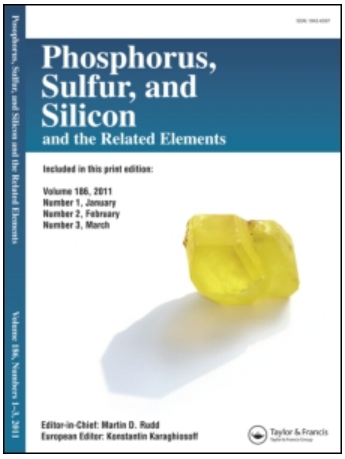

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N- vs. S-PTC ALKYLATION OF 5-CARBOETHOXY-2-THIOURACIL AND ITS REACTIVITY TOWARDS SOME NUCLEOPHILIC REAGENTS

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*The reactivity of 5-carboethoxy-2-thiouracil (**1**) toward alkylation by different organohalogen compounds under phase-transfer catalysis (PTC) conditions has been investigated to give S-monoalkylated products and/or simultaneous S- and N-dialkylated products. Also, nucleophilic additions of methylmagnesium iodide, hydroxylamine, and hydrazine to 5-carbethoxy-2-thiouracil (**1**) have been investigated. The structures of all products have been confirmed by elemental analysis and spectral data.*

Keywords: 5-Carboethoxy-2-thiouracil; phase-transfer catalysis (PTC); pyrimidothiazine; thiazolopyrimidine

In continuation of our interests[1–4] and reported PTC–alkylation[5–8] of some heterocyclic compounds, we study the reactivity of N-versus S-alkylation of 5-carboethoxy-2-thiouracil under phase-transfer catalysis conditions.

On the other hand, we synthesize some new 2-alkylthiouracil derivatives by a versatile method that might add new biological activities to their reported medicinal applications,[9] recently, as antithyroids.[10] Also, we synthesize some new condensed pyrimidines in addition to an analogous compounds with potential medicinal interest.[11]

RESULTS AND DISCUSSION

5-Carboethoxy-2-thiouracil (**1**) exists in two major tautomeric forms, (**A**) and (**B**); the keto–form (**A**) is the predominant one. This phenomena

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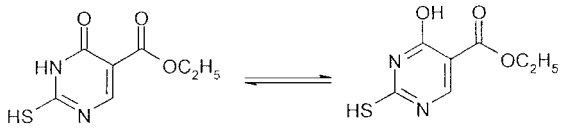
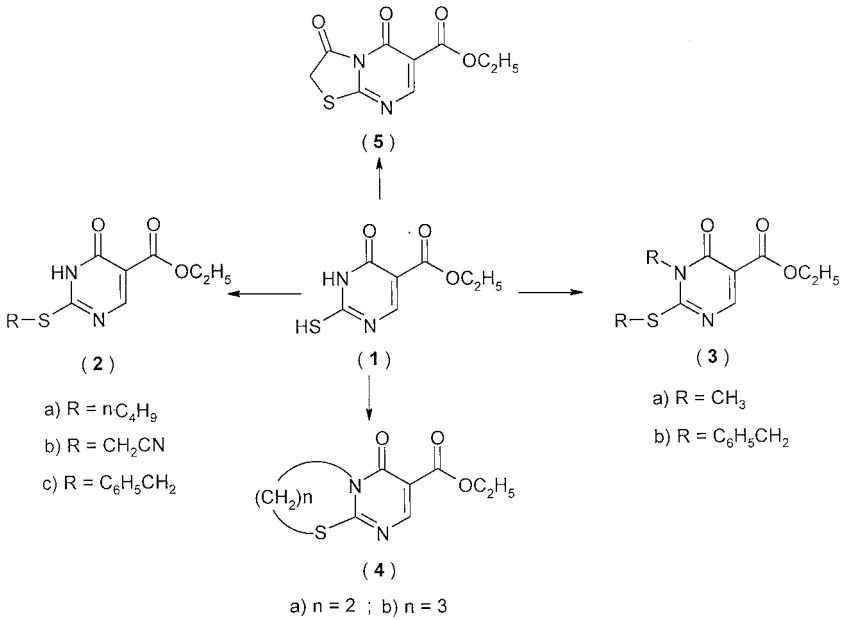
is confirmed by spectral data in addition to our results of PTC–alkylation which are afforded S-monoalkylated products and/or S- and N-dialkylated products but no O-alkylated product is obtained.



