SYNTHESIS METHODS AND DRUG MANUFACTURING TECHNOLOGY

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SYNTHESIS AND REACTIVITY OF 2-FORMYLINDOLE AND 5-FORMYLPYRROLE DERIVATIVES

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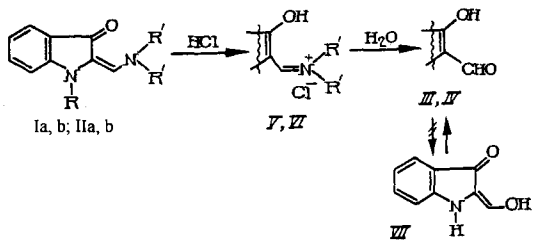
The methylation of 2-formyl-3-hydroxyindole was studied, and the sequence of introduction the methyl groups was traced by ^{1}H NMR spectroscopy. The O-methyl, N-methyl, and N,O-methyl derivatives of 2-formylindole, and also the O-methyl and N-methyl derivatives of 2-methyl-3-ethoxycarbonyl-4-hydroxypyrrole were synthesized. Novel derivatives of indolyl- and pyrrolylacrylic acids were obtained on the basis of some O- and N,O-substituted aldehydes of the indole and pyrrole series.

In the course of studying the properties and reactions of enamines of the 3-indolinone series (I, II) [1], we have found that acid hydrolysis of 2-piperidinomethylene-3-indolinone (IIb) results in 2-formyl-3-hydroxyindole (III). It was shown earlier [1] that N-acetyleneamino ketone Ib also undergoes similar hydrolysis to form the corresponding aldehyde (IV).

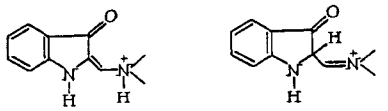


I, IV, VI: R = Ac

II, III, V: R = H; a: R′ = Me; b: R′ + R′ = $(CH_2)_5$.

O-Protonation of enamines Ia, b, IIa, b leading to the formation of immonium salts V, VI is likely to be the first step in the process. However, in the case of the hydrolysis of Ib, we failed to isolate the intermediate salt VI, but we obtained the immonium salt V in 98% yield when we treated IIb with diluted HCl. Probably, the stability of the salt V (in comparison with VI) is attributed to the absence of the electron-acceptor acetyl group. The corresponding bases, Ia and IIb, differ significantly in their basicity, which is more than an order of magniude higher for IIb than for Ib [2]. The structure of the salt V follows from the spectral data.

A comparison of the UV spectra of enamine IIb with that of salt V suggests O-protonation rather than N- or C-protonation [3]. In the case of both N- and especially C-protonation the conjugation chain decreases and a hypsochromic shift of the long-wave length absorption maxima is observed in the UV spectrum.



Actually, the spectrum of enamine IIb, [λ_{max} = 205 (log ε = 4.13), 254 (log ε = 4.03), 290 (log ε = 4.06), 338 (log ε = 4.37), 433 nm (log ε = 4.19)], is very close to that of the salt V, [λ_{max} = 205 (log ε = 4.11), 252 (log ε = 3.98), 289 (log ε = 3.91), 339 (log ε = 4.37), 429 nm (log ε = 4.06)]. This points to the low probability of N- and C-protonation [4]. The same conclusion follows from the analysis of the ^{1}H and ^{13}C NMR spectra. The PMR spectrum of chloride V contains all the signals which are observed in the PMR spectrum of the

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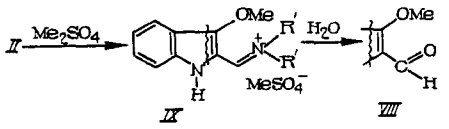
starting enamine IIb [1]. However, the proton signals from the piperidine ring, vinyl, and NH protons which are at 1.81, 1.05, 8.62, and 12.42 ppm, respectively, are shifted downfield. Such a shift of signals confirms the formation of a charged molecule V.

There is no signal at 181 ppm in the ^{13}C NMR spectra of V typical for the carbonyl carbon atom C(3), which occurs in the spectrum of IIb [1]. The signal of the carbon atom C(3) in V is shifted upfield and observed at 158.8 ppm, supporting the existence of the O-protonated form of V.

