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DIASTEREODIRECTED ALKYLATION OF KETONES AND 1,3-DIKETONES WITH N-[1H-INDOL-3-YL(PHENYL)METHYL]-N-METHYLAMINE BY THE MICHAEL REACTION

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A method has been developed for introducing the 1H-indol-3-yl(phenyl)methyl residue into position 2 of ketones and 1,3-diketones. The principle of bringing in controlled diastereoselectivity based on the configuration of intermediates is demonstrated.

Keywords: gramine, CH-acids, α-phenyl-*nor*-gramine, diastereoselectivity in the Michael reaction, X-ray structural analysis, NMR.

The present work is devoted to a study of the possibility of alkylating carbonyl compounds with α-phenyl-*nor*-gramine (**1**), and in a diastereospecific manner. Previously we showed the possibility of the nondiastereoselective alkylation of nitroalkanes with N-[1H-indol-3-yl(phenyl)methyl]-N-methylamine (α-phenyl-*nor*-gramine) (**1**) [1]. It is also known that compound **1** is readily converted into 2-(1H-indol-3-yl)-2-phenylacetonitrile on interaction with KCN [2]. Based on this we suggested that compound **1** will be a convenient reagent for introducing a 1H-indol-3-yl(phenyl)methyl residue into position 2 of ketones and 1,3-diketones. The following were used as model compounds: cyclohexanone (**3a**), cyclopentanone (**3b**), 1,2-cyclohexanedione (**3c**), 1,3-cyclohexanedione (**3d**), 5,5-dimethyl-1,3-cyclohexanedione (dimedone) (**3e**), esters of 3-oxobutyric acid: methyl (**3f**), ethyl (**3g**), isopropyl (**3h**), and benzyl (**3i**), 1,3-indanedione (**3j**), acetone (**3k**), acetophenone (**3l**), esters of cyanoacetic acid: methyl (**3m**), ethyl (**3n**), and α-tetralone (**3o**).

Compound **1** was obtained by the addition of indole at the double bond of benzylidenemethylamine by the method of Passerini [3].

The alkylation of carbonyl compounds **3** was carried out in 90% aqueous 2-propanol or ethanol using potassium carbonate as catalyst. The yields of alkylation products **4** are given in Table 1. Alkylation probably occurs through the intermediate formation of 3-[(*Z*)-phenylmethylidene]-3H-indole (**2**) with subsequent addition to it of a CH-acid enolate according to Michael.

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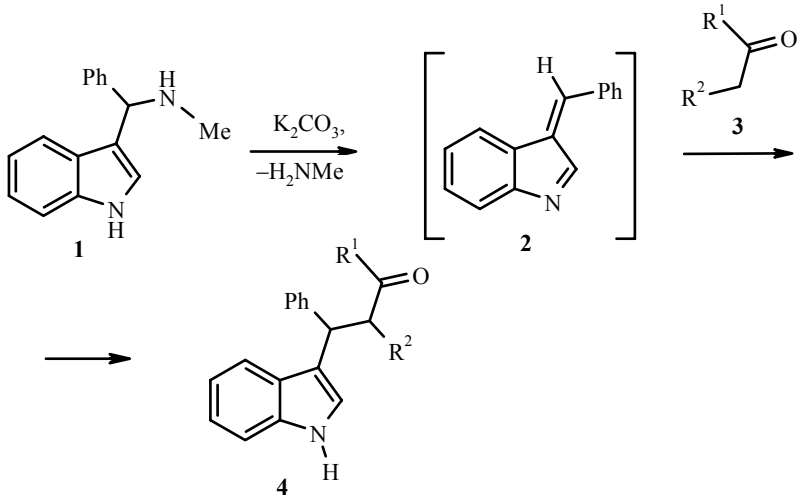


According to literature data 2-methyl-3-[(*Z*)-phenylmethylidene]-3H-indole [4] exists as one isomer. According to our *ab initio* calculations intermediate **2** also has the *Z*-configuration [5].

In the case of compounds **3d,e,i-k** the alkylation products **4d,e,i-k** were not formed under these conditions, and polymeric products of the self-condensation of the initial compound **1** were obtained. Probably the rate of polymerization in this case is higher than Michael addition of the enolates of the carbonyl compounds. For compounds **3d,e** significant steric obstacles also evidently hinder alkylation.