The proper applied PTC reaction conditions as a general procedure of alkylation of 5-carboethoxy-2-thiouracil (**1**) by haloorganic compounds[4,12,13] are benzene/anhydrous potassium carbonate as liquid/solid phases and tetrabutylammonium bromide (TBAB) as catalyst with continuous efficient stirring for 4-6 h at 70°C.

Treatment of 5-carboethoxy-2-thiouracil (**1**) with n-butyl bromide or chloroacetonitrile in 1:3 molar ratio, respectively, under the optimized PTC conditions afforded, exclusively, S-monoalkylation to give ethyl 2-(n-butylthio)-6-oxo-1,6-dihydropyrimidine-5-carboxylate (**2a**) or ethyl 2-[(cyanomethyl)thio]-6 oxo- 1,6-dihydropyrimidine-5-carboxylate (**2b**) (Scheme 1).



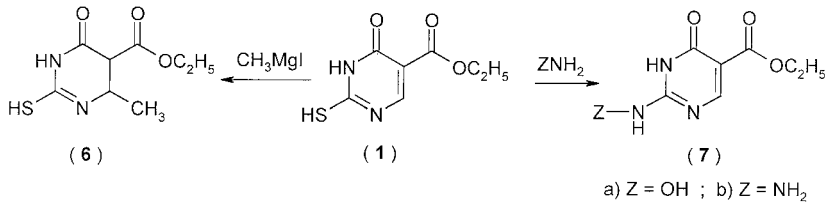
SCHEME 1

Methylation of 5-carboethoxy-2-thiouracil (**1**) by methyl iodide under the same PTC reaction conditions underwent simultaneous S- and N-dimethylation to give ethyl 1-methyl-2-(methylthio)-6-oxo-1,6-dihydropyrimidine-5-carboxylate (**3a**) (Scheme 1). Also, benzylation of thiouracil (**1**) by benzyl bromide under the same optimized PTC reaction conditions afforded a mixture of S-monobenzylated product, ethyl 2-(n-benzylthio)-6-oxo-1,6-dihydropyrimidine-5-carboxylate (**2c**) and S- and N-dibenzylated product, ethyl 1-benzyl-2-(benzylthio)-6-oxo-1,6-dihydro-pyrimidine-5-carboxylate (**3b**) in 1:3 yield ratio, which are separated by column chromatography (Scheme 1). Benzylsulfanylthiouracil (**2c)** was previously[14] synthesized by a multi-step procedure in a mild yield.

On the other hand, treatment of an equimolar amounts of 5-carboethoxy-2-thiouracil (**1**) with 1,2-dibromoethane or 1,3-dibromopropane under the same optimized phase-transfer catalysis conditions underwent simultaneous S- and N-cycloalkylation to give ethyl 5-oxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]-pyrimidine-6-carboxylate (**4a**) or ethyl 6-oxo-3,4-dihydro-2H,6H-pyrimido[2,1-b][1,3]thiazine-7-carboxylate (**4b**) respectively (Scheme 1). Also, an equimolar amounts of ethyl bromoacetate and 5-carboethoxy-2-thiouracil (**1**) under the optimized PTC reaction conditions underwent, simultaneous, S- and N-cycloalkylation to give ethyl 3,5-dioxo-2,3-dihydro-5H-[1,3]thiazolo[3,2-a]-pyrimidine-6-carboxylate (**5**) (Scheme 1).

5-Carboethoxy-2-thiouracil (**1**) is considered as an. α,.β-unsaturated ester, which is reacted with excess methylmagnesium iodide in dry ether via Michael route addition reaction to give ethyl 2-mercapto-4-methyl-6-oxo-1,4,5,6-tetra-hydropyrimidine 5-carboxylate (**6**) (Scheme 2).

Treatment of 5-caroethoxy-2-thiouracil (**1**) with nitrogen nucleophiles such as hydroxylamine or hydrazine hydrate underwent nucleophilic displacement of the mercapto group to give ethyl 2-hydroxylamino-6-oxo-1,6-dihydro-pyrimidine-5-carboxylate (**7a**) or ethyl 2-hydrazino-6-oxo-1,6-dihydropyrimidine-5-carboxylate (**7b**) respectively (Scheme 2).



