Regio- and stereochemical features of the reactions of 1,2,5-trimethylpiperidin-4-one with chalcone

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The reactions of *N*-substituted piperidin-4-ones with benzylideneacetophenone, resulting in the synthesis of a number of heterocyclic 1,5-dicarbonyl compounds, were studied. 1,2,5-Trimethylpiperidin-4-one enters into cascade-type chalcone addition accompanied by intramolecular aldol condensation giving rise to the 3-azabicyclo[3.3.1]nonane system. The conformations of the 1,5-dicarbonyl compounds and azabicyclononanes synthesized were determined; the regio- and stereochemical features of the reactions of 1,2,5-trimethylpiperidin-4-one with chalcone were studied .

Key words: Michael reaction, *N*-benzylpiperidin-4-one; 8-methyl-2-(3-oxo-1,3-diphenylpropyl)-8-azabicyclo[3.2.1]octan-3-one, 1,2,5-trimethyl-3-(3-oxo-1,3-diphenylpropyl)piperidin-4-one, 1-methyl-3-(3-oxo-1,3-diphenylpropyl)piperidin-4-one, 3-azabicyclo[3.3.1]nonan-9-ones, aldol condensation, thermodynamic control.

The Michael reaction between ketones and chalcone derivatives is a simple and facile method for the synthesis of 1,5-dicarbonyl compounds, which serve as convenient intermediates in the synthesis of dihydropyridine and pyridine systems,[1] exhibiting a broad spectrum of biological activities.

The synthetic piperidine drugs used in modern medicine as neuroleptics and analgesics, are mainly represented by 4-phenylpiperidine derivatives. In order to study the biological activities of new piperidine derivatives as potential analgesic drugs, we synthesized 1,5-dicarbonyl and azabicyclononane systems.

The reactions of aliphatic and alicyclic ketones with chalcone derivatives in the presence of bases has been studied fairly comprehensively.[2—8] However, few publications have been devoted to the reaction of benzylideneacetophenone with piperidin-4-one derivatives. It was shown[9] that 1-methylpiperidin-4-one enamine enters into [4+2] cycloaddition with benzylideneacetophenone derivatives, resulting in pyrano[3,2-*c*]piperidine systems.

We studied the reaction of 1,2,5-trimethylpiperidin-4-one (**1**)[10] with substituted chalcones under the Michael reaction conditions. The reactions were carried out in alcohol at room temperature and with continuous stirring of the reaction mixture. Two compounds were thus synthesized, 6-hydroxy-1,3,4-trimethyl-6,8-diphenyl-3-azabicyclo[3.3.1]nonan-9-one (**2**) and 1,2,5-trimethyl-3-(3-oxo-1,3-diphenylpropyl)piperidin-4-one (**3**) (Scheme 1) in 4 : 1 ratio. The mixture was separated by recrystallization, the overall yield in relation to pure products being 29.6%. In the reaction of 1,2,5-trimethylpiperidin-4-one (**1**) with *p*-bromobenzylideneacetophenone, only one product (**4**) was isolated in 14.6% yield (see Scheme 1).

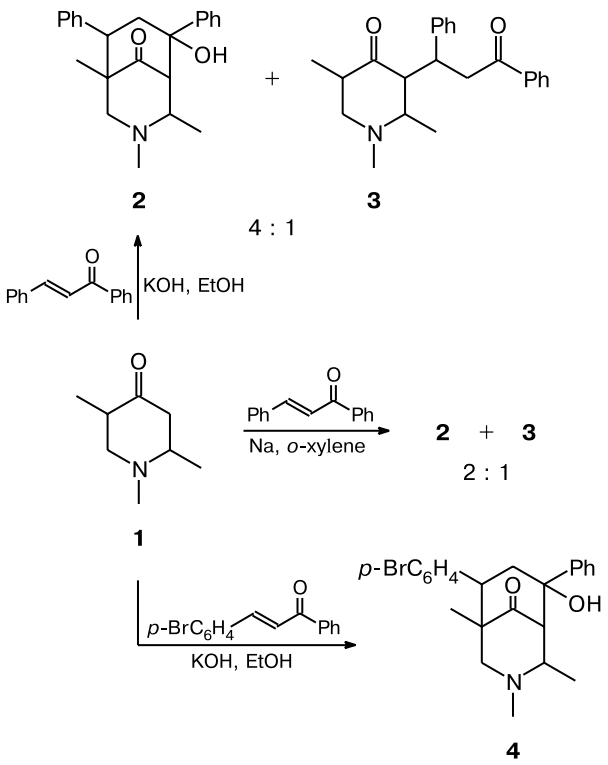
Similar reactions with two *N*-substituted piperidin-4-ones and tropinone were also carried out (Scheme 2).

