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SYNTHESIS OF DERIVATIVES OF 2-(INDOL-1-YL)PROPIONIC ACIDS*

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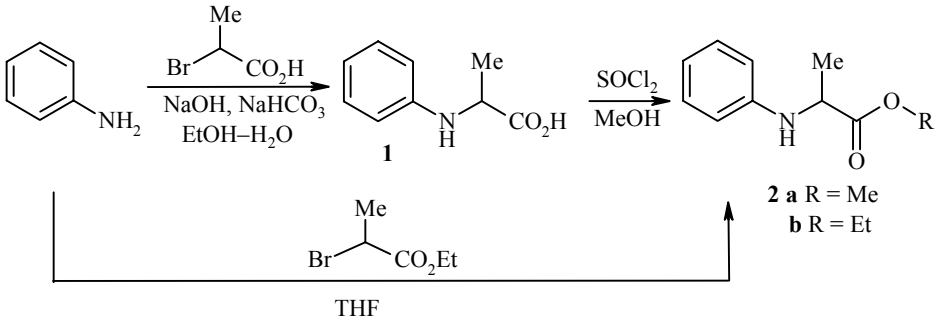
We have developed a method for synthesis of N-substituted derivatives of indole from N-phenylalanine, including Fischer cyclization of the corresponding arylalkylhydrazones. The starting hydrazines were obtained by reduction of the corresponding nitrosamines. We have established that the optimum reduction method is to use metallic zinc in a methanol–hydrochloric acid system at low temperatures.

Keywords: N-amino-N-phenylalanine esters, 2-(indol-1-yl)propionic acid esters, N-phenylalanine esters, reduction of N-nitrosamines, Fischer cyclization.

The tremendous interest in various derivatives of indole is due to the broad spectrum of biological activity exhibited by these heterocyclic compounds. Despite the fact that a large number of quite diverse compounds in the indole series have been synthesized at the moment, there is no information in the literature on synthesis of derivatives of 2-(indol-1-yl)propionic acids. Our study involves synthesis of specifically those compounds, which are of interest both from the standpoint of medicinal chemistry and in connection with the possibility of using them in the synthetic laboratory and industrial practice. In order to obtain 2-(indol-1-yl)-propionic acids, we used the Fischer method: cyclization of arylhydrazones to indoles, catalyzed by acidic reagents.



As the starting compounds, we selected N-phenylalanine esters **1**. Methyl ester **2a** was obtained in alkylation of aniline by 2-bromopropionic acid followed by esterification; ethyl ester **2b** was obtained by alkylation of aniline by 2-bromopropionic acid ethyl ester.

N-Phenylaniline esters obtained were converted to N-nitroso compounds by nitrosation of a tetrahydrofuran–alcohol mixture with ethyl nitrite. The corresponding N-nitroso compounds **3** were obtained in quantitative yields and, according to TLC data, did not contain the starting N-phenylaniline as an admixture.

* Dedicated to Professor S. Gronowitz on the occasion of his 75th birthday.

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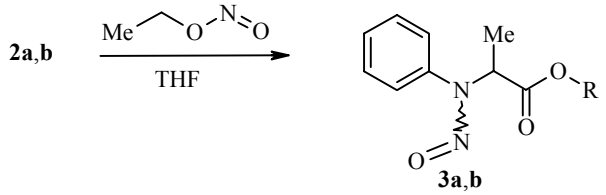
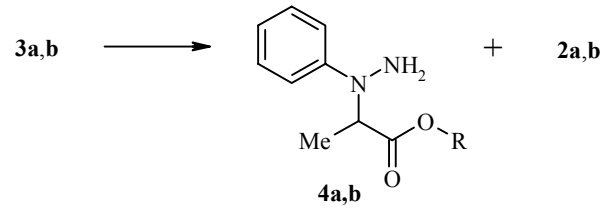
Analysis of the purity of the compounds by chromatomass-spectrometry is difficult in this case, since N-nitroso compounds decompose under the chromatography conditions. Isolation of the nitrosation products is reduced to removal of volatile impurities at low pressure. N-Nitroso compounds obtained were used in the next steps without further purification. According to ^{1}H NMR spectra, N-nitroso compounds were obtained as mixtures of two geometric isomers.



3 a R = Me, **b** R = Et

A number of methods are known for converting N-nitrosamines to asymmetric hydrazines. Thus, for example, we find descriptions of the reduction of N-nitroso compounds using $SnCl_2$ [1], using zinc dust in an aqueous ammonia solution and in acetic acid [2, 3], lithium aluminum hydride [4]; the last two methods are most often used. Generally reduction is accompanied by breaking of the N–N bond, and besides hydrazine secondary amine is formed, the ratio of the products may vary considerably depending on the reducing agent used, the process conditions, and the structure of the compound to be reduced. We tested several reducing agent systems; most of them did not give satisfactory results. Table 1 summarizes the results of these studies; the amine–hydrazine ratio is given based on chromatomass-spectrometry data.

