FORMATION OF 3,4-DIHYDRO-α-CARBOLINES FROM 2-AMINOINDOLE

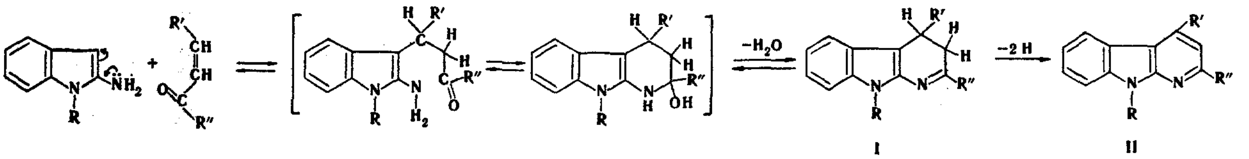
R. S. Sagitullin, A. N. Kost,
T. V. Mel'nikova, and P. A. Sharbatyan

UDC 547.754.83

In the condensation of 2-aminoindole with α,β-unsaturated oxo compounds, in contrast to ordinary aromatic amines and a number of heterocyclic amines, the direction of cyclization is reversed. The general scheme of the reaction includes the reaction of the β position of 2-aminoindole with the activated double bond of the oxo compound via a mechanism of the Michael type and condensation of the carbonyl group of the unsaturated carboline structure, which subsequently undergoes aromatization. The intermediate 3,4-dihydro-α-carbolines were produced and isolated; this made it possible in a number of cases to establish the structures of the final α-carbolines. The structures of the 3,4-dihydro compounds were confirmed by the set of spectral characteristics. Data from the UV, IR, PMR, and mass spectra are presented.

The reaction of aromatic amines with α,β-unsaturated oxo compounds (for example, in the synthesis of quinolines) proceeds as electrophilic attack by the β-carbon atom of the double bond of the unsaturated oxo compound on the amino group and subsequent ring closing [1-3]. In conformity with this, lepidine rather than quinaldine is obtained from aniline and methyl vinyl ketone. The synthesis of naphthyridines from aminopyridines proceeds similarly [4, 5]. However, two isomeric thieno[2,3-b]pyridines were isolated in the reaction of 2-aminothiophenes with methyl vinyl ketone [6], i.e., in this case it can be assumed that attack by the β-carbon atom takes place at both the amino group and the carbon atom (3-C of the thiophene ring) or that the primary process is the formation of a Schiff base, which also leads to an isomeric compound.

It has been previously demonstrated that 1-alkyl-2-aminoindoles react with benzalacetophenone to give 9-alkyl-2,4-diphenyl-α-carbolines [7]. Whereas there was no doubt about the structure of the reaction product in this case, one might have expected the formation of 2-methyl- or 4-methyl-α-carboline in the case of methyl vinyl ketone. It was not possible to unambiguously predict the structure of the reaction product, since it could have been determined either by the direction of attack or by thermodynamic factors. On the basis of the data in [8] and with allowance for the enamine character of 2-aminoindole, one could have assumed that the reaction proceeds as attack by the β-carbon atom of the unsaturated oxo compound on the 3 position of the 2-aminoindole molecule (in contrast to the amines of the benzene and pyridine series), in which case the final product is carboline II:



I, II a R=H, R'=H, R''=C_6H_5; b R=H, R'=C_6H_5, R''=C_6H_5; c R=H, R'=CH_3, R''=C_6H_5; d R=H, R'=C_6H_5; R''=CH_3; e R=H, R'=α-furyl, R''=CH_3; f R=CH_3, R=CH_3, R''= =C_6H_5; II g R=H, R'=CH_3, R''=CH_3; h R=H, R'=H, R''=CH_3; i R=H, R'=CH_3, R''=H; j R=H, R'=C_6H_5, R''=H

M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 945-951, pp. 945-951, July, 1977. Original article submitted December 5, 1976.

