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4-HYDROXYQUINOL-2-ONES. 86*. SYNTHESIS OF METHYL (ETHYL) ESTERS OF 1-SUBSTITUTED 4-AMINO-2-OXOQUINOLINE-3-CARBOXYLIC ACIDS

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Several variants of the synthesis of esters of 1-N-substituted 4-amino-2-oxoquinoline-3-carboxylic acids have been studied, one of which is recommended as preparative.

Keywords: 3-alkoxycarbonyl-4-aminoquinolin-2-one, 4-chloroquinolin-2-one, alkylation, N-debenzylation.

Esters of 1-substituted 4-amino-2-oxoquinoline-3-carboxylic acids **1** are of interest as potentially biologically active substances and also as a basis for further chemical conversions with an adequately broad synthetic potential.

The usual method of obtaining compounds of this family comprises acylation of anthranilonitrile **2** with the acid chloride of an appropriate acid, containing a fairly reactive methylene group, with subsequent closure of the 4-aminoquinoline ring under the action of basic catalysts [2, 3]. This method gives good results in the synthesis of 3-alkoxycarbonyl-1H-4-amino-2-oxoquinolines **3** [4] and, in principle, may be used for obtaining 1-N-alkyl derivatives **1** (Scheme 1, method A). Regretably alkylation of anthranilonitrile **2** does not occur quantitatively and the N-alkyl derivatives obtained always contain contamination by the starting material, effective elimination of which is only possible by chromatography (especially in the case of the lower N-alkyl substituents). Using the available N-alkylanthranilic acids in the synthesis of anthranilonitriles **4** [5] may exclude chromatographic purification, but such a modification introduces several additional stages, esterification, amidation in an autoclave, dehydration of the amide, and removal of the N-protecting group [2,3], which is not always justified by far.

A second possible variant for obtaining esters of 1-substituted 4-amino-2-oxoquinoline-3-carboxylic acids **1** is the alkylation of the previously isolated 1H-derivatives **3** (method B). As a result of lactam–lactim, enamine–imine, and keto–enol tautomerism for esters **3** it is possible that five tautomeric forms exist (Scheme 2), in which both nitrogen atoms, the oxygen of the 2-C=O group, or the carbon atom at position 3 of the quinoline ring may potentially be nucleophilic centers.

We noted previously [4] that the properties of the 4-amino group in esters **3**, judging by the chemical shift of its protons in the ^{1}H NMR spectrum (8.3 ppm), are far closer to an amide than to a normal amine (for example, for anilines the mean value is ~4 ppm [6]). It is also known that in 1H-4-amino-2-oxo-3-phenylquinolines alkylation of the 4-amino group (chemical shift 5.9 ppm) is successfully effected only in the

* For Part 85 see [1].

