ISSN 1070-4280, Russian Journal of Organic Chemistry, 2013, Vol. 49, No. 6, pp. 843–848. © Pleiades Publishing, Ltd., 2013.
Original Russian Text © D.R. Latypova, A.G. Badamshin, A.N. Lobov, V.A. Dokichev, 2013, published in Zhurnal Organicheskoi Khimii, 2013, Vol. 49, No. 6, pp. 860–865.

Reaction of Ethyl Acetoacetate with Formaldehyde and Primary Amines

D. R. Latypova, A. G. Badamshin, A. N. Lobov, and V. A. Dokichev

Institute of Organic Chemistry, Ufa Research Center, Russian Academy of Sciences, pr. Oktyabrya 71, Ufa, 450054 Bashkortostan, Russia
e-mail: dokichev@anrb.ru

Received September 15, 2012

Abstract—The condensation of ethyl acetoacetate with formaldehyde and primary amines in methanol at 65°C (Mannich reaction) gave up to 92% of hexahydropyrimidine derivatives containing ester and acetyl groups. Analogous reaction with aminopyridines stopped at the stage of formation of linear condensation products.

DOI: 10.1134/S1070428013060079

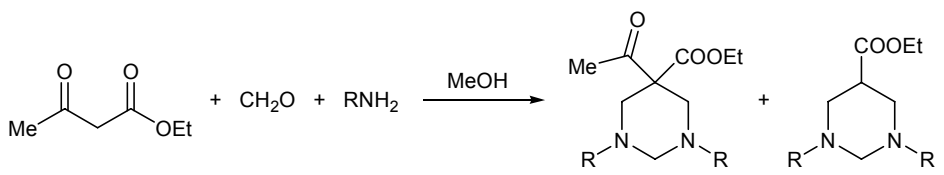
Hexahydropyrimidine derivatives are biologically active compounds exhibiting antitumor [1–4], antiplatelet [5], antibacterial [3, 6], and antiarrhythmic activity [7]. Hexahydropyrimidine fragment is a structural unit of alkaloids verbamethine and verbametrine [8]. Extensive studies are carried out on the synthesis of new hexahydropyrimidine derivatives. They are generally prepared by reaction of 1,3-diamines with aldehydes or ketones [9–11] or by condensation of CH acids with formaldehyde and primary amines [12–15]. Especially attractive is one-pot synthesis implying multi-component condensation without isolation of intermediate compounds. In the preceding communication [16] we described an efficient one-step procedure for the synthesis of hexahydropyrimidines via three-component condensation of ethyl acetoacetate with formaldehyde and natural amino acid ester hydrochlorides in an AcONa/AcOH buffer at pH 4.

In the present communication we report on the synthesis of a larger number of hexahydropyrimidines; we also examined how the initial amine structure affects the yield and composition of products of their condensation with ethyl acetoacetate and formaldehyde. Ethyl 5-acetylhexahydropyrimidine-5-carboxylate derivatives may be used as intermediate products in the synthesis of α,α-disubstituted β-amino- and β-hydroxybutyric acids [17].

As primary amines we used methylamine (**IIa**), propylamine (**IIb**), isopropylamine (**IIc**), butylamine (**IId**), benzylamine (**IIe**), 2-aminoethanol (**IIf**), pyridin-4-amine (**IIg**), and 3,5-dibromopyridin-2-amine (**IIh**). The reactions were carried out at 65°C (reaction time 5 h), the molar ratio **I**–CH_2O–**II** being 1:15:4. Ethyl acetoacetate (**I**) reacted with formaldehyde (as a 32.3% aqueous solution) and methylamine (as a 25.2% aqueous solution) in boiling methanol to produce in 5 h 5% of ethyl 5-acetyl-1,3-dimethylhexahydropyrimidine-5-carboxylate (**IIIa**) and 59% of ethyl 1,3-dimethylhexahydropyrimidine-5-carboxylate (**IVa**) (Scheme 1). When AcONa–AcOH buffer was used [16], the overall yield of **IIIa** and **IVa** decreased to 30%.