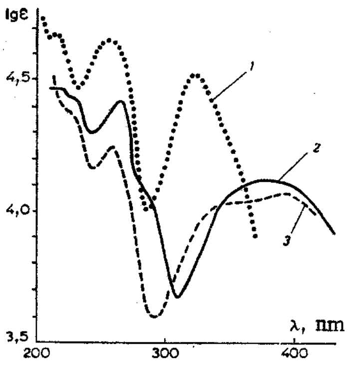


Fig. 1

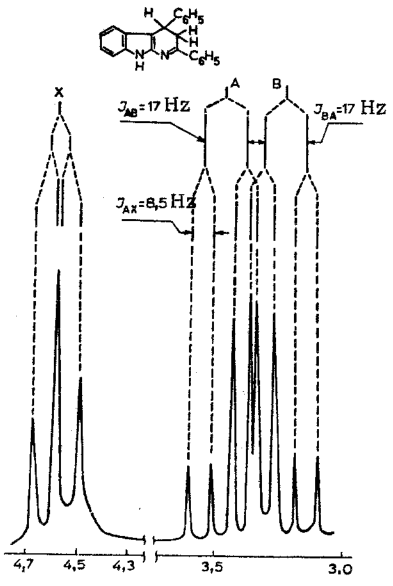


Fig. 2

Fig. 1. UV spectra: 1) 2,4-diphenyl-α-carboline; 2) 1,3-dimethyl-2-(benzylideneimino)indole; 3) 2,4-diphenyl-3,4-dihydro-α-carboline.

Fig. 2. PMR spectrum of 2,4-diphenyl-3,4-dihydro-α-carboline.

We carried out the condensation of 2-aminoindole hydrochloride with various α,β-unsaturated ketones and aldehydes. The reaction was carried out in isopropyl alcohol containing excess triethylamine (the same products were obtained in pyridine and alcoholic alkali, but they were more contaminated). Under these conditions, 2,4-dimethyl-, 4-methyl-, and 2-methyl-α-carbolines (IIg-i), respectively, were obtained from ethylidenacetone, crotonaldehyde, and methyl vinyl ketone, i.e., the carbon atom of the double bond of the unsaturated oxo compound reacts with the β position of the aminoindole. The products are colorless substances with the strong fluorescence in UV light that is characteristic for α-carbolines [9].

The general scheme of the reaction evidently includes reaction of the β position of 2-aminoindole with the activated double bond of the oxo compound via a reaction of the Michael type and condensation of the carbonyl group of the unsaturated oxo compound with the amino group of 2-aminoindole to give 3,4-dihydrocarboline structure I, which subsequently undergoes aromatization.

In a number of cases by carrying out the reaction in a nitrogen atmosphere we isolated intermediate dihydro compounds – yellow crystalline substances Ia-f, which are quite stable in the solid state and do not fluoresce in UV light. Their chromatographic mobilities on aluminum oxide in a benzene–ethyl acetate system (2 : 1) are scarcely higher than the mobility of the corresponding α-carbolines. They are quite rapidly oxidized in solution during chromatography and recrystallization to give the corresponding α-carbolines. Because of the absence of luminescence in UV light, a pyrimidoindole structure has been erroneously assigned to one of these dihydro structures (Ib) in analogy with the product of the reaction of 2-aminoindole with acetylacetone [10].

Alternatively one might have expected the formation of 1,2-, 3,4-, and 1,4-dihydro structures. Just as the structure of 1,2-dihydroquinolines was proved by the similarity between their UV spectra and the spectra of their noncyclic analogs (o-aminostyrenes) [11], the analogy between the UV spectra of the dihydro structures obtained in this research and the Schiff bases (III) from 1,3-dimethyl-2-aminoindole and benzaldehyde constitutes evidence in favor of 3,4-dihydro-α-carbolines (Fig. 1).

The IR spectra of CCl_4 solutions of Ia-e contain characteristic bands of stretching vibrations of NH groups (3480 cm^{-1}), which are not observed in the case of If, in which the indole nitrogen atom is substituted. This fact and the similarity between the UV spectra of indole nitrogen-substituted and unsubstituted dihydro compounds exclude 1,2- and 1,4-dihydro-α- carboline structures. The UV spectra also exclude the possibility of an isatinlike model.

A group of peaks of an ABX system is observed in the PMR spectrum of 2,4-diphenyl-3,4-dihydro-α-carboline (Ib) (in pyridine) for the 4-H and 3-H protons (Fig. 2). The 4-H proton shows up at weaker field (4.54 ppm) than

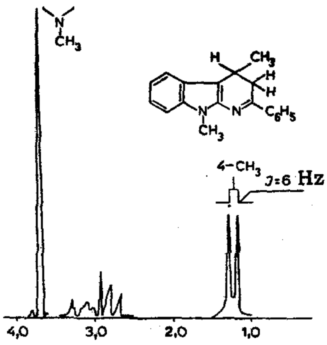


Fig. 3. PMR spectrum of 4,9-dimethyl-2-phenyl-3,4-dihydro-α-carboline.

