Diastereoselective synthesis of (*R**,*R**)-ethyl 2-[1*H*-indol-3-yl(phenyl)methyl]-3-oxobutanoate

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The benzyhydryl fragment enters into the composition of some medicines.[1]

Earlier, an analog of spasmolytin in which one of the phenyl fragments is replaced by the 3-indolyl fragment has been synthesized.[2] This replacement leads to a change in the spectrum of biological activities, to a decrease in toxicity, and to the enhancement of the local anesthetic action. With the aim of extending the range of biologically active compounds containing the α-indolyl-3-benzyl fragment, we synthesized the key compound, *viz.*, ethyl 2-[1*H*-indol-3-yl(phenyl)methyl]-3-oxobutanoate (**1**), starting from α-phenyl-*nor*-gramine and ethyl acetoacetate. We found conditions under which the reaction proceeded diastereoselectively (*de* 90%).

The structure of ethyl 2-[1*H*-indol-3-yl(phenyl)methyl]-3-oxobutanoate was confirmed by ^{1}H NMR spectroscopy, mass spectrometry, elemental analysis, and X-ray diffraction analysis. X-ray diffraction study of compound **1** (Fig. 1, Table 1) demonstrated that the C(1) and C(2) asymmetric centers have the identical (*R**,*R**) configuration. The principal geometric parameters of compound **1** are close to the expected values. The C(2)—C(1)—C(8)—C(9) and C(2)—C(1)—C(16)—C(21) torsion angles characterizing the rotation of the indole and phenyl fragments with respect to the C(1)—C(2) bond are 17.4(2) and 50.1(2)°, respectively.

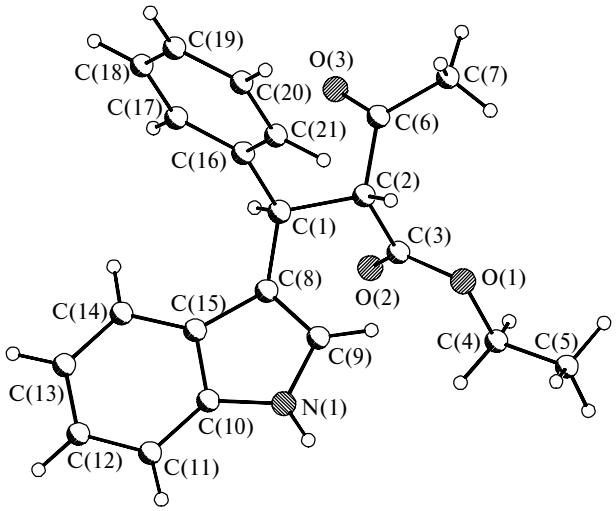

Fig. 1. Overall view of molecule **1**.

In the crystal structure, molecules **1** related by translations are linked in chains along the crystallographic axis *b* through intermolecular C(9)—H(11)...O(2^i) and C(21)—H(21)...O(3^i) interactions (H(11)...O(2), 2.55 Å; C(9)...O(2^i), 3.350(2) Å; C(9)—H(11)...O(3^i), 140.7°; H(21)...O(3^i), 2.49 Å; C(21)...O(3^i), 3.461(2) Å; C(21)—H(21)...O(3^i), 174.3°).

Table 1. Principal bond lengths and bond angles.

Bond	*d*/Å	Bond	*d*/Å	Angle	ω/deg
O(1)—C(3)	1.3379(18)	C(8)—C(15)	1.442(2)	C(8)—C(1)—C(16)	110.56(12)
O(1)—C(4)	1.4625(17)	C(10)—C(11)	1.399(2)	C(8)—C(1)—C(2)	111.44(12)
O(2)—C(3)	1.2040(17)	C(10)—C(15)	1.420(2)	C(16)—C(1)—C(2)	111.18(12)
O(3)—C(6)	1.2103(19)	C(11)—C(12)	1.380(2)	C(3)—C(2)—C(6)	106.86(12)
N(1)—C(10)	1.374(2)	C(12)—C(13)	1.404(2)	C(3)—C(2)—C(1)	110.13(12)
N(1)—C(9)	1.379(2)	C(13)—C(14)	1.382(2)	C(6)—C(2)—C(1)	112.14(12)
C(1)—C(8)	1.517(2)	C(14)—C(15)	1.405(2)	O(2)—C(3)—C(2)	123.92(14)
C(1)—C(16)	1.5324(19)	C(16)—C(17)	1.388(2)	O(1)—C(3)—C(2)	111.46(12)
C(1)—C(2)	1.534(2)	C(16)—C(21)	1.393(2)	O(3)—C(6)—C(2)	121.40(14)
C(2)—C(3)	1.5270(19)	C(17)—C(18)	1.397(2)	C(7)—C(6)—C(2)	115.62(15)
C(2)—C(6)	1.533(2)	C(18)—C(19)	1.376(2)	C(9)—C(8)—C(1)	127.51(14)
C(4)—C(5)	1.499(2)	C(19)—C(20)	1.386(2)	C(15)—C(8)—C(1)	126.06(13)
C(6)—C(7)	1.493(2)	C(20)—C(21)	1.398(2)	C(17)—C(16)—C(1)	120.23(13)
C(8)—C(9)	1.365(2)			C(21)—C(16)—C(1)	120.84(13)

