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REGIOSELECTIVE SYNTHESIS OF 1-ALKYL-5-(INDOL-3-YL- AND -2-YL)PYRROLIDIN-2-ONES FROM AVAILABLE REAGENTS

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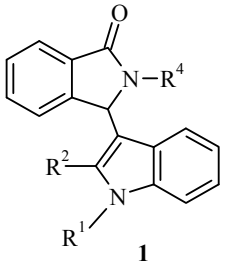
The reaction under mild conditions of 1-alkyl-5-hydroxypyrrolidin-2-ones with different indoles having a free 3 position leads exclusively to 1-alkyl-5-(indol-3-yl)pyrrolidin-2-ones but if position 3 is occupied to 1-alkyl-5-(indol-2-yl)pyrrolidin-2-ones.

Keywords: 1-alkyl-5-hydroxypyrrolidin-2-ones, 1-alkyl-5-indolylpyrrolidin-2-ones, indoles, amidoalkylation.

It is known that the combination of pharmacophoric fragments in a single molecule often leads to a strengthening and/or to a change in the pharmacological properties of the molecule. In this connection there is significant interest in studying compounds which contain indole and γ-aminobutyric acid (e.g. γ-butyrolactone) fragments in the molecule. A single compound of this type has been synthesized previously [1] but the method proposed by the authors is inconvenient and is not sufficiently general. Some time ago we carried a simple synthesis of the 2-alkyl-3-(indol-3-yl- and -2-yl)isoindol-2-ones **1** and **2** [2].



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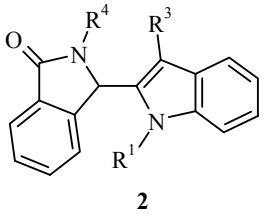

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We suggested that using this method can also prove useful for synthesizing the 1-alkyl-5-(indol-3-yl)-pyrrolidin-2-ones **3a-k**. The 5-hydroxypyrrolidin-2-ones **4a-d** needed for this were prepared from succinic anhydride and the corresponding amines **5a-d**.

The intermediate succinamic acids **6a-d** were readily prepared by mixing succinic anhydride with the corresponding amine in stoichiometric quantities in chloroform. Their cyclization to the corresponding imides **7a-d** occurs with prolonged refluxing in benzene in a Dean–Stark apparatus in the presence of equivalent

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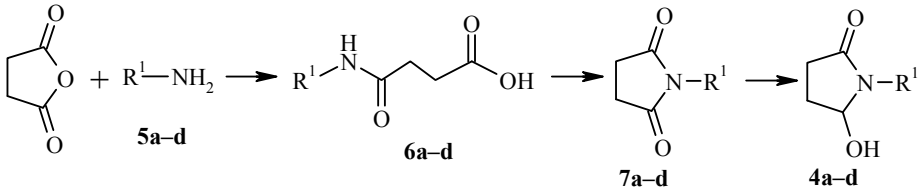
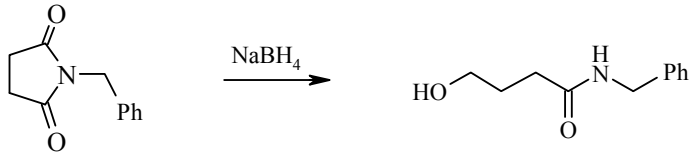


4–7 a R^1 = Bn, **b** R^1 = $CH_2CH_2C_6H_4Cl$-*p*, **c** R^1 = *sec*-Bu, **d** R^1 = CH(Me)Ph

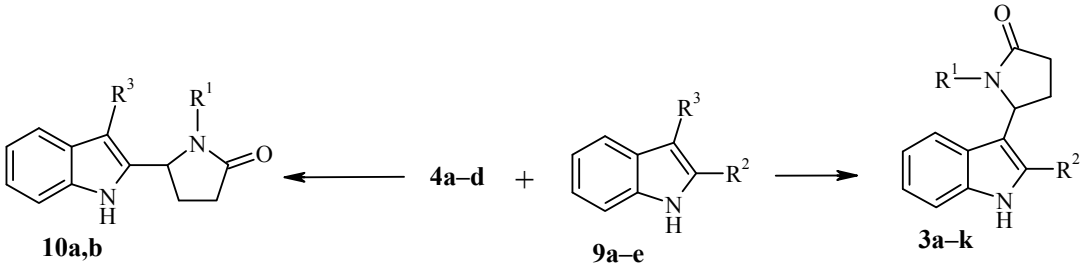
amounts of Et_3N and glacial acetic acid. A method has been reported in the literature [3] for reduction of the succinimides to the corresponding 5-hydroxypyrrolidin-2-ones using sodium borohydride in methanol but attempts to reproduce this method were unsuccessful. Hence at low temperatures imide **7a** remains undissolved in the reaction mixture and the reduction does not go to completion. On the other hand, at room temperature we obtained the 4-hydroxybutyric acid N-benzylamide (**8**) as the product of further reduction.



We have found that the target 5-hydroxypyrrolidin-2-ones are optimally prepared used a mixture of methanol and dichloromethane (3:1) as solvent in which imides **7** are completely soluble, even upon cooling.

