemical constants for the nitrostyrylquinolines agree with those given in the literature.

**2-(4-Nitro-*trans*-styryl)quinoline**, yield 65%, yellow crystals, mp 163-164°C (mp 166-168°C [15]).

**4-(4-Nitro-*trans*-styryl)quinoline**, yield 62%, yellow crystals, mp 220-222°C (mp 224°C [16]).

**6-Methyl-4-(4-nitro-*trans*-styryl)-quinoline**, yield 65%, yellow crystals, mp 210-212°C. Mass spectrum, (EI, 70 eV),  $m/z$  ( $I_{rel}$ , %): 290 [M]<sup>+</sup> (100). IR spectrum,  $\nu$ , cm<sup>-1</sup>: 1509, 1338 (NO<sub>2</sub>), 970 (CH=CH). <sup>1</sup>H NMR spectrum (200 MHz, CDCl<sub>3</sub>),  $\delta$ , ppm: 2.30 (3H, s, CH<sub>3</sub>); 6.50-8.60 (11H, m, Ar). Found, %: C 74.51; H 4.79. C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>. Calculated, %: C 74.47; H 4.86.

**Aminostyrylquinolines (General Method).** SnCl<sub>2</sub> (0.01 mol) was added to a solution of the corresponding nitrostyrylquinoline (0.001 mol) in HCl (20 ml), refluxed for 2h, cooled to room temperature, and the precipitate was filtered and dried in air. The hydrochloride yield was 75-85%. The aminostyrylquinoline hydrochloride was mixed with dry NaHCO<sub>3</sub>, water (5 ml) was added, stirred, and the precipitate filtered off. The aminostyrylquinolines obtained were purified by column chromatography using the system hexane-acetone.

**2-(4-Amino-*trans*-styryl)quinoline**, yield 75%, red crystals, mp 156-157°C (aqueous alcohol) (mp 154°C [17]).

**4-(4-Amino-*trans*-styryl)quinoline**, yield 85%, red crystals, mp 147-149°C (mp 152-154°C [18]).

**4-(4-Amino-*trans*-styryl)-6-methylquinoline**, yield 83%, red crystals, mp 146-148°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 3400 (NH<sub>2</sub>). Mass spectrum, (EI, 70 eV),  $m/z$  ( $I_{rel}$ , %): 260 [M]<sup>+</sup> (100). <sup>1</sup>H NMR spectrum (200 MHz, DMSO-d<sub>6</sub>),  $\delta$ , ppm: 2.60 (3H, s, CH<sub>3</sub>); 5.50 (2H, br. s, NH<sub>2</sub>); 6.30-6.80 (3H, m, Ar); 7.50-7.90 (6H, m, Ar, CH=CH); 8.30 (1H, s, Ar); 8.72 (1H, br. s, Ar). Found, %: C 82.91; H 6.07. C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>. Calculated, %: C 83.05; H 6.19.

**Azidostyrylquinolines (General Method).** A solution of the corresponding aminostyrylquinoline (1 mmol) in 10% HCl (5 ml) was cooled to 0°C and diazotized with a solution of NaNO<sub>2</sub> (1 mmol) in water (2 ml). The solution was filtered, cooled to 5°C, and a solution of NaN<sub>3</sub> (1 mmol) in water (2 ml) was added with stirring. After 1 h the reaction mixture was neutralized with saturated Na<sub>2</sub>CO<sub>3</sub> solution to pH 8. The precipitate was filtered off and recrystallized from petroleum ether. The compounds are yellow crystalline materials decomposing in light.

**2-(4-Azido-*trans*-styryl)quinoline (1)**, yield 80%, yellow crystals, mp 110-112°C. Mass spectrum (ES). Found:  $m/z$  273.098 [M+H]<sup>+</sup>. C<sub>17</sub>H<sub>12</sub>N<sub>4</sub>. Calculated: M 272.106. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 2120 (N<sub>3</sub>), 1290 (N<sub>3</sub>), 1596, 1578, 1400 (arom.), 1630 and 967 (CH=CH), 831 (*p*-C<sub>6</sub>H<sub>4</sub>). <sup>1</sup>H NMR spectrum (400 MHz, CDCl<sub>3</sub>),  $\delta$ , ppm ( $J$ , Hz): 8.14 (1H, d,  $J = 8.5$ , quinoline); 8.08 (1H, d,  $J = 8.5$ , quinoline); 7.80 (1H, d,  $J = 9$ , quinoline); 7.72 (1H, t, quinoline); 7.66 (3H, m, quinoline, C<sub>6</sub>H<sub>4</sub>); 7.65 (1H, d,  $J = 16.5$ , -CH=); 7.51 (1H, t, quinoline); 7.36 (1H, d,  $J = 16.5$ , -CH=); 7.01 (2H, d,  $J = 8.5$ , C<sub>6</sub>H<sub>4</sub>). UV spectrum (EtOH),  $\lambda_{max}$ , nm ( $\epsilon$ ): 296 (16700), 347 (29140), 359 (27600).