The structure of the amine component essentially affects the reaction direction. The condensation of

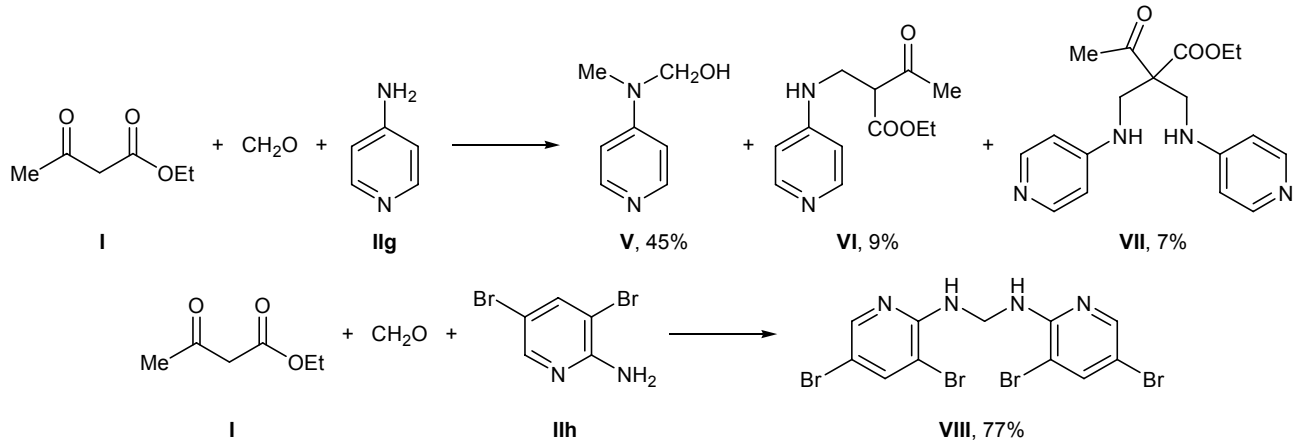
Scheme 1.



I **IIa–IIf** **IIIa**, **IIIb**, **IIId–IIIf** **IVa–IVd**, **IVf**

R = Me (**a**), Pr (**b**), *i*-Pr (**c**), Bu (**d**), $PhCH_2$ (**e**), $HO(CH_2)_2$ (**f**).

Scheme 2.



propylamine (**IIb**), butylamine (**IId**), and 2-aminoethanol (**IIf**) with formaldehyde and ester **I** at a ratio of 4:15:1 in methanol gave mixtures of the corresponding ethyl 5-acetyl-1,3-dialkylhexahydropyrimidine-5-carboxylates **IIIb**, **IIId**, and **IIIf** and ethyl 1,3-dialkylhexahydropyrimidine-5-carboxylates **IVb**, **IVd**, and **IVf**, the latter prevailing; the overall yield ranged from 36 to 72%. By contrast, in the reactions of ethyl acetoacetate (**I**) with formaldehyde and isopropylamine (**IIc**), benzylamine (**IIe**), pyridin-4-amine (**IIg**), and 3,5-dibromopyridin-2-amine (**IIh**), only one hexahydropyrimidine **III** or **IV** was formed, or the reaction stopped at the stage of formation of linear condensation products. From ester **I**, CH_2O, and isopropylamine (**IIc**) we synthesized ethyl 1,3-diisopropylhexahydropyrimidine-5-carboxylate **IVc** in 77% yield. Compound **IVc** was synthesized previously (yield 42%) together with ethyl *N*-isopropyl-3-aminopropanoate by reaction of ethyl hydrogen malonate with 1,3,5-triisopropylhexahydro-1,3,5-triazine [18]; however, no any proof for the assumed structure was given in [18].

Benzylamine (**IIe**) reacted with ester **I** and formaldehyde to give ethyl 5-acetyl-1,3-dibenzylhexahydropyrimidine-5-carboxylate (**IIIe**) as the only product (yield 92%). Compound **IIe** was synthesized previously in a lower yield (63%) [19] by $FeCl_3$-catalyzed Mannich reaction.

Presumably, compounds **IV** are formed via elimination of the acetyl group according to the retro-aldol reaction pattern in the course of generation of the hexahydropyrimidine structure. After heating an equimolar mixture of ethyl 5-acetyl-1,3-dibenzylhexahydropyrimidine-5-carboxylate (**IIIe**) and isopropylamine (**IIc**) for 5 h at 65°C, even traces of ethyl 1,3-dibenzylhexahydropyrimidine-5-carboxylate were not detected in the reaction mixture [20].

