

Nüket Öcal*, Çigdem Yolaçan and Şeniz Kaban

Yildiz Technical University, Faculty of Art and Sciences, Department of Chemistry, 80270 Şişli, Istanbul, Turkey

Leonor Vargas M. and Vladimir Kouznetsov*

Laboratory of Fine Organic Synthesis, School of Chemistry, Industrial University of Santander, A. A. 678, Bucaramanga, Colombia

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The Schiff bases derived from quinoline-8-carbaldehyde and substituted aromatic amines were used in the synthesis of C-8 substituted quinolines. 3-Aryl-2-(8-quinolinyl)-4-thiazolidinones were prepared from obtained aldimines by means of the cyclocondensation of mercapto acids. A series of 4-*N*-arylamino-4-(8-quinolinyl)-1-butenes was synthesized through the addition of the Grignard reagent (allylmagnesium bromide) to the double bond C=N of these aldimines. The structure of the prepared compounds was established on the basis of their elemental analyses and spectral data.

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Introduction.

Diverse substituted quinolines have been synthesized for a wide range of industrial, pharmaceutical, and biological purposes [1,2]. Likewise, 4-thiazolidinones have shown many useful applications. Generally, these compounds have been shown to exhibit fungicidal, pesticidal, herbicidal, antitubercular, local anaesthetic and possible antimycotic properties. They may also act as potential antiradiation and chemotherapeutic agents [3-6]. The biological significance of this kind of compounds urged us to study the synthesis of some 3-aryl-2-(8-quinolinyl)-4-thiazolidinones and 4-*N*-arylamino-4-(8-quinolinyl)-1-butenes due to their possible biological activities. Moreover, these latter homoallylamine derivatives are of particular interest due to the rich and diverse chemistry of allyl and arylamino groups. In this paper, we wish to describe the synthesis of a series of new C-8 substituted quinolines.

Results and Discussion.

For a long time imines have been used successfully in the synthesis of nitrogen containing heterocycles [7]. As part our ongoing research program aiming at the search of bioactive quinolines, we used Schiff bases **1-4**. These azomethines were obtained by the reaction of quinoline-8-carbaldehyde [8] with substituted aromatic amines such as *p*-anisidine, *p*-toluidine, 2,4-dimethylaniline and *p*-chloroaniline in refluxing dry ethanol or dry benzene. The obtained aldimines **3** and **4** are new compounds.

The new 3-aryl-2-(8-quinolinyl)-4-thiazolidinones **5-12** were prepared by refluxing equimolar amounts of the imines **1-4** and thioglycolic or thiolactic acids in dry benzene in good yields (Scheme 1, Table 1).

The ¹H nmr spectra of **5**, **7**, **9** and **11** displayed doublets at δ 3.44-4.06 due to the methylene protons H_A and H_B at C-5 in addition to other signals. The ¹H nmr spectra of the compounds **6**, **8** and **12** showed two doublets at δ 1.64-1.75 from

Scheme 1

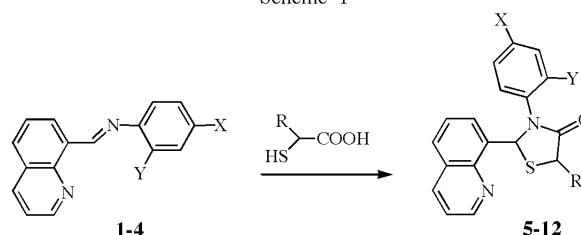


Table 1

3-Aryl-2-(8-quinolinyl)-4-thiazolidinones **5-12**

Compound No	R	X	Y	%
5	H	OCH ₃	H	61
6	CH ₃	OCH ₃	H	94
7	H	CH ₃	H	57
8	CH ₃	CH ₃	H	78
9	H	CH ₃	CH ₃	42
10	CH ₃	CH ₃	CH ₃	32
11	H	Cl	H	62
12	CH ₃	Cl	H	57

the methyl protons and two quartets at δ 3.46-4.20 from a proton at C-5 due to stereoisomerism at the chiral carbon atom.

The ir spectra of the thiazolidinones **5-12**, show the characteristic C=O stretching appearing in the region of 1680-1660 cm⁻¹. The strong sharp band at 1620-1610 cm⁻¹ corresponding to the starting azomethines was absent, which was the most characteristic evidence of the cyclocondensation.