When compared with the imides **7**, whose ^{1}H NMR spectra show all four heterocyclic ring protons in the form of a singlet, the spectra of compounds **4** are much more complex. Hence the ring protons are no longer equivalent and are shifted to higher field to different degrees (see Table 1). In addition, an H-5 proton multiplet is seen in the region of 5 ppm and the signals for the OH group and the alkyl fragment also undergo marked changes.

Compounds **4c**,**d** were synthesized as a mixture of two diastereomeric pairs, each in the ratio of about 1:1*.



3 a R^1 = Bn, R^2 = H, **b** R^1 = $CH_2CH_2C_6H_4Cl$-*p*, R^2 = H, **c** R^1 = *sec*-Bu, R^2 = H, **d** R^1 = CH(Me)Ph, R^2 = H, **e** R^1 = Bn, R^2 = Me, **f** R^1 = $CH_2CH_2C_6H_4Cl$-*p*, R^2 = Me, **g** R^1 = *sec*-Bu, R^2 = Me, **h** R^1 = CH(Me)Ph, R^2 = Me, **i** R^1 = Bn, R^2 = C_6H_4Me-*p*, **j** R^1 = *sec*-Bu, R^2 = C_6H_4Me-*p*, **k** R^1 = CH(Me)Ph, R^2 = C_6H_4Me-*p*; **9 a** R^2 = R^3 = H, **b** R^2 = Me, R^3 = H, **c** R^2 = C_6H_4Me-*p*, R^3 = H, **d** R^2 = H, R^3 = Me, **e** R^2 = H, R^3 = C_6H_4Me-*p*; **10 a** R^1 = Bn, R^3 = Me, **b** R^1 = Bn, R^3 = C_6H_4Me-*p*

* Compound **4c** was prepared and introduced in the subsequent reaction as a mixture with the starting imide **7c** in the ratio of about 3:2 because both compounds **4c** and **7c** exist as oils which could not be separated chromatographically. In addition, imide **7c** is chemically inert and does not interfere with the subsequent reaction process. The spectroscopic characteristics of compound **4c** were obtained and quoted here after subtraction of the spectrum of compound **7c** from that of the mixture of compounds produced in the reaction.

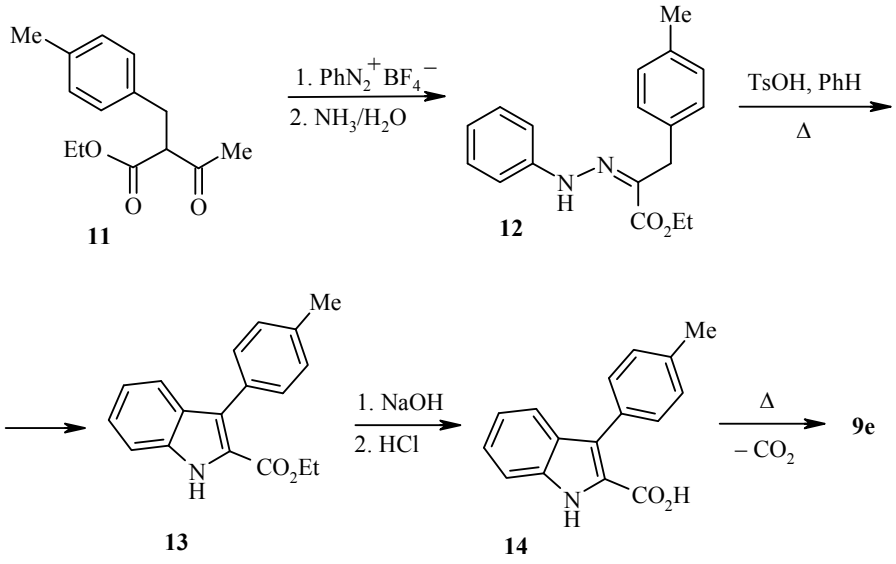
The 5-hydroxypyrrolidin-2-ones **4a-d** were introduced into the reaction with the indoles **9a-e** in similar conditions to those given in the study [2], i.e. in chloroform with a catalytic amount of boron trifluoride etherate, to give good or satisfactory yields of the corresponding indol-3-yl- (or 2-yl)pyrrolidin-2-ones **3a-k**, **10a**,**b**.

In the ^{1}H NMR spectra of the compounds obtained the characteristic broad indole NH proton signal is retained and their IR spectra show an N–H stretching band. Hence, in contrast to the study [4], the amidoalkylation occurs exclusively at a carbon atom, even in the absence of a substituent on the indole nitrogen atom. Analysis of the multiplicity of the aromatic signals shows that, by contrast with [5, 6], the attack is directed to the pyrrole ring of a neutral indole molecule and not to position 5 or 6 of the indole ring. In contrast to [7-9] substitution is directed exclusively to the 3 positions when the 2 and 3 positions of the indole ring are unoccupied (compound **9a**) as shown by the absence in the ^{1}H NMR spectra of compounds **3a-d** of the characteristic H-3 indole proton signal in the region of 6.5 ppm.

Compounds **3c**,**d**,**g**,**h**,**j**,**k** have two chiral centers and were obtained by us as a mixture of two diastereomeric pairs, each in a ratio close to 1:1.