Under similar conditions, aminopyridines **IIg** and **IIh** reacted with ethyl acetoacetate and formaldehyde, yielding linear condensation products **VII** and **VIII**, respectively (Scheme 2). The reaction of **I** with 32.3% aqueous formaldehyde and pyridin-4-amine (**IIg**) in boiling methanol gave a mixture of [methyl(pyridin-4-yl)amino]methanol (**V**), ethyl 2-acetyl-3-(pyridin-4-ylamino)propanoate (**VI**), and ethyl 3-oxo-2,2′-bis[(pyridin-4-ylamino)methyl]butanoate (**VII**) in 45, 9, and 7% yield, respectively. *N*,*N*′-Bis(3,5-dibromopyridin-2-yl)methanediamine (**VIII**) was isolated as colorless crystals in 77% yield in the reaction of **I** with formaldehyde and 3,5-dibromopyridin-2-amine.

The structure of all newly synthesized compounds was confirmed by ^1H and ^{13}C NMR spectroscopy using two-dimensional COSY, NOESY, HSQC, and HMBC techniques for signal assignment and elucidation of the hexahydropyrimidine structure. The heteroring in compounds **IV** is most likely to adopt a *chair*-like conformation with equatorial orientation of the ester group. Signals from the axial protons on C^4 and C^6 appeared as triplets at δ ~2.30 ppm ($^2J \approx 11.0$, $^3J \approx 11.0$ Hz), indicating *trans*-diaxial interaction with 5-H which resonated as a triplet of triplets at δ 2.75–2.90 ppm ($^3J \approx 11.0$, 4.2 Hz).

To conclude, we have developed a one-pot procedure for the synthesis of hexahydropyrimidine derivatives by reaction of ethyl acetoacetate with formaldehyde and primary amines. The yields and composition of the products depend on the initial amine nature.

EXPERIMENTAL

The NMR spectra were recorded at 298 K on Bruker AM-300 (300.13 MHz for ^1H and 75.47 MHz for ^{13}C) and Bruker Avance-III 500 (500.13 MHz for

^{1}H, 125.47 MHz for ^{13}C, and 50.58 MHz for ^{15}N) spectrometers using a 5-mm PABBO *Z*-gradient probe. The ^{13}C and ^{1}H chemical shifts are given relative to tetramethylsilane as internal reference; the ^{15}N chemical shifts were determined from the F_1-projection of the ^{1}H–^{15}N HMBC spectra and are given relative to ammonia. Digital resolution was improved by zero padding and multiplication of the Fourier image by the exponential function [lb = 0.1 (^{1}H), 1 Hz (^{13}C)]. The ^{13}C NMR spectra with decoupling from protons were recorded using the following parameters: spectral window 29.8 kHz, number of points 64 K, pulse duration (30°) 3.2 μs, relaxation delay 2 s, number of scans 512–2048; gsCOSY: matrix size 4 K per 512 experiments, spectral window 5.0 kHz, sine bell-shaped weight function for F_1 and F_2 projections (ssb 2); gsHSQC: relaxation delay optimized for J_{CH} = 145 and J_{NH} = 80 Hz, matrix size 2 K per 256 experiments; gsHMBC: small coupling constant evolution delay 71.4 ms for ^{1}H–^{13}C and 142.8 ms for ^{1}H–^{15}N, matrix size 2 K per 256 experiments; NOESY: matrix size 2 K per 256 experiments, spectral window 5.0 kHz, mixing time 0.5 s. The mass spectra were obtained on a Thermo Finnigan MAT 95 XP high-resolution mass spectrometer (electron impact, 70 eV, ion source temperature 250°C, direct inlet probe temperature 50–270°C, heating rate 10 deg/min). The IR spectra were measured on a Shimadzu IR Prestige-21 instrument. The melting points were determined on a Boetius melting point apparatus. TLC analyses were carried out using Silufol plates (Merck) and Sorbfil PTSKh-AF-A plates (*IMID* Ltd.); eluent chloroform–methanol (9:1) or petroleum ether–ethyl acetate (7:3). Silica gel (70–230 mesh, Macherey-Nagel) was used for column chromatography (gradient elution with chloroform–methanol, 0 to 10% of the latter or petroleum ether–ethyl acetate, 0 to 2% of the latter).

