CHEMICAL PROPERTIES OF YLIDENE DERIVATIVES OF AZINES.

2.* THE METHYLATION OF DIHYDROPYRIMIDINYLIDENECYANOACETIC ESTERS AND THEIR ANIONS

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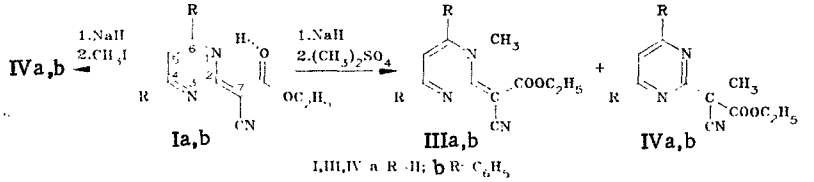
The methylation of dihydropyrimidinylidenecyanoacetic esters by various methylating reagents leads to better yields when anions of ylidene derivatives of pyrimidine are used. The structure of the products of N- and C-methylation formed and their ratio were established with the aid of the IR and UV spectra and by ^1H and ^{13}C NMR spectroscopy. The product of C-methylation contains a methyl group at the $C_{(7)}$ atom of the side chain, while the product of N-methylation contains a methyl group at the nitrogen atom of the pyrimidine ring. For 6-ylidene derivatives, N-methylation occurs at the heterocyclic atom distant from the tautomerizing chain. For 2- and 6-ylidene derivatives of pyrimidine, the ratio of the products of N- and C-methylation can be changed by varying the alkylating reagent.

Continuing a study of the reactivity of ylidene derivatives of azines [1], for which, like enaminones [2], we might expect the appearance of ambident properties of reactions with various electrophilic reagents, we investigated the direction of the methylation of dihydro-2- and dihydro-6-pyrimidinylidenecyanoacetic esters I and II and their anions under various conditions.

Methylation of 4,6-diphenyl-1,2-dihydro-2-pyrimidinylidenecyanoacetic ester (Ib) by diazomethane in benzene [3] proceeded slowly with the formation only of the N-methyl derivative — 1-methyl-4,6-diphenyl-1,2-dihydro-2-pyrimidenelyidenecyanoacetic ester (IIIb). Like the data for the original ester Ib [4], the UV spectrum of compound IIIb contains long-wave absorption maxima at $\lambda > 300$ nm, while the IR spectrum does not contain absorption bands in the region of 1700-1800 cm^{-1}. In the PMR spectrum of compound IIIb, the signal of the $N-CH_3$ group at 3.46 ppm is observed (Tables 3 and 4).

Analogously to the reactions of N- and C-alkylation of K-salts of 2-pyridyl- and 2-quinolylcyanoacetic esters described in the literature [5], it could be assumed that anions of dihydropyrimidenylidenecyanoacetic esters are capable of being alkylated either at the nitrogen atom or at the $C_{(7)}$ atom of the side chain (see the numeration of the atoms of compound I and II). Actually, in the case of methylation of the Na-salt of the ester Ib, even under conditions promoting reaction at the more "rigorous" reaction site — the nitrogen atom — using a "rigorous" methylating reagent, dimethyl sulfate in dimethoxyethane (DME) (cf. [6]), a mixture of N- and C-methylation products (IIIb and IVb) with substantial predominance of the ester IVb was isolated (Table 1). The structure of compound IVb, possessing an aromatic structure, is confirmed by its spectral characteristics (by the absence of a long-wave absorption maximum in the UV spectrum at $\lambda > 300$ nm, the presence of the νCO band at 1750 cm^{-1} in the IR spectrum, and the presence of the signal of the $C-CH_3$ group at 2.10 ppm in the PMR spectrum) (Tables 3 and 4).



*For communication 1, see [1].

