ISSN 1070-4280, Russian Journal of Organic Chemistry, 2010, Vol. 46, No. 9, pp. 1323–1326. © Pleiades Publishing, Ltd., 2010.
Original Russian Text © A.L. Kurlovich, V.A. Tarasevich, N.G. Kozlov, 2010, published in Zhurnal Organicheskoi Khimii, 2010, Vol. 46, No. 9, pp. 1324–1327.

# Synthesis of Spirocyclic Derivatives of Azaphenanthrene Containing a Hydroxy-*m*-Terphenyl Fragment

**A. L. Kurlovich [a], V. A. Tarasevich [a], and N. G. Kozlov[b]**

[a]*Institute of New Materials Chemistry, National Academy of Sciences of Belarus, Minsk, 220141 Belarus*
*e-mail: kurlovich_andrey@mail.ru*
[b]*Institute of Physical Organic Chemistry, National Academy of Sciences of Belarus, Minsk, Belarus*

Received October 28, 2009

**Abstract**—The reaction of 5'-[(2-naphthylamino)methyl]-2'-hydroxy[1,1':3',1"]terphenyl with paraformaldehyde and 1,3-cyclohexanedione, methyl 2,2-dimethyl-4,6-dioxocyclohexanecarboxylate, dimedone, furan-2,4(3*H*,5*H*)-dione, indan-1,3-dione led to the formation of spiro derivatives of azaphenanthrene.

**DOI:** 10.1134/S1070428010090101

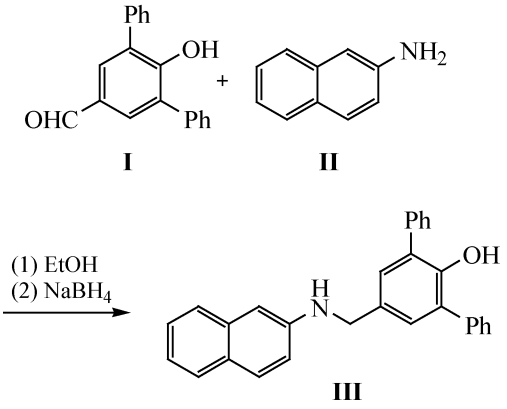
The derivatives of phenanthrene and azaphenanthrene possess a wide range of biological activity and are used as pharmaceuticals. Some publications [1–3] mention the antioxidant properties of phenanthrene derivatives. Besides the phenanthridine ring underlies the structure of certain natural alkaloids and steroids [4].

The synthesis of spiro derivatives of quinoline was formerly performed by a three-component condensation of aromatic amines with dimedone and formaldehyde [5]. Here we report on the first event of a three-component condensation involving a secondary amine containing a hydroxy-*m*-terphenyl fragment. The *m*-terphenyl dertivatives are widely used as polymer stabilizers, dyes, and also drugs and insecticides [6–8]. 2'-Hydroxy[1,1':3',1"]terphenyl-5'-carbaldehyde (**I**) we obtained by procedure [9] in 95% yield. The reductive amination of carbaldehyde **I** with 2-naphthylamine (**II**) gave 5'-[(2-naphthylamino)methyl]-2'-hydroxy[1,1':3',1"]terphenyl (**III**) (Scheme 1).