For most of the reduction methods we used, the hydrazine–amine ratio is no greater than 1:1; varying the order of mixing of the reagents and the reaction temperature do not result in an increase in the hydrazine yield. The best results were obtained upon reduction of the N-nitroso compounds by zinc dust in a methanol–hydrochloric acid system at low temperatures.



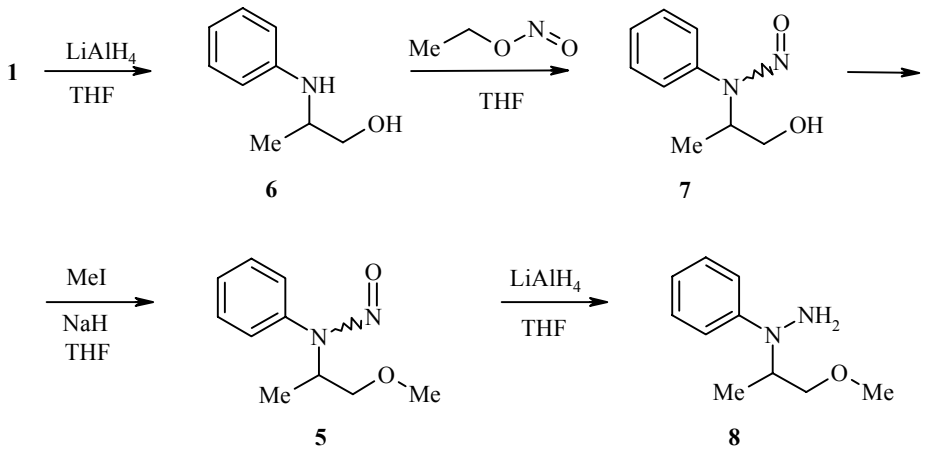
4 a R = Me, **b** R = Et

Such a procedure was used in converting methyl esters of N-nitroso-N-benzylamino acids to the corresponding hydrazines, and reduction was not accompanied by formation of the corresponding secondary amines [5]. Using such conditions for reduction of N-nitroso compound **3a**, we obtained the corresponding hydrazine containing ~5% of methyl ester **2a** according to chromatomass-spectrometry data.

TABLE 1. Results of Reduction of N-Nitrosamines **3**

Method	R	Reagents	Reaction temperature, °C	Hydrazine–amine ratio
A	Et	Zn, NH_3, $(NH_4)_2CO_3$, EtOH–H_2O	-5-0	1:2
B	Et	Zn, AcOH, EtOH	0-10	1:1
C	Et	$SnCl_2$, H_2O, HCl	20	1:100
D	Me	Zn, HCl, MeOH	-78	18:1

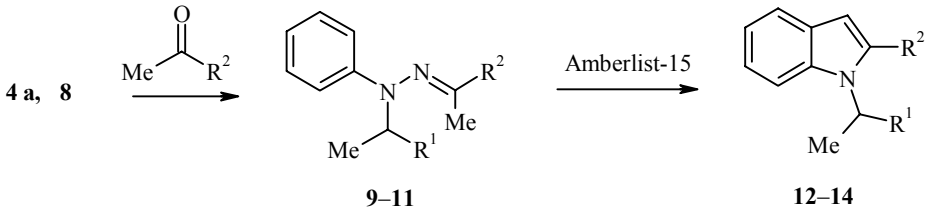
Unfortunately, the efficient and often used reducing agent [4] $LiAlH_4$ is not applicable to our compounds, containing groups capable of reduction (CO_2R). However, it in fact gives satisfactory results on suitable models. Thus reduction by lithium aluminum hydride of N-nitroso compound **5**, obtained previously by nitrosation of N-phenyl-2-aminopropanol (**6**) followed by methylation of N-nitrosamino alcohol **7** formed, led to a mixture of hydrazine **8** and the corresponding secondary amine in 9:1 ratio.



The instability of such hydrazines, noted previously in [5], was confirmed by our observations; so we used hydrazines **4a,b** (the formation of which was confirmed by mass spectrometry) in later conversions without additional purification. The more stable hydrazine **8** was converted to hydrochloride.

We should note that for methyl esters of N-phenylalanine and hydrazine **4**, related fragmentation pathways on electron impact are typical, associated with loss of the fragment CO_2Me by the molecular ion, which leads to formation of fragmentary ions with maximum intensity *m*/*z* 120 and 135 for compounds **1a** and **4** respectively. An analogous direction for the fragmentation of the molecular ion is also typical of hydrazine **8**: loss of the CH_2OMe fragment leads to formation of a fragmentary ion with *m*/*z* 135 of maximum intensity.

