Chemistry of Heterocyclic Compounds, Vol. 36, No. 10, 2000

REACTION OF 1-(R-SULFONYL)INDOLES WITH N,N-DIBENZYL-β-AMINO ALCOHOLS*

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The reaction of 1-(methylsulfonyl)- and 1-(phenylsulfonyl)indoles with N,N-dibenzylamino alcohols leads to the formation of a mixture of isomeric 1-(β-aminoethyl)indoles.

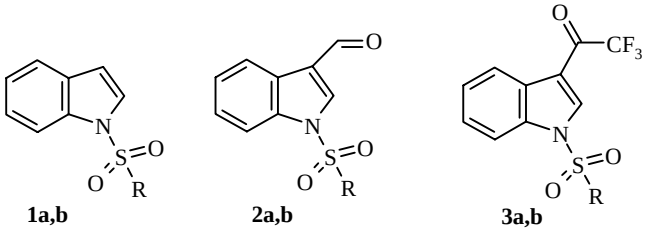
Keywords: aziridinium cation, α-amino acid, β-amino alcohols, 1-(β-aminoethyl)indoles, indoles, 1-sulfonylindoles.

1-(β-Aminoethyl)-substituted indoles are extremely interesting, like most compounds of the indole series, in connection with the search for physiologically active substances. At the present time the biological activity of compounds containing the 1-(β-aminoethyl)indole fragment is well known [1], and this has to a significant degree prompted research into the synthesis of such compounds. There are many synthetic approaches to 1-(β-aminoethyl)indoles, including the direct alkylation of indole by β-bromo(chloro)alkylamines under the conditions of phase transfer catalysis [2-4], alkylation of the previously generated indolyl anion [5], alkylation using the Mannich reaction with acrylamides followed by the Hofmann reaction [6], the synthesis of (β-aminoethyl)indoles by the Gabriel reaction [7], and other versions of the transformation of the side chain in indoles alkylated at position 1. The most promising method for the synthesis of such compounds is based on the reaction of 1-sulfonylindoles with β-amino alcohols in the presence of a base [8, 9]. The key stage of this process is the transfer of the activating sulfonyl group from the indole molecule to the anion of the β-amino alcohol generated with the participation of a base [8].

We studied the reaction of 1-sulfonylindoles with racemic β-amino alcohols in the presence of a base, leading to 1-(β-aminoethyl)indoles. As models we used 1-methyl- and 1-phenylsulfonylindoles **1-3** both with and without additional functional groups.

The reactivity of compounds with methyl and phenyl groups in the sulfonyl fragment was investigated just because of the difference in the reactivity of such derivatives in reaction with the alcoholate of the β-amino alcohol [9].

In spite the variety of approaches to the synthesis of 1-(R-sulfonyl)indoles [10-13], many of them are not universal. We therefore used various methods to find the optimum method for the synthesis of each specific R-sulfonylindole (Table 1).



1a,b **2a,b** **3a,b**

1–3 a R = Ph, **b** R = Me

* Dedicated to the memory of A. N. Kost on the 85th anniversary of his birth.

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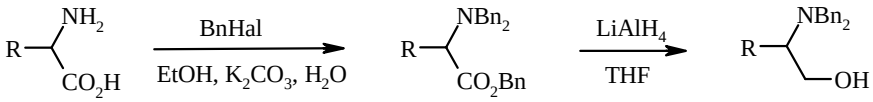
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, pp. 1321-1329, October, 2000. Original article submitted June 22, 2000.

For compounds **2b**, **3b** with low pK_a values method A (the generation of the indolyl anion under the conditions of phase-transfer catalysis) gives small yields of the sulfonylation products. The reduced basicity of indolyl anions containing electron-withdrawing groups at position 3 apparently reduces the probability of association of the indolyl anion with the quaternary ammonium salt, impeding transfer of the associate into the organic phase. In fact, the yields of the respective N-sulfonyl derivatives are fairly high for unsubstituted indole.

In method B (generation of the indolyl anion by means of a strong base, sodium hydride, DMSO, 0°C) the 1-sulfonylindoles were obtained in all cases with high yields. The exception was compound **3b** (42%), where the $COCF_3$ group was removed under the reaction conditions resulting in the formation of a mixture of compounds **1b** and **3b**, which was easily separated by chromatography.