There has been considerable recent interest in the study of the addition of allylmetal compounds to aldimines to give diverse homoallylic amines with different heterocyclic substituents. Thus, in continuation of our research program [9-11], we performed the C-allylation reaction on the Schiff bases **1-4**. The treatment of the aldimines with allylmagnesium bromide, prepared from magnesium and

allyl bromide in dry ether, gave the respective quinolines **13-16** (Scheme 2, Table 2). These quinolines are considered as versatile synthons for the construction of nitrogen containing heterocycles.

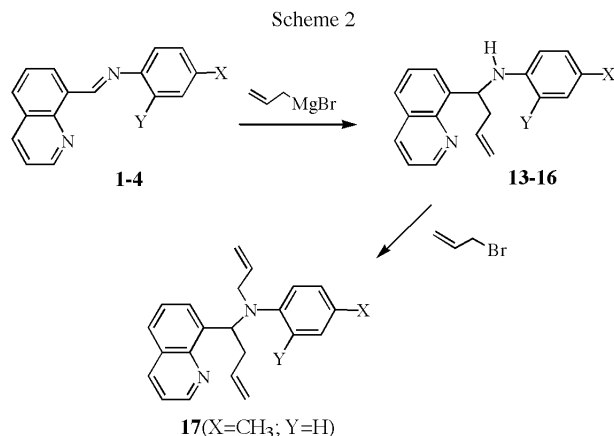


Table 2
4-*N*-Arylamino-4-(8-quinolinyl)-1-butenes **13-16**

Compound	X	Y	%
13	OCH ₃	H	83
14	CH ₃	H	87
15	CH ₃	CH ₃	94
16	Cl	H	96

After a standard work-up, this reaction furnished heterocyclic derivatives **13-16** as viscous oils in high yields. The products obtained were purified by means of a short chromatographic column (alumina). In the ¹H nmr spectra of the quinolines **13-16**, the protons of butene chain gave rise very characteristic groups of signals. The doublet of doublet from a proton at C-4 was observed at δ 2.05 ppm. The two multiplets from the 3-CH₂ (H_A and H_B are diastereotopic) appeared in the region δ 2.71-2.76 and 2.94-3.04 ppm, respectively. At low fields, the olefinic protons exhibit multiplets between δ 5.09-5.20 and δ 5.50-5.84 ppm. The ir spectra of the compounds prepared showed a characteristic band of the amine group in the 3429-3403 cm⁻¹ region.

The *N*-allylation of **14** with allyl bromide in the presence of potassium carbonate in boiling acetone afforded derivative **17** in 72% yield. Its structure was established using ir and nmr spectroscopy. As expected, in its ir spectrum, the band corresponding to the amine group was missing. The *N*-allylic protons were observed as multiplets at δ 3.92-4.00, 5.00-5.10 and 5.90-5.94 ppm (N-CH₂-CH=CH₂).

In summary, we have obtained a new series of potentially bioactive C-8 substituted quinolines with thiazolidine or aminobutene moieties. Their biological activities are under investigation and the results will be published

elsewhere. Also, these quinolines could be used in the synthesis of more complex structures such as the synthesis of leukotriene D4 antagonist analogs; that at the moment is one of our research programs.

EXPERIMENTAL

Melting points were uncorrected and measured in open capillaries with an Electrothermal IA 9100 melting point apparatus. The ir spectra were recorded on either a Philips PU 9714 (compounds **1-12**) or a Perkin Elmer 599B-FT (compounds **13-17**) spectrometer in potassium bromide pellets unless otherwise indicated. The ¹H and ¹³C nmr spectra were determined on either a Varian 200 MHz Gemini (compounds **1-12**) or a Jeol 400 MHz spectrometer (compounds **13-17**) in deuteriochloroform with tetramethylsilane as internal standard. Data are reported as follows: chemical shift (multiplicity, number of protons, coupling constants and group). The ms spectra were obtained using a Shimadzu GS/MS QP 2000 A. Elemental analyses were performed on a Leco CHN-600 analyzer. Solvents and common reagents, obtained from Merck and Aldrich, were reagent grade.

General Procedure for the Reaction of Quinoline-8-carbaldehyde with Anilines.