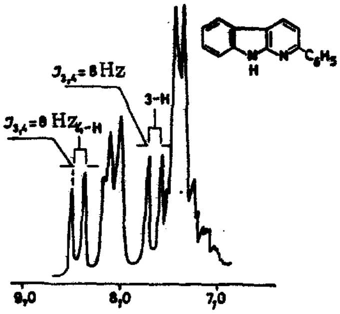


Fig. 4. PRM spectrum of 2-phenyl-α-carboline.

the 3-H and 3'-H signals (3.41 and 3.25 ppm) because of the deshielding effect of the phenyl group attached to 4-C. The following spin–spin coupling constants (SSCC) were obtained: $J_{4,3}^{\text{vic}} = 8.5$, $J_{4,3'}^{\text{vic}} = 9$, and $J_{3,3}^{\text{gem}} = 17$ Hz. The vicinal $J_{4,3}$ and $J_{4,3'}$ constants are close to one another, and this indicates a gauche conformation for the 4-H proton with respect to the 3-H and 3'-H protons. This sort of spectrum confirms a 3,4-dihydro-α-carboline structure rather than a 1,2- or 1,4-dihydro-α-carboline structure.

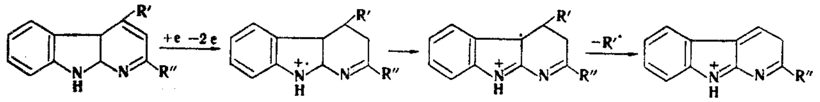
A group of peaks of an ABX system (t, 4-H, 4.28 ppm; o, 2H, 3-H, 2.15-2.96 ppm) is similarly observed in the PMR spectrum of 2-methyl-4-phenyl-3,4-dihydro-α-carboline (Id) for the 4-H and 3-H protons. The singlet at 2.0 ppm corresponds to the CH_3 group in the 2 position of the pyridine ring. When the samples are open to the air, one signal (2.6 ppm) corresponding to the methyl group of 2-methyl-4-phenyl-α-carboline (IId) remains at strong field in the spectrum after a few hours. The latter was isolated and identified by comparison with an authentic sample [12]. In the spectrum of the isomeric 2-phenyl-4-methyl-3,4-dihydro-α-carboline (Ic) the protons of the CH_3 group give a doublet at stronger field (1.32 ppm, J = 6 Hz), and the signals of the 4-H and 3-H protons are visible as a multiplet (3H, 2.42-3.42 ppm). In addition, the spectrum contains a signal at 2.78 ppm, which corresponds to the CH_3 group of the oxidized form, i.e., 2-phenyl-4-methyl-α-carboline (IIc). The latter is formed during preparation of the solution (in the case of access to the air). The α-carbolines (IIc and IId) obtained in this case made it possible to accurately assign the isomeric carbolines previously synthesized [13] from 2-aminoindole and benzoylacetone. An attempt to establish the structure of the α-carboline formed by reaction of 1-methyl-2-aminoindole with benzalacetone by means of the Skraup test [7] gave erroneous results. The conclusions that can be drawn on the basis of the chemical shifts of the protons of the CH_3 groups are also unreliable. In fact, this reaction does not give 4,9-dimethyl-2-phenyl-α-carboline (IIf) but rather the isomeric 2,9-dimethyl-4-phenyl-α-carboline (IIk). To prove this by condensation of ethylideneacetone with 1-methyl-2-aminoindole we obtained 4,9-dimethyl-2-phenyl-3,4-dihydro-α-carboline (If), the structure of which does not raise any doubts. Its PMR spectrum (Fig. 3) contains the signal of the 4-CH_3 group in the form of a doublet (1.32 ppm, J = 6 Hz), a multiplet of the protons attached to 4-C and 3-C (3H, 2.65-3.3), and a singlet of the CH_3 group attached to the indole nitrogen atom (3.7 ppm). Oxidation of If leads to carboline IIf, which is identical to the compound previously obtained from benzoylacetone [7] and differs with respect to its constants from the isomeric α-carboline obtained from benzalacetone, i.e., from carboline IIk.