Brief heating of an aqueous solution of chloride V yielded formylindole III, identical in its properties to the compound obtained previously [5] by the hydrolysis of 2-anilinomethylene-3-indolinone. The authors described the product of hydrolysis as 2-hydroxymethylene-3-indolinone (VII) [5]. However, there is a proton signal at 9.90 ppm that is related to the aldehyde group in the PMR spectra of compound III; this fact confirms the structure of this compound as III, not a tautomeric hydroxymethylene derivative.

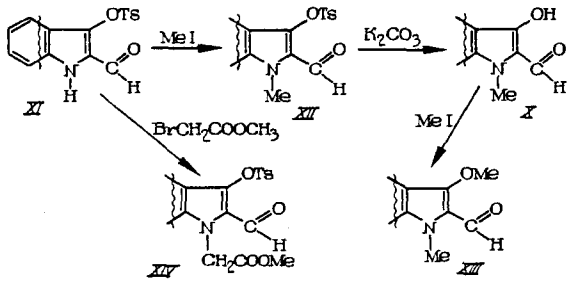
In this study, we investigated the methylation of 2-formyl-3-hydroxyindole III by methyl iodide and followed the sequence of introduction of the methyl groups using NMR spectroscopy. Samples of model compounds (O-methyl-, N-methyl-, and N,O-dimethyl-2-formylindoles) were prepared for the experiments.

2-Formyl-3-methoxyindole (VIII) was obtained by the action of dimethylsulfate on enamino indolinones II in benzene using a procedure similar to that reported in [2]. In this case, methylsulfates IX were formed, hydrolyzed to VIII by heating in water.



We obtained N-methyl-2-formyl-3-hydroxyindole (X) by the methylation of 3-tosyloxy-2-formylindone (XI) [2] with an excess of methyl iodide in dimethylformamide (DMF) in the presence of potassium carbonate, followed by the hydrolysis of the resulting N-methyl-2-formyl-3-tosyloxyindole (XII).

Hydrolysis of XII was carried out with an aqueous saturated solution of potassium carbonate in methanol. The yields of N-methylinidoles X and XII were 84 and 78%, respectively. We should emphasize that the N-methyl derivative X was described earlier in [6]. N-Methyl-2-formyl-3-methoxyindole (XIII) was obtained by methylation of X under conditions similar to those for the synthesis of XII.



We carried out three experiments (Nos. 1, 2, and 3) on the methylation of III with methyl iodide in deuterated DMF in the presence of potassium carbonate. For every experiment, 0.155 mmole of III, 0.65 mmole of K_2CO_3, and 6.2 mmole of MeI were used. The reaction times and temperatures were varied. When an experiment was completed, the excess MeI was removed *in vacuo*, and the reaction mixture was analyzed by ^1H NMR spectroscopy.

To assess the content of methylation products in the reaction mixtures (Nos. 1, 2, and 3), we recorded the ^1H NMR spectrum of a 1 : 2 : 3 mixture of the model compounds XIII, VIII, and X. The values of the chemical shifts of the aldehyde protons and methyl groups are presented in Table 1.

We determined the structure of the methylation products for compound III and their quantitative content (Table 2) based on the comparison of the ^1H NMR spectra of the reaction mixtures 1, 2, and 3 with that of the mixture of VIII, X, and XIII mentioned above.

From Table 2, we see that O-methylation is preferred; and only after the formation of VIII does its methylation at the indole nitrogen atom to the N,O-dimethyl derivative XIII begin. Under these conditions, no formation of N-methyl-2-formylindole with a free oxy group at the 3-position was observed.

Thus, in order to obtain N-alkyl derivatives of 2-formyl-3-hydroxyindole, O-substituted formylindole (for instance XI) must be used as a starting material.

We performed the alkylation of XI with methylbromoacetate and showed that methyl-(2-formyl-3-tosyloxyindol-1-yl)acetate (XIV) was formed under conditions similar to those used in the synthesis of XII, but in the presence of NaI (which is required to increase the activity of the alkylating agent). The reaction time was 35 h, and the yield of XIV – 34%.