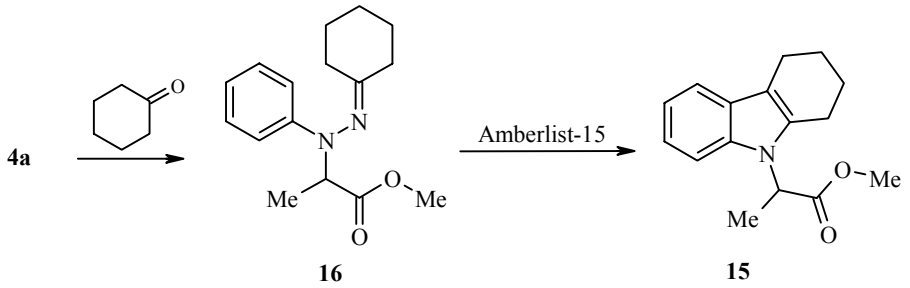
Hydrazines **4** and **8**, obtained by reduction of N-nitroso compounds, were converted by reaction with pyruvic acid ethyl ester and 4-methylacetophenone to the corresponding hydrazones. Hydrazones **9-11**, which are stable compounds, were characterized by physicochemical methods.



9, **10**, **12**, **13** $R^1 = CO_2Me$, **11**, **14** $R^1 = CH_2OMe$; **9**, **11**, **12**, **14** $R^2 = CO_2CH_2Me$, **10**, **13** $R^2 = 4\text{-}MeC_6H_4$

For further conversion of hydrazones to indoles, we used the ion-exchange resin Amberlist-15 as the acid catalyst. Such a catalyst was also successfully used previously [6] for Fischer cyclization.

Hydrazones of pyruvic acid ethyl ester **9** and **11** are converted to the corresponding indole derivatives **12** and **14** upon stirring a reaction mixture containing 2.5 mol-eq of the ion-exchange resin Amberlist-15 at 90-100°C for 3-4 h, while hydrazone of *p*-methylacetophenone **10** requires longer heating (6-8 h) for the process to go to completion.



We know that arylhydrazones of cyclohexanone are extremely easily converted to the corresponding indoles under Fischer cyclization conditions [7]. In fact, formation of appreciable amounts of indole **15** was already observed on stirring a mixture of hydrazine **4** and cyclohexanone with a catalytic amount of *p*-toluenesulfonic acid, i.e., hydrazone **16** formed easily undergoes ring closure to form the corresponding indole under the reaction conditions. These observations allowed us to synthesize indole **15** without intermediate isolation and purification of hydrazone **16**.

Thus we have developed a method for synthesis of esters of 2-(indol-1-yl)propionic acids based on Fischer cyclization, with overall yield on the order of 30% calculated on the basis of the starting aniline.

EXPERIMENTAL

The IR spectra were obtained on a UR-20 apparatus for vaseline oil suspensions or the pure compounds. Chromatomass-spectrometry studies of the reaction mixtures and the isolated compounds were performed using a Carlo Erba/Kratos Fractovap Series 4200 gas-liquid chromatograph, column Ultra-1, Hewlett Packard (25 m × 0.2 mm), thickness of the stationary phase layer 0.33 μm, carrier gas was helium (1 ml/min), stream splitter 1:10, vaporizer temperature 280°C, temperature gradient from 150 to 280°C (5°C/min). Mass spectral detector ITD-700 (Finnegan MAT), ionization by electron impact, 70 eV. ^{1}H and ^{13}C spectra were taken on a Bruker AMX-400 spectrometer (400 and 100 MHz respectively) in DMSO-d_6 solutions, if no other solvent was indicated, internal standard TMS. The melting points were measured in open capillaries; the values given are uncorrected. The course of the reactions and the purity of the isolated compounds were monitored by TLC on Silufol UV-254 plates and by gas chromatography with a mass spectral detector.

N-Phenylalanine (1). 2-Bromopropionic acid (24 ml, 260 mmol), $NaHCO_3$ (22 g, 260 mmol), and solution of aniline (26 g, 280 mmol) in ethanol (100 ml) were added sequentially with cooling to solution of NaOH (10.4 g, 260 mmol) in water (400 ml). The mixture was boiled for 24 h, the solution was concentrated down to volume of 150 ml, dilute hydrochloric acid was added until pH ~4-5 was reached, and then it was cooled down to 0°C. The precipitate was filtered off, dried in air, and recrystallized from absolute ethanol. Obtained 34 g (80%) of N-phenylalanine; mp 165°C (ethanol). According to data in [8], mp 163-164°C.

N-Phenylalanine Ethyl Ester Hydrochloride 2b. Solution of aniline (0.93 g, 10 mmol), 2-bromopropionic acid ethyl ester (1.81 g, 10 mmol) and ethyldiisopropylamine (1.29 g, 10 mmol) in THF (40 ml) was boiled for 24 h. The reaction mixture was poured into ice water (100 ml) and extracted with methylene chloride (2 × 100 ml). The organic extract was dried with anhydrous sodium sulfate, the solvent was evaporated under vacuum, the residue was dissolved in ethanol and an excess of hydrogen chloride solution in ether was added. The volatile components were removed under vacuum, and the residue was recrystallized from an ethanol–ether mixture. Obtained 1.72 g (75%) of a white crystalline material; mp 175-176°C (ethanol). Mass spectrum, *m*/*z* (*I*, %): 193 [M^+] (15), 120 [M^+-CO_2Et] (100), 77 (12). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.15 (3H, t, *J* = 7.0, $C\underline{H}_3CH_2$); 1.37 (3H, d, *J* = 7.2, CH_3); 4.06 (2H, q, *J* = 7.0, $CH_3C\underline{H}_2$); 4.17 (1H, q, *J* = 7.2, CH); 6.81 (3H, m, Ph); 7.19 (2H, t, *J* = 8.1, Ph); 8.09 (3H, br. s, NH_3^+).