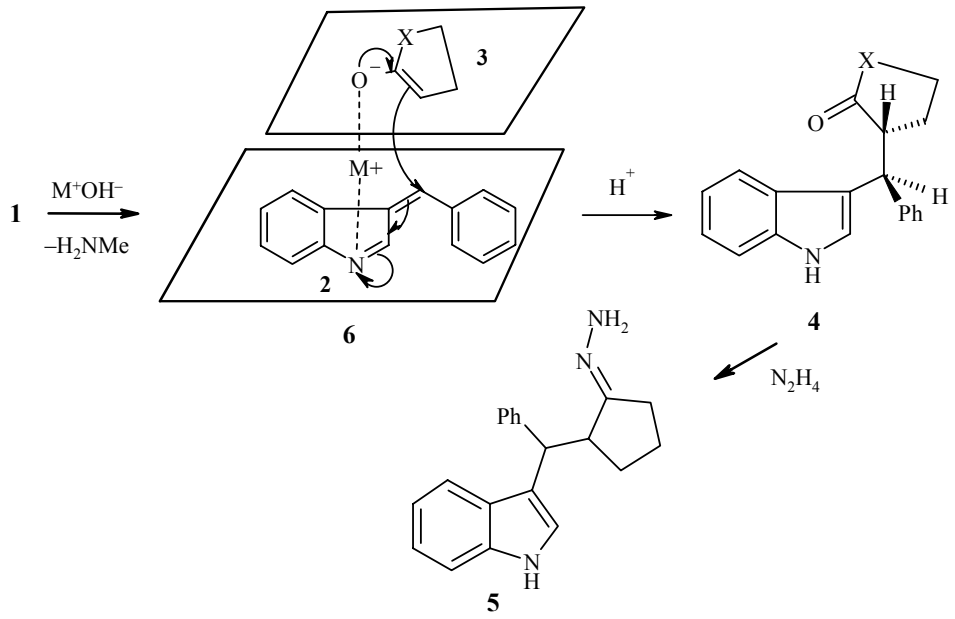
Unlike gramine [6-9], in our case only products of the monoalkylation of compounds **3a-c, f-h, l-o** were formed. The formation of bisalkylation products was not observed even chromatographically.

The method developed by us has enabled investigation of the stereochemistry of the process of alkylating cyclic ketones **3a,b,o** with α-phenyl-*nor*-gramine (**1**). Previously it was suggested that compound **1** eliminates methylamine on treatment with basic catalysts and forms an intermediate 3-[(*Z*)-phenylmethylidene]-3H-indole (**2**), having a planar structure [5]. We proposed that if in the Michael reaction the enolates of cyclopentanone or α-tetralone, having the *E*-configuration, are used as second component, then the alkylation products **4** will have an (*R**,*S**)-structure. As a result of coordination of the metal cation with a nitrogen atom of one ring and an oxygen atom of another ring both fragments are disposed to one another on the *Si* and *Re* sides, which corresponds to *unlike attack* [10-13].

We have established that for cyclohexanone the reaction does not go diastereoselectively (*de* 0%). In the case of α-tetralone enolate, having a planar rigidity in the 1,3-butadiene fragment, the reaction proved to be diastereospecific (*de* 100%), and for cyclopentanone enolate a fairly high diastereoselectivity was observed (*de* 92%).

TABLE 1. Yields of Alkylation Products

Compound	R^1	R^2	Yield, %	Compound	R^1	R^2	Yield, %
4a	$R^1 = R^2 = (CH_2)_4$		60	**4h**	Me	COOPr-*i*	65
4b	$R^1 = R^2 = (CH_2)_3$		75	**4j**	$R^1 = R^2 = C_6H_4CO$		—
4c	$R^1 = R^2 = CO(CH_2)_3$		50	**4k**	Me	H	—
4d	$R^1 = R^2 = CO(CH_2)_3$		—	**4l**	Ph	H	—
4e	$R^1 = R^2 = COCH_2CMe_2CH_2$		—	**4m**	OMe	CN	70
4f	Me	COOMe	65	**4n**	OEt	CN	65
4g	Me	COOEt	71	**4o**	$R^1 = R^2 = CH_2C_6H_4$		25



M = Li, K, Na; **3, 4 a** X = $(CH_2)_2$; **b** X = CH_2; **o** X = C_6H_4

Compound, yield, %; de, %; configuration: **4a**, 60, 0, *E*; **4b**, 75, 92, *E*; **4o**, 25, 100, *E*

Alkylation of carbonyl compounds **3a,b,o** was carried out in 90% aqueous 2-propanol or ethanol using potassium carbonate as catalyst. The use of different solvents, as was shown in the example of preparing compound **4b**, has no effect on the size of *de* and only insignificantly influenced the yield of alkylation products. The *de* was 75% in 90% aqueous isopropyl alcohol and 69% in 90% aqueous ethanol.

