Alkylation of pyrimido[5´,4´:5,6]pyrido[3,2-*b*]indol-4-one derivatives

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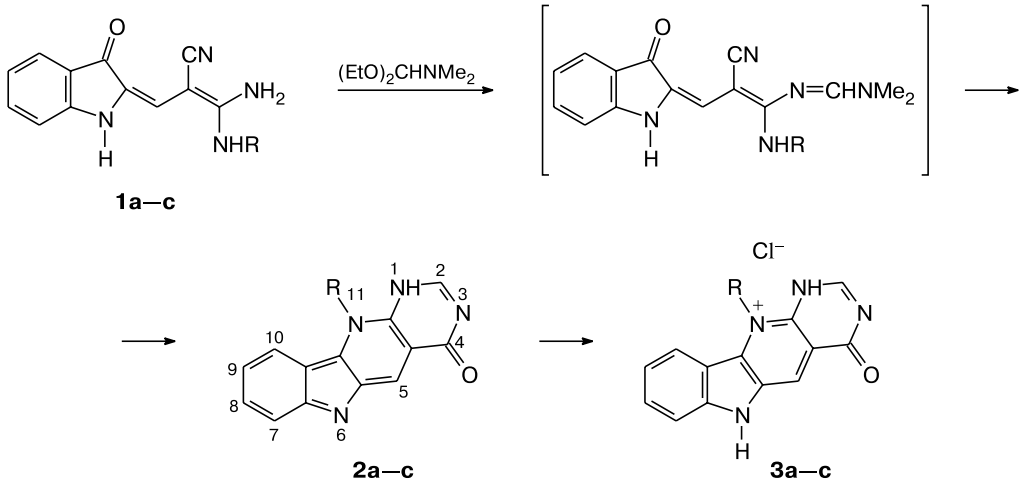
Alkylation of 11-benzyl-3,11-dihydro-4*H*-pyrimido[5´,4´:5,6]pyrido[3,2-*b*]indol-4-one with methyl iodide and methyl bromoacetate in DMF gave 3-alkylpyrimidopyridoindolones as the corresponding salts. The reaction in acetone in the presence of K_2CO_3 yielded 3,6-disubstitution products. Alkylation with DMF dimethyl acetal gave a mixture of the 3- and 6-alkylpyrimidopyridoindol-4-one bases. The structure of 4-oxo-4,6-dihydro-3*H*-pyrimido-[5´,4´:5,6]pyrido[3,2-*b*]indol-11-ium chloride (**3b**) was proved by X-ray diffraction analysis.

Key words: 11-benzyl-3,11-dihydro-4*H*-pyrimido[5´,4´:5,6]pyrido[3,2-*b*]indol-4-one, X-ray diffraction analysis, alkylation, 3- and 6-monoalkylpyrimido[5´,4´:5,6]pyrido[3,2-*b*]indol-4-ones, 3,6-dialkylpyrimido[5´,4´:5,6]pyrido[3,2-*b*]indol-4-ones, halides.

Earlier,[1] it was found that 2-(2-cyanoprop-2-enylidene)-indolin-3-ones **1a—c** containing primary and secondary amino groups in position 3 of the side chain react with DMF diethyl acetal to give derivatives **2a—c** of the novel heterocyclic system 4,11-dihydro-1*H*-pyrimido[5´,4´:5,6]-pyrido[3,2-*b*]indol-4-one (Scheme 1). The mechanism of formation of these compounds was proposed and confirmed.

The structure of compounds **2a—c** combines the δ-carboline and pyrimidine fragments. Some δ-carboline derivatives were found to exhibit antitumor, antimuscarine, antibacterial, and antiviral activities.[2—5] And such known

Scheme 1



R = Me (**a**), CH_2Ph (**b**), C_6H_4—OMe-4 (**c**)

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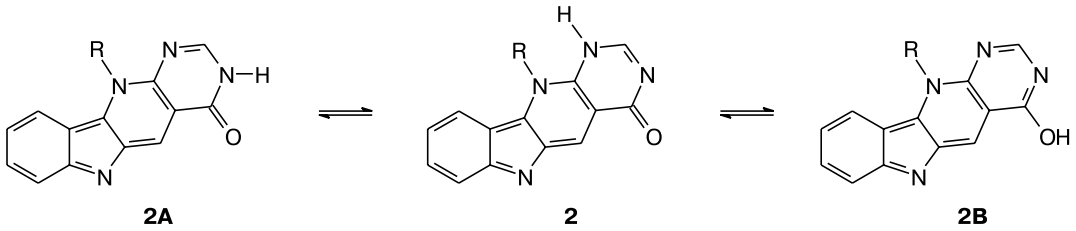


2A **2** **2B**

drugs as, *e.g.*, the bactericides sulfamonomethoxine and sulfadimethoxine, the soporific cyclobarbital, and the antitumor drug 6-mercaptopurine are pyrimidine derivatives.[6] Combination of the above fragments in a molecule can impart new biological properties to the resulting compounds. That is why here we studied alkylation of 11-benzyl-4,11-dihydro-1*H*-pyrimido[5′,4′:5,6]pyrido-[3,2-*b*]indol-4-one (**2b**) with various alkylating agents to obtain more soluble (than **2a**—**c**) compounds for pharmacological investigations.

Note that the structure of 4,11-dihydro-1*H*-pyrimidopyridoindol-4-one was assigned to compounds **2** from their IR spectra,[1] although they can exist as tautomers **2A** and **2B**.

Compounds **2** were not examined by X-ray diffraction analysis because their crystals were unsuitable for this technique.

Hydrochloride **2b** • HCl (**3b**), which is substantially more soluble than free base **2b**, was recrystallized from methanol and its single crystals were studied by X-ray diffraction analysis.

The independent part of the unit cell comprises two molecules **3b** (Fig. 1) and 3.5 molecules of water. Selected geometrical parameters of hydrochloride **3b** are given in Table 1. The poor quality of its crystals precluded location of the H atoms of solvate water molecules; however, the short distances (less than the sum of the van der Waals radii) between the atoms (Table 2) point to the water atoms probably involved in hydrogen bonding.