SCHEME 2

EXPERIMENTAL

Melting points reported are uncorrected. IR spectra were recorded on Pye-Unicam SP 2000 spectrophotometer and Maltson-1000 series FT-IR spectrophotometer using KBr Wafer technique. The NMR spectra were recorded by Varian Nova 500, using TMS as internal standard and $CDCl_3$ as solvent. The chemical shifts are recorded on δ-scale in ppm. The mass spectra were measured by AMD 604 spectrophotometer using single focusing mass spectrometer with direct inlet at beam energy 70 eV. Elemental analysis was estimated by a Carlo-Erba 1106 C,H,N analyzer. The key starting 5-carbethoxy-2-thiouracil is an Aldrich product No. 85, 525-1 and was used without further purification.

PTC-Alkylation of 5-Carboethoxy-2-thiouracil (1)

General Procedure

To a solution of 5-carboethoxy-2-thiouracil (**1**) (2.0 g, 0.01 mol) in dry benzene (50 ml), anhydrous K_2CO_3 (2.7 g, 0.02 mol) and tetrabutylammonium bromide (TBAB) (0.003 mol), the organic monohalogen compounds (0.03 mol), such as n-butyl bromide, chloroacetonitrile, methyl iodide, and benzyl bromide, and organic dihalogen compounds such as 1,2-dibromoethane and 1,3-dibromopropane or ethyl bromoacetate (0.01 mol) was added in round-bottom flask fitted with condenser and kept at 70°C. The reaction mixture was stirred vigorously and controlled by TLC over the reaction period. At the end of the reaction, the benzene layer was separated by filtration and the solvent was evaporated, then the residue was triturated with Pet. Ether 60-80 to release the excess of unreacted halogen compound. The residue was crystallized from the suitable solvent to give **2–5**. The K_2CO_3 residue was dissolved in water (50 ml) and acidified by hydrochloric acid (15% solution) to confirm if an acidic by-product also existed. In all cases, there is no by-product isolated from the K_2CO_3 residue. The physical data and yield % of the products **2–5** are listed in Table I and the spectral data are listed in Table II.

*Addition of methylmagnesium iodide on 5-carboethoxy-2-thiouracil (**1**).*

*Formation of ethyl 2-mercapto-4-methyl-6-oxo-1,4,5,6-tetrahydropyrimidine-5-carboxylate (**6**).* To a suspension of 5-carboethoxy-2-thiouracil (**1**) (2.0 g, 0.01 mol) in dry ether (50 ml), a methylmagnesium iodide (0.05 mol) in dry ether (50 ml) was added dropwise with stirring. After complete addition, the solution was refluxed on water bath for 3 h and then poured onto cold ammonium chloride solution (40 ml,

TABLE I Physical Data of Compounds **2–7**

Comp. no.	m.p.°C (color)	Solvent of cryston (yield %)	Mol. form. (m. wt.)	Elemental analysis calcd./found		
				C	H	N
2a	128–130	Pet.ether	$C_{11}H_{16}N_2O_3S$	51.50	6.24	10.92
	(white)	(48)	(256.32)	51.27	6.08	10.85
2b	170–172	Ethanol	$C_9H_9N_3O_3S$	45.14	3.76	17.55
	(pale yellow)	(58)	(239.25)	45.06	3.65	17.64
2c	88–90	Pet.ether	$C_{14}H_{14}N_2O_3S$	57.87	4.82	9.64
	(white)	(12)	(290.34)	57.75	4.74	9.55
3a	97–99	Pet.ether	$C_9H_{12}N_2O_3S$	47.31	5.26	12.27
	(pale yellow)	(71)	(228.26)	47.43	5.33	12.16
3b	107–108	Pet.ether	$C_{21}H_{21}N_2O_3S$	66.14	5.51	7.35
	(white)	(42)	(381.45)	66.08	5.54	7.50
4a	174–176	Ethanol	$C_9H_{10}N_2O_3S$	47.79	4.42	12.38
	(pale yellow)	(76)	(226.24)	47.62	4.37	12.35
4b	108–110	Benzene	$C_{10}H_{12}N_2O_3S$	49.94	4.99	11.65
	(yellow)	(62)	(240.27)	49.78	4.93	11.57
5	218	Ethanol	$C_9H_8N_2O_4S$	44.99	3.33	11.67
	(red)	(53)	(240.23)	44.84	3.27	11.33
6	138–140	Benzene	$C_8H_{12}N_2O_3S$	44.44	5.56	12.96
	(white)	(67)	(216.25)	44.31	5.48	12.84
7a	256	Ethanol	$C_7H_9N_3O_4$	42.21	4.52	21.11
	(yellow)	(85)	(199)	42.08	4.50	21.15
7b	230	Ethanol	$C_7H_{10}N_4O_3$	42.42	5.05	28.28
	(yellow)	(81)	(198)	42.33	4.93	28.35

30% solution). The organic layer was separated, dried with anhydrous Na_2SO_4, and the solvent was evaporated. The solid residue was crystallized to give methylcarboethoxypyrimidine (**6**). The results are listed in Tables I and II.