The reactions of *N*-substituted piperidin-4-ones and tropinone with benzylideneacetophenone were performed under similar conditions using KOH as the base. The products analogous to bicyclic derivatives **2** and **4** have not been isolated, although the Michael adducts **5—7** were obtained in high yields.

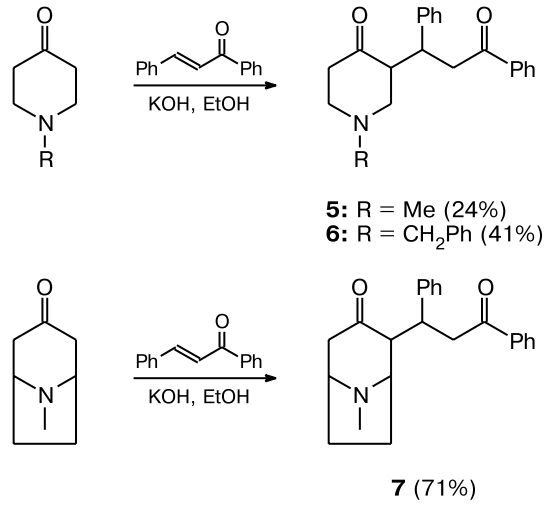
Previously,[9] compound **5** has been synthesized by the reaction of benzylideneacetophenone with *N*-methylpiperidin-4-one enamine. Parameters of the IR spectra of compound **5** obtained here coincide with those reported,[9] and the elemental analysis data confirm the proposed composition. However, it should be noted that the melting point of the compound **5** we synthesized (86—90 °C) differs from that reported in the literature[9] (140—142 °C). In the previous study,[9] the product identified as **5** was not characterized exhaustively by ^{1}H NMR spectra. The presence of multiplet signals due to the aromatic protons and signals for the N—Me group was only noted; however,

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 12, pp. 2693—2697, December, 2004.

Scheme 1



Scheme 2



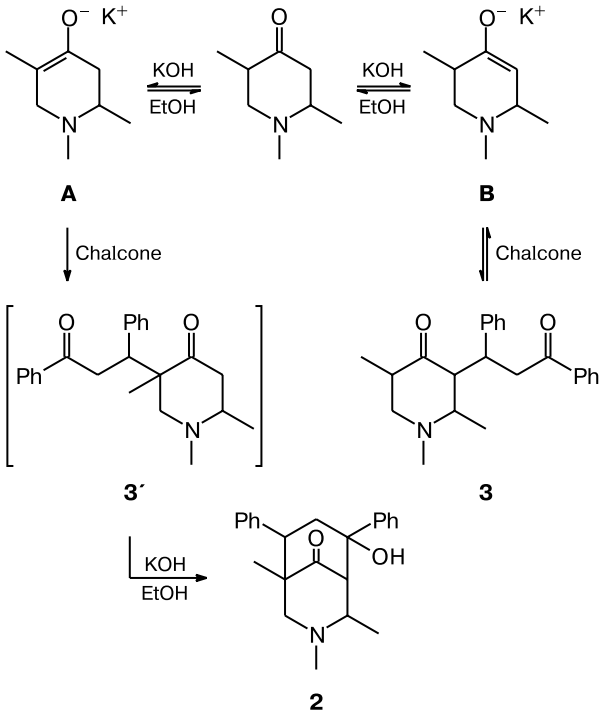
this is obviously inadequate to ultimately prove the structure of compound **5**.