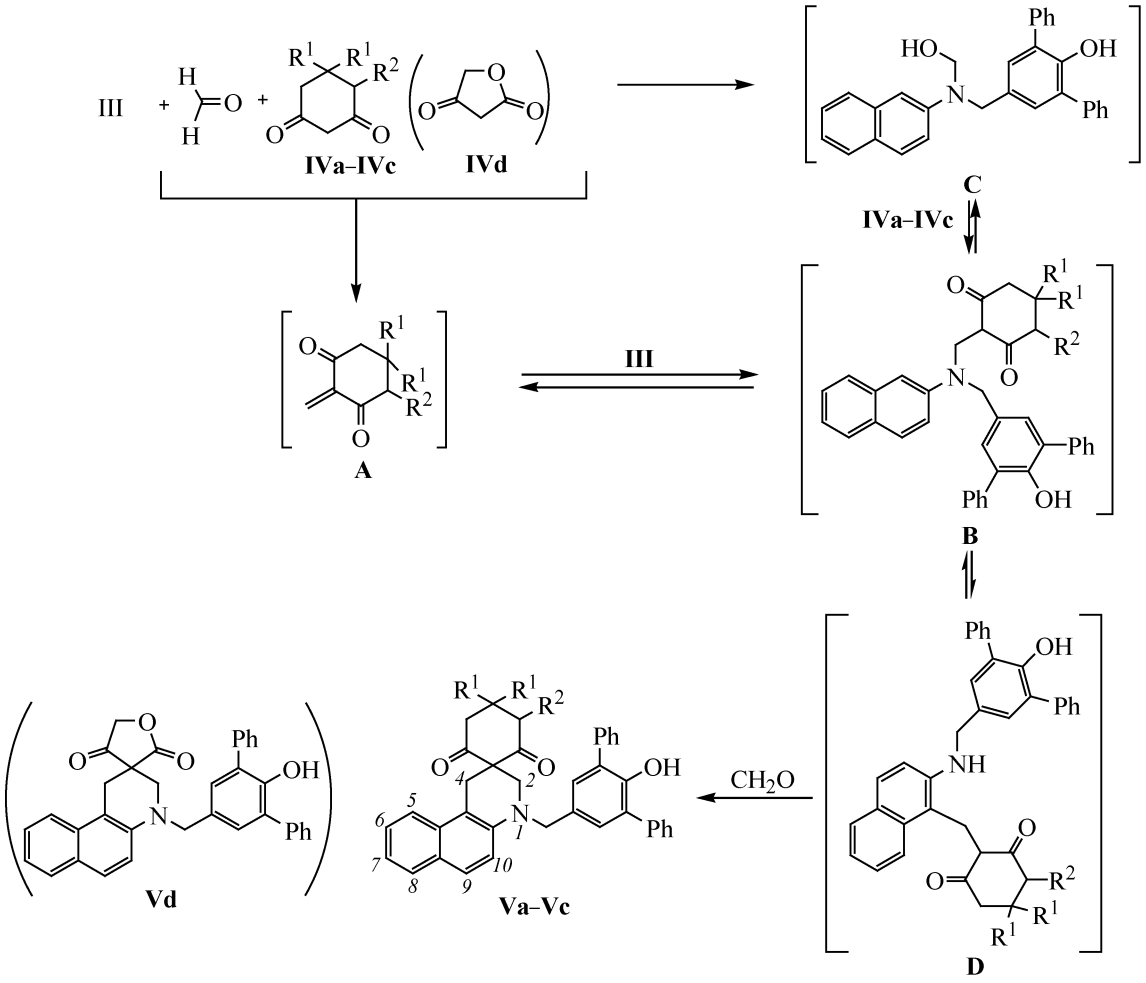
Compound **III** was brought into reaction with formaldehyde and a series of 1,3-diketones: 1,3-cyclohexanedione (**IVa**), 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (**IVb**), methyl 2,2-dimethyl-4,6-dioxocyclohexanecarboxylate (**IVc**), furan-2,4(3*H*,5*H*)-dione (**IVd**). The reaction of amine **III** with diones **IVa–IVd** was carried out by boiling in ethanol. As a result we obtained in 85–96% yield spiro[{1-(2'-hydroxy-[1,1':3',1"]terphenyl-5'-ylmethyl)-1,2,3,4-tetrahydro-1-azaphenanthrene}-3,1'-(2',6'-dioxocyclohexane)] (**Va**), spiro[{1-(2'-hydroxy[1,1':3',1''']terphenyl-5'-ylmethyl)-1,2,3,4-tetrahydro-1-azaphenanthrene}-3,1'-(4',4'-dimethyl-2',6'-dioxocyclohexane)] (**Vb**), spiro-[{1-(2'-hydroxy[1,1':3',1"]terphenyl-5'-ylmethyl)-1,2,3,4-tetrahydro-1-azaphenanthrene}-3,1'-(4',4'-dimethyl-3'-methoxycarbonyl-2',6'-dioxocyclohexane)] (**Vc**) and spiro[{1-(2'-hydroxy[1,1':3',1"]terphenyl-5'-ylmethyl)-1,2,3,4-tetrahydro-1-azaphenanthrene}-3,3'-{2',4'(1'*H*,5'*H*)-dioxofuran}] (**Vd**) (Scheme 2).