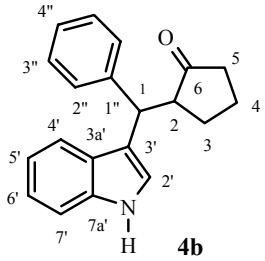
The ratio of diastereomers in the reaction to form compound **4b** was established by comparing the integral intensities of the doublets of the CH protons in the ^{1}H NMR spectra of both diastereoisomers.

We have established that this stereochemical result may not be the result of a separation of the mixture of diastereoisomers in the process of recrystallization. If the reaction is stopped 1 h after the start by the addition of water, then, according to data of ^{1}H NMR spectroscopy the ratio of diastereomers is 96:4. Consequently the reason for the diastereoselectivity is either kinetic or thermodynamic control (equilibrium isomerization of one diastereomer into the other through the enolic form of the ketone). A choice between these was made on the basis of the following experiment. If 10 mol. % C_5D_5N is added to the pure (*R**,*S**)-diastereomer in $CDCl_3$ then the formation of the second diastereomer is not observed at room temperature for 48 h. It was not successfully detected on maintaining the (*R**,*S**)-diastereomer in pure pyridine at room temperature for 96 h. In our opinion this is explained sterically by the more ready possibility of forming the enol form of compound **4b** with the participation of the protons of a methylene group of the cyclopentanone ring. However after maintaining the pure (*R**,*S**)-diastereomer in 90% aqueous 2-propanol in the presence of potassium carbonate for 30 h, we recorded a mixture of (*R**,*S**)- and (*S**,*S**)-isomers in a ratio of 75:25 (*de* 50%), but on using 90% aqueous ethanol as solvent the ratio was 60:40 (*de* 20%).

On alkylating compound **3b** in anhydrous isopropyl alcohol compound **4b** was obtained and the ratio of (*R**,*S**)- and (*S**,*S**)-diastereomers amounted to 75:25 (*de* 50%). On treating this mixture with a 20-fold excess of hydrazine hydrate the ratio of diastereomers in the resulting hydrazone **5**, according to data of ^{1}H NMR spectroscopy, was unchanged and probably the (*R**,*S**)-isomer predominates. Such a stereochemical result points to the enolization of ketone **4b** under the given conditions being in the direction of the more hydrogenated carbon atom. Consequently the reason for the diastereoselectivity is evidently kinetic control.

The configuration of the major (*R**,*S**)-diastereomer of compound **4b** was confirmed by data of ^{1}H and ^{13}C NMR spectra (Table 2) and of X-ray structural analysis (Fig. 1).

TABLE 2. NMR Spectra of Compound **4b**



4b

Numbering of atoms	^{13}C, δ, ppm		^{1}H, δ, ppm	
	*R**,*S**	*S**,*S**	*R**,*S**	*S**,*S**
1	41.6	42.1	5.05	4.95
2	53.7	53.7	2.95	2.95
3	26.4	27.6	2.30; 1.75	2.35; 1.90
4	20.8	20.7	1.70	1.70
5	38.8	38.8	2.30; 1.85	2.30; 1.85
6	219.9	220.1	—	—
2'	122.1	123.5	7.15	7.00
3'	118.4	117.1	—	—
3a'	127.1	127.1	—	—
4'	119.4	120.1	7.20	7.25
5'	119.3	119.3	6.95	6.95
6'	121.5	121.8	7.15	7.10
7'	110.9	111.0	7.35	7.35
7a'	136.4	136.2	—	—
1"	141.5	143.5	—	—
2"	129.3	128.1	7.15	7.40
3"	128.1	128.2	7.30	7.25
4"	126.4	126.1	7.20	7.15