TABLE 1. ^1H NMR Spectrum for the Mixture of Compounds VIII, X, and XIII

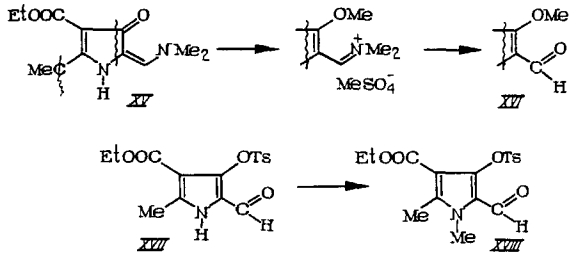
Compound	Chemical shift, δ, ppm			
	CHO	OCH_3	NCH_3	NH
VIII	9.97	4.24	–	11.19
X	10.04	–	3.92	–
XIII	9.99	4.22	3.95	–

TABLE 2. Results of Methylation of 2-Formyl-3-hydroxyindole III

Number of experiment	Temperature, °C	Reaction time, h	Percentage of products formed in the methylation process (from ^1H NMR data)			
			starting material	OMe VIII	NMe X	N,O-diMe XIII
1	20	1	~ 30	~ 65	–	~ 5
2	20	5.5	–	~ 90	–	> 10
3	Boiling	1	–	–	–	~ 100

Next we studied the O- and N-alkylation of 2-methyl-3-ethoxycarbonyl-2-pyrrolin-4-one using the results for the series of indoxyl derivatives given above.

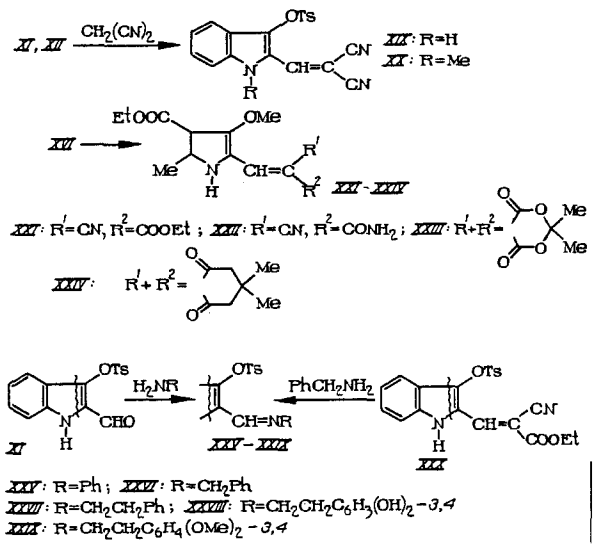
We treated the enamine of 2-pyrrolin-4-one (XV) with dimethylsulfate to convert it to methylsulfate (like the enamines of the indole series II), which underwent hydrolysis to methoxyformylpyrrole (XVI) when heated it in water; and 2-methyl-3-ethoxycarbonyl-4-tozyloxy-5-formylpyrrole (XVII) [2] was converted to the corresponding N-methyl derivative (XVIII) by the reaction of methyl iodide with XVII in DMF in the presence of sodium ethoxide. The N-methyl derivative XVIII was also prepared using an alternative technique, namely, the methylation of XVII with methyl iodide in acetone in the presence of potassium carbonate.



Thus, the results obtained makes possible the selective synthesis of O,N-alkylation products and O,N-dialkylated derivatives of 3-indolinone and 2-pyrroline-4-one, including alkylation with functionally substituted agents. The latter circumstance allows us to synthesize various indole- and pyrrole-containing heterocycles.

In conclusion, we obtained new derivatives of indolyl- and pyrrolylacrylic acids (XIX – XXIV) from some O- and N,O-substituted aldehydes of the indole and pyrrole series.

We showed that tosyloxyaldehyde XI readily formed Schiff's bases (XXV – XXIX) in the reaction with the primary amines.



The treatment of ethyl-α-cyano-β-(3-tosyloxy-2-indolyl)-acrylate (XXX) with benzylamines provided an unexpected result. Heating XXX in benzene with an equivalent amount of benzylamine did not lead to the expected hydrolysis of the tosyloxy group, but elimination of the vinyl residue occurred to give the iminomethyl derivative XXVI.