This reaction may proceed hypothetically via two mechanisms. According to the first pathway the formation of the spiro derivatives of the azaphenanthroline proceeds through the initial reaction of diketones **IVa–IVd** with formaldehyde giving the α,β-unsaturated diketone **A** where the double bond is activated owing to the conjugation with two contiguous carbonyl groups. Diketone

**Scheme 1.**



**Scheme 2.**




$R^1 = R^2 = H$ (**a**); $R^1 = Me$, $R^2 = H$ (**b**), $COOCH_3$ (**c**).

A further reacts with the molecule of amine **III** forming aminodiketone **B**.

In keeping with the second mechanism the formation of aminodiketone **B** occurs by the reaction of 1,3-diketone with the previously formed hydroxylamine **C**. Aminodiketone **B** rearranges further into intermediate **D** analogously to the transformations during the Hofmann–Martius rearrangement [10]. The subsequent intramolecular Mannich reaction results in compounds **Va–Vd**.

The involvement into the cascade cyclization of the unsymmetrical 1,3-diketone, 4-methoxycarbonyldimedone (**IVc**) (methyl 2,2-dimethyl-4,6-dioxocyclohexanecarboxylate), leads to the formation of compound **Vc** as a mixture of stereoisomers. Under the relatively mild conditions (at boiling the components in ethanol) the reaction proceeds regiospecifically and with a high degree of stereoselectivity: an exclusive formation is observed of spiro[{1-(2'-hydroxy[1,1':3',1"]terphenyl-5'-yl-methyl)-1,2,3,4-tetrahydro-1-azaphenanthrene}-3,1'-(4',4'-dimethyl-3'-methoxycarbonyl-2',6'-dioxo-cyclohexane)] (**Vc**).

The reaction of formaldehyde and amine **III** with indandione **VI** (Scheme 3) was performed by boiling in 1-butanol. As a result we obtained in 91% yield spiro[{1-(2'-hydroxy[1,1':3',1"]terphenyl-5'-yl-methyl)-1,2,3,4-tetrahydro-1-azaphenanthrene}-3,2'-(1*H*-indan-1',3'-dione)] (**VII**).

The composition and structure of obtained compounds **III, Va–Vd**, and **VII** were confirmed by elemental analysis, IR and $^1H$ NMR spectra. In the spectrum of amine **III** the characteristic absorption band of the stretching

vibrations of the secondary amino group appeared as a narrow strong band at 3365 $cm^{-1}$. The characteristic absorption bands for compounds **Va–Vd** and **VII** are those of the stretching vibrations of the C=O groups at 1695 and 1725 $cm^{-1}$.

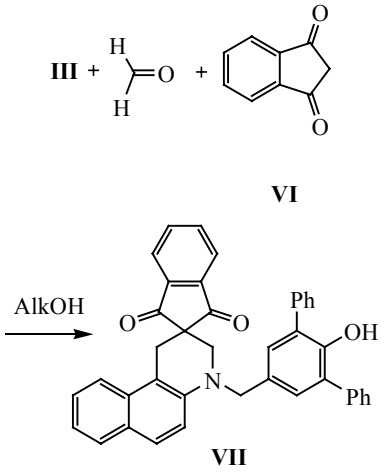
In the $^1H$ NMR spectra of azaphenanthrenes **Va–Vd**, and **VII** a singlet and a doublet were observed at δ 3.40 and 3.82 ppm corresponding to the protons attached to atoms $C^4$ and $C^2$ of the azaphenanthrene fragment. The protons of the group $N\underline{CH_2}Ar$ gave rise to a doublet at δ 4.64 ppm. In the spectrum of spiro derivative **Va** the protons of the methylene groups at the carbon atoms $C^{3'}$ and $C^{5'}$ included into the 1,3-cyclohexane fragment are observed as two multiplets at δ 2.40 and 2.75 ppm respectively. The proton of the methylene group of the 1,3-cyclohexane ring linked to the $C^{4'}$ atom appears as a multiplet at δ 1.85–1.95 ppm. The signal of protons $H^{3'}$ and $H^{5'}$ is located upfield with respect to that of the $H^{4'}$ proton due to the influence of the adjacent carbonyl groups. In the spectrum of azaphenanthrene spiro derivative **Vb** the peaks of the methyl groups of the dimedone fragment are observed at δ 1.05 and 1.20 ppm. In the $^1H$ NMR spectrum of compound **Vc** the methoxy group protons resonate at δ 3.30 ppm. The aromatic protons of the azaphenanthrene fragment give rise to a multiplet at δ 7.2 ppm and doublets at δ 7.65 and 7.90 ppm. The proton signals of the aromatic rings of the hydroxy-*m*-terphenyl fragment give triplets at δ 7.35, 7.40–7.45 ppm and a doublet at δ 7.60 ppm.

## EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Specord 75IR from pellets with KBr. $^1H$ NMR spectra were registered on spectrometers Tesla BS-567A (operating frequency 100 MHz) and Bruker Avance-500 (operating frequency 500 MHz), internal reference TMS. The melting points were measured on a Koeffler heating block.

**2'-Hydroxy[1,1':3',1"]terphenyl-5'-carbaldehyde** (**I**) was obtained from 2,6-diphenylbenzaldehyde and hexamethylenetetramine in the presence of $CF_3CO_2H$ by procedure [9]. A mixture of 12.5 g (0.051 mol) of 2'-hydroxy[1,1':3',1"]terphenyl, 14.2 g (0.101 mol) of urotropin, and 50 ml of $CF_3CO_2H$ was boiled at stirring for 12 h. On distilling off the solvent 150 ml of 3 N HCl was added, and the stirring at 80°C was continued for 3 h. The precipitate was filtered off, washed with water, and recrystallized from ethanol. Yield 13.2 g (95%), colorless crystals, mp 168–169°C. IR spectrum, ν, $cm^{-1}$: 3480 (O–H), 2850 (C–H), 1695 (C=O). $^1H$ NMR spectrum ($CDCl_3$), δ, ppm: 7.46 d ($4H_{arom}$, *J* 7.5 Hz), 7.50–7.55 t ($6H_{arom}$, *J* 7.5 Hz), 7.60 d ($4H_{arom}$, *J* 7.5 Hz), 7.84 s ($2H_{arom}$), 9.94 s (1H, CH). Found, %: C 83.17; H 5.17. $C_{19}H_{14}O_2$. Calculated, %: C 83.19; H 5.14.

**Scheme 3.**




**5'-[(2-Naphthylamino)methyl]-2'-hydroxy-[1,1':3',1"]terphenyl (III).** To a solution of 1.43 g (0.01 mol) of amine **II** in 20 ml of ethanol was added a solution of 2.74 g (0.01 mol) of aldehyde **I** in 10 ml of ethanol. The reaction mixture was boiled for 1 h. On cooling 1.52 g (0.04 mol) of $NaBH_4$ was added, and the mixture was left overnight. The mixture obtained was treated with water. The separated precipitate was filtered off and recrystallized from ethanol. Yield 3.3 g (82%), colorless crystals, mp 128°C. IR spectrum, ν, $cm^{-1}$: 3480 (O–H), 3365 (N–H). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 4.50 C (2H, $CH_2$), 6.50–6.60 m ($2H_{arom}$), 7.25–7.55 m ($10H_{arom}$; 1H, NH), 7.39–7.80 m ($7H_{arom}$ ; 1H, OH). Found, %: C 86.80; H 5.71; N 3.50. $C_{29}H_{23}NO$. Calculated, %: C 86.75; H 5.77; N 3.49.

**Spiro[{1-(2'-hydroxy[1,1':3',1"]terphenyl-5'-ylmethyl)-1,2,3,4-tetrahydro-1-azaphenanthrene}-3,1'-(2',6'-dioxocyclohexane)] (Va).** To a solution of 2.68 g (0.005 mol) of amine **III** in 30 ml of ethanol was added 0.6 g (0.02 mol) of paraformaldehyde. The mixture was boiled to complete dissolution of the precipitate, then 0.56 g (0.005 mol) of 1,3-cyclohexanedione was added, and the boiling was continued for 6–8 h. On cooling the reaction mixture the separated crystalline precipitate was filtered off, washed with ethanol, and recrystallized from benzene. Yield 5.15 g (96%), colorless crystals, mp

227°C. IR spectrum, ν, cm$^{-1}$: 3445 (O–H), 1725 (C=O), 1695 (C=O). $^1$H NMR spectrum ($CD_3COCD_3$), δ, ppm: 1.85–1.95 m (2H, $CH_2$), 2.40 m (2H, $CH_2$), 2.75 m (2H, $CH_2$), 3.40 C (2H, $CH_2$), 3.82 d (2H, $NCH_2$, *J* 13 Hz), 4.64 d (2H, $NCH_2Ar$, *J* 11 Hz), 7.20–7.25 m ($4H_{arom}$; 1H, OH), 7.35 t ($3H_{arom}$, *J* 7.5 Hz), 7.40–7.45 t ($5H_{arom}$, *J* 7.6 Hz), 7.60 d ($4H_{arom}$, *J* 7.5 Hz), 7.65 d ($1H_{arom}$, *J* 7.5 Hz), 7.90 d ($1H_{arom}$, *J* 7.6 Hz). Found, %: C 82.59; H 5.84; N 2.62. $C_{37}H_{31}NO_3$. Calculated, %: C 82.66; H 5.81; N 2.61.