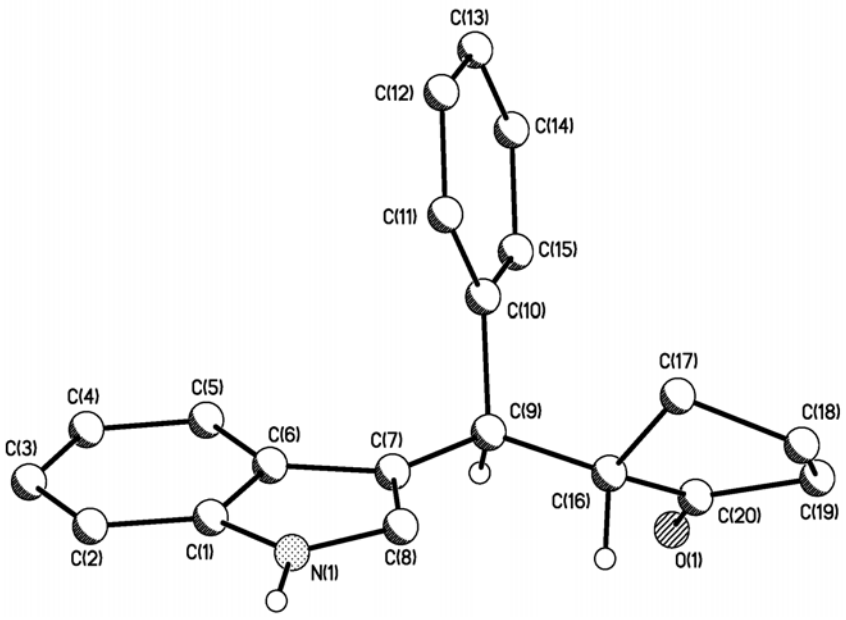


Fig. 1. General form of the compound **4b** molecule.

All the signals in the ^1H and ^{13}C NMR spectra of compound **4b** were unequivocally assigned using the ^{13}C APT (attached proton test) and the HSQC and HMBC two-dimensional heteronuclear procedures (Table 2).

Based on data of X-ray structural analysis it was established that in the crystal of the (*R**,*S**)-diastereomer of compound **4b** the cyclopentanone fragment has an envelope conformation with the $C_{(17)}$ atom emerging 0.55 Å from the plane of the remaining ring atoms. The dihedral angle between the phenyl and indole fragments was 99.6°. Analysis of the crystal packing showed that the molecules are connected by intermolecular hydrogen bonds N–H···O [N···O is 2.875(3) Å] in a spiral directed along the *c* crystal axis. The spirals interweave with one another with the formation of channels of diameter ~4.60 Å.

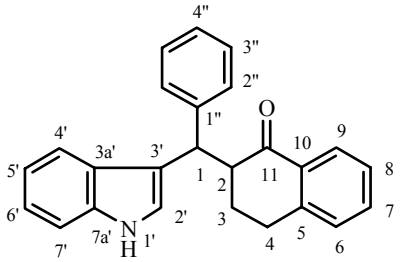
On alkylating cyclohexanone in 90% alcohol, in the presence of potassium carbonate or NaOH as catalyst, a mixture was obtained of diastereomers of compound **4a**, though the content of each diastereomer was 50% according to data of ^1H NMR spectra. This stereochemical result is probably the result of isomerization of one diastereomer into the other through the enolic form of ketone **4a**.

In the case of α-tetralone **3o** when using sodium acetate, potassium carbonate, or pyridine as base a difficultly identifiable mixture of polymeric compounds was obtained, and the use of sodium alcoholate or sodium dimsyl leads to complete resinification of the mixture. However the use of LiOH, KOH, or NaOH enabled compound **4o** to be obtained in 25% yield. According to data of ^1H NMR compound **4o** exists as only one diastereomer.

All signals in the ^1H and ^{13}C NMR spectra of compound **4o** were unequivocally assigned using the ^{13}C APT method and two-dimensional heteronuclear HSQC and HMBC procedures (Table 3).

The ^1H and ^{13}C NMR spectra were interpreted with the aid of HSQC and HMBC two-dimensional procedures in deuterochloroform at 30°C (Bruker DRX 500).

TABLE 3. NMR spectra of Compound **4o**



Numbering of atoms	^{13}C, δ, ppm	^1H, δ, ppm	Numbering of atoms	^{13}C, δ, ppm	^1H, δ, ppm
1	40.9	5.22	1'	—	8.05
2	52.4	3.45	2'	121.6	7.26
3	26.5	2.30; 1.85	3'	117.8	—
4	28.3	3.10	3a'	127.0	—
5	126.8	—	4'	119.7	7.28
6	128.7	7.22	5'	119.3	6.95
7	126.7	7.25	6'	122.1	7.13
8	133.2	7.45	7'	111.0	7.33
9	127.9	7.96	7a'	135.8	—
10	143.1	—	1"	140.7	—
11	197.3	—	2"	129.2	7.36
			3"	128.2	7.24
			4"	126.3	7.16