Method C (generation of the indolyl anion with a weak base, sodium hydroxide, methylene chloride, RSO_2Cl) proved the most suitable for 1-sulfonyl-3-formylindoles **2a,b** and 1-sulfonyl-3-trifluoroacetylindoles **3a,b** having pK_a values in the range of 12-13.

The synthesis of N,N-disubstituted β-amino alcohols was realized by the successive alkylation of α-amino acids with benzyl bromide [14] or benzyl chloride [15] and reduction with lithium aluminum hydride [16].

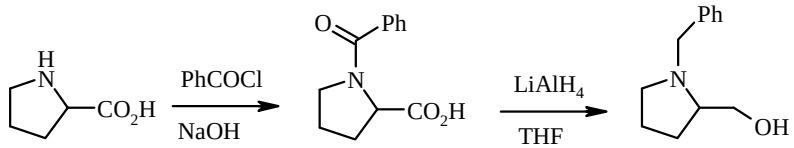


4–6 **7–9** **10–12**

4,7,10 R = Me; **5,8,11** R = $CHMe_2$; **6** R = CH_2CO_2H;
9 R = CH_2CO_2Bn; **12** R = CH_2CH_2OH

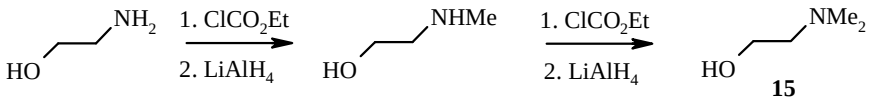
The reaction of amino acids with an excess of benzyl halides [17-19] gives the benzyl esters of N,N-dibenzylamino acids, which can be used in reduction reactions without additional purification [17, 18].

N-Benzylprolinol (**13**) was obtained through N-benzoylproline (**14**) according to the following scheme:



14 **13**

We synthesized N,N-dimethylaminoethanol (**15**) from β-aminoethanol with a total yield of 42% by the successive double reactions of ethoxycarbonylation with chloroethyl formate and reduction of the obtained carbamate with lithium aluminum hydride according to the following scheme:



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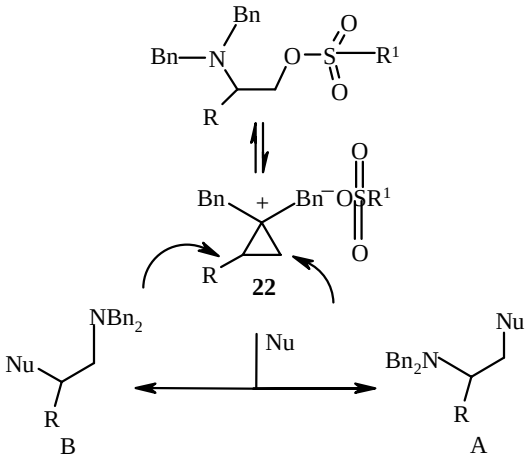
The reaction of 1-methyl(phenyl)sulfonylindoles with N,N-dibenzyl-β-amino alcohols was carried out in two stages. At the first stage the alcoholate of the β-amino alcohol was obtained by mixing its solution in toluene with sodium hydride, and in the second the alcoholate reacted with 1-sulfonylindole at 100-110°C. The 1:1.4:1.3 ratio of the reagents 1-sulfonylindole, β-amino alcohol, and sodium hydride proved optimum for the production of the highest yields (60-70%) for 1-(N,N-dimethylaminoethyl)indoles (**16**) and 1-(N,N-dibenzylaminoethyl)indoles (**17**-**21**).

