SYNTHESIS OF CONDENSED INDOLE DERIVATIVES ON THE BASIS OF 1-(2,6-DICHLOROPHENYL)-3-DIMETHYLAMINOMETHYLENEINDOLIN-2-ONE

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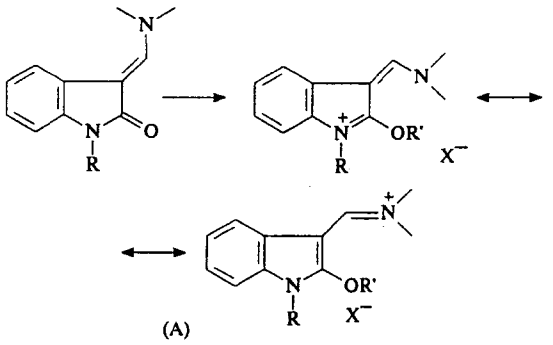
This work is a continuation of the study of synthesis, chemical and physicochemical properties, and heterocyclization pathways of 3-aminomethyleneindolin-2-one derivatives, representing enamines of the hydroxyindole series [1 – 6]. The annelation reactions of these compounds were previously performed on derivatives that were either unsubnstituted or alkyl-substituted at the N^1 atom of the indolinone cycle [3]. In this work, we have used 1-(2,6-dichlorophenyl)-3-dimethylaminomethylene hydroxyindole derivatives as the initial compounds. The choice of dichlorophenyl substituent in position 1 of the indole ring was inspired by the fact that this group, possessing high lipophilic properties, may facilitate penetration of the derivative compounds through biological membranes, thus increasing the biological activity of these compounds. Some data on the pharmacological properties of compounds of this type were published earlier [5]. At the same time, the presence of dichlorophenyl substituent at the N^1 atom in hydroxyindole derivatives may significantly change their properties as compared to those of N^1-unsubstituted or N^1-alkyl-substituted compounds.

The electron-acceptor properties of dichlorophenyl residue may differently affect the reactivity of compounds, depending on the nucleophilic or electrophylic character of the base reagent. At the same time, the large dimensions of this group create considerable steric obstacles to any process in the nearest vicinity of the substituent.

The main purpose of this work was to establish important features of the derivative compounds and study the possibility of their heterocyclization. We have outlined an approach to solving this task, which includes the following stages.

(1) Study of the O-alkylation reaction of 1-(2,6-dichlorophenyl)-3-dimethylaminomethylenehydroxyindole in order to obtain the corresponding alkoxy derivatives. It was expected that the rate of alkylation might decrease as compared to that in N^1-unsubstituted (or N^1-alkyl-substituted) hydroxyindoles because of the combined influence of electronic and steric factors on the electrophilic process.



(2) Study of the reactions of O-alkylated products. The system to be studied is rather unusual, with a cation (A) representing a resonance hybrid in which the main contribution is due to the structure with an aromatic indole cycle (see the data on polarographic reduction of enaminocxarbonyl derivatives of indole and hydroxyindole [7]). This implies that the nucleophilic agents will preferentially attack carbon atoms in the enamine fragments, rather than in the second position of the indole molecule. For N-unsubstituted or N-ethylsubstituted 2-hydroxyindole derivatives [2, 3] the reaction was observed either at the enammonium fragment alone or at both the enammonium fragment and the C^2 carbon atom, depending on the nucleophilic reagent selected (CH acid versus primary amine).

For the reactions between 1-dichlorophenyl derivatives of indolin-2-ones and nucleophilic agents, we must take into account both the electron-acceptor effect and the shielding action of dichlorophenyl substituent. Thus, the presence of this residue may either facilitate reactions at the C^2 atom of the indole cycle or hinder these reactions.

(3) Development of a method, based on the reactions of O-alkylammonium salts, for the synthesis of new derivatives of (2-alkoxy-3-indolyl)acrylic acids, which would serve as the key initial compounds for the heterocyclization reactions.