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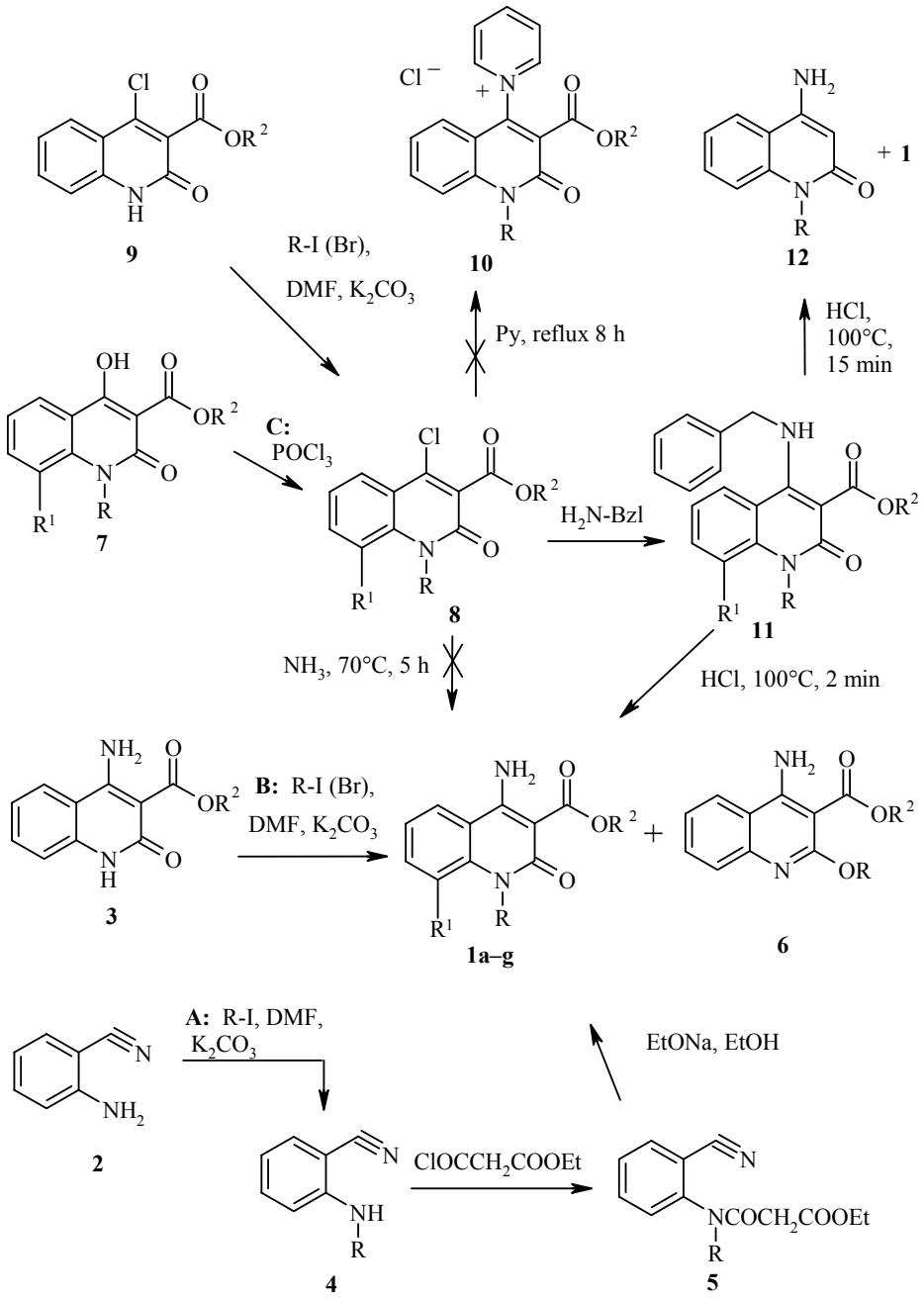
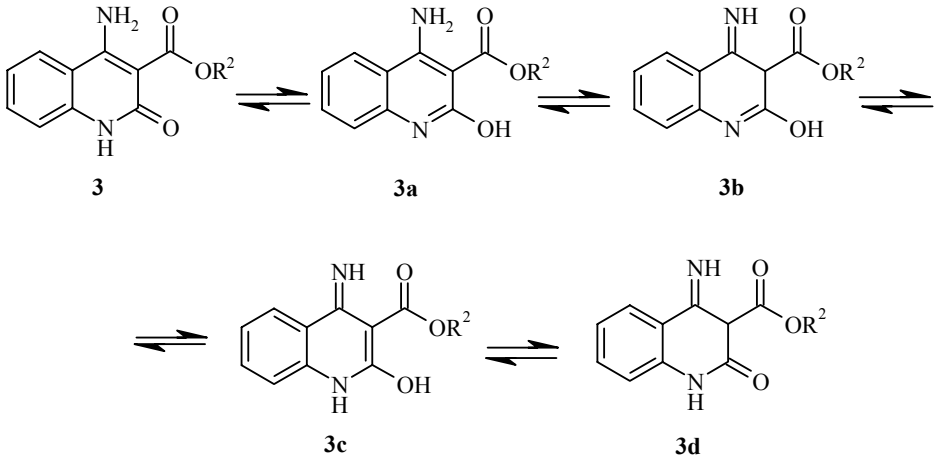
Scheme 1