**4-(4-Azido-*trans*-styryl)quinoline (2)**, yield 86%, yellow crystals, mp 85-87°C. Mass spectrum (ES). Found:  $m/z$  273.102  $[M+H]^+$ .  $C_{17}H_{12}N_4$ . Calculated: M 272.106. IR spectrum,  $\nu$ ,  $cm^{-1}$ : 2116, 2087 ( $N_3$ ), 1289 ( $N_3$ ), 1598, 1578, 1508 (arom.), 1629 and 961 (CH=CH), 831 (*p*- $C_6H_4$ ).  $^1H$  NMR spectrum (200 MHz,  $(CD_3)_2CO$ ),  $\delta$ , ppm ( $J$ , Hz): 8.55 (1H, d,  $J = 8.5$ , quinoline); 8.1 (1H, d,  $J = 8.5$ , quinoline); 7.2-7.9 (8H, m, quinoline,  $C_6H_4$ , CH=CH); 6.95 (2H, d,  $J = 8.5$ ,  $C_6H_4$ ). UV spectrum (EtOH),  $\lambda_{max}$ , nm ( $\epsilon$ ): 232 (22000), 281 (8830), 349 (24470).

**4-(4-Azido-*trans*-styryl)-6-methylquinoline (3)**, yield 80%, yellow crystals, mp 132-134°C. Mass spectrum (ES). Found:  $m/z$  287.110  $[M+H]^+$ .  $C_{18}H_{14}N_4$ . Calculated: M 286.122. IR spectrum,  $\nu$ ,  $cm^{-1}$ : 2127, 2091 ( $N_3$ ), 1303 ( $N_3$ ), 1598, 1577, 1572, 1506 (arom.), 1631, 975, and 964 (CH=CH), 1366 ( $CH_3$ ), 840 (*p*- $C_6H_4$ ).  $^1H$  NMR spectrum (400 MHz,  $CDCl_3$ ),  $\delta$ , ppm ( $J$ , Hz): 8.85 (1H, m,  $J = 8.5$ , quinoline); 8.04 (1H, d,  $J = 8.5$ , quinoline), 7.95 (1H, s, quinoline); 7.77 (1H, d,  $J = 16.5$ , CH=); 7.64 (2H, d,  $J = 8.5$ ,  $C_6H_4$ ); 7.57 (2H, m, quinoline), 7.29 (1H, d,  $J = 16.5$ , -CH=); 7.10 (2H, d,  $J = 8.5$ ,  $C_6H_4$ ); 2.72 (3H, s,  $CH_3$ ). UV spectrum (EtOH),  $\lambda_{max}$ , nm ( $\epsilon$ ): 233 (18300), 283 (8050), 346 (19800).

The authors thank V. I. Kozlovski for taking the electrospray mass spectra. The work was carried out with the financial support of the Russian Fund for Fundamental Research (grant 03-03-32116).

## REFERENCES

1. M. F. Budyka, N. V. Biktimirova, T. N. Gavrishova, and O. D. Laukhina, *Zh. Fiz. Khim.*, **79**, 1876 (2005).
2. M. F. Budyka, N. V. Biktimirova, T. N. Gavrishova, O. D. Laukhina, and D. B. Zemtsov, *J. Photochem. A: Chem.*, **173**, 70 (2005).
3. M. F. Budyka, N. V. Biktimirova, and T. N. Gavrishova, *Khimiya Vysokikh Energii*, **40**, 208 (2006).
4. R. S. Pandurangi, R. R. Kuntz, and W. A. Volkert, *Appl. Radiat. Isotop.*, **46**, 233 (1995).
5. M. J. Bouchet and M. Goeldner, *Photochem. and Photobiol.*, **65**, 195 (1997).
6. M. F. Budyka, M. M. Kantor, and R. M. Fatkulbayanov, *Khim. Geterotsykl. Soedin.* 1504 (1997). [*Chem. Heterocycl. Comp.*, **33**, 1301 (1997)].
7. M. F. Budyka, N. V. Biktimirova, T. N. Gavrishova, and O. D. Laukhina, *Izv. Akad. Nauk, Ser. Khim.*, 2655 (2005).
8. M. F. Budyka and I. V. Oshkin, *J. Mol. Struct. Theochem.*, **759**, 137 (2006).
9. G. Galiazzo, P. Bortolus, and G. Gennari, *Gazz. Chim. Ital.*, **120**, 581 (1990).
10. M. F. Budyka, M. M. Kantor, and M. F. Alfimov, *Khim. Geterotsykl. Soedin.* 1340 (1991). [*Chem. Heterocycl. Comp.*, **27**, 1072 (1991)].
11. M. E. C. Biffin, J. Miller, and D. B. Paul, in S. Patai (editor), *The Chemistry of the Azido Group*, Wiley, New York (1971), p 203.
12. P. Gordon and P. Gregory, *The Organic Chemistry of Dyes* [Russian translation], Mir, Moscow (1987).
13. A. F. Dodonov, V. I. Kozlovski, I. V. Soulimenkov, V. V. Raznikov, A. V. Loboda, Z. Zhen, T. Horwath, and H. Wollnik, *Eur. J. Mass Spectrom.*, **6**, 481 (2000).
14. A. A. Potekhin (editor), *Handbook of Properties of Organic Compounds* [in Russian], Khimiya, Moscow (1984), 520 pp.
15. S. L. Wang and T. I. Ho, *J. Photochem. Photobiol. A: Chem.*, **135**, 119 (2000).
16. G. Schulte-Frohlinde, *Z. Naturforsch. B. Anorg. Chem. Org. Chem.*, **34**, 1556 (1979).
17. E. Noeltling and E. Witte, *Chem. Ber.*, **39**, 2749 (1906).
18. C. Bahner, *J. Org. Chem.*, **23**, 1960 (1958).