Brief Communications

Introduction of the 1*H*-indol-3-yl(phenyl)methyl residue into some CH acids

B. B. Semenov* and Yu. I. Smushkevich

Department of Organic Chemistry, D. I. Mendeleev University of Chemical Technology of Russia, 9 Miusskaya pl., 125047 Moscow, Russian Federation.
Fax: +7 (095) 200 4204. E-mail: SMU@muctr.edu.ru, semenovb@mail.ru

A new method of introducing the 1*H*-indol-3-yl(phenyl)methyl residue into some CH acids was developed.

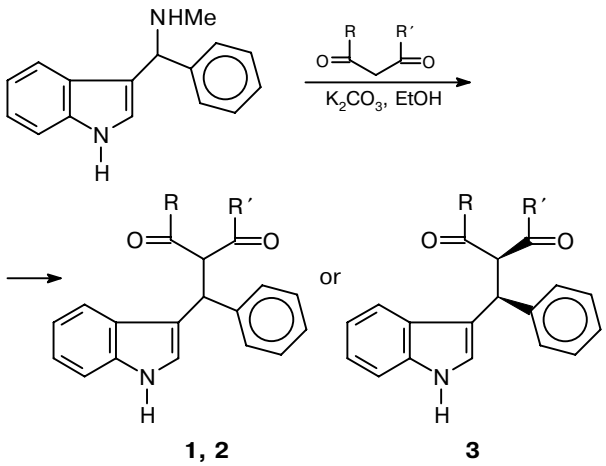
Key words: α-phenyl-*nor*-gramine, pentane-2,4-dione, ethyl malonate, ethyl 3-oxobutanoate.

The benzohydryl residue is contained in some medicaments.[1] It is also known that replacement of a phenyl fragment in spasmolytin by indol-3-yl affords a less toxic analog exhibiting a different spectrum of biological activity and enhanced local anesthetic effect.[2]

In the present work, the condensation of α-phenyl-*nor*-gramine with β-dicarbonyl compounds was described for the first time. The condensation products are potential intermediates for the synthesis of heterocyclic compounds containing the indol-3-yl(phenyl)methyl residue.

Previously, the alkylation of β-dicarbonyl compounds with gramine[3,4] and its quaternary ammonium salts[5,6] was described. The use of *nor*-gramine and α-phenyl-*nor*-gramine for these purposes remains unknown so far. α-Phenyl-*nor*-gramine was only transformed into 2-(1*H*-indol-3-yl)-2-phenylacetonitrile[7] by condensation with potassium cyanide.

It turned out that α-phenyl-*nor*-gramine[7] smoothly reacts with β-dicarbonyl compounds containing an active methylene group. Products (**1**—**3**), in which the methylamino residue is replaced by a corresponding β-dicarbonyl radical, were obtained in good yields in ethanol in the presence of K_2CO_3. The methylamine that evolves is removed from the reaction mixture by a flow of an inert gas and hence the products of its reaction with β-dicarbonyl compounds were not detected.



1: R = R′ = OEt; **2:** R = R′ = Me; **3:** R = Me, R′ = OEt

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 3, pp. 521—522, March, 2001.

^{1}H NMR spectra recorded in $CDCl_3$ revealed several specific features of the target products. Compound **3** is a mixture of diastereomers in a ratio of 95 : 5; the major (*R**,*R**)-diastereomer can be isolated by crystallization from 95% ethanol.[8] The diastereotopic ethoxycarbonyl groups in compound **1** are magnetically nonequivalent, giving two sets of signals. The same reason explains why the ^{1}H NMR spectrum of compound **2** shows different signals from two acetyl groups. The compounds obtained, especially **2**, are capable of being enolized, but no enol tautomers were detected by ^{1}H NMR spectroscopy.

Experimental

^{1}H NMR spectra were recorded on a Bruker WM-250 spectrometer in $CDCl_3$ with Me_4Si as the internal standard. Mass spectra (EI) were recorded on a Finnigan MAT SSQ-710 spectrometer (ionizing voltage 70 eV).

Reaction of *nor*-gramine with CH-acids (general procedure). A solution of potassium carbonate (0.1 g) in 1 mL of water and a CH acid (0.625 mmol) were added to a boiling solution of α-phenyl-*nor*-gramine (1.0 g, 0.42 mmol) in 10 mL of 95% EtOH. The reaction mixture was refluxed in a flow of an inert gas until the starting compound disappeared (monitored by TLC using Silufol UV-254 plates and EtOAc—CCl_4 (1 : 4)). Cooling to ~20 °C gave a white precipitate, which was filtered off and recrystallized from 95% EtOH.

