DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

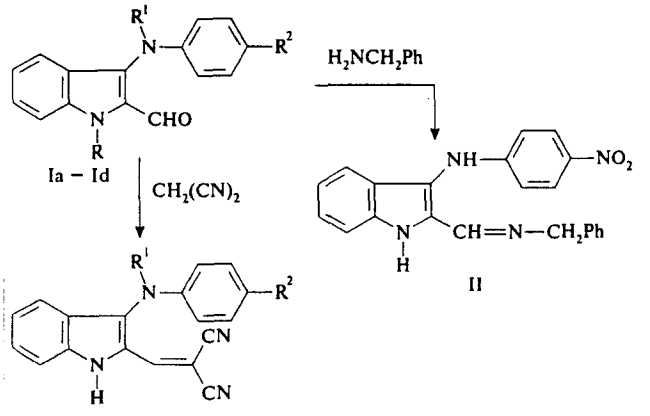
2-FORMYL-3-ARYLAMINOINDOLES IN THE SYNTHESIS OF 1,2- AND 1,4-DIHYDRO-5H-PYRIDO[3,2-b]INDOLE (δ-CARBOLINE) DERIVATIVES

S. Yu. Ryabova,[1] L. M. Alekseeva,[1] and V. G. Granik[1]

Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 30, No. 9, pp. 29 – 34, September, 1996.

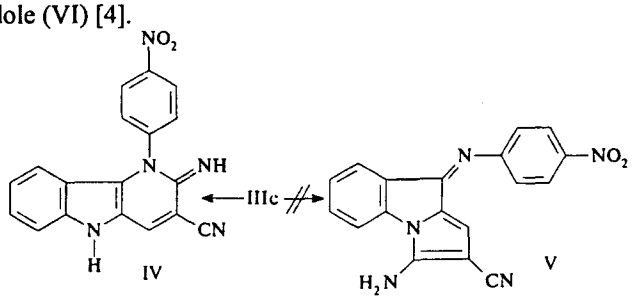
Original article submitted May 16, 1996.

In the previous paper [1] we have reported on the synthesis of 2-formyl-3-arylaminoindole derivatives Ia – Id (see the scheme below) by formylation of the corresponding 3-arylaminoindoles according to the Vilsmeier reaction. Despite the "enamine" character of some compounds (Ic, Id) of this series, the aldehyde group in position 2 is still capable of entering the reaction typical of this moiety. For example, reactions with primary amines lead to the formation of Schiff bases (e.g., compound II), and the interactions with compounds possessing an active methylene group yield 2-vinylindole derivatives. Reactions of compounds Ia – Id with malononitrile led to the formation 2-dicyanovinyl-3-arylaminoindoles IIIa – IIIc. In this work, we used these compounds as a basis for the synthesis of several new indole and condensed indole derivatives.

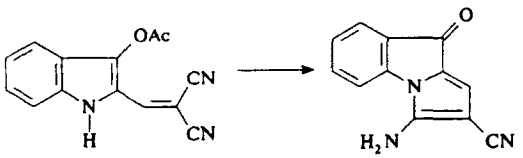


R = H, R^1 = $COCH_2Cl$, R^2 = H;
R = H, R^1 = $COCH_2Cl$, R^2 = Cl;
c: R = H, R^1 = H, R^2 = NO_2;
d: R = Ac, R^1 = H, R^2 = NO_2.

It was established that heating compound IIIc for a short time in acetone in the presence of potassium carbonate leads predominantly to the hydration of vinyl fragment with the formation of initial aldehyde Ic. However, there is an additional process of intramolecular cyclization with the participation of cyano and exocyclic NH groups resulting in a small yield (15%) of 1-(4-nitrophenyl)-2-imino-3-cyano-1,2-dihydro-δ-carboline (IV). The δ-carboline cyclization becomes the dominating process when compound IIIc is heated in a DMF – MeOH (1 : 1) mixture up to the boiling temperature; compound IV is obtained at a 73% yield. In principle, cyclization with the participation of CN group can proceed via the endocyclic NH indole fragment with the formation of the corresponding pyrrolo[1,2-a]indole derivative (V). (We have observed the latter type of closure of the pyrrole cycle in the study of properties of 2-vinyl-3-hydroxyindole[2, 3] derivatives [2, 3]). The δ-carboline (rather than pyrrolo[1,2-a]indole) structure of the product obtained in this work was confirmed by ^{1}H NMR spectroscopic data. In order to unambiguously assign the structure of the synthesized compound, we have compared the ^{1}H NMR spectrum of IV with that of the previously synthesized 2-cyano-3-amino-9-pyrrolo[1,2-a]indole (VI) [4].