To quinoline-8-carbaldehyde (1.7g, 10 mmoles) was added *p*-chloroaniline or 2,4-dimethylaniline (10 mmoles) in dry benzene (25 ml) with a small amount of potassium carbonate. The reaction mixture was refluxed for 10 hours. The crystalline solid separated at room temperature and was filtered and recrystallised from ethanol.

8-[*N*-(2,4-Dimethylphenyl)iminomethyl]quinoline (**3**).

This compound was obtained in 73% yield, mp 94°; ir (potassium bromide): ν =CH 3040, ν C=N 1610 cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.11 (s, 3H, CH₃), 2.30 (s, 3H, CH₃), 6.71-8.82 ppm (m, 10H, phenyl and quinoline protons and CH=N).

8-[*N*-(4-Chlorophenyl)iminomethyl]quinoline (**4**).

This compound was obtained in 70% yield, mp 118°; ir (potassium bromide): ν =CH 3040, ν C=N 1605 cm⁻¹; ¹H nmr (deuteriochloroform): δ 7.26-9.93 ppm (m, 11H, phenyl and quinoline protons and CH=N).

General Procedure for Reaction of Aldimines **1-4** with Mercapto Acids.

A mixture of the appropriate aldimine (**1-4**) (10 mmoles) and thioglycolic acid or thiolactic acid (15 mmoles) in dry benzene was refluxed on a water-bath for 15 hours, cooled and poured into water. The organic layer was washed with potassium bicarbonate solution (30 ml, 10%) and then with water, dried with calcium chloride and the benzene was distilled off. The residue gave the appropriate quinoline on crystallization from petroleum ether (40-60°)-EtOH (1:1).

3-(4-Methoxyphenyl)-2-(8-quinolinyl)-4-thiazolidinone (**5**).

This compound was obtained in 61% yield, mp 151°; ir (potassium bromide): ν =CH 3060-2980, ν C=O 1665 cm⁻¹; ¹H nmr (deuteriochloroform): δ 3.69 (s, 3H, OCH₃), 3.78-4.06 (d+d, 2H, 5-CH₂; H_A and H_B), 6.74-8.96 ppm (m, 11H, phenyl and quinoline protons and 2-CH); ¹³C nmr (100 MHz): δ 173.8 (C=O), 116.2-

159.8 (phenyl and quinoline carbons), 62.8 (OCH₃), 57.3 (2-CH), 35.5 ppm (5-CH₂); ms: m/z 336 (molecular ion).

Anal. Calcd. for C₁₉H₁₆N₂O₂S: C, 67.85; H, 4.79; N, 8.32. Found: C, 67.89; H, 4.81; N, 8.34.

5-Methyl-3-(4-methoxyphenyl)-2-(8-quinolinyl)-4-thiazolidinone (**6**).

This compound was obtained in 94% yield, mp 157°; ir (potassium bromide): ν =CH 3040-2980, ν C=O 1665 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.64-1.73 (dd, 6H, 5-CH₃), 3.68-3.70 (s, 6H, OCH₃), 4.13-4.20 (q+q, 2H, A and B, 5-CH), 6.73-8.96 ppm (m, 22H, phenyl and quinoline protons and 2-CH); ms: m/z 350 (molecular ion).

Anal. Calcd. for C₂₀H₁₈N₂O₂S: C, 68.56; H, 5.18; N, 7.99. Found: C, 68.58; H, 5.20; N, 7.93.

3-(4-Methylphenyl)-2-(8-quinolinyl)-4-thiazolidinone (**7**).

This compound was obtained in 57% yield, mp 141°; ir (potassium bromide): ν =CH 3040, ν C=O 1660 cm⁻¹; ¹H NMR (deuteriochloroform): δ 2.23 (s, 3H, CH₃), 3.77-4.05 (d+d, 2H, 5-CH₂; H_A and H_B), 7.03-8.97 ppm (m, 11H, phenyl and quinoline protons and 2-CH); ms: m/z 320 (molecular ion).

Anal. Calcd. for C₁₉H₁₆N₂O₂S: C, 71.24; H, 5.03; N, 8.74. Found: C, 71.26; H, 4.99; N, 8.76.

5-Methyl-3-(4-methylphenyl)-2-(8-quinolinyl)-4-thiazolidinone (**8**).

