Russian Journal of Organic Chemistry, Vol. 39, No. 9, 2003, pp. 1349–1355. Translated from Zhurnal Organicheskoi Khimii, Vol. 39, No. 9, 2003, pp. 1421–1427.

Synthesis of 1,6-Dihydro- and 4-(4-Nitrophenyl)-1,2,3,4-tetrahydropyrimidine, 1*H*- and 1-Phenyl-1*H*-pyrazole, and Isoxazole Derivatives on the Basis of Cyclopentanonopimaric Acid

E. V. Tret'yakova, O. B. Flekhter, F. Z. Galin, L. V. Spirikhin, I. P. Baikova, and G. A. Tolstikov

Institute of Organic Chemistry, Ufa Research Center, Russian Academy of Sciences, pr. Oktyabrya 71, Ufa, 450054 Bashkortostan, Russia
fax: (3472) 356 066; e-mail: obf@anrb.ru

Received December 18, 2002

Abstract—Reactions of cyclopentanonopimaric acid dimethyl ester with phosphoryl chloride, ethyl formate, and *p*-nitrobenzaldehyde afforded $\Delta^{15(16)}$-16-formyl-15-chloro, 16-hydroxymethylene-15-oxo, and 16-nitrobenzylidene-15-oxo derivatives which were subjected to heterocyclizations to obtain new diterpene pyrimidine, pyrazole, and oxazole derivatives.

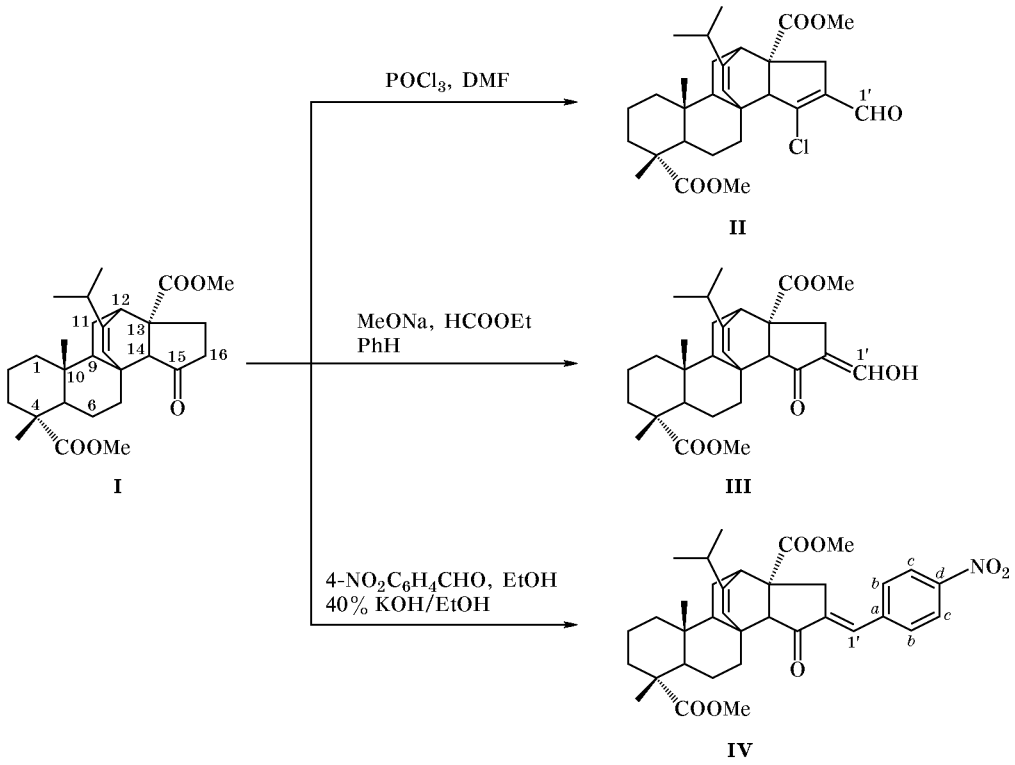
In the recent years, an interest has been revived in studying chemical transformations of diterpene acids, specifically of the abietane series, due to their use in the synthesis of biologically active compounds. Abietic acid was converted into steroids of the pregnane and androstane series [1, 2] and utilized in the total synthesis of (+)-3-deoxyaphidicolin as selective inhibitor of eukariotic DNA α-polymerase [3] and in the partial stereoselective synthesis of (+)-pisiferic acid [4]. Haslinger and Michl [5] described a multistep synthesis from abietic acid of (+)-taxodione which has a unique structure and acts as inhibitor of Walker's carcinosarcoma 256. Abietic acid is a starting compound for the preparation of highly active fragrant substances, e.g., ambrox [6] and (+)-ambrenolide [7]. Compounds possessing antifidant activity were found among derivatives of abietic and levopimaric acids [8, 9]. Diterpenoids containing a heterocyclic fragment attract a considerable interest. For example, some indoloterpenes inhibit micronimal cholesterin–acyl transferase [10], and [2,3-*d*]imidazoles containing a dehydroabietic acid moiety are potential antibacterial and antifungal agents [11]. Taking into account the importance of the problem and accessibility of the initial compounds, we have synthesized a series of diterpene heterocycles on the basis of cyclopentanonopimaric acid dimethyl ester (**I**) [12] with a view to examine their biological activity. Cyclopentanonopimaric acid is readily available from quinopimaric acid [13]; it was selected as initial diterpenoid due to its structural similarity to meroterpenoids which are inhibitors of protein harnesil transferase and antifidant metabolites [14].

As key intermediates for heterocyclizations we used compounds **II**–**IV** which were synthesized from ester **I** by the procedures reported previously [15–17] (Scheme 1). Compound **II** was prepared according to Vilsmeier–Haak by reaction of ketone **I** with phosphoryl chloride in dimethylformamide on heating. The IR spectrum of **II** contained characteristic absorption bands of the aldehyde group (1695 cm^{-1}) and C–Cl bond (785 cm^{-1}); in the ^1H NMR spectrum of this compound we observed a broadened signal from the aldehyde proton at δ 9.90 ppm. The signals from C^{15} and C^{16} in the ^{13}C NMR spectrum changed their position relative to those typical of initial compound **I** (δ_C 150.2 and 137.3 ppm against 218.1 and 30.5 ppm, respectively).