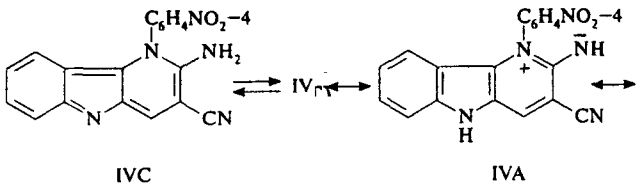


Chemical Drugs Center—All-Russia Research Institute of Pharmaceutical Chemistry, Moscow, Russia.

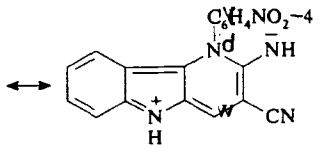


VI

The ^1H NMR spectrum of compound VI in DMSO-d_6 exhibited the following signals (δ, ppm): 7.23 (s, 1H, CH), 7.73 (bs, 2H, NH_2), 7.27 – 7.94 (m, 4H, aromatic protons). The ^1H NMR spectrum of compound IV in DMSO-d_6 contains the following signals (δ, ppm): 6.17 (bs, 2H), 5.91 (d, 1H, H-C^9), 6.74 (t, 1H, H-C^8), 7.23 (t, 1H, H-C^7) and 7.42 (q, 1H, H-C^6),[2] 7.88 and 8.55 (A_2B_2 system, 4H, $C_6H_4NO_2$), 8.25 (s, 1H, H-C^4). A characteristic feature of the latter spectrum is a considerable upfield shift of the H-C^9 proton signal (5.91 ppm) as compared to the signals of other protons of the benzene ring (6.74 – 7.42 ppm) and the analogous proton signals in the spectra of pyrrolo[1,2-a]indole VI (7.27 – 7.94 ppm) and 3-arylamino-2-formylindole Ic (6.95 – 7.59 ppm) [4]. Apparently, this shift of the H-C^9 signal toward higher field strengths can be only due to the effect of anisotropic circular currents of the 4-nitrophenyl substituent in position 1, displaced out of the plane of the molecule as a result of steric constraints (the Dreiding molecular models). Thus, the experimental data confirmed the δ-carboline structure of compound IV.[3] Note that the spectrum of compound IV contains no signal due to the proton at the indole nitrogen atom, which is probably caused by a significant contribution of the resonance IVB structure or a tautomeric equilibrium IV – IVC. This assumption agrees with the presence of a strongly broadened signal at δ = 6.17 ppm, which vanishes on adding CD_3OD.

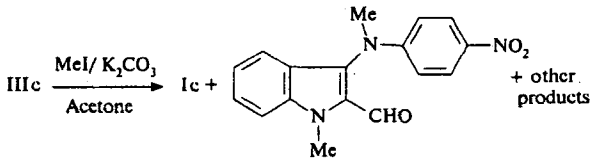


IVC IVA

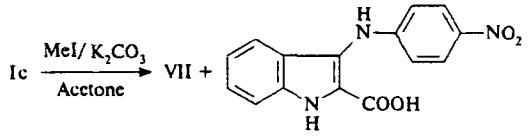


IVB

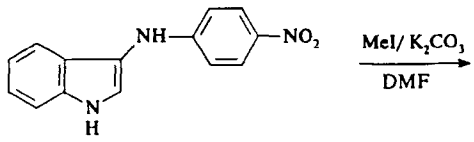
In the next stage of the work, we have studied alkylation of 3-aminoindole IX, initial aldehyde Ic, 2-vinyl derivative IIIc, and 1,2-dihydro-δ-carboline IV from the standpoint of development of a general method for the synthesis of N-alkyl derivatives. This would provide, in turn, a common approach to obtaining compounds substituted at the exocyclic amino group and the nitrogen atom of the indole cycle. In our opinion, the latter compounds can be of interest as a basis for the synthesis of new biologically active substances. According to the mass-spectrometric data, methylation of IIIc by methyl iodide in acetone in the presence of potassium carbonate leads to the formation of a mixture of mono- and dimethyl derivatives (VII), 2-formylindole Ic, and δ-carboline XIV. Using column chromatography methods, we can isolate individual aldehyde Ic and bis-dimethyl derivative VII from this mixture. The latter compound was also obtained by methylation of formylindole Ic under the same conditions. A side product in this reaction was 3-(4-nitrophenylamino)indole-2-carboxylic acid (VIII). It should be also noted that alkylation of the 3-(4-nitrophenylamino)indole (IX) described previously [1, 4] leads at a sufficiently high yield to a mixture of dimethylamino derivative X and a product of its monomethylation (XI) at the exocyclic nitrogen atom.