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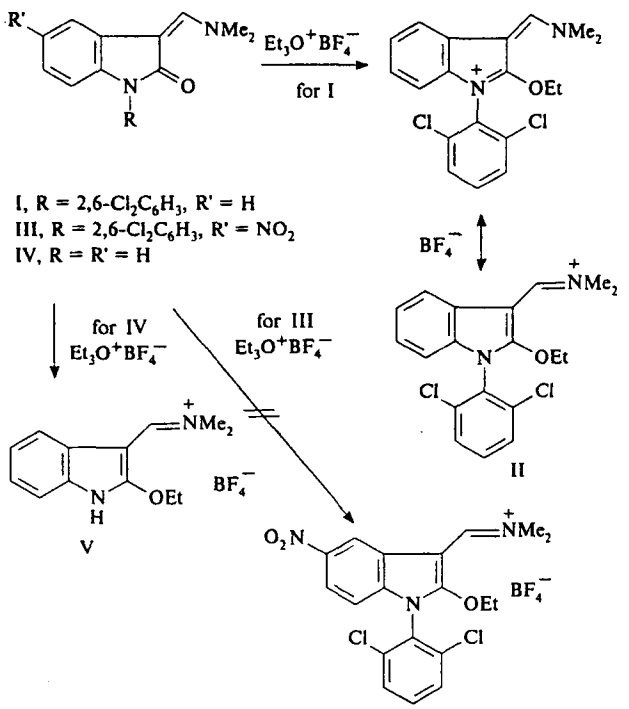
In the first stage of this work, we have studied the process of O-alkylation of the previously synthesized compound [5], 1-(2,6-dichlorophenyl)-3-dimethylaminomethyleneindolin-2- one (I), by triethyloxonium fluoroborate. It was found that the reaction proceeds rather smoothly and yields the fluoroborate salt II under the conditions used previously for the alkylation of N-unsubstituted or N-ethylsubstituted hydroxyindoles [1]. At the same time, despite the extremely high reactivity and, accordingly the low selectivity of $Et_3O^+BF_4^-$ [8], the 5-nitro derivative III was not O-alkylated under these conditions. This is evidence of the electronic factors playing an important role in the alkylation process.

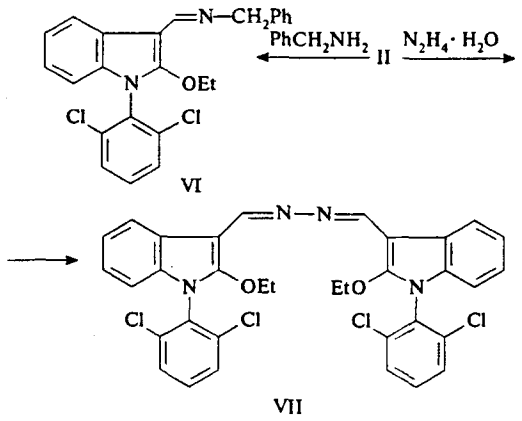
Proceeding from these results, we compared the activities of compound I and 3-dimethylaminomethylenehydroxyindole (IV) with respect to O-alkylation by conducting the process under conditions of their competition. To this end, a mixture of compounds I and IV was alkylated by triethyloxonium fluoroborate with a component ratio of 1 : 1 : 1. The course of the reaction was monitored by ^1H NMR spectroscopy using the signals from vinyl protons at 9.1 and 8.52 ppm, characteristic of the fluoroborates II and V, respectively. It was found that O-alkylation of the N^1-unsubstituted compound IV is predominant, since the ratio of salts II and V was 1 : 17.[2)]