*Reaction of hydroxylamine with 5-carboethoxy-2-thiouracil (**1**). Formation of ethyl 2-hydroxylamino-6-oxo-1,6-dihydropyrimidine-5-carboxylate (**7a**).* A solution of thiouracil (**1**) (2.0 g, 0.01 mol) and hydroxylamine hydrochloride (0.8 g, 0.011 mol) in pyridine (30 ml) was refluxed for 3 h and then poured onto crushed ice (100 g). The solid product was filtered off, dried, and crystallized from ethanol to give hydroxylaminopyrimidine (**7a**) as yellow crystals. The results are listed in Tables I and II.

*Reaction of hydrazine hydrate with 5-carboethoxy-2-thiouracil (**1**). Formation of ethyl 2-(hydrazino)-6-oxo-1,6-dihydropyrimidine-5-carboxylate (**7b**).* A solution of thiouracil (**1**) (2.0 g, 0.01 mol) and hydrazine hydrate (0.012 mol) in ethanol (50 ml) was refluxed for 4 h. The solution was concentrated and the solid product, which was

TABLE II Spectral Data of Compounds **2–7**

Comp. no.	IR (ν in cm^{-1})	^{1}H-NMR δ (ppm)	^{13}H-NMR δ (ppm)	MS (abundance %)
2a	1650 (C═O, cyclic imide), 1740 (C═O, ester), 3480 (NH or OH)	1.0 (t, 3H, C$\underline{H}_3$), 1.38 (t, 3H, C$\underline{H}_3$), 1.61 (m, 2H, C$\underline{H}_2$), 1.83 (m, 2H, C$\underline{H}_2$), 3.23 (t, 2H, S—C $\underline{H}_2$), 4.23 (q, 2H, O—C$\underline{H}_2$), 8.58 (s, 1H, C_6-$\underline{H}$), 12.34 (b, 1H, N$\underline{H}$)	13.3 (CH_3), 14.5 (CH_3), 22.2 (CH_2), 26.6 (CH_2), 29.8 (CH_2), 60.9 (OCH_2), 111.2 (C_5), 156.4 (C_4), 157.1 (C_2), 160.2 (C_6), 165.7 (CO ester)	—
2b	1665 (C═O), 1720 (C═O), 2224 (CN), 3427 (NH or OH)	1.44 (t, 3H, C$\underline{H}_3$), 3.96 (s, 2H, S—C$\underline{H}_2$), 4.48 (q, 2H, OC$\underline{H}_2$), 8.88 (s, 1H, C_6—$\underline{H}$), 11.92 (br, 1H, N$\underline{H}$)	12.7 (CH_3), 17.8 (SCH_2), 60.8 (OCH_2), 111.6 (C_5), 115.2 (CN), 156.3 (C_4),160.8 (C_6), 162.1 (C_2), 167.7 (CO ester)	—
2c	1672 (C═O), 1728 (C═O), 3427, 3535 (NH or OH)	1.32 (t, 3H, C$\underline{H}_3$), 4.31 (q, 2H, OC$\underline{H}_2$), 4.98 (s, 2H, S—C$\underline{H}_2$), 7.53 (m, 5H, Ph-$\underline{H}$), 825 (s, 1H, C_6—$\underline{H}$), 11.39 (b, 1H, N$\underline{H}$)	12.2 (CH_3), 34.3 (SCH_2), 60.9 (OCH_2), 111.8 (C_5), 127.6–136.5 (Ph-C), 157.6 (C_4), 159.7 (C_6), 161.6 (C_2), 166.3 (CO)	292 (M + 2, 19), 290 (M^+, 17), 260 (54), 145 (20), 131 (24), 91 (59), 77 (86) 65 (100), 51 (49)
3a	1653 (C═O, cyclic imide), 1735 (C═O ester)	1.38 (t, 3H, C$\underline{H}_3$), 2.64 (s, 3H, S—C$\underline{H}_3$), 3.55 (s, 3H, N—C$\underline{H}_3$), 4.35 (q, 2H, OC$\underline{H}_2$), 8.54 (s, 1H, C_6—$\underline{H}$)	14.0 (CH_3), 30.4 (S—CH_3), 49.8 (N—CH_3), 60.8 (O—CH_2), 110.7 (C_5), 156.4 (C_4), 157.7 (C_2), 158.6 (C_6), 165.0 (CO)	229 (M + 1, 6), 228 (M^+, 35), 183 (100), 156 (47), 138 (11), 82 (14)
3b	1671 (C═O, cyclic imide), 1728 (C═O, ester)	1.38 (t, 3H, C$\underline{H}_3$), 4.39 (q, 2H, OC$\underline{H}_2$), 4.46 (s, 2H, S—C$\underline{H}_2$), 5.29 (s, 2H, N—C$\underline{H}_2$), 7.26 (m,10H, Ph—$\underline{H}$), 8.59 (s, 1H, C_6—$\underline{H}$)	12.3 (CH_3), 38.8 (S—CH_2), 47.2 (N—CH_2), 60.4 (O—CH_2), 109.5 (C_5), 127.3–138.2 (Ph-C) 156.4 (C_2), 157.2 (C_4), 159.1 (C_6), 164.2 (CO ester)	382 (M + 1, 10), 381 (M^+, 63), 289 (76), 230 (28), 167 (24), 148 (43), 91 (100), 65 (29)
4a	1659 (C═O, cyclic imide), 1733 (C═O ester)	1.37 (t, 3H, C$\underline{H}_3$), 3.53 (t, 2H, S—C$\underline{H}_2$), 4.35 (q, 2H, OC$\underline{H}_2$), 4.56 (t, 2H, N—C$\underline{H}_2$), 8.52 (s, 1H, C_6—$\underline{H}$)	14.2 (CH_3), 26.6 (S—CH_2), 49.3 (NCH_2), 61.1 (O—CH_2), 112.3 (C_5), 157.3 (C_4), 160.1 (C_6), 164.3 (CO ester)168.3 (C_2)	226 (M^+, 15), 182 (25), 181 (100), 154 (85), 113 (16)