Analysis of the ^{1}H NMR spectra of the obtained compounds showed that only in the case of 1,2,5-trimethylpiperidin-4-one, can the formation of bicyclic products **2** and **4** be detected. This is indicated by different multiplicities of the signals for the Me groups, which occur as singlets (δ 0.95) and doublets (δ 0.75) (detailed analysis of the NMR spectra is presented below). The IR spectra of compounds **3** and **5—7** exhibit absorption bands for the aliphatic and aromatic C=O groups at 1700—1730 and 1680—1685 cm^{-1}, respectively. The spectra of compounds **2** and **4** contain only absorption bands for the aliphatic carbonyl group at 1710 cm^{-1}. The absorption of the second carbonyl group is not observed; instead, a band for the hydroxyl group occurs at 3480 cm^{-1}.

We monitored the reaction of piperidone **1** with chalcone. Samples taken from the reaction mixture were analyzed by GLC using products **2** and **3** and the starting reagents (**1** and chalcone) as references. It was shown that for reaction durations of less than 2.5 h, compounds **2** and **3** are accumulated in the reaction mixture in 1 : 1.8 ratio. However, after 40 h, the 1,5-dicarbonyl compound **3** becomes the minor product (the **2** : **3** ratio is 9 : 1). Subsequently the chromatograms do not change up to the end of the experiment (52 h).

These results can be explained by the existence of an equilibrium (Scheme 3, the reversibility of the Michael reaction is well-known[1,12]) between the enolate ion **B** and compounds **1** and **3**, which shifts with time toward the thermodynamically controlled product **2** through the formation of 1,2,5-trimethyl-5-(3-oxo-1,3-diphenylpropyl)piperidin-4-one (**3′**) isomeric to **3**. However, this intermediate has not been detected by GLC.

Scheme 3



The reaction of piperidone **1** with chalcone in the presence of Na as an enolyzing agent has also been studied.

The reaction (see Scheme 1) was carried out in anhydrous *o*-xylene. The end of the reaction was detected by GLC. Analysis of the chromatograms of the reaction mixtures recorded at an initial time instant and 24 and 48 h after the beginning of the reaction attests to the formation of compounds **2** and **3** whose ratio does not change in time, being equal to 2 : 1. Compound **2** was isolated in a pure state and characterized by ^{1}H NMR spectroscopy and elemental analysis. The yield was 29%.

Comparison of the reaction pathways under different conditions leads to the conclusion that in the latter case, the reaction is irreversible. The generated enolate ions are attacked by the electrophilic agent, chalcone, being converted into products **2** and **3**, whose ratio does not change with time due to the lack of equilibrium between the products and the enolates when the reaction is carried out in an aprotic solvent.

Attempts to obtain the azabicyclononane skeleton by intramolecular aldol condensation of the 1,5-dicarbonyl compounds **5** and **6** were also undertaken. The reactions were carried out in the presence of bases such as NaH and EtONa in various solvents (DMF and EtOH) at room temperature. Despite the long reaction times (72 h), no products similar in structure to compounds **2** and **4** were obtained in the experiments, the starting compounds being recovered unchanged.

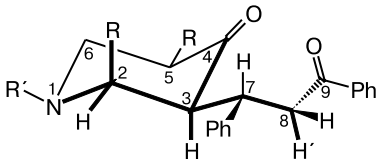
A series of previous studies[8,13—16] have been devoted to the synthesis of alicyclic 1,5-dicarbonyl compounds and bicyclononane systems based on cyclohexanone. It was shown[8] that the reaction of chalcone with cyclohexanone under Michael conditions gives rise to a mixture of 2-(3-oxo-1,3-diphenylpropyl)cyclohexanone diastereomers. The resulting diastereomers were isolated by preparative HPLC in 8 : 2 ratio and then introduced in intramolecular aldol condensation in the presence of AcOH as the solvent and catalytic amounts of HCl. This gave *exo*- and *endo*-2,4-diphenylbicyclo[3.3.1]nonen-9-ones, which were separated by fractional crystallization.

We attempted to study the stereochemistry of azabicyclononanones **2** and **4** and other reaction products by ^{1}H NMR.