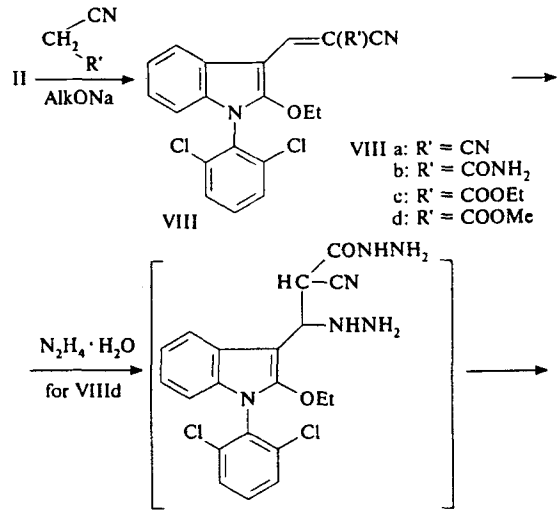
[2] The ^1H NMR spectrum of compound V was reported in [1]; ^1H NMR spectrum of fluoroborate II in DMSO-d_6 (δ, ppm): 1.18 (t, OC_2H_5), 4.31 (q, OC_2H_5), 3.68 (s, NMe_2), 3.77 (s, NMe_2), 6.96 (m, 7-CH), 7.13 (m, 5-CH), 7.40 (m, 6-CH), 7.84 (m, 4-CH), 9.1 (bs, $CH{=}N^+$). The spectrum of compound II also contains signals due to an impurity, probably 1-(2,6-dichlorophenyl)-2-ethoxy-3-formylindole formed by hydrolysis of II (δ, ppm): 1.24 (t, OC_2H_5), 4.60 (q, OC_2H_5), 6.78 (m, 7-CH), 7.18 (m, 5-CH), 7.26 (m, 6-CH), 8.12 (m, 4-CH), 10.2 (s, CHO). On standing, the amount of formyl derivative increases and eventually formylindole becomes the main product.

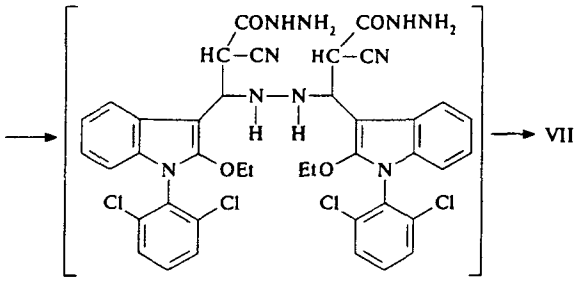
The experimental data showed the important role of substituents at the N^1 atom in enaminoindolin-2-ones. The combined steric and electron-acceptor (in this case, synergstic) effect of the dichlorophenyl residue markedly reduces (as compared to the case of indolinone IV) the probability of the electrophilic attack (including the O-alkylation process) of compound I at the oxygen atom.

Previously [1] we have demonstrated that salt V and its N^1-ethylsubstituted analog react with primary amines both at the α-position of the enammonium fragment and position 2 of the indole cycle. In compound II, however, the similar process proceeds (even in the presence of excess amine) with the formation of only 3-iminomethyl-20alkoxyindole (VI). Interaction of II with hydrazine hydrate, even under rigid conditions, yields azine VII as the only reaction product. In other words, the steric effect of dichlorophenyl residue in our system is apparently the dominating factor that hinders the attack of nucleophilic agents at the C^2 carbon atom.



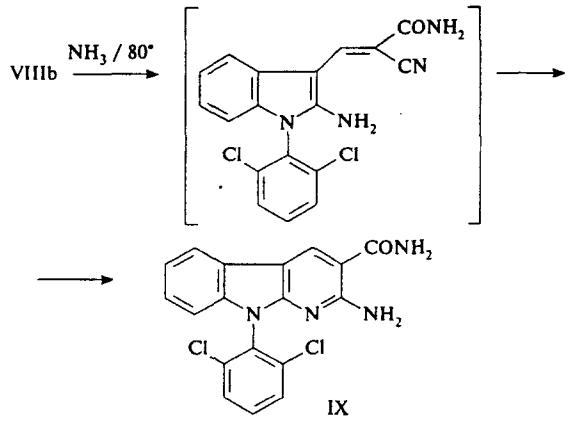
Interaction of fluoroborate II in the presence of sodium alkoholate with compounds containing active methylene groups (malonodinitrile, cyanoacetamide, cyanoacetic asters) occurs (as was also reported in [2]) only at the α-position of the enamine fragment, which leads to the formation of 3-[1-(2, 6-dichlorophenyl)-2-ethoxy-3-indolyl]acrylic acid derivatives (VIIIa – VIIId).