According to X-ray diffraction data, chloride **3b** exists in the crystal as a quasi-centrosymmetric dimer. The planes of its tetracycles are above each other (if viewed along the normal) and are spaced at, on average, 3.35 Å.

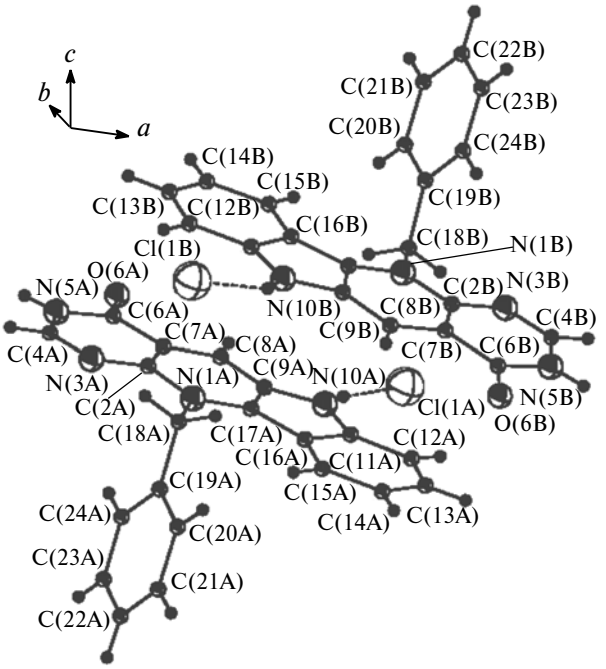


Fig. 1. General view of two crystallographically independent molecules in chloride **3bA**. Solvate water molecules are omitted because they mask the positions of the atoms in the solvated molecules.

In the crystal, the chloride anions Cl(lA) and Cl(lB) link the organic cations (A and B, respectively) to form chains along the crystallographic axis *a* by means of the hydrogen bonds N(10A,B)—H(10A,B)...Cl(1A,B) and C(4A,B)—H(4A,B)...Cl(1A,B) (Fig. 2). The chains of molecules A and B are united through the hydrogen bonds N(5A)—H(5A)...O(6B) (1 − *x*, 0.5 + *y*, 1.5 − *z*) and a complex

Table 1. Bond lengths (*d*) and angles (ω) in structure **3b**

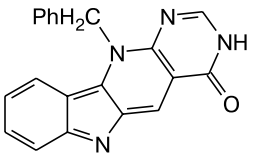
Bond	*d*/Å	Bond	*d*/Å	Parameter	Value	Angle	ω/deg
N(1A)—C(17A)	1.357(8)	N(10A)—C(11A)	1.377(8)	Bond	*d*/Å	C(9A)—N(10A)—C(11A)	108.8(6)
N(1A)—C(2A)	1.377(7)	N(1B)—C(2B)	1.353(8)	C(9B)—N(10B)	1.379(8)	C(2B)—N(1B)—C(17B)	119.7(6)
N(1A)—C(18A)	1.470(7)	N(1B)—C(17B)	1.355(8)	N(10B)—C(11B)	1.361(8)	C(2B)—N(1B)—C(18B)	120.0(6)
C(2A)—N(3A)	1.370(9)	N(1B)—C(18B)	1.478(7)	Angle	ω/deg	C(17B)—N(1B)—C(18B)	120.3(6)
N(3A)—C(4A)	1.272(8)	C(2B)—N(3B)	1.354(8)	C(17A)—N(1A)—C(2A)	120.5(6)	C(4B)—N(3B)—C(2B)	116.5(7)
C(4A)—N(5A)	1.361(9)	N(3B)—C(4B)	1.280(8)	C(17A)—N(1A)—C(18A)	119.1(6)	C(4B)—N(5B)—C(6B)	122.3(6)
N(5A)—C(6A)	1.390(9)	C(4B)—N(5B)	1.361(8)	C(2A)—N(1A)—C(18A)	120.4(6)	C(11B)—N(10B)—C(9B)	110.4(6)
C(6A)—O(6A)	1.233(9)	N(5B)—C(6B)	1.399(8)	C(4A)—N(3A)—C(2A)	113.4(7)		
C(9A)—N(10A)	1.374(8)	C(6B)—O(6B)	1.217(7)	C(4A)—N(5A)—C(6A)	121.2(7)		

Table 2. Parameters of the hydrogen bonds in structure **3b** and the shortest distances around the O(1), O(2), O(3), and O(4) atoms of the solvate water molecules that suggest possible hydrogen bonding (the H atoms in the solvate water molecules were not located)*

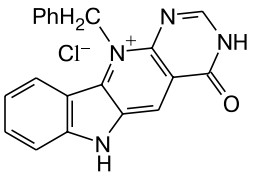
D—H....A	Distance D...A/Å	Angle D—H...A/deg	Distance D...A	*d*/Å	Distance D...A	*d*/Å
N(10A)—H(10A)...Cl(1A)	3.156(7)	172	O(1)...O(3)	3.348(9)	O(3)...N(5B)	2.744(9)
N(10B)—H(10B)...Cl(1B)	3.189(7)	153	O(1)...O(2)[d]	2.759(8)	O(4)...C(11B)	3.21(1)
N(5A)—H(5A)...O(6B)[a]	2.738(7)	161	O(1)...Cl(1A)	3.293(7)	O(4)...O(2)	3.48(1)
C(4B)—H(4B)...Cl(1B)[b]	3.621(9)	166	O(3)...Cl(1A)	3.010(6)	O(4)...O(2)[f]	3.20(1)
C(4A)—H(4A)...Cl(1A)[c]	3.99(1)	173	O(3)...O(4)[e]	2.80(1)		

* Symmetry operation codes: [a] (1 − *x*, 0.5 + *y*, 1.5 − *z*); [b] (1 + *x*, *y*, *z*); [c] (−1 + *x*, *y*, *z*); [d] (1 − *x*, 0.5 + *y*, 1.5 − *z*); [e] (*x*, 0.5 − *y*, −0.5 + *z*); [f] (1 − *x*, −*y*, 2 − *z*).

system of hydrogen bonds involving water molecules (see Table 2). In addition, X-ray diffraction data provide convincing evidence that compounds **3** (as well as **2**) exist in the crystal as tautomer **3A** (**2A**); *i.e.*, they are 4,11-dihydro-3*H*-pyrimido[5′,4′:5,6]pyrido[3,2-*b*]indol-4-one derivatives.