The study [7] reported a double Wagner-Meerwein type rearrangement which occurred under mild conditions during the amidoalkylation process. As a result of this rearrangement the substituent at position 2 of the indole ring shifts to position 3 and the new substituent now occupies its place. We did not observe such a rearrangement in [2] (compounds **1**, **2**). In order to reveal whether this rearrangement can occur in the reactions studied by us here we have compared the compounds pairs **3e**, **10a** and **3i**, **10b** which were respectively obtained from the isomeric indole pairs **9b**,**d** and **9c**,**e** and the hydroxypyrrolidin-2-one **4a**. The pairs of compounds indicated have different physicochemical properties. While their ^{1}H NMR spectra are very similar they, none the less, have no common signals. We did not observe isomeric reaction products in any of the examples. Hence it can be considered as confirmed that in this reaction and in the conditions studied the double Wagner-Meerwein reaction referred to does not occur and the reaction takes place regioselectively. We suggest that the intermediate carbocation in the literature example [7] has a high stability as a result of the appearance of the α-effect of the neighboring nitrogen atom in the pyrazolidine derivatives.

Indole **9e** used for this proof was prepared by us using the following scheme (Experimental).



According to ^{1}H NMR data (Table 1) and TLC, compound **9e** does not contain an admixture of the isomeric 2-(*p*-tolyl)indole **9c**.