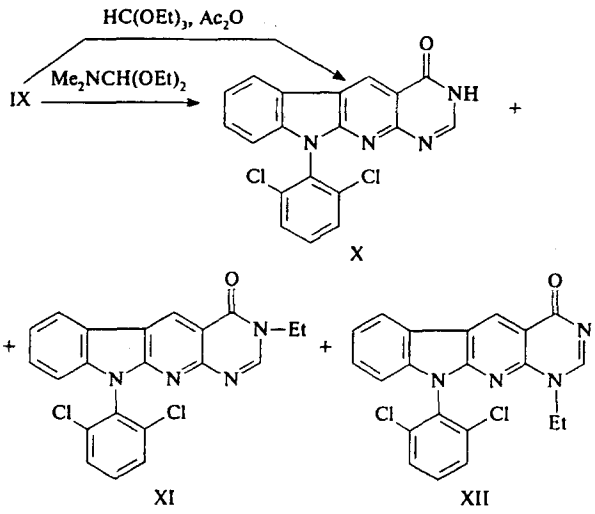
It must be noted that the reaction of compound II with malonodinitrile proceeds at a low yield (and involves the formation of impurities). Therefore, dinitrile VIIIa is more reliably obtained by boiling amide VIIIb with phosphorus chloroxide.

Boiling of acrylic ester VIIId with hydrazine hydrate does not lead to substitution of the 2-ethoxy group; instead, the C=C group is ruptured and azine VII is formed (a possible scheme of this transformation is depicted above). The difference between compounds of the type VIII and their N-ethyl analogs is clearly revealed by interaction with ammonia. For example, ethyl ester of 3-(1-ethyl-2-ethoxy-3-indolyl)-2-cyanoacrylic acid readily reacts with ammonia at room temperature with the formation of the corresponding 2-amino derivative [3]. On the contrary, the reaction of ester VIIId with ammonia under the same conditions yields only carbamide VIIIb. This is evidence of the considerable steric obstacles produced by aryl substituents in position 1, which can be surmounted only by conducting the reaction under more severe conditions, that is, by heating VIIIb in saturated methanol solution of ammonia in an autoclave at 80°C for 22 h. However, in this case the reaction does not terminate on forming the 2-amino derivative, and is followed by a cyclization process with participation of cyano and amino groups, leading to the formation of a new α-carboline derivative (IX) at a 57% yield.



The presence of two functional substituents (NH_2 and $CONH_2$) in the neighboring positions allows us to close another heterocycle, thus forming a new tetracyclic system containing annelated indole and pyrido[2,3-d]pyrimidine fragments.

However, the use of dimethylformamide diacetal as cyclization agent leads to certain complications caused by the well-known ability of this compound to act as the alkylating agent as well. Note that the N-alkylation products are not formed if the acetal is introduced at a nearly equimolar amount, while a large excess of the acetal results in predominant formation of two possible N-ethylation products, XI and XII (by ^1H NMR data, in the 4.5 : 1 ratio).[3]



It was established that a more convenient method consists in closing the pyrimidine cycle with the aid of orthoformic ester. Heating the reagents in acetic anhydride, followed by hydrolysis of partly formed O- and/or N-methyl derivatives, leads to a high yield of compound X.

Thus, our experiments revealed certain features in the chemical behavior of 1-(2,6-dichlorophenyl) hydroxyindole derivatives and led to the first representative of a new heterocyclic system, pyrimido[4,5-b]-α-carbolines.

EXPERIMENTAL PART

The IR spectra of synthesized compounds were measured on a Perkin-Elmer spectrophotometer using samples prepared as vaseline oil suspensions. The mass spectra were obtained on a Varian MAT-112 mass spectrometer with direct injection of samples into the ion source (electron impact ionization energy, 70 eV; ionization chamber temperature, 180°C). The ^1H NMRT spectra were measured on the Varian XL-200 and Unity Plus 400 spectrometers using TMS as the internal standard. The course of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates in the chloroform – methanol 10 : 1 system (spot development in the UV light). The results of elemental analyses agreed with the calculated values.

1-(2,6-Dichlorophenyl)-2-ethoxy-3-dimethylaminomethyleneindolenium fluoroborate (II). A mixture of 42 g (126.1 mmole) of 1-(2,6-dichlorophenyl)-3-dimethylami-

[3] Within the framework of this study, no attempts were made to isolate individual isomers XI and XII. The major isomer in the mixture was assigned to structure XI on the basis of general considerations, proceeding from greater steric accessibility of the NH group in position 3.

nomethylenehydroxyindolin-2-one and 66 g (347.3 mmole) of trioxonium fluoroborate in 380 ml of dry distilled dichloroethane was boiled for 4.5 h and allowed to stand for 16 h at room temperature. Then the solvent was distilled in vacuum and the residue triturated with 100 ml of 2-propanol. The precipitate was separated by filtration and washed with methanol (2 × 50 ml) to obtain 44.86 compound II. Yields and physicochemical properties of synthesized compounds are listed in Table 1.