This compound was obtained in 78% yield, mp 162°; ir (potassium bromide): ν =CH 3040, ν C=O 1665 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.60-1.72 (d+d, 6H, 5-CH₃), 2.01-2.22 (d+d, 6H, CH₃), 3.46-4.20 (q+q, 2H, A and B, 5-CH), 7.00-8.96 ppm (m, 22H, phenyl and quinoline protons and 2-CH); ¹³C nmr (100 MHz): δ 176.6 (C=O), 123.6-151.8 (phenyl and quinoline carbons), 59.8-60.2 (2-CH), 43.4-45.0 (5-CH), 22.88-23.28 (5-CH₃), 19.81 ppm (CH₃); ms: m/z 334 (molecular ion).

Anal. Calcd. for C₂₀H₁₈N₂O₂S: C, 71.80; H, 5.42; N, 8.38. Found: C, 71.82; H, 5.40; N, 8.40.

3-(2,4-Dimethylphenyl)-2-(8-quinolinyl)-4-thiazolidinone (**9**).

This compound was obtained in 42% yield, mp 165°; ir (potassium bromide): ν =CH 3040, ν C=O 1670 cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.20 (s, 3H, CH₃), 2.36 (s, 3H, CH₃), 3.44-3.90 (d+d, 2H, 5-CH₂; H_A and H_B), 6.70-8.92 ppm (m, 10H, phenyl and quinoline protons and 2-CH); ms: m/z 334 (molecular ion).

Anal. Calcd. for C₂₀H₁₈N₂O₂S: C, 71.80; H, 5.42; N, 8.38. Found: C, 71.83; H, 5.44; N, 8.34.

5-Methyl-3-(2,4-dimethylphenyl)-2-(8-quinolinyl)-4-thiazolidinone (**10**).

This compound was obtained in 32% yield, mp 168°; ir (potassium bromide): ν =CH 3040, ν C=O 1665 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.76-1.79 (d, 3H, 5-CH₃), 2.14 (s, 3H, CH₃), 2.33 (s, 3H, CH₃), 4.13-4.23 (q, 1H, 5-CH), 6.72-8.85 ppm (m, 10H, phenyl and quinoline protons and 2-CH); ms: m/z 348 (molecular ion).

Anal. Calcd. for C₂₁H₂₀N₂O₂S: C, 72.40; H, 5.78; N, 8.04. Found: C, 72.45; H, 5.75; N, 8.01.

3-(4-Chlorophenyl)-2-(8-quinolinyl)-4-thiazolidinone (**11**).

This compound was obtained in 62% yield, mp 181°; ir (potassium bromide): ν =CH 3060, ν C=O 1680 cm⁻¹; ¹H nmr

(deuteriochloroform): δ 3.78-4.05 (d+d, 2H, 5-CH₂; H_A and H_B), 7.17-8.98 ppm (m, 11H, phenyl and quinoline protons and 2-CH); ms: m/z 340 (molecular ion).

Anal. Calcd. for C₁₈H₁₃ClN₂O₂S: C, 63.43; H, 3.84; N, 8.21. Found: C, 63.40; H, 3.80; N, 8.26.

5-Methyl-3-(4-chlorophenyl)-2-(8-quinolinyl)-4-thiazolidinone (**12**).

This compound was obtained in 57% yield, mp 157°; ir (potassium bromide): ν =CH 3060, ν C=O 1675 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.64-1.72 (d+d, 6H, CH₃), 4.09-4.20 (q+q, 2H, 5-CH), 7.14-8.98 ppm (m, 22H, phenyl and quinoline protons and 2-CH); ¹³C nmr (100 MHz): δ 176.0 (C=O), 122.1-150.0 (phenyl and quinoline carbons), 60.3 (2-CH), 42.0 (5-CH), 20.0 ppm (CH₃); ms: m/z 354 (molecular ion).

Anal. Calcd. for C₁₉H₁₅ClN₂O₂S: C, 64.31; H, 4.26; N, 7.89. Found: C, 64.36; H, 4.22; N, 7.91.

General Procedure for Reaction of Aldimines 1-4 with Allylmagnesium Bromide.