2-Phenyl-3,4-dihydro-α-carboline (Ia), the PMR spectrum of which (in pyridine) has a multiplet of 4-H and 3-H protons at 2.8-3.2 ppm, was similarly obtained from phenyl vinyl ketone. Aromatization of Ia gives 2-phenyl-α-carboline (IIa), the PMR spectrum of which [in dimethyl sulfoxide (DMSO)] contains two multiplets of aromatic protons at 7.33-7.50 (5H) and 7.93-8.30 ppm (4H), which can be assigned to the protons of the phenyl and benzene rings, respectively. The 3-H and 4-H protons appear in the form of two doublets (7.63 ppm, $J_{3,4} = 8$ Hz, and 8.43 ppm, $J_{3,4} = 8$ Hz) (Fig. 4). The PMR spectrum of a DMSO solution of the isomeric 4-phenyl-α-carboline (IIj), obtained from 2-aminoindole and cinnamaldehyde, contains a multiplet of aromatic protons at 6.98-8.5 ppm, from which a doublet at 7 ppm (J ~ 5 Hz), which corresponds to the proton in the 3 position of the pyridine ring of the α-carboline, can be isolated at strongest field. The $J_{3,4}$ constant for the α-carbolines differs from the $J_{2,3}$ constant (5 Hz), and, according to the data in [14], is 8 Hz. This ratio of the constants, which is characteristic for pyridine, is almost independent of the substituent [15] and is retained on passing to condensed systems containing a pyridine ring [6].

The mass spectra of the α-carbolines at 20-50 eV contain practically only intense molecular ion peaks, and only low-intensity (up to 2%) noncharacteristic peaks of fragment and doubly charged molecular ions appear in addition to them at higher energies (70 eV). Elimination of benzonitrile and acetonitrile, which could make it possible to determine the positions of the substituents, was not observed.

In contrast to this, the principal peak in the mass spectrum of 2-methyl-4-phenyl-3,4-dihydro-α-carboline (Id) is the $[M-Ph]^+$ ion peak at 183.* This process is confirmed by the metastable transition (apparent mass 128.9). The principal characteristic of this process is detachment of CH_3CN from the molecular ion (219, 15%); this indicates unambiguously that the CH_3 group is in the 2 position. Elimination of $H^\cdot$ and H_2 by the molecular ion to give $[M-H]^+$ (46%) and $[M-H_2]^+$ (35%) ions, respectively, is also observed. Both of these ions also eliminate acetonitrile. The fragmentation of the molecular ion of the isomeric 2-phenyl-4-methyl-3,4-dihydro-α-carboline (Ic) differs markedly. The principal peak in this case is the $[M-CH_3]^+$ ion peak at 245; this is confirmed by the metastable transition. Moreover, $[M-PhCN]^+$ ions are not observed. Detachment of $H^\cdot$ and H_2 by the molecular ion is also characteristic. The molecular ion of 4,9-dimethyl-2-phenyl-3,4-dihydro-α-carboline (If) undergoes fragmentation with subsequent splitting out of two methyl radicals to give ions at 259 (the maximum peak) and 244 (6.6%). Both processes are confirmed by the peaks of the corresponding metastable ions. Detachment of $H^\cdot$ and H_2 is also observed. In the case of 2,4-diphenyl-3,4-dihydro-α-carboline (Ib) the principal peak in the mass spectrum is the molecular ion peak, and the $[M-H_2]^+$ (62%) and $[M-Ph]^+$ (68%) peaks are also intense; the processes involved in their formation are confirmed by the peaks of the corresponding metastable ions. The peaks of the ions formed as a result of elimination of benzonitrile by the molecular ions and as a result of the $[(M-H)^+-PhCN]$ process constitute 8 and 5.5%, respectively, of the intensity of the maximum ion. The mass spectrum of 2-methyl-4-(α-furyl)-3,4-dihydro-α-carboline (Ie) contains, in addition to ions that characterize the processes M^+-H (249), M^+-H_2 (248, the maximum peak), M^+-HCO (221), and $[M-H_2]^+-HCO$ (219), a peak of an ion at 209 that is formed as a result of elimination of CH_3CN from the molecular ions. The intensity of the peak of these ions constitutes 20% of the M^+ peak and 8% of the maximum peak. A molecular ion peak and an $[M-H]^+$ ion peak (36%) are observed in the mass spectrum of 2-phenyl-3,4-dihydro-α-carboline (Ia).

Consequently, the principal diagnostic characteristic of the mass spectral fragmentation of dihydrocarbolines is splitting out of the substituent in the 4 position and of benzonitrile or acetonitrile. The formation of very stable ions during the elimination of the substituent in the 4 position, the peak of which is most frequently the maximum peak in the mass spectrum, can be represented as follows:



Thus the set of spectral characteristics of the dihydro structures and their oxidation to the corresponding α-carbolines give an unambiguous answer regarding the structures of α-carbolines formed from unsaturated oxo compounds.