N-Phenyalanine Methyl Ester Hydrochloride 2a. Thionyl chloride (17.85 g, 150 mmol) was added dropwise over 5-10 minutes to suspension of N-phenylalanine (16.6 g, 100 mmol) in absolute methanol (75 ml) with stirring and cooling. Obtained mixture was stirred at room temperature for 15 min and then boiled for 6 h. The reaction mixture was evaporated to dryness under vacuum, the residue was recrystallized from a methanol–ether mixture, dried under vacuum over alkali. Obtained 18.77 g (87%) of white crystals; mp 137°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.39 (3H, d, *J* = 7.1, CH_3); 3.63 (3H, s, CH_3O); 4.15 (1H, q, *J* = 7.1, CH); 6.70 (3H, m, Ph); 7.14 (2H, d, *J* = 8.1, Ph); 8.56 (3H, br. s, NH_3^+). Mass spectrum, *m*/*z* (*I*, %): 179 [M^+] (10), 120 [M^+-CO_2Me] (100), 104 (4), 77 (9).

N-Nitroso-N-phenylalanine Ethyl Ester (3b). Hydrochloride **2b** (1.2 g, 5.2 mmol) was added all at once with cooling and vigorous stirring to 50 ml of cold solution of potassium hydroxide (0.29 g, 5.2 mmol) in water. Amine was extracted with ether (3 × 50 ml), washed with water and a saturated sodium chloride solution, the extract was dried with anhydrous sodium sulfate. The solvent was removed at reduced pressure, the residue (1 g) was dissolved in anhydrous THF (10 ml), and 14% solution of ethyl nitrite in alcohol (~7.2 mmol) was added in portions with cooling and stirring to the solution obtained. The reaction mixture was held for 12 h at room temperature in the dark. The volatile components were removed under vacuum with bath temperature of 40°C, 1.14 g (99%) of a yellowish oily liquid were obtained. The compound was used in later conversions without additional purification. IR spectrum, ν, cm^{-1}: 1730 (C=O), 1430 (N=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.12 (3H, t, *J* = 7.1, $C\underline{H}_3CH_2$); 1.34 (3H, d, *J* = 7.1, CH_3); 4.08 (2H, m, $CH_3C\underline{H}_2$); 5.16 (1H, q, *J* = 7.1, CH); 7.46-7.60 (5H, m, Ph). Mass spectrum, *m*/*z* (*I*, %): 222 [M^+] (5), 192 [M^+-N=O] (20), 177 (5), 148 (11), 120 (100), 104 (38), 91 (5), 77 (43).

N-Nitroso-N-phenylalanine Methyl Ester (3a) was synthesized similarly in 98% yield. IR spectrum, ν, cm^{-1}: 1730 (C=O), 1430 (N=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.41 (3H, d, *J* = 7.1, CH_3); 3.63 (3H, s, CH_3O); 5.15 (1H, q, *J* = 7.1, CH); 7.31-7.60 (5H, m, Ph). Mass spectrum, *m*/*z* (*I*, %): 208 [M^+] (7), 178 [M^+-N=O] (23), 120 (100), 104 (38), 91 (7), 77 (32).

Reduction of N-Nitroso-N-phenylalanine Ethyl Ester (3b). A. Solution of ammonium carbonate (2 g) in water (5 ml) was added to solution of compound **2b** (1.18 g, 5.3 mmol) in ethanol (5 ml), this was cooled down to -5 to 0°C, zinc dust (1 g) was added, and 7.5 ml of aqueous solution of ammonia (*d* = 0.91 g/ml) were added dropwise for 20 min with vigorous stirring. Another 1 g of zinc dust was added after 40 min and it was stirred for 3 h at 0°C, after which the precipitate was filtered off and washed with ethanol (30 ml), the filtrate was poured into ice water (100 ml), the aqueous phase was extracted with methylene chloride (5 × 50 ml). The extract was washed with water and dried with anhydrous sodium sulfate. After removal of the solvent under vacuum, we obtained 1.1 g of yellowish oil which, according to chromatomass-spectrometry data, was a mixture of 32% of 1-(1-ethoxycarbonylethyl)-1-phenylhydrazine (**4b**) and 62% of compound **2b**.

B. Glacial acetic acid (6 g, 5.7 ml, 100 mmol) was added dropwise with vigorous stirring and cooling (0 to 10°C) to suspension of zinc dust (5.85 g, 90 mmol) in solution of ethyl ester **3b** (3.32 g) in ethanol (75 ml). Stirring was continued for 6 h at the same temperature, after which the excess zinc was filtered out of the reaction mixture and the latter was poured into water with ice (100 ml), neutralized with ammonia solution, and extracted with chloroform (6 × 50 ml). The organic extract was washed with a saturated solution of sodium chloride and dried with anhydrous sodium sulfate. After evaporation of the solvent under vacuum, we obtained 2.62 g of a yellowish oil which, according to chromatographic/mass spectrometry data, contained 50% of hydrazine **4b** and 50% of compound **2b**.