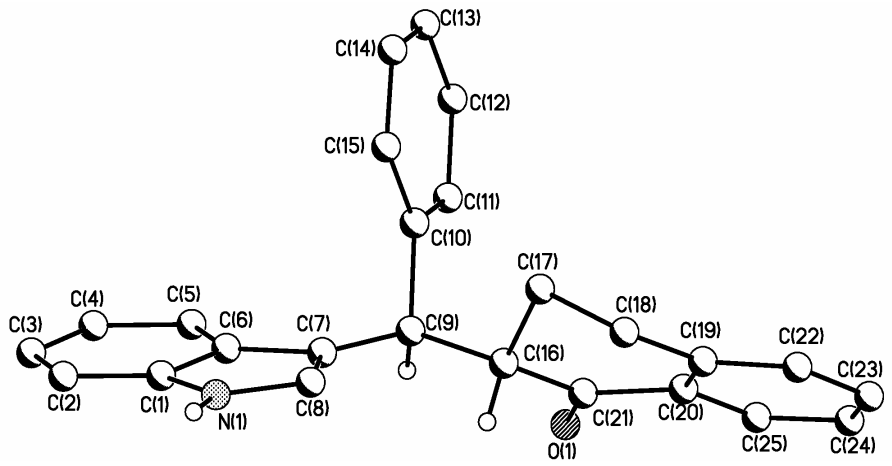


Fig. 2. General form of the compound **4o** molecule.

The configurations of the asymmetric carbon atoms in compound **4o** were established on the basis of X-ray structural analysis (Fig. 2). The main geometric parameters of compound **4b** were close to the corresponding parameters of the **4o** molecule. The cyclohexane ring has a chair conformation with atom $C_{(17)}$ emerging by 0.68 Å. The dihedral angle between the phenyl and indole fragments was unchanged and in the **4o** molecule was 95°. We note that apart from the molecular geometry the supramolecular organization also remains unchanged. In compound **4o** the molecules are connected by intermolecular hydrogen bonds N–H···O [N···O is 2.995(3) Å] in spirals which interweave with one another forming channels of a scarcely lesser diameter (4.34 Å).

TABLE 4. Main Crystallographic Parameters and Refinement Characteristics for Compounds **4b** and **4o**

	4b	**4o**
Formula	$C_{20}H_{19}NO$	$C_{25}H_{21}NO$
M	308.28	351.43
T, K	110	110
Space group	*Fdd*2	*C*2/*c*
a, Å	29.272(7)	23.555(7)
b, Å	33.235(8)	6.971(1)
c, Å	6.368(1)	23.488(7)
β, °	87.89(2)	108.79(2)
V, Å^3, *Z*	6195(2)	3651(1), 8
F(000)	2464	1488
ρ_{calc}, cm^{-3}	1.241	1.279
$2\theta_{max}$, °	56	50
Number of reflections		
measured (R_{int})	10519 (0.0366)	4389 (0.0686)
independent	3669	2895
observed with $I > 2\sigma(I)$	2631	1209
R_1	0.0485	0.0815
WR_2	0.1091	0.1774
GOF	0.985	1.119

Attempts to obtain the second diastereomer by heating in 90% ethanol or isopropyl alcohol in the presence of alkali gave no result. The reaction forming compound **4o** is probably subject to kinetic control.

Compound **4g** [14] was isolated as a mixture of two diastereomers with a predominance of the (*R**,*R**)-isomer (*de* 90%). It is curious that compound **4c** exists only in the enolic form. Compounds **4a,f,h,m,n** were isolated as mixtures of diastereomers, the content of each isomer was 50%.

On attempting to alkylate the benzyl ester of 3-oxobutyric acid **3i** in 90% isopropyl alcohol we unexpectedly isolated compound **3h**, which may be the result of transesterification.

The method proposed by us enables the preparation of compounds **4** containing an indolylphenylmethyl fragment in the position α to the carbonyl group with a known diastereomeric excess. In the *Z/E* case predominantly (*R**,*S**)-diastereomers are formed. The introduction of planes of rigidity enables the Michael reaction to be carried out with 100% *de*. In the *Z/Z* case predominantly (*R**,*R**)-diastereomers are formed.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Bruker WP 200 (200 MHz) instrument in acetonitrile-d_3 (**4a,f,h, 5**), deuterochloroform (**4c**), pyridine-d_5 (**4m**), DMSO-d_6 (**4n**), internal standard was TMS. The ^{1}H and ^{13}C NMR spectra of compounds **4b,o** were recorded on a BRX 500 instrument (500 and 125 MHz respectively) in deuterochloroform at 30°C. All experiments were conducted according to standard Bruker procedures. Two-dimensional HSQC and HMBC spectra were obtained using the gradient method. The ^{13}C spectra were recorded in APT mode, number of accumulations 34000. Mass spectra were recorded on a Finnigan MAT SSQ 710 spectrometer at an energy of the ionizing radiation of 70eV. Analysis by TLC was carried out on Silufol UV 254 plates. The X-ray diffraction investigations were carried out on a Smart CCD diffractometer (MoKα radiation, graphite monochromator, ω-scanning). The main crystallographic parameters and the refinement characteristics are given in Table 4. Structures were solved by the direct method and refined by a full matrix least squares method in an anisotropic approach according to F^2. All calculations were carried out with the SHELXTL PLUS set of programs Ver. 5.1.