TABLE 1. ^{1}H NMR Spectra of the Compounds Prepared

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
1	2
3a	2.20-2.29 (1H, m, H-4); 2.38-2.47 (1H, m, H'-4); 2.56-2.65 (1H, m, H-3); 2.70-2.78 (1H, m, H'-3); 3.61 (1H, d, *J* = 14.7, CHH'Ph); 4.81 (1H, dd, *J* = 8.0, *J* = 6.6, H-5); 5.12 (1H, d, *J* = 14.6, CHH'Ph); 7.05 (1H, d, *J* = 2, arom); 7.10-7.17 (3H, m, arom); 7.24-7.34 (4H, m, arom); 7.45 (1H, d, *J* = 7.5, arom); 7.51 (1H, d, *J* = 7.9, arom); 8.43 (1H, br. s, NH)
3b	2.15-2.25, 2.34-2.44 (2H, two m, H-4); 2.45-2.55, 2.60-2.65 (2H, two m, H-3); 2.65-2.70, 2.78-2.88 (2H, two m, $CH_2C_6H_4$); 2.90-3.00, 3.81-3.91 (2H, two m, CH_2N); 4.71-4.79 (1H, m, H-5); 6.98-7.54 (9H, m, arom); 8.15 (1H, br. s, NH)
3c	0.76-0.82 (3H, m, CH_3CH_2); 0.82-0.89, 1.20-1.25 (3H, 2 m, ~3:4, CH_3CH); 1.25-1.29, 1.36-1.39, 1.54-1.67, 1.67-1.79 (2H, four m, CH_2CH_3); 2.10-2.26, 2.39-2.48 (2H, two m, H-4); 2.48-2.55, 2.65-2.79 (2H, two m, H-3); 3.56-3.65, 3.92-4.04 (1H, two m, ~4:3, $CHCH_3$); 4.99-5.05 (1H, m, H-5); 7.12-7.19 (2H, m, arom); 7.20-7.27 (1H, m, arom + $CDCl_3$); 7.39-7.44 (1H, m, arom); 7.58-7.64 (1H, m, arom); 8.15-8.29 (1H, br., NH)
3d	1.65 (3H, d, *J* = 7.6, CH_3); 2.18-2.28, 2.43-2.48 (2H, two m, H-4); 2.48-2.53, 2.66-2.76 (2H, two m, H-3); 4.76-4.82 (1H, m, $CHCH_3$); 4.96-5.06 (1H, m, H-5); 6.84-7.61 (10H, m, arom); 8.29 (1H, br. s, NH)
3e	2.06 (3H, br. s, CH_3Ar); 2.21-2.39 (2H, br. m, H-4); 2.58-2.67, 2.69-2.79 (2H, two m, H-3); 3.41 (1H, d, *J* = 13.8, CHH'Ph); 4.68 (1H, t, *J* = 7.9, H-5); 5.13 (1H, d, *J* = 14.3, CHH'Ph); 7.01-7.50 (9H, m, arom); 7.90 (1H, br. s, NH)
3f	2.12-2.22, 2.25-2.35 (2H, 2 m, H-4); 2.39 (3H, s, CH_3); 2.44-2.54, 2.56-2.66 (2H, two m, H-3); 2.56-2.66 (1H, m, high field part of CH_2N); 2.75-2.85 (2H, m, $CH_2C_6H_4$); 3.78-3.88 (1H, m, low field part of CH_2N); 4.63-4.73 (1H, m, H-5); 6.98-7.54 (8H, m, arom); 7.88 (1H, br. s, NH)
3g	0.72-0.95 (4.6H, m, CH_3CH_2 + high field part of CH_3CH); 1.10-1.31 (2.5H, m, low field part of CH_3CH + high field part of CH_2CH_3); 1.47-1.74 (1.1H, two m, low field part of CH_2CH_3); 2.15-2.42 (2H, two m, H-4); 2.45 (3H, s, CH_3Ar); 2.50-2.63, 2.65-2.81 (2H, two m, H-3); 3.40-3.53, 3.86-3.98 (1H, two m, ~3:2 NCH); 4.90-5.07 (1H, br. m, H-5); 7.03-7.58 (4H, m, arom + $CDCl_3$); 7.94 (1H, br. s, NH)
3h	1.04, 1.71 (3H, two br. d, J_1 = 7.3, J_2 = 6.9, ~1:1, CH_3CH); 1.74, 2.31 (3H, two s, ~1:1, CH_3Ar); 2.13-2.46, 2.47-2.58, 2.58-2.73, 2.77-2.89 (4H, four m, ~1.5:1:1:0.5, H-3,4); 4.36-4.55, 5.58 (1H, br. s + q, *J* = 7.3, $CHCH_3$); 4.55, 4.75-4.95 (1H, t + br. s, ~1:1, *J* = 7.5, H-5); 6.85-7.55 (9H, m, arom); 7.76, 7.82 (1H, two br. s, ~1:1, NH)
3i	2.28-2.36 (2H, m, H-4); 2.36 (3H, s, CH_3); 2.52-2.60, 2.60-2.68 (2H, two m, H-3); 3.49 (1H, d, *J* = 14.7, CHH'Ph); 4.85-4.91 (1H, m, H-5); 5.10 (1H, d, *J* = 14.7, CHH'Ph); 6.88-7.57 (13H, m, arom); 8.26 (1H, br. s, NH)
3j	0.56-0.74 (4.4H, m, CH_3CH_2 + high field part of CH_3CH); 1.00 (1.6H, d, *J* = 6.9, low field part of CH_3CH); 1.09-1.18, 1.28-1.40, 1.49-1.60 (2H, three m, ~2:3:2, CH_3CH_2); 2.31-2.62, 2.45, 2.45 (6H, m + two s, 2H-3+CH_3Ar+H-4); 2.68-2.87 (1H, br. m, H'-4); 3.32-3.42, 3.76-3.86 (1H, two m, ~4:3, NCH); 5.03-5.13 (1H, m, H-5); 7.09-7.65 (8H, m, arom); 8.20, 8.22 (1H, two s, ~4:3, NH)
3k	1.03, 1.57 (3H, two d, ~6:7, *J* = 7.2, $CHCH_3$); 2.42, 2.44 (3H, two s, ~6:7, $ArCH_3$); 2.18-2.30, 2.32-2.50 (2H, two m, ~1:3, H-4); 2.51-2.62, 2.66-2.79, 2.82-2.94 (2H, three m, ~2:1:1, H-3); 4.54, 5.53 (1H, two q, ~7:6, *J* = 7.3, $CHCH_3$); 4.83 (0.46H, dd, J_1 = 5.6, J_2 = 3.1, H-5); 5.06 (0.54H, t, *J* = 7.8, H-5); 6.92-7.63 (13H, m, arom); 8.53 (1H, br. s, NH)
4a	1.84-1.94 (1H, m, H-4); 2.12-2.32 (2H, m, H'-4 + H-3); 2.52-2.65 (1H, m, H'-3); 4.14 (1H, d, *J* = 14.8, CHH'Ph); 4.83 (1H, d, *J* = 14.8, CHH'Ph); 5.06 (1H, t, *J* = 6.5, H-5); 5.50 (1H, br. s, OH); 7.18-7.36 (5H, m, arom)
4b	1.80-1.90, 2.26-2.36, 2.51-2.61 (4H, three m, ~1:2:1, H-3 + H-4); 2.08 (1H, d, *J* = 8.3, OH); 2.85-2.95 (2H, m, $CH_2C_6H_4$); 3.40-3.50 (1H, m, CHH'N); 3.67-3.77 (1H, m, CHH'N); 5.01 (1H, t, *J* = 7.8, H-5); 7.15-7.34 (4H, m, arom)
4c	0.55-0.61 (3H, m, $MeCH_2$); 1.01-1.07 (3H, m, MeCH); 1.30-1.40, 1.44-1.54, 1.56-1.66 (2H, three m, ~1:2:1, $MeCH_2$); 1.67-1.77, 2.00-2.07 (2H, two m, H-4); 2.07-2.10, 2.38-2.48 (2H, two m, H-3); 5.01-5.04 (1H, m, H-5)

TABLE 1 (continued)