4b	1664 (C=O, cyclic imide), 1737 (C=O ester)	1.30 (t, 3H, C$\underline{H}_3$), 2.25 (m, 2H, 3a-C$\underline{H}_2$), 3.19 (t, 2H, S–C$\underline{H}_2$), 4.11 (t, 2H, N–C$\underline{H}_2$), 4.27 (q, 2H, OC$\underline{H}_2$), 8.40 (s, 1H, C_6–$\underline{H}$)	13.4 (CH_3), 22.6 (3a-CH_2), 28.8 (S–CH_2), 43.4 (N–CH_2), 61.5 (O–CH_2), 111.6 (C_5), 157.6 (C_4), 158.4 (C_6), 165.1 (CO ester) 167.3 (C_2)	—
5	1686 (C=O, cyclic imide), 1744 (C=O ester)	1.33 (t, 3H, C$\underline{H}_3$), 4.13 (q, 2H, OC$\underline{H}_2$), 4.28 (s, 2H, S–C$\underline{H}_2$), 8.74 (s, 1H, C_6–$\underline{H}$)	13.2 (CH_3), 32.7 (S–CH_2), 61.4 (O–CH_2), 111.2 (C_5), 156.2 (C_4), 157.4 (C_2), 160.9 (C_6), 164.3 (CO ester) 171.3 (3a-CO)	—
6	1693 (C=O cyclic imide), 1742 (C=O, ester), 3387 (NH or OH)	1.35 (t, 3H, C$\underline{H}_3$), 1.39 (d, 3H, C_6-C$\underline{H}_3$), 3.42 (d, 1H, C_5–$\underline{H}$), 4.35 (q, 2H, OC$\underline{H}_2$), 4.22 (m, 1H, C_6–$\underline{H}$), 7.62 (b, 1H, N$\underline{H}$), 8.76 (b, 1H, N$\underline{H}$ or S$\underline{H}$)	11.8 (CH_3), 16.2 (6-CH_3), 46.3 (C_5), 50.8 (C_6), 60.4 (OCH_2), 156.3 (C_4), 161.5 (C_2) 166.3 (C=O ester)	217 (M + 1, 18), 216 (M^+, 56), 171 (25), 144 (34), 143 (100), 129 (33), 86 (26), 69 (54)
7a	1665 (C=O, cyclic imide), 1735 (C=O), 3340, 3348 (NH or OH)	1.39 (t, 3H, C$\underline{H}_3$), 4.29 (q, 2H, OC$\underline{H}_2$), 8.82 (s, 1H, C_6–$\underline{H}$), 9.11, 9.31 (b, 2H, O$\underline{H}$, N$\underline{H}$), 11.87 (b, 1H, N$\underline{H}$)	13.2 (CH_3), 61.6 (OCH_2), 111.7 (C_5), 151.5 (C_2), 155.3 (C_4), 157.6 (C_6), 164.2 (C=O ester)	—
7b	1675 (C=O cyclic imide), 1728 (C=O ester), 3348, 3542 (NH or OH)	1.38 (t, 3H, C$\underline{H}_3$), 4.39 (q, 2H, OC$\underline{H}_2$), 7.2 (b, 3H, N$\underline{H}$, N$\underline{H}_2$), 8.63 (s, 1H, C_6–$\underline{H}$), 10.44 (b, 1H, N$\underline{H}$)	12.8 (CH_3), 61.8 (OCH_2), 111.5 (C_5), 150.2 (C_2), 152.3 (C_4), 156.4 (C_6), 164.5 (C=O ester)	199 (M + 1, 58), 198 (M^+, 100), 156 (29), 155 (44), 128 (58), 84 (31), 69 (80)