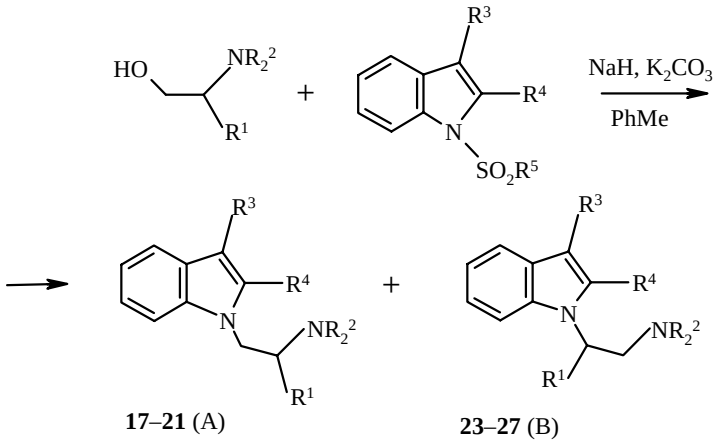
The question of the regioselectivity in the alkylation of the indolyl anion is important, since the formation of the unsymmetrical aziridinium ion (**22**) as intermediate is possible. It can be opened during attack by a nucleophile in two directions, leading to isomeric products of types A and B:

TABLE 1. 1-R-Sulfonylindoles

Compound	Empirical formula	Found, % / Calculated, % C	Found, % / Calculated, % H	mp, bp, °C (published data)	^{1}H NMR spectrum, δ, ppm, (*J*), Hz	Yield, % (method)
1a				78-80 (78-79) [12]		76(A) 93(B) 33(C)
1b				176-179/10 mm Hg 125-126/0.2 mm Hg [24]		82(A) 90(B)
2a	$C_{16}H_{10}F_3NO_3S$	54.42 54.39	3.03 2.85	127-128	6.95 (2H, m, *p*-H_{Ph}); 7.55 (1H, t, *J* = 7.62, 6-H); 7.65 (1H, t, *J* = 7.62, 5-H); 7.95 (3H, m, H_{arom}); 8.35 (1H, s, 2-H); 8.45 (2H, m, H_{arom})	60(A) 20(B) 84(C)
2b	$C_{11}H_8F_3NO_3S$	45.48 45.36	2.44 2.77	142-145	3.35 (3H, s, CH_3); 7.55 (2H, m, H_{arom}); 7.95 (1H, d, *J* = 7.67, 6-H); 8.35 (1H, s, 2-H); 8.95 (1H, d, *J* = 7.54, 4-H)	74(B) 80(C)
3a	$C_{17}H_{18}N_2O_2S$	65.12 64.94	5.89 5.77	86-89	2.20 (6H, s, $N(\underline{CH_3})_2$); 3.52 (2H, s, CH_2); 7.07 (1H, t, *J* = 7.44, 6-H); 7.26 (1H, t, 5-H); 7.32-7.54 (4H, m); 7.58 (1H, d, *J* = 7.44, 7-H); 7.81 (2H, d, *J* = 9, *o*-H_{Ph}); 7.94 (1H, d, *J* = 8.19, 4-H)	32(A) 63(B)
3b	$C_{12}H_{16}N_2O_2S$	57.40 57.12	6.23 6.39	152-154	2.25 (6H, s, $N(\underline{CH_3})_2$); 3.42 (3H, s, CH_3); 3.61 (2H, s, CH_2); 7.48 (2H, m); 7.89 (1H, d, *J* = 8.2, 7-H), 8.28 (1H, s, 2-H); 8.90 (1H, d, *J* = 8.2, 4-H)	20(A) 42(B 67(C)



A similar process was observed during nucleophilic substitution of the chlorine atom in 1-benzyl-2-chloromorpholine by the phenolate ion [9]. Indeed, the ^{1}H NMR spectra of all the obtained 1-(N,N-dibenzyl-β-aminoethyl)indoles contain a double set of signals of unequal intensity, corresponding to a mixture of the two possible isomers (**17**-**21**) (A) and (**23**-**27**) (B) (Table 2).