1	2
4d	1.59, 2.25 (1H, two d, ~1:1, *J* = 7.1, OH); 1.65, 1.70 (3H, two d, ~1:1, *J* = 7.6, CH_3); 1.82-1.92, 2.12-2.22 (2H, two m, H-4); 2.30-2.40, 2.62-2.72 (1H, two m, H-3); 4.95, 5.43 (1H, two t, ~1:1, *J* = 7.0, H-5); 5.40-5.46 (1H, m, C<u>H</u>Ph); 7.27-7.53 (5H, m, arom)
7b	2.67 (4H, s, $COCH_2CH_2CO$); 2.87 (2H, t, *J* = 7.7, C<u>H</u>$_2C_6H_4$); 3.74 (2H, t, *J* = 7.7, NCH_2); 7.16 (2H, d, *J* = 8.3, arom); 7.27 (2H, d, *J* = 8.3, arom)
7c	0.65 (3H, two t, ~1:1, *J* = 7.5, C<u>H</u>$_3CH_2$); 1.18 (3H, two d, ~1:1, *J* = 7.0, C<u>H</u>$_3$CH); 1.53 (1H, m, C<u>H</u>H'); 1.75 (1H, m, CH<u>H</u>'); 2.50 (4H, two s, ~1:1, CH_2CH_2); 3.94 (1H, m, CHN)
8	1.87 (2H, m, CH_2C<u>H</u>$_2CH_2$); 2.36 (2H, t, *J* = 6.8, CH_2CON); 3.42 (1H, br. t, OH); 3.66 (2H, br. m, C<u>H</u>$_2$OH); 4.41 (2H, d, *J* = 5.7, CH_2Ph); 6.44 (1H, br. s, NH); 7.23-7.39 (5H, m, arom)
9e	2.42 (3H, s, CH_3); 7.18-7.22 (1H, dt, J_1 = 6.9, J_2 = 1.1); 7.24-7.29 (3H, m); 7.35 (1H, d, *J* = 2.5); 7.44 (1H, d, *J* = 8.7); 7.58 (2H, d, *J* = 8.1); 7.94 (1H, d, *J* = 8.7); 8.20 (1H, br. s, NH)
10a	2.09 (3H, s, CH_3); 2.13-2.22 (1H, m, H-4); 2.36-2.47 (1H, m, H'-4); 2.55-2.66 (1H, m, H-3); 2.67-2.78 (1H, m, H'-3); 3.49 (1H, d, *J* = 14.6, C<u>H</u>H'Ph); 4.79 (1H, t, *J* = 7.6, H-5); 5.07 (1H, d, *J* = 14.3, CH<u>H</u>'Ph); 7.09-7.16 (3H, m, arom); 7.21 (1H, dt, J_1 = 7.5, J_2 = 1.1, arom); 7.26-7.34 (3H, m, arom); 7.38 (1H, d, *J* = 8.1, arom); 7.55 (1H, br. d, *J* = 7.8, arom); 8.96 (1H, br. s, NH)
10b	2.31-2.41 (1H, m, H-4); 2.49 (3H, s, CH_3); 2.51-2.61 (1H, m, H'-4); 2.63-2.71 (1H, m, H-3); 2.80-2.88 (1H, m, H'-3); 3.69 (1H, d, *J* = 14.4, C<u>H</u>H'Ph); 5.00 (1H, dd, J_1 = 8.2, J_2 = 6.8, H-5); 5.07 (1H, d, *J* = 14.4, CH<u>H</u>'Ph); 7.06 (2H, d, *J* = 7.0, arom); 7.18-7.29 (6H, m, arom); 7.31-7.39 (3H, m, arom); 7.52 (1H, d, *J* = 8.1, arom); 7.75 (1H, d, *J* = 7.9, arom); 9.53 (1H, br. s, NH)
14	2.46 (3H, s, CH_3); 7.17 (1H, t, *J* = 7.5, arom); 7.30 (2H, d, *J* = 7.7, arom); 7.40 (1H, t, *J* = 7.4, arom); 7.45 (1H, d, *J* = 8.2, arom); 7.49 (2H, d, *J* = 7.9, arom); 7.65 (1H, d, *J* = 8.2, arom); 8.99 (1H, br. s, NH)

In [2] there were discovered rotational isomers of compound **1** with a high barrier to internal rotation around the σ-bond between the indole C-3 and the isoindolone C-3 when there was a substituent in position 2 of the indole ring. We expected that, in our case, a similar effect might occur. However, no indications of hindered internal rotation were observed in any of the obtained compounds **3**, **10**. Hence it can be proposed that the rotational isomerism occurring in compounds **1** compared with compounds **3**, **10** is due to the presence of the additional condensed aromatic ring in the isoindolone fragment of these compounds.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument as a thin layer. ^{1}H NMR spectra were taken on a Varian Avance-400 spectrometer (400 MHz) using DMSO-d_6 with the residual signals for DMSO-d_6 (δ 2.50 ppm) and $CDCl_3$ (δ 7.27 ppm) as internal standards. Mass spectra were recorded on a Bruker Autoflex II instrument. Elemental analysis for C, H, and N was carried out on a Carlo-Erba ER-20 analyzer. Monitoring of the course of the reaction and the compounds purity were performed on Silufol UV-254 and Merck Silicagel 60 F_{254} plates. Compounds purification was carried out on Merck silica gel (column chromatography, 0.035-0.070 nm, 6 nm pore diameter, 500 m^2/g).

N-Benzylsuccinamic Acid (6a). An equivalent amount of succinic anhydride was added rapidly with stirring to a solution of benzylamine (**5a**) in a fivefold excess of chloroform (by volume). After cooling the hot reaction mixture to room temperature the precipitate formed was filtered off, washed with chloroform, and dried in air to give white crystals (93%) with mp 135-137ºC (mp 137-139º [10]).