The structure of compounds XVI, XVIII – XXIV, and XXV – XXIX was confirmed by elemental analysis, IR, and mass-spectra.

EXPERIMENTAL PART

The IR spectra were recorded using Vaseline oil on a Perkin – Elmer-457 spectrometer; mass-spectra were obtained on a Varian MAT-112 instrument by electron impact (70 eV) with direct injection of the sample into the ion source. The temperature of the ionization chamber was 180°C. The ^{1}H NMR spectra were recorded on a Varian XL-200 instrument with TMS as an internal standard. The course of the reaction and the purity of the compounds were monitored by TLC on Silufol UV-254 plates in chloroform (for X, XII, and XIII); in a chloroform – methanol (10 : 1) system (for VIII, IX, XIX, XX, XXV, and XXVI), in a benzene – methanol (9 : 1) system (for XIV, XVI, XVIII, XXI – XXIV, and XXVII – XXIX). Visualization was done using UV light. The values of M^+ and the elemental analysis were consistent with calculated values for the assigned structures. The properties of the compounds synthesized are given in Table 3.

2-Piperidinium-methylene-3-hydroxyindole chloride (Vb). A mixture of 2-piperidinomethylene-3-indolinone (IIb) (1.14 g, 5 mmole) and 30 ml dilute HCl solution (1 : 10) was stirred for 1 h at 20°C. The substance was dissolved, and a new precipitate was formed. The precipitate was filtered off and washed with acetone and ether. The yield was 1.3 g. PMR (DMSO-d_6): 1.81 (6H, m, 3′, 4′, 5′-CH_2; 4.05 (4H, m, 2′, 6′-CH2); 8.62 (1H, s, vinyl proton); 7.07, 7.69, 8.08 (4H, m, 4,5,6,7-CH), 12.42 ppm (1H, br. s, NH, OH). ^{13}C NMR (DMSO-d_6): 22.5 (4′-C); 26.4 (3′, 5′-C); 55.4 (2′, 6′-C), 146.7 (C vinyl); 116.5 (2-CC), 158.8 (3-C); 110.8 (3a-C); 142.9 (7a-C); 113.4 (4-C); 120.0 (5-C); 122.5 (6-C); 131.5 ppm (7-C).

2-Formyl-3-hydroxyindole (III). Chloride Vb (1.3 g, 5 mmole) was dissolved in 40 ml of water with stirring and heating, and boiled for 5 min and then cooled; the precipitate formed was filtered off, washed with water, and crystallized from water (80 ml) with activated carbon. The yield of III was 0.5 g. PMR (DMF-d_7): 6.97, 7.26, 7.78 (4H, m, 4 – 7-CH); 9.90 (1H, 2-C, CHO); 10.85 ppm (1H, br. s, NH).

2-Formyl-3-methoxyindole (VIII). To a suspension of enamino ketone IIa or IIb (10 mmole) in benzene (40 ml), dimethylsulfate was added (2.5 g, 20 mmole) and boiled with stirring for 0.5 h. The suspension was cooled, the precipitate of methylsulfate IX was filtered off, washed with benzene and acetone, then dissolved in water (100 ml), mixed with activated carbon, filtered, and heated to 50 – 80°C (a precipitate was formed from the hot solution). The mixture was cooled, the precipitate was filtered off, washed with water, and dried. The yield of VIII was 0.6 g (from IIa) and 0.9 g (from

IIb). ^{1}H NMR (DMSO-d_6): 4.21 (3H, s, 3-OCH_3); 9.95 (1H, s, 2-CHO); 11.23 ppm (1H, br. s, NH).

1-Methyl-2-formyl-3-tosyloxyindole (XII). A mixture of 2-formyl-3-tosyloxyindole XI (6.65 g, 20 mmole) [2], DMF (30 ml), anhydrous potassium carbonate (5.4 g, 40 mmole), and methyl iodide (10 ml, 160 mmole) was boiled and stirred for 2 h, then cooled. The potassium carbonate was filtered off , the DMF was evaporated, and the residue was crystallized from isopropanol. The yield of XII was 5.8 g. PMR (DMSO-d_6): 2.43 (3H, s, $C_6H_4CH_3$); 3.97 (1H, s, 1-CH_3); 7.12, 7.27, 7.45, 7.62 (4H, m, 4, 5, 6, 7-CH); 7.65 (4H, A_2B_2, OTs); 9.57 ppm (1H, s, 2-CHO).