Hydroxymethylene-substituted ketone **III** was synthesized by reaction of **I** with ethyl formate in benzene in the presence of sodium methoxide. In the IR spectrum of **III** we observed absorption bands belonging to the hydroxy group (3220–3440 cm^{-1}). The NMR spectra of **III** contained additional signals from the hydroxymethylene group at δ_C 166.4 ppm ($C^{1'}$) and δ 8.71 (1′-H) and 8.15 ppm (OH). The reaction of compound **I** with *p*-nitrobenzaldehyde in ethanolic potassium hydroxide afforded *p*-nitrobenzylidene derivative **IV**. The product showed in the

1070-4280/03/3909-1349 $25.00 © 2003 MAIK "Nauka / Interperiodica"

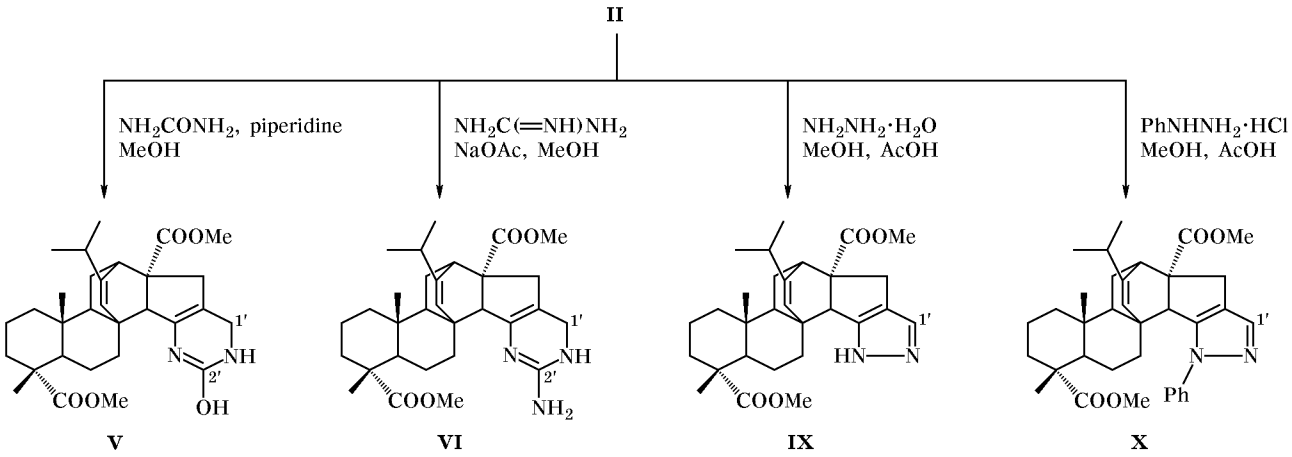
Scheme 1.



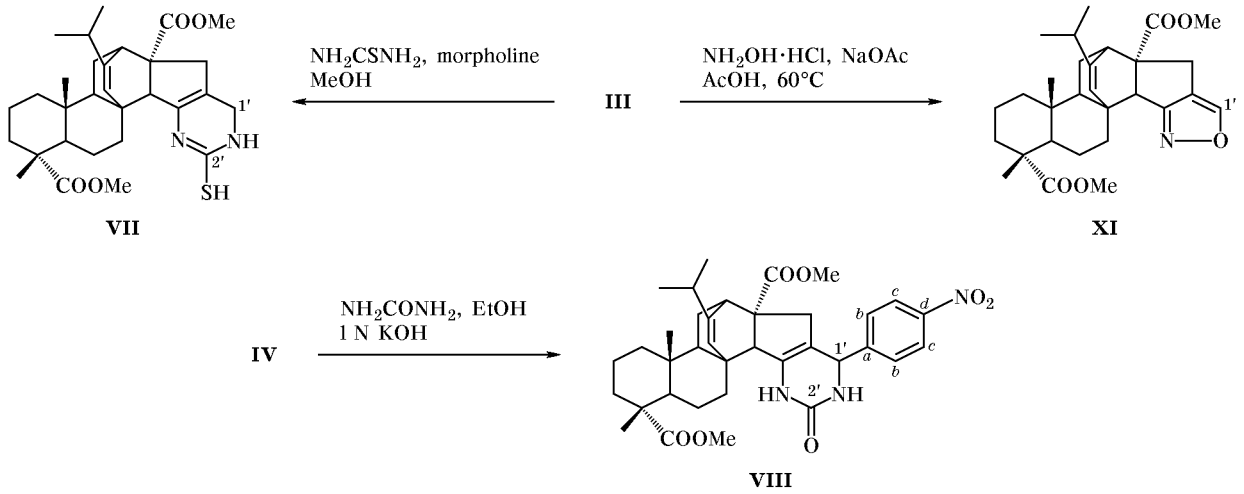
IR spectrum a band at 1580 cm^{-1}, corresponding to the aromatic substituent. In the ^1H NMR spectrum, signals from the aromatic protons appeared at δ 6.80–7.00 and 7.25–7.55 ppm, and the 1′-H signal was observed at δ 8.00–8.05 ppm as a multiplet with small long-range coupling constants. The corresponding ^{13}C signals were located in the δ_C range from 121.1 to 145.5 ppm.

As might be expected, the reactions of aldehyde **II** with urea and guanidine hydrochloride in methanol resulted in formation of fused 2-hydroxy- and 2-aminopyrimidine derivatives **V** and **VI** in 58–62% yield (Scheme 2). Their structure was determined by spectral methods. The IR spectra of **V** and **VI** contained absorption bands in the region 3265–3390 cm^{-1} due to stretching vibrations of the NH, NH_2, and OH groups. The corresponding protons appeared in the ^1H NMR spectra as downfield broadened signals at δ 9.70–9.95 ppm. Resonance of the 1′-H proton was observed at δ 5.90 and 6.05 ppm as a singlet.

Scheme 2.



Scheme 3.