N-(2-*p*-Chlorophenylethyl)succinamic Acid (6b). Prepared similarly from succinic anhydride and 2-chlorophenylethylamine (**5b**) as white crystals (97%) with mp 137-138ºC. IR spectrum, δ, cm^{-1}: 1640 (HNC=O); 1695 (HOC=O); 2670 (OH), 3330 (NH). Found, %: C 56.46; H 5.66; N 5.51. $C_{12}H_{14}ClNO_3$. Calculated, %: C 56.37; H 5.52; N 5.48.

N-*sec*-Butylsuccinamic Acid (6c). Prepared from succinic anhydride and *sec*-butylamine (**5c**). The product was cooled and solvent removed *in vacuo* to give a yellowish, oily residue in about 100% yield which was used without further purification.

N-(1-Phenylethyl)succinamic Acid (6d). Prepared similarly from succinic anhydride and 1-phenylethylamine (**5d**). Removal of most of the solvent *in vacuo* gave white crystals (87%) with mp 99-100ºC (mp 100.9-101.1ºC [11]).

Preparation of Imides 7a-d (General Method). Equimolar amounts of acetic acid and triethylamine were added to a suspension of the corresponding succinamic acid in a tenfold excess of benzene and the product was refluxed in a Dean and Stark apparatus until the separation of water had ceased (~ 24 h). The mixture obtained was washed with water, saturated $NaHCO_3$ solution, and then water again. The aqueous phases were combined and extracted with benzene (2×50 ml). The benzene fractions were combined, dried over $MgSO_4$, passed through a thin layer of silica, and the solvent was distilled off *in vacuo*.

N-Benzylsuccinimide (7a). Yield 65%; mp 102-103ºC (mp 102.5-103.5ºC [10]).

N-[2-(*p*-Chlorophenyl)ethyl]succinimide (7b). Yield 37%; mp 113-115ºC (mp 113-114ºC [12]). IR spectrum, δ, cm^{-1}: 1690 (C=O).

N-*sec*-Butylsuccinimide (7c). Yield ~ 95%. Yellow oil, used without further purification.

N-(1-Phenylethyl)succinimide (7d). Yield 56%; mp 65-66ºC (mp 67-68.5ºC [13]).

Preparation of 1-Alkyl-5-hydroxypyrrolidin-2-ones 4a-d (General Method). Sodium borohydride (2.36 g, 62.5 mmol) was added over 2 h with stirring keeping at 0 to 5°C to a solution of imide **7a-d** (25 mmol) in a mixture of dichloromethane (30 ml) and methanol (90 ml) which was cooled to 2-3ºC. The reaction mixture was left overnight at ~ -15ºC, water (30 ml) was added, and the organic solvent was removed by distillation *in vacuo*. The precipitate formed was washed several times with water and dried in air. The filtrate was extracted with dichloromethane (4×20 ml), the extract was dried over $MgSO_4$, and the solvent was distilled off *in vacuo*. Both fraction of the reaction product were combined and recrystallized from benzene.

1-Benzyl-5-hydroxypyrrolidin-2-one (4a). White crystals, yield 62%; mp 105-106ºC. IR spectrum, ν, cm^{-1}: 1640 (C=O), 3175 (OH). Found, %: C 68.91; H 6.72; N 7.14. $C_{11}H_{13}NO_2$. Calculated, %: C 69.09; H 6.85; N 7.32.

5-Hydroxy-1-[2-(*p*-chlorophenyl)ethyl]pyrrolidin-2-one (4b). White crystals, yield 37%; mp 149-150ºC. IR spectrum, ν, cm^{-1}: 1650 (C=O), 3210 (OH). Found, %: C 60.25; H 5.80; N 5.82. $C_{12}H_{14}ClNO_2$. Calculated, %: C 60.13; H 5.89; N 5.84.

1-*sec*-Butyl-5-hydroxypyrrolidin-2-one (4c). A precipitate did not form upon dilution with water but a yellow oil was formed which was used without further purification. According to ^1H NMR spectroscopy the yield was ~ 50%.

5-Hydroxy-1-(1-phenylethyl)pyrrolidin-2-one (4d). White crystals, yield 50%; mp 75-76ºC. IR spectrum, ν, cm^{-1}: 1645 (C=O), 3260 (OH). Found, %: C 69.99; H 7.15; N 6.77. $C_{12}H_{15}NO_2$. Calculated, %: C 70.22; H 7.37; N 6.82.

N-Benzyl-4-hydroxybutaneamide (8). An equimolar amount of $NaBH_4$ was added in several aliquots with stirring to a suspension of the N-benzylsuccinimide **7a** (4.73 g, 25 mmol) in methanol (50 ml). The suspension dissolved and the solution heated noticeably. The mixture was left overnight at room temperature, water (30 ml) was added, and the methanol was distilled off *in vacuo*. The residue was extracted with chloroform (3×20 ml), the organic layer was dried over $MgSO_4$, passed through a thin silica layer, and solvent was distilled off *in vacuo*. The residue was triturated with ether and the crystals formed were filtered off, washed with ether, and dried in air. The colorless crystals (67%) had mp 70-71ºC (mp 70-72ºC [14]). Found, %: C 68.80; H 7.46; N 7.11. $C_{11}H_{15}NO_2$. Calculated, %: C 68.37; H 7.82; N 7.25.