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TABLE 1. Conditions of the Reaction and Yields of the Products of Methylation of Na-Salts of the Esters Ia, b and IIa-c

Initial compound	Reagent	Reaction time, h	Yield of reaction products,%		Recovery of substrate,%
			III or V	IV or VI	
Ia	$(CH_3)_2SO_4$	120	30	10	50
Ia	CH_3I	24	—	60	20
Ib	$(CH_3)_2SO_4$	120	7	56	25
Ib	CH_3I	24	—	90	—
IIa	CH_3OTs	5	75	10	—
IIb	CH_3OTs	5	75	10	—
IIb	CH_3I	24	65	15	—
IIc	CH_3OTs	120	44	15	20
IIc	CH_3I	24	30	45	10

TABLE 2. Analytical Characteristics of Compounds II-VIII

Compound	Mp, °C	Found, %			Gross Formula	Calculated %		
		C	H	N(S)		C	H	N(S)
IIc	173—175	67,6	5,2	15,6	$C_{15}H_{13}N_3O_2$	67,4	4,3	15,8
IIIa	152—154	58,3	5,3	20,2	$C_{10}H_{11}N_3O_2$	58,5	5,4	20,5
IVa	Oil	58,6	5,3	20,6	$C_{10}H_{11}N_3O_2$	58,5	5,4	20,5
IVb	100—103	74,1	5,3	11,5	$C_{22}H_{19}N_3O_2$	73,9	5,4	11,7
Va	236—237	58,2	5,5	20,4	$C_{10}H_{11}N_3O_2$	58,5	5,4	20,5
Vb	205—207	60,3	5,9	19,4	$C_{11}H_{13}N_3O_2$	60,3	6,0	19,2
Vc	184,5—185	68,9	5,5	14,5	$C_{16}H_{15}N_3O_2$	68,3	5,4	14,9
VIb	Oil	61,0	6,2	19,9	$C_{11}H_{13}N_3O_2$	60,3	6,0	19,2
VIc	Oil	68,5	5,0	14,4	$C_{16}H_{15}N_3O_2$	68,3	5,4	14,9
VIIb	159—161	55,3	5,5	10,3 (7,8)	$C_{18}H_{21}N_3O_5S$	55,2	5,4	10,7 (8,2)
VIIIa	211—220	53,0	4,8	12,0 (8,7)	$C_{16}H_{17}N_3O_5S$	52,9	4,7	11,6 (8,5)
VIIIb	198—202	53,9	5,1	11,2 (9,0)	$C_{17}H_{19}N_3O_5S$	54,1	5,1	11,1 (8,8)

*Compounds IIc, IIIa, IVb, and Va-c were recrystallized from ethanol; VIIb and VIIIa, b were recrystallized from absolute ethanol, with decomposition.

TABLE 3. IR (region of 1400-2300 cm^{-1}) and UV Spectra of Compounds III-VIII

Compound	ν, cm^{-1} (in KBr)	λ_{max}, nm (log ε (in ethanol)
IIIa	1410, 1500, 1545, 1620, 1680, 2200	308 (4,29), 385 (3,70)
IIIb	1495, 1530, 1600, 1610, 1670, 2200	312 (4,55), 424 (3,83) [3]
IVa	1420, 1450, 1580, 1680, 1760, 2255	245 (3,43), 290 (2,04)
IVb	1420, 1530, 1585, 1590, 1750, 2250	252 (4,41), 290 (4,31)
Va	1450, 1480, 1630, 1680, 2200	352 (4,52); 313 (4,38)*
Vb	1450, 1490, 1640, 1680, 2200	352 (4,48); 313 (4,37)*
Vc	1430, 1480, 1625, 1690, 2200	362 (4,46)
VIb	1400, 1450, 1580, 1770, 2250	253 (3,62)
VIc	1400, 1430, 1570, 1770, 2260	262 (4,35)
VIIb	1550, 1600, 1660, 1680, 2220	315 (4,38)*
VIIIa	1550, 1610, 1680, 1690, 2220	313 (4,30)*
VIIIb	1580, 1650, 1660, 1680, 2220	315 (4,36)*

*In CF_3COOH.

By using a substantially "milder" methylating reagent, methyl iodide in DME, we obtained only the C-methyl-substituted compound IVb from the anion of the ester Ib. Analogously the compound IVa was obtained from the anion of the unsubstituted ester Ia, while methylation of the ester Ia by dimethyl sulfate in DME leads to a mixture of N- and C-derivatives in a 1:3 ratio. An increase in the amount of the N-derivative IIIa in comparison with the amount of the compound IIIb formed under the same conditions is evidently explained by fewer steric hindrances to the reaction at the nitrogen atom in the case of methylation of the Na-salt of compound Ia in comparison with compound Ib. The spectral characteristics (IR, UV, and PMR) of compound IIIa are similar to the data for compound IIIb, and those of IV to the data for IVb (see Tables 3 and 4).