Reaction of ethyl acetoacetate (I) with formaldehyde and primary amines IIa–IIh (*general procedure*). Ethyl acetoacetate, 1 mmol, was dissolved in methanol, 4 mmol of amine **IIa**–**IIh** and 15 mmol of formaldehyde (as a 32.3% aqueous solution) were added under stirring, and the mixture was heated for 5 h under reflux. The solvent was distilled off under reduced pressure, 20 ml of methylene chloride was added to the residue, the mixture was washed with water (3 × 10 ml) and dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was subjected to column chromatography on silica gel.

Ethyl 5-acetyl-1,3-dimethylhexahydropyrimidine-5-carboxylate (IIIa) and ethyl 1,3-dimethylhexahydropyrimidine-5-carboxylate (IVa) were obtained from 0.95 g (7.6 mmol) of ester **I** in 21 ml of MeOH, 9.7 ml (114 mmol) of 32% aqueous formaldehyde, and 3.68 g (30 mmol) of 25.2% aqueous methylamine.

Compound **IIIa** was isolated using petroleum ether–ethyl acetate (7:3) as eluent. Yield 0.06 g (5%), light yellow oily substance. IR spectrum (film), ν, cm^{-1}: 2791, 1740, 1712, 1350, 1200. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.13 t (3H, Me, ^3J = 7.1), 2.15 s (6H, MeN), 2.20 s (3H, MeC=O), 2.45–2.60 m (2H, CH_2N), 2.60–2.75 m (1H, 2-H), 2.82–3.11 m (3H, CH_2N, 5-H), 4.13 q (2H, OCH_2, ^3J = 7.1). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ_C, ppm: 13.61 (Me), 26.30 (MeC=O), 42.51 (MeN), 56.92 (NCH_2), 56.52 (C), 61.25 (OCH_2), 78.40 (C^2), 168.65 (C=O, ester), 202.96 (C=O). Found: *m*/*z* 228.1462 $[M]^+$. $C_{11}H_{20}N_2O_3$. Calculated: *M* 228.1468.

Compound **IVa** was isolated using petroleum ether–ethyl acetate (7:3) as eluent. Yield 0.65 g (59%), light yellow oily substance. IR spectrum (film), ν, cm^{-1}: 2791, 1730, 1180. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.15 t (3H, Me, ^3J = 7.1), 2.15 d (2H, 4-H$_{ax}$, 6-H$_{ax}$, ^2J = 11.3), 2.22 s (6H, MeN), 2.55 d (1H, 2-H$_{ax}$, ^2J = 9.4), 2.85 m (1H, CH), 2.98 d.d (2H, 4-H$_{eq}$, 6-H$_{eq}$, ^2J = 11.3, ^3J = 3.7), 3.40 d (1H, 2-H$_{eq}$, ^2J = 9.4), 4.03 q (2H, OCH_2, ^3J = 7.1). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ_C, ppm: 13.95 (Me), 38.15 (CH), 42.04 (NMe), 54.71 (CH_2N), 60.37 (OCH_2), 77.42 (C^2), 171.91 (C=O). Found: *m*/*z* 186.1348 $[M]^+$. $C_9H_{18}N_2O_2$. Calculated: *M* 186.1363.

Ethyl 5-acetyl-1,3-dipropylhexahydropyrimidine-5-carboxylate (IIIb) and ethyl 1,3-dipropylhexahydropyrimidine-5-carboxylate (IVb) were synthesized from 0.5 g (4 mmol) of ester **I** in 27 ml of MeOH, 0.9 g (15 mmol) of propylamine, and 5.8 ml (68 mmol) of 32.3% aqueous formaldehyde.

Compound **IIIb** was isolated using petroleum ether as eluent. Yield 0.29 g (27%), light yellow oily substance. IR spectrum (film), ν, cm^{-1}: 2966, 1730, 1714, 1369, 1207, 731. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.97 t (6H, Me, ^3J = 7.1), 1.32 t (3H, OCH_2**Me**, ^3J = 7.1), 1.71–1.82 m (4H, NCH_2C**H**$_2$), 2.33 s (3H, MeC=O), 3.71 t (4H, N**C**H$_2$CH$_2$, ^3J = 6.8), 3.79 br.d (2H, 4-H$_{ax}$, 6-H$_{ax}$, ^2J = 13.5), 3.86 br.d (2H, 4-H$_{eq}$, 6-H$_{eq}$, ^2J = 13.5), 4.19–4.26 m (2H, 2-H), 4.29 q (2H, OCH_2, ^2J = 7.1). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ_C, ppm: 10.62