A convenient method for building up a pyrimidine ring is based on the reaction of formyl ketones with urea derivatives. By heating compound **III** with thiourea in methanol containing a catalytic amount of morpholine we obtained 2-sulfanylpyrimidine **VII** (Scheme 3). Unlike 2-hydroxy derivative **V**, the $C^{2'}$ signal in the ^{13}C NMR spectrum of **VII** is displaced to 145.3 ppm. Nitrophenyl-substituted pyrimidine **VIII** was synthesized by cyclization of compound **IV** with urea in boiling ethanol. The spectral parameters of product **VIII** indicated the presence of fused pyrimidine ring. Carbon atoms of the heteroring (C^{15}, C^{16}, $C^{2'}$, and $C^{1'}$) gave signals at δ_C 145.6, 123.5, 156.9, and 54.9 ppm, respectively. In the ^1H NMR spectrum we observed coupling between the NH proton and 1′-H with a constant J of 4.5 Hz. Signals from the aromatic ring appeared at δ 6.80–7.00 and 7.25–7.55 ppm and δ_C 121.2–140.3 ppm. The IR spectrum contained absorption bands at 3380 (NH), 1720 (C=O, pyrimidine ring), and 1540 cm^{-1} ($C-C_{arom}$).

Pyrazole derivatives **IX** and **X** were synthesized by reaction of aldehyde **II** with hydrazine hydrate and phenylhydrazine hydrochloride, respectively, in methanol in the presence of acetic acid (Scheme 2). Their yields were 61–69%. Signals from the pyrazole ring carbon atoms (C^{15}, C^{16}, and $C^{1'}$) in **IX** were observed in the ^{13}C NMR spectra at δ_C 137.3–134.6, 111.3–111.0, and 154.8–154.9 ppm, and the 1′-H proton signal was located in a weak field (δ 7.20 and 7.23 ppm) as a singlet. Compound **X** having a phenyl group on the nitrogen is characterized by more downfield signals, δ 6.75–7.19 ppm (a multiplet) and δ_C 123.8–134.5 ppm.

Treatment of compound **III** with hydroxylamine hydrochloride in acetic acid at 60°C afforded isoxazole derivative **XI** (Scheme 3). The 1′-H signal in the ^1H NMR spectrum of **XI** was observed in a stronger field relative to the corresponding signal of **III**, and the C^{15}, C^{16}, and $C^{1'}$ signals were located at δ_C 167.1, 122.6, and 148.9 ppm, respectively.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples dispersed in mineral oil. The ^{13}C and ^1H NMR spectra were obtained on a Bruker AM-300 spectrometer (75.5 and 300 MHz, respectively) using tetramethylsilane as internal reference. The optical rotations were measured on a Perkin–Elmer MC-241 polarimeter (in $CHCl_3$). The melting points were determined on a Boetius device. TLC analysis was performed on Silufol plates (Chemapol, Czechia) using chloroform–methanol (20 : 1) as eluent; spots were visualized by treatment with a 10% solution of phosphotungstic acid in ethanol, followed by heating for 2–3 min at 100–120°C. Dimethyl ester **I** was synthesized by the procedure described in [13].

Dimethyl 16-chloro-15-formyl-19-isopropyl-5,9-dimethylpentacyclo[10.5.2.0^{1,10}.0^{4,9}.0^{13,17}]nonadec-18-ene-5,13-dicarboxylate (II). A cold mixture of 2 ml of $POCl_3$ and 2 ml of DMF was added with stirring to a solution of 1 mmol (0.47 g) of compound **I** in 10 ml of chloroform. The mixture was allowed to warm up to room temperature and was then heated for 4 h under reflux in a nitrogen atmosphere. The mixture was concentrated under reduced pressure to a half of the initial volume, poured into cold water, and extracted with chloroform (3 × 10 ml). The combined extracts were washed with water (3 × 50 ml), dried over $CaCl_2$, and evaporated under reduced

pressure, and the residue was subjected to chromatography on aluminum oxide using chloroform as eluent. Yield 0.44 g (88%), mp 153–155°C. IR spectrum, ν, cm^{-1}: 1730, 1695 (CHO), 1635, 1495, 1390, 1290, 1270, 1245, 1205, 1150, 1120, 1080, 1030, 1005, 970, 890, 855, 820, 785 (C–Cl), 740. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.49 s (3H, 10-CH_3), 0.80 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.85 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.89–0.98 m (2H, 1-H$_{ax}$, 11-H$_{ax}$), 1.05 s (3H, 5-CH_3), 1.17–1.50 m (8H, 1-H$_{eq}$, 2-H$_{ax}$, 2-H$_{eq}$, 3-H$_{eq}$, 6-H$_{ax}$, 6-H$_{eq}$, 7-H$_{ax}$, 7-H$_{eq}$), 1.51–1.72 m (4H, 3-H$_{ax}$, 5-H, 9-H, 11-H$_{eq}$), 2.00 sept [1H, C**H**$(CH_3)_2$, J = 6.8], 2.35 d.d.d (1H, 12-H, $^4J_{12,19}$ = 1.6, $^3J_{12,11\text{-}ax}$ = 2.2, $^3J_{12,11\text{-}eq}$ = 13.2), 2.85 br.s (1H, 14-H), 3.40 d (2H, 17-H$_{ax}$, 17-H$_{eq}$, J = 2.6), 3.55 s (3H, $COOCH_3$), 3.65 s (3H, $COOCH_3$), 5.19 br.s (1H, 19-H), 9.90 br.s (1H, 1′-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 38.5 (C^1), 16.9 (C^2), 37.5 (C^3), 46.9 (C^4), 51.8 (C^5), 21.8 (C^6), 36.6 (C^7), 43.1 (C^8), 52.4 (C^9), 37.9 (C^{10}), 25.1 (C^{11}), 41.8 (C^{12}), 66.3 (C^{13}), 53.5 (C^{14}), 150.2 (C^{15}), 137.3 (C^{16}), 34.2 (C^{17}), 146.8 (C^{18}), 125.5 (C^{19}), 36.1 (C^{20}), 20.9 (C^{21}), 19.8 (C^{22}), 16.7 (C^{23}), 15.6 (C^{24}), 179.1 (C^{25}), 176.0 (C^{26}), 48.8 (C^{27}), 54.5 (C^{28}), 187.5 (C$^{1'}$). Found, %: C 69.05; H 7.70; Cl 7.20. $C_{29}H_{39}ClO_5$. Calculated, %: C 69.24; H 7.81; Cl 7.05.