1-(2,6-Dichlorophenyl)-2-ethoxy-3-benzyliminomethylindole (VI). To a suspension of 0.5 g (1.1 mmole) of compound II in 5 ml of 2-propanol was added 0.36 ml (3.3 ml) of benzylamine, and the mixture was stirred for 23 h at 20°C. Then the mixture was cooled on ice and the precipitate was filtered and washed with 2-propanol to obtain 0.37 g of compound VI.

1-(2,6-Dichlorophenyl)-2-ethoxy-3-formylindole azine (VII).

Method 1. A suspension of 0.5 g (1.2 mmole) of compound VIIId in 10 ml of hydrazine hydrate was boiled for 2.5 h and allowed to stand for 16 h at 20°C. The precipitate was separated by filtration and washed sequentially with petroleum ether, diethyl ether, water, and 2-propanol to obtain 0.32 of compound VII.

Method 2. To a solution of 0.37 g (11 mmole) of hydrazine hydrate in 10 ml of 2-propanol was added 0.5 g (1.1 mmole) of compound II and the mixture was stirred for 2.5 h at 20°C. The precipitate was separated by filtration and washed with 2-propanol. The mother liquor was evaporated and the residue triturated with 2-propanol. The precipitate was separated by filtration and washed with 2-propanol. The two precipitates were combined and washed sequentially with water, 2-propanol, and diethyl ether to obtain 0.17 g od compound VII. The melting temperature of a mixture of this product with that obtained by method 1 showed no evidence of depression.

TABLE 1. Yields and Physicochemical Properties of Synthesized Compounds

Compound	M.p., °C (solvent)	Yield, %	Mass spectrum (M^+)	Empirical formula	IR spectrum, ν_{max}, cm^{-1}	^1H NMR spectrum, DMSO-d_6, δ, ppm
II	167 – 170 (2-propanol)	79	–	$C_{19}H_{19}N_2Cl_2OBF_4$	1680,	
VI	86 – 86.5 (2-propanol)	79	422	$C_{24}H_{20}N_2Cl_2O$	1640	1.15 (t, $OCH_2\underline{CH_3}$), 4.25 (q, $O\underline{CH_2}CH_3$), 4.73 (s, CH_2Ph), 6.73* (7-CH), 7.25 – 7.43 (m, $CH_2\underline{Ph}$), 7.62 – 7.74** (Ar), 7.12* (5-CH), 7.17* (6-CH), 8.27* (4-CH), 8.75 (s, vinyl proton)
VII	245 – 246 (acetonitrile – DMF, 1 : 1.25)	80 (1***) 42.5 (2***)	662	$C_{34}H_{26}N_4Cl_2O_2$	1620, 1550	1.21 (t, $OCH_2\underline{CH_3}$), 4.33 (q, $O\underline{CH_2}CH_3$), 6.79* (7-CH), 7.19* (5-CH), 7.27* (6-CH), 7.69 – 7.83** (Ar), 8.41* (4-CH), 9.02 (s, vinyl proton)
VIIIa	154 —156 (2-propanol)	30(1***), 83(2***)	381	$C_{20}H_{13}N_3Cl_2O$	2210, 1610, 1565	1.16 (t, $OCH_2\underline{CH_3}$), 4.28 (q, $O\underline{CH_2}CH_3$), 6.87* (7-CH), 7.27* (5-CH), 7.34* (6-CH), 7.74 – 7.86** (Ar), 8.06* (4-CH), 8.40 (s, vinyl proton)
VIIIb	197 – 198 (benzene)	88(1***), 21(2***)	399	$C_{20}H_{15}N_3Cl_2O_2$	3380, 3180, 2200, 1705, 1650, 1610	1.16 (t, $OCH_2\underline{CH_3}$), 4.18 (q, $O\underline{CH_2}CH_3$), 6.84* (7-CH), 7.23* (5-CH), 7.29* (6-CH), 7.60 (bs, $CONH_2$), 7.71 – 7.84** (Ar), 8.04* (4-CH), 8.33 (s, vinyl proton)
VIIIc	143 – 145 (heptane – benzene, 2 : 1)	85	428	$C_{22}H_{18}N_2Cl_2O_3$	2200, 1730, 1585	1.18 (t, $COOCH_2\underline{CH_3}$) 1.31 (t, $OCH_2\underline{CH_3}$) 4.21 (q, $COOCH_2\underline{CH_3}$), 4.29 (q, $OCH_2\underline{CH_3}$), 6.88* (7-CH), 7.27* (5-CH), 7.33* (6-CH), 8.21* (4-CH), 8.43 (s, vinyl proton)
VIIId	176 – 177.5 (methanol)	89	414	$C_{21}H_{16}N_2Cl_2O_3$	2200, 1715, 1585	1.18 (t, $OCH_2\underline{CH_3}$), 4.21 (q, $O\underline{CH_2}CH_3$), 3.84 (s, $COO\underline{CH_3}$), 6.88* (7-CH), 7.27* (5-CH), 7.33* (6-CH), 7.74 – 7.86** (Ar), 8.21* (4-CH), 8.43 (s, vinyl proton)
IX	261 – 262 (acetonitrile)	57	370	$C_{18}H_{12}N_4Cl_2O$	3410b, 3300, 3190, 1655, 1630, 1610	6.28 (m, 8-CH), 7.26, 7.66, 7.97 (bs, $CONH_2$, NH_2), 7.64 – 7.78** (Ar), 7.90* (m, 5-CH), 7.26 (m, 6- and 7-CH), 8.81* (4-CH)
X	325 (acetonitrile)	90(1***), 99(2***)	380	$C_{19}H_{10}N_4Cl_2O$	3600 – 3350b	7.09* (9-CH), 7.56 (m, 7- and 8-CH), 7.75 – 7.87** (Ar), 8.51 (6-CH), 8.28* (s, 2-CH), 9.44 (d, 5-CH), 12.5 (bs, NH)