1 a R = Me, **b** R = C_3H_7, **c** R = C_6H_{13}, **d** R = C_7H_{15}, **e** R = C_8H_{17}, **f** R = Ph, **g** R+R^1 = –$(CH_2)_3$–;
a-f R^1 = H; **a**, **b**, **f**, **g** R^2 = Et, **c-e** R^2 = Me

presence of very strong bases (potassium hexamethyldisilazide) and only after introducing a 1-N protecting group [2]. Consequently on alkylating esters **3** in the system DMF–K_2CO_3 the 4-amino group may be excluded from the number of probable targets for electrophilic attack. Due to steric difficulties the formation of 3-alkyl derivatives is also not very likely. Experiments carried out by us show that on interacting esters **3** with alkyl halides the 4-amino group is indeed not affected. Two types of reaction product are formed, *viz*. the desired

Scheme 2



1-N-alkyl derivatives **1** and esters of 4-amino-2-alkoxyquinoline-3-carboxylic acids **6** isomeric with them. The higher yields of the latter indicate the significant contribution of the 4-amino-2-hydroxy form **3a** to the resonance hybrid of esters **3** in an alkaline medium.

In view of the above arguments a different approach to the synthesis of amino esters **1** seemed of interest, based on the use of the easily accessible ethyl esters of 1-substituted 4-hydroxy-2-oxoquinoline-3-carboxylic acids **7** [7]. Modification of the 4-hydroxy substituent of such compounds into a primary amino group, theoretically at least, is not inconsistent. Several practical procedures are known for such a conversion. First of all, there is direct replacement of a 4-hydroxy group by NH_2 by the reaction of 3-R-4-hydroxyquinol-2-ones with benzylammonium chloride at 300°C [8]. With benzylamine a similar reaction occurs under comparatively mild conditions (180°C), but leads only to 4-benzylaminoquinolone and only subsequent catalytic hydrogenation gives 4-amino derivatives [9]. It is evident that the methods given are unsuitable for obtaining amino esters **1** because of the thermal instability of the initial 4-hydroxy derivatives **7** [10] in the first case, and the high reactivity of their ester groupings [11] in the second, and consequently were not considered by us.

TABLE 1. Characteristics of Esters of 1-R-4-Amino-2-oxoquinoline-3-carboxylic Acids **1a-g**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, % (method)
		C	H	N		
1a	$C_{13}H_{14}N_2O_3$	63.31 / 63.40	5.85 / 5.73	11.51 / 11.38	173-175 (ethanol)	83 (C)
1b	$C_{15}H_{18}N_2O_3$	65.50 / 65.68	6.79 / 6.61	10.10 / 10.21	154-156 (ethanol)	46 (A)
1c	$C_{17}H_{22}N_2O_3$	67.66 / 67.53	7.47 / 7.33	9.15 / 9.26	137-139 (methanol)	72 (C)
1d	$C_{18}H_{24}N_2O_3$	68.28 / 68.33	7.54 / 7.65	8.93 / 8.85	133-135 (methanol)	70 (C)
1e	$C_{19}H_{26}N_2O_3$	69.22 / 69.06	7.81 / 7.93	8.62 / 8.48	136-138 (methanol)	35 (B)
1f	$C_{18}H_{16}N_2O_3$	70.29 / 70.12	5.34 / 5.23	9.16 / 9.09	215-217 (ethanol)	87 (C)
1g	$C_{14}H_{14}N_2O_3$	65.18 / 65.11	5.37 / 5.46	10.76 / 10.85	237-239 (ethanol)	81 (C)