α-Phenyl-*nor*-gramine (1). A 33% methylamine solution (150 g, 1.59 mol) was added to benzaldehyde (106 g, 1 mol) during 20 min. Reaction occurs with a significant evolution of heat. To complete the reaction the mixture was kept for 12 h at ~20°C. The mixture was then saturated with sodium chloride solution, and extracted with ether. The ether extract was dried over $MgSO_4$, and the ether distilled. The residue was then distilled. Benzylidenemethylamine (83 g, 70%) was obtained; bp 183-185°C {bp 92-93°C (34 mm) [15]}.

A solution of indole (30 g, 0.26 mol) in benzylidenemethylamine (36 g, 0.30 mol) was heated at 70°C for 40 h, then maintained at room temperature until crytallization was complete. The solid was filtered off. After recrystallization from benzene a white crystalline substance was obtained, turning pink in the air. Yield 49 g (65%); mp 139-141°C (mp 139-141°C [16]).

Preparation of Compounds 4 (General Procedure). A solution of potassium carbonate (0.1 g) in water (1 ml) and CH-acid **3** (0.625 mmol) were added to a boiling solution of α-phenyl-*nor*-gramine 1 (1.0 g, 0.42 mmol) in 90% alcohol (10 ml). The mixture was boiled in a current of inert gas until disappearance of the starting material (check by TLC on Silufol UV 254, ethyl acetate–CCl_4, 1:4). The reaction mixture was cooled to room temperature. Compounds **4a-c,f-h,o** crystallized from aqueous alcohol, **4m-n** from aqueous acetic acid.

2-[1H-Indol-3-yl(phenyl)methyl]cyclohexanone (4a). White crystals; mp 118-119°C (aqueous 2-propanol). ^{1}H NMR spectrum, δ, ppm: 1.7-2.37 (8H, m, cyclohexane); 3.38-3.58 (1H, m, IndCHPhC<u>H</u>); 4.57-4.59 (1H, m, IndC<u>H</u>Ph); 6.9-7.3 (9H, m, Ind and Ph); 7.18 (1H, m, H-2_{Ind}); 9.09-9.15 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 303 (11) $[M]^+$, 206 (100) $[IndCHPh]^+$. Found, %: C 83.43; H 7.04; N 4.32. $C_{21}H_{21}NO$. Calculated, %: C 83.13; H 6.98; N 4.62.

2-[1H-Indol-3-yl(phenyl)methyl]cyclopentanone (4b) (*R,*S**).** White crystals; mp 182-184°C (aqueous 2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.6-1.9 [6H, m, $(CH_2)_3$]; 3.02 (1H, m, C<u>H</u>CHPh); 4.72 (1H, d, *J* = 5.37, C<u>H</u>Ph); 6.86 (1H, m, H-5$_{Ind}$); 7.06 (1H, m, H-6$_{Ind}$); 7.1-7.2 (6H, m, Ph and Ind); 7.29 (1H, d, *J* = 2.19, H-2$_{Ind}$); 7.36 (1H, m, H-7$_{Ind}$); 10.77 (1H, s, NH). ^{1}H NMR spectrum (C_5D_5N), δ, ppm (*J*, Hz): 1.5-2.2 [6H, m, $(CH_2)_3$]; 3.12 (1H, m, C<u>H</u>CHPh); 5.28 (1H, d, *J* = 3.97, C<u>H</u>Ph); 7.05 (1H, m, H-5$_{Ind}$); 7.25 (3H, m, H$_{Ph}$); 7.25 (1H, m, H-6$_{Ind}$); 7.43 (2H, m, *o*-H$_{Ph}$); 7.48 (1H, m, H-4$_{Ind}$); 7.55 (1H, m, H-7$_{Ind}$); 7.62 (1H, dd, *J* = 2.45, *J* = 0.6, H-2$_{Ind}$); 11.97 (1H, s, NH). Characteristic signal for the (*R**,*R**)-isomer in the ^{1}H NMR spectrum (C_5D_5N), δ, ppm: 5.14 (1H, d, *J* = 3.97, C<u>H</u>Ph). Mass spectrum, *m/z* (I_{rel}, %): 289 (22) $[M]^+$, 205 (100) $[IndCHPh]^+$. Found, %: C 83.2; H 6.73; N 4.41. $C_{20}H_{19}NO$. Calculated, %: C 83.01; H 6.62; N 4.84.