* The multiplicity of proton signals from benzene fragments was as follows: 4-CH and 7-CH, doublets (Jortho 8 Hz) with each component split into (J_{meta} 2 Hz, J_{para} 1 Hz); 5-CH and 6-CH tripets of (J_{ortho}, 8 Hz, J_{meta} 2 Hz) doublets. The character of splitting and spin – spin coupling constants are similar for the 4-CH, 5-CH, 6-CH, 7-CH proton signals in compounds VI, VII, VIIIa – VIIId and 6-CH, 7-CH, 8-CH, 9-CH proton signals in compound X;

** The proton signals from the aryl substituent (2,6-dixhlorophenyl) in the spectra of compounds II, VIIIa – VIIId, VI, VII, IX, and X have the form of an A_2B system observed in the interval 7.74 – 7.89 ppm (A_2) and 7.62 – 7.86 ppm (B);

*** For the method of synthesis, see the experimental part.

Method 3. To a suspension of 0.5 g (1.1 mmole) of compound II in 5 ml of 2-propanol was added 0.11 ml (3.3 mmole) of hydrazine hydrate and the mixture was stirred for 1.5 h at 20°C. The precipitate was separated by filtration, washed with 2-propanol, and dissolved in dichloroethane. The dichloroethane solution was washed with water and dried over magnesium sulfate. Then the solvent was distilled off in vacuum and the residue recrystallized from benzene. The resulting compound VII had IR spectrum identical with those of the products obtained by methods 1 and 2.

3-[1-(2,6-dichlorophenyl)-2-ethoxy-3-indolyl]-2-cyanoacrylic acid nitrile (VIIIa).

Method 1. To a sodium methylate solution, prepared from 0.025 g (1.1 mmole) sodium and 5 ml methanol, was added on stirring 0.073 g (1.1 mmole) of malonodinitrile and 0.5 g (1.1 mmole) of compound II. A precipitate formed in this solution within 2 min and the mixture was stirred for another 2 h at 20°C. Then the precipitate was separated fy filtration and washed with methanol and water to obtain 0.13 g of compound VIIIa.