TABLE 2. ^{1}H NMR Spectra of Esters of 1-R-4-Amino-2-oxoquinoline-3-carboxylic Acids **1a-g**

Compound	Chemical shifts, δ, ppm						
	4-NH_2 (2H, s)	H arom.				R	R^2
		H-5 (1H, d)	H-8 (1H, d)	H-7 (1H, t)	H-6 (1H, t)		
1a	8.00	8.15	7.41	7.64	7.21	3.46 (3H, s, NCH_3)	4.21 (2H, q, OCH_2); 1.19 (3H, t, CH_3)
1b	7.99	8.14	7.41	7.62	7.22	4.02 (2H, t, NCH_2); 1.54 (2H, m, $NCH_2C\underline{H}_2$); 0.90 (3H, t, CH_3)	4.20 (2H, q, OCH_2); 1.20 (3H, t, CH_3)
1c	8.06	8.17	7.39	7.65	7.20	4.09 (2H, t, NCH_2); 1.53 (2H, q, $NCH_2C\underline{H}_2$); 1.30 (6H, m, $C\underline{H}_2)_3CH_3$); 0.85 (3H, t, CH_3)	3.73 (3H, s, OCH_3)
1d	8.07	8.16	7.39	7.63	7.19	4.07 (2H, t, NCH_2); 1.52 (2H, q, $NCH_2C\underline{H}_2$); 1.21 (8H, m, $(C\underline{H}_2)_4CH_3$); 0.80 (3H, t, CH_3)	3.71 (3H, s, OCH_3)
1e	8.07	8.16	7.39	7.64	7.20	4.06 (2H, t, NCH_2); 1.51 (2H, q, $NCH_2C\underline{H}_2$); 1.22 (10H, m, $(C\underline{H}_2)_5CH_3$); 0.83 (3H, t, CH_3)	3.77 (3H, s, OCH_3)
1f	8.36	8.20	6.36	7.64-7.10 (7H, m, H-7,6 + N–C_6H_5)		see. H-7 and H-6	4.18 (2H, q, OCH_2); 1.21 (3H, t, CH_3)
1g	7.98	7.93	—	7.38 (d)	7.07	3.87 (2H, t, NCH_2); 2.84 (2H, t, $NCH_2CH_2C\underline{H}_2$); 1.87 (2H, q, $NCH_2C\underline{H}_2CH_2$)	4.20 (2H, q, OCH_2); 1.23 (3H, t, CH_3)

It is more preferred to convert the 4-hydroxy esters **7** into chloro derivatives **8**, the synthesis of which is also possible by alkylating 1H-4-chloro-2-oxoquinolines **9** [12]. Nucleophilic substitution of the chlorine atom in these compounds under the action of primary and secondary alkyl- and arylamines occurs readily [13]. However ammonia does not react, after passing dry gaseous ammonia into a solution of chloro-substituted ester **8** in alcohol or DMF for 5 h only the starting material was isolated. At atmospheric pressure such a replacement was successfully effected only for the highly reactive 4-chloro-3-nitroquinol-2-ones [14], while in the remaining cases treatment with ammonia in an autoclave is necessary [8]. This is not acceptable for the synthesis of amino esters **1** due to the inevitable amidation of the alkoxycarbonyl group.

Another method giving no positive result is that used successfully by us for the synthesis of esters of 1H-4-amino-2-oxoquinoline-3-carboxylic acids **2**, which was the treatment of N-(1H-3-alkoxycarbonyl-2-oxoquinolin-4-yl)pyridinium chlorides with alkyl- or arylamines [4]. It turned out that, unlike the 1H-derivative, the ethyl esters of 1-alkyl-4-chloro-2-oxoquinoline-3-carboxylic acids **8** did not form the corresponding quaternary salts **10** with pyridine.