EXPERIMENTAL†

The IR spectra of CCl_4 solutions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of methanol solutions were recorded with a Cary-15 spectrophotometer. The PMR spectra were recorded with T-60 and XL-100 spectrometers. The mass spectra were recorded with an MKh-1303 mass spectrometer with introduction of the samples into the ion source.

2,4-Dimethyl-α-carboline (IIg). A mixture of 0.084 g (0.5 mmole) of 2-aminoindole hydrochloride, 0.052 g (0.62 mmole) of ethylideneacetone, 0.14 ml (1 mmole) of triethylamine, and 1.5 ml of isopropyl alcohol was refluxed in a stream of nitrogen for 30 min, after which it was cooled and treated with water. The resulting precipitate was removed by filtration and washed with alcohol to give 0.06 g (61%) of 2,4-dimethyl-α-carboline with mp 222-224°. UV spectrum: λ_{max} 218, 239, 296, and 322 nm (log ε 4.45, 4.02, 4.13, and 3.60) (mp 223-223.5° [16]).

2-Methyl-α-carboline (IIh). A mixture of 0.084 g (0.5 mmole) of 2-aminoindole hydrochloride, 0.1 g (1.5 mmole) of methyl vinyl ketone, 0.14 ml (1 mmole) of triethylamine, and 1.5 ml of isopropyl alcohol was refluxed in a stream of nitrogen for 1 h, after which the solvent was evaporated, and the residue was dissolved in benzene. The benzene solution was subjected to preparative chromatography on activity II aluminum oxide in a

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* Here and subsequently, the m/e values are presented for the ion peaks.

† E. N. Frenkel', a student, participated in the experiments.

TABLE 1. 3,4-Dihydro-α-carbolines (Ib-f)

Compound I	Isolation meth.	mp, °C	Found, %		Empirical formula	Calc., %		UV spectrum		Yield, %
			C	H		C	H	λ_{max}, nm	lg ε	
b	1	189—191	85,5	5,6	$C_{23}H_{18}N_2$	85,7	5,6	258 390 shoulder 330	4,27 4,07 4,03	94
c	2	180—181	82,5	6,1	$C_{18}H_{16}N_2$	83,0	6,1	241 302 382	4,46 4,36 3,75	85
d	1	210—212	*		$C_{18}H_{16}N_2$			205 240 319	4,5 4,38 3,97	76
e	1	230—231	†		$C_{16}H_{14}N_2$			216 270 325	4,3 4,03 3,97	85
f	2	100—101	82,3	6,8	$C_{19}H_{18}N_2$	83,2	6,6	262 348 396	4,29 4,11 4,07	98

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*Molecular weight 260 (by mass spectrometry).

†Molecular weight 250 (by mass spectrometry).

TABLE 2. α-Carbolines (IIb-f)

Compound II	Oxidation meth.	mp, °C	Found, %		Empirical formula	Calc., %		UV spectrum		Yield, %
			C	H		C	H	λ_{max}, nm	lg ε	
b	1	222—224	86,2	5,0	$C_{23}H_{16}N_2$	86,2	5,0	217 253 321	4,67 4,65 4,53	99
c	1	190—192	83,3	5,5	$C_{18}H_{14}N_2$	83,7	5,4	218 250 312	4,54 4,6 4,58	80
d	2	230—231*	83,4	5,5	$C_{18}H_{14}N_2$	83,7	5,4	220 251 305	4,75 4,38 4,19	40
e	2	242—243	77,5	4,9	$C_{16}H_{12}N_2$	77,4	4,8	214 320 shoulder 237 shoulder 255	4,46 4,06 4,22 4,0	85
f	1	139—140	83,4	6,2	$C_{19}H_{16}N_2$	83,7	5,9	219 250 310	4,48 4,54 4,53	80

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*According to the data in [12], this compound has mp 229-229.5°C.

benzene–ethyl acetate system (3 : 1) to give 0.027 g (30%) of 2-methyl-α-carboline with mp 252° (mp 252-254° [14]). With respect to its IR spectrum and chromatographic mobility, the product was identical to an authentic sample.