Dimethyl 15-hydroxymethylene-19-isopropyl-5,9-dimethyl-16-oxopentacyclo[10.5.2.0^{1,10}.0^{4,9}.0^{13,17}]-nonadec-18-ene-5,13-dicarboxylate (III). Freshly distilled (over P_2O_5) ethyl formate, 1 ml, was added with stirring at 20°C to a suspension of 0.5 g of sodium methoxide in 10 ml of dry benzene, and 20 min after a solution of 1 mmol (0.47 g) of compound **I** in 20 ml of dry benzene was added dropwise. The mixture was stirred for 4 h at room temperature, left to stand for 15 h, and poured into 50 ml of 5% hydrochloric acid. The organic phase was separated, the aqueous phase was extracted with benzene (2 × 50 ml), and the combined extracts were washed with water (3 × 30 ml), dried over $MgSO_4$, and evaporated under reduced pressure. Yield 0.44 g (90%), mp 77–79°C. IR spectrum, ν, cm^{-1}: 3440–3220 (OH), 1740, 1680, 1635, 1470, 1390, 1310, 1260, 1205, 1150, 1120, 1090, 1040, 1005, 950, 890, 840, 740. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.48 s (3H, 10-CH_3), 0.80 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.85 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.91–0.99 m (2H, 1-H$_{ax}$, 11-H$_{ax}$), 1.05 s (3H, 5-CH_3), 1.15–1.45 m (8H, 1-H$_{eq}$, 2-H$_{ax}$, 2-H$_{eq}$, 3-H$_{eq}$, 6-H$_{ax}$, 6-H$_{eq}$, 7-H$_{ax}$, 7-H$_{eq}$), 1.50–1.70 m (4H, 3-H$_{ax}$, 5-H, 9-H, 11-H$_{eq}$), 2.00 sept [1H, C**H**$(CH_3)_2$, J = 6.8], 2.35 d.d.d (1H, 12-H, $^4J_{12,19}$ = 1.6, $^3J_{12,11\text{-}ax}$ = 2.2, $^3J_{12,11\text{-}eq}$ = 13.2), 2.51 s (2H, 17-H$_{ax}$, 17-H$_{eq}$), 2.88 br.s (1H, 14-H), 3.55 s (3H, $COOCH_3$), 3.65 s (3H, $COOCH_3$), 5.20 br.s (1H, 19-H), 8.15 br.s (1H, OH), 8.70 s (1H, 1′-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 37.9 (C^1), 17.0 (C^2), 36.6 (C^3), 47.1 (C^4), 51.9 (C^5), 21.7 (C^6), 34.3 (C^7), 42.4 (C^8), 52.4 (C^9), 37.5 (C^{10}), 25.4 (C^{11}), 41.8 (C^{12}), 62.5 (C^{13}), 53.3 (C^{14}), 208.1 (C^{15}), 112.5 (C^{16}), 23.9 (C^{17}), 146.7 (C^{18}), 126.1 (C^{19}), 33.0 (C^{20}), 21.1 (C^{21}), 19.9 (C^{22}), 16.8 (C^{23}), 15.6 (C^{24}), 179.2 (C^{25}), 176.9 (C^{26}), 49.2 (C^{27}), 58.2 (C^{28}), 166.4 (C$^{1'}$). Found, %: C 70.69; H 8.40. $C_{29}H_{40}O_6$. Calculated, %: C 71.87; H 8.32.

Dimethyl 19-isopropyl-5,9-dimethyl-15-(4-nitrophenylmethylene)-16-oxopentacyclo[10.5.2.0^{1,10}.0^{4,9}.0^{13,17}]nonadec-18-ene-5,13-dicarboxylate (IV). To a solution of 1 mmol (0.47 g) of compound **I** and 10 mmol (0.16 g) of *p*-nitrobenzaldehyde in 10 ml of EtOH we added on cooling to 10°C 2.5 ml of a 40% solution of potassium hydroxide in EtOH. After 30 min, the mixture was allowed to warm up to room temperature, stirred for 24 h, and poured into 50 ml of 5% aqueous acetic acid. The precipitate was filtered off, washed with water, dried, and purified by chromatography on aluminum oxide using benzene as eluent. Yield 0.50 g (85%), mp 130–132°C. IR spectrum, ν, cm^{-1}: 1720, 1654, 1630, 1580 (C–C$_{arom}$), 1460, 1380, 1350, 1245, 1190, 1140, 1100, 1065, 760, 730. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.47 s (3H, 10-CH_3), 0.80 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.82 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.85–0.98 m (2H, 1-H$_{ax}$, 11-H$_{ax}$), 1.03 s (3H, 5-CH_3), 1.18–1.51 m (8H, 1-H$_{eq}$, 2-H$_{ax}$, 2-H$_{eq}$, 3-H$_{eq}$, 6-H$_{ax}$, 6-H$_{eq}$, 7-H$_{ax}$, 7-H$_{eq}$), 1.55–1.72 m (4H, 3-H$_{ax}$, 5-H, 9-H, 11-H$_{eq}$), 2.05 sept [1H, C**H**$(CH_3)_2$ J = 6.8], 2.37 d.d.d (1H, 12-H, $^4J_{12,19}$ = 1.6, $^3J_{12,11\text{-}ax}$ = 2.2, $^3J_{12,11\text{-}eq}$ = 13.2), 2.88 br.s (1H, 14-H), 3.40 d (2H, 17-H$_{ax}$, 17-H$_{eq}$, J = 2.6), 3.55 s (3H, $COOCH_3$), 3.65 s (3H, $COOCH_3$), 5.19 br.s (1H, 19-H), 6.80–7.00 m (2H, H$_c$), 7.25–7.55 m (2H, H$_b$), 8.00–8.05 m (1H, 1′-H). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 37.5 (C^1), 15.6 (C^2), 34.5 (C^3), 42.1 (C^4), 49.3 (C^5), 20.0 (C^6), 33.0 (C^7), 40.6 (C^8), 51.8 (C^9), 36.7 (C^{10}), 25.3 (C^{11}), 38.2 (C^{12}), 60.5 (C^{13}), 53.2 (C^{14}), 206.2 (C^{15}), 123.5 (C^{16}), 30.7 (C^{17}), 148.3 (C^{18}), 124.2 (C^{19}), 32.7 (C^{20}), 20.5 (C^{21}), 21.7 (C^{22}), 17.8 (C^{23}), 17.0 (C^{24}), 179.3 (C^{25}), 173.5 (C^{26}), 46.9 (C^{27}), 56.9 (C^{28}), 145.5 (C$^{1'}$), 135.1 (C^a), 129.1 and 129.3 (C^b), 121.1 and 121.4 (C^c), 140.4 (C^d). Found, %: C 70.99; H 7.40; N 2.50. $C_{35}H_{43}NO_7$. Calculated, %: C 71.28; H 7.35; N 2.38.