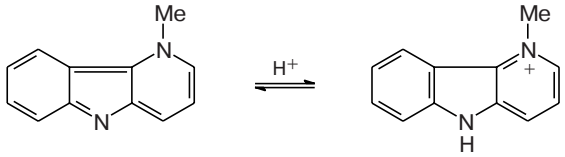


2bA



3bA

Alkylation of tetracyclic compound **2bA** with methyl iodide and methyl bromoacetate was carried out under different conditions. For instance, reactions of compound **2bA** with alkyl halides in DMF in the absence of bases could be expected to occur at the indole N atom because of a considerable energy gain resulting from the formation of the aromatic indole system. This assumption was supported by the high basicity of *N*-methyl-δ-carboline **4** (pK_a = 10.77).[7]



4

However, moderate heating (40—50 °C) of compound **2bA** with methyl iodide or methyl bromoacetate in DMF

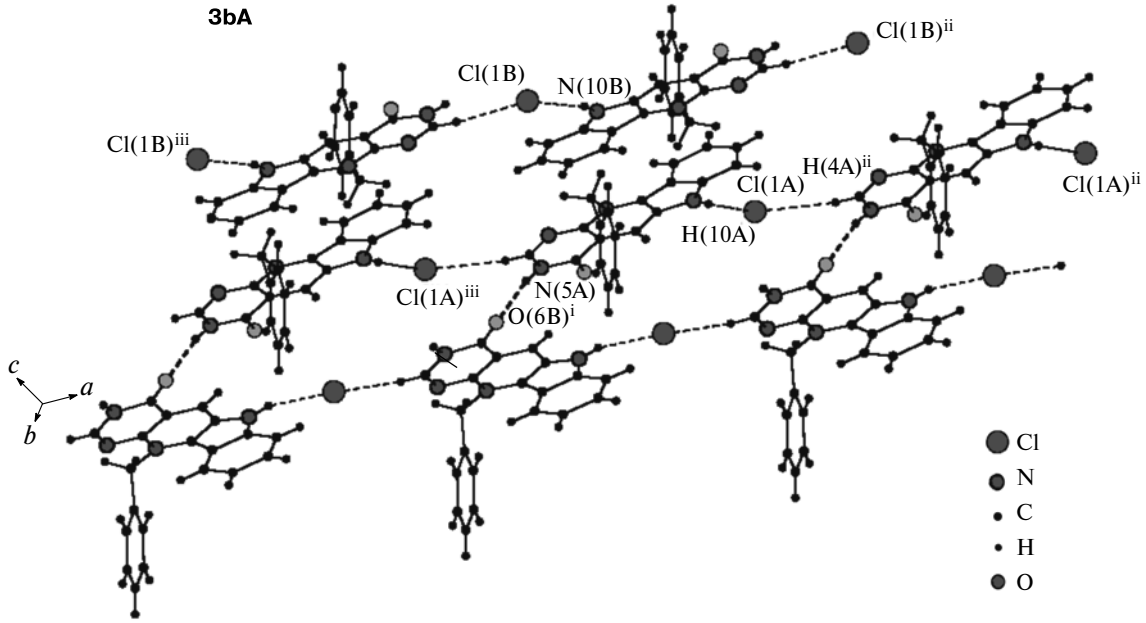
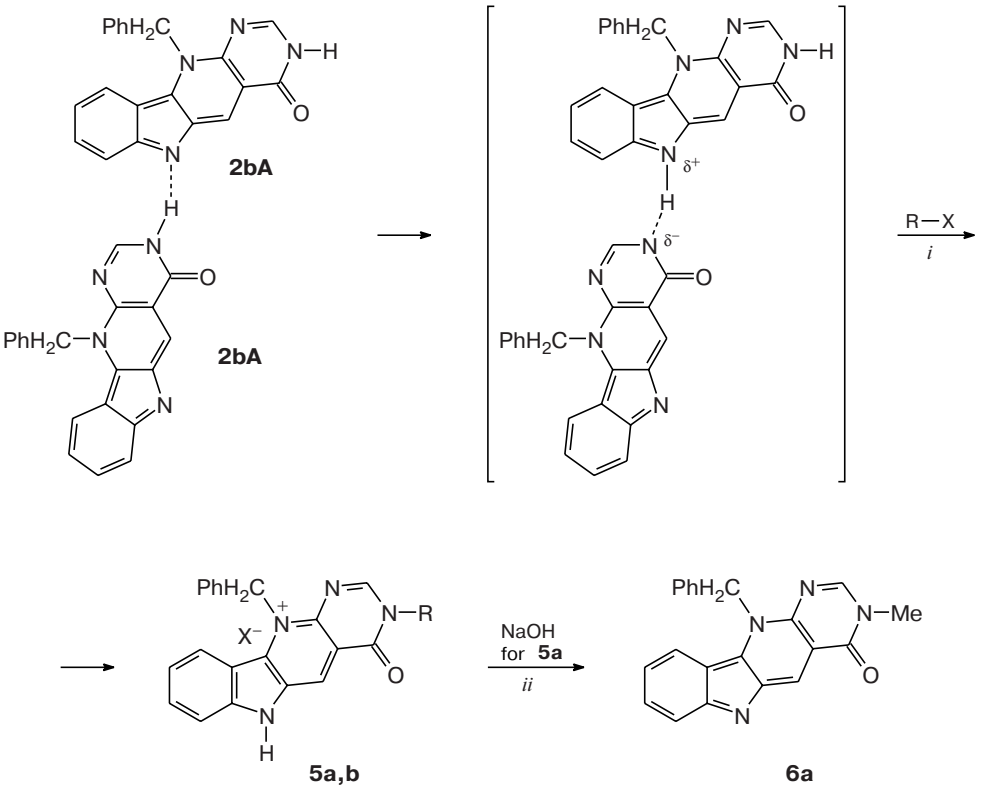


Fig. 2. Fragment of the molecular packing in the crystal structure **3bA**. Hydrogen bonds between the atoms of adjacent molecules are indicated with dashed lines.