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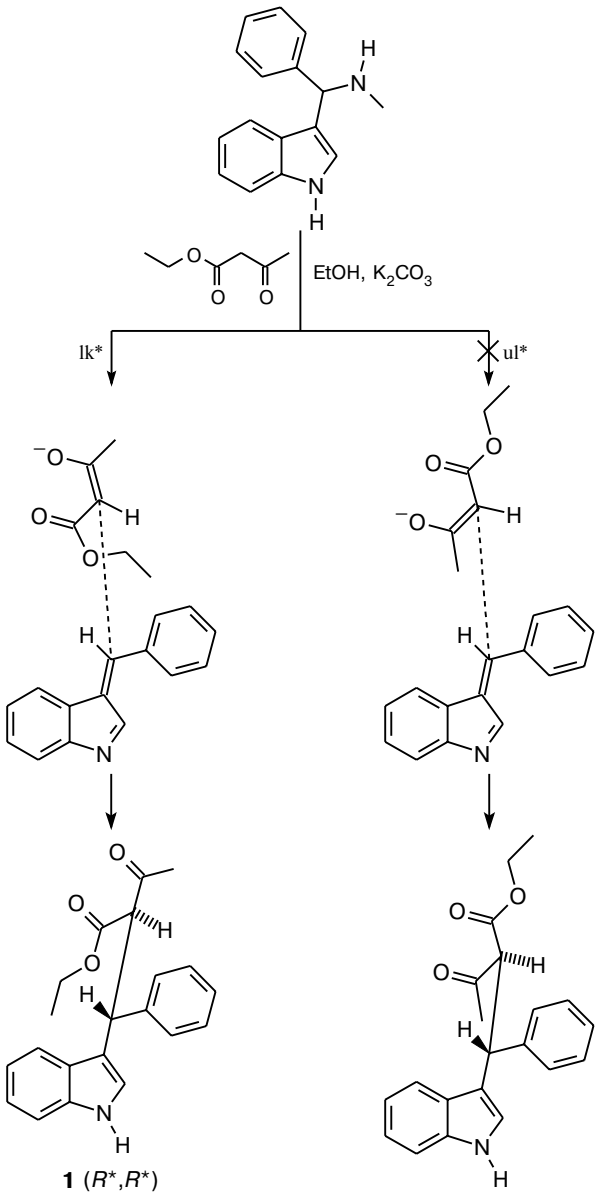
Scheme 1



* lk is the "like attack", and ul is the "unlike attack".[3]

(*R**,*R**)-Ethyl 2-[1*H*-indol-3-yl(phenyl)methyl]-3-oxobutanoate was obtained in 71% yield. This stereochemistry could be a consequence either of the kinetic or thermodynamic control over the reaction (the equilibrium isomerization of one diastereomer into another through the enol form of the ester). At ~20 °C, the equilibrium between two diastereomers (50% each) was established within 48 h after the addition of pyridine (10 mol.%) to the pure (*R**,*R**)-diastereomer in $CDCl_3$. This ratio remained unchanged upon storage of the resulting mixture of the diastereomers (after removal of the pyridine) under the conditions of the synthesis of compound **1** for 5.5 h. Therefore, the kinetic control is responsible for the diastereoselectivity of the reaction. As can be seen from Scheme 1, the "like attack"* is less sterically hindered.[3,4,5,6]

Experimental

The ^1H NMR spectra were recorded on a Bruker WM-250 spectrometer in $CDCl_3$ with Me_4Si as the internal standard. The mass spectra (EI) were obtained on a Finigan MAT SSQ-710 spectrometer; the energy of ionizing electrons was 70 eV.