Nevertheless replacement of a chlorine atom in esters **8** by a primary amino group was successfully effected, although indirectly, through the 4-benzylamino derivatives **11**. Catalytic hydrogenation [9, 15] or catalyzed acid hydrolysis [16, 17] are most frequently used in organic chemistry to remove benzyl protection.The first method as a rule is fairly extended in time (6-12 h) and moreover unsafe. On the other hand hydrolysis of 1-R-3-alkoxycarbonyl-4-benzylamino-2-oxoquinolines **11** with conc. HCl occurs in 2 min. It is interesting to note that the ester group is not affected by this. It is however necessary to take into account the fact that too extended a treatment of 4-benzylaminoquinolones **11** with boiling conc. HCl is accompanied not

only by debenzylation but also by decomposition of the alkoxycarbonyl group with the formation of 1-R-4-amino-2-oxoquinolines **12**. After 15 min their content in the mixture, judging by the ^{1}H NMR spectrum, amounted to ~40% in relation to esters **1**. The whole chain of conversions of 4-hydroxy esters **7** into the final 4-amino derivatives **1** (method C) is readily effectable without isolating the intermediate 4-chloro- and 4-benzylaminoquinolones. Apart from the mentioned hydrogenation and acid hydrolysis used by us the final stage where necessary may be carried out by any other suitable method. Choices of N-debenzylating agent and the conditions for using them are fairly wide [18-25], which on the whole makes the proposed method practically universal and enables it to be recommended as a practical method.

EXPERIMENTAL

The ^{1}H NMR spectra of the synthesized compounds were recorded on a Varian Mercury VX 200 (200 MHz) instrument, solvent was DMSO-d_6, internal standard TMS.

4-Amino-2-oxo-1-propylquinoline-3-carboxylic Acid Ethyl Ester (1b). 1-Iodopropane (6.83 ml, 0.07 mol) was added to a mixture of anthranilonitrile **2** (5.91 g, 0.05 mol) and anhydrous K_2CO_3 (13.8 g, 0.1 mol) in DMF (80 ml) and the mixture stirred for 5 h at 90°C. The mixture was cooled, and diluted with water. The precipitated oily residue of N-propylanthranilonitrile **4** was extracted with CH_2Cl_2 (3 × 50 ml). The organic extracts were combined, the solvent distilled off, and the residue chromatographed on a column (silica gel L 100/250) in the solvent system CH_2Cl_2–hexane, 3:1.

N-Propylanthranilonitrile **4** R_f 0.60; (Silufol UV 254, CH_2Cl_2–hexane, 3:1); initial anthranilonitrile **2** (under the same conditions) R_f 0.31. The obtained N-propylanthranilonitrile **4** (4.25 g, 0.026 mol) was dissolved in CH_2Cl_2 (50 ml), triethylamine (4.2 ml, 0.03 mol) was added, and then ethoxymalonyl chloride (4.52 g, 0.03 mol) was added in small portions with stirring and cooling. After 4-5 h the reaction mixture was poured into cold water (100 ml), thoroughly stirred, and transferred to a separating funnel. The organic layer was separated, dried over $CaCl_2$, and the solvent removed, finally at reduced pressure. A solution of sodium ethylate, from metallic sodium (1.15 g, 0.05 mol) and absolute ethanol (50 ml), was added to the residue of anilide **5** and the mixture boiled for 1 h (use of sodium methylate in methanol as basic catalyst is accompanied by transesterification). The mixture was cooled, and poured into water (200 ml). The precipitated solid amino ester **1b** was filtered off, washed with water, and dried. Yield 6.34 g (46% calculated on anthranilonitrile **2**).

4-Amino-1-octyl-2-oxoquinoline-3-carboxylic Acid Methyl Ester (1e). B. Amino ester **3** (R^2 = Me) was alkylated with 1-bromooctane by the procedure in the previous experiment, reaction time was 8 h. At the end of the reaction the mixture was poured into water, and the alkylation products extracted with CH_2Cl_2. The unreacted amino ester **3** (~7%) is separated in the residue insoluble in CH_2Cl_2. It was filtered off and dried. The solvent was distilled from the filtrate, hexane was added to the residue, the mixture was rubbed thoroughly, and filtered. The solid on the filter (amino ester **1e**) was washed several times with hexane, and dried. Yield was 35%.