C. Tin(II) chloride dihydrate (2.38 g, 10.4 mmol) was added to suspension of compound **3b** (1.2 g, 5.4 mmol) in 1.1 N HCl (55 ml). This was stirred at room temperature for 12 h, then pyruvic acid ethyl ester (0.63 g, 5.4 mmol) and catalytic amounts of tetrabutylammonium hydrosulfate were added; this was stirred for 3 h and extracted with chloroform (5 × 50 ml). After drying with anhydrous sodium sulfate and removing the solvent under vacuum, we obtained 1.05 g of a yellowish oily compound that, according to

chromatomass-spectrometry data, contained only trace amounts of the desired 1-phenyl-1-(2-ethoxycarbonylethyl)hydrazone of pyruvic acid ethyl ester. The major reduction product was compound **2b**. Mass spectrum, *m*/*z* (*I*, %): 208 [M^+] (32), 135 [M^+-CO_2Et] (100), 118 (24), 104 (26), 91 (19), 77 (50).

2-(1-Phenylhydrazino)propionic Acid Methyl Ester (4a). D. Concentrated HCl (6 ml, 72 mmol) and (in portions with vigorous stirring) zinc dust (4.68 g) were added to solution of nitrosamine **3a** (9 mmol) in absolute methanol (100 ml) with cooling down to -80°C in argon atmosphere. The reaction mixture was stirred vigorously for 6-8 h at temperature from -80 to -70°C in argon atmosphere. The completeness of reduction was monitored by TLC (silica gel, ethyl acetate–petroleum ether, 1:3, visualization by an alcoholic solution of ferric trichloride). The excess of zinc was filtered off, the residue was washed with methanol (20 ml), the filtrate was evaporated under vacuum at room temperature down to volume of ~20 ml, poured into ice water (100 ml) and made alkaline by adding of 24% aqueous solution of ammonia (20 ml) (pH ~12). This was extracted with methylene chloride (4 × 50 ml), the extract was washed with saturated sodium chloride solution (30 ml) and dried with anhydrous sodium sulfate. After removing the solvent under vacuum, we obtained 1.65 g (95%) of a yellow-brown oily substance which was used to obtain hydrazones without additional purification. Mass spectrum, *m*/*z* (*I*, %): 194 [M^+] (25), 135 [M^+-CO_2Me] (100), 118 (26), 104 (20), 91 (18), 77 (45).

N-Phenyl-2-aminopropanol Hydrochloride (6). N-Phenylalanine (16 g, 97 mmol) was added in portions, without allowing the boiling to become too rapid, to suspension of lithium aluminum hydride (7.37 g, 190 mmol) in absolute THF (250 ml). The reaction mixture was boiled for 6 h and cooled down to room temperature, then water (10 ml) was added carefully followed by 10% KOH solution (10 ml) and water (10 ml), after which it was stirred for 1 h at ~ 20°C. The residue was filtered off and washed with THF (250 ml), the filtrate was evaporated under vacuum. The residue was dissolved in 250 ml of methylene chloride, washed with saturated sodium chloride solution (50 ml), and dried with anhydrous sodium sulfate. The solvent was evaporated under vacuum, the residue was dissolved in a small amount of absolute ether, and excess hydrogen chloride solution in ether was added. After removing the volatile components under vacuum and holding in a desiccator over KOH, the residue was recrystallized from an acetone–ether mixture. Obtained 14 g (76%) of white crystals; mp 112°C (acetone–ether). IR spectrum, ν, cm^{-1}: 690, 750 (Ar), 2570 (br, NH), 3400 (br, OH). ^{1}H NMR spectrum (D_2O), δ, ppm (*J*, Hz): 1.35 (3H, d, *J* = 6.3, CH_3); [3.70 (1H, dd, *J* = 5.6, *J* = 12.4), 3.78-3.90 (2H, m), CH+CH_2]; 7.53 (2H, d, *J* = 7.5, Ar); 7.62-7.70 (3H, m, Ar). Found, %: C 57.58; H 7.51; N 7.59. $C_9H_{13}NO$·HCl. Calculated, %: C 57.60; H 7.52; N 7.46.