1-Methyl-2-formyl-3-hydroxyindole (X). 1-Methyl-2-formyl-3-tosyloxyindole XII (6.5 g, 20 mmole) was dissolved in methanol (230 ml) with heating, and an aqueous saturated solution of potassium carbonate (40 ml) was added with stirring, boiled for 5 min, and cooled. The potassium carbonate was filtered off, the methanol was evaporated, the residue was dissolved in water and acidified with 6 N HCl. The precipitate formed was filtered off, washed with water, and dried. The yield of X was 2.7 g. PMR (DMF-d_7): 3.91 (1H, s, 1-CH_3); 7.08 – 8.81 (4H, m, 4, 5, 6, 7-CH); 10.04 ppm (1H, s, 2-CHO).

1-Methyl-2-formyl-3-methoxyindole (XIII). A mixture of 1-methyl-2-formyl-3-hydroxyindole X (0.5 g, 3 mmole), DMF (10 ml), anhydrous potassium carbonate (2 g, 15 mmole), and 5 ml (80 mmole) of methyl iodide was boiled for 45 min, and cooled. The potassium carbonate was filtered off, the DMF was evaporated, the residue was mixed with chloroform, and the potassium carbonate was filtered off once more. The chloroform was evaporated. The residue was cooled (in an ice bath), and the solid formed was filtered off and washed with petroleum ether to yield XIII (0.15 g). PMR (DMSO-d_6): 3.90 (3H, s, 1-CH_3); 4.21 (3H, s, 3-OCH_3); 7.08 – 8.81 (4H, m, 4, 5, 6, 7-CH); 9.98 ppm (1H, s, 2-CHO).

Methyl-2-formyl-3-tosyloxyindolyl-1-acetate (XIV). A mixture of 2-formyl-3-tosyloxyindole XII (2.31 g, 7.33 mmole), methylbromoacetate (8 g, 52.3 mmole), melted NaI (0.33 g), and 15 ml of distilled DMF was heated at 100°C for 35 h. The precipitate was filtered off, the filtrate was evaporated, the residue was dissolved in benzene and transferred to a column with silicagel (40/100 mesh). The column was first eluted with heptane and then with a benzene-heptane mixture (1 : 1). The yield of XIV was 0.96 g.

2-Methyl-3-ethoxycarbonyl-4-methoxy-5-formylpyrrole (XVI). Dimethylsulfate (6.1 g, 48 mmole) was added dropwise to a boiling suspension (8.96 g, 40 mmole) of enamino ketone XV in 200 ml of benzene, boiled for 1.5 h, and cooled; the methylsulfate (12.9 g) was filtered off, then it was dissolved in 30 ml of distilled water, boiled for 5 min, and cooled. The precipitate formed was filtered and dried to yield XVI (5.2 g).

1,2-Dimethyl-3-ethoxycarbonyl-4-tosyloxy-5-formylpyrrole (XVIII). *Procedure A.* A solution of tosyloxyaldehyde XVII (1.75 g, 5 mmole) in 30 ml of anhydrous DMF was added to the residue of solid sodium ethoxide prepared from metallic sodium (0.24 g, 6 mmole) and 30 ml of ethanol, and stirred for 1 h at 20°C. The resulting N-sodium derivative solution was mixed with a solution of methyl iodide (2.56 g,

TABLE 3. Properties of the Synthesized Compounds III, V, VII, X, XII, XIII,XIV, XVI, and XVIII – XXIX