The signals in the ^{1}H NMR spectra of compounds **2—6** were assigned using double resonance experiments. The conformational behavior of piperidones **3**, **5**, and **6** was analyzed using data on the chemical shifts and the coupling constants of related systems described in a monograph.[17]

The spin-spin coupling constants for compounds **3**, **5**, and **6** (see Experimental) indicate that all compounds exist as the predominant chair conformation with the equatorial 3-oxo-1,3-diphenylpropyl fragment.

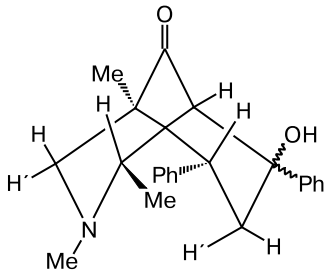
Using the data on the spin-spin coupling constants, it was found that in compound **3**, the piperidine ring protons at the C(2), C(3) (J = 1.4 Hz) and C(5), C(6) atoms (J = 10.5 Hz) occupy eq,ax and ax,ax positions, respectively, the Me group at the C(2) atom occupies the axial position, while that at C(5) occurs in the equatorial position in the ring. The 3-oxo-1,3-diphenylpropyl radical at the C(3) occurs in the equatorial position in the piperidine ring, the protons at C(3) and C(7) (J = 11.5 Hz) being predominantly in the antiperiplanar positions with respect to each other.



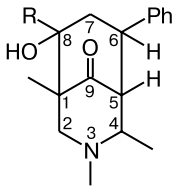
3: R = R′ = Me; **5:** R = H′, R′ = Me; **6:** R = H′, R′ = CH_2Ph

In compound **5**, the protons at the C(3), C(2) (J = 8.3 Hz) and C(5), C(6) atoms (J = 4.9 Hz) of the piperidine ring occupy ax,ax and ax,eq positions, respectively. The protons at C(3) and C(7) (J = 10.5 Hz) occur predominantly in the antiperiplanar positions relative to each other.

The spin-spin coupling constants of compound **6** are similar to those for compounds **3** and **5**. The signals for the protons at C(5) and C(6) have not been identified, as the signals in this region of the ^{1}H NMR spectrum overlap. However, the available data indicate that in compound **6**, too, the piperidone ring is in the chair conformation with the equatorial 3-oxo-1,3-diphenylpropyl fragment.



2



2′: R = Ph
4′: R = 4-BrC_6H_4

The presence of compounds **2** and **4** in the reaction mixture indicates that the reactions do not stop after the formation of 1,5-dicarbonyl compounds and result in the products of intramolecular aldol condensation (see Scheme 3). The ^{1}H NMR spectra of compound **4** are similar to the spectra of **2**, differences being observed only in the aromatic region. The signals of protons of one Me group are recorded as a singlet, whereas the proton signals of the second Me group are responsible for a doublet. This implies that the proton at the C(1) atom is replaced by a chalcone fragment. However, the question of whether this takes place in the first step (*i.e.*, during the formation of 1,5-diketone **3**, which subsequently cyclizes) or results from the attack by the enolate ion formed from com-

pound **3´** on the aromatic carbonyl group remains open. The spectra of products **2** and **4** do not exhibit additional signals for the C(5)H and C(6)H protons, which would show themselves as dd and ddd, respectively, if isomeric bicyclic derivatives **2´** and **4´** were formed. In addition, as noted above, attempts to carry out the intramolecular cyclization of the isolated compound **3** has not met with success. Therefore, we believe that azabicyclononanones **2** and **4** are formed from thermodynamically more stable enolate **A** (see Scheme 3).

A special challenge is to elucidate the orientation of the Me group at the C(4) atom in the azabicyclononane system, as the measured coupling constant between the proton at C(4) and the vicinal proton at C(5) (3.9 Hz) can correspond to both the ax,eq and the eq,eq arrangements of these protons. However, by comparing the spectra of the free base and its hydrochloride, we found that protonation of the N atom induces the most pronounced changes in the chemical shift and substantial line broadening for the axial proton at C(2) and the proton at C(4). We attributed this to the spin-spin coupling between the proton at nitrogen and the axial protons at neighboring carbons in the hydrochloride. Therefore, we assign the equatorial position to the Me group at C(4).