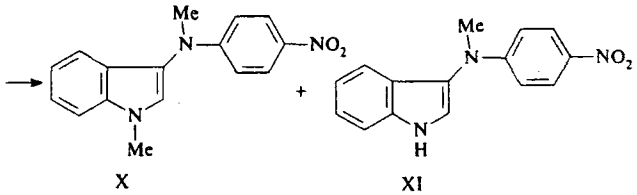
VII



VIII



IX



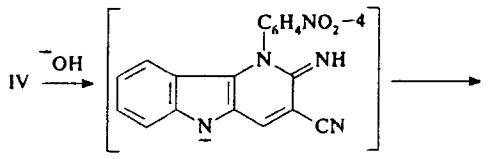
X XI

It is worth noting the interesting and rather unexpected results obtained from the study of properties of tricyclic compound IV. On heating in the presence of an aqueous alkali with dimethyl sulfate in acetone, this compound exhibits methylation with respect to the endo- and exocyclic nitrogen atoms (probably, via the stage of formation of the corresponding anion XII) with the yield of δ-carboline (XIII) from the reaction mixture. In order to confirm the proposed struc-

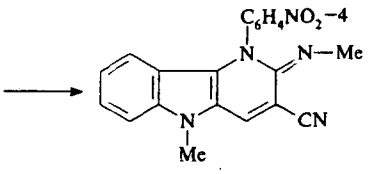
[2] The proton signals have the form of triplets and doublets (J_{ortho} 8 – 9 Hz), with each component additionally split into J_{meta} 3 Hz and J_{para} < 1 Hz.

[3] An additional evidence for the δ-carboline structure of synthesized tricycles is provided by analysis of the ^1H NMR spectrum of the 2,5-dimethyl derivative XIV (see below).

ture of this compound, we have studied the homonuclear Overhauser effect (NOE) in the system.



XII

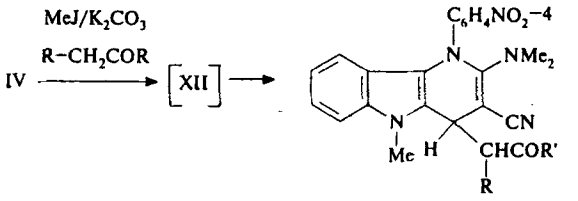


XIII

The ^{1}H NMR spectrum of compound XIII (Table 2) contains signals from two methyl groups: δ = 3.18 ppm (s, 3H, 2-NMe) and 3.81 ppm (s, 3H, 5-NMe). On saturation of the low-field N-methyl group signal, the intensity of the doublet at δ = 7.45 ppm increases by 8%, and that of the singlet at δ = 8.50 increases by 14%. In contrast, saturation of the signal of the other methyl group leads to no increase in the intensity of signals from aromatic protons. At the same time, saturation of the low-field part (δ = 7.70 ppm) of the A_2B_2 system of signals from protons of the 4-nitrophenyl fragment increases by 4% the intensity of a doublet (δ = 5.82 ppm) belonging to the proton at C^9. The above NOE estimates unambiguously confirm the proposed structure of compound XIII (and, hence, the carboline structure of IV), in which the methyl group at N^5 approaches the positions of H-C^4 and H-C^6, while the proton at C^9 is close to protons of the 4-nitrophenyl substituent in position 1. The comparatively small increase in intensity of the doublet due to C_9 protons (δ = 5.82 ppm), observed on saturation of the signal from *ortho* protons of the nitrophenyl fragment, is probably explained by increasing distance to this proton system as a result of displacement of the N^1-aryl substituent out of the molecular plane (as indicated above, this also leads to the upfield shift of the signal from H-C^9).

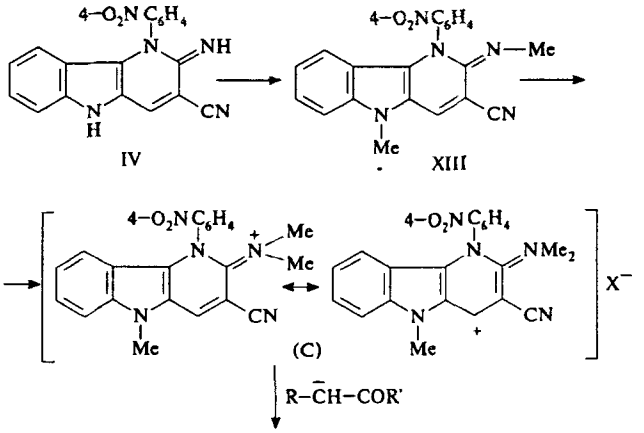
A different reaction of compound IV with methyl iodide is observed in the presence of potassium carbonate, whereby the final result is determined by the methylation medium. For example, prolonged heating of the components in acetone leads to trimethylation of the initial carboline, accompanied by attachment of the acetonyl anion in position 4. As a result, we obtain tricyclic compound XIV, in which the indole cycle is linked to the 1,4-dihydropyridine ring having a new functional substituent in position 4.