Ethyl 3-(*p*-Tolyl)pyruvate Phenylhydrazone (12). Phenyldiazonium fluoroborate previously prepared and dried at room temperature (4.86 g, 25.3 mmol) was added with stirring to a solution of 3-(*p*-methylbenzyl)acetoacetic ester (4.93 g, 21.0 mmol) cooled to 2ºC. Et_3N (3.5 ml, 25.2 mmol) was added with stirring and cooling to 3-5ºC to the colorless suspension obtained. The suspension dissolved during the addition process and became intensely red in color. The mixture was left overnight at room temperature. A 25% solution of NH_3 (6.4 ml, 85 mmol) was added portionwise with stirring. The emulsion formed was left overnight and the partially crystalline precipitate was filtered off, washed with ethanol and then petroleum ether, and dried to give light-red crystals (0.52 g); mp 73-74ºC and R_f 0.9 (EtOAc–petroleum ether, 2: 3). The organic solvent was distilled off *in vacuo* from the combined filtrate. The residual dark-red oil was treated with water, stirred, the aqueous layer decanted, and the oil was treated with methanol and left overnight to give less pure compound (0.61 g). A second similar treatment of the filtrate gave further compound (0.22 g). Overall yield 1.35 g (22%). The compound was used in the subsequent reaction without additional purification.

Ethyl 3-(*p*-Tolyl)-1H-indole-2-carboxylate (13). A solution of anhydrous *p*-toluenesulfonic acid in benzene was prepared by refluxing a suspension of *p*-toluenesulfonic acid monohydrate (1.04 g, 5.5 mmol) in benzene (50 ml) with a Dean–Stark apparatus until the separation of water ceased and the suspension dissolved. The solution obtained was cooled to room temperature, compound **12** (1.35 g, 4.6 mmol) was added, and the mixture obtained was refluxed for 4 h with stirring. The mixture with the ammonium tosylate precipitate produced was cooled to room temperature, washed with water (3×50 ml), the organic layer was dried over $MgSO_4$, and passed through a silica layer. The adsorbent was washed with benzene and then chloroform. Solvent was removed from the combined eluate *in vacuo* and the residue was triturated with ether. The precipitate formed was filtered off and washed with ether to give a yellow powder with mp 142-144ºC and R_f 0.5 (chloroform). The filtrate was diluted with petroleum ether and most of the solvent was distilled off *in vacuo*. Trituration of the residue gave less pure reaction product. Overall yield 0.62 g (49%). The compound was used in the subsequent reaction without further purification.

3-(*p*-Tolyl)-1H-indole-2-carboxylic Acid (14). A solution of NaOH (0.17 g, 4.25 mmol) in water (2 ml) was added to a suspension of ester **13** (0.61 g, 2.2 mmol) in methanol (15 ml). The mixture was refluxed for 5 h, cooled, methanol distilled off *in vacuo*, and the semicrystalline residue was treated with water (15 ml) and filtered hot. The filtrate was cooled to room temperature, acidified with stirring using dilute HCl (1:1), and the suspension obtained was stirred for 2 h, the precipitate filtered off, washed several times with water, and dried. Light-yellow powder, yield 0.47 g (85%); mp 222-226ºC (decomp.) and R_f 0.05 (chloroform). Found, %: C 76.03; H 4.77; N 5.71. $C_{16}H_{13}NO_2$. Calculated, %: C 76.48; H 5.21; N 5.57.

3-(*p*-Tolyl)-1H-indole (9e). Acid **14** (0.43 g, 1.7 mmol) was heated for 3 h at 210-220ºC in a test tube filled with inert gas. The vessel contents darkened and decomposed with the evolution of gas. The reaction products were removed using chloroform, solvent was distilled off *in vacuo*, the residue was treated with warm benzene, the solution passed through a silica layer, the solvent was removed *in vacuo*, and the residue was recrystallized from heptane. Yield 0.24 g (69%); mp 100-101ºC (mp 107-108ºC [15]). R_f 0.62 (chloroform), 0.56 (EtOAc–hexane, 2:3)*. Found, %: C 87.41; H 6.64; N 6.52. $C_{15}H_{13}N$. Calculated, %: C 86.92; H 6.32; N 6.76.

According to ^{1}H NMR and TLC data the compound is pure and does not contain an admixture of the 2-(*p*-tolyl)-1H-indole **9c**.

Preparation of 1-Alkyl-5-indolylpyrrolidin-2-ones 3a-k, 10a,b (General Method). Indole **9a-e** (1 mmol) and about 0.01 ml (~ 0.1 mmol) of boron trifluoride etherate were added with stirring to a solution of the 1-alkyl-5-hydroxypyrrolidin-2-one **4a-d** (1 mmol) in chloroform (8 ml). The reaction mixture was stirred for several hours at room temperature, left overnight, and then passed through a thin silica layer. Solvent was evaporated *in vacuo*, the residue was triturated with ether, and the precipitate was filtered off, washed with ether, and dried.

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* For the isomeric 2-(*p*-tolyl)-1H-indole (**9c**) in this system R_f = 0.75.

1-Benzyl-5-(1H-indol-3-yl)pyrrolidin-2-one (3a). Yield 43%; mp 192-194ºC. IR spectrum, ν, cm^{-1}: 1670 (C=O), 3260 (NH). Found, %: C 78.64; H 6.31; N 9.44. $C_{19}H_{18}N_2O$. Calculated, %: C 78.59; H 6.25; N 9.65.