Ethyl 2-[1*H*-indol-3-yl(phenyl)methyl]malonate (1), yield 36%, m.p.165—167 °C (from EtOH). ^{1}H NMR, δ: 8.00 (br.s, 1 H, NH); 7.55 (dd, 1 H, $H(4)_{Ind}$, J = 7.7 and 1.5 Hz); 7.29 (dd, 1 H, $H(7)_{Ind}$, J = 7.7 and 1.5 Hz); 7.18 (d, 1 H, $H(2)_{Ind}$, J = 2.2 Hz); 7.02—7.36 (m, 7 H, Ph and Ind); 5.08 (d, 1 H, CHPh, J = 12.1 Hz); 4.28 (m, 1 H, PhCHCH); 4.01 (q, 2 H, CH_2CH_3, J = 7.1 Hz); 3.97 (q, 2 H, CH_2CH_3, J = 7.1 Hz); 1.00 (t, 3 H, Me); 0.98 (t, 3 H, Me). MS, *m*/*z* (I_{rel} (%)): 365 $[M]^+$ (42), 320 $[M - OEt]^+$ (2), 292 $[M - COOEt]^+$ (5), 206 $[IndCHPh]^+$ (100). Found (%): C, 72.51; H, 6.24; N, 3.63. $C_{22}H_{23}NO_4$. Calculated (%): C, 72.31; H, 6.34; N, 3.83.

3-[1*H*-Indol-3-yl(phenyl)methyl]pentane-2,4-dione (2), yield 71%, m.p. 150—152 °C (from EtOH). ^{1}H NMR, δ: 8.08 (br.s, 1 H, NH); 7.53 (dd, 1 H, $H(4)_{Ind}$, J = 7.7 and 1.5 Hz); 7.12 (d, 1 H, $H(2)_{Ind}$, J = 2.2 Hz); 7.05—7.31 (m, 8 H, Ph and Ind); 5.10 (d, 1 H, CHCHAc$_2$, J = 12.1 Hz); 4.64 (d, 1 H, CHCHAc$_2$); 2.06 (s, 3 H, Me); 1.93 (s, 3 H, Me). MS, *m*/*z* (I_{rel} (%)): 305 $[M]^+$ (8), 262 $[M - Ac]^+$ (14), 206 $[IndCHPh]^+$ (70). Found (%): C, 78.87; H, 6.18; N, 4.39. $C_{20}H_{19}NO_2$. Calculated (%): C, 78.66; H, 6.27; N, 4.59.

Ethyl 2-[1*H*-indol-3-yl(phenyl)methyl]-3-oxobutanoate (3), yield 71%, m.p. 162—163 °C (from EtOH). ^{1}H NMR, δ for (*R**,*R**)-isomer: 7.99 (br.s, 1 H, NH); 7.54 (dd, 1 H, $H(4)_{Ind}$, J = 7.7 and 1.5 Hz); 7.19 (d, 1 H, $H(2)_{Ind}$, J = 2.20 Hz); 7.03 —7.34 (m, 8 H, Ph and Ind); 5.09 (d, 1 H, CHPh, J = 12.1 Hz); 4.50 (d, 1 H, CHC(3)H, J = 12.1 Hz); 3.98 (q, 2 H, CH_2CH_3, J = 7.13 Hz); 2.04 (s, 3 H, COMe); 0.97 (t, 3 H, Me, 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.

Below are the characteristic signals of the minor (*R**,*S**)-diastereomer. ^{1}H NMR, δ: 5.05 (d, 1 H, CHPh, J = 12.1 Hz); 4.49 (d, 1 H, CHC(3)H, J = 12.1 Hz); 3.96 (q, 2 H, CH_2CH_3, J = 7.1 Hz); 2.14 (s, 3 H, COMe); 0.99 (t, 3 H, Me, J = 7.1 Hz).

References

1. M. D. Mashkovskii, *Lekarstvennye preparaty* [*Medicaments*], Khar´kov, 1997, **1**, 215 (in Russian).
2. K. A. Zaitseva, V. N. Rusinova, Yu. I. Smushkevich, N. N. Suvorov, and M. D. Mashkovskii, *Khim.-Farm. Zh.*, 1973, **10**, 17.
3. D. A. Lyttle and D. L. Weisblat, *J. Am. Chem. Soc.*, 1949, **71**, 3079.
4. M. Nettekoven and M. Priorz, *Tetrahedron Lett.*, 1955, **36**, 1425.
5. H. R. Snyder, *J. Am. Chem. Chem. Soc.*, 1944, **66**, 350.
6. A. Albertson, *J. Am. Chem. Soc.*, 1944, **66**, 500.
7. V. N. Rusinova, Yu. I. Smushkevich, O. V. Telenkova, M. V. Vasin, and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, 1974, **2**, 211 [*Chem. Heterocycl. Comp.*, 1974, **2**, 211 (Engl. Transl.)].
8. B. B. Semenov, Yu. I. Smushkevich, G. V. Grintselev-Knyazev, and M. Yu. Antipin, *Izv. Akad. Nauk, Ser. Khim.*, 2001, 543 [*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 571].

Received April 28, 2000;
in revised form February 7, 2001