Dimethyl 18-hydroxy-23-isopropyl-5,9-dimethyl-17,19-diazahexacyclo[10.9.2.0^{1,10}.0^{4,9}.0^{13,21}.0^{15,20}]-tricosa-15(20),18,22-triene-5,13-dicarboxylate (V). To a solution of 1 mmol (0.50 g) of compound **II** in 25 ml of methanol we added 0.48 g (8 mmol) of urea and 2 drops of freshly distilled piperidine. The mixture was heated for 10 h under reflux, evaporated by half under reduced pressure, and poured into 100 ml of cold water. The precipitate was filtered off, washed with water, dried, and purified by chromatography on aluminum oxide using benzene as eluent. Yield 0.32 g (62%), mp 105–107°C. IR spectrum, ν, cm^{-1}: 3360 (OH), 1740, 1690 (C=N), 1480, 1390, 1260, 1240, 1200, 1170, 1120, 1080, 1040, 970, 910, 825, 740. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.49 s (3H, 10-CH_3), 0.80 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.85 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.89–0.98 m (2H, 1-H$_{ax}$, 11-H$_{ax}$), 1.05 s (3H, 5-CH_3), 1.17–1.50 m (8H, 1-H$_{eq}$, 2-H$_{ax}$, 2-H$_{eq}$, 3-H$_{eq}$, 6-H$_{ax}$, 6-H$_{eq}$, 7-H$_{ax}$, 7-H$_{eq}$), 1.51–1.72 m (4H, 3-H$_{ax}$, 5-H, 9-H, 11-H$_{eq}$), 2.00 sept [1H, C**H**(CH$_3$)$_2$, J = 6.8], 2.35 d.d.d (1H, 12-H, $^4J_{12,19}$ = 1.6, $^3J_{12,11\text{-}ax}$ = 2.2, $^3J_{12,11\text{-}eq}$ = 13.2), 2.85 br.s (1H, 14-H), 3.40 t (2H, 17-H$_{ax}$, 17-H$_{eq}$, J = 3.9), 3.55 s (3H, $COOCH_3$), 3.65 s (3H, $COOCH_3$), 5.19 br.s (1H, 19-H), 6.05 s (2H, 1′-H$_{ax}$, 1′-H$_{eq}$), 9.95 br.s (2H, OH, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 37.9 (C^1), 16.9 (C^2), 36.4 (C^3), 46.9 (C^4), 51.7 (C^5), 20.9 (C^6), 33.9 (C^7), 41.3 (C^8), 52.5 (C^9), 37.3 (C^{10}), 21.6 (C^{11}), 38.3 (C^{12}), 61.1 (C^{13}), 58.0 (C^{14}), 136.4 (C^{15}), 111.9 (C^{16}), 25.2 (C^{17}), 146.6 (C^{18}), 126.4 (C^{19}), 33.0 (C^{20}), 20.8 (C^{21}), 20.3 (C^{22}), 16.6 (C^{23}), 15.3 (C^{24}), 178.9 (C^{25}), 172.5 (C^{26}), 48.9 (C^{27}), 53.0 (C^{28}), 61.8 (C$^{1'}$), 158.9 (C$^{2'}$). Found, %: C 70.05; H 8.10; N 5.30. $C_{30}H_{42}N_2O_5$. Calculated, %: C 70.56; H 8.29; N 5.49.

Dimethyl 18-amino-23-isopropyl-5,9-dimethyl-17,19-diazahexacyclo[10.9.2.0^{1,10}.0^{4,9}.0^{13,21}.0^{15,20}]-tricosa-15(20),18,22-triene-5,13-dicarboxylate (VI). A mixture of 1 mmol (0.50 g) of compound **II**, 0.76 g (8 mmol) of guanidine hydrochloride, and 0.66 g (8 mmol) of sodium acetate in 30 ml of methanol was heated for 10 h under reflux. The mixture was then treated as described above for the synthesis of **V**. Yield 0.29 g (58%), mp 138–140°C. IR spectrum, ν, cm^{-1}: 3390, 3265 (NH), 1740, 1660 (C=N), 1480, 1390, 1310, 1260, 1200, 1175, 1125, 1080, 1040, 1000, 930, 880, 825, 805, 740. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.45 s (3H, 10-CH_3), 0.80 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.83 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.88–0.98 m (2H, 1-H$_{ax}$, 11-H$_{ax}$), 1.02 s (3H, 5-CH_3), 1.19–1.50 m (8H, 1-H$_{eq}$, 2-H$_{ax}$, 2-H$_{eq}$, 3-H$_{eq}$, 6-H$_{ax}$, 6-H$_{eq}$, 7-H$_{ax}$, 7-H$_{eq}$), 1.57–1.72 m (4H, 3-H$_{ax}$, 5-H, 9-H, 11-H$_{eq}$), 2.00 sept [1H, C**H**(CH$_3$)$_2$, J = 6.8], 2.33 d.d.d (1H, 12-H, $^4J_{12,19}$ = 1.6, $^3J_{12,11\text{-}ax}$ = 2.2, $^3J_{12,11\text{-}eq}$ = 13.2), 2.81 br.s (1H, 14-H), 3.40 t (2H, 17-H$_{ax}$, 17-H$_{eq}$, J = 3.9), 3.56 s (3H, $COOCH_3$), 3.65 s (3H, $COOCH_3$), 5.17 br.s (1H, 19-H), 5.90 s (2H, 1′-H$_{ax}$, 1′-H$_{eq}$), 9.70 br.s (3H, NH, NH_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 37.4 (C^1), 16.8 (C^2), 36.4 (C^3), 46.8 (C^4), 49.0 (C^5), 20.8 (C^6), 33.9 (C^7), 40.5 (C^8), 51.6 (C^9), 37.2 (C^{10}), 23.7 (C^{11}), 38.0 (C^{12}), 61.2 (C^{13}), 57.8 (C^{14}), 134.3 (C^{15}), 111.8 (C^{16}), 24.9 (C^{17}), 145.5 (C^{18}), 123.9 (C^{19}), 32.5 (C^{20}), 20.7 (C^{21}), 20.5 (C^{22}), 16.8 (C^{23}), 15.4 (C^{24}), 178.8 (C^{25}), 172.3 (C^{26}), 48.6 (C^{27}), 52.4 (C^{28}), 66.1 (C$^{1'}$), 161.8 (C$^{2'}$). Found, %: C 70.05; H 8.00; N 8.50. $C_{30}H_{43}N_3O_4$. Calculated, %: C 70.70; H 8.50; N 8.24.