The appropriate aldimine (**1-4**) (4.06 mmoles) in 40 ml of ether was added slowly to 25 ml of an ether solution of allylmagnesium bromide prepared from 48.8 mmoles of magnesium and 32.5 mmoles of allyl bromide. The mixture was stirred for 4 hours at room temperature and then cooled and treated with saturated ammonium chloride solution. The products were extracted with ether (3 x 10 ml). The organic layer was dried (sodium sulfate) and the residue purified by chromatographic column (alumina). The compounds **13-16** were obtained as brownish oils except compound **15**, which is a brown solid.

4-N-(4-Methoxyphenyl)amino-4-(8-quinolinyl)-1-butene (**13**).

This compound was obtained in 83% yield, oil; ir (neat): ν NH 3403, 1639, ν C=C 1599, 917 cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.08 (dd, J = 7 Hz, 1H, 4-H), 2.71, 2.95 (m, each, 1H, 3-CH₂; H_A and H_B), 3.66 (s, 3H, OCH₃), 5.10-5.13 (m, 2H, =CH₂), 5.43-5.87 (m, 1H, -CH=), 6.58-6.64 (AA'BB'-system, 4H, phenyl protons), 6.97-8.02 ppm (m, 6H, quinoline protons); ¹³C nmr (100 MHz): δ 118.6-154.7 (phenyl and quinoline carbons and =CH), 114.9 (=CH₂); 55.7 (OCH₃), 55.8 (4-CH), 41.7 ppm (3-CH₂); ms: m/z 304 (molecular ion).

Anal. Calcd. for C₂₀H₂₀N₂O: C, 78.95; H, 6.58; N, 9.21. Found: C, 78.90; H, 6.68; N, 9.25.

4-N-(4-Methylphenyl)amino-4-(8-quinolinyl)-1-butene (**14**).

This compound was obtained in 87% yield, oil; ir (neat): ν NH 3412, 1639, ν C=C 1599, 916 cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.06 (dd, J = 7 Hz, 1H, 4-H), 2.18 (s, 3H, CH₃), 2.77, 2.98 (m, each, 1H, 3-CH₂; H_A and H_B), 5.11-5.21 (m, 2H, =CH₂), 5.56-5.86 (m, 1H, -CH=), 6.51-6.87 (AA'BB'-system, 4H, phenyl protons), 6.97-8.05 ppm (m, 6H, quinoline protons); ¹³C nmr (100 MHz): δ 118.9-155.1 (phenyl and quinoline carbons and =CH), 113.9 (=CH₂), 54.9 (4-CH), 41.6 (5-CH₂), 20.5 ppm (CH₃); ms: m/z 288 (molecular ion).

Anal. Calcd. for C₂₀H₂₀N₂: C, 83.33; H, 6.94; N, 9.72. Found: C, 83.15; H, 7.23; N, 9.83.

4-N-(2,4-Dimethylphenyl)amino-4-(8-quinolinyl)-1-butene (**15**).

This compound was obtained in 94% yield, mp 66-68° (heptane); ir (potassium bromide): ν NH 3429, 1639, ν C=C 1599, 916 cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.05 (dd, J = 7 Hz, 1H, 4-H), 2.18, 2.24 (s, each, 3H, CH₃), 2.77, 3.04 (m, each, 1H, 3-CH₂; H_A and

H_B), 5.11-5.25 (m, 2H, =CH₂), 5.50-5.91 (m, 1H, -CH=), 6.25-8.05 ppm (m, 10H, phenyl and quinoline protons); ¹³C nmr (100 MHz): δ 118.9-155.2 (phenyl and quinoline carbons and =CH), 113.8 (=CH₂), 53.9 (4-CH), 41.8 (3-CH₂), 18.7 ppm (CH₃); ms: m/z 302 (molecular ion).

Anal. Calcd. for C₂₁H₂₂N₂: C, 83.44; H, 7.28; N, 9.27. Found: C, 83.48; H, 7.30; N, 9.20.

4-*N*-(4-Chlorophenyl)amino-4-(8-quinolinyl)-1-butene (**16**).