Scheme 2



R = Me, X = I (**a**); R = CH_2COOMe, X = Br (**b**)

Reagents and conditions: *i*. **2bA**, DMF, MeI, 40—50 °C, 14 h; **2bA**, DMF, $BrCH_2COMe$, 50 °C, 0.5 h, 20 °C, 64 h; *ii*. MeOH, 4 *N* NaOH.

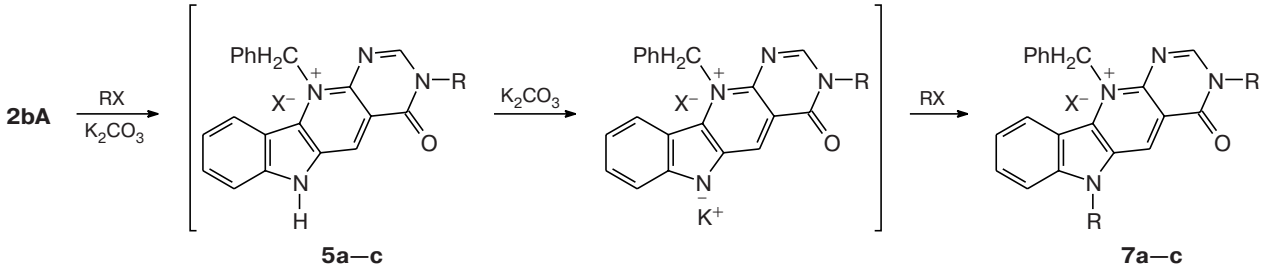
gave alkylation products only at the pyrimidine NH group: 11-benzyl-3-methyl- and 11-benzyl-3-methoxycarbonylmethyl-4,11-dihydro-3*H*-pyrimido[5′,4′:5,6]pyrido[3,2-*b*]indol-4-ones (iodide **5a** and bromide **5b**, respectively). Apparently, this unexpected outcome can be explained by the sufficiently high acidity of the pyrimidine NH group (pK_a = 8.59 for pyrimidin-4-one[8]) and the presence of the highly basic N atom in position 6 (see above).

The alkylation of compound **2bA** is probably preceded by the formation of the strong intermolecular hydrogen bond N(3)H...N(6)= between the highly basic N(6) atom and the sufficiently acid N(3)H atom. As the result, a significant partial negative charge on the pyrimidine N(3) atom favors alkylation at this position and a partial positive charge on the N(6) atom hinders N(6)—C bonding (Scheme 2).

Treatment of iodide **5a** with NaOH in aqueous methanol gave free base **6a**.

Alkylation of tetracyclic compound **2bA** with methyl iodide, methyl bromoacetate, or dimethyl sulfate in acetone in the presence of K_2CO_3 occurred at both the pyrimidine and indole N atoms to give dialkyl derivatives **7a—c** as the corresponding salts. The first step of the

Scheme 3



R = Me, X = I (**a**); R = CH_2COOMe, X = Br (**b**); R = Me, X = $[MeSO_4]^-$ (**c**)

reaction involves the formation of monoalkyl derivatives **5a—c**; in this case, K_2CO_3 (rather than compound **2bA**) seems to act as an acceptor of the N(3)H proton. Then, K_2CO_3 abstracts the proton from the indole N atom of compounds **5a—c**, which gives rise to an integer negative charge on it and favors secondary alkylation (Scheme 3).

Replacement of K_2CO_3 by NaOH in the methylation of compound **2bA** with methyl iodide in acetone does not affect the final outcome of the reaction. We isolated 3,6-dimethyl derivative **7a** as an iodide salt in 18% yield. Interestingly, the final product in the alkylation with methyl bromoacetate under similar conditions was 3-monoalkyl derivative **5b** (as bromide) identical in physicochemical characteristics with the compound synthesized according to Scheme 2. An increase in either the reaction time or the excess of methyl bromoacetate did not lead to a dialkylation product. Apparently, NaOH (which is a stronger base than K_2CO_3) promotes a rapid transformation of bromide **5b** into base **6b** incapable of producing an anion. In addition, one can assume that the alkali reacts with methyl bromoacetate more rapidly than does with compound **5b**, methyl bromoacetate undergoes hydrolysis of the ester group and replacement of the Br atom by the hydroxy group, and, consequently, the reaction does not proceed any further.

For unambiguous determination of the structures of monoalkyl derivatives **5a,b**, we recorded the HSQC, HMBC, and NOESY spectra of compound **5a** and compared them with analogous spectra of 3,6-dimethylpyrimidopyridoindolium iodide **7a**. The HMBC spectrum shows correlation peaks of the ^{1}H NMR signals for two methyl groups (δ 3.67 and 4.26) in compound **7a** with the signals for the C(2) (δ 153.6) and C(4) atoms (δ 159.6) and with the signals for the C(5a) (δ 134.2) and C(6a) atoms (δ 145.5), respectively. The NOESY spectrum of compound **7a** exhibits a correlation peak of the low-field N(6)Me group with the H(5) (δ 9.66) and H(7) atoms (δ 8.03) and a correlation peak of the high-field N(3)Me group with the singlet for the H(2) atom (δ 8.94). According to our signal assignment, the methyl group with the signal at δ 3.67 should be in position 3 of monomethyl indolium iodide **5a**. Indeed, the HMBC spectrum of compound **5a** shows a correlation peak of the signal for the methyl group (δ 3.67) with the signals for the C(2) (δ 153.5) and C(4) atoms (δ 159.6) and the NOESY spectrum shows a correlation peak of the same signal with the signal for the H(2) atom (δ 8.95). Structure **5b** was determined from the NOEDIFF data: when the signal for the methylene group (δ 5.06) is saturated, the intensity of the singlet for the H(2) atom (δ 8.96) changes by 10%.