Experimental

The reactions were monitored and the product purity was checked by TLC (Silufol UV-254) and GLC on a Tsvet-152 chromatograph (a 0.7-m long column of diameter 3 mm, SE-30/5% liquid phase on Chromaton N-AW 0.16—0.20 mm). Nitrogen was the carrier gas, temperature programming in the 75—325 °C range, 22 °C min^{-1}. IR spectra were measured on a Perkin—Elmer instrument in KBr, ^1H NMR spectra were recorded on a Bruker A-250 instrument (operating frequency 250 MHz). $CDCl_3$ and DMSO-d_6 were used as solvents. The chemical shifts are presented in ppm in the δ scale relative to internal HMDS. The melting points of substances were determined on a Boetius hot stage (Kofler system).

All solvents were purified by standard procedures.[18]

6-Hydroxy-1,3,4-trimethyl-6,8-diphenyl-3-azabicyclo[3.3.1]nonan-9-one (2) and 1,2,5-trimethyl-3-(3-oxo-1,3-diphenylpropyl)piperidin-4-one (3). 1,2,5-Trimethylpiperidin-4-one (3.75 g, 0.026 mol) and KOH (1.52 g) in 3.81 mL of water were added subsequently to a solution of benzylideneacetophenone (4.92 g, 0.023 mol) in 30 mL of ethanol. The reaction mixture was stirred for 5 h and kept in a refrigerator (−3 °C) for ~14 h. The oily layer was separated from the ethanol solution. The ethanol solution was concentrated on a rotary evaporator, and benzene and water were added successively to the residue. The benzene layer was thoroughly washed with water to remove 1,2,5-trimethylpiperidin-4-one and alkali. The benzene fraction was dried with $CaCl_2$ and the hydrochloride was prepared by adding an ether solution of HCl to the benzene solution with monitoring the pH to a slightly acidic medium using universal indicator. The resulting crystals were recrystallized from Pr^iOH to give 2.32 g (23.2%) of the hydrochloride of compound **2**, m.p. 215—217 °C (from Pr^iOH). Benzene was added to the oily layer (see above) and the mixture was repeatedly washed with water to remove the starting ketone impurity. The benzene extract was dried with $CaCl_2$, the solvent was evaporated, and the residue was recrystallized from Pr^iOH to give 0.57 g (6.39%) of compound **3**, m.p. 115—118 °C (from Pr^iOH).

Compound **2** (hydrochloride). Found (%): C, 71.32; H, 7.09; Cl, 9.24; N, 3.42. $C_{23}H_{27}NO_2 \cdot HCl$. Calculated (%): C, 71.59; H, 7.26; Cl, 9.20; N, 3.63. ^1H NMR (DMSO-d_6—CF_3COOD), δ: 0.79 (d, 3 H, C(4)Me, $J_{C(4)Me,H(4)}$ = 6.2 Hz); 0.96 (s, 3 H, C(1)Me); 1.98 (dd, 1 H, H(8), $J_{C(8)H,C(7)H}$ = 3.0 Hz, $J_{C(8)H,C(7)H´}$ = 14.0 Hz); 2.64 (d, 1 H, H(5), $J_{C(5)H,C(4)H}$ = 3.90 Hz); 2.77 (s, 3 H, NMe); 3.04 (d, 1 H, H´(2), $J_{C(2)H´,C(2)H}$ = 13.4 Hz); 3.21 (dd, 1 H, H(7), $J_{C(7)H,C(7)H´}$ = 12.5 Hz, $J_{C(7)H,C(8)H}$ = 3.0 Hz); 3.48 (dq, 1 H, H(4), $J_{C(4)H,C(4)Me}$ = 6.20 Hz, $J_{C(4)H,C(5)H}$ = 3.90 Hz); 3.74 (dd, 1 H, H´(7), $J_{C(7)H´,C(7)H}$ = 12.5 Hz, $J_{C(7)H´,C(8)H}$ = 14.0 Hz); 4.21 (d, 1 H, H(2), $J_{C(2)H,C(2)H´}$ = 13.4 Hz); 7.25—7.80 (m, 10 H, H_{Ar}); 10.5 (br.s, 1 H, NH^+).