This compound was obtained in 96% yield, oil; ir (neat): ν NH 3415, 1639, ν C=C 1599, 918 cm⁻¹; ¹H nmr (deuteriochloroform): δ 2.05 (dd, J = 7 Hz, 1H, 4-H), 2.76, 2.94 (m, each, 1H, 3-CH₂; H_A and H_B), 5.09-5.20 (m, 2H, =CH₂), 5.52-5.84 (m, 1H, -CH=), 6.48-6.97 (AA'BB'-system, 4H, phenyl protons), 6.94-8.05 ppm (m, 6H, quinoline protons); ¹³C nmr (100 MHz): δ 118.9-154.9 (phenyl and quinoline carbons and =CH), 114.8 (=CH₂), 54.2 (4-CH), 41.5 ppm (3-CH₂); ms: m/z 308 (molecular ion for ³⁵Cl).

Anal. Calcd. for C₁₉H₁₇N₂Cl: C, 73.91; H, 5.51; N, 9.07. Found: C, 73.88; H, 5.81; N, 9.21.

4-[*N*-Allyl, *N*-(4-methylphenyl)]amino-4-(8-quinolinyl)-1-butene (**17**).

A suspension of **14** (0.38 g, 1.31 mmoles) in 10 ml acetone with allyl bromide (1.58 g, 13.10 mmoles) and potassium carbonate (0.90 g, 6.50 mmoles) was allowed to reflux for 4 days. The reaction was monitored by tlc. The mixture was treated with water. The products were extracted and the organic layer was dried (sodium sulfate) and the residue purified by a short chromatographic column (alumina). The *N*-allyl derivative **17** was obtained 0.34 g (78%) as brownish oil; ir (neat): ν C=C 1600, 914 cm⁻¹; ¹H nmr (deuteriochloroform): δ 1.92 (dd, J = 7 Hz, 1H, 4-H), 2.26 (s, 3H, CH₃), 2.98 (m, 2H, 3-CH₂), 3.97 (m, 2H, N-CH₂), 4.96-5.20 (m, 4H, =CH₂), 5.57-6.00 (m, 2H, -CH=), 6.67-7.03 (AA'BB'-system, 4H, phenyl protons), 7.00-8.01 ppm (m, 6H, quinoline protons); ms: m/z 328 (molecular ion).

Anal. Calcd. for C₂₃H₂₄N₂: C, 84.15; H, 7.32; N, 8.54. Found: C, 84.10; H, 7.30; N, 8.49.

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REFERENCES AND NOTES

- [*] Fax 5776-346149 or 90212- 2245013. E-mail: kouznet@uis.edu.co or nocal@yildiz.edu.tr
- [1] F. S. Yates, in *Comprehensive Heterocyclic Chemistry*, Vol. 2, A. J. Boulton and A. McKillop, eds, Pergamon Press, Oxford, 1984, p. 511.
- [2] V. Kouznetsov, A. Palma, C. Ewert, A. Varlamov, *J. Heterocyclic Chem.*, **35**, 761 (1998).
- [3] F. C. Brown, *Chem. Rev.* **61**, 463 (1961).
- [4] M. S. Raasch, *J. Heterocyclic Chem.* **11**, 587 (1974).
- [5] S. P. Singh, S. S. Parmar, K. Raman, V. Stenberg, *Chem. Rev.* **81**, 175 (1981).
- [6] V. P. Singh, G. S. Upadhyay, H. Singh, *Asian J. Chem. Rev.*, **3**, 12 (1992).
- [7] V. V. Kuznetsov, N. S. Prostakov, *Khim. Geterotsikl. Soed.*, **5** (1990); *Chem. Abst.*, **113**, 40.347 (1990).
- [8] V. M. Rodionov, M. A. Berkengeim, *J. Gen. Chem. (U.S.S.R.)*, **14**, 330 (1944); *Chem. Abstr.*, **39**, 4076-9 (1945).
- [9] V. V. Kuznetsov, A. E. Aliev, N. S. Prostakov, *Khim. Geterotsikl. Soed.*, **73** (1994); *Chem. Abst.*, **121**, 300.738 (1994).
- [10] V. V. Kuznetsov, E. I. Andreeva, N. S. Prostakov, *Khim. Farm. Zh.*, **29**, 61 (1995); *Chem. Abst.*, **124**, 48.290 (1996).
- [11] V. Kouznetsov, N. Öcal, Z. Turgut, F. Zubkov, Ş. Kaban, A. V. Varlamov, *Mon. Chem.*, **129**, 671 (1998).