4-Amino-2-octyloxyquinoline-3-carboxylic Acid Methyl Ester (6, R = C_8H_{17}, R^2 = Me). The hexane filtrate remaining after separation of amino ester **1e** (see previous experiment) was purified with carbon, after which the solvent was removed. Ester **6** was obtained as a light yellow oily liquid. Yield 52%. ^{1}H NMR spectrum, δ, ppm: 8.14 (1H, d, H-5); 7.71 (2H, s, NH_2); 7.55 (1H, t, H-7); 7.45 (1H, d, H-8); 7.23 (1H, t, H-6); 4.25 (1H, t, OCH_2); 3.76 (3H, s, $COOCH_3$); 1.64 (2H, q, $OCH_2C\underline{H}_2$); 1.35 (2H, q, $OCH_2CH_2C\underline{H}_2$); 1.13 [8H, m, $(C\underline{H}_2)_4CH_3$]; 0.76 (3H, s, CH_3). Found, %: C 69.10; H 7.78; N 8.64. $C_{19}H_{26}N_2O_3$. Calculated, %: C 69.06; H 7.93; N 8.48.

4-Amino-1-methyl-2-oxoquinoline-3-carboxylic Acid Ethyl Ester (1a). C. A solution of 4-hydroxy-1-methyl-2-oxoquinoline-3-carboxylic acid ethyl ester (**7**) (2.47 g, 0.01 mol) in $POCl_3$ (15 ml) was boiled for 2 h. The excess of $POCl_3$ was distilled off, finally at reduced pressure. The residue was treated with a mixture of ice and water. After decomposing the $POCl_3$, Na_2CO_3 was added to the reaction mixture to pH 8 in the aqueous

layer. The separated 4-chloro substituted ester **8** may be filtered off and characterized. However it is more expedient to extract it with CH_2Cl_2 (3 × 30 ml). The pH of the aqueous layer was checked and Na_2CO_3 was added if necessary. The solvent was removed, and to the residue were added ethanol (30 ml), benzylamine (1.31 ml, 0.012 mol), and triethylamine (1.4 ml, 0.01 mol), and the mixture boiled for 5 h. The reflux condenser was changed to a downward condenser and the alcohol was distilled off. The obtained 4-benzylaminoquinolone **11** may also be separated in the pure state [13]. If there is no need the reaction mixture is treated with water, and the resulting 4-benzylaminoquinolone **11** extracted with CH_2Cl_2 (3 × 30 ml). The organic extracts were combined, washed with water, and the solvent distilled. Conc. HCl (15 ml) was added to the residue, rapidly heated to boiling, boiled for 2 min, after which the mixture was poured directly into cold water. The reaction mixture was neutralized with Na_2CO_3. After several hours the precipitated solid 4-amino ester **1a** was filtered off, washed with water, and dried. Yield 2.04 g (83%).

The esters of 1-substituted 4-amino-2-oxoquinoline-3-carboxylic acids **1c,d,f,g** were obtained analogously (Tables 1 and 2).