Compounds **Vb–Vd** were similarly prepared.

**Spiro[{1-(2'-hydroxy[1,1':3',1"]terphenyl-5'-ylmethyl)-1,2,3,4-tetrahydro-1-azaphenanthrene}-3,1'-(4',4'-dimethyl-2',6'-dioxocyclohexane)] (Vb)** was obtained from amine **III** and dimedone (**IVb**). Yield 5.2 g (92%), colorless crystals, mp 229°C. IR spectrum, ν, cm$^{-1}$: 3445 (O–H), 1724 (C=O), 1695 (C=O). $^1$H NMR spectrum ($CD_3COCD_3$), δ, ppm: 1.05 s (3H, $CH_3$), 1.20 s (3H, $CH_3$), 2.50 m (2H, $CH_2$), 3.25 m (2H, $CH_2$), 3.40 s (2H, $CH_2$), 3.80 d (2H, $NCH_2$, *J* 13 Hz), 4.60 d (2H, $NCH_2Ar$, *J* 11 Hz), 7.20–7.25 m ($4H_{arom}$, 1H, OH), 7.35 t ($3H_{arom}$, *J* 7.5 Hz), 7.40–7.45 t ($5H_{arom}$, *J* 7.6 Hz), 7.60 d ($4H_{arom}$, *J* 7.5 Hz), 7.65 d ($1H_{arom}$, *J* 7.5 Hz), 7.90 d ($1H_{arom}$, *J* 7.6 Hz). Found, %: C 82.75; H 6.26; N 2.46. $C_{39}H_{35}NO_3$. Calculated, %: C 82.80; H 6.24; N 2.48.

**Spiro[{1-(2'-hydroxy[1,1':3',1"]terphenyl-5'-ylmethyl)-1,2,3,4-tetrahydro-1-azaphenanthrene}-3,1'-(4',4'-dimethyl-3'-methoxycarbonyl-2',6'-dioxocyclohexane)] (Vc)** was obtained from amine **III** and methyl 2,2-dimethyl-4,6-dioxocyclohexanecarboxylate (**IVc**). Yield 5.3 g (85%), Grey crystals, mp 219°C. IR spectrum, ν, cm$^{-1}$: 3450 (O–H), 1724 (C=O), 1705 (C=O), 1695 (C=O), 1233 (C–O–C). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 0.90 s (3H, $CH_3$), 0.98 s (3H, $CH_3$), 1.05 s (3H, $CH_3$), 1.20 s (3H, $CH_3$), 2.40 s (1H, $CH_2$), 2.45 s (1H, $CH_2$), 3.20 m (4H, $CH_2$), 3/30 s (3H, $CH_3$), 3,35 s (3H, $CH_3$), 3.45 m (4H, $CH_2$), 3.85 m (4H, $NCH_2$), 4.64 m (4H, $NCH_2Ar$), 7.20–7.25 m ($8H_{arom}$; 1H, OH), 7.35 m ($6H_{arom}$), 7.40–7.45 m ($10H_{arom}$), 7.60 m ($8H_{arom}$), 7.65 m ($2H_{arom}$), 7.90 m ($2H_{arom}$). Found, %: C 78.91; H 5.94; N 2.22. $C_{41}H_{37}NO_5$. Calculated, %: C 78.95; H 5.98; N 2.25.