Dimethyl 23-isopropyl-5,9-dimethyl-18-sulfanyl-17,19-diazahexacyclo[10.9.2.0^{1,10}.0^{4,9}.0^{13,21}.0^{15,20}]-tricosa-15(20),18,22-triene-5,13-dicarboxylate (VII). To a solution of 1 mmol (0.48 g) of compound **III** in 25 ml of methanol we added 0.48 g (6 mmol) of thiourea and 2 drops of freshly distilled morpholine, and the mixture was heated for 10 h under reflux and was then treated as described above for the synthesis of compound **V**. Yield 0.43 g (82%), mp 110–112°C. IR spectrum, ν, cm^{-1}: 3420 (SH), 1740, 1670 (C=N), 1480, 1400, 1370, 1260, 1200, 1170, 1080, 1050, 860, 760. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.80 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.85 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.89–0.98 m (2H, 1-H$_{ax}$, 11-H$_{ax}$), 1.05 s (3H, 5-CH_3), 1.17–1.50 m (8H, 1-H$_{eq}$, 2-H$_{ax}$, 2-H$_{eq}$, 3-H$_{eq}$, 6-H$_{ax}$, 6-H$_{eq}$, 7-H$_{ax}$, 7-H$_{eq}$), 1.51–1.72 m (4H, 3-H$_{ax}$, 5-H, 9-H, 11-H$_{eq}$), 2.00 sept [1H, C**H**(CH$_3$)$_2$, J = 6.8], 2.35 d.d.d (1H, 12-H, $^4J_{12,19}$ = 1.6, $^3J_{12,11\text{-}ax}$ = 2.2, $^3J_{12,11\text{-}eq}$ = 13.2), 2.51 s (2H, 17-H$_{ax}$, 17-H$_{eq}$), 2.85 br.s (1H, 14-H), 3.55 s (3H, $COOCH_3$), 3.65 s (3H, $COOCH_3$), 5.19 br.s (1H, 19-H), 7.15 br.s (1H, SH), 9.90 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 37.9 (C^1), 16.9 (C^2), 36.4 (C^3), 46.9 (C^4), 51.7 (C^5), 20.9 (C^6), 33.9 (C^7), 41.3 (C^8), 52.5 (C^9), 37.3 (C^{10}), 21.6 (C^{11}), 38.3 (C^{12}), 61.1 (C^{13}), 58.0 (C^{14}), 134.9 (C^{15}), 103.6 (C^{16}), 25.2 (C^{17}), 146.6 (C^{18}), 126.4 (C^{19}), 33.0 (C^{20}), 20.8 (C^{21}), 20.3 (C^{22}), 16.6 (C^{23}), 15.3 (C^{24}), 178.9 (C^{25}), 172.5 (C^{26}), 48.9 (C^{27}), 53.0 (C^{28}), 66.5 (C$^{1'}$), 145.3 (C$^{2'}$). Found, %: C 68.99; H 8.12; N 5.12; S 6.00. $C_{30}H_{42}N_2O_4S$. Calculated, %: C 68.41; H 8.04; N 5.32; S 6.09.

Dimethyl 23-isopropyl-5,9-dimethyl-16-(4-nitrophenyl)-18-oxo-17,19-diazahexacyclo[10.9.2.0^{1,10}.-

$0^{4,9}.0^{13,21}.0^{15,20}$]tricosa-15(20),18,22-triene-5,13-dicarboxylate (VIII). To a solution of 1 mmol (0.59 g) of compound **IV** in 10 ml of ethanol we added 0.8 g (10 mmol) of urea, and the mixture was heated for 15 h under reflux. The mixture was cooled, 5 ml of 1 N aqueous potassium hydroxide was added in small portions, and the mixture was evaporated by half and poured into 50 ml of cold water. The precipitate was filtered off, washed with water, dried, and purified by chromatography on aluminum oxide using benzene as eluent. Yield 0.37 g (59%), mp 123–125°C. IR spectrum, ν, cm^{-1}: 3380 (NH), 1730, 1720 (C=O, pyrimidine), 1630, 1540 (C–C_{arom}), 1455, 1380, 1350, 1240, 1190, 1140, 1080, 1020, 990, 840, 760, 735. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.49 s (3H, 10-CH_3), 0.77 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.82 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.88–0.98 m (2H, 1-H_{ax}, 11-H_{ax}), 1.05 s (3H, 5-CH_3), 1.20– 1.50 m (8H, 1-H_{eq}, 2-H_{ax}, 2-H_{eq}, 3-H_{eq}, 6-H_{ax}, 6-H_{eq}, 7-H_{ax}, 7-H_{eq}), 1.55–1.72 m (4H, 3-H_{ax}, 5-H, 9-H, 11-H_{eq}), 2.02 sept [1H, C**H**(CH$_3$)$_2$, J = 6.8], 2.37 d.d.d (1H, 12-H, $^4J_{12,19}$ = 1.6, $^3J_{12,11\text{-}ax}$ = 2.2, $^3J_{12,11\text{-}eq}$ = 13.2), 2.86 br.s (1H, 14-H), 3.43 d (2H, 17-H_{ax}, 17-H_{eq}, J = 2.6), 3.55 s (3H, $COOCH_3$), 3.65 s (3H, $COOCH_3$), 4.45 d (1H, 1′-H, J = 4.5), 5.19 br.s (1H, 19-H), 6.80–7.00 m (2H, H_c), 7.25–7.55 m (2H, H_b), 7.95 br.s (1H, NH), 8.10 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 38.2 (C^1), 17.0 (C^2), 36.7 (C^3), 46.9 (C^4), 49.2 (C^5), 21.7 (C^6), 34.5 (C^7), 42.1 (C^8), 51.9 (C^9), 37.5 (C^{10}), 25.3 (C^{11}), 40.6 (C^{12}), 60.6 (C^{13}), 53.1 (C^{14}), 145.6 (C^{15}), 123.5 (C^{16}), 30.7 (C^{17}), 146.9 (C^{18}), 124.3 (C^{19}), 33.0 (C^{20}), 20.9 (C^{21}), 20.0 (C^{22}), 16.7 (C^{23}), 15.5 (C^{24}), 179.4 (C^{25}), 177.7 (C^{26}), 47.1 (C^{27}), 58.8 (C^{28}), 54.9 ($C^{1'}$), 156.9 ($C^{2'}$), 135.1 (C^a), 129.1 and 129.3 (C^b), 121.2 and 121.5 (C^c), 140.3 (C^d). Found, %: C 68.05; H 7.10; N 6.20. $C_{36}H_{45}N_3O_7$. Calculated, %: C 68.44; H 7.18; N 6.65.