(Me), 13.96 (OCH_2**Me**), 20.66 (NCH_2**C**H_2), 26.35 (**Me**C=O), 45.64 (C^4, C^6), 56.32 (C^5), 56.57 (1-CH_2, 3-CH_2), 62.00 (C^2), 63.74 (OCH_2), 166.60 (C=O, ester), 197.98 (C=O). Found: *m*/*z* 284.2086 $[M]^+$. $C_{15}H_{28}N_2O_3$. Calculated: *M* 284.2094.

Compound **IVb** was isolated using petroleum ether–ethyl acetate (50 : 1) as eluent. Yield 0.41 g (45%), light yellow oily substance. IR spectrum (film), ν, cm^{-1}: 1730, 1207. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.88 t (6H, Me, ^3J = 7.3), 1.23 t (3H, OCH_2**Me**, ^3J = 7.1), 1.50 m (4H, NCH_2C**H**$_2$), 2.30 d.d (2H, 4-H_{ax}, 6-H_{ax}, $^2J = {}^3J$ = 10.5), 2.35 m (4H, NC**H**$_2$$CH_2$), 2.72 d (1H, 2-$H_{ax}$, ^2J = 9.5), 2.88 t.t (1H, 5-H, ^3J = 10.5, 4.2), 3.11 d.d (2H, 4-H_{eq}, 6-H_{eq}, ^2J = 10.5, ^3J = 4.2), 3.60 d (1H, 2-H_{eq}, ^2J = 9.5), 4.11 q (2H, OCH_2, ^3J = 7.1). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ_C, ppm: 11.82 (Me), 14.19 (OCH_2**Me**), 20.12 (NCH_2**C**H_2), 37.95 (C^5), 53.39 (CH_2N), 56.49 (N**C**H_2), 60.67 (OCH_2), 74.60 (C^2), 172.40 (C=O). Found: *m*/*z* 242.1980 $[M]^+$. $C_{13}H_{26}N_2O_2$. Calculated: *M* 242.1989.

Ethyl 1,3-diisopropylhexahydropyrimidine-5-carboxylate (IVc) was synthesized from 0.5 g (4 mmol) of ester **I** in 27 ml of MeOH, 0.94 g (16 mmol) of isopropylamine, and 5.1 ml (60 mmol) of 32.3% aqueous formaldehyde; the product was purified by column chromatography using chloroform–methanol (9 : 1) as eluent. Yield 0.88 g (77%), light yellow oily substance. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.06 d and 1.08 d (6H each, Me, ^3J = 6.6), 1.27 t (3H, CH_2**Me**, ^3J = 7.1), 2.37 t (2H, 4-H_{ax}, 6-H_{ax}, ^2J = 11.0, ^3J = 11.0), 2.80–2.87 m (2H, C**H**Me_2, 5-H), 2.93 br.d (1H, 2-H_{ax}, ^2J = 9.1), 3.14–3.17 m (2H, 4-H_{eq}, 6-H_{eq}), 3.74 br.d (1H, 2-H_{eq}, ^2J = 9.1), 4.14 q (2H, OCH_2, ^3J = 7.1). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ_C, ppm: 14.23 (CH_2**Me**), 18.65 and 19.45 (CH**Me**$_2$), 39.92 (C^5), 49.42 (CH_2N), 52.17 (**C**HMe_2), 60.47 (OCH_2), 69.63 (C^2), 173.03 (C=O). ^{15}N NMR spectrum (50 MHz, $CDCl_3$): δ_N 52.83 ppm. Found: *m*/*z* 241.1918 $[M - H]^+$. $C_{13}H_{25}N_2O_2$. Calculated: *M* 241.1911.

Ethyl 5-acetyl-1,3-dibutylhexahydropyrimidine-5-carboxylate (IIId) and ethyl 1,3-dibutylhexahydropyrimidine-5-carboxylate (IVd) were obtained from 0.5 g (4 mmol) of ester **I** in 27 ml of methanol, 0.9 g (15 mmol) of butylamine, and 5.8 ml (68 mmol) of 32.3% aqueous formaldehyde.