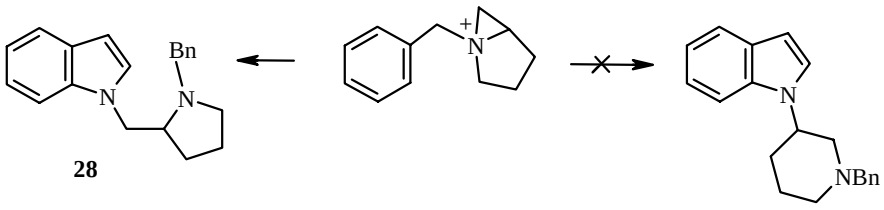
To assign the signals in the spectra to one or the other isomer we used the difference in the chemical shifts of the methylene protons in the 1-β-aminoethyl substituent. For the major isomer the multiplet signals of the two magnetically nonequivalent protons of the CH_2 group appear at 3.87 and 4.15 ppm, while those for the minor isomer appear in the upfield region at 2.70 and 2.92 ppm. In view of this we suggest that the major isomer corresponds to structure B, since the N-alkyl substituents in indole are characterized by a downfield shift of the signals of the α-protons [20, 21]. Thus, in all the investigated cases attack by the indolyl anion on the aziridinium cation is directed mainly at the least sterically hindered methylene group, and this leads to the formation of isomers B.

We confirmed that a mixture of isomers was formed by chromato-mass spectral investigation of compound **18**. Two isomers in a ratio of 1.8:1 were clearly detected on the chromatogram. There is no peak for the molecular ion in the spectrum of the major isomer, and there is a weak peak for the molecular ion in the spectrum of the minor isomer. Further support for our assignment of the major isomer to structure B on the basis of the ^{1}H NMR spectra is the presence of a strong ion peak with *m/z* 224, corresponding to the $[CH(CH_3)NBn_2]^+$ fragment, in the mass spectrum of this compound, whereas the spectrum of the minor isomer A contains a strong peak with *m/z* 210, corresponding to the $[CH_2NBn_2]^+$ ion.

As seen from Table 2, the substituent at the sulfonyl group does not have a significant effect on the yield of the reaction products and the ratio of the isomers. Our attempts at chromatographic separation of the mixture of isomeric indoles were unsuccessful.