separated after cooling, was filtered off and recrystallized from ethanol to give hydrazinopyrimidine (**7b**) as yellow crystals. The results are listed in Tables I and II.

REFERENCES

[1] S. A. Shiba, N. M. S. Harb, M. A. El-Kasaby, M. A. Hassan, and M. K. Abou El-Regal, *Phosphorus, Sulfur, and Silicon*, **104,** 15 (1995).
[2] M. A. Hassan and D. Döpp, *Heterocycles*, **45,** 451 (1997).
[3] M. A. Hassan, M. M. Mohamed, and S. A. Shiba, *Phosphorus, Sulfur, and Silicon,* **157,** 97 (2000).
[4] S. A. Shiba, M. M. Mohamed, M. A. Hassan, and A. M. El-Sayed, *Phosphorus, Sulfur, and Silicon,* **158,** 91 (2000).
[5] M. Lissel, S. Schmidt, and B. Neumann, *Synthesis*, 382 (1986).
[6] H. J.-M. Dou, P. Hassanaly, and J. Metzger, *J. Heterocycl. Chem.*, **14,** 321 (1977).
[7] H. J.-M. Dou, P. Hassanaly, J. Kister, G. Vernin, and J. Metzger, *Helv. Chim. Acta*, **61,** 3143 (1978).
[8] P. Hassanaly, H. J.-M. Dou, and M. Ludwikow, *Bull. Soc. Chim. Belg.*, **91,** 661 (1982).
[9] R. H. Koppel, R. H. Springer, R. K. Robins, and C. C. Cheng, *J. Org. Chem.,* **27,** 3614 (1962).
[10] a) A. Palumbo and M. d'Ischia, *Biochem. & Biophys. Res. Comm.*, **282,** 793 (2001); b) D. M. Saleh, G. K. Barrel, C. I. Bailey, and C. M. A. Frampton, *Small Ruminant Research*, **30,** 49 (1998).
[11] a) H. Armstrong et al. (Merck and Co., Inc., USA). WO 0100213, A1 20010104 (2001); *Chem. Abstr.*, **134,** 12273 (2001); b) M. Barvian et al., *J. Med. Chem.*, **43,** 4606 (2000); c) D. H. Kim, *J. Heterocycl. Chem.*, **22,** 173 (1985); d) R. S. Shadbolt and T. L. Ulbricht, *J. Chem. Soc.*, **13,** 1172 (1967).
[12] D. Landini, F. Montanari, and A. Maia, *J. Amer. Chem. Soc.,* **100,** 2796 (1978).
[13] J. E. Gorden and R. Z. Kutina, *J. Amer. Chem. Soc.*, **99,** 3903 (1977).
[14] Yu. M. Volovenko and E. V. Blyumin, *Khim. Geterotsikl. Soedin* (in English), **33,** 1696 (1998).