Method 2. A mixture of 0.5 g (1.2 mmole) of compound VIIIb and 10 ml of phosphorus chloroxide was boiled for 25 min and then evaporated in vacuum. The residue was dissolved in chloroform, washed with saturated potassium carbonate solution and water, and dried over magnesium sulfate. Then chloroform was distilled offf in vacuum, the residue was triturated with heptane, and the precipitate was separated by filtration and washed with heptane to obtain 0.4 g of compound VIIIa. The product was identcal with that obtained by method 1.

3-[1-(2,6-dichlorophenyl)-2-ethoxy-3-indolyl]-2-cyanoacrylic acid amide (VIIIb).

Method 1. Compound VIIIb was obtained similarly to compound VIIIa from 2.33 g (101.3 mmole) sodium, 330 ml methanol, 8.95 g (102.1 mmole) cyanoacetamide, and 44.86 g (99.9 mmole) of compound II. Yield of compound VIIIb, 29.4 g. Together with an additional yield of 5.61 g from mother liquors, the total yield of compound VIIIb was 35.01 g.

Method 2. A mixture of 0.5 g (1.2 mmole) of compound VIIId and 25 ml of a 10% ammonia solution in methanol was stirred for 23 h at 20°C. Then methanol was distilled off, the residue dissolved in 30 ml of boiling benzene, benzene distilled off, and the residue recrystallized from 5 ml of benzene to obtain 0.1 g od compound VIIIb. The melting temperature of a mixture of this product with that obtained by method 1 showed no evidence of depression.

Ethyl ester of 3-[1-(2,6-dichlorophenyl)-2-ethoxy-3-indolyl]-2-cyanoacrylic acid (VIIIc).

Compound VIIIc was obtained similarly to compound VIIIa from 0.025 g (1.1 mmole) sodium, 10 ml absolute ethanol, 0.12 ml (1.1 mmole) cyanoacetic ester, and 0.5 g (1.1 mmole) of compound II. Yield of compound VIIIc, 0.41 g.

Methyl ester of 3-[1-(2,6-dichlorophenyl)-2-ethoxy-3-indolyl]-2-cyanoacrylic acid (VIIId).

Compound VIIId was obtained similarly to compound VIIIa from 0.025 g (1.1 mmole) sodium, 6 ml methanol, 0.12 ml (1.1 mmole) cyanoacetic ester, and 0.5 g (1.1 mmole) of compound II. Yield of compound VIIId, 0.41 g.

2-Amino-3-carbamoyl-9-(2,6-dichlorophenyl)-α-carboline (IX). A mixture of 10 g (24.9 mmole) of compound VIIIb and 140 ml of ammonia-saturated methanol was treated for 23 h at 80°C in an autoclave. Then the mixture was cooled and the residue was separated by filtration and washed with methanol to obtain 5.28 g of compound IX.

10-(2,6-dichlorophenyl)-4,10-dihydro-3H-pyrimido[4,5-b]-α-carbolin-4-one (X).

Method 1. A mixture of 0.1 g (0.269 mmole) of compound IX, 0.35 ml ethyl ester of orthoformic acid, and 0.71 ml acetic anhydride was boiled for 2 h and cooled to 20°C. The precipitate was separated by filtration, washed sequentially with a mixture of 0.1 ml ethyl ester of orthoformic acid and 0.2 ml acetic anhydride and then with water, and boiled in 1 ml of water for 1 h. The precipitate was separated by filtration and washed with water to obtain 0.05 g of compound X. In addition, 0.04 g of the product can be obtained from the mother liquor. Total yield of compound X, 0.09 g.

Method 2. A mixture of 0.1 g (0.269 mmole) of compound IX, 0.051 ml (0.296 mmole) of dimethylformamide diacetal, and 1 ml of dimethylformamide (E-Merck, water < 0.2%) was boiled for 2.5 h and allowed to stand for 48 h at – 6°C. The precipitate was separated by filtration and washed with dimethylformamide and acetonitrile to obtain 0.05 g of compound X. The mother liquor was evaporated in vacuum, the residue triturated with heptane, and the precipitate filtered and washed with heptane to obtain additionally 0.05 g of the product. Total yield of compound X, 0.1 g.

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