TABLE 2. β-Aminoethylindoles

Com-pound	R^1	R^2	R^3	R^4	R^5	^1H and ^{13}C NMR spectrum, δ, ppm, (*J*), Hz	Ratio A : B	Yield, %
16	H	Me	H	H	Ph	2.31 (6H, s, N($\underline{CH_2}$)$_2$); 2.72 (2H, t, *J* = 8.14, $CH_2\underline{CH_2}$); 4.28 (2H, t, *J* = 8.16); 6.51 (1H, d, *J* = 4.56); 7.08–7.26 (3H, m); 7.36 (1H, d, *J* = 9.11); 7.64 (1H, d, *J* = 8.76)		72
17 (A),	Me	Bn	Bn	Bn	Ph	major, 0.97 (3H, d, *J* = 6.59); 3.32 (1H, m, $\underline{CH}$); 3.41, 3.78 (2H each, d each,	1 : 1.7	62
23 (B)	Me	Bn	Bn	Bn	Me	*J* = 13.73, $\underline{CH_2}$Ph); 3.87, 4.14 (2H each, m each, $\underline{CH_2}$CH); 6.51 (1H, d, *J* = 8.31); 6.78-7.58 (14H, m); 7.67 (1H, d, *J* = 7.62); minor, 1.05 (3H, d, *J* = 7.01); 3.37, 3.41 (2H each, m each, $\underline{CH_2}$CH); 4.24 (1H, m, $\underline{CH}$)	1 : 1.8	67
18 (A),	Me	Me	CHO	H	Ph	major, 1.07 (3H, d, *J* = 6.76, $\underline{CH_3}$); 3.28 (1H, m, $\underline{CH}$); 3.47, 3.78 (2H each, d each,	1:3.2	56
24 (B)	Me	Me	CHO	H	Me	*J* = 13.72, $\underline{CH_2}$Ph); 3.83, 4.15 (2H each, m each, $\underline{CH_2}$CH); 6.81 (1H, d, *J* = 8.1); 6.91-7.43 (13 H, m); 8.27 (1H, d, *J* = 7.69); 9.89 (1H, s, C$\underline{H}$O); minor, 1.36 (3H, d, *J* = 7.24); 2.64, 2.91 (2H each, m each, $\underline{CH_2}$CH); 3.65 (2H, d, $\underline{CH_2}$Ph, *J* = 13.2); 4.57 (1H, m); 9.81 (1H, s, C$\underline{H}$O)	1:3.0	64
19 (A),	Me	Bn	$COCF_3$	H	Ph	major, 0.87 (3H, d, *J* = 6.31, $\underline{CH_3}$); 3.24 (1H, m, $\underline{CH}$); 3.48, 3.75 (2H each, d each,	1:2.6	65
25 (B)	Me	Bn	$COCF_3$	H	Me	*J* = 12.87, $\underline{CH_2}$Ph); 3.87, 4.21 (2H each, m each, $\underline{CH_2}$CH); 6.43 (1H, m); 6.81-7.28 (13 H, m); 7.32 (1H, s, 2-H); 7.57 (1H, d, *J* = 7.29); minor, 1.21 (3H, d, *J* = 7.19, $\underline{CH_3}$); 2.68, 2.81 (2H each, m each, $\underline{CH_2}$CH); 3.42 (1H, m, $\underline{CH_2}$Ph); 4.51 (1H, m, $\underline{CH}$)	1:2.5	42
20 (A),	$CHMe_2$	Me	H	H	Ph	major, 0.91, 1.14 (3H each, d each, *J* = 7.56, $\underline{CH_3}$); 2.12 (1H, m, $\underline{CH}$);	1:1.3	55
26 (B)						3.45, 3.58 (2H each, m each, $\underline{CH_2}$CH); 3.76, 3.91 (2H each, d each, *J* = 13.71, $\underline{CH_2}$Ph); 6.d, *J* = 7.72, $\underline{CH_3}$); 2.61 (2H, m, $\underline{CH_2}$CH); 4.21 (1H, m, $\underline{CH}$)		
21 (A),	$CHMe_2$	Bn	H	H	Ph	major, 0.88, 1.12 (3H each, д each, *J* = 7.14, $\underline{CH_3}$); 2.08 (1H, m, $\underline{CH}$);	1:1.6	57
27 (B)	$CHMe_2$	Bn	H	H	Me	3.43, 3.52 (2H each, m each, $\underline{CH_2}$CH); 3.72, 3.89 (2H each, d each, *J* = 12.12, $\underline{CH_2}$Ph); 6.94-7.62 (15H, m); minor, 0.82 (3H, d, *J* = 8.11, $\underline{CH_3}$); 2.52 (2H, m, $\underline{CH_2}$CH); 4.15 (1H, m, $\underline{CH}$)	1:1.5	61



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In the case of N-benzylprolinol **13** together with the usual product of nucleophilic substitution the formation of the isomeric compound formed as a result of ring enlargement could be expected. However, the ^{1}H NMR spectrum of the product from the reaction of 1-sulfonylindole with N-benzylprolinol **13** indicates that only one isomer **28** is formed in this case, and according to the criteria discussed above this corresponds to structure B. The multiplets of the protons of the methylene group at the nitrogen atom of the indole appear at 3.98 and 4.14 ppm.

Thus, the method for the production of 1-(β-aminoethyl)indoles using the reaction of 1-sulfonylindoles and the anion of N,N-dialkyl-β-amino alcohol is restricted to amino alcohols that lead to the formation of a symmetrical aziridinium cation as intermediate in the reaction (as, for example, in the case of N,N-dimethylethanolamine). The result obtained in the reaction with N-benzylprolinol was fairly unexpected. Steric control by the pyrrolidine ring probably directs attack by the indolyl cation at only one of the two possible carbon atoms of the respective aziridinium cation.

EXPERIMENTAL

The NMR spectra were recorded on Varian VXR-400 and Bruker AM-360 instruments for solutions in deuterochloroform. The chromato-mass spectral investigations were carried out on a Finnegan MAT 90 instrument. The melting points were determined in open capillaries; the presented data were not corrected. The reactions and the purity of the obtained compounds were monitored by analytical TLC on Silufol plates in benzene, hexane, benzene–ethyl acetate, and chloroform–methanol.