Dimethyl 22-isopropyl-5,9-dimethyl-17,18-diazahexacyclo[10.8.2.$0^{1,10}$.$0^{4,9}$.$0^{13,20}$.$0^{15,19}$]docosa-15(19),16,21-triene-5,13-dicarboxylate (IX). To a solution of 1 mmol (0.50 g) of compound **II** and 0.49 g (8 mmol) of hydrazine hydrate in 25 ml of methanol we added 2–3 drops of acetic acid, and the mixture was heated for 5 h under reflux and was then treated as described above for the synthesis of compound **V**. Yield 0.33 g (69%), mp 79–81°C. IR spectrum, ν, cm^{-1}: 3395 (NH), 1740, 1670 (C=N), 1480, 1380, 1280, 1255, 1200, 1160, 1120, 1090, 1020, 960, 920, 880, 820, 740. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.49 s (3H, 10-CH_3), 0.80 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.85 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.89–0.98 m (2H, 1-H_{ax}, 11-H_{ax}), 1.05 s (3H, 5-CH_3), 1.17–1.50 m (8H, 1-H_{eq}, 2-H_{ax}, 2-H_{eq}, 3-H_{eq}, 6-H_{ax}, 6-H_{eq}, 7-H_{ax}, 7-H_{eq}), 1.51–1.72 m (4H, 3-H_{ax}, 5-H, 9-H, 11-H_{eq}), 2.00 sept [1H, C**H**(CH$_3$)$_2$, J = 6.8], 2.35 d.d.d (1H, 12-H, $^4J_{12,19}$ = 1.6, $^3J_{12,11\text{-}ax}$ = 2.2, $^3J_{12,11\text{-}eq}$ = 13.2), 2.85 br.s (1H, 14-H), 3.40 s (2H, 17-H_{ax}, 17-H_{eq}), 3.55 s (3H, $COOCH_3$), 3.65 s (3H, $COOCH_3$), 5.19 br.s (1H, 19-H), 7.20 s (1H, 1′-H), 9.90 br.s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 38.7 (C^1), 16.8 (C^2), 37.6 (C^3), 42.1 (C^4), 49.2 (C^5), 21.7 (C^6), 36.4 (C^7), 43.1 (C^8), 49.5 (C^9), 38.0 (C^{10}), 25.0 (C^{11}), 41.8 (C^{12}), 65.7 (C^{13}), 51.9 (C^{14}), 137.3 (C^{15}), 111.3 (C^{16}), 34.0 (C^{17}), 146.7 (C^{18}), 125.8 (C^{19}), 35.9 (C^{20}), 20.7 (C^{21}), 19.8 (C^{22}), 16.8 (C^{23}), 15.9 (C^{24}), 179.1 (C^{25}), 176.1 (C^{26}), 48.9 (C^{27}), 52.5 (C^{28}), 154.8 ($C^{1'}$). Found, %: C 72.11; H 8.50; N 5.66. $C_{29}H_{40}N_2O_4$. Calculated, %: C 72.47; H 8.39; N 5.83.

Dimethyl 22-isopropyl-5,9-dimethyl-18-phenyl-17,18-diazahexacyclo[10.8.2.$0^{1,10}$.$0^{4,9}$.$0^{13,20}$.$0^{15,19}$]-docosa-15(19),16,21-triene-5,13-dicarboxylate (X). To a solution of 1 mmol (0.50 g) of compound **II** in 30 ml of methanol we added 1.20 g (8.30 mmol) of phenylhydrazine hydrochloride and 2–3 drops of acetic acid, and the mixture was heated for 6 h under reflux. The mixture was then treated as described above for the synthesis of compound **V**. Yield 0.34 g (61%), mp 85–87°C. IR spectrum, ν, cm^{-1}: 1740, 1670 (C=N), 1585 (C=C), 1480, 1390, 1290, 1260, 1205, 1160, 1120, 1090, 1025, 960, 940, 920, 820, 740. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.49 s (3H, 10-CH_3), 0.80 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.85 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.89–0.98 m (2H, 1-H_{ax}, 11-H_{ax}), 1.05 s (3H, 5-CH_3), 1.17–1.50 m (8H, 1-H_{eq}, 2-H_{ax}, 2-H_{eq}, 3-H_{eq}, 6-H_{ax}, 6-H_{eq}, 7-H_{ax}, 7-H_{eq}), 1.51–1.72 m (4H, 3-H_{ax}, 5-H, 9-H, 11-H_{eq}), 2.00 sept [1H, C**H**(CH$_3$)$_2$, J = 6.8], 2.35 d.d.d (1H, 12-H, $^4J_{12,19}$ = 1.6, $^3J_{12,11\text{-}ax}$ = 2.2, $^3J_{12,11\text{-}eq}$ = 13.2), 2.85 br.s (1H, 14-H), 3.40 s (2H, 17-H_{ax}, 17-H_{eq}), 3.55 s (3H, $COOCH_3$), 3.65 s (3H, $COOCH_3$), 5.19 br.s (1H, 19-H), 6.75–7.19 m (5H, H_{arom}), 7.23 s (1H, 1′-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 36.1 (C^1), 16.9 (C^2), 36.6 (C^3), 47.0 (C^4), 51.8 (C^5), 21.6 (C^6), 34.3 (C^7), 44.7 (C^8), 52.6 (C^9), 37.6 (C^{10}), 23.8 (C^{11}), 42.0 (C^{12}), 61.8 (C^{13}), 57.7 (C^{14}), 134.6 (C^{15}), 111.0 (C^{16}), 29.8 (C^{17}), 146.1 (C^{18}), 125.6 (C^{19}), 32.9 (C^{20}), 20.9 (C^{21}), 20.4 (C^{22}), 16.7 (C^{23}), 15.4 (C^{24}), 179.1 (C^{25}), 172.1 (C^{26}), 49.1 (C^{27}), 58.0 (C^{28}), 154.9 ($C^{1'}$), 134.3 (C^a), 124.6 and 123.8 (C^b), 124.8 and 124.0 (C^c), 128.2 (C^d). Found, %: C 75.05; H 7.82; N 5.00. $C_{35}H_{44}N_2O_4$. Calculated, %: C 75.51; H 7.97; N 5.03.