Compound **2** (base). ^1H NMR (DMSO-d_6), δ: 0.59 (s, 3 H, C(1)Me); 0.65 (d, 3 H, C(4)Me, $J_{C(4)Me,C(4)H}$ = 6.6 Hz); 1.77 (dd, 1 H, H(8), $J_{C(8)H,C(7)H}$ = 5.1 Hz, $J_{C(8)H,C(7)H´}$ = 13.2 Hz); 2.25 (s, 3 H, NMe); 2.25 (d, 1 H, H´(2), $J_{C(2)H´,C(2)H}$ = 12.5 Hz); 2.25 (d, 1 H, H(5), $J_{C(5)H,C(4)H}$ < 1.0 Hz); 2.76 (d, 1 H, H(2), $J_{C(2)H,C(2)H´}$ = 12.5 Hz); 2.86 (dq, 1 H, H(4), $J_{C(4)H,C(4)Me}$ = 6.6 Hz, $J_{C(4)H,C(5)H}$ < 1.0 Hz); 3.17 (dd, 1 H, H(7), $J_{C(7)H,C(7)H´}$ = 12.5 Hz, $J_{C(7)H,C(8)H}$ = 5.1 Hz); 4.28 (dd, 1 H, H´(7), $J_{C(7)H´,C(7)H}$ = 12.5 Hz, $J_{C(7)H´,C(8)H}$ = 13.2 Hz); 5.26 (s, 1 H, C(6)OH); 7.19—7.66 (m, 10 H, H_{Ar}).

Compound **3** (base). Found (%): C, 79.18; H, 7.57; N, 4.15. $C_{23}H_{27}NO_2$. Calculated (%): C, 79.05; H, 7.79; N, 4.01. ^1H NMR ($CDCl_3$), δ: 0.68 (d, 3 H, C(2)Me, $J_{C(2)Me,C(2)H}$ = 6.8 Hz); 0.95 (d, 3 H, C(5)Me, $J_{C(5)Me,C(5)H}$ = 6.3 Hz); 2.24 (s, 3 H, NMe); 2.35 (dd, 1 H, H(3), $J_{C(2)H,C(3)H}$ = 1.4 Hz, $J_{C(3)H,C(7)H}$ = 11.5 Hz); 2.40 (dd, 1 H, H´(6), $J_{C(6)H´,C(6)H}$ = 10.5 Hz, $J_{C(6)H´,C(5)H}$ = 10.5 Hz); 2.65 (dq, 1 H, H(2), $J_{C(2)H,C(2)Me}$ = 6.8 Hz, $J_{C(2)H,C(3)H}$ = 1.4 Hz); 2.89 (dd, 1 H, C(8)H, $J_{C(8)H,C(8)H´}$ = 17.40 Hz, $J_{C(8)H,C(7)H}$ = 4.3 Hz); 2.90 (dd, 1 H, H(6), $J_{C(6)H,C(6)H´}$ = 10.5 Hz, $J_{C(6)H,C(5)H}$ = 7.4 Hz); 3.02 (ddq, 1 H, H(5), $J_{C(5)H,C(6)H´}$ = 10.5 Hz, $J_{C(5)H,C(6)H}$ = 7.4 Hz, $J_{C(5)H,C(5)Me}$ = 6.3 Hz); 3.43 (dd, 1 H, C(8)H´, $J_{C(8)H´,C(8)H}$ = 17.40 Hz, $J_{C(8)H´,C(7)H}$ = 9.6 Hz); 4.30 (ddd, 1 H, C(7)H, $J_{C(7)H,C(3)H}$ = 11.5 Hz, $J_{C(7)H,C(8)H´}$ = 9.6 Hz, $J_{C(7)H,C(8)H}$ = 4.30 Hz); 7.08—7.90 (m, 10 H, H_{Ar}).