TABLE 4. PMR Spectra of Compounds III-VIII

Compound	Solvent	δ, ppm					
		2-H (4-H)	6-H	5-H and Ar	CH_2CH_3	CH_2CH_3	Other CH_3 groups
IIIa	$CDCl_3$	(8,65)	8,00	6,83	4,23	1,33	3,70 (N—CH_3)
IIIb	$CDCl_3$	—	—	7,10; 7,50—8,45	4,33	1,36	3,46 (N—CH_3)
IVa	CCl_4	(8,83)	8,83	7,38	4,33	1,30	1,95 (C—CH_3)
IVb	CCl_4	—	—	7,40—8,30	4,32	1,33	2,10 (C—CH_3)
Va	$CDCl_3$	8,18	8,01	7,04	4,18	1,29	3,63 (N—CH_3)
	DMSO-D_6	8,55	8,00	8,00	4,20	1,30	3,75 (N—CH_3)
	CF_3COOH	9,06	7,68	7,32	4,40	1,38	4,00 (N—CH_3)
Vb	$CDCl_3$	—	7,85	7,08	4,18	1,30	2,50 (2-CH_3); 3,61 (N—CH_3)
	DMSO-D_6	—	7,85	7,85	4,20	1,30	2,52 (2-CH_3); 3,64 (N—CH_3)
	CF_3COOH	—	7,64	7,18	4,38	1,38	2,93 (2-CH_3); 3,90 (N—CH_3)
Vc	$CDCl_3$	—	7,95	7,30; 7,40—7,70	4,27	1,30	3,50 (N—CH_3)
VIb	CCl_4	—	8,70	7,43	4,28	1,25	1,90 (C—CH_3); 2,65 (2-CH_3)
VIc	CCl_4	—	8,80	7,30—7,60; 8,30—8,60	4,25	1,20	1,95 (C—CH_3)
VIIb	CF_3COOH	—	7,00—7,85		4,25	1,22	2,20 (CH_3, tosyl); 2,78 (2-CH_3); 3,74 (N—CH_3)
VIIIa	CF_3COOH	—	7,00—7,75		4,20	1,16	2,15 (CH_3, tosyl);
VIIIb	CF_3COOH	—	6,90—7,80		4,28	1,22	2,22 (CH_3, tosyl); 2,78 (2-CH_3)

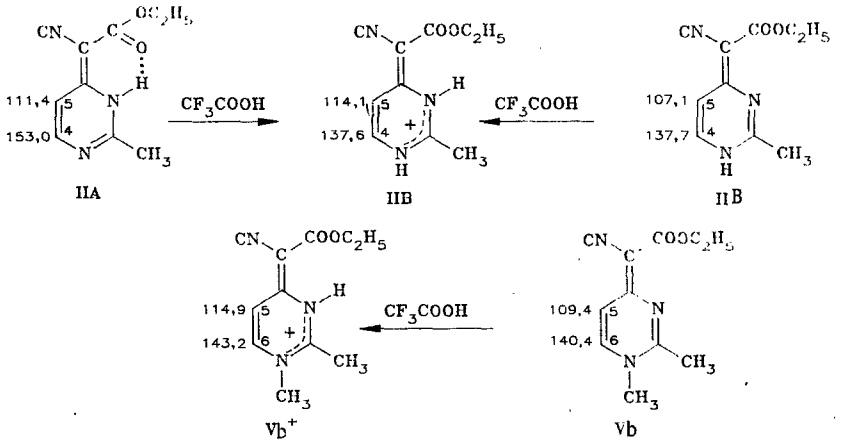


Fig. 1. Protonation of tautomeric forms of compound IIb (IIA ⇄ IIB) and the product of its N-methylation Vb. Chemical shifts in the ^{13}C NMR spectra in various solvents are cited: IIA and Vb in $CDCl_3$, IIB in a mixture of $CDCL_3$—DMSO, IIC and Vb^+ in CF_3COOH.