Dimethyl 22-isopropyl-5,9-dimethyl-17-oxa-18-azahexacyclo[10.8.2.$0^{1,10}$.$0^{4,9}$.$0^{13,20}$.$0^{15,19}$]docosa-15,18,21-triene-5,13-dicarboxylate (XI). To a solution of 0.5 g of hydroxylamine hydrochloride and 0.5 g of sodium acetate in 5 ml of water at 60°C we added with stirring over a period of 10 min a solution of 1 mmol (0.48 g) of compound **III** in 25 ml of acetic acid. After 1 h, the mixture was cooled to room temperature and poured into 50 ml of cold water, and the precipitate was filtered off, washed with water, dried, and purified by chromatography on aluminum oxide using chloroform as eluent. Yield 0.35 g (73%), mp 138–140°C. IR spectrum, ν, cm^{-1}: 1730, 1705, 1625, 1575, 1520, 1465, 1375, 1250, 1190, 1125, 1105, 1075, 1020, 790, 720. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.49 s (3H, 10-CH_3), 0.80 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.85 d [3H, CH(C**H**$_3$)$_2$, J = 6.8], 0.89–0.98 m (2H, 1-H_{ax}, 11-H_{ax}), 1.05 s (3H, 5-CH_3), 1.17–1.50 m (8H, 1-H_{eq}, 2-H_{ax}, 2-H_{eq}, 3-H_{eq}, 6-H_{ax}, 6-H_{eq}, 7-H_{ax}, 7-H_{eq}), 1.51–1.72 m (4H, 3-H_{ax}, 5-H, 9-H, 11-H_{eq}), 2.00 sept [1H, C**H**(CH_3)$_2$, J = 6.8], 2.35 d.d.d (1H, 12-H, $^4J_{12,19}$ 1.6, $^3J_{12,11\text{-}ax}$ = 2.2, $^3J_{12,11\text{-}eq}$ = 13.2), 2.51 s (2H, 17-H_{ax}, 17-H_{eq}), 2.85 br.s (1H, 14-H), 3.55 s (3H, $COOCH_3$), 3.65 s (3H, $COOCH_3$), 5.30 br.s (1H, 19-H), 7.52 s (1H, 1′-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 37.1 (C^1), 16.6 (C^2), 35.6 (C^3), 46.7 (C^4), 51.7 (C^5), 21.7 (C^6), 34.3 (C^7), 41.6 (C^8), 52.1 (C^9), 36.3 (C^{10}), 25.2 (C^{11}), 37.5 (C^{12}), 63.5 (C^{13}), 52.4 (C^{14}), 167.1 (C^{15}), 122.6 (C^{16}), 42.3 (C^{17}), 145.7 (C^{18}), 126.2 (C^{19}), 33.9 (C^{20}), 21.6 (C^{21}), 19.6 (C^{22}), 16.3 (C^{23}), 15.2 (C^{24}), 178.9 (C^{25}), 176.7 (C^{26}), 48.8 (C^{27}), 52.9 (C^{28}), 148.9 ($C^{1'}$). Found, %: C 73.55; H 8.40; N 2.66. $C_{29}H_{39}NO_5$. Calculated, %: C 72.32; H 8.16; N 2.91.

REFERENCES

1. Abad, A., Agullo, C., Arno, M., Domingo, L.R., Rozalen, J., and Zaragoza, R.J., *Can. J. Chem.*, 1991, vol. 69, p. 379.
2. Abad, A., Agullo, C., Arno, M., Domingo, L.R., and Zaragoza, R.J., *J. Org. Chem.*, 1990, vol. 55, p. 2369.
3. Koyama, H., Okawara, H., Kobayashi, S., and Ohno, M., *Tetrahedron Lett.*, 1985, vol. 22, p. 2685.
4. Geiwiz, J. and Haslinger, E., *Helv. Chim. Acta*, 1995, vol. 78, p. 818.
5. Haslinger, E. and Michl, G., *Tetrahedron Lett.*, 1988, vol. 29, p. 5751.
6. Koyama, H., Kaku, Y., and Ohno, M., *Tetrahedron Lett.*, 1987, vol. 28, p. 2863.
7. Abad, A., Agullo, C., Arno, M., Cunat, A.C., and Zaragoza, R.J., *J. Org. Chem.*, 1989, vol. 54, p. 5123.
8. Michl, G., Rettenbacher, C., and Haslinger, E., *Monatsh. Chem.*, 1988, vol. 119, p. 833.
9. Ayer, W.A. and Talamas, F.X., *Can. J. Chem.*, 1988, vol. 66, p. 1675.
10. Chernov, S.V., Shul'ts, E.E., Shakirov, M.M., Gatilov, Yu.V., Bagryanskaya, I.Yu., and Tolstikov, G.A., *Russ. J. Org. Chem.*, 2000, vol. 36, p. 1623.
11. Fonseca, T., Gigante, B., and Gilchrist, T.L., *Tetrahedron*, 2001, vol. 57, p. 1793.
12. Tret'yakova, E.V., Flekhter, O.B., Galin, F.Z., Spirikhin, L.V., and Tolstikov, G.A., *Khim. Prirodn. Soedin.*, 2002, no. 3, p. 206.
13. Herz, W. and Nair, M.G., *J. Org. Chem.*, 1969, vol. 34, p. 4016.
14. Kosemura, S. and Yamamura, S., *Tetrahedron Lett.*, 1997, vol. 38, p. 6221.
15. Siddiqui, A.U., Rao, V.U. Maheshwar, Maimirani, M., and Siddiqui, A.H., *J. Heterocycl. Chem.*, 1995, vol. 32, p. 353.
16. Rapole Keshava, R., Siddiqui, A.H., Dayal, B., Batta, A.K., Rao, S.J., Kumar, P., and Salen, G., *Synth. Commun.*, 1996, vol. 26, p. 3511.
17. Govardhan, Ch., Reddy, R.P., Ramaiah, T.S., and Rao, T.V., *J. Indian Chem. Soc.*, 1983, vol. 60, p. 858.