REFERENCES

1. I. V. Ukrainets, O. V. Gorokhova, and L. V. Sidorenko, *Khim. Geterotsikl. Soedin.*, 1195 (2005).
2. R. W. Carling, P. D. Leeson, K. W. Moore, C. R. Moyes, M. Duncton, M. L. Hudson, R. Baker, A. C. Foster, S. Grinwood, J. A. Kemp, G. R. Marshall, M. D. Tricklebank, and K. L. Saywell, *J. Med. Chem.*, **40**, 754 (1997).
3. M. Rowley, J. J. Kulagowski, A. P. Watt, D. Rathbone, G. I. Stevenson, R. W. Carling, R. Baker, G. R. Marshall, J. A. Kemp, A. C. Foster, S. Grinwood, R. Hargreaves, C. Hurley, K. L. Saywell, M. D. Tricklebank, and P. D. Leeson, *J. Med. Chem.*, **40**, 4053 (1997).
4. I. V. Ukrainets, P. A. Bezuglyi, N. Skaif, O. V. Gorokhova, and L. V. Sidorenko, *Zh. Org. Farm. Khim.*, **2**, Part 1, (2004).
5. N. A. Jaradat, Dissertation for Candidate of Pharmaceutical Sciences, Kharkov (2000).
6. H. Gunther, *NMR Spectroscopy: Basic Principles, Concepts, and Applications in Chemistry*, John Wiley & Sons, Chichester (1995).
7. I. V. Ukrainets, O. V. Gorokhova, S. G. Taran, P. A. Bezuglyi, A. V. Turov, N. A. Marusenko, and O. A. Evtifeeva, *Khim. Geterotsikl. Soedin.*, 958 (1994).
8. W. Stadlbauer and T. Kappe, *Monatsh. Chem.*, **113**, 751 (1982).
9. W. Stadlbauer and T. Kappe, *Bull. Slov. Chem. Soc. (Vestn. Slov. Kem. Drus)*, **33**, 271 (1986).
10. I. V. Ukrainets, E. A. Taran, O. V. Shishkin, O. V. Gorokhova, S. G. Taran, N. A. Dzharadat, and A. V. Turov, *Khim. Geterotsikl. Soedin.*, 516 (2000).
11. I. V. Ukrainets, Dissertation for Doctor of Chemical Sciences, Kharkov (1992).
12. I. V. Ukrainets, S. G. Taran, O. V. Gorokhova, I. V. Gorlacheva, P. A. Bezuglyi, and A. V. Turov, *Khim. Geterotsikl. Soedin.*, 1104 (1996).
13. P. A. Bezugly, I. V. Ukrainets, Skaif Nicola, O. V. Gorokhova, L. V. Sidorenko, *Pharmacom*, No. 3, 23 (2003).
14. P. Roschger, W. Fiala, and W. Stadlbauer, *J. Heterocycl. Chem.*, **29**, 225 (1992).
15. A. Marinetti, P. Hubert, and J.-P.Genet, *Eur. J. Org. Chem.*, 1815 (2000).
16. P. Kowalski, Z. Majka, and T. Kowalska, *Khim. Geterotsikl. Soedin.*, 845 (1998).
17. M. Pawlowski and M. Gorczyca, *Pol. J. Chem.*, **55**, 837 (1981).
18. N. M. Howarth, J. R. Malpass, and C. R. Smith, *Tetrahedron*, **54**, 10899, (1998).
19. H. Suzuki, A. Tsukuda, M. Kondo, M. Aizawa, Y. Senoo, N. Megumi, W. Toshiko, Y. Yuusaku, and M. Yasuoki, *Tetrahedron Lett.*, **36**, 1671 (1995).
20. P. Q. Huang, X. Zheng, S. L. Wang, J. L. Ye, and L. R. Jin, *Tetrahedron Asymmetry,* **10**, 3309 (1999).

21. M. K. H. Doll, A. Guggisberg, and M. Hesse, *Helv. Chim. Acta*, **79**, 1379 (1996).
22. J. V. B. Kanth, C. K. Reddy, and M. Periasamy, *Synth. Commun.*, **24**, 313 (1994).
23. A. A. Haddach, A. Kelleman, and M. V. Deaton-Rewolinski, *Tetrahedron Lett.*, **43**, 399 (2002).
24. S. D. Bull, S. G. Davies, G. Fenton, A. W. Mulvaney, R. S. Prasad, and A. D. Smith, *J. Chem. Soc., Chem. Commun.*, 337 (2000).
25. L. Cipolla, A. Palma, B. L. Ferla, and F. Nicotra, *J. Chem. Soc., Perkin Trans. 1,* 2161 (2002).