1-[2-(*p*-Chlorophenyl)ethyl]-5-(1H-indol-3-yl)pyrrolidin-2-one (3b). Yield 25%; mp 245-246ºC. IR spectrum, ν, cm^{-1}: 1665 (C=O); 3170 (NH). Found, %: C 71.34; H 5.51; N 8.21. $C_{20}H_{19}ClN_2O$. Calculated, %: C 70.90; H 5.65; N 8.27.

1-*sec*-Butyl-5-(1H-indol-3-yl)pyrrolidin-2-one (3c). Yield 31%; mp 170-172ºC. IR spectrum, ν, cm^{-1}: 1660 (C=O); 3230 (NH). Found, %: C 74.89; H 8.03; N 10.59. $C_{16}H_{20}N_2O$. Calculated, %: C 74.97; H 7.86; N 10.93.

5-(1H-Indol-3-yl)-1-(1-phenylethyl)pyrrolidin-2-one (3d). Yield 25%; mp 187-189ºC. IR spectrum, ν, cm^{-1}: 1665 (C=O), 3180 (NH). Found, %: C 78.70; H 6.45; N 9.11. $C_{20}H_{20}N_2O$. Calculated, %: C 78.92; H 6.62; N 9.20.

1-Benzyl-5-(2-methyl-1H-indol-3-yl)pyrrolidin-2-one (3e). Yield 33%; mp 228-230ºC. IR spectrum, ν, cm^{-1}: 1670 (C=O), 3200 (NH). Found, %: C 78.56; H 6.72; N 8.94. $C_{20}H_{20}N_2O$. Calculated, %: C 78.92; H 6.62; N 9.20.

5-(2-Methyl-1H-indol-3-yl)-1-[2-(p-chlorophenyl)ethyl]pyrrolidin-2-one (3f). Yield 21%; mp 199-200ºC. IR spectrum, ν, cm^{-1}: 1665 (C=O), 3165 (NH). Found, %: C 71.75; H 6.72; N 7.84. $C_{21}H_{21}ClN_2O$. Calculated, %: C 71.48; H 6.00; N 7.94.

1-*sec*-Butyl-5-(2-methyl-1H-indol-3-yl)pyrrolidin-2-one (3g). Yield 19%; mp 151-152ºC. IR spectrum, ν, cm^{-1}: 1665, 1670 (C=O), 3200 (NH). Found, %: C 75.46; H 8.48; N 10.01. $C_{17}H_{22}N_2O$. Calculated, %: C 75.52; H 8.20; N 10.36.

5-(2-Methyl-1H-indol-3-yl)-1-(1-phenylethyl)pyrrolidin-2-one (3h). Yield 27%; mp 180-182ºC. IR spectrum, ν, cm^{-1}: 1665 (C=O), 3195 (NH). Found, %: C 79.47; H 7.18; N 8.66. $C_{21}H_{22}N_2O$. Calculated, %: C 79.21; H 6.96; N 8.80.

1-Benzyl-5-(2-*p*-tolyl-1H-indol-3-yl)pyrrolidin-2-one (3i). Yield 66%; mp 230-232ºC. IR spectrum, ν, cm^{-1}: 1655 (C=O), 3160 (NH). Found, %: C 82.32; H 6.38; N 7.29. $C_{26}H_{24}N_2O$. Calculated, %: C 82.07; H 6.36; N 7.36.

1-*sec*-Butyl-5-(2-*p*-tolyl-1H-indol-3-yl)pyrrolidin-2-one (3j). Yield 39%; mp 201-202ºC. IR spectrum, ν, cm^{-1}: 1660 (C=O), 3235 (NH). Found, %: C 80.22; H 7.66; N 8.06. $C_{23}H_{26}N_2O$. Calculated, %: C 79.73; H 7.56; N 8.09.

5-(2-*p*-Tolyl-1H-indol-3-yl)-1-(1-phenylethyl)pyrrolidin-2-one (3k). Yield 28%; mp 226-227ºC. IR spectrum, ν, cm^{-1}: 1660 (C=O), 3260 (NH). Mass spectrum (MALDI). Found: *m/z* 362. $C_{27}H_{26}N_2O$. Calculated: M_{calc} = 394. M_{calc}-55 (C_3H_3O) + 23 (Na) = 362.

1-Benzyl-5-(3-methyl-1H-indol-2-yl)pyrrolidin-2-one (10a). Yield 22%; mp 140-142ºC. IR spectrum, ν, cm^{-1}: 1655 (C=O), 3200 (NH). Found, %: C 78.86; H 6.77; N 8.98. $C_{20}H_{20}N_2O$. Calculated, %: C 78.92; H 6.62; N 9.20.

1-Benzyl-5-(3-*p*-tolyl-1H-indol-2-yl)pyrrolidin-2-one (10b). Yield 22%; mp 202-203ºC. IR spectrum, ν, cm^{-1}: 1665 (C=O), 3200 (NH). Found, %: C 81.78; H 6.92; N 7.20. $C_{26}H_{24}N_2O$. Calculated, %: C 82.07; H 6.36; N 7.36.

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