**Spiro[{1-(2'-hydroxy[1,1':3',1"]terphenyl-5'-ylmethyl)-1,2,3,4-tetrahydro-1-azaphenanthrene}-3,3'-{2',4'(1'H,5'H)-dioxofuran}] (Vd)** was obtained from amine **III** and furan-2,4(3*H*,5*H*)-dione (**IVd**). Yield 4.9 g (93%), colorless crystals, mp 230°C. IR spectrum, ν, cm$^{-1}$: 3450 (O–H), 1780 (C=O), 1720 (C=O), 1265 (C–O–C). $^1$H NMR spectrum ($CD_3COCD_3$ and DMSO-$d_6$), δ, ppm: 3.40 s (2H, $CH_2$), 3.82 d (2H, $NCH_2$, *J* 13 Hz), 4.64 d (2H, $NCH_2Ar$, *J* 11 Hz), 5.20 m (2H, $CH_2$), 7.20–7.25 m ($4H_{arom}$; 1H, OH), 7.35 t ($3H_{arom}$, *J* 7.5 Hz), 7.40–7.45 t ($5H_{arom}$, *J* 7.6 Hz), 7.60 d ($4H_{arom}$, *J* 7.5 Hz), 7.65 d ($1H_{arom}$, *J* 7.5 Hz), 7.90 d ($1H_{arom}$, *J* 7.6 Hz). Found, %: C 79.96; H 5.14; N 2.62. $C_{35}H_{27}NO_4$. Calculated, %: C 79.98; H 5.18; N 2.66.

**Spiro[{1-(2'-hydroxy[1,1':3',1"]terphenyl-5'-ylmethyl)-1,2,3,4-tetrahydro-1-azaphenanthrene}-3,2'-(H-indan-1',3'-dione)] (VII)**. To a solution of 1.37 g (0.005 mol) of paraformaldehyde in 20 ml of 1-butanol was added a solution of 2.68 g (0.005 mol) of amine **III** in 10 ml of 1-butanol and a solution of 0.73 g (0.005 mol) of indandione **VI** in 10 ml of 1-butanol. The reaction mixture was boiled for 4 h. On cooling the reaction mixture the separated crystalline precipitate was filtered off and three times washed with hot acetone. Yield 5.2 g (91%), colorless crystals, mp 227°C. IR spectrum, ν, cm$^{-1}$: 3450 (O–H), 1724 (C=O), 1695 (C=O). $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 3.40 s (2H, $CH_2$), 3.80 d (2H, $NCH_2$, *J* 13 Hz), 4.60 d (2H, $NCH_2CHAr$, *J* 11 Hz), 7.20–7.25 m ($6H_{arom}$; 1H, OH), 7.35 t ($3H_{arom}$, *J* 7.5 Hz), 7.40–7.45 t ($5H_{arom}$, *J* 7.6 Hz), 7.60 d ($4H_{arom}$, *J* 7.5 Hz), 7.65 d ($1H_{arom}$, *J* 7.5 Hz), 7.90 d ($1H_{arom}$, *J* 7.6 Hz). Found, %: C 84.06; H 5.18; N 2.42. $C_{40}H_{29}NO_3$. Calculated, %: C 84.04; H 5.11; N 2.45.

## REFERENCES


1. Hon-Yi, Chen, Ming-Shi, Shiao, and Yu-Lin, Huang. *J. Nat. Prod*., 1999, vol. 62, p. 1225.
2. Milian, L., Estelles, R., and Abarca, B., *Chem. Pharm. Bull.*, 2004, vol. 52, 696.
3. Dovgopolyi, E.E., Eminov, E.A., Zimina, K.I., and Siryuk, A.G., *Chem. Technol. Fuels Oils*, 1972, vol. 8, p. 22.
4. Fieser, L.F. and Fieser, M., *Natural Products Related to Phenanthrene,* New York: Reinhold, 1949.
5. Kozlov, N.G. and Kadutskii, A.P., *Tetrahedron Lett.*, 2008, vol. 49, p. 4560.
6. Barnekow, A., *Bioscience Reports*, 1983, vol. 3, 153.
7. Jacobs, S., Kull, F.C., Earp, H.S., Svoboda, M.E., Yan, Wyk, J.J., and Cuatrecasas, P., *J. Biol. Chem*., 1983, vol. 258, p. 958.
8. Westermark, B., Wasteson, A., and Heldin, C.-H., *Nature,* 1982, vol. 295, p. 419.
9. Cortes, E., Martinez, R., Avila, J.G., and Toscano, R.A., *J. Heterocyclic. Chem.*, 1988, vol. 25, p. 895.
10. Gauptman, Z., Grefe, Yu., and Remane, Kh., *Organicheskaya khimiya* (Organic Chemistry), Moscow: Khimiya, 1979, p. 487.