Compound **IIId** was isolated using petroleum ether as eluent. Yield 0.21 g (18%), light yellow oily substance. IR spectrum (film), ν, cm^{-1}: 1730, 1712, 1371, 1201. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.76–0.99 m (6H, CH_2**Me**), 1.17–1.36 m (7H, CH_2C**H**$_2$Me, OCH_2**Me**), 1.40–1.58 m (4H, NCH_2C**H**$_2$), 2.30 s (3H, MeC=O), 2.39–3.23 m (4H, 4-H, 6-H), 3.48–3.55 m (2H, 2-H), 3.49–3.71 m (4H, NC**H**$_2$$CH_2$), 4.15 q (2H, OCH_2, ^2J = 7.1). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ_C, ppm: 13.59 and 13.90 (CH_2**Me**, OCH_2**Me**), 20.53 (**C**H_2Me), 26.70 [C(O)**Me**], 28.81 (**C**H_2CH_2Me), 55.00 (C^4, C^6), 55.58 (CH_2**C**H_2N), 57.52 (C^5), 61.48 (OCH_2), 76.34 (C^2), 169.22 (C=O, ester), 203.77 (C=O). Found: *m*/*z* 312.2520 $[M]^+$. $C_{17}H_{32}N_2O_3$. Calculated: *M* 312.2529.

Compound **IVd** was isolated using petroleum ether–ethyl acetate (50 : 1) as eluent. Yield 0.46 g (44%), light yellow oily substance. IR spectrum (film), ν, cm^{-1}: 1730 (C=O), 1199 (C–O). ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.89 t (6H, Me, ^3J = 7.3), 1.23 t (3H, OCH_2**Me**, ^3J = 7.1), 1.32 m (4H, NCH_2CH_2C**H**$_2$), 1.46 m (4H, NCH_2C**H**$_2$), 2.29 t (2H, 4-H_{ax}, 6-H_{ax}, ^2J = 10.5, ^3J = 10.5), 2.38 m (4H, NC**H**$_2$$CH_2$), 2.70 d (1H, 2-$H_{ax}$, ^2J = 9.5), 2.86 t.t (1H, 5-H, ^3J = 10.5, 4.2), 3.11 d.d (2H, 4-H_{eq}, 6-H_{eq}, ^2J = 10.5, ^3J = 4.2), 3.59 d (1H, 2-H_{eq}, ^2J = 9.5), 4.11 q (2H, OCH_2, ^3J = 7.1). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ_C, ppm: 13.25 (CH_2**Me**), 13.70 (OCH_2**Me**), 19.04 (NCH_2CH_2**C**H_2), 29.05 (NCH_2**C**H_2), 34.74 (C^5), 43.24 (N**C**H_2CH_2), 54.46 (C^4, C^6), 61.91 (OCH_2), 76.45 (C^2), 168.83 (C=O). Found: *m*/*z* 270.2312 $[M]^+$. $C_{15}H_{30}N_2O_2$. Calculated: *M* 270.2302.

Ethyl 5-acetyl-1,3-dibenzylhexahydropyrimidine-5-carboxylate (IIIe) was synthesized from 0.5 g (4 mmol) of ester **I** in 27 ml of MeOH, 1.7 g (16 mmol) of benzylamine, and 5.1 ml (60 mmol) of 32.3% aqueous formaldehyde. The product was purified by column chromatography using chloroform as eluent. Yield 1.35 g (92%), light yellow oily liquid. IR spectrum (film), ν, cm^{-1}: 3600–3200, 2827, 2941, 1732, 1712, 1454, 1359, 1199, 1168, 1028, 752. ^{1}H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.23 t (3H, Me, ^3J = 6), 2.23 s (3H, MeC=O), 2.84 d (2H, 4-H_{ax}, 6-H_{ax}, ^2J = 12), 3.02 d (1H, 2-H_{ax}, ^2J = 9), 3.20 d (2H, 4-H_{eq}, 6-H_{eq}, ^2J = 12), 3.36 d (1H, 2-H_{eq}, ^2J = 9), 3.57 s and 3.70 s (2H each, C**H**$_2$Ph), 4.18 q (2H, OCH_2, ^3J = 6), 7.24–7.38 m (10H, Ph). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ_C, ppm: 13.75 (OCH_2**Me**), 26.59 (**Me**C=O), 56.85 and 59.58 (C^4, C^5, C^6), 61.36 (OCH_2), 73.57 (C^2); 126.82, 127.00, 128.03, 128.69, 128.80 (C^o, C^m, C^p); 137.37 and 138.27 (C^i), 169.21 (C=O, ester), 203.57 (C=O). Found: *m*/*z* 380.2109 $[M]^+$. $C_{23}H_{28}N_2O_3$. Calculated: *M* 380.2094.