It is known that amide acetals can serve as alkylating agents.[9—11] Substrates containing both N- and O-alkylation centers yield mixtures of N- and O-alkylation products, the O-alkylation usually being dominant.

Scheme 4

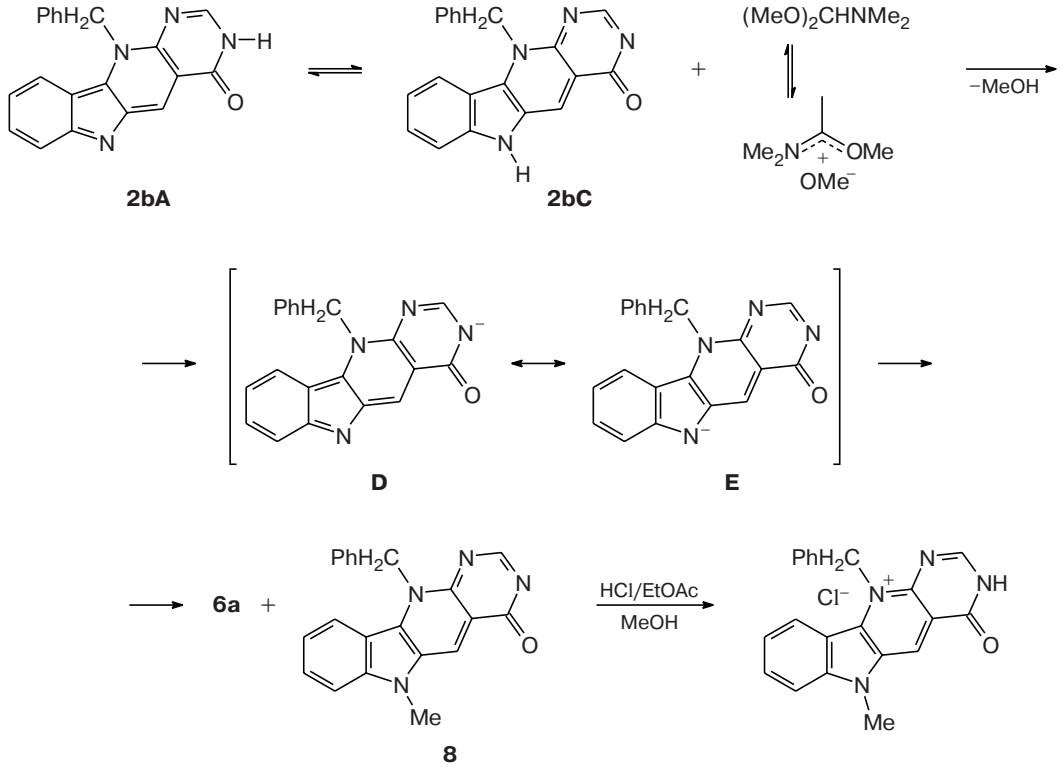


Table 3. Yields, elemental analysis data, and physicochemical and spectroscopic characteristics of the compounds obtained

Compound	Yield (%)	M.p./°C[a]	M	Found / Calculated (%)				Molecular formula	IR, ν_{max}/cm^{-1} (CO)	MS, *m/z*
				C	H	N	I			
5a	53	240—244 (Pr^i : H_2O, 2 : 1)	468	53.88 53.86	3.61 3.66	—	26.99 27.10	$C_{21}H_{17}IN_4O$	1689	341 $[M - HI + H]^+$, 250 $[M - HI + H - 91]^+$
5b	43 (*A*) 41 (*B*)	240—242 (MeOH)	488	56.55 56.57	4.71 4.13	11.46 11.47	—	$C_{23}H_{19}BrN_4O_3 \cdot$ $\cdot 0.5\ H_2O$[b]	1755, 1707	399 $[M - HBr + H]^+$, 797 $[2\ (M - HBr) + H]^+$
6a	59 (*A*) 11.5 (*B*)	244—246	340	73.61 74.10	5.241 4.74	16.12 16.46	—	$C_{21}H_{16}N_4O$	1685	341 $[M + H]^+$, 681 $[2\ M + H]^+$
7a	68 (*A*) 18 (*B*)	250—252 (H_2O : MeCN, 2 : 1)	482	54.68 54.78	4.10 3.97	—	26.29 26.31	$C_{22}H_{19}IN_4O$	1691	355 $[M - HI + H]^+$
7b	55	194—198 (H_2O)	551	56.88 56.63	5.30 4.80	10.40 10.16	—	$C_{26}H_{23}BrN_4O_5$	1681, 1749	471 $[M - HBr + H]^+$, 379 $[M - HBr + H - 92]^+$
7c	45	250—254 (Pr^i : H_2O, 2 : 1)	466	59.22 59.22	4.93 4.75	12.06 12.01	—	$C_{23}H_{22}N_4O_5S$	1689	355 $[M - HMeSO_4 + H]^+$, 264 $[M - HMeSO_4 +$ $+ H - 91]^+$
8	13.5	240—244 (MeOH)	340	73.56 74.10	4.95 4.74	16.33 16.46	—	$C_{21}H_{16}N_4O$	1627	341 $[M + H]^+$, 363 $[M + Na]^+$, 681 $[2\ M + H]^+$, 703 $[2\ M + Na]^+$
9	57	>330 (MeOH)	385	64.80 65.37	5.53 4.70	14.43 14.52	—	$C_{21}H_{17}ClN_4O \cdot$ $\cdot 0.5\ H_2O$	1712	341 $[M - HCl + H]^+$, 363 $[M - HCl + Na]^+$, 681 $[2\ (M - HCl) + H]^+$, 703 $[2\ (M - HCl) + Na]^+$

[a] The solvent for recrystallization is given in parentheses. [b] Found (%): H_2O, 1.38. Calculated (%): H_2O, 1.84. [c] Found (%): S, 6.85. Calculated (%): S, 6.87.