N-Nitroso-N-phenyl-2-aminopropanol (7). N-Phenylalaninol hydrochloride **6** (1.5 g, 8 mmol) in methanol (20 ml) was dissolved in methanol (20 ml) and then cooled solution of KOH (0.45 g, 8 mmol) in methanol (10 ml) was added with cooling. The precipitate was filtered off and the filtrate was evaporated under vacuum. The residue was dissolved in methylene chloride (50 ml), washed with saturated sodium chloride solution (20 ml), and dried with anhydrous sodium sulfate. After the solvent was removed at reduced pressure, we obtained 1.15 g of N-phenylalaninol, which was converted to N-nitroso-N-phenylalaninol similarly to the way N-nitroso-N-phenylalanine ethyl ester was obtained. We isolated 1.35 g (99%) of a brownish viscous liquid which was used in later conversions without additional purification. ^{1}H NMR spectrum ($CDCl_3$, mixture of isomers in 1:1.3 ratio), δ, ppm (*J*, Hz): 1.17 and 1.38 (3H, 2 d, *J* = 7.1 and *J* = 6.8 respectively, CH_3); [3.69 and 5.15 (2H, 2 m), 4.91 and 5.15 (1H, 2 m), CH+CH_2]; 7.05 (2H, d, *J* = 7.5, Ar); 7.41-7.55 (3H, m, Ar).

N-(1-Methoxy-2-propyl)-N-nitrosoaniline (5). Nitrosaminopropanol **7** (3.43 g, 19 mmol) was dissolved in freshly distilled THF (40 ml), cooled down to -80°C, then methyl iodide (4 g, 285 mmol) and sodium hydride (0.62 g, 26 mmol) were added; the reaction mixture was slowly heated to room temperature and stirred for 1 h. The completeness of reaction was monitored by TLC (silica gel, 1:1 ethyl acetate–hexane). The reaction mixture was decomposed by adding water (2 ml), after which THF was removed under vacuum and the residue was diluted with water (25 ml) and extracted with chloroform (4 × 25 ml). The organic extract was dried with anhydrous sodium sulfate; after removal of the solvent under vacuum, we obtained 3.5 g (93%) of a yellow-brown substance, which was introduced to the reduction reaction without additional purification.

^{1}H NMR spectrum (mixture of isomers in 1:1.3 ratio), δ, ppm (*J*, Hz): 1.08 and 1.30 (3H, 2 d, *J* = 7.2 and *J* = 7.1, respectively, CH_3); 3.16 and 3.33 (3H, 2 s, CH_3O); [3.34-3.54 (2H, 2 m), 5.10-5.25 (1H, 2 m), CH+CH_2]; 6.99-7.59 (5H, 2 m, Ar).

1-(1-Methoxy-2-propyl)-1-phenylhydrazine (8). Solution of nitrosoaniline **5** (3.5 g, 18 mmol) in THF (40 ml) was added dropwise over a 30 min period with stirring to suspension of lithium aluminum hydride (0.76 g, 20 mmol) in absolute THF (30 ml). The reaction mixture was stirred for 1 h at room temperature and allowed to stand for 12 h. Water (1 ml) and 10% aqueous solution of KOH (0.5 ml) were added for decomposition, the precipitate was filtered off and washed with THF (3 × 50 ml). The filtrate was evaporated, the residue was dissolved in chloroform (50 ml), washed with saturated sodium chloride solution, and dried with anhydrous sodium sulfate. After removal of the solvent under vacuum, we obtained 3 g (75%) of a dark yellow oil. To obtain an analytical sample, hydrazine obtained was converted to the corresponding hydrochoride. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.07 (3H, d, *J* = 6.5, CH_3); 3.27 (3H, s, CH_3O); 3.37 (1H, dd, *J* = 4.7, *J* = 10.3, CH_2); 3.49 (1H, dd, *J* = 7.2, *J* = 10.3, CH_2); 3.87 (1H, m, CH); 7.17 (1H, t, *J* = 7.2, Ar); 7.26 (2H, d, *J* = 7.5, Ar); 7.40 (2H, t, *J* = 7.4, Ar); 10.17 (3H, br. s, NH_3). Mass spectrum, *m*/*z* (*I*, %): 180 [M^+] (20), 135 [M^+-CH_2OMe] (100), 118 (40), 104 (27), 91 (27), 77 (55).

(1-Methoxycarbonylethyl)phenylhydrazone of Pyruvic Acid Ethyl Ester (9). Pyruvic acid ethyl ester (0.55 g, 4.7 mmol) was added with stirring to 2-(1-phenylhydrazino)propionic acid methyl ester (0.92 g, 4.7 mmol), a catalytic amount of *p*-toluenesulfonic acid was added, and this was stirred at room temperature for 1 h; the reaction mixture was allowed to stand for 12 h, then it was diluted with benzene (30 ml) and stirred with anhydrous sodium sulfate (1 g) for 2 h. The drying agent was filtered off and the solvent was distilled off at reduced pressure. The residue was chromatographed on a dry column in the system petroleum ether–ethyl acetate with concentration gradient up to 15 vol.% of the latter; we obtained 0.9 g (64%) of hydrazone in the form of a viscous yellowish liquid. IR spectrum, ν, cm^{-1}: 1600 (Ar), 1705, 1750 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (3H, t, *J* = 7.1, C<u>H</u>$_3$CH$_2$); 1.28 (3H, d, *J* = 7.1, C<u>H</u>$_3$CH); 1.50 (3H, s, CCH_3); 3.61 (3H, s, CH_3O); 4.18 (2H, q, *J* = 7.1, CH_3C<u>H</u>$_2$); 4.58 (1H, q, *J* = 7.1, CH_3C<u>H</u>); 7.00 (2H, d, *J* = 7.8, Ar); 7.12 (1H, t, *J* = 7.2, Ar); 7.33 (2H, t, *J* = 8.4, Ar). ^{13}C NMR spectrum, δ, ppm: 14.10 (CH_3); 15.70 (CH_3); 16.82 (CH_3). 51.72, 60.73, 65.72, 123.16 (2C, CH); 124.63, 128.99 (2C, CH); 144.25, 146.98, 164.54 (C=O); 171.83 (C=O). Mass spectrum, *m*/*z* (*I*, %): 292 [M^+] (25), 233 [M^+-CO_2Me] (100), 159 (23), 118 (70), 104 (35), 77 (33), 42 (55).

