9-Methylisoquinolino[7,6-f]quinoline (VIII). A solution of 2.48 g (0.01 mole) of substituted quinoline II in 60 ml of benzene was passed at a constant rate in the course of 2 h through K-16 catalyst (10 cm^3). The temperature in the catalyst zone was 580°C. The residue from the catalyzate was crystallized from petroleum ether to give 0.7 g of starting II. Chromatography (H = 30 cm, d = 2.5 cm, elution with ether) of the residue from the mother liquor gave an additional 0.8 g of II (R_f 0.4) and 0.15 g (16% on the basis of the converted II) of dehydrocyclization product VIII as pale-orange crystals with mp 177-178°C [from carbon tetrachloride–chloroform (1:1)] and R_f 0.18. PMR spectrum, δ, ppm: 9.26 s (11-H), 8.80 d (3-H), 8.70 d (1-H), 7.97 s (7-H), 7.41 dd (2-H), and 2.62 s (9-CH_3). UV spectrum, λ_{max} (log ε): 210 (4.6), 264 (4.45), 296 (4.21), 330 (2.84) sh, and 380 (2.42) sh. Found: N 11.2%; M^+ 244. $C_{17}H_{12}N_2$. Calculated: N 11.4%; M 244.

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AMINOMETHYLATION OF SUBSTITUTED 5-HYDROXYPYRIMIDINES

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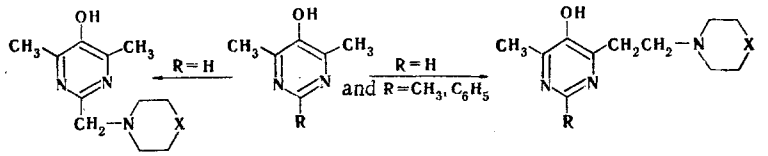
Conditions that make it possible to obtain aminomethyl derivatives of 2-R-4,6-dimethyl-5-hydroxypyrimidine that are substituted both in the pyrimidine ring (R = H) and at the methyl group of the side chain (R = H, CH_3, C_6H_5) were found. The facts established in this research make it possible to propose various substitution mechanisms.

We have shown the fundamental possibility of the incorporation of an electrophilic substituent in the 2 position of 4,6-dimethyl-5-hydroxypyrimidine (Ia) by aminomethylation and diazo coupling [1]. However, methyl groups bonded to a pyridine or pyrimidine ring have increased activity [2]. For example, the formation of products of substitution in the side chain have been noted for 4-nitro-2-methyl- and 2-nitro-6-methyl-3-hydroxypyridines [3].

Using piperidine and morpholine as the secondary amines we investigated the aminomethylation of 2,4,6-trimethyl- (Ib) and 2-phenyl-4,6-dimethyl-5-hydroxypyrimidine (Ic),



IIIa, b Ia-c IIa-d

Ia, IIa, b R=H; Ib, IIc R=CH_3; Ic, IId R=C_6H_5; IIa, c, d, IIIb X=O; IIb, IIIa X=CH_2

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TABLE 1. Characteristics of the Synthesized Compounds

Compound	mp, °C (crystallization solvent)	PMR spectra, ppm								Found, %		Empirical formula	Calc., %		Yield, %
		2-H	2-CH_3	4-CH_3	6-CH_3	CH_2NCH_2	CH_2OCH_2	CH_2CH_2	Other substituents	C	H		C	H	
IIa	110—111 (ether—hexane)	8,12s	—	—	2,25s	1,6m	2,56m	1,6m; 2,9m	—	59,3	7,4	$C_{11}H_{17}N_3O_2$	59,2	7,7	21
IIb	109—110 (ether—hexane)	8,02s	—	—	2,37s	—	—	3,00m; 3,12m	1,8m (β,γ-CH_2); 3,1m (α-CH_2)	64,8	8,9	$C_{12}H_{19}N_3O$	65,1	8,6	14
IIc	141—142 (benzene)	—	2,61s	—	2,48s	1,83m	3,28m	2,00m; 2,6m	—	60,3	7,6	$C_{12}H_{19}N_3O_2$	60,7	8,1	12
IId	168—169 (ether)	—	—	—	2,50s	2,42m	3,58m	2,55m; 3,00m	7,4m 8,5m (C_6H_5) 5,6brs (OH)	67,8	7,2	$C_{17}H_{21}N_3O_2$	68,2	7,1	20
IIIa	211—212 (methyl ethyl ketone)	—	—	2,31s	2,31s	—	—	—	2,58m (α-CH_2); 1,52m (β,γ-CH_2); 3,60s (CH_2); 5,0brs (OH)	65,2	8,8	$C_{12}H_{19}N_3O$	65,1	8,6	53
IIIb	211—212 (methyl ethyl ketone)	—	—	2,35s	2,35 m	2,46m	3,60m	—	3,50s (CH_2)	59,6	7,4	$C_{11}H_{17}N_3O_2$	59,2	7,7	40

in which the methyl groups in the 2 and 4(6) positions have similar reactivities, but the possibility of condensation in the 2 position of the ring is excluded. In this case we observed the facile formation of condensation products (IIa-d), the PMR spectra of which contain signals of protons of the morpholine (or piperidine) ring and of $-CH_2CH_2-$ groups, whereas the integral intensity of the CH_3 group in the 4(6) position corresponds to only three protons. Thus, the aminomethylation of Ib and Ic takes place at the methyl group in the 4(6) position.