The dimethyl derivative XIII is apparently an intermediate involved in the formation of the acetonitrile derivative XIV. This is confirmed by the fact that methylation of compound XIII under the conditions indicated above leads to a 65% yield of compound XIV. A similar pattern is observed if cyclohexanone or methylethylketone are used as solvents instead of acetone: in this case the process leads to 1-(4-nitrophenyl)-2-dimethylamino-3-cyano-4-(2-oxocyclohexyl) (XV) and (3-oxo-2-butyl)-5-methyl-1,4-dihydro-δ-carbolines (XVI), respectively.



XIV: R = H, R' = Me
XV: RR' = $(CH_2)_4$
XVI: R = R' = Me

We may suggest that the initial stage involves exhaustive methylation of 2-imino-1,2-dihydro-δ-carboline IV with the formation of a cation (C), in which the positive charge is delocalized between a dimethylamino group and position 4 of the molecule. It is this position to which the anion of a ketone (present in the reaction mass) is attached in the following stage with the formation of 1,4-dihydro-δ-carbolines (XV – XVI).



XIV, XV, or XVI

The proposed structure of synthesized δ-carbolines was confirmed by spectroscopic data, primarily by the results of NMR measurements (Tables 1 and 2). For example, let us consider the results of spectroscopic characterization of compound XIV. The IR spectrum of this compound, measured as a Nujol mull, showed the absorption bands at 1720 cm^{-1} (nonconjugated ketone) and 2190 cm^{-1} (CN group); mass spectrum (*m/z*): 429 [M^+], 372 [M^+–CH_2COCH_3]; ^{1}H NMR spectrum in DMSO-d_6 (δ, ppm): 3.75 (s, 3H, NMe), 2.90 (bs, 6H, NMe), 2.10 (s, 3H, $CH_2CO\underline{CH_3}$), 2.69 (AB-system, 2H, J_{hem} 17 Hz, J^1_{vic} 9 Hz, J^2_{vic} 5 Hz, $\underline{CH_2}COCH_3$), 4.31 (q, 1H, H-C^4), 7.89 (A_2B_2-system, 4H, $C_6H_4NO_2$), 7.08 – 7.53 (4H, aromatic protons). It is worth noting the fact that the ^{1}H NMR spectrum of this compound, unlike that of compound IV, contains no high-field signal of protons in position C^9.

The 1,4-dihydropyridine cycle is not planar (according to some data, it has a "boat" conformation [5, 6]). Attempts to construct molecular models of the synthesized compounds XIV – XVI with an allowance for these data showed that the 4-nitrophenyl cycle produces no anisotropic effect; as a result, the signals from all protons of the annelated benzene ring are observed in the same region (7.08 – 7.53 ppm).

In concluding, it must be noted that, taking into account the high biological activity of some 1,4-dihydropyridine derivatives [7, 8] and the antitumor and antibacterial activity of substituted δ-carbolines [9, 10], a combination of both fragments in one molecule may be of interest with a view to searching for new biologically active compounds in the δ-carboline series.

EXPERIMENTAL PART

The IR spectra of synthesized compounds were measured on a Perkin-Elmer Model 457 spectrophotometer using samples prepared as Nujol mulls. The mass spectra were obtained on a Varian MAT-112 mass spectrometer with direct introduction of samples into the ion source operated at an ionizing electron energy of 70 eV. The NMR spectra were recorded on a Varian XL-200 instrument (USA) using TMS as the internal standard. The course of reactions was monitored and the samples were identified by thin-layer chromatography on Silufol UV-254 plates eluted in the chloroform – methanol system (10 : 1). Physicochemical properties and yields of all new compounds are given in Table 1, and the parameters of ^{1}H NMR spectra, in Table 2. The data of elemental analyses coincided with the results of analytical calculations.

2-Benzyliminomethyl-3-(4-nitrophenylamino)indole (II). A mixture of 0.3 g (1 mmole) of compound Ic [1], 10 ml 2-propanol, and 0.22 ml (2 mmole) benzylamine was boiled for 4 h. Then 0.22 ml benzylamine was added and the reaction mixture was boiled for another 13 h. Then the mixture was cooled, and the precipitate was separated by filtering and washed with 2-propanol. Yield of compound II, 0.2 g.

2-Cyano-3-[3-(N-chloroacetyl-N-phenylamino)-2-indolyl]acrylic acid nitrile (IIIa). Compound Ia (2.35 g, 7.5 mmole) was dissolved in 80 ml of boiling 2-propanol. Then the solution was cooled to 20°C (which was accompanied by the appearance of turbidity). To this solution was added 0.55 g (8 mmole) of malononitrile and 1.1 ml (8 mmole) of triethylamine, and the mixture was stirred for 1 h at 20°C. The precipitate was separated by filtering and washed with propanol. Yield of compound IIIa, 2.5 g.