2-Hydroxy-3-[1H-indol-3-yl(phenyl)methyl]-2-cyclohexen-1-one (4c). White crystals; mp 121-123°C (aqueous 2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.92-2.50 (6H, m, cyclohexane); 5.9 (1H, s, IndCHPh); 6.32 (1H, s, OH); 6.86 (1H, d, *J* = 7.2, H-2$_{Ind}$); 7.05 (1H, m, H-5$_{Ind}$); 7.2-7.3 (7H, m, Ind and Ph); 7.37 (1H, m, H-4$_{Ind}$); 7.57 (1H, m, H-7$_{Ind}$); 8.08 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 317 (20) $[M]^+$, 206 (100) $[IndCHPh]^+$. Found, %: C 80.2; H 6.43; N 4.21. $C_{21}H_{19}NO_2$. Calculated, %: C 79.47; H 6.03; N 4.41.

2-[1H-Indol-3-yl(phenyl)methyl]-3-oxobutyric Acid Methyl Ester (4f). White crystals; mp 147-149°C (aqueous 2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.07-2.16 (3H, m, $COCH_3$); 3.51-3.55 (3H, m, OCH_3); 4.64-4.73 (1H, m, IndCHPhC<u>H</u>); 5.01-5.03 (1H, m, IndC<u>H</u>Ph); 7.01 (1H, m, H-5$_{Ind}$); 7.11 (1H, m, H-6$_{Ind}$); 7.17 (1H, m, *p*-H$_{Ph}$); 7.27 (2H, m, *m*-H$_{Ph}$); 7.29 (1H, m, H-2$_{Ind}$); 7.37 (1H, m, H-7$_{Ind}$); 7.42 (2H, m, *o*-H$_{Ph}$); 7.57 (1H, m, H-4$_{Ind}$); 9.02 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 321 (24) $[M]^+$, 206 (100) $[IndCHPh]^+$. Found, %: C 74.95; H 6.07; N 4.26. $C_{20}H_{19}NO_3$. Calculated, %: C 74.75; H 5.96; N 4.36.

2-[1H-Indol-3-yl(phenyl)methyl]-3-oxobutyric Acid Isopropyl Ester (4h). White crystals; mp 111-119°C (aqueous 2-propanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.94-1.11 [6H, m, $(CH_3)_2$]; 2.10-2.18 (3H, m, $COCH_3$); 4.79 (1H, m, OCH); 4.58-4.68 (1H, m, IndCHPhC<u>H</u>); 4.99-5.01 (1H, m, IndC<u>H</u>Ph); 7.00 (1H, m, H-5$_{Ind}$); 7.11 (1H, m, H-6$_{Ind}$); 7.16 (1H, m, *p*-H$_{Ph}$); 7.27 (2H, m, *m*-H$_{Ph}$); 7.31 (1H, m, H-2$_{Ind}$); 7.37 (1H, m, H-7$_{Ind}$); 7.43 (2H, m, *o*-H$_{Ph}$); 7.59 (1H, m, H-4$_{Ind}$); 9.21 (1H, br. s, NH). Mass spectrum, (I_{rel}, %): 349 (18) $[M]^+$, 206 (100) $[IndCHPh]^+$. Found, %: C 75.82; H 6.83; N 3.93. $C_{22}H_{23}NO_3$. Calculated, %: C 75.62; H 6.63; N 4.01.

2-Cyano-3-(1H-indol-3-yl)-3-phenylpropionic Acid Methyl Ester (4m). White crystals; mp 146-147°C (aqueous AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.56 (3H, s, CH_3); 5.25 (1H, d, *J* = 7.2, CNC<u>H</u>$COCH_3$); 5.57 (1H, d, *J* = 7.2, IndC<u>H</u>Ph); 7.1-7.7 (9H, m, Ind and Ph); 8.11 (1H, m, H-2$_{Ind}$); 12.36 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 304 (14) $[M]^+$, 206 (90) $[IndCHPh]^+$. Found, %: C 75.01; H 5.2; N 9.15. $C_{19}H_{16}N_2O_2$. Calculated, %: C 74.98; H 5.3; N 9.2.