However, a reaction of compound **2bA** with DMF dimethyl acetal gave a mixture of two monomethyl derivatives (at the N(3) and N(6) atoms): 11-benzyl-3-methyl-4,11-dihydro-3*H*-pyrimido[5′,4′:5,6]pyrido-[3,2-*b*]indol-4-one (**6a**) and 11-benzyl-6-methyl-6,11-dihydro-4*H*-pyrimido[5′,4′:5,6]pyrido[3,2-*b*]indol-4-one (**8**). These products were separated by column chromatography. The formation of a mixture of monomethyl derivatives can be explained by the existence of another tautomer **2bC** (apart from the aforementioned tautomers **2b**, **2bA** and **2bB** of the starting reagent). In this case, the alkylating agent is an ambident cation; this cation and the alkoxy anion are in equilibrium with the amide acetal. The alkylation proceeds through anions **D** and **E** formed by means of abstraction of the NH protons by the alkoxy anion. Note that when treated with HCl in methanol, compound **8** is transformed into chloride **9** because of the formation of the thermodynamically favorable aromatic indole system (Scheme 4).

Compound **6a** obtained according to Scheme 4 was identical in all physicochemical characteristics with the compound synthesized from iodide **5b**. The *N*-alkylation is confirmed by the NOEDIFF spectrum of compound **8**: when the signal for the methyl group (δ 4.19) is saturated, two signals resonate (NOE up to 10%): the doublet at δ 7.78 (H(7)) and the singlet at δ 9.37 (H(5)). We tried to obtain an *O*-alkyl derivative in a reaction with triethyloxonium fluoroborate tending toward O-alkylation.[12] However, $Et_3O^+BF_4^-$ did not react with compound **2bA** under these conditions at all, probably because the latter is virtually insoluble in nonpolar solvents (chloroform, dichloromethane, dichloroethane, *etc.*) usually employed for such reactions.

Experimental

IR spectra were recorded on an FSM-1201 instrument (Nujol). Mass spectra were recorded on a Waters ZQ-2000 mass spectrometer (electrospray ionization, direct inlet probe). ^1H NMR spectra were recorded on Bruker DRX-500 and Bruker AC-300 spectrometers. The course of the reactions was monitored and the purity of the products was checked by TLC on Merck 60 F_{254} plates in chloroform—methanol (10 : 1) and ethyl acetate—Pr^iOH—ammonia (5 : 3 : 1). Spots were visualized under UV light. The yields, melting points, elemental analysis data, and mass and IR spectra of the compounds obtained are given in Table 3.

Single crystals of salt **3b** were obtained by crystallization from methanol. X-ray diffraction analysis was carried out on

Table 4. Crystallographic parameters and a summary of data collection for structure **3b**

Parameter	Value
Molecular formula	$2(C_{20}H_{15}H_4OCl) \cdot 3.5H_2O$
Molecular mass	783
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell parameters	
a/Å	12.596(13)
b/Å	20.568(2)
c/Å	15.350(7)
β/deg	3635.3(2)
V/Å^3	3635.3(2)
Z	4
ρ_{calc}/g cm^{-3}	1.448
Scan range/deg	$2\theta < 61$
Number of measured reflections	5254
Number of reflections with $I > 2\sigma$	1737
Number of parameters refined	488
R_{int}	0.04
R	0.061
R_w	0.12

an Enraf Nonius CAD-4 diffractometer (graphite monochromator, λ = 1.54061 Å (Cu, Kα$_1$), ω-scan mode). Selected crystallographic parameters and a summary of data collection for structure **3b** are given in Table 4. Selected geometrical parameters of chloride **3b** are given in Table 1. The structure was solved by the direct method. The coordinates and thermal parameters of the non-hydrogen atoms were refined in the full-matrix anisotropic approximation. The hydrogen atoms were located geometrically and refined in the rider model. The H atoms of solvate water molecules were not located from difference electron-density maps because of the poor quality of crystals and probably because of alternative ways of hydrogen bonding in the crystal with participation of water molecules (see Table 2). All calculations were performed with the SHELX97 program package.[13] The drawings were made with the DIAMOND program.[14]

11-Benzyl-3-methyl-4-oxo-4,6-dihydro-3*H*-pyrimido-[5′,4′:5,6]pyrido[3,2-*b*]indol-11-ium iodide (5a). Methyl iodide (1 mL) was added to a suspension of pyrimidopyridoindole **2bA** (0.3 g, 0.92 mmol) in DMF (7 mL). The reaction mixture was stirred at 40 °C for 14 h. The resulting solution gradually settled to give a new precipitate. The suspension was stirred at 20 °C for 14 h and the precipitate was filtered off, washed with DMF, ethyl acetate, and acetone. The yield of compound **5a** was 0.1 g. The mother liquor was stirred with another portion of MeI (0.3 mL) at 40 °C for 9 days, MeI (0.3 mL) being added every next day. The solution was concentrated by half *in vacuo* and triturated with acetone (1 mL). The precipitate was filtered off and washed with DMF and acetone. An additional crop of compound **5a** was 0.13 g (its total yield was 0.26 g). ^{1}H NMR (DMSO-d$_6$), δ: 3.67 (s, 3 H, N(3)Me); 6.75 (s, 2 H, C$\underline{H}_2$Ph); 7.22—7.34 (m, 5 H, CH$_2\underline{Ph}$); 7.40 (t, 1 H, H(9), J_o = 8.2 Hz); 7.86 (t, 1 H, H(8), J_o = 8.2 Hz); 7.92 (d, 1 H, H(7), J_o = 8.2 Hz); 8.25 (d, 1 H, H(10), J_o = 8.2 Hz); 8.95 (s, 1 H, H(2)); 9.38 (s, 1 H, H(5)); 13.13 (br.s, 1 H, N(6)H). ^{13}C NMR (DMSO-d$_6$), δ: 34.4 N(3)Me); 52.3 (C$\underline{H}_2$Ph); 112.1 (C(7)); 112.9 (C(10a)); 113.9 (C(7)); 115.1 (C(4a)); 122.2 (C(9)); 124.4 (C(10)); 125.3 (C(5)); 126.0, 128.0, 129.0, 133.0 (Ph); 133.4 (C(5a)); 133.6 (C(8)); 135.6 (C(10b)); 144.9 (C(6a)); 147.0 (C(11a)); 153.5 (C(2)); 159.6 (C(4)).