2-Cyano-3-[3-[N-chloroacetyl-N-(4-chlorophenyl)amino]-2-indolyl]-acrylic acid nitrile (IIIb). Compound IIIb (with a yield of 0.35 g) was obtained similarly to IIIc, using 0.4 g (1.2 mmole) of compound Ib, 0.1 g (1.5 mmole) of malononitrile, 0.2 g (1.5 mmole) of triethylamine, and 10 ml of 2-propanol.

2-Cyano-3-[3-(4-nitrophenylamino)-2-indolyl]acrylic acid nitrile (IIIc).

Method 1. A mixture of 3.65 g (13 mmole) of compound Ic, 1.6 g (24 mmole) malononitrile, 0.25 ml (2 mmole) triethylamine, and 73 ml of 2-propanol was stirred for 5 h at 20°C and allowed to stand at this temperature for 16 h. The precipitate was separated by filtration and washed with 2-propanol to obtain 3.3 g of compound IIIc.

Method 2. A mixture of 3 g (11 mmole) of compound Ic, 1.5 g (22 mmole) malononitrile, and 60 ml of 2-propanol was boiled for 4 h and allowed to stand for 16 h at 20°C. Then the reaction mixture is treated as in method 1 to obtain 2.7 g of compound IIIc identical with the product obtained by method 1.

Method 3. A suspension of 0.3 g (1 mmole) of compound Id, 0.1 g (1.5 mmole) malononitrile, and 0.13 g (1.5 mmole) fused sodium acetate in 5 ml of acetic acid was stirred for 0.5 h at 20°C, followed by 3 h at 80°C. Then 0.1 g

TABLE 1. Yields and Physicochemical Characteristics of Synthesized Compounds

Compound	Yield, %	M.p., °C (solvent)	Mass spectrum (M^+)	Empirical formula	IR spectrum, ν, cm^{-1}
II	50	167 – 168 (*iso*-PrOH, decomp.)	370	$C_{22}H_{18}N_4O_2$	3400, 3000 – 3150, 1630, 1600
IIIa	92	226 –227 (MeOH – dioxane, decomp.)	360	$C_{20}H_{13}ClN_4O$	3280, 2230, 1680, 1590
IIIb	76	241 (MeCN, decomp.)	395	$C_{20}H_{12}Cl_2N_4O$	3300, 2230, 1680, 1590
IIIc	77 (1), 71 (2), 14.5 (3)	(MeOH – dioxane)	329	$C_{18}H_{11}N_5O_2$	3390, 3290, 2210, 1570
IV	73 (1), 15 (2)	280 (MeOH – DMF, decomp.)	329	$C_{18}H_{11}N_5O_2$	3320, 2200, 1620, 1600, 1580
VI	50	325 (DMF)	209	$C_{12}H_7N_3O_2$	3320, 3200, 2210, 1650, 1610
VII	81 (2)	133 (MeOH)	309	$C_{17}H_{15}N_3O_3$	–
VIII	3.4	255 – 256	297	$C_{15}H_{11}N_3O_4$	1710, 1670, 1610
X	42	100 – 102 (*iso*-PrOH)	281	$C_{16}H_{15}N_3O_2$	1590
XI	30	151 – 153 (*iso*-PrOH)	267 (M_2^+ 281)	$C_{15}H_{13}N_3O_2$	3360, 1590
XIII	58	179 – 180 (MeOH)	357	$C_{20}H_{15}N_5O_2$	2200, 1615, 1580
XIV	53 (1), 65 (2)	198 – 199 (*iso*-PrOH, decomp.)	429	$C_{24}H_{23}N_5O_3$	2180, 1720, 1595
XV	79	236 (*iso*-PrOH, decomp.)	469	$C_{27}H_{27}N_5O_3$	2190, 1720, 1590
XVI	23	231 (*iso*-PrOH, decomp.)	443	$C_{25}H_{25}N_5O_3$	2190, 1720, 1590

of malononitrile was added and the mixture was stirred for another 5 h at 80°C. Then the mixture was cooled, and the precipitate was separated by filtering and washed with AcOH, water, and MeOH to obtain 0.05 g of compound IIIc identical with the product obtained by method 1.

1-(4-Nitrophenyl)-2-imino-3-cyano-1,2-dihydro-5H-pyrido[3,2-b]-indole (IV).