4-Methyl-α-carboline (IIi). Similarly, reaction of 0.084 g (0.5 mmole) of 2-aminoindole hydrochloride, 0.1 g (1.5 mmole) of crotonaldehyde, 0.14 ml (1 mmole) of triethylamine, and 1.5 ml of isopropyl alcohol gave (after refluxing for 4 h in a stream of nitrogen) 0.03 g (33%) of 4-methyl-α-carboline with mp 216° (from methanol) (mp 217-219° [14]). The product was identical to an authentic sample with respect to its IR spectrum and chromatographic mobility.

2-Phenyl-α-carboline (IIj). Similarly, the reaction of 0.5 g (3 mmole) of 2-aminoindole hydrochloride, 0.4 g (9 mmole) of cinnamaldehyde, 6 ml of isopropyl alcohol, and 0.84 ml (6 mmole) of triethylamine gave (after refluxing for 3 h) 0.13 g (18%) of 4-phenyl-α-carboline [preparative separation with toluene–ethyl acetate (3 : 2)] with mp 223-225°. UV spectrum: λ_{max} 218, 247, and 300 nm (log ε 4.63, 4.26, and 4.09). Found: C 83.9; H 5.7%. $C_{17}H_{12}N_2$. Calculated: C 83.6; H 5.7%.

2-Phenyl-3,4-dihydro-α-carboline (Ia). A mixture of 0.084 g (0.5 mmole) of 2-aminoindole hydrochloride, 0.079 g (0.6 mmole) of freshly distilled phenyl vinyl ketone, 1.5 ml of isopropyl alcohol, and 0.14 ml (1 mmole) of triethylamine was refluxed in a stream of nitrogen for 30 min, after which the solvent was evaporated rapidly, and the residue was dissolved in benzene. Preparative separation on an activity II aluminum oxide plate [elution with benzene–ethylacetate (17 : 1)] gave 0.066 g (52.5%) of 2-phenyl-3,4-dihydro-α-carboline. Trituration with petroleum ether gave yellow crystals with mp 218-220°. UV spectrum: λ_{max} 218, 258, and 322-327 nm (log ε 4.31, 4.19, and 4.02). Found: C 82.4; H 5.8%. $C_{17}H_{14}N_2$. Calculated: C 82.9; H 5.7%.

Compounds Ib-f, the yields, physical constants, and methods for the isolation of which are presented in Table 1, were similarly obtained.

The following methods of isolation of the products were used: 1) the precipitate that formed after the reaction mixture was cooled was removed rapidly by filtration and washed with isopropyl alcohol; 2) the solvent was evaporated, the residue was dissolved in benzene, the benzene solution was filtered, the solvent was removed from the filtrate by evaporation, and the residue was triturated with petroleum ether.

2-Phenyl-α-carboline (IIa). A mixture of 0.03 g (0.12 mmole) of 2-phenyl-3,4-dihydro-α-carboline and 2 ml of pyridine was heated with a few drops of DMSO for 15 min as air was bubbled into the mixture, after which it was cooled and treated with water. The resulting precipitate was removed by filtration to give 2-phenyl-α-carboline, with mp 242° (from benzene), in quantitative yield. UV spectrum: λ_{max} 218, 252, and 318 nm (log ε 4.73, 4.74, and 4.67). Found: C 83.7; H 5.2%. $C_{17}H_{12}N_2$. Calculated: C 83.6; H 4.9%.

Compounds IIb-f, the yields, physical constants, and methods for the isolation of which are presented in Table 2, were similarly obtained.

The following oxidation methods were used: 1) heating to pyridine with a few drops of DMSO; 2) recrystallization of the 3,4-dihydro compound with access to air.

1,3-Dimethyl-2-(benzylideneimino)indole (III). A 0.4-g (2 mmole) sample of 1,3-dimethyl-2-aminoindole hydrochloride was dissolved by heating in 10 ml of alcohol containing 0.145 g (30% excess) of potassium hydroxide, after which 0.21 g (2 mmole) of benzaldehyde was added to the hot solutions as nitrogen was bubbled through it, and the mixture was allowed to stand for 24 h. The precipitated crystals were separated, washed with alcohol, and dissolved in benzene. The benzene solution was filtered, and the solvent was evaporated from the filtrate to give 0.28 g (56%) of yellow crystals of 1,3-dimethyl-2-(benzylideneimino)indole with mp 85-86° (from methanol). UV spectrum: λ_{max} 267-268 and 372-390 nm (log ε 4.41 and 4.11). Found: C 82.4; H 6.6%. $C_{17}H_{16}N_2$. Calculated: C 82.3; H 6.4%.

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