Compound	Yield, %	M. p., °C	Solvent for recrystallization	M^+	Empirical formula	M	IR spectra, ν_{max}, cm^{-1}
III	62	175, decomp	Chloroform	161	$C_9H_7NO_2$	161	3300, 1620, 1600
V	98	250, decomp	Ethanol	228	$C_{14}H_{16}ClN_2O$	264	3120, 2700 – 2300, 1655, 1640
VIII	34[1], 50[2]	130 – 131	–"–	175	$C_{10}H_9NO_2$	175	3300, 1610, 1570
XII	84	124 – 125	Isopropanol	329	$C_{17}H_{15}NO_4S$	329	1660, 1610, 1590
X	78	129, 531	–"–	175	$C_{10}H_9NO_2$	175	3600 – 3280, 2700 – 2300, 1615, 1600, 1590
XIII	26	50	Petroleum ether	189	$C_{11}H_{11}NO_2$	189	1635, 1620, 1600
XIV	34	129 – 131	Isopropanol	387	$C_{19}H_{17}NO_6S$	387	
XVI	68	153 – 154	Benzene – isopropanol, 4 : 1	211	$C_{10}H_{13}NO_4$	211	3220, 1710, 1640, 1560
XVIII	47[3], 65[4]	136 – 137	Benzene – petroleum ether, 10 : 1	365	$C_{17}H_{19}NO_6S$	365	1700, 1670, 1600
XIX	73	193 – 5, decomp	Isopropanol – DMF, 10 : 1,5	363	$C_{19}H_{13}N_3O_3S$	363	3400, 2210, 1660, 1620, 1590
XX	90	188 – 90, decomp	Methanol – DMF, 1 : 1	377	$C_{20}H_{15}N_3O_3S$	377	2210, 1610, 1580
XXI	82	147 – 148	Methanol	306	$C_{15}H_{18}N_2O_5$	306	3300, 2220, 1720 – 1700, 1600
XXII	83	222 – 223	–"–	277	$C_{13}H_{15}N_3O_4$	277	3420, 3260, 2200, 1670, 1620, 1550
XXIII	66	154 – 155	Ethanol	337	$C_{16}H_{19}NO_7$	377	3200, 1710, 1680, 1560
XXIV	64	118 – 119	Benzene – petroleum ether, 10 : 1	333	$C_{18}H_{23}NO_5$	333	3220, 1710, 1670, 1550
XXV	32	150 – 150,5	Isopropanol	390	$C_{22}H_{18}N_2O_3S$	390	
XXVI	62[3], 46[4]	145 – 147	Methanol	404	$C_{23}H_{20}N_2O_3S$	404	3280, 1650
XXVII	63.5	149 – 151	Isopropanol	418	$C_{24}H_{22}N_2O_3S$	418	
XXVIII	65	169 – 171	–"–	451	$C_0H_{22}N_2O_5S$	450	
XXIX	71	140 – 142	–"–	478	$C_{26}H_{26}N_2O_5S$	478	3500 – 3100, 1640, 1590

Note. [1] From compound IIa; [2] from compound IIb; [3] by procedure A; [4] by procedure B. The mass-spectrum of XXIII was recorded on a Finnigan SSQ-710 mass-spectrometer with fast Xe atom ionization (8 keV). The spectrum was obtained in a glycerine matrix on a gold target. The pressure in the ionization chamber was 2×10^{-6} Torr, the incidence angle for primary ions was 20°.

18 mmole) in DMF (15 ml) for 1 h at 20°C, poured into ice water, and kept for 1 h at 20°C. The precipitate was filtered off, washed with water, and dried to yield 0.95 g of XVIII.

Procedure B. To a solution of tosyloxyaldehyde XVII (1.75 g, 5 mmole) in 30 ml of acetone, calcined potassium carbonate (3.5 g, 25 mmole), and methyl iodide (1.13 ml, 15 mmole) was added. The mixture was boiled for 1 h, the hot solution was filtered, the precipitate was washed with 20 ml of boiling methanol. The combined organic phase was evaporated *in vacuo*, and product XVIII (1.2 g) was isolated, which did not show a depression of the melting point when mixed with the sample of XVIII obtained by procedure A.

Nitrile of α-cyano-β-(3-tosyloxy-2-indolyl)-acrylic acid (XIX). To a mixture of 2-formyl-3-tosyloxyindole (XI) (3.15 g, 10 mmole) and malononitrile (1 g, 15 mmole) in 100 ml of benzene, triethylamine (2.2 ml, 15 mmole) was added at 20°C with stirring. In 4 h the precipitate formed was filtered off, washed with benzene and isopropanol to yield 2.65 g of XIX.