It is well known that the aminomethylation of the aromatic ring is regarded as an electrophilic reaction that proceeds via an S_E2 mechanism, in which an immonium carbonium cation acts as the electrophilic reagent [4]. In addition, the aminomethylation of methylpyridines and other compounds that have a labile aliphatic proton is classified as nucleophilic substitution that proceeds via an S_N2 mechanism [5]. Summing up the indicated facts, one may conclude that conditions that include the formation of the anionic form of 5-hydroxypyrimidine will favor aminomethylation in the ring, since in this case the reactivity of the ring 2 position will increase. On the other hand, aminomethylation in the side chain requires that the synthesis be carried out in aqueous media, in which the ring nitrogen atom can be protonated, and this promotes an increase in the lability of the proton of the side chain.

In fact, in this case, when the reaction was carried out with aminals $R_2NCH_2OCH_3$ in benzene or dioxane or in excess amine with paraformaldehyde in an anhydrous medium or in chlorobenzene, substitution occurred in the 2 position of the pyrimidine ring to give IIIa,b. The reaction in the latter case (with chlorobenzene and paraformaldehyde) is accelerated and gives the product in good yield in the presence of a tertiary amine, whereas the addition of butyl alcohol slows it down.

The formation of products of substitution in the side chain was observed when the reaction was carried out with formalin and an amine in the base form or in the hydrochloride form in an aqueous medium. The addition of a tertiary amine markedly inhibited the course of the reaction as a consequence of a decrease in the lability of the protons of the methyl groups of the side chain.

The signal of a proton in the 2 position is absent in the PMR spectra of the IIIa and IIIb obtained by this method, but signals due to the protons of a dialkylaminomethyl group do appear in the spectra.

Thus, taking into account the various factors that affect the direction of the Mannich condensation, one can selectively direct the aminomethylation of 4,6-dimethyl-5-hydroxypyrimidines to the ring or to the side chain.

EXPERIMENTAL

The PMR spectra of 8-10% solutions of the compounds in CCl_4, CD_3OD, C_6D_6, C_6D_5N were recorded with HA-100 and Tesla BS-487C spectrometers at 29°C with hexamethyldisiloxane as the internal standard.

4-Methyl-5-hydroxy-6-morpholinoethylpyrimidine (IIa). A mixture of 3.1 g (0.025 mole) of 4,6-dimethyl-5-hydroxypyrimidine (Ia), 6 ml of morpholine, and 6 ml of 25% formalin was heated at 100°C for 1 h, after which it was evaporated to dryness in vacuo. Compounds Ia and IIa were isolated with a column filled with silica gel (40/100 μ) in an acetone–methanol system (in ether for IId).

Compounds IIb-d were similarly obtained; the data from the experiments are presented in Table 1.

2-Morpholinomethyl-4,6-dimethyl-5-hydroxypyrimidine (IIIb). A) A mixture of 2 g (14.5 mmole) of Ia, 1 g of previously dried paraformaldehyde, and 10 ml of morpholine was refluxed for 4 h. After 12 h, the precipitated crystals were removed by filtration and washed with ether.

Compound IIIa was similarly obtained using the same amount of piperidine.

Compounds IIIa and IIIb were identical to the compounds previously synthesized [1] through the corresponding methoxymethylamines, according to the results of thin-layer chromatography (TLC) and the absence of melting-point depressions for mixtures of the products.

B) A 10-ml sample of dry chlorobenzene was added to a mixture of 0.2 g of Ia, 0.2 ml of morpholine, and 0.2 g of dry paraformaldehyde, and the mixture was stirred with refluxing for 1.5 h. After 12 h, the precipitated dark crystals were removed by filtration, washed with ether, and recrystallized to give the product in 46% yield.

Similar experiments were carried out with the addition of 1 ml of n-butanol (1 ml of triethylamine in another case) to the reaction mixtures. The addition of triethylamine increases the yield (68%) and shortens the reaction time up to 15-20 min. The presence of n-butanol inhibits the reaction (according to chromatographic monitoring) almost completely.

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