Method 1. A mixture of 3.3 g (10 mmole) of nitrile IIIc, 15 ml MeOH, and 15 ml DMF was heated to boiling. As a result, compound IIIc dissolved and a new precipitate appeared. This suspension was boiled for 5 min and cooled. The precipitate was separated by filtering and washed with MeOH to obtain 2.4 g of compound IV; ^{13}C NMR spectrum in DMSO-d_6 (δ, ppm): 154.9 (C^2), 99.8 (C^3), 133.9 (C^4), 119.8 (C^{4a}), 114.5 (C^{9b}), 139.9 (C^{5a}), 128.8 (C^{9a}), 113.1, 119.9, 126.2, 127.1 (C^6–C^9), 119.9, 131.1 ($C^{2'}$, $C^{3'}$, $C^{5'}$, $C^{6'}$), 148.1, 144.1 ($C^{1'}$, $C^{4'}$), 117.7 (CN).

Method 2. A mixture of 0.33 g (1 mmole) of nitrile IIIc and 0.4 g (3 mmole) of calcined potassium carbonate in 10 ml of acetone was boiled for 15 min. The precipitate was separated by filtering and washed with water to obtain 0.05 g of compound IV identical to the product obtained by method 1. The acetone mother liquor was evaporated, and the residue triturated with diethyl ether to obtain 0.17 g (61%) of compound Ic (m.p., 230°C, decomp.; M^+, 281) with the IR spectrum identical with that of a compound described in [1].

1-Amino-4-oxo-2-cyano-4H-pyrrolo[1,2-a]indole (VI). A mixture of 0.25 g (1 mmole) of 2-cyano-3-(3-acetoxy-2-indolyl)acrylic acid nitrile [11], 10 ml MeOH, and 0.15 ml (1.5 mmole) triethylamine was boiled for 5 h and cooled. The precipitate was separated by filtering and washed with MeOH to obtain 0.1 g of compound VI.

1-Methyl-2-formyl-3-[N-methyl-N-(4-nitrophenyl)amino]indole (VII).

Method 1. To a mixture of 0.33 g (1 mmole) of nitrile IIIc and 0.4 g (3 mmole) of calcined potassium carbonate in 10 ml of acetone was added 2 ml methyl iodide and the mixture was boiled for 20 h, with 2 ml MeI added each 5 h. Then the mixture was cooled and the remainder of potash separated by filtering. The filtrate was evaporated, and the residue dissolved in 20 ml of boiling 2-propanol. The solution was filtered and evaporated, and the residue chromatographed on a silica gel column with chloroform. Sequential 50 – 70 ml fractions were collected and analyzed by TLC. The fractions containing individual products (1 and 5 – 8) were evaporated. Fraction 1 yielded compound VII (m.p., 135°C; M^+, 309), and combined fractions 5 – 8 yielded compound Ic (m.p., 230°C, decomp.) [1].

Method 2. To a mixture of 0.56 g (2 mmole) of compound Ic and 0.83 g (6 mmole) of calcined potassium carbonate in 20 ml of acetone was added 2 ml methyl iodide and the mixture was boiled for 30 h, with 2 ml MeI added each 7 h. Then the remainder of potash was separated by filtering, the filtrate was evaporated, and the residue chromatographed on a silica gel column with chloroform. Three sequential fractions of 250, 40, and 130 ml were collected, and the first of these used to obtain 0.5 g of compound VII having the melting point, IR, and ^1H NMR spectra identical with those of the final product of method 1. The third fraction was re-chromatographed on the silica gel column and the same three fractions were collected. The second of these fractions was evaporated, and the residue triturated with diethyl ether on adding 3 drops of MeOH. The precipitate was separated by filtering to obtain 0.02 g of 2-carboxy-3-(4-nitrophenylamino)indole (VIII).

Methylation of 3-(4-nitrophenylamino)indole. To a mixture of 1.3 g (5 mmole) of 3-(4-nitrophenylamino)indole, 16 ml DMF, and 2.1 g (15 mmole) of calcined potassium carbonate was added 2 ml methyl iodide and the mixture was