8-(4-Bromophenyl)-6-hydroxy-1,3,4-trimethyl-6-phenyl-3-azabicyclo[3.3.1]nonan-9-one (4). 1,2,5-Trimethylpiperidin-4-one (1.5 g, 0.01 mol) and KOH (0.65 g) in 1.46 mL of water were added subsequently with continuous stirring to a solution of *p*-bromobenzylideneacetophenone (2.29 g, 0.008 mol) in 50 mL of ethanol and 15 mL of benzene. The mixture was left for 48 h. The solvent was evaporated, and benzene and brine were added to the residue. The benzene layer was separated, washed repeatedly with water, and dried with $CaCl_2$, the solvent was evaporated, and an ether solution of HCl was added to the residue. The crystals were recrystallized from a petroleum ether—ethanol mixture (1 : 1.5) to give 0.54 g (14.6%) of compound **4** as the hydrochloride, m.p. (hydrochloride) 213—216 °C (from a petroleum ether—ethanol mixture), m.p. (base) 178—182 °C (from ethanol). Compound **4** (hydrochloride). Found (%): C, 59.26; H, 5.96; Cl + Br, 24.99; N, 3.46. $C_{23}H_{26}BrNO_2 \cdot HCl$. Calculated (%): C, 59.43; H, 5.85; Cl + Br, 24.82; N, 3.01. ^1H NMR (DMSO-d_6—CF_3COOD), δ: 0.79 (d, 3 H, C(4)Me,

$J_{C(4)Me,H(4)}$ = 6.2 Hz); 0.96 (s, 3 H, C(1)Me); 1.98 (dd, 1 H, H(8), $J_{C(8)H,C(7)H}$ = 3.0 Hz, $J_{C(8)H,C(7)H'}$ = 14.0 Hz); 2.64 (d, 1 H, H(5), $J_{C(5)H,C(4)H}$ = 3.90 Hz); 2.77 (s, 3 H, NMe); 3.04 (d, 1 H, H´(2), $J_{C(2)H',C(2)H}$ = 13.4 Hz); 3.21 (dd, 1 H, H(7), $J_{C(7)H,C(7)H'}$ = 12.5 Hz, $J_{C(7)H,C(8)H}$ = 3.0 Hz); 3.48 (dq, 1 H, H(4), $J_{C(4)H,C(4)Me}$ = 6.20 Hz, $J_{C(4)H,C(5)H}$ = 3.90 Hz); 3.74 (dd, 1 H, H´(7), $J_{C(7)H',C(7)H}$ = 12.5 Hz, $J_{C(7)H',C(8)H}$ = 14.0 Hz); 4.21 (d, 1 H, H(2), $J_{C(2)H,C(2)H'}$ = 13.4 Hz); 7.25—7.80 (m, 9 H, H_{Ar}); 10.5 (br.s, 1 H, NH^+).

1-Methyl-3-(3-oxo-1,3-diphenylpropyl)piperidin-4-one (5). Potassium hydroxide (1.11 g) in 2.5 mL of water was added with stirring to a solution of benzylideneacetophenone (2.89 g, 0.014 mol) and *N*-methylpiperidin-4-one 2 g (0.017 mol) in 25 mL of ethanol. The mixture was left for 48 h and poured into water. The resulting suspension was extracted with benzene (2×30 mL). Then the solvent was evaporated and the residue was recrystallized from Pr^iOH and kept for ~14 h at −3 °C. The yellow crystals that precipitated were filtered off and washed 4 times with cold Pr^iOH to give 1.30 g (24%) of compound **5**, m.p. 86—90 °C (from Pr^iOH). Found (%): C, 78.33; H, 7.04; N, 4.42. $C_{21}H_{23}NO_2$. Calculated (%): C, 78.47; H, 7.21; N, 4.36. ^{1}H NMR ($CDCl_3$), δ: 2.0—2.80 (m, 4 H, H(5), H(6) piper. ring); 2.06 (dd, 1 H, H´(2) piper. ring, $J_{C(2)H',C(2)H}$ = 11.5 Hz, $J_{C(2)H',C(3)H}$ = 8.3 Hz); 2.19 (s, 3 H, NMe); 2.40 (dd, 1 H, H(2) piper. ring, $J_{C(2)H,C(2)H'}$ = 11.5 Hz, $J_{C(2)H,C(3)H}$ = 4.9 Hz); 2.82 (ddd, 1 H, H(3) piper. ring, $J_{C(3)H,C(2)H'}$ = 8.3 Hz, $J_{C(3)H,C(2)H'}$ = 4.9 Hz, $J_{C(3)H,C(7)H}$ = 10.5 Hz); 3.25 (dd, 1 H, C(8)H´, $J_{C(8)H',C(8)H}$ = 16.6 Hz, $J_{C(8)H',C(7)H}$ = 9.5 Hz); 3.48 (dd, 1 H, C(8)H, $J_{C(8)H,C(8)H'}$ = 16.6 Hz, $J_{C(8)H,C(7)H}$ = 4.5 Hz); 3.87 (ddd, 1 H, C(7)H, $J_{C(7)H,C(3)H}$ = 10.5 Hz, $J_{C(7)H,C(8)H}$ = 4.5 Hz, $J_{C(7)H,C(8)H'}$ = 9.5 Hz); 7.08—7.98 (m, 10 H, H_{Ar}).