Indole, 3-formylindole, 2-aminoethanol, benzenesulfonyl chloride, methanesulfonyl chloride, trifluoroacetic anhydride, ethyl chloroformate, racemic α-amino acids, benzyl chloride, and benzoyl chloride from the firm Lancaster were used without previous purification. The benzene, toluene, DMSO, and THF were purified by the usual procedures [22] just before use.

3-Trifluoroacetylindole was obtained by the method in [23].

1-R-sulfonylindoles (1-3a,b) (General Procedures). A. A 50% solution of sodium hydroxide (10 ml) was added to a vigorously stirred solution of indole (10 mmol) and tetrabutylammonium chloride (1 mmol) in benzene (30 ml). After 5 min a solution of sulfonyl chloride (15 mmol) in benzene (15 ml) was added dropwise to the obtained two-phase system over 20 min at 20°C. The solution was stirred for 20 min, while the reaction was monitored by TLC. The organic layer was separated, washed with water (3×20 ml), and dried with sodium sulfate. Benzene was distilled off. The residue was purified by chromatography with a 1:1 mixture of petroleum ether and benzene as eluent. The eluate was evaporated to dryness, and the residue was treated with hexane (15 ml), decanted, and dried.

B. A solution of sodium methylsulfonylmeside was prepared from sodium hydride (12 mmol) and DMSO (10 ml). The solution was cooled on an ice bath, a solution of indole (10 mmol) in absolute ether (50 ml) was added dropwise with stirring, and the mixture was stirred for 1.5 h. The solution was then cooled again to 0°C, and sulfonyl chloride (12 mmol) was added. The mixture was stirred for 30 min, poured into water, and extracted several times with methylene chloride. The combined extracts were washed with a large amount of water and dried with sodium sulfate. The solvent was distilled off, and the residue was recrystallized from methanol.

C. A mixture of indole (10 mmol), methylene chloride (10 ml), and sodium hydroxide (10 mmol) was stirred for 15 min until the solution was completely uniform. Sulfonyl chloride (12 mmol) was then added, and the mixture was again stirred for 25 min; the reaction mixture was extracted several times with benzene, the combined

benzene extracts were dried with sodium sulfate, and the solvent was distilled off. The residue was purified by chromatography with benzene as eluent.

Benzyl Esters of N,N-Dibenzyl-α-amino Acids (7-9) were obtained by the methods in [16, 17].

N,N-Disubstituted β-Amino Alcohols (10-12). These compounds were obtained by the methods in [14, 16, 17]. The data from the ^{1}H NMR spectra agreed with the published data.

1-Benzoylproline (14) was obtained by the method in [25].

1-Benzylprolinol (13). A solution of 1-benzoylproline (11.66 g, 53 mmol) in THF (30 ml) was added dropwise with stirring and cooling to a suspension of lithium aluminum hydride (4.05 g, 0.106 mol) in absolute THF (20 ml). The mixture was then heated to boiling for 4 h and cooled, and water (4 ml), a 15% solution of sodium hydroxide (4 ml), and water (12 ml) were added with stirring. Aluminum oxide that formed was filtered off, and the solution was dried with sodium sulfate and evaporated under reduced pressure. Yield 8.6 g (85%) of a light-yellow oil; bp 169°C (5 mm Hg). ^{1}H NMR spectrum, δ, ppm, *J*, Hz: 1.48-1.86 (4H, m); 2.21 (1H, m, CH_2); 2.63 (1H, m, CH_2); 2.92 (1H, m,CH_2); 3.16 (1H, d, *J* = 12); 3.42 (1H, d, *J* = 13); 3.68 (1H, m); 3.88 (1H, s); 6.81-7.28 (5H, m, H arom.). Found %: C 74.98; H 9.27. $C_{12}H_{17}NO$. Calculated %: C 75.35; H 8.96.

N,N-Dimethyl-2-aminoethanol (15). A. Ethyl chloroformate (32.5 g, 30 ml, 0.3 mol) was added dropwise in five equal portions (every 20-30 min) to a cooled mixture of 2-aminoethanol (15.33 g, 0.25 mol) and sodium hydrocarbonate (40 g) in water (100 ml) with stirring. The solution was then stirred at room temperature for 1 h, extracted with ethyl acetate, and dried with sodium sulfate. The solvent was evaporated at reduced pressure. The residue was used in the next stage without further purification.