TABLE 2. Parameters of ^1H NMR Spectra of Synthesized Compounds

Compound	Chemical shifts, δ, ppm (shape, intensity, proton type)
II	11.75 (bs, 1H, NH), 8.49 (s, 1H, CH), 4.79 (s, 2H, NCH_2Ph), 9.20 (bs, 1H, N'H), 6.74, 8.04 (A_2B_2, 4H, $C_6H_4NO_2$), 6.88 – 7.42 (9H, Ph, H-C^4 – H-C^7)**
IIIa	11.61 (bs, 1H, NH), 8.55 (s, 1H, CH), 4.32 (s, 2H, $COCH_2Cl$), 7.16 – 7.72 (m, 9H, Ph, H-C^4 – H-C^7)*
IIIb	11.67 (bs, 1H, NH), 8.56 (s, 1H, CH), 4.32 (bs, 2H, $COCH_2Cl$), 7.20 – 7.72 (m, 8H, C_6H_4Cl, H-C^4 – C^7)*
IIIc	11.17 (bs, 1H, NH), 8.19 (bs, 1H, CH), 9.68 (bs, 1H, N'H), 6.93, 8.12 (A_2B_2, 4H, $C_6H_4NO_2$), 7.11, 7.26, 7.43, 7.67 (4H, H-C^4 – H-C^7)**
VII	4.08 (s, 3H, NMe), 3.54 (s, 3H, N'Me), 9.89 (s, 1H, CHO), 6.77, 8.05 (A_2B_2, 4H, $C_6H_4NO_2$), 7.15, 7.38, 7.47, 7.83 (4H, H-C^4 – H-C^7)**
VIII	7.67, 8.35 (A_2B_2, 4H, $C_6H_4NO_2$), 7.35, 7.54, 7.83, 8.07 (4H, H-C^4 – H-C^7)**
X	3.83 (s, 3H, NMe), 3.44 (s, 3H, N'Me), 7.52 (s, 1H, H-C^2), 6.73, 8.02 (A_2B_2, 4H, $C_6H_4NO_2$), 6.89 – 7.35 (3H) and 7.54 (1H) (H-C^4 – H-C^7)**
XI	3.45 (s, 3H, NMe), 7.48 (d, 1H, J 2.6 Hz, H-C^2), 6.72, 8.01 (A_2B_2, 4H, $C_6H_4NO_2$), 6.99, 7.15, 7.46 (4H, H-C^4 – H-C^7)**, 11.37 (bs, 1H, NH)
XIII	3.81 (s, 3H, N_5Me), 3.18 (s, 3H, NMe), 8.50 (s, 1H, H-C^4), 7.70, 8.44 (A_2B_2, 4H, $C_6H_4NO_2$), 5.82, 6.75, 7.32, 7.45, (4H, H-C_6 – H-C^9)**
XVI	3.80, 3.99 (2s, 3H, N_5Me), 3.00 (bs, 6H, NMe_2), 3.85, 4.05 (2d, 2H, H-C^4), 1.20 – 2.45 (m, 9H, cyclohexane ring protons), 7.0 – 8.20 (m, 8H, aromatic protons)
XVI	3.79 (s, 3H, NMe), 2.92 (bs, 6H, NMe_2), 2.39 (m, 1H, H-$C^{2'}$), 0.98 (d, 3H, J 7.2 Hz, CH_3-$C^{2'}$), 2.07 (s, 3H, $COCH_3$), 4.00 (d, 1H, J 9.2 Hz, H-C^4), 7.40, 8.28 (A_2B_2, 4H, $C_6H_4NO_2$), 7.14, 7.23, 7.45, 7.48 (4H, H-C^6 – H-C^9)***

* Signals from aromatic protons of the phenyl and 4-substituted phenyl rings overlap with the signals from aromatic protons in positions 4 – 7.

** Signals in the form of doublets and triplets (J_a = 8 – 9 Hz) with each component additionally split into J_m = 3 Hz and J_p = 1 Hz.

*** Compound XVI represents a mixture of diastereomers (1 : 1); the table gives chemical shifts for H-C^4 and endo-N-methyl group of diastereomers.

stirred at 80°C for 60 h, with 2 ml MeI added each 6 h (to a total of 20 ml). Then the mixture was cooled, the remainder of potash separated by filtering and washed with DMF, and the filtrate was evaporated. The residue was triturated with diethyl ether on adding a minimum amount of MeOH and filtered. The filtrate was evaporated, and the residue chromatographed on a silica gel column with chloroform. Five sequential 100 ml fractions were collected, and the third and fifth fractions containing individual products were evaporated. Fraction 1 yielded 0.6 g (42%) of 1-methyl-3-[N-methyl-N-(4-nitrophenyl)amino]indole (X), and fraction 3 yielded 0.4 g of 3-[N-methyl-N-(4-nitrophenyl)amino]indole (XI).

1-(4-Nitrophenyl)-2-methylimino-3-cyano-5-methyl-1,2-dihydro-5H-pyrido[3,2-b]indole (XIII). To a solution of 2 g (50 mmole) of NaOH in 2 ml water was added 100 ml acetone and 3.3 g (10 mmole) of compound IV, and the mixture was heated to boiling on stirring and boiled for 5 min. To this mixture was added 4 ml (40 mmole) of Me_2SO_4 and the boiling was continued on stirring for 6 h, another 4 ml of Me_2SO_4 was added and the mixture was boiled for another 6 h. Then the mixture was cooled, the precipitate separated by filtration, washed with acetone, and dissolved in 500 ml of boiling water. The solution was filtered hot, cooled, and alkalified with 1 N KOH (15 ml). The precipitate was filtered and washed sequentially with water, 2-propanol, and diethyl ether to obtain 2.1 g of compound XIII.