Methylation of Na-salts of 1,6-dihydro-6-pyrimideneylidenecyanoacetic esters* IIa, b, which do not contain voluminous substituents in the 2-position, under various conditions occurs chiefly at the nitrogen atom. At the same time, 2-phenyl-1,6-dihydro-6-pyrimidinylidenecyanoacetic ester (IIc), the phenyl group of which hinders the reaction at the nitrogen atom, is methylated analogously to compounds Ia, b, with the formation both of N- and of C-derivatives in comparable amounts. Thus, in the methylation of Na-salts of the esters IIa, b by dimethyl sulfate (or methyl tosylate) in DME, chiefly the N-methyl derivatives Va and Vb were isolated. The C-methyl-substituted compound VIb was isolated under the action of methyl iodide in DME on the ester IIb (analogously to the production of IVa, b); in this case the ester VIb is formed in a mixture with the N-methyl derivative Vb in a 1:5 ratio. Under the same conditions the ester IIc forms the esters VIc and Vc in a 1.5:1 ratio (see Table 1).

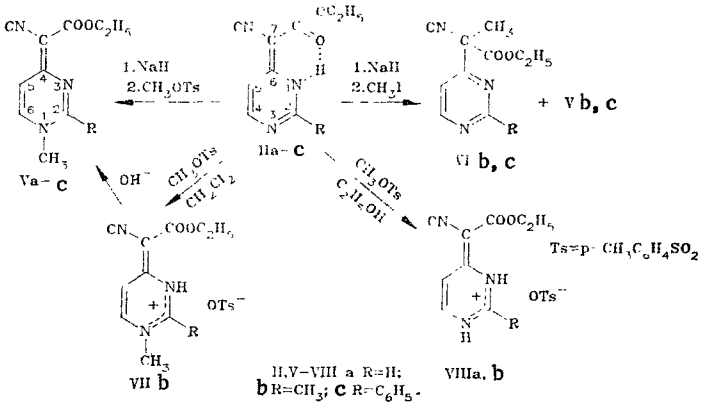
The possibility of using a wide assortment of different solvents for the methylation of Na-salts of the investigated compounds is limited by their poor solubility in nonpolar solvents; therefore, we selected DME with an addition of DMFA as the solvent in which the various reagents were compared.

*In the numeration of the atoms in compounds I and II, the ylidene tautomer, which predominates in the equilibrium mixture, was taken as the basis.

TABLE 5. ^{13}C NMR Spectra of Compounds Va-c

Compound	Solvent	δ, ppm										
		$C_{(2)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	CN	CO	OCH_2	$N-CH_3$	CH_2CH_3	$2-CH_3$ or $2-C_6H_5$
Va	$CDCl_3$	149,1	163,8*	110,6	138.0	—	—	—	60,0	40,7	14,3	
	$CDCl_3$—DMSO-D_6	149,1	163,8*	110,1	138,5	77,0	119,1	—	59,4	39,0	14,0	
	CF_3COOH	152,3	153,0	118,3	142,4	79,4	—	168,7	66,0	45,0	13,9	
Vb	$CDCl_3$	157,4	164,8*	109,4	140,4	—	119,6	166,7*	59,7	41,0	14,4	22,2
	$CDCl_3$—DMSO-D_6	156,7	163,5*	106,7	141,0	72,6	117,8	164,6*	57,2	39,0	12,7	20,3
	CF_3COOH	162,9	153,8	114,9	143,2	77,0	112,9	168,4	64,8	42,8	13,0	19,7
Vc	$CDCl_3$	158,0	164,4*	109,4	141,0	77,0	119,5	166,4*	59,6	42,5	14,4	132,4; 130,7; 128,6; 128,3
	CF_3COOH	154,3	164,1*	116,0	143,7	78,1	113,3	168,9*	65,5	44,9	13,5	137,2; 131,8; 129,8; 125,3

*The assignment of the signal to CO or $C_{(4)}$ is tentative.