Ethyl 5-acetyl-1,3-bis(2-hydroxyethyl)hexahydropyrimidine-5-carboxylate (IIIf) and ethyl 1,3-bis(2-hydroxyethyl)hexahydropyrimidine-5-carboxylate (IVf) were synthesized from 1 g (8 mmol) of ester **I** in 35 ml of MeOH, 1.85 g (30 mmol) of 2-aminoethanol, and 9.8 ml (114 mmol) of 32.3% aqueous formaldehyde.

Compound **IIIf** was isolated using chloroform–methanol (10:1) as eluent. Yield 0.33 g (15%), yellow oily substance. IR spectrum (film), ν, cm^{-1}: 3600–3100, 1728, 1367, 1184. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.16 t (3H, Me, ^3J = 7.1), 2.15 s (3H, MeC=O), 2.40–2.47 m (6H, NC**H**$_2$CH$_2$, 4-H$_{ax}$, 6-H$_{ax}$), 2.90 br.s (2H, 4-H$_{eq}$, 6-H$_{eq}$), 3.05 m (1H, 2-H$_{ax}$), 3.14 m (1H, 2-H$_{eq}$), 3.47–3.56 m (4H, C**H**$_2$OH), 4.10 q (2H, OCH_2, ^3J = 7.1). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ_C, ppm: 13.65 (Me), 26.22 (**Me**C=O), 54.76 (C^4, C^6), 55.77 (N**C**H$_2$CH$_2$), 58.10 (**C**H$_2$OH), 59.87 (C^5), 61.74 (OCH_2), 75.14 (C^2), 169.06 (C=O, ester), 202.76 (C=O). ^{15}N NMR spectrum (50 MHz, $CDCl_3$): δ_N 37.57 ppm. Found: *m*/*z* 287.1598 $[M - H]^+$. $C_{13}H_{23}N_2O_5$. Calculated: *M* 287.1601.

Compound **IVf** was isolated using chloroform–methanol (9:1) as eluent. Yield 0.40 g (21%), yellow oily substance. IR spectrum (film), ν, cm^{-1}: 3600–3100, 1731, 1180. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.14 t (3H, Me, ^3J = 7.1), 2.15 s (3H, MeC=O), 2.49–2.54 m (6H, NCH$_2$C**H**$_2$, 4-H$_{ax}$, 6-H$_{ax}$), 2.75 m (1H, 5-H), 2.92–3.01 m (3H, 2-H$_{ax}$, 4-H$_{eq}$, 6-H$_{eq}$), 3.45–3.57 m (5H, 2-H$_{eq}$, C**H**$_2$OH), 4.03 q (2H, OCH_2, ^3J = 7.1). ^{13}C NMR spectrum (125 MHz, $CDCl_3$), δ_C, ppm: 13.88 (Me), 38.49 (C^5), 52.95 (C^4, C^6), 55.93 (CH$_2$**C**H$_2$N), 58.48 (CH_2OH), 60.44 (OCH_2), 74.34 (C^2), 172.00 (C=O). ^{15}N NMR spectrum (50 MHz, $CDCl_3$): δ_N 38.21 ppm. Found: *m*/*z* 245.1462 $[M - H]^+$. $C_{11}H_{21}N_2O_4$. Calculated: *M* 245.1496.

[Methyl(pyridin-4-yl)amino]methanol (V), ethyl 2-acetyl-3-(pyridin-4-ylamino)propanoate (VI), and ethyl 3-oxo-2,2-bis[(pyridin-4-ylamino)methyl]-butanoate (VII) were synthesized from 0.17 g (1.3 mmol) of ester **I** in 9 ml of MeOH, 0.5 g (5.3 mmol) of pyridin-4-amine, and 1.7 ml (20 mmol) of 32.3% aqueous formaldehyde.