1-(4-Nitrophenyl)-2-dimethylamino-3-cyano-4-(2-oxopropyl)-5-methyl-1,4-dihydro-5H-pyrido-[3,2-b]indole (XIV).

Method 1. To a suspension of 2.15 g (6.5 mmole) of compound IV and 3.6 g (26 mmole) of calcined potassium carbonate in 80 ml of acetone was added 2 ml methyl iodide and the mixture was boiled on stirring for 60 h, with 2 ml MeI added each 7 – 8 h. Then the mixture was cooled and the remainder of potash separated by filtering and washed with acetone. The filtrate was evaporated, and the residue triturated with water, filtered, and washed with water and methanol to obtain 2.1 g of a technical-purity product XIV. The product was purified by boiling with 20 ml MeOH, after which the insoluble precipitate was filtered to obtain 1.5 g of compound XIV.

Method 2. A mixture of 1.07 g (3 mmole) of compound XIII, 0.83 g (6 mmole) calcined potassium carbonate, 70 ml acetone, and 2 ml methyl iodide was boiled on stirring for 45 h, followed by a procedure similar to that in method 1. This yielded 0.85 g of compound XIV, which was identical to the product obtained by method 1.

1-(4-Nitrophenyl)-2-dimethylamino-3-cyano-4-(2-oxocyclohexyl)-5-methyl-1,4-dihydro-5H-pyri-do[3,2-b]indole (XV). Compound XV was obtained similarly to compound XIV, by treating a mixture containing 0.33 g (1 mmole) of compound IV, 0.55 g (4 mmole) potassium carbonate, 10 ml cyclohexanone, and 2 ml methyl iodide at 60°C for 40 h. The filtrate was evaporated, the residue dissolved in chloroform, and the solution filtered and evaporated. The new residue was triturated with water, and the precipitate was filtered and washed with water and methanol to obtain 0.37 g of compound XV.

1-(4-Nitrophenyl)-2-dimethylamino-3-cyano-4-(2-oxo-2-butyl)-5-methyl-1,4-dihydro-5H-pyrido-[3,2-b]indole (XVI). To a suspension of 0.33 g (1 mmole) of compound IV and 0.65 g (4.7 mmole) of calcined potassium carbonate in 20 ml of methylethylketone was added 2 ml methyl iodide and the mixture was boiled on stirring for 41 h, with 2 ml MeI added each 6 h. Then the mixture was cooled and the remainder of potash separated by filtering and washed with diethyl ether, water, and methanol. The residue was mixed with chloroform, and the solution was filtered and evaporated. The residue was triturated with ether, and the precipitate was filtered and washed with ether to obtain 0.1 g of compound XVI.

REFERENCES

1. S. Yu. Ryabova, N. Z. Tugusheva, L. M. Alekseeva, et al., *Khim.-Farm. Zh.*, **30**(7), 42 – 45 (1996).
2. S. Yu. Ryabova, L. M. Alekseeva, and V. G. Granik, *Khim. Geterotsikl. Soedin.*, No. 9, 1191 – 1204 (1991).
3. S. Yu. Ryabova, Yu. I. Trofimkin, L. M. Alekseeva, et al., *Khim.-Farm. Zh.*, **29**(9), 22 – 29 (1995).
4. S. Yu. Ryabova, L. M. Alekseeva, and V. G. Granik, *Mendeleev Commun.*, No. 3, 107 – 109 (1995).
5. V. H. Quast, K. H. Ros, E. Spiegel, et al., *Angew. Chem.*, **89**(3), 202 – 203 (1977).
6. A. F. Mishnev, A. E. Shvets, Ya. Ya. Bleidelis, et al., *Khim. Geterotsikl. Soedin.*, No. 9, 1229 – 1234 (1977).
7. A. Sausins and G. Duburs, *Heterocycles*, **27**(1), 269 – 289 (1988).
8. A. Sausins and G. Duburs, *Khim. Geterotsikl. Soedin.*, No. 4, 435 – 467 (1992).
9. N. N. Suvorov, V. A. Chernov, V. S. Velezheva, et al., *Khim.-Farm. Zh.*, **15**(9), 27 – 34 (1981).
10. S. Minami, S. Yamade, H. Sakurai, et al., Japan Kokai 76, 136, 698; *Chem Abstr.*, 87: 5937 (1977).
11. S. Yu. Ryabova, Yu. I. Trofimkin, L. M. Alekseeva, et al., *Khim. Geterotsikl. Soedin.*, No. 3, 343 – 348 (1991).