(1-Methoxy-2-propyl)phenylhydrazone of Pyruvic Acid Ethyl Ester (11) was obtained similarly to hydrazone **9**, in the form of a viscous oil in 73% yield. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.23 (3H, d, *J* = 6.8, C<u>H</u>$_3$CH); 1.34 (3H, t, *J* = 7.1, C<u>H</u>$_3$CH$_2$); 1.55 (3H, s, CCH_3); 3.36 (3H, s, CH_3O); [3.44 (1H, m), 3.72 (1H, dd, *J* = 9.8, 7.2), 3.88 (1H, m), CH+CH_2]; 4.27 (2H, q, *J* = 7.1, CH_3C<u>H</u>$_2$); 6.98 (2H, d, *J* = 7.3, Ar); 7.09 (1H, t, *J* = 7.5, Ar); 7.28 (2H, t, *J* = 7.5, Ar). Mass spectrum, *m*/*z* (*I*, %): 278 [M^+] (10), 233 [M^+-CH_2OMe] (100), 201 (7), 159 (12), 118 (42), 104 (12), 77 (17), 45 (53).

(1-Methoxycarbonylethyl)phenylhydrazone of *p*-Methylacetophenone (10). *p*-Methylacetophenone (0.47 g, 3.5 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added to solution of 2-(1-phenylhydrazino)propionic acid methyl ester (0.68 g, 3.5 mmol) in benzene (10 ml). The reaction mixture was boiled for 8 h with a Dean–Stark attachment. The solvent was evaporated under vacuum, the residue was chromatographed on silica gel, eluting with a mixture of hexane–ethyl acetate with concentration gradient up to 5 vol.% of the latter. Obtained 0.76 g (70%) of hydrazone in the form of a yellowish oil that crystallized upon standing; mp 57°C (ethanol). IR spectrum, ν, cm^{-1}: 1600 (Ar), 1740 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.35 (3H, d, *J* = 6.8, C<u>H</u>$_3$CH); 2.01 (3H, s, CH_3); 2.34 (3H, s, CH_3); 3.57 (3H, s, CH_3O); 4.73 (1H, q, *J* = 6.8, CH_3C<u>H</u>); 6.80-6.91 (3H, m, Ar); 7.18-7.23 (4H, m, Ar); 7.26 (2H, d, *J* = 8.1, Ar). Mass spectrum, *m*/*z* (*I*, %): 310 [M^+] (28), 251 [M^+-CO_2Me] (59), 223 (8), 167 (9), 132 (100), 118 (13), 104 (9), 91 (28), 77 (12).

Cyclization of Hydrazones (General Procedure). Hydrazone (1.55 mmol) was dissolved in toluene (15 ml), then ion-exchange resin Amberlist-15 (0.8 g, 3.5 mmol-eq.) was added and the reaction mixture was held at 90-100°C for 4-8 h with vigorous stirring; the resin was filtered off, washed with ethyl acetate (30 ml), the filtrate was evaporated under vacuum, the residue was filtered through a layer of silica gel and recrystallized as needed.

2-(2-Ethoxycarbonylindol-1-yl)propionic acid methyl ester (12). Yield 87%; mp 53-55°C (ether–petroleum ether). IR spectrum, ν, cm^{-1}: 1705, 1745 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.31 (3H, t, *J* = 7.2, C<u>H</u>$_3$CH$_2$); 1.65 (3H, d, *J* = 6.8, CH$_3$C<u>H</u>); 3.60 (3H, s, CH$_3$O); 4.29 (2H, q, *J* = 7.2, CH$_3$C<u>H</u>$_2$); 6.02 (1H, q, *J* = 6.8, CH$_3$C<u>H</u>); 7.16 (1H, t, *J* = 7.4); 7.34 (1H, t, *J* = 7.5); 7.36 (1H, s, 3-H); 7.69 (1H, d, *J* = 8.7); 7.71 (1H, d, *J* = 8.1). ^{13}C NMR spectrum, δ, ppm: 14.11, 17.22, 52.11, 52.72, 60.63, 110.84, 111.30, 120.84, 122.58, 125.25, 125.46, 126.62, 138.58, 161.27 (C=O); 170.88 (C=O). Found, %: C 65.40; H 6.11; N 5.03. $C_{15}H_{17}NO_4$. Calculated, %: C 65.44; H 5.09; N 5.09.