The structure of the methylation products Va-c and VIb, c was confirmed by the data of the IR, UV and PMR spectra, which correspond well to ylidene or aromatic structures, respectively (see Tables 3 and 4). Actually, in the IR spectra of compounds Va-c, intense absorption bands of the conjugated ester and nitrile groups are observed (at 1680 and 2200 cm^{-1}), whereas compounds VIb, c are characterized by the presence of an intense band νCO at 1750-1760 cm^{-1} and a low-intensity band of the unconjugated νCN at 2250 cm^{-1}. The UV spectra of compounds Va-c contain a long-wave absorption maximum at 350 nm, which is absent in products of C-methylation VIb, c. In the PMR spectra of the esters Va-c, the signals of the $N-CH_3$ groups are observed at 3.50-4.00 ppm, and for compounds VIb, c those of the $C-CH_3$ groups at 1.95-2.65 ppm. We should mention the substantial change in the position of the signal of 5-H for the esters Va-c as we go from solution in $CDCl_3$ to DMSO (weak-field shift by ~1 ppm), which is evidently associated with the solvation influence of DMSO on compounds of this type [7].

However, the data cited do not permit a selection to be made between the isomeric $N_{(1)}$- and $N_{(3)}$-derivatives for products of N-methylation. Therefore, a final demonstration of the structure of N-methyl-derivatives Va-c was performed on the basis of the ^{13}C NMR spectra of these compounds and the products of their protonation, enlisting the well-known principles of [1, 8, 9]. Below are cited the chemical shifts of the $C_{(4)}$ and $C_{(5)}$ atoms of the ester IIb in the ^{13}C NMR spectra, recorded in various solvents.

As was shown earlier [1, 8], the ester IIb exists in an "orthoquinoid" form (IIA) in $CDCl_3$, in a "para-quinoid" form (IIB) in a mixture of $CDCl_3$—DMSO, and in a protonated ylidene form (IIC) in CF_3COOH. Evidently transition to the protonated form IIC from the structure IIA is accompanied by a substantial decrease in the value of the chemical shift of the $C_{(4)}$ atom (15.4 ppm) next to the nitrogen atom at which protonation occurs; such a pattern is known in the literature as a strong-field α-shift [9]. A small weak-field shift, known as the β-shift [9], occurs for the signal of the $C_{(5)}$ atom (2.7 ppm). At the same

time, in the protonation of compound IIB, the changes in the chemical shift of the $C_{(4)}$ atom are appreciably lower (0.1 ppm), and of the $C_{(5)}$ atom higher (7.0 ppm). The nature of the change in the positions of the signals of the $C_{(6)}$* and $C_{(5)}$ atoms of the N-methyl derivative Vb in the transition from solution in $CDCl_3$ to CF_3COOH (2.8 and 5.5 ppm) is similar precisely to these data, which is in good agreement with the structure of Vb. Analogous changes in the ^{13}C NMR spectra are also observed for compounds Va, c (see Table 5). It can also be noted that, in contrast to the action of DMSO on the position of the signals in the PMR spectra, the addition of DMSO-D_6 to solutions of compounds Va-c in $CDCl_3$ does not cause any significant change in the signals of the carbon atoms.

We were unable to perform the quaternization of the esters Ia, b and IIa by dimethyl sulfate (or methyl tosylate) even with heating to 150°C in sulfolane, evidently on account of their low basicity. The more basic compound IIb [1] is quaternized by methyl tosylate in solution in methylene chloride. The selection of methyl tosylate as the methylating reagent is due in this case to the stability of the crystalline salt VIIb formed. In quaternization of the ester IIb in solution in methylene chloride, where it has an "ortho-quinoid" structure [8], we might have expected the formation of products of the reaction of the $N_{(3)}$ atom, in accordance with the rule confirmed in [10]. According to this rule, methylation of prototropic ambident nucleophiles occurs at the heteroatom that does not contain a proton. And actually, N-methyl derivatives of compound IIb, obtained both by treatment of the quaternization product VIIb with an aqueous solution of sodium hydroxide and by methylation of the Na-salt of IIb by methyl tosylate in DME, proved identical and had the structure Vb.

We also performed the quaternization of the esters IIa, b by methyl tosylate in solution in ethanol, in which a substantial amount of the "para-quinoid" tautomer is formed [8]. According to the rules cited earlier [10], compounds IIa, b might be quaternized at the $N_{(1)}$ atom under these conditions. However, only the formation of tosylates VIIIa, b was noted. The structure of the salts VIIb and VIIa, b is confirmed by the similarity of their spectral characteristics of the data that we described earlier for perchlorates of the esters IIa, b [1] (see Tables 3 and 4).