11-Benzyl-3-(2-methoxy-2-oxoethyl)-4-oxo-4,6-dihydro-3*H*-pyrimido[5′,4′:5,6]pyrido[3,2-*b*]indol-11-ium bromide (5b). Method *A*. Methyl bromoacetate (0.13 mL, 1.38 mmol) was added to a suspension of pyrimidopyridoindole **2bA** (0.3 g, 0.92 mmol) in DMF (7 mL). After 30-min stirring at 50 °C, another portion of methyl bromoacetate (0.13 mL) was added, which caused a new precipitate to form. The suspension was left for 64 h. The precipitate was filtered off, washed with DMF and acetone, and dried to give compound **5b** (0.19 g). ^{1}H NMR (DMSO-d$_6$), δ: 3.77 (s, 3 H, OMe); 5.06 (s, 2 H, C$\underline{H}_2$COOMe); 6.76 (s, 2 H, C$\underline{H}_2$Ph); 7.23—7.34 (m, 5 H, CH$_2\underline{Ph}$); 7.42 (t, 1 H, H(9), J_o = 8.2 Hz); 7.92 (m, 2 H, H(7), H(8)); 8.24 (d, 1 H, H(10), J_o = 8.2 Hz); 8.96 (s, 1 H, H(2)); 9.40 (s, 1 H, H(5)); 13.30 (br.s, 1 H, N(6)H).

Method *B*. Potassium hydroxide (0.07 g, 1.22 mmol) and methyl bromoacetate (0.14 mL, 1.53 mmol) were added to a suspension of pyrimidopyridoindole **2bA** (0.2 g, 0.61 mmol) in anhydrous acetone (7 mL). The suspension was refluxed with stirring for 2 h and then for an additional 14 h with another portion of methyl bromoacetate (0.14 mL). The precipitate was filtered off, washed with acetone, water, and again acetone, and dried to give compound **5b** (0.12 g). A mixture of the samples obtained according to methods ***A*** and ***B*** did not depress the melting point.

11-Benzyl-3-methyl-4,11-dihydro-3*H*-pyrimido[5′,4′:5,6]-pyrido[3,2-*b*]indol-4-one (6a). Method *A*. A suspension of compound **5a** (0.17 g, 0.36 mmol) in methanol (30 ml) was brought to boiling. The resulting solution was cooled to room temperature and alkalified with 4 *N* NaOH (7 mL) to pH 10—11. The red precipitate that formed was filtered off, washed with water and isopropyl alcohol, and dried to give compound **6a** (0.1 g).

Method *B*. A suspension of pyrimidopyridoindole **2bA** (0.5 g) in DMF dimethyl acetal (6 mL) was refluxed with stirring for 5.5 h. On cooling, the precipitate that formed was filtered off and washed with Pr^{i}OH and ethyl acetate to give a mixture (0.15 g) of compound **6a** and **11-benzyl-6-methyl-6,11-dihydro-4*H*-pyrimido[5′,4′:5,6]pyrido[3,2-*b*]indol-4-one (8)**. The mixture was separated by column chromatography on SiO_2 with chloroform—methanol (10 : 1), chloroform—methanol (10 : 2), and methanol as eluents. The yields of compounds **6a** and **8** were 0.06 and 0.07 g, respectively. A mixture of compounds **6a** obtained according to methods ***A*** and ***B*** did not depress the melting point.

A mixture of compounds **6a** (methods ***A*** and ***B***): ^{1}H NMR (DMSO-d$_6$ + CCl_4), δ: 3.61 (s, 3 H, N(3)Me); 6.63 (s, 2 H, C$\underline{H}_2$Ph); 6.95 (t, 1 H, H(9), J_o = 8.2 Hz); 7.09—7.26 (m, 5 H, CH$_2\underline{Ph}$); 7.44 (t, 1 H, H(8), J_o = 8.2 Hz); 7.68 (d, 1 H, H(7), J_o = 8.2 Hz); 8.00 (d, 1 H, H(10), J_o = 8.2 Hz); 8.64 (s, 1 H, H(2)); 8.97 (s, 1 H, H(5)).

Compound **8**: ^{1}H NMR (DMSO-d$_6$ + CCl_4), δ: 4.19 (s, N(6)Me); 6.62 (s, 2 H, C$\underline{H}_2$Ph); 7.10—7.29 (m, 6 H, H(9), CH$_2\underline{Ph}$); 7.71 (t, 1 H, H(8), J_o = 8.2 Hz); 7.78 (d, 1 H, H(7), J_o = 8.2 Hz); 8.10 (d, 1 H, H(10), J_o = 8.2 Hz); 8.35 (s, 1 H, H(2)); 9.37 (s, 1 H, H(5)).

11-Benzyl-3,6-dimethyl-4-oxo-4,6-dihydro-3*H*-pyrimido-[5′,4′:5,6]pyrido[3,2-*b*]indol-11-ium iodide (7a). Method *A*. Potassium carbonate (0.43 g, 3.1 mmol) and methyl iodide

(1 mL) were added to a suspension of pyrimidopyridoindole **2Ab** (1 g, 3.1 mmol) in anhydrous acetone (30 mL). The reaction mixture was refluxed with stirring for 6 h. The precipitate was filtered off hot, washed with acetone, water, methanol, and again acetone, and dried. The yield of compound **7a** was 1.01 g. ^{1}H NMR (DMSO-d_6), δ: 3.67 (s, 3 H, N(3)Me); 4.26 (s, 3 H, N(6)Me); 6.77 (s, 2 H, C$\underline{H}_2$Ph); 7.20—7.33 (m, 5 H, CH$_2$$\underline{Ph}$); 7.45 (t, 1 H, H(9), J_o = 8.2 Hz); 7.94 (t, 1 H, H(8), J_o = 8.2 Hz); 8.03 (d, 1 H, H(7), J_o = 8.2 Hz); 8.28 (d, 1 H, H(10), J_o = 8.2 Hz); 8.94 (s, 1 H, H(2)); 9.66 (s, 1 H, H(5)). ^{13}C NMR (DMSO-d_6), δ: 30.3 (N(6)Me); 34.4 (N(3)Me); 52.3 (C$\underline{H}_2$Ph); 112.1 (C(7)); 112.6 (C(10a)); 115.1 (C(4a)); 122.4 (C(9)); 124.3 (C(5)); 124.6 (C(10)); 126.0, 128.0, 129.0, 133.3 (Ph); 133.7 (C(8)); 134.2 (C(5a)); 135.1 (C(10b)); 145.5 (C(6a)); 146.9 (C(11a)); 153.6 (C(2)); 159.6 (C(4)).