2-(2-(4-Tolyl)indol-1-yl)propionic Acid Methyl Ester (13). Yield 71%; mp 92-93°C (methanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.60 (3H, d, *J* = 6.9, C<u>H</u>$_3$CH); 2.38 (3H, s, CH$_3$); 3.62 (3H, s, CH$_3$O); 5.27 (1H, q, *J* = 6.9, CH$_3$C<u>H</u>); 6.50 (1H, s, 3-H); 7.08 (1H, t, *J* = 6.8); 7.15 (1H, t, *J* = 7.8); 7.27 (1H, d, *J* = 8.1); 7.33 (2H, d, *J* = 7.5); 7.39 (2H, d, *J* = 7.5); 7.58 (1H, d, *J* = 7.8). ^{13}C NMR spectrum, δ, ppm: 16.17, 20.87, 52.54, 52.70, 102.24, 110.87, 119.90, 120.55, 121.68, 128.30, 129.15 (2C); 129.25, 129.48 (2C); 135.76, 137.45, 141.08, 171.15 (C=O). Mass spectrum, *m*/*z* (*I*, %): 293 [M^+] (100), 234 [M^+-CO_2Me] (83), 220 (22), 204 (17), 179 (7). Found, %: C 77.97; H 6.57; N 4.78. $C_{19}H_{19}NO_2$. Calculated, %: C77.79; H 6.53; N 4.77.

1-(1-Methoxy-2-propyl)indol-2-ylcarboxylic Acid Ethyl Ester (14). Yield 53%. Viscous liquid. IR spectrum, ν, cm^{-1}: 1710 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.33 (3H, t, *J* = 7.1 C<u>H</u>$_3$CH$_2$); 1.55 (3H, d, *J* = 7.2, C<u>H</u>$_3$CH); 3.14 (3H, s, CH$_3$O); 3.71 (1H, dd, *J* = 10.0, *J* = 5.6, CH$_2$); 3.96 (1H, dd, *J* = 10.0, *J* = 8.4, CH$_2$); 4.30 (2H, q, *J* =7.1, CH$_3$C<u>H</u>$_2$); 5.74 (1H, m, CH$_3$C<u>H</u>); 7.11 (1H, t, *J* = 7.1); 7.24-7.32 (2H, m); 7.68 (1H, d, *J* = 8.1); 7.71 (1H, d, *J* = 8.4). ^{13}C NMR spectrum, δ, ppm: 14.15, 16.42, 51.00, 58.06, 60.51, 73.66, 110.94, 113.04, 122.66, 123.30, 124.62, 126.11, 127.98, 137.88, 161.59 (C=O). Mass spectrum, *m*/*z* (*I*, %): 261 [M^+] (90), 229 (11), 216 [M^+-CH_2OCH_3] (60), 201 (7), 170 (100), 144 (54), 116 (25), 89 (18), 45 (70). Found, %: C 68.91; H 7.38. $C_{15}H_{19}NO_3$. Calculated, %: C 68.94; H 7.33.

1-(1-Methoxycarbonylethyl)-2,3,4,5-tetrahydrocarbazole (15). Cyclohexanone (0.39 g, 4 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added to solution of methyl ester of compound **4a** (0.78 g, 4 mmol) in benzene (10 ml); this was boiled for 8 h with a Dean–Stark attachment. Formation of hydrazone **16** was confirmed by chromatomass-spectrometry (*m*/*z* (*I*, %): 274 [M^+] (5), 215 [M^+-CO_2Me] (100), 118 (50), 104 (15), 96 (80), 77 (63), 69 (18), 55 (30)). Benzene was removed at reduced pressure, the residue was dissolved in toluene (40 ml), ion-exchange resin Amberlist-15 (2 g) was added, and it was vigorously stirred for 3 h at 90-100°C. The resin was filtered off, washed with ethyl acetate (60 ml), the filtrate was evaporated under vacuum, the residue was chromatographed on a column with silica gel in a hexane–ethyl acetate system with concentration gradient up to 5 vol.% of the latter. Obtained 0.63 g (61%) of a viscous liquid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.59 (3H, d, *J* = 7.2, C<u>H</u>$_3$CH); 1.73-1.92 (4H, m); 2.54-2.74 (4H, m); 3.64 (3H, s, CH$_3$O); 5.40 (1H, q, *J* = 7.2, CH$_3$C<u>H</u>); 6.98 (1H, t, *J* = 7.4); 7.02 (1H, t, *J* = 7.1); 7.22 (1H, d, *J* = 8.1); 7.38 (1H, d, *J* = 7.1). Mass spectrum, *m*/*z* (*I*, %): 257 [M^+] (35), 198 [M^+-CO_2Me] (100), 170 (30), 156 (5), 143 (3), 128 (4), 115 (4), 98 (3), 77 (3). Found, %: C 74.73; H 7.50; N 5.35. $C_{16}H_{19}NO_2$. Calculated, %: C 74.68; H 7.44; N 5.44.

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