Compound **V** was isolated using chloroform–methanol (9:1) as eluent. Yield 0.17 g (45%), yellow oily substance. IR spectrum (film), ν, cm^{-1}: 3250–3000, 2930, 2818, 1601, 1518 (Py). ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.28 s (3H, Me), 4.62 d (2H, C**H**$_2$OH, ^3J = 6.8), 5.82 br.s (1H, OH), 6.60–6.62 m (2H, 2-H, 6-H), 8.20–8.22 m (2H, 3-H, 5-H). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ_C, ppm: 54.34 (Me), 75.06 (CH_2OH), 108.48 (C^2, C^6), 149.46 (C^3, C^5), 152.65 (C^4). Found: *m*/*z* 138.0796 $[M]^+$. $C_7H_{10}N_2O$. Calculated: *M* 138.0802.

Compounds **VI** and **VII** were isolated using chloroform–methanol (95:5) as eluent. Yield 0.06 g (16%), mixture **VI**/**VII** at a ratio of 4:5 [determined from the intensity ratio of the OCH_2 signals in the ^1H NMR spectrum, δ 4.06 (m) and 4.16 ppm (q)]. ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.06–1.16 m and 1.18–1.32 m (3H each, OCH_2**Me**), 2.18 s and 2.56 s (3H each, MeC=O), 3.33–3.36 m (6H, CH_2NH), 3.96–4.11 m (1H, $CHCO_2$), 4.06 m (2H, OCH_2), 4.16 q (2H, OCH_2, ^3J = 6), 5.87 br.s (3H, NH), 6.35–6.41 m (2H, 3-H, 5-H), 6.55–6.63 m (4H, 3-H, 5-H), 8.08–8.29 m (6H, 2-H, 6-H). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ_C, ppm: **VI**: 13.84 (CH_2**Me**), 28.41 (**Me**C=O), 43.65 (**C**H$_2$NH), 54.52 (**C**HCO$_2$), 62.42 (OCH_2), 107.62 (C^2, C^6), 149.83 (C^3, C^5), 153.28 (C^4), 174.06 (C=O, ester), 204.67 (C=O); **VII**: 14.11 (CH_2**Me**), 28.39 (**Me**C=O), 46.22 (CH_2NH), 52.88 (**C**CO$_2$), 61.35 (OCH_2), 108.64 (C^2, C^6), 149.90 (C^3, C^5), 152.52 (C^4), 170.22 (C=O, ester), 204.51 (C=O). Found for **VI**: *m*/*z* 236.1002 $[M]^+$. $C_{12}H_{16}N_2O_3$. Calculated: *M* 236.1007. Found for **VII**: *m*/*z* 342.1973 $[M]^+$. $C_{18}H_{22}N_4O_3$. Calculated: *M* 342.1981.

***N*,*N*′-Bis(3,5-dibromopyridin-2-yl)methanediamine (VIII)** was synthesized from 0.5 g (4 mmol) of ester **I** in 27 ml of MeOH, 4.06 g (16 mmol) of 3,5-dibromopyridin-2-amine, and 5.1 ml (60 mmol) of 32.3% aqueous formaldehyde. The product was isolated by column chromatography using chloroform as eluent. Yield 3.08 g (77%), colorless crystals, mp 196–198°C (decomp.). IR spectrum (mineral oil), ν, cm^{-1}: 3421, 1579, 1311, 1224, 1093, 889. ^1H NMR spectrum (300 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 5.10 t (2H, CH_2), 7.14 d (2H, 4-H, ^4J = 2.1), 8.13 d (2H, 2-H, 6-H, ^4J = 2.2). ^{13}C NMR spectrum (75 MHz, $CDCl_3$), δ_C, ppm: 49.12 ($HNCH_2NH$), 106.11 and 106.98 (C^3, C^5), 141.70 (C^4), 147.03 and 152.91 (C^2, C^6). Found, %: C 25.75; H 1.55; Br 61.86; N 10.84. $C_{11}H_8Br_4N_4$. Calculated, %: C 25.61; H 1.56; Br 61.96; N 10.86.

This study was performed under financial support by the Presidium of the Russian Academy of Sciences, Basic Research Program "Development of Methods for the Preparation of Chemical Substances and Design of New Materials" in the framework of the guideline

"Development of Methodology of Organic Synthesis and Design of Compounds with Valuable Applied Properties."

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