Method *B*. Compound **7a** was obtained analogously from pyrimidopyridoindole **2bA** (0.3 g, 0.92 mmol), methyl iodide (1 mL), and KOH (0.01 g, 1.84 mmol) in anhydrous acetone (10 mL). The yield was 0.08 g. A mixture of compounds **7a** obtained according to methods ***A*** and ***B*** did not depress the melting point.

11-Benzyl-3,6-bis(2-methoxy-2-oxoethyl)-4-oxo-4,6-dihydro-3*H*-pyrimido[5′,4′:5,6]pyrido[3,2-*b*]indol-11-ium bromide (7b). **Method *A*.** Potassium carbonate (0.13 g, 0.92 mmol) and methyl bromoacetate (0.2 mL, 2.3 mmol) were added to a suspension of pyrimidopyridoindole **2bA** (0.3 g, 0.92 mmol) in anhydrous acetone (10 mL). The reaction mixture was refluxed with stirring for 2 h and another portion of methyl bromoacetate (0.2 mL) was added. The suspension was kept at 20 °C for 64 h. The precipitate that formed was filtered off, washed with acetone, water, and again acetone, and dried. The yield of compound **7b** was 0.28 g. ^{1}H NMR (DMSO-d_6 + CCl_4), δ: 3.77, 3.80 (both s, 3 H each, OMe, OMe); 5.09, 5.89 (both s, 2 H each, C$\underline{H}_2$COOMe, C$\underline{H}_2$COOMe); 6.83 (s, 2 H, C$\underline{H}_2$Ph); 7.23—7.33 (m, 5 H, CH$_2$$\underline{Ph}$); 7.46 (t, 1 H, H(9), J_o = 8.2 Hz); 7.94 (t, 1 H, H(8), J_o = 8.2 Hz); 8.00 (d, 1 H, H(7), J_o = 8.2 Hz); 8.31 (d, 1 H, H(10), J_o = 8.2 Hz); 9.03 (s, 1 H, H(2)); 9.86 (s, 1 H, H(5)).

Method *B*. Compound **7b** was obtained analogously from pyrimidopyridoindole **2bA** (0.2 g, 0.61 mmol), methyl bromoacetate (0.14 mL, 1.53 mmol), and KOH (0.07 g, 1.23 mmol) in anhydrous acetone (7 mL). The yield was 0.12 g. A mixture of compounds **7b** obtained according to methods ***A*** and ***B*** did not depress the melting point.

11-Benzyl-3,6-dimethyl-4-oxo-4,6-dihydro-3*H*-pyrimido-[5′,4′:5,6]pyrido[3,2-*b*]indol-11-ium methyl sulfate (7c). Potassium carbonate (0.08 g, 0.61 mmol) and dimethyl sulfate (0.09 mL, 0.92 mmol) were added to a suspension of pyrimidopyridoindole **2bA** (0.2 g, 0.61 mmol) in anhydrous acetone (10 mL). The reaction mixture was refluxed with stirring for 5 h and then for an additional 1 h with another portion of dimethyl sulfate (0.09 mL). The suspension was cooled and the precipitate that formed was filtered off, washed with acetone, water, and again acetone, and dried. The yield of compound **7c** was 0.13 g. ^{1}H NMR (DMSO-d_6 + CCl_4), δ: 3.37 (s, 3 H, [$\underline{Me}SO_4$]$^-$); 3.71 (s, 3 H, N(3)Me); 4.28 (s, 3 H, N(6)Me); 6.80 (s, 2 H, C$\underline{H}_2$Ph); 7.20—7.29 (m, 5 H, CH$_2$$\underline{Ph}$); 7.43 (t, 1 H, H(9), J_o = 8.2 Hz); 7.93 (t, 1 H, H(8), J_o = 8.2 Hz); 8.00 (d, 1 H, H(7), J_o = 8.2 Hz); 8.31 (d, 1 H, H(10), J_o = 8.2 Hz); 8.94 (s, 1 H, H(2)); 9.71 (s, 1 H, H(5)).

11-Benzyl-6-methyl-4-oxo-4,6-dihydro-3*H*-pyrimido[5′,4′:5,6]-pyrido[3,2-*b*]indol-11-ium chloride (9). A saturated solution of HCl in ethyl acetate (0.1 mL) was added to a suspension of compound **8** (0.08 g, 0.26 mmol) in methanol (4 mL). The reaction mixture was brought to boiling. The resulting solution was filtered, cooled, and triturated. The precipitate that formed was filtered off and washed with methanol and acetone. The yield of chloride **9** was 0.05 g. ^{1}H NMR (DMSO-d_6 + CCl_4), δ: 4.27 (s, N(6)Me); 6.79 (s, 2 H, C$\underline{H}_2$Ph); 7.20—7.29 (m, 5 H, CH$_2$$\underline{Ph}$); 7.42 (t, 1 H, H(9), J_o = 8.2 Hz); 7.92 (t, 1 H, H(8), J_o = 8.2 Hz); 8.01 (d, 1 H, H(7), J_o = 8.2 Hz); 8.29 (d, 1 H, H(10), J_o = 8.2 Hz); 8.67 (s, 1 H, H(2)); 9.68 (s, 1 H, H(5)); 13.75 (br.s, 1 H, N(3)H).

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