1-Benzyl-3-(3-oxo-1,3-diphenylpropyl)piperidin-4-one (6). *N*-Benzylpiperidin-4-one (5.63 g, 0.025 mol) and KOH (2 g) in 5 mL of H_2O were added with stirring to a solution of benzylideneacetophenone (5.28 g, 0.025 mol) in 50 mL of ethanol. The reaction mixture was left for 3 days. The precipitated crystals were filtered off and recrystallized from Pr^iOH to give 3.68 g (+1.5 g from the mother liquor) of compound **6**. Yield 41%, m.p. 118—122 °C (from Pr^iOH). Found (%): C, 81.39; H, 7.04; N, 3.81. $C_{27}H_{27}NO_2$. Calculated (%): C, 81.61; H, 6.80; N, 3.52. ^{1}H NMR ($CDCl_3$), δ: 2.25—2.70 (m, 4 H, H(2), H(5), H(6) piper. ring); 2.76 (ddd, 1 H, H(3), $J_{C(3)H,C(2)H}$ ≈ 5.0 Hz, $J_{C(3)H,C(2)H'}$ ≈ 8.0 Hz, $J_{C(3)H,C(7)H}$ = 10.7 Hz); 3.33 (d, 2 H, C(8)H, C(8)H´, $J_{C(8)H,C(7)H}$ ≈ 6.7 Hz, $J_{C(8)H',C(7)H}$ ≈ 6.7 Hz); 3.37, 3.45 (both d, 2 H, NCH_2Ph, $J_1 = J_2$ = 14 Hz); 4.00 (dt, 1 H, C(7)H, $J_{C(7)H,C(3)H}$ = 10.70 Hz, $J_{C(7)H,C(8)H}$ ≈ 6.7 Hz, $J_{C(7)H,C(8)H'}$ ≈ 6.7 Hz); 7.08—7.90 (m, 10 H, H_{Ar}).

8-Methyl-2-(3-oxo-1,3-diphenylpropyl)-8-azabicyclo[3.2.1]octan-3-one (7). Tropan-3-one (14 g, 0.1 mol) and a solution of KOH (5.76 g) in 15 mL of water were added with stirring to a solution of benzylideneacetophenone (17.86 g, 0.085 mol) in 134 mL of ethanol. The mixture was left for 3 days, and the precipitate was filtered off, washed with ethanol, and recrystallized from Pr^iOH to give 19 g of compound **7** (and additional 2 g from the mother liquor). Yield 71%, m.p. 148—150 °C (from Pr^iOH). Found (%): C, 79.66; H, 7.11; N, 4.46. $C_{23}H_{25}NO_2$. Calculated (%): C, 79.51; H, 7.25; N, 4.03. ^{1}H NMR ($CDCl_3$), δ: 1.25—2.15 (m, 2 H each, H(6), H(7), H(4) tropane ring); 2.2 (s, 3 H, NMe); 2.65—2.75 (m, 1 H, H(2) tropane ring); 2.90—3.05 (m, 2 H, H(1), H(5) tropane ring); 3.25—3.40 (m, 2 H, —C$\underline{H}_2$—COPh); 4.15—4.30 (m, 1 H, Ar—C$\underline{H}$—); 7.15—7.90 (m, 10 H, H_{Ar}).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 03-03-32401).

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Received April 27, 2004;
in revised form June 16, 2004