B. A solution of urethane obtained at the previous stage in THF (100 ml) was added dropwise with cooling and stirring to a suspension of lithium aluminum hydride (15 g, 0.4 mol) in absolute THF (100 ml). The reaction mixture was left for 24 h, decomposed by the successive addition of water (15 ml), a 15% solution of sodium hydroxide (15 ml), and water (45 ml) with stirring and cooling. The solution obtained after filtration of the aluminum oxide was dried with sodium sulfate and evaporated at reduced pressure, and the oily residue was used without further purification.

C. Ethyl chloroformate (32.5 g, 30 ml, 0.3 mol) we added dropwise in five equal portions (every 20-30 min) to a cooled mixture of N-methyl-2-aminoethanol and sodium hydrocarbonate (40 g) in water (100 ml) with stirring. The solution was stirred at room temperature for 1 h, extracted with ethyl acetate, and dried with sodium sulfate. The solvent was evaporated at reduced pressure, and the residue was used in the next stage without further purification.

D. A solution of N-ethoxycarbonyl-N-methyl-2-aminoethanol obtained in the previous stage in THF (70 ml) was added dropwise with cooling and stirring to a suspension of lithium aluminum hydride (10 g, 0.26 mol) in absolute THF (70 ml). The reaction mixture was left for 24 h, decomposed by the successive addition of water (10 ml), a 15% solution of sodium hydroxide (10 ml), and water (30 ml) with cooling and stirring. The solution obtained after filtration of the aluminum oxide was dried with sodium sulfate and evaporated at reduced pressure at 25°C. The residue was distilled, and the fraction boiling at 130-134°C (133-134°C [26]) was collected. Yield 9.35 g (42% calculated on 2-aminoethanol).

β-Aminoethylindoles (1-21, 23-27). Anhydrous potassium carbonate (2 mmol) and then sodium hydride (1.3 mmol) in the form of a 60% suspension in mineral oil were added to a solution of N,N-dibenzyl-β-amino alcohol (0.1 mmol) in toluene (10 ml). The solution was stirred at room temperature, and after 30 min the sulfonylindole was added (1 mmol). The mixture was boiled for 12 h, diluted with water (40 ml), and extracted with benzene (4×20 ml). The combined benzene extracts were dried with sodium sulfate, the solvent was distilled off, and the residue was separated by chromatography. The ratio of the isomers, determined by ^{1}H NMR and chromato-mass spectrometry, and the yields are given in Table 2.

1-(2-N,N-Dibenzylaminopropyl)-3-formylindole (17) and 1-(1-Methyl-2-N,N-dibenzylaminoethyl)-3-formylindole (23). Mass spectrum, *m/z* (I_{rel}, %): **17** (A): 21 A: 354 (10), 281 (8), 211 (15), 210 (85), 181 (11), 144 (13), 117 (8), 92 (8), 91 (100). **23** (B): 225 (11), 224 (72), 181 (8), 91 (100).

1-[(1-Benzyltetrahydro-2-pyrrolyl)methyl]indole (28). Yield 60%, colorless oil that darkened on storage. ^{1}H NMR spectrum, δ, ppm, *J*, Hz: 1.64 (2H, m); 1.79 (2H, m); 2.24 (1H, m, CH); 3.37 (2H, d, *J* = 12.91, CH_2Ph); 3.74 (2H, d, *J* = 12.88, CH_2Ph); 3.96, 4.14 (2H each, m each, CH_2CH); 6.41 (1H, d, *J* = 4.16); 7.01-7.33

(9H, m); 7.53 (1H, d, J = 7.76). ^{13}C NMR spectrum, δ, ppm: 23.13; 29.52; 50.09; 54.97; 59.99; 63.40; 96.23; 101.26; 109.34; 119.30; 121.05; 121.37; 127.07; 128.22; 128.28; 128.57; 128.89 Found %: C 82.42; H 8.48. $C_{20}H_{24}N_2$. Calculated %: C 82.15; H 8.27.

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