2-Cyano-3-(1H-indol-3-yl)-3-phenylpropionic Acid Ethyl Ester (4n). White crystals; mp 91-93°C (aqueous AcOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.97-1.00 (3H, m, CH_2CH_3); 4.02-4.05 (2H, m, CH_2CH_3); 4.92-4.95 (1H, m, CNC<u>H</u>COEt); 5.00-5.09 (1H, m, IndC<u>H</u>Ph); 7.1-7.8 (10H, m, Ind and Ph); 10.97 (1H, br. s, NH). Mass spectrum *m/z*, (I_{rel}, %): 318 (8) $[M]^+$, 206 (90) $[IndCHPh]^+$. Found, %: C 75.57; H 5.58; N 8.70. $C_{20}H_{18}N_2O_2$. Calculated, %: C 75.45; H 5.70; N 8.80.

(2*S)-2-[(*R**)-1H-Indol-3-yl(phenyl)methyl]-3,4-dihydro-1-(2H)-naphthalenone (4o).** White crystals; mp 138-139°C (aqueous 2-propanol). Mass spectrum *m/z* (I_{rel}, %): 351 (17) $[M]^+$, 206 (100) $[IndCHPh]^+$. Found, %: C 85.63; H 6.04; 3.87. $C_{25}H_{21}NO$. Calculated, %: C 85.44; H 6.02; N 3.99.

2-[1H-Indol-3-yl(phenyl)methyl]cyclopentanone Hydrazone (5). Compound **4b** (0.303 g, 0.1 mmol) and anhydrous hydrazine hydrate (0.64 g, 20 mmol) were mixed in alcohol (5 ml). The mixture was maintained at room temperature until disappearance of the starting material (check by TLC on Silufol UV 254, ethyl acetate–CCl_4, 1:4). The reaction mixture was poured into water and the white crystals were filtered off; mp 162-163°C (aqueous 2-propanol). ^{1}H NMR spectrum, δ, ppm: 1.65-2.4 (6H, m, cyclopentyl); 3.35-3.6 (1H, m, IndCHPhCH); 4.57-4.59 (1H, m, IndCHPh); 6.9-7.3 (9H, m, Ind and Ph); 7.2 (1H, m, H-2$_{Ind}$); 9.1-9.18 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 303 (25) $[M]^+$, 206 (100) $[IndCHPh]^+$. Found, %: C 80.03; H 7.04; N 12.93. $C_{20}H_{21}N_3$. Calculated, %: C 79.17; H 6.98; N 13.85.

REFERENCES

1. B. B. Semenov and Yu. I. Smushkevich, *Izv. Akad. Nauk, Ser. Khim.*, 334 (2002).
2. V. N. Rusinova, Yu. I. Smushkevich, O, V. Telenkova, M. V. Vasin, and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, 211 (1974).
3. M. Passerini, *Gazz. Chim. Ital.*, **65**, 933 (1935).
4. T. Moriya, K. Hagio, and N. Yoneda, *Chem. Pharm. Bull.*, **28**, 1711 (1980).
5. B. B. Semenov, Author's Abstract of Dissertation for Candidate of Chemical Sciences, Moscow (2002).
6. H. Snyder, C. Smith, and J. Stewart, *J. Am. Chem. Soc.*, **66**, 200 (1944).
7. A. Kamal, A. A. Qureshi, and I. Ahmad, *Tetrahedron*, **19**, 681 (1963).
8. M. Suzuki, T. Miyahara, R. Yoshioka, M. Miyoshii, and K. Matsumoto, *Agric. Biol. Chem.*, **38**, 1709 (1974).
9. B. B. Semenov and V. G. Granik, *Khim.-farm. Zh.*, **38**, No. 6, 3 (2004).
10. R. Aitken and S. N. Kilenyi, *Asymmetric Synthesis*, Chapman & Hall, New York (1992).
11. V. Prelog and G. Helmchen, *Angew. Chem., Int. Ed. Eng.*, **94**, 614 (1982).
12. D. Seebach and V. Prelog, *Angew. Chem., Int. Ed. Eng.*, **94**, 696 (1982).
13. K. Mislow and J. Siegel, *J. Am. Chem. Soc.*, **106**, 3319 (1984).
14. B. B. Semenov, Yu. I. Smushkevich, G. V. Grintselev-Knyazev, and M. Yu. Antipin, *Izv. Akad. Nauk, Ser. Khim.*, 543 (2001).
15. *Organic Syntheses*, Vol. 6 [Russian translation], *Izd. Inostr. Lit.*, Moscow (1956), p. 50.
16. V. N. Borisova, E. N. Gordeev, and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, 357 (1976).