Nitrile of α-cyano-β-(1-methyl-3-tosyloxy-2-indolyl)acrylic acid (XX). A mixture of 1-methyl-2-formyl-3-tosyloxyindole XII (3.3 g, 10 mmole), malononitrile (1 g, 15 mmole), benzene (90 ml), and triethylamine (2.2 ml, 15 mmole) was stirred for 15 min at 25 – 30°C. The precipitate formed was filtered off and washed with benzene and ether. Yield of XX was 3.4 g.

Ethyl-α-cyano-β-(2-methyl-3-ethoxycarbonyl-4-methoxypyrrol-2-ylacrylate (XXI). A solution of methoxyaldehyde XVI (0.5 g, 2.4 mmole), ethylcyanoacetate (0.32 g, 2.84 mmole), and triethylamine (0.24 g, 2.4 mmole) in 15 ml of isopropanol was boiled for 2 h and cooled. The precipitate formed was filtered off, washed with isopropanol, and dried to yield 0.7 g of XXI.

Amide of α-cyano-β-(2-methyl-3-ethoxycarbonyl-4-methoxypyrrol-2-yl)acrylic acid (XXII), 1′-(2-methyl-3-ethoxycarbonyl-4-methoxypyrrol-5-ylmethylene)-2′,6′-dioxo-3′,5′-dioxa-4′,4′-dimethylcyclohexane (XXIII), and 1′-(2-methyl-3-ethoxycarbonyl-4-methoxypyrrol-5-ylmethylene)-2′,6′-dioxo-4′,4′-dimethylcyclohexane (XXIV) were obtained from methoxyaldehyde XVI (1 g, 4.73 mmole), cyanoacetamide (5 mmole), Meldrum's acid, and dimedone, respectively, triethylamine (0.67 ml, 4.8 mmole) in 20 ml of isopropanol in a manner similar to that for XXI; the yields were 1.1 g (XXII), 1.06 g (XXIII), and 0.9 g (XXIV).

2-Phenyliminomethyl-3-tosyloxyindole (XXV). A mixture of 2-formyl-3-tosyloxyindole XI (0.5 g, 1.6 mmole), aniline (0.2 g, 2 mmole), and benzene (10 ml) was boiled for 45 min; 0.1 g (1 mmole) of aniline was added and it was boiled for 30 min. After evaporating the benzene, the residue was stirred with ether, the precipitate was filtered off and washed with ether to yield 0.2 g of XXV.

2-Benzyliminomethyl-3-tosyloxyindole (XXVI). *Procedure A.* A mixture of 2-formyl-3-tosyloxyindole XI (0.63 g, 2 mmole), benzylamine (0.24 g, 2.2 mmole), and benzene (10 ml) was boiled for 15 min and cooled; the precipitate was filtered off and washed with benzene and ether to yield 0.5 g of XXVI.

Procedure B. A mixture of ethyl-α-cyano-β-(3-tosyloxyindolyl-2)acrylate XXX [2] (1.2 g, 3 mmole), methanol (15 ml), and benzylamine (0.96 g, 9 mmole) was boiled for 1 h and then cooled. The precipitate formed was filtered off, washed with methanol and ether to yield 0.55 g of XXVI. There is no depression of the melting point for a mixture of the samples obtained according the procedures A and B.

2-(β-Phenylethylaminomethyl)-3-tosyloxyindole (XXVII), 2-[β-(3,4-dihydroxy)phenylethylaminomethyl]-3-tosyloxyindole (XXVIII), and 2-[(-(3,4-dimethoxy)phenylethyliminomethyl]-3-tosyloxyindole (XXIX) were obtained from 2-formyl-3-tosyloxyindole XI (0.6 g, 2 mmole) and the corresponding amine (2.2 mmole) by boiling for 2 – 3 h. After removing the benzene *in vacuo*, the residue was recrystallized from propanol. The yields were 0.5 g (XXVII), 0.56 g (XXVIII), and 0.65 g (XXIX).

Physical and chemical properties of the compounds synthesized are given in Table 3.

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