Thus, methylation of the esters I and II themselves is difficult on account of their low basicity, or it occurs slowly under the conditions used. In the case of methylation of the Na-salts of 2- and 6-ylidene derivatives of pyrimidine, however, products of N- and C-methylation are formed, the ratio of which can be changed by varying the leaving group of the alkylating reagent. Moreover, in the absence of any significant steric hindrances, methylation may occur primarily both at the carbon atom of the side chain and at the nitrogen atom of the heterocycle. In dihydro-6-pyrimidinylidenecyanoacetic esters, methylation occurs at the $N_{(3)}$ atom away from the tautomerizing chain, even in the presence of a voluminous phenyl substituent in the position next to it.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrophotometer in tablets of KBr; the UV spectra were recorded on a Specord UV-vis instrument (concentration of the substance 10^{-4} M); the PMR spectra were recorded on a Varian A-56/60 instrument (60 MHz) for 7-10% solutions at 20°C. The ^{13}C NMR spectra were recorded in a pulsed system, followed by Fourier-transformation on a Bruker WP200SY spectrometer (50.3 MHz) at room temperature (concentration of the substance <1 M).

2-Phenyl-1,6-dihydro-6-pyrmidinylidenecyanoacetic ester (IIc) was produced from 2-phenyl-4-chloropyrimidine [11] according to the procedure of [12] with a 60% yield.

General Procedure for the Methylation of Na-Salts of Compounds I and II. To a solution of 2 mmoles of the ester I or II in 15 ml DME and 3 ml DMFA at room temperature, 0.06 g (2.5 mmoles) NaH was gradually added and mixed for 30 min. Then 2-3 mmoles of the methylating reagent was added, and the reaction mixture was mixed at room temperature (the reaction time is indicated in Table 1), monitoring the course of the reaction by thin-layer chromatography on Silufol UV-254 plates. The residue after the solvent was distilled off was washed with water, extracted with chloroform, dried, and isolated from chloroform by distilling off the solvent under vacuum. Then it was separated on a column with silica gel (330 ×

*According to the rules of the IUPAC nomenclature, N-methyl derivatives V have a different numeration of the atoms than compounds I and II; therefore not the atom $C_{(4)}$ but the atom $C_{(6)}$ is next to the nitrogen atom being methylated.

15 mm) with a mixture of chloroform and ethanol (10:1) as the eluent, collecting the products of C-methylation in the first colorless zone and the starting material and products of N-methylation in the two subsequent yellow zones. The ratio of the products of N- and C-methylation in the residue before separation on a column was determined according to the signal intensity of the N- and C-methyl groups in the PMR spectra recorded in $CDCl_3$.

The conditions of the reaction and yields of the methylation products are cited in Table 1, the characteristics of the compounds obtained in Tables 2-5.

Quaternization of 2-Methyl-1,6-dihydro-6-pyrimidinylidenecyanoacetic ester (IIb). We dissolved 0.5 g (2.4 mmoles) of the ester IIb with heating in 7 ml of methylene chloride, added 3.1 g (17 mmoles) methyl tosylate to the solution, and sealed into an ampule. The reaction mixture was heated for 11 h at 80°C. After removal of the solvent, the residue was washed with dry $CHCl_3$, 0.2 g (21%) 1,2-dimethyldihydro-4-pyrimidinylidenecyanoacetic ester (VIIb) was obtained, and after removal of chloroform, 0.22 g (50%) of the starting material IIb. When ethanol was used instead of methylene chloride, a precipitate of the salt VIIIb was isolated with a yield of 70%. The salt VIIIa was produced analogously.

When the salt VIb was treated with a 0.1 N solution of sodium chloride, 1,2-dimethyl-1,4-dihydro-4-pyrimidinylidenecyanoacetic ester (Vb) was formed in a yield of 0.1 g (19%) with mp 203-205°C, identical according to a mixed melting point test and the IR spectrum with the sample obtained in methylation of the Na-salt of the ester IIb.

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