A solution of potassium carbonate (0.1 g) in H_2O (1 mL) and ethyl acetoacetate (0.8 g, 6.15 mmol) was added to a boiling solution of α-phenyl-*nor*-gramine (1.0 g, 4.2 mmol) in EtOH (10 mL). The reaction mixture was refluxed under a stream of an inert gas until the starting compound was consumed. The course of the reaction was monitored by TLC (Silufol UV-254, the 1 : 4 AcOEt—CCl_4 system). Then the reaction mixture was cooled to ~20 °C. The white precipitate that formed was filtered off and recrystallized from EtOH.

Ethyl 2-[1*H*-indol-3-yl(phenyl)methyl]-3-oxobutanoate (1), the yield was 71%, m.p. 162—163 °C (EtOH). ^1H NMR, δ: 0.97 (t, 3 H, Me); 2.04 (s, 3 H, COMe); 3.98 (m, 2 H, C$\underline{H}_2$Me); 4.50 (d, 1 H, CHC(3)$\underline{H}$, J = 12.1 Hz); 5.09 (d, 1 H, C$\underline{H}$Ph, J = 12.1 Hz); 7.03—7.34 (m, 8 H, Ph and Ind); 7.19 (d, 1 H, $H(2)_{Ind}$, J = 2.2 Hz); 7.54 (dd, 1 H, $H(4)_{Ind}$, J = 7.7 Hz, J = 1.5 Hz); 7.99 (br.s, 1 H, N$\underline{H}$, J = 7.1 Hz). MS, m/z (I_{rel} (%)): 335 $[M]^+$ (5), 292 $[M - COMe]^+$ (1), 206 $[IndCHPh]^+$ (86). Found (%): C, 75.31; H, 6.19; N, 4.09. $C_{21}H_{21}NO_3$. Calculated (%): C, 75.20; H, 6.31; N, 4.18.

Single crystals of compound **1** were obtained by recrystallization from EtOH. The crystallographic data and the details of X-ray diffraction analysis for the structure of **1**: at 110 K, the crystals of $C_{21}H_{21}NO_3$ are monoclinic, space group $P2_1/c$, a = 9.580(2) Å, b = 5.5438(12) Å, c = 32.878(8) Å, β = 94.138(6)°, V = 1741.7(7) Å^3, Z = 4, M = 335.39, d_{calc} = 1.279 g cm^{-3}, μ(Mo-$K\alpha$) = 0.85 cm^{-1}, F(000) = 712. The intensities of 12860 reflections were measured on a Smart 1000 CCD diffractometer at 110 K (λ(Mo-$K\alpha$) = 0.71073 Å, the ω scan step was 0.4°; frames were exposed for 30 s, 2θ < 60°) of which 4873 reflections were independent (R_{int} = 0.0420). The structure was solved by the direct method. The positions and the thermal parameters of the nonhydrogen atoms were refined first isotropically and then anisotropically based on F^2 by the full-matrix least-squares method. The positions of the hydrogen atoms were located from the difference Fourier synthesis and refined isotropically. The final R factors were as follows: wR_2 = 0.1150 and GOF = 0.865 for independent reflections (R_1 = 0.0493 was calculated based on F for 2746 independent reflections with $I > 2\sigma(I)$). The number of the parameters in the refinement was 310 (more than 15 observed reflections per parameter refined). All calculations were carried out on IBM PC AT with the use of the SHELXTL PLUS 5.1 program package.

References

1. A. Von Kleemann and J. Engel, *Pharmazeutische Wirkstoffe*, New York, 1982, 1039.
2. V. N. Borisova, E. N. Gordeev, and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, 1976, **3**, 357 [*Chem. Heterocycl. Compd.*, 1976, **3** (Engl. Transl.)].
3. R. Aitken and S. N. Kilenyi, *Asymmetric Synthesis*, Chapman and Hall, London—New York, 1992, 28.
4. V. Prelog and G. Helmchen, *Angew. Chem., Int. Ed.*, 1982, 614.
5. D. Seebach and V. Prelog, *Angew. Chem.*, 1982, 696.
6. K. Mislow and J. Siegel, *J. Am. Chem. Soc.*, 1984, **106**, 3319.

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